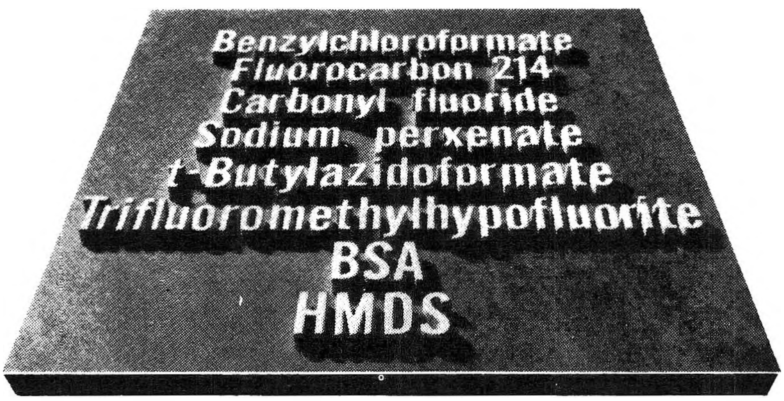
VOLUME 36 APRIL 9, 1971 NUMBER 7 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

PCR RESEARCH PRODUCTS



These and many other research products are always at your fingertips through our latest Catalog G6. If you don't have your copy . . . write now, it's FREE. If you already have our catalog call in your next order and test our service. We know you will be impressed by our quality products and fast delivery.

PCR, INCORPORATED
P.O. Box 1466 / Gainesville, Fla. 32601 / (904) 376-7522

Directory of Graduate Research 1969

Biennial publication of the ACS Committee on Professional Training

Covers the universities and colleges in the United States and Canada known to offer an organized curriculum leading to the doctoral degree in chemistry, biochemistry, chemical engineering, and pharmaceutical or medicinal chemistry.

The guide to graduate schools, research, and personnel in these areas.

201 Departments of Chemistry
165 Departments offering Biochemistry
106 Departments of Chemical Engineering
29 Departments of Pharmaceutical or Medicinal Chemistry

Lists 2807 full- and part-time staff members, each with outline of career, teaching and research specialties, and list of publications for the past two or five years.

Statistical data on departments include number of Ph.D. degrees conferred during the previous two years, number of staff members, and number of postdoctoral appointments.

Other listings include interdisciplinary programs and doctoral theses accepted during previous two years.

1213 pp. with index of names
paper bound (1970) $10.00
postpaid in U.S., plus 50 cents Canada and Pan America, plus 75 cents foreign.

Order from:
Special Issue Sales
American Chemical Society
1155 Sixteenth St., N.W.
Washington, D. C. 20036

THE JOURNAL OF Organic Chemistry

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

EDITOR-IN-CHIEF: FREDERICK D. GREENE

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

SENIOR EDITORS

GLENN A. BERCHTOLD, *Massachusetts Institute of Technology, Cambridge, Massachusetts*
WERNER HERZ, *Florida State University, Tallahassee, Florida*
JAMES A. MOORE, *University of Delaware, Newark, Delaware*
ALEX NICKON, *Johns Hopkins University, Baltimore, Maryland*

ASSISTANT EDITOR: THEODORA W. GREENE

BOARD OF EDITORS

DOUGLAS E. APPLEQUIST
MYRON L. BENDER
RONALD C. D. BRESLOW
ARNOLD BROSSI
JOSEPH F. BUNNETT
CLIFFORD A. BUNTON
MICHAEL P. CAVA
GERHARD L. CLOSS
ALEXANDER D. CROSS
CHARLES H. DEPUY
JACK J. FOX
ROBERT J. HIGHET
EARL S. HUYSER
FREDERICK R. JENSEN
WALTER LWOWSKI
GEORGE A. OLAH
HOWARD E. SIMMONS
EDWARD C. TAYLOR
DAVID J. TRECKER
EDWIN F. ULLMAN
EDGAR W. WARNHOFF
KENNETH B. WIBERG
HOWARD E. ZIMMERMAN

EX-OFFICIO MEMBERS: GEORGE H. COLEMAN, *Wayne State University*
JEREMIAH P. FREEMAN, *University of Notre Dame (Secretary–Treasurer of the Division of Organic Chemistry of the American Chemical Society)*

FOREIGN EDITORS: ROBERT ROBINSON, *170 Piccadilly, London, W.1.*
P. KARRER, *Zurich*

MANAGER, EDITORIAL PRODUCTION: CHARLES R. BERTSCH

Editorial Production Office, American Chemical Society, 20th and Northampton Sts., Easton, Pennsylvania 18042

© Copyright, 1971, by the American Chemical Society.

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

AMERICAN CHEMICAL SOCIETY, *1155 Sixteenth Street, N.W., Washington, D. C. 20036*

Executive Director: FREDERICK T. WALL

BOOKS AND JOURNALS DIVISION

JOHN K CRUM, *Director (ad interim)*
JOSEPH H. KUNEY, *Head, Business Operations Department*
RUTH REYNARD, *Assistant to the Director*

ห้องสมุด กรมวิทยาศาสตร์
4 มิ.ย. 2514

B&N INTERNATIONAL TEXTBOOK SERIES ANNOUNCES ITS FIRST ORGANIC CHEMISTRY TEXTBOOK

COMING IN APRIL 1971 — *GENERAL ORGANIC CHEMISTRY* by Raymond B. Seymour, Professor of Chemistry, University of Houston. Approx.: 525 pp. *Tent.: $5.95*

Designed for a one semester organic chemistry course for non chemistry majors, GENERAL ORGANIC CHEMISTRY emphasizes the practical with up-to-date applications; however, the classical discoveries and chemical aspects are not neglected. Simplicity is maintained throughout the text to retain a high interest level on the part of the non chemistry major, while enough information on mechanisms is provided to meet the needs of the more sophisticated student. Experience with calculus and other instrumental techniques is *not* assumed. A lab text, EXPERIMENTAL ORGANIC CHEMISTRY, by Dr. Jerry Higgins, Illinois State University, will be available for fall classes.

CONTENTS

Preface

1. Introduction
2. Hydrocarbons, Alkanes
3. Cycloalkanes and Alkenes
4. Alkapolyenes and Alkynes
5. Aromatic Hydrocarbons
6. Organic Halides and Cyanides
7. Water, Alcohols, Ethers, Epoxides and Sulfur Compounds
8. Aldehydes and Ketones
9. Carboxylic Acids, Acyl Halides, Anhycrides and Esters
10. Nitro Compounds, Ammonia, Amines, Azo Compounds and Amides
11. Carbohydrates
12. Heterocyclic Compounds, Alkaloids
13. Steroids, Proteins, Nucleic Acids
14. The Characterization of Organic Compounds

For a complimentary examination copy for adoption consideration, write on your college letterhead to: David Richerson, Marketing Manager

Barnes & Noble International Textbook Series, 105 Fifth Avenue, New York, N. Y. 10003

Designed for the potential scientist in your family...

Chemistry magazine

For the high school or college student whose curiosity of chemistry extends *beyond* required course work.

Eleven issues a year, including a special Summer issue, bring the reader
... experimental projects and investigations
... news items on recent research developments
... feature articles on theoretical and applied science
... book reviews
... chemical puzzles
... reader's column

Order CHEMISTRY now and start an exciting adventure for a young member in your family!

All adding up to an exciting opportunity to see chemistry in *action—out of the textbook and in the real laboratory.*

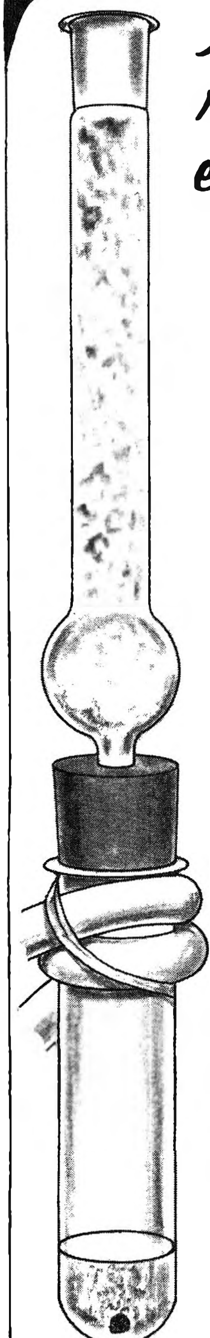
Yes—start a subscription to CHEMISTRY at the low yearly rate of $6.
☐ Canada, PUAS $7.00 ☐ Foreign $7.50
Payment must be made in U.S. currency, by international money order, UNESCO coupons, or U.S. bank draft; or order through your book dealer.
Send CHEMISTRY to:
Name ____
Address ____
City ____ State ____ Zip ____
Recipient is a ☐ student. ☐ teacher. ☐ other ____
☐ Check enclosed (payable to American Chemical Society) ☐ Send bill to:
Name ____
Address ____
City ____ State ____ Zip ____

American Chemical Society
1155 Sixteenth Street, N.W.
Washington, D.C. 20036

E28

THE JOURNAL OF Organic Chemistry®

VOLUME 36, NUMBER 7 APRIL 9, 1971



Mirrors the research lab experience ...

A New Book! Published Jan., 1971

Moore & Dalrymple:

EXPERIMENTAL METHODS IN ORGANIC CHEMISTRY

By JAMES A. MOORE and DAVID L. DALRYMPLE, *both of University of Delaware*

This new text is designed for the laboratory work accompanying a two-semester organic chemistry course taken by chemistry, chemical engineering, and other science majors, and by pre-medical students.

The first group of experiments provides experience in general laboratory procedures and separation methods. Chapters are devoted to the theory and practice of vapor phase, thin layer, and column chromatography, and to IR and NMR spectroscopy.

Organic synthesis, structure determination, and comparison of reactivities are included in the second part of the text. The experiments on reactivity involve both qualitative tests of reactivity and quantitative studies of reaction rates and product mixtures.

The final section describes the identification of organic compounds —emphasizing the use of spectroscopy. The student is shown how to deduce a tentative structure from spectra, physical constants, and solubility properties, and how to complete the identification by the preparation of derivatives or degradation products.

233 pages, 86 figures. $7.75. Published January, 1971. A 69-page *Instructor's Guide* contains a discussion of the individual experiments and lists of chemicals and equipment required for each. Answers to all questions are given in full. The guide includes a table of 193 compounds suitable for use as unknowns.

Moore & Dalrymple: NMR SPECTRA OF UNKNOWNS

For the instructor's convenience, the authors have recorded the nmr spectra (with integration curves) of the 193 dompounds listed in the *Instructor's Guide*. One copy of this set of spectra will be provided free to instructors adopting the text. Sets may also be purchased separately. *Instructors may reproduce these spectra as often as desired* for distribution to students along with samples of unknowns. The spectra are large enough to permit measurement of integral steps and coupling constants. *198 pages. $18.00. Published January, 1971.*

To request copies for adoption consideration, please write Educational Department,

W. B. Saunders Company

West Washington Square, Philadelphia, Pa. 19105

from Cambridge

ORGANIC CHEMISTRY

F. W. EASTWOOD, J. M. SWAN and JEAN B. YOUATT

Second edition of a highly successful programmed learning text, covering all the topics usually found in a first-year organic chemistry course. It can be used both as a class text and as a guide for independent study and home review. $4.95

CAMBRIDGE UNIVERSITY PRESS

32 East 57th Street

New York, N.Y. 10022

Directory of Graduate Research 1969

Biennial publication of the ACS Committee on Professional Training

Covers the universities and colleges in the United States and Canada known to offer an organized curriculum leading to the doctoral degree in chemistry, biochemistry, chemical engineering, and pharmaceutical or medicinal chemistry.

The guide to graduate schools, research, and personnel in these areas.

201 Departments of Chemistry
165 Departments offering Biochemistry
106 Departments of Chemical Engineering
29 Departments of Pharmaceutical or Medicinal Chemistry

Lists 2807 full- and part-time staff members, each with outline of career, teaching and research specialties, and list of publications for the past two or five years.

Statistical data on departments include number of Ph.D. degrees conferred during the previous two years, number of staff members, and number of postdoctoral appointments.

Other listings include interdisciplinary programs and doctoral theses accepted during previous two years.

1213 pp. with index of names paper bound (1970)
$10.00 postpaid in U.S., plus 50 cents Canada and Pan America, plus 75 cents foreign.

Order from: Special Issues Sales, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036

AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

VOLUME 36, NUMBER 7 APRIL 9, 1971

© Copyright 1971 by the American Chemical Society

Steroid Conjugates. VI.[1a] An Improved Koenigs–Knorr Synthesis of Aryl Glucuronides Using Cadmium Carbonate, a New and Effective Catalyst[1b]

R. B. CONROW AND SEYMOUR BERNSTEIN*

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

Received September 1, 1970

The 3-β-D-glucuronide triacetate methyl esters of estrone, 17β-estradiol, estriol, equilin, and equilenin and the 3-β-D-glucoside tetraacetate of estrone were obtained in yields of 46–71% by direct crystallization from a Koenigs-Knorr reaction using a glycosyl halide and the novel catalyst, cadmium carbonate. This represents an approximately tenfold improvement in yield over previously reported methods. Evidence was obtained which suggests that the actual catalyst in these reactions is the resulting cadmium halide. Among the identified by-products were small amounts of the corresponding α anomers and the steroidal 3-acetates. A 4-C-glucuronosyl derivative of equilenin was also obtained in 14% yield. The products were deblocked by standard methods to give the corresponding glucuronides and glucoside.

The importance of glycoside synthesis in many areas of natural product chemistry is well documented.[2] Recently, steroid conjugates,[3] consisting primarily of sulfates and glucuronides, have attracted increasing attention. This stems largely from the growing awareness that their role in the body is not merely one of detoxification.[4] As a result, improved methods for preparing these compounds have assumed greater importance.

Generally, steroidal alicyclic glucuronides are reasonably accessible by present methods.[5] This, however, is not true with steroidal aryl glucuronides.[6,7] For example, reported[6a–c] yields of methyl [17-oxoestra-1,3,5(10)-trien-3-yl-2,3,4-tri-O-acetyl-β-D-glucopyranosid]uronate (4) (henceforth abbreviated, estrone-3-β-D-glucuronide triacetate methyl ester) using silver carbonate in the standard Koenigs–Knorr reaction have not exceeded approximately 7%. Consequently, the isolation of product from such low yield reactions often necessitates tedious crystallization and countercurrent or chromatographic procedures. In connection with our investigation of the biological function of steroid conjugates, a more convenient method for obtaining these compounds was required. Toward this end, an investigation of the catalytic effect of various metals,[8] mainly as their carbonates or oxides, on the glucuronidation of estrone was undertaken. Next in

(1) (a) Part V: J. P. Joseph, J. P. Dusza, E. W. Cantrall, and S. Bernstein, *Steroids*, **14**, 591 (1969); (b) S. Bernstein, presented in part at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969.

(2) For a recent, extensive review of glycosides, see (a) L. Hough and A. C. Richardson in "Rodd's Chemistry of Carbon Compounds," Vol. I^F, S. Coffey, Ed., Elsevier, Amsterdam, 1967, p 320. For additional reviews relating to the Koenigs–Knorr Synthesis, see (b) C. A. Marsh in "Glucuronic Acid," G. J. Dutton, Ed., Academic Press, New York, and London, 1966, p 62; (c) J. Conchie, G. A. Levvy, and C. A. Marsh, *Advan. Carbohyd. Chem.*, **12**, 157 (1957); (d) R. U. Lemieux, *ibid.*, **9**, 1 (1954); (e) W. W. Zorbach and K. V. Bhat, *ibid.*, **21**, 273 (1966); and (f) W. L. Evans, D. D. Reynolds, and E. A. Tally, *ibid.*, **6**, 41 (1951).

(3) For extensive references and reviews pertaining to steroid glucuronide conjugates, see (a) S. Bernstein, E. W. Cantrall, J. P. Dusza, and J. P. Joseph, "Steroid Conjugates, a Bibliography," Chemical Abstracts Service, American Chemical Society, 1966; (b) H. E. Hadd and R. T. Blickenstaff, "Conjugates of Steroid Hormones," Academic Press, New York and London, 1969; (c) S. Bernstein and S. Solomon, Ed., "Chemical and Biological Aspects of Steroid Conjugates," Springer-Verlag, New York, N. Y., 1970, in press; (d) S. Bernstein, J. P. Dusza, and J. P. Joseph, "Physical Properties of Steroid Conjugates," Springer-Verlag, New York, N. Y., 1968; and e) R. Hähnel and N. bin Muslim, *Chromatogr. Rev.*, **11** (3), 215 (1969).

(4) Reference 3b, p 293, and references therein.

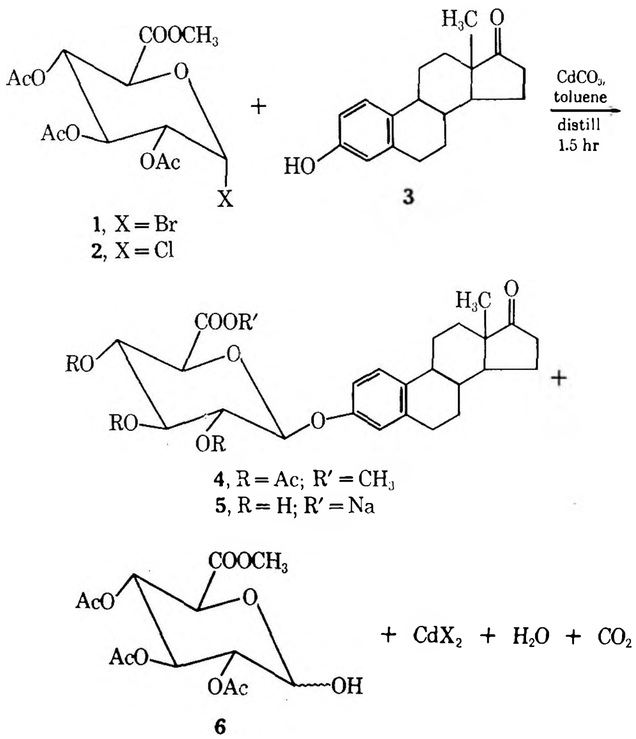
(5) For some examples of the preparation of steroid alicyclic glucuronides in good yield, see (a) J. J. Schneider and N. S. Bhacca, *J. Org. Chem.*, **34**, 1990 (1969); (b) J. F. Becker, *Biochim. Biophys. Acta*, **100**, 574 (1965); (c) V. R. Mattox, J. E. Goodrich, and W. D. Vrieze, *Biochemistry*, **8**, 1188 (1969); (d) Ch. Meystre and K. Miescher, *Helv. Chim. Acta*, **27**, 231 (1944).

(6) (a) E. Schapiro, *Biochem. J.*, **33**, 385 (1939); (b) J. S. Elce, J. G. D. Carpenter, and A. E. Kellie, *J. Chem. Soc.*, 542 (1967); (c) H. H. Wotiz, E. Smakula, N. N. Lichtin, and J. H. Leftin, *J. Amer. Chem. Soc.*, **81**, 1704 (1959); (d) T. Nambara and K. Imai, *Chem. Pharm. Bull.*, **15**, 1232 (1967).

(7) A. Hagedorn, F. Johannessohn, E. Rabald, and H. E. Voss, *Z. Physiol. Chem.*, **264**, 23 (1940) [*Chem. Abstr.*, **34**, 4783^2 (1940)], report the preparation of estrone-3-β-glucoside Ac$_4$ (**7**) in 63% yield from acetobromoglucose using quinoline–Ag_2CO_3 as condensing agent. Other workers [*e.g.*, (b) C. A. Marsh and L. M. Reid, *Biochim. Biophys. Acta*, **97**, 597 (1965); (c) F. G. Muhtadi and M. J. R. Moss, *Tetrahedron Lett.*, 3751 (1969); and (d) H. Tanino, S. Inoue, K. Nishikawa, and Y. Hirata, *Tetrahedron*, **25**, 3033 (1969)], have also found the combination of Ag_2CO_3 or Ag_2O with quinoline useful for the preparation of various aromatic glycosides. However, in our hands the glucuronidation of estrone by this method gave a thick dark mixture from which product could not be crystallized directly. Purification of a sample by tlc (system A) gave **4** in 23% yield.

(8) Helferich and coworkers investigated a variety of materials including the oxides of zinc, cadmium, and mercury as glycosidation catalysts, but mainly for primary alcohols: (a) B. Helferich and K. F. Wedemeyer, *Justus Liebigs Ann. Chem.*, **563**, 139 (1949) [*Chem. Abstr.*, **43**, 7430g (1949)]; (b) B. Helferich and K. F. Wedemeyer, *Chem. Ber.*, **83**, 538 (1950) [*Chem. Abstr.*, **45**, 3336b (1951)]; (c) B. Helferich and A. Berger, *Chem. Ber.*, **90**, 2492 (1957) [*Chem. Abstr.*, **52**, 16224c (1958)]. These workers found that $Hg(CN)_2$ was a particularly effective catalyst and it has since proved of value, expecially where Ag_2CO_3 or Ag_2O gave poor results. See ref 2e, p 278; 2c, p 166; and 2a, p 23.

importance to silver carbonate and oxide as glycosidation catalysts are various salts of mercury, *e.g.*, $Hg(CN)_2$[8] and HgO–$HgBr_2$.[9] While use of the HgO catalyst system with methyl (2,3,4-tri-*O*-acetyl-1-bromo-1-deoxy-α-D-glucopyran)uronate (**1**)[10] (henceforth referred to as bromo sugar **1**) in refluxing toluene (procedure A) gave an improved yield (25%) of estrone-3-β-D-glucuronide triacetate methyl ester, the product was contaminated with organomercury complexes which were difficult to remove. The next element investigated was cadmium[8] inasmuch as this metal is in the same periodic group as mercury. The glucuronidation of estrone in the presence of $CdCO_3$ using procedure A afforded a 54% yield of the glucuronide **4**. Moreover, tlc indicated that the mixture was relatively uncom-



plex, containing chiefly unreacted estrone (28%) in addition to the desired product. Further evidence for the catalytic superiority of cadmium carbonate under these conditions (procedure A) was exemplified by the results obtained with the following compounds: $ZnCO_3$, CdO,[8] CdS, $CoCO_3$, $NiCO_3$, $PbCO_3$,[11] $CuCO_3 \cdot Cu(OH)_2$, and NaOAc. Only the first three compounds gave any product, the yields being approximately 19, 38, and 20%, respectively. With $ZnCO_3$, a dark brown gum precipitated halfway through the reaction, due probably to decomposition of the bromo sugar **1**. It was not surprising that CdO and CdS gave some product since it was reasoned that, as with $CdCO_3$, the resulting $CdBr_2$ was probably the effective catalyst[12] in these reactions. This aspect will be discussed further in conjunction with other factors affecting the reaction.

The initial results obtained with $CdCO_3$ were very encouraging and suggested that a proper selection of reaction conditions would result in complete reaction of the starting steroid. This was desirable not only to obtain a good yield of product but also to facilitate its isolation by direct crystallization from the crude mixture. Efforts in this direction showed that continuous distillation[13] of toluene from the mixture was more effective in bringing the reaction to completion than successive increases in the amount of bromo sugar **1**. A limited investigation of other reaction variables determined that complete reaction of the estrone was achieved when 2 equiv of bromo sugar were added dropwise, over 1 hr, to a mixture of the steroid and $CdCO_3$ in distilling toluene followed by an additional 0.5-hr reaction time. At this stage the organic soluble components of the mixture were predominately product and methyl (2,3,4-tri-*O*-acetyl-D-glucopyran)uronate (**6**).[14] Since the latter compound is water soluble, this allowed an initial purification of the product by dissolving it in dimethylformamide (or, better, acetone) and pouring the solution into water. The desired glucuronide **4** was precipitated in sufficient purity that three crystallizations from methylene chloride–ethanol provided pure material in an isolated yield of 71%. That this method is generally applicable to the preparation of other steroidal phenolic glycosides in good yield is demonstrated by the results in Table I.[15]

TABLE I

PREPARATION OF STEROIDAL PHENOLIC GLYCOSIDES *via* A $CdCO_3$ MEDIATED KOENIGS–KNORR REACTION

Products[a]	Compd no.	Yield, %[b]		Color of reaction
Estrone-3-β-GAc3Me[c]	4		71.0	Pink
Estrone-3-β-GlAc4[d]	7	61.0	67.5	Pink
Estrone-3-α-GlAc4	9	6.5[e]		
Estradiol-17β-formate-3-β-GAc3Me	10		71.0	Pale tan
Estriol-16α,17β-diformate-3-β-GAc3Me	12		65.0	Pale tan
Equilin-3-β-GAc3Me	14		68.0	Pink
Equilenin-3-β-GAc3Me	16	46.0		
Equilenin-3-α-GAc3Me	18	2.0[e]	62.0	Pink changing to pale tan
Equilenin-4-ξ-glucuronosyl Ac3Me	19	14.0[f]		

[a] All products are new compounds except **4** and **7**. [b] Actual yield of product isolated by crystallization, unless otherwise indicated. [c] Stands for estrone-3-β-D-glucuronide triacetate methyl ester. [d] Stands for estrone-3-β-D-glucoside tetraacetate. [e] Isolated by chromatography. [f] Isolated by crystallization and chromatography.

(9) L. R. Schroeder and J. W. Green, *J. Chem. Soc. C*, 530 (1966).

(10) G. N. Bollenback, J. W. Long, D. G. Benjamin, and J. A. Lindquist, *J. Amer. Chem. Soc.*, **77**, 3310 (1955).

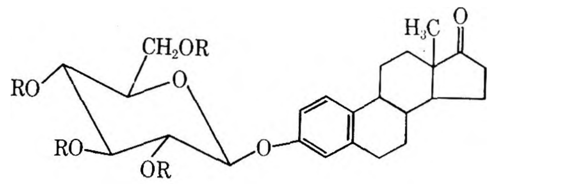
(11) Lead carbonate has been used as a catalyst for the preparation of ortho esters: N. K. Kochetkov, A. J. Khorlin, and A. F. Bachkov, *Tetrahedron Lett.*, 289 (1964).

(12) In glycosidations using mercuric compounds, such as $Hg(CN)_2$ and HgO, the resulting halide is considered to be the active catalyst. See, for example, ref 9.

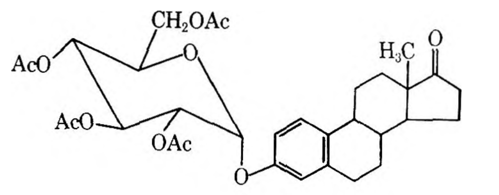
(13) This presumably removes water formed during the reaction and is the basis of the Meystre–Miescher[5d] modification of the Koenigs–Knorr reaction. Other workers have also noted that anhydrous conditions had a beneficial effect on yield. See, for example, ref 6b.

(14) In a similar run, a polar non-uv-absorbing band was isolated as a glass by preparative tlc. Although this material was still somewhat impure, its spectral properties (ir, nmr, and rotation) indicated that it was an anomeric mixture of **6** when compared to an authentic sample of the α anomer of **6** prepared by the method of N. Pravdić and D. Keglević, *J. Chem. Soc.*, 4633 (1964).

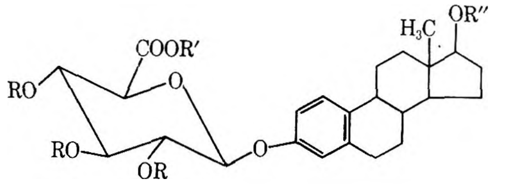
(15) In the limited number of examples tried, the method also gives good yields of steroidal alicyclic glucuronides, except where easily eliminated hydroxyls were involved, as in androsterone, digitoxigenin, and 17α-estradiol. Also, the formation of by-products, such as α anomers, *tends to be greater* than in the aromatic series: R. B. Conrow and S. Bernstein, unpublished results. Cadmium carbonate has also found use in the preparation of the anomeric *N*-acetylglucosaminides of 17α- and 17β-estradiol: J. P. Joseph, J. P. Dusza and S. Bernstein, Steroid Conjugates VII, submitted for publication in *Biochemistry*.



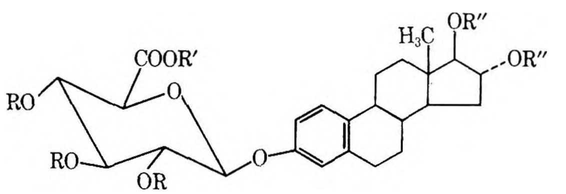
7, R = Ac
8, R = H



9



10, R = Ac; R′ = CH_3; R″ = CHO
11, R = R″ = H; R′ = Na



12, R = Ac; R′ = CH_3; R″ = CHO
13, R = R″ = H; R′ = Na

An interesting feature of the reaction is the development of color on the surface of the cadmium carbonate. This occurs with most of the substrates and in some cases is quite vivid, as indicated in Table I. This aspect will also be discussed further.

The structure of the acetylated β-D-glucuronides and glucosides were fully supported by elemental analysis and spectral studies,[16] including the mass spectrum.[17] Although isolation of all products formed in these reactions was not attempted, some of the more accessible steroid-containing by-products were investigated. In all of the reactions, a weakly polar, uv-absorbing product was observed. In the glucuronidation of estrone and equilenin this was identified as the corresponding steroid 3-acetate, obtained in a yield of approximately 2%. In the preparation of estrone-3-β-D-glucoside tetraacetate (7)[7a] and equilenin-3-β-D-glucuronide triacetate methyl ester (16), the corresponding α anomers[18] 9 and 18 were isolated in yields of 6.5 and 2%, respectively. It is likely that the other reaction mixtures also contained some of the α anomer, but these were either not evident by tlc or could not be isolated in sufficient purity for a positive identification. Initial evidence for the structure of the α anomers was provided by their infrared spectrum,[19] which showed distinct differences in the glycosidic bond region at 1000–1110 cm^{-1}, compared to the β anomer. Thus, the β anomer contains absorption in this region, as a peak or shoulder, which is absent in the α anomer. The net effect is to make the glycosidic bond–ester complex between 1010 and 1110 cm^{-1} appear sharper and somewhat more intense in the α anomer than in the β. The large difference in optical rotations[20] also suggested anomeric pairs. The most conclusive evidence, however, was provided by the nmr spectra which indicated an equatorial–axial relationship ($J_{1',2'}$ = 3.5 Hz)[21] for the C-1,2 sugar protons of the α anomers. It is feasible that the α anomers could be derived from the β as a result of the catalytic effect[22] of $CdBr_2$, or any free hydrogen bromide, formed in the reaction. A most interesting by-product, obtained in significant yield (14%) from the glucuronidation of equilenin, was the *C*-glycosyl compound[23] 4-ξ-glucuronosyl triacetate methyl ester, 19. Its ir spectrum was similar to that of the glucuronide 16 except that it appeared to contain a hydroxyl group and showed differences in the glycosidic bond region.[19] The hydroxyl was confirmed and shown to be phenolic by the uv spectrum which evidenced a bathochromic shift on basification.[24] The failure to detect any equilenin on strong acid hydrolysis[23] of 19 (1:1 2 *N* HCl–EtOH, 4-hr reflux) decreased the possibility that it could have an *O*-glucuronide, ortho ester, or acetal type structure. Moreover, in the mass spectrum[25] of 19 the most abundant ions were those in which the sugar moiety was retained, whereas in the glucuronide 16 the most abundant ions were derived from the eliminated sugar moiety. These

(16) See, ref 2a, p 125, for a review of the structural determination of monosaccharides by physical methods.

(17) A majority of the abundant fragments in the mass spectrum of the glucuronide triacetate methyl esters could be interpreted as arising from loss of OMe, COOMe, acetic acid, and ketene fragments, and cleavage of the glucuronosidic bond. In the glucoside tetraacetate derivatives, the major fragments were associated with loss of OAc, CH_2OAc, acetic acid, and ketene together with cleavage of the glucosidic bond.[2] The fragments are listed (see Experimental Section) in order of decreasing abundance. The first series of numbers represents abundant fragments and the second series represents less abundant fragments in the high mass range.

(18) The formation of α anomers of simple glycosides has been reported when mercuric salts have been used in conjunction with glycosyl halides: see, *e.g.*, ref 2c, p 166; ref 2f, p 46; and ref 8c. Schneider and Bhacca[5a] report the presence of traces of cholesterol-α-D-glucosiduronate Ac_3Me in a preparation of the β anomer from bromo sugar 1 and Ag_2O in benzene at room temperature.

(19) Various absorption bands, mainly in the range of *ca.* 800–950 cm^{-1}, have been attributed to the α- and β-glycosidic linkages. Recently, J. J. Schneider, *Carbohyd. Res.*, **12**, 369 (1970), has reported a band at 1146–1140 cm^{-1} as diagnostic for the α anomers of a series of anomeric, steroidal, aliphatic glucuronide triacetate methyl esters, and glucoside tetraacetates. Effects of the environment of the glycosidic bond on the band contours between 1125 and 1000 cm^{-1} has been demonstrated by E. Smakula, J. H. Leftin, and H. H. Wotiz, *J. Amer. Chem. Soc.*, **81**, 1708 (1959). It was only in this region that obvious and consistent differences existed between the steroidal, anomeric glycosides isolated by the present authors.

(20) Poor absolute agreement was obtained between the calculated and found molecular rotations. However, the figures clearly differentiate between the anomers when considered as differences in orders of magnitude: W. Klyne in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1955, p 98.

(21) L. D. Hall, *Advan. Carbohyd. Chem.*, **19**, 51 (1964).

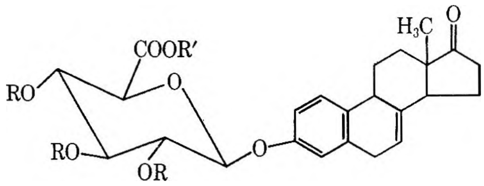
(22) Various Lewis acids have been used to anomerize β- to α-glycosides: E. Pacsu, J. Janson, and B. Lindberg, "Methods in Carbohydrate Chemistry," Vol. II, R. L. Whistler and M. L. Wolfrom, Ed., 1963, p 376. Schneider[19] has recently applied the $TiCl_4$ reagent to the preparation of a series of acetylated, steroidal α-glucuronides, and glucosides from the acetylated β-glucuronide. Several metal halides, including cadmium chloride, have also been shown to cause glycoside anomerization and O → *N*-glycosyl rearrangement: D. Thacker and T. L. V. Ulbricht, *Chem. Commun.*, 122 (1967).

(23) This is believed to be the first reported example of a *C*-glycosyl derivative of a steroid. For a review of *C*-glycosyl derivatives, see L. J. Haynes, *Advan. Carbohydrate Chem.*, **20**, 357 (1965).

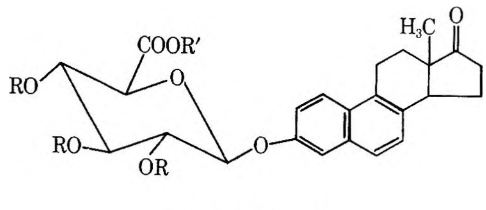
(24) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, New York, N. Y., 1964, p 95.

(25) A. Prox, *Tetrahedron*, **24**, 3697 (1968), discusses the mass spectrum of *C*-glucoside derivatives of flavonoids.

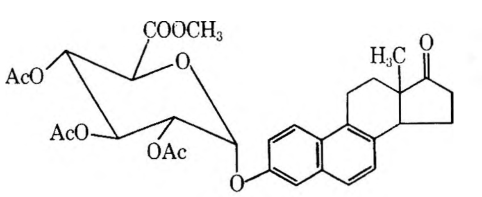
results indicated an exceptionally stable sugar–steroid linkage. The nmr spectrum of **19** revealed two sugar acetates in normal positions at δ 2.01 and 2.09, and a third methyl group far upfield at δ 1.3. This value was appreciably outside the range of δ 1.67–1.75 reported for the C-2 acetate methyl signal of *C*-glucosyl derivatives of flavonoids.[26,27] Thus, some doubt re-



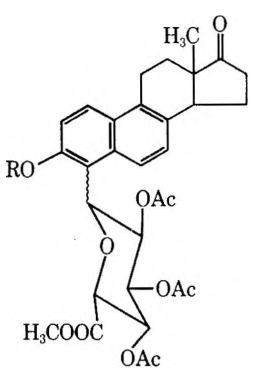
14, R = Ac; R′ = CH_3
15, R = H; R′ = Na



16, R = Ac; R′ = CH_3
17, R = H; R′ = Na



18



19, R = H
20, R = CH_3

mained about the actual structure of the unknown. Methylation of the product with diazomethane gave **20** whose nmr spectrum proved easier to interpret than that of the phenol **19**. Furthermore the sugar C-2 acetate methyl was found at δ 1.62 which was more consistent with the previously mentioned values[26,27] for related compounds. Two pairs of ortho aromatic protons were clearly evident in the nmr spectrum of **20** and this showed that the sugar must be substituted at C-4 of the steroid.[28] By using field-sweep decoupling techniques, it was shown that doublets at δ 8.0 and 7.25 were associated, and these were assigned to the C-1 and C-2 protons, respectively. Similarly, doublets at δ 8.38 and 7.42 were associated and these were assigned to the C-6 and C-7 protons, respectively. Significantly, the doublet at δ 8.38 was very diffuse at ambient temperature (40°), whereas at 90° it sharpened to a normal pattern. This indicated steric hindrance between the sugar and C-6 proton and confirmed the assignment for the aromatic protons. The configuration of the glucuronosyl–steroid bond is the only structural feature which remains in doubt because of the obscurity of the C-1 sugar proton[29] in the nmr spectrum. The formation of **19** in significant yield indicates that cadmium carbonate may have value for the preparation[30] of other *C*-glycosyl derivatives of reactive aromatic compounds.

Additional information on the nature and limitations of the cadmium carbonate promoted glycosidation reaction was obtained during the course of our investigations. While the glucuronidation of estrone was run successfully in benzene, toluene, or chlorobenzene, no reaction was obtained in toluene when dimethylacetamide (17%), sulfolane (17%), or pyridine (1 equiv with respect to the halo sugar) were present. The reason for failure of the reaction under these conditions is unknown, but complexing[31] of the cadmium halide with the polar additive is one possibility. Evidence suggesting that the cadmium halide, or a cadmium halide species, produced in the reaction is the actual catalyst[12] was obtained in experiments with the chloro sugar **2**.[32] Thus, when **2** was used in the glucuronidation of estrone, the yield (75%) of product compared favorably to that obtained with bromo sugar **1**. However, initiation of the reaction, as manifested by a change in color[33] (colorless to pale tan and finally red), did not occur until 30 min after the addition of chloro sugar was started. In reactions with bromo sugar, color change was evident after 3–5 min. It seemed likely that the longer induction period was the result of the greater thermal stability of the chloro sugar and, hence, the longer time required for the formation of trace amounts of hydrogen halide and, hence, of cadmium halide before the reaction could become autocatalytic. Indeed, when the reaction mixture was treated with a trace of anhydrous hydrogen chloride prior to the dropwise addition of chloro sugar **2**, the formation of product was evident after 5 min. Moreover, when the cadmium carbonate was pretreated with excess anhydrous hydrogen chloride, the glucuroni-

(26) W. E. Hillis and D. H. S. Horn, *Aust. J. Chem.*, **18**, 531 (1965).

(27) At a recent conference, however, it was learned that the C-2 acetate methyl of the 1-glucosyl-Ac4 derivative of naphthalene[30a] resonates at δ 1.5: L. J. Haynes, CIC–ACS Joint Conference, Toronto, May 1970.

(28) This is also the expected position of substitution by analogy with electrophilic substitution in naphthalene which goes almost exclusively in the α position: H. Zollinger, "Azo and Diazo Chemistry," Interscience, New York, N. Y., 1961, p 231, and references therein.

(29) The C-1,2,3,4 sugar protons of **20** are grouped together over the range of δ 5.42–5.92.

(30) Aromatic *C*-glycosyl derivatives have been prepared *via* glycosyl halides using (a) Friedel-Crafts catalysts or Grignard reagents [W. A. Bonner, *Advan. Carbohyd. Chem.*, **6**, 251 (1951)] and (b) metal alkoxides. See, for example, V. K. Bhatia and T. R. Seshadri, *Tetrahedron Lett.*, 1741 (1968).

(31) Stable complexes of cadmium halides with a variety of nucleophiles have been reported. For example, see, J. C. Barnes and C. S. Duncan, *J. Chem. Soc. A*, 1746 (1969), and B. Paul and D. V. R. Rao, *Can. J. Chem.*, **46**, 334 (1968).

(32) W. D. S. Bowering and T. E. Timell, *J. Amer. Chem. Soc.*, **82**, 2827 (1960).

(33) That the appearance of color did in fact correspond to the initiation of the reaction was verified by tlc monitoring of the reaction.

dation reaction again proceeded smoothly, and to completion, with little or no apparent induction period. In view of this, it was surprising to find that commercial anhydrous $CdCl_2$ or $CdBr_2$ were ineffective as catalysts.[34] The reason for this is obscure and requires further investigation. Inasmuch as the reaction is apparently heterogeneous, one possibility could be a difference in surface properties, such as surface area. Thus, when different brands[35] of cadmium carbonate were used, it was observed that the particle size and, hence, surface area of the catalyst had a large effect on the rate of the reaction. This effect is consistent with a heterogeneous reaction.

The free glucuronides were obtained by alkaline hydrolysis of the acetylated products, avoiding vigorous conditions. Thus, the glucuronide triacetate methyl esters were treated with a 1.0 molar excess of aqueous sodium hydroxide in methanol or ethanol at room temperature for 1 hr. Generally the product precipitated and was readily crystallized from aqueous ethanol. However, attempts to crystallize equilin-3-glucuronide (**15**) were unsuccessful. The product was purified reasonably well (tlc evidence) by precipitation but failed to give a satisfactory elemental analysis. Estrone-3-β-D-glucoside tetraacetate (**7**) was treated with saturated ammonia–methanol solution overnight at 4° to give the deblocked glucoside **8** in good yield.

Experimental Section[36]

Procedure A. Trial Glucuronidations of Estrone.—A mixture of 250 mg (0.925 mmol) of estrone and 1.5 mmol of the catalyst in 14 ml of toluene was distilled until *ca.* 2 ml of toluene had been removed. The mixture was cooled slightly and 600 mg (1.51 mmol) of bromo sugar[10] **1** was added. The mixture was stirred and refluxed for 1 hr and then filtered through Celite and evaporated to an oil. Half of the crude product was purified by preparative tlc (system A) and material from the product band was crystallized once from CH_2Cl_2–EtOH. With NaOAc, 3.0 mmol were used. With CdS as catalyst, the mole ratio of estrone: bromo sugar:CdS was 1:2:4. In the reaction with HgO–$HgBr_2$ (1.5:0.07 mmol) the product was partially obscured on the tlc plate by strongly uv-absorbing materials, and it was necessary to purify the product again by tlc.

Procedure B. General Glucuronidation Procedure Using $CdCO_3$.—All equipment and reagents were thoroughly dried before use. A mixture of the steroid (5.0 mmol), cadmium carbonate[35] (1.72 g, 10.0 mmol), and 100 ml of toluene was distilled until *ca.* 25 ml of toluene had been removed, thus ensuring dryness of the reagents and equipment. A solution of the bromo sugar[10] **1** (3.97 g, 10.0 mmol) in 100 ml of toluene was added dropwise to the stirred mixture over 1 hr and an equal volume of toluene was distilled from the flask at the same rate. Distillation was continued for a further 0.5 hr during which an equal volume (50 ml) of makeup toluene was added dropwise. The mixture was filtered through a pad of Celite, and the filtrate was evaporated to an oil. The oil was dissolved in dimethylformamide or acetone (25–50 ml) and poured into water (200 ml). The mixture was filtered through a pad of Celite and the precipitate was washed on the filter with water and then dissolved in CH_2Cl_2. The resulting solution was dried and evaporated to give the crude product as an easily crystallizable oil. Additional purification is outlined below under the individual compounds.

Methyl [17-Oxoestra-1,3,5(10)-trien-3-yl-2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosid]uronate (**4**).—The crude product (3.15 g) obtained from the general procedure B using 1.35 g (5.0 mmol) of estrone was crystallized three times from CH_2Cl_2–EtOH to give 2.09 g (71%) colorless plates, mp 222–230°. Analytical material was obtained by further purification of a sample by tlc (system A). The product was crystallized twice from CH_2Cl_2–EtOH to give colorless plates: mp 230–233°; $[\alpha]^{25}D$ +55° (*c* 0.70, $CHCl_3$); ir (KBr) 1754 (ester + C-17, C=O), 1493 (aromatic), 1220 (ester COC), 1094 sh (glycosidic COC), 1040 cm^{-1} (ester); uv max (MeOH) 217, 278 mμ (ε 10,500, 1470); nmr ($CDCl_3$) δ 7.18 (d, 1, H-1), 6.78 (m, 2, H-2,4), 5.25 (m, 4, H-1′,2′,3′,4′), 4.17 (m, 1, H-5′), 3.73 (s, 3, COOMe), 2.85 (m, 2′, C-6 CH_2), 2.05 (s, 9, three OAc), 0.90 (s, 3, H-18); mass spectrum[17] *m/e* 127, 155, 197, 257, 317, 215, 270, *m/e* 365, 407, 393, 527, 467, 586 (M^+), 425, 423, 555, 569.

Anal. Calcd for $C_{31}H_{38}O_{11}$: C, 63.47; H, 6.53. Found: C, 63.24; H, 6.44.

17-Oxoestra-1,3,5(10)-trien-3-yl-2′,3′,4′,6′-tetra-*O*-acetyl-D-glucopyranoside, β and α Anomers (7 and 9).—The crude product (3.43 g) obtained from the general procedure B using 1.35 g (5.0 mmol) of estrone and 3.95 g (9.61 mmol) of acetobromoglucose[37] was crystallized once from CH_2Cl_2–EtOH to give 1.85 g (61%) colorless needles, mp 212–216°. Analytical material was obtained as follows. The product, in CH_2Cl_2 solution, was filtered through a bed of Magnesol (20 g) using 300 ml of CH_2Cl_2 wash. Material from the filtrate was crystallized once from CH_2Cl_2–EtOH to give the β anomer **7** as fine colorless needles: 1.55 g; mp 214–217°; $[\alpha]^{25}D$ +65° (*c* 1.02, $CHCl_3$); ir (KBr) 1761 (acetate and C-17, C=O), 1504 (aromatic), 1232 (acetate COC), 1081 sh, 1067 sh (glycosidic COC), 1047 cm^{-1} (acetate); uv max (MeOH) 215, 275 mμ (ε 11,400, 1560); nmr ($CDCl_3$) δ 7.18 (d, 1, H-1), 6.78 (m, 2, H-2,4), 5.17 (m, 4, H-1′,2′,3′,4′), 4.23 (m, 2, H-6′CH_2), 3.90 (m, 1, H-5′), 2.85 (m, 2, H-6 CH_2), 2.08, 2.05, 2.03 (t, 12, four OAc), 0.90 (s, 3, H-18); mass spectrum[17] *m/e* 169, 109, 331, 127, 170, 145, 139, 271, *m/e* 379, 365, 353, 407, 421, 541, 600 (M^+), 527, 437.

Anal. Calcd for $C_{32}H_{40}O_{11}$: C, 64.00; H, 6.71. Found: C, 63.73; H, 6.62.

All mother liquors from the isolation of **7** were evaporated to a glass which was purified by partition chromatography on Celite using heptane:chloroform:methanol:water 50:1:10:2.5. In order of elution, there was obtained estrone 3-acetate (37 mg), α anomer **9** (244 mg), and β anomer **7** (404 mg) as uncrystallized glasses. The α-anomer fraction was crystallized from ether–hexane to give 194 mg (6.5%) colorless crystals, mp 95–100° (partial) and 125–135° (final). Material of analytical purity was obtained by an additional crystallization from ether–hexane followed by a final crystallization from isopropyl ether. Slow cooling gave colorless needles solvated with isopropyl ether. Drying overnight at 100° *in vacuo* gave unsolvated needles of α anomer **9**: mp 133–136°; $[\alpha]^{25}D$ +203° (*c* 0.64, $CHCl_3$); ir (KBr) 1757 (acetate + C-17, C=O), 1499 (aromatic), 1229 (acetate COC), 1075 sh (glycosidic COC), 1044 cm^{-1} (acetate); uv max (MeOH) 215, 275 mμ (ε 11,000, 1380); nmr ($CDCl_3$ +

(34) Interestingly, in a similar case Helferich[8a] observed that, whereas $HgBr_2$ was practically inactive as a glycosidation catalyst, it had a net rate-enhancing effect when used in conjunction with the active catalyst $Hg(CN)_2$ (in methanol).

(35) When $CdCO_3$ from Fisher Scientific Co. was used for the glucuronidation of estrone, the reaction was incomplete at 48% yield of **4**, whereas under the same conditions Baker Analyzed $CdCO_3$ gave a 71% yield of product. However, when the Fisher material was vigorously ground in a mortar, it gave a 58% yield of product. In view of this, the reaction time and/or amount of $CdCO_3$ outlined in the general procedure (see Experimental Section) may have to be increased for optimum yields in some cases.

(36) The $CdCO_3$ used throughtout was Baker Analyzed material unless otherwise indicated.[35] The toluene was distilled over CaH_2 and stored over molecular sieves (Linde, type 4A). Magnesol (Food Machinery Chemical Corp.) is a hydrous magnesium sulicate, decolorizing adsorbent. Celite (Johns-Manville Co.) is a diatomaceous silica filter aid. Solutions were dried over anhydrous Na_2SO_4 and all evaporations were under reduced pressure. In crystallizations from CH_2Cl_2–EtOH, the material was dissolved in CH_2Cl_2 and absolute EtOH added to the boiling solution until all of the CH_2Cl_2 had been removed. Thin layer chromatography (tlc) was carried out on 250-μ-thick, silica gel GF Uniplates (Analtech Inc.). In preparative tlc, 20 × 20 cm plates with 500–1000-μ layers of silica gel GF were used. For the acetylated glucuronides, the plates were developed twice with 5% acetone–benzene (system A) unless otherwise indicated. A useful system for the deblocked glucuronides was $CHCl_3$–HOAc–H_2O, 30:35:3 (system B). Visualization was by uv light and 10% phosphomolybdic acid–methanol spray. Melting points were determined on a Mel-Temp apparatus in open capillaries and are uncorrected. The infrared spectra were run in pressed KBr disks on a Perkin-Elmer Model 21 spectrophotometer. Ultraviolet spectra were run on a Cary Model 11 recording spectrophotometer. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer with tetramethylsilane as internal standard. The mass spectra were determined at 70 eV on an Associated Electrical Industries MS-9 instrument.

(37) C. E. Redemann and C. Niemann, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 11.

C_6D_6) δ 7.00 (m, 3, H-1,2,4), 5.82 (t, 1, *J* = 9.0 Hz, H-3′), 5.75 (d, 1, *J* = 3.5 Hz, H-1′), 5.38 (m, 1, H-4′), 5.08 (q, 1, *J* = 10.0 Hz, H-2′), 4.12 (m, 2, H-5′ CH_2), 2.73 (m, 2, H-6 CH_2), 1.88, 1.87, 1.85, 1.82 (q, 12, four OAc), 0.88 (s, 3, H-18); mass spectrum[17] *m/e* 169, 109, 331, 127, 170, 270, 145 139, 271, *m/e* 600 (M^+), 379, 365, 353, 541, 421, 395, 407, 437, 439.

Anal. Calcd for $C_{32}H_{40}O_{11}$: C, 64.00; H, 6.71. Found: C, 63.82; H, 6.60.

Methyl [17β-Formyloxyestra-1,3,5(10)-trien-3-yl-2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosid]uronate (10).—The crude product (3.4 g) obtained from the general procedure B using 1.50 g (5.0 mmol) of estradiol-17β-formate[38] was crystallized three times from CH_2Cl_2–EtOH and then filtered through a bed of Magnesol (24 g) using 300 ml of CH_2Cl_2 wash. The filtrate was evaporated, and the residue was crystallized twice from CH_2Cl_2–EtOH to give 10 as colorless crystals (2.18 g, 71%) of analytcal purity and mp 260–263°: $[\alpha]^{25}D$ 0° (*c* 0.73, $CHCl_3$); ir (KBr) 1764 (ester C=O), 1724 (formate C=O), 1502 (aromatic), 1222 (ester COC), 1183 sh (formate COC), 1096 (glycosidic COC), 1045 cm^{-1} (ester); uv max (MeOH) 215, 278 mμ (ε 13,000, 1540); nmr ($CDCl_3$) δ 8.10 (s, 1, OCHO), 7.17 (d, 1, H-1), 6.78 (m, 2, H-2,4), 5.25 (m, 4, H-1′,2′,3′,4′), 4.77 (m, 1, H-17), 4.23 (m, 1, H-5′), 3.73 (s, 3, COOMe), 2.82 (m, 2, C-6 CH_2), 2.03 (s, 9, three OAc), 0.85 (s, 3, H-18); mass spectrum[17] *m/e* 127, 155, 197, 257, 317, 215, 300, *m/e* 395, 437, 423, 557, 497, 585, 571, 616 (M^+).

Anal. Calcd for $C_{32}H_{40}O_{12}$: C, 62.32; H, 6.54. Found: C, 62.31; H, 6.55.

Methyl [16α,17β-Diformyloxyestra-1,3,5(10)-trien-3-yl-2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosid]uronate (12).—The crude product (1.8 g) obtained from half the scale of the general procedure B using 861 mg (2.5 mmol) of estriol-16α,17β-diformate[38] was crystallized three times from CH_2Cl_2–EtOH in presence of activated carbon to provide 1.08 g (65%) of colorless crystals, mp 225–230°. The analytical sample was obtained by an additional crystallization from CH_2Cl_2–EtOH followed by filtering the product through a small bed of Magnesol, in CH_2Cl_2 solution. The resulting material was given a final crystallization from CH_2Cl_2–EtOH to afford 12 as colorless needles: mp 225–233°; $[\alpha]^{25}D$ −34° (*c* 0.71, $CHCl_3$); ir (KBr) 1770 (ester C=O), 1736 (formate C=O), 1506 (aromatic), 1232 (ester COC), 1172 (formate COC), 1100 sh, 1075 sh (glycosidic COC), 1047 cm^{-1} (ester); uv max (MeOH) 215, 275 mμ (ε 14,200, 1650); nmr ($CDCl_3$) δ 8.10 (s, 1, C-17 OCHO), 8.01 (s, 1, C-16 OCHO), 7.17 (d, 1, H-1), 6.77 (m, 2, H-2,4), 5.25 (m, 6, H-1′,2′,3′,4′ + H-16,17), 4.18 (m, 1, H-5′), 3.72 (s, 3, COOMe), 2.82 (m, 2, H-6 CH_2), 2.03 (s, 9, three OAc), 0.88 (s, 3, H-18); mass spectrum[17] *m/e* 155, 127, 317, 257, 197, 215, 344, *m/e* 439, 386, 481, 601, 467, 541, 660 (M^+), 497, 629, 569, 615.

Anal. Calcd for $C_{33}H_{40}O_{14}$: C, 59.99; H, 6.10. Found: C, 59.82; H, 6.08.

Methyl [17-Oxoestra-1,3,5(10),7-tetraen-3-yl-2′,3′,4′-tri-*O*-acetyl-β-D-glucopyranosid]uronate (14).—The crude product (3.38 g) obtained from the general procedure B using 1.34 g (5.0 mmol) of equilin was crystallized three times from CH_2Cl_2–EtOH to give 2.0 g (68.5%, two crops) of colorless needles, mp 154–159°. The analytical sample was obtained as follows. The product was crystallized from CH_2Cl_2–EtOH and then filtered through a bed of Magnesol in methylene chloride solution. Material from the filtrate was crystallized twice from ether–hexane to give 14 as colorless crystals: mp 165–169°; $[\alpha]^{25}D$ +119° (*c* 0.80, $CHCl_3$); ir (KBr) 1764 (ester + C-17 C=O), 1504 (aromatic), 1224 (ester COC), 1099 (glycosidic COC), 1046 cm^{-1} (ester); uv max (MeOH) 275, 283 mμ (ε 1520, 1400); nmr ($CDCl_3$) δ 7.20 (d, 1, H-1), 6.88 (m, 2, H-2,4), 5.55 (m, 1, H-7), 5.30 (m, 4, H-1′,2′,3′,4′), 4.22 (m, 1, H-5′), 3.75 (s, 3, COOMe), 3.47 (m, 2, H-6 CH_2), 2.05, 2.03 (d, 9, three OAc), 0.78 (s, 3, H-18); mass spectrum[17] *m/e* 187, 155, 317, 257, 197, 215, 268, 266, *m/e* 363, 582, 584 (M^+), 405, 525, 391, 465.

Anal. Calcd for $C_{31}H_{36}O_{11}$: C, 63.69; H, 6.20. Found: C, 63.59; H, 6.10.

Methyl [17-Oxoestra-1,3,5(10),6,8-pentaen-3-yl-2′,3′,4′-tri-*O*-acetyl-D-glucopyranosid]uronate, β and α Anomers (16 and 18). Methyl [3-Hydroxy-17-oxoestra-1,3,5(10),6,8-pentaen-4-yl-2′,-3′,4′-tri-*O*-acetyl-1′-deoxy-1′-ξ-D-glucopyran]uronate (19).—The crude product (3.05 g) obtained from the general procedure B using 1.33 g (5.0 mmol) of equilenin was crystallized from CH_2Cl_2–EtOH (30–35 ml) to give 1.38 g, mp 210–216°, of almost pure β-glucuronide 16 by tlc (system A). On concentration of the mother liquor to 10–15 ml, there was obtained 267 mg of crystalline material, mp 248–262° dec, which was substantially pure *C*-glucuronosyl derivative 19 by tlc (system A).

The β-glucuronide 16 was crystallized again from CH_2Cl_2–EtOH to provide 1.35 g (46%) of colorless crystals, mp 212–216°. Analytical material was obtained by filtering the product through a bed of Magnesol using CH_2Cl_2 as eluent followed by a final crystallization from CH_2Cl_2–EtOH to give 16 as colorless crystals: mp 215–218°; $[\alpha]^{25}D$ +13° (*c* 0.87, $CHCl_3$); ir (KBr) 1767 (ester + C-17 C=O), 1631, 1608 (aromatic), 1229 (ester COC), 1099 (glycosidic COC), 1044 cm^{-1} (ester); uv max (MeOH), 232 (ε 74,500), 269 (4600), 280 (5530), 291 (4360), 318 (1750), 332 mμ (2040); nmr ($CDCl_3$) δ 7.93 (d, 1, *J* = 8.0 Hz, H-6), 7.27 (m, 3, H-2,4,7), 5.37 (m, 4, H-1′,2′,3′,4′), 4.27 (m, 1, H-5′), 3.75 (s, 3, COOMe), 2.07 (s, 9, three OAc), 0.78 (s, 3, H-18); mass spectrum[17] *m/e* 155, 127, 317, 197, 257, 266, 215, 223, 210, *m/e* 582 (M^+), 361, 522, 523, 403, 462, 463.

Anal. Calcd for $C_{31}H_{34}O_{11}$: C, 63.90; H, 5.88. Found: C, 63.76; H, 5.76.

The *C*-glucuronosyl compound 19 was crystallized twice from CH_2Cl_2–EtOH to give 205 mg (7.0%) of analytical material as off-white crystals: mp 265–268°; $[\alpha]^{26}D$ +83° (*c* 0.86 $CHCl_3$); ir (KBr) 3436 (OH), 1767 (ester + C-17 C=O), 1626, 1608 (aromatic), 1224 (ester COC), 1105, 1037 cm^{-1} (ester); uv max (MeOH) 236 (ε 61,750), 276 (4950), 287 (6700), 299 (6110), 333 (3500), 345 mμ (3780); uv max (0.1 *N* NaOH, MeOH), 216 (ε 51,250), 247 (50,400), 279 (7000), 290 (7560), 301 sh (4360), 363 mμ (4360); nmr ($CDCl_3$) δ 8.10 (br m, 1, H-6), 7.92 (d, 1, *J* = 9.5 Hz, H-1), 7.28 (d, 1, *J* = 8.5 Hz H-7), 7.18 (d, 1, *J* = 9.5 Hz, H-2), 5.57 (m, 4, H-1′,2′,3′,4′), 4.33 (m, 1, H-5′), 3.80 (s, 3, COOMe), 2.08, 2.00 (d, 6, C-3′, C-4′ OAc), 0.13 (s, 3, C-2′ OAc) 0.72 (s, 3, H-18); mass spectrum[17] *m/e* 582 (M^+), 319, 343, 361, 303, 403, 331, 279, 308, 294, 238, 251, 197, *m/e* 522, 540, 420, 480.

Anal. Calcd for $C_{31}H_{34}O_{11}$: C, 63.90; H, 5.88. Found: C, 63.64; H, 5.76.

Filtrates from the crystallization of 16 and 19 were evaporated and the residue (*ca.* 1.6 g) was chromatographed on silica gel (150 g, Mallinckrodt SilicAR CC-7, 100–200 mesh). Elution with 5% then 10% acetone–hexane gave 40 mg (2.6%) of material which on crystallization from ether–hexane afforded tan crystals, mp 140–153°, of equilenin 3-acetate by ir. Elution with 15% acetone–hexane gave the next fraction of 328 mg which on crystallization from acetone–benzene provided 192 mg (14.5%), mp 240–250°, of yellow solid which was equilenin by ir and tlc. Elution with 20% acetone–hexane gave 125 mg of crude α anomer 18 (see preparation of analytical material below). Increasing the polarity of the eluent to 30% acetone–hexane provided 203 mg of material as the next component. This was crystallized from CH_2Cl_2–EtOH to give 84 mg (2.9%), mp 206–212°, of additional β-glucuronide 16. Continuing with 30% acetone–hexane gave 363 mg of solid which on crystallization from CH_2Cl_2–EtOH provided 225 mg (7.7%), mp 254–265°, of tan crystals of additional *C*-glucuronosyl derivative 19.

The α anomer 18, obtained above, was purified further by tlc (developed six times with 25% acetone–hexane) to give 66 mg (2.3%) of product. Crystallization from ether followed by two crystallizations from EtOH provided the α-glucuronide 18 as colorless needles: mp 226–230°; $[\alpha]^{25}D$ +183° (*c* 0.45 $CHCl_3$); ir (KBr) 1757 (ester + C-17 C=O), 1629, 1608 (aromatic), 1229 (ester COC), 1078 sh (glycosidic COC), 1053 cm^{-1} (ester); uv max (MeOH) 232 (ε 71,600), 268 (4360), 280 (5240), 291 (4075), 317 (1750), 332 mμ (1800); nmr ($CDCl_3$) δ 7.93 (d, 1, *J* = 9.5 Hz, H-1), 7.65 (d, 1, *J* = 8.5 Hz, H-6), 7.37 (m, 3, H-2, 4, 7), 5.98 (d, 1, *J* = 3.5 Hz, H-1′), 5.82 (t, 1, *J* = 10.0 Hz, H-3′), 5.30 (t, 1, *J* = 10.0 Hz, H-4′), 5.15 (q, 1, *J* = 10.0 Hz, H-2′), 4.50 (d, 1, *J* = 10.0 Hz, H-5′), 3.72 (s, 3, COOMe), 2.07, 2.05, 2.03 (t, 9, three OAc), 0.79 (s, 3, H-18); mass spectrum[17] *m/e* 155, 127, 266, 197, 257, 317, 215, 156, 210, 223, 209, 582 (M^+), *m/e* 522, 523, 403.

Anal. Calcd for $C_{31}H_{34}O_{11}$: C, 63.90; H, 5.88. Found: C, 63.75; H, 5.77.

Methyl [3-Methoxy-17-oxoestra-1,3,5(10),6,8-pentaen-4-yl-2′,3′,4′-tri-*O*-acetyl-1′-deoxy-1′-ξ-D-glucopyran]uronate (20).—To a solution of 150 mg (0.257 mmol) of the *C*-glucuronosyl phenol 19 in 2 ml of CH_2Cl_2 and 2 ml of MeOH was added a solution of diazomethane (*ca.* 2.7 mmol) in 10 ml of ether. The

(38) J. P. Dusza and J. P. Joseph (unpublished work) prepared these compounds by selective formylation of the parent steroid with 88% formic acid on the steam bath.

solution was stored overnight in the dark at room temperature. Evaporation of the solution gave a solid which was only 50% reacted by tlc. The product was reacted again as above using 10 ml of 1:1 CH_2Cl_2:CH_3OH and a solution of diazomethane (*ca.* 4.1 mmol) in 15 ml of ether. The excess CH_2N_2 was decomposed with a small amount of HOAc and the solution evaporated. The residue was purified by tlc (developed twice with 10% acetone–benzene) and crystallized from CH_2Cl_2–EtOH and finally from CH_2Cl_2–CH_3OH to give 104 mg of **20** as a colorless solid: mp 290–303°; $[\alpha]^{25}D$ −3.5° (*c* 0.86 $CHCl_3$); ir (KBr) 1754 (ester + C-17 C=O), 1621, 1600 (aromatic), 1241, 1218 (ester COC), 1103 sh, 1034 cm^{-1} (ester); uv max (MeOH) 236 (ϵ 94,000), 276 (6260), 287 (8640), 299 (7750), 330 (4470), 344 mμ (4780); nmr ($CDCl_3$) δ 8.38 (br m, 1, H-6), 8.00 (d, 1, *J* = 9.5 Hz, H-1), 7.42 (d, 1, *J* = 8.5 Hz, H-7), 7.25 (d, 1, *J* = 9.5 Hz, H-2), 5.67 (m, 4, H-1',2',3',4'), 4.28 (m, 1, H-5'), 3.96 (s, 3, C-3 OMe), 3.74 (s, 3, COOMe), 2.08, 2.01 (d, 6, C-3',4' OAc), 1.62 (s, 3, C-2' OAc), 0.78 (s, 3, H-18); nmr ($CDCl_3$ + C_6D_6 at 90°) δ 8.37 (d, 1, *J* = 9.0 Hz, H-6); mass spectrum[17] *m/e* 375, 596 (M^+), 143, 357, 309, 127, 417, *m/e* 477, 536, 527, 610, 553, 565.

Anal. Calcd for $C_{32}H_{36}O_{11}$: C, 64.42; H, 6.08. Found: C, 64.40; H, 6.06.

Hydrolysis of Acetylated Glycosides. Sodium [17-Oxoestra-1,3,5(10)-trien-3-yl-β-D-glucopyranosid]uronate (5).—To a suspension of 1.17 g (2.0 mmol) of the glucuronide triacetate methyl ester **4** in 30 ml of absolute MeOH was added 2.0 ml (10.0 mmol) of 5 *N* NaOH. The mixture was stirred at room temperature for 1 hr then coevaporated several times with EtOH to a small volume. The product was filtered and crystallized from 90% aqueous EtOH to give 635 mg (64%) colorless plates, 270–288° dec. The analytical sample was obtained by an additional crystallization from 90% EtOH to give **5** as colorless plates: 287–297° dec; $[\alpha]^{25}D$ +26° (*c* 0.92, H_2O); ir (KBr) 3413 (OH), 1739 (C-17 C=O), 1618 (carboxylate C=O), 1497 (aromatic), 1404 (COO^-), 1060 cm^{-1} (hydroxyl CO); uv max (MeOH) 215, 275 mμ (ϵ 9700, 1240); nmr (DMSO-d_6) δ 7.20 (d, 1, H-1), 6.83 (m, 2, H-2,4), 5.40 (br s, 3, OH), 4.80 (m, 2, sugar H's), 0.83 (s, 3, H-18).

Anal. Calcd for $C_{24}H_{29}O_8Na\cdot1^1/_2H_2O$: C, 58.17; H, 6.51; H_2O, 5.45. Found: C, 58.46; H, 6.25; H_2O,[39] 4.1.

Sodium [17β-Hydroxyestra-1,3,5(10)-trien-3-yl-β-D-glucopyranosid]uronate (11).—To a suspension of 1.23 g (2.0 mmol) of the formylglucuronide triacetate methyl ester, **10**, in 60 ml of absolute MeOH was added 2.8 ml (14.0 mmol) of 5 *N* NaOH. The mixture was stirred at room temperature for 1 hr then coevaporated several times with EtOH to small volume and filtered. The product was crystallized from 70% aqueous acetone to give 666 mg (65%) of **11** as colorless crystals, 270–279° dec. An additional crystallization from aqueous acetone gave analytical material as colorless plates: 271–280° dec; $[\alpha]^{26}D$ −13° (*c* 0.99 H_2O); ir (KBr) 3390 (OH), 1616 (carboxylate C=O), 1497 (aromatic), 1418 (COO^-), 1060 cm^{-1} (hydroxyl CO); uv max (MeOH) 215, 275 mμ (ϵ 10,000, 1300); nmr (DMSO-d_6) δ 7.17 (d, 1, H-1), 6.78 (m, 2, H-2,4), 6.55 (m, 1, C-17 OH?), 5,35 (s, 3, OH), 4.77 (m, 1, sugar H?), 4.53 (m, 1, sugar H?), 0.67 (s, 3, H-18).

Anal. Calcd for $C_{24}H_{31}O_8Na\cdot2^1/_2H_2O$: C, 55.91; H, 7.04; H_2O, 8.5. Found: C, 56.15; H, 6.81; H_2O, 7.2.

Sodium [16α,17β-Dihydroxyestra-1,3,5(10)-trien-3-yl-β-D-glucopyranosid]uronate (13).—A mixture of 660 mg (1.0 mmol) of the diformylglucuronide triacetate methyl ester, **12**, 30 ml of absolute EtOH and 1.4 ml (7.0 mmol) of 5 *N* NaOH was stirred at room temperature for 1 hr. The mixture was filtered and the product was crystallized from 70% aqueous EtOH to give 339 mg (65%) of colorless needles, 265–275° dec. Antlytical material was obtained by an additional crystallization from aqueous EtOH to give **13** as colorless needles: 270–280° dec; $[\alpha]^{25}D$ −23° (*c* 0.75, H_2O); ir (KBr) 3390 (OH) 1613 (carboxylate C=O), 1497 (aromatic), 1416 (COO^-), 1053 cm^{-1} (hydroxyl CO); uv max (MeOH) 215, 276 mμ (ϵ 10,000, 1300); nmr (DMSO-d_6) δ 7.17 (d, 1, H-1), 6.80 (m, 2, H-2,4), 5.35 (s, 3, OH), 4.82 (m, 3, sugar H?), 0.68 (s, 3, H-18).

Anal. Calcd for $C_{24}H_{31}O_9Na\cdot2H_2O$: C, 55.17; H, 6.76; H_2O, 6.9. Found: C, 54.86; H, 6.64; H_2O, 3.90.

Sodium [17-Oxoestra-1,3,5(10),7-tetraen-3-yl-β-D-glucopyranosid]uronate (15).—To a solution of 468 mg (0.8 mmol) of the glucuronide triacetate methyl ester, **14**, in 24 ml of absolute EtOH and 3 ml of CH_2Cl_2 was added 0.8 ml (4.0 mmol) of 5 *N* NaOH. The mixture was stirred at room temperature for 1 hr and filtered to give 270 mg (72%) of tan solid. All attempts to crystallize the product from a variety of systems resulted in the formation of a gum. The product was dissolved in refluxing anhydrous MeOH, treated with activated carbon, and filtered. The filtrate was concentrated to 5 ml and diluted at reflux with 5 ml of acetone. The resulting precipitate, plus a second crop from the filtrate, was precipitated again from methanol to give 139 mg of **15** as a tan solid which had only a trace of organic impurity by tlc (system B). Melting point of the product was 214–228°; $[\alpha]^{25}D$ +108° (*c* 0.97, H_2O); ir (KBr) 3367 (OH), 1739 (C-17 C=O), 1618 (carboxylate C=O), 1506 (aromatic), 1414 (COO^-), 1063 cm^{-1} (hydroxyl CO); uv max (MeOH) 276, 283 (sh) mμ (ϵ 1740, 1550); nmr (DMSO-d_6) δ 7.22 (d, 1, H-1), 6.88 (m, 2, H-2,4), 5.52 (br s, 2, H-7 + sugar H?), 4.82 (m, 1, H-1'), 3.33 (m, 10, sugar OH + H_2O?), 0.68 (s, 3, H-18).

Anal. Calcd for $C_{24}H_{27}O_8Na\cdot H_2O$: C, 59.50; H, 6.03; Na, 4.74; H_2O, 3.72. Found: C, 58.09; H, 5.86; Na, 5.92; H_2O, 2.7.

Sodium [17-Oxoestra-1,3,5(10),6,8-pentaen-3-yl-β-D-glucopyranosid]uronate (17).—A mixture of 582 mg (1.0 mmol) of the glucuronide triacetate methyl ester, **16**, 30 ml of absolute EtOH and 1.0 ml of 5 *N* NaOH (5.0 mmol) was stirred at room temperature for 1 hr. The mixture was evaporated to small volume and filtered, and the product was crystallized from 40% aqueous EtOH to give 300 mg (65%) of colorless crystals, mp 275–290°. The product was crystallized from 60% aqueous EtOH followed by two crystallizations from water (approx 2 ml) to provide an analytical sample (129 mg) of **17** as colorless needles: mp 288–295° dec; $[\alpha]^{25}D$ −8.5° (*c* 0.99, H_2O); ir (KBr) 3367 (OH), 1739 (C-17 C=O), 1623, 1600 (carboxylate C=O), 1508 (aromatic), 1429 (COO^-), 1064 cm^{-1} (hydroxyl CO); uv max (MeOH) 232 (ϵ 79,000), 268 (4825), 280 (5550), 290 (4100), 318 (1690), 333 mμ (1810); nmr (DMSO-d_6) δ 7.93 (d, 1, *J* = 9.5 Hz H-1), 7.67 (d, 1, *J* = 8.5 Hz H-6), 7.35 (m, 3, H-2, 4, 7), 5.17 (m, 3, sugar OH), 0.67 (s, 3, H-18).

Anal. Calcd for $C_{24}H_{25}O_8Na\cdot H_2O$: C, 59.74; H, 5.64; Na, 4.77; H_2O, 3.73. Found: C, 59.90; H, 5.57; Na, 4.46; H_2O, 4.4.

17-Oxoestra-1,3,5(10)-trien-3-yl-β-D-glucopyranoside (8).—To a solution of 348 mg (0.58 mmol) of the glucoside tetraacetate, **7**, in 1.0 ml of CH_2Cl_2 was added 20 ml of methanol which had been saturated with anhydrous ammonia at 0°. The solution was refrigerated at 4° overnight and then evaporated to a colorless glass. The glass was triturated with water and filtered, and the resulting solid was crystallized from 25% aqueous EtOH to give 238 mg (94%) of **8** in analytical purity as colorless crystals: mp 150–170°; $[\alpha]^{25}D$ +63° (*c* 0.72, MeOH); ir (KBr) 3390 (OH), 1724 (C-17 C=O), 1499 (aromatic), 1072 cm^{-1} (hydroxyl C-O); uv max (MeOH) 275, 283 (sh) mμ (ϵ 1470, 1310); nmr (DMSO-d_6) δ 7.22 (d, 1, H-1), 6.80 (m, 2, H-2,4), 5.20–4.33 (m, 5, sugar H'), 0.86 (s, 3, H-18); mass spectrum[17] *m/e* 270, 146, 185, 162, 172, *m/e* 312, 323, 317, 365, 432 (M^+).

Anal. Calcd for $C_{24}H_{32}O_7\cdot{}^1/_4H_2O$: C, 65.96; H, 7.49. Found: C, 65.96; H, 7.65.

Glucuronidation of Estrone in Presence of Cadmium Halides. A. $CdCl_2$ Generated *in Situ*.—A small amount (*ca.* 10 bubbles) of anhydrous HCl was passed into a stirred and distilling mixture of 270 mg (1.0 mmol) of estrone, 345 mg (2.0 mmol) of $CdCO_3$, and 20 ml of toluene. A solution of 705 mg (2.0 mmol) of chloro sugar **2**[32] in 20 ml of toluene was then added dropwise over 1 hr according to general procedure B except on $^1/_5$th the scale. The reaction was monitored by tlc (system A), samples being taken every 5 min for the first 30 min and then every 10 min for the next 90 min. A trace of product was evident after 5 min and definitely present after 10 min. At this time a change in color (colorless to pale tan) of the mixture was observed. The product uniformly increased with time, and the estrone decreased until the reaction was complete after a total of 90 min.

In another reaction, using the same quantities of reagents, anhydrous HCl was bubbled through the distilling mixture of estrone, $CdCO_3$, and toluene for 1 hr during which makeup toluene (20 ml) was added. A solution of the chloro sugar in toluene was added dropwise over 1 hr as in the general procedure B. The results, as determined by tlc monitoring, were indistinguishable from those above except that the initial color change occurred during treatment with HCl. In an identical

(39) The Karl Fischer water analyses are approximate values due to the nature of the determination; however, they are given here as additional justification for the inclusion of water in the molecular formula.

reaction which was not pretreated with anhydrous HCl, the appearance of color and of product (tlc monitoring) was not evident until 25–30 min. Repetition of this showed a color change after 22 min. After 90 min a sample (1/4) of the mixture was purified by tlc (system A), and the product was crystallized from CH_2Cl_2–EtOH to give 110 mg (75%) of **4** as colorless plates, mp 227–230°.

B. **CdX_2 Added.**—Estrone (270 mg, 1.0 mmol) was glucuronidated with chloro sugar **2** (705 mg, 2.0 mmol) using $CdCO_3$ (345 mg, 2.0 mmol) and 18 mg (0.1 mmol) of anhydrous $CdCl_2$ (Coleman and Bell Co., Norwood, Ohio) according to the general procedure B. The mixture changed color after 30 min. Separation of a sample (1/4) of the mixture by tlc (system A) and crystallization of the product from CH_2Cl_2–EtOH gave 91.7 mg (62.5%) of **4**, mp 226–231°.

In another experiment, estrone (250 mg, 0.925 mmol) was reacted with bromo sugar **1** according to procedure A using 410 mg (1.51 mmol) of anhydrous $CdBr_2$ (Alfa Inorganics) and 208 mg (1.50 mmol) of anhydrous K_2CO_3 as the catalyst–acid acceptor system. However, no product was evident by tlc (system A) and work-up of the mixture gave back 79% of the estrone and 96% of the bromo sugar.

Registry No.—**4**, 27537-72-0; **5**, 15087-01-1; **7**, 27610-08-8; **8**, 25591-03-1; **9**, 27610-09-9; **10**, 27537-75-3; **11**, 14982-12-8; **12**, 27537-76-4; **13**, 15087-06-6; **14**, 27570-87-2; **15**, 27610-12-4; **16**, 27537-77-5; **17**, 27537-78-6; **18**, 27537-79-7; **19**, 27537-80-0; **20**, 27537-81-1; cadmium carbonate, 513-78-0.

Acknowledgments.—We thank Louis M. Brancone and associates for the elemental analyses and William Fulmor and associates for the spectral data. Special thanks go to Dr. George E. Van Lear for the mass spectra and to George O. Morton for his most helpful interpretations of the nmr data.

Synthesis of Tobacco Mosaic Virus Protein Sequence 81–85[1]

GEORGE R. PETTIT* AND WILLIAM R. JONES

Department of Chemistry, Arizona State University, Tempe, Arizona 85281

Received July 10, 1970

The 81–85 segment of tobacco mosaic virus protein has been prepared by two different synthetic approaches. Synthesis of the protected pentapeptide *N*-benzyloxycarbonyl-L-threonyl-L-alanyl-L-leucyl-L-leucyl-glycine hydrazide corresponding to TMV protein 81–85 was accomplished employing as key step coupling of *N*-Z-Thr-Ala azide with Leu-Leu-Gly-OMe. The product was identical with the same pentapeptide obtained by a Merrifield solid-phase synthesis.

Synthesis of the tobacco mosaic virus protein would represent an important step toward the first total synthesis of an organism capable of replication. With this objective in view, we began a program concerned with synthesis of, at that time (1962) known, segments of the TMV protein. By 1964 the complete structure of TMV protein had been proposed with reasonable certainty.[2] Subsequently, the 120–124[3a] (solution polymer method) and 151–154[3b] (fragment condensation) units were prepared in our laboratory and units 42–46[4a] and 103–112[4b] have been prepared (solid phase technique) elsewhere. Concurrent with preparation of TMV protein fragments, we have been using certain of these peptides in an immunological[5] study of steroidal peptides[6a] and in preparation of alkaloidal peptides.[6b] The preparation reported herein of the fully protected pentapeptide *N*-Z-Thr-Ala-Leu-Leu-Gly hydrazide corresponding to TMV protein sequence 81–85 was accomplished by both conventional methods of peptide synthesis in solution and by a Merrifield solid-phase[7] synthesis.

Synthesis of pentapeptide **6** by a fragment condensation approach proceeded as follows. Condensation of *tert*-butoxycarbonyl-L-leucine with glycine methyl ester proceeded well in the presence of 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (EDCI)[8] and gave protected dipeptide **1**. Attempts at cleaving the *tert*-butoxycarbonyl group of dipeptide **1** using trifluoroacetic acid and hydrogen chloride in methylene chloride or in methanol gave a two-component mixture. However, use of 98% formic acid[9] gave a pure product (**2**). A mixed carbonic anhydride[10] coupling procedure was used to condense *tert*-butoxycarbonyl-L-leucine with dipeptide ester **2**. By this means, the protected tripeptide **3a** was obtained in good yield. By contrast, the use of dicyclohexylcarbodiimide in methylene chloride afforded a low yield of tripeptide **3a**. The dipeptide fragment *N*-Z-Thr-Ala-OMe (**4**) was conveniently obtained as described by Hofmann, *et al.*,[11] using dicyclohexylcarbodiimide. Noteworthy at this stage of the synthesis was the observation that *N*-ethyl-5-phenylisoxazolium 3′-sulfonate (WRK)[12] in acetonitrile or nitromethane, or EDCI in methylene chloride, led to consistently low yields of the protected dipeptide **4**. Hydrazinolysis of Z-Thr-Ala-OMe **4** to

(1) Contribution XI of the series Structural Biochemistry. For part X, see P. Brown and G. R. Pettit, *Org. Mass Spectrom.*, **3**, 67 (1970). We are grateful to the National Science Foundation for financial support by Grants GB-4939 and GB-8250.

(2) G. Funatsu, A. Tsugita, and H. Fraenkel-Conrat, *Arch. Biochim. Biophys.*, **105**, 25 (1964).

(3) (a) B. Green and L. Garson, *J. Chem. Soc. C*, 401 (1969); (b) G. R. Pettit and S. K. Gupta, *J. Chem. Soc.*, 1208 (1968).

(4) (a) J. D. Young, C. Y. Leung, and W. A. Rombauts, *Biochemistry*, **7**, 2475 (1968). (b) J. M. Stewart, J. D. Young, E. Benjamini, M. Shimizu, and C. Y. Leung, *ibid.*, **5**, 3396 (1966); J. D. Young, E. Benjamini, J. M. Stewart, and C. Y. Leung, *ibid.*, **6**, 1455 (1967).

(5) For example, the 93–112 and 102–112 units of TMV protein have been reported to be antigenic areas: J. D. Young, E. Benjamini, M. Shimizu, and C. Y. Leung, *ibid.*, **5**, 1481 (1966); E. Benjamini, M. Shimizu, J. D. Young, and C. Y. Leung, *ibid.*, **8**, 2242 (1969).

(6) (a) G. R. Pettit, R. L. Smith, and H. Klinger, *J. Med. Chem.*, **10**, 145 (1967); G. R. Pettit and N. H. Rogers, *J. Org. Chem.*, manuscript in preparation. (b) G. R. Pettit and S. K. Gupta, *J. Chem. Soc. C*, 1208 (1968).

(7) R. B. Merrifield, *Advan. Enzymol. Relat. Subj. Biochem.*, **32**, 221 (1969).

(8) J. C. Sheehan, P. A. Cruickshank, and G. L. Boshart, *J. Org. Chem.*, **26**, 2525 (1961). The abbreviations for amino acids, peptides, and coupling reagents are those recommended by the IUPAC Commission on nomenclature, *Biochemistry*, **5**, 2485 (1966), and those adopted by G. R. Pettit in "Synthetic Peptides," Vol. I, Van Nostrand–Reinhold, New York, N. Y., 1970.

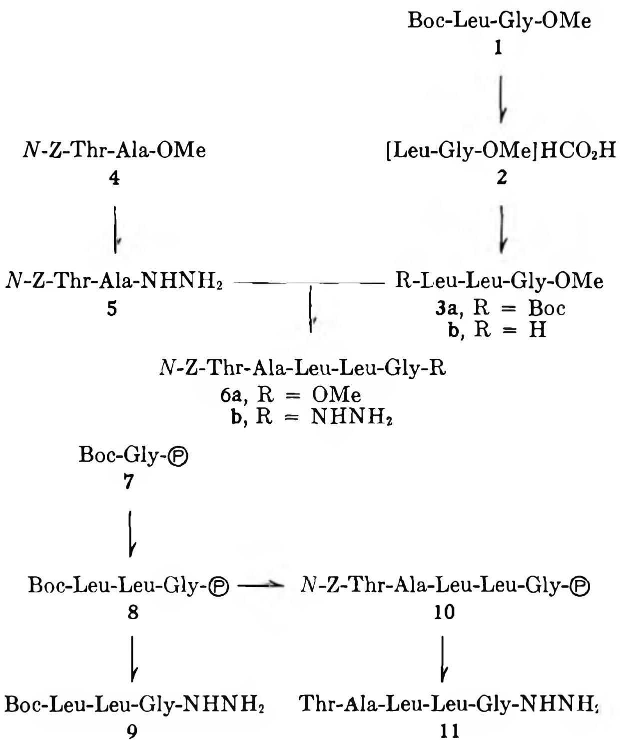
(9) B. Halpern and D. E. Nitecki, *Tetrahedron Lett.*, 3031 (1967).

(10) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Amer. Chem. Soc.*, **89**, 5012 (1967).

(11) K. Hofmann, R. Schmiechen, R. D. Wells, Y. Wolman, and N. Yanaihara, *ibid.*, **87**, 611 (1965).

(12) R. B. Woodward and D. J. Woodman, *J. Org. Chem.*, **34**, 2742 (1969); R. B. Woodward, R. A. Olofson, and H. Mayer, *Tetrahedron*, **S8**, 321 (1966).

yield the corresponding hydrazide **5** was easily performed employing hydrazine in methanol.[11] Condensation of protected dipeptide **5** with tripeptide ester **3b** was achieved, albeit in low yield, by an azide procedure. The protected pentapeptide **6a** was obtained as an amorphous powder which, as evidenced by thin layer chromatography, was homogeneous. A quantitative amino acid analysis demonstrated the presence of threonine, alanine, leucine, and glycine in the molar ratios 1.0, 1.0, 2.1, and 1.1, respectively. The structure of pentapeptide **6a** was further confirmed by a diagnostic field ionization mass spectrometry study which we have already summarized.[1]



For the solid-phase synthesis of protected pentapeptide **6a**, a styrene–2% divinylbenzene copolymer was washed and chloromethylated as described by Merrifield.[7,13] The polymeric benzyl ester **7** was formed by reaction between Boc-Gly triethylammonium salt and the chloromethylated polymer. The approximate yield was determined by weight increase as suggested by Khosla.[14] The deprotection, washing, and coupling sequence with addition of each amino acid was also similar to that outlined by Khosla. Except for the last step, in which the *p*-nitrophenyl active ester technique was used,[15] the coupling method was DCCI in methylene chloride.

The growing peptide chain was analyzed at the protected tripeptide stage by subjecting an aliquot of resin to hydrazinolysis and comparison of the cleavage product with an authentic specimen of tripeptide hydrazide **9**. A several-component mixture was detected by tlc but the most prominent component had the same R_f value as a specimen of hydrazide **9** prepared from protected tripeptide **3a**. Hydrazinolysis at the pentapeptide stage (**10**) afforded hydrazide **6b** in 17% overall yield based on the Boc-Gly-polymer. The amorphous product **6b** displayed a single spot on a thin layer chromatogram as did the N-deprotected derivative **11**. By thin layer chromatographic and mass spectral comparison, as well as amino acid analysis, the solid-phase product **6b** was identical with the substance obtained by the fragment condensation approach. In both syntheses the only evidence for a side product reflecting some racemization was detected during purification of protected dipeptide **4**. Preparation of pentapeptide hydrazide **6b** by the solid-phase approach proved to be most economical in terms of time and yield.

(13) R. B. Merrifield, *Biochemistry*, **3**, 1385 (1964).

(14) M. C. Khosla, R. B. Smelby, and F. M. Bumpus, *ibid.*, **6**, 754 (1967).

(15) M. Bodanszky and M. A. Ondetti, *Chem. Ind.* (*London*), 26 (1966).

Experimental Section

Alanine, leucine, and threonine were of the L configuration. The resin was styrene–2% divinylbenzene copolymer beads-X2, 200–400 mesh, lot no. 6075-31 from the Dow Chemical Co. The beads were washed thoroughly with 1 *N* sodium hydroxide, 1 *N* hydrochloric acid, water, dimethylformamide, and methanol. After drying at 95° (0.3 mm) for 48 hr, the polymer was stored in a desiccator over phosphorus pentoxide and used as required. Chloromethylation of the resin was conducted essentially as described by Merrifield.[13] The product was found to contain 5.42% chlorine.

Extracts of aqueous solutions were dried over magnesium sulfate. Thin layer chromatograms were prepared with silica gel HF-254 (E. Merck, AG, Darmstadt, Germany) unless otherwise noted. The thin layer plates were developed by ultraviolet light and/or ninhydrin. Each analytical sample was colorless and homogeneous as evidenced by tlc. Melting points were determined using a Kofler melting point apparatus and are corrected. Elemental microanalyses were provided by Dr. A. Bernhardt, Mikroanalytisches Laboratorium, 5251 Elbach uber Engelskirchen, West Germany. Proton magnetic resonance and optical rotatory dispersion measurements were conducted by Miss K. Reimer employing, respectively, an A-60 Varian spectrometer (deuteriochloroform solution with tetramethylsilane as internal standard) and a Jasco ORD-UV-5 instrument at 25° (ethanol solution). The amino acid analyses were performed by Mr. R. Storm, of our department, using a Beckman Spinco 120-C amino acid analyzer. All solvents were removed at temperatures below 25° using a rotating evaporator.

Boc-Leu-Gly-OMe (**1**).—Triethylamine (1.92 ml) was added to a mixture of Boc-L-leucine[16] monohydrate (4.2 g) and methyl glycinate hydrochloride (2.25 g) in methylene chloride (70 ml) at 0°. After 5 min 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (4.0 g) was added. The homogeneous reaction mixture was kept at 0° for 5.5 hr and then washed successively with water (two 40-ml portions), 2% sodium carbonate solution (two 30-ml portions), and water (one 20-ml portion). Removal of solvent gave a white solid which crystallized from methylene chloride–hexane as needles (3.4 g) of methyl Boc-leucyl glycinate: mp 132.5–133° [two further crystallizations from the same solvent combination raised the melting point to 132.8–133° (lit.[17] mp 128–131°)]; pmr δ 0.93 (d, J = 5 Hz, isopropyl methyls), 1.45 (*tert*-butyl methyl groups), 1.6 (br hump, $(CH_3)_2CHCH_2$), 3.75 (s, $CH_3OC{=}O$), 4.05 (d, J = 5.5 Hz, $NHCH_2C{=}O$), 4.3 (unresolved m, C═ONHCH); RD $[\alpha]_{589}$ −24.9°, $[\alpha]_{400}$ −66.4°, $[\alpha]_{300}$ −166° (*c* 0.723).

Anal. Calcd for $C_{14}H_{26}N_2O_5$: C, 55.6; H, 8.6; N, 9.27. Found: C, 55.22; H, 8.89; N, 9.3.

Cleavage of the N-Protecting Group from Boc-Leu-Gly-OMe (**1**). **A. Trifluoracetic Acid.**—The acid (3 ml) was added to peptide **1** (0.13 g) at 25°. After 25 min the TFA was removed (*in vacuo* at 25°), and the residue examined by tlc. Two components of comparable intensity (R_f values 0.5 and 0.6 in 5:1:4 1-butanol–water–acetic acid) were revealed. The N-protected dipeptide had an R_f value of 0.93 in the same tlc system. When the reaction was repeated with TFA for 1 min, a similar pattern on tlc was observed.

B. By Hydrogen Chloride.—The dipeptide **1** (80 mg) was dissolved in methylene chloride (5 ml) at 25°, and methylene chloride saturated with HCl gas at 0° was added. After 30 min

(16) E. Schnabel, *Justus Liebigs Ann. Chem.*, **702**, 188 (1967).

(17) F. C. McKay and N. F. Albertson, *J. Amer. Chem. Soc.*, **79**, 4686 (1957).

ห้องสมุด กรมวิทยาศาสตร์

at 25° the solvent was removed. Tlc (see method A) showed a component at R_f 0.5 and a less intense one at R_f 0.35. The reaction was repeated as follows. Methanol saturated with hydrogen chloride gas at 10° (1 ml) was added to Boc-Leu-Gly-OMe (70 mg). Effervescence was immediate and subsided over 5 sec. After a total time elapse of 1 min the methanol was removed (*in vacuo*) and the residual yellow oil examined by tlc. One component at R_f 0.5 and a trace of another at R_f 0.4 was revealed.

C. **By 98% Formic Acid.**—A solution of Boc-Leu-Gly-OMe (0.60 g) in 98% formic acid (10 ml) was kept at 17° for 3 hr. Removal (*in vacuo*) of the formic acid at 23° gave a clear oil which did not solidify on trituration with dry ether. Tlc (see method A) showed one component at R_f 0.5. The ether was removed at 20° and the residue of formate **2** was stored *in vacuo* over sodium hydroxide pellets for 48 hr. The formate partially solidified and was noticeably hygroscopic.

Boc-Leu-Leu-Gly-OMe (3a).—Boc-leucine monohydrate (1.47 g, 5.8 mmol) was dissolved in ethyl acetate (10 ml) and benzene (100 ml). The solvents were removed *in vacuo*, the vitreous residue was dissolved in dry tetrahydrofuran (100 ml) and cooled to −15°, and N-methylmorpholine (0.65 ml, 5.8 mmol) was added and followed in 4 min by isobutyl chloroformate (0.8 ml, 5.8 mmol). After an activation time of 2 min at −10°, a solution derived from methyl L-leucylglycinate formic acid salt (from 5.8 mmol of Boc-Leu-Gly-OMe) and *N*-methylmorpholine (0.65 ml) in tetrahydrofuran (20 ml at 0°) was added. The reaction mixture was stirred at −10° for 5 min and then allowed to warm to 21° during 50 min. Most of the solvent was removed and the residue partitioned between ethyl acetate (100 ml) and water (50 ml). Successive washing of the organic phase with 2% citric acid (three 15-ml portions), water (one 10-ml portion), 2% sodium carbonate (four 20-ml portions), and saturated sodium chloride (one 10-ml portion) gave, after removal of solvent, a clear oil (2.1 g) which separated from benzene–ligroin (during 18 hr) as very small needles (1.24 g, first crop). The Boc-Leu-Leu-Gly-OMe melted at 139–140°. The melting point was unchanged on recrystallization from benzene–ligroin and a tlc (R_f 0.77) using 9:1 chloroform–ethanol showed only one component.

Anal. Calcd for $C_{20}H_{37}O_6N_3$: C, 58.74; H, 9.1; N, 9.8. Found: C, 58.86; H, 8.90; N, 10.01.

N-**Z-Thr-Ala-OMe (4). A. DCCI Method.**—Essentially as previously reported[11] DCCI (2.2 g) was used to condense carbobenzoxy-L-threonine (2.53 g) with L-alanine methyl ester hydrochloride (1.4 g) in the presence of *N*-methylmorpholine (1.15 ml) and dry methylene chloride at 0°. The resulting white solid (3.4 g, 100% yield crude) upon tlc showed one component at an R_f value of 0.7 (chloroform–ethanol 9:1) and a trace (*ca.* 1–5%) of another component at a slightly higher R_f value. More product (0.35 g) was isolated from the mother liquors. Crystallization from ethyl acetate–ligroin gave needles (2.0 g, first crop) of Z-Thr-Ala-OMe: mp 128–129° [two further crystallizations from benzene–hexane raised the melting point to 130–130.5° (lit.[11] mp 127–129°)]; pmr δ 1.2 (d, J = 6.5 Hz), 1.39 (d, J = 7.5 Hz), 3.6 (br hump, hydroxyl), 3.75 (s, methyl ester), 5.14 (s, benzyl), 7.38 (aromatic protons); RD $[\alpha]_{589}$ −13.3°, $[\alpha]_{400}$ −31.5°, $[\alpha]_{300}$ −76.0 (*c* 0.476).

Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.51; N, 8.28. Found: C, 56.77; H, 6.66; N, 8.26.

B. **EDCI Method.**—Triethylamine (0.7 ml) was added to a mixture of *N*-benzyloxycarbonyl-L-threonine (0.77 g, 3 mmol) and L-alanine methyl ester hydrochloride (0.42 g, 3 mmol) in methylene chloride (30 ml) at 0°. After 10 min 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride (0.768 g, 4 mmol) was added and after 4 hr at 0° methylene chloride (20 ml). The solution was washed with water (two 20-ml portions) and 2% sodium carbonate (five 15-ml portions). Removal of the solvent gave a solid (0.80 g, 74% crude) which separated from methylene chloride–hexane as colorless blades (0.48 g) of dipeptide **4**, mp 127.5–129.2°.

C. **WRK Method.**—To *N*-ethyl-5-phenylisoxazolium 3′-sulfonate (1.01 g) in acetonitrile (18 ml) at 0° was added *N*-benzyloxycarbonyl-L-threonine (1.012 g, 4 mmol) and *N*-methylmorpholine (0.4 ml) in acetonitrile (14 ml). The cooling bath was removed and the stirred reaction mixture was allowed to warm to 25°. After 65 min the solution had clarified, and a solution of L-alanine methyl ester hydrochloride (0.56 g) in *N*-methylmorpholine (0.4 ml)–acetonitrile (12 ml) was added. Stirring was contiued at 25° for 22.5 hr. The acetonitrile was removed and replaced by ethyl acetate (100 ml), and the solution was washed with successive portions of water (one 20-ml portion), 4% sodium carbonate (two 30-ml portions), water (one 10-ml portion), 4% hydrochloric acid (two 20-ml portions), and finally with water (two 25-ml portions). Removal of solvent afforded a solid which formed hair-like crystals from methylene chloride–ligroin, 0.34 g, mp 129–129.8°. A second crop (0.14 g) had mp 124–128°.

N-**Z-Thr-Ala-Leu-Leu-Gly-OMe (6a).**—Sodium nitrite (0.22 g) in water (1 ml) at 0° was added to a solution of hydrazide **5** (0.46 g, 1.36 mmol)[11] in cold (ice bath) dimethylformamide (20 ml) and 2 *N* hydrochloric acid (10 ml). The mixture was kept at 0–5° for 6 min and then extracted with ice-cold ethyl acetate (20 ml). The extract was washed with cold saturated sodium bicarbonate solution and with cold saturated sodium chloride solution. The ethyl acetate solution was *dried* (sodium sulfate) and added to a cold solution derived from Leu-Leu-Gly-OMe formate (from 0.58 g of protected tripeptide **3a**) and *N*-methylmorpholine (0.15 ml) in ethyl acetate (15 ml). The reaction mixture was maintained at 0° for 21 hr, and the gelatinous white precipitate which formed was dissolved by addition of ethyl acetate (50 ml). The solution was washed with successive portions of ice-cold 2% citric acid (four 15-ml portions), saturated sodium chloride solution (one 10-ml portions), 1 *N* sodium bicarbonate (two 15-ml portions), and saturated sodium chloride solution (one 10-ml portion). Removal of solvent gave a gelatinous solid which led to a powder (0.14 g, 16% yield) on storage *in vacuo*. Tlc showed essentially one component (R_f 0.5, chloroform–ethanol 9:1); attempted crystallization from methanol gave a white powder, mp 227–230°. The amino acid analysis was performed as summarized below for hydrazide **6b** (obtained *via* solid-phase synthesis) and gave values of 1.0, 1.01, 2.13, and 1.07, respectively, for Thr, Ala, Leu, and Gly. The mass spectrum of pentapeptide **6a** has already been described in detail.[1]

Preparation of hydrazide **6b** was easily achieved by the method noted for obtaining dipeptide **5**. The hydrazide **6b** was identical (tlc, mass spectrum, and amino acid analysis) with a sample obtained by the resin method (see below).

Boc-Gly-Polymer (7).—Boc-glycine (2.70 g) was condensed with the chloromethylated resin (14.4 g) in absolute ethanol (30 ml) containing triethylamine (2.2 ml). The mixture was heated at reflux for 23 hr with protection from moisture. The resin was collected and washed with successive portions of ethanol (200 ml), water (200 ml), and methanol (200 ml) and dried at 25° (1 mm) for 24 hr. The dried resin weighed 15.7 g. The increase in weight represented incorporation of 7.2 mmol of Boc-glycine or 0.46 mmol of Boc-glycine per gram of *N*-Boc-Gly-resin.

Boc-Gly-Polymer to Boc-Ala-Leu-Leu-Gly-Polymer.—Starting with Boc-glycyl-polymer (15.1 g containing 6.9 mmol of Boc-Gly), the following series of reactions was performed. The resin was washed with acetic acid (three 75-ml portions), and the protecting group was cleaved with 1 *N* hydrochloric acid in acetic acid (75 ml) during 30 min. The resin was again washed with acetic acid (three 75-ml portions), absolute ethanol (three 75-ml portions), and dimethylformamide (three 75-ml portions). The hydrochloride salt was removed with triethylamine (7.5 ml) in dimethylformamide (over a 10–15-min period). The resin was washed with dimethylformamide (three 75-ml portions) and methylene chloride (three 75-ml portions). At this point 14 mmol of the appropriate Boc-amino acid in methylene chloride (75 ml) was added with ice cooling. After 10 min of mixing, 14 mmol of DCCI in methylene chloride (20 ml) was added, and the mixture shaken for 2 hr with ice cooling and overnight at ambient temperatures. Next, the resin was washed with methylene chloride (three 75-ml portions) and ethanol (three 75-ml portions). The same cycle was repeated for each addition of an amino acid unit to the growing peptide chain on the resin except that with Boc-Ala no ice cooling was used in the coupling reaction. Also, 10 min after the first addition of DCCI the resin had turned bright yellow and remained highly colored (either yellow or brown) thereafter.

Analysis of the peptide-resin after the addition of the third amino acid unit was accomplished as follows. The dried resin (80 mg) was treated with anhydrous hydrazine (0.4 ml) in absolute ethanol (3 ml) for 48 hr at 25°. The solution was filtered, the filtrate evaporated, and the residue stored *in vacuo* over phosphorus pentoxide for 12 hr. A silica gel G tlc in the system 1-butanol–acetic acid–water (5:1:4) and vizualization by brief exposure to hydrogen chloride vapor followed by ninhydrin spray showed that the main component, an orange spot, had the same R_f value as the Boc-Leu-Leu-Gly hydrazide, prepared by alternate synthesis (*vide infra*).

Boc-Leu-Leu-Gly Hydrazide (9).—To Boc-Leu-Leu-Gly-OMe (70 mg) in methanol (1 ml) was added hydrazine hydrate (4 drops). After 24 hr at 25° the solvent was removed giving a clear oil which showed one component on tlc (silica gel G, 1-butanol–acetic acid–water, 5:1:4, R_f 0.6).

***N*-Z-Thr-Ala-Leu-Leu-Gly-Polymer (10).**—To a solution of *N*-carbobenzoxy-L-threonine (3.2 g, 12 mmol) in cold (ice bath) dry ethyl acetate (30 ml) was added *p*-nitrophenol (1.83 g, 13.2 mmol). The cold solution was stirred 5 min and dicyclohexylcarbodiimide (2.72 g, 13.2 mmol) in dry ethyl acetate (10 ml) was added. Stirring was continued 65 min at ice-bath temperature. After removing the ice bath, for 15 min glacial acetic acid (2 drops) was added. The precipitated dicyclohexylurea was collected and washed with ethyl acetate (10 ml). Solvent was removed giving a yellow oil which did not crystallize. The oil, which showed predominently one component on tlc (silica gel G, chloroform–ethanol, 18:1, R_f 0.5), was used in the peptide-forming reaction without further purification. Coupling to the tetrapeptide-polymer was performed using the Z-Thr-ONp (14 mmol) in DMF (50 ml). The reaction was allowed to proceed 17 hr at 25°. At that point the resin was collected and washed with dimethylformamide (five 80-ml portions) and ethanol (three 75-ml portions).

***N*-Z-Thr-Ala-Leu-Leu-Gly Hydrazide (6b).**—The pentapeptide-polymer (10) was treated with dimethylformamide (50 ml) for 60 min. Anhydrous hydrazine (14 ml) was added and agitation continued 67 hr. The resin was collected and washed with dimethylformamide (two 50-ml portions). The combined filtrate and washings were evaporated at 45° *in vacuo* to a yellow residue which was triturated with water (30 ml). Precipitation of the solid from ethanol gave an amorphous powder (0.70 g), 17% yield based on Boc-Gly-polymer which showed one spot on tlc (silica gel G, 1-butanol–acetic acid–water 5:1:4) with R_f value identical with that of *N*-Z-Thr-Ala-Leu-Leu-Gly hydrazide obtained from methyl ester **6a**.

The residual polymer was treated with anhydrous hydrazine (50 ml) for 48 hr. Evaporation of the filtrate after addition of water did not leave a residue. Hydrazinolysis of the pentapeptide-resin was therefore complete after the first treatment with hydrazine.

Hydrazide **6b** (7.63 mg) was treated with 2 *N* hydrogen bromide–acetic acid (10 ml), in which it slowly dissolved. After 110 min the solvent was removed at 40° *in vacuo* after water (1 ml) added to the residue. Tlc (silica gel G, 1-butanol–acetic acid–water 5:1:4) and vizualization with ninhydrin showed one pink spot at R_f 0.41. Concentrated hydrochloric acid (5 ml) and water (4 ml) were added to the solution which was then heated at reflux for 21 hr. The water was removed at 50° *in vacuo* and the residue dissolved in citrate buffer ("sample diluter" 100 ml). A 1-ml aliquot was used in the amino acid analysis which showed the presence of threonone, alanine, leucine, and glycine only, in the molar ratio 1:1.09:2.19:1.03, respectively.

Registry No.—**1**, 27610-07-7; **3a**, 27545-11-5; **4**, 2483-53-6; **6a**, 27545-13-7; **6b**, 27545-14-8; **7**, 27536-85-2.

The Structure of Viomycidine

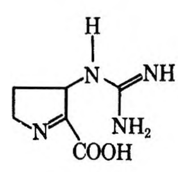
G. BÜCHI* AND JAMES A. RALEIGH

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

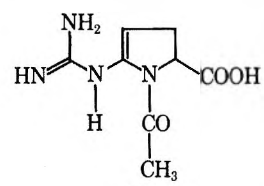
Received September 17, 1970

Viomycidine, a guanidino amino acid obtained from the antibiotic vioymcin by acid hydrolysis, has been shown to be 7-*endo*-carboxy-3-imino-2,4,6-triazabicyclo[3.2.1]octane. The structural assignment was made primarily on the basis of nuclear magnetic resonance evidence and oxidation of viomycidine to 3-guanidinopyrrole and of viomycidine methyl ester to 2-carbomethoxy-3-guanidinopyrrole. Earlier degradative evidence is discussed in terms of the new structure.

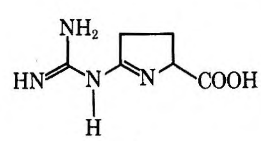
Viomycin, a polypeptide produced by *Streptomyces puniceous* and *Streptomyces floridae*,[1] shows marked tuberculostatic activity[2,3] but because of its toxicity has remained a secondary drug in the chemotherapy of tuberculosis.[4] Structural work on viomycin is being pursued in several laboratories and should be completed in the near future. Vigorous acid hydrolysis of viomycin gave some known amino acids and a new one which has been named viomycidine.[5-7] This fragment is optically active, has pK_a values of 1.3 (estimated), 5.50, and 12.6 (in water) and a composition of $C_6H_{10}O_2N_4$, and forms well-defined salts. Oxidation with nitric acid or with permanganate gave guanidine **15**, while alkaline hydrolysis led to pyrrole-2-carboxylic acid (**14**), 2-aminopyrimidine (**16**), and glycine (**17**). Viomycidine was reported to be susceptible to catalytic hydrogenation[6,7] and this finding led to the suggestion that the molecule contains a second carbon–nitrogen double bond in addition to the nonreducible double bond of the guanido group. Based on these findings and some physical properties structure **1** was proposed for viomycidine.[6,8] Later on, in an experiment designed to serve the twofold purpose of locating the



1



2



3

double bond in the ring and the point of attachment of the guanido group, acetylviomycidine was ozonized.

(1) V. Ševcik, "Antibiotica aus Actinomyceten," Gustav Fischer Verlag, Jena, 1963.

(2) A. C. Finlay, G. L. Hobby, F. Hochstein, T. M. Lees, F. F. Lenert, J. A. Means, S. Y. P'an, P. P. Regna, J. B. Rontien, B. A. Sobin, K. B. Tate, and J. H. Kane, *Amer. Rev. Tuberc.*, **63**, 1 (1951).

(3) Q. R. Bartz, J. Ehrlich, J. D. Mold, M. A. Penner, and R. M. Smith, *ibid.*, **63**, 4 (1951).

(4) R. S. Mitchell and J. C. Bell, "Modern Chemotherapy of Tuberculosis," Medical Encyclopedia, Inc., New York, N. Y., 1958.

(5) T. H. Haskell, S. A. Fusari, R. P. Frohardt, and Q. R. Bartz, *J. Amer. Chem. Soc.*, **74**, 599 (1952).

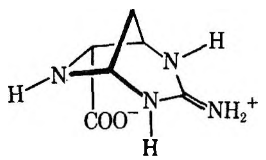
(6) J. H. Bowie, A. W. Johnson, and G. Thomas, *Tetrahedron Lett.*, 863 (1964).

(7) J. R. Dyer, H. B. Hayes, E. G. Miller, Jr., and R. F. Nassar, *J. Amer. Chem. Soc.*, **86**, 5363 (1964).

(8) J. R. Dyer, H. B. Hayes, and E. G. Miller, Jr., 3rd Interscience Conference for Antimicrobial Agents and Chemotherapy, Washington, D. C., Oct 1963; *cf.* D. Perlman, *Nature*, **201**, 456 (1964).

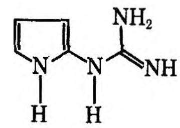
Guanidine and racemic aspartic acid were the only observable products suggesting that acetylviomycidine and viomycidine were represented by structures **2** and **3**, respectively.[7]

We had reservations concerning the stabilities of compounds such as **1** and **3** to vigorous acid hydrolysis and in this paper describe evidence in favor of structure **4** for viomycidine.

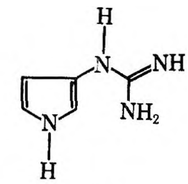


4

We began our own thinking on the structure of viomycidine by accepting the presence of a 2-carboxypyrrolidine moiety, and new evidence in favor of this postulate was provided by the mass spectrum which agreed with that of pyrrole-2-carboxylic acid with an additional peak at m/e 59 corresponding to the molecular ion of guanidine. On the other hand the existing evidence was not sufficient to permit placing of the guanidine group with any degree of confidence. Our hope that dehydrogenation of viomycidine would lead to a pyrrole whose substitution pattern could be ascertained by nuclear magnetic resonance spectroscopy was confirmed by experiment. Oxidation with mercuric acetate in aqueous acetic acid gave a crystalline acetate $C_7H_{12}N_4O_2$. A violet color with Ehrlich reagent and a positive Sakaguchi[9,10] test indicated the presence of a pyrrole and a monosubstituted guanidine, respectively. That the oxidation product lacked the original carboxyl group of viomycidine was evident from the ultraviolet spectrum which displayed end absorption only while pyrrole-2-carboxylic acid has a maximum at 258 nm (ϵ 12,600).[11] This was confirmed by a nuclear magnetic resonance spectrum which in D_2O displayed in addition to the three-proton singlet due to the acetate ion three aromatic protons at δ 6.12 (1 H, t, J = 2 Hz) and 6.82 (2 H, d, J = 2 Hz). Although the nmr spectra of neither amino- nor guanidinopyrroles seem to be recorded in the literature, we tentatively concluded from the absence of coupling constants larger than 3 Hz[12-14] and the presence of two low field aromatic protons that the oxidation product was 3-guanidinopyrrole acetate (**6**). This was confirmed by synthesis. Catalytic reduction of 2- and 3-nitropyrrole[13] separately over a platinum catalyst in ethanol containing 1 equiv of sodium ethoxide (required to suppress decomposition of the reduction products[15]) gave the exceptionally unstable 2- and 3-aminopyrroles, respectively. Immediate condensation with *S*-methylisothiuronium sulfate[16] produced the corresponding guanidinopyrroles **5** and **6** in low yield. Preliminary comparison by chromatographic techniques and Ehrlich color tests led to the conclusion that the oxidation product of viomycidine is 3-guanidinopyrrole (**6**).

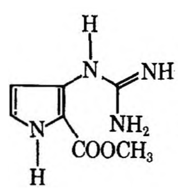


5

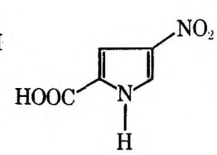


6

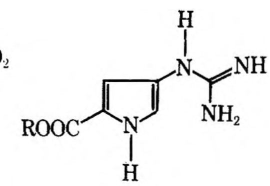
On the basis of the preceding discussion the carboxyl group in viomycidine must be attached to either C_2 or C_5 of the pyrrolidine ring. To differentiate between these alternatives, viomycidine had to be transformed to a pyrrole retaining both guanido and carboxy groups. Oxidation of viomycidine methyl ester dihydrochloride with mercuric acetate resulted in the pyrrole **7** with ultraviolet absorption at 266 nm (ϵ 13,500). The nuclear magnetic resonance spectrum in D_2O confirmed the presence of a methyl ester and the appearance of one-proton signals at δ 6.38 (d, J = 3 Hz) and 7.17 (d, J = 3 Hz) favored a 2,3-disubstituted pyrrole because proton coupling between C_2 and C_4 positions in pyrroles is smaller than 2 Hz. To verify this, 2-carboxy-4-nitropyrrole (**8**)[13,17] was hydrogenated and the resulting 2-carboxy-4-aminopyrrole which was much more stable than 3-aminopyrrole condensed with *S*-methylisothiuronium sulfate. 2-Carboxy-4-guanidinopyrrole (**9**) when heated in acetic acid gave 3-guanidinopyrrole (**6**) identified beyond doubt with material prepared by oxidation of viomycidine. Methylation of the acid **9** gave the methyl ester **10** different from its isomer **7** from viomycidine. In agreement with anticipation the two aromatic protons at δ 6.87 and 7.12 in the nmr spectrum of **10** are split by only 1.8 Hz. Furthermore, the difference in chemical shift between α and β pyrrole protons (0.3 ppm) is much smaller than in **7** (0.8 ppm) and in pyrrole (0.65 ppm) due to deshielding of the β proton by the carbomethoxy group.[12,13]



7



8

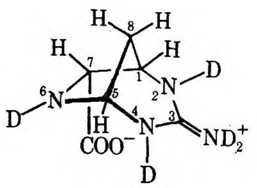


9, R = H
10, R = CH_3

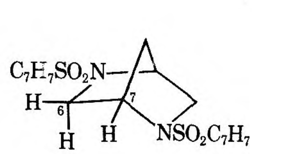
With the ambiguity concerning the position of the guanido group removed, there seemed little question that viomycidine contains a 2-carboxy-3-guanidinopyrrolidine part structure. The nuclear magnetic resonance spectrum of viomycidine contains five nonexchangeable protons, and if the substance is indeed a pyrroline it should have structure **1** or **12**. The absence of an absorption pattern expected from vicinal methylene protons eliminated the former and lack of resonances at approximately δ 7 caused by a proton attached to

(9) S. Sakaguchi, *J. Biochem.* (*Tokyo*), **5**, 13, 25 (1925).
(10) J. D. Mold, J. M. Ladino, and E. J. Schantz, *J. Amer. Chem. Soc.*, **75**, 6321 (1953); A. Heesing and K. Hoppe, *Chem. Ber.*, **100**, 3649 (1967).
(11) R. Andrisano and G. Pappalardo, *Gazz. Chim. Ital.*, **85**, 1430 (1955).
(12) S. Gronowitz, A. Hornfeldt, B. Gestblom, and R. A. Hoffman, *Ark. Kemi*, **18**, 133 (1961).
(13) K. J. Morgan and D. P. Morrey, *Tetrahedron*, **22**, 57 (1966).
(14) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, England, 1969, pp 209, 306.
(15) H. Fischer and F. Rothweiler, *Ber.*, **56**, 512 (1923).
(16) R. A. B. Bannard, A. A. Casselman, W. F. Cockburn, and G. M. Brown, *Can. J. Chem.*, **36**, 1541 (1958).
(17) W. J. Hale, and W. V. Hoyt, *J. Amer. Chem. Soc.*, **37**, 2538 (1915).

the imino group[18] removed the latter from further consideration. The bridged structure **4** on the other hand accommodates the nuclear magnetic resonance spectrum (in D_2O) with ease: C_8, δ 2.18, AB of ABXY pattern; C_7, 3.86, d, J = 4 Hz; C_1, 4.18, m; C_5,

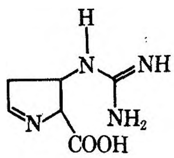


4

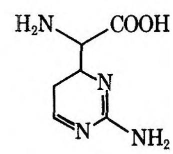


11

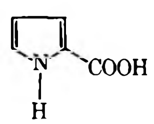
4.73, d of d. Comparison of J_{17} coupling (4 Hz) with those of exo C_6–C_7 (2.2 Hz) and endo C_6–C_7 (0 Hz) in **11** indicates endo configuration of the carboxy group in viomycidine.[19] The bicyclic aminoacetal structure **4** is entirely consistent with the degradation products resulting from treatment of viomycidine with base. Opening of the pyrrolidine ring leads to the dihydropyrimidine **13** which should not need much provocation to fragment into 2-aminopyrimidine (**16**) and glycine (**17**). Cleavage of the six-membered ring leads to the imine **12** which within the corresponding enamine can eject guanidine (**15**) to give pyrrole-2-carboxylic acid (**14**).



12

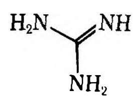


13

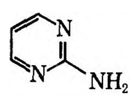


14

+



15



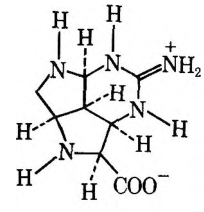
16

+ NH_2CH_2COOH

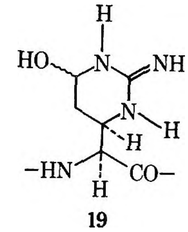
17

Structure **4** also accounts for the observed pK_a values of viomycidine. The highest value is characteristic of the guanidino group which when protonated is expected to have a drastic base weakening effect on the secondary amine function. (For example the pK_a values for ethylenediamine are 9.89 and 6.97.[20]) The lowest pK_a value is assigned to the carboxyl group of viomycidine. Oxidation of viomycidine (**4**) to pyrroles proceed *via* the pyrroline **12**, the result of an acid-catalyzed ring opening. Since the new formulation no longer contains a double bond, we reinvestigated the catalytic reduction of viomycidine. Hydrogenation over platinum in acetic acid[7] or palladium in an unspecified solvent[6] reportedly proceeds with uptake of 1 equiv of hydrogen, but no products were described and the time required for complete hydrogenation was not reported. In our hands hydrogenation of viomycidine over platinum in 0.5 N hydrochloric acid and over W-7 Raney nickel in water were exceedingly slow and gave two ninhydrin-positive products which were not characterized. This finding is not in disagreement with structure **4** but the formation of aspartic acid by ozonization of acetylviomycidine remains an enigma.[7]

After this investigation was completed[21] and the results quoted,[22] the structure of viomycidine was confirmed by a single-crystal X-ray structure determination of the corresponding hydrobromide.[23] The absolute configuration was not determined but it follows as shown in **4** with a high degree of certainty from that of viocidic acid **18**,[22,24] another degradation product of viomycin.



18



19

Both viomycidine (**4**) and viocidic acid (**18**) seem to be artifacts produced from the unit **19**[22,25] present in the intact antibiotic viomycin. Viomycidine (**4**) belongs to a family of guanidino acids discovered in antibiotics, comprising roseonine[26] (from *Streptomyces roseochromogenes*), blasticidic acid[27] (from *Streptomyces griseochromogenes*), and capreomycidine[22,28,29] (from *Streptomyces capreolus*).

Experimental Section

General.—Melting points were determined on a hot-stage microscope and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 237 grating instrument and peak intensities are given as very strong (vs), strong (s), medium (m), or weak (w). Ultraviolet spectra were recorded on a Cary Model 14 recording spectrophotometer. Nuclear magnetic resonance spectra were measured on a Varian A-60 spectrometer. The standards used were tetramethylsilane (TMS) and sodium 3-(trimethylsilyl)-1-propanesulfonate (TSPS). Thin layer chromatography (tlc) was used extensively with Merck silica gel G and aluminum oxide G, and MN 300 G cellulose powder serving as adsorbents and 1-propanol–acetic acid–water 44:12:44 (solvent A), methanol–concentrated ammonium hydroxide–water 32:1:8 (solvent B), and 1-butanol–acetic acid–water 73:10:17 (solvent C) serving as the main solvent combinations. Ninhydrin and Ehrlich spray reagents and iodine vapor were used separately and in concert to develop the plates. High voltage electrophoresis was a useful analytical tool with Whatman No. 3 MM filter paper serving as the support and acetic acid–formic acid–water 20:2:78 (pH 1.81) serving as the sole electrolyte. Typically, a potential of 35 V/cm was applied resulting in a current of 50 mA, the paper being immersed in a water-cooled bath of varsol. After 2 hr the chromatogram was retrieved, dried, and soaked by immersion with a 0.1% solution of ninhydrin in 1-butanol. Air-drying revealed most of the hydrolysate com-

(18) R. Bonnett and D. McGreer, *Can. J. Chem.*, **40**, 177 (1962).
(19) P. S. Portoghese and A. A. Mikhail, *J. Org. Chem.*, **31**, 1059 (1966).
(20) M. Kotake, "Constants of Organic Compounds," Asakura Publication Co., Tokyo, 1963.

(21) J. A. Raleigh, Ph.D. Dissertation, Massachusetts Institute of Technology, Oct 1966.
(22) B. W. Bycroft, D. Cameron, L. R. Croft, A. W. Johnson, T. Webb, and P. Coggon, *Tetrahedron Lett.*, 2925 (1968).
(23) J. C. Floyd, J. A. Bertrand, and J. R. Dyer, *Chem. Commun.*, 998 (1968).
(24) P. Coggon, *J. Chem. Soc. B*, 838 (1970).
(25) T. Takita and K. Maeda, *J. Antibiot.*, **21**, 512 (1968).
(26) H. E. Carter, C. C. Sweeley, E. E. Daniels, J. E. McNary, C. P. Schaffner, C. A. West, E. E. van Tamelen, J. R. Dyer, and H. A. Whaley, *J. Amer. Chem. Soc.*, **83**, 4296 (1961).
(27) N. Otake, S. Takeuchi, T. Endo, and H. Yonehara, *Tetrahedron Lett.*, 1411 (1965).
(28) E. B. Herr, Jr., in J. C. Sylvester, "Antimicrobial Agents and Chemotherapy," American Society for Microbiology, 1962, p 201.
(29) E. B. Herr and M. O. Redstone, *Ann. N. Y. Acad. Sci.*, **135**, 940 (1966).

ponents from viomycin while heating briefly at 110° was required to develop the spot corresponding to viomycidine; urea was detected by Ehrlich spray reagent (a bright yellow color).

Viomycidine. Isolation and Characterization.—In a typical procedure viomycin sulfate (15.7 g) was hydrolyzed in 600 ml of 6 *N* hydrochloric acid at 100° (steam bath) for 6 hr (complete hydrolysis of the antibiotic was observed in this time). The deep red hydrolysate was diluted in half with distilled water and taken to dryness repeatedly *in vacuo* (at 50–60° on rotary evaporator). The last traces of hydrochloric acid were removed by passage of the hydrolysate through an Amberlite IR 4B (OH^-) column (2 × 25 cm). The column was washed with 100 ml of distilled water (effluent becomes neutral, subsequent elution of the column with dilute aqueous acid and base produced no material), the wash combined with the rest of the neutralized hydrolysate, and the combination (300 ml, pH 8) passed onto an Amberlite IRA 400 (OH^-) column (3 × 45 cm, conditioned in the usual manner). The column was eluted with distilled water and the first 500 ml of effluent combined (electrophoresis showed this fraction to be a mixture of urea and viomycidine contaminated with other components of the hydrolysate), concentrated *in vacuo* to 300 ml, and rechromatographed on an Amberlite IRA 400 (OH^-) column (3 × 45 cm). The first 450 ml of effluent from the second chromatography was largely a mixture of urea and viomycidine, the next 300 ml contained slightly impure viomycidine, and the last 600 ml of effluent (effluent was collected until it no longer gave a positive Sakaguchi reaction) contained an almost equal mixture of viomycidine and a closely related substance. The first and third fractions were combined and rechromatographed. The second fraction was taken to dryness *in vacuo* to give a crystalline residue which was subjected to fractional precipitation from an ethanol–water pair. The forecrops (132 mg) were set aside for further purification and the mother liquor was taken to dryness *in vacuo* to yield 1.48 g of purified viomycidine, mp 178–180° dec. Tlc on silica gel G (solvent A) showed this material to be of high purity with only traces of slower moving materials being present. Repeated recrystallization from a methanol–ethyl acetate solvent pair gave pure viomycidine: mp 181–182° dec; homogeneous by tlc on silica gel G (solvent A and solvent B) and by electrophoresis; $[\alpha]^{32.2}D$ −151° (c 1.25 in H_2O), $[\alpha]^{32.2}D$ −38° (c ~0.8 in aqueous HCl); $pK_a' < 2.2$, = 5.2, > 12.4 (50% aqueous EtOH); ir (KBr) 1705 (shoulder), 1670 (vs), 1608 (vs), 1600 (vs), 1575 cm^{-1} (shoulder); uv (H_2O) end absorption only; nmr (D_2O, TSPS internal standard) δ 2.18 (2 H, approximates AB of ABXY pattern), 3.86 (1 H, d, J = 4 Hz), 4.18 (1 H, m), 4.73 (1 H, d of d).

Viomycidine Monohydrochloride.—Viomycidine (337 mg) in 2 ml of water (pH 8–9 pHydrion paper) was neutralized (dilute hydrochloric acid) and the solution taken to dryness *in vacuo*: yield of monohydrochloride 290 mg; mp 200–205° dec (lit.[7] 200–208° dec); ir (KBr) 3500, 3240, 2940, 1700 (vs), 1655 (s), 1640 (shoulder), 1585 cm^{-1}; uv (H_2O) end absorption.

Viomycidine Methyl Ester Dihydrochloride.—Viomycidine monohydrochloride (290 mg) was added to 1.0 ml of thionyl chloride which had been dissolved in 5.0 ml of absolute methanol at −10°. After standing overnight at room temperature in a sealed flask, the reaction solution was taken to dryness *in vacuo*. Tlc (aluminum oxide G, methanol) showed incomplete conversion of the starting material, and the reaction mixture was treated with a further 0.25 ml of thionyl chloride in 5.0 ml of methanol as above. The methyl ester dihydrochloride was precipitated directly from the reaction mixture by the addition of ethyl ether: yield 200 mg; mp 195–200° dec; ir (KBr) 3250, 3100, 1760, 1670, 1630, 1585 cm^{-1}; uv (H_2O) end absorption only; nmr (D_2O, TSPS internal standard) δ 2.57 (2 H, t, J = 2.3 Hz), 4.02 (3 H, s), 5.77 (2 H, t, J = 3.1 Hz), the remaining CH was under the HOD peak; nmr (DMSO-d_6, TMS internal standard) δ 2.28 (2 H, s), 3.82 (3 H, s), 4.61 (2 H, t, J = 2.5 and 4.5 Hz), 5.33 (1 H, s broad), 8.04–9.29 (6 H, exchangeable NH protons). Upon hydrolysis (12 *N* hydrochloric acid, 100°, 10 hr) the methyl ester gave viomycidine as the only observable product (electrophoresis, tlc). The methyl ester was purified for analysis by recrystallization from methanol–ethyl ether.

Anal. Calcd for $C_7H_{14}N_4O_2Cl_2$: C, 32.68; H, 5.45; N, 21.79. Found: C, 32.40; H, 5.77; N, 22.02.

Viomycidine Dihydrochloride.—A solution of viomycidine (120 mg) in 5 ml of 3 *N* hydrochloric acid was taken to dryness repeatedly *in vacuo* (40°) until excess hydrochloric acid had been removed. After storage over $KOH/CaCl_2$ overnight, the crude dihydrochloride was recrystallized from methanol–ethyl ether: first crop 40 mg, mp 210–220° dec, sinter 90–100°; second crop 30 mg, mp 190–210° dec, sinter 157–160°; third crop 34 mg, white crystalline feathers, mp 190–195° dec, sinter 159–160°, and ir (KBr) 3250, 3075, 1745, 1670, 1625, 1575 cm^{-1}.

Anal. Calcd for $C_6H_{12}N_4O_2Cl_2 \cdot CH_3OH$: C, 30.56; H, 5.86; N, 20.37. Found: C, 30.38; H, 5.82; N, 20.85.

Mercuric Acetate Oxidation of Viomycidine to 3-Guanidinopyrrole Acetate (6).—Viomycidine (170 mg, 0.0010 mol) and mercuric acetate (350 mg, 0.0011 mol) were dissolved in 5% aqueous acetic acid (15 ml) and the solution was heated at 100° (oil bath) for 3 hr with stirring. The precipitated mercurous acetate was filtered off and the filtrate (pH 7) saturated with hydrogen sulfide. The precipitated mercuric sulfide was filtered off and the filtrate once again saturated with hydrogen sulfide. After filtration of the mercuric sulfide, the filtrate was taken to dryness *in vacuo* (50°, rotary evaporator) to give a partially crystalline residue which was purified by chromatography on cellulose powder. Standard grade Whatman cellulose powder (20 g) was slurried with solvent C and made into a column (2 × 20 cm) which was then washed with 150 ml of the slurry solvent. The sample (dissolved in a small amount of water) was introduced to the top of the column. Fractions (10–15 ml) were collected with the major product coming off the column after the passage of 150 ml of eluent. Evaporation of the fractions containing the major product gave 3-guanidinopyrrole acetate (6) which was homogeneous according to tlc (cellulose powder, solvent C): yield 51 mg (28%); mp 165–175° dec; recrystallized from methanol–ethyl ether, mp 168–175° dec; ir (KBr) 3450, 1680, 1640, 1535 cm^{-1}; uv (H_2O) end absorption only; nmr (D_2O, TSPS external standard) δ 2.05 (3 H, s, $OCOCH_3$), 6.12 (1 H, t, J = 2 Hz), 6.82 (2 H, d, J = 2 Hz). The compound gave a violet color with Ehrlich reagent, a purple color with a pine splint saturated with hydrochloric acid vapors, and a green color with the Sakaguchi reagent.

Anal. Calcd for $C_7H_{12}N_4O_2$: C, 45.64; H, 6.57; N, 30.42. Found: C, 45.56; H, 6.76; N, 30.22.

Mercuric Acetate Oxidation of Viomycidine Methyl Ester Dihydrochloride to 2-Carbomethoxy-3-guanidinopyrrole Hydrochloride (7).—Viomycidine methyl ester dihydrochloride (300 mg, 0.0012 mol) and mercuric acetate (440 mg, 0.0014 mol) were dissolved in 5% aqueous acetic acid (25 ml), and the solution was stirred at 75–80° for 1 hr (within 25 min ultraviolet absorption at 267 nm appeared to reach maximum intensity). The precipitated mercurous acetate was filtered off and the filtrate treated with hydrogen sulfide. Mercuric sulfide was filtered off, the filtrate treated with hydrogen sulfide, and the mercuric sulfide once again filtered. The filtrate and 5% aqueous acetic acid washings of the precipitated mercuric sulfide were combined and taken to dryness *in vacuo* to give a solid residue, yield 255 mg. The crude product was triturated with absolute ethanol (three 5-ml portions), the filtered ethanolic triturate taken to dryness *in vacuo*, and the solid residue dried over $KOH/CaCl_2$ for 12 hr. This partially purified material was chromatographed on cellulose powder (30 g of Whatman standard grade cellulose powder in ethanol–chloroform 1:1 slurry made up into a column 2 × 27 cm) after being introduced to the top of the column adsorbed on cellulose powder. Fractions containing the chromophore (267 nm, eluent ethanol–chloroform 1:1) were collected, combined, and evaporated to dryness *in vacuo*, yield 45 mg (18%). This material was slightly contaminated with components of low R_f on tlc. The product was recrystallized from ethanol–carbon tetrachloride: mp 195–198° dec (crystalline residue mp >300°); ir (KBr) 1690, 1665, 1650, 1600 cm^{-1}; uv (EtOH) 266 nm (ε 13,500); uv (H_2O) 267.5 nm; nmr (D_2O, TSPS external standard) δ 3.92 (3 H, s), 6.38 (1 H, d, J = 3 Hz), 7.17 (1 H, d, J = 3 Hz).

2-Carboxy-4-guanidinopyrrole Sulfate (9).—To 2 *N* sodium hydroxide (2.25 ml, 0.0045 mol) in distilled water (8 ml) containing platinum oxide (237 mg) was added 2-carboxy-4-nitropyrrole[13] (702 mg, 0.0045 mol) and hydrogenation commenced with vigorous stirring. Within 2 hr the hydrogenation was complete (98% of the theoretical uptake) and the pale yellow solution was decanted from the catalyst in a closed system onto powdered *S*-methylisothiouronium sulfate (417 mg, 0.030 equiv) mixed with a pinch of sodium metabisulfite and contained in a nitrogen-flushed flask. The solution was stirred at 95° (oil bath) under a stream of nitrogen for 7 hr. The dark solution was filtered and neutralized with 5 *N* sulfuric acid and a copious, crystalline precipitate formed. The reaction mixture was chilled

(0°) for 48 hr and the olive green crystals were collected by filtration, washed with a little ice-water, and air-dried, yielding 504 mg (77%): mp 203–205° dec; faint yellow Ehrlich test; insoluble in water and common organic solvents; ir (KBr) 1710, 1675 (vs), 1625 cm^{-1} (s); nmr (D_2O/NaOD, TSPS external standard) δ 6.43 (1 H, d, J = 1.6 Hz), 6.72 (1 H, d, J = 1.6 Hz). Because of its insolubility this material was used without further purification.

3-Guanidinopyrrole Acetate (6).—To anhydrous barium acetate (127.8 mg, 0.50 mmol) in 5% aqueous acetic acid (15 ml) was added 2-carboxy-4-guanidinopyrrole sulfate (9) (217 mg, 0.50 mmol) followed by mercuric acetate (175 mg, 0.55 mmol). The heterogeneous mixture was heated at 93° (oil bath) with stirring for 3 hr (the reaction mixture darkened quickly and within 15 min gave a violet color with Ehrlich reagent). The reaction mixture was cooled and filtered and the filtrate treated with hydrogen sulfide. The small amount of mercuric sulfide precipitate was filtered off and the filtrate taken to dryness *in vacuo*. Crystallization and recrystallization from methanol–ethyl ether gave 119 mg of crystalline 3-guanidinopyrrole acetate: mp 170–178° dec; ir (KBr) 1680, 1640, 1535 cm^{-1}. The synthetic product was homogeneous and identical with material obtained by oxidation of viomycidine (tlc on cellulose powder, solvent C, Ehrlich reagent, and ir spectrum).

Anal. Calcd for $C_7H_{12}N_4O_2$: C, 45.64; H, 6.57. Found: C, 45.69; H, 6.64.

2-Carboxy-4-guanidinopyrrole Hydrochloride (9).—A saturated barium hydroxide solution was added with vigorous mixing to 2-carboxy-4-guanidinopyrrole sulfate (245 mg) suspended in 10 ml of distilled water until a pH of 8–9 (Hydrion pH paper) was attained. The precipitated barium sulfate was centrifuged down and the supernatant liquid drawn off. The barium sulfate was washed with a few milliliters of distilled water and the wash combined with the supernatant liquid; the combination was acidified (carefully with dilute hydrochloric acid) and taken to dryness *in vacuo*. The residue was extracted with boiling methanol (three 3-ml portions), the extract taken to dryness *in vacuo*, and the residue recrystallized from methanol–ethyl ether. The first recrystallization gave 65 mg of impure hydrochloride. Further recrystallization from methanol–ethyl ether gave 40 mg of pure 2-carboxy-4-guanidinopyrrole hydrochloride as granular crystals: mp 179–180° dec; homogeneous upon tlc (cellulose powder, solvent C); extremely weak Ehrlich test (yellow color); ir (KBr) 3460, 3325, 3165, 1690, 1670, 1604 cm^{-1}; nmr (D_2O, TSPS external standard) δ 6.61 (1 H, d, J = 1.7 Hz), 6.89 (1 H, d, J = 1.7 Hz).

2-Carbomethoxy-4-guanidinopyrrole Hydrochloride (10).—A solution of 2-carboxy-4-guanidinopyrole hydrochloride (9) (40 mg) in 5 ml of absolute methanol was saturated with hydrogen chloride gas. After 12 hr at room temperature in a sealed flask the methanolic solution was taken to dryness *in vacuo*, and the residual hydrogen chloride removed by repeated evaporations with methanol. The final residue was recrystallized from methanol–ethyl ether to give 24 mg of hydroscopic granular crystals: mp 103–107°; homogeneous by tlc (silica gel G, solvent A); ir (KBr) 1700, 1675, 1635, 1600, 1510 cm^{-1}; nmr (D_2O, TSPS external standard) δ 3.83 (3 H, s), 6.87 (1 H, d, J = 1.8 Hz), 7.12 (1 H, d, J = 1.8 Hz). The extremely hydroscopic nature of this compound prevented a satisfactory elemental analysis.

Anal. Calcd for $C_7H_{11}N_4O_2Cl$: C, 38.45; H, 5.07; N, 25.63. Found: C, 37.93; H, 5.38; N, 24.89.

Registry No.—**4**, 24250-74-6; **4** 2HCl, 27557-44-4; **4** Me ester 2HCl, 27557-45-5; **6** acetate, 27557-46-6; **7** HCl, 27557-47-7; **9** sulfate, 27557-48-8; **9** HCl, 27617-87-4; **10** HCl, 27557-49-9.

Acknowledgment.—We are indebted to the National Institutes of Health for generous financial support and to Dr. F. A. Hochstein, Chas. Pfizer Inc., Groton, Conn., for a supply of viomycin sulfate.

The Stereoselective Total Synthesis of Racemic Fukinone

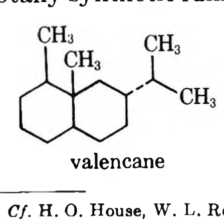
JAMES A. MARSHALL* AND GARY M. COHEN

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

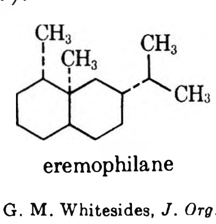
Received October 10, 1970

Two synthetic approaches to racemic fukinone, a sesquiterpene ketone of the eremophilane–valencane type, are described. Both utilize a decalone intermediate **12** synthesized from the known unsaturated alcohol **7** *via* acetylation, allylic oxidation, conjugate methylation, Wolff–Kishner reduction, and oxidation. The stereochemically crucial step of this sequence, conjugate methylation of enone **9**, was effected cleanly with lithium dimethylcopper(I). A reaction sequence involving a novel reduction–fragmentation of a β,γ-epoxynitrile (**15** → **16**) failed for lack of a suitable method for oxidizing the resulting allylic alcohol **16**. An alternative route involving addition of isopropenyllithium to the acetoxy ketone **20** and hydrogenolysis of the derived α-acetoxy ketone **23** was accordingly examined. This route led to a mixture of unsaturated ketones which isomerized to racemic fukinone (**17**) upon chromatography.

Considerable effort has been invested over the past several years in the development of rational schemes for the synthesis of sesquiterpenes related to the valencane–eremophilane family.[1] One of the difficulties in designing a synthetic approach to such compounds stems from the need for stereochemically selective methods for introducing the distinctive cis-related vicinal methyl substituents. In the case of fukinone (**17**), a sesquiterpene ketone isolated from the flower stalks of a cultivated variety of *Petasites japonicus* Maxim,[2] the presence of a cis-fused decalin system led us to consider the application of lithium dimethylcopper 1,4 addition[3] to an angularly methylated 1-octal-3-one (*e.g.*, **9**) as a means for achieving this task.[4] This report details the successful execution of that plan and the subsequent chemical transformations leading to totally synthetic fukinone (**17**).[5]



valencane



eremophilane

(1) *Cf.* J. A. Marshall, H. Faubl, and T. M. Warne, Jr., *Chem. Commun.*, 753 (1967); R. M. Coates and E. J. Shaw, *ibid.*, **47**, 515 (1968); *Tetrahedron Lett.* 5405 (1968); C. Berger, M. Franck-Neumann, and G. Ourisson, *ibid.*, 3451 (1968); E. Piers and R. J. Keziere, *ibid.*, 583 (1968); S. Murayama, D. Chan, and M. Brown, *ibid.*, 3715 (1968).

(2) K. Naya, I. Takagi, Y. Kawaguchi, Y. Asada, Y. Hirose, and N. Shinoda, *Tetrahedron*, **24**, 5871 (1968).

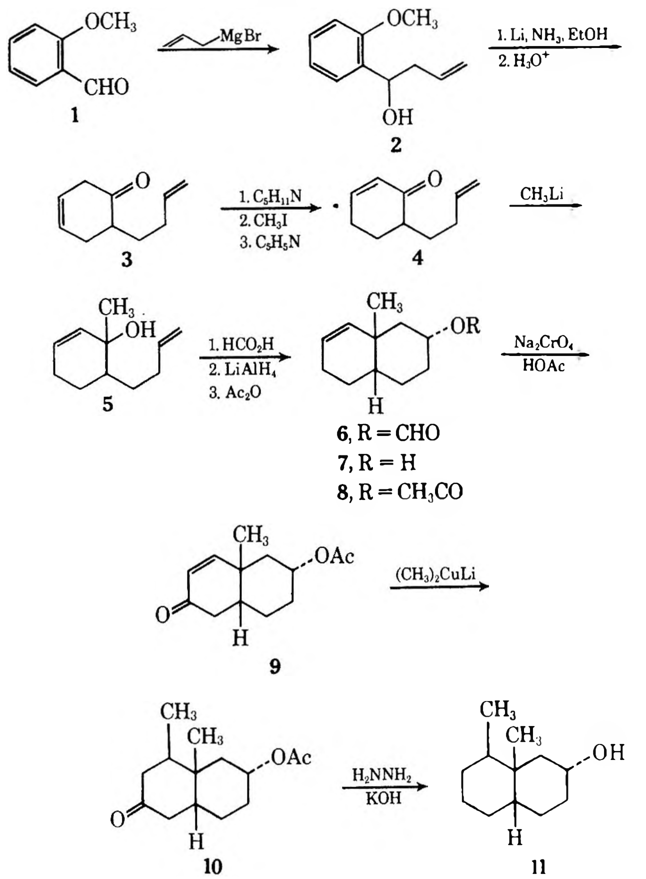
(3) *Cf.* H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).

(4) Related trans-fused decalin enones undergo 1,4 additions with this reagent to give trans-related methyl groups. *Cf.* M. Pesaro, G. Bozatto, and P. Schudel, *Chem. Commun.*, 1152 (1968).

(5) For a preliminary report of this work, see J. A. Marshall and G. M. Cohen, *Tetrahedron Lett.*, in press.

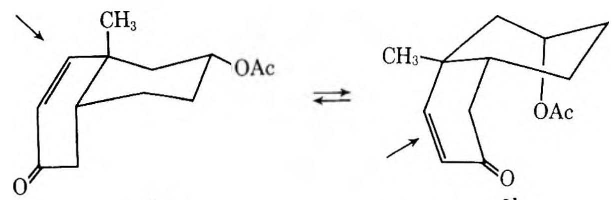
An attractive starting material for this project, the cis-fused octalyl formate 6, had already been synthesized by Johnson and coworkers through an elegant application of their allyl-cation-initiated olefin cyclization method.[6] We utilized their approach but chose 1-methyl-2-(3-butenyl)-5-cyclohexen-1-ol (5) as the allyl cation precursor rather than the isomeric 5-methyl-2-(3-butenyl)-5-cyclohexen-1-ol employed by them in their synthesis. In this way we were able to simplify the reaction sequence leading to formate 6 (Scheme I).

SCHEME I



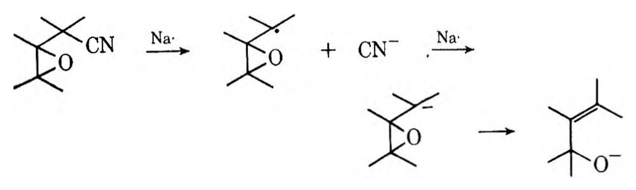
The main complication in our sequence, reduction of the butenyl and cyclohexenyl double bonds in the Birch reduction of the benzylic alcohol 2, was likewise experienced by Johnson.[6] We employed his method[7] for the separation of cyclohexene-reduced material from enone 4 wherein the piperidine 1,4 adduct of the enone is prepared and separated from the neutral by-product *via* acid extraction. Basic treatment of the corresponding methiodide then affords the enone 4 contaminated only with butenyl-reduced material. The alcohol 7 secured *via* cyclization of allylic alcohol 5 and subsequent cleavage of the formate derivative 6 exhibited the properties reported by Johnson and coworkers[6] for the alcohol obtained through cyclization of the allylic isomer of dienol 5.

Oxidation of the unsaturated acetate 8 with sodium chromate in acetic acid–acetic anhydride[8] afforded the crystalline enone 9 in high yield. Conformational analysis of this enone suggests that the steroid conformation 9a should be favored over the nonsteroid conformation 9b by an energy of 0.6 kcal/mol plus an additional increment arising from interaction of the acetoxyl grouping with the C-1 vinylic carbon. These interactions would be present to perhaps an even greater extent in the transition state for the conjugate addition of lithium dimethylcopper(I) to enone 9.[9] Previous studies have shown that steric and stereoelectronic factors control the stereochemical outcome of this reaction.[10] In the case of conformer 9a both factors favor formation of the cis adduct 10. In conformer 9b the stereoelectronically favored antiparallel attack[11] appears effectively blocked by the acetoxyl grouping and the concave cis-fused bicyclic geometry. Hence the cis adduct 10 might likewise be expected to predominate in 1,4 additions whose transition state geometry resembles this conformer. In any case, only a single stereoisomer was obtained upon treatment of enone 9 with lithium dimethylcopper(I). This product was assigned the cis stereochemistry in consideration of the foregoing arguments.



9a 9b

With a solution to the stereochemical problem of fukinone in hand we were able to attack the second synthetic problem presented by this molecule, introduction of the α-isopropylidene ketone functionality. For this task the ketone 12, secured *via* Wolff–Kishner reduction of keto acetate 10 and oxidation of the resulting alcohol 11, seemed like a promising intermediate. Our initial plan called for the application of an interesting reduction–fragmentation reaction of the β,γ-epoxynitrile 15. The expected formation of allylic alcohol 16 by this route was based on the finding of Arapakos, Scott, and Hubert that tertiary nitriles readily undergo reductive decyanation upon treatment with sodium in ammonia.[12] The following sequence illustrates the basis for our proposed fragmentation reaction.



Ketone 12 yielded a 1:1 mixture of geometrically isomeric unsaturated nitriles 13 upon condensation with diethyl cyanomethylphosphonate. Alkylation of this mixture with methyl iodide using triphenylmethyllithium as the base afforded the dimethylated nitrile 14 as the major product. The major by-product of this reaction appeared to be the monomethylated

(6) W. S. Johnson and K. E. Harding, *J. Org. Chem.*, **32**, 478 (1967).

(7) The method was developed by G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4604 (1956).

(8) *Cf.* W. G. Dauben and A. C. Ashcraft, *ibid.*, **85**, 3673 (1963).

(9) *Cf.* J. A. Marshall, W. I. Fanta, and H. Roebke, *J. Org. Chem.*, **31**, 1016 (1966).

(10) *Cf.* J. A. Marshall and N. H. Andersen, *ibid.*, **31**, 667 (1966); H. O. House and W. F. Fischer, Jr., *ibid.*, **33**, 949 (1968).

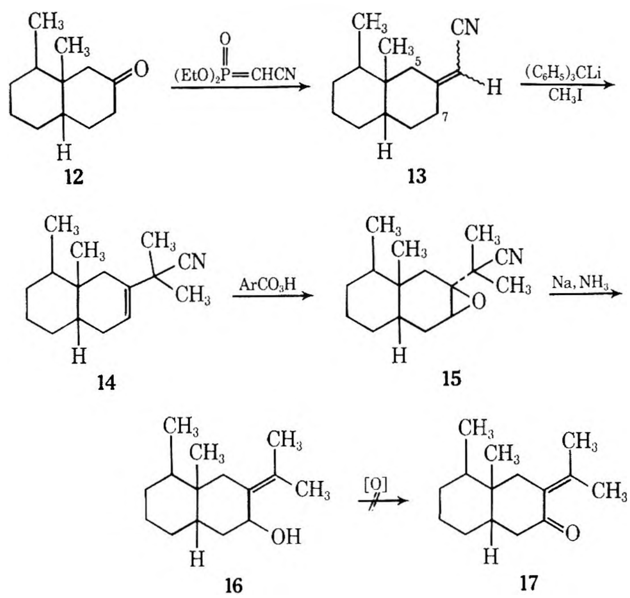
(11) *Cf.* E. Toromanoff, *Bull. Soc. Chim. Fr.*, 708 (1962).

(12) P. G. Arapakos, M. K. Scott, and F. E. Hubert, Jr., *J. Amer. Chem. Soc.*, **91**, 2059 (1969).

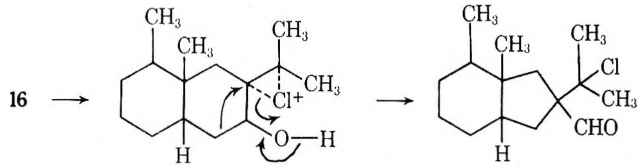
counterpart of nitrile **14**. We could find no indication that the *a priori* possible double bond isomer of nitrile **14** was formed to any extent. Our selection of a bulky base for the methylation reaction was made with this outcome in mind on the premise that proton abstraction from C-5 would involve appreciably greater steric interactions than abstraction at C-7. The use of potassium *tert*-butoxide in *tert*-butyl alcohol for this reaction led only to recovered starting material.

Expoxidation of the unsaturated nitrile **14** with *m*-chloroperoxybenzoic acid afforded material consisting largely of an isomer assigned structure **15** on the basis of spectral evidence and conformational considerations (attack of peroxy acid on the less hindered face of the double bond of olefin **14** in the steroid conformation). Treatment of the epoxynitrile **15** with sodium in ammonia gave the unsaturated alcohol **16** in 94% yield. Consideration of a probable mechanism for this cleavage (see Scheme II) leads to the indicated stereochemical assignment for this product.

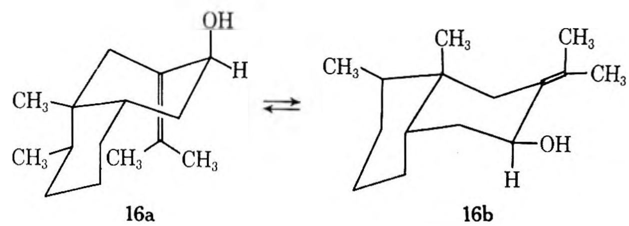
SCHEME II



Unfortunately, the seemingly trivial final step of this synthetic sequence, oxidation of alcohol **16** to racemic fukinone (**17**), could not be effected in our hands despite a considerable effort. The following reagents gave the results indicated: manganese dioxide[13] and Oppenauer oxidation[14] (recovered starting material); Collins reagent[15] (epoxide and epoxy ketone formation); Jones reagent,[16] ceric ammonium nitrate,[17] silver(II) picolinate,[18] dimethyl sulfoxide–acetic anhydride[19] (dehydration); chlorobenzotriazole[20] (rearrangement). This last reaction was of some interest as it afforded an aldehyde whose formation can be envisioned as follows.



Of the two major conformations **16a** and **16b** available to alcohol **16** the former should be of substantially lower energy. In addition to an axially oriented secondary methyl group (1.8 kcal/mol)[21] the latter also suffers from an $A^{(1,3)}$ interaction between the equatorial hydroxyl group and a vinyl methyl group.[22] Conformer **16a** suffers from two major drawbacks with regard to oxidation reactions: (1) acidic reagents should readily promote dehydration of the axial allylic hydroxy group, and (2) abstraction of the carbinyl hydrogen should be difficult owing to steric hindrance by the *syn*-vinyl methyl group.



Finding no way to effect the oxidation of alcohol **16**, we turned to an alternative plan for introducing the isopropylidene ketone grouping of fukinone. To this end, ketone **17** was treated first with triphenylmethyllithium and then acetic anhydride to give the enol acetate **18**. The use of a bulky base in this reaction to direct enolate formation in the desired direction was decided by consideration of steric factors as discussed above for the unsaturated nitrile **7**. Acid-catalyzed enol acetylation[23] led to a mixture of double bond isomers.

Epoxidation of the enol acetate **18** with *m*-chloroperoxybenzoic acid followed by thermal rearrangement[24] of the resulting epoxy acetate **19** afforded the acetoxy ketone **20**, an apparent mixture of epimers. Addition of isopropenyllithium gave the acid-labile diol **21** which was oxidized directly by the dimethyl sulfoxide–pyridine–sulfur trioxide method.[25] Acetylation then afforded the acetoxy ketone **23** as a mixture of epimers. Reduction with calcium in ammonia removed the acetoxy function from this compound and led to a mixture of α,β- and β,γ-unsaturated ketones **24**. Isomerization of the latter to racemic fukinone was effected upon chromatography of the mixture on alkaline alumina. Material thus secured was spectroscopically and chromatographically identical with natural fukinone[1,26] (Scheme III).

(13) *Cf.* P. J. Neustaedter in "Steroid Reactions," C. Djerassi, Ed., Holden-Day, San Francisco, Calif., 1963, pp 104–110.

(14) Reference 13, pp 92–104; C. Djerassi, *Org. React.*, **6**, 235 (1951); R. B. Woodward, N. L. Wendler, and F. J. Brutschy, *J. Amer. Chem. Soc.*, **67**, 1425 (1945).

(15) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(16) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **39** (1946).

(17) W. S. Trahanovsky, L. B. Young, and G. L. Brown, *J. Org. Chem.*, **32**, 3865 (1967).

(18) J. B. Lee and T. G. Clarke, *Tetrahedron Lett.*, 415 (1967).

(19) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **87**, 4214 (1965).

(20) C. W. Rees and R. C. Storr, *Chem. Commun.*, 1305 (1968).

(21) *Cf.* E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformationl Analysis," Interscience, New York, N. Y., 1965, p 44.

(22) F. Johnson and S. K. Malhotra, *J. Amer. Chem. Soc.*, **87**, 5492 (1965).

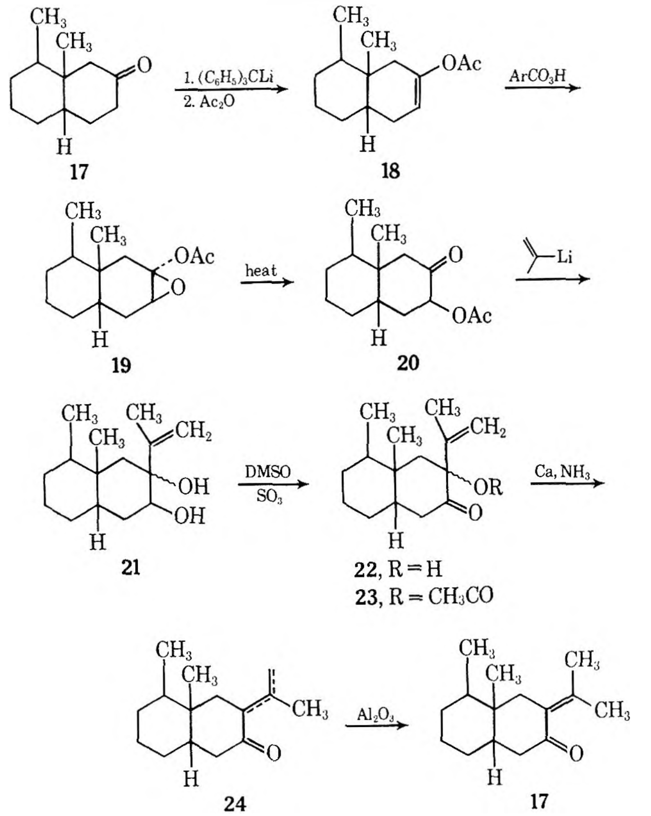
(23) B. E. Edwards and P. N. Rao, *J. Org. Chem.*, **31**, 324 (1966).

(24) *Cf.* K. L. Williamson and W. S. Johnson, *ibid.*, **26**, 4563 (1961).

(25) J. R. Parikh and W. von E. Doering, *J. Amer. Chem. Soc.*, **89**, 5505 (1967).

(26) We are indebted to Dr. K. Naya and Dr. Y. Hirose for a sample of natural fukinone.

SCHEME III



Experimental Section[27]

1-(o-Methoxyphenyl)-3-buten-1-ol (2).—To a solution of allylmagnesium bromide (prepared from 30.0 g of Mg and 57.1 g of allyl bromide in 370 ml of ether)[28] at 0° was added, with stirring, 55.8 g of o-anisaldehyde in 200 ml of ether over a period of 1.5 hr. Stirring was continued for 20 min and aqueous ammonium chloride and 1:1 aqueous HCl were added to dissolve the precipitated salts. The product was isolated with ether[27] and distilled affording 57.8 g (78%) of alcohol 2: bp 80–92° (0.02 mm); λ_{max}^{film} 6.09, 6.24, 8.08, 9.02, 10.89, and 13.18 μm; $\delta_{TMS}^{CCl_4}$ 2.34 (CH_2, broad triplet, $J = 6$ Hz), 2.75 (OH), 3.63 (OCH_3), 4.7–5.1 (=CH_2 and CHOH), 5.3–5.9 (CH=), and 6.5–7.3 ppm (aryl CH).

The analytical sample was secured by preparative gas chromatography on a 13.5 ft by 0.5 in. column of DC-550 silicone oil on 70–80 mesh Chromosorb G (AW-DMCS).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.1; H, 7.7.

Conversion of Alcohol 2 to Octalol 7.—The following sequence was patterned after an analogous conversion reported by Johnson.[6] A solution of 62.2 g of alcohol 2 in 800 ml of 1,2-dimethoxyethane and 1600 ml of ammonia cooled in a Dry Ice–acetone bath was treated with 13.8 g of Li wire in small pieces over a period of 0.5 hr. Ethanol (40.7 ml) was added dropwise to the efficiently stirred solution over a period of 0.5 hr and, 10 min after complete addition, excess ammonium chloride was added to discharge the blue color. The ammonia was allowed to evaporate and the product was isolated with ether affording 51.9 g (89%) of material comprised chiefly of the enol ether but containing considerable (~20–30%) amounts of material with reduced vinyl and cyclohexene double bonds.

A solution of 26.6 g of the above material and 3.3 g of oxalic acid dihydrate in 25 ml of 1,2-dimethoxyethane and 40 ml of water was stirred briskly for 22 hr. The product was isolated with ether affording 16.7 g (69%) of β,γ-unsaturated ketone 3 contaminated with saturated ketone and butenyl-reduced material according to the nmr spectrum.

A solution of 30.4 g of enone, comparable to that described above, in 125 ml of piperidine was stirred at reflux for 4 hr. The cooled solution was poured into 440 ml of 10% HCl and washed with ether. The aqueous phase was made basic with 220 ml of 20% NaOH and extracted with ether affording 33.3 g of β-amino ketone: λ_{max}^{film} 5.84 μm; $\delta_{TMS}^{CCl_4}$ 4.8–5.2 (=CH_2) and 5.4–6.1 ppm (CH=).

The above amino ketone was cooled in an ice bath during the careful addition of 67 ml of methyl iodide. The mixture was allowed to reach room temperature over 3 hr and excess methyl iodide was removed from the crushed mass under vacuum.

The above methiodide in 50 ml of pyridine was heated on a steam bath for 1.7 hr and the cooled solution was poured into 430 ml of 10% HCl. The product was isolated with ether and treated with activated charcoal to remove colored impurities. Distillation at 87–89° (1.7 mm) afforded 17.0 g (74%) of enone 4 contaminated with 30% of the butenyl-reduced enone according to gas chromatography: λ_{max}^{film} 5.96, 6.08, and 10.92 μm; $\delta_{TMS}^{CCl_4}$ 4.7–5.3 (=CH_2), 5.4–6.2 (CH=), 5.88 (t of d, CH=CHC=O, J = 1 and 10 Hz), and 6.86 ppm (t of d, CH=CHC=O, J = 7 and 10 Hz).

A solution of 17.0 g of the above enone in 110 ml of ether was added to 150 ml of 1.37 *M* methyllithium in ether at 0° with stirring. After 2.5 hr the ice bath was removed and the product was isolated with ether. The crude alcohol 5 thus secured was poured into 300 ml of rapidly stirred formic acid. After several minutes, the product was isolated with hexane affording 14.2 g (65% based on enone 4) of formate 6: λ_{max}^{film} 5.80, 6.02, and 8.47 μm.

A mixture of 10.2 g of the above formate and 3.22 g of lithium aluminum hydride in 350 ml of ether was stirred at 0° for 0.5 hr and at room temperature for 0.5 hr. The mixture was cooled to 0° and 6.4 ml of water and 5.1 ml of 10% NaOH were added carefully with stirring. After 4 hr the mixture was filtered and the solvent was removed *in vacuo* affording 9.30 g (100%) of alcohol 7: λ_{max}^{film} 3.1, 6.05, and 9.55 μm. The 3,5-dinitrobenzoate had mp 127–128° (lit.[6] mp 128–129°) after recrystallization from ethanol.

***cis*-10β-Methyl-3-octal-6α-yl Acetate (8).**—A solution of 3.22 g of alcohol 7, 6 ml of acetic anhydride, and 23 ml of pyridine was stirred for 23 hr at room temperature. The solution was poured into 100 ml of cold 10% sulfuric acid and the product was isolated with ether affording 3.67 g (91%) of acetate 8: bp 50–60° (0.03 mm); λ_{max}^{film} 5.87, 6.05, 8.02, 8.12, and 9.72 μm; $\delta_{TMS}^{CCl_4}$ 1.08 (CH_3), 1.90 (CH_3CO), 4.5–5.0 (H-6), and 5.1–5.7 ppm (vinyl H multiplet). The analytical sample was secured *via* preparative gas chromatography on an 18 ft by 0.25 in. column of 5% Carbowax 20M on Chromosorb W.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.0; H, 9.7.

***cis*-10β-Methyl-6α-acetoxy-3-octal-2-one (9).**—The procedure of Dauben[8] was modified. To a solution of 7.77 g of octalin 8 in 92 ml of acetic acid and 64 ml of acetic anhydride was slowly added, with mechanical stirring and intermittent cooling, 44 g of anhydrous sodium chromate. After 7 hr of heating at 60°, 30 ml of water was added, the solution was cooled, and the product was isolated with ether affording 6.68 g (81%) of an oil which crystallized upon cooling. Recrystallization from hexane–ether afforded the analytical sample: mp 63.5–65.5°; λ_{max}^{KBr} 5.78, 5.96, 6.19, 8.18, 9.69, 13.28, and 13.99 μm; $\delta_{TMS}^{CCl_4}$ 1.23 (CH_3), 1.93 (CH_3CO), 2.2–2.5 (H-1), 4.7–5.7 (H-6), 5.72 (H-3 doublet, J = 10 Hz), and 6.48 ppm (H-4 doublet, J = 10 Hz).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.5; H, 8.3.

***cis*-6α-Acetoxy-4β,10β-dimethyl-2-decalone (10).**—The method of House[3] was employed. A solution of lithium dimethylcopper(I) was prepared from 13.6 g of Cu(I) in 300 ml of ether to which 100 ml of 1.36 *M* methyllithium was added at 0°. To this solution was added with stirring a solution of 7.56 g of keto acetate 9 in 100 ml of anhydrous ether. After 0.5 hr, the mixture was poured into 700 ml of saturated ammonium chloride and ammonium hydroxide was added to dissolve the precipitated salts. The product was isolated with ether and distilled, bp 92–132° (0.05 mm). The distilled material was chromatographed on 244 g of Merck alumina. The keto acetate 10 (4.50 g, 55%) was eluted with 1% ether–benzene: λ_{max}^{film} 5.73, 5.82, 8.05, 8.78, 9.60, and 9.79 μm; $\delta_{TMS}^{CCl_4}$ 0.87 (CH_3 doublet, J = 6 Hz), 1.05 (CH_3), 1.92 (CH_3CO), and 4.6–5.1 ppm. The analytical sample

(27) Reactions were conducted under a nitrogen atmosphere using the apparatus described by W. S. Johnson and W. P. Schneider, "Organic Syntheses," Collect Vol. IV, Wiley, New York, N. Y., 1963, p 132. Reaction products were isolated by addition of water and extraction with the specified solvent. The combined extracts were washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed from the filtered solutions on a rotary evaporator.

(28) O. Grummitt, E. P. Budewitz, and C. C. Chudd, *ibid.*, p 748.

was secured by preparative gas chromatography on a 7 ft × 0.25 in. column of DC-550 silicone oil on 60–70 mesh Chromosorb G (AW-DMCS).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.4; H, 9.3.

cis-4β,10β-**Dimethyl-6α-decalol (11)**.—A modified Huang-Minlon[29] procedure was used. A solution of 537 mg of keto acetate **10**, 596 mg of KOH, 0.4 ml of 85% hydrazine hydrate, and 20 ml of diethylene glycol was heated at 120° for 18 hr and then at reflux for 3 hr with a Dean–Stark trap. The product was isolated with hexane affording 304 mg (74%) of alcohol **11**. The analytical sample, mp 72–74°, was secured by preparative gas chromatography on a 13.5 ft × 0.5 in. column of 9% DC-550 silicone oil on 70–80 mesh Chromosorb G (AW-DMCS), and sublimation at 70° (0.2 mm): λ_{max}^{KBr} 3.05, 9.59, 9.68, 10.11, 10.48, 10.69, and 10.84 μm; $\delta_{TMS}^{CCl_4}$ 0.85 (CH_3), 0.86 (CH_3 doublet, J = 7 Hz), and 3.90 ppm (H-6).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.3; H, 12.4.

cis-4β,10β-**Dimethyl-6-decalone (12)**.—The Jones oxidation procedure was used.[16] To a solution of 301 mg of alcohol **11** in 12 ml of acetone at 0° was added dropwise 0.52 ml of Jones reagent.[16] After 3 min isopropyl alcohol was added and the product was isolated with ether affording 274 mg (92%) of ketone **12**: bp 73° (bath temperature) (0.1 mm); λ_{max}^{film} 5.85, 7.62, and 8.01 μm; $\delta_{TMS}^{CCl_4}$ 0.85 (CH_3 doublet, J = 6 Hz) and 0.95 ppm (CH_3).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.0; H, 11.2.

(*Z*)- **and** (*E*)-(*cis*-4β,10β-**Dimethyl-6-decalylidene)cyanoacetate (13)**.—The method of Wadsworth and Emmons[30] was employed. To 58.5 mg of pentane-washed NaH (from a 53% dispersion in oil) was added 2.0 ml of DME and 259 mg of diethyl cyanomethylphosphonate with stirring and cooling. After hydrogen evolution ceased, 208 mg of ketone **12** and 0.4 ml of DME was added and the solution was allowed to reach room temperature. After 22 hr the product was isolated with ether and chromatographed on silica gel. Elution with 25% benzene–hexane afforded 185 mg (79%) of nitrile **13**: bp 100° (bath temperature) (0.02 mm); λ_{max}^{film} 4.49, 6.12, and 12.12 μm; $\delta_{TMS}^{CCl_4}$ 0.79 (CH_3 doublet, J = 6 Hz), 0.90 and 0.96 (CH_3's of *Z* and *E* isomers), 4.86 and 4.97 ppm (vinyl H's of *Z* and *E* isomers, $W_{h/2}$ = 5 Hz).

cis-4β,10β-**Dimethyl-6-(dimethylcyanomethyl)-6-octalin (14)**.—Triphenylmethyllithium was prepared according to House.[31] The solvent from 2.39 ml of 1.76 *M* methyllithium was removed *in vacuo* and replaced by 4.0 ml of DME. To this solution was added 1.13 g of triphenylmethane. After 3 hr, 188 mg of nitrile **13** was added with stirring and, after 0.5 hr, the solution was cooled in an ice bath and 0.435 ml of methyl iodide was slowly added. After addition was complete the ice bath was removed and after 0.5 hr the product was isolated with ether and chromatographed on 150 g of silica gel. The fractions eluted with 85% hexane–benzene were combined and distilled affording 183 mg (85%) of nitrile **14**: bp 90° (bath temperature) (0.02 mm); λ_{max}^{film} 4.47, 7.26, and 7.35 μm; $\delta_{TMS}^{CCl_4}$ 0.88 (CH_3), 1.23 (gem CH_3's), and 5.67 ppm (H-7, $W_{h/2}$ = 10 Hz). Gas chromatography on a 6 ft × 0.125 in. column of 10% SE-30 silicone gum rubber on 80–100 mesh Diatoport S revealed an 80:20 mixture of nitrile **14** and its monomethylated counterpart.

cis-4β,10β-**Dimethyl-6-isopropylidenedecal-7β-ol (16)**.—A solution of 150 mg of nitrile **14** and 235 mg of *m*-chloroperoxybenzoic acid (97%) in 10 ml of methylene chloride was stirred at room temperature for 6 hr. The solution was treated with 2.5 ml of 10% aqueous sodium sulfite and the product was isolated with ether affording 159 mg (99%) of epoxynitrile **15**: λ_{max}^{film} 4.46, 7.24 and 7.35 μm; $\delta_{TMS}^{CCl_4}$ 0.86 (CH_3), 1.26 and 1.36 (gem CH_3's), and 3.27 ppm (H-7, $W_{h/2}$ = 11 Hz). The gas chromatogram indicated a purity of 73% and contained minor peaks amounting to 7 and 19% along with trace impurity peaks.

The reduction procedure of Arapakos, Scott, and Hubert was followed.[12] To a solution of 217 mg of Na in 15 ml of liquid ammonia was added a solution of 159 mg of epoxy nitrile **15** in 1.6 ml of ether over a period of 5 min. After 20 min excess ammonium chloride was added to discharge the color, the ammonia was allowed to evaporate, and the product was isolated with ether affording 134 mg (94%) of alcohol **16**: λ_{max}^{film} 3.00 μm; $\delta_{TMS}^{CCl_4}$ 0.90 (CH_3), 1.67 and 1.73 [$(CH_3)_2C$=], and 4.70 ppm (H-7, $W_{h/2}$ = 8 Hz).

cis-4β,10β-**Dimethyl-6-octal-6-yl Acetate (18)**.—The method of House[31] was utilized. Triphenylmethyllithium was prepared as described above from 7.8 ml of 1.08 *M* methyllithium and 2.56 g of triphenylmethane in 10 ml of DME. To this solution was added 949 mg of ketone **17**, a quantity which just discharged the red color of the basic solution. After 0.5 hr this enolate solution was added dropwise to 25 ml of acetic anhydride. The solution was stirred for 0.5 hr, poured into hexane, and treated with aqueous and then solid sodium bicarbonate. The product was isolated with hexane and chromatographed on 140 g of silica gel. Elution with 75% benzene–hexane afforded 669 mg (57%) of enol acetate **18**: bp 68° (bath temperature) (0.02 mm); λ_{max}^{film} 5.70, 5.92, 8.24, 9.15, and 9.93 μm; $\delta_{TMS}^{CCl_4}$ 0.93 (CH_3), 0.91 (CH_3 doublet, J = 6 Hz), 1.98 (CH_3CO), and 5.07 ppm (H-7, $W_{h/2}$ = 17 Hz). The analytical sample was secured by preparative gas chromatography on a 7 ft × 0.25 in. of column of DC-550 silicone oil on 60–70 mesh Chromosorb G (AW-DMCS).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.7; H, 9.9.

cis-**7-Acetoxy-4β,10β-dimethyl-6-decalone (20)**.—A solution of 97.8 mg of enol acetate **18**, 166 mg of *m*-chloroperoxybenzoic acid (97%), and 17.7 mg of 2,6-di-*tert*-butylphenol in 1.55 ml of benzene was stirred at room temperature for 4 hr. The solution was treated with 3.5 ml of 10% aqueous sodium sulfite and the product was isolated with ether, after an initial wash with 10% aqueous NaOH, and distilled affording 94.5 mg of epoxy acetate **19**: bp 75–100° (bath temperature); λ_{max}^{film} 5.72 μm, contaminated with 2,6-di-*tert*-butylphenol.

The above sample of epoxy acetate **19** was heated at 170–180° for 10 min and distilled, 110° (bath temperature) (0.02 mm), to yield 79 mg of an oil that was chromatographed on silica gel. Elution with 2% ether–benzene afforded 50 mg (48%) of keto acetate **20**: λ_{max}^{film} 5.72, 5.82, 8.12, and 9.48 μm; $\delta_{TMS}^{CCl_4}$ 0.90 and 0.96 (CH_3), 2.03 (CH_3CO), and 4.9–5.3 ppm (H-7). The C-4 methyl doublets were partially obscured by the angular methyl signals. The analytical sample, mp 96–104°, was secured by repeated crystallization from hexane of one chromatographic fraction.

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.7; H, 9.4.

cis-4β,10β-**Dimethyl-6-hydroxy-6-isopropenyl-7-decalone (22)**.—A solution of isopropenyllithium was prepared from 401 mg of lithium (1% Na) and 1.42 ml of isopropenyl bromide in 23 ml of ether according to the procedure of Braude and Evans.[32] To this solution at 0° was added with stirring 191 mg of keto acetate **20** and 2 ml of ether. After 1 hr the product was isolated with ether (dried over potassium carbonate) and oxidized by treatment with 1.95 g of sulfur trioxide–pyridine complex in 8.8 ml of dimethyl sulfoxide and 4.15 ml of triethylamine for 4 hr.[25] The product was isolated with hexane and distilled to give 137 mg of ketol **22**. Chromatography on 13 g of silica gel afforded on elution with 2% ether–benzene 84 mg (44%) of product: λ_{max}^{film} 2.90, 5.87, 6.08, and 11.06 μm; $\delta_{TMS}^{CCl_4}$ 0.89 (two overlapping CH_3 doublets, J = 7 Hz), 1.05 (CH_3), 1.83 (vinyl CH_3), and 4.6–4.9 ppm (CH_2=). The analytical sample was secured by distillation, 105° (bath temperature) (0.2 mm).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.3; H, 10.3.

cis-**6-Acetoxy-4β,10β-dimethyl-6-isopropenyl-7-decalone (23)**.—The procedure of Huang-Minlon, Wilson, Wendler, and Tishler was employed.[33] A solution of 83.9 mg of ketol **22** and 64.9 mg of *p*-toluenesulfonic acid monohydrate in 4.7 ml of acetic anhydride was stirred for 19 hr at room temperature. The solution was poured into saturated aqueous sodium bicarbonate and hexane, and solid sodium bicarbonate was added. The product was isolated with hexane and distilled to give 88 mg of keto acetate **23**: bp 90° (bath temperature) (0.02 mm); λ_{max}^{film} 5.74, 5.78, 6.08, 8.10, 9.80, and 10.97 μm; $\delta_{TMS}^{CCl_4}$ 0.80 (CH_3 doublet, J = 6 Hz), 0.93 and 0.96 (CH_3), 1.8 (vinyl CH_3), 1.96 and 2.02 (CH_3CO), and 4.7–5.1 ppm (CH_2=). The analytical sample was eluted from silica gel with 2% ether–benzene and distilled, bp 80° (bath temperature) (0.1 mm).

Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.5; H, 9.6.

(29) Huang-Minlon, *J. Amer. Chem. Soc.*, **71**, 3301 (1949).

(30) W. S. Wadsworth, Jr., and W. D. Emmons, *ibid.*, **83**, 1733 (1961).

(31) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965).

(32) E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 3333 (1956).

(33) Huang-Minlon, E. Wilson, N. L. Wendler, and M. Tishler, *J. Amer. Chem. Soc.*, **74**, 5394 (1952).

(±)-**Fukinone** (**17**).—A stirred solution of 82.8 mg of Ca in 5 ml of liquid ammonia was treated with a solution of 48 mg of keto acetate **23** in 0.8 ml of ether. After 10 min, excess ammonium chloride was added and the ammonia was allowed to evaporate through a Mercury bubbler. The product was isolated with ether and distilled affording 33 mg of an oil, bp 75° (bath temperature) (0.01 mm). Elution from 10 g of Merck alumina with 50% benzene–hexane afforded 15 mg (39%) of (±)-fukinone: λ_{max}^{film} 5.93, 6.12, 6.93, 7.33, 7.88, 8.21, 8.61, and 9.39 μm; $\delta_{TMS}^{CDCl_3}$ 0.85 (CH_3 doublet, J = 7 Hz), 0.97 (CH_3), 1.79 and 1.94 ppm [$(CH_3)_2C$=].[34] The infrared and nmr spectra matched those of natural fukinone and the gas chromatographic behavior of the two substances was identical on three columns (peak enhancement).[1,26]

Registry No.—**2**, 27693-90-9; **8**, 27755-32-4; **9**, 27693-91-0; **10**, 27693-92-1; **11**, 27755-33-5; **12**, 27693-93-2; (*E*)-**13**, 27693-94-3; (*Z*)-**13**, 27693-95-4; **14**, 27693-96-5; **16**, 27693-97-6; **17**, 25828-19-7; **18**, 27693-99-8; **20**, 27694-00-4; **22**, 27694-01-5; **23**, 27694-02-6.

Acknowledgments.—We are grateful to the National Institutes of Health for a research fellowship (5-F01-GM42762, Division of General Medical Sciences to G.M.C., 1969–1970) and a research grant (5-R01-CA11089, National Cancer Institute).

(34) This spectrum was secured using a Brucker 90-MHz spectrometer.

The Nature of the Ortho Effect. VIII. Composition of the Ortho Effect as a Function of Side-Chain Structure

MARVIN CHARTON

Department of Chemistry, School of Engineering and Science, Pratt Institute, Brooklyn, New York 11205

Received May 18, 1970

Twenty-two sets of ionization constants, in water, for ortho-substituted compounds of the type XGZY (where X is a substituent; Z, a side chain; Y, the reaction site; and G, a skeletal group to which X and Z are attached) were correlated with the equation $Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi_{V,X} + h$, and 27 sets were correlated with the equation $Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h$. Significant correlations were obtained in most cases. Steric effects were absent in most of those sets which were of diagnostic value. Examination of the ϵ values obtained shows that the composition of the ortho electrical effect is indeed a function of the side chain. It is shown that this implies the existence of electrical proximity effects. The delocalized electrical proximity effect is found to be a function of the side chain. No conclusion can be reached as to whether or not the localized electrical proximity effect is a function of the side chain. In the majority of the sets studied, the value for the unsubstituted compound does lie on the correlation line.

In a further extension of our work on the nature of the ortho effect,[1–7] we consider here the variation of the composition of the ortho electrical effect as a function of side-chain structure in sets of the type $2XC_6H_4ZY$, in which X is the substituent, Y is the reaction site, and Z is the side chain. For this purpose, it is advisable to consider the composition of the overall effect of an ortho substituent on some reaction site. This overall effect is composed of the normal electrical effect of the substituent at the ortho position and of a proximity effect which results from the nearness of the substituent to the reaction site. This proximity effect can be separated into three possible contributions.

I. Proximity Electrical Effects.—These electrical effects are a property of the proximity effect and are exerted in addition to the normal electrical effects of the substituent. They may be resolved into (1) localized effects, which are a function of the σ_I constants, and (2) delocalized effects, which are a function of the σ_R constants.

II. Steric Effects.—These effects are a function of the size of the substituent. They may consist of (1) steric hindrance to solvation of the substituent and/or the reaction site, (2) steric hindrance of the reaction site to attack by a reagent, (3) steric inhibition of resonance in the substituent and/or the reaction site, and (4) steric control of the reacting conformation.

III. Intramolecular Secondary Bonding Forces.—(1) Hydrogen bonding, (2) Keesom (dipole–dipole), Debye (dipole–induced dipole), and London (induced dipole–induced dipole), and (3) charge transfer interactions comprise this group.

It is readily seen that not all ortho-substituted sets will show a proximity effect. The existence of the proximity effect depends on the closeness in space of the substituent to the reaction site. In sets of the type $2XC_6H_4ZY$, the closeness of X to Y is a function of the size and geometry of the side chain Z. For a sufficiently large Z, X and Y must be far enough apart to exclude the possibility of proximity effects. Furthermore, the magnitude of the proximity effect must be a function of the distance between the reaction site and the substituent. We would predict then a dependence of the overall substituent effect upon the size of Z. We may quantitatively represent the overall substituent effect of an ortho substituent by the expression

$$Q_X = \alpha_{norm}\sigma_{I,X} + \beta_{norm}\sigma_{R,X} + \alpha_{prox}\sigma_{I,X} + \beta_{prox}\sigma_{R,X} + \psi r_{V,X} + \nu\omega_X + d \quad (1)$$

where $\alpha_{norm}\sigma_{I,X} + \beta_{norm}\sigma_{R,X}$ represents the proximity electrical effect, $\psi r_{V,X}$ signifies the steric effect, and $\nu\omega_X$ denotes the contribution due to secondary bonding. Equation 1 simplifies to

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi r_{V,X} + \nu\omega_X + h \quad (2)$$

Of the types of secondary bonding considered above, hydrogen bonding and charge transfer occur only in

(1) M. Charton, *J. Org. Chem.*, **34**, 278 (1969).
(2) M. Charton, *J. Amer. Chem. Soc.*, **91**, 615 (1969).
(3) M. Charton, *ibid.*, **91**, 619 (1969).
(4) M. Charton, *ibid.*, **91**, 674 (1969).
(5) M. Charton, *ibid.*, **91**, 6649 (1969).
(6) M. Charton and B. I. Charton, *J. Org. Chem.*, **36**, 260 (1971).
(7) M. Charton, *ibid.*, **36**, 266 (1971).

TABLE I

DATA USED IN CORRELATIONS[a]

1. pK_a, 2-substituted pyridinium ions, 25°[b]
OMe, 3.06; $PhCH_2$, 5.13; C_2H_3, 4.98; *H*, 5.17; F, −0.44; Cl, 0.72; Br, 0.90; I, 1.82; Me, 5.97; Et, 5.97; Pr, 5.97; *i*-Pr, 5.83; *tert*-Bu, 5.76; NH_2, 6.71
2. pK_a, 2-substituted pyridinium ions, 20°[b]
CN, −0.26; $CONH_2$, 2.10; CO_2Me, 2.21; Me, 5.97; Et, 5.99; OMe, 3.40; MeS, 3.59; NH_2, 6.82; NHAc, 4.09; NHBz, 3.33; *H*, 5.28
3. pK_a, 2-substituted quinolinium ions, 25°[b]
MeS, 3.71; OMe, 3.17; OEt, 3.04; *H*, 4.959; Me, 5.832; CO_2Me, 1.755; NH_2, 7.25
4. pK_a, 2-substituted imidazolinium ions, 25°[c]
H, 6.95; Me, 7.86; Et, 8.00; Ph, 6.39; NO_2, −0.81; NH_2, 8.46
5. pK_a, 2-substituted benzimidazolinium ions, 25°[c]
H, 5.58; Me, 6.29; Et, 6.27; CH_2OH, 5.40; OEt, 4.18; Ph, 4.23; NH_2, 7.54
6. pK_b, 2-substituted benzimidazoles, 25°[c]
H, 8.6; Me, 8.3; Ph, 9.2; $PhCH_2$, 8.9; Cl, 11.4; Me_2N, 6.6; CH_2OH, 8.4; $AcOCH_2$, 9.4; $PhCH_2CH_2$, 7.9; PhC_2H_3, 8.8
7. pK_a, 2-substituted 5,6,7,8-tetrahydronaphth[2,3]imidazolinium ions, 20°[c]
H, 5.98; Et, 6.64; Cl, 2.68; NH_2, 7.69; Me_2N, 7.65; MeS, 5
8. pK_a, 2-substituted phenols, 25°[d]
H, 10.00; F, 8.705; Cl, 8.53; Br, 8.44; I, 8.51; Me, 10.29; OMe, 9.98
9. pK_a, 2-substituted phenols, 0.1 *M* KCl, 20°[e]
NMe_2, 10.62; *i*-Pr, 10.31; Et, 10.27; OMe, 9.90; I, 8.44; Br, 8.33; Cl, 8.46; *NO_2*, 7.21; *H*, 9.89
10. pK_a, 2-substituted anilinium ions, 25°[d]
H, 4.60; F, 3.20; Cl, 2.65; Br, 2.53; I, 2.60; OMe, 4.52; Me, 4.45
11. pK_a, 2-substituted 1-hydroxypyridinium ions, 25°[f]
H, 0.79; $PhCH_2S$, −0.23; NHAc, −0.42; NHBz, −0.44; NH_2, 2.67; OMe, 1.23; OEt, 1.18; NO_2, −2.71; CN, −2.08; Ac, −0.45; Cl, −0.77
12. pK_a, 2-substituted benzoic acids, 25°[g]
F, 3.267; Cl, 2.9215; Br, 2.854; I, 2.863; Me, 3.9083; Et, 3.793; OMe, 4.094; Ph, 3.460; *H*, 4.203; *NO_2*, 2.173
13. pK_b, 2-substituted phenylhydrazines, 25°[h,i]
OMe, 8.47; OEt, 8.64; Me, 8.68; *H*, 8.73; Cl, 9.35; Br, 9.46; CO_2Et, 9.34; NO_2, 10.50
14. pK_b, 2-substituted *N*-methylphenylhydrazines, 25°[i,j]
OMe, 8.58; OEt, 8.75; *H*, 9.02; Cl, 9.22; Br, 9.32; *CO_2Et*, 9.09; NO_2, 9.68; Me, 8.71
15. pK_{bH^+}, 2-substituted benzoic acids[k]
H, 7.18; Me, 7.13; Et, 7.15; *i*-Pr, 7.23; *tert-Bu*, 7.56; F, 7.60; Cl, 7.68; Br, 7.75; I, 7.78; OH, 6.78; OMe, 6.10; OEt, 6.10; *NO_2*, 7.03; *CO_2H*, 5.95
16. pK_a, 2-substituted benzene phosphonic acids, 25°[l]
H, 1.83; Me, 2.10; F, 1.64; Cl, 1.63; Br, 1.64; I, 1.74; OMe, 2.16
17. pK_{a2}, 2-substituted benzene phosphonate ions, 25°[l]
H, 7.07; Me, 7.68; *Ph*, 8.13; F, 6.80; Cl, 6.98; Br, 7.00; I, 7.06; OMe, 7.77
19. pK_a, 2-substituted mandelic acids, 25°[m]
F, 3.30; Cl, 3.31; Br, 3.32; OMe, 3.64
20. pK_a, 3-(2′-substituted phenyl)propanic acids, 25°[n]
H, 4.66; Me, 4.66; F, 4.60; Cl, 4.58; Br, 4.58; NO_2, 4.50; OMe, 4.80; *OH*, 4.75
21. pK_a, 2-substituted cinnamic acids, 25°[n]
H, 4.44; Me, 4.50; F, 4.28; Cl, 4.23; Br, 4.23; NO_2, 4.15; OMe, 4.46; *OH*, 4.61
22. 10^4 K_a, 2-substituted phenoxyacetic acids, 25°[o]
H, 6.75; Me, 5.93; OMe, 5.88; NO_2, 12.7; CN, 10.6; F, 8.22; Cl, 8.90; Br, 7.53; I, 6.72
23. 10^4 K_a, 2-substituted phenoxyacetic acids, 25°[p]
OMe, 5.8; Me, 6.8; Cl, 10.2; NO_2, 15.8
24. 10^4 K_a, 2-substituted phenylthioacetic acids, 25°[p]
OMe, 1.8; Me, 2.8; Cl, 3.0; NO_2, 5.5
25. pK_a, 2-substituted phenylthioacetic acids, 20°[q]
H, 3.38; Me, 3.38; Cl, 3.23; OMe, 3.59; NO_2, 3.10; SMe, 3.57
26. 10^4 K_a, 2-substituted phenylselenoacetic acids, 25°[q]
OMe, 1.4; Me, 1.5; Cl, 2.3; NO_2, 3.2
27. pK_a, 2-substituted phenylselenoacetic acids, 20°[q]
H, 3.75; Me, 3.76; Cl, 3.57; OMe, 3.87; OEt, 3.90; NO_2, 3.42; Br, 3.58; SMe, 3.80

[a] Substituents in italics were excluded from the correlations. [b] M. Charton, *J. Amer. Chem. Soc.*, **86**, 2033 (1964). [c] M. Charton, *J. Org. Chem.*, **30**, 3346 (1965). [d] A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961). [e] C. van Hooidonk and L. Ginjaar, *Recl. Trav. Chim. Pays-Bas*, **86**, 449 (1967). [f] D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965. [g] Reference 8. [h] H. H. Stroh and G. Westphal, *Chem. Ber.*, **96**, 184 (1963). [i] G. Westphal and H. H. Stroh, *Z. Chem.* **7**, 192 (1967). [j] H. H. Stroh and G. Westphal, *Chem. Ber.*, **97**, 83 (1964). [k] R. Stewart and M. R. Granger, *Can. J. Chem.*, **39**, 2508 (1961). [l] G. Kortum, W. Vogel, and K. Andrussow, *Pure Appl. Chem.*, **1**, 190 (1961). [m] J. J. Klingenberg, J. P. Thole, and R. D. Lingg, *J. Chem. Eng. Data*, **11**, 94 (1966). [n] K. Bowden and D. C. Parkin, *Can. J. Chem.*, **46**, 3909 (1968). [o] N. V. Hayes and G. E. K. Branch, *J. Amer. Chem. Soc.*, **65**, 1555 (1943). [p] O. Behagel and M. Rollman, *Chem. Ber.*, **62**, 2693 (1929). [q] L. D. Petit, A. Royston, C. Sherrington, and R. J. Whewell, *J. Chem. Soc. B*, 588 (1968).

certain cases; they are not observed for all substituents. Keesom, Debye, and London forces may be proportional to the σ_I constants if they do in fact make a significant contribution to the proximity effect. Then, excluding from consideration any substituent for which hydrogen bonding or charge transfer interaction may be important, eq 2 either reduces to

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi r_{V,X} + h \quad (3)$$

or its equivalent.

If the steric effect is zero or negligible, eq 3 reduces to the extended Hammett equation

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h \quad (4)$$

Let us now consider the composition of the ortho electrical effect which may be represented as

$$\epsilon = \beta/\alpha \quad (5)$$

Now

$$\beta = \beta_{norm} + \beta_{prox} \quad (6)$$

where

$$\beta_{prox} = f_1(Z) \quad (7)$$

TABLE II

SUBSTITUENT CONSTANTS

X	σ_I	σ_R	Ref	X	σ_I	σ_R	Ref
C_2H_3		−0.11	*a, b*	CH_2OH		−0.06	*a, f*
$CONH_2$		0.09	*a, c*	CH_2OAc	0.14	−0.05	*a, f*
CO_2Me		0.10	*a, d*	$PhCH_2CH_2$		−0.15	*a, f*
$PhCH_2S$		−0.16	*a, e*	PhC_2H_2	0.06	−0.06	*a, f*

[a] Calculated from the equation $\sigma_R = \sigma_p - \sigma_I$. [b] σ_p from M. Charton, *J. Org. Chem.*, **30**, 552 (1965). [c] σ_p from M. Charton, *ibid.*, **28**, 3121 (1963). [d] σ_p from M. Charton and H. Meislich, *J. Amer. Chem. Soc.*, **80**, 5940 (1958). [e] σ_p from M. Charton, *J. Org. Chem.*, **34**, 1871 (1969). [f] M. Charton, *ibid.*, **30**, 3346 (1965).

and

$$\alpha = \alpha_{norm} + \alpha_{prox} \quad (8)$$

where

$$\alpha_{prox} = f_2(Z) \quad (9)$$

It is highly probable that

$$f_1(Z) \neq cf_2(Z) \quad (10)$$

Table III
Results of Correlations

Set	$-\alpha$	$-\beta$	ψ	h	R^a	F^b	r_{12}^c	r_{13}^c	r_{23}^c
1A	11.3	2.31	−0.00254	5.28	0.979	70.57[g]	0.339	0.243	0.526
1B	11.3	2.31		5.28	0.979	117.6[g]	0.339		
2A	9.50	2.38	−1.27	7.47	0.997	41.35[g]	0.317	0.286	0.451
2B	9.18	2.64		5.25	0.976	69.18[g]	0.317		
3A	10.7	3.62	3.22	−0.372	0.950	6.115[h]	0.120	0.107	0.654
3B	11.2	2.77		5.30	0.939	11.22[m]	0.120		
4A	10.7	3.57	1.12	5.08	0.9998	893.1[k]	0.370	0.653	0.361
4B	11.0	3.32		7.05	0.9997	1957.0[g]	0.370		
5A	13.0	3.88	−2.41	9.51	0.982	17.83[m]	0.583	0.702	0.910
5B	12.4	4.54		5.27	0.979	35.31[i]	0.583		
6A	−6.71	−1.96	4.37	10.12	0.982	45.21[g]	0.123	0.115	0.909
6B	−7.15	−2.95		8.68	0.979	69.10[g]	0.123		
7A	8.37	2.87	−0.337	6.59	0.995	36.67[n]	0.179	0.437	0.864
7B	8.43	2.96		5.99	0.995	109.3[i]	0.179		
8A	4.05	2.19	−0.0187	9.87	0.999	236.7[h]	0.295	0.020	0.866
8B	4.06	2.21		9.83	0.999	531.9[g]	0.295		
9A	4.01	1.09	−0.644	11.13	0.997	200.7[g]	0.348	0.086	0.406
9B	3.98	1.23		9.99	0.994	198.4[g]	0.348		
10A	4.24	3.21	−0.218	4.24	0.998	193.3[i]	0.295	0.020	0.866
10B	4.30	3.45		3.82	0.998	395.2[g]	0.295		
11A	5.04	2.52	−0.244	1.35	0.968	29.56[g]	0.676	0.033	0.401
11B	4.98	2.57		0.923	0.968	51.57[g]	0.676		
12A	2.47	2.51	0.193	3.11	0.998	297.7[g]	0.503	0.023	0.790
12B	2.40	2.31		3.47	0.997	475.4[g]	0.503		
13A	−2.05	−1.42	−0.0537	8.87	0.971	16.68[k]	0.327	0.033	0.327
13B	−2.05	−1.41		8.78	0.971	33.30[h]	0.327		
14A	−1.30	−0.562	0.568	7.77	0.972	17.04[k]	0.327	0.053	0.327
14B	−1.24	−0.671		8.76	0.956	21.25[i]	0.327		
15A	3.22	6.49	−3.01	13.21	0.986	58.30[g]	0.466	0.010	0.807
15B	2.22	3.61		7.59	0.932	19.87[h]	0.466		
16A	1.38	1.58	0.848	0.387	0.995	62.56[k]	0.295	0.020	0.866
16B	1.14	0.660		2.02	0.956	16.09[k]	0.295		
17A	2.32	2.72	1.69	4.34	0.986	23.45[l]	0.295	0.020	0.866
17B	1.85	0.889		7.59	0.929	9.505[m]	0.295		
18B	−0.704	−0.658		0.767	0.99994	385.6[l]	0.680		
19B	1.20	0.252		3.81	0.9998	1003.0[k]	0.505		
20A	0.240	0.241	0.129	4.87	0.907	3.079[h]	0.199	0.235	0.317
20B	0.216	0.274		4.64	0.890	5.724[m]	0.199		
21A	0.529	0.0978	−0.241	4.88	0.994	53.64[k]	0.199	0.235	0.317
21B	0.484	0.159		4.46	0.966	21.00[k]	0.199		
22A	−0.337	−0.262	−0.198	1.15	0.974	25.11[h]	0.309	0.214	0.236
22B	−0.386	−0.210		0.786	0.936	17.64[i]	0.309		
23B	0.391	0.427		0.902	0.996	57.09[m]	0.390		
24B	0.208	0.638		0.534	0.99998	13123.0[i]	0.390		
25A	0.282	0.661	−0.0559	3.41	0.932	2.215[h]	0.411	0.353	0.059
25B	0.272	0.664		3.31	0.932	6.592[n]	0.411		
26B	0.377	0.314		0.231	0.992	32.83[n]	0.390		
27A	0.408	0.499	−0.224	4.08	0.984	30.06[i]	0.408	0.091	0.203
27B	0.379	0.540		3.68	0.969	31.01[h]	0.408		

Set	s_{est}^d	s_α^d	s_β^d	s_φ^d	s_h^d	n^e	t_α^f	t_β^f	t_ψ^f	t_h^f
1A	0.577	0.789	0.973	0.806	1.57	13	14.32[g]	2.375[l]	0.033[r]	3.373[i]
1B	0.547	0.746	0.807		0.244	13	15.15[g]	2.866[j]	21.64[g]	
2A	0.561	1.22	0.873	2.49	4.35	10	7.787[g]	2.724[l]	0.512[q]	1.719[o]
2B	0.531	0.995	0.663		0.342	10	9.230[g]	3.988[i]		15.35[g]
3A	1.01	3.28	1.99	5.10	9.03	6	3.271[m]	1.820[p]	0.632[q]	0.041[r]
3B	0.899	2.84	1.31		0.849	6	3.955[l]	3.114[o]		6.244[i]
4A	0.150	0.637	0.478	1.84	3.23	5	16.78[l]	7.461[m]	0.608[q]	1.537[p]
4B	0.124	0.220	0.204		0.0831	5	50.09[g]	16.28[i]		84.81[g]
5A	0.394	2.11	1.49	4.72	8.31	6	6.142[l]	2.603[o]	0.511[q]	1.144[p]
5B	0.342	1.58	0.651		0.202	6	7.870[j]	6.981[j]		26.04[i]
6A	0.308	0.872	1.14	4.74	8.31	9	7.703[g]	1.731[o]	0.923[p]	0.122[r]
6B	0.304	0.721	0.394		0.145	9	9.924[g]	7.469[g]		59.87[g]
7A	0.403	1.27	1.26	4.17	7.39	5	6.606[m]	2.279[p]	0.081[r]	0.891[q]
7B	0.286	0.738	0.411		0.283	5	11.41[i]	7.20[j]		21.18[i]
8A	0.0696	0.188	0.466	0.394	0.761	6	21.49[i]	4.687[l]	0.047[r]	12.97[i]
8B	0.0569	0.126	0.156		0.0562	6	32.25[g]	14.18[g]		175.0[g]
9A	0.133	0.206	0.184	0.342	0.615	8	19.44[g]	5.921[i]	1.882[o]	18.09[g]
9B	0.163	0.253	0.206		0.119	8	15.76[g]	5.940[i]		83.62[g]

TABLE III
(*Continued*)

Set	s_{est}[d]	s_α[d]	s_β[d]	s_ψ[d]	s_h[d]	n[e]	t_α[f]	t_β[f]	t_ψ[f]	t_h[f]
10A	0.0862	0.233	0.577	0.487	0.942	6	18.19[i]	5.563[l]	0.448[q]	4.498[l]
10B	0.0738	0.163	0.202		0.0729	6	26.37[g]	17.08[g]		52.35[g]
11A	0.488	1.33	0.836	1.85	3.29	10	3.785[i]	3.009[l]	0.132[r]	0.411[q]
11B	0.452	1.16	0.665		0.533	10	4.308[i]	3.866[i]		1.732[o]
12A	0.0439	0.116	0.267	0.232	0.436	8	21.29[g]	9.396[g]	0.832[p]	7.130[i]
12B	0.0426	0.0796	0.112		0.0284	8	30.20[g]	20.58[g]		122.4[g]
13A	0.235	0.451	0.424	0.792	1.38	7	4.549[j]	3.347[l]	0.068[r]	6.409[i]
13B	0.203	0.386	0.343		0.185	7	5.326[i]	4.105[j]		47.42[g]
14A	0.131	0.252	0.236	0.442	0.772	7	5.145[j]	2.377[m]	1.286[p]	10.07[i]
14B	0.141	0.268	0.238		0.129	7	4.639[i]	2.815[l]		68.09[g]
15A	0.138	0.331	0.735	0.698	1.31	9	9.722[g]	8.830[g]	4.312[i]	10.11[g]
15B	0.275	0.468	0.614		0.176	9	4.736[i]	5.890[i]		43.10[g]
16A	0.0399	0.108	0.267	0.225	0.435	6	12.76[i]	5.908[i]	3.765[l]	0.890[p]
16B	0.0925	0.205	0.253		0.0914	6	5.583[j]	2.607[m]		22.11[g]
17A	0.107	0.289	0.714	0.603	1.16	6	8.043[j]	3.805[m]	2.804[o]	3.728[m]
17B	0.193	0.427	0.529		0.191	6	4.339[l]	1.683[o]		39.80[g]
18B	0.00920	0.0295	0.113		0.0158	4	23.86[l]	5.823[o]		58.54[j]
19B	0.00639	0.0360	0.0281		0.0223	4	33.33[j]	8.967[m]		170.9[i]
20A	0.0680	0.129	0.148	0.224	0.404	6	1.864[p]	1.627[p]	0.577[q]	12.04[i]
20B	0.0600	0.108	0.121		0.0607	6	2.010[o]	2.267[o]		76.45[g]
21A	0.0245	0.0464	0.0534	0.0808	0.146	6	11.40[i]	1.833[p]	2.977[m]	33.53[g]
21B	0.0466	0.0836	0.0939		0.0472	6	5.794[j]	1.689[o]		94.52[g]
22A	0.0353	0.0653	0.0661	0.0817	0.153	8	5.162[i]	3.963[j]	2.418[m]	7.483[i]
22B	0.0495	0.0871	0.0877		0.0472	8	4.431[i]	2.394[m]		16.65[g]
23B	0.0314	0.0631	0.0763		0.0342	4	6.196[o]	5.596[o]		26.37[l]
24B	0.00213	0.00428	0.00518		0.00232	4	48.59[j]	127.6[i]		230.2[i]
25A	0.154	0.331	0.362	0.660	1.16	5	0.853[q]	1.826[p]	0.085[r]	2.940[p]
25B	0.109	0.219	0.256		0.118	5	1.243[p]	2.599[o]		28.02[i]
26B	0.0357	0.0716	0.0866		0.0388	4	5.265[o]	3.626[o]		59.53[j]
27A	0.0454	0.0900	0.0959	0.138	0.248	7	4.530[l]	5.201[j]	1.627[p]	16.44[g]
27B	0.0540	0.105	0.110		0.0575	7	3.615[l]	4.915[i]		64.06[g]

[a] Multiple correlation coefficient. [b] F test for significance of correlation. [c] Partial correlation coefficients for σ_I on σ_R, σ_I on r_V, and σ_R on r_V, respectively. [d] Standard errors of the estimate, α, β, ψ, and h. [e] Number of points in set. [f] "Student's t" tests for signifiance of α, β, ψ, and h. [g] 99.9% confidence level (CL). [h] 99.5% CL. [i] 99.0% CL. [j] 98.0% CL. [k] 97.5% CL. [l] 95.0% CL. [m] 90.0% CL. [n] <90.0% CL. [o] 80.0% CL. [p] 50.0% CL. [q] 20.0% CL. [r] <20.0% CL.

Then we would predict that if there are proximity electrical effects

$$\epsilon = \frac{\beta_{norm} + f_1(Z)}{\alpha_{norm} + f_2(Z)} \quad (11)$$

A dependence of ϵ on Z may therefore be taken as evidence that proximity electrical effects do in fact exist. Furthermore, such a dependence of ϵ on Z would once and for all preclude the definition of σ_0 constants for use with ortho substituents, as no single set of σ_0 constants could be expected to represent data for various $2XC_6H_4ZY$.

To test the validity of eq 11, we have correlated data for 27 sets of proton transfer reactions with eq 3 and 4. The data used are set forth in Table I. Only data obtained in water as solvent have been considered, as we have previously established a dependence of ϵ on solvent composition in the case of the ionization constants of 2-substituted benozic acids.[8] The sources of the substituent constants and van der Waals radii used in the correlations are set forth in previous papers of this series.[1-7] Substituent constants from other sources are reported in Table II. The data have been correlated with eq 3 and 4 by means of multiple linear regression analysis.[9]

(8) M. Charton and B. I. Charton, *J. Org. Chem.*, **33**, 3872 (1968).

(9) K. A. Brownlee, "Statistical Theory and Methodology in Science and Engineering," 2nd ed, Wiley, New York, N. Y., 1965; E. L. Crow, F. A. Davis, and M. W. Maxfield, "Statistical Manual," Dover Publications, New York, N. Y., 1960.

The value for X = H was excluded from all the sets studied as this value often does not lie on the correlation line for ortho-substituted compounds.

Results

Results of the correlations are presented in Table III. Sets labeled A were correlated with eq 3. Sets labeled B were correlated with eq 4. Of the 22 sets correlated with eq 3, nine sets gave excellent, two gave very good, five gave good, one gave fair, and one gave poor correlation. Four sets did not give significant results. Of the 27 sets correlated with eq 4, 12 sets gave excellent, five gave very good, three gave good, one gave fair, and four gave poor results. Two sets did not give significant correlations.

Discussion

Steric Effects.—Of the 22 sets correlated with eq 5, 13 gave significant correlation and did not have a significant value of r_{13} or r_{23} (that is, neither σ_I and r_V nor σ_R and r_V are related to each other). Only these sets are of diagnostic value. Of these 13 sets, ten did not give significant values of t_ψ, whereas three did give significant values. We conclude, therefore, that in most cases proton transfer reactions of ortho-substituted compounds are free of steric effects. This result is in accord with our previous findings.[1-7] Lending credence to this conclusion is the generally better correlation obtained with eq 4 as compared with eq 3.

Variation of the Composition of the Electrical Effect with the Side Chain.—Values of ϵ are reported in Table IV. It is convenient for the purpose of discussing the variation of ϵ with Z to classify Z according to the number of atoms n intervening between the aromatic ring and the ionizable proton. Examination of the results in Table IV certainly show considerable variation with Z. There seems to be a possible dependence on n, with low values of ϵ at $n = 0$, and higher values of ϵ at $n > 0$. The results are not yet conclusive however. For para-substituted benzene derivatives of the type $4XC_6H_4ZY$, the value of ϵ_p is dependent on the electronic demands of Y and the degree to which Z can transmit resonance effects. Thus, ϵ_p for para-substituted benzene derivatives may range from a value of 0.74 for $4XPnCH_2CO_2H$ to 1.47 for $4XC_6H_4OH$. It is necessary, therefore, to correct for the electronic demands of Y and the variable resonance effect transmission of Z. For this purpose only those sets will be considered for which $\epsilon_p = 1.0 \pm 0.1$. Thus, the sets considered are those for which the para-substituted analogs are best correlated by the σ_p constants. Sets which meet this requirement are given in italics in Table IV. Their ϵ values show a dependence on Z, with $\bar{\epsilon} = 0.2$ for $n = 0$, $\bar{\epsilon} = 0.8$ for $n = 2$, and $\bar{\epsilon} = 1.0$ for $n = 4$, where n is the number of atoms between the ring and the ionizable proton.

TABLE IV

VALUES OF ϵ

Set	ϵ	n[a]	Set	ϵ	n	Set	ϵ	n
1	*0.20*	0	10	0.80	1	19	0.21	3
2	*0.29*	0	11	...[c]	1	20	...[d]	4
3	...[b]	0	12	*0.96*	2	21	...[b]	4
4	0.30	0	13	0.69	2	22	*0.54*	4
5	0.37	0	14	0.54	2	23	...[d]	4
6	0.41	0	15	1.6	2	24	3.1	4
7	0.35	0	16	*0.58*	2	25	...[e]	4
8	0.54	1	17	...[b]	2	26	...[e]	4
9	0.32	1	18	...[b]	3	27	*1.4*	4

[a] n is the number of atoms separating the ring and the ionizable proton. Values of ϵ are calculated from correlations with eq 8. Values in italics are for sets for which $\epsilon_p \cong 1.0$. [b] Value of β is not significant. [c] r_{12} shows $\sigma_I = f(\sigma_R)$. [d] Values of α and β are not significant. [e] Correlation with eq 4 was not significant.

The Existence of Proximity Electrical Effects.—The variation of ϵ with Z shows the existence of proximity electrical effects. Further evidence of their existence may be inferred as follows. Consider β as a function of ZY in the species XGZY where G is the skeletal group to which the substituent X and the side chain Z are attached. We may write for β

$$\beta = (\beta_N + \beta_P)\gamma_R\eta_R \quad (12)$$

where β_N is the normal delocalized electric effect through the group G, β_P is the delocalized proximity electrical effect, η_R represents the factor which accounts for the electronic demands of Y, and γ_R represents the factor which accounts for the transmission of the resonance effect by the group Z. The quantities γ_R and η_R are assumed to be characteristic of Z and Y, respectively, and independent of G. They are defined by the equations

$$\gamma_R = \frac{\beta GZY}{\beta GZ^0Y} \quad (13)$$

and

$$\eta_R = \frac{\beta GZY}{\beta GZY^0} \quad (14)$$

where Z^0 is a reference side chain and Y^0 is a reference reaction site. Then for the 2-substituted benzene derivatives we may write

$$\beta_2 = (\beta^2{}_N + \beta_P)\gamma_R\eta_R \quad (15)$$

and for the 4-substituted benzene derivatives we may write

$$\beta_4 = \beta^4{}_N\gamma_R\eta_R \quad (16)$$

Then

$$\frac{\beta_2}{\beta_4} = \frac{\beta^2{}_N + \beta_P}{\beta^4{}_N} \quad (17)$$

where β_{2N} is a constant characteristic of the o-phenylene group and β_{4N} is a constant characteristic of the p-phenylene group. β in general may conceivably be a function of Z, Y, reagent, medium, temperature, and pressure. As in the sets studied, the only reaction is proton transfer in water at 20–25° and 1 atm. β can in these sets vary only as a function of Y and Z. The quantity β_2/β_4 is independent of the electronic demands of Y and the extent of transmission of the resonance effect by Z. If this quantity varies with Z, then this can only be due to β_P being a function of Z. Thus examination of the quantity β_2/β_4 for various side chains Z will show whether or not β_P is dependent on Z. Values of β_2/β_4 are given in Table V. There is obviously variation of β_2/β_4 with Z. Excluding the values for pK_a and pK_{bH^+} of benzoic acids, which seem anomalously large, there seems to be a trend toward an increasing value of β_2/β_4 with increasing n.

TABLE V

VALUES OF β_2/β_4

Set	$-\beta_2$	$-\beta_4$	β_2/β_4	n
1	2.64	5.11[a]	0.52	0
2	2.31	5.63[b]	0.41	0
8	2.21	2.99[b]	0.74	1
9	1.23	1.61[b]	0.76	1
10	3.45	4.38[b]	0.79	1
12	2.31	1.00[c]	2.3	2
13	−1.41	−1.78[c]	0.79	2
14	−0.671	−2.74[c]	0.25	2
15	3.62	1.41[b]	2.6	2
16	0.660	0.755[c]	0.87	2
22	−0.210	−0.297[b]	0.71	4
24	0.638	0.528[b]	1.2	4
27	0.540	0.430[b]	1.3	4

[a] M. Charton, Abstracts, 154th National Meeting of the American Chemical Socieity, Chicago, Ill., 1967, S-137. [b] M. Charton, unpublished results. [c] Calculated from $\beta = \rho\delta$.

These results may be taken as evidence for the existence of a delocalized proximity electrical effect which is a function of the side chain Z. The exact nature of this delocalized proximity electrical effect remains to be established.

Deviation of the Unsubstituted Compound.—We have excluded the value for X = H from the correlations as this value often deviates from the correlation line obtained for ortho-substituted compounds. It was shown, however, that, in the case of polarographic half-wave potentials of ortho-substituted compounds, h_{calcd} was not significantly different from h_{obsd} (the value for the unsubstituted compound). In the case of nmr data of ortho-substituted compounds, 16 of 18 sets studied showed no significant difference between h_{calcd} and h_{obsd}.[7] It seemed of interest to determine whether h_{calcd} and h_{obsd} are significantly different in the case of the proton transfer equilibria studied here. A Student's t test was carried out for the significance of h_{calcd} for all sets for which significant correlation with eq 4 was obtained and h_{obsd} values were available. The results are given in Table VI. Of the 23 sets studied, 17 did not give significant differences between h_{obsd} and h_{calcd}. It would seem that the unsubstituted compound more often than not does lie on the correlation line for ortho-substituted compounds. It seems to deviate in some examples, however.

TABLE VI

SIGNIFICANCE OF h_{calcd}

Set	h_{obsd}	h_{calcd}	$\|\Delta\|h^a$	s_h^b	t^c	n^d	CL[e]
1	5.17	5.28	0.11	0.244	0.451	13	20.0
2	5.28	5.25	0.03	0.342	0.088	10	<20.0
3	4.959	5.30	0.34	0.849	0.400	6	20.0
4	6.95	7.05	0.10	0.0831	1.203	5	50.0
5	5.58	5.27	0.31	0.202	1.535	6	50.0
6	8.6	8.68	0.08	0.145	0.552	9	20.0
7	5.98	5.99	0.01	0.283	0.035	5	<20.0
8	10.00	9.83	0.17	0.0562	3.024	6	90.0
9	9.89	9.99	0.10	0.119	0.840	8	50.0
10	4.60	3.82	0.78	0.0729	10.70	6	99.0
11	0.79	0.923	0.13	0.533	0.244	10	<20.0
12	4.203	3.47	0.73	0.0284	25.70	8	99.9
13	8.73	8.78	0.05	0.185	0.280	7	20.0
14	9.02	8.76	0.26	0.129	2.016	7	80.0
15	7.18	7.59	0.41	0.176	2.330	9	90.0
16	1.83	2.02	0.19	0.0914	2.079	6	80.0
17	7.07	7.59	0.52	0.191	2.723	6	90.0
18	0.340	0.767	0.43	0.0158	27.22	4	95.0
20	4.66	4.64	0.02	0.0607	0.329	6	20.0
21	4.44	4.46	0.02	0.0472	0.424	6	20.0
22	0.829	0.786	0.04	0.0472	0.847	8	50.0
27	3.75	3.68	0.07	0.0575	1.217	7	50.0

[a] Absolute value of the difference between h_{obsd} and h_{calcd}. [b] Standard error of h_{calcd}. [c] Student's t test for the significance of h_{calcd}. [d] Number of points in the set. [e] Confidence levels for the significance of h_{calcd}.

Specific Salt Effects upon the Rates of SN1 Solvolyses[1]

C. A. BUNTON,* T. W. DEL PESCO,[2] A. M. DUNLOP, AND K-U. YANG

Department of Chemistry, University of California, Santa Barbara, California 93106, and The William Ramsay and Ralph Forster Laboratories, University College, London, W.C.1, England

Received August 20, 1970

Specific kinetic salt effects upon the solvolyses of *tert*-butyl bromide, 1- and 2-methyl-*exo*-2-chloronorbornane, isobornyl chloride, and camphene hydrochloride have been examined in methanol, aqueous methanol, acetone, 1,2-dimethoxyethane, and methanol–1,2-dimethoxyethane. Anion effects are important but cation effects are small (for Li^+, Na^+, and Et_4N^+). The anion order is $ClO_4^- > OTos^- \approx NO_3^- \approx Br^- > Cl^- \approx$ no salt $> F^- > OH^-$. Isotopic and azide trapping experiments show that carbonium ions or ion pairs can return in solvolyses of camphene hydrochloride and *tert*-butyl chloride, but return is not large enough to explain the salt effects. This conclusion is supported by the observation of specific salt effects upon solvolyses of isobornyl chloride and 1-methyl-*exo*-2-chloronorbornane. Retention of configuration in the methanolysis of isobornyl chloride and camphene hydrochloride shows that methyl or hydride shifts do not occur during the lifetime of the carbonium ions. Experiments on isobornyl chloride in aqueous methanol and acetone show that chloride and perchlorate ions have little effect upon the activity coefficient of the substrate. The transition state effects appear to be related, at least in part, to solvent structure induced interactions between the carbonium-like transition state, especially with a large anion such as perchlorate.

Salt effects upon the SN1 solvolyses of alkyl halides and sulfonic esters in polar hydroxylic solvents have been widely studied. It was postulated that increase of ionic strength should assist any reaction in which a neutral molecule dissociates into ions,[3,4] and Ingold and his coworkers observed such an effect in SN1 solvolyses of secondary and tertiary alkyl halides in aqueous organic solvents. They used a simple electrostatic model to explain stabilization of the dipolar transition state, and for a limited number of salts obtained a reasonable fit between experiment and theory by assuming that the transition state could be represented as a dipole in which the carbon–halogen bond was stretched by *ca.* 0.4 Å.[4]

They also observed a rate retardation for some SN1 solvolyses when the common halide ion competed with the solvent for the carbonium ion.[3-5] This common ion retardation becomes very important with relatively stable carbonium ions and in solvents of low nucleophilicity.[4,6]

The simple electrostatic theory of the ionic strength effect assumed that ions acted nonspecifically, as point

(1) Support of this work by the National Science Foundation and the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

(2) NDEA Fellow, University of California, Santa Barbara, 1965–1968.

(3) L. C. Bateman, M. G. Church, E. D. Hughes, C. K. Ingold, and N. A. Taher, *J. Chem. Soc.*, 979 (1940).

(4) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Chapter VII.

(5) O. T. Benfey, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2488 (1952).

(6) (a) C. G. Swain, C. B. Scott, and K. H. Lohmann, *J. Amer. Chem. Soc.*, **75**, 136 (1953); (b) T. H. Bailey, J. R. Fox, E. Jackson, G. Kohnstam, and A. Queen, *Chem. Commun.*, 123 (1966).

charges, and that the whole effect was on the dipolar transition state.[3,4] However, salts have specific effects upon the activity coefficients of nonelectrolytes in water,[7] and therefore could well have specific effects upon both the initial and transition states of an SN1 solvolysis even in polar hydroxylic solvents. There are specific effects upon the rates of SN1 solvolyses,[8-10] and Hammett, in particular, drew attention to the possibility that small ions of high charge density might "dry" the solvent and so reduce the reaction rate.[8] Rate retardations or unexpectedly small enhancements by lyate and other small high charge density ions have been observed for several SN1 solvolyses in polar hydroxylic solvents.[5,8-13]

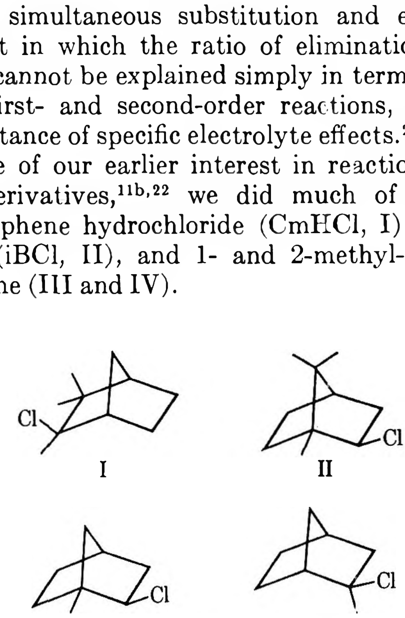
Taft and his coworkers showed that the activity coefficient of *tert*-butyl chloride in water was dependent upon the nature and concentration of electrolytes, but that for many, but not all salts, there was an approximate cancellation between the specific effects on the initial and transition states, and that the net effect fitted the simple electrostatic theory reasonably well.[14] Nonetheless, difficulties remained because there are specific salt effects upon the activity coefficients of the transition state for the solvolysis of *exo*-norbornyl bromide in aqueous dioxane.[15] Another example of specific kinetic salt effects which cannot be explained wholly in terms of initial state effects is the SN1 solvolysis of 4-nitro-4′-phenyl diphenyl methyl chloride.[16] Also the electrostatic theory predicts a logarithmic relationship between rate and ionic strength whereas for many reactions the relationship is linear,[10] even in solvents of low dielectric constant.[17]

Perrin and Pressing have recently put forward a theoretical treatment of kinetic salt effects, based on dipole–dipole interactions between the transition state and the ion-paired electrolytes, which explains the specificity of these salt effects.[18] A special salt effect has been observed in some acetolyses, where a salt, *e.g.*, lithium perchlorate, may assist dissociation of an ion pair,[17,19] and ion pair return in, for example, the hydrolysis of *exo*-norbornyl bromide[15] or a diarylmethyl chloride[5,16] could be affected specifically by added electrolytes.

Electrolyte effects are used extensively as mechanistic tests, and it is therefore important to find whether the specific salt effects which are observed in SN1 solvolyses in polar hydroxylic solvents depend upon mechanistic complexity of the reaction or upon the limitations of the simple ionic atmosphere treatment of kinetic salt effects.

Bunnett and his coworkers have observed reactions in which simultaneous substitution and elimination occur, but in which the ratio of elimination to substitution cannot be explained simply in terms of simultaneous first- and second-order reactions, suggesting the importance of specific electrolyte effects.[20,21]

Because of our earlier interest in reactions of norbornyl derivatives,[11b,22] we did much of our work with camphene hydrochloride (CmHCl, I), isobornyl chloride (iBCl, II), and 1- and 2-methyl-*exo*-chloronorbornane (III and IV).



Sneen and his coworkers have studied the reaction rates and products in the presence of added nucleophiles using substrates which give "borderline" kinetic behavior[23] and explain their results in terms of simultaneous dissociation of an ion pair to give products and nucleophilic attack upon the ion pair, rather than in terms of the classical explanations based on simultaneous uni- and bimolecular mechanisms. Added salts could affect the partitioning of such an ion pair. One method of eliminating return of intermediates to reactants as a cause of specific salt effects is to use substrates, such as II and III which generate carbonium ions, which on return give the more reactive alkyl chlorides (I and IV). There are several other methods which can give information on the possible importance of return of intermediates to reactants and on the lifetime of such intermediates in reactive hydroxylic solvents: (1) examination of kinetic salt effects in solvents varying from polar hydroxylic solvents such as methanol ($Y = -1.09$) and methanol–water, 70:30 v/v ($Y = 0.96$), to relatively nonpolar solvents such as acetone–water, 90:10 v/v ($Y = -1.86$),[24] where ion pairing of electrolytes and reaction intermediates could be important; (2) rate measurements in heterogeneous systems in order to exclude effects on the activity coefficient of the substrate;[14,15] (3) solvolysis in the presence of $^{36}Cl^-$ in order to detect return of a carbonium ion or ion pair to substrate;[17b,25] (4) examination of the stereochemistry of solvolysis of the trimethylnorbornyl chlorides, to find whether the in-

(7) F. A. Long and W. F. McDevit, *Chem. Rev.*, **51**, 119 (1952).
(8) G. R. Lucas and L. P. Hammett, *J. Amer. Chem. Soc.*, **64**, 1928 (1942).
(9) F. Spieth and A. R. Olson, *ibid.*, **77**, 1412 (1955).
(10) A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2763 (1956).
(11) (a) C. A. Bunton and A. Konasiewicz, *J. Chem. Soc.*, 1354 (1955); (b) P. Beltramé, C. A. Bunton, A. Dunlop, and D. Whittaker, *ibid.*, 658 (1964).
(12) C. G. Swain, T. E. C. Knee, and A. MacLachan, *J. Amer. Chem. Soc.*, **82**, 6107 (1960).
(13) E. F. J. Duynstee, E. Grunwald, and M. L. Kaplan, *ibid.*, **82**, 5654 (1960).
(14) G. A. Clarke, T. R. Williams, and R. W. Taft, *ibid.*, **84**, 2292 (1962); G. A. Clarke and R. W. Taft, *ibid.*, **84**, 2295 (1962).
(15) K. D. Michael and R. A. Clement, *Can. J. Chem.*, **39**, 957 (1961).
(16) E. Jackson and G. Kohnstam, *Chem. Commun.*, 279 (1965).
(17) (a) A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 2780 (1956); (b) S. Winstein, B. Appel, R. Baker, and A. Diaz, *J. Chem. Soc., London, Spec. Publ.*, No. 19, 109 (1965).
(18) C. L. Perrin and J. Pressing, unpublished results.
(19) S. Winstein, P. E. Klinedinst, and G. C. Robinson, *J. Amer. Chem. Soc.*, **83**, 885 (1961); S. Winstein, P. E. Klinedinst, and E. Clippinger, *ibid.*, **83**, 4986 (1961).
(20) J. F. Bunnett, G. T. Davis, and H. Tanida, *ibid.*, **84**, 1606 (1962).
(21) Accompanying paper: J. F. Bunnett and D. L. Eck, *J. Org. Chem.*, **36**, 897 (1971).
(22) (a) C. A. Bunton and C. J. O'Connor, *Chem. Ind. (London)*, 1182 (1965); (b) C. A. Bunton, C. J. O'Connor, and D. Whittaker, *J. Org. Chem.*, **33**, 2812 (1967).
(23) R. A. Sneen and J. W. Larsen, *J. Amer. Chem. Soc.*, **91**, 362, 6031 (1969); R. A. Sneen and H. M. Robbins, *ibid.*, **91**, 3100 (1969).
(24) A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2770 (1956).
(25) C. A. Bunton and B. Nayak, *J. Chem. Soc.*, 3854 (1958).

termediates last long enough for methyl or hydride shifts to occur.[26]

Examination of the kinetic salt effects showed that added chlorides did not increase reaction rate markedly, irrespective of any contribution of a common-ion effect, whereas perchlorate ions always markedly increased the rate. We therefore used 1 and 2 in the presence of chloride and perchlorate ions.

Experimental Section

Materials.—The preparation and purification of most of the alkyl chlorides has already been described. D-(+)-Camphor was converted into (+)-camphene by the method of Meerwein and Wortmann, which involves some loss of optical purity.[29] The products had values of $[\alpha]_D$ between +58 and +64°. (The specific rotation of optically pure camphene appears to be $[\alpha]^{25}_D$ 117.5° in toluene, and 108° in ethanol[30] showing that our material had 54–60% optical purity.) Methanol was dried by Bjerrum's method,[31] distilled, and then treated with molecular sieve. Acetone and dioxane were purified by standard methods,[31] and 1,2-dimethoxyethane (DME) was dried over sodium and then fractionally distilled.

The salts were commercial samples or were prepared by acid–base neutralization and were dried either in an oven at 150° or under vacuum in an Abderhalden drying pistol over P_2O_5.

The mixed solvents were generally made up by weight to correspond to the quoted volume:volume compositions, except for 1,2-dimethoxyethane–methanol, 80:20 v/v, which was made up by volume.

Kinetics.—Most of the reactions were followed titrimetrically by acid–base titration using lacmoid as indicator. Because of the high reactivity of camphene hydrochloride, its solvolyses in polar solvents were followed by withdrawing samples from a water-jacketed automatic pipet and quenching them in acetone at −80°.[11b] The first-order rate constants were calculated using the integrated form of the first-order rate equation and are in sec^{-1}. A few reactions in the absence of added electrolyte were followed conductrimetrically. Rate constants determined conductrimetrically agreed to within ±1% and the titrimetric rate constants within ±5%.

Isobornyl chloride was allowed to react in both homogeneous and heterogeneous conditions using methanol–water, 70:30 v/v, and acetone–water, 55:45 v/v. Aqueous dioxane could not be used as solvent under heterogeneous conditions because emulsions were formed, and the solvent compositions were chosen so that the reactions were relatively slow, but the water contents were sufficiently high that the concentration of isobornyl chloride in a saturated solution was low. For each pair of experiments, the reaction solution at 0° was divided into two equal portions, one for the homogeneous and one for the heterogeneous experiments. For the former, powdered isobornyl chloride was added, and the mixture was shaken at 0°, and then placed in a vessel, also at 0°, which contained a sintered glass filter to retain undissolved substrate, so that the filtered solution could be sucked into the reaction vessel. Atmospheric moisture was excluded by using drying tubes.

A similar type of apparatus was used for the heterogeneous experiments where solvolysis was allowed to occur at 0° in the presence of solid isobornyl chloride which was excluded from the sampling chamber by a sintered glass filter. For these experiments the reaction rate, v, was determined by plotting % reaction against time. The reaction was followed for 2–3 hr, and good linear plots were obtained; the mean values of v, calculated between points, agreed with the graphical value within ±2%.

Isotopic Exchange.—The general procedure has already been described.[25] Radioactive inorganic chloride was used, and the unreacted alkyl chloride was extracted into petroleum ether. The alkyl chloride was solvolyzed, the chloride ion was determined by potentiometric titration, and the solution was counted using an Ekco Autoscaler N530 F. Corrections were made for background counts. Control experiments using $Li^{36}Cl$ showed that no inorganic chloride was extracted using this procedure, and in the experiments with camphene hydrochloride the conditions for the final solvolysis were such that any isobornyl chloride would not react and could be removed by a second extraction with petroleum ether.

The relative values of the first-order rate constants of exchange, k_e, and chemical reaction, k_c, are given by

$$k_e/k_c = \log [100/(100 - \%\ \text{exchange})]/\log [a/(a - x)]$$

where a and $(a - x)$ are the substrate concentrations at the initial time and the time of sampling.

Stereochemistry.—The optical rotations were determined using either a conventional visual polarimeter or a Bendix–Ericcson electronic polarimeter. Because of a small sample size needed for the electronic polarimeter, it was used for determination of the rotations of the products, using either the Na D line or the Hg green line at 5461 Å at 20°. The rotations were all measured using ethanol solutions, excepting camphene hydrochloride whose rotation was measured in ether. For camphene they were reproducible to 3%. The starting materials and products were purified or isolated by preparative glc.

Camphene hydrochloride was prepared from camphene in the usual way, and it was converted into isobornyl chloride by dissolving it in liquid SO_2 and allowing the solvent to evaporate. Partial racemization occurred during this step, and when we converted camphene into isobornyl chloride by dissolving it in liquid SO_2 and bubbling hydrogen chloride into the solution, the isobornyl chloride was almost wholly racemized.

The details of a solvolysis are given in Table I, and Table II summarizes the results of solvolyses done under various conditions. The extent of racemization of isobornyl chloride varied from one preparation to another, and in one preparation, that used for solvolysis in the presence of Ag_2O, there was little racemization (Table II).

TABLE I

SOLVOLYSIS OF OPTICALLY ACTIVE CAMPHENE HYDROCHLORIDE[a]

Compd	$[\alpha]$Hg, deg	$[\alpha]_D$, deg	$[M]_D$, deg	% retention
Camphene hydrochloride[b]		−26.7	−46.1	
Camphene[c]	+67.5	+57.1	+77.8	99
Camphene hydrate Methyl ether[c]	−18.6	−16.8	−28.2	

[a] At 0° in MeOH with $NaHCO_3$. [b] Starting material; the camphene used in the initial preparation had $[\alpha]$Hg +68.4°; $[\alpha]_D$ +57.9°; $[M]_D$ +78.9°. [c] Products.

TABLE II

STEREOCHEMICAL COURSE OF SOLVOLYSIS OF CAMPHENE HYDROCHLORIDE AND ISOBORNYL CHLORIDE[a]

Substrate	Reagent	% optical purity of product: Cm	CmOMe
CmHCl[b]	0.2 M NaOMe	54.8 (+59.2°)	52.0 (−15.9°)
CmHCl[b]	$NaHCO_3$	52.9 (+57.1°)	55.0 (−16.8°)
CmHCl[c]	Ag_2O	58.7 (+63.4°)	61.0 (−18.7°)
iBCl[b]	0.2 M NaOMe[d]	25.9 (+27.9°)	24.3 (−7.44°)
iBCl[b]	0.2 M NaOMe[e]	27.6 (+29.8°)	28.4 (−8.7°)
iBCl[c]	Ag_2O	53.4 (+58.0°)	55.7 (−17.0°)

[a] In MeOH at 0° unless specified: Cm = camphene; CmHCl = camphene hydrochloride; CmOMe = camphene hydrate methyl ether; iBCl = isobornyl chloride. The values in parentheses are for $[\alpha]_D$. [b] Prepared from camphene of 53.6% optical purity, $[\alpha]_D$ +57.9°. [c] Prepared from camphene of 59.1% optical purity, $[\alpha]_D$ +63.8°. [d] At 59.3°. [e] At 45.1° in 1,2-dimethoxyethane–methanol, 50:50 v/v.

(26) These shifts occur readily in aprotic solvents.[27,28]

(27) W. R. Vaughan and R. Perry, *J. Amer. Chem. Soc.*, **75**, 3168 (1953); W. R. Vaughan, C. T. Godschel, M. H. Goodnow, and C. L. Warren, *ibid.*, **85**, 2282 (1963).

(28) P. v. R. Schleyer, W. E. Watts, R. C. Fort, M. B. Comisarow, and G. A. Olah, *ibid.*, **86**, 5679 (1964); M. Saunders, P. v. R. Schleyer, and G. A. Olah, *ibid.*, **86**, 5680 (1964); G. A. Olah and J. Lukas, *ibid.*, **90**, 933 (1968); F. R. Jensen and B. H. Beck, *Tetrahedron Lett.*, 4287 (1966).

(29) H. Meerwein and R. Wortmann, *Justus Liebigs Ann. Chem.*, **435**, 190 (1923).

(30) J. P. Bain, A. H. Best, B. L. Hampton, G. A. Hawkins, and L. J. Kitchen, *J. Amer. Chem. Soc.*, **72**, 3124 (1950).

(31) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1948, Chapter 2.

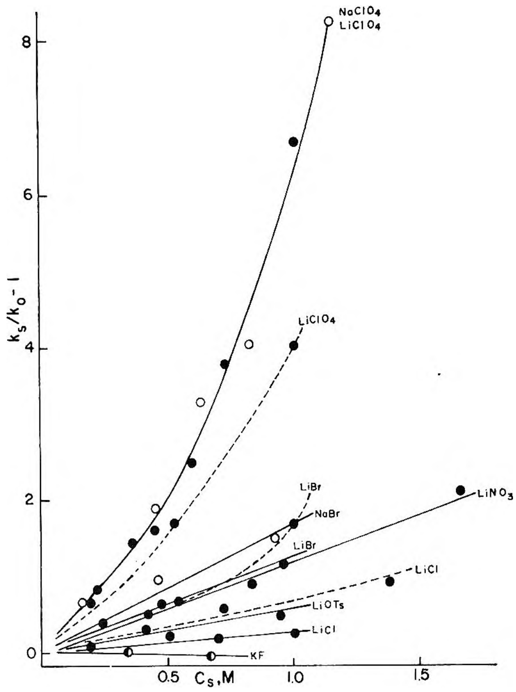


Figure 1.—Salt effects upon the methanolysis of 1-methyl-*exo*-2-chloronorbornane at 80.0° (broken line) and 2-methyl-*exo*-2-chloronorbornane at 25.0° (solid line): ●, lithium salts; ○, sodium salts; ◐, potassium salts.

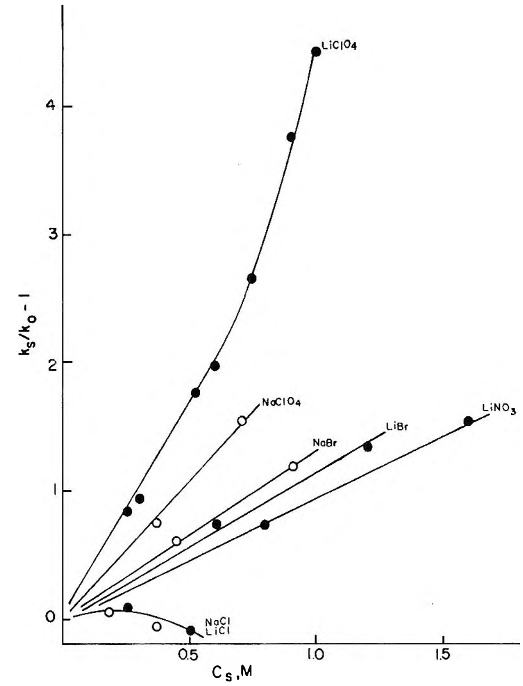


Figure 2.—Salt effects upon the methanolysis of *tert*-butyl bromide at 25.0°: ●, lithium salts; ○, sodium salts.

The conversion of camphene into its hydrochloride and back to camphene occurs with no loss of optical activity (Tables I and II), suggesting that both steps occur without racemization and that therefore the formation of camphene hydrate methyl ether probably also occurs without racemization. In one experiment camphene with $[\alpha]_D$ +57.9° gave isobornyl chloride with $[\alpha]_D$ −16.0° and $[\alpha]_{Hg}$ −16.6°, and in another camphene with $[\alpha]_D$ +63.8° gave isobornyl chloride with $[\alpha]_D$ −31.5° and $[\alpha]_{Hg}$ −32.8°. Taking $[\alpha]_D$ +108° for optically pure camphene in ethanol[30] we calculate the optical purities given in Table II, $[\alpha]_D$ −50° for optically pure camphene hydrochloride, and a mean value of $[\alpha]_D$ −30.6° for camphene hydrate methyl ether. On the assumption that the solvolysis of isobornyl chloride proceeds without racemization, we estimate $[\alpha]_D$ −59.2° and $[\alpha]_{Hg}$ −63° for optically pure material.

Independent experiments showed that the products were optically stable in the reaction solutions, and on a Tween 60–Celite glc column at 120°.

In the course of this work, we compared the rotations of some of the materials at two wavelengths (Table III). The results for camphene confirm Hückel's earlier measurements.[32]

TABLE III
OPTICAL ACTIVITIES AT TWO WAVELENGTHS

Compd	$[\alpha]_D/[\alpha]_{Hg}$
Camphene	0.846[a]
Camphene hydrate methyl ether	0.899
Isobornyl chloride	0.979

[a] A value of 0.825 is reported by Hückel.[32]

Products.—The salt effects upon the products of methanolysis of isobornyl chloride and camphene hydrochloride were determined using glc by methods already described.[11b] Because of the insensitivity of the thermal conductivity detector used in our glc, we did not measure the amounts of the minor products such at tricyclene and isobornyl methyl ether which are formed in these solvolyses.[22,33]

Methanolysis of isobornyl chloride and camphene hydrochloride in the presence of sodium or tetraethylammonium azide gave what we assume is 2,3,3-trimethylnorbornyl 2-azide, and it was extracted with the other neutral products. We were unable to separate it from camphene hydrate methyl ether by elution from an alumina column using petroleum ether, but it could be isolated by glc at 130° using a Tween–Celite column. It decomposed on heating at atmospheric pressure at *ca.* 170° but had a sharp melting point of 55° in a sealed tube. It had ir peaks at 4.8 and 8.0 μ characteristic of an azide.[34] *Anal.* Calcd for $C_{10}H_{17}N_3$: C, 63.5; H, 14.3; N, 22.2. Found: C, 63.3; H, 14.5; N, 22.0. In most experiments the amount of azide intervention was determined using glc, but with isobornyl chloride in aqueous 1,2-dimethoxyethane titration was used.

Results

Rates of Solvolysis.—Salt effects upon rate constant are illustrated for a number of reactions by plotting or tabulating $(k_s/k_0) - 1$ against C_s (Figures 1–4 and Tables IV–VIII), where k_s and k_0 are the first-order rate constants in the presence and absence of salt, and C_s is the molar concentration of salt. The values of the first-order rate constants in the absence of salt are given in Table IX.

TABLE IV
METHANOLYSIS OF ISOBORNYL CHLORIDE[a]

Salt	C_s, M	$(k_s/k_0) - 1$	b
LiCl	0.51	0.30	0.59
LiCl	1.00	0.60	0.60
$LiNO_3$	0.50	2.02	4.0
$LiNO_3$	1.19	4.11	3.5
$LiNO_3$	0.50	0.42[b]	0.84[b]
$LiNO_3$	1.19	1.15[b]	0.97[b]
$LiClO_4$	0.093	0.76	8.2
$LiClO_4$	0.52	3.09	6.0
$LiClO_4$	0.51	2.06[b]	4.0[b]
$LiClO_4$	1.03	5.20[b]	5.0[b]
$NaClO_4$	0.28	1.84	6.6
$NaClO_4$	0.56	3.60	6.4

[a] In MeOH at 0° unless specified; at 0° $k_0 = 1.84 \times 10^{-7}$ sec^{-1}. [b] At 45.0°, $k_0 = 9.65 \times 10^{-5}$ sec^{-1}.

(32) W. Hückel, *J. Prakt. Chem.*, **157**, 225 (1941).

(33) T. W. Del Pesco, Thesis, University of California, Santa Barbara, 1968.

(34) R. T. Cowley, "Infrared Spectroscopy," Allyn and Bacon, Boston, 1966, Chapter V.

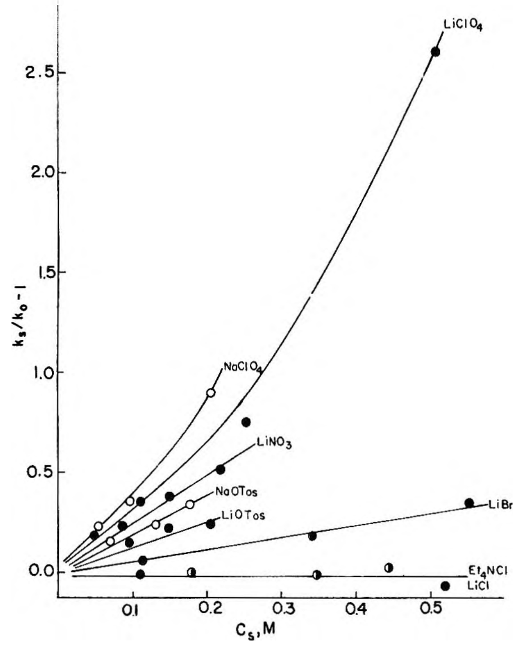


Figure 3.—Salt effects upon the methanolysis of camphene hydrochloride at 0°: ●, lithium salts; ○, sodium salts; ◑, tetraethylammonium salts.

TABLE V

SALT EFFECTS UPON THE METHANOLYSIS OF 2-METHYL-*exo*-2-NORBORNYL CHLORIDE[a]

Salt	C_s, M	10^5k, sec^{-1}	b
		1.52	
		47.0[b]	
LiCl	0.69	2.14	0.59
LiCl	1.47	2.38	0.39
LiBr	0.47	2.66	1.6
LiBr	1.17	4.45	1.6
$LiNO_3$	0.58	2.70	1.3
$LiNO_3$	1.00	3.60	1.4
$LiClO_4$	0.53	6.55	6.3
$LiClO_4$	1.18	21.7	11.3
KOMe	0.05	43.4[b]	
NaOAc	0.17	50.5[b]	

[a] In MeOH at 0° unless specified. [b] At 25.0°.

TABLE VI

SOLVOLYSIS OF ISOBORNYL CHLORIDE IN AQUEOUS METHANOL[a]

Salt	C_s	10^6k, sec^{-1b}	b	10^7v, mol l.$^{-1}$ sec^{-1c}	f_{RCl}	f^*
		3.52		3.00		
LiCl	0.14	3.27		3.03	0.92	0.99
LiCl	0.30	3.45		2.95	1.00	1.02
LiCl	0.38	3.70		3.09	1.02	0.97
LiCl	1.05	4.23		3.00	1.20	1.00
NaCl	0.12	3.21		3.03	0.90	0.99
NaCl	0.37	3.46		3.09	0.95	0.97
Et_4NCl	0.10	3.48		2.95	1.05	1.02
Et_4NCl	0.22	3.48		2.89	1.03	1.04
NaBr	0.10	3.44		2.84	1.04	1.06
NaBr	0.23	3.53		3.07	0.98	0.98
$LiClO_4$	0.44	5.73		4.64	1.06	0.65
$NaClO_4$	0.10	4.32	2.3	3.34	1.10	0.90
$NaClO_4$	0.23	5.05	1.9	3.61	1.19	0.83
$NaClO_4$	0.33	4.90	1.2	4.42	0.82	0.68
$NaClO_4$	0.45	5.44	1.5	4.61	1.00	0.65
$NaClO_4$	1.14	9.48	1.4	7.77	1.05	0.39

[a] In $MeOH-H_2O$, 70:30 v/v, at 0°. [b] Homogeneous solution. [c] Heterogeneous conditions.

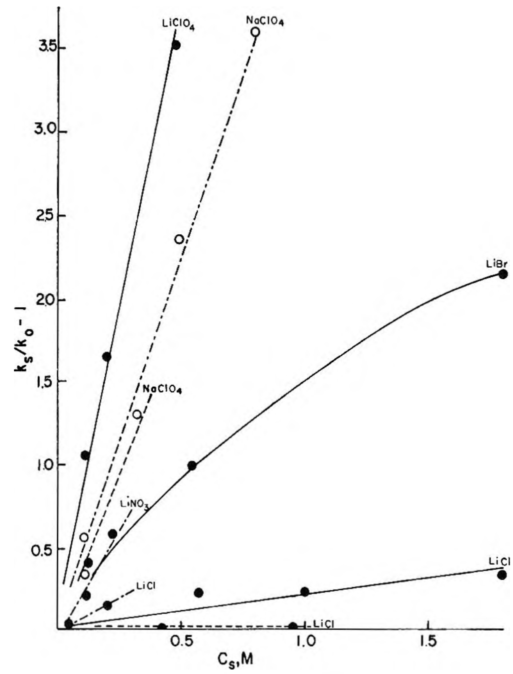


Figure 4.—Salt effects upon the methanolysis of camphene hydrochloride in 1,2-dimethoxyethane–methanol, 80:20, v/v, at 25.3° (solid line), and 0° (-----), and in acetone–water, 90:10 v/v, at 0° (–·–): ●, lithium salts; ○, sodium salts.

TABLE VII

SOLVOLYSIS OF ISOBORNYL CHLORIDE IN AQUEOUS ACETONE[a]

Salt	C_s, M	10^6k, sec^{-1b}	b	10^7v, mol l.$^{-1}$ sec^{-1c}	f_{RCl}	f^*
		2.35		2.32		
LiCl	0.47	2.37		2.02	1.16	1.15
LiCl	1.00	2.30		1.83	1.24	1.27
$LiClO_4$	0.57	4.58	1.7	2.92	1.56	0.80
$LiClO_4$	0.74	6.08	2.1	3.38	1.78	0.69
$LiClO_4$	1.06	8.01	2.3	4.06	1.95	0.57

[a] In acetone–H_2O, 55:45 v/v, at 0°. [b] Homogeneous solution. [c] Heterogeneous conditions.

The simple electrostatic theory and the empirical extension of the Debye–Hückel treatment both predict linear relationships between log k and ionic strength.[3,4,35] Our kinetic results support Winstein's conclusion that the relationship between rate and salt concentration is linear rather than logarithmic[10,17] at least for relatively low concentrations of salt, and Tables IV–VIII and X–XIII give the initial slopes, b, of plots of $(k_s/k_0) - 1$ against salt concentration, C_s. There is a spread of b values, which are close to zero for chlorides, fluorides, and acetates, and which are always largest for perchlorates. However, the actual b values differ, even for substrates of similar structure, *e.g.*, camphene hydrochloride and 2-methyl-*exo*-2-chloronorbornane. Although the data are not extensive, they indicate that some of the b values decrease with increasing temperature. There is no simple relation between the b values and solvent composition, except that for the solvolysis of isobornyl chloride they decrease for perchlorates in going from methanol to aqueous methanol.

(35) E. M. Kosower, "An Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., 1968, Part 2.8.

TABLE VIII

SALT EFFECTS ON SOLVOLYSES OF CAMPHENE HYDROCHLORIDE[a]

		Solvent			
		Me_2CO-H_2O[b]		DMe-MeOH[c]	
Salt	C_s, M	$(k_s/k_0) - 1$	b	$(k_s/k_0) - 1$	b
LiCl	0.028	0.03	1.0		
LiCl	0.099	0.16	1.6		
LiCl	0.410			−0.02	
LiCl	0.573			0.23[d]	0.4[d]
LiCl	0.942			−0.03	
LiCl	1.00			0.24[d]	0.2[d]
LiCl	2.36			0.43[d]	0.2[d]
Et_4NCl	0.075	−0.03			
Et_4NCl	0.13			0.22	
LiBr	0.545			0.98	1.8
LiBr	1.93			2.33	1.4
$LiNO_3$	0.104	0.20	1.9		
$LiNO_3$	0.210	0.57	2.7		
$NaClO_4$	0.108	0.55	5.1		
$NaClO_4$	0.115			0.35	3.0
$NaClO_4$	0.315			1.3	4.1
$NaClO_4$	0.491	2.33	4.7		
$NaClO_4$	0.977	4.44	4.6		
$LiClO_4$	0.103			1.06[d]	10.2[d]
$LiClO_4$	0.201			1.65[d]	8.2[d]
$LiClO_4$	0.481			3.52[d]	7.3[d]
Bu_4NPF_6	0.101			0.20[d]	2.0

[a] At 0° unless specified. [b] Me_2CO-H_2O, 90:10 v/v, at 0° $k = 6.80 \times 10^{-5}$ sec^{-1}. [c] 1,2-Dimethoxyethane–MeOH, 80:20 v/v, at 0° $k = 8.29 \times 10^{-6}$ sec^{-1}, at 25.3° $k = 1.06 \times 10^{-4}$ sec^{-1}. [d] At 25.3°.

TABLE IX

FIRST-ORDER RATE CONSTANTS IN THE ABSENCE OF ADDED SALT[a]

	Solvent					
Substrate	MeOH	70% MeOH–H_2O	20% MeOH–DME	55% Me_2CO–H_2O	90% Me_2CO–H_2O	80% DME–H_2O
tert-BuBr	36.7[b]					
1-MBCl (III)	320[c]					
2-MBCl (IV)	15.2					
	470[b]					
iBCl (II)	0.18	35.2		23.5		
	96.5[d]					
CmHCl (I)	72.7		8.3		68.0	148
			104[b]			

[a] Values of 10^6k sec^{-1}, at 0° unless specified; the solvent compositions are in vol %, *i.e.*, 70% MeOH–H_2O is 70:30 MeOH–H_2O v/v. [b] At 25.0°. [c] At 80.0°. [d] At 45.0°.

TABLE X

VALUES OF *b* PARAMETERS FOR SOLVOLYSIS OF *tert*-BUTYL BROMIDE[a]

Salt	b
LiCl	~0
NaCl	~0
LiBr	1.2
NaBr	1.4
$LiNO_3$	0.9
$LiClO_4$	3.4
$NaClO_4$	2.2

[a] In MeOH at 25.0°.

For small rate enhancements most of the data are fitted equally well by linear or logarithmic relationships, but for the larger rate enhancements plots of log k against salt concentration curve downward.

We used few cations, but the anion order is generally $ClO_4^- > NO_3^- \approx Br^- \approx OTos^- \approx PF_6^- > Cl^- \approx OAc^- > F^- > OR^-$ with perchlorate being

TABLE XI

VALUES OF *b* PARAMETERS OF SOLVOLYSIS OF 1- AND 2-METHYL-*exo*-2-CHLORONORBORNANE[a]

	Substrate	
Salt	*sec*-RCl[b]	*tert*-RCl
LiCl	0.8	0.3
LiCl		0.5[c]
LiBr	1.1	1.6
LiBr		1.6[c]
NaBr		2.0
$LiNO_3$		1.2
$LiNO_3$		1.4[c]
LiOTos		0.7
$LiClO_4$	3.3	3.7
$LiClO_4$		6.3[c]
$NaClO_4$		4.3
NaOAc		0.4
KOMe		−1.6
KF		~0

[a] In MeOH at 25.0° unless specified; *sec*- and *tert*- denote the secondary 1,2 derivative and the tertiary 2,2 derivative, respectively. [b] At 80.0°. [c] At 0°.

TABLE XII

VALUES OF *b* PARAMETERS FOR SOLVOLYSIS OF ISOBORNYL CHLORIDE[a]

	Solvent		
Salt	MeOH	70:30 MeOH–H_2O	55:45 Me_2CO–H_2O
LiCl	0.6	~0	~0
Et_4NCl		~0	
NaCl		~0	
NaBr		~0	
$LiNO_3$	4.0		
$LiNO_3$	0.9[b]		
$LiClO_4$	6.5		
$LiClO_4$	4.0[b]	1.5	1.7
$NaClO_4$	6.5	2.0	

[a] At 0° unless specified. [b] At 45.0°.

TABLE XIII

VALUES OF *b* PARAMETERS FOR SOLVOLYSIS OF CAMPHENE HYDROCHLORIDE[a]

	Solvent		
Salt	MeOH	90:10 Me_2CO–H_2O	80:20 DME–MeOH
LiCl	~0	1.0	~0
LiCl			0.1[b]
Et_4NCl	~0	~0	
LiBr	0.6		1.3[b]
LiOTos	1.6		
NaOTos	1.8		
$LiNO_3$	2.4	3.7	
Bu_4NPF_6	1.9		
Bu_4NPF_6			
$LiClO_4$	3.0		
$LiClO_4$			
$NaClO_4$	4.1	4.5	4.2
$NaClO_4$			4.8[b]

[a] At 0° unless specified. [b] At 25.3°.

much more effective than the other anions. Chloride ion generally has little effect except for the methanolysis of 1-methyl-*exo*-2-chloronorbornane (III) at 80°, and it sometimes retards reaction, even when a common ion retardation is improbable. This salt order is qualitatively similar to that upon the relative stabilities of the trianisyl cation and the *p*-nitroanilinium ion.[36]

(36) C. A. Bunton, J. Crabtree, and L. Robinson, *J. Amer. Chem. Soc.*, **90**, 1258 (1968).

Ionic association can be very important; for example, specific salt effects upon the rates of SN2 reactions can be explained in terms of ion pairing of the nucleophilic anion with a cation to give an unreactive ion pair,[37] and an ion-paired salt might show no rate-enhancing ionic strength effect for the SN1 reactions considered in this discussion, but ion pairing appears not to be all important in our systems, because lithium and sodium perchlorate and lithium nitrate are strong electrolytes in methanol, and lithium and sodium chloride are strong in methanol–water containing 0.8 mol fraction of methanol,[38] but nonetheless exhibit very different kinetic salt effects. Conductance measurements show that tetraethylammonium chloride is a stronger electrolyte than either lithium chloride or bromide in methanol, and conductivity measurements on lithium halides in aqueous acetone suggest that lithium chloride exists as a tight ion pair whereas, with lithium bromide and especially iodide, some solvent molecules are bound in the ion pair,[39,40] but there is again no simple relation between the kinetic salt effects and ion pairing of the electrolyte.

For salts in which the cation is large, *e.g.*, tetrabutylammonium, there can be considerable association even in water, because disruption of the water structure is minimized by ion pairing, and this association appears to be important in hydroxylic solvents but not in an aprotic solvent such as acetonitrile.[41]

Another factor which suggests that ionic association is not all important is that the salt order upon reaction rate is qualitatively similar in solvents ranging from good ionizing solvents like methanol and aqueous acetone to poor ionizing solvents such as 1,2-dimethoxyethane–methanol.

The specificity of these kinetic salt effects cannot therefore be ascribed wholly to ionic association, and its role seems to be relatively small for the better ionizing solvents.

Initial and Transition State Effects.—In methanol–water, 70:30 v/v, and acetone–water, 55:45 v/v, the solvolysis of isobornyl chloride is slow, compared with its rate of dissolution. In a saturated solution the activity of isobornyl chloride is constant and the Brønsted–Bjerrum rate equation gives[14,15]

$$v_s/v_0 = 1/f^*$$

where v_s and v_0 are the rates in the presence and absence of salt, and f^* is the activity coefficient in the presence of salt, taking the pure solvent as the standard state.

For homogeneous solutions

$$k_s/k_0 = f_{\mathrm{RCl}}/f^*$$

where k_s and k_0 are the first-order rate constants in the presence and absence of salt, and f_{RCl} is the activity coefficient of the substrate.

(37) S. Winstein, L. Savedoff, S. Smith, I. D. R. Stevens, and J. S. Gall, *Tetrahedron Lett.*, 24 (1960); N. N. Lichtin and K. N. Rao, *J. Amer. Chem. Soc.*, **83**, 2417 (1961), and references cited.

(38) C. W. Davies, "Ionic Association," Butterworths, London, 1962, Chapter 1; H. S. Harned and B. O. Owen, "The Physical Chemistry of Electrolyte Solutions," 3rd ed, Reinhold, New York, N. Y., 1957, Chapter 6; L. G. Longsworth and D. A. MacInnes, *J. Phys. Chem.*, **43**, 239 (1939).

(39) R. E. Jervis, D. R. Muir, J. P. Butler, and A. R. Gordon, *J. Amer. Chem. Soc.*, **75**, 2855 (1953); P. G. Sears, R. L. McNeer, and L. R. Dawson, *J. Electrochem. Soc.*, **102**, 269 (1955).

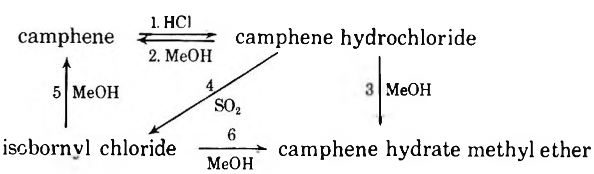
(40) L. G. Savedoff, *J. Amer. Chem. Soc.*, **88**, 654 (1966).

(41) (a) R. M. Diamond, *J. Phys. Chem.*, **67**, 2513 (1963). (b) R. L. Kay and D. F. Evans, *J. Amer. Chem. Soc.*, **86**, 2748 (1964); J. L. Hawes and R. L. Kay, *J. Phys. Chem.*, **69**, 2420 (1965).

From the reaction rates in the saturated heterogeneous system (Tables VI and VII), we calculate the salt effects upon the transition state, and hence can calculate the activity coefficients of the initial state. The values of f_{RCl} are much less accurate than those of f^*, because they depend upon two separate sets of experiments, but in aqueous methanol only the activity coefficient of the transition state is affected by added salts. In aqueous acetone both f_{RCl} and f^* depend on the salt, but with lithium chloride the effects on f_{RCl} and f^* cancel and with lithium perchlorate they augment each other.

In these systems, return of a carbonium ion intermediate cannot be responsible for the relatively low rate in lithium chloride solution, because return would give very reactive camphene hydrochloride.

Stereochemistry.—One of the questions which arises regarding kinetic salt effects hinges on the lifetimes of the carbonium ion intermediates in the hydroxylic solvents used in this work, and in acetic acid hydride shifts occur more rapidly than solvent attack upon a number of bicyclic alkyl cations.[42] There is qualitative evidence for retention of configuration in solvolyses of camphene hydrochloride in polar hydroxylic solvents,[43] and we used methanolysis to relate the stereochemistry of trimethylnorbornyl chlorides, and their solvolysis products.



The fact that camphene can be converted into camphene hydrochloride which gives camphene with no loss of optical activity suggests that steps 1 and 2 and probably 3 occur without racemization (Tables I and II). However, the conversion of camphene hydrochloride into isobornyl chloride in liquid sulfur dioxide, step 4, causes partial racemization, but we note that the overall optical properties concerned in steps 4 and 5 and 4 and 6 are the same, suggesting that all the racemization occurs in step 4, and that the solvolyses 5 and 6 occur without racemization.

Our evidence is consistent with existing evidence that the camphene hydro cation racemizes by hydride and methyl shifts when it is generated in aprotic solvents[27] (but not in the reaction of camphene with hydrogen chloride), and that it retains its optical purity in a reactive solvent such as methanol, where the lifetime of the carbonium ion is shorter than the time required for methyl or hydride shifts. In the norbornyl system, these shifts are fast on the nmr time scale except at low temperatures.[28] In various solvolyses in reactive solvents, the lifetimes of the carbonium ion like species have been estimated to be $<10^{-5}$ sec,[44] and therefore the absence of racemization in our systems is consistent with these estimates.

(42) J. D. Roberts and C. C. Lee, *J. Amer. Chem. Soc.*, **73**, 5009 (1951); J. D. Roberts, C. C. Lee, and W. H. Sanders, *ibid.*, **76**, 4501 (1954); P. D. Bartlett, "Non-Classical Ions," W. A. Benjamin, New York, N. Y., 1965.

(43) J. L. Simonsen, "The Terpenes," Vol. II, Cambridge University Press, Cambridge, England, 1957, p 317.

(44) S. Winstein, *J. Amer. Chem. Soc.*, **87**, 381 (1965); D. S. Noyce and S. K. Brauman, *ibid.*, **90**, 5218 (1968).

Products.—Added lyate ion increases the amount of elimination in E1–S_N1 solvolyses of isobornyl chloride and camphene hydrochloride without increasing the overall rate of solvolysis, suggesting either that the lyate ion removes the proton from the carbonium ion, whereas the solvent attacks the cationic center, or that the lyate ion changes the properties of the solvent so as to favor loss of the proton. Moreover, the loss of the proton from relatively stable carbonium ions has an enthalpy of activation of 4 kcal mol^{-1} greater than that for addition of solvent,[45] and these results suggest that a strongly basic lyate ion may be more effective than a solvent molecule in removing the proton.[11b]

The salt effects upon amount of elimination in methanolyses of isobornyl chloride and camphene hydrochloride are simple: bromide has no effect; chloride, nitrite, and acetate increase elimination; perchlorate reduces it (Table XIV and XV), and elimination increases with increasing temperature. Salt effects upon the amount of elimination have also been observed by Lucas and Hammett for the S_N1–E1 solvolysis of *tert*-butyl nitrate in aqueous dioxane.[8] For solvolysis of α,α'-dimethyl benzyl chloride in the presence of methoxide and perchlorate ions, the amount of elimination is greater than that expected in terms of the net rates of elimination and substitution, but in this reaction salt effects upon the bimolecular component of reaction also have to be considered.[20]

Table XIV

Electrolyte Effects on the Formation of Camphene from Isobornyl Chloride[a]

c_{OMe^-}	Salt	C_s, *M*	[Camphene], mol %
0.05			30[b]
0.05	$NaNO_2$	0.30	41[b]
0.05	LiOAc	0.84	48[b]
0.20			35
0.20	$NaClO_4$	1.50	29
0.50			46
0.50	$NaClO_4$	1.50	36
1.50			70
1.50	$NaClO_4$	1.50	66
0.20			42[b]
0.20	$NaClO_4$	1.50	33[b]
0.20	$LiClO_4$	1.50	36[b,c]
0.20	$LiNO_3$	1.50	43[b,c]
0.20	LiBr	1.50	41[b,c]
0.20	LiCl	1.00	46[b,c]
0.20	Et_4NCl	1.50	58[b,c]

[a] At 45.1° in MeOH with NaOMe unless specified. [b] At 59.8°. [c] LiOMe.

Table XV

Electrolyte Effects on the Formation of Camphene from Camphene Hydrochloride[a]

c_{OMe^-}	Salt	C_s, *M*	[Camphene], mol %
0.20			20
0.20	$NaClO_4$	1.50	15
0.50			31
0.50	$NaClO_4$	1.50	22
1.50			50
1.50	$NaClO_4$	1.50	31
0.20			22[b]
0.20	$NaClO_4$	1.50	16[b]
0.20[c]	LiCl	1.00	35[b,c]
0.50			35[b]
0.50	$NaClO_4$	1.50	25[b]

[a] At 0° in MeOH with NaOMe unless specified. [b] At 25.3°. [c] LiOMe.

The ability of the salt to increase elimination decreases with increasing acidity of the conjugate acid of the anion (Tables XIV and XV). Nitrite or acetate could act as bases toward a carbonium ion, but chloride ion would not be expected to extract a proton from a carbonium ion in a polar hydroxylic solvent.[46] It is also possible that the salt is modifying the properties of the solvent so that it attacked the carbonium ion as a base rather than a nucleophile. The salt order on the amount of elimination, $Cl^- > NO_3^- > Br^- > ClO_4^-$, follows the ability of the anion to orient water molecules about itself, and disruption of the water structure decreases in the sequence from ClO_4^- to Cl^-.[48] These anions could have a similar effect on the structure of methanol.

If the O–H dipoles of the hydroxylic solvent molecules are oriented toward the anion, the lone pair electrons will be more effective at removing a proton from the carbonium ion; alternatively we could suppose that solvation of the chloride ion (or other small anion) reduces the ability of the solvent to solvate the lyate ion and thereby increases its ability to extract a proton from the carbonium ion.

Anion Intervention in Solvolyses of Trimethylnorbornyl Chlorides.—One of the problems in considering the effect of electrolytes upon the fate of the carbonium ion or ion pair hinges upon the question of their lifetimes in a polar solvent. We had earlier found that addition of 1,2-dimethoxyethane increased the amount of camphene formed in the methanolysis of isobornyl chloride and camphene hydrochloride[11b] and suggested that (1) the aprotic ether could increase the basicity of the methoxide ion, by reducing hydrogen bonding between it and methanol,[49] or (2) it could solvate the carbonium ion[50] which would therefore be less susceptible to nucleophilic attack by a hydroxylic solvent but not to loss of a proton. Our observations on azide intervention support the second of these explanations, because, although 2,2,3-trimethylnorbornyl-2-azide is not formed from camphene hydrochloride and azide ion in methanol–1,2-dimethoxyethane, 10:90 v/v, it is formed in water–1,2-dimethoxyethane, 20:80 v/v, although the azide ion should be less nucleophilic in the more hydroxylic solvent.[49] (The reaction in methanolic 1,2-dimethoxyethane was not studied in detail, but the main products were camphene and isobornyl chloride.)

The results in Table XVI confirm earlier results in showing that elimination and azide attack upon the carbonium ion have enthalpies of activation which are 2–3 kcal mol^{-1} higher than that for nucleophilic attack by the solvent molecules.[45]

(45) Reference 4, Chapter VIII.

(46) There is, however, considerable evidence that proton transfer from a carbonium to a chloride ion can occur within an ion pair.[47]

(47) M. Cocivera and S. Winstein, *J. Amer. Chem. Soc.*, **85**, 1702 (1963).

(48) H. S. Frank and H. G. Evans, *J. Chem. Phys.*, **13**, 507 (1945); G. R. Choppin and K. Buijs, *ibid.*, **39**, 2042 (1963).

(49) A. J. Parker, *Quart. Rev.* (*London*), **16**, 163 (1962).

(50) A. Streitweiser and W. D. Schaeffer, *J. Amer. Chem. Soc.*, **79**, 2888, 6233 (1957); A. Streitweiser and S. Andreades, *ibid.*, **80**, 6553 (1958).

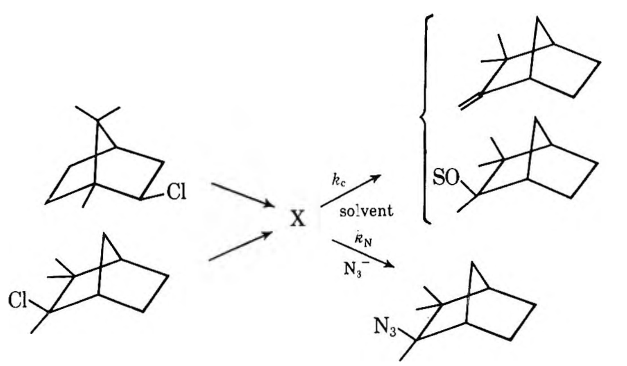
TABLE XVI
INTERVENTION BY AZIDE ION[a]

Substrate	Products, mol %		
	Cm	CmOMe	$CmHN_3$
CmHCl[b]	20.5	64.0	15.5
CmHCl	26.5	54.5	19.0
iBCl	25.3	54.0	20.5
iBCl[c]	36.5	40.5	23.0
iBCl[c,d]	41.0	47.0	12.0
iBCl[c,e]			16.0

[a] In methanol with 0.05 *M* NaOMe, 0.28 *M* NaN_3, and 0.04 *M* substrate, at 25.3° unless specified. [b] At 0°. [c] At 59.8°. [d] With 0.14 *M* NaN_3. [e] Water:1,2-dimethoxyethane, 20:80 v/v.

In methanolic sodium azide the products are almost the same whether the starting material is isobornyl chloride or camphene hydrochloride, showing that both substrates generate the same intermediates, either directly or by a rapid equilibration.

The simplest picture of azide intervention is shown below.



At 0° in methanol $k_N/k_c = 0.65$, whereas the experiments with ^{36}Cl give for the attack of chloride ion and methanol $k_e/k_c = 0.16$ (calculated for 1 *M* nucleophilic anions, using data in Tables XVI and XVII),

TABLE XVII
ISOTOPIC EXCHANGE BETWEEN
LITHIUM CHLORIDE AND ALKYL CHLORIDES[a]

Substrate	Solvent[b]	C_{LiCl}, *M*	α_{ex}[c]	α_k[d]
tert-BuCl	60% aq ac	0.131	0.32	
CmHCl	MeOH	1.88	0.16[e]	0.11
CmHCl	80% aq dme	0.166	0.92 (0.60)	

[a] At 25.0° unless specified. [b] Solvents are ac = acetone, diox = dioxane, and dme = 1,2-dimethoxyethane, and the volume percentage refers to the organic component. [c] The values in parentheses are for *ca.* 25% reaction, the others are for 50% reaction unless specified. [d] Calculated from the rates of solvolysis using eq 2. [e] At 0°.

i.e., the chloride ion is a less effective reagent than azide ion toward the camphene hydro cation or ion pair. For solvolyses of *tert*-butyl chloride, azide and chloride have similar reactivities,[21] and, in so far as it is the less reactive carbonium ions which discriminate most between nucleophiles, these results suggest that the camphene hydro cation is less reactive than the *tert*-butyl cation toward nucleophiles. The reactivity difference could arise from both electronic and steric effects,[22b,44,51,52] and X may be a free ion or an ion pair, or a mixture of the two, and chloride and azide ions and the solvent molecules may discriminate between the various cationic intermediates represented by X. The absence of azide attack in methanol–1,2-dimethoxyethane, 10:90 v/v, suggests that here an ion pair within a solvent cage is eliminating camphene and collapsing to isobornyl chloride, probably by the mechanism suggested by Cocivera and Winstein.[47] (We note that the situation may be different for attack upon an ion pair generated from a primary or secondary alkyl halide or tosylate in a more nucleophilic solvent.[23])

(51) N. C. Brown, *J. Chem. Soc., London, Spec. Publ.*, No. 16, 140, 175 (1962); *Chem. Brit.*, **2**, 199 (1966).

(52) P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 699, 701 (1967); F. R. Jensen and B. E. Smart, *ibid.*, **91**, 5688 (1969).

Isotopic Exchange.—The similarities of the salt effects upon the solvolyses of isobornyl chloride and 1-methyl-*exo*-chloronorbornane where return is kinetically unimportant and the other solvolyses where return is possible suggest that return is not the cause of this salt specificity, but it seemed desirable to examine the possibility of recombination of a *tert*-butyl or camphene hydro cation and a chloride ion by carrying out the solvolysis in the presence of isotopically labeled chloride ion. Only a small amount of exchange was observed (Table XVII) and the values of k_e/k_c are similar to those found earlier for solvolyses of *tert*-butyl chloride in aqueous methanol.[25]

Exchange could arise either by capture of a free carbonium ion by an external chloride ion or by isotopic exchange involving an ion pair intermediate,

$$R{-}Cl \rightleftharpoons \overset{+}{R} + Cl^-$$

followed by return of the ion pair to substrate.[17] Sneen

$$^{36}Cl^- + \overset{+}{R}Cl^- \rightleftharpoons {}^{36}Cl^-R^+ + Cl^-$$

and his coworkers have considerable evidence for bimolecular reactions between nucleophiles and ion pairs generated by secondary alkyl halides,[23] and return of an ion pair generated from *p*-chlorodiphenyl methyl chloride has also been observed.[17]

On the assumption that the exchange and chemical reactions involve an intermediate I, which may be

$$R{-}Cl \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} I \xrightarrow{k_2} \text{products}$$

an ion pair or a carbonium ion, and assuming that *every* return of I involves isotopic exchange, the relative values of the rate constants k_e and k_c are given by

$$k_e/k_c = k_{-1}\,[Cl^-]/k_2, \quad (1)$$

If I is a free carbonium ion, $k_{-1}/k_2 = \alpha$, where α is the common ion parameter.[3–5]

$$k = k_1/(1 + \alpha[Cl^-]) \quad (2)$$

and then

$$\alpha_{ex} = k_e/k_c[Cl^-] \quad (3)$$

Therefore, our exchange results give maximum values for capture of a free carbonium ion by chloride ion and show that return is never large enough to produce the specific salt effects which we observe with added perchlorates, *e.g.*, in the presence of 1 *M* chloride ion no more than 10% of the camphene hydro cations or ion pairs return with exchange to substrate in 1,2-dimethoxyethane–water, 80:20 v/v (Table XVII), and the rate enhancement would be small even if all this return were eliminated by an added salt. Similar conclusions can be drawn regarding solvolyses of *tert*-butyl chloride (Table XVII and ref 21).

Discussion

Kinetic Salt Effects.—The pattern of the overall kinetic salt effects is simple and is generally similar to those observed earlier, and, at least for the uniunivalent salts which we used, the nature of the cation is relatively unimportant. The salt order upon the rates of solvolysis of a given substrate does not depend markedly upon the temperature, the solvent, or substrate structure or upon the possibility of carbonium ion return to substrate, although these factors influence the magnitude of the kinetic salt effect.

Our experiments with isobornyl chloride under heterogeneous conditions show that initial state effects are not particularly important in mixed solvents, in agreement with experiments using *exo*-norbornyl bromide in aqueous dioxane,[15] although they are important for hydrolyses in water.[14]

Any explanation of these specific salt effects must take into account the fact that they can be observed both in systems in which there may be return of intermediates to starting material and in systems where there is no return and in which the life time of the carbonium ion is too short for methyl or hydride shifts to occur. Therefore we cannot explain all these specific salt effects in terms of a special salt effect upon the dissociation of a solvent separated ion pair, as for acetolyses,[17,19] or upon recombination of carbonium and chloride ion, or nucleophilic attack on an ion pair.[23]

The absence of a salt effect upon the activity coefficient of isobornyl chloride in aqueous methanol or acetone is understandable because the organic component of the solvent should interact most strongly with the organic substrate, whereas the salt should interact with the water. The situation in the mixed solvents is therefore completely different from that in water.[14,15]

We note also that cation effects are not large in these polar aqueous organic solvents, although in nonpolar solvents such as ether and acetic acid, a small high charge density cation such as lithium can electrophilically assist ionization.[17] Presumably small cations are so strongly solvated in polar hydroxylic solvents that they are ineffective catalysts, and the importance of such catalysis should be reduced by solvation of the departing anion. One notable exception to this generalization is the observation that the rate of hydrolysis of *p*-chlorodiphenylmethyl chloride in 80% acetone–water increases linearly with concentration of lithium perchlorate but is little affected by tetrabutyl ammonium perchlorate,[53] possibly because the latter salt is a weak electrolyte so that the perchlorate ion is less available to stabilize the carbonium ion (*cf.* ref 18).

Some workers have noted that these and other similar specific salt effects upon transition state stability in hydroxylic solvents appear to be caused by direct interactions between the transition state and the electrolyte.[13,36,54] Large low charge density anions and cations can bond hydrophobically in water, so as to maximize water–water interactions, and minimize the disruption of the water structure by the large ions,[41,48,55] and such an effect could be an important factor in the specificity of kinetic salt effects. Carbonium ions are generally large and have low charge densities and are probably not strongly solvated by hydroxylic solvents, particularly if the positive charge is delocalized, and therefore they might interact with a large low charge density anion such as perchlorate, and such stabilization of the carbonium ion may be a major factor in the differential effects of salts and strong acids, upon the H_0 and H_R acidity functions and on the rates of A1 as compared with A2 solvolyses.[36] Somewhat similarly large, low charge density cations, such as tetraalkylammonium ions, stabilize the transition state of SN2 reactions relative to the nucleophilic anion.[13,54]

Effects upon the initial state have to be considered, but once this is done the salt order which we observe on these SN1 and A1 reactions is very similar to that found for anion effects upon water structure. Solvent structure dictated that ion pairing is quite different from that observed in the more usual type of Bjerrum electrostatic ion pairing which is most important in solvents of low dielectric constant and with ions of high charge density.[41]

Anion effects upon the rates of SN1 methanolysis of *tert*-butyl chloride or bromide follow the order $ClO_4^- > Br^- > NO_3^- > Cl^- \approx$ no salt $> OR^-$, and for anion effects upon water structure, measured by infrared spectral shifts, it is structure breaking anions; $ClO_4^- > Br^- > NO_3^- > Cl^-$, with OH^- and F^- being structure-making anions.[48]

Although the cation effects are generally small, several solvolyses in aqueous organic solvents are slightly faster in solutions of sodium than in lithium salts, in the opposite direction to that expected for electrophilic catalysis. Sodium disrupts the structure of water more than does lithium,[48] and to this extent the cation order is also explicable in terms of effects upon the solvent.

Much of the evidence on hydrophobic bonding relates to aqueous solutions, but protic solvents such as methanol also have considerable structure,[56] and structure could still be important in mixed aqueous organic solvents, even though the basic water structure is disrupted by addition of appreciable amounts of organic solvents (initial addition of many aprotic solvents actually enhances water–water interactions.)[57] In these organic or aqueous organic solvents it is understandable that initial state salt effects should be less important than in water, where the organic substrate must be in a cavity surrounded by water molecules instead of being solvated preferentially by the organic solvent. These solvent-structure-enforced ion pairings will depend very critically upon both the nature of the solvent and the sizes of the anion and the transition state. We should not therefore expect any simple relationship between rate and salt concentration over a wide range of solvents and substrates.

Our results also show that, as pointed out earlier,[8,9]

(53) S. Winstein, M. Hojo and S. G. Smith, *Tetrahedron Lett.*, 12 (1960).

(54) C. A. Bunton and L. Robinson, *J. Amer. Chem. Soc.*, **90**, 5965 (1968); C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34**, 783 (1969).

(55) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, Chapter VIII.

(56) Reference 35, Parts 2.5 and 2.6.

(57) D. N. Glew, H. D. Mark, and N. S. Rath, *Chem. Commun.*, 265 (1968).

we must be cautious in calculating the amount of common ion return kinetically, because small high charge density anions, such as hydroxide and fluoride, can retard reaction, and estimation of any rate enhancing effect of the common ion is fraught with uncertainty.[58] Use of an isotopically labeled common ion is also not the answer, because it could exchange with the leaving anion at the ion pair stage.[17]

Although we conclude that interactions between an anion and a carbonium-ion-like transition state are important factors in determining kinetic salt orders in polar hydroxylic solvents, other factors including the conventional ionic atmosphere effects and dipole-dipole effects undoubtedly contribute to the overall effect.[18] The relation between rate constant and salt concentration also suggests that more than one factor is at work.

Except for the treatment used by Perrin and Pressing,[18] most of the electrostatic treatments of kinetic salt effects predict a linear relation between log k and ionic strength (or its square root for interionic reactions).[3,35] However, Winstein and his coworkers found that kinetic salt effects in many nonpolar solvents were linear with ionic strength,[17a] as would be expected if there were direct 1:1 interactions between say a lithium cation and the anionic leaving group (*cf.* ref 13).

As we noted earlier our results fit neither a linear nor a logarithmic relationship between rate and ionic strength, although for many electrolytes k varies linearly with ionic strength up to moderate salt concentrations and then increases more sharply.

That part of the salt effect which involves solvent-structure-induced (hydrophobic) ion pairing could very well lead to linear relations between rate and ionic strength, whereas those caused by ionic atmosphere effects[3] and by salt effects upon the activity coefficient of the substrate[7] should follow a logarithmic relationship. Insofar as all the effects contribute to the overall effect it is not surprising that the relation between rate and ionic strength is in between linear and logarithmic.

Registry No.—I, 27720-68-9; II, 27720-69-0; III, 27720-70-3; IV, 27720-71-4; *tert*-butyl bromide, 507-19-7.

Acknowledgment.—We acknowledge helpful discussions and the exchange of unpublished results with Professors J. F. Bunnett and C. L. Perrin.

(58) The small rate retardations observed with fluoride or acetate ions could in principle be caused by return of a reaction intermediate to an unreactive alkyl fluoride or acetate.

Reactions of 2-Halo-2,3,3-trimethylbutanes in Methanol Solution. Rates and Product Ratios in Solvolysis and in Reactions with Anionic Bases[1]

J. F. BUNNETT* AND DAVID L. ECK

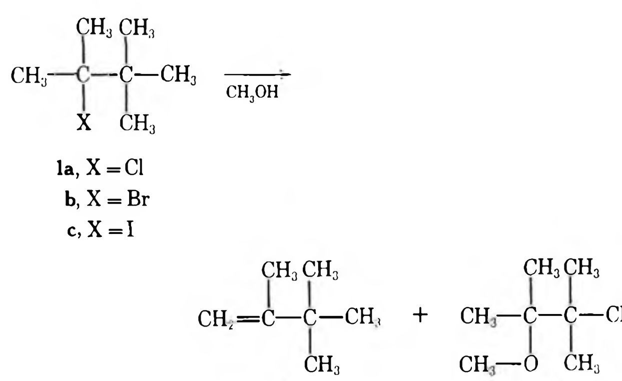
University of California, Santa Cruz, California 95060

Received August 24, 1970

Reactions of 2-chloro-2,3,3-trimethylbutane (**1a**) in CH_3OH to form 2,3,3-trimethyl-1-butene (**2**) and 2,3,3-trimethyl-2-butyl methyl ether (**3**) are accelerated by added electrolytes in the order $NaClO_4 > NaSC_2H_5 > NaOCH_3$. The kinetic effects of $NaClO_4$ plus $NaOCH_3$ or $NaSC_2H_5$ are not additive. Low concentrations of $NaOCH_3$ cause a small rate increase but larger concentrations cause the rate to diminish. $NaClO_4$ does not affect the proportions of **2** and **3** formed from **1a**, but $NaOCH_3$ and especially $NaSC_2H_5$ cause an increase in the fraction of olefin in the products. **1a** and its bromo and iodo analogs differ, in solvolysis and in reactions with $NaOCH_3$ or $NaSC_2H_5$, in the proportions of **2** and **3** formed. The data suggest reaction in part by E1–SN1 solvolysis and in part by the E2 mechanism, but no model to give a satisfactory quantitative account of the data has been found.

Part A

Much scientific interpretation consists of the fitting of experimental data to conceptual models, often with demonstration that certain models can and that other models cannot accommodate the data. Sometimes new models are devised *ad hoc* when none of the older ones seems adequate. However, there are occasions when experimental data outrun the supply of models; we now present data of this character.



1a, X = Cl
b, X = Br
c, X = I

2 **3**

These data concern principally rate and product studies on the solvolysis of 2-chloro-2,3,3-trimethylbutane (**1a**) in methanol, both in the absence and in the presence of sodium perchlorate, and on its reactions with sodium methoxide and sodium thioethoxide. For reactions of the bromo and iodo analogs of **1a**, we have studied only product compositions, except for a short series of kinetic data on the iodo compound, presented in Part B. The products obtained from all reactions are an olefin, 2,3,3-trimethyl-1-butene (**2**), and an ether, 2,3,3-trimethyl-2-butyl methyl ether (**3**). No dialkyl sulfide product was detectable in the sodium thioethoxide reactions. Our original purpose was to compare CH_3O^- and $C_2H_5S^-$ as to their effectiveness in bringing about E2 elimination

(1) Financial support by the Petroleum Research Fund of the American Chemical Society is gratefully acknowledged.

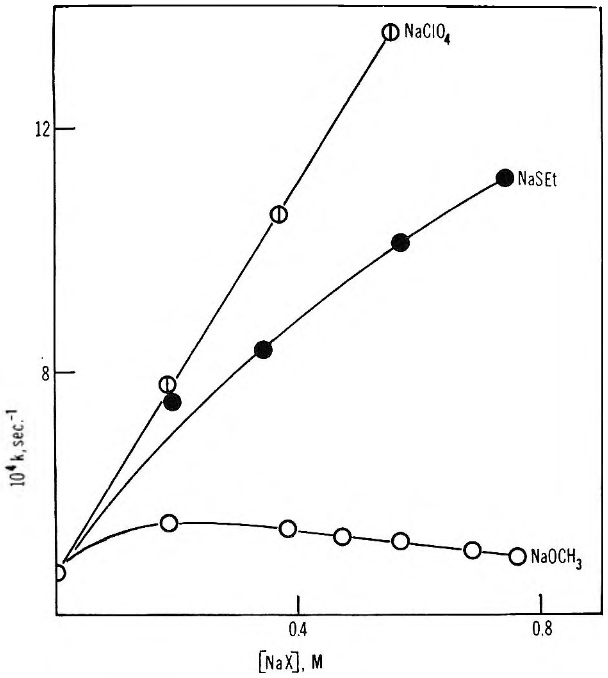


Figure 1.—Pseudo-first-order rate coefficients for reaction of 2-chloro-2,3,3-trimethylbutane (**1a**) with various sodium salts at several concentrations in methanol at 69.9°: open circles, solvolysis or $NaOCH_3$; filled circles, $NaSC_2H_5$; barred circles, $NaClO_4$.

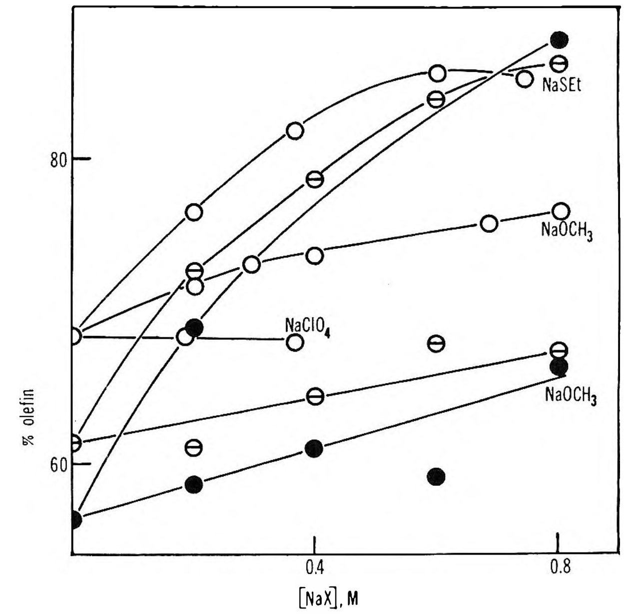


Figure 2.—Per cent of olefin **2** formed from **1a**, **1b**, and **1c** in solvolysis and in reaction with $NaOCH_3$ or $NaSC_2H_5$, and from solvolysis of **1a** in the presence of $NaClO_4$: open circles, chloride **1a**; barred circles, bromide **1b**; filled circles, iodide **1c**. The sodium salts involved are designated at the right.

to **2**, but the data turn out to be only marginally useful for that purpose.

All reactions were conducted with the base in large excess over the substrate, and clean pseudo-first-order kinetics were observed. In solvolysis reaction mixtures, 2,6-lutidine was included to neutralize the hydrogen halide by-product; both in a previous study[2] and in the present work it was shown that the inclusion of 2,6-lutidine affects neither rates nor product compositions. Rates were followed by argentimetric titration of halide ion. Products were determined by glpc. There was no evidence for any product other than **2** and **3**, and the absolute yields of **2** and **3** when occasionally checked against an internal standard totaled 100%.

In Figure 1, many of our kinetic data are displayed. It is noteworthy that $NaOCH_3$ had but a modest effect on overall reaction rate: a slight increase up to about 0.2 *M* $NaOCH_3$, and then a gentle and nearly linear *decrease*. The kinetic effect of the mercaptide base was considerably greater; 0.75 *M* $NaSC_2H_5$ caused the rate to more than double.[3] The kinetic response shows a gentle downward curvature. Sodium perchlorate had the strongest kinetic effect; 0.55 *M* $NaClO_4$ caused an approximate tripling of solvolysis rate, the response being strictly linear.

The effects of these sodium salts on the product composition from all three alkyl halides (**1a**, **1b**, and **1c**) are shown, as per cent olefin (**2**), in Figure 2.

Further sets of experiments involved constant concentrations of either $NaOCH_3$ or $NaSC_2H_5$ and variable concentrations of $NaClO_4$, with determination both of rates and product compositions. Results are set forth in Table I.

Table I

Reactions of 2-Chloro-2,3,3-trimethylbutane (1a) with $NaOCH_3$ or $NaSC_2H_5$ in the Presence of $NaClO_4$ in Methanol at 69.9°

Base	[Base],[a] M	[$NaClO_4$],[a] M	10^4k_ψ, sec^{-1}	Yields, % 2	3
$NaOCH_3$	0.802		(4.93)[b]	76.6	23.4
	0.802	0.184	6.69	75.8	24.2
	0.802	0.368	7.94	74.8	25.2
	0.802	0.552	10.37	73.7	26.3
	0.802	0.736		72.9	27.1
$NaSC_2H_5$	0.368[c]		(8.58)[b]	81.8	18.2
	0.368[c]	0.184	11.10	80.1	19.9
	0.368[c]	0.368	13.98	78.4	21.6
	0.368[c]	0.552	16.36	77.1	22.9
	0.368[c]	0.736		75.8	24.2

[a] Concentrations are corrected for solvent expansion. [b] Interpolated or extrapolated in Figure 1. [c] C_2H_5SH, 0.184 *M*, also present.

Discussion

A leaving group effect on solvolysis products is evident in Figure 2: the more basic the leaving group, the greater the fraction of olefin that is formed. This is a further example of an effect noted by Cocivera and Winstein.[4] It is attributed to reaction within the initial intimate ion pair; the anion, if basic, can take a proton from the carbonium ion, forming some olefin before the two ions become separated by solvent.

Although $NaClO_4$ greatly affects solvolysis rate, it does not affect the product ratio (see Figure 2). This was also observed in a previous study involving benzyldimethylcarbinyl chloride.[2] This implies that the kinetic effect of $NaClO_4$ does not involve either transformation of R^+Cl^- to $R^+ClO_4^-$ intimate ion pairs or alteration of the extents to which products are

(2) J. F. Bunnett, G. T. Davis, and H. Tanida, *J. Amer. Chem. Soc.*, **84**, 1606 (1962).

(3) Ethanethiol, usually at about half the concentration of $NaSC_2H_5$, was present in all reactions involving the mercaptide base.

(4) M. Cocivera and S. Winstein, *J. Amer. Chem. Soc.*, **85**, 1702 (1963).

formed from R^+Cl^- intimate ion pairs and from solvent-separated ions. This implication is based on assumptions that the proportions of products **2** and **3** from R^+X^- intimate ion pairs would differ when X^- was chloride or perchlorate, just as they do when X^- is chloride, bromide, or iodide, and that the product proportions from R^+Cl^- intimate ion pairs and from solvent-separated ions would differ. It therefore seems necessary to assign $NaClO_4$ the role of accelerating, through a salt effect, the initial ionization to intimate ion pairs.

We have sought to fit our data to various conceptual models for this system, but we have been unable to find a model which gives a satisfactory quantitative account of both the kinetic and product data. One model that was tried was a combination of E1–SN1 solvolysis, subject to linear acceleration or deceleration by the various salts present, and an E2 component not subject to salt effects. Another was similar, except that it allowed for the possibility that a negative salt effect by $NaOCH_3$ might be superimposed on a positive salt effect by $NaClO_4$. As discussed in Part B, neither of these models was satisfactory.

No doubt it would be possible to fit our data to a model having a large number of adjustable parameters. Conceivably the chemical situation requires such a complex model. We have not pursued this approach because of the difficulty of verifying such a model, even if it does accommodate the data.

The possibility that there is no E2 component in these systems has been considered, and is disfavored for reasons we shall now discuss. In this model, products would be formed exclusively from ion pair or free carbonium ion intermediates. The model is disfavored on considerations of analogy, and because of the fact that olefin yield in the presence of $NaOCH_3$ or $NaSC_2H_5$ depends on $NaClO_4$ concentration (Table I).

In the analogous system of benzyldimethylcarbinyl chlorides, both hydrogen isotope effects[2] and Hammett ρ parameters[5] call for an E2 component.[6] Qualitatively, many phenomena in that system resemble observations made in the present study. An E2 component is therefore probable in the present system.

Inasmuch as $NaClO_4$ is judged not to affect the relative amounts of product formation from intimate ion pairs and from free ions in the absence of $NaOCH_3$ and $NaSC_2H_5$, it is unlikely to affect the relative amounts of olefin and ether formed from intimate ion pairs or free ions in the presence of these bases. Therefore, without an E2 component, the yield of olefin in the presence of $NaOCH_3$ or $NaSC_2H_5$ should not depend on the concentration of $NaClO_4$. However, the yield of olefin does depend on $NaClO_4$ concentration, both in 0.8 *M* $NaOCH_3$ and in 0.37 *M* $NaSC_2H_5$ (Table I). It follows that the reaction involves an E2 component.

Experimental support for this reasoning is provided by a recent study of the reaction of 2,2,2-triphenylethyl tosylate with $NaOCH_3$-CH_3OH, which forms 1,1,2-triphenylethene and 1,1,2-triphenylethyl methyl ether; the product ratio with 0.85 *M* $NaOCH_3$ is unaffected by $NaClO_4$ in concentrations as high as 0.6 *M*.[7] Both products have rearranged carbon skeletons, and it is unlikely that recombination of tosylate ion with the 1,1,2-triphenylethyl cation occurred after rearrangement. There was almost certainly no E2 component; the lack of effect of $NaClO_4$ on products supports our reasoning above.

On the other hand, $NaClO_4$ does affect the ratio of camphene to camphene hydrate methyl ether from reaction of isobornyl chloride or camphene hydrochloride with $NaOCH_3$ in CH_3OH.[8] Here also an E2 component is unlikely. Therefore our conclusion that the reactions of **1a** with $NaOCH_3$ and $NaSC_2H_5$ involve an E2 component can only be advanced with some qualification.

Part B

Experimental Section

Materials. 2-Chloro-2,3,3-trimethylbutane (1a), from Aldrich Chemical Co., was purified by the method of Calingaert, *et al.*[9] The corresponding bromide (**1b**) and iodide (**1c**) were made by reaction of 2,3,3-trimethyl-2-butanol[9] with aqueous HBr and HI, respectively. All three halides had physical properties in agreement with those recorded in the literature;[9–11] for each, the nmr spectrum comprised the expected two singlets, in relative areas 3:2. **2,3,3-Trimethyl-1-butene (2)** was obtained by sulfuric acid catalyzed dehydration of 2,3,3-trimethyl-2-butanol; its boiling point (78°) is consistent with the literature;[12] its purity was >99% as judged by glpc; δ^{CCl_4} 1.05 (s, 9) *tert*-C_4H_9, 1.70–1.73 (m, 3) CH_3, 4.53–4.68 (m, 2) vinyl CH_2.

Methyl 2,3,3-Trimethyl-2-butyl Ether (3).—To a stirred suspension of 0.12 g (0.06 mol) of NaH in 10 ml of dimethyl sulfoxide (DMSO) was added dropwise a solution of 3.48 g (0.03 mol) of 2,3,3-trimethyl-2-butanol in 15 ml of DMSO. The mixture was stirred overnight at 40–50°, a solution of 5.68 g (0.04 mol) of CH_3I in 10 ml of DMSO was added, and stirring was continued for 24 hr. Pentane (20 ml) and water (20 ml) were added, and a yellow liquid (2.86 g, 73%) was isolated by standard procedures. The product was purified by glpc on a column of 15% Carbowax on Chromosorb W operated at 75°. **3** was obtained as a colorless solid: mp 26.5–27°; δ^{CCl_4} 3.13 (s, 3) OCH_3, 1.05 (s, 6) CH_3, 0.90 (s, 9) *tert*-C_4H_9.

Anal. Calcd for $C_8H_{18}O$: C, 73.78; H, 13.93. Found:[13] C, 73.95; H, 13.95.

Rate Measurements.—Reaction solutions were 0.02 to 0.04 *M* in alkyl halide, arranged so that the base was always in at least tenfold excess. Solutions were prepared as previously described,[2] except that for $NaSC_2H_5$ runs neat ethanethiol was used, being measured by pipet. In $NaSC_2H_5$ runs, free ethanethiol was always present, from 1.5 to 2.0 equiv of C_2H_5SH being used per equivalent of $NaOCH_3$. In solvolysis runs, excess 2,6-lutidine was always present to neutralize the hydrogen chloride formed. Aliquots (5.0 ml) of the reaction solution were sealed in glass ampoules which had been flushed with nitrogen before sealing.

For $NaOCH_3$ and solvolysis runs, the contents of the chilled ampoules were poured into 30 ml of hexane, to which 5 ml of 15% nitric acid and 40 ml of water were then added. After stirring, potentiometric titration with standard $AgNO_3$ solution was carried out directly. For $NaSC_2H_5$ runs, the contents of the chilled ampoules were poured into 10 ml of hexane in a separatory funnel, 20 ml of water was added, the aqueous phase was separated and washed with 10 ml of diethyl ether, 1 ml each of concentrated nitric acid and of 30% hydrogen peroxide were added, the solutions were allowed to stand overnight, and they were

(5) L. F. Blackwell, A. Fischer, and J. Vaughan, *J. Chem. Soc. B*, 1084 (1967).

(6) J. F. Bunnett, *Surv. Prog. Chem.*, **5**, 61 (1969).

(7) D. L. Eck, unpublished work at Washington State University.

(8) C. A. Bunton, T. W. Del Pesco, A. M. Dunlop, and K.-U. Yang, *J. Org. Chem.*, **36**, 887 (1971).

(9) G. Calingaert, H. Soroos, V. Hnizda, and H. Shapiro, *J. Amer. Chem. Soc.*, **66**, 1389 (1944).

(10) H. C. Brown and A. Stern, *ibid.*, **72**, 5068 (1950).

(11) Butlerow, *Justus Liebigs Ann. Chem.*, **177**, 184 (1875); Beilstein, **I**, 159.

(12) J. Timmermans, "Physico-Chemical Constants of Pure Organic Compounds," Elsevier, Amsterdam, Netherlands, 1950, p 133.

(13) Analysis was by Micro-Tech Laboratories, Skokie, Ill.

then titrated with standard $AgNO_3$ solution. Plots of ln ($V_\infty - V_t$) *vs.* time were linear and the negatives of their slopes, obtained by linear regression analysis, were taken as pseudo-first-order rate coefficients (k_ψ).

Product Analysis.—Reaction solutions prepared as for kinetics were sealed in ampoules which were kept in the thermostat for at least 10 half-lives. The ampoules were cooled and the contents poured into 15 ml of chlorobenzene. The organic phase was extracted with water (one 25-ml and two 10-ml portions), the organic phase was dried over anhydrous Na_2SO_4 (for $NaOCH_3$ and solvolysis runs) or over KOH (for $NaSC_2H_5$ runs), and portions were analyzed by glpc. An Aerograph Model 204 apparatus was used, with a 91-cm column of 5% SE-30 silicone rubber and 5% Bentone 34 clay on Chromosorb P, operated at a temperature of 55°. Molar responses were determined *vs.* benzene as internal standard. Samples taken at various time intervals showed no variation of product composition with time; the products are thus stable under the reaction conditions. The reaction temperature for both kinetic and product studies was 69.9° unless otherwise stated.

Because **1b** and **1c** are more reactive than **1a**, it was probable that appreciable reaction occurred at room temperature during preparation and sealing in ampoules of reaction solutions. In a few experiments, the technique was altered so as to effect mixing at 69.9°, but the product proportions observed were substantially the same as by the usual technique.

Results

In addition to results presented in Part A, we set forth in Table II kinetic data concerning the reaction

TABLE II
REACTION OF 2-IODO-2,3,3-TRIMETHYLBUTANE (1c) WITH $NaOCH_3$ IN METHANOL AT 25.0°

$[NaOCH_3]$, *M*	10^4k_ψ, sec^{-1}
Nil[a]	8.54
0.108	8.40
0.216	8.20
0.432	7.29
0.810	6.89

[a] 2,6-Lutidine present.

of iodide **1c** with $NaOCH_3$ in CH_3OH at 25.0°. It is to be noted that the rate coefficient *drops* continuously; the drop is somewhat steeper at higher $NaOCH_3$ concentrations.

Discussion

We first examine two models to which we tried to fit our data, and then discuss the relevance of the data to some other problems.

The Simple Model of E1–SN1 Solvolysis Plus E2.—The essential feature of this model is that it provides for independent E1–SN1 and E2 components of reaction, according to eq 1, in which k_S^* pertains to

$$k_\psi = k_S^* + k_E[B] \quad (1)$$

solvolysis and k_E to the E2 component. The effect of salts on k_S^* is not specified, except that the effects of two or more salts be additive. Whether or not anionic bases affect the proportions of olefin and ether formed from the carbonium ion intermediate is also not specified. A model of this type gave an excellent account of the $NaSC_2H_5$ data in an analogous study involving benzyldimethylcarbinyl chloride and a fair account of the $NaOCH_3$ data.[2]

This model calls for the kinetic effects of $NaClO_4$ and $NaOCH_3$, or of $NaClO_4$ and $NaSC_2H_5$, admixed, to be additive. Experimentally, however, they are less than additive. This is shown in Table III. Clearly models of this type are not serviceable.

TABLE III

	10^4k_ψ, sec^{-1}	10^4k_ψ, sec^{-1}
0.552 *M* $NaClO_4$	13.6	13.6
0.802 *M* $NaOCH_3$	4.9	
0.368 *M* $NaSC_2H_5$		8.6
Sums	18.5	22.2
Actual for mixtures (Table I)	10.4	16.4

A Model of E1–SN1 Plus E2, with Anionic Bases Allowed to Have Negative Salt Effects.—Figure 1 and studies by Bunton and coworkers[8,14] indicate that $NaOCH_3$ may have a negative salt effect on solvolysis rates in methanol. This suggests the possibility that a negative salt effect by $NaOCH_3$ might be superimposed on a positive salt effect by $NaClO_4$ according to eq 2,

$$k_\psi = k_S(1 + b[NaClO_4])(1 - m[NaOCH_3]) + k_E[NaOCH_3] \quad (2)$$

in which k_S is the rate coefficient for solvolysis in the absence of salts, k_E is the E2 coefficient, and b and m are salt effect parameters.[15] Apart from the fact that a model of this sort cannot account for the rate maximum for $NaOCH_3$ in Figure 1 or the curvature for $NaSC_2H_5$, it leads to inconsistent estimates of k_E from reactions at various $NaClO_4$ concentrations.

Relevance to the Scheme of Sneen and Robbins.—Our results are reason for caution in accepting the mechanistic conclusions of Sneen and Robbins,[16] who aver that E2 and SN2 reactions of α-phenylethyl bromide proceed *via* a common intermediate, an ion pair. A principal element of support for their interpretation was their finding that the apparent second-order rate coefficient for reaction with $NaOC_2H_5$ in ethanol diminishes in relative magnitude from 1.0 at 0.1 *M* $NaOC_2H_5$ to 0.4 at 1.1 *M* $NaOC_2H_5$. They assumed that "normal salt effects" are minimal at the levels of $NaOC_2H_5$ concentration used in their investigation. The present work suggests that *abnormal* salt effects may also need to be taken into account.

If one sought to fit the present cases to the interpretation of Sneen and Robbins, he might take the downward slope of the $NaSC_2H_5$ plot in Figure 1 as evidence of approach to a rate plateau at which rate would be limited by the rate of ionization of **1a**. The curved plot for $NaOCH_3$ might be given a similar interpretation, the approach to a rate plateau being thought to be superimposed on a slight overall negative salt effect. However, rate plateaus at different heights would need to be assigned to the two plots, but that is inconsistent if both plateaus pertain to the same ionization process.

$NaSC_2H_5$ *vs.* $NaOCH_3$ as Elimination-Inducing Reagents.—As discussed in Part A, the drop in the fraction of olefin **2** in the product mixture caused by addition of $NaClO_4$ to reaction mixtures 0.802 *M* in $NaOCH_3$ or 0.368 *M* in $NaSC_2H_5$ (Table I) suggests a substantial E2 component. It remains to consider

(14) P. Beltrame, C. A. Bunton, A. Dunlop, and D. Whittaker, *J. Chem. Soc.*, 658 (1964).

(15) A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 2763 (1956).

(16) R. A. Sneen and H. M. Robbins, *ibid.*, **91**, 3100 (1969).

why the plot in Figure 1 for the mercaptide base is so much steeper than for the alkoxide base. Is it because the E2 rate coefficient for the sulfur base is very much greater? Or is it because $NaSC_2H_5$ has a very favorable salt effect on ionization, whereas $NaOCH_3$ has a rather unfavorable one? We do not feel that a firm decision can be made because of the unsatisfactoriness of the various models. On the whole, however, it appears that the data are better explained in terms of a distinctly higher E2 rate coefficient for the sulfur base. Thus, the rate of change of olefin fraction in Table I is greater for $NaSC_2H_5$ than for $NaOCH_3$, and the former is less than half the concentration of the latter.

If this judgment is correct, it is noteworthy that the higher E2 reactivity of $C_2H_5S^-$ than of CH_3O^- persists even when the substrate is highly hindered about C_α; the carbon to which chlorine is attached in **1a** is both tertiary and neopentylic. Such an outcome is not compatible with the "E2C" mechanism which has been proposed by other workers for certain eliminations induced by reagents of relatively low basicity.[17] We have earlier reported that **1b** undergoes E2 elimination with chloride ion in acetone or dioxane faster than with its less hindered analog, *tert*-butyl bromide,[18] and we have made similar observations with respect to secondary alkyl halides and tosylates.[19] These studies provide no support for the E2C mechanism. Reasons for the surprisingly high E2 reactivity of mercaptide ions in certain eliminations have been discussed elsewhere.[6]

Registry No.—**1a,** 918-07-0; **1b,** 16468-75-0; **1c,** 27705-19-7; **2,** 594-56-9; **3,** 27705-21-1.

(17) A. J. Parker, M. Ruane, G. Biale, and S. Winstein, *Tetrahedron Lett.*, 2113 (1968); G. Biale, A. J. Parker, S. G. Smith, I. D. R. Stevens, and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 115 (1970).
(18) D. Eck and J. F. Bunnett, *ibid.*, **91**, 3099 (1969).
(19) J. F. Bunnett and D. L. Eck, unpublished observations.

Reactions of Bicyclo[2.1.0]pentane and Bicyclo[4.1.0]heptane with Hydrogen Chloride. Cleavage of Cyclopropane Rings[1a]

ROBERT S. BOIKESS*[1b] AND MARY MACKAY[1c]

Department of Chemistry, Douglass College, Rutgers—The State University, New Brunswick, New Jersey 08903, and Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11790

Received August 17, 1970

The products of the reaction of bicyclo[2.1.0]pentane (I) and bicyclo[4.1.0]heptane (II) with HCl in the vapor phase and with concentrated hydrochloric acid in a two-phase system have been studied. In the case of I, both cyclopentene and cyclopentyl chloride were obtained. In the case of II, nonthermodynamic mixtures of six-membered and seven-membered olefins and chlorides were obtained. It is proposed that the olefins arise primarily *via* quasiheterolytic six-membered cyclic transition states and that the chlorides arise *via* pathways of somewhat greater heterolytic character. Relief of strain in the ground state and nonbonded interactions and strain in the transition state are invoked to explain the relative amounts of internal and external cleavage of the three-membered ring as well as product distributions.

In connection with our work on the chlorination of bicyclo[*n*.1.0]alkanes,[1c,2] we have also investigated the reaction of hydrogen chloride with bicyclo[2.1.0]pentane (I) and bicyclo[4.1.0]heptane (II). We wish to report our results since they are divergent from previously reported ones in at least one important respect, and since they serve to further elucidate the behavior of cyclopropanes in ring-opening reactions.

Cleavages of cyclopropyl compounds by acids or other electrophiles have been extensively studied.[3-9] Where rationales have been advanced,[4,6a] the course of the reaction has been discussed in terms of polarization of the three-membered ring by the incoming electrophile. More recently[9] anti-Markovnikov ring opening of the cyclopropane in a tricyclo[3.2.2.0^{2,4}]nonyl system has been interpreted in terms of steric inhibition to normal collapse of a protonated cyclopropyl intermediate.

We have studied the reactions of I and II with HCl under conditions which are not conducive to normal ionic modes of reaction. Nevertheless, the results parallel those obtained under more ionic conditions[4] in many ways.

Results

Reaction between HCl and bicyclo[2.1.0]pentane (I) and bicyclo[4.1.0]heptane (II) was brought about in several ways. In one approach, HCl vapor was added slowly to an excess of refluxing hydrocarbon and the two vapors were mixed, under anhydrous conditions, in a glass reaction chamber heated by sun lamps. These reactions were performed in a modification[1c] of a vapor phase chlorination apparatus designed by Roberts and Mazur.[10] In another approach, equimolar amounts of 12 *M* hydrochloric acid and I at 10° or II at 25° were shaken vigorously for 6 hr. In addition II was reacted with a twofold excess of anhydrous HCl in a glass ampoule, filled on a vacuum line, sealed, and heated

(1) (a) This research was supported in part by a grant from The Research Council of Rutgers University and by AFOSR (SRC) OAR, USAF, Grant No. 837-67. (b) To whom correspondence should be addressed at Douglass College, New Brunswick, N. J. (c) Abstracted, in part, from the thesis of M. M. submitted in partial fulfillment of the requirements for the M.S. Degree, State University of New York at Stony Brook, 1966.
(2) (a) R. Boikess and M. Mackay, *Tetrahedron Lett.*, 5991 (1968); (b) R. Boikess and M. Mackay, unpublished results.
(3) (a) C. J. Collins, *Chem. Rev.*, **69**, 543 (1969); (b) E. E. Royals, "Advanced Organic Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1954, pp 210–218.
(4) R. T. LaLonde and L. S. Forney, *J. Amer. Chem. Soc.*, **85**, 3767 (1963).
(5) (a) R. T. LaLonde, J. Ping, and M. A. Tobias, *ibid.*, **89**, 6651 (1967), and earlier papers; (b) A. C. Cope and G. L. Woo, *ibid.*, **85**, 3601 (1963).
(6) (a) R. J. Ouellette, A. South, Jr., and D. L. Shaw, *ibid.*, **87**, 2602 (1965); (b) S. Moon, *J. Org. Chem.*, **29**, 3456 (1964).
(7) R. Criegee and A. Rimmelin, *Chem. Ber.*, **90**, 414 (1957).
(8) R. C. Cookson, D. P. G. Hamon, and J. Hudec, *J. Chem. Soc.*, 5782 (1963).
(9) J. B. Hendrickson and R. K. Boeckman, Jr., *J. Amer. Chem. Soc.*, **91**, 3269 (1969).
(10) J. D. Roberts and R. H. Mazur, *ibid.*, **73**, 2509, (1957).

TABLE I

PER CENT DISTRIBUTION OF OLEFIN PRODUCTS FROM HYDROCHLORINATION REACTIONS

Reaction	Reactants	Reaction, %	Olefin, %	Cyclopentene	1-Methyl-cyclohexene	3-Methyl-cyclohexene	Cyclo-heptene
A	HCl (g) + I	98	40	100			
B	HCl (12 *M*) + I	86	46	100			
C	HCl (g) + II	68	21		3.8	90	6.6
C	HCl (g) + II[a]	87	13		3.7	90	6.7
D	HCl (12 *M*) + II	87	24[b]		5.3	87	7.7
E	HCl (g) + II (sealed tube)	99	39		5.4	85	9.3

[a] Same reaction run in the dark. [b] An additional component here is toluene which accounts for 13% of the olefin fraction. The relative percentages of the three olefins are calculated after toluene is subtracted out and represent 87% of the olefin fraction.

at 160° for 24 hr. In all cases the reaction mixtures were worked up in standard ways and analyzed by vapor phase chromatography.

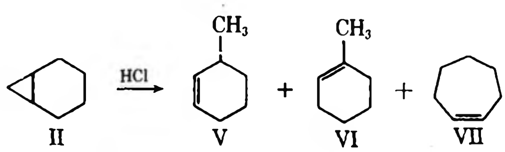
All the products obtained were known compounds, and identifications were made by comparisons of vpc retention times, infrared spectra, and nmr spectra with those of independently synthesized authentic compounds. Control experiments, using cycloheptyl chloride as an internal standard, showed that 99% of the products were accounted for by the vpc analyses. The products do not react or react much more slowly with HCl under the reaction conditions and survive unchanged through the work-up procedure. Both I and II could be recovered unchanged when subjected to the reaction conditions in the absence of HCl. Neither the starting materials nor the products decomposed under the vpc conditions.

Under both sets of conditions, bicyclo[2.1.0]pentane (I) yielded approximately equal amounts of cyclopentene (III) and cyclopentyl chloride (IV) in contrast to

I III IV

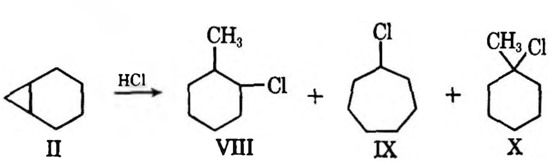
the report[4] that only cyclopentyl acetate was obtained on treating I with *p*-toluenesulfonic acid in acetic acid.

Similarly, under all three sets of conditions bicyclo[4.1.0]heptane (II) yielded both olefin products and chloride products. The same products were obtained in all cases with the exception that a small amount of toluene was formed when conditions were not anhydrous. The fraction of olefin in the total product varied but in all cases consisted of a major product, 3-methylcyclohexene (V), and two minor products, 1-methylcyclohexene (VI) and cycloheptene (VII). The chloride



II V VI VII

fraction consisted in all cases of three compounds, which were, in order of relative abundance, *trans*-2-methylcyclohexyl chloride (VIII), the major product, cycloheptyl chloride (IX), and 1-methylcyclohexyl chloride (X).



II VIII IX X

The relative percentages of the products are summarized in Tables I and II.

TABLE II

PER CENT DISTRIBUTION OF CHLORIDE PRODUCTS FROM HYDROCHLORINATION REACTIONS

Reaction	Chloride, %	Cyclopentyl chloride	*trans*-2-Methyl-cyclohexyl chloride	1-Methyl-cyclohexyl chloride	Cyclo-heptyl chloride
A	60	100			
B	54	100			
C	79		63	15	22
C	87		55	15	30
D	76		72	7	21
E	61		62	15	23

Discussion

The conditions of the vapor phase reaction (slow addition of HCl to maintain an excess of hydrocarbon, absence of a proton source, and relatively low temperatures[11]) support an explanation for the course of the reaction in terms of quasiheterolytic processes involving only one molecule of HCl. The fact that the same products, in similar proportions, are obtained from the two-phase reactions with hydrochloric acid is not totally unexpected given the negligible solubility of hydrocarbons in water and the small solubility[12] of HCl in hydrocarbons. The formation of a small amount of toluene is puzzling but may be due to some ionic interfacial side reaction.

In contrast with our observation of almost equal amounts of cyclopentene (III) and cyclopentyl chloride (IV) from the reaction of HCl and I, Criegee and Rimmelin[7] reported only cyclopentyl bromide from treatment of I with hydrobromic acid, and LaLonde and Forney[4] reported only cyclopentyl acetate from treatment of I with *p*-toluenesulfonic acid in acetic acid. One possible explanation for this discrepancy is a changeover in mechanism under nonionic conditions. We postulate a six-membered cyclic transition state similar to those postulated for the HCl-catalyzed gas phase decompositions of 1,1-dimethylcyclopropane[13] and a variety of oxygenated compounds.[14] This transi-

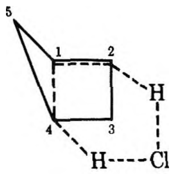
(11) The reaction temperatures must be close to the boiling point of I, 45°, and the boiling point of II, 116°.

(12) R. P. Bell, *J. Chem. Soc.*, 1371 (1931).

(13) J. Bullivant, J. S. Shapiro, and E. S. Swinbourne, *J. Amer. Chem. Soc.*, **91**, 7703 (1969).

(14) D. A. Kairaitis and V. R. Stimson, *Aust. J. Chem.*, **21**, 1711 (1968), and earlier papers.

tion state must have some heterolytic character[15,16] but can be represented as the extreme form, XI. Although



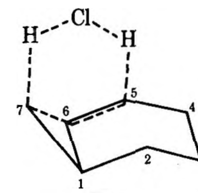
XI

the hydrogen of the HCl is drawn as attacking a corner of the three-membered ring in XI and other related transition states, *vide infra*, this need not be required. Consistent with the well-known formation of bridged protonated cyclopropane intermediates,[3a] it is possible to conceive that the initial overlap between the partially bound hydrogen of HCl and the three-membered ring is along an edge. Its exact location would be determined by the balance between better overlap, nonbonded repulsions, and angle strain in the transition state. An alternative cyclic transition state is possible involving removal of H-5, but we prefer XI on steric grounds.

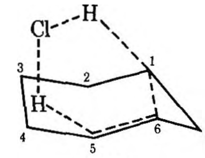
Cyclopentyl chloride (IV) can be envisaged to form by two possible pathways: a four-center concerted 1,3 addition of HCl across the very strained central bond or 1,2 addition of HCl between C-1 and C-5 with a simultaneous hydride shift from C-5 to C-4. Although both types of processes seem reasonable, the former possibility seems preferable for I since it leads to greater relief of strain in the transition state and requires less drastic reorganizations.

The absence of any methyl cyclobutyl products is consistent with previous work[4,7] as well as with the tremendous relief of strain which occurs on cleavage of the very weak[17] bond between C-1 and C-4.

As has been previously observed,[4] but not fully accounted for, the addition of electrophiles to bicyclo[4.1.0]heptane (II) leads to a distribution of olefin products which does not reflect their relative thermodynamic stabilities. Under our conditions this discrepancy is even more pronounced. From available thermodynamic data,[18] it is possible to calculate approximate heats of formation for 3-methylcyclohexene (V), 1-methylcyclohexene (VI), and cycloheptene (VII) which are −9.6 kcal/mol, −11.6 kcal/mol, and −5.2 kcal/mol, respectively. Although the preponderance of six-membered olefins, from external cleavage, over seven-membered olefin, from internal cleavage, is expected on the basis of relative stabilities and favorable statistics, we believe, as have previous workers,[4] that this is to a large extent fortuitous. However, rather than rationalizing the relative amounts of internal and external cleavage by an argument involving the most favorable direction for polarization of a three-membered ring by a perturbing electrophile,[4,6a] we suggest that, at least under the present conditions, simple steric arguments serve to account for not only the relative amounts of internal and external cleavage but also the preponderance of V, the less stable six-membered olefin, in the products. Reasonable quasiheterolytic cyclic six-membered transition states which lead to V and VII can be visualized and are represented in one extreme form as XII and XIII, respectively.



XII



XIII

It can be readily seen that XII, which leads to the major product, is the less strained transition state, since the attacking HCl lies near the edge of the cyclohexane ring, thus minimizing nonbonded repulsions with hydrogens on C-2, C-3, and C-4, while at the same time the HCl easily spans the distance between C-7 and the hydrogen to be eliminated at C-5. On the other hand in XIII, which leads to cycloheptene (VII) by internal cleavage, the HCl must lie across the face of the cyclohexane ring leading to more serious interactions with hydrogens on C-2, C-3, and C-4, although here too the HCl easily spans the distance between C-2 and the hydrogen to be eliminated at C-5. It is not easy to visualize the formation of VI, the most stable and least abundant olefin, through a similar process since no reasonable cyclic transition state of the type shown above can be formulated which leads to this olefin. A six-center transition state leading to this product would involve a solid bridge between C-7 and C-1, making it unlikely. More reasonably, formation of VI occurs through a competing process of greater heterolytic character[19] rather than through direct collapse of a cyclic transition state. This hypothesis leads to the expectation that under more ionic conditions greater amounts of VI relative to VII should be formed. It has been found that in acetic acid the relative amounts of VI and VII are reversed, more than twice as much of the former being formed than the latter.[4]

The composition of the mixture of chlorides is also somewhat unexpected. The preponderance of external over internal opening is not surprising, but here greater than 20% of the product comes from internal opening compared to less than 8% in the olefins. In addition, the relative amount of 1-methylcyclohexyl derivative has increased by a factor of between three and four. This suggests that the formation of the chlorides is less sterically controlled and proceeds by way of processes with more heterolytic character than those which lead to olefins. Formation of 1-methylcyclohexyl chloride (X) which formally requires a hydride shift is not anomalous; such shifts have been observed in quasiheterolytic reactions.[15b]

(15) (a) C. J. Harding, A. G. Loudon, A. Maccoll, P. G. Rodgers, R. A. Ross, S. K. Wong, J. S. Shapiro, E. S. Swinbourne, V. R. Stimson, and P. J. Thomas, *Chem. Commun.*, 1187 (1967); (b) A. Maccoll in, "Advances in Physical Organic Chemistry," Vol. 3, V. Gold, Ed., Academic Press, New York, N. Y., 1965.

(16) S. W. Benson and A. N. Bose, *J. Chem. Phys.*, **39**, 3463 (1963).

(17) M. L. Halberstadt and J. P. Chesick, *J. Amer. Chem. Soc.*, **84**, 2688 (1962).

(18) (a) American Petroleum Institute, "Tables of Thermodynamic Properties," Project 44, Carnegie Institute of Technology, 1952; (b) J. Coops, H. Van Kamp, W. A. Lambgrets, B. J. Visser, and H. Dekker, *Recl. Trav. Chim. Pays-Bas*, **79**, 1226 (1960); (c) R. B. Turner in "Kekule Symposium on Theoretical Organic Chemistry," Butterworths, London, 1959, p 67.

(19) Similarities between quasiheterolytic gas phase reactions and normal ionic processes in solution are well known.[15b]

The stereospecificity of the addition to give the trans isomer VIII as the only 1,2-disubstituted cyclohexyl product has also been noted under ionic conditions[4] and has been rationalized by comparison to the well-known preference for diaxial opening in epoxides.[20] However more recent work[8] indicates that cyclopropanes do not seem to have this same preference for diaxial opening, and the explanation must lie elsewhere. Inspection of models of a bicyclo[4.1.0]heptane in its preferred[21] half-chair conformation suggests that concerted attack of HCl, concurrent with conformational changes from the half-chair toward a chair, should lead to trans addition of HCl, although the argument is not overwhelming. Since the timing and extent of electrophile addition, bond breaking, and nucleophile addition in such a process is not understood, it is difficult to make convincing arguments to explain the stereospecificity.

Experimental Section

Analytical and preparative vapor phase chromatography were carried out on an Aerograph A-90P fitted with 0.25 in. × 2 m columns. All infrared spectra were obtained on a Perkin-Elmer Model 21 spectrometer using a microcavity cell filled with neat liquids. Proton nmr spectra were recorded on a Varian Model A-60 spectrometer. The samples were either neat liquids or 20 vol % solutions in CCl_4. Tetramethylsilane was used as the internal standard. All the products obtained were known compounds and identifications were made by comparison of vpc retention times, infrared spectra, and nmr spectra with those of independently synthesized compounds.

Vapor Phase Hydrochlorinations. A. Bicyclo[2.1.0]pentane. Reaction A.—The reaction assembly was a modification[1c] of that of Roberts and Mazur.[13] A one-piece all-Pyrex apparatus consisted of a 50-ml round-bottom boiler fitted with a magnetic stirring bar, a rubber septum for withdrawing samples, and an inlet assembly fitted with two stopcocks for introducing the hydrocarbon. To the boiler was attached a vertical 4-in. Vigreux column. Atop this column was a reaction chamber fitted with a thermometer inlet. A gas inlet tube led directly into this chamber, which consisted of a 50-ml round bulb surmounted by three Pyrex loops 2 in. in diameter. Above the reaction chamber was a fitting for a condenser, arranged in such a way that condensate bypassed the reaction chamber and returned directly to the boiler at the bottom. To this one-piece assembly was fitted a spiral Dry Ice–acetone condenser. The top of the condenser was connected to a 1-l. flask, vented through a barium oxide–silica gel drying tube. All of the reaction chamber and its connections, except the spiral and the Vigreux column, were covered with asbestos paper. Gases (HCl or N_2) introduced into the reaction chamber were first passed through a concentrated sulfuric acid drying tower, a Dry Ice–acetone cooled trap, and a calibrated gas flow meter, all connected by polyethylene tubing.

Before the reaction was begun, all glass surfaces were flamed for 30 min, while maintaining a slow stream of nitrogen through the system. The bicyclo[2.1.0]pentane (0.1 mol), prepared by the method of Cohen, *et al.*,[22] and free of cyclopentene, was placed in a flask containing calcium hydride and allowed to stand overnight. The flask was connected to the boiler and the hydrocarbon distilled directly into it through the inlet assembly. During this transfer the entire system was closed by placing a glass stopper in the drying tube. After the transfer the stopper was removed and the entire assembly swept for a few minutes with a stream of dried nitrogen. The glass spiral was heated by two aluminum foil covered Sylvania 275-W sun lamps placed at a distance of 5 cm from the spiral. The Vigreux column was heated to 48° with a heating tape, whose temperature was measured with a chromel–alumel thermocouple. The boiler was heated to 70° with an oil bath. The hydrocarbon boiled vigorously, filling the apparatus with vapors which were condensed by the Dry Ice–acetone condenser and recycled back to the boiler. Dry hydrogen chloride gas was added at a rate of roughly 2–4 cm^3/min. The reaction was stopped after 6.7 hr. The reaction mixture was poured into pyridine, washed with water and 5% sodium bicarbonate solution, and dried. Analysis was performed by vpc on a 20% squalane on a 60–40 mesh Chromosorb P column at 40° and on a 20% Apiezon L on a 60–80 mesh Chromosorb W column at 98°.

A small portion of the reaction mixture was mixed with an equal weight of cycloheptyl chloride as internal standard and analyzed by vpc under the same conditions. The calculated percentage of internal standard was within 0.0% of that measured. The products of the reaction were collected in the usual way in small test tubes fitted with side arms and compared with authentic samples. Reinjection of the collected products into the vapor phase chromatograph under the same conditions showed no detectable decomposition. When the reaction products were resubjected to the conditions of the work-up, they were recovered unchanged.

B. Bicyclo[4.1.0]heptane. Reaction C.—Following the above-described procedure, 5.8 g (0.06 mol) of bicyclo[4.1.0]-heptane, prepared by the method of Simmons and Smith[23] and free of olefins, was allowed to react with an average hydrogen chloride flow of roughly 5 cm^3/min for 3.7 hr. After work-up the reaction mixture was analyzed by vpc on a 20% Apiezon L on a 60–80 mesh Chromosorb W column at 98° and a 20% squalane on a 60–40 mesh Chromosorb P column at 60°.

A small portion of the reaction mixture was mixed with an equal weight of cycloheptyl chloride as internal standard and analyzed by vpc under the same conditions. The calculated percentage of internal standard was within 0.1% of that measured. The products of the reaction were collected as above and compared with authentic samples. Reinjection of the collected products into the vapor phase chromatograph under the same conditions showed no detectable decomposition.

In other runs the lights used to heat the reaction spiral were eliminated and the reaction was run in the dark. No significant change in products occurred.

Liquid Phase Hydrochlorinations. A. Bicyclo[2.1.0]pentane. Reaction B.—An equimolar mixture of I (1.1×10^{-2} mol) and 12 *M* hydrochloric acid was stirred for 1.5 hr at 10°. The organic layer was separated, worked up in the usual way, and analyzed by vpc, as above.

B. Bicyclo[4.1.0]heptane. Reaction D.—An equimolar mixture of II (0.1 mol) and 12 *M* hydrochloric acid was shaken for 6 hr at room temperature. The organic layer was separated, worked up in the usual way, and analyzed by vpc as above.

C.—Each of the product hydrocarbons was stirred with a large excess of 12 *M* hydrochloric acid for 24 hr. Analysis in the usual way showed that none of them showed greater than 5% decomposition.

Hydrochlorination in a Sealed Ampoule. Reaction E.—A 7-cm^3 ampoule covered with black tape was fitted to a vacuum line. It was filled with 1.22×10^{-3} mol of II and 2.30×10^{-3} mol of dry hydrogen chloride, sealed, and heated in an oven at 160° for 24 hr. At the end of this time the vial was cooled and opened, and the contents were poured into pyridine. The mixture was washed with water and 5% aqueous sodium bicarbonate solution, and the organic layer was separated, dried over anhydrous sodium sulfate, and analyzed by vpc as above.

Authentic Samples.—Samples of cyclopentene (III), $n^{20}D$ 1.4220, cycloheptene (VII), $n^{20}D$ 1.4565, and 3-methylcyclohexene (V), $n^{20}D$ 1.4438, were all obtained from Aldrich Chemical Co., and were used without further purification. A sample of 1-methylcyclohexene (VI), $n^{20}D$ 1.4506, was obtained from K and K Laboratories and used without further purification.

Cyclopentyl chloride (IV), $n^{20}D$ 1.4511, was prepared by refluxing cyclopentene with an excess of 12 *M* hydrochloric acid and an excess of calcium chloride for 20 hr. Purification was effected by distillation. Cycloheptyl chloride (IX), $n^{20}D$ 1.4752, was similarly prepared from cycloheptene and purified by distillation.

trans-2-Methylcyclohexyl chloride (VIII) was prepared from 2-methylcyclohexanol by the method of Botteron and Shulman.[24] Purification by preparative vpc on a 20% Apiezon L on a 60–80

(20) D. H. R. Barton in "Kekule Symposium on Theoretical Organic Chemistry," Butterworths, London, 1959, p 129.

(21) (a) W. G. Kumler, R. S. Boikess, P. Bruck, and S. Winstein, *J. Amer. Chem. Soc.*, **86**, 3126 (1964); (b) S. Winstein, R. S. Boikess, and J. I. Brauman, unpublished results.

(22) S. G. Cohen, R. Zand, and G. Steel, *J. Amer. Chem. Soc.*, **83**, 2895 (1961).

(23) R. O. Smith and H. E. Simmons, *Org. Syn.*, **41**, 72 (1961).

(24) D. G. Botteron and G. P. Shulman, *J. Org. Chem.*, **27**, 2007 (1962).

mesh Chromosorb W column yielded material, $n^{20}D$ 1.4584 (lit.[24] $n^{20}D$ 1.4588).

1-Methylcyclohexyl chloride (X) was prepared by the method of Russell[25] from 1-methylcyclohexanol and thionyl chloride.

(25) G. Russell, *J. Amer. Chem. Soc.*, **74**, 3882 (1952).

Purification was effected by distillation to yield material, $n^{17}D$ 1.4580 (lit.[25] $n^{17}D$ 1.4580).

Registry No.—I, 185-94-4; II, 286-08-8; HCl 7647-01-0.

Reactive Intermediates in the Bicyclo[3.1.0]hexyl and Bicyclo[3.1.0]hexylidene Systems. VI.[1] The Free-Radical Addition of Methanethiol and Methanethiol-*d* to Bicyclo[3.1.0]hexene-2

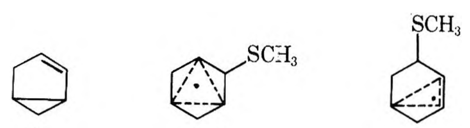
PETER K. FREEMAN,*[2] MARVIN F. GROSTIC,[3] AND FLOYD A. RAYMOND

Department of Chemistry, University of Idaho, Moscow, Idaho 83843

Received August 14, 1970

Free-radical addition of methanethiol to bicyclo[3.1.0]hexene-2 results in a mixture of *cis*-3-methylthiobicyclo-[3.1.0]hexane, *trans*-2-methylthiobicyclo[3.1.0]hexane, *trans*-3-methylthiobicyclo[3.1.0]hexane, and *cis*- and *trans*-3-methyl-5-methylthiocyclopentene. The dependence of product composition upon concentration of methanethiol suggests that an equilibrium of substituted 2-bicyclo[3.1.0]hexyl and Δ^2-cyclopentylmethyl radicals are involved rather than the related delocalized intermediate. The stereochemistry of the radical addition of methanethiol-*d* leading to 3-deuterio-*trans*-2-methylthiobicyclo[3.1.0]hexane was investigated and found to be predominantly trans (81–91%).

Our interests in carbonium ion[4] and carbene[5] intermediates in the bicyclo[3.1.0]hexyl and bicyclo-[3.1.0]hexylidene systems provided the impetus to investigate the nature of analogous free-radical intermediates. We have recently discussed free-radical abstraction reactions of bicyclo[3.1.0]hexane,[6] and now report on a complementary study of radical addition of methanethiol to bicyclo[3.1.0]hexene-2 (**1**). In terms of orientation, there are two possible reaction pathways. Addition of the methylthio radical to C-2 might generate a delocalized radical (2) analogous to the trishomocyclopropenyl carbonium ion[7] (or a related set of equilibrating classical radicals), while addition at C-3 might produce a delocalized radical analogous to either the bicyclobutonium ion[8] (**3**) or the closely



1 2 3

related symmetrical bisected cyclopropylcarbinyl carbonium ion[9] (or, alternatively a related set of equilibrating classical radicals).

Radical addition of methanethiol to bicyclo[3.1.0]-hexene-2 proceeded smoothly upon irradiation to give an 85–95% yield of 1:1 addition products. Vapor phase chromatography on a Carbowax 1500 column showed that four components were present in a 1.5:33:59:6.5 composition. The 6.5% component was isolated by vapor phase chromatography and infrared analysis suggested a bicyclic structure (CH absorption at 3060, 3040, and 3000 cm^{-1}, no C=C absorption, and cyclopropane at 1020 cm^{-1}). In particular, the 3040-cm^{-1} CH absorption was enhanced, which indicates a cis isomer.[4] Consistent with this picture, the 6.5% component was identified as *cis*-3-methylthiobicyclo[3.1.0]hexane (**4**) by comparison of its infrared spectrum with that of an authentic standard. The 59% component was isolated by vapor phase chromatography and its infrared spectra also suggested a [3.1.0] ring system (CH at 3070, 3040, and 3005 cm^{-1}, no C=C absorption, and cyclopropane absorption at 1020 cm^{-1}). The nmr spectrum exhibited two *S*-methyl peaks at τ 7.94 and 8.02 with a relative ratio of 80:20. With this accurate lead, the composition of the 59% component was determined to be a mixture of *trans*-2-methylthiobicyclo[3.1.0]hexane (**5**) and *trans*-3-methylthiobicyclo[3.1.0]hexane (**6**), with the *trans*-2 thio ether present as the major component, by preparation of authentic standards and infrared spectral comparison.

Infrared analysis of the 33% component, isolated by vapor phase chromatography, gives a clear indication of a cyclopentene ring (3050, 3045, 1600, and 750 cm^{-1}) with a *C*-methyl group (1375 cm^{-1}). The nmr spectrum exhibits absorption for olefinic protons at τ 4.30–4.58 (2 H), hydrogen α to *S*-methyl at 6.08–6.48, hydrogen α to *C*-methyl at 6.90–7.50, *S*-methyl at 8.02 and 8.07 (two singlets, 3 H), methylene hydrogens at 7.58–8.80 (2 H), and *C*-methyl at 8.90 and 8.97 (two doublets in a 20:80 ratio). That the hydrogens α to *S*-methyl and α to *C*-methyl are allylic is indicated by comparison with the analogous hydrogens in 3-methylthiocyclopentene, τ 6.08–6.46, and 3-methylcyclopentene, 7.02–7.48. Confirmation of the methylcyclopentene ring structure was achieved by the desulfurization of the methylthiomethylcyclopentenes with deactivated Raney nickel catalyst in 3-pentanone, which produced a mixture of 1-methyl-, 3-methyl-, and 4-methylcyclo-

(1) Part V: P. K. Freeman, F. A. Raymond, and J. N. Blazevich, *J. Org. Chem.*, **34**, 1175 (1969).

(2) Address all correspondence to this author at the Department of Chemistry, Oregon State University, Corvallis, Ore. 97331.

(3) NDEA Fellow, University of Idaho, 1961–1964.

(4) (a) P. K. Freeman, F. A. Raymond, and M. F. Grostic, *J. Org. Chem.*, **32**, 24 (1967); (b) P. K. Freeman, M. F. Grostic, and F. A. Raymond, *ibid.*, **30**, 771 (1965).

(5) P. K. Freeman and D. G. Kuper, *ibid.*, **30**, 1047 (1965).

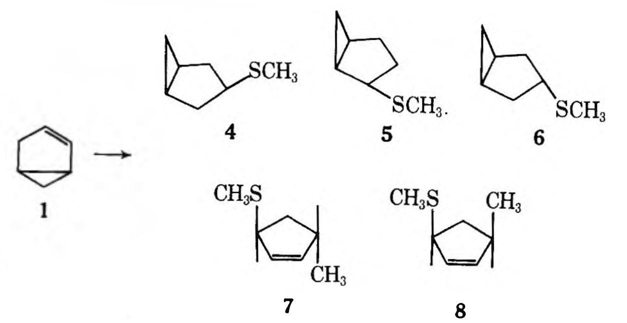
(6) P. K. Freeman, F. A. Raymond, J. C. Sutton, and W. R. Kindley, *ibid.*, **33**, 1448 (1968).

(7) (a) S. Winstein, E. C. Friedrich, R. Baker, and Y.-I Lin, *Tetrahedron*, 621 (1966). (b) S. Winstein and J. Sonnenberg, *J. Amer. Chem. Soc.*, **83**, 3235 (1961); **83**, 3244 (1961); S. Winstein, *ibid.*, **81**, 6524 (1959); S. Winstein, J. Sonnenberg, and L. de Vries, *ibid.*, **81**, 6523 (1959).

(8) M. S. Silver, M. C. Caserio, H. E. Rice, and J. D. Roberts, *ibid.*, **83**, 3671 (1961).

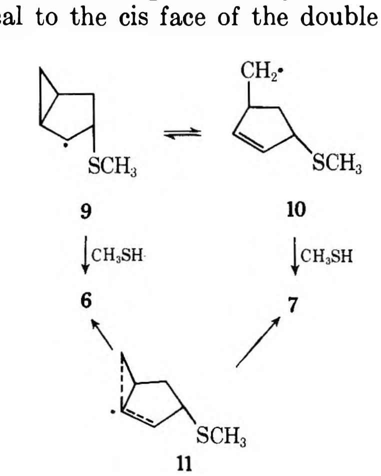
(9) P. v. R. Schleyer and G. W. Van Dine, *ibid.*, **88**, 2321 (1966).

pentene. Since an experiment demonstrated that 3-methylcyclopentene isomerized to 1-methyl- and 4-methylcyclopentene under the reaction conditions, the desulfurization served only to establish the ring skeleton. Thus the 33% component is most reasonably identified as an 80:20 mixture of *trans*- and *cis*-3-methyl-5-methylthiocyclopentene (**7** and **8**). Since the cyclopropane methylene sterically shields electrophilic addition to the cis face of the bicyclo[3.1.0]hexene double bond,[4] hydride transfer to 2- and 3-bicyclo-[3.1.0]hexanone,[7b,10] and capture of the 2-bicyclo-[3.1.0]hexyl radical and carbonium ion,[6,10] and since bicyclic *trans*-3 thio ether predominates over bicyclic *cis*-3 thio ether, the major isomer in the 33% vpc component is assigned as the trans compound. The 1.5% component was isolated and gave a satisfactory analysis for a $C_7H_{12}S$ isomer but was not characterized further due to its low product concentration.



The cis–trans pairs of 2- and 3-methylthiobicyclo[3.1.0]hexane epimers necessary for standards were synthesized by SN2 displacement of the appropriate chlorides by thiomethoxide. Starting with a mixture of 27% *trans*- and 73% *cis*-3-chlorobicyclo[3.1.0]hexane,[4a] treatment with the potassium salt of methanethiol gave a 55% yield of *trans*-3 and *cis*-3 thio ethers (**6** and **4**) in a ratio of 72:28. The cis–trans nature of the epimers was established by infrared and nmr analyses. The infrared spectrum of the *trans*-3 thio ether exhibits absorption at 3070, 3040, 3000, and 1025 cm^{-1}, while the analogous bands for the *cis*-3 thio ether appear at 3070, 3035, 3000, and 1020 cm^{-1}. The 3035-cm^{-1} band is enhanced in the cis structure relative to the trans, as we have found to be typical for *cis*- and *trans*-3- and -2-bicyclo[3.1.0]hexane epimers.[4b] The assignment is reinforced by a consideration of the nmr spectra, since the absorption for the cyclopropane methylene protons of the *trans*-3 thio ether appears at τ 9.47–9.94, while the analogous region for the *cis*-3 thio ether is shifted downfield to τ 9.30–9.75, in accord with data on the cyclopropane region in related [3.1.0] substrates.[4b] Treatment of a mixture of 30% *trans*- and 70% *cis*-2-chlorobicyclo[3.1.0]hexane with the potassium salt of methanethiol gave a 65% yield of a mixture of thio ethers which was 77% *trans*-2 and 23% *cis*-2. The infrared spectrum of the *trans*-2 thio ether exhibits characteristic [3.1.0] absorption at 3070, 3040, 3000, and 1020 cm^{-1}, while the analogous bands for the *cis*-2 epimer appear at 3070, 3035, 3000, and 1020 cm^{-1}, with the expected enhancement of the 3035-cm^{-1} band. The nmr data is in accord with this assignment with the cyclopropane methylene absorption appearing at τ 9.38–9.97 for the *trans*-2 thio ether, while the upfield proton is shifted downfield in the *cis*-2 thio ether (τ 9.50–9.80).

At first glance the reaction pathways followed as a consequence of addition of methylthio radical to bicyclo[3.1.0]hexene-2 would appear to involve either an equilibrium of radicals (**9** and **10**) or a delocalized radical **11** for which **9** and **10** are the resonance structures. A decision between these two alternatives is possible using the method, introduced by Seubold[11] and extended by Cristol and others,[12] of increasing the, concentration of the chain transfer agent in order to attempt to trap the initially formed intermediate. Thus, in the present case, in radical addition to the trans face of the double bond, an increase of methanethiol concentration might increase the ratio of **6**:**7** if an equilibrium, **9** ⇌ **10** obtains, whereas the ratio of **6**:**7** will remain uneffected if delocalized **11** is the sole product determining intermediate. A similar analysis can be applied to the intermediate(s) generated by addition of methylthio radical to the cis face of the double bond. The



results of the application of this test to determine the nature of the radical intermediate(s) using varying ratios of bicyclo[3.1.0]hexene-2:methanethiol are recorded in Table I.

TABLE I

METHANETHIOL ADDITION TO BICYCLO[3.1.0]HEXENE-2[a]

Run	Thiol, mol	Reaction composition, % **7**	**8**	**6**	**4**	**5**
1[b]	0.010	44.9	11.2	8.1	3.5	32.3
2[c]	0.015	43.1	10.8	8.3	4.8	33.2
3[b]	0.020	16.2	4.0	17.4	7.5	54.9
4[c]	0.020	16.9	4.2	16.8	8.8	53.3
5[b]	0.040	7.4	1.9	24.3	9.5	56.7
6[c]	0.040	6.4	1.6	25.2	8.0	58.8

[a] Bicyclo[3.1.0]hexene (0.010 mol) was used in each run. [b] Vapor phase chromatographic analysis on a 25-ft Carbowax 1500 column gave three peaks corresponding to **7** and **8**, **5** and **6**, and **4**. The ratio of **7**:**8** was determined by isolation and nmr determination of the ratio of the two *C*-methyl doublets at τ 8.97 and 8.90, while the ratio of **6**:**5** was determined by nmr measurement of the ratio of the two *S*-methyl absorptions at τ 7.94 and 8.02. [c] The ratios of **7**:**8** and **6**:**5** are assumed to be the same as the repeat or closest run.

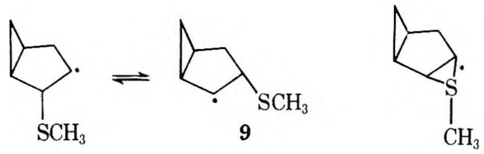
(10) E. J. Corey and R. L. Dawson, *J. Amer. Chem. Soc.*, **85**, 1782 (1963).

(11) F. H. Seubold, *ibid.*, **75**, 2532 (1953).

(12) S. J. Cristol and R. V. Barbour, *ibid.*, **90**, 2832 (1968); S. J. Cristol and R. V. Barbour, *ibid.*, **88**, 4262 (1966); C. R. Warner, R. J. Strunk, and H. G. Kuivila, *J. Org. Chem.*, **31**, 3381 (1966); M. L. Poutsma, *J. Amer. Chem. Soc.*, **87**, 4293 (1965); S. J. Cristol, T. W. Russell, and D. I. Davies, *J. Org. Chem.*, **30**, 207 (1965); S. J. Cristol and D. I. Davies, *ibid.*, **29**, 1282 (1964); E. E. Huyser and J. D. Taliaferro, *ibid.*, **28**, 3442 (1963); S. J. Cristol, G. D. Brindell, and J. A. Reeder, *J. Amer. Chem. Soc.*, **80**, 635 (1958).

Discussion

As the concentration of methanethiol was increased the first formed radical intermediates were trapped and the ratio of **6**:**7** as well as that of **4**:**8** increased. The results of Table I clearly favor equilibria such as **9** ⇌ **10**, rather than a single delocalized radical such as **11** for the addition of thiyl radical to both faces of the bicyclo-[3.1.0]hexene double bond. It is interesting to note, however, that as the concentration of methanethiol is increased the ratio of (**6** + **7**):**5** is not constant but decreases. It appears that the radical precursor(s) for both *trans*-2-methylthio- and *trans*-3-methylthiobicyclo[3.1.0]hexane (**5** and **6**) rearranges to **10**. This suggests that a rapid equilibrium of *trans*-methylthio radicals **12** and **9** or alternatively a single bridged thiyl radi-



12 9 13

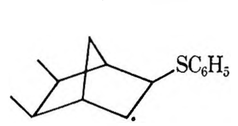
cal[13] (**13**) may be the product determining intermediates or intermediate.

In order to provide further evidence bearing on these alternatives, a study of the addition of methanethiol-*d* to bicyclo[3.1.0]hexene-2 was carried out. Radical addition of methanethiol-*d* gave the expected vpc components: *cis*- and *trans*-3-methyl-5-methylthiocyclopentene, *trans*-2 and *trans*-3 thio ether, and *cis*-3 thio ether. Nmr analysis of the deuterated 3-methyl-5-methylthiocyclopentenes gave an integration of two protons for the *C*-methyl region at τ 8.97 and 8.90, which is consistent with the cyclopropylcarbinyl–allylcarbinyl β fission process (**9** ⇌ **10**) drawn above.

The nmr spectrum of undeuterated standard, *trans*-2-methylthiobicyclo[3.1.0]hexane, exhibits a doublet of doublets for the proton α to methylthio (J = 5, 2 Hz) centered at τ 6.96. The stronger J = 5 Hz coupling is due to coupling with the *cis*-3 proton[4] and the weaker J = 2 Hz is apparently due to coupling with the bridgehead proton, since, as noted below, the doublet of doublets pattern persists in the addition product resulting from the cis addition of CH_3SD to the trans face of the double bond. The nmr spectrum of the vpc fraction containing the mixture of deuterated *trans*-2 and *trans*-3 thio ethers provided evidence for a stereoselective, but not a stereospecific radical addition process. The proton α to methylthio in the *trans*-2 thio ether is resolved from the analogous *trans*-3 thio ether proton, and the normal doublet of doublet of absorption for the cis-2 proton is replaced with a broad singlet ($W_{1/2}$ = 3 Hz) with two small shoulders corresponding to the outside peaks of the doublet of doublets. Analysis of this pattern reveals that the *trans*-2 thio ether component is 81–91% *cis*-3-deuterio- and 9–19% *trans*-3-deuterio-*trans*-2-methylthiobicyclo[3.1.0]hexane. Thus the elements of CH_3SD are added 81–91% in the trans manner.

(13) See, for example, P. D. Readio and P. S. Skell, *J. Org. Chem.*, **31**, 759 (1966). The role of analogous bromine bridged radical intermediates is a matter of divergent opinions: D. D. Tanner, D. Darwish, M. W. Mosher, and N. J. Bunce, *J. Amer. Chem. Soc.*, **91**, 7398 (1969); J. G. Traynham and W. G. Hines, *ibid.*, **90**, 5208 (1968); P. S. Skell and P. D. Readio, *ibid.*, **86**, 3334 (1964); P. S. Skell, D. L. Tuleen, and P. D. Readio, *ibid.*, **85**, 2849 (1963); W. Thaler, *ibid.*, **85**, 2607 (1963).

As noted above, the concave side of bicyclo[3.1.0]-hexane is sterically shielded by the cyclopropane methylene. One might expect, in fact, that the ratio of trans:cis attack in the chain transfer step for the 3-bicyclo[3.1.0]hexyl radical might be similar to the ratio of exo:endo attack in the chain transfer reactions of the 2-norbornyl radical, based on the similar stereoselectivities exhibited in lithium aluminum hydride reduction (3-bicyclo[3.1.0]hexanone,[7b] trans:cis attack = 89:11; 2-norbornanone,[14] exo:endo attack = 89:11) and epoxidation (bicyclo[3.1.0]hexene,[7b] trans:cis attack ≥ 100:1, norbornene,[15] exo:endo attack = 200). However in the case of *trans*-2-methylthio radical **12**, the most accessible convex side of the bicyclohexane skeleton is blocked by the methylthio substituent. One might, therefore, consider for purposes of comparison the steric course of chain transfer for *exo*-3-phenylthio-2-norbornyl radical and the analogous aldrinyl radical, since in these radicals (**14**), the most accessible exo side



14

is similarly blocked by a thiyl substituent. As the radical additions of *S*-deuteriothiophenol to both aldrin[16] and norbornene[17] proceed to form predominantly cis–exo addition products, one might argue that the trans addition of the elements of methanethiol leading to **5** suggests a 1,2-bridged thiyl radical **13** or a trans-substituted trishomocyclopropenyl radical 2.

Neither bridged thiyl radical **13** nor trans-substituted **2** can be the sole product determining intermediate leading to **5**, since the reaction is not completely stereospecific, and the necessity for involving either intermediate as part of an equilibrium with classical radicals **12** and **9** is reduced by the possibility that steric access to the concave side of bicyclo[3.1.0]hexane may be greater than to the endo side of norbornane. We see some evidence of this in this work in the ratios of thio ethers **6**, **4**, and **5** formed in the addition of methanethiol to **1**, while, in contrast, in analogous radical additions of *p*-thiocresol (no endo attack observed)[18] and thiophenol (99.5% exo attack)[15] to norbornene, steric control appears to be more severe.[19] Similarly, electrophilic addition of DCl to bicyclo[3.1.0]hexene-2 proceeds by a route involving cis addition of the elements of DCl to the double bond, but with attack at both the trans and cis faces of the double bond in a ratio of 66:31,[4a] while similar additions of DCl to norbornene[20] or HCl to 2,3-dideuterionorbornene[21] pro-

(14) H. C. Brown, W. J. Hammar, J. H. Kawakami, I. Rothberg, and D. L. Vander Jagt, *ibid.*, **89**, 6381 (1967).

(15) H. C. Brown and J. H. Kawakami, *ibid.*, **92**, 201 (1970).

(16) S. J. Cristol and T. W. Russell, quoted by D. I. Davies and S. J. Cristol, *Advan. Free Radical Chem.*, **1**, 162 (1965).

(17) D. I. Davies and J. A. Claisse, quoted by S. J. Cristol and D. I. Davies, *ibid.*, **1**, 162 (1965).

(18) S. J. Cristol and G. D. Brindell, *J. Amer. Chem. Soc.*, **76**, 5699 (1954).

(19) Some endo attack of thiyl radicals upon norbornadiene has recently been uncovered [T. V. Van Auken and E. A. Rick, *Tetrahedron Lett.*, 2709 (1968)], which reinforces the cautionary comment on assuming complete exo attack of thiyl radicals on norbornene derivatives voiced by D. I. Davies and S. J. Cristol, *Advan. Free Radical Chem.*, **1**, 155 (1965).

(20) H. C. Brown and K-T. Lin, *J. Amer. Chem. Soc.*, **89**, 3900 (1967).

(21) J. K. Stille, F. M. Sonnenberg, and T. H. Kinstle, *ibid.*, **88**, 4922 (1966).

ceed *via* cis–exo stereochemistry for that portion of reaction leading to unrearranged product.

Thus, it appears most reasonable to represent the radical addition of methanethiol to bicyclo[3.1.0]hexene-2 in terms of attack at the trans face of the double bond, which generates an equilibrium of **12** and **9**, with **9** rearranging to **10** by a cyclopropylcarbinyl–allylcarbinyl β fission process, while attack at the cis face produces an equilibrium of radicals analogous to **12** $\rightleftharpoons$ **9**, although one cannot rule out a role for bridged radical intermediates analogous to **13** and **2**.

Experimental Section

Methanethiol Addition to Bicyclo[3.1.0]hexene-2.—Into a 50-ml reaction flask was placed 0.80 g (0.010 mol) of bicyclo[3.1.0]-hexene-2 and the flask placed on a vacuum line. The flask was cooled in a Dry Ice–isopropyl alcohol bath and the system evacuated. Methanethiol (0.020 mol, measured as a gas) was introduced into the system and condensed in the reaction flask. The Dry Ice trap was removed and the reaction mixture irradiated for about 2 min with a General Electric sun lamp and then immersed in the cold trap. These 2-min irradiations followed by cooling were continued for a total of about 2 hr of irradiation time. Following the completion of the reaction time, the reaction flask was removed from the vacuum line and the product mixture allowed to warm to room temperature leaving 1.1 g of (0.0094 mol, 94%) product.

Vapor phase chromatographic analysis on a 25-ft Carbowax 1500 column showed four peaks in the ratio of 1.5:33:59:6.5. The 33% peak was collected by vpc and the infrared and nmr spectra were recorded. The nmr spectrum contained two olefinic protons (τ 4.30–4.58), one hydrogen α to *S*-methyl (6.08–6.48), one hydrogen α to *C*-methyl (6.90–7.50), two types of *S*-methyl absorption (8.02 and 8.07), methylene hydrogens (7.58–8.80, 2 H, part of this region falling under the *S*-methyl absorption), and two types of *C*-methyl absorption (doublet at 8.90 and a doublet at 8.97, J = 7 Hz). The relative ratio of the two types of *C*-methyl absorption was 80:20. The infrared spectra showed olefinic CH absorption at 3050 and 3045 cm^{-1}, C=C absorption at 1600 cm^{-1}, cis hydrogens on a double bond at 750 cm^{-1}, and absorption at 1375 cm^{-1} assignable to a *C*-methyl group. An analytical sample was isolated by vpc.

Anal. Calcd for $C_7H_{12}S$: C, 65.56; H, 9.44. Found: C, 65.36; H, 9.33.

The infrared spectra of the 59% component had absorption indicating that the bicyclo[3.1.0]hexane ring structure was present (CH at 3070, 3040, and 3005 cm^{-1}, no C=C absorption, and cyclopropane at 1020 cm^{-1}).[4] The nmr spectrum of this component contained one tertiary proton (doublet of doublets at τ 6.82–6.96), two types of *S*-methyl absorption at 7.94 and 8.02, four methylene protons and two tertiary protons (8.17–8.75 region), and two methylene protons on a cyclopropane ring (τ 9.33–9.87). The two *S*-methyl absorptions were in the ratio of 80:20. An analytical sample was isolated by vpc.

Anal. Calcd for $C_7H_{12}S$: C, 65.56; H, 9.44. Found: C, 65.56; H, 9.56.

The infrared spectra of the 6.5% component (containing about 10% of the 59% component) had absorption supporting the bicyclo[3.1.0]hexane ring structure (CH at 3060, 3040, and 3000 cm^{-1}, no C=C absorption, and cyclopropane at 1020 cm^{-1}). An enhancement of the band at 3040 cm^{-1} indicated that this component was the cis isomer. Spectral comparisons with the 2- and 3-methylthiobicyclo[3.1.0]hexanes described below established the 6.5% component as the *cis*-3-methylthiobicyclo[3.1.0]-hexane isomer. An analytical sample free of the 59% component was isolated by vpc.

Anal. Calcd for $C_7H_{12}S$: C, 65.56; H, 9.44. Found: C, 65.46; H, 9.37.

The 1.5% component was not completely characterized due to its low concentration in the product fraction. An analytical sample was isolated by vpc.

Anal. Calcd for $C_7H_{12}S$: C, 65.56; H, 9.44. Found: C, 65.43; H, 9.53.

Other addition reactions were run in a similar manner and using the various concentrations of methanethiol (Table I). The cyclopentenyl products were isolated by vpc from three of these runs (1, 3, and 5, Table I) and the ratios of the trans to cis isomers analyzed by nmr using the ratio of the two *C*-methyl doublets at τ 8.90 and 8.97. This ratio was found to be 80:20 for all three runs studied.

The peak corresponding to the *trans*-2 and *trans*-3 thio ether mixture was isolated by vpc and analyzed by nmr using the ratio of the *S*-methyl peaks at τ 7.94 and 8.02. The ratio of *trans*-2 to *trans*-3 thio ether was found to be 80:20 at 0.01 mol of methanethiol (run 1), 76:24 at 0.02 mol of methanethiol (run 3), and 70:30 at 0.04 mol of methanethiol (run 5).

Desulfurization of 3-Methylthiocyclopentene.—Raney nickel catalyst was deactivated by a modification of the method described by Spero, McIntosh, and Levin.[22] The catalyst (9 g) was washed five times with 20–30-ml portions of 3-pentanone to remove the ethyl alcohol. The catalyst was transfered to a 100-ml flask with approximately 60 ml of 3-pentanone. The catalyst was deactivated by refluxing the mixture for a period of 2 hr. To the mixture of deactivated catalyst in 3-pentanone was added 1.0 g of 3-methylthiocyclopentene, and the mixture was heated at reflux for a period of 4–5 hr.

After refluxing, the reaction was arranged for simple distillation and 3 ml of distillate was collected in a graduate cyclinder immersed in an ice bath. The distillate showed two peaks corresponding to cyclopentane and cyclopentene in the ratio of 3:1 when analyzed by vpc on a 30-ft Carbowax 1500 column.

Desulfurization of *cis*- and *trans*-3-Methyl-5-methylthiocyclopentene.—Raney nickel catalyst (6 g) was washed five times with 20–30 ml-portions of 3-pentanone and then transferred with approximately 50 ml of 3-pentanone to a 100-ml round-bottom flask equipped with a magnetic stirrer. The catalyst was deactivated by refluxing for 1 hr and 0.5 ml of methylthiomethylcyclopentenes (collected by vpc from the methanethiol–bicyclo[3.1.0]hexene-2 reaction mixture) was added at reflux temperature. The mixture was allowed to cool to 70° at which temperature it was heated for 9 hr. After the heating period was completed, the flask was cooled and arranged for simple distillation. A total of 2.5 ml of distillate was collected in a graduate cylinder immersed in an ice bath.

Vpc analysis of the distillate on a 30-ft aluminum column of 25% Carbowax 1500 on Chromosorb P (30–60 mesh) revealed two peaks which corresponded to methylcyclopentenes and indicated an overall yield of 10–15%. The largest peak of the methylcyclopentenes had a retention time of 11.5 min, and it corresponded in retention time to 3-methylcyclopentene and 4-methylcyclopentene. The second peak had a retention time of 13.7 min corresponding to that of 1-methylcyclopentene. The two peaks were collected and analyzed on a 1-m silver nitrate column. The 11.5-min peak showed two peaks in a 1:1 ratio corresponding in retention times to those of 3-methylcyclopentene and 4-methylcyclopentene. The 13.7-min peak had a retention time corresponding to that of 1-methylcyclopentene.

Stability of 3-Methylcyclopentene to Desulfurization Conditions.—To 6 g of deactivated Raney nickel catalyst in 50 ml of 3-pentanone was added 0.4 ml of 3-methylcyclopentene, and the mixture was heated at 70° for 9.5 hr. After the heating period was completed, the apparatus was arranged for simple distillation and a total of 4 ml of distillate was collected in a graduate cylinder immersed in an ice bath. Analysis of the distillate by vpc using a 30-ft Carbowax 1500 column showed two products peaks in the ratio of 40:60. The two peaks corresponded to methylcyclopentane, with a shoulder for 3- and 4-methylcyclopentene, and 1-methylcyclopentene. The two peaks were collected and the infrared spectra of the 60% component showed it to be 1-methylcyclopentene by comparison with the infrared of an authentic sample. The 40% components were analyzed by vpc using a 1-m silver nitrate column. The analysis showed it to be mostly methylcyclopentane with small amounts of 3- and 4-methylcyclopentene in the ratio of 2:1.

Preparation of the Potassium Salt of Methanethiol.—Metallic potassium (0.78 g, 0.02 g-atom) was added to 50 ml of anhydrous ether in a three-necked reaction flask equipped with a gas bubbler, stirrer, and Dry Ice condenser. The reaction flask was cooled with a Dry Ice–isopropyl alcohol bath and methanethiol (about 0.03 mol) bubbled into this solution over a 2-hr period. The flask was allowed to warm slowly to room temperature and the solution stirred overnight. The ether was removed by distillation leaving 1.4 g (0.018 mol, 93%) of product.

(22) G. B. Spero, A. V. McIntosh, and R. H. Levin, *J. Amer. Chem. Soc.*, **70**, 1907 (1948).

cis- and *trans-*3-**Methylthiobicyclo[3.1.0]hexane.**—A solution of 2.0 g (0.017 mol) of a mixture of 27% *trans-* and 73% *cis-*3-chlorobicyclo[3.1.0]hexane[4a] in 10 ml of acetone was added dropwise with stirring to a slurry of 1.72 g (0.02 mol) of the potassium salt of methanethiol in 40 ml of acetone. The mixture was stirred at room temperature for 12 hr and then heated at reflux temperature for 2 hr. The solution was filtered and the residue thoroughly washed with ether. The solvent was removed from the combined washings and filtrate, and the residue was distilled under vacuum to give 1.0 g (0.009 mol, 55%) of the thio ether product. The vpc analysis of this product on a 25-ft Carbowax 1500 column showed it to be a mixture of 72% trans and 28% cis. The infrared spectrum of the *trans*-3 methylthio substrate shows CH stretching absorptions at 3070, 3040 and 3000 cm^{-1} and an absorption at 1025 cm^{-1} for cyclopropane, while the analogous absorptions for the *cis*-3 methylthio substrate appear at 3070, 3035, 3000, and 1020, with the absorption at 3035 enhanced relative to the trans epimer as is typical for 3-substituted epimers on the bicyclo[3.1.0]hexane skeleton.[4] A comparison of the infrared spectrum of *trans*-3-methylthiobicyclo[3.1.0]hexane with that of the 59% component from the thiol addition reaction showed that the minor component was the *trans*-3 thio ether, while the spectrum of *cis*-3-methylthiobicyclo[3.1.0]hexane was identical with that of the 6.5% component from the thiol addition reaction.

The nmr spectrum of the *trans*-3-methylthiobicyclo[3.1.0]-hexane shows high-field cyclopropane methylene absorption (τ 9.47–9.94), which is typical for a trans-3 epimer,[4b] an *S*-methyl peak at τ 8.02, a complex splitting pattern in the region τ 7.10–7.90 for the proton α to the thiol group, and a complex splitting pattern from τ 7.90 to 8.90 for six protons. Since the *trans*-2 and *trans*-3 thio ethers could not be separated by vpc, one could still analyze for the proton α to the thiyl group in the *trans*-2 thio ether without any interference from the complex absorption for the analogous proton in the *trans*-3 thio ether.

The nmr spectrum of the *cis*-3-thiomethoxybicyclo[3.1.0]-hexane shows high-field cyclopropane methylene absorption (τ 9.30–9.75) which is typical for a cis-3 epimer,[4] an *S*-methyl peak at τ 8.00, a complex splitting pattern for the proton α to the thiyl group in the region τ 6.67–7.17, and a complex splitting pattern for six protons in the region τ 7.40–8.90.

cis- and *trans-*2-**Methylthiobicyclo[3.1.0]hexane.**—A solution of 2.0 g (0.017 mol) of a mixture of 30% *trans-* and 70% *cis-*2-chlorobicyclo[3.1.0]hexane[4a] in 10 ml of acetone was added dropwise with stirring to a slurry of 1.72 g (0.02 mol) of the potassium salt of methanethiol in 40 ml of acetone. The mixture was stirred at room temperature for 12 hr and then heated at reflux temperature for 2 hr. The solution was filtered and the residue thoroughly washed with ether. The solvent was removed from the combined washings and filtrate, and the product was distilled under vacuum to give 1.24 g (0.011 mol, 65%) of the thio ether product. The vpc analysis of this product using a 25-ft Carbowax 1500 column showed it to be a mixture of 77% trans and 23% cis. The infrared spectrum of the *trans*-2-methylthio epimer exhibits CH stretching absorptions at 3070, 3040, 3000 cm^{-1} and cyclopropane absorption at 1020 cm^{-1}, while the *cis*-2-methylthio epimer shows absorptions at 3070, 3035, 3000, and 1020 cm^{-1}, with the 3035 absorption enhanced relative to the trans epimer.

A comparison of the infrared spectrum of the *trans*-2 thio ether with that of the 59% component mixture from the thiol addition reaction demonstrated that *trans*-2-methylthiobicyclo[3.1.0]-hexane represents the major isomer present in the 59% peak. A comparison of the infrared spectra of the *cis*-2 thio ether with that of the components isolated from the thiol addition reaction indicated that *cis*-2-methylthiobicyclo[3.1.0]hexane was not formed to any great extent in the reaction (<3%).

The nmr spectrum for the trans isomer shows high-field cyclopropane absorption (τ 9.38–9.97), which is typical for *trans*-2-bicyclohexane epimers,[4b] an *S*-methyl peak at τ 7.94, a complex splitting pattern in the region τ 9.00–8.88 for six protons, and a doublet of doublets (J = 5 and 2 Hz) for the proton α to SCH_3.

The nmr spectrum of the *cis*-2 thio ether shows high-field cyclopropane methylene absorption (τ 9.50–9.80), which is typical for *cis*-2-bicyclohexane epimers, an *S*-methyl peak at τ 7.94, a complex splitting pattern for the proton α to the thiyl group in the region τ 6.58–7.03, and a complex splitting pattern for six protons in the region τ 8.00–9.30.

3-Methylthiocyclopentene.—3-Methylthiocyclopentene was prepared by the reaction of the potassium salt of methanethiol with 3-chlorocyclopentene in acetone. To 0.13 mol of the potassium salt of methanethiol in 100 ml of acetone was added dropwise with stirring 10.0 g (0.10 mol) of 3-chlorocyclopentene. After the addition was completed, the reaction mixture was stirred at room temperature for an additional 30 hr. The salts were filtered off and the acetone was evaporated under reduced pressure. The residue was distilled through a 6-in. Vigreux column yielding 4.50 g (40%) of product which had bp 49–52° (25 mm).

Anal. Calcd for $C_6H_{10}S$: C, 63.07; H, 8.82. Found: C, 62.72; H, 8.44.

The nmr spectrum of methylthiocyclopentene shows the *S*-methyl peak at τ 8.02, two olefinic protons with a complex splitting pattern in the region τ 4.03–4.50, an allylic proton α to the thiyl group represented by a complex splitting pattern in the region τ 6.08–6.46, and two allylic methylene and two methylene protons represented by a complex splitting pattern in the region τ 7.33–8.30. The infrared spectrum shows high energy CH absorption above 3000 cm^{-1}, a double bond absorption band at 1600 cm^{-1}, cis hydrogen out-of-plane deformation absorption bands at 740 cm^{-1}, and other strong bands at 1415, 1205, 1015, 950, and 905 cm^{-1}.

Preparation of Methanethiol-*d*.—The potassium salt of methanethiol (0.1 mol) was prepared as described above. Deuterium oxide (8 ml, 99.5%) was added dropwise to the potassium salt under a gentle flow of carbon dioxide gas. The methanethiol-*d* was collected at −80° in a cold trap, which was fitted with ground glass joints and a high vacuum stopcock. The cold trap was fitted to a vacuum system and the methanethiol-*d* was distilled into a storage flask, whereupon it was purified by several distillations in the vacuum system.

Nmr analysis of the deuterated mercaptan showed complete disappearance of the SH peak at *ca.* τ 9.0, and it was concluded that the deuteration was greater than 98%. Infrared analysis indicated complete deuteration of the mercaptan by the complete disappearance of the SH band at 3.79 μ and the appearance of the SD band at 5.24 μ.

Addition of Methanethiol-*d* to Bicyclo[3.1.0]hexene-2.—Methanethiol-*d* (12.6 mmol) was allowed to react with 0.8 g (10.0 mmol) of bicyclo[3.1.0]hexene-2 in the manner described above. After 60 min of irradiation an 80% yield of thio ethers was obtained. Analysis on a 30-ft aluminum column of 25% Carbowax 1500 at 150° showed peaks for methylthiomethylcyclopentenes, *trans*-2- and *trans*-3-thiomethoxybicyclo[3.1.0]-hexane, and *cis*-3-thiomethoxybicyclo[3.1.0]hexane. The cyclopentenes and trans bicyclic compounds were collected for nmr and infrared analysis.

The nmr spectrum of the mixture of 3-methyl-5-methylthiocyclopentenes shows it to be a 70:30 mixture of the trans and cis isomers. The spectrum exhibits a total integration equivalent to 11 protons with the region for the two methyl doublets (τ 8.92 and 8.97) integrating for an area of two protons. The other protons appeared as in the undeuterated compounds. The integration of 11 protons also gave evidence for complete deuteration of the methanethiol. The infrared spectrum shows a strong CD stretching frequency at 2180 cm^{-1} and C=C band at 1600 cm^{-1}.

The nmr spectrum of the vpc collection for the *trans*-2- and *trans*-3-methylthiobicyclo[3.1.0]hexane showed them to be in the ratio of 72:28 as determined from the ratio of the *S*-methyl peaks at τ 7.94 and 8.02. The spectrum shows typical high-field cyclopropane methylene absorption (τ 9.40–10.00) for a *trans*-bicyclo[3.1.0]hexane isomer. The doublet of doublets in the nmr spectrum for the proton α to the thiyl group in the undeuterated *trans*-2 thio ether now is reduced to a somewhat broadened singlet ($W_{1/2}$ = 3 Hz) with two small shoulders corresponding to the outside peaks of the doublet of doublets. The singlet corresponds to trans addition of the elements of CH_3SD across the double bond, while the doublet of doublets represents the cis addition product. Analysis of the absorption region for hydrogen α to methylthio allows one to estimate that trans addition occurs to an extent greater than 81% and less than 91%.

Registry No.—**1,** 694-01-9; **4,** 27557-67-1; **5,** 27557-65-9; **6,** 27557-66-0; **7,** 27557-70-6; **8,** 27557-71-7; methanethiol, 74-93-1; methanethiol-*d*, 16978-68-0; 3-methylthiocyclopentene, 27557-68-2.

Acknowledgment.—The authors gratefully acknowledge the generous support of this work by the Air Force Office of Scientific Research and the National Science Foundation and express their appreciation to F. A. MacKeller of the Upjohn Co. for nmr spectral measurements and analyses.

Preparation and Pyrolysis of Some 2,6-Dimethyl-4-pyrone–Alkyne Photoadducts. Bicyclic Claisen Rearrangement

J. WILLIAM HANIFIN* AND ELLIOTT COHEN

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

Received July 29, 1970

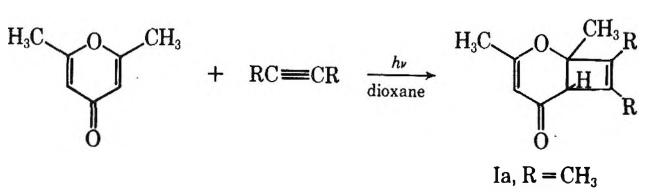
The photoaddition reaction of 2,6-dimethyl-4-pyrone with acetylenes has produced the desired 1:1 photoadducts. The pyrolysis of these cyclobutene derivatives was carried out in an attempt to convert them to the oxacyclooctatrienone ring system. However, the adducts underwent a symmetry-allowed bicyclic Claisen rearrangement followed by aromatization to substituted phenols.

Several examples of addition reactions of photochemically excited molecules to substituted acetylenes to produce cyclobutene derivatives have been reported in the literature.[1-3] The photoaddition reaction of 2-cyclopentenone with butyne-2 was the first reported example of this type reaction.[1] Recently we have shown that chromone undergoes a similar photoaddition with butyne-2.[4,5]

We would now like to report the unsensitized photoaddition reaction of 2,6-dimethyl-4-pyrone with substituted acetylenes to produce the cyclobutene derivatives. The purpose of this work was to prepare these 1:1 adducts in the hope that they would serve as useful intermediates in the preparation of medium-sized oxygen heterocycles. The results of pyrolysis experiments carried out on the photoadducts are described.

Results

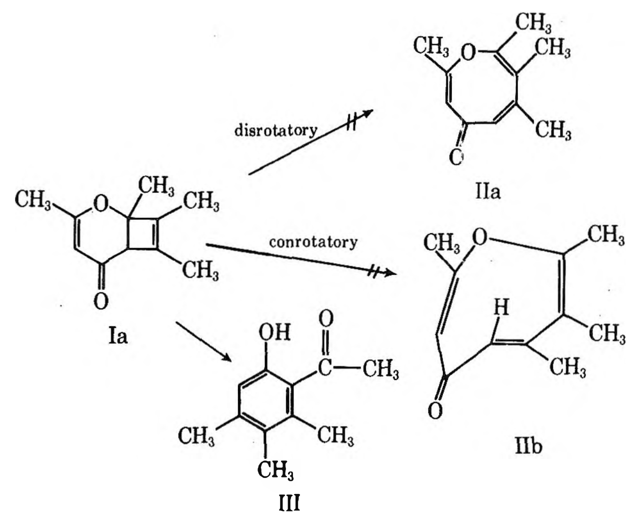
A solution of 2,6-dimethyl-4-pyrone, butyne-2, and dioxane was irradiated with the 450-W mercury arc lamp. Gas–liquid chromatography indicated that only one major product was produced. The major product was isolated by liquid–liquid partition chromatography (llpc) and shown to be the desired 2,6-dimethyl-4-pyrone–butyne-2 adduct (Ia) by nmr, ir, uv, and mass spectral analysis.



Ia, R = CH_3
b, R = CH_3

The pyrolysis of Ia was undertaken in an attempt to convert it to the *cis,cis,cis*-oxa-2,5,7-cyclooctatrien-4-one ring system, IIa. Such a ring opening would have to occur by a symmetry-forbidden disrotatory mode, or by a heterolytic or homolytic pathway, all of which are predicted to require highly energetic conditions. It was hoped that the reaction might occur under the forcing conditions of high temperature since the allowed conrotatory opening of the cyclobutene ring should be very difficult due to the formation of a trans double bond in the product, *cis,trans,cis*-oxa-2,5,7-cyclooctatrien-4-one (IIb).

The pyrolysis of adduct Ia was accomplished by refluxing in *o*-dichlorobenzene for 2 days. By glpc it was shown that one major and one very minor product were formed during the pyrolysis. The major product isolated by llpc was identified as 2-acetyl-3,4,5-trimethylphenol (III). The structure of this product was determined by nmr, ir, uv, mass spectrum, and comparison with an authentic sample prepared by an independent route.[6]



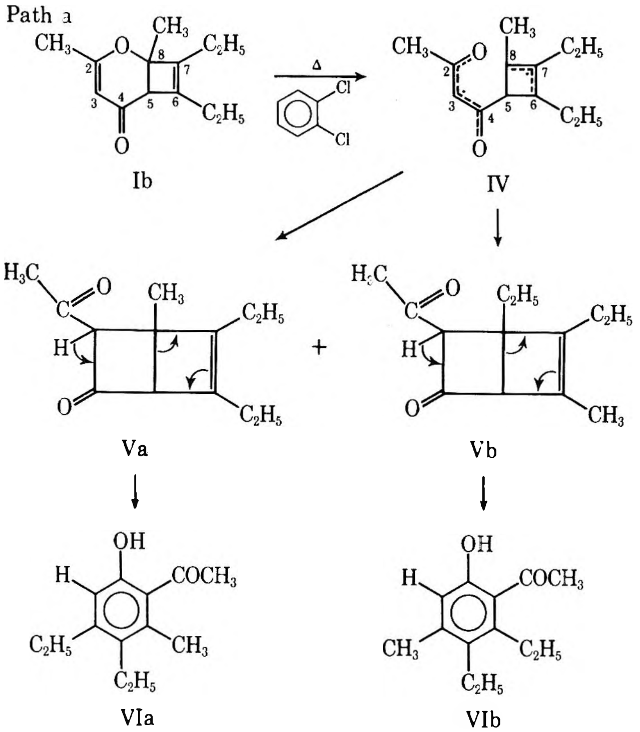
One can envision two different pathways for the pyrolysis reaction leading to the formation of III. In order to distinguish between these two different pathways, it was necessary to carry out the pyrolysis of the **2,6-dimethyl-4-pyrone–hexyne-3 adduct (Ib)**. The preparation of Ib was carried out *via* the photoaddition reaction and its structure determined by nmr, ir, uv, and mass spectrum.

Path a involves initial cleavage of the ether oxygen–C_8 bond to give the diradical intermediate IV. This is followed by bond formation between C_3 and C_8

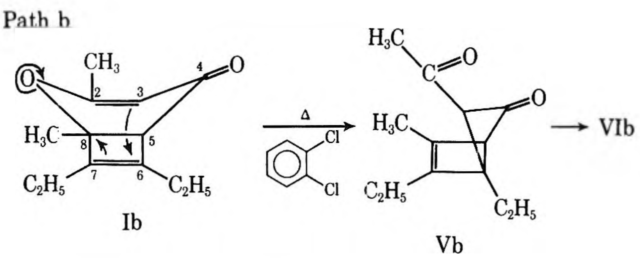
(1) P. E. Eaton, *Tetrahedron Lett.*, 3695 (1964).
(2) R. Criegee, U. Zirngibl, H. Furrer, D. Seebach, and G. Freund, *Chem. Ber.*, **97**, 2942 (1964).
(3) G. O. Schenck and R. Steinmetz, *Bull. Soc. Chim. Belg.*, **71**, 781 (1962).
(4) J. W. Hanifin and E. Cohen, *Tetrahedron Lett.*, 5421 (1966).
(5) J. W. Hanifin and E. Cohen, *J. Amer. Chem. Soc.*, **91**, 4494 (1969).

(6) An authentic sample of 2-acetyl-3,4,5-trimethylphenol was obtained *via* a Fries rearrangement on 3,4,5-trimethylphenyl acetate.

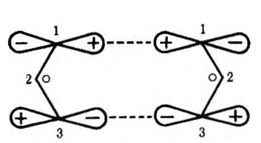
or C_3 and C_6 to give Va and Vb, respectively. Rearrangement of Va and Vb followed by enolization should yield the two isomer phenols VIa and VIb.



Path b involves the concerted intramolecular conversion of Ib to Vb by a reaction mechanism analogous to the Claisen rearrangement,[7] the thermal transformation of an allyl vinyl ether to a homoallylic carbonyl compound. Rearrangement and enolization of Vb would give only the phenol VIb.



The Claisen and Cope rearrangements have recently been classified by Woodward and Hoffman[8] as sigmatropic changes of the order $[i,j]$ where i and j corresponds to 3. It can be shown by use of the phase relationships of the highest occupied molecular orbital that for rearrangements of the order $[i,j]$ in which both i and j are greater than unity, thermal changes are symmetry-allowed when $i + j = 4n + 2$. If it is assumed that the Cope rearrangement proceeds by formation and combination of allyl quasiradicals in the transition state, the picture of the highest occupied molecular orbitals shows that the [3,3] change



(7) For a review of the Claisen rearrangement, see A. Jefferson and F. Scheinmann, *Quart. Rev. Chem. Soc.*, **22**, 391 (1968).

(8) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 2511, 4389 (1965).

is allowed. Experimentally, it has been shown that the conclusions are the same for the Claisen rearrangement.[9]

This picture is in agreement with the stereochemical requirements for intramolecular allylic rearrangements which demand that bond breaking and bond formation both occur on the same face of the allyl group, classifying it is a suprafacial migration.

The pyrolysis of Ib was carried out and the reaction products examined by glpc and llpc. It was shown that only one phenol was produced. This product, isolated by llpc, was positively identified as VIb by nmr, ir, uv, and mass spectral analysis. The nmr spectrum contained two methyl groups at δ 1.13 and 1.22 (triplets, $J = 7$ cps), one aromatic methyl at δ 2.32 (doublet, $J = 0.3$ cps), one acetyl methyl at δ 2.66 (singlet), two methylene groups at δ 2.62 (quartet, $J = 7$ cps) and 2.85 (quartet, $J = 7$ cps), one aromatic hydrogen at δ 6.62 (quartet, $J = 0.3$ cps), and one broad phenolic hydrogen at δ 9.50. Double irradiation experiments were carried out on VIb such that strong irradiation of the aromatic hydrogen collapsed the aromatic methyl to a singlet.[10] The ir spectrum contained the expected absorption bands at 3.03 and 5.96 μ, analogous to III. The uv spectrum showed absorption maxima at 219, 260, and 290 mμ, again analogous to III. The mass spectrum gave the expected molecular ion at m/e 206. This experiment indicates that the reaction proceeds *via* path B.[11]

In conclusion, pyrolysis of the 2,6-dimethyl-4-pyrone–alkyne photoadducts yields a 2-acetyl-3,4,5-trialkylphenol *via* path b, a concerted reaction analogous to the Claisen rearrangement.

Experimental Section

Procedure for Photoaddition Reactions.—The photoaddition reactions were carried out using the immersion apparatus supplied by the Hanovia Lamp Division of Engelhard Industries. This consisted of an irradiation vessel fitted with a water-cooled quartz immersion well, magnetic stirring bar, and a side arm connected to a mercury seal. A freshly prepared solution of the reactants to be irradiated was added to the vessel and then the solution was flushed with nitrogen for several minutes. The irradiation vessel was immersed in a large beaker of water for additional cooling. The solution was irradiated with a 450-W, medium-pressure mercury arc, type no. 679A-10.

The course of the reaction was followed by removing samples from the irradiation vessel and examining them by gas–liquid chromatography. The F & M Model 720 gas chromatograph fitted with a 6-ft 20% silicon rubber Se-30 column was used for the analysis.

Spectra.—Nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Infrared spectra were determined on a Perkin-Elmer Infracord spectrophotometer. Ultraviolet spectra were measured on a Cary Model 11 MS spectrophotometer. Mass spectra were determined on a AEIMS9 mass spectrometer. Melting points were determined in a capillary tube in a Mel-Temp apparatus and are uncorrected.

Materials.—2,6-Dimethyl-4-pyrone from Aldrich Chemical Co. was used without further purification. Butyne-2 and hexyne-3 from Farchan Research Laboratories were also used without

(9) Y. Pocker, *Proc. Chem. Soc., London*, 141 (1961).

(10) Double irradiation experiments were also conducted on III. The results served to verify our nmr analysis of VIb.

(11) Some additional evidence for the proposed mechanism was obtained from the pyrolysis of Ia which yielded a minor product along with III. Only a trace amount of this product could be obtained as an impure oil; however, its ir spectrum contained two carbonyl bands at 5.65 and 5.85 μ, suggestive of the bicyclo[2.2.0]hex-5-en-2-one system V. The mass spectrum of the material gave a molecular ion at m/e 170.

further purification. Dioxane from Matheson Coleman and Bell was purified by distillation from the sodium ketyl of benzophenone and stored frozen under nitrogen.

1,3,7,8-Tetramethyl-2-oxabicyclo[4.2.0]octa-3,7-dien-5-one (2,6-Dimethyl-4-pyrone-Butyne-2 Adduct) (Ia).—A solution of 0.08 mol of 2,6-dimethyl-4-pyrone, 1.85 mol of 2-butyne, and 1.14 mol of dioxane was prepared. This solution was then added to the outer jacket of the 450-W mercury arc immersion apparatus. The solution was flushed with nitrogen for several minutes and irradiation begun. The course of the reaction was followed by gas-liquid partition chromatography using the 6-ft 20% SE-30 column at 220°. After 48 hr the irradiation was stopped. By glpc and llpc it was shown that the 1:1 adduct was the only major product. Some white crystals which precipitated to the bottom of the flask were filtered and shown to be the known dimer. The volatile materials were removed on the rotating evaporator; the product was isolated by llpc using a heptane-methanol system. The infrared spectrum of the adduct showed strong carbonyl absorption at 6.1 μ. The nmr spectrum contained one methyl group at δ 1.53 (singlet), two vinyl methyl groups at δ 1.62 (multiplet), one vinyl methyl group at δ 1.95 (singlet), one tertiary hydrogen at δ 3.02 (multiplet), and one vinyl hydrogen at δ 5.15 (singlet). The uv spectrum of this product showed λ_{max}^{MeOH} 273 mμ (ϵ 7700). The mass spectrum of the compound gave a molecular ion at *m/e* 178.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.1; H, 7.9. Found: C, 73.5; H, 8.2.

2-Acetyl-3,4,5-trimethylphenol (III).—To 8.0 g (0.045 mol) of 3,4,5-trimethylphenyl acetate was added 6.0 g (0.045 mol) of aluminum chloride. This mixture was shaken together and then heated to 130° in an oil bath. After cooling, the contents of the flask were added to a mixture of 30 g of ice and 15 ml of concentrated hydrochloric acid. A yellow oil formed which was extracted with ether. The ether solution was dried over calcium chloride and then the ether was removed. The residue was taken up in hot petroleum ether (bp 30-60°) and approximately 4.0 g of product was obtained on cooling. The product was further purified by llpc and recrystallized again from petroleum ether to give a white solid, mp 58-60°. The mass spectrum of the compound showed a molecular ion at *m/e* 178. The infrared spectrum of the product contained carbonyl absorption at 5.94 μ and strong hydroxyl absorption at 3.0 μ. The uv spectrum showed λ_{max}^{MeOH} 218, 258, and 290 mμ. The nmr spectrum contained three aromatic methyl groups at δ 2.12, 2.25, and 2.40, one methyl group at δ 2.57, one aromatic hydrogen at δ 6.63, and one phenolic hydrogen at δ 10.70.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.1; H, 7.9. Found: C, 74.4; H, 8.1.

2-Acetyl-3,4,5-trimethylphenol (III) *via* Pyrolysis of Ia.—A solution of 0.5 g (0.003 mol) of Ia in 3.5 ml of *o*-dichlorobenzene was heated to reflux. The course of the pyrolysis was followed by glpc using the 6-ft 20% SE-30 column at 200°. After refluxing for 72 hr, it was shown that no starting material remained. By glpc it was shown that one major and one minor product were formed during the pyrolysis. The *o*-dichlorobenzene was removed on the spinning band. The two products were then isolated by llpc. The major product was identified as 2-acetyl-3,4,5-trimethylphenol. The structure of this product was determined by comparison of its spectral data with that from the authentic sample prepared by the independent route above. The minor product could only be isolated as an impure oil. Attempts to further purify it were unsuccessful. The mass spectrum of the compound showed a molecular ion at *m/e* 178. The infrared spectrum contains two strong carbonyl bands at 5.65 and 5.85 μ, suggestive of the bicyclo[2.2.0]hex-5-en-2-one system.

7,8-Diethyl-1,3-dimethyl-2-oxabicyclo[4.2.0]octa-3,7-dien-5-one (2,6-dimethyl-4-pyrone-Hexyne-3 Adduct) (Ib).—A solution of 10.0 g (0.08 mol) of 2,6-dimethyl-4-pyrone, 100 g (1.2 mol) of 3-hexyne, and 150 ml of dioxane was prepared and added to the outer jacket of the immersion apparatus. The solution was flushed with nitrogen and irradiation begun. After 24 hr of irradiation, the solution was examined by glpc using the 6-ft 20% SE-30 column at 220°. It was seen that the desired adduct was present in a large yield and that little starting material remained. The volatile materials were removed on the rotating evaporator and the product was isolated by llpc using a heptane-Methyl Cellosolve system. The infrared spectrum of the product showed strong absorption bands at 6.05 and 6.20 μ. The nmr spectrum contained two methyl groups at δ 1.08 (triplets, J = 7 cps), one methyl group at δ 1.58 (singlet), one vinyl methyl group at δ 1.95 (singlet), two groups of methylene hydrogens centered at δ 2.12 (multiplet), one tertiary ring hydrogen at δ 3.10 (multiplet), and one vinyl hydrogen at δ 5.18 (singlet). The mass spectrum of the compound showed a molecular ion at *m/e* 206.

Anal. Cacld for $C_{13}H_{18}O_2$: C, 75.7; H, 8.8. Found: C, 76.0; H, 9.4.

2-Acetyl-3,4-diethyl-5-methylphenol (VIb) *via* Pyrolysis of Ib.—A solution of 0.15 g (0.001 mol) of Ib and 5 ml of *o*-dichlorobenzene was heated to reflux. The course of the reaction was followed by glpc, using the 6-ft 20% SE-30 column at 220°. After refluxing for 72 hr, it was shown that no starting material remained. The *o*-dichlorobenzene was removed by distillation and the product was isolated by llpc using a heptane-methanol system. By glpc and llpc it was shown that only one phenol was produced. The infrared spectrum of the product showed strong absorption bands at 3.03, 5.96, and 6.26 μ. The uv spectrum showed λ_{max}^{MeOH} 219, 260, and 290 mμ. The mass spectrum gave a molecular ion at *m/e* 206.

Registry No.—Ia, 27192-99-0; Ib, 27192-98-9; III, 27192-97-8; VIb, 27193-00-6; 2,6-dimethyl-4-pyrone, 1004-36-0.

Acknowledgments.—We thank Mr. L. Brancone and staff for the microanalyses, Mr. Fulmor and staff for the uv and nmr spectra, Mr. C. Pidacks and staff for the liquid-liquid partition chromatography, Drs. J. Karliner and G. Van Lear for the mass spectra, and Dr. J. Lancaster of the Central Research Division, American Cyanamid Co., Stamford, Conn., for the double irradiation experiments. We are also indebted to Professor H. Zimmerman, University of Wisconsin, for helpful discussions relating to this work.

Thermal Transformations of Medium-Ring Olefins

J. K. CRANDALL*[1a] AND R. J. WATKINS[1b]

Contribution Number 1893 from the Department of Chemistry, Indiana University, Bloomington, Indiana 47401

Received August 26, 1970

The pyrolysis of cycloheptene, cyclooctene, cyclononene, and cyclododecene has been studied in a flow system at relatively high temperatures. Two major reaction processes obtain, namely isomerization of the cycloalkene to an α,ω-diene and to a ring-contracted vinylcycloalkane. Both of these reactions are reversible. Related transformations occur with 3- and 4-cyclooctenone. The details of these reactions are discussed.

In connection with photochemical studies on medium-ring ketones possessing nonconjugated double bonds,[2,3] it was of interest to compare the thermally induced transformations of such substrates. Two examples are described at the end of the present paper. In order to provide perspective for this work, a product survey on the pyrolysis of simple medium-ring olefins was performed.

Pyrolysis of either *cis*-cyclononene or *trans*-cyclononene at 720° in a flow system at reduced pressure promoted complete conversion to 1,8-nonadiene and vinylcycloheptane in a 4:1 ratio. The reaction was remarkably clean in that no other important products were observed. Resubmission of 1,8-nonadiene to the reaction conditions resulted in 65% conversion to 1,5-hexadiene and, significantly, a trace of both *cis*-cyclononene and vinylcycloheptane. The vinyl compound, on the other hand, was not substantially decomposed under the thermolysis conditions, although it gave detectable amounts of *cis*-cyclononene and 1,8-nonadiene. No *trans*-cyclononene was observed from the pyrolysis of either product. Thermolysis of *cis*- and *trans*-cyclononene at various temperatures led to variations in the product mixtures as summarized in Table I.

TABLE I
PYROLYSIS OF CYCLONONENE AT VARIOUS TEMPERATURES

Temp, °C	1	2	3	4	Ratio of 3/4
720	0[a]	0	80	20	4
620	54[a]	0	43	3	14
520	93[a]	0	67	0.3	23
720	0	0[a]	80	20	4
620	0	1[a]	92	7	13
520	0	49[a]	49	2	24

[a] Starting material.

Rearrangement of either *cis*-cyclododecene or *trans*-cyclododecene at 720° yielded 1,8-nonadiene, 1,11-dodecadiene, vinylcyclodecane, *cis*-cyclododecene, and *trans*-cyclododecene in the same 5:34:3:20:32 ratio. Resubmission of vinylcyclodecane to the reaction conditions produced 1,8-nonadiene, 1,11-dodecadiene, *cis*-cyclododecene, and *trans*-cyclododecene in a 5:34:20:32 ratio. 1,11-Dodecadiene, on the other hand, was 35% converted to 1,8-nonadiene as the sole product.

Pyrolysis of *cis*-cyclooctene produced 1,5-hexadiene, 1,7-octadiene, and vinylcyclohexane in a 3:78:14 ratio plus about 5% of uncharacterized lower molecular weight products. The vinyl compound was not substantially transformed to other materials under the reaction conditions, but careful gc analysis indicated a trace of cyclooctene and 1,7-octadiene. Thermolysis of 1,7-octadiene resulted in 35% conversion to 1,5-hexadiene and minute amounts of cyclooctene and vinylcyclohexane.

Pyrolysis of cycloheptene at 800° generated a complex product mixture. Six components in a 55:14:3:6:15:5 ratio were isolated in addition to 25% unreacted starting material and identified as vinylcyclopentane, 1,6-heptadiene, 4-methylcyclohexene, cyclopentadiene, benzene, and toluene. Submission of vinylcyclopentane or 1,6-heptadiene to the reaction conditions afforded essentially the same product mixture obtained from cycloheptene. At 800°, 4-methylcyclohexene was transformed completely to benzene and toluene in a 4:1 ratio and cyclopentene was converted to cyclopentadiene.

The isomerization of medium-ring olefins (**1** or **2**) to α,ω-dienes (**3**) was first reported by Blomquist[4] and later extended by Rienäcker.[5] The latter author also noted that pyrolysis of *cis*-cyclodecene under certain conditions gave about 5% of vinylcyclooctane in addition to 1,9-decadiene. The present work, which was performed at reduced pressure and generally higher temperatures, extends the range of observed transformation to α,ω-dienes and demonstrates the universal nature of the allylic rearrangement leading to ring-contracted vinylcycloalkanes (**4**). Considering the sum total of the data, it seems secure to conclude that both of these reactions are reversible. Reconversion of the α,ω-dienes to cycloalkenes is appreciable for the C_7 compound and small but clearly demonstrated reversion was observed for the C_8 and C_9 dienes. The reversibility of the C_8 system has been explored previously.[6] The C_{12} diene did not reclose but this is probably a result of its more facile fragmentation to give 1,9-nonadiene. The vinyl compounds showed trace reconversion to cycloalkenes for C_8 and C_9 systems and appreciable amounts with the C_7 and C_{12} compounds.

The identical nature of the product mixtures obtained from either geometrical isomer of cyclododecene or cyclononene (see Table I) is noteworthy and could indicate preequilibration ($1 \rightleftarrows 2$) or a common intermediate in these reactions. Geometrical isomerism is indeed observed for the C_{12} system. The trans C_8[6] and C_9 olefins are more reactive than their cis isomers as expected on the basis of the more strained nature of the smaller *trans*-cycloalkenes. The higher reactivity and lower thermodynamic stability of these trans olefins accounts for their nonaccumulation in the pyrolysates, but the

(1) (a) Alfred P. Sloan Research Fellow 1968–1970; (b) Petroleum Research Fund Graduate Fellow.

(2) J. K. Crandall, J. P. Arrington, and J. Hen, *J. Amer. Chem. Soc.*, **89**, 6208 (1967).

(3) J. K. Crandall, J. P. Arrington, and R. J. Watkins, *Chem. Commun.*, 1052 (1967).

(4) A. T. Blomquist and P. R. Taussig, *J. Amer. Chem. Soc.*, **79**, 3505 (1957); see also A. C. Cope and M. J. Youngquist, *ibid.*, **84**, 2411 (1962).

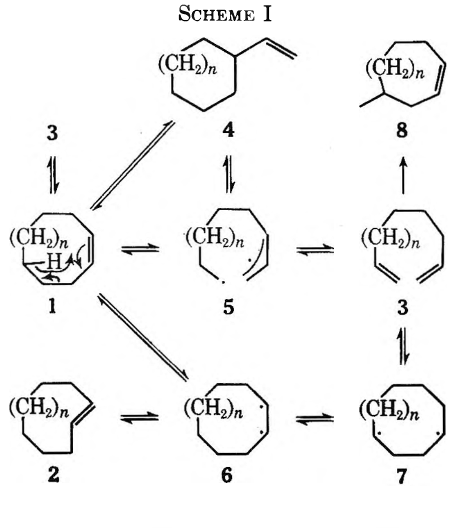
(5) R. Rienäcker, *Brennst.-Chem.*, **45**, 206 (1964).

(6) W. R. Roth, *Chimia*, **20**, 229 (1966).

lack of favorable trans to cis isomerization in the C_9 series speaks against cycloalkene preequilibration, unless only the trans isomer is reactive and it is transformed to products much more readily than it is isomerized to cis olefin. A more likely alternative is that the reaction pathway involves a common reactive intermediate which can be achieved from either cis or trans starting olefin.

The isomerization of cyclic olefins to α,ω-dienes is formally a reverse ene reaction.[7] This type of transformation is customarily considered to proceed by a concerted six-center mechanism, but stepwise, biradical conversions may obtain in certain instances. One such pathway involves homolysis of the allylic bond of the cycloalkene to give biradical **5** and disproportionation of this species (in just one of three possible ways) to yield α,ω-diene **3**. A second scheme proceeds by thermal activation of the olefin moiety to a vibrationally excited state best represented by biradical structure **6**; 1,5-hydrogen transfer (in one of two possible ways) then leads to 1,4-biradical **7** which can collapse to α,ω-diene in a straightforward fashion. Biradical **6**, of course, is the logical intermediate for cycloalkene geometrical isomerism[8] which was experimentally demonstrated for the C_{12} system. The reverse reaction (**3** → **1**) can be accommodated by any of the above mechanisms without insurmountable difficulty. It is interesting that the alternate ene reaction orientation (**3** → **8**) has been characterized only for the C_7 diene where 4-methylcyclohexene and its transformation products benzene and toluene are important components of the pyrolysis mixture. However, the minor extent of the cyclization reaction for the other α,ω-dienes may have obscured similar processes (see Scheme I).

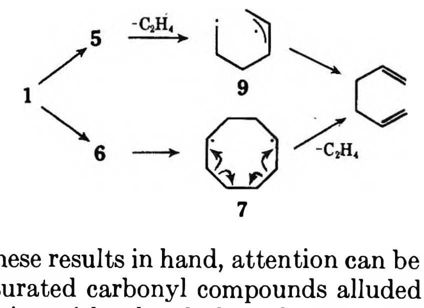
Scheme I



The two more obvious mechanistic routes from cycloalkene to vinylcycloalkane **4** are concerted [1,3]-sigmatropic rearrangement[9] in which a methylene group migrates from one end of an allylic moiety to the other, or the nonconcerted equivalent proceeding through intermediate biradical **5**. Current dogma requires that the concerted process occurs with inversion of configuration at the migrating center.

If generalization from the data obtained for cyclononene (Table I) is valid, there is a strong temperature dependence on the **3**:**4** ratio, which decreases with increasing temperature in the C_9 system. This situation is best rationalized by competition between two processes with reasonably different activation parameters *at the product determining stage* of the reaction. Attractive possibilities include competition between (a) the two concerted reactions, (b) a concerted pathway to **3** and the biradical route to **4**, (c) two biradical pathways involving partitioning between alternate biradicals **5** and **6**, and (d) the two different decomposition modes of biradical **5**. A small bias in favor of the last alternative derives from the discussion above regarding the likelihood of a common intermediate from the *cis-* and *trans-*cycloalkene. However, clear distinction among the various possibilities must await more incisive experimentation, particularly the quantitative determination of activation parameters and further discussion is best deferred until this data is available.

In addition to the isomerization reactions induced by thermolysis of the cycloalkenes, various amounts of fragmentation to smaller hydrocarbons were observed. One relatively important such process involves conversion of the α,ω-diene to a lower α,ω-diene by the loss of a three-carbon fragment, propene. This reaction is a simple ene fragmentation and was characterized in the present study for the C_9 and C_{12} compounds. A less obvious fragmentation is the elimination of ethylene to give 1,5-hexadiene in the C_8 system. The formation of cyclopentadiene from cycloheptene is probably the result of a similar process involving the intermediacy of pentadienes[10] and cyclopentene.[11] It is interesting and perhaps significant that the loss of ethylene was not an important reaction with the higher homologs. One direct explanation for the loss of ethylene utilizes biradical **5** which can split out this small molecule with the formation of a new biradical **9**, a potential precursor of 1,5-hexadiene.[12] However, the operation of this mode of reaction of **9** to the exclusion of the other disproportionation and combination possibilities seems a little peculiar. Cyclohexene, which is not substantially decomposed by the pyrolysis conditions, is especially anticipated from **9**. An alternate and intriguing possibility invokes the indicated fragmentation of biradical **7**. A similar process can obtain for the C_7 system but not for the higher homologs, in accord with experimental observation.



With these results in hand, attention can be turned to the unsaturated carbonyl compounds alluded to above in connection with related photochemical studies. Pyrolysis of 4-cyclooctenone (**10**) at 720° gave 63% 3-

(7) H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).

(8) S. W. Benson, "Thermochemical Kinetics," Wiley, New York, N. Y., 1968, pp 72–75.

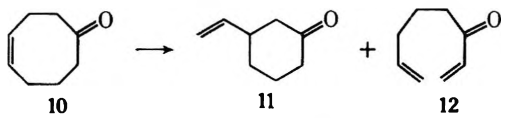
(9) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(10) For example, pyrolysis of piperylene under the indicated conditions gives partial conversion to cyclopentadiene.

(11) J. E. Baldwin, *Tetrahedron Lett.*, 2953 (1966); D. W. Vanas and W. D. Walters, *J. Amer. Chem. Soc.*, **70**, 4035 (1948).

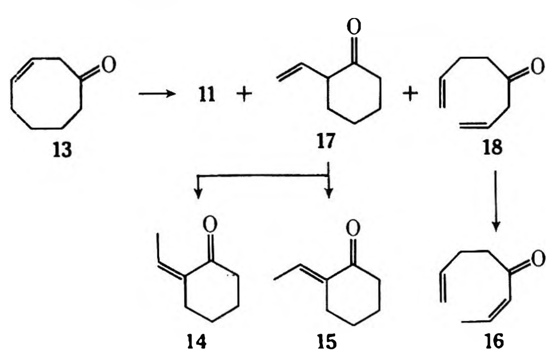
(12) Reference 8, pp 121–129.

vinylcyclohexanone (11), 10% octa-1,7-dien-3-one (12), and a host of uncharacterized minor components.[3] Thus the rearrangement of 10 parallels that of cyclooctene itself. The placement of the carbonyl function allows for only one mode for reverse ene reaction in this unsymmetrical system. The major product is the allylic rearrangement product 11 in which the migrating



methylene group has an adjacent carbonyl function, presumably a beneficial situation. Little, if any of the other possible allylic isomerization product, 4-vinylcyclohexanone, is present. Interestingly, pyrolysis of 3-vinylcyclohexanone under these conditions was without effect.

The thermolysis of 3-cyclooctenone (13) at 720° yielded *cis*- and *trans*-2-ethylidenecyclohexanone (14 and 15), 3-vinylcyclohexanone (11), and *cis*-octa-2,7-dien-4-one (16) in a 19:28:12:15 ratio. A plethora of minor products accompanied these important constituents. Compounds 14 and 15 are almost certainly secondary products derived from 2-vinylcyclohexanone (17), which is known to isomerize readily to these materials.[2] The acyclic ketone is probably also formed by secondary isomerization of octa-1,7-dien-4-one (18), the expected ene fragmentation product. In fact, careful examination of the spectral data indicates that there was about 20% 18 in the sample of 16. Enolization and subsequent 1,5-hydrogen transfer accounts for the 18 → 16 transformation including the less stable cis stereochemistry of 16. Insofar as the allylic isomerization is concerned, both possible processes appear to obtain. It is noteworthy that migration of the carbonyl carbon (13 → 17) is favored over that of the methylene group (13 → 18) though only by a factor of about 4.



Comparison of these results with the photochemical studies lead to the conclusion that, although there is some overlap of product from the two types of reactions, the thermal processes are much less specific and, furthermore, these appear to be regulated by the double bond and not by the carbonyl function as in the photochemical transformations.

Experimental Section

General.—Nmr spectra were obtained with a Varian HR-100 instrument (CCl_4) and infrared spectra (ir) with a Perkin-Elmer 137 spectrophotometer (neat samples). Gas chromatography (gc) was performed on Aerograph A1200 (analtyical) and A90-P3 (preparative) instruments. The analytical column was 10 ft × 1/8 in. 15% Carbowax 20M on 60–80 Chromosorb W; the preparative column was 20 ft × 1/8 in. 15% Carbowax 20M on 60–80 Chromosorb W. Percentage composition data on product mixtures were estimated by peak areas and are uncorrected. Mass spectra were obtained at 70 eV on an AEI-MS9 instrument. Starting materials were purified by preparative gas chromatography.

General Pyrolysis Procedure.—The thermal rearrangements were effected on a vacuum pyrolysis system consisting of a quartz column, 10 × 170 mm, packed with quartz chips passing through an E. H. Sargent and Co. tube furnace. The sample was placed in a 5-ml flask attached at one end of the tube and a trap, 20 × 150 mm, cooled with Dry Ice–acetone was attached to the other end of the tube. Vacuum was applied at the trap and the pyrolysate collected in the trap. Analysis of product mixtures was by analytical gc, while product separation was achieved by preparative gc.

***trans*-Cyclononene.**—A stirred solution of 6 g of *cis*-cyclononene[13] in 650 ml of benzene was irradiated for 7 hr using a 450 W Hanovia Type L mercury lamp without a filter. Removal of the solvent by distillation through a glass-helices packed column yielded 6 g of a mixture of *cis*-cyclononene and *trans*-cyclononene in a 4:1 ratio. The mixture was placed on a column containing 350 g of 20% silver nitrate–silica gel[14] and elution with pentane afforded, after evaporation of the solvent, 0.9 g (15%) of *trans*-cyclononene: ir 6.1 and 10.3 μ; nmr δ 5.3 (m, 2, CH=CH), 2.2 (m, 4, $C{=}CCH_2$), and 1.6 (m, 10, CH_2).

Pyrolysis of *cis*-Cyclononene.—Pyrolysis of 0.7 g of *cis*-cyclononene at 720° resulted in complete conversion to two products in a 4:1 ratio. The major product was identified as 1,8-nonadiene: ir 3.3, 6.07, 10.1, and 11.0 μ; nmr δ 5.7 (m, 2, C=CH), 4.9 (m, 4, $C{=}CH_2$), 2.05 (m, 4, $C{=}CCH_2$), and 1.35 (m, 6, CH_2). The minor product was identified as vinylcycloheptane:[15] ir 3.3, 6.1, 10.1, and 11.0 μ; nmr δ 5.7 (m, 1, C=CH), 4.8 (m, 2, $C{=}CH_2$), and a broad resonance from 2.2 to 1.2 accounting for thirteen ring protons; mass spectrum *m/e* (rel intensity) 124 (5), 109 (11), 96 (62), 95 (100), 81 (56), 67 (97), 55 (67), 54 (68), and 41 (69). No *trans*-cyclononene was observed.

Pyrolysis of *trans*-Cyclononene.—Pyrolysis of 0.3 g of *trans*-cyclononene at 720° resulted in complete conversion to 1,7-nonadiene and vinylcycloheptane in a 4:1 ratio. No *cis*-cyclononene was observed.

Pyrolysis of 1,8-Nonadiene.—Pyrolysis of 50 mg of 1,8-nonadiene at 720° resulted in 65% conversion to 1,5-hexadiene as well as a trace of *cis*-cyclononene and vinylcycloheptane.

Pyrolysis of Vinylcycloheptane.—A 25-mg sample of vinylcycloheptane was pyrolyzed under the reaction conditions and produced 1% *cis*-cyclononene and 1% 1,8-nonadiene.

***cis*-Cyclododecene and *trans*-Cyclododecene.**—A commercial sample of cyclododecene (Columbian Carbon Co.) was separated by preparative gc.

Pyrolysis of *cis*-Cyclododecene.—Pyrolysis of 1.1 g of *cis*-cyclododecene at 720° resulted in the formation of four products and starting material in the ratio 5:34:3:32:20. The products were separated by preparative gc from the 0.95 g (86%) of pyrolysate. The 5, 34, 32, and 20% products were identified as 1,8-nonadiene, 1,11-dodecadiene, *trans*-cyclododecene, and *cis*-cyclodododecene, respectively, by comparison with authentic samples. The 3% product was identified as vinylcyclodecane: ir 3.3, 6.1, 10.05, and 11.0 μ; nmr δ 5.7 (m, 1, C=CH), 4.9 (m, 2, $C{=}CH_2$), a broad resonance from 2.3 to 2.1 (1, C=CCH), and a broad singlet at 1.55 (s, 18, CH_2); mass spectrum *m/e* (rel intensity) 166 (3), 137 (53), 109 (40), 95 (61), 81 (100), 67 (90), 55 (95), and 41 (94).

Pyrolysis of *trans*-Cyclododecene.—Pyrolysis of 0.5 g at 720° produced the same products in the same ratios as were observed from rearrangement of *cis*-cyclododecene.

Pyrolysis of 1,11-Dodecadiene.—Pyrolysis of a 10-mg sample of 1,11-dodecadiene under the reaction conditions resulted in 35% conversion to 1,8-nonadiene. No *cis*- or *trans*-cyclododecene was observed.

Pyrolysis of Vinylcyclodecane.—Pyrolysis of 5 mg of vinylcyclodecane at 720° produced 1,8-nonadiene, 1,11-dodecadiene, and *cis*- and *trans*-cyclododecene in a 5:34:32:20 ratio.

Pyrolysis of *cis*-Cyclooctene.—Pyrolysis of 1.5 g at 720° pro-

(13) P. D. Gardner and M. Narayana, *J. Org. Chem.*, **26**, 3518 (1951).

(14) E. C. Murray and R. N. Keller, *ibid.*, **34**, 2234 (1969).

(15) Prepared by the method of G. Zweifel, H. Arzoumanian, and C. C. Whitney, *J. Amer. Chem. Soc.*, **89**, 3652 (1967).

duced 1.3 g (86%) of pyrolysate. Gc analysis indicated 91% conversion to three products in a 78:14:3 ratio plus 5% of uncharacterized fragmentation products.

The major product was identified as 1,7-octadiene by comparison with an authentic sample. The 14% product was identified as vinylcyclohexane: ir 3.3, 6.1, 10.1, and 11.0 μ; nmr δ 5.7 (m, 1, C=CH), 4.85 (m, 2, $C=CH_2$), and broad multiplets at 1.7 and 1.2 accounting for eleven ring protons; mass spectrum m/e (rel intensity) 110 (29), 95 (18), 81 (100), 67 (68), 54 (36), and 41 (40). The minor product was 1,5-hexadiene.

Pyrolysis of Vinylcyclohexane.—A 0.3-g sample was pyrolyzed at 720° and found to be stable. Only 1% each of 1,7-octadiene and cyclooctene were produced.

Pyrolysis of 1,7-Octadiene.—Pyrolysis of 0.9 g under the reaction conditions resulted in 35% conversion to 1,5-hexadiene as well as a trace of cyclooctene and vinylcyclohexane.

Pyrolysis of Cycloheptene.—Pyrolysis of 1.2 g at 800° resulted in 75% conversion to six products in the ratio 55:14:6:15:5:3. The products were isolated by preparative gc from the 1.0 g (84%) of pyrolysate.

The major product was identified as vinylcyclopentane: ir 3.3, 6.1, 10.1, and 11.0 μ; nmr δ 5.75 (m, 1, C=CH), 4.85 (m, 2, $C=CH_2$), and a broad, nine-proton resonance from 2.6 to 1.2 (ring protons); mass spectrum m/e (rel intensity) 96 (18), 81 (18), 68 (31), 67 (100), 54 (26), and 41 (16).

The 14% product was identified as 1,6-heptadiene: ir 3.3, 6.1, 10.1, and 11.0 μ; nmr δ 5.75 (m, 2, C=CH), 4.85 (m, 4, $C=CH_2$), 2.0 (m, 4, $C=CCH_2$), and 1.5 (m, 2, CH_2); mass spectrum m/e (rel intensity 96 (6), 81 (61), 68 (31), 67 (57), 55 (99), 54 (100), 39 (57), and 29 (76).

The other minor products were identified as cyclopentadiene, benzene, toluene, and 3-methylcyclohexane by comparison of their spectral properties with authentic samples.

1,6-Heptadiene.—The apparatus described by Bailey and King[16] was used for the pyrolysis at 525° of 17 g of 1,7-diacetoxyheptane. The crude pyrolysate was treated in the usual manner and removal of the solvent yielded 1,6-heptadiene,[17] bp 89–91°, and 7-acetoxy-1-heptene, bp 92–95° (22 mm), in a 3:2 ratio.

Pyrolysis of 1,6-Heptadiene.—A 1.2-g sample was pyrolyzed at 800° and gave 0.85 g (71%) of yellow pyrolysate. Gc analysis indicated vinylcyclopentane, 1,6-heptadiene, cycloheptene, cyclopentadiene, benzene, toluene, and 4-methylcyclohexene in a 55:12:14:3:10:3:3 ratio.

Pyrolysis of Vinylcyclopentane.—Pyrolysis of 0.7 g at 800° produced 0.55 g (79%) of pyrolysate. Gc analysis indicated the same products in the same ratios as obtained from thermolysis of 1,6-heptadiene.

Pyrolysis of Cyclopentene.—Pyrolysis of 1.1 g of cyclopentene at 800° resulted in 86% conversion to cyclopentadiene.

Pyrolysis of 4-Methylcyclohexene.—Pyrolysis of 15 mg at 800° gave 97% conversion to benzene and toluene in a 4:1 ratio.

4-Cyclooctenone.—To a cooled, stirred solution of 70 g of 4-cyclooctenol[18] in 500 ml of acetone was added dropwise 160 ml of 8 *N* chromic acid. The addition required 1.5 hr, and stirring was continued for an additional 45 min at room temperature. The mixture was poured into 500 ml of water and extracted with five 150-ml portions of pentane. The pentane extracts were combined, washed twice with water, dried, and concentrated. The residue was distilled through an annular Teflon spinning-band column to give 44 g (64%) of 4-cyclooctenone: bp 75–85° (10 mm); ir 3.3, 5.87, and 6.1 μ; nmr δ 5.65 (m, 2, CH=CH), 2.5 to 1.9 (m, 8, CH_2), and 1.5 (m, 2, CH_2).

Pyrolysis of 4-Cyclooctenone.—Pyrolysis of 1.1 g at 720° gave 0.9 g (82%) of pyrolysate which contained 63% 3-vinylcyclohexanone[8] and 10% octa-1,7-dien-3-one plus a host of minor products. Octa-1,7-dien-3-one was identified on the basis of spectral properties: uv max (hexane) 217 mμ (ϵ 8700); ir 5.93, 6.1, 6.2, 10.1, and 11.0 μ; nmr δ 6.2, 5.7, and 4.9 (m, 6, $CH=CH_2$), 2.53 (t, 2, J = 7 Hz, $COCH_2$), 2.0 (m, 2, $C=CCH_2$), and 1.67 (m, 2, CH_2).

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.13; H, 9.58.

Pyrolysis of 3-Cyclooctenone[2] (13).—Pyrolysis of 1.3 g of **13** at 720° yielded 1.1 g (85%) of pyrolysate which contained *cis*-2-ethylidenecyclohexanone (**14**), *trans*-2-ethylidenecyclohexanone (**15**), 3-vinylcyclohexanone (**11**), and an unknown material in a 19:28:12:15 ratio as well as a plethora of minor products. Authentic samples were available.[2] The remaining compound displayed the following spectral properties consistent with assignment as **16**: uv max (hexane) 224 mμ (ϵ 12,900); ir 5.89, 6.09. 6.16, 10.1, and 11.0 μ; nmr (220 MHz) δ 6.03 (close m, *cis*-COCH=CH),[19] 5.8 (m, $CH=CH_2$), 5.0 (m, $CH=CH_2$), 2.4 (m, CH_2), 2.3 (m, CH_2), and 2.06 (d, $C=CHCH_3$). The presence of about 20% **18** was indicated by an ir band at 5.81 μ, nmr integral deviations, and a very characteristic nmr doublet at δ 3.06 (J = 8 Hz) attributed to a methylene group substituted by carbonyl and olefin moieties (see nmr of **13**).[2]

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.43; H, 9.63.

Upon catalytic hydrogenation this material produced 4-octanone.

Registry No.—**10**, 6925-14-0; **13**, 4734-90-1; cycloheptene, 628-92-2; *cis*-cyclooctene, 931-87-3; *cis*-cyclononene, 933-21-1; *trans*-cyclononene, 3958-38-1; *cis*-cyclododecene, 1129-89-1; *trans*-cyclododecene, 1486-75-5.

Acknowledgment.—We thank Dr. C. F. Mayer for advice and experimental assistance.

(16) W. J. Bailey and C. King, *J. Amer. Chem. Soc.*, **77**, 75 (1955).

(17) A. Maccioni and M. Secci, *Ann. Chim. (Rome)*, **54**, 266 (1964).

(18) J. K. Crandall, D. B. Banks, R. A. Colyer, R. J. Watkins, and J. P. Arrington, *J. Org. Chem.*, **33**, 423 (1968).

(19) This assignment follows from comparison with the distinctive nmr spectra of *cis*- and *trans*-3,7-octadien-2-one: J. K. Crandall and C. F. Mayer, *ibid.*, **35**, 3049 (1970).

Acid-Catalyzed and Thermal Isomerization in the Methylcyclohexadiene System. Elimination of Ethanol from Ethyl Methylcyclohexenyl Ethers

CHARLES W. SPANGLER*[1] AND RONALD P. HENNIS

The Michael Faraday Laboratories, Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115

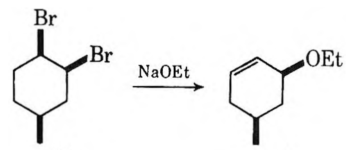
Received July 1, 1970

Acid-catalyzed elimination of ethanol from various ethyl methylcyclohexenyl ethers by either activated alumina at elevated temperatures or potassium hydrogen sulfate yields complex mixtures of all possible methyl-1,3-cyclohexadienes, 3-methylenecyclohexene, and toluene. At 250 and 300°, the products are consistent with simple eliminations involving intermediary allylic carbonium ions, followed by alumina-catalyzed isomerization of the diene mixture, although the mechanism by which this occurs is obscure. Thermal isomerization of the product methyl-1,3-cyclohexadienes *via* [1,5]-sigmatropic hydrogen migration is not important at temperatures much below 325° under nonequilibrium fast-flow conditions, although alumina-catalyzed isomerization is extensive.

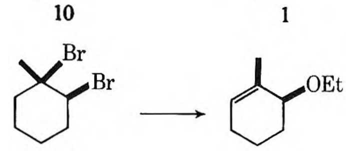
In our investigations of the various mechanistic pathways involved in the alumina-catalyzed vapor phase dehydration of substituted hexadienols,[2] we recently postulated that the complex product mixtures can be rationalized on the basis of electrocyclic ring closure of intermediate trienes followed by cyclohexadiene isomerization resulting from intramolecular [1,5]-sigmatropic hydrogen shifts. At that time, however, we had no direct experimental evidence for the latter portion of this mechanism, nor could we estimate the relative contribution of acid-catalyzed isomerization of the product methyl-1,3-cyclohexadienes. We would now like to report on the magnitude and relative contributions of both acid-catalyzed and thermal isomerization in the generation of the methyl-1,3-cyclohexadiene system.

Most preparations of alkyl-1,3-cyclohexadienes reported in the literature involve, as the final step, an acid-catalyzed elimination reaction. One procedure which can be utilized is that of Hofmann and Damm,[3] which generates the diene system by acid-catalyzed decomposition of an appropriately substituted cyclohexenyl ethyl ether. Pines and coworkers[4,5] reported the synthesis of several substituted 1,3-cyclohexadienes by this procedure. In some instances isomerization occurred,[5] but for the most part unrearranged cyclohexadienes were reported as primary products. Thus this system seemed to be well suited to determine the extent of acid-catalyzed isomerization of the cyclohexadiene products by comparison of the alumina and potassium hydrogen sulfate product ratios.

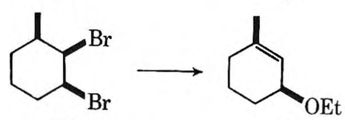
Bromination of the three isomeric methylcyclohexenes was accomplished in good yield. Reaction of the resulting purified bromides with sodium ethoxide yielded the desired methylcyclohexenyl ethyl ethers whose structures and purities were confirmed by nmr and glpc. The results are illustrated in eq 1–3.



10 1 (1)



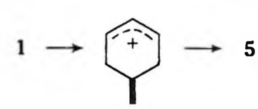
11 2 (2)



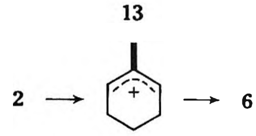
12 3 (3)

Methylcyclohexadienes were generated from ethyl methylcyclohexenyl ethers or methylcyclohexenols by either of the following: (1) distillation from potassium hydrogen sulfate, or (2) vapor phase passage over alumina (250–300°). Similarly, isomerization of methyl-1,3-cyclohexadiene mixtures of known composition was accomplished by passage through a dehydration column packed with either Pyrex helices or alumina (300–350°). Table I summarizes the results of the elimination reactions, while the thermolytic results are shown in Table II.

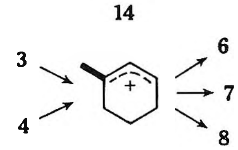
Distillation of either **1**, **2**, or **3** from potassium hydrogen sulfate or passage through an activated alumina column at 250–300° produced mixtures of the desired methyl-1,3-cyclohexadienes. In no case was a pure product obtained, although the major product in each was that predicted on the basis of simple 1,2 elimination. A much more reasonable supposition, however, is that each ether procedes through an allylic carbonium ion from which the dienic products are then formed. This would explain the product distribution obtained from alumina-catalyzed elimination to a first approximation.



13



14



15

Examination of the results obtained in Table I shows that **1** and **2** do yield the expected methyl-1,3-cyclohexadienes **5** and **6** in good yield at 250°. In confirmation of the intermediacy of **15**, both **3** and **4** were passed over alumina at 250°, and similar product distributions were obtained. The differences in minor product for-

(1) Author to whom inquiries are to be addressed.

(2) C. W. Spangler and N. Johnson, *J. Org. Chem.*, **34**, 1444 (1969).

(3) F. Hofmann and P. Damm, *Mitt Kohlenforschungsmit Breslau*, **2**, 113, 127 (1925); *Chem. Abstr.*, **22**, 1249 (1928).

(4) H. Pines and R. H. Koslowski, *J. Amer. Chem. Soc.*, **78**, 3776 (1956).

(5) H. Pines and C. Chen, *ibid.*, **81**, 928 (1959).

Table I

Acid-Catalyzed Elimination Products

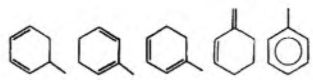
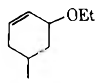
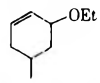
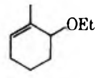
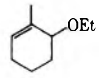
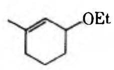
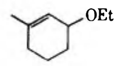
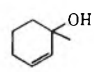
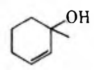
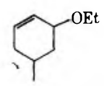
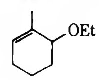
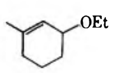
Compd (no.)		Catalyst (temp, °C)	% of total product				
			 5	6	7	8	9
	(1)	Al_2O_3 (250)	73	6	10	4	7
	(1)	Al_2O_3 (300)	73	7	11	3	5
	(2)	Al_2O_3 (250)	8	69	8	9	6
	(2)	Al_2O_3 (300)	7	29	41	14	9
	(3)	Al_2O_3 (250)	12	24	41	14	9
	(3)	Al_2O_3 (300)	13	24	39	15	9
	(4)	Al_2O_3 (250)	0	39	27	34	0
	(4)	Al_2O_3 (300)	1	33	46	20	0
	(1)	$KHSO_4$ (100)	73	8	14	4	1
	(2)	$KHSO_4$ (100)	0	41	35	22	2
	(3)	$KHSO_4$ (100)	18	18	46	14	2

Table II

Thermolyses of Methyl-1,3-cyclohexadienes[a]

Support (temp, °C)	Feed mixture, % of total			Product mixture, % of total		
	1-Me	2-Me	5-Me	1-Me	2-Me	5-Me
Helices (300)	12	8	80	13	8	79
Al_2O_3 (300)[b]	12	8	80	35	25	26
Helices (325)	12	8	80	41	12	47
Al_2O_3 (325)[c]	12	8	80	41	27	15
Helices (350)	15	8	77	61	25	13
Al_2O_3 (350)[d]	15	8	77	42	28	11
Helices (350)	46	54	0	51	41	8
Helices (350)	56	22	22	57	29	14

[a] Sealed tube, 150°, 24 hr or until no further change: 70% 1-Me, 20% 2-Me, 10% 5-Me. [b] 7% **8** and 7% **9** also formed. [c] 9% **8** and 7% **9** also formed. [d] 9% **8** and 10% **9** also formed.

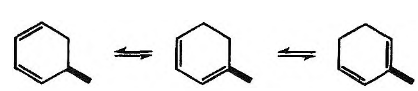
mation (**5** and **9**) can be attributed to kinetic control in the major product formation step, followed by separate isomerization reactions leading to **5** and **9**.

Elimination of ethanol from **1**, **2**, and **3** by the action of potassium hydrogen sulfate yields results similar to those obtained from alumina, indicating extensive isomerization of the initial product or rearrangement of the intermediate carbonium ions. One major difference between the alumina and $KHSO_4$ reactions is the percentage of toluene. The methylcyclohexadiene to toluene conversion over alumina is well known[6] and can be a serious side reaction; hence this variance in products is to be expected.

In order to estimate the magnitude of acid-catalyzed isomerization of methyl-1,3-cyclohexadienes formed by the elimination of ethanol or water, a mixture of known composition was thermolyzed at 300, 325, and 350° over both alumina and Pyrex helices. It can readily be seen that at 300 and 325° the quantity of thermal isomerization is much less than the corresponding passage over alumina. While the absolute numbers are obviously dependent on type of alumina, flow rate,[7] porosity, etc., it does indicate that the more important mode of cyclohexadiene isomerization at temperatures much below 350° is alumina-catalyzed as opposed to [1,5]-sigmatropic hydrogen migration which is dominant at temperatures of 350° or higher.

These results substantiate, to a large degree, our previous postulate that substituted 1,3-cyclohexadienes undergo rapid reversible isomerization resulting in a dynamic mixture of positional isomers in any reaction in which these structures are generated at elevated temperatures. However, we tended to ascribe this isomerization almost exclusively to rapid reversible thermal [1,5]-sigmatropic rearrangement of hydrogen. As can readily be seen from the thermal studies, this is a facile process at 350°, and possible at 325°, but becomes much less important at 300 and 250°. That the process is a dynamic set of equilibria is apparent from examination of initial *vs.* final product ratios. Isomerization occurs in the direction one would predict for the expected thermodynamic distributions,[8] although it would be entirely fortuitous and quite unexpected if these values actually correspond to equilibrium values at 350°. It must be kept in mind that all of these experiments attempt to duplicate on-column nonequilibrium flow conditions followed by rapid quenching. It would therefore be unrealistic to expect equilibrium to be achieved during the relatively short residence times[9] in the hot zones.

The appearance of the less stable 5-methyl-1,3-cyclohexadiene in all cases regardless of its presence or absence in the feed mixture indicates the reversibility of the [1,5] shifts under thermolytic conditions. The possibility of carbonium mechanisms operating at these tem-



5 **7** **6**

peratures (325° and above) was eliminated by adding 3-methylenecyclohexene to any of the above mixtures. In all cases, the exocyclic diene survives quantitatively. This, we feel, further substantiates the sigmatropic nature of the isomerization in the absence of alumina in that this diene cannot assume the necessary cisoid configuration.[10] Further, Bates and coworkers[8] have defi-

(6) C. W. Spangler, *J. Org. Chem.*, **31**, 346 (1966).

(7) It is of particular importance in comparing results between alumina and helices that the flow rates be matched quite accurately and maintained throughout the course of the reaction.

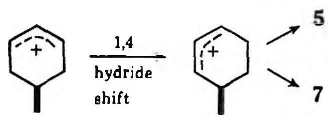
(8) R. B. Bates, E. S. Caldwell, and H. P. Klein, *ibid.*, **34**, 2615 (1969).

(9) It has been estimated here and previously (see ref 1) that contact or residence times in the heated zone is *ca.* 45 sec.

(10) (a) H. M. Frey and R. Walsh, *Chem. Rev.*, **69**, 103 (1969); (b) R. B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry," Verlag Chemie–Academic Press, Weinheim/Bergstr., 1970, pp 114–140.

nitely shown that exocyclic and endocyclic dienes will equilibrate under either acid or base catalysis.

The question remains, once one eliminates sigmatropic hydrogen migration as a specific cause, as to the probable source of cyclohexadiene isomerization at temperatures below 300°. Alumina, presumably *via* acid catalysis, is capable of causing such isomerization and in so doing also generates **8** and **9**. A comparison of product distributions (Table II) at 250 and 300° shows an apparent anomally for **1** in that the product ratios appear to be independent of temperature. In fact, $KHSO_4$ elimination produces an almost identical distribution for **1** at a temperature at least 100° lower. A somewhat similar observance may be made for **3**, while for **2** there is a large temperature dependence and nonsimilar results with $KHSO_4$. These observations of product distributions indicate that kinetic control of product formation is operative. If such is the case, an alternative explanation to acid-catalyzed isomerization would be rearrangement of the intermediate allylic carbonium ions **13**, **14**, and **15**, probably *via* hydride shifts, for example



13

It is indeed possible, if not probable, that rearrangements involving 1,2-, 1,3-, and 1,4-hydride shifts compete with acid catalysis throughout the whole range of temperatures normally utilized in cyclohexadiene production, and that the observed product distributions at various temperatures are the sum of several independent kinetically controlled isomerization pathways. Therefore, even though we have shown that alumina can cause isomerization, the exact mechanism, if indeed only one exists, remains obscure. Sigmatropic isomerization, however, does not assume major proportions until reactions approach 325° in a nonequilibrium flow situation.

Experimental Section[11]

3-Ethoxy-5-methylcyclohexene (**1**).—1,2-Dibromo-4-methylcyclohexane[12] (384 g, 1.5 mol) was added to a mixture of sodium (4 g-atoms) in 1200 ml of absolute alcohol. The mixture was refluxed for 4 hr, cooled, and filtered to remove precipitated sodium bromide. The salt was washed with several 200–300-ml portions of ether, and the combined organic solution was washed with several 200-ml portions of water. The resulting ether solution of **1** was then separated and dried with anhydrous magnesium sulfate. Distillation at reduced pressure yielded **1** (130 g, 62%), bp 60–62° (14 mm), n^{27}D 1.4464 (lit.[13] bp 155°, n^{18}D 1.4490). Glpc indicated a purity of at least 96%, with a trace of the isomeric 3-ethoxy-6-methylcyclohexene. The nmr spectrum revealed a multiplet, τ 4.3 (2 vinyl protons); multiplet, τ 5.9–6.7 (3 protons α to ether linkage); broad multiplet, 7.8–8.6 (5 protons, methylene and methyne); triplet, τ 8.8 (3 protons, ether methyl, J = 6 Hz); multiplet, τ 9.1 (3 protons, alicyclic methyl).

3-Ethoxy-2-methylcyclohexene (**2**).—1,2-Dibromo-1-methylcyclohexane[14] (243 g, 0.95 mol) was treated as described above for **1**. Distillation at reduced pressure yielded **2** (67 g, 51%), bp 54–56° (14 mm), n^{25}D 1.4535 [lit.[15] bp 61–62° (15 mm), n^{21}D 1.4550]. Glpc indicated a purity of at least 97%, with a trace of the isomeric 3-ethoxy-3-methylcyclohexene. The nmr spectrum revealed a broad singlet, τ 4.4 (1 vinyl proton); multiplet, τ 6.1–6.8 (3 protons α to ether linkage); broad multiplet, 8.3 (9 allylic and methylene protons); triplet, τ 8.8 (3 protons, ether methyl, J = 7 Hz).

3-Ethoxy-1-methylcyclohexene (**3**).—1,2-Dibromo-3-methylcyclohexane[16] (266 g, 1.04 mol) was treated as described above for **1** and **2**. Distillation at reduced pressure yielded **3** (56 g, 43%), bp 58–60° (11 mm), n^{25}D 1.4533. Glpc indicated a purity of at least 95% with a trace of 3-ethoxy-4-methylcyclohexene. The nmr spectrum revealed a multiplet, τ 4.2–4.6 (1 vinyl proton); multiplet, τ 6.1–6.8 (3 protons α to ether linkage); multiplet, τ 7.9–8.6 (9 allylic and methylene protons); triplet, τ 8.8 (3 protons, ether methyl, J = 7 Hz).

Alumina-Catalyzed Eliminations. A.—Through a 22-mm Pyrex tube packed to a depth of 12 in. with activated alumina[17] (8–14 mesh) and externally heated at 250° with a Lindberg Hevi-duty split-tube electric furnace was dropped 3-ethoxy-5-methylcyclohexene (20 g, 0.16 mol) at the rate of 0.5 ml/min. The alumina had been dried previously by heating the column at 300° under vacuum for 1 hr. A pressure of 20–25 mm was maintained in the system to facilitate rapid removal of the product from the column. The product was trapped in a flask immersed in a Dry Ice–acetone bath and subsequently warmed to room temperature, washed with water, and dried by filtration through anhydrous magnesium sulfate. After filtration the clear yellow liquid was distilled at reduced pressure and the volatile fraction collected. No attempt was made to maximize the yield (14 g, 93%). Glpc analysis showed the presence of five products. Each peak emanating from the chromatograph was trapped in a V tube immersed in a Dry Ice bath and identified by characteristic and known uv and nmr spectra:[2] 73% **5**, 6% **6**, 10% **7**, 4% **8**, and 7% **9**.

B.—3-Ethoxy-5-methylcyclohexene (20 g, 0.16 mol) was allowed to react as above at 300°. The crude product was isolated and purified (85% yield). Glpc analysis revealed the presence of the same five products: 73% **5**, 7% **6**, 11% **7**, 3% **8**, and 5% **9**.

C.—3-Ethoxy-2-methylcyclohexene (15 g, 0.12 mol) was allowed to react as above at 250°. Glpc analysis of the purified product (80%) yielded 8% **5**, 69% **6**, 8% **7**, 9% **8**, and 6% **9**.

D.—3-Ethoxy-2-methylcyclohexene (20 g, 0.16 mol) was allowed to react as above at 300°. Glpc analysis of the purified product (83%) yielded 7% **5**, 29% **6**, 41% **7**, 14% **8**, and 9% **9**.

E.—3-Ethoxy-1-methylcyclohexene (20 g, 0.16 mol) was allowed to react as above at 250°. Glpc analysis of the purified product (92%) yielded 12% **5**, 24% **6**, 41% **7**, 14% **8**, and 9% **9**.

F.—3-Ethoxy-1-methylcyclohexene (20 g, 0.16 mol) was allowed to react as above at 300°. Glpc analysis of the purified product (90%) yielded 13% **5**, 24% **6**, 39% **7**, 15% **8**, and 9% **9**.

G.—1-Methyl-2-cyclohexen-1-ol (20 g, 0.18 mol) was allowed to react as above at 250°. The crude product was filtered directly through anhydrous magnesium sulfate and distilled (12.9 g, 76%). Glpc analysis of the product yielded 39% **6**, 27% **7**, and 34% **8**.

H.—1-Methyl-2-cyclohexen-1-ol (20 g, 0.18 mol) was allowed to react at 300° and isolated as in G (13.2 g, 78%). Glpc analysis of the product yielded 1% **5**, 33% **6**, 46% **7**, and 20% **8**.

$KHSO_4$-Catalyzed Eliminations. A.—3-Ethoxy-5-methylcyclohexene (0.18 mol) was distilled from potassium hydrogen sulfate (0.036 mol). The distillate was collected in an ice-cooled flask and washed with dilute bicarbonate solution and the organic product was dried with anhydrous magnesium sulfate. The product (7.0 g, 41%) was distilled, bp 98–108°. Glpc analysis revealed 73% **5**, 8% **6**, 14% **7**, 4% **8**, and 1% **9**.

(11) Gas–liquid partition chromatography was performed with an Aerograph Model 202-1B dual column instrument equipped with a Hewlett-Packard Model 3370 electronic integrator for peak area measurement; dual 6'-15% Carbowax 20M on 60–80 mesh Chromosorb W columns were utilized for the determination of ether purity, dual 15'-15% TCEP on 60–80 mesh Chromosorb W columns for the analysis of the methycyclohexadiene product mixtures. Ultraviolet spectra were obtained with a Perkin-Elmer Model 202, nmr spectra with a Varian A60-A using TMS as an internal standard ($CDCl_3$ solvent). All spectra were consistent with the assigned structures, and satisfactory C and H analyses were obtained for all compounds.

(12) M. Mousseron and R. Granger, *C. R. Acad. Sci.*, **205**, 327 (1937).

(13) M. Mousseron and F. Winternitz, *Bull. Soc. Chim. Fr.*, **13**, 232 (1946).

(14) M. Mousseron and F. Winternitz, *ibid.*, **13**, 604 (1946).

(15) E. Urion, *C. R. Acad. Sci.*, **199**, 363 (1934).

(16) A. Berlande, *Bull. Soc. Chim. Fr.*, **9**, 644 (1942).

(17) Kaiser active alumina KA-101 (Matheson Scientific); chemical analysis and physical properties available for supplier upon request.

B.—3-Ethoxy-2-methylcyclohexene (0.18 mol) was treated as described above, yielding 6.6 g (38%) of mixed dienes. Glpc analysis yielded 41% **6**, 35% **7**, 22% **8**, and 2% **9**.

C.—3-Ethoxy-1-methylcyclohexene (0.18 mol) was treated as above yielding 7.0 g (41%) of mixed dienes. Glpc analysis yielded 18% **5**, 18% **6**, 46% **7**, 14% **8**, and 2% **9**.

Thermal Isomerization Reactions. General Procedure.—Mixtures of the three isomeric methyl-1,3-cyclohexadienes of known composition were added dropwise through a 22-mm Pyrex tube packed to a depth of 12 in. with $^1/_{16}$-in. Pyrex helices and externally heated at either 300, 325, or 350° as in the above elimination studies. The thermolysis products were isolated in a similar manner (90–95% recovery) and submitted to glpc analys is (Table II). Addition of 3-methylenecyclohexene did not affect the above reactions, and **8** survived quantitatively in all cases. Alumina studies were carried out under identical conditions of temperature and flow rate.

Registry No.—**1**, 27525-90-2; **2**, 27525-91-3; **3**, 27525-92-4; **4**, 23758-27-2; ethanol, 64-17-5.

The Molecular Structure of Perfluorobutyne-2 and Perfluorobutadiene-1,3 as Studied by Gas Phase Electron Diffraction

C. H. CHANG, A. L. ANDREASSEN, AND S. H. BAUER*

Department of Chemistry, Cornell University, Ithaca, New York 14850

Received July 6, 1970

The structures of two C_4F_6 isomers, perfluorobutadiene-1,3 and perfluorobutyne-2, have been determined by gas phase electron diffraction. The perfluorobutyne-2 was found to be linear with freely rotating CF_3 groups. The following parameters were determined: r_g values for (C≡C) = 1.199 ± 0.009 Å; (C–F) = 1.333 ± 0.003 Å; (C–C) = 1.472 ± 0.006 Å; and ∠CCF = 110.8 ± 0.3°. In contrast to the trans planar structure of butadiene-1,3, the perfluoro compound is in a nonplanar cisoid conformation, with a CCCC dihedral angle of 47.4 ± 2.4°. For the other structural parameters (r_g values): (C=C) = 1.336 ± 0.018 Å; (C–F) = 1.323 ± 0.006 Å; (C–C) = 1.488 ± 0.018 Å; ∠C=C–C = 125.8 ± 0.6°; $\angle F_7–C_2=C_1$ = 121.0 ± 1.8°; and $\angle F_6–C_1=C_2$ = 124.5 ± 0.6°. The above uncertainties were estimated errors set at three times the standard deviations as obtained from the converged least squares fitting of the calculated to the observed $qM(q)$ function.

Recent developments in experimental techniques, both diffraction and spectroscopic, and in computer reductions of data have led to accurate determinations of molecular structures and systematic studies of geometrical parameters as influenced by various types of substitution. It was recognized more than a decade ago[1,2] that C–C bond lengths vary with environment. Stoicheff[3] found empirical relations for C–C and C=C bond lengths in hydrocarbons as a function of the number of adjacent bonds or adjacent atoms. Little is known about the secondary effect,[4] of deviations due to adjacent heteroatoms, although Stoicheff[3] did notice a small change on the C=C bond length when Cl, Br, or F atoms were substituted for hydrogen. There is a suggestion of an "inductive" effect through two or more bonds by heteroatoms, but it has not been adequately documented. Of course, Stoicheff's relations do not apply to highly strained small ring molecules.[5,6]

Studies of fluoro compounds made in this laboratory have shown that substitution not only changes the length of the bond β to the site of substitution, but also alters the entire molecular conformation. For instance, perfluoroazomethane[7] was found to be cis instead of trans, as is the conformation for azomethane, and the third carbon atom of perfluoropropene may not be in the plane containing the F_2C=C group.[8] This is a report on the molecular structures of two fluorocarbons, $F_3CC≡CCF_3$ and $F_2C=CFCF=CF_2$, which were investigated in order to shed additional light on the inductive effect produced by fluorine atom substitution.

Perfluorobutyne-2 was first studied by Sheehan and Schomaker,[9] who used visual estimates of plate densities. They reported (C–F) as 1.340 ± 0.020 Å, (C–C) as 1.465 ± 0.055 Å, (C≡C) as 1.22 ± 0.09 Å, and ∠FCF as 107.5 ± 1.0°, in agreement with corresponding geometrical parameters in $F_3CC≡CH$.[9] Infrared and raman spectra of $F_3CC≡CCF_3$ were obtained by Miller and Bauman.[10] Their data clearly indicate that D_{3d} selection rules were followed. Hence either the molecule has free internal rotation or a staggered conformation; they were unable to distinguish between them.

The structure of butadiene-1,3 with various degrees and types of substitution has been extensively investigated. In general, these were found to be in the trans-planar conformation.[11–14] However, in the cases with trihalogenation at the 1,1, and 3 positions, skew conformations were observed.[15] For the hexasubstituted species, there is strong evidence for a cisoid structure.[16,17] Robin and Brundle recorded the optical spectra of perfluorobutadiene-1,3 and interpreted their data as indicative of a cisoid structure, with the skeleton carbon dihedral angle of approximately 42°.[18] In view of this departure from the expected behavior of a conjugated system, it was

(1) G. Herzberg and B. P. Stoicheff, *Nature*, **175**, 79 (1955).
(2) C. C. Costain and B. P. Stoicheff, *J. Chem. Phys.*, **30**, 777 (1959).
(3) B. P. Stoicheff, *Tetrahedron*, **17**, 135 (1962).
(4) M. Tanimoto, K. Kuchitsu, and Y. Morino, *Bull. Chem. Soc. Jap.*, **42**, 2519 (1969).
(5) C. H. Chang, R. F. Porter, and S. H. Bauer, *J. Mol. Struct.*, in press.
(6) M. Cardillo and S. H. Bauer, *J. Amer. Chem. Soc.*, **92**, 2399 (1970).
(7) C. H. Chang, R. F. Porter, and S. H. Bauer, *ibid.*, **92**, 5313 (1970).
(8) (a) J. Karle, A. H. Lowrey, C. F. George, and P. D'Antonio, private communication; (b) C. H. Chang, R. F. Porter, and S. H. Bauer, unpublished work.
(9) W. F. Sheehan, Jr., and V. Schomaker, *J. Amer. Chem. Soc.*, **74**, 4468 (1952).
(10) F. A. Miller and R. P. Bauman, *J. Chem. Phys.*, **22**, 1544 (1954).
(11) D. R. Lide, Jr., *ibid.*, **37**, 2074 (1962).
(12) D. R. Lide, Jr., and M. Jen, *ibid.*, **40**, 252 (1964).
(13) R. A. Beaudet, *ibid.*, **42**, 3758 (1965).
(14) R. A. Beaudet, *J. Amer. Chem. Soc.*, **87**, 1390 (1965).
(15) A. B. Aothner-by and D. Jung, *ibid.*, **90**, 2342 (1968).
(16) G. Szasz and N. Sheppard, *Trans. Faraday Soc.*, **49**, 358 (1953).
(17) J. C. Albright and J. Rud Nielsen, *J. Chem. Phys.*, **26**, 370 (1957).
(18) M. Robin and C. R. Brundle, *J. Amer. Chem. Soc.*, **92**, 5550 (1970).

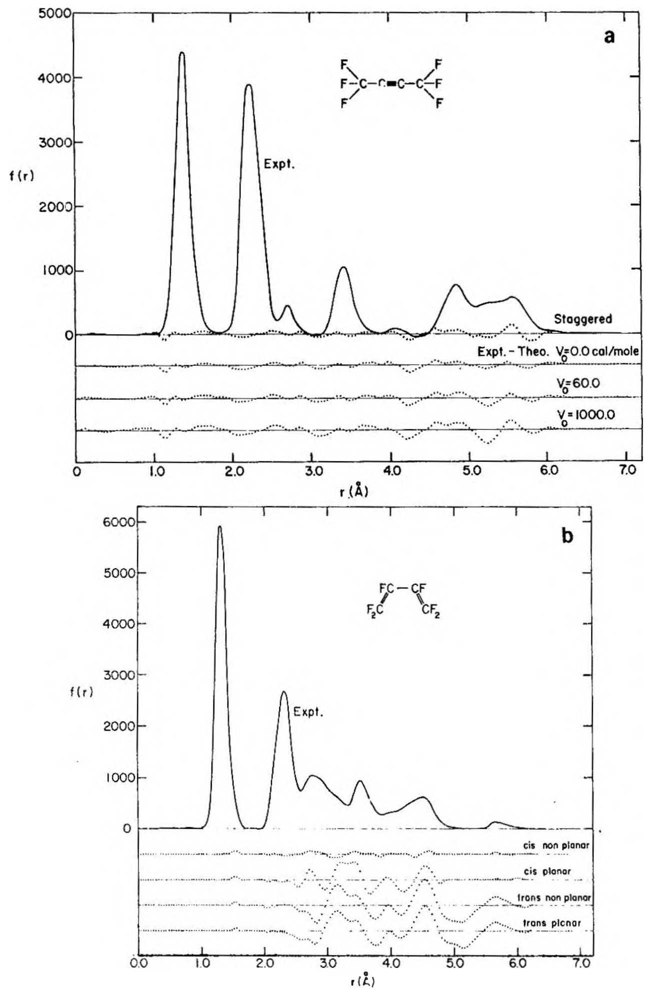


Figure 1.—The refined experimental radial distribution curves and difference curves between the experimental and calculated values for various models. In Figure 1a, the staggered conformation ($V_0 \rightarrow \infty$) appears to give a slightly better fit then does the curve with $V_0 = 1000$. This was possible only with unacceptably large l_{ij}'s.

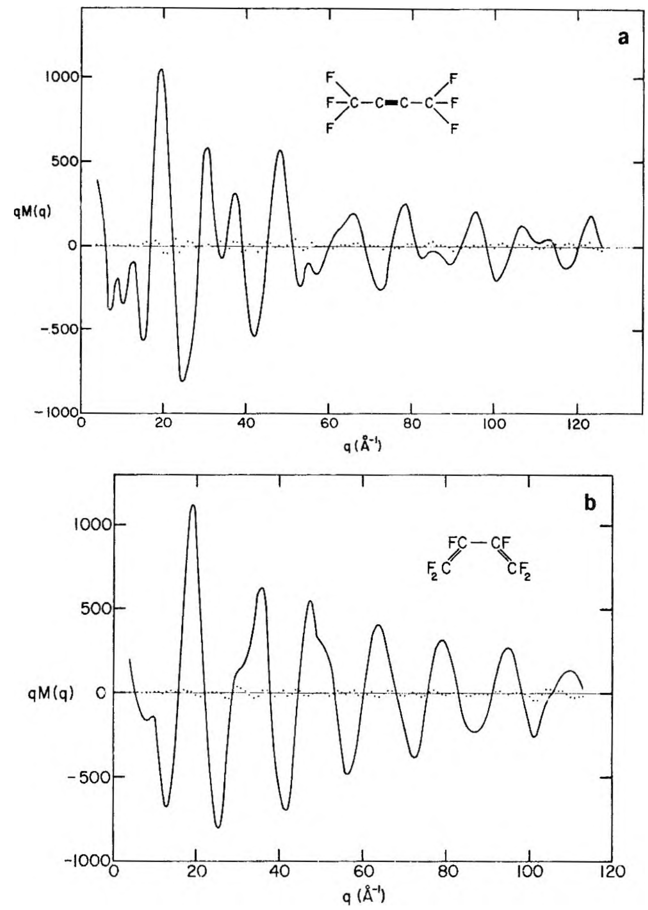


Figure 2.—The reduced experimental molecular scattering curves, $qM(q)$, and the difference curves between the experimental and the calculated values.

decided to investigate the structure of this molecule more fully by electron diffraction.

Experimental Section

Both C_4F_6 were available commercially from Pennisular Chem-Research, Gainesville, Fla. Infrared spectra of the gases agreed with published data.[10,17] For each compound, three sets of convergent mode diffraction photographs were recorded with the Cornell dual mode apparatus.[19] Data were obtained for q = 4–30 Å^{-1} at 25 kV, at a nozzle-to-plate distance of 253 mm; q = 15–60 Å^{-1} at 60 kV, at a nozzle-to-plate distance of 253 mm; and q = 40–126 Å^{-1} at 60 kV, at a distance of 125 mm. All patterns were recorded on 4 × 5 in. Kodak electron image plates. Wavelengths and nozzle-to-plate distances were determined from analyses of magnesium oxide powder patterns taken concurrently with the sample photographs.

For each set of experimental conditions, a pair of plates, one light and one dark, were microphotometered on a modified double-beam Jarrel-Ash densitometer, fitted with a rotating stage.[20] The digital signal was recorded on punched paper tape at intervals of 100 μ for the short nozzle-to-plate distance and at 200 μ for the long distance. The conversion of the recorded transmittances to optical densities and then to intensities[21] was carried out on a modified DEC PDP-9 computer.

Structure Analysis.—The reduced diffracted intensities were analyzed by least squares fitting of the experimental $qM(q)$ curve[22] $[q \equiv (40/\lambda)\sin(\phi/2)]$. The atomic elastic and inelastic scattering factors of Tavard, *et al.*,[23] were used, as was the phase shift correction of Bonham and Ukaji.[24] In the least squares analysis a nondiagonal weighting matrix was inserted in the manner described by Morino.[25] Corrections were introduced to compensate for the anharmonicity of the molecular vibrations.[26,27] A very simple and rapid algorithm[28] for the calculation of the molecular cartesian coordinates was employed throughout the analysis. The radial distribution curve was used for background refinement;[29] the curve was also used to obtain initial parameter estimates.

Perfluorobutyne-2.—Reduced experimental data from q = 4–126 Å^{-1} have been included in the microfilm edition (Table IVa);[30] they have also been plotted along with the reduced backgrounds in Figure 4a.[30] The corresponding radial distribution curve is shown in Figure 1a, and the experimental molecular intensity curve $qM(q)$ is shown in Figure 2a. "Static" models were constructed in the preliminary least squares refinements by as-

(19) S. H. Bauer and K. Kimura, *J. Phys. Soc. Jap.*, **17**, 300 (1962).
(20) S. H. Bauer, R. Jenkins, and R. L. Hilderbrandt, unpublished work.
(21) J. L. Hencher and S. H. Bauer, *J. Amer. Chem. Soc.*, **89**, 5527 (1967).
(22) K. Hedberg and M. Iwasaki, *Acta Crystallogr.*, **17**, 529 (1964).
(23) C. Tavard, D. Nicholas, and M. Rouault, *J. Chim. Phys. Physico-chim. Biol.*, **64**, 540 (1967).
(24) R. A. Bonham and T. Ukaji, *J. Chem. Phys.*, **36**, 72 (1962).
(25) Y. Murata and Y. Morino, *Acta Crystallogr.*, **20**, 605 (1966).
(26) K. Kuchitsu and L. S. Bartell, *J. Chem. Phys.*, **35**, 1945 (1961).
(27) K. Kuchitsu, *Bull. Chem. Soc. Jap.*, **40**, 498 (1967).
(28) R. L. Hilderbrandt, *J. Chem. Phys.*, **51**, 1654 (1969).
(29) I. L. Karle and J. Karle, *ibid.*, **17**, 1052 (1949).
(30) Table IVa,b, Table Va,b, and Figures 4a,b will appear immediately following this article in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N. W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

suming that the molecule had either D_{3h} (eclipsed) symmetry, D_{3d} (staggered) symmetry, or an intermediate conformation with very large mean square amplitudes in the region 5.0–6.0 Å, contributed by long nonbonded F···F distances. Three bond lengths, C–C, C≡C, and C–F, and the valence angle CCF were inserted as independent geometrical parameters; these were refined simultaneously with seven root mean square amplitude parameters, l_{ij}'s. They are l_{C-C}, $l_{C_1 \cdots C_3}$, l_{C-F}, $l_{C_2 \cdots F_5}$, $l_{C_3 \cdots F_5}$, $l_{C_4 \cdots F_5}$, $l_{F_5 \cdots F_6}$; the atom designations are shown in Figure 3.

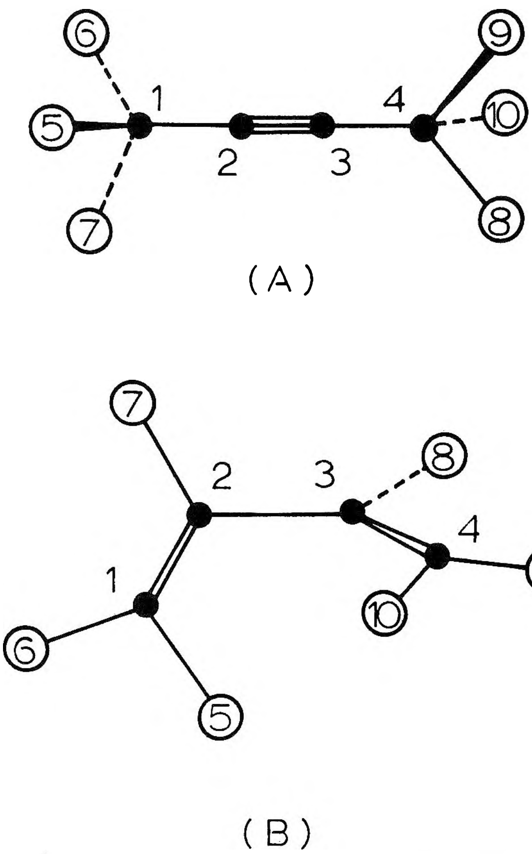


Figure 3.—Atom designation for $F_3CC{\equiv}CCF_3$ (A) and $CF_2{=}CFCF{=}CF_2$ (B).

Initial values for these 11 parameters were obtained from the RDR curves, reported bond lengths, and calculated root mean square amplitudes.[31] Since the l_{ij}'s for the long F···F atom pairs are relatively insensitive to the least squares refinement, their values were constrained to those calculated by Elvebredd.[31] The optinum set of parameters for $F_3CC{\equiv}CCF_3$ are listed in Table I. As shown in Table Va,[30] correlations between the selected 11 parameters are small.

The question whether this molecule is best represented by a staggered conformation or by a free internal rotation model was investigated by careful study of the RDR curve in the region from r = 5.0–6.0 Å, contributed solely by the nonbonded F···F distances. A threefold potential function, $V(\phi) = (1/2)V_0\,(1 + \cos 3\phi)$, was used to approximate the rotational barrier, and a Boltzmann satistical weight function inserted to weight all rotational conformations. The staggered form was assumed to be the minimum energy conformation. Then a sequence of "dynamic" models was tested by choosing a range of V_0's, while constraining the $l_{F \cdots F}$'s = 0.140 Å. The difference curves shown in Figure 1 indicate that, within the limits of our analysis, $V_0 \approx 0$; *i.e.*, the molecule has free internal rotation.

Perfluorobutadiene-1,3.—The experimental intensity curve for this model has been plotted in Figure 4b.[30] Several conformations were investigated, ranging in torsional angle from trans planar to cis planar. The experimental RDR and difference

TABLE I

LEAST SQUARES STRUCTURE PARAMETERS FOR $F_3CC{\equiv}CCF_3$ AND $F_2C{=}CFCF{=}CF_2$

$F_3CC{\equiv}CCF_3$		$F_2C{=}CFCF{=}CF_2$	
C–C	1.472 ± 0.002[a]	C–C	1.488 ± 0.006
C≡C	1.199 ± 0.003	C=C	1.336 ± 0.006
C–F	1.333 ± 0.001	C–F	1.323 ± 0.002
∠CCF	110.8 ± 0.1	∠CCC	125.8 ± 0.2
l_{C-C}	0.053 ± 0.004 (0.046)[b]	$\angle C_1C_2C_7$	121.0 ± 0.2
$l_{C{\equiv}C}$	0.036 (fixed) (0.036)	$\angle C_3C_1F_6$	124.5 ± 0.6
$l_{C_1 \cdots C_3}$	0.055 ± 0.006 (0.050)	∠CCCC	47.4 ± 0.8
$l_{C_1 \cdots C_4}$	0.058 (fixed) (0.058)	l_{C-C}	0.051 (fixed)
l_{C-F}	0.046 ± 0.001 (0.044)	$l_{C{=}C}$	0.039 (fixed)
$l_{F_5 \cdots F_6}$	0.058 ± 0.001 (0.058)	l_{C-F}	0.054 ± 0.001
$l_{C_2 \cdots F_5}$	0.062 ± 0.002 (0.073)	$l_{C_2 \cdots F_6}$	0.074 ± 0.002
$l_{C_3 \cdots F_5}$	0.098 ± 0.003 (0.099)	$l_{F_7 \cdots F_8}$	0.079 ± 0.003
$l_{C_4 \cdots F_5}$	0.115 ± 0.006 (0.128)	$l_{C_1 \cdots F_8}$	0.093 ± 0.006
		$l_{F_6 \cdots F_7}$	0.077 (fixed)
		$l_{F_5 \cdots F_6}$	0.054 (fixed)
		$l_{F_7 \cdots F_9}$	0.134 (fixed)
		$l_{C_3 \cdots F_{10}}$	0.128 (fixed)
		$l_{C_2 \cdots F_9}$	0.109 (fixed)
		$l_{C_1 \cdots C_3}$	0.107 (fixed)
		$l_{F_5 \cdots F_{10}}$	0.129 (fixed)
		$l_{F_6 \cdots F_9}$	0.135 (fixed)
		$l_{C_3 \cdots C_4}$	0.110 (fixed)

[a] These are least squares standard deviations. [b] Calculated value from I. Elvebredd, *Acta Chem. Scand.*, **22**, 1606 (1968).

curves for these models are plotted in Figure 1b. All the trans models predict a sizable peak in the RDR curve which is 0.3 Å beyond the last peak in the experimental curve. Least squares analysis of the angular parameters proceeded without difficulty. However, determination of the bonded parameters proved troublesome. Examination of the correlation matrix (Table Vb)[30] reveals that the C–F and C=C bond lengths are −0.97 correlated. An iterative process was followed, in which first one of these two distances was constrained and all other parameters allowed to vary, and then the other distance was constrained, again allowing all parameters to vary. After several iterations it was possible to insert concurrent variations in both the C–F and C=C distances, along with the other parameters. It was essential that the initially inserted approximate values be quite close to the final model before this simultaneous variation converged. The RDR difference curve for the final model is labeled cis nonplanar in Figure 1b. The experimental $qM(q)$ curve and difference curve are shown in Figure 2b.

Discussion

Perfluorobutyne-2.—The C–F bond length of 1.333 ± 0.003 Å agrees well with previous studies of $F_3CC{\equiv}CH$[9] (1.335 ± 0.01 Å), $F_3CC{\equiv}CCH_3$[32] (1.340 Å), and $F_3CC{\equiv}CCF_3$[9] (1.340 ± 0.020 Å). However, the C≡C separation is shorter and the C–C bond lengths are longer in $F_3CC{\equiv}CCF_3$ than in $H_3CC{\equiv}CCH_3$.[4] As shown in Table II, this parallels the relative magnitudes in HC≡CF and $HC{\equiv}CCF_3$, and it is also interesting to notice that in the N=N system, the N=N bond is shortened and the N–C bond is lengthened by fluorine substitution. More accurate determinations of bond lengths in these molecules are required to substantiate these comparisons. Except for $l_{C_2 \cdots F_5}$ the mean square amplitudes of vibration obtained in this study agree with those calculated by Elvebredd, within the experimental uncertainties.

Perfluorobutadiene-1,3.—The C–F bond length in this compound (1.323 ± 0.006 Å) is consistent with dimensions reported for similar species; its magnitude does not appear to be particularly sensitive to its molecular environment. Twisting of the molecules

(31) Irene Elvebredd, *Acta Chem. Scand.*, **22**, 1606 (1968).

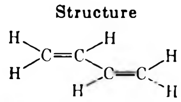
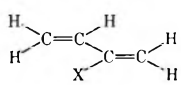
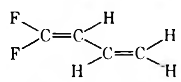
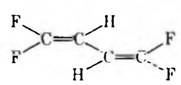
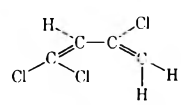
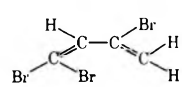
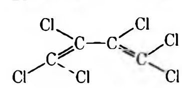
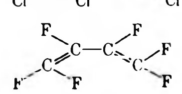
(32) V. W. Laurie, *J. Chem. Phys.*, **30**, 1101 (1959).

TABLE II

Compd	C≡C {N=N}	Δ (C≡C) Δ {N=N}	C–C {C–N}	Δ (C–C)	∠XCC	Ref
HC≡CH (r_0)	1.207					*a*
		−0.009				
HC≡CF (r_0)	1.198					*b*
$HC{\equiv}CCH_3$ (r_0)	1.207		1.458		110° 30′	*c*
		−0.006		+0.006		
$HC{\equiv}CCF_3$ (r_0)	1.201		1.464		107.5 ± 1.0° (FCF)	*d*
$H_3CC{\equiv}CCH_3$ (r_g)	1.213 ± 0.001		1.467 ± 0.001		110.7 ± 0.4°	*e*
		−0.014		+0.005		
$F_3CC{\equiv}CCF_3$ (r_g)	1.199 ± 0.009		1.472 ± 0.006		110.8 ± 0.3°	*f*
HN=NH (trans)	{1.238 ± 0.007}					*g*
		−0.024				
FN=NF (cis)	{1.214 ± 0.010}					*h*
$H_3CN{=}NCH_3$ (trans) (r_g)	{1.254 ± 0.003}		{1.474 ± 0.002}			*i*
		−0.018		+0.016		
$F_3CN{=}NCF_3$ (cis) (r_g)	{1.236 ± 0.015}		{1.490 ± 0.006}			*i*

[a] M. T. Christensen, D. R. Easton, B. A. Green, and H. W. Thompson, *Proc. Roy. Soc., Ser. A*, **238,** 15 (1956). [b] J. K. Tyler and J. Sheridan, *Proc. Chem. Soc.*, 119 (1960). [c] L. F. Thomas, E. I. Sherrard, and J. Sheridan, *Trans. Faraday Soc.*, **51,** 619 (1955). [d] W. F. Sheehan, Jr., and V. Schomaker, *J. Amer. Chem. Soc.*, **74,** 4468 (1952). [e] See ref 31. [f] This work. [g] A. Trombetti, *Can. J. Phys.*, **46,** 1005 (1968). [h] R. K. Bohn and S. H. Bauer, *Inorg. Chem.*, **6,** 309 (1967). [i] C. H. Chang, R. F. Porter, and S. H. Bauer, *J. Amer. Chem. Soc.*, **92,** 5313 (1970).

TABLE III

Compd	Structure	Dihedral angle (φ = 0° cis planar)	Ref
Butadiene-1,3		φ = 180°	*a, b*
Haloprene X = F, Cl, Br, I		φ = 180°	*c, e*
1,1-Difluorobutadiene-1,3		φ = 180°	*f*
1,1,4,4-Tetrafluorobutadiene-1,3		φ = 180°	*g*
1,1,3-Trichlorobutadiene-1,3		φ = 50°	*e*
1,1,3-Tribromobutadiene-1,3		φ = 50°	*e*
Perchlorobutadiene-1,3		0° < φ < 90°	*d*
Perfluorobutadiene-1,3		φ = 42° φ = 47°	*h* *i*

[a] A. Almenningen, O. Bastiansen, and M. Traetteberg, *Acta Chem. Scand.*, **12,** 1221 (1958). [b] D. J. Marais, N. Sheppard, and B. P. Stoicheff, *Tetrahedron*, **17,** 163 (1962). [c] D. R. Lide, Jr., *J. Chem. Phys.*, **37,** 2074 (1962). [d] G. Szasz and N. Sheppard, *Trans. Faraday Soc.*, **49,** 358 (1953). [e] A. A. Bothner-by and D. Jung, *J. Amer. Chem. Soc.*, **90,** 2342 (1968). [f] R. A. Beaudet, *J. Chem. Phys.*, **42,** 3758 (1965). [g] R. A. Beaudet, *J. Amer. Chem. Soc.*, **87,** 1390 (1965). [h] C. R. Brundle and M. Robin, private communication. [i] This work.

from a planar conformation minimizes the π overlap conjugation; this accounts for the shortening of the C=C separation from 1.344 Å in butadiene-1,3[33] to 1.336 ± 0.018 and lengthening of Å, the C–C distance from 1.467 Å to 1.488 ± 0.018 Å. The large uncertainties in the two carbon–carbon bond lengths is attributed to the fact that their scattering is greatly overshadowed by the scattering from the six carbon–fluorine pairs.

The 47.4 ± 2.4° dihedral angle for the cisoid model is in quantitative agreement with the spectroscopic work of Brundle and Robin.[18] The unlikelihood of a completely cis structure due to fluorine–fluorine overlap has been discussed.[34] Examination of Table III documents the trend from trans planar to cisoid. It appears that 1,1,3 type of interaction is necessary for twisting the molecule out of the trans conformation. Perfluorobutadiene-1,3 has in effect two 1,1,3 interactions.

Registry No.—Perfluorobutyne-2, 692-50-2; perfluorobutadiene-1,3, 685-63-2.

Acknowledgments.—We wish to thank Dr. H. Mair for his initial work on perfluorobutyne-2. This work was supported partly by the National Science Foundation under Grant No. GP-7794 and the Material Science Center, Cornell University.

(33) W. Haugen and M. Traetteberg, "Selected Topics in Structure Chemistry," P. Andersen, O. Bastiansen, and S. Furberg, Ed., Universitet Forlaget, Oslo, 1967.

(34) R. M. Conrad and D. A. Dows, *Spectrochim. Acta*, **21,** 1039 (1965).

Aluminum Chloride Catalyzed Diene Condensation. VI.[1,2] Partial Rate Factors of 2-Phenyl-, 2-Chloro-, 2-Trifluoromethyl-, and 2-Cyanobutadienes in Reactions with Methyl Acrylate. A Differential Hammett Correlation

TAKASHI INUKAI* AND TAKESHI KOJIMA

The Central Research Laboratories, Chisso Corporation, Kamariya, Kanazawa-ku, Yokohama, Japan

Received July 27, 1970

The para:meta ratios of the adducts and relative rates, 2-substituted butadiene as opposed to butadiene, of the aluminum chloride catalyzed and the uncatalyzed Diels-Alder reactions of 2-substituted butadienes (RC_4H_5, R = Ph, Cl, CF_3, and CN) with methyl acrylate at 20° were determined to obtain the partial rate factors, $prf^{(c)}$ and $prf^{(u)}$, for the formation of the respective adducts in both modes of the reactions. These two sets of prf's, including the prf's for 2-methyl-, 2,3-dimethyl-, and *trans*-1-methylbutadienes, were successfully correlated by a differential form of the Hammett equation, $\log prf^{(c)} - \log prf^{(u)} = \rho\sigma^+$. This correlation is regarded as a consequence of the electronic interaction between the diene substituent R and the dienophile substituent through a quasibenzene conjugation system that is conceived of in the four-center transition state.

In contrast to their recent importance in the theoretical studies of the multicenter reactions, the Diels-Alder reactions have not been sufficiently supplied with reliable exact experimental data on the substituent effects on their rates. Although the systematic study by Sauer, *et al.*,[3] among other less extensive studies, recently gave quantitative data supporting the well-known Alder rule on the rate,[4] the problem of orientation in the Diels-Alder reactions remains open yet. The preferential ortho/para orientation, irrespective of the electron-releasing or electron-withdrawing characteristics of the diene substituents, may be assumed to be a rule, but many of the reported isomer ratios are suspect or at best only semiquantitative.[5] Yet these orientation phenomena seem to have been regarded as indicating the failure of the polarity consideration of the electronic theory in understanding the characteristics of the Diels-Alder reactions.

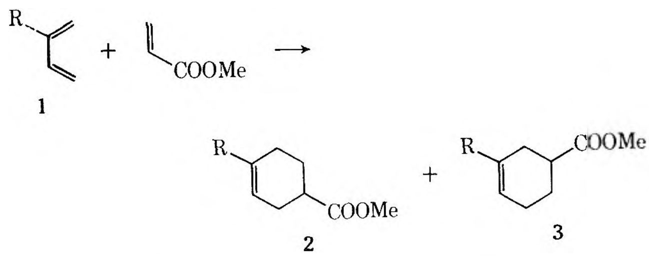
Therefore, it is of interest to obtain the kinetically controlled isomer ratios of high accuracy on which the theoretical arguments can be safely based. In this article the reactions of 2-phenyl-, 2-chloro, 2-trifluoromethyl-, and 2-cyanobutadienes with methyl acrylate, both uncatalyzed and aluminum chloride catalyzed, are studied with respect to the para:meta product ratios and the rates relative to unsubstituted butadiene, as the continuation of our previous studies on the isoprene[6] and *trans*-piperylene[7] cases.

Method and Results

The reactions for the isomer ratio and relative rate determinations were carried out at 20°,[8] and the general pattern of the experimental design is analogous with that described in the previous papers.[6,7]

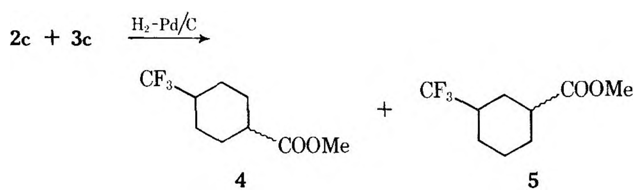
Para:Meta Ratio.—The products from reactions with 2-phenylbutadiene (**1a**) were hydrolyzed with alkali to obtain the mixture of **2a** (acid) and **3a** (acid) freed from some neutral by-products. After removing pure **2a** (acid) by recrystallization, the remainder was reconverted to the ester (**2a** + **3a**) and the isomeric composition was determined by the nmr spectroscopy.

The **2b**:**3b** ratio was determined by glpc assuming an equal molar ion current intensity of the isomers. The **2c**:**3c** ratio was determined in a similar way, except that some additional experiments were required for assignment of the glpc peaks because the authentic



a, R = Ph; **b**, R = Cl; **c**, R = CF_3; **d**, R = CN

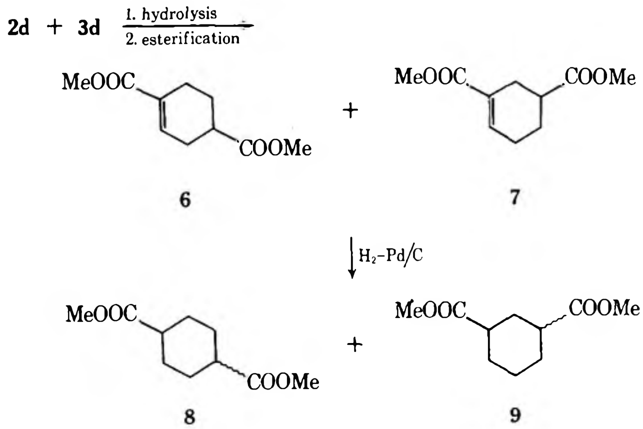
specimen of neither isomer was accessible. Thus the mixture (**2c** + **3c**) was quantitatively converted to the saturated derivatives (**4** + **5**) whose glpc peaks were identified by comparison with those of **4** and **5** derived from authentic *p*- and *m*-trifluoromethylbenzoic acids, respectively.



Since the mixture, **2d** + **3d**, could not be separated under all the glpc conditions we tried, it was converted to **8** + **9** by the process shown in Scheme I and their glpc peaks were identified by comparison of the retention times with those of authentic specimens of **8** and **9** which were synthesized from *trans*-cyclohexane-1,4-dicarboxylic acid and isophthalic acid, respectively. Both the conversions, from **2d** + **3d** to **6** + **7** and from **6** + **7** to **8** + **9**, were satisfactorily quantitative. This allowed us to assign each of the peaks of the **6** + **7** mixture to one or the other of **6** and **7** unambiguously and to adopt their ratio as the desired ratio of **2d**:**3d**.

(1) Paper V: T. Kojima and T. Inukai, *J. Org. Chem.*, **35**, 1342 (1970).
(2) Preliminary communication: T. Inukai and T. Kojima, *Chem. Commun.*, 1334 (1969).
(3) J. Sauer, D. Lang, and A. Mielert, *Angew. Chem.*, **74**, 352 (1962).
(4) K. Alder, *Experientia, Suppl.*, **2**, 86 (1955).
(5) See, for example, J. Sauer, *Angew. Chem.*, **79**, 76 (1967).
(6) T. Inukai and T. Kojima, *J. Org. Chem.*, **31**, 1121 (1966).
(7) T. Inukai and T. Kojima, *ibid.*, **32**, 869 (1967).
(8) Some of the uncatalyzed reactions were carried out in the dark in an air-conditioned room (about 20°), for they required a few months to afford a sufficient amount of the adduct for further study.

SCHEME I



The isomer ratios thus determined, together with some previous results, are summarized in Table I.

TABLE I
ISOMER RATIOS OF PRODUCTS FROM REACTIONS AT 20°

Substituent	Uncatalyzed, para:meta	Catalyzed,[a] para:meta
2-Ph	80:20[b,c]	97:3
2-Cl	87:13[b,d]	98:2
$2\text{-}CF_3$	55:45[b]	51:49
2-CN	84:16[a]	73:27
2-Me[e]	69.5:30.5[f]	95:5
	ortho:meta	ortho:meta
1-Me[f]	90:10[b]	98:2

[a] In benzene solution. [b] No solvent was used. [c] The ratio has been reported [I. N. Nazarov, Yu. A. Titov, and A. I. Kuznetsova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1270 (1959); *Chem. Abstr.*, **54**, 1410 (1960)] to be 4.5:1 (at 150°) and 7.3:1 (at room temperature). [d] The para isomer was reported as the main product.[30] [e] Reference 6. [f] Reference 7.

Relative Rates.—The competitive reaction techniques were employed for the determination of relative rates of 2-substituted butadiene as opposed to butadiene. In the case of 2-cyanobutadiene, however, they were calculated from the second-order rate constants of the respective Diels–Alder reactions, because the competitive reactions might be complicated by the probable concomitant condensation between 2-cyanobutadiene and butadiene.

The second-order rate constants, k^u, of the uncatalyzed reaction between 2-cyanobutadiene and methyl acrylate (MA) in benzene are shown in Table II. The

TABLE II
SECOND-ORDER RATE CONSTANTS, k^u, OF UNCATALYZED REACTION BETWEEN **1d** AND MA IN BENZENE[a,b]

Temp, °C	k^u, l./(mol sec) × 10^7
20	1.38
36.4	7.78
45.3	15.0
60.5	31.5

[a] Initial concentration of **1d**, 1.30–2.57 mol/l.; that of MA, 3.62–5.06 mol/l. [b] Rate of formation of the product (**2d** + **3d**) was followed with glpc analysis with 1,2-diphenylbutane as the internal standard.

Arrhenius parameters are calculated to be E_a = 15.0 kcal/mol, log A (l./mol sec) = 4.4.

The second-order rate constants, k^c, of the aluminum chloride catalyzed reaction of **1d** with MA (the MA–$AlCl_3$ complex as the dienophile[9]) were determined according to the method described previously.[9] The pseudo-first-order rate constants at several levels of aluminum chloride concentration were determined, and the second-order rate constants, k^c, were calculated (Table III). It should be noted that the contribution

TABLE III
DETERMINATION OF CATALYZED RATE CONSTANT, k^c, OF REACTION OF **1d** WITH MA–$AlCl_3$ IN BENZENE AT 40° [a]

$AlCl_3$,[b] mmol/l.	$AlCl_3$,[c] mmol/l.	MA, mmol/l.	$k_1 \times 10^6$ (sec^{-1})[d]	$k^c \times 10^4$ [e] (l./mol sec)
5.8	5.1	101	1.90	3.70
11.6	10.9	20.2	4.22	3.86
18.3	17.6	89.6	6.90	3.91
25.4	24.7	198.0	9.37	3.79

[a] Initial concentration of **1d**, 32.1 mmol/l. [b] Uncorrected. [c] Corrected for partial deterioration of $AlCl_3$ (0.7 mmol/l.), which was determined from the intercept of $[AlCl_3]$ on extrapolation to zero k_1. [d] $k_1 = t\ (\text{sec})^{-1} \times 2.303 \log (a/a - x)$ where a is the initial concentration of **1d**. [e] $k^c = k_1$ divided by $[AlCl_3]_{cor}$.

of the uncatalyzed reaction to the total rate is negligible and the rate of an individual kinetic run is first order to the concentration of **1d** alone, since the concentration of MA–$AlCl_3$ is determined by the analytical concentration of aluminum chloride and hence is essentially constant throughout a kinetic run.

The temperature dependence of k^c is shown in Table IV and the Arrhenius parameters are calculated to be E_a = 11.3 kcal/mol, log A (l./mol sec) = 4.4.

TABLE IV
SECOND-ORDER RATE CONSTANTS, k^c, OF CATALYZED REACTION BETWEEN **1d** AND MA–$AlCl_3$ IN BENZENE[a]

Temp, °C	k^c, l./(mol sec) × 10^5
10.0	5.79
20.0	11.6
30.0	18.9
40.0	38.1

[a] Initial concentration of **1d**, 32–62 mmol/l.; that of MA, 87–521 mmol/l.; $[AlCl_3]_{cor}$, 5.13–46.1 mmol/l.

The corresponding k^u and k^c of the reactions with butadiene as the diene component at 20° are 1.00 × 10^{-8} l./(mol sec) and 1.15 × 10^{-3} l./(mol sec), respectively,[9] and these values are used for calculation of the relative rates of **1d**. The relative rates of 2-substituted butadienes, as well as some other previous data for ready reference, are listed in Table V.

TABLE V
RELATIVE RATES AT 20°[a,b]

Substituent	Uncatalyzed reaction	Catalyzed reaction
2-Ph	23.1	94.5
2-Cl	1.29[c]	0.553
$2\text{-}CF_3$[d]	17.7[c]	0.320
2-CN	13.8	0.101
2-Me	1.89[e,f]	12.1[g]
$2,3\text{-}Me_2$	3.43[f]	36.2[g]
1-Me[h]	1.19[c]	6.47

[a] Reactivity of unsubstituted butadiene is taken as unity for each set of relative rate data; note that the rate constants for the catalyzed reactions are 10^5 times as large as those for the corresponding members of the uncatalyzed reactions.[9] [b] In benzene solution unless otherwise indicated. [c] In absence of solvent. [d] Reference 1. [e] 2.16 in absence of solvent, ref 6. [f] Present work. [g] Reference 6. [h] Reference 7.

(9) T. Inukai and T. Kojima, *J. Org. Chem.*, **32**, 872 (1967).

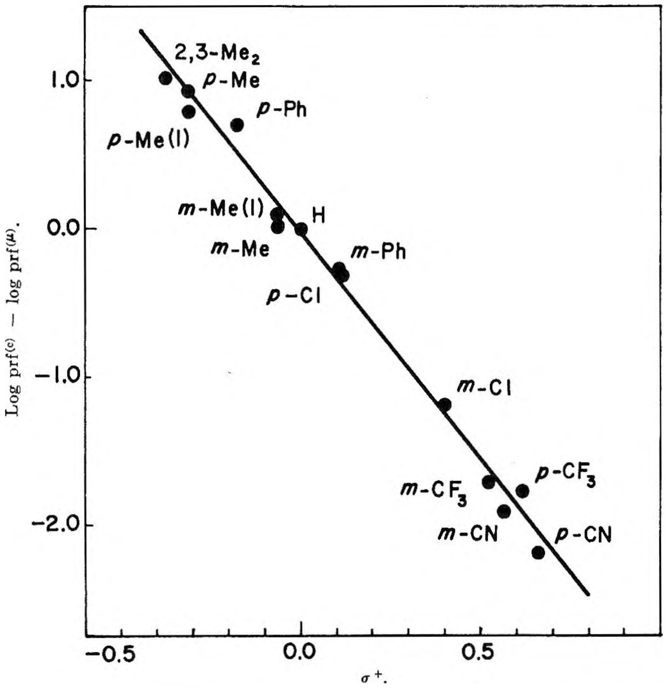


Figure 1.—Plot of log $prf^{(c)}$ − log $prf^{(u)}$ *vs.* σ^+. The points for 1-methylbutadiene have the mark (1) attached.

Discussion

Since the isomer ratios and relative rates were obtained from reactions at 20° at which temperature the products are thermally stable, it can be safely assumed that these results are kinetically controlled.

As to the isomer ratios the following rules are observed. (1) With the substituents capable of electron release by the inductive or mesomeric mechanism (Me, Ph, and Cl), the degree of para (or ortho) orientation is enhanced by the change of the dienophile from MA to MA–$AlCl_3$. (2) The percentage of meta for the dienes with the electron-withdrawing substituents increases, but to a relatively lesser degree, by the same change of the dienophile. (3) In no case does the meta exceed the para however.

Rules 1 and 2 are apparently in harmony with the expectation from the electronic theory, since MA–$AlCl_3$ is more electrophilic than MA.[1] However, the fact that the meta per cent of 2-Ph or 2-Me is greater than that of 2-CN in the uncatalyzed reactions is peculiar. The rule 3 agrees with, and reconfirms, the accepted general ortho or para orientation in the Diels–Alder reactions[5] and obviously contradicts the prediction from the polarity consideration.[10] It may be argued that the steric hindrance in the transition state prevents the predominance of the meta product,[11] the orientation that would otherwise be the case. This view cannot be born out, however, since the less bulky CN group gives less meta per cent than the CF_3 group; note that the difference of the substituent constants $\sigma_p^+ - \sigma_m^+$, of CN group (0.097) is about the same as that of the CF_3 group (0.092),[12] suggesting a similar isomer ratio for both groups on the electronic basis. Consequently, this peculiar orientation is deemed to be a genuine property of the Diels–Alder reactions.

The relative rate is related to the reactivities of the s-cis subspecies of the diene, $\bar{k}_{cis}$, and the cisoid–transoid equilibrium constant, K = [s-cis]/[s-trans], by eq 1.[1]

$$\text{relative rate} = [\bar{k}_{cis}{}^R/\bar{k}_{cis}{}^H][K^R/(1 + K^R)]/[(1 + K^H)/K^H] \quad (1)$$

Alder's generalization that electron-releasing diene substituents facilitate the reaction[4] should apply to $\bar{k}_{cis}$. However, since the effect of R on the K value will be manifold in origin, the observed relative rates may not follow a simple trend as will be seen by inspection of Table V. Unfortunately, the ratio of $\bar{k}_{cis}{}^R/\bar{k}_{cis}{}^H$ cannot be evaluated because the K values are not known to a required accuracy.

It is possible to qualitatively rationalize the results if we assume that K's for 2-Ph-, 2-Cl-, 2-CN-, and 2-CF_3-butadienes are greater than K^H.[13] Thus the conformational factor is dominant in determining the relative rates of the uncatalyzed reactions, whereas in the catalyzed reactions this factor is heavily overshadowed by the other factor, $\bar{k}_{cis}{}^R/\bar{k}_{cis}{}^H$, since MA–$AlCl_3$ is more sensitive to the substituent effect than free MA.[1]

For the convenience of the quantitative analysis of the reactivities that follows, the partial rate factors, $prf^{(u)}$ and $prf^{(c)}$, for the uncatalyzed and catalyzed reactions, respectively, were calculated from the isomer ratio and relative rate data. The results are shown in Table VI.

TABLE VI

PARTIAL RATE FACTORS AT 20°[a]

R	Uncatalyzed		Catalyzed	
	$prf_{para}^{(u)}$	$prf_{meta}^{(u)}$	$prf_{para}^{(c)}$	$prf_{meta}^{(c)}$
2-Ph	37	9.2	183	5.7
2-Cl	2.2	0.34	1.1	0.022
2-CF_3	19.5	16	0.33	0.31
2-CN	23	4.4	0.15	0.055
2-Me	2.7	1.15	23	1.2
2,3-Me_2	3.4	3.4	36	36
	$prf_{ortho}^{(u)}$	$prf_{meta}^{(u)}$	$prf_{ortho}^{(c)}$	$prf_{meta}^{(c)}$
1-Me	2.1	0.24	13	0.30

[a] $prf_{para}^{(u)}$, for example, means the relative rate of formation of the para isomer, in units of the uncatalyzed reactivity of unsubstituted butadiene in one of the two degenerate orientations. The partial rate factors for the catalyzed reactions are in units of the catalyzed reactivity of butadiene. *Cf.* footnote *a* to Table V.

Differential Hammett Correlation.—It is easy to eliminate the unknown conformational factors appearing in eq 1 and to derive eq 2, in which $k_{cis}{}^R$'s are the rates

$$prf^{(c)}/prf^{(u)} = [k_{cis}{}^{R(c)}/k_{cis}{}^{H(c)}]/[k_{cis}{}^{R(u)}/k_{cis}{}^{H(u)}] \quad (2)$$

of formation of isomeric products based on the normalized concentration of the s-cis subspecies of the

(10) Some articles of interest in this connection are J. Kazan and F. D. Greene, *J. Org. Chem.*, **28**, 2965 (1963); D. L. Fields, T. H. Regan, and J. C. Dignan, *ibid.*, **33**, 390 (1968); C. K. Bradsher and J. A. Stone, *ibid.*, **33**, 519 (1968); and T. L. Kwa, O. Korver, J. W. Hartgering, and C. Boelhouwer, *Tetrahedron*, **24**, 5711 (1968).

(11) The steric strain between the carboxylate and R group will be greater, if it is of any significance, in the transition state toward the meta isomer than the para when the diene and dienophile approach to each other in parallel planes in the endo fashion.

(12) The same can be shown in terms of Hammett σ constants.

(13) Steric repulsion in the s-trans conformation is generally assumed when R is bulky. 2-Cyanobutadiene in hexane shows uv absorption of ϵ_{max} 11,500 (λ_{max} 217 mμ), which extinction coefficient is more compatible with the s-cis rather than the s-trans conformation. The electronic effect of the cyano group on ϵ_{max} will not be great since 1-cyanobutadienes show normal extinction coefficients for transoid 1,3-dienes: *trans*-1-cyanobutadiene, ϵ_{max} 25,500 (λ_{max} 240 mμ); *cis*-1-cyanobutadiene, ϵ_{max} 25,400 (λ_{max} 240 mμ), both in hexane solution.

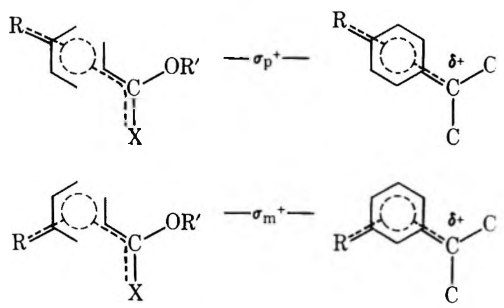
dienes. It is of interest to examine the interrelation of the two sets of prf's by means of eq 3, so to say a

$$\log \text{prf}^{(c)} - \log \text{prf}^{(u)} = \rho\sigma^+ \quad (3)$$

differential Hammett correlation. Figure 1 shows the plot ($\rho = -3.07$, $r = 0.994$, $s^2 = 0.015$). In this correlation σ_p^+ and σ_m^+ are used for prf_{para} and prf_{meta}, respectively, of 2-substituted butadienes, and $\sigma_{p\text{-Me}}^+$ (as a substitute for $\sigma_{o\text{-Me}}^+$)[14] and $\sigma_{m\text{-Me}}^+$ for prf_{ortho} and prf_{meta}, respectively, of 1-methylbutadiene.[16]

Such a way of application of σ_p^+ and σ_m^+ will be rationalized by contrasting the four-center transition states of the Diels–Alder reactions with the transition states of SN1 solvolysis of the aryldimethylcarbinyl chlorides on whose rates σ^+ were defined (Scheme II).

SCHEME II



Diels–Alder reaction (X = O or O:AlCl$_3$) solvolysis

The success of the correlation in a differential form, eq 3, means that the *change* of the substituent effects on the free energy of activation due to the change of the electronic characteristics of the dienophile substituent, from COOMe to COOMe–AlCl$_3$, is linearly correlated with σ_R^+. This will be regarded as resulting from the transmission of the substituent effects in both series of the reactions through a benzene-like conjugation system, though it may not be planar, that is conceived of in the four-center or multicenter transition state.[17a]

It should be noted that neither eq 4 nor 5 hold, as will be evident from the fact that the isomer ratios in both the reaction series do not follow the correlation

$$\log k_{cis}^{R(c)}/k_{cis}^{H(c)} = \rho^{(c)}\sigma^+ \quad (4)$$

$$\log k_{cis}^{R(u)}k_{cis}^{H(u)} = \rho^{(u)}\sigma^+ \quad (5)$$

$\log \text{prf}_{para} - \log \text{prf}_{meta} = \rho(\sigma_p^+ - \sigma_m^+)$. It is concluded, therefore, that, although the *interrelation* between the two sets of the reactivity data for the catalyzed and uncatalyzed Diels–Alder reactions is electronically intelligible in terms of eq 3, the orientation phenomena in none of these reactions are explicable by the conventional electronic considerations.[17b] A perturbational molecular orbital treatment for the orientation has been reported to give good predictions for methyl- and phenylbutadienes,[18] but the exactly same calculation on 2-cyanobutadiene that presents a more diagnostic case turned out to give meta orientation in disagreement with the experimental results.[19] Therefore, more elaborate MO calculations are required in order to obtain a satisfactory solution of the problem using one-step transition models.

Experimental Section

Melting points are uncorrected. Identification of the products, either pure specimens or uncontaminated binary mixtures of isomers, were made by their satisfactory nmr spectra (a Varian A-60A spectrometer) and elemental analyses.

Substituted 1,3-Butadienes.—1a was prepared by the published procedure,[20] bp 64–66° (15 mm) [lit.[21] bp 60° (15 mm)]. **1b** was prepared according to the known method,[22] bp 58° (lit.[22] bp 59.4°). 1c is the same as that described previously.[1] 3-Hydroxy-3-cyano-1-butene was prepared in 70% yield by addition of hydrogen cyanide to methyl vinyl ketone in methanol below −5°,[23,24] and its acetate[27] was pyrolyzed[27] to obtain **1d**, bp 34–36° (40 mm) [lit.[27] bp 34–36° (33 mm)]. **1-Cyanobutadiene** was synthesized from crotonaldehyde by the method of Gudgeon, *et al.*,[28] bp 47–56° (31.5 mm) [lit.[28] bp 48–58° (24 mm)]. Cis (pure) and trans (containing about 4% cis) isomers separated by preparative glpc (polyethylene glycol column)[29] were used for uv measurements.

Authentic Diels–Alder Adducts.—A. **2a** (acid) and **3a** (acid) were prepared from **1a** and acrylic acid by the known method:[20] **2a** (acid), mp 157–159.7° (lit.[20] mp 157–158°); **3a** (acid), mp 96.5–97.5° (lit.[20] mp 87–88°). These were converted to the methyl esters with diazomethane: **2a**, mp 58.7–59.7° (lit.[20] mp 57–58°); **3a**, bp 154–155° (6 mm). B. **2b** (acid) was obtained by alkaline hydrolysis[30] of the adduct of **1b** and methyl acrylate by the method of Meek and Trapp,[30] mp 109.5–110.5° (lit.[30] mp 113–114°). Its methyl ester, **2b**, showed bp 98–101.5° (10 mm). The oily by-product, **2b** (acid) plus **3a** (acid),[30] of the alkaline hydrolysis of the above adduct was passed through a silica gel column and was converted to the methyl ester, bp 94–95.6° (8 mm), which was found to consist 60% of **2b** and 40% **3b** by glpc. C. See ref 1 for **2c** and **3c**. D. The mixture of **2d** plus **3d** was obtained from reaction of **1d** with methyl acrylate in benzene at 20°, 2 months, bp 150°–151.5° (15 mm).

Other Authentic Samples. Methyl 4-Trifluoromethylcyclohexane-1-carboxylate (*cis*-**4** and *trans*-**4**).—α,α,α-Trifluoro-*p*-toluic acid (Aldrich Co.) was hydrogenated in acetic acid with platinum oxide catalyst at 80° under hydrogen pressure of 40 atm, and the product was converted (MeOH and H_2SO_4) to the methyl ester, bp 90–90.5° (20 mm), whose isomeric composition was 77:23, presumably rich in the cis isomer.

Methyl 3-trifluoromethylcyclohexane-1-carboxylate (*cis*-**5** and *trans*-**5**) was prepared from α,α,α-trifluoro-*m*-toluic acid (Aldrich Co.) in the same way as above, bp 90–91° (20 mm), and had an isomeric composition of 88:12, presumably rich in the cis isomer.

Dimethyl *trans*-**1,4-cyclohexanedicarboxylate** (*trans*-**8**) was prepared by esterification (MeOH and H_2SO_4) of *trans*-1,4-cyclo-

(14) Evidently $\sigma^+_{o\text{-Me}}$, free from proximity effects, is ideal if it were available. Recently a $\sigma^+_{o\text{-Me}}$ value (−0.233) was claimed[15] from the rate study of the pyrolytic elimination reactions of esters on the assumption that the proximity effects are negligible. This value also fits nicely in the correlation line.

(15) G. G. Smith, K. K. Lum, J. A. Kirby, and J. Posposil, *J. Org. Chem.*, **34**, 2090 (1969).

(16) Brown and Okamoto's σ^+ [H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958)] was used.

(17) (a) See ref 1 for the evidence and discussions against the cationic two-step mechanism for the aluminum chloride catalyzed reactions. (b) For some previous works on structural effects of the Diels–Alder reactions in terms of the Hammett-type equations, see M. Charton, *J. Org. Chem.*, **31**, 3745 (1966), and references therein.

(18) J. Feuer, W. C. Herndon, and L. H. Hall, *Tetrahedron*, **24**, 2575 (1968).

(19) Unpublished work with H. Sato.

(20) J. S. Meek, R. T. Merrow, D. E. Ramey, and S. J. Cristol, *J. Amer. Chem. Soc.*, **73**, 5563 (1951).

(21) C. C. Price, F. L. Benton, and C. J. Schmidle, *ibid.*, **71**, 2860 (1949).

(22) W. H. Carothers, I. Williams, A. M. Collins, and J. E. Kirby, *ibid.*, **53**, 4203 (1931).

(23) M. Tanaka and J. Murata, *Kogyo Kagaku Zasshi*, **60**, 433 (1957).

(24) Levulinonitrile was the main product when the addition of hydrogen cyanide was carried out by the descriptions of ref 25 and 26.

(25) E. O. Leopold and H. Vollmann, U. S. Patent 2,166,600 (July 18, 1939).

(26) C. S. Marvel and N. O. Brace, *J. Amer. Chem. Soc.*, **70**, 1775 (1948).

(27) M. Tanaka, T. Nishimura, and J. Murata, *Kogyo Kagaku Zasshi*, **60**, 435 (1957).

(28) H. Gudgeon, R. Hill, and E. Isaac, *J. Chem. Soc.*, 1926 (1951).

(29) J. G. Grasselli, B. L. Ross, H. F. Huber, and J. M. Augl, *Chem. Ind. (London)*, 162 (1963).

(30) J. S. Meek and W. B. Trapp, *J. Amer. Chem. Soc.*, **74**, 2686 (1952).

hexanedicarboxylic acid (Aldrich Co.) and showed mp 66–66.3° (lit.[31] mp 69°). The ester was epimerized (MeONa in absolute MeOH) to a mixture *trans*-**8** (75%) and *cis*-**8** (25%).

Dimethyl 1,3-cyclohexanedicarboxylate (9) was obtained from isophthalic acid by hydrogenation with platinum oxide catalyst at 60°, 40 atm, in acetic acid, followed by esterification, bp 129.5–130.5° (10 mm) [lit.[31] *cis*-**9**, bp 130.6° (10 mm); *trans*-**9**, bp 140° (20 mm)]. The product consisted of 84% of *cis*-**9** and 16% of *trans*-**9**.

Determination of Isomer Ratios.—The Diels–Alder reactions were carried out at 20° starting from approximately equimolecular amounts of the dienes and dienophiles in a similar way as in the previous work.[6,7] The assumption was made that the isomer ratios were equal to the glpc peak area ratios (FID by a Hitachi K 53 instrument equipped with a suitable Golay column).

R = Phenyl.—The adduct, 11.0 g, from the aluminum chloride catalyzed reaction was heated in aqueous methanolic sodium hydroxide (NaOH 4 g, MeOH 15 ml, H_2O 25 ml) for 16 hr. After dilution with water the mixture was washed with ether, and the aqueous layer acidified with dilute hydrochloric acid to precipitate the acids. The precipitates were recrystallized from benzene to obtain 6.1 g of pure **2a** (acid). The benzene mother liquor on vacuum evaporation to dryness left 3.5 g of crystals, which was treated with diazomethane in ether to recover the mixture of **2a** plus **3a**, 3.1 g, by vacuum distillation. The **2a**:**3a** ratio of this mixture was found to be 92:8 by the relative nmr peak heights at τ 7.60 and 7.37 (characteristic of **2a** and **3a**, respectively, in 10 wt % benzene solution with tetramethylsilane as internal standard), by referring to the calibration curve prepared by use of known artificial mixtures of **2a** and **3a**. The product from the uncatalyzed reaction was treated similarly but no attempt was made to set aside pure **2a** (acid) before nmr analysis. The limit of experimental uncertainty is estimated at ±1% absolute.

R = Cl.—An R-45 Golay column (45 meter polypropylene glycol 550, Hitachi) was used for the glpc analysis of **2b**:**3b** ratio; **3b** eluted faster than **2b**.

R = CF_3.—The glpc analysis of the adduct from the uncatalyzed reaction by means of a PEG 4000-45 Golay column (45-m polyethylene glycol 4000, Hitachi) gave two peaks, peak A (faster elute, 55%) and peak B (45%). The adduct was hydrogenated at NTP with Pd on carbon to obtain the **4** plus **5** mixture in over 96% yield. It exhibited four glpc peaks, in order of elution, of trans-**5** (4.6%), *cis*-**4** (38.1%), *trans*-**4** (15.5%), and *cis*-**5** (41.8%), all being identified by coincidence of retention times with those of the authentic samples. Therefore the ratio of **2c**:**3c** in the original adduct is reckoned to be 53.6:46.4 in good agreement with that directly found by peak A and peak B above, which are now ascribed to **2c** and **3c**, respectively.

R = CN.—The adduct, 2.00 g, was heated with aqueous sodium hydroxide (7.4 g of NaOH in 35 ml of H_2O) under reflux for 45 hr, and the resulting solution was acidified with hydrochloric acid to precipitate almost all of the dicarboxylic acids. The precipitates were collected by filtration and washed with a small volume of water, and the combined aqueous solution was treated in order to recover further crops of the hydrolysis product, which were proved to be minute. The combined product weighed 2.57 g; so it must contain some sodium chloride. It was converted to **6** + **7** by treatment with diazomethane in methanol, bp 95–101° (2 mm); overall yield from **2d** + **3d** was 92%. This mixture gave on glpc with a Golay column HB 2000-45 (polypropylene glycol, Hitachi) two peaks, peak A (faster elute, 73%) and peak B (27%), which were identified with **6** and **7**, respectively, in the following way. The mixture, **6** plus **7**, was hydrogenated at NTP with Pd on carbon to afford **8** plus **9** in 95% yield. The saturated product gave, on glpc analysis with the same column, four peaks, *trans*-**9** (9.1%), *cis*-**8** (57.9%), *trans*-**8** (17.9%), and *cis*-**9** (15.1%). The predominant isomer of the Diels–Alder reaction therefore belongs to the para series.

Competitive Reactions.—The reaction conditions used were quite similar to those described in the previous papers.[1,6,7] For the cases of **1a** and 2,3-dimethylbutadiene was used isoprene as the competitor in place of the standard substrate butadiene. The ratios of the products from two dienes were determined by quantitative glpc using appropriate calibration curves for peak area ratio *vs.* molar ratio.

Kinetic experiments were carried out in a similar manner to the previous work,[1,9] and some of experimental details are summarized in Tables II, III, and IV.

Registry No.—**2b**, 27705-05-1; **2d**, 20594-59-6; **3a**, 27705-07-3; **3b**, 27705-08-4; **3d**, 27705-09-5; *cis*-**4**, 27705-10-8; *trans*-**4**, 27705-11-9; *cis*-**5**, 27705-12-0; *trans*-**5**, 27705-13-1; aluminum chloride, 7446-70-0; 2-phenylbutadiene, 2288-18-8; 2-chlorobutadiene, 126-99-8; 2-trifluoromethylbutadiene, 381-81-7; 2-cyanobutadiene, 5167-62-4; methyl acrylate, 96-33-3.

Acknowledgment.—The authors express their sincere thanks to Professor O. Simamura of Tokyo University for his kind interest and encouragement throughout this series of study. They also thank Mr. T. Nakamura for his valuable technical assistance.

(31) H. A. Smith, K. G. Scrogham, and B. L. Stump, *J. Org. Chem.*, **26**, 1408 (1961).

J. Org. Chem., Vol. 36, No. 7, 1971 929

The Diels–Alder Reaction of α,β-Unsaturated Trihalosilanes with Cyclopentadiene

Robert F. Cunico

Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115

Received July 27, 1970

The Diels–Alder reaction of cyclopentadiene with some ethylenic and acetylenic α,β-unsaturated silanes was investigated to determine the synthetic potential of such compounds as dienophiles. Although trimethylsilyl species displayed low reactivity in these reactions, the corresponding trichloro and trifluorosilyl analogs were quite reactive. Trifluorosilyl compounds induced polymerization of cyclopentadiene, and in the case of ethynyltrifluorosilane this polymerization precluded the formation of cycloaddition product. The geometrical isomers of β-chlorovinyltrichlorosilane were characterized for the first time, and the lowest member of a new class of compounds, alkynyltrifluorosilanes, was prepared.

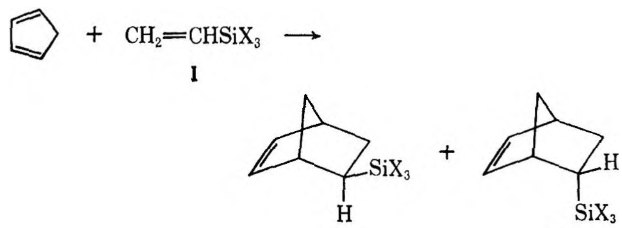
Organosilicon compounds possessing unsaturation adjacent to the heteroatom have not enjoyed widespread use as dienophilic participants in Diels–Alder reactions.[1] This neglect may be due to the reluctance of many such organosilicon compounds to readily undergo 1,4 cycloaddition with diene systems such as cyclopentadiene and 1,3-butadiene. Most reports in this area thus involve either dienes which are reactive by virtue of "inverse electron demand,"[2] or reaction conditions of high temperatures and long reaction times have been employed.[3]

In the latter cases, a trimethylsilyl group was usually present in the dienophile. Since Diels–Alder reactions of electron-rich dienes are favored by electron-withdrawing substituents in the dienophile,[4] the electrical effect of the trimethylsilyl group ($\sigma_p = -0.07$)[5] would dampen the dienophilicity of an unsaturated site. Conversely, a group such as trichlorosilyl ($\sigma_p = +0.24$)[6] should enhance the reactivity of an olefin or acetylene.

Although this latter point has been confirmed by the observation that vinyltrichlorosilane (**1a**) and cyclopentadiene react exothermically to give a near-quantitative yield of Diels–Alder adduct,[7] no extension of this principle to similarly substituted alkynes has been attempted. Moreover, it was of interest to investigate the behavior of α,β-unsaturated trifluorosilanes in order to assess the value of the trifluorosilyl group ($\sigma_p = +0.30$) as an activating moiety.

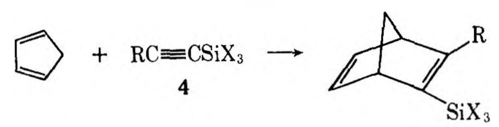
Results and Discussion

Vinylsilanes.—To establish a reference point against which to judge the dienophilic reactivity of some trihalovinylsilanes (**1a, 1b**), the Diels–Alder reaction of trimethylvinylsilane (**1c**) and cyclopentadiene was carried out. The cycloaddition afforded only a 4% yield of adduct after 8 hr at 100°, but at 170° a 58% yield of product was obtained, identified as a 1:1 mixture of 5-*exo*-trimethylsilylbicyclo[2.2.1]hept-2-ene (**2c**) and the corresponding endo isomer **3c**. Since the reactivity of other highly α-branched dienophiles is very low,[8] this result suggests that additional parameters not measured by σ_p values may contribute to the behavior of **1c**.[9]



1 2 3

a, X = Cl
b, X = F
c, X = CH$_3$



4 5

a, X = Cl; R = H d, X = Cl; R = Ph
b, X = F; R = H e, X = CH$_3$; R = Ph
c, X = CH$_3$; R = H

The exo (**2a**) and endo (**3a**) adducts of cyclopentadiene and vinyltrichlorosilane (**1a**) were easily prepared and individually characterized for the first time. The ratio of 24:76 for the exo to endo distribution in the product (obtained in 93% yield) agrees well with the 20:80 ratio determined previously for this mixture by indirect methods.[7b] Inasmuch as the steric requirements of the trichlorosilyl and trimethylsilyl groups should be similar,[12] the predominant influence on the promoting effect of the former is probably its electron-withdrawing capability.

The reaction between vinyltrifluorosilane (**1b**) and cyclopentadiene occurred readily (a mildly exothermic

(1) Recent reviews in this area include (a) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **5**, 211 (1966); (b) *ibid.*, **6**, 16 (1967); (c) S. Seltzer, *Advan. Alicyclic Chem.*, **2**, 1 (1968).

(2) (a) For a discussion, see ref 1b, pp 26–27. (b) Dienes used, this category have usually been hexahalocyclopentadienes.

(3) (a) D. Seyferth, C. Sarafidis, and A. B. Evnin, *J. Organometal. Chem.*, **2**, 417 (1964); (b) M. E. Freeburger and L. Spialter, *J. Org. Chem.*, **35**, 652 (1970); (c) C. S. Kraihanzel and M. L. Losee, *ibid.*, **33**, 1983 (1968); (d) D. Seyferth, D. R. Blank, and A. B. Evnin, *J. Amer. Chem. Soc.*, **89**, 4793 (1967); (e) C. S. Kraihanzel and Losee, *ibid.*, **90**, 4701 (1968).

(4) See ref 1b, pp 24–26.

(5) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).

(6) J. Hradil and V. Chvalovsky, *Collect. Czech. Chem. Commun.*, **32**, 171 (1967).

(7) (a) G. H. Wagner, D. L. Bailey, A. N. Pines, D. L. Dunham, and D. B. McIntire, *Ind. Eng. Chem.*, **45**, 367 (1953); (b) H. G. Kuivila and C. R. Warner, *J. Org. Chem.*, **29**, 2845 (1964).

(8) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961); also, see ref 1c, pp 26–29.

(9) A vinylsilane may well be less hindered than in its carbon analog because of the longer silicon–(vinyl) carbon bond, said to be 1.853 Å in vinylsilane,[10] for example, as compared with 1.448 Å in propene.[11]

(10) J. M. O'Reilly and L. Pierce, *J. Chem. Phys.*, **34**, 1176 (1961).

(11) D. R. Lide and D. E. Mann, *ibid.*, **27**, 868 (1957).

(12) Calculations based on reported bond lengths[13] and van der Waals radii[14] of the atoms involved give 4.2, 3.8, and 2.9 Å, respectively, for the effective radii of trimethylsilyl, trichlorosilyl, and trifluorosilyl groups.

(13) C. Eaborn, "Organosilicon Compounds," Butterworths, London, 1960, Chapter 16.

(14) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 260.

reaction ensued spontaneously at ambient temperatures) to afford a 77% yield of product. Although the enhanced reactivity of **1b** *vs.* its trimethyl analog **1c** (possibly due to a combination of electrical and steric[12] effects) is thus evident, the answer to a similar comparison with vinyltrichlorosilane awaits further information of a more quantitative nature. Again, the cycloaddition produced more endo isomer **3b** than exo isomer **2b**, obtained in a ratio of 69:31. During this preparation, **1b** apparently initiated the polymerization of cyclopentadiene.[15] This was not a serious complication in the present case, since the use of excess diene led to good yields of adducts, but less reactive alkenyltrifluorosilanes might not afford useful quantities of Diels-Alder products from cyclopentadiene.

Ethynylsilanes.—Kraihanzel and Losee[3c] have reported that ethynyltrimethylsilane (**4c**) and cyclopentadiene in benzene yielded only 10% **5c** after 50 hr at 180°, but 87% after similar treatment at 270°. In contrast to the behavior of **4c**, its trichloro analog **4a** undergoes reaction with cyclopentadiene within 2 hr at 70° to give 93% bicycloheptadiene **5a**.

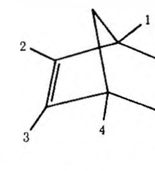
When ethynyltrifluorosilane (**4b**) was employed in this reaction, polymerization of the diene occurred to the exclusion of cycloaddition. Since alkynes are less potent dienophiles than corresponding alkenes,[19] it appears that the balance in rates between cycloaddition and polymerization which existed in the case of **1b** has with **4b** become much more favorable for polymer formation.

In order to estimate the difference in reactivity between trimethylsilyl- and trichlorosilyl-substituted dienophiles possessing increased steric requirements, the reactions of cyclopentadiene with acetylenes **4e** and **4d** were also investigated. Although phenylethynyltrimethylsilane (**4e**) afforded adduct **5e** in only 10% yield after 8 hr at 170°, the trichloro analog **4d** underwent cycloaddition at 100° to afford a 50% yield (96% based on recovered **4d**) of **5d** within 5.5 hr. Although excess cyclopentadiene was used in the reactions carried out at 100°, conversion of **4d** to adduct was only about half complete. A higher conversion of **4d** to **5d** was not realized by operating above the dissociation temperature of dicyclopentadiene (170–180°), since higher boiling materials were then formed at the expense of **5d**.

Spectral Assignment of Structure.—Kuivila and Warner have assigned exo and endo configurations to several 5-silyl-substituted bicyclo[2.2.1]hept-2-enes on the basis of chemical and pmr evidence.[7b] Although most compounds studied were obtained as mixtures of epimers, characteristic differences in the vinylic and bridgehead proton regions of their pmr spectra allowed for spectral identification of the two isomers in each case. Of special significance was the conclusion that the exo isomers exhibited two separate unsymmetrical doublet of doublets in the vinylic region, while in the spectra of the endo isomers the absorptions due to the two vinylic protons had merged to afford an apparent triplet. This method of epimer assignment was used here to identify **2a** and **3a** and has been extended to assign the stereochemistry of the corresponding trifluorosilyl isomers **2b** and **3b** (Table I).

TABLE I

PMR DATA FOR 5-TRIHALOSILYLBICYCLO[2.2.1]HEPT-2-ENES[a-c]



	2a	2b	3a	3b
H_1	3.09 (bs)	3.10 (bs)	3.02 (bs)	3.06 (bs)
H_2, H_3	6.01 (dd) or 6.29 (dd)	5.97 (dd) or 6.13 (dd)	6.02 (t)	6.12 (t)
H_4	3.09 (bs)	3.10 (bs)	3.22 (bs)	3.18 (bs)
Other	0.92–1.69 (c)	0.55–2.1 (c)	1.07–2.35 (cm)	0.93–2.23 (c)

[a] Data obtained on *ca.* 30% CCl_4 solutions with TMS as internal standard and reported as δ values. [b] In all cases, integrated peak areas were consistent with the assignments made. [c] Chemical shifts are measured to the estimated center of a singlet or multiplet.

One discordant observation intrudes upon the configurational assignments thus made however. In all other examples of exo-endo pairs of 5-substituted bicyclo[2.2.1]hept-2-enes for which pmr data has been found, the difference in chemical shifts between the two vinylic protons is larger for the endo than for the exo isomer.[20] As can be seen from Table I and the data reported by Kuivila and Warner,[7b] the assignments originally made lead to an inversion of this relationship for the corresponding silyl-substituted compounds. The explanation for this disparity is beyond the scope of the present investigation and will be the subject of a future report.

The pmr spectra of several 2-silyl-substituted bicyclo-[2.2.1]hepta-2,5-dienes have been discussed previously.[3c] Pmr data for similar compounds prepared in this study are recorded in Table II; no unusual features were observed in these spectra.

Experimental Section

General.—Cyclopentadiene was prepared from its dimer just prior to use by a standard procedure.[21] Dicyclopentadiene was obtained from the redimerization of freshly cracked cyclopentadiene upon overnight standing. The following stainless steel 0.25-in. columns were used for vpc analyses: A, 10-ft FFAP; B, 12-ft QF-1; C, 16-ft QF-1 ($^3/_8$ in.); D, 5-ft SE-30. For halosilane analysis, columns were preconditioned by the injection of *ca.* 10 μl of ethyltrichlorosilane. Compositions obtained from vpc data are based on relative peak areas. All infrared data was obtained on neat films employing a Beckman IR-8 spectrophotometer, except the ir spectrum of **4b** which was recorded by a Beckman IR-12 spectrophotometer. Pmr spectra were obtained on *ca.* 30%

(15) The cationic polymerization of cyclopentadiene can be initiated by a variety of protonic[16] or nonprotonic[17] acids. However, the observed effect of **1b** in this regard appears to be the first report of a halosilane acting in this capacity.[18] Evidence of such extensive polymerization was absent from any of the cycloaddition reactions involving organotrichlorosilanes.

(16) (a) H. Staudinger and H. A. Bruson, *Justus Liebigs Ann. Chem.*, **447**, 97 (1926); (b) J. Upadhyay, P. Gaston, A. A. Levy, and A. Wasserman, *ibid.*, 3252 (1965), and references therein.

(17) (a) H. Staudinger and H. A. Bruson, *ibid.*, **447**, 110 (1926); (b) P. V. French and A. Wasserman, *J. Chem. Soc.*, 1044 (1963).

(18) The possibility that traces of hydrogen fluoride were inducing the polymerization cannot be rigorously excluded.

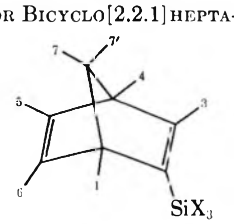
(19) Reference 1b, p 25.

(20) (a) J. C. Davis, Jr., and T. V. Van Auken, *J. Amer. Chem. Soc.*, **87**, 3900 (1965); (b) W. L. Dilling, R. D. Kroening, and J. C. Little, *ibid.*, **92**, 928 (1970); (c) J. Paasivirta, *Soumen Kemistilehti*, *B*, **38**, 130 (1965); (d) R. V. Moen and H. S. Makowski, *Anal. Chem.*, **39**, 1860 (1967); (e) R. J. Ouellette and G. E. Booth, *J. Org. Chem.*, **30**, 423 (1965); (f) L. A. Paquette, *ibid.*, **29**, 2851 (1964).

(21) R. B. Moffett in "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 238.

Table II

Pmr Data for Bicyclo[2.2.1]hepta-2,5-Dienes[a]



	5a	5d	5e[b]
H_1, H_4	3.82 (bs) or 3.92 (bs)	3.87 (bs) or 4.13 (bs)	3.92 (bs) or 4.05 (bs)
H_3	7.64 (dd)		
H_5, H_6	6.65 (ddd) or 6.82 (ddd)	6.86 (t)	7.01 (m)
H_7, $H_{7'}$	2.03 (t)	2.00 (dt) or 2.22 (dt)	2.21 (cm)
$SiCH_3$			0.25 (s)
3-Ph		7.26 (s)	7.39 (s)

[a] Footnotes to Table I apply. [b] CH_2Cl_2 as internal standard.

CCl_4 solutions with tetramethylsilane as internal standard using a Varian A-60A spectrometer. The pmr spectra of halosilanes could be conveniently recorded (and the samples then stored indefinitely) by sealing the solution in a melting point capillary tube. The sample and some CCl_4 were then put into an nmr tube and the spectrum obtained as usual.[22] Unless stated otherwise, distillations were carried out by the use of short-path apparatus.

5-*exo*- and 5-*endo*-Trimethylsilylbicyclo[2.2.1]hept-2-ene (2c and 3c).—A mixture of 4.0 g (0.04 mol) of vinyltrimethylsilane (1c) and 2.9 g (0.044 mol) of cyclopentadiene was sealed in a glass ampoule and held at 170° for 8 hr. Distillation gave 3.8 g (58%) of a 1:1 mixture[23] of 2c and 3c, bp 75–79° (21 mm). These isomers were inseparable on a variety of vpc columns and were collected together from column A (90°).

Anal. Calcd for $C_{10}H_{18}Si$: C, 72.22; H, 10.91. Found: C, 72.19; H, 10.98.

In another run as above, but at 100°, vpc showed that only a 4% yield of an exo-endo mixture of adducts was obtained.

5-*exo*- and 5-*endo*-Trichlorosilylbicyclo[2.2.1]hept-2-ene (2a and 3a).—A mixture of 8.1 g (0.05 mol) of 1a and 4.0 g (0.06 mol) of cyclopentadiene became mildly exothermic upon gentle heating. After 1 hr, followed by 10 min at 100°, distillation gave 10.6 g (93%) of adduct, bp 77–81° (8 mm) [lit.[7a] bp 116–117° (49 mm)]. This distillate consisted of 24% exo isomer 2a and 76% endo isomer 3a (order of elution from column B, 165°). Preparative vpc (column C, 140°) afforded pure 2a: ir 3.25 (w), 7.47 (m), 11.23 (s), 12.30 (m), 13.55 (s), 14.33 μ (s).

Anal. Calcd for $C_7H_9Cl_3Si$: C, 36.94; H, 3.99. Found: C, 36.79; H, 4.00.

The endo isomer 3a was similarly obtained: ir 3.25 (w), 7.47 (m); 11.23 (s), 12.10 (m), 13.81 (s), 14.07 μ (m).

Anal. Calcd for $C_7H_9Cl_3Si$: C, 36.94; H, 3.99. Found: C, 37.10; H, 3.91.

5-*exo*- and 5-*endo*-Trifluorosilylbicyclo[2.2.1]hept-2-ene (2b and 3b).—An ampoule containing 6.2 g (0.094 mol) of cyclopentadiene at −78° was charged with 4.0 g (0.036 mol) of 1b[24] (distilled into the ampoule from anhydrous KF or calcium hydride). After sealing, the ampoule was warmed to 25°, initiating a mildly exothermic reaction of 10-min duration. After 13 hr, the ampoule was opened, allowing a low boiler to distil off (unreacted 1b?). The residue consisted of a rubbery white gel and a mobile, water-white liquid. Distillation of the latter gave 4.9 g (77%) of adduct, bp 115–121° (740 mm). Vpc showed it to contain 31% exo isomer 2b and 69% endo isomer 3b (order of elution from column B, 115°).

Preparative vpc[25] (column C, 130°) afforded pure 2b: ir 3.24 (w), 7.47 (m), 10.5–10.7 (vs), 11.16 (s), 11.74 (s), 12.51 (m), 13.70 (s), 14.46 μ (m).

Anal. Calcd for $C_7H_9F_3Si$: C, 47.18; H, 5.09. Found: C, 46.98; H, 4.93.

The endo isomer 3b was similarly obtained: ir 3.24 (w), 7.47 (m), 10.5–10.7 (vs), 11.14 (s), 11.84 (vs), 12.39 (m), 13.82 μ (s).

Anal. Calcd for $C_7H_9F_3Si$: C, 47.18; H, 5.09. Found: C, 47.53; H, 4.83.

Freshly distilled or vpc-collected samples of 2b or 3b were initially colorless but soon became dark when stored.[26] However, redistillation of this mobile liquid led to excellent recovery of colorless material. A mixture of 2b and 3b which was sealed in a capillary tube soon darkened but afforded identical nmr spectra over a period of 3 months.

Reaction of 1,2-Dichloroethylene with Trichlorosilane. Ethynyltrichlorosilane and *cis* and *trans*-β-Chlorovinyltrichlorosilane.—Because of the brevity of experimental detail in the published procedure,[27] a description of technique and results is given here.

A 30-mm-diameter Vycor tube filled to a height of 30 cm with 5-mm Kimax glass beads was mounted vertically and heated by an electric furnace. The mixed reactants were added under a slow flow of nitrogen; pyrolysate was collected in a −78° trap. A mixture of 97 g (1.0 mol) of *trans*-1,2-dichloroethylene and 68 g (0.50 mol) of trichlorosilane was passed dropwide through the hot zone at 630° over 2 hr to give 119.3 g of dark pyrolysate. Fractionation of this material (760 mm) on a 24-in. annular Teflon spinning-band column[28] gave the following fractions: bp 48.5–74° (39.3 g, mixed dichloroethylenes); bp 74–76° (lit.[27] bp 73°) [34.3 g (43%), ethynyltrichlorosilane (purity in excess of 99%); ir 3.01 (s), 4.84 (s), 7.20 (m), 14.2 μ (s, br); pmr δ 2.88 (s)]; bp 131.5–132° [21.5 g, *trans*-β-chlorovinyltrichlorosilane (98% pure)]; bp 132–136° (5.8 g, 1:3 ratio of *trans*- to *cis*-β-chlorovinyltrichlorosilane). Pure samples of the geometric isomers were obtained by preparative vpc (column D, 75°). The trans isomer eluted first and had ir 3.24 (vw), 3.28 (vw), 6.16 (m), 6.44 (s), 8.49 (s), 10.60 (s),[29] 12.54 (s), 12.99 μ (m), and pmr δ 6.30 (d, 1, J = 15.5 cps, C=CHSi), 7.07 (d, 1, J = 15.5 cps, ClCH=C).[30]

Anal. Calcd for $C_2H_2Cl_4Si$: C, 12.26; H, 1.03. Found: C, 12.34; H, 1.00.

The cis isomer had ir 3.23 (vw), 3.28 (vw), 6.07 (w), 6.40 (s), 7.61 (m), 12.25 (s), 14.4–14.9 μ (s, br), and pmr δ 6.12 (d, 1, J = 9.5 cps, C=CHSi), 7.07 (d, 1, J = 9.5 cps, ClCH=C).[30]

Anal. Calcd for $C_2H_2Cl_4Si$: C, 12.26; H, 1.03. Found: C, 11.94; H, 1.08.

When the pyrolysis was carried out as above, but at 540°, 95.4 g of starting material was recovered, and only about 1 g of ethynyltrichlorosilane was obtained. The major product of the reaction was 40.5 g of a 4:1 mixture of *trans*- and *cis*-β-chlorovinyltrichlorosilane. This material could be pyrolyzed in turn (at 640°) to afford 9.9 g (39%) of ethynyltrichlorosilane.

2-Trichlorosilylbicyclo[2.2.1]hepta-2,5-diene (5a).—A mixture of 1.6 g (0.01 mol) of 4a and 0.8 g (0.012 mol) of cyclopentadiene was heated at 70° for 2 hr under nitrogen. Distillation gave 2.1 g (93%) of 5a, bp 60–64° (4 mm), which vpc (column B, 170°) showed was at least 95% pure: ir 3.23 (w), 6.36 (w), 6.48 (m), 7.71 (s), 9.74 (s), 14.29 μ (vs).

Anal. Calcd for $C_7H_7Cl_3Si$: C, 37.27; H, 3.13. Found: C, 37.43; H, 2.80.

2-Trimethylsilylbicyclo[2.2.1]hepta-2,5-diene (5c).—A solution of 2.1 g (0.0094 mol) of 5a in 20 ml of dry ethyl ether was slowly treated with 0.038 mol of ethereal methylmagnesium bromide. After a 3.5-hr reflux, the reaction mixture was worked up to give 1.1 g (73%) of 5c: bp 73–74° (30 mm) [lit.[3c] bp 58.5–59.5° (18 mm)]; vpc (column A, 150°) showed a purity of 96%. A vpc-collected sample had $n^{27}D$ 1.4645; ir 3.23 (w), 3.26 (w),

(22) The author wishes to thank Mr. E. M. Dexheimer for bringing this technique to his attention.

(23) The isomer content was determined *via* the nmr technique detailed in ref 7b.

(24) Prepared from 1a by the method of L. Spialter, R. S. Towers, and M. M. Kent, *Tetrahedron Lett.*, 11 (1960); see R. Mueller, H. Witte, and C. Dathe, *Z. Chem.*, 3, 391 (1963).

(25) The temperature of the thermal conductivity detector was 200°. Material obtained at 300° contained cyclopentadiene, as evidenced by nmr, presumably formed *via* a partial retrodiene reaction.

(26) This dark material may be similar to the polymer described by J. Upadhyay, P. Gaston, A. A. Levy, and A. Wasserman, *J. Chem. Soc.*, 3252 (1965).

(27) E. A. Chernyshev and G. F. Pavelko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 12, 2205 (1966).

(28) Nester Faust Mfg. Co., Newark, Del.

(29) Strong absorption in this region is indicative of a *trans*-substituted ethylene: see R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass., 1966, pp 101–102.

(30) The observed J values suggest the *cis–trans* assignments made: see L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, London, 1969, pp 301–302.

6.35 (vw), 6.48 (w), 7.69 (m), 8.01 (s), 10.03 (m), 12.0 (vs), 13.34 (s), 14.42 μ (s). Confirmation of structure was provided by spectra comparison with published data.[3c]

Ethynyltrifluorosilane (4b).—A flask was fitted with a train of apparatus consisting of a water condenser, glass tubing to a −78° trap, and a drying tube. The flask was charged with 6.8 g (0.038 mol) of powdered SbF_3, 30 ml of dry heptane, and 5.0 g (0.031 mol) of **4a**. No observable reaction occurred upon stirring for 1 hr at 25°, but reaction was rapid at 65–70°. After all volatile material had condensed, the product was purified by trap to trap distillation at 25 and −78°. This afforded 2.2 g (64%) of ethynyltrifluorosilane (**4b**): ir (gas, 20 mm, 10-cm cell) 3.01 (m), 4.80 (m), 7.12 (w), 8.52 (w, br), 9.20 (w, br), 10.0 (s), 11.2 (s), 13.7 μ (s); pmr (neat plus TMS) δ 2.46 (s); mass spectrum (70 eV) *m/e* (rel intensity) 110 (75), 91 (65), 90 (11) 85 (100), 47 (12); vapor pressure 84 mm at −63.5° (chloroform slush).

An attempt to prepare **4b** by the use of aqueous HF[24] produced a rush of gas, noncondensable at −78°, and afforded no detectable amount of product.

2-Trifluorosilylbicyclo[2.2.1]hepta-2,5-diene (5b) (Attempted).—An ampoule containing 3.0 g (0.046 mol) of cyclopentadiene was cooled in liquid nitrogen, and 1.5 g (0.014 mol) of **4b** was allowed to distill in. The sealed ampoule was then agitated 3 hr at 25°. After recovery of 1.0 g of **4b**, a residue of stringy, water-white polymer was extracted with pentane, and this solution was examined by vpc (column D, 100°). The only solutes present were dicyclopentadiene and a trace (estimated at no more than 0.03 g) of unknown material.

Reaction of Phenylethynyltrimethylsilane (4e) with Cyclopentadiene.—A mixture of **4e** and cyclopentadiene (threefold molar excess) was heated in an ampoule 8 hr at 170°. Vpc (column D, 190°) then indicated that only 17% of the reaction mixture consisted of material boiling higher than starting acetylene. This material was represented by two closely spaced peaks in the chromatogram, the first of which to elute (10%) was identified as **5e** by retention time comparison with an authentic sample.

3-Phenyl-2-trichlorosilylbicyclo[2.2.1]hepta-2,5-diene (5d).—A flask fitted with a condenser and nitrogen inlet was charged with 4.2 g (0.018 mol) of phenylethynyltrichlorosilane (**4d**)[31] and 1.2 g (0.018 mol) of cyclopentadiene and then held at 100°. Two more identical increments of diene were added at 2-hr intervals, followed by a 1.5-hr heating period. Distillation then gave two fractions: bp 66–73° (0.25 mm), 2.0 g, and bp 98–100° (0.25 mm), 2.7 g. The former cut was recovered **4d**, and the latter adduct **5d** (96% yield based on recovered acetylene). Vpc (column D, 230°) indicated a purity in excess of 95% for the adduct: ir 3.23 (w), 6.30 (m), 6.43 (m), 6.71 (m), 7.69 (m), 9.78 (m), 13.11 (s), 13.84 μ (s). A peak of variable intensity at 4.58 μ always appeared in vpc-collected samples of **5d**. Re-vpc of such samples showed the presence of *ca.* 4% **4d**. This impurity probably arose *via* a retrodiene reaction induced by the high temperature (300°) of the thermal conductivity detector.

Anal. Calcd for $C_{13}H_{11}Cl_3Si$: C, 51.76; H, 3.68. Found: C, 51.57; H, 3.75.

In another run, a mixture of 2.4 g (0.010 mol) of **4d** and 0.72 g (0.0055 mol) of dicyclopentadiene was heated under nitrogen at 170° for 1.5 hr. Vpc then showed dicyclcpentadiene (**4d**) and adduct **5d** in a ratio of 1.0:2.7:3.0. An additional 0.5 hr at 170° did not alter this distribution; the mixture was distilled to give 0.9 g of recovered **4d** and 1.0 g (53% based on recovered **4d**) of adduct. Increasing the amount of dicyclopentadiene relative to **4d** in an attempt to maximize conversion led to the formation of higher boiling products. When a mixture of 3.0 g (0.013 mol) of **4d** and 1.3 g (0.0099 mol) of dicyclopentadiene was treated as above for 1 hr, vpc showed only 2% of starting acetylene, and distillation gave 1.8 g (47%) of adduct **5d** and 2.0 g of a viscous yellow liquid, bp 160–170° (0.4 mm).

3-Phenyl-2-trimethylsilylbicyclo[2.2.1]hepta-2,5-diene (5e).—A solution of 2.2 g (0.0073 mol) of **5d** in 20 ml of dry benzene was treated with 0.030 mol of ethereal methylmagnesium bromide. More benzene was then introduced (20 ml), and 30 ml of distillate was removed over a 1-hr period. After an additional 1.5 hr at reflux, the reaction mixture was worked up. Distillation gave 1.4 g (80%) of **5e**: bp 78–84° (0.5 mm); $n^{27}D$ 1.5435; ir 3.23 (w), 6.29 (w), 6.43 (w), 6.70 (w), 8.01 (s), 11.57 (s), 12.04 (vs), 13.26 (s), 14.00 (s), 14.39 (s), 15.32 μ (s).

Anal. Calcd for $C_{16}H_{20}Si$: C, 79.74; H, 8.39. Found: C, 79.84; H, 8.54.

Registry No.—**2a,** 27610-02-2; **2b,** 27544-80-5; **2c,** 27544-81-6; **3a,** 27544-82-7; **3b,** 27544-83-8; **3c,** 27544-84-9; **4b,** 27544-85-0; **5a,** 27544-86-1; **5d,** 27544-87-2; **5e,** 27544-88-3; *cis*-β-chlorovinyltrichlorosilane, 27544-89-4; *trans*-β-chlorovinyltrichlorosilane, 27544-90-7; cyclopentadiene, 542-92-7.

Acknowledgment.—The author wishes to acknowledge financial support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, as well as from Northern Illinois University in the form of a faculty research grant. Thanks are also due to Drs. M. E. Russell and M. J. Biallas for mass spectral and vapor pressure determinations, and to Mr. G. Martinie for elemental analyses.

(31) A. D. Petrov and L. L. Shchukovskaya, *Zh. Obshch. Khim.*, **25**, 1128 (1955); *Chem. Abstr.*, **50**, 3275 (1956).

Physical Organosilicon Chemistry. II. The Mass Spectral Cracking Patterns of Phenylsilane and Ortho-, Meta-, and Para-Substituted Benzyl- and Phenyltrimethylsilanes

MICHAEL E. FREEBURGER,* B. MASON HUGHES, GLEN R. BUELL, THOMAS O. TIERNAN, AND LEONARD SPIALTER

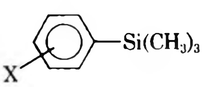
Aerospace Research Laboratories, Chemistry Research Laboratory, Wright-Patterson Air Force Base, Ohio 45433

Received June 16, 1970

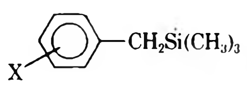
The mass spectral cracking patterns of 29 organosilicon compounds ($PhSiH_3$, $XC_6H_4CH_2SiMe_3$, $XC_6H_4SiMe_3$) were investigated. They are similar to the analogous carbon compounds except (a) no cracking which would require a carbon–silicon double bond in either the ion or the neutral is observed, and (b) extensive rearrangements occur in the $XC_6H_4SiMe_3$ series which result in the formation of $C_7H_7^+$ and SiX^+ species. Anomalies also appear when a particularly stable ion (as from o-$PhC_6H_4SiMe_3$) may be formed.

The mass spectra of organosilicon compounds (*e.g.*, those containing only carbon bonded to silicon) have received little attention, in spite of the growing accumulation of information concerning organosilicon reactions and reaction mechanisms. Studies of compounds containing silicon–oxygen,[1–5] silicon–nitrogen,[1,2,5] and silicon–sulfur[1] bonds have been conducted as an offspring of the utility of the trimethylsilyl group, $SiMe_3$, in derivativization of functional groups (alcohols, thiols, acids, amines). A "silyl McLafferty rearrangement" been observed in two organosilicon compounds, methyl 4-trimethylsilylbutyrate[6] and 4-trimethylsilylbutyronitrile, but other information on the mass spectra of organosilicon compounds is rare, other than an occasional reference in mass spectral tables.

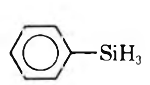
The interest of this laboratory in physical organosilicon chemistry led to the investigation of the mass spectral cracking patterns of a series of substituted phenyltrimethylsilanes (**1**), benzyltrimethylsilanes (**2**), and phenylsilane (**3**). It was expected that information



1



2



3

concerning the facility and nature of rearrangements, if any, could be obtained by varying the electronic character of the substituent. In several of the cases, the analogous *tert*-butylbenzenes were available for comparison, and the rearrangement aptitudes of silicon relative to carbon could be determined.

Experimental Section

Mass Spectra.—All mass spectra were obtained on a CEC 21-491 double-focusing mass spectrometer equipped with variable collector slits. While the maximum resolution of the instrument was $m/\Delta m$ = 3000 with a 10% valley, all spectra recorded were determined with a resolution of *ca.* $m/\Delta m$ = 300. Samples were separated from trace impurities on a 20 ft × 3/8 in. gas chromatography column packed with 20% SE-30 on Chromosorb W, and the effluent was introduced directly into the mass spectrometer's ionization chamber. All spectra were obtained at a source temperature of 190° and an electron energy of 70 eV.

The mass of all significant fragments was determined by the introduction of appropriate mass standards. When there was more than one logically possible structure for a nominal mass number, the exact mass number was determined to permit precise determination of the molecular species. Thus, in the tables of ion intensities, molecular formulas are listed rather than mass/charge ratio. Although all ions were counted when determining the per cent of total ionization, only those of intensity greater than 1% are listed in the tables.

Substituted Phenyltrimethylsilanes.—The preparation and purification of *o*-, *m*-, and *p*-$XC_6H_4SiMe_3$ (X = F, Cl, Me, MeO, Ph, CF_3, NO_2, H) and *m*- and *p*-bis(trimethylsilyl)benzene are reported elsewhere.[7] All compounds gave correct carbon, hydrogen, and silicon analyses.

Benzyltrimethylsilane (8).—To a stirred solution of 1.2 g (0.05 g-atom) of magnesium metal, 5.4 g (0.05 mol) of chlorotrimethylsilane and 100 ml of tetrahydrofuran (THF) was added 6.1 g (0.05 mol) of benzyl chloride at a rate which maintained the solution at its reflux temperature. After addition was complete, heat was applied to maintain the condition of reflux for 12 hr. The solution was treated with 50 ml of a saturated aqueous ammonium chloride solution, the salts were removed by filtration, and the organic layer was separated. After drying with magnesium sulfate, the center cut of the proper distillate was further purified by preparative gas chromatography (20 ft × 3/8 in. 20% SE-30 on Chromosorb W, Varian Aerograph Model 1868). The yield of **8** was 3.3 g (40%). *Anal.* Calcd for $C_{10}H_{16}Si$: C, 73.09; H, 9.81; Si, 17.92. Found: C, 73.25; H, 9.94; Si, 17.65.

***o*-Fluorobenzyltrimethylsilane.**—This compound was prepared as **8** above but from *o*-fluorobenzyl chloride in 42% yield. *Anal.* Calcd for $C_{10}H_{15}SiF$: C, 65.88; H, 8.28; Si, 15.40. Found: C, 65.70; H, 8.30; Si, 15.26.

***m*-Fluorobenzyltrimethylsilane.**—A yield of 33% was achieved as **8** above but starting with *m*-fluorobenzyl chloride. *Anal.* Calcd for $C_{10}H_{15}SiF$: C, 65.88; H, 8.28; Si, 15.40. Found: C, 65.72; H, 8.24; Si, 15.79.

***p*-Fluorobenzyltrimethylsilane.**—From *p*-fluorobenzyl chloride, this compound was prepared as **8** above in 44% yield. *Anal.* Calcd for $C_{10}H_{15}SiF$: C, 65.88; H, 8.28; Si, 15.40. Found: C, 66.06; H, 8.30; Si, 15.56.

Phenylsilane (3).—A solution of 21.1 g (0.10 mol) of phenyltrichlorosilane in 50 ml of THF was added dropwise to a slurry of 3.8 g (0.10 mol) of lithium aluminum hydride in 100 ml of THF. After the addition was complete, the mixture was heated at the reflux temperature for 12 hr. Following decomposition of excess $LiAlH_4$ with 50 ml of dilute hydrochloric acid, the organic layer was separated, dried with magnesium sulfate, and distilled. The yield of **3**, bp 118–120° (760 mm) (reported[8] bp 120°), was 2.5 g (23%). *Anal.* Calcd for C_6H_8Si: C, 66.59; H, 7.45; Si, 25.96. Found: C, 66.78; H, 7.65; Si, 26.19.

Results and Discussion

A. Phenylsilane.—The mass spectral cracking pattern of phenylsilane (**3**) and toluene (**4**) are compared in Table I. The pattern of toluene is quite simple, exhibiting predominantly the parent ion M^+ and $(M - 1)^+$. The large $(M - 1)^+$ ion has been identified as the

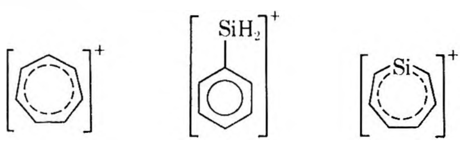
(1) J. Diekman, J. B. Thomson, and C. Djerassi, *J. Org. Chem.*, **32**, 3904 (1967).
(2) J. Diekman, J. B. Thomson, and C. Djerassi, *ibid.*, **33**, 2271 (1968).
(3) J. Diekman, J. B. Thomson, and C. Djerassi, *ibid.*, **34**, 3147 (1969).
(4) W. J. Richter and A. L. Burlingame, *Chem. Commun.*, 1158 (1968).
(5) K. M. Baker, M. A. Shaw, and D. H. Williams, *ibid.*, 1108 (1969).
(6) W. P. Weber, R. A. Felix, and A. K. Willard, *J. Amer. Chem. Soc.*, **92**, 1420 (1970).
(7) M. E. Freeburger and L. Spialter, *J. Amer. Chem. Soc.*, in press.
(8) A. E. Finholt, A. C. Bond, K. E. Wilzbach, and H. I. Schlesinger, *J. Amer. Chem. Soc.*, **69**, 2692 (1947).

TABLE I
PROMINENT IONS IN THE MASS SPECTRA OF PHENYLSILANE (3), TOLUENE (4), BENZYLTRIMETHYLSILANE (8), AND NEOPENTYLBENZENE (9)

Ion	% of total ionization 3	% of total ionization 4[a]	Ion	% of total ionization 8	% of total ionization 9[b]
M^+	17.4	24.1	M^+	8.4	2.8
$(M - 1)^+$	16.8	34.4	$(M - 15)^+$	6.1	2.2
$(M - 2)^+$	15.6	2.6	$C_7H_8^+$	1.0	18.4
$(M - 3)^+$	12.7	1.8	$C_7H_7^+$	9.2	10.0
$C_6H_7^+$	2.8	1.0	$C(CH_3)_3^+$		25.2
$C_6H_6^+$	2.1	1.0	$Si(CH_3)_3^+$	49.7	
$C_6H_5^+$	1.8	1.0	$C_3H_5^+$		7.0
$C_5H_5^+$	2.8	1.0	$C_2H_5^+$		5.8
$C_5H_4^+$	2.3	1.0	$SiCH_3^+$	4.7	
$C_5H_3^+$	2.2	3.3			
SiH^+	2.3				

[a] "Atlas of Mass Spectral Data," Vol. I, E. Stenhagen, S. Abrahamsson, and F. W. McLafferty, Ed., Interscience, New York, N.Y., 1969, p 189. [b] Reference a, Vol. II, 1969, p 862.

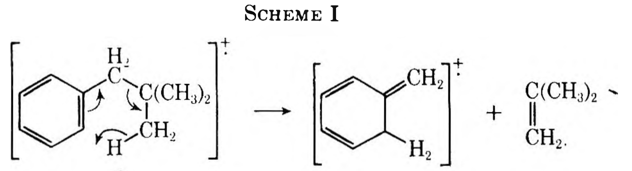
tropylium ion 5[9] and is common to almost all alkylbenzenes. If an analogous ion were produced from 3, the formal resonance structures would include a carbon–silicon double bond, a system which is extremely unstable.[10] The silicon-containing ions from 3, M^+, $(M - 1)^+$, $(M - 2^+)$, and $(M - 3)^+$ are of approximately equal intensity, suggesting that no resonance stabilization of the $(M - 1)^+$ ion occurs. The structure of the $SiC_6H_7^+$ ion is probably best described as being analogous to the benzyl ion 6, rather than to the tropylium ion 7.



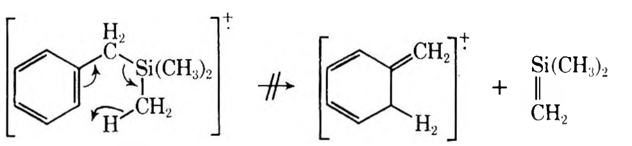
5 6 7

B. Benzylsilanes.—In comparing the data of benzyltrimethylsilane (8) with that of neopentylbenzene (9) (Table I), a striking difference is observed. There is a large amount of $C_7H_8^+$ formed from 9 while only a trace of this ion is produced from 8. The mechanism of $C_7H_8^+$ formation is presented in Scheme I.[9] The generation of this ion from 8 would require the formation of a carbon–silicon double bond in the neutral compound, a process which is not favorable (Scheme II). An es-

SCHEME I



SCHEME II



(9) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, New York, N. Y., 1967, p 76.

(10) W. J. Bailey and M. S. Kaufman, Abstracts, 157th National Meeting of the American Chemical Society, April 1969, ORGN 57.

sentially equivalent amount of tropylium ion is formed from both 8 and 9; the larger amount of $SiMe_3^+$ from 8, relative to the CMe_3^+ from 9, may reflect either the greater stability of $SiMe_3^+$ or the fact that 8 cannot form the $C_7H_8^+$ ion [note that for 8 ($C_7H_8^+ + C_7H_7^+ + SiMe_3^+$) is 60% of the ion current, for 9 ($C_7H_8^+ + C_7H_7^+ + CMe_3^+$) is 54% of the ion current].

The $(M - 15)^+$ fragment is larger in 8 than in 9, but this is to be expected. Loss of CH_3 from silicon is common in the cracking patterns of trimethylsilyl ethers,[1,2,4,5] esters,[3] and amines[5]; indeed, the following discussion will provide evidence that it is also a predominant fragmentation mode in phenyltrimethylsilanes.

The ion $C_3H_5^+$, the allylic cation 10, present in aromatic systems possessing a *tert*-butyl group, is absent in all of the trimethylsilyl systems; the analogous silicon-containing ion, $SiC_2H_5^+$, is also absent. Again, for 8 to generate such an ion (11) would require the formation of a carbon–silicon double bond, which appears not to occur.

$$\overset{+}{C}H_2CH{=}CH_2 \longleftrightarrow CH_2{=}CH\overset{+}{C}H_2$$
10

$$\overset{+}{C}H_2SiH{=}CH_2 \longleftrightarrow CH_2{=}SiH\overset{+}{C}H_2$$
11

Substitution of a fluoro group in the ortho, meta, or para position of 8 causes a substantial change in their cracking patterns (Table II). The ion $C_7H_6F^+$, presumably a fluorotropylium ion, is formed, as well as $C_7H_6^+$, which is the second most abundant ion. The appearance of the ion $SiMe_2F^+$ suggests that the substituent is able to migrate to the silicon atom. (This

TABLE II
PROMINENT IONS IN THE MASS SPECTRA OF *o*-, *m*-, AND *p*-FLUOROBENZYLTRIMETHYLSILANE

Ion	% of total ionization Ortho	Meta	Para
M^+	4.0	3.1	3.7
$(M - 15)^+$	0.5	3.6	3.8
$Si(CH_3)_3^+$	27.2	30.7	30.1
$SiCH_3^+$	3.7	4.2	4.7
$C_7H_6F^+$	5.1	5.7	9.6
$C_7H_6^+$	23.0	22.5	23.0
$Si(CH_3)_2F^+$	6.6	3.1	1.9

will be seen to be very common in the cracking of substituted phenyltrimethylsilanes.) As might be expected, this ion is most common for the ortho isomer which has the more favorable group juxtaposition. Concomitantly, the $C_7H_6F^+$ species is most abundant in the para case.

These data lead to the conclusions that for the benzyltrimethylsilanes (a) fragmentation is similar to that of the carbon analogs except when the fragmentation would produce a carbon–silicon double bond in either the neutral or ionic product species, and (b) if the aromatic ring is substituted, the substituent may migrate to the silicon atom.

C. Substituted Phenyltrimethylsilanes.—The cracking patterns of phenyltrimethylsilane (12), *m*- and *p*-bis(trimethylsilyl)benzene (13 and 14), and *p*-bis(*tert*-butyl)benzene (16) are compared in Table III. They are quite similar, M^+ and $(M - 15)^+$ appearing

TABLE III
PROMINENT IONS IN THE MASS SPECTRA OF PHENYLTRIMETHYLSILANE (12), *m*- AND *p*-BIS(TRIMETHYLSILYL)BENZENE (13 AND 14), *tert*-BUTYLBENZENE (15), AND *p*-BIS(*tert*-BUTYL)BENZENE (16)

Ion	% of total ionization 12	13	14	15[a]	16[b]
M^+	9.3	11.9	11.3	10.3	4.4
$(M - 15)^+$	62.5	72.0	71.9	36.9	32.9
$C_7H_7^+$	1.0	1.0	1.0	16.8	2.1
$C_4H_9^+$	1.0	1.0	1.0	1.0	6.4
$Si(CH_3)_3^+$	1.0	6.3	5.4		
$C_3H_5^+$	1.0	1.0	1.0	5.8	6.4
$SiCH_3^+$	5.1	1.0	1.0		
$(M - 30)^{2+}$		4.9	3.2		1.6

[a] "Atlas of Mass Spectral Data," Vol. I, E. Stenhagen, S. Abrahamsson, and F. W. McLafferty, Ed., Interscience, New York, N. Y., 1969, p 670. [b] Reference *a*, Vol. II, 1969, p 1331.

as the predominant ionic species. The loss of methyl from the silane [affording the $(M - 15)^+$ ion] is the most common fragmentation in all of the substituted species with the exception of some ortho compounds. The $C_3H_5^+$ appears only for the *tert*-butyl species; $SiC_2H_5^+$ is not observed for the silicon species (*vide supra*).

It is interesting to note that virtually no tropylium ion is formed from **12**, **13**, or **14**. Although the formation of $C_7H_7^+$ would require the migration of a methyl fragment into the ring, preceding or concurrent with the loss of a silicon fragment, this ion is observed only when the phenyl ring is substituted (see following discussion). The necessary requirement for this migration appears to be the substituent on the ring. Both bis(trimethylsilyl) compounds afford unusually large doubly charged ions, $(M - 30)^{2+}$, as does *p*-bis(*tert*-butyl)benzene.

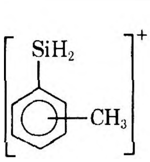
Upon comparison of *o*-, *m*-, and *p*-methylphenyltrimethylsilane (**17**, **18**, and **19**) with *m*-methyl-*tert*-butylbenzene (**20**) (Table IV), similarities are again observed.

TABLE IV
PROMINENT IONS IN THE MASS SPECTRA OF *o*-, *m*-, AND *p*-METHYLPHENYLTRIMETHYLSILANE (17, 18, AND 19) AND *m*-METHYL-*tert*-BUTYLBENZENE (20)

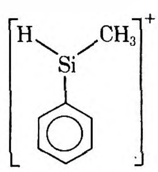
Ion	% of total ionization 17	18	19	20[a]
M^+	5.2	4.8	4.2	7.9
$(M - 15)^+$	21.3	26.1	28.9	32.1
$C_7H_9^+$	1.5	1.6	1.4	4.3
$C_7H_7^+$	3.4	4.4	5.5	4.1
$C_7H_6CH_3^+$	1.9	1.8	1.1	10.4
$SiC_6H_6CH_3^+$	7.9	3.2	2.4	
$Si(CH_3)_3^+$	6.1	3.4	1.5	
$C_3H_5^+$	1.0	1.0	1.0	5.6
$C_3H_3^+$	2.2	3.0	3.0	4.0

[a] "Atlas of Mass Spectral Data," Vol. II, E. Stenhagen, S. Abrahamsson, and F. W. McLafferty, Ed., Interscience, New York, N. Y., 1969, p 864.

The ion $SiC_6H_6CH_3^+$, analogous to $C_7H_6CH_3^+$, is much larger for the ortho isomer than for the meta or para isomer. The most probable structure(s) for this ion are **21** and/or **22**, if one excludes the silicon analog of the



21



22

tropylium ion, *vide supra*. No choice is possible on the basis of the present investigation.

The chlorophenyltrimethylsilanes show interesting effects (Table V) of substituent position. The tropyl-

TABLE V
PROMINENT IONS IN THE MASS SPECTRA OF *o*-, *m*-, AND *p*-CHLOROPHENYLTRIMETHYLSILANE (23, 24, AND 25) AND CHLORO-*tert*-BUTYLBENZENE (26)

Ion	% of total ionization 23	24	25	26[a]
M^+	8.7	12.2	11.2	10.0
$(M - 15)^+$	44.0	76.0	76.9	37.0
$C_7H_7^+$	14.2	3.4	2.5	0.9
$C_7H_6Cl^+$	1.0	1.0	1.0	15.8
$SiC_6H_6Cl^+$	14.0	1.0	1.0	
$SiC_8H_9^+$	8.4	1.0	1.0	
$C_3H_5^+$	1.0	1.0	1.0	6.5
$SiCl^+$	3.3	2.6	2.5	

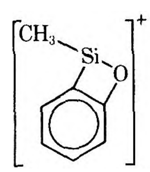
[a] "Atlas of Mass Spectral Data," Vol. II, E. Stenhagen, S. Abrahamsson, and F. W. McLafferty, Ed., Interscience, New York, N. Y., 1969, p 1099. The position of the chloro group is not specified.

ium ion is formed in all cases, but in the highest percentage from the ortho isomer. This requires both the migration of methyl from silicon to the ring and removal of chlorine from the ring. The ortho isomer also affords appreciable amounts of $SiC_6H_6Cl^+$ and $SiC_8H_9^+$, the former being the chlorine analog of **21** or **22** and the latter involving loss of CH_3 and Cl (possibly as CH_3Cl) from the parent. Unlike the *tert*-butyl case, no chlorotropylium ion, $C_7H_6Cl^+$, is formed from the silanes. All of the chloro isomers produce some $SiCl^+$, indicating a migration of chlorine to silicon.

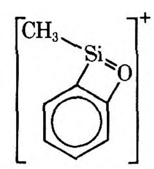
Data for the substituents fluoro, methoxy, phenyl, and trifluoromethyl are presented in Table VI. Corresponding data for the *tert*-butyl compounds are not available.

The fluoro case parallels the chloro case. Tropylium ion is formed from all isomers but in the highest percentage from the ortho; $SiC_6H_6F^+$ (fluoro **21** or **22**) is also large for the ortho. A constant, and unexpectedly large, amount of SiF^+ is formed from all the isomers.

The methoxy series shows the same trend, $C_7H_7^+$ being largest for the ortho; however, the methoxy analog of **21** or **22** is not detected. The ortho isomer has a prominent ion of the formula $SiC_6H_4OCH_3^+$, a very strange product requiring loss of three methyl groups which may be formulated as **23** or **24**. Other possibili-



23



24

ties exist, but these two appear the most reasonable in light of data from trimethylsilyl ethers.[1,2] Strangely, no $SiOMe^+$ was observed.

The biphenyl series (*i.e.*, with phenyl as the substituent) afford very simple patterns, possibly due to the strength of the phenyl–phenyl bond. The ortho isomer produces a large fragment corresponding to $C_{12}H_8$-$SiCH_3^+$ which is presumed to have the fluorene-type

TABLE VI

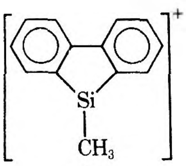
PROMINENT IONS IN THE MASS SPECTRA OF SUBSTITUTED PHENYLTRIMETHYLSILANES

Ion	Fluorophenyltrimethylsilane (% of total ionization) Ortho[a]	Meta[b]	Para[c]	Methoxyphenyltrimethylsilane Ortho[d]	Meta[e]	Para[f]
M^+	3.8	3.8	3.6	8.0	18.8	10.2
$(M - 15)^+$	8.9	21.9	27.1	21.5	49.7	64.1
$C_7H_7^+$	17.0	6.6	5.2	6.4	2.8	2.5
$Si(CH_3)_3^+$	1.4	2.3	1.7	1.5	4.0	2.0
$SiCH_3^+$	2.6	6.0	5.9	3.1	2.9	3.5
SiF^+	14.4	14.0	14.9			
$SiC_6H_6F^+$	9.5	0.8	1.3			
$SiC_6H_4OCH_3^+$				39.6	5.6	2.8

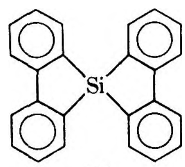
Ion	Phenylphenyltrimethylsilane Ortho[g]	Meta[h]	Para[i]	Trifluoromethylphenyltrimethylsilane Ortho[j]	Meta[k]	Para[l]
M^+	12.9	20.6	14.5	1.9	3.5	5.6
$(M - 15)^+$	43.8	48.7	47.5	9.1	56.1	54.6
$C_7H_7^+$	1.0	1.0	1.0	5.6	1.0	0.7
$Si(CH_3)_3^+$	1.0	1.9	2.5	1.9	1.2	1.2
$SiCH_3^+$	1.0	3.1	4.2	0.9	1.2	1.5
$C_{12}H_8SiCH_3^+$	25.9	3.5	4.0			
SiF^+				2.1	1.1	0.9
$SiF(CH_3)_2^+$				10.0	2.50	2.40
$C_3F_2SiCH_3^+$				8.0	1.0	1.0
$C_3F_2SiH^+$				11.9	1.0	1.0

Registry No.: [a] 1842-26-8; [b] 7217-41-6; [c] 455-17-4; [d] 704-43-8; [e] 17876-90-3; [f] 877-68-9; [g] 17049-39-7; [h] 17938-21-5; [i] 1625-88-3; [j] 312-92-5; [k] 4405-40-7; [l] 312-75-4.

structure **25**. The closely related compound, bis(*o*-biphenyl)silane (**28**), has been reported to afford[11] only



25

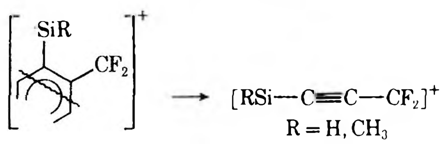


28

the parent ion under electron impact, an observation confirmed by this laboratory.

The trifluoromethyl compounds show the typical fragments M, $(M - 15)^+$, and $C_7H_7^+$, but the fragments $C_7H_6CF_3^+$ and $SiC_6H_6CF_3^+$, analogous to those formed in the halogen substituted compounds, are absent. A fragment in which fluorine has migrated to the silicon, $SiFMe_2^+$, is present in all three isomers although in largest amount for the ortho. Two additional fragments, $C_3F_2SiCH_3^+$ and $C_3F_2SiH^+$, are formed from the ortho, presumably the result of scission of the aromatic ring (Scheme III).

SCHEME III



The three nitrophenyltrimethylsilane isomers produce fragments dissimilar to the other compounds (Table VII). Tropylium ion is still present, but the parent ion is substantially reduced, particularly in the ortho case. This ortho compound produces fragments corresponding to $SiC_6H_5NO_2^+$ and $SiC_6H_5NO^+$ which can be depicted by structures **26** and **27**, respectively. When the nitro group is meta or para, fragments which

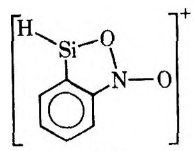
(11) R. Coutant and M. Levy, Aerospace Research Laboratories, Technical Report 69-0213, 1969.

TABLE VII

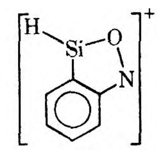
PROMINENT IONS IN THE MASS SPECTRA OF *o*-, *m*-, AND *p*-NITROPHENYLTRIMETHYLSILANE

Ion	Ortho (% of total ionization)	Meta	Para
M^+	1.0	1.0	1.7
$(M - 15)^+$	17.9	20.4	22.4
$C_7H_7^+$	4.6	1.2	1.0
$Si(CH_3)_3^+$	4.0	9.1	8.7
$SiCH_3$	6.3	5.5	8.6
$SiC_6H_5NO_2^+$	8.1	0.5	0.9
$SiC_6H_9^+$	1.0	7.3	1.8
$SiC_6H_{10}^+$	1.0	3.0	8.1
$SiC_6H_5NO^+$	9.9	1.2	2.2
$C_7H_6NO_2^+$	1.8	1.0	1.0
$C_4H_5^+$	0.3	4.3	3.7
$C_7H_7Si^+$	0.6	10.0	8.1
$C_7H_8Si^+$	0.7	1.3	2.1

have lost the NO_2 group are produced, *e.g.*, $SiC_6H_9^+$, $SiC_6H_{10}^+$ (because of the large H/C ratio of these ions, they probably contain methyl groups and represent scission of the aromatic ring), and $SiC_7H_7^+$.



26



27

In summary, the cracking patterns of all the substituted phenyltrimethylsilanes appear similar to the *tert*-butylbenzene analogs with the following exceptions. First, a methyl group may migrate from silicon into the ring producing the tropylium ion. This happens only if the ring is substituted, is most prevalent for halogen substitution, and, for any given substituent, is greatest for the ortho isomer. A direct corollary of this observation is the fact that in the case of halogen substituents, the substituent may migrate to the silicon atom. The degree of this migration, insofar as is measured by the amount of SiX^+ produced, is independent of the position of the substituent. Second, no ion corresponding to allyl (*e.g.*, $SiC_2H_5^+$) is formed in any of the cases. This would require a carbon–silicon double bond, the resulting fragments of which are never observed. Third, ions of the general formula $SiC_6H_6X^+$ are observed when methyl or halogen is the substituent corresponding to the structures **21** or **22**. A distinction between which of these is present (ineeed, both may be) is not possible at this time. Fourth, anomalies appear in the ortho cases when a particularly stable ion may be formed, for example, **23**, **24**, or **25**. The nitro and the trifluoromethyl derivatives appear to undergo a fragmentation of the aromatic ring which does not occur in the other compounds.

Registry No.—**3,** 69-45-31; **4,** 108-88-3; **8,** 770-09-2; **9,** 1007-26-7; **12,** 768-32-1; **13,** 2060-89-1; **14,** 13183-70-5; **15,** 98-06-6; **16,** 1012-72-2; **17,** 7450-03-5; **18,** 3728-44-7; **19,** 3728-43-6; **20,** 1075-38-3; **23,** 15842-76-9; **24,** 4405-42-9; **25,** 10557-71-8; **26,** 27378-66-1; *o*-fluorobenzyltrimethylsilane, 1833-40-5; *m*-fluorobenzyltrimethylsilane, 772-48-5; *p*-fluorobenzyltrimethylsilane, 706-25-2; *o*-nitrophenyltrimethylsilane, 15290-22-9; *m*-nitrophenyltrimethylsilane, 15290-24-1; *p*-nitrophenyltrimethylsilane, 4405-33-8.

Studies in Boron Hydrides. IV. Stable Hydride Meisenheimer Adducts[1]

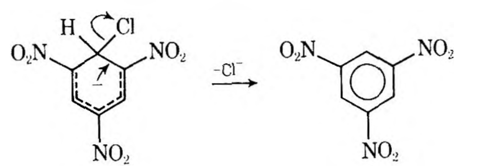
LLOYD A. KAPLAN* AND ALLEN R. SIEDLE

The Advanced Chemistry Division, U. S. Naval Ordnance Laboratory, Silver Spring, Maryland 20910, and the Department of Chemistry, Norfolk State College, Norfolk, Virginia 23504

Received September 4, 1970

The addition of hydride from the octahydrotriborate ion to 1-substituted 2,4,6-trinitrobenzenes affords a stable C_3-hydride Meisenheimer adduct. Concurrent with this addition reaction is hydride displacement of the C_1 substituent to form 1,3,5-trinitrobenzene. Under the reaction conditions, 1,3,5-trinitrobenzene is reduced to a monohydride Meisenheimer adduct. Displacement of the C_1 substituent by hydride is favored by substituents which can coordinate with the developing B_3H_7 moiety in the transition state.

Severin[2-4] demonstrated that the reduction of nitroaromatic compounds with sodium tetrahydroborate under alkaline conditions produced the dihydro or polyhydro product. Thus, 1,3,5-trinitrobenzene (**1**), and 1-X-2,4-dinitrobenzene (X = Cl, CH_3, H, etc.) afforded 1,3,5-trinitrocyclohexane and 2-X-3,5-dinitrocyclohex-1-ene, respectively. Kaplan[5] has shown that the reduction of 1-X- or 1,3-X,Y-2,4,6-trinitrobenzenes (X,Y = Br, Cl, OCH_3) under identical conditions yields 1,3,5-trinitrocyclohexane as the sole product. This transformation was formulated[5] for 1-chloro-2,4,6-trinitrobenzene as occurring by attack of hydride at C_1 to produce the anion **2** which rearomatizes by loss of chloride to form **1**. Subsequent reduction of **1** affords 1,3,5-trinitrocyclohexane.

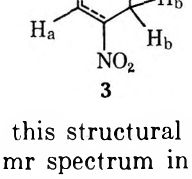


2 **1**

To test this suggested mechanism for the conversion of **1** and mono- and disubstituted trinitrobenzenes to 1,3,5-trinitrocyclohexane, the reaction of these substrates with some hydropolyborate ions which would be weaker hydride donors than tetrahydroborate ion was investigated. By decreasing the formal reduction potential of the hydride donor, it might be possible to interrupt the reduction at an intermediate stage, thereby permitting the isolation of cyclohexadienyl-type products.

Results and Discussion

The reaction of **1** with the *nido*hydropolyborate ions $B_3H_8^-$, $B_9H_{14}^-$, $B_{10}H_{13}^-$, $B_{10}H_{14}^{2-}$, and $B_{10}H_{15}^-$ [6] in such solvents as acetone, acetonitrile, dimethyl sulfoxide, and nitromethane resulted in the formation of dark purple solutions which had absorption maxima at 478 and 582 nm. The position of these absorption maxima are similar to those displayed by 1:1 Meisenheimer adducts of **1** with cyanide,[7] thiophenoxide,[8] and sulfite[9] ions, and piperidine.[10] For preparative work, tetramethylammonium octahydrotriborate proved to be the most convenient reducing agent. On mixing chilled acetonitrile solutions of the reactants, glistening, purple-black crystals separated which analyzed for the tetramethylammonium salt of the hydride Meisenheimer adduct **3**.



3

Confirmation of this structural assignment was obtained from the nmr spectrum in dimethyl sulfoxide. This spectrum exhibited lines at $\delta_{Me_4N^+}$ 3.12 (6),[11] δ_{H_b} 3.87 (1.1), and δ_{H_a} 8.24 (1). The line position found for H_a is almost identical with those reported for H_a in the Meisenheimer adducts of **1** with hydroxide

(1) Part III: A. R. Siedle and T. R. Hill, *J. Inorg. Nucl. Chem.*, **31**, 3874 (1969).

(2) T. Severin and R. Schmitz, *Chem. Ber.*, **95**, 1417 (1962).

(3) T. Severin and M. Adam, *ibid.*, **96**, 448 (1963).

(4) T. Severin, R. Schmitz, and M. Adam, *ibid.*, **96**, 3076 (1963).

(5) L. A. Kaplan, *J. Amer. Chem. Soc.*, **86**, 740 (1964).

(6) The ions $B_6H_6^{2-}$, $B_9H_{19}^{2-}$, $B_{10}H_{10}^{2-}$, and $B_{20}H_{18}^{2-}$ were found to be unreactive.

(7) A. R. Norris, *Can. J. Chem.*, **45**, 2703 (1967).

(8) M. R. Crampton, *J. Chem. Soc. B*, 1208 (1968).

(9) M. R. Crampton, *ibid.*, 1341 (1967).

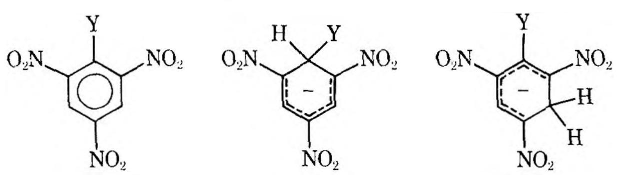
(10) M. R. Crampton and V. Gold, *ibid.*, 23 (1967).

(11) Chemical shifts are in parts per million downfield from internal tetramethylsilane. Relative intensities are in parentheses; H_a is used as reference.

(δ 8.42),[12] ethoxide (δ 8.41),[13] ammonia, and alkyl and dialkylamines (δ 8.32–8.50)[9] in dimethyl sulfoxide solutions. The slight upfield shift found for H_a in the adduct **3**, relative to the average value for H_a, δ 8.4, in the hydroxide, ethoxide, and amido Meisenheimer adducts of **1**, can be attributed to increased shielding of H_a on replacing an electronegative nitrogen or oxygen atom on the ring by hydrogen.

The assignment of H_b to the line at δ 3.87 can not be made by analogy with the reported values[9,12,13] for the "aliphatic" proton in other Meisenheimer adducts as this structural moiety is a methinyl proton, δ 5.8 ± 0.4, whereas in **3**, it is a methylene proton. An upfield shift of about 2 ppm could be expected on going from a methinyl to a methylene proton, and a shift of similar magnitude is found when one compares the methylene protons in 2,2′,4,4′,6-pentanitrodiphenylmethane, δ 4.95, with the methinyl proton of 2,2′,4,4′,6-pentanitrodiphenylchloromethane, δ 7.67.[14]

Having defined **3** as the structure of the hydride adduct of **1**, the reduction procedure was extended to 1-Y-2,4,6-trinitrobenzenes, **4**, with the expectation of isolating a C_1-hydride adduct **5**, the proposed precursor of 1,3,5-trinitrocyclohexane formed in reductions with tetrahydroborate ion.[5] When **4** (Y = Cl) was reduced with tetramethylammonium octahydrotriborate in acetonitrile solution, the nmr spectrum of the isolated purple-black crystals indicated the presence of two components. Lines at δ 8.24 (1.0) and 3.87 (1.2) are coincident with those found for **3**. Two additional lines at δ 8.35 (1.0) and 4.04 (2.2) (Table I) could not be reconciled with the spectrum expected for the C_1-adduct **5** (Y = Cl[9,12,13]), but they did have the proper position and intensity ratio for the C_3 adduct **6** (Y = Cl. The line for the tetramethylammonium cation,



4 **5** **6**

δ 3.12, was used as an internal reference in interpreting these spectra by subtracting from its area the contribution due to **3** and normalizing the residual area to the observed area of the H_a line in the adduct **6** (Y = Cl). Thus, the areas of the lines for H_a, H_b, and the tetramethylammonium cation were found to be in the ratio of 1:2.2:13. This agrees well with the calculated ratio, 1:2:12, for the adduct **6** (Y = Cl).

When **4** (Y = OCH_3) is reduced under similar conditions, a mixture composed of 65% of the C_3 adduct **6** (Y = OCH_3), and 35% of the adduct **3**. By contrast, *N,N*-dimethylpicramide yields only **3** and 2,4,6-trinitrotoluene forms the C_3 adduct **6** (Y = CH_3) exclusively.

The formation of mixed products from picryl chloride and 2,4,6-trinitroanisole suggested, by analogy with previously observed[15,16] transformations of C_3 Meisenheimer adducts to the C_1 isomers, that hydride initially

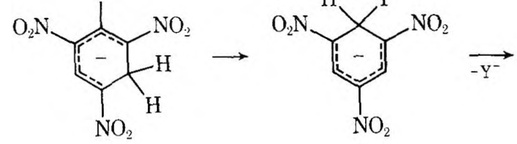
TABLE I

PROTON MAGNETIC RESONANCE SPECTRA OF HYDRIDE MEISENHEIMER ADDUCTS[a]

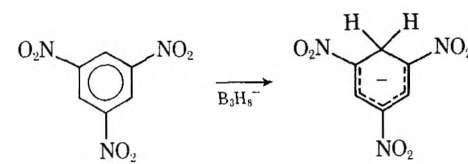
Substrate[b]	δ_{H_a}[c]	δ_{H_b}[c]	$\delta_{(CH_3)_4N^+}$[c]	% C_3 adduct[g]
Pi-H	8.24 (1)	3.87 (1.1)	3.12 (6.8)	
Pi-Cl	8.35 (1)	4.04 (2.2)	3.12 (13)[f]	75
	8.24 (1)	3.87 (1.2)	3.12 (6)	
Pi-OCH_3[d]	8.35 (1)	3.92 (2.4)	3.12 (12.6)[f]	65
	8.24 (1)	3.87 (1.0)	3.12 (6)	
Pi-$N(CH_3)_2$	8.24 (1)	3.86 (1.2)	3.12 (6)	0
Pi-CH_3[e]	8.38 (1)	3.90 (2.0)	3.12 (13.0)	100

[a] In dimethyl sulfoxide-d_6; δ in ppm downfield from internal tetramethylsilane. [b] Pi = 2,4,6-trinitrophenyl. [c] Relative intensities, H_a = 1, in parentheses. [d] δ_{OCH_3} 3.76 (3.2). [e] δ_{CH_3} 2.58 (4.2); integral not accurate due to some overlap with dimethyl sulfoxide-d_5, δ 2.50. [f] By subtracting the area due to **3** from total and normalizing remainder. [g] Calculated from the areas of the respective H_a lines.

added at C_3 to form the adduct **6** which during the course of the reaction reverses to **4** and readds hydride at C_1 to form **5**. Though C_1 adducts are reported to be more thermodynamically stable than the C_3 adducts, like the C_3 adducts, they too are in equilibrium with their progenitors.[17] For the adduct **5**, this should involve the loss of the better leaving group, Cl^-, OCH_3^-, or $(CH_3)_2N^-$ rather than H^-, to form **1** which would be subsequently reduced to **3** under the reaction conditions.



6 **5**



1 **3**

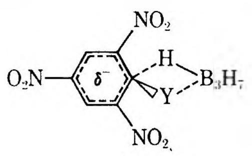
Evidence to support the above reaction sequence could not be obtained. We have observed that the adducts **3** and **6** undergo slow decomposition in dimethyl sulfoxide solution. However, inspection of the nmr spectra of these aged solutions showed neither a change in the ratio of **6** to **3** nor a new line attributable to 1,3,5-trinitrobenzene. These observations tend to rule out the above proposed C_3 to C_1 hydride equilibration. Furthermore, when **4** (Y = Cl or OCH_3) is reduced using a twofold excess of tetramethylammonium octahydrotriborate, the product ratio (**6**:**3**) is unchanged. Thus, the product composition appears to be subject to kinetic rather than thermodynamic control as is observed in reactions leading to the formation of other Meisenheimer adducts.[15,16]

Unlike other nucleophiles, hydride would have to produce the C_1 and C_3 adducts concurrently, by separate nonequilibrating paths, with the former eliminating the C_1 substituent to form **1** which is subsequently reduced to the hydride adduct **3**. A perhaps more attractive route to **3** would not involve the intermediacy of the C_1 adduct **5**, but would require displacement of the

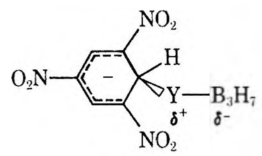
(12) M. R. Crampton and V. Gold, *J. Chem. Soc.*, 4293 (1964).
(13) R. Foster and C. A. Fyfe, *Tetrahedron*, **21**, 3363 (1965).
(14) K. G. Shipp and L. A. Kaplan, unpublished results.
(15) K. L. Servis, *J. Amer. Chem. Soc.*, **87**, 5495 (1965).
(16) M. R. Crampton and V. Gold, *J. Chem. Soc. B*, 893 (1966).

(17) The methoxide Meisenheimer adduct of 2,4,6-trinitroanisole is converted to the acetonyl adduct by dissolution in acetone; *cf.* ref 13.

C_1 substituent by hydride to form **1**. In this reaction, the participation of the developing B_3H_7 moiety as an electrophile in the transition state is involved. A reasonable transition state geometry would be **7** in



7



8

which B–Y bond formation occurs concurrently with C–H bond formation. Collapse of this transition state to the tetrahedral intermediate **8** is followed by loss of $B_3H_7Y^-$ which results in rearomatization to produce **1**.[18] Relative to rearomatization to **1**, the reversal of **8** to its progenitors should be kinetically disfavored as C–Y bond cleavage should be energetically more favorable than B–Y bond cleavage. For a reaction sequence involving participation of B_3H_7 as an electrophile, the product yield from reaction at C_1 should be, as is observed, a function of the B–Y bond strengths which are in the order B–N > B–O > B–Cl.[19] This ordering is to be contrasted with the ordering of the C_1 substituents as leaving groups in other SN2 displacements at aromatic carbon, Cl > OMe > NMe_2.[20] In support of this hypothesis is the observation that 2,4,6-trinitrotoluene forms neither a C_1 Meisenheimer adduct[21] nor the 1,3,5-trinitrobenzene adduct **3**. The lack of hydride attack at C_1 in 2,4,6-trinitrotoluene can be attributed to the inability of the methyl group to coordinate with the developing B_3H_7 moiety in the transition state.

(18) An alternate route involves synchronous C–Y bond breaking in the transition state **7**. Collapse of this transition state affords **1** and $B_3H_7Y^-$ directly. We have no preference for either sequence based on the data. However, we do feel that the data, *vide infra*, support the proposal that the B_3H_7 moiety participates as an electrophile in the reaction. The coproduct in these reductions, the species $B_3H_7Y^-$, is isoelectronic with the stable $B_3H_8^-$ and should therefore be capable of being isolated from the reaction. We are continuing our so far unsuccessful attempts to isolate this coproduct.

(19) E. L. Muetteries and W. H. Knoth, "Polyhedral Boranes," Marcel Dekker, New York, N. Y., 1968, p 13.

(20) J. Miller, "Aromatic Nucleophilic Substitution," Elsevier, Amsterdam, 1968, p 138.

(21) By analogy with other Meisenheimer systems, the C-1 adduct should be more stable but kinetically less favored.[15,16]

Experimental Section

These reactions involve powerful oxidizing and reducing agents. Precooled solutions should be employed and solvents should not be added to the dry premixed reactants. The reaction mediums from which the Meisenheimer adducts have crystallized should not be further concentrated as an explosion can result.

Reactions were carried out under nitrogen. Acetonitrile was dried by distillation from phosphorus pentoxide. The nitroaromatics used were of a good commercial grade and not purified further. Nmr spectra were obtained with the Varian HA-100 spectrometer at 23487 G and 30°. Chemical shifts reported are accurate to better than ±0.02 ppm.

$(CH_3)_4N^+C_6H_3(NO_2)_3^-$, 3.—Acetonitrile solutions, 0.3 *M*, were prepared from 0.23 g (2 mmol) of tetramethylammonium octahydrotriborate and 0.43 gm (2 mmol) of 1,3,5-trinitrobenzene. The solutions were cooled to about −10° and mixed. After standing for several minutes at this temperature, **3** separated as dark lustrous needles. It was collected by filtration, washed with a small amount of cold acetonitrile, and dried *in vacuo*. The yield was 0.34 g (57%): λ_{max} (CH_3CN) 262 nm (ϵ 15,000), 478 (27,600), 582 (33,500); the infrared spectrum (KBr) exhibited bands at 1325, 1490, 1550 and 1623 cm^{-1}. *Anal.* Calcd for $C_{10}H_{16}N_4O_6$: C, 41.7; H, 5.5; N, 19.4; B, 0.0. Found: C, 41.1, 41.1; H, 5.9, 6.1; N, 17.4, 17.9; B, 0.1.[22]

The order of addition of the reactants did not affect the yield. The Meisenheimer adduct **3** is stable for several days in the solid state, but in solution its decomposition is much more rapid.

$(CH_3)_4N^+C_6H_2CH_3(NO_2)_3^-$, 6 (Y = CH_3).—This compound was prepared from tetramethylammonium octahydrotriborate and 2,4,6-trinitrotoluene as described above: λ_{max} (CH_3CN) 256 nm (ϵ 11,000), 478 (25,000), 580 (34,000);[23] yield 62%. *Anal.* Calcd for $C_{11}H_{18}N_4O_6$: C, 43.7; H, 6.0; N, 18.5. Found: C, 43.5, 43.2; H, 6.1, 6.2; N, 18.2, 18.6.

Reduction of 2,4,6-Trinitroanisole and Picryl Chloride.—The reduction of these substrates with 1 and 3 equiv of tetramethylammonium octahydrotriborate was carried out in acetonitrile solution as described above.

Registry No.—**3,** 27554-58-1; **6** (Y = Cl), 27554-59-2; **6** (Y = OCH_3), 27554-60-5; **6** [Y = $N(CH_3)_2$], 27554-61-6; **6** (Y = CH_3), 27554-62-7.

Acknowledgment.—This work was supported in part by the Independent Research Fund of the U. S. Naval Ordnance Laboratory, Task IR-44.

(22) Analysis of these compounds is cometimes difficult as they tend to explode on combustion.

(23) Dilute solutions of these adducts are moisture sensitive and not particularly stable. This makes an accurate determination of their extinction coefficients quite difficult.

Some Reactions of Pyrosulfuryl Fluoride[1]

MAX M. BOUDAKIAN,*[2a] GENE A. HYDE,[2b] AND SANTAD KONGPRICHA[2c]

Olin Corporation, Chemicals Division, New Haven, Connecticut 06504

Received April 29, 1970

The reaction of pyrosulfuryl fluoride (1) with chloroethanol and phenol gave 2-chloroethyl fluorosulfate and phenyl fluorosulfate, respectively. Although benzene has been reported to be inert to 1 under ambient conditions, higher temperatures provided benzenesulfonyl fluoride in 51% yield. Treatment of benzoic acid with 1 gave a 7% yield of benzoyl fluoride. While published observations report exclusive formation of diethyl sulfate from diethyl ether and 1, reversal of the mode of addition furnished ethyl fluorosulfate in 64% yield. Bulk polymerization of tetrahydrofuran was effected by 1. Nonprotic anhydrides of halogenated oxy acids represent a new class of catalysts for the polymerization of cyclic ethers. Vinylidine fluoride and 1 react at 300° to give a complex mixture of products including sulfuryl fluoride, trifluoroethane sulfonyl fluoride, difluorovinyl sulfonyl fluoride, trifluoroethane, and difluoroethyl fluorosulfate. Autocondensation of acetone was effected by 1 to give water, mesityl oxide, and other condensation products.

Since its initial preparation in 1951,[3] relatively few reactions involving pyrosulfuryl fluoride, FSO_2OSO_2F (**1**), with organic substrates have been reported.[4] Heterolytic cleavage of **1** by secondary amines gave aminosulfuryl fluorides and fluorosulfate salts.[5,6] Lustig recently found that reactions of fluoro-organic anions with **1** provided fluoroalkyl fluorosulfate esters.[7] Fluorine-free sulfate esters were obtained by Sokol'skii from dialkyl ethers and **1**.[8] (Solvents such as benzene,[3] chloro- and chlorofluorohydrocarbons,[3] acetonitrile,[5,9] diethyl ether,[5,6] and nitro organics[7,9] are miscible with **1** under ambient conditions.)

Discussion

A brief study demonstrated that **1** reacts with a variety of substrates. Table I summarizes the reactions of **1** in comparison with those of the parent acid, fluorosulfuric acid.

Hayek and Koller[3] reported a violent reaction when ethanol and **1** were mixed at room temperature; no product(s) were identified. It was observed that **1** could effect fluorosulfation of 2-chloroethanol at 0° to give 2-chloroethyl fluorosulfate (**2**) in 40% yield.

$$ClCH_2CH_2OH + \underset{\mathbf{1}}{FSO_2OSO_2F} \xrightarrow{0^\circ} \underset{\mathbf{2}}{ClCH_2CH_2OSO_2F}$$

In a similar fashion, phenol was converted by **1** to phenyl fluorosulfate, $C_6H_5OSO_2F$ (**3**), in 23% yield.

The reaction of **1** and benzoic acid in benzene solvent

$$C_6H_5CO_2H + 1 \xrightarrow{C_6H_6} \underset{\mathbf{4}}{C_6H_5C(=O)F} + \underset{\mathbf{5}}{C_6H_5SO_2F}$$

gave a mixture of benzoyl fluoride (**4**) and benzenesulfonyl fluoride (**5**). The formation of **5** from benzene was quite pronounced (51% yield) at elevated temperatures (170°, monel autoclave); the gas phase consisted of sulfuryl fluoride (**6**). (In contrast, Hayek observed that benzene and **1** were miscible under ambient conditions without any apparent reaction.[3]) Since Ruff and Lustig effected thermolysis of **1** at 150° (monel autoclave) to give sulfuryl fluoride (**6**) in 50% conversion,[10,11] the formation of **5** may be envisaged as fluorosulfonation by **6**. The inertness of

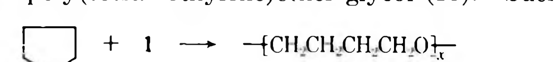
$$1 \longrightarrow \underset{\mathbf{6}}{SO_2F_2} + \underset{\mathbf{7}}{SO_3}$$

toluene to sulfuryl fluoride (**6**) (benzoyl peroxide catalyst at reflux)[12] does not appear to support this interpretation.

While diethyl ether can be employed as a solvent for ammonolysis reactions of **1** from −30 to +25°,[5,6] Sokol'skii[8] obtained a 55% yield of diethyl sulfate (**8**) upon the addition of **1** to refluxing diethyl ether; any ethyl fluorosulfate (**9**) formed immediately reacted with diethyl ether to give **8**. However, it was demonstrated in the present study that reversal of the mode of addition of reactants, *i.e.*, addition of diethyl ether to refluxing **1**, provided ethyl fluorosulfate (**9**) in 64% yield.

$$C_2H_5OC_2H_5 + 1 \begin{cases} \xrightarrow{55\%} \underset{\mathbf{8}}{C_2H_5OSO_2OC_2H_5} \\ \xrightarrow{64\%} \underset{\mathbf{9}}{C_2H_5OSO_2F} \end{cases}$$

Bulk polymerization of tetrahydrofuran was effected by **1** or pyrosulfuryl chloride fluoride to give 60–70% yields of poly(tetramethylene)ether glycol (**10**). Such



10

nonprotic anhydrides of halogen-containing oxy acids represent a new class of catalysts for the polymerization of cyclic ethers. A related anhydride, pyrophosphoryl

(1) Presented at the 158th National Meeting of the American Chemical Society, Division of Fluorine Chemistry, Sept 1969, New York, N. Y.

(2) (a) Olin Corp., Rochester, N. Y.; (b) Olin Corp., New Haven, Conn.; (c) Olin Corp., Joliet, Ill.

(3) (a) E. Hayek and W. Koller, *Monatsh. Chem.*, **82**, 942 (1951); (b) E. Hayek and A. Czaloun, *ibid.*, **87**, 790 (1956).

(4) Even long-known pyrosulfuryl halides have been ignored in such reactions: "Little attention has been paid to pyrosulfuryl chloride, although it has attractive possibilities as a reagent in organic chemistry." E. de B. Barnett and C. L. Wilson, "Inorganic Chemistry,' Longmans, Green and Co., London, 1953, p 434.

(5) (a) R. Appel and G. Eisenhauer, *Angew. Chem.*, **70**, 742 (1958); (b) *Z. Anorg. Allg. Chem.*, **310**, 90 (1961).

(6) S. Kongpricha, W. C. Preusse, and R. Schwarer, 148th National Meeting of the American Chemical Society, Division of Fluorine Chemistry, Chicago, Ill., Sept 1964, Abstracts, p 3K.

(7) M. Lustig, *Inorg. Chem.*, **9**, 104 (1970).

(8) G. A. Sokol'skii, *J. Gen. Chem. USSR*, **36**, 817 (1966).

(9) J. K. Ruff, *Inorg. Chem.*, **4**, 567 (1965).

(10) J. K. Ruff and M. Lustig, *ibid.*, **3**, 1422 (1964). Since treatment of **1** with cesium fluoride at 50° gave **6** and $CsSO_3F$, these authors suggested that the thermolysis of **1** at 150° in a "clean prefluorinated' monel bomb might have been initiated by metal fluorides present in the autoclave.

(11) In contrast, pyrolysis of **1** in a Hastelloy C-lined vessel to give **6** did not occur at a measurable rate at 200° (10 hr): E. L. Muetterties and D. D. Coffman, *J. Amer. Chem. Soc.*, **80**, 5914 (1958).

(12) H. J. Emeléus and J. F. Wood, *J. Chem. Soc.*, 2183 (1948).

TABLE I

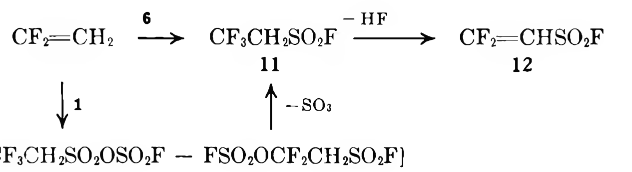
COMPARATIVE REACTIONS OF PYROSULFURYL FLUORIDE AND FLUOROSULFURIC ACID

	$S_2O_5F_2$ (1)	HSO_3F
Alcohols	$ROSO_2F$ (40%)	$ROSO_2F$ (trace)[a]
Phenols	$C_6H_5OSO_2F$ (23%)	p-$HOC_6H_4SO_2F$ (58%)[b]
Benzoic acid	$C_6H_5C(=O)F$ (7%)	No reaction[c]
Benzene	$C_6H_5SO_2F$ (51%)	$C_6H_5SO_3H$,[a,d] $C_6H_5SO_2F$,[b] $C_6H_5SO_2C_6H_5$[b,d]
Alkyl ether	$ROSO_2OR$ (55–62%)[e] $ROSO_2F$ (64%)	$ROSO_2F$ (30%)[a]
Tetrahydrofuran	$\mathrm{-[CH_2CH_2CH_2CH_2O]_x-}$ (60–70%)	$\mathrm{-[CH_2CH_2CH_2CH_2O]_x-}$[f]
Vinylidene fluoride	See text	$CH_3CF_2OSO_2F$[g]
Acetone	H_2O, mesityl oxide, other condensation products (red solution)	Red color test for HSO_3F[a]

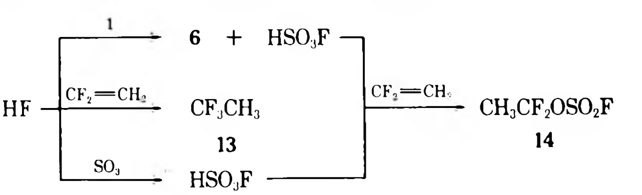
[a] Reference 19. [b] Reference 26. [c] W. Baker, G. E. Coates, and F. Glockling, *J. Chem. Soc.*, 1376 (1951). [d] J. H. Simons, H. J. Passino, and S. Archer, *J. Amer. Chem. Soc.*, **63**, 608 (1941). [e] Reference 8. [f] H. Meerwein, D. Delfs, and H. Morschel, *Angew. Chem.*, **72**, 927 (1960). These investigators found that pyrosulfuric acid also polymerized tetrahydrofuran. [g] Reference 18.

tetrafluoride, $F_2P(O)O(O)PF_2$, was less effective as a polymerization catalyst; the yield of **10** was only 5%.

Vinylidene fluoride and **1** react at 300° to give <5% yield of **6** and **11–14**. One postulated sequence to **6**, **11**, and **12** involves pyrolysis of **1** to form **6** and **7**, subsequent addition of **6** to vinylidine fluoride to give 2,2,2-trifluoroethane sulfonyl fluoride **11**, and dehydrofluorination of the latter to provide difluorovinyl sulfonyl fluoride with the probable structure **12**.[13] However, we were unable to add **6** to vinylidene fluoride at 300–400° to give **11**.[14] An alternate route to **11** might involve addition of **1** to vinylidene fluoride, followed by expulsion of sulfur trioxide.[15,16] Sulfuryl



fluoride (**6**), 1,1,1-trifluoroethane (**13**), and 1,1-difluoroethyl fluorosulfate (**14**) may arise by reactions similar to those previously reported: **6** and fluorosulfuric acid from hydrogen fluoride and **1**;[8] **13** from hydrogen fluoride and vinylidene fluoride;[17] and **14** from vinylidene fluoride and fluorosulfuric acid.[18]



Autocondensation of acetone was effected by **1** to give a dark red solution containing water, mesityl oxide, phorone, isophorone, and other condensation products. Meyer and Schramm's diagnostic test for fluorosulfuric acid involves addition of acetone to give a dark red solution of unknown composition.[19] The red color noted in the reaction of **1** and acetone may be due to fluorosulfuric acid arising by hydrolysis of **1** as a consequence of the above autocondensation.

Experimental Section

Chemicals.—Pyrosulfuryl fluoride (**1**) and pyrosulfuryl chloride fluoride were prepared from the reaction of fluorosulfuric acid and cyanuric chloride.[6,20] *Pyrosulfuryl fluoride has been reported to be toxic!*[3,11]

2-Chloroethyl Fluorosulfate (2).—**1** (36.4 g, 0.20 mol) was added slowly with stirring to 2-chloroethanol (16.1 g, 0.20 mol) kept at 0°. The reaction mixture was allowed to warm to 25° and then heated at 45–50° (2 hr). Volatiles were removed at 55° (1 mm); distillation of the latter provided 14 g of **2** (40% yield), bp 32° (2.6 mm).

Anal. Calcd for $C_2H_4ClSO_3F$: C, 14.77; H, 2.48; Cl, 21.81; F, 11.69. Found: C, 14.70; H, 2.48; Cl, 22.1; F, 11.9.

Phenyl Fluorosulfate (3).—Phenol (12.3 g, 0.13 mol) and **1** (23.8 g, 0.13 mol) were mixed at 10° and successively stirred at 25° (2 hr) and 53° (3 hr). Distillation provided 5.5 g of **3** (23.2% yield), bp 34–38° (2.7 mm), $n^{25.5}_D$ 1.4688 (reported for **3**:[21] bp 180°; $n^{25.6}_D$ 1.4628). Product identification (95% **3**, 5% phenol) was corroborated by comparison with the standard infrared spectrum of **3**,[21,22] by mass spectroscopy (*m/e* 65, 93, and 176), and by nmr (^{19}F singlet at −48.65 ppm). The distillation residue consisted of a nonvolatile [300° (0.05 mm)], fluorine-free (^{19}F nmr) solid; the infrared spectrum showed bands at 3.1 (OH), 5.9–6.3 (C=C), 6.5–7.2, 13–15 (phenyl), and 7.65, 8.65 μ (SO_2).

Reaction of 1 and Benzoic Acid in Benzene. A mixture of **1** (0.11 mol, 20.2 g), benzoic acid (0.074 mol, 9.1 g), and benzene (150 ml) was refluxed for 20 hr. After removal of benzene and unreacted **1**, 0.61 g (6.6% yield) of a liquid, bp <25° (4.5 mm), n^{25}_D 1.4980 (reported for **4**:[23] n^{25}_D 1.4988), was obtained. The product had the characteristic infrared spectrum of **4**,[24] along with the weak absorption indicative of **5**.[25] Further identification of **4** was obtained by nmr (^{19}F and ^1H) and mass spectroscopy (molecular weight ion peak at *m/e* 124). Unreacted benzoic acid (8.2 g, 90% recovery) was isolated by sublimation of the distillation residue. The sublimation residue (1.55 g) consisted of a fluorine-free (^{19}F nmr) liquid containing benzenesul-

(13) M. M. Boudakian, G. A. Hyde, and E. H. Kober, U. S. Patent 3,492,348 (Jan 27, 1970).

(14) The addition of **6** to vinylidene fluoride could not be effected under ionic conditions (cesium fluoride/diglyme, 100–150°): S. Temple, Fourth International Fluorine Chemistry Symposium, Estes Park, Colo., July 1967, Paper No. 49.

(15) We thank Dr. D. D. DesMarteau of Northeastern University for this suggestion.

(16) The decomposition of methyl disulfuryl fluoride or perfluoroacetyl fluorosulfate to give methane sulfonyl fluoride and perfluoroacetyl fluoride, respectively, has been interpreted on the basis of sulfur trioxide expulsion: W. M. Johnson, H. A. Carter, and F. Aubke, *Inorg. Nucl. Chem. Lett.*, **5**, 719 (1969); D. D. DesMarteau and G. H. Cady, *Inorg. Chem.*, **5**, 169 (1966).

(17) C. B. Miller and L. B. Smith, U. S. Patent 2,669,590 (Feb 16, 1954).

(18) J. D. Calfee and P. A. Florio, U. S. Patent 2,628,972 (Feb 17, 1953).

(19) J. Meyer and G. Schramm, *Z. Anorg. Allg. Chem.*, **206**, 24 (1932).

(20) (a) R. F. Schwarer, S. Kongpricha, and W. C. Preusse, U. S. Patent 3,275,413 (Sept. 27, 1966); (b) *Inorg. Syn.*, **11**, 151 (1968).

(21) R. Cramer and D. D. Coffman, *J. Org. Chem.*, **26**, 4164 (1961).

(22) F. K. Butcher, J. Charlambous, M. J. Frazer, and W. Gerrard, *Spectrochim. Acta, Part A*, **23**, 2399 (1967).

(23) A. I. Mashentsev, *Zh. Obshch. Khim.*, **15**, 915 (1945); *Chem. Abstr.*, **40**, 6443 (1946).

(24) F. Seel and J. Langer, *Chem. Ber.*, **91**, 2553 (1958).

(25) N. S. Ham, A. N. Hambly, and R. H. Laby, *Aust. J. Chem.*, **13**, 443 (1960).

fonic acid and/or hydrate based on infrared and mass spectral analysis (molecular weight ion peak, m/e 158; peaks at m/e 48, 50, 64, 66, and 81 were suggestive of the $-SO_3H$ group).

Benzoic acid (0.5 mol, 61.1 g), **1** (0.4 mol, 76.8 g), and benzene (0.62 mol, 55 ml) were heated in a rocking 300-ml autoclave (monel) at 170° for 1.5 hr. The autoclave was cooled to 25° (100 psig); mass spectral analysis of the gaseous products showed only sulfuryl fluoride (**6**). Distillation did not give any unreacted **1**. The product, bp 107–110° (35 mm), consisted primarily of benzenesulfonyl fluoride (**5**) and small quantities of benzoyl fluoride (**4**) (ir). Redistillation provided 37 g of **5** (51% yield), bp 62–63° (3.5 mm), $n^{25}D$ 1.4894 (vpc 99.8%) [reported for **5**: bp 90–91° (14 mm);[26] $n^{18}D$ 1.4932;[26] $n^{20}D$ 1.4922[27]]. The product had the characteristic infrared spectrum of **5**;[25] mass spectral assay showed a molecular weight ion peak at m/e 160. Unreacted benzoic acid (>90% recovery) was isolated by sublimation of the distillation residue. The viscous sublimation residue (67.2 g) was not analyzed.

Ethyl Fluorosulfate (9).—Diethyl ether (18.5 g, 0.25 mol) was added dropwise to **1** (45.0 g, 0.25 mol) (initial temperature, 51°; final temperature, 95°). The reaction product was fractionally distilled to give 42 g of **9** (64% yield), bp 42°(51.5 mm) [reported[19] for **9**: bp 24° (12 mm)].

Anal. Calcd for $C_2H_5SO_3F$: C, 18.7; H, 3.9; S, 24.99; F, 14.8. Found: C, 19.11; H, 4.05; S, 24.99; F, 15.0.

Pyrosulfuryl Fluoride as Polymerization Catalyst.—Tetrahydrofuran was refluxed over sodium hydroxide pellets for 3 hr and distilled. The fraction, bp 66°, was stored over calcium hydride and redistilled under nitrogen prior to use.

A mixture of tetrahydrofuran (173.0 g, 2.39 mol) and **1** (2.89 g, 1.64 wt %) was stirred under a nitrogen atmosphere at 25°; within 2 hr, stirring had ceased. After 3.5 hr, 250 ml of water was added to the semisolid gel, the mixture was heated, and the aqueous layer was decanted. The opaque polymer was dissolved in 1.5 l. of hot tetrahydrofuran, the solution poured into 1 l. of water with stirring, and the precipitated polymer dried *in vacuo* to give 105 g of **10** (60.7% yield), mp 35–40°. The polymer had the characteristic infrared spectrum of polytetrahydrofuran.[28] Other properties of the polymer include intrinsic viscosity (30°), 0.50 (tetrahydrofuran), 0.52 (benzene); hydroxyl number, 10.0 mg KOH/g; number-average molecular weight, 8038 (benzene, 39°; vapor-pressure osmometer, Mechrolab, Inc., Model 302).

From tetrahydrofuran (149.7 g) and pyrosulfuryl chloride fluoride (1.41 g, 0.93 wt %) under a nitrogen atmosphere (25°, 20 hr), 101.2 g of polymer **10** (67% yield), mp 36–39°, was obtained.

From pyrophosphoryl tetrafluoride[29] (1.0 g, 0.95 wt %) and tetrahydrofuran (103 g) under nitrogen (25°, 22 hr), 5.1 g of **10** (5% yield), mp 30.2°, was obtained.

Reaction of 1 and Vinylidene Fluoride.—A mixture of **1** (21.8 g, 0.12 mol) and vinylidene fluoride (7.8 g, 0.12 mol, Matheson Co.) was heated in a 150-ml monel cylinder at different stages: 100° (1.5 hr), 200° (2 hr), and 300° (6 hr). During the first two stages, there was no evidence of reaction based on pressure change. At 300°, the pressure rose to 420 psig (1 hr) and gradually decreased to 310 psig.

The reactor was cooled to −94° and 6.9 g of volatiles collected [ir primarily SO_2F_2 (**6**), with trace quantities of vinylidene fluoride and CF_3CH_3 (**13**)]. The reactor was then warmed to 25° and 12.7 g of volatiles collected. The latter consisted of a fraction (wt 2.6 g) volatile at −23°; infrared and mass spectral analysis revealed the presence of **6** and **13**. Vpc trapping of the nonvolatile fraction (at −23°) provided unreacted **1** and the following compounds in decreasing order of magnitude (<5% yield).

CF_2=$CHSO_2F$ (12): mass spectral analysis, molecular weight ion peak at m/e 146; infrared spectrum showed bands at 3.2 (CH), 5.8 (C=C), 7.35 and 8.45 (SO_2F), and 12.5 μ (RR′C=CHR″); nmr (^1H) revealed the presence of a component containing a single proton.

$CF_3CH_2SO_2F$ (11): mass spectral analysis showed a molecular weight ion peak at m/e 166; both ir and nmr (^{19}F, ^1H) were consistent with structure **11**.

$CH_3CF_2OSO_2F$ (14): infrared spectrum showed bands at 6.75 and 7.95 (OSO_2F), 7.1, 8.8, and 10.5 μ (CF_2); mass spectral analysis indicated a fragmentation pattern suggestive of **14**; nmr (^1H) analysis was consistent with structure **14**.

The nonvolatile (at 25°) components (7.1 g) in the reactor consisted of a liquid and solid. The former was a complex mixture of high-boiling products which decomposed in the mass spectral hot inlet to give the following fragments: m/e 61 (CHSO), 67 (SOF), 83 (SO_2F), 97 (CH_2SO_2F or $C_2H_3F_2S$), and 147 ($C_2H_2SO_2F_3$). The solid had an infrared spectrum characteristic of polyvinylidene fluoride.

Attempted Reaction of Sulfuryl Fluoride (6) and Vinylidene Fluoride.—A mixture of **6** (3.8 g, 0.037 mol, Matheson Co.) and vinylidene fluoride (20.6 g, 0.32 mol) was heated in a 150-ml monel cylinder at 300–400° (5 hr). The pressure (810 psig) remained constant during this period. The reactor was cooled to −78° and volatiles removed (24.2 g, 99% of initial charge). Infrared and mass spectral analysis showed only starting materials.

Reaction of 1 and Acetone.—During an 0.5-hr period, acetone (26.8 g, 0.46 mol) was added to **1** (19.0 g, 0.46 mol) dissolved in 100 ml of benzene cooled to 5°. The solution was stirred 4 hr (5 to 25°); two dark red layers were formed. Distillation of the lower layer provided a fraction, bp 25° (2.5 mm), wt 2.1 g, consisting of water and a fluorine-free (^{19}F nmr) lower layer. Infrared analysis indicated that the latter consisted of mesityl oxide, as well as lesser amounts of isophorone, phorone, and unidentified components. Infrared analysis of the initial upper layer revealed the presence of unreacted starting materials and mesityl oxide.

Registry No.—**1**, 13036-75-4; **2**, 27669-92-7; **9**, 371-69-7; benzoic acid, 65-85-0; vinylidene fluoride, 75-38-7.

(26) W. Steinkopf, K. Buchheim, K. Beythien, H. Dudek, J. Eisold, J. Gall, P. Jaeger, H. Reumuth, A. Semenoff, and A. Wemme, *J. Prakt. Chem.*, **117**, 1 (1927).

(27) W. Davis and J. H. Dick, *J. Chem. Soc.*, 2104 (1931).

(28) T. Saegusa, H. Imai, and J. Furakawa, *Makromol. Chem.*, **56**, 55 (1962).

(29) E. A. Robinson, *Can. J. Chem.*, **40**, 1725 (1962).

Neighboring Oxide Ion and Fragmentation Reactions of 1,3-Chlorohydrins

W. H. RICHARDSON,* C. M. GOLINO, R. H. WACHS, AND M. B. YELVINGTON

Department of Chemistry, San Diego State College, San Diego, California 92115

Received August 26, 1970

The rates of disappearance of a series of 1,3-chlorohydrins in basic aqueous methanol at various temperatures are reported along with yields of the products. From these data, rate coefficients and the corresponding activation parameters for ring closure, fragmentation, substitution, and elimination are calculated. Fragmentation is observed when the 1,3-chlorohydrin is substituted with a *gem*-dimethyl group so that isobutylene results. In contrast, no fragmentation occurs if the *gem*-dimethyl grouping is moved so that the potential fragmentation products would have these methyl groups at the carbonyl rather than the olefinic fragmentation unit. It is found that the entropy of activation is responsible for the rate of fragmentation of **3** being slightly greater than ring closure, which is consistent with previous reports that these competing reactions are solvent dependent. Rates of ring closure and yields of oxetanes decrease in the order 4-chloro-2-methyl-2-butanol (**2**) > **3** ~ 3-chloro-1-propanol (**1**). Possible reasons for this order are discussed. A comparison of the effect of ring size on the rates of ring closure for a series of ω-hydroxyalkyl chlorides with base is made.

The kinetics of the neighboring oxide ion reactions of 1,2-chlorohydrins [ND_I-($^-$O-3)],[1] to give oxiranes, have been studied extensively.[4,5] Kinetic data for the basic decomposition of other ω-hydroxyalkyl halides, where n is greater than 3 in the ND_I-($^-$O-n) reaction, are not as prevalent.[4k,n,5a,b,6] We are particularly interested in the ND_I-($^-$O-4) reaction as a model for the neighboring peroxide anion reaction [ND_I-($^-$OO-4)].[7] In the few instances where kinetic data are presented for the ND_I-($^-$O-4) reaction, quantitative product studies are not reported[4k,6b] with one exception.[6d] Quantitative product studies are essential to evaluate the kinetic data, since fragmentation accompanies the ND_I-($^-$O-4) reaction.[4k,5a,6d,8] We now report a systematic kinetic and product study of the basic decomposition of a series of methyl-substituted 1,3-chlorohydrins in aqueous methanol. From these data, kinetic parameters for the ND_I-($^-$O-4), fragmentation, substitution, and elimination reactions are obtained.

(1) ND_I refers to "internal nucleophilic displacement"[2] and $^-$O-3 refers to the participating group and the ring size that is developed at the transition state.[3]

(2) W. Hanstein, H. J. Berwin, and T. G. Traylor, *J. Amer. Chem. Soc.*, **92**, 829 (1970).

(3) See R. Heck and S. Winstein, *ibid.*, **79**, 3105 (1957).

(4) (a) W. P. Evans, *Z. Phys. Chem.*, **7**, 335 (1891); (b) L. Smith, *ibid.*, **81**, 339 (1912); **A152**, 153 (1931); (c) H. Nilsson and L. Smith, *ibid.*, **A166**, 136 (1933); (d) L. Smith and B. Platon, *Chem. Ber.*, **61**, 1709 (1928); (e) L. O. Winstrom and J. C. Warner, *J. Amer. Chem. Soc.*, **61**, 1205 (1939); (f) D. Porret, *Helv. Chim. Acta*, **24**, 80E (1941); (g) R. G. Kadesch, *J. Amer. Chem. Soc.*, **68**, 46 (1946); (h) T. Bergkvist, *Svensk Kem. Tidskr.*, **64**, 18? (1952): *Chem. Abstr.*, **46**, 8942*g* (1952), and earlier references cited therein; (i) A. G. Ogston, E. R. Holiday, J. S. L. Philpot, and L. A. Stocken, *Trans. Faraday Soc.*, **44**, 45 (1948); (j) J. E. Stevens, C. L. McCabe, and J. C. Warner, *J. Amer. Chem. Soc.*, **70**, 2449 (1948); (k) G. Forsberg, *Acta Chem. Scand.*, **8**, 135 (1954); (l) P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **81**, 2347 (1959); (m) C. G. Swain, A. D. Ketley, and R. F. W. Bader, *ibid.*, **81**, 2353 (1959); (n) H. W. Heine and W. Siegfried, *ibid.*, **76**, 489 (1954).

(5) For reviews, see (a) B. Capon, *Quart. Rev.*, **18**, 45 (1964); (b) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 110; (c) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1961, p 288.

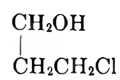
(6) (a) C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Amer. Chem. Soc.*, **87**, 1553 (1965); (b) G. Forsberg, *Nord. Kemikermoede, 9th*, **7**, 170 (1950); *Chem. Abstr.*, **48**, 7405 (1954); (c) H. W. Heine, *J. Amer. Chem. Soc.*, **79**, 6268 (1957); (d) R. B. Clayton, H. B. Henbest, and M. Smith, *J. Chem. Soc.*, 1982 (1957).

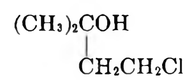
(7) (a) W. H. Richardson, J. W. Peters, and W. P. Konopka, *Tetrahedron Lett.*, 5531 (1966); (b) W. H. Richardson, Abstracts, *Int. Symp., Chem. Organischen Peroxide, Berlin, DDR*, 81 (Sept 1967); (c) W. H. Richardson and V. F. Hodge, *Tetrahedron Lett.*, 2271 (1970); (d) R. Curci and J. O. Edwards, "Organic Peroxides," Vol. 1, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1970, p 256.

(8) (a) S. Searles, *Chem. Heterocycl. Compounds*, **19**, 983 (1964); (b) H. B. Henbest and B. B. Millward, *J. Chem. Soc.*, 3575 (1960); (c) S. Searles, R. G. Nickerson, and W. K. Witsiepe, *J. Org. Chem.*, **24**, 1839 (1959); (d) G. Adam, *Angew. Chem.*, **79**, 619 (1967); (e) S. Searles and M. J. Gortatowski, *J. Amer. Chem. Soc.*, **75**, 3030 (1953); (f) P. S. Wharton and G. A. Hiegel, *J. Org. Chem.*, **30**, 3254 (1965); (g) P. S. Wharton, *ibid.*, **26**, 4781 (1961); (h) C. H. Issidorides and A. I. Matar, *J. Amer. Chem. Soc.*, **77**, 6382 (1955); (i) E. J. Corey, R. B. Mitra, and H. Uda, *ibid.*, **86**, 485 (1964); (j) R. R. Burford, F. R. Hewgill, and P. R. Jefferies, *J. Chem. Soc.*, 1983 (1957).

Results

Products.—The condensable product yields were determined by gas–liquid chromatography (glc) by the internal standard method.[9] The yields of gaseous products were obtained by standard vacuum line procedures,[10] coupled with mass spectral analyses. Product analyses are reported in Tables I–III for the reaction of 3-chloro-1-propanol (**1**), 4-chloro-2-methyl-2-butanol (**2**), and 3-chloro-2,2-dimethyl-1-propanol (**3**)


1


2

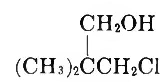
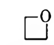
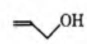
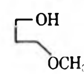
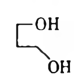

3

TABLE I

PRODUCTS FROM THE REACTION OF 1[a] WITH SODIUM HYDROXIDE[b] IN 40% AQUEOUS METHANOL

Product	% yield 100°	85°	75°	65°
 **4**	14.6	13.5	13.4	13.0
 **5**	4.65	3.77	2.43	2.49
 **6**	53.5	50.0	49.2	48.2
 **7**	28.5	28.9	25.8	27.2
% product balance	101	96.2	90.8	90.9
% reaction[c]	58.0	61.7	45.7	41.7

[a] $[1]_0$ = 0.0546 M. [b] $[NaOH]_0$ = 0.1063 M. [c] Calculated from the difference between the initial and final concentrations of **1**.

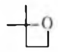
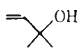
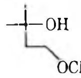
with base in 40% aqueous methanol. Analyses could be made with excess **3** after 10–20 half-lives; however, under similar conditions with **1** and **2**, the corresponding oxetanes were not stable. Apparently hydrogen chloride is produced from **1** and **2** by a β elimination,

(9) S. Dal Nogare and R. S. Juvet, Jr., "Gas–Liquid Chromatography," Interscience, New York, N. Y., 1962, p 256.

(10) (a) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill, New York, N. Y., 1960, Chapter 3; (b) R. T. Sanderson, "Vacuum Manipulation of Volatile Compounds," Wiley, New York, N. Y., 1948.

TABLE II

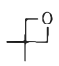
PRODUCTS FROM THE REACTION OF 2[a] WITH SODIUM HYDROXIDE[b] IN 40% AQUEOUS METHANOL

Product	% yield 100°	85°	75°	65°
 8	81.7	82.6	79.1	75.9
 9	1.5	1.2	1.8	2.3
 10	16.4	14.6	19.4	23.4
% product balance	99.1	98.4	100.3	101.6
% reaction[c]	37.8	43.3	40.6	36.0

[a] $[2]_0$ = 0.0652 *M*. [b] $[NaOH]_0$ = 0.1049 *M*. [c] Calculated from the difference between the initial and final concentrations of 2.

TABLE III

PRODUCTS FROM THE REACTION OF 3[a] WITH SODIUM HYDROXIDE[b] IN 40% AQUEOUS METHANOL

Product	% yield 95°	85°	75°	65°
 11	40.0, 39.7	46.4	49.0	54.3, 54.3
 12	54.0		54.6	57.2
% product balance	94.0		103.6	111.5
No. of half-lives	10.6, 20.6	10.4	9.9	10.3, 20.3

[a] $[3]_0$ = 0.194–0.207 *M*. [b] $[NaOH]_0$ = 0.0188 *M*.

which is not possible with **3** after the base is expended and the acid catalyzes the opening of the oxetane ring.[8a,11] For this reason, product analyses from **1** and **2** were conducted with excess base and the reaction was allowed to proceed for about 1 half-life. Yields are based on the amount of **1** and **2** that underwent reaction. Small amounts of the glycol (2-methyl-2,4-butanediol) were detected from the reaction of **2** with base, but quantitative analyses were not pursued. Control experiments with base and the oxetanes **4** and **8**, as well as allyl alcohol (**5**) under conditions which approximated those of the reaction of **1** and **2** with base, showed that these products were stable. The constancy in yield of oxetane **11** with variation in reaction time (Table III) shows that **11** is stable under the reaction conditions. Ethylene would be produced from the basic fragmentation of **1**, but the *maximum* possible yield was 0.2%. Acetone, which would arise from the basic fragmentation of **2**, was not observed.

Kinetic Data.—The overall rates of basic decomposition of **1**, **2**, and **3** were determined by acidometric methods through approximately 3 half-lives. The orders in the 1,3-chlorohydrin and base were established with **3** and the data are given in Table IV. The results indicate first-order dependence on both **3** and base. Kinetic data from which activation parameters were calculated for the overall reaction are given in Table V along with these parameters. The reactions of 1,3-chlorohydrins with base fall into the category of parallel second-order reactions, where the overall rate coefficient (k_2) equals the sum of the second-order rate

TABLE IV

ORDER IN 3-CHLORO-2,2-DIMETHYL-1-PROPANOL (3) AND SODIUM HYDROXIDE IN 40% AQUEOUS METHANOL AT 85.00°[a]

$[3]_0$, *M*	$10^2[NaOH]_0$, *M*	10^4k_1,[b] sec^{-1}	10^4k_2,[c] l. mol^{-1} sec^{-1}
0.1006	0.938	0.365 ± 0.005	3.62 ± 0.05
0.2224	0.938	0.890 ± 0.016	4.01 ± 0.07
0.4012	0.938	1.53 ± 0.02	3.81 ± 0.04
0.6085	0.938	2.10 ± 0.04	3.45 ± 0.06
0.7999	0.938	2.99 ± 0.03	3.74 ± 0.04
1.007	0.938	3.54 ± 0.06	3.51 ± 0.06
			Av 3.69 ± 0.14
1.019	1.88	3.46 ± 0.04	3.53 ± 0.04
1.008	2.81	3.43 ± 0.03	3.40 ± 0.03
1.004	5.63	3.47 ± 0.02	3.46 ± 0.02
1.000	9.38	3.26 ± 0.04	3.26 ± 0.04
			Av 3.43 ± 0.06

[a] Ionic strength adjusted to 0.499 *M* with sodium perchlorate. Individual rate coefficients are given with probable error and the calculations were made with the aid of a standard first-order computer program. [c] Calculated from $k_2 = k_1/[3]_0$.

coefficients for the ND_I reaction (k_r), fragmentation (k_f), substitution (k_N), and elimination (k_E) (eq 1).[12]

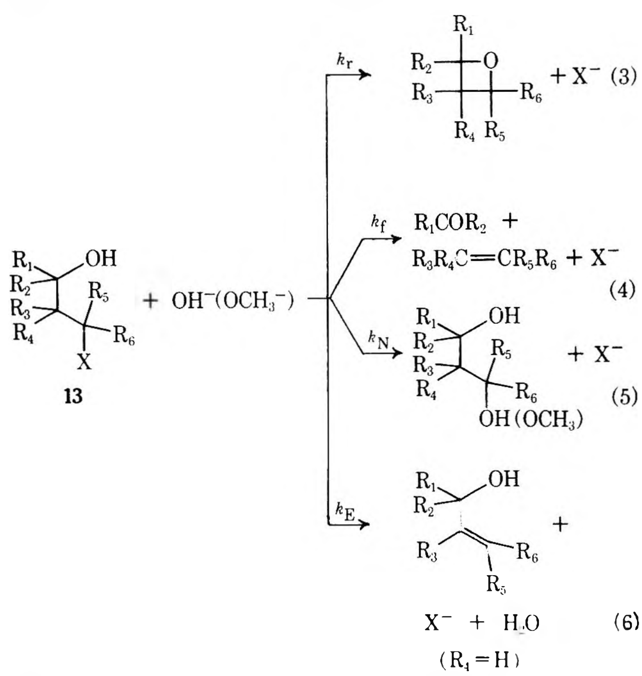
$$k_2 = k_r + k_f + k_N + k_E = \sum_i k_i \qquad (1)$$

$$k_i = k_2 \left(\frac{\%\ \text{yield i}}{100}\right) \qquad (2)$$

The individual rate coefficients (k_i) are then calculated, with the aid of eq 2, from data in the preceding tables. The k_i values at various temperatures and their corresponding activation parameters are given in Table VI.

Discussion

The possible reactions of 1,3-halohydrins are generalized in eq 3–6. In the present investigation, 1,3-



chlorohydrins **1** and **2** exhibited reactions 3, 5, and 6, while **3** underwent reactions 3 and 4. Usually a complete product study was not made in previous investigations of the basic reaction of 1,3-halohydrins, or

(11) (a) R. T. Keen, *Anal. Chem.*, **29**, 1041 (1957); (b) H. Rupe and O. Klemm, *Helv. Chim. Acta*, **21**, 1538 (1938); (c) S. Searles, D. G. Hummel, P. O. Throckmorton, and S. Nukina, *J. Amer. Chem. Soc.*, **82**, 2928 (1960).

(12) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1961, p 164.

TABLE V

ACTIVATION PARAMETERS FOR THE OVERALL REACTION OF 1,3-CHLOROHYDRINS WITH SODIUM HYDROXIDE IN 40% AQUEOUS METHANOL[a]

1,3-Chlorohydrin	Temp, °C	10^4k_2[b]	E_a[c]	Log A	$\Delta H^{\ddagger}$[c]	$\Delta S^{\ddagger}$[d]
1[e]	65.00	1.15 ± 0.01				
	75.00	3.31 ± 0.04				
	85.00	8.27 ± 0.15				
	100.00	32.4 ± 0.9	23.9 ± 0.2	11.5	23.2 ± 0.1	−8.2 ± 0.3
2[f,g]	55.00	1.51 ± 0.06				
	65.00	4.45 ± 0.03				
	75.00	12.2 ± 0.1				
	85.00	31.6 ± 0.2	23.6 ± 0.04	11.9	23.0 ± 0.1	−6.2 ± 0.2
3[g,h]	65.00	0.455 ± 0.004				
	75.00	1.39 ± 0.02				
	85.00	3.69 ± 0.14[i]				
	95.00	10.4 ± 0.3	25.6 ± 0.3	12.2	24.9 ± 0.3	−5.0 ± 0.9

[a] Ionic strength adjusted to 0.499 M with sodium perchlorate. [b] Units in l. mol^{-1} sec^{-1}. Each entry is an average of two measurements. [c] In kcal/mol with probable error. [d] In eu. [e] $[1]_0$ = 0.120–0.125 M, $[NaOH]_0$ = 0.0528 M, and k_2 is calculated from a second-order computer program. [f] $[2]_0$ = 0.317–0.322 M, $[NaOH]_0$ = 0.02814 M. [g] Second-order rate constant calculated from $k_2 = k_1/[\text{1,3-chlorohydrin}]_0$. [h] $[3]_0$ = 0.208–0.194 M, $[NaOH]_0$ = 0.0188 M. [i] Average from $[3]_0$ = 0.1006–1.007 M, $[NaOH]_0$ = 0.00938 M, Table IV.

TABLE VI

ACTIVATION PARAMETERS FOR INDIVIDUAL RATE COEFFICIENTS (k_i) IN THE BASIC REACTION OF 1,3-CHLOROHYDRINS IN 40% AQUEOUS METHANOL

1,3-Chlorohydrin	Temp, °C		10^4k_i[a]	E_a[b]	Log A	$\Delta H^{\ddagger}$[b]	$\Delta S^{\ddagger}$[c]
		k_r[d]					
1	65.0		0.150				
	75.0		0.444				
	85.0		1.12				
	100.0		4.73	24.6 ± 0.2	11.1	23.9 ± 0.2	−10.2 ± 0.8
		k_{Nm}[e]					
1	65.0		0.554				
	75.0		1.63				
	85.0		4.14				
	100.0		17.3	25. ± 0.2	11.6	23.8 ± 0.2	−7.8 ± 0.7
		k_{Nh}[f]					
1	65.0		0.313				
	75.0		0.854				
	85.0		2.39				
	100.0		9.23	24.3 ± 0.2	11.2	23.6 ± 0.2	−9.6 ± 0.6
		k_E[g]					
1	65.0		0.0286				
	75.0		0.0804				
	85.0		0.312				
	100.0		1.51	28.8 ± 0.7	13.1	28.1 ± 0.7	−1.1 ± 2.5
		k_r[h]					
2	65.0		3.38				
	75.0		9.65				
	85.0		26.1				
	100.0[i]		103	24.5 ± 0.1	12.3	23.7 ± 0.1	−4.4 ± 0.2
		k_{Nm}[j]					
2	65.0		1.04				
	75.0		2.37				
	85.0		4.61				
	100.0[i]		20.6	21.1 ± 1.1	9.63	20.4 ± 1.1	−16.8 ± 3.7
		k_E[k]					
2	65.0		0.102				
	75.0		0.220				
	85.0		0.379				
	100.0[i]		1.89	20.5 ± 1.6	8.21	19.8 ± 1.6	−23.3 ± 5.5
		k_r[l]					
3	65.0		0.247				
	75.0		0.681				
	85.0		1.71				
	95.0		4.15	23.2 ± 0.1	10.4	22.5 ± 0.1	−13.3 ± 0.3
		k_I[m]					
3	65.0		0.260				
	75.0		0.759				
	95.0		5.61	25.3 ± 0.1	11.8	24.6 ± 0.1	−6.9 ± 0.3

[a] Units in l. mol^{-1} sec^{-1}. [b] In kcal/mol with probable error. [c] In eu. For appearance of [d] 4; [e] 6; [f] 7; [g] 5; [h] 8. [i] Calculated from an overall rate coefficient which is extrapolated from the 55–85° range to 100°. For appearance of [j] 10; [k] 9; [l] 11; [m] 12.

product yields were determined by isolation which may be subject to error. The lack of a complete product study by some previous workers was due, in part, to their interest in the basic reaction of 1,3-chlorohydrins solely as a synthetic route to oxetanes.[8a,13] Unfortunately the yield data for oxetanes did not allow one to assign the unreported products to fragmentation, substitution, or elimination products. With the quantitative product study and kinetic data presented here, a more complete evaluation of the relative importance of eq 3–6 can be made.

The fragmentation reaction (eq 4) is of particular interest.[4k,5a,6d,8,14] In a detailed product study of the basic reaction of 2,2-disubstituted 1,3-bromohydrins (**13**, X = Br; $R_1 = R_2 = R_5 = R_6 = H$), the yield of the olefinic fragmentation product increased in the order of increasing stability of the olefin.[8c] Product distribution from 1- or 3-substituted 1,3-halohydrins has not been as thoroughly studied. Fragmentation has been reported for 3-substituted 1,3-chlorohydrins (**13**, R_5 = alkyl; $R_1 = R_2 = R_3 = R_4 = R_6 = H$; X = Cl),[4k] but not with 1-substituted 1,3-halohydrins.[4k,13a,c] In the latter instances, it cannot be ascertained if fragmentation occurred, but was simply not reported. Fragmentation was reported (55–60% yield) from 1,3-disubstituted hydroxy brosylates (**13**, $R_1 = R_5 = CH_3$; $R_2 = R_3 = R_4 = R_6 = H$; X = OBs).[8b] From our data, it is clear that fragmentation occurs only when a substituted olefin can be formed. In principle, fragmentation could be facilitated by 1 substitution of **13**, as in **2**, to generate a more stable carbonyl fragment. Yet no fragmentation was observed with **2**, whereas 2 substitution (as in **3**) does result in fragmentation where a more stable olefin is produced. In changing from 2 to 1 substitution (**3** *vs.* **2**), not only is fragmentation suppressed, but ring-closure (eq 3) and substitution (eq 5) are markedly increased (*cf.* Table VI). The rate of fragmentation of **3** is slightly greater than ring closure; yet $\Delta H^{\ddagger}$ is *greater* for fragmentation (25.3 kcal/mol) than for ring closure (23.2 kcal/mol). Thus, it is $\Delta S^{\ddagger}$ that determines the rate sequence of $k_f \gtrsim k_r$ for **3**. This is consistent with the observation[8c] that fragmentation *vs.* ring closure is solvent dependent. Thus, there appears to be less solvent reorganization for fragmentation of **3** ($\Delta S^{\ddagger} = -6.9$ eu) where there is greater charge dispersion in proceeding to the transition state than in ring closure ($\Delta S^{\ddagger} = -13.3$ eu) with less charge dispersion.

The rates of ring closure and yields of oxetanes decrease in the order of **2** > **3** ~ **1**. On the basis of the Thorpe–Ingold effect,[15] it is expected that the rate of ring closure of **3** should be significantly greater than for **1** due to the *gem*-dimethyl group in **3**, which should decrease the proximity between oxygen and the carbon bearing chlorine.[16] There is then little basis for support of the Thorpe–Ingold hypothesis in these reactions. The reason that the k_r values are in the order **2** > **3** is found in the $\Delta S^{\ddagger}$ term, since $\Delta H^{\ddagger}$ is greater for **2** (23.7 kcal/mol) than **3** (22.5 kcal/mol). Although the differences in activation parameters between **2** and **3** are reasonably attributed to a change from a tertiary to a primary hydroxy grouping, the interpretation is complicated by the inability to assess the mechanistic details. Isotope studies indicate that the $N D_I$-($^-$O-3) reaction of ethylene chlorohydrin is a two-step process with an acid–base preequilibrium, while the $N D_I$-($^-$O-5) reaction of 4-chloro-1-butanol is a concerted process.[6a] The present $N D_I$-($^-$O-4) reaction occupies an intermediate position between these two studied examples. A larger positive contribution to $\Delta H^{\ddagger}$ from the possible preequilibrium may occur for **3** as compared to **2**, since tertiary alcohols are weaker acids than primary alcohols in protic solvents.[6d] However, a similar ordering of $\Delta H^{\ddagger}$ values for **2** and **3** would also be expected with the concerted reaction. Another possibility exists, namely that a change from a two-step to a concerted mechanism occurs. Indeed, the $\Delta S^{\ddagger}$ value for **2** (−4.4 eu) is considerably more positive than the values for **1** (−10.2 eu) or **3** (−13.3 eu). The $\Delta S^{\ddagger}$ term for the basic aqueous reaction of ethylene chlorohydrin (10 eu) is significantly more positive than the corresponding term for the basic reaction of 4-chloro-1-butanol (−5 eu).[4n] This may suggest that **2**, with a tertiary hydroxyl group, proceeds *via* the two-step mechanism, while **1** and **3**, with primary hydroxyl groups, follow the concerted mechanism.

Capon[5a] previously compared the rates of ring closure for a series of ω-hydroxyalkyl chlorides in aqueous sodium hydroxide at 30°, but 3-chloro-1-propanol (**1**) was missing from the series. Our activation parameters for the ring-closure reaction of **1** allow comparison of an extrapolated value in 40% aqueous methanol with this series. A previous study[4j] of the effect of solvent on the rate of ring closure for the basic reaction of ethylene chlorohydrin showed that the rate was approximately doubled in proceeding from water to 40.9 wt % ethanol at 30°. With this correction, the comparison of ring-closure reactions is given in Table VII. The k_{rel}^{cor}

TABLE VII

EFFECT OF RING SIZE ON THE $N D_I$ REACTION FOR A SERIES OF CHLOROHYDRINS IN AQUEOUS SODIUM HYDROXIDE AT 30°

Chlorohydrin	n in $N D_I$-($^-$O-n)	$10^3 k_r$, mol^{-1} sec^{-1}	k_{rel}^{uncor}	$k_{rel}^{cor\,a}$
$Cl(CH_2)_2OH^b$	3	2.16	4300	2000
$Cl(CH_2)_3OH$ (1)	4	$5 \times 10^{-4\,c}$	≡1	≡1
$Cl(CH_2)_4OH^b$	5	2.86	5700	(5700)[d]
$Cl(CH_2)_5OH^b$	6	$10^{-2\,e}$	20	20

[a] Corrected by comparison to the corresponding alcohol where Cl is replaced by CH_3 in each case. [b] From ref 5a, data of Capon and Farazmand, and from ref 4n. [c] Extrapolated value at 30° in 40% aqueous methanol is 9×10^{-4} l. mol^{-1} sec^{-1} and this is corrected to 5×10^{-4} l. mol^{-1} sec^{-1} in H_2O (see text). [d] Uncorrected, since 4-chloro-1-butanol is reported to undergo ring closure by a concerted process.[6a] The k_{rel}^{cor} value, assuming a two-step mechanism, is 4700. [e] Extrapolated.

(13) (a) C. Moureu and G. Barrett, *Bull. Soc. Chim. Fr.*, **29**, 994 (1921); (b) G. M. Bennett and W. G. Philip, *J. Chem. Soc.*, 1937 (1928); (c) F. Covaert and M. Beyaert, *Natuurwetensch. Tijdschr.*, **22**, 78 (1940); (d) R. Lespieau, *Bull. Soc. Chim. Fr.*, **7**, 254 (1940); (e) D. C. Dittmer, W. R. Hertler, and H. Winicov, *J. Amer. Chem. Soc.*, **79**, 4431 (1957).

(14) For a general review, see C. A. Grab and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, **6**, 1 (1967).

(15) (a) R. M. Beesley, C. K. Ingold, and J. F. Thorpe, *J. Chem. Soc.*, **107**, 1080 (1915). (b) See ref 8c for a discussion of the Thorpe–Ingold effect in basic decomposition of 1,3-halohydrins.

(16) The Thorpe–Ingold effect is a potential energy factor and the rate (or $\Delta G^{\ddagger}$) argument presumes that potential energy is represented by $\Delta G^{\ddagger}$. See (a) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 665; (b) C. D. Ritchie and W. F. Sager, "Progress in Physical Organic Chemistry," S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, Jr., Ed., Vol. 2, Interscience, New York, N. Y., 1964, p 378.

values are obtained by assuming a two-step mechanism and correcting the equilibrium constant associated with alkoxide ion formation for polar effects. For each ω-hydroxyalkyl chloride, a new equilibrium constant is calculated, where chlorine is replaced by methyl, with the aid of the Taft equation[17] and Ballinger and Long's value of $\rho^* = 1.42$[18] for the pK_a of alcohols. Although a change from a two-step to a concerted mechanism may occur in the series,[6a] the trend in the k_{rel}^{cor} may not be greatly altered. Thus, the magnitude of the neighboring group reaction with ethylene chlorohydrin is not simply due to the increased acidity of the hydroxy group, which results from the proximity of the electronegative chlorine atom.[5a] With regard to the relative rate of ring closure/substitution for the reference compound 1, Table VI may be consulted. Substitution is favored over ring closure, and the relative value is $k_r/k_N = 0.179$ ($= 0.444 \times 10^{-4}/2.48 \times 10^{-4}$) at 75°, where $k_N = k_{N_m} + k_{N_h}$.

Experimental Section[19]

Materials.—The aqueous methanol solvent was prepared as volume/volume per cent at 25° or by weight corresponding to the volumes. Methanol (ACS, reagent) was purified by refluxing over magnesium turnings with a catalytic amount of iodine followed by distillation.[20] Anhydrous sodium perchlorate was prepared from the hydrated salt by drying under vacuum at 110° for 48 hr. Oxetane (4) (Aldrich) was distilled from potassium hydroxide pellets and the heart-cut was collected (bp 47–48°, lit.[13c] 47–48°). 3-Chloro-1-propanol (1) [Matheson Coleman and Bell (MCB)] was distilled and a heart-cut was collected: bp 159.0–159.5° (lit.[21] 165°); ir (CCl_4) 3630, 3330, 2960–2882 cm^{-1}. Nmr (CCl_4) follows: CCH_2C, 1.97, 5, 2.0; $ClCH_2$ and $HOCH_2$, 3.71, m, 4.1; OH, 4.26, s, 1.1. 1,3-Propanediol (7) was fractionally distilled on an annular Teflor spinning-band column (Nester and Faust Co.): heart-cut bp 98–99° (6 mm) (lit.[22a] 214°); $n^{23.5}$D 1.4390 (lit.[22b] n^{20}D 1.4389). Allyl alcohol (MCB) was distilled, heart-cut bp 97–98° (lit.[23] 97.2°). 2-Methyl-3-buten-2-ol (Aldrich) was used without further purification.

4-Chloro-2-methyl-2-butanol (2).—The preparation was the same as that reported previously.[13b] The chlorohydrin was obtained in 72% yield from ethyl 3-chloropropionate (Aldrich) and methylmagnesium iodide, bp 66–67° (14 mm) [lit.[13b] 72° (13 mm)]. The ir (CCl_4) showed the following significant absorptions: 3612, 3485, 2880–2972 cm^{-1}. The nmr (CCl_4) consisted of the following absorptions: $(CH_3)_2$, 1.20, s, 5.8; CH_2CH_2Cl, 1.89, t (J = 8 cps), 1.7; CH_2CH_2Cl, 3.57, t (J = 8 cps), 2.0; and OH, 2.48, s, 1.0. Glc shows only one significant component (>99.9% pure). The molecular ion (M) of 2 was not observed in the mass spectrum, but the following significant fragments were detected and they are given with relative abundance: (M − CH_3) m/e 109, 107 (7.90%/23.6% = 0.33); (M − CH_2CH_2Cl) 59 (100%).

3-Chloro-2,2-dimethyl-1-propanol (3).—The method of preparation of 3 was adapted from a procedure for the preparation of pentaerythrityl trichloride.[24] To 25.8 g (0.248 mol) of 2,2-dimethyl-1,3-propanediol (MCB, practical grade) and 17.8 g (0.225 mol) of pyridine, 26.8 g (0.226 mol) of thionyl chloride was added as quickly as possible commensurate with the exothermic reaction. The reaction mixture was allowed to reflux for 135 min and then allowed to stand overnight at room temperature. Ether (200 ml) was added and the organic phase was washed with 6 N hydrochloric acid and then dried over magnesium sulfate. Rotary evaporation of the ether gave 28.68 g of a dark oil which was distilled. The forerun [0.63 g, bp 24–83° (30 mm)] was discarded and the heart-cut [18.62 g, bp 83–86° (30 mm), 86% 3 by glc, 58% yield based on thionyl chloride] was collected. Fractional distillation improved the purity of 3, but column chromatography proved to be the most successful method to obtain high purity 3 in quantity. Chromatography was carried out on alumina (Merck acid washed, dried 1.5 hr at 110° in a vacuum oven) with a ratio of 8.5 g of alumina/1.0 g of crude 3. The column was progressively eluted with n-hexane, benzene, and then 85% benzene–15% methanol. Glc analyses showed that essentially pure (99.9% minimum) fractions of 3 were obtained after the initial n-hexane elution. The combined fractions of 3, after removal of solvent, were distilled through a 4 in. Vigreux column to give a low melting white solid (mp ~30°), bp 87° (35 mm). A 70% recovery of 3 was realized by this method. The ir (CS_2) of 3 showed the following absorptions: OH, 3620 and 3365 cm^{-1}; CH, 2960, 2872 cm^{-1}; CCl, 721 cm^{-1}. The nmr (CS_2) spectrum of 3 showed $(CH_3)_2$, 1.01, s, 6; CH_2Cl and CH_2OH, 3.46, two singlets partially resolved, 4; OH, 3.82, s (broad), 1.1.

Anal. Calcd for $C_5H_{11}OCl$: C, 48.99; H, 9.05; Cl, 28.91. Found: C, 48.62; H, 8.72; Cl, 28.78.

3-Methoxy-1-propanol (6).—A previously reported method[25] was used to prepare 6 in 44% yield. The product, obtained by fractional distillation on an annular spinning-band column, bp 144–145° (lit.[25] 148–149°), gave an ir (CCl_4) spectrum with absorptions at 3630 and 3475 cm^{-1}. The nmr ($CDCl_3$) spectrum showed the following: $CH_2CH_2CH_2$, 1.87, sextuplet (J = 6 cps), 2.0; OH, 2.83, s, 1.35; OCH_3, 3.36, s, 2.95; CH_2OCH_3, 3.66, triplet (J = 6 cps), 2.0; CH_2OH, 3.73, triplet (J = 6 cps), 2.0.

2,2-Dimethyloxethane (8).[26]—The method of Bennett and Philip[13b] was used to prepare 8 in quantitative yield, bp 70–71° (lit.[13b] 71°) from 2 and sodium hydroxide pellets. The nmr (CCl_4) spectrum showed $(CH_3)_2$, 1.27, s, 6.0; 3-CH_2, 2.26, triplet (J = 8 cps), 2.0; and 4-CH_2, 4.25, triplet (J = 8 cps), 2.0.

4-Methoxy-2-methyl-2-butanol (10).—A mixture of 2.45 g (20.0 mmol) of 2, 1.19 g (22.0 mmol) of sodium methoxide (MCB), and 8 ml of anhydrous methanol was allowed to reflux for 20 hr under anhydrous conditions. The mixture was then filtered, the precipitate of sodium chloride was washed with anhydrous ether, and the filtrate was distilled. The forerun was discarded and a cut was collected at 147–148° (lit.[28] 144°), which corresponded to 0.469 g of 10 (20% yield). The nmr (CCl_4) spectrum of 10 showed $(CH_3)_2$, 1.17, s, 5.9; $CH_2CH_2OCH_3$, 1.68, triplet (J = 6 cps), 2.0; OH, 2.93, s, 1.1; OCH_3, 3.30, s, 2.9; and $CH_2CH_2OCH_3$, 3.54, triplet (J = 6 cps), 1.9.

3,3-Dimethyloxethane (11).[26]—A previously reported method[29] was used to prepare 11 in 4% yield from 2,2-dimethyl-1,3-propanediol (MCB, practial grade) and concentrated sulfuric acid, bp 78–80° (lit.[29] 79.2–80.3°). Glc analysis indicated that the product was 96% pure. The nmr (CCl_4) spectrum gave the following absorptions: $(CH_3)_2$, 1.18, s, 6.0 and CH_2, 4.16, s, 4.0.

Product Analysis.—Condensable products were analyzed by glc using the internal standard method[9] with comparison to a known mixture of the components and the internal standard. Low boiling products from 1 and base were analyzed with a 5 ft × $^1/_8$ in. Porapak Q column at 110° (flow 25 ml/min) and the high boiling components were analyzed on the same column at 165° with *tert*-butyl alcohol as the internal standard. Products from 2 and base were analyzed on a 10 ft × $^1/_8$ in. 15% DIDP on Variport column at 80° (flow 25 ml/min). A 20 ft × $^1/_8$ in. 20% XF-1150 on firebrick column at 86° (flow 15 ml/min) was

(17) Reference 16a, Chapter 13.

(18) P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, **82**, 795 (1960).

(19) All melting points are corrected and boiling points are uncorrected. Nuclear magnetic resonance (nmr) spectra were obtained with a Varian A-60 spectrometer. Chemical shifts are expressed in parts per million (ppm) relative to the internal tetramethylsilane standard as 0 ppm (δ scale). The nmr absorptions are given as ppm, coupling, relative area. Infrared (ir) spectra were determined with a Perkin-Elmer 621 or 337 spectrometer and mass spectra were obtained with a Hitachi RMU-6E instrument. Gas-liquid chromatography (glc) analyses were performed on Varian-Aerograph 1520 and Hy-Fi III instruments. Elemental analyses were performed by C. F. Geiger, Ontario, Calif., or by R. Steed of these laboratories.

(20) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath, Boston, Mass., 1941, p 359.

(21) C. W. Gayler and H. M. Waddle, *J. Amer. Chem. Soc.*, **63**, 3359 (1941).

(22) (a) H. J. Bernstein, *ibid.*, **74**, 2674 (1952); (b) A. F. Gallagher and H. Hibbert, *ibid.*, **58**, 813 (1936).

(23) M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky, E. A. Smith, and W. E. Vaughan, *ibid.*, **60**, 440 (1938).

(24) A. Mooradian and J. B. Cloke, *ibid.*, **67**, 942 (1945).

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

(26) The numbering system of oxetanes is not uniform. The "Ring Index" system is used here, where oxygen is given the number one.[27]

(27) A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index," American Chemical Society Publication, 1960, p 6.

(28) F. Straus and W. Thiel, *Justus Liebigs Ann. Chem.*, **525**, 151 (1936).

(29) L. F. Schmoyer and L. C. Case, *Nature*, **183**, 389 (1959).

used to analyze the products from the reaction of **3** with base. The internal standard for the product analyses, resulting from **2** and **3**, was *n*-butyl alcohol.

Kinetic Method.—Sealed ampoules of the reaction mixture were periodically removed from a thermostated oil bath, quenched in ice-water, warmed to room temperature, shaken, and opened, and a 1.00-ml aliquot was transferred to a 125-ml erlenmeyer flask under a nitrogen atmosphere. The aliquots were titrated to the phenolphthalein end point with standardized hydrochloric acid. The data were processed with standard computer programs.

Registry No.—**2**, 1985-88-2; **3**, 13401-56-4; **6**, 1589-49-7; **8**, 6245-99-4; **10**, 27557-84-2; **11**, 6921-35-3.

Acknowledgment.—This investigation was supported by the Petroleum Research Fund, administered by the American Chemical Society, and by the U. S. Army Research Office (Durham). We thank Mr. R. Cuneo and Mr. W. Koskinen for their assistance.

Mass Spectral Fragmentation of Spiro Ketones and Olefins[1]

G. D. CHRISTIANSEN AND D. A. LIGHTNER*

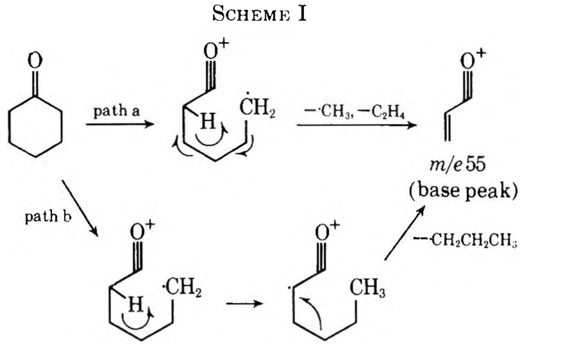
Contribution No. 2586 from the Department of Chemistry, University of California, Los Angeles, California 90024

Received August 31, 1970

The mass spectra of spiro ketones with varying ring size have been recorded. An unusual fragmentation resulting in the loss of an olefinic radical in a hydrogen-transfer mechanism was observed to be an important decomposition pathway. Deuterium labeling determined the site of the fragmentation to be the nonketone ring. However, in several cases the preferred path of fragmentation was loss of the ketone ring. High-resolution data (Table I) defined the exact composition of the principal fragment peaks. The mass spectra of seven spiro olefins were investigated, and their fragmentation behavior was interpreted in terms of the loss of a series of alkyl radicals correlated with ring size.

Spiro Ketones.—The mass spectra of spiro ketones are found to exhibit a behavior unlike that of simple cycloalkyl ketones such as cyclohexanone or cyclopentanone.[2] The mass spectrum of cyclohexanone, for example, contains significant peaks arising from α cleavage followed by further fragmentation. In particular, the base peak at *m/e* 55 (M − 43) for cyclohexanone arises *via* one or both of the pathways shown in Scheme I. A related scheme can be written for cyclopentanone in which the base peak is also *m/e* 55 (M − 29). It might therefore be expected that a similar mode of fragmentation should occur for the

SCHEME I



spiro ketones which contain a cyclohexanone or a cyclopentanone ring. However, the prominent M − 43 ion (*m/e* 55) from cyclohexanone is extremely weak (*m/e* 123) in the mass spectrum of spiro[5.5]undecan-1-one (**1**) (Figure 1), whereas the M − 55 (*m/e* 111, $C_7H_{11}O$) peak, which is very small in cyclohexanone, is the base peak. Similarly, in the mass spectrum of spiro[4.5]decan-6-one (**2**) (Figure 2) *m/e* 111 ($C_7H_{11}O$) again appears as one of the two significant peaks (70% of the base peak at *m/e* 67, C_5H_7) but now corresponds to the loss of 41 amu. (See Table I.)

In order of establish the structure parameters required for the formation of the intense *m/e* 111 peak, two spiro ketones containing five-membered carbonyl-bearing rings were prepared and analyzed. The mass spectrum of spiro[4.5]decan-1-one (**3**) (Figure 3) exhibits an intense peak (70% of the base peak) corresponding to M − 55 (*m/e* 97, C_6H_9O), and spiro[4.4]nonan-1-one (**4**) (Figure 4) also shows a major peak (50% of the base peak) at *m/e* 97 (C_6H_9O), which corresponds to the loss of 41 amu. The origin of the neutral fragment from the *saturated ring* is consistent with a mass shift of 14 amu (*m/e* 97 going to *m/e* 111) when the carbonyl-bearing ring is increased from five (**3** or **4**) to six carbons (**1** or **2**). Moreover, this correlation is also consistent with the observation that the neutral fragment is 41 amu when the *saturated* ring is five-membered, but 55 amu when the saturated ring is six-membered.

To define more precisely the mechanism and ions involved, the α hydrogens of **2** and **4** were exchanged for deuterium by repeated equilibration with D_2O in the presence of base. In the mass spectra of 7,7-dideuteriospiro[4.5]decan-6-one (**5**) (Figure 5) and 2,2-dideuteriospiro[4.4]nonan-1-one (**6**) (Figure 6), *m/e* 111 and *m/e* 97 are shifted completely to *m/e* 113 and *m/e* 99, respectively. We conclude therefore that the neutral fragments under discussion in the foregoing come entirely from the saturated ring and presumably by similar mechanisms.

One pathway, which is consistent with the data above, for the decomposition leading to the *m/e* 97 or *m/e* 111 peaks is postulated in Scheme II. Thus, the molecular ion undergoes β cleavage at the spiro junction followed by transfer of a δ hydrogen[3] to the carbonyl and C–C bond cleavage with loss of an allylic radical (*m* = 1) or a homoallylic radical (*m* = 2). An alternative mechanism might be written in which the spiro carbon carries the positive charge and abstracts the hydrogen.

(1) We are indebted to the National Science Foundation for financial aid (Grants No. GP-9533 and GP-7193).

(2) For leading references, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967. Chapter 3.

(3) S. D. Sample, D. A. Lightner, O. Buchardt, and C. Djerassi, *J. Org. Chem.*, **32**, 997 (1967).

TABLE I

HIGH RESOLUTION (1:12,500) MASS MEASUREMENTS OF THE PRINCIPAL FRAGMENT PEAKS OF SPIRO KETONES

Name	m/e	Composition	Multiplet ratio	Obsd mass	Calcd mass
Spiro[5.5]undecan-1-one (1)	111	$C_7H_{11}O$		111.08107	111.08099
	109	C_8H_{13}	9	109.1021	109.10172
	109	C_7H_9O	10	109.06574	109.06534
	98	$C_6H_{10}O$		98.07499	98.07316
	95	C_7H_{11}	1	95.08584	95.08607
	95	C_6H_7O	10	95.04910	95.04969
	81	C_6H_9		81.06999	81.07042
	69	C_5H_9		69.07041	69.07042
Spiro[4.5]decan-6-one (2)	111	$C_7H_{11}O$		111.08085	111.08099
	109	C_8H_{13}	1	109.10207	109.10172
	109	C_7H_9O	5	109.06499	109.06534
	95	C_7H_{11}	5	95.08537	95.08607
	95	C_6H_7O	1	95.04882	95.04969
	81	C_6H_9		81.06999	81.07042
	67	C_5H_7		67.05478	67.05477
Spiro[4.5]decan-1-one (3)	97	C_6H_9O		97.06581	97.06534
	84	C_5H_8O		84.0580	84.05751
	81	C_6H_9		81.07027	81.07042
	79	C_6H_7		79.05457	79.05477
	68	C_5H_8		68.06262	68.06260
	67	C_5H_7		67.05478	67.05477
Spiro[4.4]nonan-1-one (4)	97	C_6H_9O		97.06609	97.06534
	95	C_6H_7O	10	95.04966	95.04969
	95	C_7H_{11}	7	95.08398	95.08607
	94	C_7H_{10}		94.07805	94.07825
	67	C_5H_7		67.05479	67.05477
Spiro[5.6]dodecan-7-one (7)	162	$C_{12}H_{18}$		162.14058	162.14084
	125	$C_8H_{13}O$		125.09660	125.09664
	109	C_8H_{13}		109.10173	109.10172
	96	C_7H_{12}		96.09376	96.09390
	81	C_6H_9		81.07034	81.07042
	79	C_6H_7		79.05450	79.05477
	67	C_5H_7		67.05478	67.05477
Spiro[3.4]octan-5-one (8)	96	C_6H_8O		96.05754	96.05751
	68	C_5H_6		68.06254	68.06260
	67	C_5H_7		67.05478	67.05477
Spiro[2.4]heptan-4-one (9)	68	C_5H_8		68.06261	68.06260
	67	C_5H_7		67.05484	67.05477
	54	C_4H_6		54.04714	54.04695

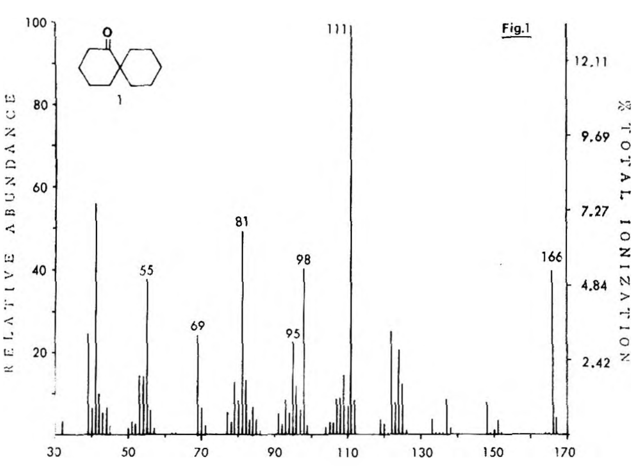


Figure 1.—Mass spectrum of spiro[5.5]undecan-1-one, 70 eV.

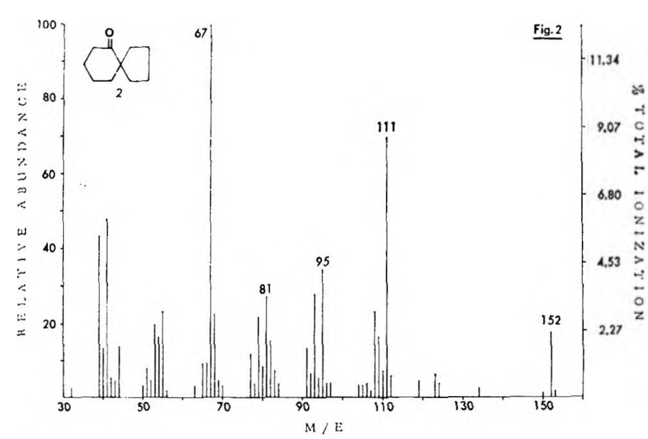
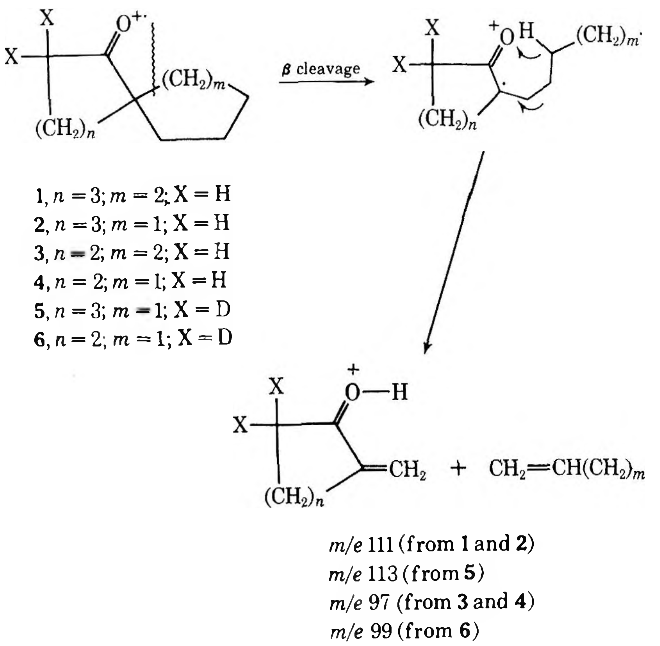


Figure 2.—Mass spectrum of spiro[4.5]decan-6-one, 70 eV.

The generality of this mechanism was examined for spiro ketones containing rings which varied in size from cyclopropane to cycloheptane. As the size of the ketone ring increases, the mass spectrum becomes somewhat more complex, *e.g.*, spiro[5.6]dodecan-7-one (**7**) (Figure 7). However, the prominent (M − 55) fragmentation of the five- (**3**) and six- (**1**) membered ring ketones is found to be a major contributor to the mass spectrum (*cf.* *m/e* 125) of the seven-membered ring ketone (**7**). The effect of decreasing the size of the *hydrocarbon* ring may be seen in the mass spectra of spiro[3.4]octan-5-one (**8**) (Figure 8) and spiro[2.4]-heptan-4-one (**9**) (Figure 9). Spiro[3.4]octan-5-one (**8**) gives only an extremely weak peak at *m/e* 97. The mechanism of Scheme II is unlikely to contribute

SCHEME II



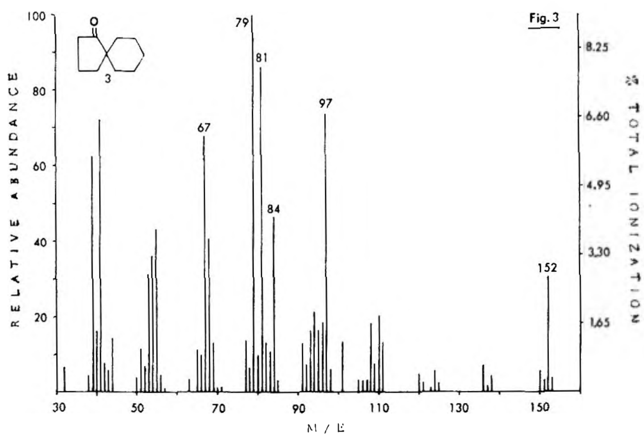


Figure 3.—Mass spectrum of spiro[4.5]decan-1-one, 70 eV.

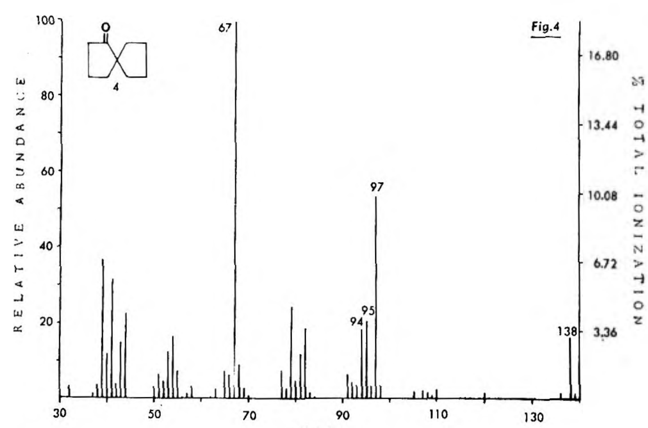


Figure 4.—Mass spectrum of spiro[4.4]nonan-1-one, 70 eV.

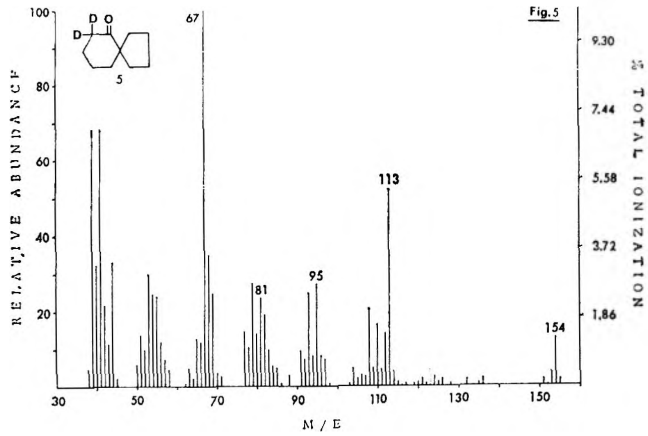


Figure 5.—Mass spectrum of 7,7-dideuteriospiro[4.5]decan-6-one, 70 eV.

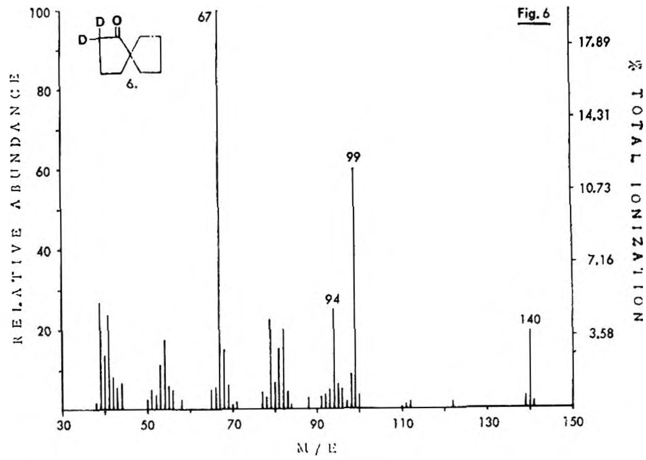


Figure 6.—Mass spectrum of 2,2-dideuteriospiro[4.4]nonan-1-one, 70 eV.

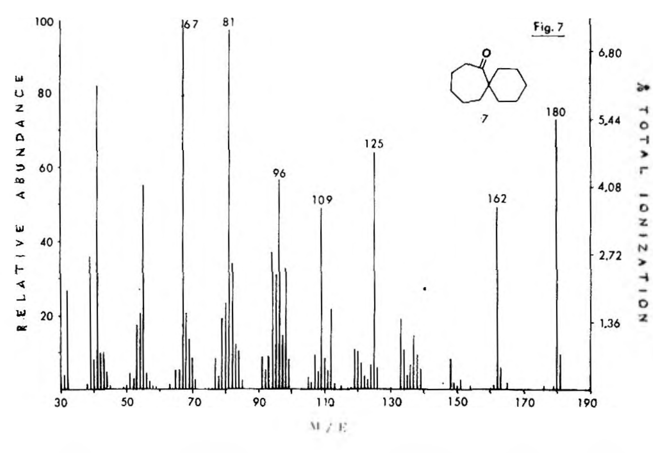


Figure 7.—Mass spectrum of spiro[5.6]dodecan-7-one, 70 eV.

greatly in the mass spectrum of **8** for such a mechanism in this instance requires the expulsion of a vinylic and not an allylic or homoallylic radical and is presumably a higher energy pathway than that in **3** or **4**. Spirocyclopropyl ketone **9** can provide no δ hydrogen for the mechanism of Scheme II. However, the mechanism can be successfully invoked to explain the base peak (*m/e* 97) in the spectrum of spiro[4.4]-nona-1,6-dione (**10**) (Figure 10). For this compound the structure of the fragment expelled is $CH_2=CHC{\equiv}O$.

The mass spectra of the various spiro ketones also display several other intense peaks. An ion at *m/e* 67 appears as a major contributor to the total ion current (in some cases, the base peak) in the spectra of **2**, **4**, **5**, and **6**, all of which contain a five-membered saturated ring. The homologous ion at *m/e* 81 appears in the spectra of **1**, **3**, and **7**, all of which contain a six-membered saturated ring. It may be noted, however,

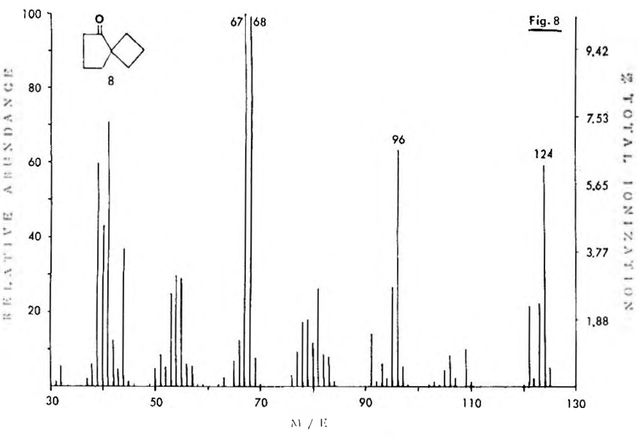


Figure 8.—Mass spectrum of spiro[3.4]octane-5-one, 70 eV.

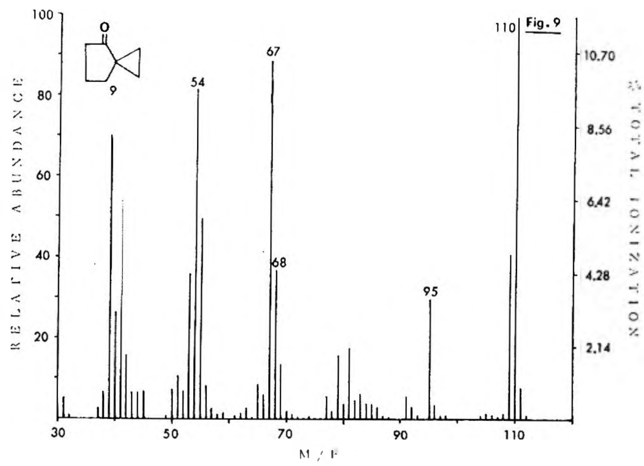


Figure 9.—Mass spectrum of spiro[2.4]heptane-4-one, 70 eV.

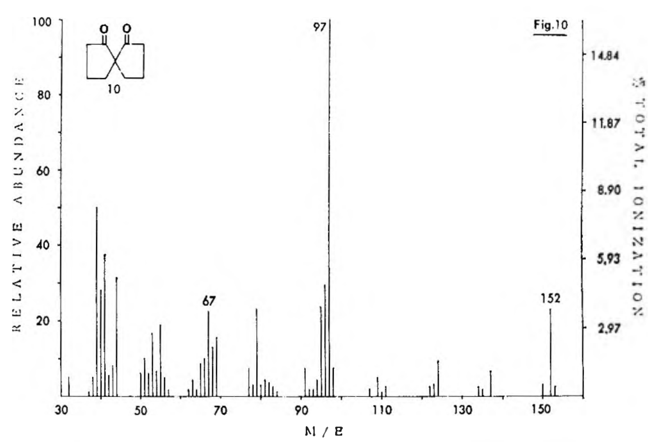
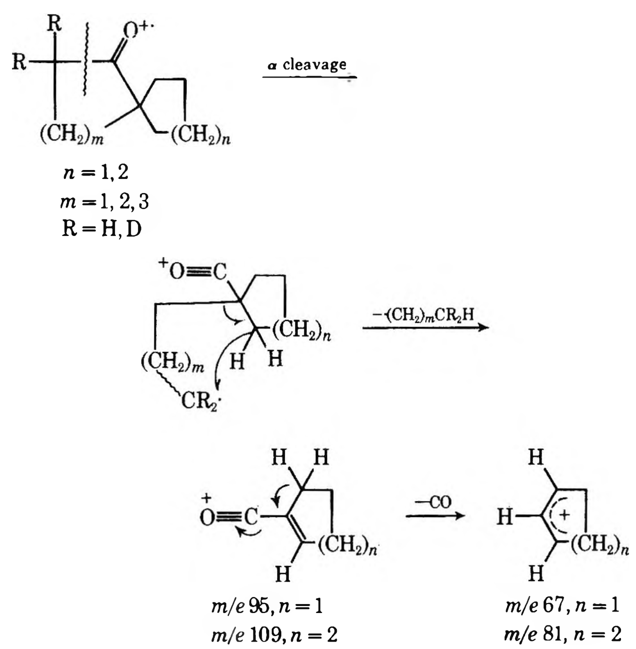


Figure 10.—Mass spectrum of spiro[4.4]nona-1,6-dione, 70 eV.

that m/e 67 as well as m/e 81 appears in the mass spectra of **1** and **7**. The fragment of m/e 67 is assigned $C_5H_7^+$ and that at m/e 81 is assigned $C_6H_9^+$ by high resolution measurements (see Table I). Based on the fact that the peak remains at m/e 67 when **2** and **4** are deuterated α to the carbonyl group, it is assumed that the fragment originated from the saturated ring.

A mechanisms is suggested in Scheme III which

Scheme III

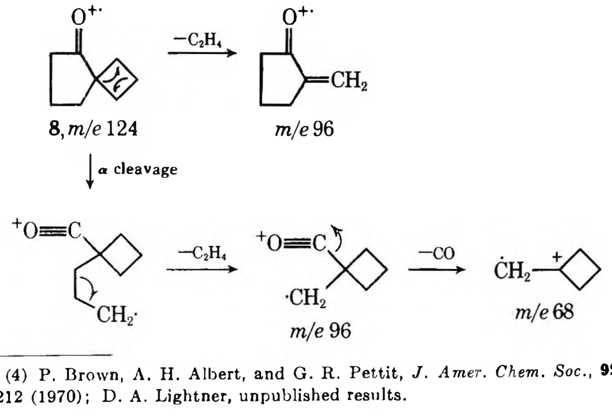


explains the origin of both the m/e 67 and m/e 81 fragments and involves α cleavage of the parent ion followed by hydrogen abstraction from the saturated ring and loss of an alkyl radical. The ion that is formed at this stage is observed at m/e 95 or 109 (Table I) in the mass spectrum, albeit to a small extent (*ca.* 20% of the base peak). The next step is shown as a concerted 1,2-hydrogen shift with loss of carbon monoxide to leave an allylic carbonium ion (m/e 67 or 81). Unfortunately, the paucity of metastable ions in all the mass spectra of our spiro ketones precludes the customary method of confirming the mechanism in this instance.

The mechanism shown in Scheme III is consistent with the observation that per cent ionization at m/e 67 in **4** (18.5%) is greater than that at m/e 81 in **2** (12.5%). In **4** the ketone-containing ring is five membered and, in its opened form following α cleavage, the cyclic transition state for hydrogen abstraction is a six-membered ring. In **2**, however, the hydrogen abstraction step involves a less favorable seven-membered transition state.[4]

The more strained spiro ketones **8** and **9** [as well as the seven-membered ring ketone (**7**)] display a unique behavior. The mass spectrum of spiro[3.4]-octan-5-one (**8**) exhibits two major contributors to the total ion current at m/e 68 (C_5H_8) and m/e 96 (C_6H_8O) which do not appear to any large extent in the spectra of the other spiro ketones. The peak at m/e 96 is readily interpreted (Scheme IV) as the

Scheme IV



(4) P. Brown, A. H. Albert, and G. R. Pettit, *J. Amer. Chem. Soc.*, **92**, 3212 (1970); D. A. Lightner, unpublished results.

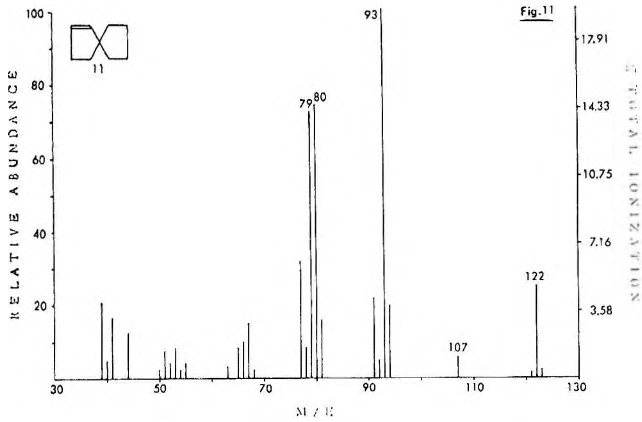


Figure 11.—Mass spectrum of spiro[4.4]non-1-ene, 70 eV.

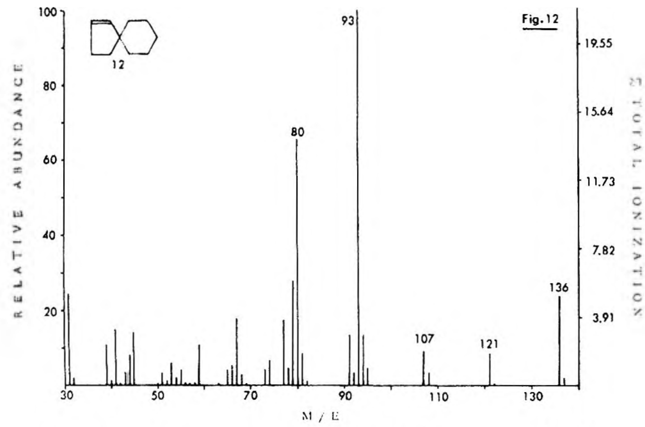
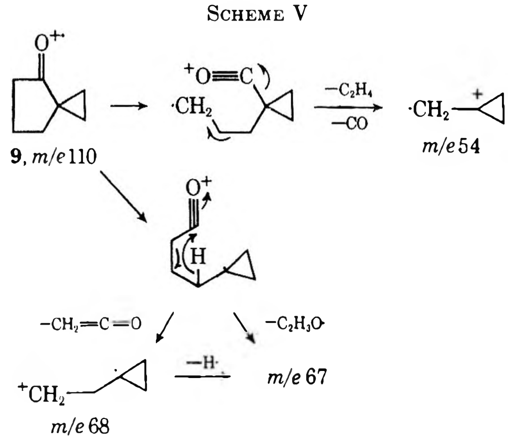


Figure 12.—Mass spectrum of spiro[4.5]dec-1-ene, 70 eV.

expulsion of ethylene, a common decomposition route for cyclobutane rings.[2,5] An alternative pathway to m/e 96 involves α cleavage followed by the loss of ethylene from the five-membered ring. Subsequent expulsion of carbon monoxide from this ion leads to m/e 68. Again, the absence of metastable ions in the mass spectrum of **8** renders the correlation between m/e 96 and 68 tenuous.

Spiro[2.4]heptan-4-one (**9**) (Figure 9) exhibits a peak at m/e 67 of the same composition (C_5H_7) as that of the m/e peaks found in the spectra of the less highly strained spiro ketones (Scheme III). A rational pathway leading to the m/e 67 fragment is shown in Scheme V. Here α cleavage occurs followed by loss of ketene

SCHEME V



(5) "Catalog of Mass Spectral Data," American Petroleum Institute, Research Project 44, Carnegie Institute of Technology, Pittsburgh, Pa., spectrum no. 416.

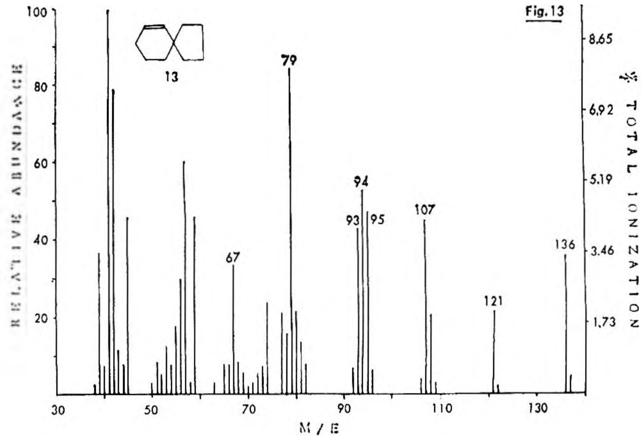


Figure 13.—Mass spectrum of spiro[4.5]dec-6-ene, 70 eV.

leads to m/e 68 (C_5H_8) which may in turn lose a hydrogen atom. Alternatively, the concerted loss of C_2H_3O *via* hydrogen transfer may account for m/e 67 directly. Another important contributor is the ion at m/e 54 whose occurrence might be explained by α cleavage followed by loss of ethylene and carbon monoxide.

Spiro[5.6]dodecan-7-one (**7**) (Figure 7) shows a moderately intense fragment ion at m/e 162 (loss of H_2O). The loss of H_2O is found to a smaller extent in the mass spectra of **1** and **2** and is extremely weak or absent in the other ketones presented here. Moreover, the (M − 18) fragmentation is much stronger in the mass spectrum of **7** than that of cycloheptanone.[6] The fragment ion at m/e 96 might arise by loss of five carbons of the ketone ring, including the carbonyl group, in a manner akin to the formation of m/e 68 from **8** (see Scheme IV). Subsequent losses of hydrogen atoms would lead to m/e 95 and 94.

Spiro Olefins.—The mass spectra of spiro olefins exhibited a behavior typical of cyclic alkenes.[7] Two general types of spiro olefins were studied and included olefins containing an exocyclic methylene group and those containing an endocyclic double bond. The *exo*-methylene olefins were prepared in a Wittig reaction from the corresponding ketones and the methylene triphenylphosphine.[8] The endocyclic olefins were prepared by decomposition of the tosylhydrazones of the corresponding ketones with methyllithium.[9] Where the carbon–carbon double bond is in a five-membered ring, as in spiro[4.4]non-1-ene (**11**) and spiro[4.5]dec-1-ene (**12**), the mass spectra are relatively uncomplicated by large numbers of fragmentation peaks (see Figures 11 and 12). The origin of the major fragment peaks, m/e 93, 80, and 79, is interpreted in Scheme VI, which also accounts for the homologous fragment ions (m/e 107, 94, and 93) in the mass spectra (see Figures 13 and 14) of spiro[4.5]dec-6-ene (**13**) and spiro[5.5]undec-1-ene (**14**). Thus, initial allylic cleavage followed by a second carbon–carbon cleavage, route a, yields m/e 80 (or 94), whereas the alternative second step involving a hydrogen transfer, route b, yields

(6) R. T. Aplin, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 3180 (1965).

(7) See ref 2, Chapter 1.

(8) R. Greenwald, M. Chaykowsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(9) W. G. Dauben, M. E. Lorber, N. D. Vietmeyer, R. H. Shapiro, J. H. Duncan, and K. Tomer, *J. Amer. Chem. Soc.*, **90**, 4762 (1968).

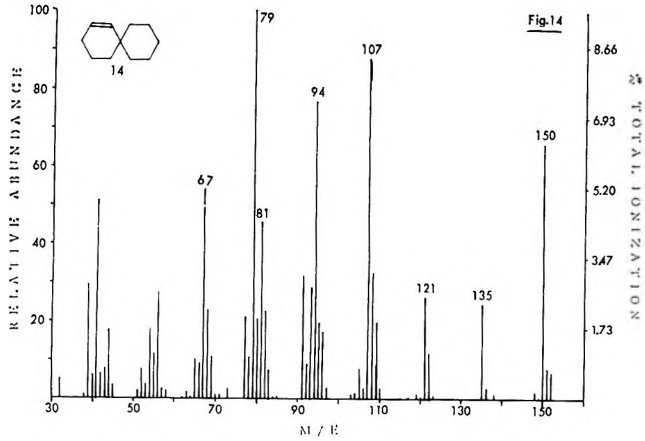


Figure 14.—Mass spectrum of spiro[5.5]undec-1-ene, 70 eV.

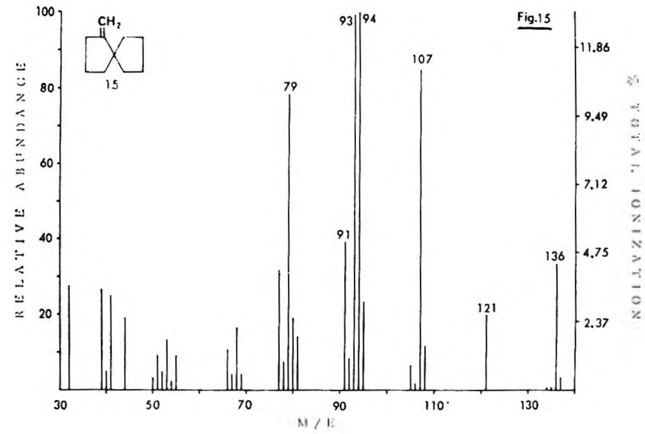
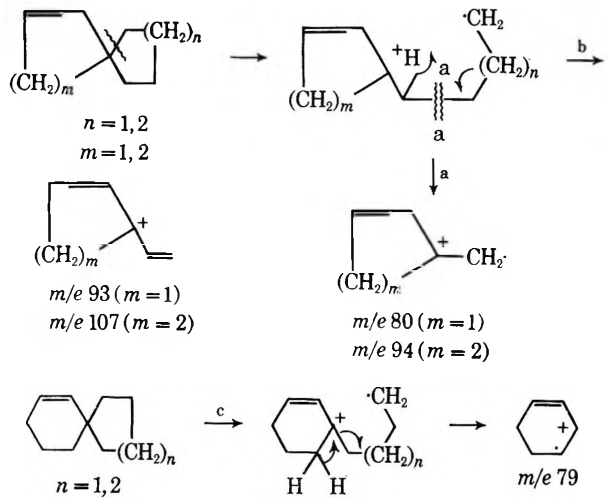


Figure 15.—Mass spectrum of 1-methylenospiro[4.4]nonane, 70 eV.

SCHEME VI



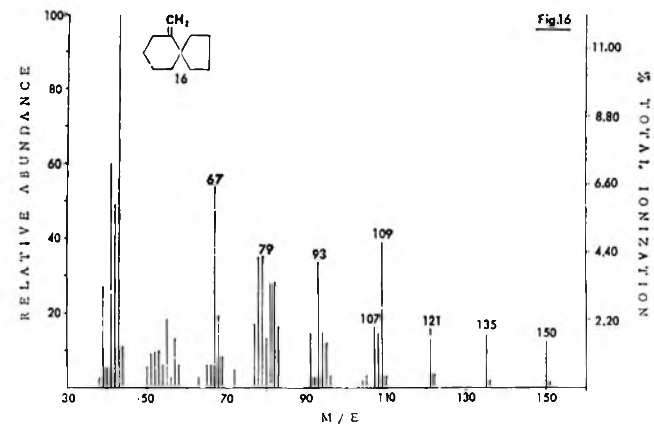


Figure 16.—Mass spectrum of 6-methylenopsiro[4·5]decane, 70 eV.

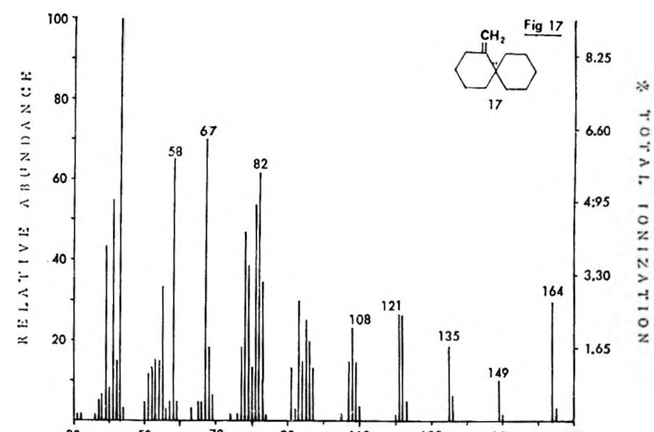


Figure 17.—Mass spectrum of 1-methylenospiro[5·5]undecane, 70 eV.

m/e 93 (or 107). The fragment ions *m/e* 80 and 94 mentioned above may lose a hydrogen atom to give observed ions at *m/e* 79 and 93, respectively. The large *m/e* 79 peak in the cyclohexene spectra (Figures 13 and 14) may be accounted for by route c of Scheme VI. Both cyclohexene derivatives show very weak retro-Diels–Alder fragment ions at *m/e* 108 (from **13**) and 122 (from **14**).

The *exo*-methylene spiro olefins (**15**–**17**) display fragment peaks (see Figures 15–17) at similar *m/e* to the endocyclic olefins (Figures 11–14). The higher mass fragment peaks in the spectra of the exocyclic olefins appear to arise by the loss of a series of alkyl radicals, such as $\cdot CH_3$, $\cdot CH_2CH_3$, $\cdot CH_2CH_2CH_3$, etc. The origin of these alkyl fragments is not well defined and can be postulated to originate from either ring. However, as shown in Scheme VI, one of the most favorable cleavages would be allylic bond breaking at the spiro center. This cleavage could be followed by a hydrogen abstraction from one of several sites and further decomposition would result in ions corresponding to the loss of alkyl radicals. The same general mechanisms shown in Scheme VI might apply also with the exocyclic olefins, and in fact leads to the observed major fragment ions in the high mass region.

In summary, the π-electron groups in both the spiro ketones and spiro olefins serve to direct fragmentation. The ketone fragmentations are unusual, and in one instance a seven-membered cyclic transition state is implicated for hydrogen transfer.

Experimental Section[10]

Synthesis of the Spiro Ketones.—Spiro[2.4]heptan-4-one (9), bp 79–81° (50 mm) [lit.[11] 54–55° (14 mm), 160° (760 mm)], was

(10) All gas chromatographic sample purity checks were performed on a Carle Instruments basic gas chromatograph using a 5 ft, 1/8 in. diameter SE-30 column (10% on Chromosorb W). Nmr spectra were measured using a Varian A-60 instrument. All mass spectra were measured on an AEI MS-9 mass spectrometer by Miss E. Irwin. The inlet system and source temperatures were maintained at 180–200°. The ionizing energy was 70 eV and the ionizing current was 100 μA.

prepared in 34% yield from 2-(β-bromoethyl)cyclopentanone by the procedure described by Mayer and Schubert.[11] Spiro[3.4]-octan-5-one (8), bp 59–61° (12 mm) [lit.[12] 67–69° (18 mm)], was prepared in 23% yield from 2-(γ-bromopropyl)cyclopentanone, and spiro[4.5] decan-1-one (3), bp 120–130° (12 mm) [lit.[12] 105–106° (3 mm)], was prepared in 73% yield from 2-(ω-bromopentyl)cyclopentanone by the method of Mayer, Wenschuh, and Töpelmann.[12] Spiro[4.4]nonan-1-one (4), bp 96–97° (25 mm) [lit.[13] 90° (22 mm)], was prepared in 55% yield by the alkylation of 1-piperidone-1-cyclopentene with 1,4-dibromobutane by the method of Krieger, Ruotsalainen, and Montin.[13] Spiro[4.5]-decan-6-one (2), bp 94–99° (12 mm) [lit.[14] 120° (45 mm)], was prepared by the rearrangement of 1,1′-dihydroxybicyclopentyl in 57% yield by the method of Zelinski and Elagina.[14] Spiro-[5.5]undecan-1-one (1), bp 58–63° (0.3 mm) [lit.[15] 130–132° (25 mm)], was prepared by the alkylation of cyclohexanone with 1,5-dibromopentane in the presence of potassium *tert*-butoxide in 53% yield, and spiro[5.6]dodecan-7-one (7), bp 121–122° (12 mm) [lit.[15] 133–135° (18 mm)], was prepared in 50% yield by the rearrangement of 1,1′-dihydroxybicyclohexyl as described by Cristol, Jacquier, and Mousseron.[15] Spiro[4.4]nona-1,6-dione (10) was previously prepared by Cram and Steinberg.[16] The deuterated ketones were prepared as follows.

7,7-Dideuteriospiro[4.5]decan-6-one (5).—To a mixture of 10 ml of D_2O and 1.2 g of sodium methoxide was added 1.50 g (0.010 mol) of spiro[4.5]decan-6-one (2). The mixture was refluxed 3 hr and then cooled and extracted three times with ether. The ether extracts were combined, washed with D_2O, dried, and filtered. The ether was removed by distillation through a 6 in. Vigreux column and the residual ketone was treated as described four more times. Distillation of the product afforded 0.71 g (46% yield) of a colorless liquid which showed no α hydrogens in the nmr and was found to be 95% dideuterated and about 5% monodeuterated by mass spectrometric analysis.

2,2-Dideuteriospiro[4.4]nonan-1-one (6).—The deuteration of 2.40 g (0.0174 mol) of spiro[4.4]nonan-1-one (4) was accomplished by mixing the ketone with 10 ml of dioxane and 2.0 g of sodium methoxide and refluxing the mixture for 3 hr. The reaction mixture was cooled and extracted three times with ether. The ether extracts were combined and washed once with D_2O, dried with magnesium sulfate, and filtered, and the ether was removed by distillation through a 6 in. Vigreux column. This process was repeated three more times on the residual ketone. The deuterated ketone was vacuum distilled to give 0.907 g (37% yield) of product which showed no α hydrogen in the nmr spectrum and was found to be 88% dideuterated, 12% monodeuterated, and less than 1% nondeuterated by mass spectrometric analysis.

(11) R. Mayer and H. J. Schubert, *Chem. Ber.*, **91**, 768 (1958).
(12) R. Mayer, G. Wenschuh, and W. Töpelmann, *ibid.*, **91**, 1616 (1958).
(13) H. Krieger, H. Ruotsalainen, and J. Montin, *ibid.*, **99**, 3715 (1966).
(14) N. D. Zelinski and H. V. Elagina, *C. R. Acad. Sci., URSS*, **49**, 568 (1945); *Chem. Abstr.*, **40**, 6058 (1946).
(15) H. Cristol, R. Jacquier, and M. Mousseron, *Bull. Chim. Soc. Fr.*, 346 (1957).
(16) D. J. Cram and H. Steinberg, *J. Amer. Chem. Soc.*, **76**, 2753 (1954).

Synthesis of the Endocyclic Spiro Olefins.—These olefins were prepared by decomposing the tosylhydrazones of the corresponding spiro ketones by the method of Dauben, *et al.*[8] The olefins prepared in this manner were found to have identical physical properties with those prepared by Krapcho and Donn.[17] Those prepared for this study were spiro[4.4]non-1-ene (11), bp 139–143° (760 mm) (lit.[17] bath temperature 140°), spiro[4.5]dec-1-ene (12), bath temperature 200° [lit.[17] bp 177° (740 mm)], spiro[4.5]-dec-6-ene (13), bp 178–179° (760 mm) [lit.[17] bp 181° (740 mm)], and spiro[5.5]undec-1-ene (14), bath temperature 210° [lit.[17] bp 205–207° (740 mm)].

Synthesis of the *exo*-Methylene Spiro Olefins.—These olefins were prepared from the corresponding spiro ketones by the Corey modification[7] of the Wittig reaction.[18] A typical preparation follows.

6-Methylenospiro[4.5]decane (16).—To 25 ml of dry dimethyl sulfoxide (DMSO) was added 1.5 g of sodium hydride followed by 8.0 (0.0225 mol) of methyltripenylphosphonium bromide. This mixture was stirred at 50–55° for 1 hr before 3.04 g (0.020 mol) of spiro[4.5]decan-6-one (2) was added as a solution in 20 ml of DMSO. After the mixture had stirred at 55° overnight, it was added to 50 ml of water and extracted four times with pentane. The pentane extracts were combined, washed with 1:1 DMSO-water and saturated NaCl solution, and then dried and filtered. The pentane was removed by distillation. The residue was distilled in a Hickman distillation apparatus at a bath temperature of 200° to give 1.08 g (36% yield) of colorless liquid: infrared (neat, NaCl plates) 3.6 μ (s), 6.2 (m), and 7.0 (s); nmr (CCl_4 solution) δ 4.60 (singlet, olefinic protons), 2.16 (broad singlet, allylic protons), and 1.7–1.4 (broad multiplet, aliphatic protons) in the ratio 1:1:7. The vpc analysis on a 5 ft SE-30 column showed only one component.

Also prepared by this procedure were 1-methylenospiro[4.4]-nonane (15) [bp 162–165° (760 nm)] and 1-methylenospiro[5.5]-undecane (17) (bath temperature 250°).

Registry No.—1, 1781-83-5; 2, 13388-94-8; 3, 4728-91-0; 4, 14727-58-3; 5, 27723-38-2; 6, 27723-39-3; 7, 4728-90-9; 8, 10468-36-7; 9, 5771-32-4; 10, 27723-43-9; 11, 873-12-1; 12, 697-27-8; 13, 697-28-9; 14, 699-56-9; 15, 19144-06-0; 16, 19144-01-5; 17, 27723-50-8.

Acknowledgment.—The AEI mass spectrometer used in the measurements was purchased with funds made available from the National Science Foundation Grant GP-3672. The authors are grateful to Miss E. Irwin for determining the mass spectra and to the Campus Computing Network at UCLA for a generous gift of computer time.

(17) A. P. Krapcho and R. Donn, *J. Org. Chem.*, **30**, 641 (1965).
(18) G. Wittig and U. Schöllkopf, *Chem. Ber.*, **87**, 1318 (1954).

Medium-Ring 3-Carboxycycloalkanones. Synthesis and Keto–Enol Equilibria

JERRY A. HIRSCH*[1] AND FREDRIC J. CROSS

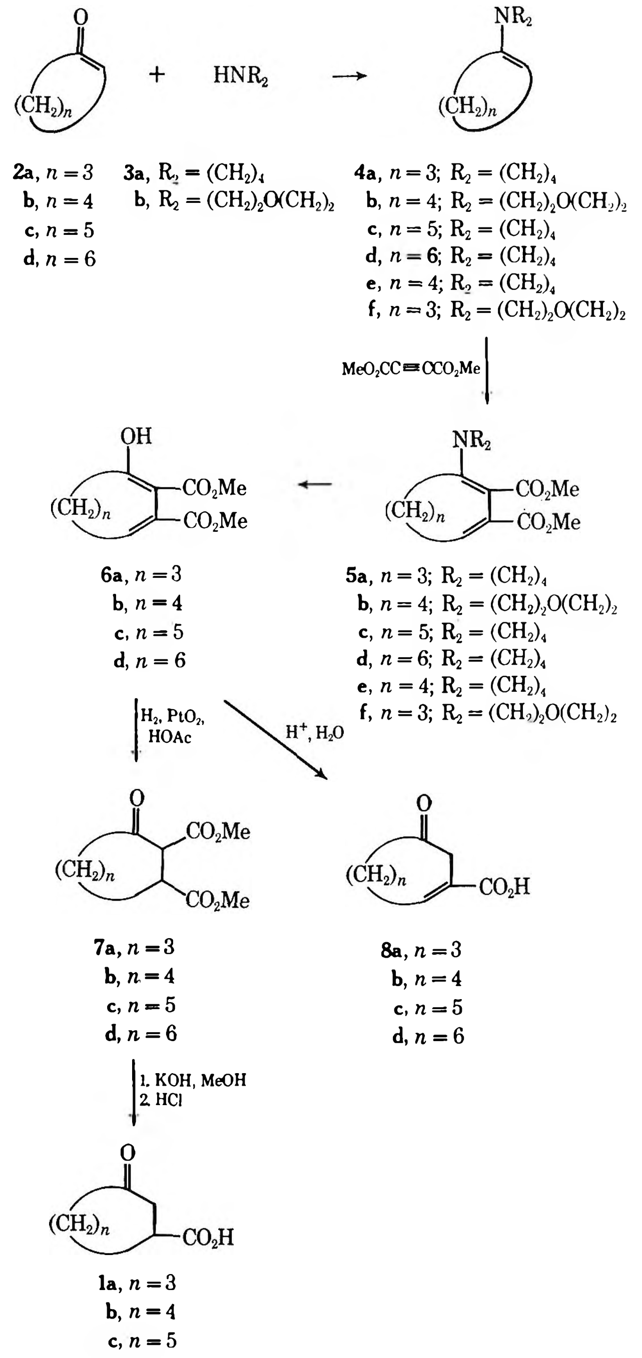
Department of Chemistry, Seton Hall University, South Orange, New Jersey 07079

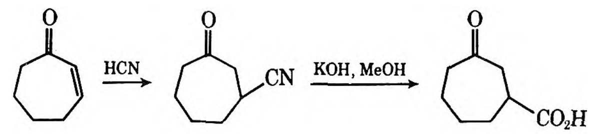
Received July 29, 1970

The title compounds with ring sizes seven to ten were prepared by several synthetic routes, exposing instances of reactivity extremely sensitive to ring size. Trends in enol content of the 3-carboxycycloalkanones and various unsaturated and 2,3-dicarboxycycloalkanone precursors are evaluated.

The 3-carboxycycloalkanones (**1a–d**) provide attractive synthetic precursors for a variety of medium-sized ring systems. Berchtold and Uhlig[2] have reported the preparation of 3-carboxycycloheptanone (**1a**) by two routes. The first route (Scheme I) was lengthier, but involved more readily available starting materials. The pyrrolidino or morpholino enamines of cyclopentanone (**4a** or **4f**) were treated with dimethyl acetylenedicarboxylate to effect expansion of the carbocyclic ring by two carbon atoms.[2-5] The resulting adducts, **5a** and **5f**, were hydrolyzed to dimethyl 7-hydroxy-2,7-cycloheptadiene-1,2-dicarboxylate (**6a**). Catalytic reduction with prereduced platinum oxide in glacial acetic acid to the saturated keto dicarboxylic ester **7a** was followed by saponification and acidic monodecarboxylation to 3-carboxycycloheptanone (**1a**). Alternatively, Berchtold and Uhlig[2] prepared the 3-carboxycycloheptanone by hydrolysis of 3-cyanocycloheptanone, the result of a Michael addition of hydrogen cyanide to 2-cycloheptenone. The products from the two routes exhibited identical infrared spectra.[2]

SCHEME I





1a

The ring-expanded enamines **5a–e** were prepared by the methods of Berchtold and Uhlig[2] and Paquette and Begland.[6] The morpholino enamine in the eight-membered ring system, **5b**, was used instead of the corresponding pyrrolidino enamine because of poor yields in the ring expansion of the 1-*N*-(pyrrolidino)cyclohexenone (**4e**). Hydrolysis with acidic methanol[2,6] produced good yields of the crystalline seven-, eight-, and ten-membered unsaturated keto dicarboxylic esters **6a**, **6b**, and **6d**. The first two compounds were essentially 100% enolic, while the ten-membered ring compound[7] after 2 days at room temperature was found to be 53% enolic in a 10% solution in deuteriochloroform and 65% enolic in a 10% solution in carbon tetrachloride (by integration of the proton magnetic resonance spectra).[8] The oily material obtained by Paquette and Begland[6] corresponding to **6d** exhibited 41% and 57% enol in deuteriochloroform and carbon tetrachloride, respectively. The nine-membered ring compound **6c** was obtained only as an oil in poor yield. The spectral characteristics of this compound agree with those of Paquette,[6]

(1) Author to whom correspondence should be directed.

(2) G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, **28**, 1459 (1963).

(3) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *ibid.*, **28**, 1464 (1963).

(4) C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson, and P. Strachan, *ibid.*, **28**, 3134 (1963).

(5) A. K. Bose, G. Mina, M. S. Manhas, and E. Rzucidlo, *Tetrahedron Lett.*, 1467 (1963).

(6) L. A. Paquette and R. W. Begland, *J. Amer. Chem. Soc.*, **88**, 4685 (1966).

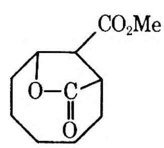
(7) Recrystallization of this ten-membered unsaturated keto diester **6d** from varying proportions of methanol and water produced isomeric material with slightly different physical properties and slightly different behavior toward thin layer chromatography. See the Experimental Section for details.

(8) Enol content refers to [enol]/[keto] ratios calculated from integrated nmr signal intensities unless otherwise noted. See Table I.

but the compound was shown to be impure by elemental analysis even after repeated attempts at purification. The major product from this reaction mixture was identified as 8-oxo-1-cyclononenecarboxylic acid (**8c**) (*vide infra*).

Catalytic reduction of dimethyl 7-hydroxy-2,7-cycloheptadiene-1,2-dicarboxylate (**6a**) by the method of Berchtold[2] proceeded with difficulty to give impure saturated **7a**, which was the major component when hydrogen absorption effectively ceased, but which we could not purify. Increased hydrogenation pressures[9] or a change to 5% palladium on carbon in ethanol at 40 psig[10] did not improve the results. When various purification procedures failed, the crude **7a** was subjected to the Berchtold–Uhlig saponification–decarboxylation sequence.[2] A low yield of a mixture containing at least four components was produced. Because of the possibility of ring opening under the alkaline conditions,[11] the conversion of **7a** to **1a** was attempted under acidic conditions. The infrared and proton magnetic resonance spectra of the crude reaction product suggested the presence of starting material and a lactone, but little of the desired keto carboxylic acid.

Catalytic hydrogenation of dimethyl 8-hydroxy-2,8-cyclooctadiene-1,2-dicarboxylate (**6b**) with prereduced platinum oxide in glacial acetic acid at 40 psig proceeded in a somewhat more satisfactory fashion than with the lower homolog **6a**. Hydrogen absorption did not show a reproducible inflection point or cease at the equimolar ratio, the products after 100, 120, or 200% hydrogen absorption being dimethyl 8-oxocyclooctane-1,2-dicarboxylate (**7b**), unreacted starting material, and lactonic material. Fractional distillation followed by column chromatography on silica gel effected separation of the saturated keto dicarboxylate ester **7b**, starting material, and a lactone identified as **9**. Acidic hydrolysis and de-



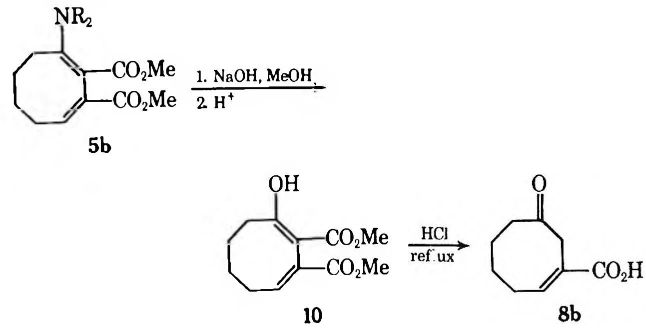
9

carboxylation of **7b** produced pure 3-carboxycyclooctanone (**1b**).

Catalytic hydrogenation of the unsaturated ten-membered ring compound **6d** was performed as for the lower homolog **6b**. The hydrogenation stopped at 93.5% of theoretical hydrogen absorption to give a good yield of the desired dimethyl 10-oxocyclodecane-1,2-dicarboxylate (**7d**) with a slight lactonic contaminant. Purified **7d** was hydrolyzed and decarboxylated under acidic conditions to produce good yields of pure 3-carboxycyclodecanone (**1d**).

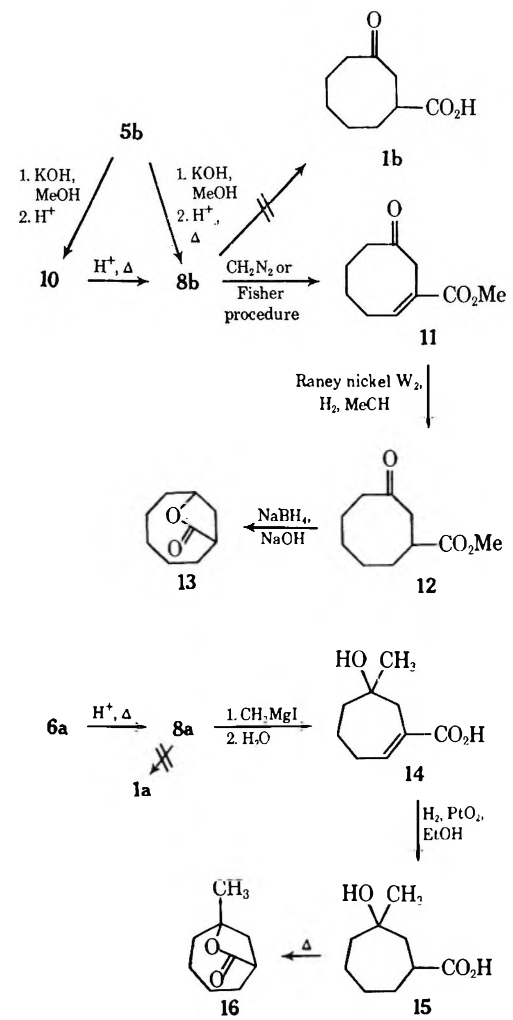
Having succeeded only in preparing the 3-carboxycycloalkanones with even ring sizes in good yield and purity, the challenge remained to prepare the odd ring size analogs. Isolation of 8-oxo-1-cyclononenecarboxylic acid (**8c**) recalled the work of Bose and coworkers[5] (Scheme II) and Cope and coworkers[12] (Scheme III).

SCHEME II[a]



[a] See ref 12.

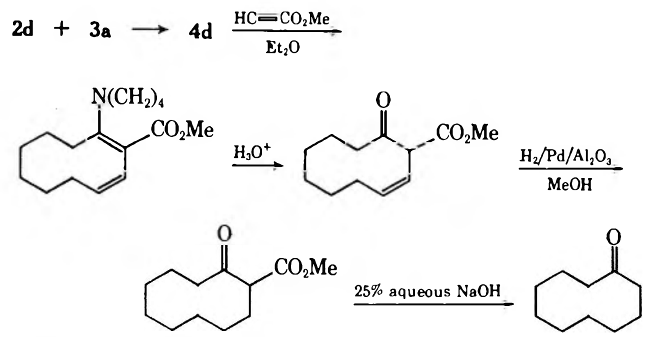
SCHEME III[a]



[a] See ref 5.

(9) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965.

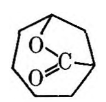
(10) Since completion of this phase of this work, the Pd/Al_2O_3 hydrogenation shown below has been reported by R. Burpitt and J. Thweatt, *Org. Syn.*, **48**, 56 (1968).



(11) R. D. Sands, *J. Org. Chem.*, **34**, 2794 (1969), and earlier papers; H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 170, but see a successful alkaline decarboxylation in ref 10.

(12) A. C. Cope, J. M. McIntosh, and M. A. McKervey, *J. Amer. Chem. Soc.*, **89**, 4020 (1967).

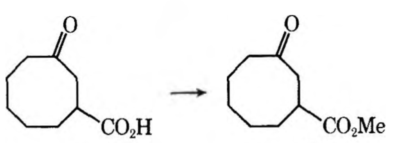
Unfortunately, Cope's group had reported no success on attempted catalytic hydrogenation of either 6-oxo-1-cycloheptenecarboxylic acid (**8a**) or 7-oxo-1-cyclooctenecarboxylic acid (**8b**). Nevertheless, we decided to investigate a sequence **5** → (**6** →) **8** → **1** in the cycloheptane series. 6-Oxo-1-cycloheptenecarboxylic acid (**8a**) was obtained in good yield from the unsaturated diester **6a** by Cope's procedure[12] (refluxing 20% aqueous hydrochloric acid) and, in better yield, directly from the pyrrolidino adduct **5a** (refluxing 10% aqueous hydrochloric acid). Both methods resulted in a product, **8a**, which was contaminated with unsaturated diester **6a** and which was slightly unstable in either reaction mixture. Surprisingly enough, the purified 6-oxo-1-cycloheptenecarboxylic acid (**8a**) could be smoothly hydrogenated (at a faster rate than the unsaturated keto dicarboxylate esters, **6**) over either prereduced platinum oxide or 5% palladium on carbon in glacial acetic acid at 40 psig. The palladium-catalyzed hydrogenation cleanly produced the desired 3-carboxycycloheptanone (**1a**), while the platinum-catalyzed reaction produced a 2:1 mixture of **1a** and 3-hydroxycycloheptanecarboxylic acid lactone (**17**), which could be separated by chromatography on a silica gel column.



17

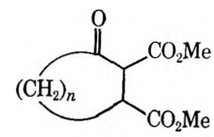
Because of this success in the cycloheptane series, the 8-oxo-1-cyclononenecarboxylic acid (**8c**) isolated previously (*vide supra*) was prepared in larger amounts using the aqueous hydrochloric acid reaction conditions, in which it also was slightly unstable. Hydrogenation of **8c** to 3-carboxycyclononanone (**1c**) proceeded smoothly on platinum oxide but inconsistently over the palladium catalyst system.

3-Carboxycyclooctanone (**1b**) was also prepared by this variation of Cope's procedure.[12] Unsaturated diester **6b** was hydrolyzed and decarboxylated in refluxing 20% aqueous hydrochloric acid to 7-oxo-1-cyclooctenecarboxylic acid (**8b**),[13] which was subjected to hydrogenation over palladium to the desired 3-carboxycyclooctanone (**1b**), identical in all respects with that prepared by the modified Berchtold–Uhlig procedure.[2] A sample of 3-carboxycyclooctanone (**1b**) was converted with boron trifluoride–methanol complex[14] to its methyl ester, **12**, a compound identical in its properties with that reported by Cope and coworkers.[12]

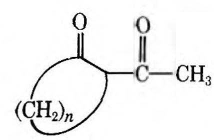


1b **12**

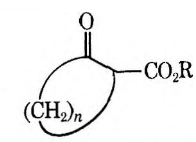
Keto–Enol Equilibria.—Keto–enol equilibria in mesocyclic systems are known to vary markedly with structure and ring size. Paquette and Begland[6] have reported (Table I) 100% enolization for the unsaturated keto diesters **6a** and **6b** and roughly 50% for the larger rings **6c** and **6d**, results which are reinforced by our data. Increased enol content was discovered upon introduction of another double bond into the larger rings or upon replacement of a tetrahedral carbon atom with an oxygen atom. Because of the known flexibility of medium-ring systems[15] and the necessary rigidity associated with the presence of double bonds,[15] it is impossible at the present stage of sophistication to accurately analyze the relative importance of nonbonded interactions, angle strain, and hybridization with respect to one another. The absence of measurable amounts of enol (using proton magnetic resonance spectroscopy) for compounds **8** independent of ring size suggests that the presence of one double bond in a position suitable for conjugation in the enolic form is not sufficient to promote significant enolization in such cycloalkanones. A comparison of the enol content of similar ring sizes in the 2,3-dicarbomethoxycycloalkanones (**7**), the 2-acetylcycloalkanones (**18**),[16] and the 2-carbethoxy- or 2-carbomethoxycycloalkanones (**19**),[17] although measured by different methods with differing precision and accuracy (Table I), suggests slightly decreased enol content upon introduction



7



18

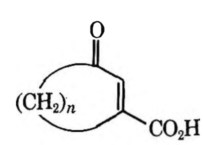


R = Me, Et

19

of a 3 substituent (**7** *vs.* **18** or **19**). A Δ^3 double bond does cause an enormous increase in enol content in dimethyl 8-hydroxy-2,8-cyclooctadiene-1,2-dicarboxylate (**6b**) relative to 2,3-dicarbomethoxycyclooctanone (**7b**), but not for the ten-membered ring analog. One can only surmise that decreased nonbonded interactions in the enol of **6b** relative to the enol of **7b** are more significant than in the enol of **6d** relative to the enol of **7d**. Why such a situation exists in the less flexible eight-membered ring and not in the more flexible ten-membered ring is extremely puzzling.

As indicated by Bose and coworkers,[5] it is somewhat surprising that the unsaturated keto carboxylic acids isolated from the hydrolysis and decarboxylation of **6** possess structures **8** to the exclusion of the more highly conjugated isomeric structures **20**. Heap and Whitham[18] have reported the equilibrium compositions for



20

the unsubstituted medium-ring cycloalkanone isomers (Table II). Since the acid-catalyzed decarboxylation of β-keto acids[19,20] is believed to involve the enol of the

(13) **8b** may also be prepared directly from the morpholino adduct **5b**: W. A. Meresak, unpublished results.

(14) G. Hallas, *J. Chem. Soc.*, 5770 (1965).

(15) J. Dale, *Angew. Chem., Int. Ed. Engl.*, **5**, 1000 (1966); J. D. Dunitz in "Perspectives in Structural Chemistry," Vol. II, J. D. Dunitz and J. A. Ibers, Ed., Wiley, New York, N. Y., 1968, p 1.

(16) Table I, ref *a*.

(17) Table I, ref *b–d*.

(18) N. Heap and G. H. Whitham, *J. Chem. Soc. B*, 164 (1966).

(19) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 303.

(20) J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N. Y., 1968, p 478.

TABLE I
PER CENT ENOL CONTENT

Structure	Ring size 7	8	9	10	Technique	Ref
6	100	100	46	57	Pmr in CCl_4	6
	100	100	31	41	Pmr in $CDCl_3$	6
	100	100		65	Pmr in CCl_4	This work
	100	100		53	Pmr in $CDCl_3$	This work
2-Acetylcycloalkanones (18)	70	95	57	50	Uv	a
2-Carbethoxycycloalkanones (19)	31	64	38	70	Pmr in CCl_4	b
	14	42	19	49	Titrimetric in EtOH	c
	12				Titrimetric in EtOH	d
2-Carbomethoxycycloalkanones (19)		40	15	50	Titrimetric in EtOH	d
7		30[f]		35[f]	Pmr in $CDCl_3$	This work
1	0	0	0	0	Pmr in $CDCl_3$	This work
8	0	0	0		Pmr in $CDCl_3$	This work
1,3-Cycloalkanediones	0	0	0	10	Various	e

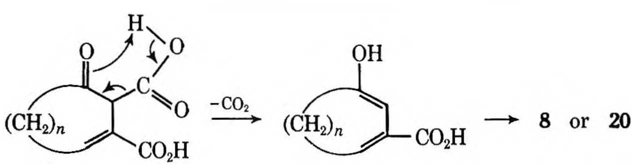
[a] S. Hunig and H. Hoch, *Justus Liebigs Ann. Chem.*, **716**, 68 (1968). [b] S. J. Rhoads, *J. Org. Chem.*, **31**, 171 (1966). [c] S. J. Rhoads and C. Pryde, *ibid.*, **30**, 3212 (1965). [d] G. Schwarzenbach, M. Zimmerman, and V. Prelog, *Helv. Chim. Acta*, **34**, 1954 (1951). [e] I. Maclean and R. P. A. Sneeden, *Tetrahedron*, **21**, 31 (1965); B. Eistert and K. Schank, *Tetrahedron Lett.*, 429 (1964); B. Eistert, F. Haupter, and K. Schank, *Justus Liebigs Ann. Chem.*, **665**, 55 (1963); K. Schank, B. Eistert, and H. J. Felzmann, *Chem. Ber.*, **99**, 1414 (1966). [f] Calculated from area under enol peak relative to total integral.

TABLE II
EQUILIBRIA BETWEEN CYCLOALK-2- AND -3-ENONES[a]

Ring size	Equilibrium composition, % Δ^2	Δ^3
7	73	27
8	20	80
9	<0.3	>99.7

[a] See ref 18.

decarboxylation product, conditions for equilibration of the double bond position would seem to be present prior to the isolation of the products. Inspection of Dreiding models suggests that nonbonded interactions might account for the lack of evidence for **20** as a product in these reactions, particularly as the rings become larger, as suggested by Heap and Whitham.[18] The exocyclic carboxy group does not appear to provide any stabilization which might favor either **8** or **20** relative to the equilibrium composition of the unsubstituted compounds.[18]



Experimental Section

Melting points and boiling points are uncorrected. Nmr spectra were recorded on a Varian A-60A instrument using 10% solutions in deuteriochloroform, unless otherwise noted, and are reported in parts per million downfield from tetramethylsilane as an internal standard. Only distinct absorptions will be listed herein. Infrared spectra were determined with a Beckman IR-10 spectrophotometer on 5–7% solutions in chloroform unless otherwise specified. Only major absorptions are listed herein. Ultraviolet spectra were measured with a Cary 15 spectrophotometer. Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Elbach, West Germany.

1-(*N*-Pyrrolidino)-2,3-dicarbomethoxy-*cis,cis*-1,3-cycloheptadiene (5a).—This product was prepared in 39.1% overall yield from cyclopentanone by the method of Berchtold and Uhlig[2] and was obtained as white crystals from acetone, mp 144.5–146.5° (lit. 145–146°,[2] 147–148°,[3] 135–138°[4]).

1-(*N*-Morpholino)-2,3-dicarbomethoxy-*cis,cis*-1,3-cyclooctadiene (5b).—This compound was prepared from cyclohexanone in 32.7% yield by the method of Berchtold and Uhlig[2] and was obtained as a pale yellow solid from acetone, mp 210–212.5° (lit. 210–211°[2], 210–212°[4]).

1-(*N*-Pyrrolidino)-2,3-dicarbomethoxy-*cis,cis*-1,3-cyclooctadiene (5e).—This compound was prepared from cyclohexanone in 5.7% yield by the method of Berchtold and Uhlig.[2] The poor overall yield[3] results from the 14% conversion of 1-(*N*-pyrrolidino)cyclohexenone (4e) to **5e**.

1-(*N*-Pyrrolidino)-2,3-dicarbomethoxy-*cis,cis*-1,3-cyclononadiene (5c).—This compound was prepared in 37.4% yield from cycloheptanone by the method of Brannock, *et al.*,[3] and was obtained from ether as pale yellow crystals, mp 140–142° (lit. 109.5–110.5°,[3] 139–141°[6]).

1-(*N*-Pyrrolidino)-2,3-dicarbomethoxy-*cis,cis*-1,3-cyclodecadiene (5d).—This product was prepared in 44.4% yield from cyclooctanone by the method of Brannock, *et al.*,[3] and was obtained from ether as white crystals, mp 104–106° (lit.[6] 104–105°).

Dimethyl 7-Hydroxy-2,7-*cis,cis*-cycloheptadiene-1,2-dicarboxylate (6a).—This compound was prepared from **5a** by the method of Berchtold and Uhlig[2] in 88.5% yield as white, needle-like crystals, mp 60.5–63.0° (recrystallized from 2:1 aqueous methanol) (lit. 63.5–64.0°,[2] 61–62°,[6] 55–57°[3]), spectra in agreement with those reported.[6]

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.37; H, 6.24. Found: C, 58.23; H, 6.23.

Dimethyl 8-Hydroxy-2,8-*cis,cis*-cyclooctadiene-1,2-dicarboxylate (6b).—This product was prepared from **5b** by the method of Berchtold and Uhlig,[2] and was obtained as a 91.9% yield of white needle-like crystals, mp 75.0–77.5° (lit. 75.4–76.3°,[2] 74–75°,[6] 74–75°,[3] 60–64°[4]), spectra as reported.[6]

Anal. Calcd for $C_{12}H_{16}O_5$: C, 60.00; H, 6.70. Found: C, 60.11; H, 6.73.

Identical material was obtained by the same procedure from the pyrrolidino compound **5e** in 79.6% yield.

Dimethyl 10-Hydroxy-2,10-*cis,cis*-cyclodecadiene-1,2-dicarboxylate (6d).—This compound was prepared from **5d** by the method of Berchtold and Uhlig[2] and was obtained as a 68.3% yield of pale yellow, slightly gummy solids. Recrystallization from 1:2 aqueous methanol resulted in a 60% recovery of white, needle-like crystals: mp 55–59°; ir 1750, 1710, 1650, 1600 cm^{-1} [lit.[6] (CCl_4) 1765, 1725, 1655, 1606 cm^{-1}]; uv max (C_6H_{12}) 254 mμ (ϵ 9800) [lit.[6] 255 mμ (ϵ 5330)]; nmr δ 3.67 (s, 3), 3.75 (s, 3), 4.64 (s, 0.46), 6.14 (m, 1.) 12.30 (s, 0.53), 53% enol[8] (lit.[6] δ 3.74, 3.83, 4.73, 6.30, 12.45, 41% enol); nmr (CCl_4), δ 3.71 (s, 3), 3.82 (s, 3), 4.58 (s, 0.65), 5.98 (d, J = 4 Hz), 6.20 (d, J = 4 Hz), 12.33 (s, 0.35), 65.4% enol (lit.[6] δ 3.67, 3.78, 4.59, 6.18, 12.33, 57% enol).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.69; H, 7.53. Found: C, 63.03; H, 7.40.

Crude product recrystallized from 3:1 aqueous methanol produced a 67% yield of a crystalline product identical with that reported above except for an additional large nmr singlet absorption at δ 1.85, a 55% enol content in $CDCl_3$, uv max (C_6H_{12}) 257 mμ (ϵ 11,516), and a higher retention factor on tlc analysis on silica gel plates.

Dimethyl 7-Oxocycloheptane-1,2-dicarboxylate (7a).—A solution of 9.6 g (43 mmol) of **6a** in 12 ml of glacial acetic acid was hydrogenated at 15 psig at room temperature using 96.8 mg of prereduced platinum (IV) oxide (Engelhard) until hydrogen absorption ceased (106% theoretical). The catalyst was removed by filtration, and the filtrate was neutralized ($NaHCO_3$) and extracted with ether. The ethereal extract was dried ($MgSO_4$), concentrated, and distilled, giving 6.8 g of a viscous, colorless oil, bp 126–132° (0.5–0.6 mm). Gas chromatographic analysis[21] indicated three components at 77, 20, and 3% approximate concentration levels. The effluent from the main peak was collected and found to be impure **7a** by spectral analysis. Attempts to prepare this compound by other hydrogenation routes gave lower yields of impure material.

Dimethyl 8-Oxocyclooctane-1,2-dicarboxylate (7b).—A solution of 2.40 g (10 mmol) of **6b** in 30 ml of glacial acetic acid was hydrogenated over 502.4 mg of prereduced platinum(IV) oxide at 40 psig at room temperature. The reaction was stopped after 125% of the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure. The concentrated filtrate was extracted with ether, and the ether layer was dried ($MgSO_4$), concentrated, and distilled at reduced pressure. The lower boiling fraction, 1.34 g (55.4%) of a viscous, colorless oil, bp 123–125° (0.4 mm), contained starting material, product **7b**, and a lactone by spectral analysis. The higher boiling fraction, 0.38 g (15.7%) of a viscous, colorless oil, bp 125–127° (0.4 mm), contained product and a considerable amount of the lactonic byproduct.

The lower boiling fraction was separated in an inefficient manner on a silica gel (Woelm) column using benzene–acetone mixture as eluent. The desired product, **7b**, was isolated as a colorless, viscous oil: ir 1735, 1710, 1650, 1615 cm^{-1}; nmr δ 3.63–3.74 (3 peaks, 6), 12.41–12.52 (two, d, 0.29), enol content[22] 30%.

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.40; H, 7.34.

The lactone was isolated from the later fractions of the column chromatography as a pure compound and identified as 2-carbomethoxy-3-hydroxycyclooctanecarboxylic acid lactone (**9**). After recrystallization from ether, **9** exhibited mp 88–90°; ir 1770, 1740 cm^{-1}; nmr δ 2.04 (broad s, 2), 3.74 (s, 5), 4.95 (m, 1).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.10; H, 7.91.

Hydrogenation of **6b** under these conditions to 100 or 200% of the theoretical hydrogen untake did not improve the conversion of **6b** to **7b**.

Dimethyl 10-Oxocyclodecane-1,2-dicarboxylate (7d).—A solution of 25.6 g (95.4 mmol) of **6d** in 285 ml of glacial acetic acid was hydrogenated over 4.75 g of prereduced platinum(IV) oxide at 40 psig at room temperature until hydrogen absorption ceased (93.5% theoretical). The catalyst was removed by filtration and the acetic acid by distillation under reduced pressure. Distillation of the residue through a Vigreux column gave 22.05 g (85.7%) of a viscous oil: bp 139–140° (0.3 mm); ir 1810, 1730, 1710, 1650, 1605 cm^{-1}; nmr δ 3.60–3.75 (complex pattern, 6.5), 12.70 and 12.80 (two d, 0.36), enol content 35%.[22]

Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.08; H, 8.06.

6-Oxo-1-cycloheptenecarboxylic Acid (8a). Method 1.—A solution of 5.0 g (1.79 mmol) of **5a** in 100 ml of 10% HCl was refluxed for 16 hr, cooled to 0–2°, and aged overnight. Fine, amorphous, brown solids (0.2 g) were removed by filtration. The filtrate was extracted three times with ether and the combined ethereal extracts were dried ($MgSO_4$) and partially concentrated under reduced pressure. The resulting slurry was filtered to give, after drying overnight at reduced pressure, 1.10 g (39.7%) of white, needle-like crystals: mp 73–75° (lit.[12] 73.5–75.0°); ir 1710, 1690, 1640 cm^{-1} (as reported[12]); nmr δ 3.65 (s, 2), 7.35 (t, 1, J = 5.0 Hz), 11.30 (s, 1) (as reported[12]).

Anal. Calcd for $C_{18}H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.62; H, 6.59.

Evaporation of the ethereal liquors gave 0.8 g of waxy orange solids whose spectra indicated the presence of **6a** along with the desired **8a**.

Method 2.—This product (**8a**) was prepared from **6a** by the method of Cope, *et al.*,[12] and was obtained as a 23.4% yield of pale yellow crystalline agglomerates, mp 68.0–71.5°, with spectra identical with those reported above. Evaporation of the mother liquors resulted in a clear amber oil consisting of a mixture of **6a** and **8a**.

7-Oxo-1-cyclooctenecarboxylic Acid (8b).—A solution of 9.8 g (40.7 mmol) of **6b** in 41 ml of 20% HCl was refluxed for 8 hr, cooled to 0–2°, and aged for 1 hr. The resulting slurry was filtered and washed exhaustively with H_2O. The tan solids were dried overnight at 39° under reduced pressure to give 4.3 g of product, and an additional 1.0 g was obtained from CH_2Cl_2 extracts of the mother liquors taken to dryness. Combined crops were recrystallized from benzene to produce 3.84 g (63.5% yield) of **8b**: mp 103.0–105.0° (lit.[12] 108–109°); ir 1700–1680, 1645 cm^{-1} (as reported[12]); nmr δ 3.45 (s, 2), 7.20 (t, 1, J = 9.0 Hz), 11.16 (s, 1) (similar to reported data[12]).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.15; H, 7.06.

8-Oxo-1-cyclononenecarboxylic Acid (8c).—A solution of 7.7 g (25 mmol) of **5c** in 154 ml of 10% HCl was refluxed for 20 hr, cooled to 0–2°, and aged for 2 hr. The resulting slurry was filtered and washed exhaustively with ice water. Tan needlelike crystals (3.4 g, 74.3%) were obtained after drying overnight at 39° and reduced pressure. A sample recrystallized from ether exhibited mp 111.0–112.5°; ir 1695, 1640 cm^{-1}; nmr δ 3.54 (s, 2), 7.22 (t, 1, J = 8.5 Hz), 11.45 (s, 1).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.75. Found: C, 65.69; H, 7.94.

Extraction of the mother liquors with ether followed by drying of the ethereal extract ($MgSO_4$) and removal of the ether gave 0.6 g of pale yellow needles, spectra identical with those of desired product except for a small nmr absorption at δ 3.78 (s, 0.2).

3-Carboxycycloheptanone (1a).—Hydrogenation of a solution of 1.00 g (6.5 mmol) of **8a** in 15 ml of glacial acetic acid at room temperature and 40 psig over 100 mg of prereduced platinum(IV) oxide was performed until hydrogen absorption ceased (142% theory). After removal of the catalyst by filtration and the acetic acid by distillation under reduced pressure, the residue was dissolved in ether and dried ($MgSO_4$). The ether was removed and the residue distilled to give 0.64 g of a viscous colorless oil, bp 120–130° (0.2 mm), which partially solidified. Tlc indicated the presence of two components.

A solution of 0.418 g of the above material in chloroform was separated into two components by column chromatography on silica gel (Davison Chemical). The first material obtained was 0.109 g of a white, waxy solid. A 50-mg portion of this solid was sublimed at room temperature and 0.2 mm to give 41 mg of 3-hydroxy-cycloheptanecarboxylic acid lactone (**17**), a white crystalline solid: mp 102–104°; ir 1760 cm^{-1}; nmr δ 4.90 (broad d, 1).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.61; H, 8.76.

The second component was 0.236 g of the desired **1a**, a viscous, clear, colorless oil: ir 1705 cm^{-1}; nmr δ 8.95 (s, 1) [lit.[2] bp 200° (0.65 mm); mp 40–41°; ir 1700, 1550 cm^{-1}].

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.34; H, 7.80.

The desired product **1a** was also prepared from the hydrogenation of 0.882 g (5.13 mmol) of **8a** in 12 ml of glacial acetic acid at 40 psig and room temperature over 88.5 mg of 5% palladium on carbon (Engelhard). The same work-up as above (without the chromatography) produced 0.569 g (64.4%) of pure **1a** as a clear, slightly yellow oil, bp 120–121° (2 mm), with spectra identical with those exhibited by the material purified by chromatography (*vide supra*).

3-Carboxycyclooctanone (1b). Method 1.—A solution of 0.80 g (4.75 mmol) of **8b** in 10 ml of glacial acetic acid was treated with hydrogen at 40 psig and room temperature over 100 mg of 5% palladium on carbon until hydrogen absorption ceased (139% theoretical). The catalyst was removed by filtration and the filtrate concentrated at reduced pressure. An ethereal solution of the residue was dried ($MgSO_4$) and evaporated to dryness under reduced pressure, leaving 0.73 g (90.5%) of white, crystalline solids: mp 96.5–100.0°; ir 1705 cm^{-1}; nmr δ 10.51 (s, 1).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.36; H, 8.39.

Method 2.—A solution of 29.0 g (0.120 mol) of the low-boiling fraction of impure **7b** in 250 ml of 10% HCl was refluxed for 28 hr and the solvent removed by distillation at reduced pressure. The residue was dissolved in ether, dried ($MgSO_4$), and concentrated under reduced pressure to a heavy slurry. After aging for 2 hr at 0–2°, the slurry was filtered and the cake washed with

(21) A 6 ft × 0.25 in. 3% SE-52 column at 170° on F & M Series 810 gas chromatograph.

(22) Enol content was calculated from the area under the enol absorptions relative to the total pmr integral.

0–2° ether to give 9.55 g (46.1%) of white, crystalline **1b**. The ir and pmr spectra of this solid, as well as the behavior on tlc, presented evidence for the presence of 7-oxo-1-cyclooctenecarboxylic acid (**8b**) as an impurity, even though elemental analysis was satisfactory for pure **1b**.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.42; H, 8.09.

Hydrogenation of 1.703 g of this solid material as in method 1 (above) produced 1.601 g (94.0%) of white, crystalline solids corresponding to pure **1b**: mp 96.5–100.0°; ir 1705 cm^{-1}; nmr δ 10.51 (s, 1).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.61; H, 8.38.

3-Carbomethoxycyclooctanone (12).—A solution of 2.00 g (11.7 mmol) of **1b** in 10 ml of methanol was refluxed for 2 hr with 40 ml of 1:2 BF_3-MeOH complex[14] under a nitrogen atmosphere. The solution was cooled, poured into $CHCl_3$, extracted with H_2O, washed with saturated NaCl solution, dried ($MgSO_4$), concentrated, and distilled under reduced pressure to give 1.82 g (84.1%) of a colorless oil: bp 74–75° (0.25 mm); ir 1730, 1700 cm^{-1} (as reported[12]); nmr δ 3.67 (s, 3) (as reported[12]).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.06; H, 8.87.

3-Carboxycyclononanone (1c).—A solution of 0.85 g (4.56 mmol) of **8c** in 25 ml of glacial acetic acid was hydrogenated at 40 psig and room temperature over 180 mg of prereduced platinum(IV) oxide until hydrogen absorption ceased (136% theoretical). Work-up as for **1b** (method 1) above gave 0.48 g (55.9%) of a viscous, clear and colorless oil: bp 135–136° (0.2 mm); ir 1700 cm^{-1}; nmr δ 10.30 (s, 1). This oil solidified to a waxy, white solid after storage overnight at 4°.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.12; H, 8.98.

Similar results were produced on hydrogenation of **8c** over 5% palladium on carbon except that the product **1c**, was contaminated with unreacted starting material even after repeated hydrogenation.

3-Carboxycyclodecanone (1d).—Hydrolysis and decarboxylation of **7d** was performed by refluxing 20.7 g (76.5 mmol) of **7d** in 250 ml of 10% HCl for 29 hr. Most of the H_2O was removed under reduced pressure. The residue was dissolved in ether, dried ($MgSO_4$), and concentrated under reduced pressure to a heavy slurry, from which 15.8 g (104%) of waxy material was separated by filtration. Recrystallization from ether gave 9.25 g (60.9%) of white crystalline solids: mp 56.0–58.5°; ir 1700 cm^{-1}; nmr δ 11.20 (s, 1).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.48; H. 9.06.

The ethereal mother liquors were concentrated further to give 1.45 g (9.5%) of white solids identical in all respects with the above product.

Registry No.—**1a**, 27531-68-6; **1b**, 27531-69-7; **1c**, 27531-70-0; **1d**, 27531-71-1; **6d**, 27531-72-2; **7a**, 27531-73-3; **7b**, 27531-74-4; **7d**, 27531-75-5; **8a**, 17606-97-2; **8b**, 17606-93-8; **8c**, 27531-78-8; **9**, 27531-79-9; **12**, 17606-96-1; **17**, 18543-37-8.

Absolute Configurations of the *p*-Menthane-2,5-diones and *p*-Menthane-2,5-diols[1]

ROBERT D. STOLOW* AND KRISHNA SACHDEV

Department of Chemistry, Tufts University, Medford, Massachusetts 02155

Received July 22, 1970

The eight diastereoisomeric *p*-menthane-2,5-diols (**1–8**), the four diastereoisomeric *p*-menth-1-ene-3,6-diols (**9–12**), and the two (+)-*p*-menthane-2,5-diones (**13** and **14**), which all have the same absolute configuration at the isopropyl group as (−)-α-phellandrene (**15**), have been prepared, characterized, and interrelated. Absolute configurations have been established for **1–14** by stereoselective chemical interconversions, including hydrogenation of diols **9–12**, Jones oxidation of diols **1–6**, lithium aluminum hydride reduction of diones **13** and **14**, and displacements by formate and hydride ions on monotosylates of diol **4**.

The configurational assignments presented here for the optically active *p*-menthane-2,5-diones and *p*-menthane-2,5-diols formed the basis of our previous definitive report on the *p*-menth-1-ene-3,6-diols.[2] The configurational relationships among the eight diastereoisomeric *p*-menthane-2,5-diols (**1–8**), the four diastereoisomeric *p*-menth-1-ene-3,6-diols[2] (**9–12**), and the two (+)-*p*-menthane-2,5-diones (**13** and **14**), which all have the same absolute configuration at C-4 as (−)-α-phellandrene (**15**), are shown in Scheme I.

Racemic Diones and Diols.—Racemic mixtures containing diones **13** and **14** and diols **3** and **4** have been prepared previously. Lithium–liquid ammonia–ethanol reduction of 2,5-dimethoxy-*p*-cymene followed by acid-catalyzed hydrolysis of the reduction product gave in 96% yield an equilibrium mixture of diones (±)-**13** and (±)-**14**, from which the more stable isomer, (±)-*cis-p*-menthane-2,5-dione [(±)-**13**], mp 72–73°, was isolated by fractional crystallization.[3] Hydrogenation of dione (±)-**13** gave (±)-*cis,cis,cis-p*-menthane-2,5-diol [(±)-**3**], mp 105°. Assignment of the all-cis configuration, (±)-**3**, to the racemic diol, mp 105°, was based unequivocally upon infrared spectroscopic studies of intramolecular hydrogen bonding.[3,4] Among the *p*-menthane-2,5-diols with hydroxyl groups cis to one another (**1–4**), only diol **3** exhibits detectable intramolecular hydrogen bonding.[4] Diol (±)-**3** has also been prepared by hydrogenation of thymoquinone with rhodium on alumina catalyst at 25°.[5] In addition, a (±)-*p*-menthane-2,5-diol, mp 144°, was isolated from the product of reduction of thymoquinone.[5] The cis configuration of the more stable racemic dione [(±)-**13**], mp 72–73°, was confirmed by its preparation by stereospecific Jones oxidation[6] of the all-cis diol (±)-**3**.[5] Jones oxidation[6] of the racemic diol, mp 144°, gave (±)-*trans-p*-menthane-2,5-dione [(±)-**14**], mp 43–43.5°.[5] Therefore, the racemic diol, mp 144°,

(1) Taken from the Doctoral Dissertation of Krishna Sachdev, Tufts University, June 1966. This paper is dedicated to the memory of the late Dr. Arnold Blumann whose kind encouragement and cooperation contributed in great measure to the successful completion of this work, and the previously reported study of the *p*-menth-1-ene-3,6-diols.[2] This work was supported in part by Public Health Service Research Grant GM-08813 from the National Institutes of Health, in part by the National Science Foundation, and in part by the Research Corporation, and was presented at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965.

(2) R. D. Stolow and K. Sachdev, *Tetrahedron*, **21**, 1889 (1965).

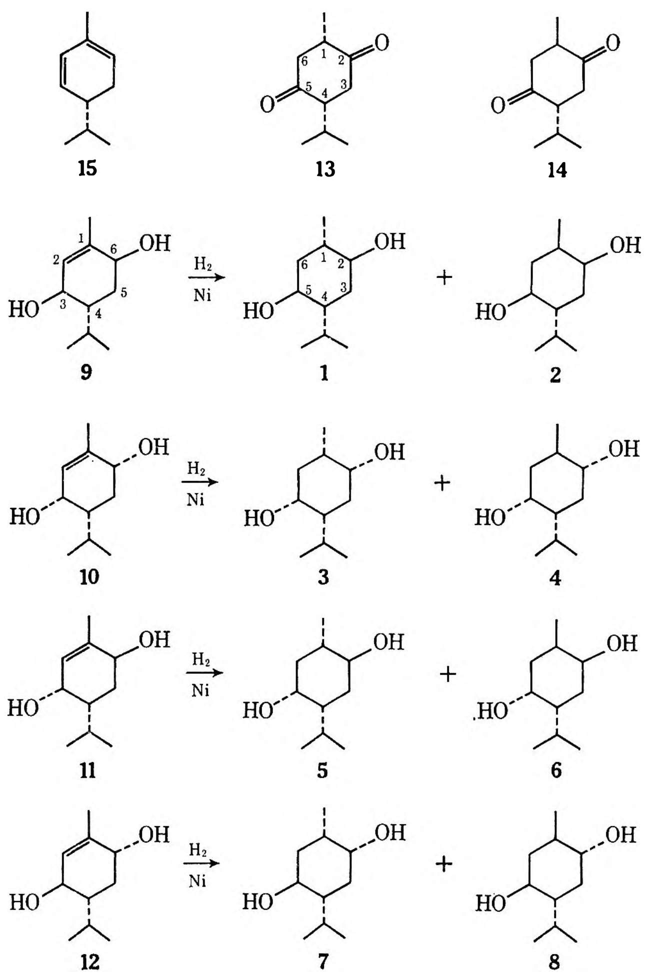
(3) R. D. Stolow, P. M. McDonagh, and M. M. Bonaventura, *J. Amer Chem. Soc.*, **86**, 2165 (1964).

(4) R. D. Stolow, *ibid.*, **86**, 2170 (1964).

(5) R. D. Stolow and R. R. Krikorian, *Org. Prep. Proced.*, **3**, 39 (1971).

(6) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

SCHEME I



must have its alkyl groups trans to one another.[5] The (±)-p-menthane-2,5-diol, mp 144°, is here assigned structure (±)-4 on the basis of its nmr and infrared spectra which are identical with those of optically active diol 4, described below.[7]

The Optically Active Diols and Diones.—Of the optically active diols (1–12), nine had been described before this work began.[8,9] However, all but four (diols 1, 2, 9, and 10) had been reported erroneously.[10]

Although the related monoalcohols, the menthols and carvomenthols, had been studied extensively for many years, the last vestige of confusion concerning structure lingered until recent work was published from several laboratories.[11] In their review of the problem, Schroeter and Eliel[11a] cite work of Blumann, *et al.*,[9] and others,[12] concerning (+)-p-menthane-2,5-diols, mp "134°" and "176°," diols 1 and 2, respectively. Blumann, *et al.*, degraded diol 1 to monoalcohols, isomenthol and isocarvomenthol.[9] Since firm independent evidence for the structures of the monoalcohols has been provided,[11] assignment of structure 1 to the (+)-p-menthane-2,5-diol, reported mp "134°," has been established beyond reasonable doubt.[9]

Results and Discussion

Preparation.—The eight optically active diastereoisomeric p-menthane-2,5-diols (1–8) have been prepared by hydrogenation of the four optically active diastereoisomeric p-menth-1-ene-3,6-diols (9–12).[2] Hydrogenation of each p-menth-1-ene-3,6-diol[2] yielded a corresponding pair of p-menthane-2,5-diols epimeric at C-1 (Scheme I). Hydrogenation of diol 9 to give diols 1 and 2 has been reported[8,9] and confirmed[4] previously. Similarly, hydrogenation of diol 10 gave diols 3 and 4, as mentioned earlier.[4] Hydrogenation of diol 11 gave diols 5 and 6, and hydrogenation of diol 12 gave diols 7 and 8.[2]

Upon hydrogenation with Raney nickel catalyst at *ca.* 25° and 2-atm hydrogen pressure in ethanol solution, diols 9 and 10, in which the hydroxyl groups are cis to one another, each gave predominantly the product in which hydrogen had added cis to the hydroxyl groups. Diol 9 showed the greatest stereoselectivity, yielding 90% of 1 and 10% of 2. Diol 9 has its isopropyl group on the opposite side of the ring from its two hydroxyl groups. When the isopropyl group and the two hydroxyl groups are on the same side of the ring (diol 10), the stereoselectivity is reduced somewhat, but steric hindrance caused by the isopropyl group is not sufficient to overcome the preference for hydrogen addition cis to the hydroxyl groups. Thus diol 10 gave 70% of 4, and 30% of 3. This result supports the idea that a net attractive interaction between allylic hydroxyl groups and the catalyst surface exerts a significant influence upon the stereochemistry of the Raney nickel-catalyzed hydrogenation of a carbon–carbon double bond. Related examples have been reported.[13]

Similar hydrogenation of diols 11 and 12, each of which has one hydroxyl group on each side of the ring, showed little stereoselectivity. In each case, a little more of the product resulted from hydrogen addition cis to the 3-hydroxyl group than from addition cis to the 6-hydroxyl group. Thus diol 11 gave 35% of diol 5 and 65% of diol 6, while diol 12 gave 60% of diol 7 and 40% of diol 8.

Each of the four binary mixtures of p-menthane-2,5-diols described above was separable by chromatography on alumina. Four-component diol mixtures, 1, 2, 3, and 4, and also 1, 2, 5, and 6 were also separable by chromatography on alumina. Therefore, rather than separate the mixture of diols 9 and 10 (prepared as reported previously[2]), it was found advantageous to hydrogenate the mixture of diols 9 and 10 and then separate the four product diols (1–4) in one operation by chromatography on alumina. The all-cis diol 3, eluted first, was followed by diols 2, 4, and 1.

(+)-p-Menthane-2,5-diols 7 and 8 were prepared by lithium aluminum hydride reduction of (+)-*cis*- and

(7) About 60 years ago, hydrogenation of thymohydroquinone was reported to give a mixture from which was isolated a product, mp 112°, a p-menthane-2,5-diol: G. G. Henderson and M. M. J. Sutherland, *ibid.*, **97**, 1616 (1910). We have no clue to the identity of this product.

(8) G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957); see p 592 therein.

(9) A. Blumann, E. W. Della, C. A. Henrick, J. Hodgkin, and P. R. Jefferies, *Aust. J. Chem.*, **15**, 290 (1962), and references cited therein.

(10) Samples previously reported[8] as diols 3 and 4 have been shown to be mixtures.[4] Those previously reported[9] as diols 5 and 11 have been shown to be 1,2-diols,[2] and the diol reported[9] as 12 has been reassigned structure 11.[2]

(11) (a) S. H. Schroeter and E. L. Eliel, *J. Org. Chem.*, **30**, 1 (1965), and references cited; (b) E. E. Royals and J. C. Leffingwell, *ibid.*, **31**, 1937 (1966), and references cited.

(12) Reference 11a, and ref 49 therein.

(13) M. C. Dart and H. B. Henbest, *J. Chem. Soc.*, 3563 (1960); S. Nishimura and K. Mori, *Bull. Chem. Soc. Jap.*, **36**, 318 (1963); J. E. Anderson, F. G. Riddell, J. P. Fleury, and J. Morgen, *Chem. Commun.*, 128 (1966); S. Mitsui, Y. Senda, and H. Saito, *Bull. Chem. Soc. Jap.*, **39**, 694 (1966), and ref 1 and 2 therein; T. J. Howard and B. Morley, *Chem. Ind. (London)*, 73 (1967); S. Mitsui, K. Hebiguchi, and H. Saito, *ibid.*, 1746 (1967).

(+)-*trans*-*p*-menthane-2,5-dione (**13** and **14**), respectively, before the alternate precursor, diol **12**, had been isolated.[2] The (+)-*trans*-dione **14** gave a mixture of the four expected *p*-menthane-2,5-diols: **2** + **4**, 44%; **6**, 6%; and **8**, 50%. The all-equatorial diol **8**, the major product, was isolated by fractional crystallization. The (+)-*cis*-dione **13** gave diols **1**, **3**, **5**, and **7** in the ratio 1:47:33:19. The major product was the all-cis diol **3**. Diol **7** was isolated from the mixture by fractional crystallization. Reduction product mixtures were analyzed by gas chromatography.

The very low yield of diol **1** (1%) from the lithium aluminum hydride reduction of the (+)-*cis*-dione **13** is of interest because it requires at least one highly stereoselective hydride addition step. This point will be discussed more fully elsewhere.

The (+)-*cis*-dione **13** was prepared by Jones oxidation of diol **1**, **3**, or **5**. The (+)-*trans*-dione **14** was prepared by Jones oxidation of diol **4** or **6**. In both the Jones oxidations[6] of diols to diones, and in the lithium aluminum hydride reductions of diones to diols, no significant epimerization of alkyl groups was detected by careful gas chromatographic analysis. In the Raney nickel catalyzed hydrogenations of diols **9–12** described above, in no case was there any detectable epimerization at C-2, C-4, or C-5.

The equilibration of diones (±)-**13** and (±)-**14** has been studied and methods for gas chromatographic analysis of diols **1–8** have been developed.[14] Indeed, the key to the preparative work reported above was analysis by gas chromatography, using columns developed specifically for this purpose by Arthur Clements.[14] Key physical properties and yields of diols **1–8** are summarized in Table I. Conformational studies of diols **1–8** provide the subject for a subsequent publication in which physical properties are treated more fully.

TABLE I
MELTING POINTS, MOLECULAR ROTATIONS, RETENTION TIMES, AND YIELDS OF THE OPTICALLY ACTIVE *p*-MENTHANE-2,5-DIOLS (1–8)

Diol	Mp, °C	$[M]_D$,[a] deg	Time,[b] min	Yield, %,[c] H_2/Ni	Yield, %,[d] $LiAlH_4$
1	137	+58	16.8	90	1
2	177	+150	13.2	10	*e*
3	132	+40	14.5	30	47
4	157	−72	13.2	70	*e*
5	121	+34	12.1	35	33
6	129	+34	9.4	65	6
7	169	+112	18.2	60	19
8	144	+34	15.9	40	50

[a] For diols **1–8**, $[M]_D = 1.723\ [\alpha]_D$. [b] Gas chromatographic retention times in a typical case. [c] Per cent yield upon hydrogenation of the corresponding *p*-menth-1-ene-3,6-diol (**9–12**). [d] Per cent yield from lithium aluminum hydride reduction of the corresponding *p*-menthane-2,5-dione (**13** or **14**). [e] The sum of **2** plus **4** (which have the same retention time) was 44%.

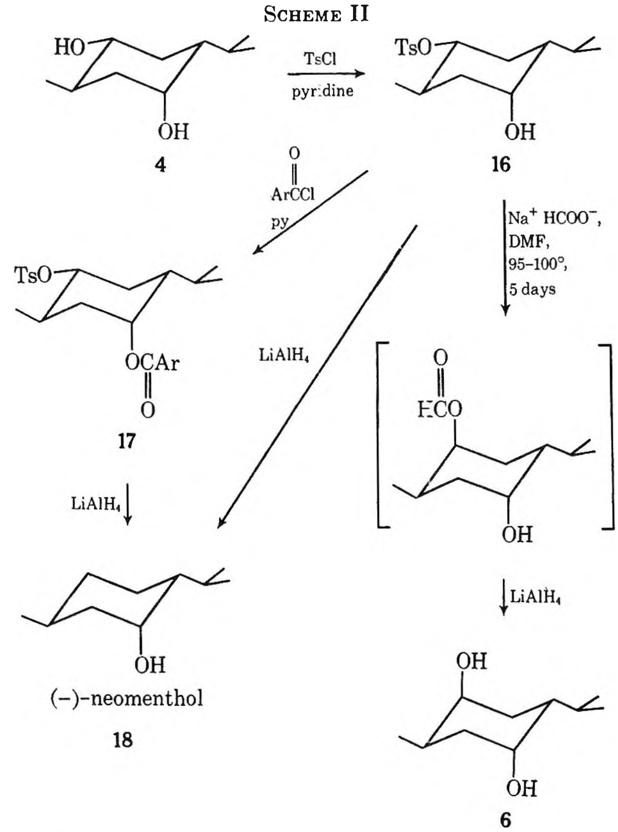
Absolute Configuration.—Diols **9** and **10**, each prepared by opening the oxygen–oxygen linkage of the corresponding cyclic peroxide of (−)-α-phellandrene,[2,8] must each be a *p*-menth-1-ene-3,6-diol with hydroxyl groups cis to one another. Therefore, diols **1–4**, prepared by hydrogenation of diols **9** and **10**, each must have its hydroxyl groups cis to one another.

(14) A. E. Clements, M.S. Thesis, Tufts University, 1965.

As described above, Blumann, *et al.*, showed unequivocally that the (+)-*p*-menthane-2,5-diol, observed mp 137°, has structure **1**.[2,8] Assignment of structure **9** to the (−)-*p*-menth-1-ene-3,6-diol, mp 168°, precursor of diol **1**, is therefore required.[2,9] Assignment of structure **2** to the (+)-*p*-menthane-2,5-diol, mp 177°, follows from the fact that it is the coproduct of diol **1** formed upon hydrogenation of diol **9**, and therefore the diol, mp 177°, must have structure **2**, the C-1 epimer of **1**.[2,8,9]

Assignment of structure **4** to the (−)-*p*-menthane-2,5-diol, mp 157°, was based upon its degradation to (−)-neomenthol (**18**) as shown in Scheme II. The

SCHEME II



objective was removal of the C-2 hydroxyl group without affecting the stereochemistry at C-1, C-4, or C-5. Treatment of diol **4** with 1 equiv of *p*-toluenesulfonyl chloride in pyridine at *ca.* 25° gave a monotosylate **16**, mp 97°, in 80% yield. The monotosylate **16** was converted to a monotosylate mono-3,5-dinitrobenzoate (**17**), mp 193° dec. Reaction of either **16** or **17** with excess lithium aluminum hydride to bring about displacement of tosylate by hydride gave a total product which contained small amounts of the starting diol **4**, none of the carvomenthols, no neoisomenthol, no isomenthol, <6% of menthol, and >94% of neomenthol, as shown by gas chromatographic comparison with an eight-component mixture containing the four carvomenthols plus the four menthols. Neomenthol had the shortest retention time. The minor component which had the same retention time as menthol was not isolated or identified; the possibility that it was an elimination product has not been ruled out. The major component of the product from **17**, isolated by preparative gas chromatography, gave an infrared spectrum identical with that of an authentic sample of (+)-neomenthol. The neomenthol isolated as the major component from **16** was shown to be (−)-neomenthol (**18**) by conversion into its 3,5-dinitrobenzoate, **19**, mp 154°, $[\alpha]^{27}D$ −22°, which gave an nmr spectrum identical in all respects with that of an authentic sample of its enantiomer, mp 156°, $[\alpha]^{27}D$ +23°, prepared from authentic (+)-neomenthol. The isolation of (−)-neomenthol (**18**) requires that the monotosylate of diol **4** must have structure **16** as shown, with the tosyloxy group at C-2 rather than at C-5.[15]

It follows from the unequivocal assignment of structure **4** above that the immediate precursor of diol **4**, the (−)-p-menth-1-ene-3,6-diol, mp 149°, with its hydroxyl groups cis to one another, must have structure **10**, as assigned.[2,8,9] Therefore, the (+)-p-menthane-2,5-diol, mp 132°, the coproduct of diol **4** formed upon hydrogenation of diol **10**, must have structure **3**, the C-1 epimer of **4**. The all-cis configuration (structure **3**) was confirmed for the (+)-p-menthane-2,5-diol, mp 132°, by infrared spectroscopy.[4] Diol **3**, which exhibits significant intramolecular hydrogen bonding, is unique among the p-menthane-2,5-diols.[4]

The configuration of diol **6** was established by its preparation from diol **4** by a stereospecific route (Scheme II). The monotosylate **16**, upon treatment with sodium formate in dimethylformamide at 95–100° for 5 days, yielded a monoformate. Reduction of the monoformate with lithium aluminum hydride gave a (+)-p-menthane-2,5-diol, mp 129°, assigned structure **6**. When the total product of reaction of the monotosylate **16** with formate ion in dimethylformamide was treated with lithium aluminum hydride, analysis of the resultant total product mixture by gas chromatography showed no detectable amount of diols **1**, **3**, **5**, **7**, and **8**, and showed the presence of diols **4** and **6** in the ratio 1:34. Attack by formate ion upon C-2 of tosylate **16** with inversion of configuration, followed by hydride reduction of the formate without change in configuration, would convert **16** into diol **6**.[16]

The coproducts of hydrogenation of the (−)-p-menth-1-ene-3,6-diol, mp 112°, are the (+)-p-menthane-2,5-diols, mp 121 and 129°. The latter was identical with diol **6** (prepared from diol **4** as described above) as shown by melting point, mixture melting point, and gas chromatography. The (−)-p-menth-1-ene-3,6-diol, mp 112°, which gives diol **6** upon hydrogenation, must therefore have structure **11**, as assigned.[2] The (+)-p-menthane-2,5-diol, mp 121°, coproduct of **6** in the hydrogenation of **11**, has been assigned structure **5**, the C-1 epimer of diol **6**.

(15) The equatorial hydroxyl group at C-2 of diol **4** reacted faster to form the mono-p-toluenesulfonate ester (**16**) than did the more sterically hindered axial hydroxyl group at C-5. Comparison of the nmr spectra of diol **4** and its monotosylate showed a large downfield shift for the axial C-2 proton of the monotosylate (δ, C-2 proton: **4**, 2.90 ppm; **16**, 4.1 ppm), while the equatorial C-5 proton was affected only slightly. Thus the nmr spectrum of the monotosylate of diol **4** is also consistent with structure **16**, with the electron-attracting tosyloxy group at C-2 rather than C-5.

(16) F. C. Chang and R. T. Blickenstaff, *J. Amer. Chem. Soc.*, **80**, 2906 (1958), reported that β-cholestanyl tosylate, 2.5% in dimethylformamide, 23 hr at 78°, gave 75% of α-cholestanyl formate. This reaction was tested by using it to convert menthol into neomenthol. The total product of the reaction of menthyl tosylate with dimethylformamide for 6 days at 75–80°, still containing some starting tosylate (thin layer chromatography), was reacted with lithium aluminum hydride to give two major components corresponding in gas chromatographic retention time to the expected product, neomenthol, plus menthol. The menthol presumably was formed from the unreacted tosylate. If so, its formation may be analogous to the formation of 57% cholestan-6α-ol (and 38% of cholestane) upon treatment of cholestan-6α-yl tosylate with lithium aluminum hydride, as reported by N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interchemical Corp., New York, N. Y., 1956, pp 855–873.

(+)-*cis*-p-Menthane-2,5-dione (**13**) (prepared unequivocally by Jones oxidation of diols **1**, **3**, and **5**), upon lithium aluminum hydride reduction, would be expected to give diols **1**, **3**, **5**, and **7**. The reduction gave a four-component product mixture which contained 19% of a (+)-p-menthane-2,5-diol, mp 168–169°, different from diols **1**, **3**, and **5**. The diol, mp 168–169°, was therefore assigned structure **7**.

(+)-*trans*-p-Menthane-2,5-dione (**14**) (prepared unequivocally by Jones oxidation of diols **4** and **6**) would be expected to give diols **2**, **4**, **6**, and **8** upon reduction with lithium aluminum hydride. The major component of the product mixture, 50% of a (+)-p-menthane-2,5-diol, mp 144°, isolated by fractional crystallization, was different from diols **2**, **4**, and **6**. The diol, mp 144°, was therefore assigned structure **8**.

The coproducts of hydrogenation of the (+)-p-menth-1-ene-3,6-diol, mp 123°, gave the same retention times upon gas chromatography as diols **7** and **8**. One of the coproducts, mp 168–169°, isolated by chromatography on alumina, gave the same melting point, optical rotation, and retention time as diol **7** prepared from dione **13** as described above. Therefore, the (+)-p-menth-1-ene-3,6-diol, mp 123°, must have structure **12**, as assigned.[2]

The chemical interconversions reported or cited above are more than adequate to establish the absolute configurations of the p-menthane-2,5-diols (**1**–**8**), the p-menth-1-ene-3,6-diols (**9**–**12**), the (+)-p-menthane-2,5-diones (**13** and **14**), and, of course, the complete set of their enantiomers. The configurational relationships among compounds **1**–**15** are shown in Scheme I.

Since the completion of our work,[1] a communication has appeared which reports isolation of diol **8**, mp 143–144°, in 0.003% yield from a natural source.[17] The six infrared absorption peaks reported for this sample[17] are probably consistent with those we found for diol **8**. Jones oxidation was reported[17] to yield a dione, mp 56–57°. Both reported melting points[17] are in excellent agreement with our own values for diol **8**, mp 144–144.5°, and its expected oxidation product, dione **14**, mp 55.5–56°. However, the diol sample isolated from natural sources is reported[17] to give $[\alpha]^{16}D$ −17.8° (c 1.065, ethanol), whereas our sample, the absolute configuration of which has been established above, gave $[\alpha]^{25}D$ +20° (c 0.876, ethanol). If in fact the sample isolated from natural sources is levorotatory, then it *cannot* have structure **8** as claimed.[17,18]

(17) T. Hashizume and I. Sakata, *Tetrahedron Lett.*, 3355 (1967).

(18) The optical rotation expected for diol **8** may be estimated simply by taking the sum of the observed molecular rotations of the corresponding monoalcohols. Taking (+)-menthol, [M]D +77°, and (−)-carvomenthol, [M]D −43°, from J. H. Brewster, *J. Amer. Chem. Soc.*, **81**, 5483 (1959), Table VII, the sum, [M]D +34°, is the molecular rotation expected for diol **8**. Diol **8**, prepared in this work, gave [M]D +34°, as expected (Table I). Similarly, optical rotations for (+)-menthyl acetate, $[\alpha]D$ +80° (*Beil.*, **6**, III, 143) and (−)-carvomenthyl acetate, $[\alpha]D$ −28° (*Beil.*, **6**, I, 19), can be used to estimate the expected optical rotation of the diacetate of diol **8**. It was reported[17] that the levorotatory diol gave a dextrorotatory diacetate. mp 66–67°, $[\alpha]^{10}D$ +15°, a value inconsistent with that expected for either the diacetate of diol **8**, $[\alpha]D$ *ca.* +40°, or its enantiomer, *ca.* −40°. Unfortunately, no optical rotation was reported for the dione sample prepared from the levorotatory diol.[17] If diol, dione, and diacetate had all been levorotatory, one would have been forced to consider the possibility that the diol reported[17] was the enantiomer of diol **8**. However, this possibility seems very unlikely. From a natural source rich in derivatives of (−)-α-phellandrene,[17] isolation of diol (−)-**8** with absolute configuration at C-4 opposite to that of (−)-α-phellandrene (**15**) would be astounding. In the absence of additional information, the identity of the sample isolated from natural sources[17] remains in question.

Experimental Section

Routine spectral data and analyses by gas chromatography were recorded as described previously.[2,19] Retention times for diols 1–8 are given in Table I. Optical rotations at 589 mμ were measured by use of Zeiss and Perkin-Elmer Model 141 polarimeters. ORD curves of diones 13 and 14 were recorded on a Cary Model 60 spectropolarimeter.

Analytical thin layer chromatograms were carried out on 5 × 20 or 10 × 20 cm glass plates uniformly coated with a 0.25-mm layer of aluminum oxide G or silica gel G (E. Merck).[20] The plates were activated by heating at *ca.* 75° for 1 hr. Exposure of the developed plates to iodine vapor allowed detection of separated components.

Melting points were determined in open Pyrex glass capillary tubes by use of an oil bath apparatus and are corrected. Microanalyses were determined by Dr. S. M. Nagy.

Reactions involving lithium aluminum hydride were carried out in a dry nitrogen atmosphere.

(+)-*p*-Menthane-2,5-diols, mp 137 and 177° (1 and 2). Hydrogenation of Diol 9.—The reported procedure[4] gave diol 1 {mp 136.5–137°; $[\alpha]^{27}D$ +34° (*c* 7.46, ethanol); ir (KBr) 1037, 1002, 984, 962 cm^{-1}} and diol 2 {mp 177–177.5°; $[\alpha]^{25}D$ +87° (*c* 0.874, ethanol); ir (KBr) 1073, 1025, 998, 979 cm^{-1}} (reported[8,9] for diol 1, mp 134°, $[\alpha]D$ +32°; for diol 2, mp 176°, $[\alpha]D$ +80°).

(+)-*cis,cis,cis*-*p*-Menthane-2,5-diol, mp 132° (3), and (−)-*p*-Menthane-2,5-diol, mp 157° (4). A. Hydrogenation of a Mixture of Diols 9 and 10.—Preparation in relatively large quantity of a mixture of diols 9 and 10, mp 132–145°, has been reported.[2] To a solution of 3.00 g (0.0174 mol) of the mixture in 150 ml of 95% ethanol was added 4.5 g of neutral Raney nickel catalyst (moist with ethanol). Hydrogenation, as above, followed by removal of catalyst and solvent, gave 3.0 g of white solid. Three recrystallizations from benzene gave 1.0 g of diol 4: mp 156.5–157°; $[\alpha]^{27}D$ −42° (*c* 6.88, ethanol); ir (KBr) 1049, 1033, 1023 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.90; H, 11.82.

The combined filtrates were evaporated to dryness. Part of the residue, 1.5 g, was chromatographed on 150 g of alumina (Fisher, A-540). Elution with 1% methanol in ether gave first 0.60 g of diol 3, mp 130–132°, free from detectable amounts of the other diols (gas chromatography). Two recrystallizations from benzene gave diol 3, mp 132–132.5°, $[\alpha]^{26}D$ +23° (*c* 7.70, ethanol), which gave infrared spectra (KBr and CCl_4) and a retention time in gas chromatography identical with those of its racemate, (±)-3, mp 105°,[3,4] ir (KBr) 1048, 1032, 958 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 70.09; H, 11.80.

Further elution gave 30 mg of solid, mp 176° (diol 2), followed by 100 mg of solid, mp 146–148° (mixture of diols 2 and 4: gas chromatography, and thin layer chromatography on alumina), followed by 350 mg of solid, mp 156–157° (diol 4). Finally, elution with 2% methanol in ether gave 400 mg of solid, mp 137° (diol 1).

Thin layer chromatography of a mixture of diols 1–4 on aluminum oxide plates activated by heating at 73° for 1 hr gave, with 2% methanol in ether, the following R_f values for each diol: 1, 0.39; 4, 0.52; 2, 0.58; 3, 0.69. These values correspond to the elution order observed during column chromatography on alumina, described above.

B. Hydrogenation of Diol 10.—To a solution of 0.500 g (2.94 mmol) of (−)-*p*-menth-1-ene-3,6-diol (10), mp 147–149°,[2] in 30 ml of 95% ethanol was added 0.8 g of neutral Raney nickel catalyst (moist with ethanol). Hydrogenation as above, followed by removal of catalyst and solvent, gave a 3:7 mixture (gas chromatogram of total product) of diols 3 and 4. Crystallization from 40 ml of benzene gave diol 4, 0.250 g (50%), mp 156.5–157°. The filtrate, upon evaporation, gave 0.230 g of a mixture of diols 3 and 4, mp 105–115°, saved for future separation by chromatography on alumina by the method above which gave clean separation of diols 3 and 4.

(+)-*p*-Menthane-2,5-diols, mp 121 and 129° (5 and 6). A. Hydrogenation of a Mixture of Diols 9 and 11.—To a solution of 2.00 g (0.0118 mol) of a mixture[2] containing 88% of (−)-*p*-menth-1-ene-3,6-diol (11), mp 112°, plus 12% of impurity identified by gas chromatography[2] as (−)-*p*-menth-1-ene-3,6-diol (9), mp 168°, in 100 ml of 95% ethanol was added 3 g of neutral Raney nickel catalyst (moist with ethanol). At 22° and *ca.* 3-atm hydrogen pressure (Parr apparatus Model 3911), hydrogenation was *ca.* 80% complete in 1 hr and was stopped after 8 hr. Removal of catalyst and solvent gave 2.0 g of colorless semisolid. Upon gas chromatography, a sample of the total product gave two major and two minor peaks, the latter with the same retention times as diols 1 and 2, the known products of hydrogenation of diol 9 (the impurity[2]). Attempts to isolate diols 5 and 6 by crystallization from ether–hexane or benzene were unsuccessful, since diols 1 and 2 were less soluble. Only diol 1 was isolated. However, chromatography on 140 g of alumina (Fisher Scientific Co., A-540) of the 1.20-g residue, obtained from the combined filtrates of three crystallizations of the product mixture, gave clean separation of the four colorless component diols: 1, 2, 5, and 6. Elution first with redistilled benzene gave 0.52 g of diol 6, mp 129°; 1:1 anhydrous ether–benzene next gave 0.50 g of diol 5, mp 121°; 1% methanol in anhydrous ether then gave 0.02 g of diol 2, mp 176°, followed by 0.08 g of diol 1, mp 137°.

Diol 5 after crystallization from 3:1 hexane–ether, gave mp 120.5–121°; $[\alpha]^{28}D$ +20° (*c* 5.53, ethanol); ir (KBr) 1110, 1048, 1032, 939 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.61; H, 11.45.

Diol 6 after two crystallizations from 10:1 hexane–ether gave mp 128.5–129°; $[\alpha]^{26}D$ +20° (*c* 7.86 or 0.96, ethanol); ir (KBr) 1030, 998, 972 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.98; H, 11.85.

A second run in which the total hydrogenation product, 2.0 g, was chromatographed as above, gave 0.80 g of recrystallized diol 6, mp 129°, and 0.39 g of recrystallized diol 5, mp 121°.

B. Hydrogenation of Diol 11.—To a solution of 0.52 g (3.3 mmol) of pure diol 11, mp 112°,[2] in 40 ml of 95% ethanol was added 1.1 g of neutral Raney nickel catalyst (moist with ethanol). Hydrogenation, as above, gave 0.50 g of white solid product, containing about 35% of diol 5 and 65% of diol 6 (gas chromatography). Column chromatography on alumina, as above, followed by recrystallization gave 0.120 g of diol 5, mp 121°, and 0.280 g of diol 6, mp 129°.

5-Hydroxy-2-*p*-menthyl *p*-Toluenesulfonate 16, a Monotosylate from Diol 4.—To a solution of 0.50 g (2.9 mmol) of diol 4 in 8 ml of dry pyridine in an ice bath was added with stirring, 0.55 g (2.9 mmol) of *p*-toluenesulfonyl chloride over a period of 10 min. The clear solution was stored for 3 days at room temperature. Pyridine was removed at 25° (reduced pressure). The viscous residue was triturated with crushed ice. A white solid, 0.82 g (86%), mp 90–93°, was obtained, Crystallization from hexane gave 0.70 g (67%) of long thin needle-like crystals, mp 96°. Two recrystallizations from hexane gave crystals: mp 97–97.5°, $[\alpha]^{26}D$ −60° (*c* 0.202, ethanol); nmr peaks (10% solution in $CDCl_3$) at δ (ppm) 7.85, 7.71, 7.37, 7.23 (4 H quartet, aromatic), 4.32–3.89 (2 H), 2.42 (3 H singlet, H_3CAr), 2.18–1.02 (8 H), 0.933, 0.817, 0.71 (9 H, three overlapping doublets, $(CH_3)_2CH$ and CH_3CH). The C-2 proton multiplet centered at 4.1 ppm overlapped the C-5 proton multiplet centered at 3.95 ppm.

Anal. Calcd for $C_{17}H_{26}O_4S$: C, 62.55; H, 8.03. Found: C, 62.60; H, 7.99.

The 3,5-Dinitrobenzoate 17, Derived from 16.—To a solution of 0.326 g (1.00 mmol) of the monotosylate 16, mp 96°, in 5 ml of dry pyridine stirred in an ice bath, was added a solution of 0.250 g (1.08 mmol) of 3,5-dinitrobenzoyl chloride in 5 ml of benzene. The mixture was stirred for 2 days at room temperature. The solvent was removed at 25° (reduced pressure). The residue was triturated with crushed ice. The white solid which separated was collected and washed with four 5-ml portions of water at ~0°. Crystallization of the dried solid from benzene gave 0.350 g (67%) of needle-like crystals, mp 188–191° dec. Two recrystallizations from benzene gave 17, mp 193° dec, ν_{max}^{Nujol} 1725 cm^{-1}.

Anal. Calcd for $C_{24}H_{28}N_2O_9S$: C, 55.40; H, 5.38; N, 5.38. Found: C, 55.54; H, 5.47; N, 5.27.

Degradation of Diol 4 to Neomenthol (18). A. Reaction of the Monotosylate–Monodinitrobenzoate 17 with Lithium Aluminum Hydride.—To a stirred suspension of 0.60 g (0.016 mol) of lithium aluminum hydride in 150 ml of anhydrous ether was added a solution of 0.280 g (0.538 mmol) of 17 in 80 ml of tetra-

(19) Nmr and infrared spectra of diols 1–12 have been reproduced in the Doctoral Dissertation of K. Sachdev, Tufts University, 1966.

(20) E. Stahl, Ed., "Thin-Layer Chromatography," Academic Press, New York, N. Y., 1965.

hydrofuran (freshly distilled from lithium aluminum hydride)[21] during 7 min. The mixture was heated under reflux for 2 days. Most of the tetrahydrofuran was removed by distillation. To the residue was added 100 ml of ether followed by 4 ml of saturated aqueous sodium sulfate. The salt was separated by filtration and was washed several times with ether. The ether was removed from the filtrate and the residue was crystallized from hexane to give 25 mg of diol **4**, mp 155–156°, identified by mixture melting point, gas chromatography, and infrared spectroscopy. The hexane filtrate was analyzed by gas chromatography on a column[14] capable of resolution of an eight-component mixture of the four menthols and the four carvomenthols. The reaction product showed no detectable amount of any of the carvomenthols or of isomenthol or neoisomenthol (direct comparison by gas chromatography). Two components were observed with a peak ratio of 17:1. The major component was collected. Its retention time and infrared spectrum were identical with those of an authentic sample of (+)-neomenthol.[22] The minor component which had the same retention time as menthol, was not isolated or identified.

B. Reaction of the Monotosylate 16 with Lithium Aluminum Hydride.—To a stirred suspension of 150 mg (3.84 mmol) of lithium aluminum hydride in 70 ml of anhydrous ether was added a solution of 254 mg (0.78 mmol) of monotosylate **16** in 15 ml of ether during 5 min. The mixture was heated gently under reflux for 24 hr. The excess hydride was decomposed with 1 ml of saturated aqueous sodium sulfate. The mixture of salts was collected by filtration and was washed thoroughly with ether. The filtrate was dried ($MgSO_4$). Removal of the solvent (reduced pressure) gave 0.152 g of colorless oil. Analysis by thin layer chromatography on silica gel with 1:1 ether–hexane showed three spots, R_f 0.08, corresponding to diol **4**, 0.48, unidentified, and 0.59, corresponding to neomenthol. No monotosylate **16** was detected. After separation of 5 mg of diol **4**, mp 156.5–157°, by crystallization, the filtrate was subjected to preparative thin layer chromatography on silica gel PF_{254} (E. Merck), to remove the remaining diol **4**. The resulting two component mixture gave a major peak in gas chromatography with the same retention time as neomenthol, and a minor peak, *ca.* 6%, unidentified, but with the same retention time as menthol. The two-component mixture gave $[\alpha]^{27}D$ −13° (*c* 0.539, methanol), whereas authentic (+)-neomenthol[22] gave $[\alpha]^{27}D$ +20.4° (c 0.673, methanol) (reported[23] (+)-neomenthol, $[\alpha]D$ +19.7°).

(−)-Neomenthyl 3,5-Dinitrobenzoate (19).—To a stirred solution of 27.8 mg (0.178 mmol) of the above two-component mixture in 0.5 ml of dry pyridine cooled in an ice–salt bath, was added 50 mg (0.22 mmol) of 3,5-dinitrobenzoyl chloride dissolved in 1 ml of dry benzene. The mixture was allowed to attain room temperature. After 44 hr, most of the solvent was removed at 25–30° under reduced pressure. Trituration of the residue with crushed ice gave 48 mg of solid. Two crystallizations from 5:1 hexane–ether gave 12 mg of **19**, white needle-like crystals, mp 154°, $[\alpha]^{27}_{589}$ −22°, $[\alpha]^{27}_{436}$ −42.2° (*c* 1.027, chloroform). The sample gave the same R_f in thin layer chromatography and the same nmr spectrum (in deuteriochloroform) as an authentic sample of (+)-neomenthyl 3,5-dinitrobenzoate, described below.

(+)-Neomenthyl 3,5-Dinitrobenzoate.—The procedure above was used to prepare the ester from authentic (+)-neomenthol.[22] The derivative gave mp 155.5–156° (reported[23] mp 153°), $[\alpha]^{27}_{589}$ +23°, $[\alpha]^{27}_{436}$ +45.6° (*c* 1.152, chloroform).

Diol 6 from Diol 4 *via* Monotosylate 16.—To a solution of 163 mg (0.500 mmol) of **16**, mp 96°, in 5 ml of dimethylformamide (Fisher reagent) was added 68 mg (0.50 mmol) of sodium formate. The mixture was stirred and heated at 95–100° in a nitrogen atmosphere for 5 days. The product mixture was diluted with 5 ml of water and was extracted with three 40-ml portions of ether. The ether extract was washed with two 15-ml portions of water and then dried ($MgSO_4$). Evaporation of the ether gave 80 mg of yellowish oil, which gave carbonyl absorption at 5.8 μ and two spots on thin layer chromatography on silica gel with anhydrous ether as solvent. The spot of lower R_f corresponded to unreacted tosylate **16**.

To a stirred suspension of 0.100 g of lithium aluminum hydride in 50 ml of anhydrous ether was added slowly a solution of the yellow oil (presumably containing crude monoformate) in 10 ml of ether. The mixture was heated under reflux for 6 hr. Excess hydride was decomposed by addition of 1 ml of saturated aqueous sodium sulfate. The semisolid product, upon gas chromatography, gave three peaks, two of which corresponded in retention time to diols **6** (8 2 min) and **4** (11.4 min) with peak height ratio of 34:1; the third peak, with very short retention time (1.4 min), was not a *p*-menthane-2,5-diol. No detectable amount of diols **1**, **3**, **5**, **7**, or **8** was observed in the product. Crystallization from hexane gave diol **6**, 35 mg (41%), mp 129°, containing a trace of diol **4**. The sample gave the same melting point, mixture melting point, infrared spectrum, and retention time in gas chromatography as the sample of diol **6** prepared above by hydrogenation of diol **11**.

(+)-*cis-p*-Menthane-2,5-dione (13). A. Oxidation of Diol 1.—To a solution of 0.50 g (2.9 mmol) of diol 1, mp 135–136°, in 25 ml of acetone (redistilled from potassium permanganate) at 0–5°, was added dropwise during 15 min with vigorous stirring, 2.8 ml (100% excess) of 2.8 *M* chromium trioxide solution.[6] After 10 min more, the reaction mixture was combined with a solution of 0.8 g of sodium hydrogen sulfite in 20 ml of water and the mixture was extracted immediately with three 150-ml portions of ether. The combined ether extract was washed with 50 ml of 10% aqueous ammonium chloride, 50 ml of 10% aqueous sodium bicarbonate, and 30 ml of water. The ether solution was dried ($MgSO_4$). Removal of the ether and recrystallization of the residue from hexane gave 0.40 g (82%) of shiny white plates, mp 68–69°, containing <1% (detected by gas chromatography) of the *trans*-dione **14**. Two recrystallizations from hexane gave the (+)-*cis*-dione **13**: mp 69–69.5°; $[\alpha]D$ +294° (*c* 1.58, benzene); ORD [A] +183° (*c* 1.05, hexane), extrema 325, 275 mμ.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.25; H, 9.71.

B. Oxidation of Diol 5.—A solution of 0.100 g (0.58 mmol) of diol **5**, mp 120.5–121°, in 8 ml of acetone was treated, as above, with 0.55 ml of 2.8 *M* chromium trioxide solution (100% excess) added during 10 min. The total product contained *ca.* 1% (detected by gas chromatography) of *trans*-dione **14**. Crystallization from hexane gave a first crop of 50 mg (50%) of (+)-*cis*-dione **13**, mp 68–69°, mixture melting point with the analytical sample, mp 68–69°, infrared spectrum identical with that of the analytical sample, $[\alpha]^{26}D$ +280° (*c* 0.129, benzene).

(+)-*trans-p*-Menthane-2,5-dione (14). A. Oxidation of Diol 4.—A solution of 0.50 g (2.9 mmol) of diol **4**, mp 156.5–157°, in 35 ml of acetone, was treated exactly as above (for part A, preparation of **13**). The total oxidation product contained <1% (detected by gas chromatography) of the *cis*-dione **13**. Crystallization from hexane gave 0.40 g (82%) of the (+)-*trans*-dione **14**, mp 55–56°. Two recrystallizations from hexane gave **14**: mp 55.5–56°; $[\alpha]^{26}D$ +49° (*c* 1.29, benzene); ORD [A] +30.4° (*c* 0.803, *n*-hexane), extrema 317, 278 mμ.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.28; H, 9.76.

B. Oxidation of Diol 6.—A solution of 0.100 g (0.58 mmol) of diol **6**, mp 128.5–129°, in 8 ml of acetone was treated, as above, with 0.55 ml of 2.8 *M* chromium trioxide solution (100% excess) added during 10 min. The total product contained a small amount of *cis*-dione **13**. Crystallization from hexane gave 65 mg (67%) of **14**, mp 56°, undepressed mixture melting point with analytical sample.

Reduction of (+)-*cis-p*-Menthane-2,5-dione (13) with Lithium Aluminum Hydride.—To a stirred suspension of 0.300 g (8.1 mmol) of lithium aluminum hydride in 80 ml of anhydrous ether was added slowly a solution of 0.280 g (1.67 mmol) of (+)-*cis*-dione **13** in 10 ml of ether during 5 min. The mixture was heated under reflux for 3 hr. Excess hydride was decomposed by addition of 2 ml of saturated aqueous sodium sulfate. The semisolid total product, isolated as usual, gave four peaks upon gas chromatography, with the same retention times as diols **1**, **3**, **5**, and **7**. Diols **2**, **4**, **6**, and **8** were not detected. The gas chromatogram is consistent with the following diol composition: **1**, 1%; **3**, 47%; **5**, 33%; **7**, 19%.

(+)-*p*-Menthane-2,5-diol, mp 169° (7).—Three recrystallizations from hexane–ether of the above mixture of diols **1**, **3**, **5**, and **7**, gave thin white needle-like crystals of diol **7**: 20 mg (7%); mp 168.5–169.5°; uncontaminated by detectable amounts of diols 1–6 or **8** (gas chromatography); $[\alpha]^{26}D$ +65° (*c* 0.942, ethanol); ir (KBr) 1081, 1052, 1036, 1016 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.60; H, 11.75.

(21) *Caution!* See *Org. Syn.*, **46**, 105 (1966).

(22) The authors are grateful to Mr. F. Porsch, Dragoco, Holzminden, Germany, for his kindness in supplying a generous sample of authentic (+)-neomenthol.

(23) H. Phillips, *J. Chem. Soc.*, **127**, 2584 (1925).

Reduction of (+)-*trans*-*p*-Menthane-2,5-dione (14) with Lithium Aluminum Hydride.—As above for **13**, 0.160 g (0.95 mmol) of (+)-*trans*-dione **14**, mp 56°, plus 0.150 g (4 mmol) of lithium aluminum hydride, gave a total product which showed three peaks upon gas chromatography, corresponding in retention time to a mixture of diols **2**, **4**, **6**, and **8**. Diols **1**, **3**, **5**, and **7** were not detected. The gas chromatogram is consistent with the following diol composition: **2**, plus **4**, 44%; **6**, 6%; **8**, 50%.

(+)-*p*-Menthane-2,5-diol, mp 144° (8).—Three recrystallizations from hexane-ether of the above mixture of diols **2**, **4**, **6**, and **8**, gave colorless needle-like crystals of diol **8**: 20 mg (12%); mp 144-144.5°; uncontaminated by detectable amounts of diols **1-7** (gas chromatography); $[\alpha]^{25}D$ +20° (*c* 0.876, ethanol); ir (KBr) 1097, 1046, 1030 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.93; H, 11.80.

(+)-*p*-Menthane-2,5-diol, mp 169° (7), from Hydrogenation of Diol 12.—The hydrogenation product[2] of diol **12**, a mixture of diols **7** (59%) and **8** (41%, analysis by gas chromatography), mp 142-153°, 90 mg, was recrystallized five times from benzene-hexane-ether (5:3:2). The crystals, 11 mg, mp 169°, contained 96% diol **7** and 4% diol **8**. The mixture recovered from the combined filtrates was chromatographed on 20 g of alumina (Fisher A-540). Elution with benzene gave white solid. One crystallization from ether-hexane gave diol **8**, 20 mg, mp 142-144°, contaminated with 5% of diol **7**. Further elution with ether-benzene (1:9) gave fractions which after crystallization from hexane-ether yielded 13 mg of diol **7**, contaminated with 5% of diol **8**. The two fractions of impure diol **7**, totaling 24 mg, were combined and rechromatographed on 7 g of alumina. The last fraction obtained by elution with ether-benzene (1:9) was crystallized from hexane-ether to give 5 mg of diol **7**, mp 169°, of 99% purity, $[\alpha]^{26}D$ +63° (*c* 0.302, ethanol).

(−)-Menthyl Tosylate (20).—(−)-Menthol (Aldrich) gave (−)-menthyl tosylate (**20**), mp 95-96° (reported[24] mp 94°).

Neomenthol from (−)-Menthyl Tosylate (20).—A solution of 1.03 g of (−)-menthyl tosylate (**20**) in 30 ml of dimethylformamide (Fisher reagent grade) was heated for 6 days at 75-80°. The reaction mixture, cooled to 25°, was diluted with 100 ml of water and was extracted with three 150-ml portions of ether. The ether extract was washed with two 50-ml portions of water and then was dried over anhydrous magnesium sulfate. Evaporation of the ether left 0.35 g of yellowish oil which showed a peak at 5.8 μ (presumably neomenthyl formate carbonyl absorption). Thin layer chromatography showed two major spots, one corresponding in R_f value to the starting tosylate **20**. To a stirred suspension of 0.305 g of lithium aluminum hydride in 100 ml of anhydrous ether was added slowly a solution of the above reaction product mixture in 10 ml of ether. After heating under reflux for 5 hr, excess hydride was decomposed by addition of 2 ml of saturated aqueous sodium sulfate solution. The product, isolated by ether extraction, yielded a yellowish oil which gave a gas chromatogram with two major peaks with the same retention times as neomenthol and menthol.[16] Two unidentified minor peaks were also detected.

Registry No.—**1**, 27525-51-5; **2**, 27525-52-6; **3**, 27525-53-7; **4**, 27525-54-8; **5**, 27525-55-9; **6**, 27525-56-0; **7**, 27525-57-1; **8**, 27525-58-2; **9**, 4031-55-4; **10**, 4031-54-3; **11**, 4031-53-2; **12**, 27570-89-4; **13**, 27525-61-7; **14**, 27525-62-8; **16**, 27570-90-7; **17**, 27570-91-8; **19**, 27525-63-9.

(24) W. Hückel and C.-M. Jennewein, *Justus Liebigs Ann. Chem.*, **683**, 100 (1965).

A New Synthesis of 7,12-Dimethylbenz[*a*]anthracene[1]

MELVIN S. NEWMAN*[2] AND ZIA UD DIN

Evans Chemistry Laboratory, The Ohio State University, Columbus, Ohio 43210

Received August 7, 1970

A new synthesis, which may prove general for the synthesis of 7,12-dimethylbenz[*a*]anthracenes from the corresponding benz[*a*]anthracenes, is described. Benz[*a*]anthracene (II) was condensed with vinylene carbonate to yield 7,12-dihydro-7,12-ethanobenz[*a*]anthracene-13,14-diol cyclic carbonate (III). Hydrolysis yielded 7,12-dihydro-7,12-ethanobenz[*a*]anthracene-13,14-diol (IV) which on treatment with lead tetraacetate afforded 7,12-dialdehydo-7,12-dihydrobenz[*a*]anthracene (V). Reduction of V with lithium aluminum hydride yielded 7,12-bis(hydroxymethyl)-7,12-dihydrobenz[*a*]anthracene (VI), the bismethanesulfonyl derivative of which was reduced to 7,12-dihydro-7,12-dimethylbenz[*a*]anthracene (VIII) by lithium aluminum hydride. Aromatization of VIII by heating with sulfur afforded 7,12-dimethylbenz[*a*]anthracene (I). The yields in each step were high. Similarly, 5-fluoro-7,12-dimethylbenz[*a*]anthracene (I_F) was synthesized from 5-fluorobenz[*a*]anthracene (II_F) in high yield.

Three general syntheses of 7,12-dimethylbenz[*a*]-anthracene (I) are known. One involves addition of methylmagnesium iodide to benz[*a*]anthraquinone followed by conversion of the resulting diol with acidic methanol to the corresponding dimethoxy derivative which is reduced with metallic sodium (or potassium) to I[3] or to 7,12-dihydro-7,12-dimethylbenz[*a*]anthracene. The latter is converted to I by heating with sulfur.[3] A second method involves treating the above-mentioned dimethyldiol with hydrogen iodide to yield 12-methyl-7-iodomethylbenz[*a*]anthracene which is reduced to I with stannous chloride.[4] The third method involves treatment of 12-methylbenz[*a*]anthrone (not isolated) with methylmagnesium bromide, followed by dehydration of the crude carbinol to I.[5]

Each of these methods has potential drawbacks if variously substituted 7,12-dimethylbenz[*a*]anthracenes are desired: the first two, because of possible difficulties in the synthesis of the desired quinones and in finding proper conditions for transforming the dimethyldiols to the desired analogs of I; and the third because benzanthrones are often too sensitive to give high yields on reaction with methylmagnesium halides. For these reasons a new synthesis was deemed desirable. In this paper, such a new route is illustrated in Scheme I.

Since anthracene was known to react with vinylene carbonate to give a Diels-Alder type addition product in good yield,[6] we heated benz[*a*]anthracene in excess vinylene carbonate to produce the adduct III[7] in high

(1) This research was supported by Grant 5 RO 1 CA07394-Ob from the U. S. Public Health Service.

(2) To whom correspondence should be directed.

(3) W. E. Bachmann and J. M. Chermerda, *J. Amer. Chem. Soc.*, **60**, 1023 (1938). Similar reductions were carried out by B. M. Mikhailov and coworkers, *Chem. Abstr.*, 5842 (1939); 6350i (1948).

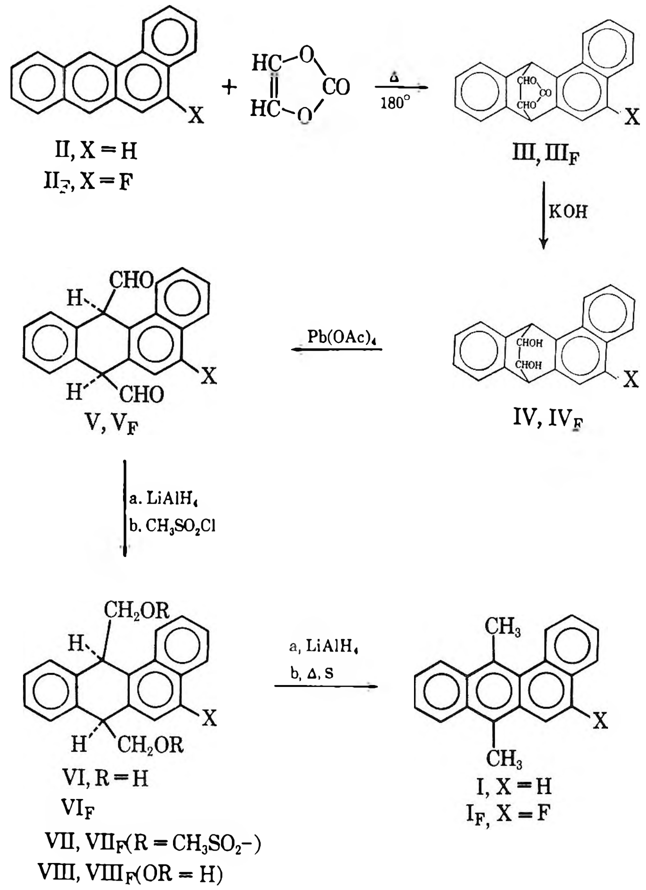
(4) R. B. Sandin and L. F. Fieser, *J. Amer. Chem. Soc.*, **62**, 3098 (1940).

(5) M. S. Newman, *ibid.*, **60**, 1141 (1938).

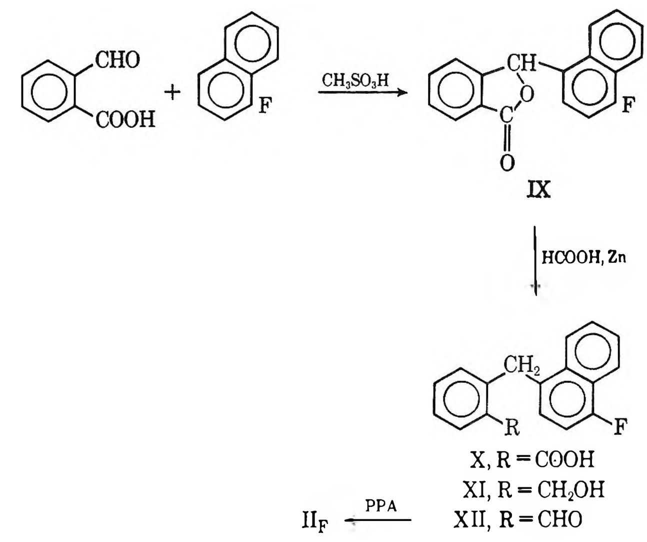
(6) M. S. Newman and R. W. Addor, *ibid.*, **77**, 3789 (1955).

(7) This product was probably a mixture of stereoisomers, but we made no attempts at separation or purification of individual isomers.

SCHEME I



SCHEME II



yield. Alkaline hydrolysis of III yielded the diol IV[7] which was cleaved to the dialdehyde V by lead tetraacetate. Attempts to reduce the aldehyde groups by the Wolff-Kishner method led surprisingly to 7-methylbenz[a]anthracene. However, the desired 7,12-dimethylbenz[a]anthracene (I) was obtained from V by reduction with lithium aluminum hydride to the diol VI, conversion of the latter to the dimesyl derivative VII, reduction of the latter to VIII with lithium aluminum hydride, and dehydrogenation by heating with sulfur. The yields in each step were very good.

In order to test the above series of reactions with a substituted benz[a]anthracene, 5-fluorobenz[a]anthracene (II$_F$) was chosen. All of the above reactions went successfully and the overall yield from II$_F$ to I$_F$ was good. The desired II$_F$[8] was prepared as shown in Scheme II.

The condensation of 1-fluoronaphthalene with phthalaldehydic acid[9] was best effected at room temperature in concentrated methanesulfonic acid.[10] The conditions necessary to cause condensation of phthalaldehydic acid with fluorobenzene were about the same as those required for condensation of o-acetylbenzoic acid with 1,2-dimethoxynaphthalene.[11] That condensation occurred para to the fluorine was established by the fact that X was identical with an authentic sample.[12] Attempts to cyclize XI to 7,12-dihydro-5-fluorobenz[a]anthracene by heating with polyphosphoric acid (PPA) followed by heating with sulfur to dehydrogenate afforded only a 10% yield of II$_F$. However, oxidation of XI to XII, using Sarett's reagent,[13] followed by heating of XII with PPA resulted in high yields of II$_F$, which was shown to be identical with II$_F$ prepared as described.[12] The above method of converting X to II$_F$ is to be preferred to the earlier synthesis[12] as a higher overall yield of II$_F$ is more reliably obtained. In our experience, routes which involve a benz[a]anthrone are liable to give erratic yields, especially on larger scale runs.

Experimental Section[14]

7,12-Dihydro-7,12-ethanobenz[a]anthracene-13,14-diol Cyclic Carbonate (III).—A solution of 6.8 g (0.03 mol) of benz[a]anthracene[15] in 25.8 g (0.3 mol) of vinylene carbonate[16] was held at reflux (about 175–180°) under nitrogen for 18 hr. On vacuum distillation about 22 g of vinylene carbonate suitable for reuse was recovered. The residue (9.38 g), a brown solid, mp 205–210°, yielded 7.5 g (80%) of yellowish adduct III,[7] mp 219–224°, ir band at 5.55 μ, on crystallization from benzene-petroleum ether (bp 60–110°).

Anal. Calcd for $C_{21}H_{14}O_3$: C, 80.3; H, 4.5. Found: C, 80.5; H, 4.6.

In an experiment essentially the same as the above, the fluorine analog[7] III$_F$, mp 228–231°, ir band at 5.55 μ, was obtained in 85% yield.

Anal. Calcd for $C_{21}H_{13}FO_3$: C, 75.9; H, 3.9; F, 5.7. Found: C, 76.0; H, 4.0; F, 5.5.

7,12-Bis(hydroxymethyl)-7,12-dihydrobenz[a]anthracene (IV).—In a typical experiment a mixture of 3.14 g of III, 2.3 g of potassium hydroxide, 3 ml of water, and 25 ml of ethanol was held at 70–75° for 2 hr. After the usual work-up, the product was crystallized from benzene–petroleum ether to yield 2.60 g (93%) of IV, mp 196–198°, ir broad band at 2.75 μ.

Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.3; H, 5.6. Found: C, 83.5; H, 5.4.

(8) M. S. Newman and K. Naiki, *J. Org. Chem.*, **27**, 863 (1962).

(9) V. W. Floutz, *ibid.*, **25**, 643 (1960), and references therein.

(10) We thank the Pennwalt Manufacturing Co., for a generous gift of 70% methanesulfonic acid. Concentrated acid is easily obtained from this by vacuum distillation.

(11) M. S. Newman and C. C. Davis, *J. Org. Chem.*, **32**, 66 (1967).

(12) M. S. Newman, D. MacDowell, and S. Swaminathan, *ibid.*, **24**, 509 (1959).

(13) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(14) All melting points are uncorrected. All microanalyses were by Galbraith Laboratories, Knoxville, Tenn. The nmr spectra of all compounds were consistent with the postulated structure. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian Model A-60 instrument at 60 Mc with tetramethylsilane as an internal reference. The term "worked up in the usual way" means that an ether–benzene solution of the reaction products was washed with dilute acid and/or base, with saturated salt solution and was filtered through a cone of anhydrous $MgSO_4$. The solvent was then removed by either distillation or a rotary evaporator.

(15) Used as obtained from Henley and Co., New York, N. Y.

(16) We thank the Union Carbide Plastics Co., Bound Brook, N. J., and the American Cyanamide Corp. for generous gifts of vinylene carbonate.

In a similar way, pure IV_F,[7] mp 230–235°, ir broad band at 2.75 μ, was obtained in 99% yield.

Anal. Calcd for $C_{20}H_{15}FO_2$: C, 78.5; H, 4.9; F, 6.2. Found: C, 78.6; H, 4.8; F, 6.0.

7,12-Dialdehydo-7,12-dihydrobenz[*a*]anthracene (V).—To a stirred solution of 36.5 g of IV in 1.5 l. of benzene and 25 ml of acetic acid at 30–35° was added 92 g of lead tetraacetate in portions during 15 min. After 2 hr the lead oxide was removed by filtration. The filtrate was worked up as usual to yield 32.4 g (89%) of V,[7] mp 175–177°, ir band at 5.75 μ, suitable for the next step. The analytical sample of V, mp 178–180°, was obtained by one recrystallization from benzene–petroleum ether.

Anal. Calcd for $C_{20}H_{14}O_2$: C, 84.0; H, 4.9. Found: C, 84.1; H, 4.8.

7,12-Dialdehydo-7,12-dihydro-5-fluorobenz[*a*]anthracene (V_F).—In a similar way V_F, mp 129–130°, was obtained in 91% yield from IV_F.

Anal. Calcd for $C_{20}H_{13}FO_2$: C, 78.9; , 4.3; F, 6.3. Found: C, 79.0; H, 4.3; F, 6.1.

7,12-Bis(hydroxymethyl)-7,12-dihydrobenz[*a*]anthracene (VI).—To the solution formed by heating a mixture of 2 g of $LiAlH_4$ and 50 ml of dry ether for 4 hr was added a solution of 5.0 g of V in 25 ml of ether and 140 ml of pure tetrahydrofuran during 15 min. After holding at reflux for 6 hr, the usual work-up afforded 4.7 g (94%) of pure VI, mp 172–173°, ir broad band at 3.05 μ, on crystallization from benzene–THF.

Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.8; H, 6.2. Found: C, 83.1; H, 6.4.

7,12-Dihydroxymethyl-7,12-dihydro-5-fluorobenz[*a*]anthracene (VI_F).—In a similar way VI_F, mp 180–181.5°, ir broad band at 3.05 μ, was obtained in 84% yield.

Anal. Calcd for $C_{20}H_{17}FO_2$: C, 77.8; H, 5.5; F, 6.2. Found: C, 78.0; H, 5.7; F, 5.9.

7,12-Dihydro-7,12-dimethylbenz[*a*]anthracene (VIII).—To a suspension of 5.0 g of VI in 125 ml of methylene chloride was added rapidly a stirred mixture formed by adding 6 g of methanesulfonyl chloride to 5 ml of dry pyridine. The reaction mixture was stirred at room temperature overnight and poured into a mixture of ice and concentrated HCl. The CH_2Cl_2 solution was washed with dilute HCl and worked up as usual. The crude reaction product was heated with 0.05-ml pressure at 60° to remove traces of methanesulfonyl chloride. A solution of this product (8.3 g, yellowish oil) in 50 ml of THF and 60 ml of ether was added during 15 min to the solution formed by refluxing a mixture of 7.5 g of lithium aluminum hydride in 150 ml of ether for 12 hr. After being held at reflux for 18 hr, the reaction mixture was cooled and treated with 7.5 ml of water, 7.5 ml of 15% NaOH, and 23 ml of water. After the usual work-up, the crude product (4.8 g) was chromatographed on 100 g of Woelm grade A neutral alumina using a mixture of petroleum ether and benzene, 1:1, to elute 3.2 g (70%) of pure VIII as colorless crystals suitable for the next step. Recrystallization of a portion from petroleum ether yielded the analytical sample of VIII, mp 103–105°.

Anal. Calcd for $C_{20}H_{18}$: C, 93.1; H, 6.9. Found, C, 93.1; H, 7.0.

When the above reduction with $LiAlH_4$ was conducted in 1:1 ether–THF, the yield of VIII fell to 58%. A mixture of the two possible methyl, hydroxymethyl analogs of VIII was obtained. By mesylation and $LiAlH_4$ reduction, additional VIII could be obtained.

7,12-Dihydro-7,12-dimethyl-5-fluorobenz[*a*]anthracene ($VIII_F$).—By a procedure similar to that described above, $VIII_F$ was obtained in 90% yield. The analytical sample, mp 59–62°, was obtained by recrystallization from methanol.

Anal. Calcd for $C_{20}H_{17}F$: C, 87.0; H, 6.2; F, 6.9. Found: C, 87.1; H, 6.6; F, 6.9.

7,12-Dimethylbenz[*a*]anthracene (I).—In a typical experiment a mixture of 1.00 g of VIII and 0.12 g of sulfur was heated to 150° (when H_2S began to be evolved) and then rapidly to 270° for 15 min. The crude hydrocarbon was purified by formation and recrystallization of the picrate to yield 0.90 g (90%) of pure I, mp and mmp (with an authentic sample[17]) 122–123°, prepared by a slight modification of a previous method.[4]

5-Fluoro-7,12-dimethylbenz[*a*]anthracene (I_F).—All solvents used in processing the product of reactions involving I_F were distilled under nitrogen and a nitrogen atmosphere was maintained throughout because I_F reacts readily with oxygen to form a peroxide, probably transannular.[18] The melting point of I_F is not sharp, probably because of traces of peroxide. However, the ir and nmr spectra are consistent with the structure.

In the best of several experiments, a mixture of 1.20 g of $VIII_F$ and 0.128 g of sulfur was heated slowly to 170° when H_2S was evolved. The mixture was then heated at 195° for 3 hr and at 260° for 5 min. The product was purified by recrystallization of the picrate followed by chromatography over alumina to yield 0.90 g (75%) of VIII, mp 89–91° alone and mixed with a sample previously prepared.[19]

7-Methylbenz[*a*]anthracene.—A solution of 1.2 g of V in 220 ml of alcohol containing 16 g of 85% hydrazine hydrate was refluxed for 30 min. On cooling 1.3 g of crude dihydrazone (no carbonyl absorption in the ir) was obtained as a yellow solid, mp 58–80°. A solution of 1.2 g of this in 40 ml of diethylene glycol containing 1 g of KOH was heated at reflux for 3 hr during which time the theoretical amount of nitrogen was evolved. After the usual work-up 0.5 g of 7-methylbenz[*a*]anthracene, mp and mmp 137.5–139.0°, with authentic hydrocarbon[20] was obtained. The mixture melting point with 12-methylbenz[*a*]anthracene was depressed. In an attempt to effect the reduction with potassium *tert*-butoxide in DMSO,[21] only tar was obtained.

3-(4-Fluoro-1-naphthyl)phthalide (IX).—To a solution of 55 g (0.366 mol) of phthalaldehydic acid in 415 ml of methanesulfonic acid (prepared by adding 13.6 ml of water to 400 ml of concentrated methanesulfonic acid)[10] was added 53 g (0.363 mol) of 1-fluoronaphthalene. After stirring at room temperature overnight the mixture was poured on ice and worked up as usual to yield 91 g (91%) of IX pure enough for the next step. The analytical sample of IX, mp 154.0–154.5°, was obtained by recrystallization from benzene–petroleum ether.

Anal. Calcd for $C_{18}H_{11}FO_2$: C, 77.8; H, 4.0; F, 6.8. Found: C, 77.5; H, 4.0; F, 6.6.

***o*-(4-Fluoro-1-naphthylmethyl)benzoic Acid (X).**—A solution of 6.0 g of IX in 100 ml of 90% formic acid was refluxed over 12 g of zinc dust[22] for 10 hr to yield 5.5 g (91.5%) of pure X, mp and mmp (with an authentic sample[8]) 176–177°.

***o*-(4-Fluoro-1-naphthylmethyl)benzyl Alcohol (XI).**—A solution of 54.5 g of X in 700 ml of ether and 100 ml of THF was added to the mixture formed by refluxing 10 g of $LiAlH_4$ in 200 ml of ether for 2 hr. After refluxing for 3 hr the mixture was decomposed by addition of water. The usual work-up afforded 51.3 g (99%) of XI pure enough for further use. The analytical sample, mp 92.0–93.5°, was obtained by crystallization from benzene-petroleum ether.

Anal. Calcd for $C_{18}H_{15}FO$: C, 81.2; H, 5.6; F, 7.1. Found: C, 81.2; H, 5.6; F, 7.0

5-Fluorobenz[*a*]anthracene (II*).—To a solution ot 20° of 25 g of CrO_3 in 250 ml of pyridine[23] was added a solution of 25 g of XI in 250 ml of pyridine during 15–20 min. The temperature was held near 20° for a further 2 hr and the suspended inorganic matter was removed by filtration. An ether–CH_2Cl_2 solution of the products was well washed with dilute HCl and then K_2CO_3. The crude brownish aldehyde XII (ir band at 5.8 μ) was not purified but dissolved in 75 ml of CH_2Cl_2 and added to 250 ml of PPA with stirring. The CH_2Cl_2 was distilled and the mixture heated on a steam bath for 20 min. After pouring on ice the usual work-up afforded a solid which was purified *via* the picrate to yield 20.4 g (88%) of II_F, mp 129–130°. The melting point was not depressed by an authentic sample.[12]

Registry No.—I, 57-97-6; III, 27525-64-0; III_F, 27525-65-1; IV, 27570-93-0; IV_F, 27525-66-2; V, 27570-94-1; V_F, 27525-67-3; VI, 27525-68-4; VI_F, 27525-69-5; VIII, 24316-23-2; $VIII_F$, 27525-71-9; IX, 27525-72-0; XI, 27525-73-1.

(17) M. S. Newman and R. Gaertner, *J. Amer. Chem. Soc.*, **72**, 264 (1950).

(18) J. W. Cook and R. H. Martin, *J. Chem. Soc.*, 1125 (1940).

(19) M. S. Newman and K. Naiki, *J. Org. Chem.*, **27**, 863 (1962). The melting point of the sample prepared in this work had decreased from the reported 92.5–93.0°, undoubtedly due to a small amount of peroxide formation. However, the ir and nmr spectra were identical.

(20) L. F. Fieser and M. S. Newman, *J. Amer. Chem. Soc.*, **58**, 2376 (1936).

(21) D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *ibid.*, **84**, 1734 (1962).

(22) R. L. Letsinger, J. D. Jamison, and A. S. Hussey, *J. Org. Chem.*, **26**, 97 (1961).

(23) Note the precautions described in "Reagents for Organic Synthesis," L. F. Fieser and M. Fieser, Wiley, New York, N. Y., 1967, p 146.

Rates of Addition of Styrene to 9-Substituted Acridizinium Ions

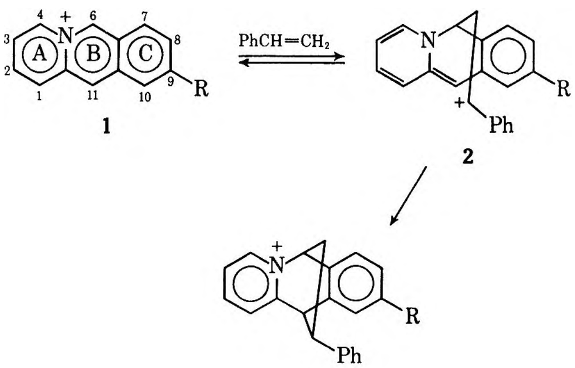
I. JOHN WESTERMAN[1] AND CHARLES K. BRADSHER*

Department of Chemistry, Duke University, Durham, North Carolina 27706

Received August 10, 1970

The rates of cycloaddition of styrene with acridizinium perchlorate and with nine 9-substituted acridizinium derivatives 1 have been determined. A well-correlated Hammett plot was obtained and interpreted as being consistent with a two-step mechanism.

Earlier evidence showed that the addition of ethylene derivatives to the acridizinium ion 1 occurred with "inverse electron demand."[2,3] It also suggested that the reaction does not fall into the classical pattern of a concerted (but two stage) reaction[4] but has reached the limiting case in which two discrete steps are involved and configuration may not be retained.[5]



The first step in the proposed mechanism involves a nucleophilic attack by the alkene on the electron-deficient 6 position of the acridizinium ion (1). Presumably factors influencing the electron deficiency at position 6 would also influence the rates. Frost and Saylor[6] have shown that the polarographic reduction of the acridizinium ion (presumably at position 6) occurs at lower negative potential when electron-attracting groups are present in ring C.

The purpose of the present work was to measure the rate of addition of styrene to acridizinium salts having substituents at position 9. This orientation was selected because resonance effects could be readily transmitted to position 6 while steric effects would be minimal. Fortunately the nine-substituted acridizinium salts required had been synthesized previously in this laboratory.[7] As in previous studies[3,5] reaction rates were followed by measuring the disappearance of the longer wavelength absorptions in the acridizinium spectrum rather than by isolation of addition products.

Experimental Section

Rate Determinations.—Rate determinations were carried out by a slight modification of that described earlier.[3] Stock solutions were made in dimethyl sulfoxide.[8] Due to the rapidity with which some salts reacted, samples slightly large than 0.1 ml were withdrawn rapidly using disposable pipets fitted with eye-dropper bulbs, the resulting sample was cooled rapidly in an ice bath, and then exactly 100 μl of cool liquid was withdrawn carefully with a microsyringe and diluted to 50 ml immediately with either water or 95% ethanol. The concentration of the acridizinium salt remaining was determined by measuring the absorbance (A) at the wavelength of maximum absorption beyond 300 mμ. Good pseudo-first-order plots were obtained, and in nearly all cases rates were reproducible to within 5%. An average trial followed the rate over 1–2 half-lives and, as judged by the linearity of the plots, pseudo-first-order conditions were maintained. The rate reported is a simple average of the trials.

9-Substituted Acridizinium Perchlorates (1).—The salts, with the exception of the 9-isopropyl, were prepared by methods published earlier,[7] and the observed and literature melting points are recorded in Table I.

9-Isopropylacridizinium Perchlorate [1, R = $(Me)_2CH$].[9]—The quaternization of 6.04 g of 2-(1,3-dioxolan-2-yl)pyridine[10] with 8.52 g of *p*-isopropylbenzyl bromide in 4 ml of tetramethylene sulfone was carried out in 3 days. Addition of ethyl acetate precipitated an oil which was dissolved in 40 ml of 48% hydrobromic acid and heated on a steam bath for 6 hr. Removal of the acid under reduced pressure left an oil which crystallized on addition of 35% perchloric acid. The salt (51% yield) was crystallized as pale yellow needles from methanol–ethyl acetate, mp 144–146°.

Anal. Calcd for $C_{16}H_{16}ClNO_4$: C, 59.72; H, 5.01; N, 4.35. Found: C, 59.93; H, 5.11; N, 4.65.

Results

As may be seen in Table I, changes in the substituent at position 9 have a significant effect (up to 50-fold) on the rate of addition. The compounds when tabulated in the order of their increasing Hammett substituent constants are approximately in the order of their increasing rate of reaction. A Hammett plot using the available primary σ values of the McDaniels and Brown[11] as well as the recommended[11,12] consistent treatment of the data is shown in Figure 1.

An analysis of the significance of the plot was made as recommended by Jaffé,[13] and in Table II will be seen the results obtained when only the seven primary σ values were used and when the three secondary values were used in addition. The standard deviation of ρ is less than 4% of the total value of ρ, an excellent agreement.

Discussion

Both the sign and magnitude of the reaction constant (ρ) are unusual for a 4 + 2 cycloaddition reaction.

(1) National Science Foundation Trainee, 1967–1969.
(2) D. L. Fields, T. H. Regan, and J. C. Dignan, *J. Org. Chem.*, **33**, 390 (1968).
(3) C. K. Bradsher and J. A. Stone, *ibid.*, **33**, 519 (1968).
(4) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).
(5) C. K. Bradsher and J. A. Stone, *J. Org. Chem.*, **34**, 1700 (1969).
(6) J. Frost and J. H. Saylor, *Recl. Trav. Chem. Pays-Bas*, **83**, 340 (1964).
(7) (a) C. K. Bradsher and L. E. Beavers, *J. Amer. Chem. Soc.*, **77**, 4812 (1955); (b) C. K. Bradsher and J. C. Parham, *J. Heterocycl. Chem.*, **1**, 30 (1964); (c) C. K. Bradsher, J. P. Shearer, and J. C. Parham, *J. Chem. Eng. Data*, **10**, 180 (1965); (d) J. C. Parham, Ph.D. Dissertation, Duke University, 1963.
(8) An obvious typographical error in the published directions: ". . . placed in a 2-ml volumetric flask . . . was made up to 20 ml." This should read ". . . to 2 ml."
(9) Based in part upon the work of J. C. Parham, ref 7d.
(10) C. K. Bradsher and J. C. Parham, *J. Org. Chem.*, **28**, 83 (1963).
(11) D. H. McDaniel and H. C. Brown, *ibid.*, **23**, 420 (1958).
(12) J. F. Bunnett, "Techniques of Organic Chemistry," part I, Vol. VIII, Interscience, New York, N. Y., 1961, pp 177–278.
(13) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

TABLE I
RATES OF ADDITION OF STYRENES TO 9-SUBSTITUTED ACRIDIZINIUM PERCHLORATES (1) AT 65°

R	Mp, °C	Lit. mp, °C	Lit. ref	n^c	$k \times 10^{-3}$ min$^{-1\,d}$	$\sigma_p{}^e$
Me	196–198	203–205	7a	4	2.0 ± 0.1	−0.170 ± 0.02[f]
CH(Me)$_2$	144–146	145–146	7d	3	2.8 ± 0.1	−0.151 ± 0.02[f]
H		205–206	7a	4	5.0 ± 0.2	0.000
F	173–178	177–178	7c	4	5.4 ± 0.2	0.062 ± 0.02[f]
I	258–260	257–258	7c	5	10.6 ± 0.6	0.18 ± 0.01[g]
Cl	223–224	224.5–226	7c	5	10.1 ± 0.5	0.227 ± 0.02[f]
Br	216–218	218–220	7c	5	11.2 ± 0.8	0.232 ± 0.02[f]
COOH	270–272[a]	250–253[b]	7b	3	18.1 ± 0.7	0.406 ± 0.04[h]
COOMe	233–239	236–237	7b	2	24.7 ± 1.0	0.463 ± 0.02[h]
NO$_2$	241–242[a]	240–242[a]	7b	4	105 ± 5	0.778 ± 0.02[f]

[a] With decomposition. [b] It is believed that the earlier report may have been a typographical error since the methyl esters melt in the same general range. [c] Number of trials. [d] Range includes the standard deviation. [e] Para substituent constants. [f] Primary σ values (ref 11). [g] Secondary σ value (ref 11). [h] Secondary σ value: H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **78**, 815 (1959).

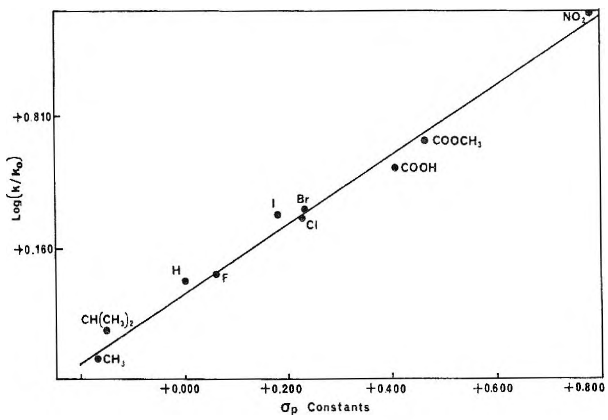


Figure 1.—Hammett plot of reaction rate data from Table I.

TABLE II
CONSTANTS AND STATISTICAL VALUES CALCULATED FOR THE HAMMETT PLOT

Calculated quantity	Substituents considered: Primary only	All
ρ, reaction constant	1.74	1.69
Sρ, standard deviation of ρ	0.06	0.07
S, standard deviation from regression line	0.05	0.06
γ, correlation factor	0.997	0.994
Log k_0	0.650	0.650

The positive sign further substantiates the inverse electron demand character of the addition of styrene to the acridizinium ion, while the magnitude of the reaction constant implies that the addition is more ionic and less synchronous than in the conventional Diels–Alder reaction. Concerted reactions usually fail to give a significant Hammett plot and very few Diels–Alder reactions have been so represented. For most of this small group of additions, low and uncertain values of ρ have been recorded.[14]

The two-step mechanism proposed for the cycloaddition reaction gains additional support from the present work. The 9 position is not symmetrically located with respect to the 6 and 11 (meso) positions of the acridizinium ion, but is para to position 6 and meta to position 11. Significantly, the Hammett para substituent constants gave an excellent correlation, whereas the meta constants failed to give a significant plot. This would seem to imply that initially the 6 position is either the exclusive or principal bonding site, and if the reaction is in any way concerted it must be approaching the limiting case in which the cycloaddition occurs in two separate steps.[15]

Registry No.—1 (R = Me), 27705-56-2; 1 [R = CH(Me)$_2$], 27705-57-3; 1 (R = H), 18507-95-4; 1 (R = F), 1695-36-9; 1 (R = I), 1695-42-7; 1 (R = Cl), 1695-37-0; 1 (R = Br), 1695-39-2; 1 (R = COOH) 27705-63-1; 1 (R = COOMe), 27705-64-2; 1 (R = NO$_2$), 27755-38-0; styrene, 100-42-5.

(14) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).
(15) The authors are indebted to Professor N. A. Porter for helpful discussions concerning this problem.

Cyclopropylcarbinyl Radical Reactions in the Cycloprop[2,3]indene System

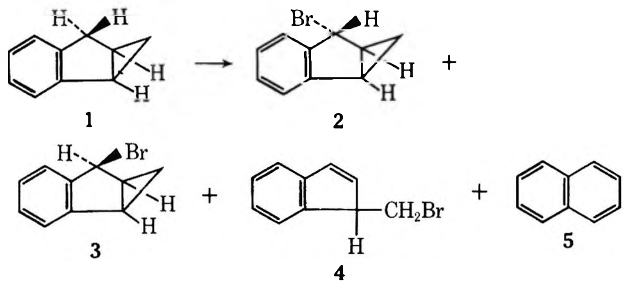
EDWIN C. FRIEDRICH* AND ROY L. HOLMSTEAD

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

Received August 5, 1970

An investigation of the use of different brominating agents and reaction conditions in free-radical α bromination of cycloprop[2,3]indene (**1**) is reported. Room temperature light-initiated brominations with either *N*-bromosuccinimide or molecular bromine in carbon tetrachloride solution give both higher conversions of the starting material and higher yields of cyclopropylcarbinyl bromide products than are obtained at 77° using either light or chemical initiation. Light-initiated bromination with bromotrichloromethane, however, is unsatisfactory even at low temperatures because of extensive side-product formation. Tri-*n*-butyltin and triphenyltin hydride reductions of a mixture of *exo*- and *endo*-1-bromocycloprop[2,3]indenes (**2** and **3**) and of a pure sample of 1-bromomethylindene (**4**) were also carried out to obtain detailed information regarding the nature of the cyclopropylcarbinyl–allylcarbinyl radical rearrangement processes in the cycloprop[2,3]indene system. Evidence was obtained for the intermediacy of the 1,2-dihydronaphthyl radical in the formation of at least part of the naphthalene produced in the free-radical bromination of cycloprop[2,3]indene (**1**). Also, the formation of **1** from the tin hydride reductions of **4** demonstrated the reversibility of the cyclopropylcarbinyl–allylcarbinyl rearrangement of the cycloprop[2,3]indenyl radical to the 1-methylindenyl radical.

A preliminary investigation of the possibility of carrying out free-radical α brominations of cyclopropyl hydrocarbons by *N*-bromosuccinimide (NBS) was reported[1] recently from these laboratories. One of the compounds investigated briefly in the preliminary study was cycloprop[2,3]indene (**1**). Because of its ready availability[2] and because of the relative ease of handling



and identifying its bromination products (**2**, **3**, **4**, and **5**),[1] this compound was chosen for use in the present study for investigation of the effects of different brominating agents and reaction conditions in free-radical cyclopropane α brominations. Also, we wished to carry out a detailed examination of the free-radical rearrangement processes occurring in this system.

Results and Discussion

Bromination Studies.—In the present study of the free-radical α bromination of **1**, ultraviolet light initiation was used in each case. Bromination using 1 equiv of NBS in CCl_4 solvent was carried out both at 77 and 28°, and bromination using 1 equiv of molecular bromine in CCl_4 solvent under a nitrogen sweep to remove HBr[3] was done at 28°. Finally light-initiated bromination using 5 equiv of bromotrichloromethane[4] in the absence of a solvent was examined at 28°. The results of these studies are shown in Table I along with those obtained earlier[1] for NBS bromination at 77° using azobisisobutyronitrile (AIBN) initiation.

(1) E. C. Friedrich, *J. Org. Chem.*, **34**, 528 (1969).

(2) A. L. Goodman and R. H. Eastman, *J. Amer. Chem. Soc.*, **86**, 908 (1964).

(3) B. P. McGrath and J. M. Tedder, *Proc. Chem. Soc., London*, 80 (1961).

(4) (a) G. J. Gleicher, *J. Org. Chem.*, **33**, 332 (1968); (b) B. B. Jarvis, *ibid.*, **35**, 924 (1970).

TABLE I

FREE-RADICAL BROMINATION OF CYCLOPROP[2,3]INDENE (1)

Reaction conditions	% conversion[a] of 1	Product composition,[b] % 2	3	4	5	Unknown
1 equiv NBS, CCl_4, AIBN, 77°, 10 min	65	37	25	27	5	6[c]
1 equiv NBS, CCl_4, $h\nu$, 77°, 1 hr	67	43	27	14	8	8[c]
1 equiv NBS, CCl_4, $h\nu$, 28°, 2 hr	87	56	32	0	4	8[c]
1 equiv Br_2, CCl_4, $h\nu$, 28°, 20 min	82	53	30	0	3	14[c]
5 equiv $BrCCl_3$, neat, $h\nu$, 28°, 4 hr	54	44	23	0	2	31

[a] Brominations with NBS and Br_2 were carried to complete reaction of the brominating agent. [b] Average values, based on reacted **1**, of runs carried out in duplicate or triplicate. The per cent yields shown in each case are reproducible to *ca.* ±2%. [c] High boiling, presumed di- or tribrominated materials.

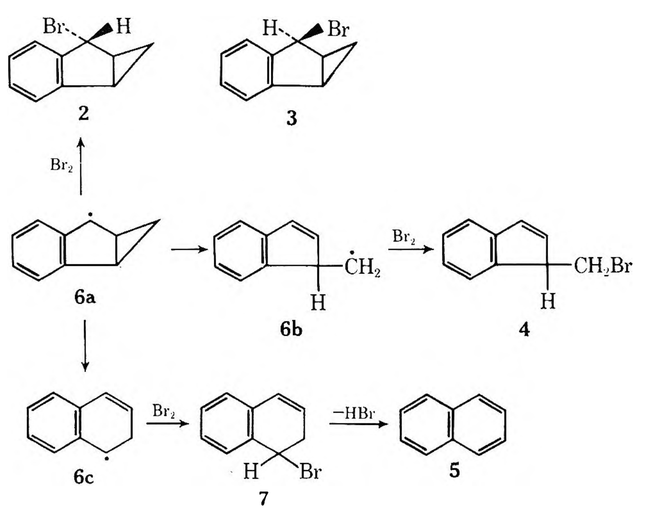
In the brominations with NBS at 77° using either light or AIBN initiation, the same four products are obtained. However, in the light-initiated process less of the cyclopropylcarbinyl–allylcarbinyl radical rearrangement product 1-bromomethylindene (**4**) is formed. This is not due to subsequent ion-pair rearrangement of the cyclopropylcarbinyl bromides **2** and **3** in the AIBN-initiated reaction since the products were shown to be stable under the reaction conditions.[1] Moreover, the reaction conditions for the AIBN-initiated reaction were less vigorous than those using light initiation. A possible, although unsupported, explanation which can be offered for this behavior is that in the light-initiated reaction the steady state concentration of molecular bromine is higher than in the AIBN-initiated reaction. Thus, the initially formed cyclopropylcarbinyl radical intermediate would be more likely to react with the bromine to form the cyclopropylcarbinyl bromides **2** and **3** in competition with rearrangement to the radical precursor of **4**.

In the light-initiated free-radical brominations at 28°, significant differences in product composition were observed from those obtained at 77°. Both Br_2 and NBS bromination gave essentially identical product mixtures consisting almost entirely of the unrearranged cyclopropylcarbinyl bromides **2** and **3**.[5] Also, considerably greater conversions of the cycloprop[2,3]-indene were obtained.[6] These variations are most likely due to differences in the activation energies for the various processes which can take place during the bromination reactions. In practice, the light-initiated room temperature bromination of **1** with molecular bromine has proved to be a highly satisfactory procedure for preparation of a mixture of the *exo*- and *endo*-bromides **2** and **3** which we needed for the tin hydride reduction studies to be discussed later.

The final method for cyclopropane α bromination which was investigated in the present study involved the use of bromotrichloromethane as the source of bromine. Although light-initiated bromination of **1** at 28° with the bromotrichloromethane did proceed readily, it was unsatisfactory due to the formation of large amounts of side products (see Table I). The nature of these side products was not investigated; however, it is presumed that they result from addition of the chain carrying trichloromethyl radicals to the cyclopropane ring of **1**.[4b]

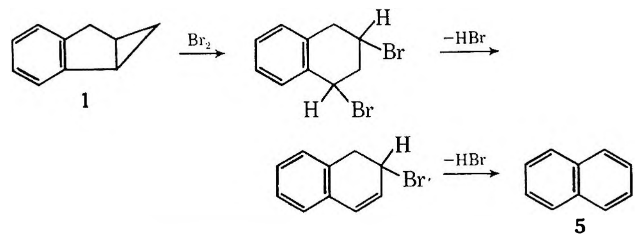
Free-Radical Rearrangement Studies.—A possible mechanistic scheme for the formation of each of the products obtained from the free-radical bromination of cycloprop[2,3]indene (**1**) is given in Scheme I. The

Scheme I



exo- and *endo*-1-bromocycloprop[2,3]indenes (**2** and **3**) are formed *via* the cyclopropylcarbinyl radical intermediate **6a**, resulting from initial abstraction of a hydrogen atom from the 1 position of cycloprop[2,3]indene. 1-Bromomethylindene (**4**) results *via* bromine attack on the rearranged allylcarbinyl radical **6b**. Finally, a probable pathway for the formation of naphthalene is *via* reaction of the allylcarbinyl radical **6c** with bromine to give 1-bromo-1,2-dihydronaphthalene (**7**). This material would be expected to immediately eliminate HBr under the reaction conditions by an ionic mechanism to give naphthalene (**5**).

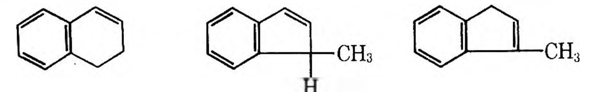
To test the validity of this free-radical bromination mechanism, it was necessary to carry out an investigation in which certain of the postulated radical intermediates were generated by independent processes. For example, besides the scheme shown earlier for the formation of naphthalene, another pathway might be *via* the process shown below. It was also of considerable



theoretical interest to determine whether the proposed cyclopropylcarbinyl–allylcarbinyl radical rearrangement of **6a** to **6b** is reversible. Furthermore, we wished to obtain additional information regarding the observation that, in the free-radical bromination of **1**, rearrangement of the initially formed cyclopropylcarbinyl radical **6a** to the primary homoallyl radical **6b** apparently proceeds in preference to rearrangement to the benzylic radical **6c**.

Since tin hydride reductions of organic halides are known to proceed by free-radical mechanisms,[7] and have also been used in a number of cases for studying cyclopropylcarbinyl–allylcarbinyl radical rearrangements,[8] this process was chosen as the alternative to free-radical bromination for use in obtaining further information regarding the problems posed above. Reductions of a 65:35 mixture[9] of the *exo*- and *endo*-1-bromocycloprop[2,3]indenes (**2** and **3**) and of a pure sample of 1-bromomethylindene (**4**) were carried out using equimolar amounts of tri-*n*-butyltin hydride or triphenyltin hydride and the bromide in the absence of a solvent. Controls showed that a maximum of 7% rearrangement of the bromides **2** and **3** to bromide **4** occurred on irradiation at 26° for 4 hr in the presence of tri-*n*-butyltin bromide.

The products observed from the tin hydride reduction studies were cycloprop[2,3]indene (**1**), 1,2-dihydronaphthalene (**8**), 1-methylindene (**9**), and 3-methylindene (**10**). These were identified by isolation and



8 **9** **10**

comparison with known samples, and the yields were determined using a combination of nmr and glpc techniques as are described in the Experimental Section. In all cases studied the total yields of hydrocarbon products accounted for amounted to greater than 95%.

(5) A similar temperature dependence of product composition was observed in free-radical chlorination of methylcyclopropane: C. Walling and P. S. Fredricks, *J. Amer. Chem. Soc.*, **84**, 3326 (1962).

(6) It was shown in the previous study[1] that the low conversion of **1** in the AIBN-initiated reaction with NBS at 77° was due predominately to a side rearrangement of a portion of the NBS to β-bromopropionyl isocyanate.

(7) H. G. Kuivila, "Advances in Organometallic Chemistry," Vol. 1, Academic Press, New York, N. Y., 1964, p 47.

(8) For example, see C. R. Warner, R. J. Strunk, and H. G. Kuivila, *J. Org. Chem.* **31**, 3381 (1966).

(9) It was necessary to use the mixture of bromides **2** and **3** obtained from free-radical bromination of **1** for this study because they were too unstable for separation into the individual isomers. However, both **2** and **3** were observed to be reduced at identical rates, and for the purposes of this study starting with the mixture or with one pure isomer does not affect the conclusions which are drawn from the results.

The results obtained are summarized in Table II and are the averages of duplicate runs.

Table II
Tin Hydride Reductions[a,b]

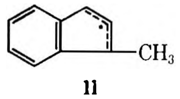
Bromide	Hydride	Relative yields of products, % 1	8	9	10
2 + 3[c]	$(n\text{-Bu})_3SnH$	35	3	62	0
2 + 3[c]	$(C_6H_5)_3SnH$	64	4	32	0
4	$(n\text{-Bu})_3SnH$	15	3	73	9
4	$(C_6H_5)_3SnH$	18	2	72	8

[a] Reductions were carried in the absence of a solvent using 1 mmol each of the tin hydride and the bromide. [b] $(n\text{-Bu})_3SnH$ reductions were carried out at 26 ± 1° using light initiation. In the $(C_6H_5)_3SnH$ reductions of 2 and 3, the reactants were mixed at room temperature and the moderately exothermic reactions did not require light initiation. Reduction of 4 with $(C_6H_5)_3SnH$, however, required light initiation. [c] A 65% exo and 35% endo mixture.

1,2-Dihydronaphthalene (**8**) is obtained from the tin hydride reductions of both the isomeric 1-bromocycloprop[2,3]indenes (**2** and **3**) and the 1-bromomethylindene (**4**). Thus, the formation of this material supports the proposed intermediacy of the 1,2-dihydronaphthyl radical **6c**, as the source of at least part of the naphthalene in the free-radical bromination of cycloprop[2,3]indene (**1**). Also, the formation of **1** from the tin hydride reductions of 1-bromomethylindene (**4**) demonstrates the reversibility of the cyclopropylcarbinyl–allylcarbinyl radical rearrangement of **6a** to **6c**.[10]

In the reduction of the cyclopropylcarbinyl bromides **2** and **3** with triphenyltin hydride, much higher yields of the unrearranged product cycloprop[2,3]indene (**1**) were obtained than in the case using the tri-*n*-butyltin hydride. This must be due to the greater ability of the triphenyltin hydride to capture the initially formed cyclopropylcarbinyl radical **6a** before it undergoes rearrangement to the homoallyl radicals **6b** or **6c**.[7] In the case of the reduction of the homoallyl bromide (**4**), however, both tin hydrides gave within experimental error an identical product composition. It is likely that the product composition obtained here reflects the equilibrium composition of the radical intermediates **6a–c**, and thus allowing the radicals a longer lifetime would not change the final product composition.

The formation of 3-methylindene (**10**) from the reductions of 1-bromomethylindene (**4**) must be *via* reaction between the 1-methylindenyl radical **6b** and 1-methylindene (**9**) to give the allylic radical **11**. Upon reduction of **11** a mixture of **9** and **10** would be expected.



11

Finally, it is interesting to note that in the tin hydride reduction studies, as well as in the free-radical bromination studies, rearrangement of the cyclopropylcarbinyl radical **6a** to the primary homoallyl radical **6b** apparently proceeds in preference to rearrangement to the benzylic radical **6c**. Based on the stabilities expected for the radical products, the opposite behavior would have been anticipated. For example, in the free-radical NBS bromination of *trans*-1-benzyl-2-methylcyclopropane,[1] the secondary and primary homoallylic bromide products were obtained in the ratio of 5:1. Also, Cristol and Barbour[11] observed that the reaction of 3,5-cyclocholestan-6-yl chloride with triphenyltin hydride or with sodium biphenyl radical anion leads exclusively to 5-cholestene, resulting from rearrangement to the secondary homoallylic radical. However, Freeman and coworkers[12] observed that free-radical chloroformylation of bicyclo[3.1.0]hexane with oxalyl chloride leads to approximately equivalent amounts of Δ^2-cyclopentenylmethylacetyl chloride and 3-cyclohexenylacetyl chloride along with other products. Also, Slaugh[13] found that the generation of the Δ^2-cyclopentenylmethyl radical by thermal decomposition of *tert*-butyl Δ^2-cyclopentenyl peracetate in the presence of *p*-cymene or benzotrichloride resulted in rearrangement, probably *via* a bicyclo[3.1.0.]hexyl radical, to produce the 4-cyclohexenyl radical.

An attempt was made to generate the dihydronaphthyl radical **6c** by an independent process to determine whether it might be involved in an equilibrium which is strongly directed toward the cyclopropylcarbinyl radical **6a**. This was done by means of light-initiated NBS bromination of 1,2-dihydronaphthalene (**8**) at 26° in CCl_4 solution. However, nmr examination of the product mixture showed the absence of any cyclopropyl products.

A possible explanation for the unexpected direction of rearrangement of the cyclopropylcarbinyl radical **6a** in the cycloprop[2,3]indene system is that the phenyl substituent on carbon 3 in the activated complex for rearrangement of **6a** to **6c** is providing a destabilizing electron-withdrawing inductive effect rather than a stabilizing electron-releasing resonance effect. We plan to test this explanation by means of cyclopropylcarbinyl radical rearrangement studies in the benzobicyclo[4.1.0.]heptyl homolog of the cycloprop[2,3]indene system.

Experimental Section

Boiling points are uncorrected. Mass spectra were run on a CEC Model 21-104 single focusing instrument by Mr. J. Voth.

Nuclear Magnetic Resonance Spectra.—All nmr spectra were obtained using a Varian Associates Model A-60A instrument. They were run either directly on the crude or distilled reaction mixtures or, in the case of pure compounds, as 5–10% solutions in carbon tetrachloride. Tetramethylsilane (TMS) was used as an internal standard, and chemical shift values are reported in parts per million (δ) downfield from the TMS. For quantitative nmr analyses, at least four integrations were obtained for the peak areas of each different proton absorption. Integral amplitudes were maximized so as to obtain the highest possible accuracy. Average values of the integrations were used for calculation of the product compositions.

Gas–Liquid Partition Chromatography.—Both analytical and preparative scale gas–liquid partition chromatography were carried out using an Aerograph A90-P3 instrument equipped with a Pyrex injector insert. Analyses of the bromination products were done as described previously.[1] Analyses of the hydrocarbon products obtained from the tin hydride reduction studies were done using a 3.5 m × 0.25 in. copper column with a 20% 3-nitro-3-methylpimelonitrile (NMPN) on 60–80 mesh Chromosorb W

(10) Similar behavior has been observed in the simple Δ^2-cyclopentenylmethyl system: L. H. Slaugh, *J. Amer. Chem. Soc.*, **87**, 1522 (1965).

(11) S. J. Cristol and R. V. Barbour, *ibid.*, **90**, 2832 (1968).

(12) P. K. Freeman, F. A. Raymond, J. C. Sutton, and W. R. Kindley, *J. Org. Chem.*, **33**, 1448 (1968).

(13) L. H. Slaugh, *J. Amer. Chem. Soc.*, **87**, 1522 (1965).

packing. Helium (60 ml/min) was employed as the carrier gas. The retention times in minutes, using a column operating temperature of 112°, of certain of the compounds encountered in this work are as follows: 1-methylindene, 27; cycloprop[2,3]indene, 33; 3-methylindene, 45; and 1,2-dihydronaphthalene, 47.

Photolysis Equipment.—Light-initiated brominations and tin hydride reductions were carried out using a 275-W General Electric sun lamp placed approximately 10 cm from the object being irradiated. All glassware employed was Pyrex.

Cycloprop[2,3]indene (1).—This material was prepared using the Le Goff modification[14] of the procedure employed by Goodman and Eastman.[2] The reaction of a zinc-copper couple, prepared from 58.8 g (0.9 mol) of 30-mesh zinc granules, with 121.8 g (0.7 mol) of dibromomethane and 58 g (0.5 mol) of freshly distilled indene in 300 ml of anhydrous ether at reflux for 68 hr gave, after work-up and distillation through a 60-cm spinning-band column, 14.1 g (22%) of pure cycloprop[2,3]indene: bp 85° (18.5 mm); $n^{23}D$ 1.5583 [lit.[2] bp 104° (40 mm); $n^{26}D$ 1.5545]; mass spectrum (70 eV) *m/e* (rel intensity) 131 (11), 130 (100), 129 (99), 128 (57), 127 (26), 115 (67), and 102 (7).

Light-Initiated Bromination of Cycloprop[2,3]indene by NBS.—Light-initiated brominations at 28° were carried out by placing 0.34 g (1.91 mmol) of NBS along with 0.237 g (1.82 mmol) of cycloprop[2,3]indene and 5 ml of carbon tetrachloride solvent in an 18 × 150 mm test tube fitted with a thermometer. The mixture was stirred magnetically and the reaction temperature was maintained by running a stream of tap water over the tube. Brominations at 77° were carried out using the same quantities of starting materials as shown above. However, a 10-ml two-necked ₮ 14/20 flask fitted with a thermometer, a reflux condenser, and a calcium chloride drying tube was used as the reaction vessel. The magnetically stirred reaction mixture was brought to reflux temperature within 2–3 min by irradiating without cooling. The temperature was maintained by blowing a stream of air over the flask. After the reactions were completed, as indicated by the absence of NBS at the bottom of the reaction vessel, the product mixtures were analyzed using a combination of nmr and glpc techniques as described earlier.[1]

Light-Initiated Bromination of Cycloprop[2,3]indene Using Br_2.—Cycloprop[2,3]indene (0.237 g, 1.82 mmol) was weighed into a 10-ml two-necked ₮ 14/20 flask containing 1 ml of carbon tetrachloride solvent. The flask was fitted with a gas inlet tube and a dropping funnel. Dry nitrogen was then slowly bubbled through the mixture while the flask was irradiated and cooled by a stream of tap water, and 3.6 ml of a 0.5 *M* solution of bromine (1.8 mmol) in carbon tetrachloride solution was added slowly in a dropwise manner. Decoloration of the bromine solution occurred immediately upon addition of each drop. HBr was evolved as evidenced by the dense white fumes, which were strongly acidic to moist pHydrion paper, emitted from the top of the dropping funnel. After addition of the bromine solution was complete, irradiation was stopped but the nitrogen bubbling was continued for 1–2 min longer. The product mixture was then analyzed in the usual manner.[1]

Light-Initiated Bromination of Cycloprop[2,3]indene with Bromotrichloromethane.—Cycloprop[2,3]indene (0.13 g, 1 mmol) and bromotrichloromethane (0.99 g, 5 mmol) were carefully weighed into a polished glass, thin-wall nmr tube. The tube was then irradiated for 4 hr while being cooled by a stream of tap water. The product mixture was analyzed in the usual manner.[1]

***exo*- and *endo*-1-Bromocycloprop[2,3]indene Mixture (2 and 3).**—The reaction of 1.5 g (11.5 mmol) of cycloprop[2,3]indene (1) in 5 ml of carbon tetrachloride solvent with 35 ml of a 0.5 *M* solution of bromine (17.5 mmol) in carbon tetrachloride was carried out at 28° over a period of 15 min by a procedure similar to that described above. The carbon tetrachloride was then removed on a rotary vacuum evaporator and the resulting light yellow product was distilled, using an oil bath which was preheated to 95°, through a small short-path microdistillation apparatus. The 1-bromocycloprop[2,3]indene (1.92 g, 80%) was collected from 75 to 80° (0.5 mm): $n^{22.5}D$ 1.6097; nmr analysis[1] showed that the material consisted of a 65:35 mixture of 2 and 3; mass spectrum (70 eV) *m/e* (rel intensity) 210 (5), 208 (6), 130 (11), 129 (100), 128 (57), and 127 (19).

1-Hydroxymethylindene.—The procedure used for preparation of this material, the precursor for 1-bromomethylindene (4), essentially followed that described by Courtot[15] involving the reaction of indenylmagnesium bromide with paraformaldehyde. 1-Hydroxymethylindene was obtained in a 62% yield based on reacted indene: bp 95–96° (1.0 mm); $n^{23}D$ 1.5865 [lit.[14] bp 134° (10 mm)]; nmr (CCl_4) δ 3.55 (m, 3 H), 6.4 (d, 1 H, *J* = 5 Hz, vinyl), 6.65 (d, 1 H, *J* = 5 Hz, vinyl), and 7.1 ppm (m, 4 H, aromatic).

1-Bromomethylindene (4).—The procedure used essentially followed that of Smith.[16] The reaction of 5.6 g (20.7 mmol) of phosphorus tribromide and 10.0 g (62.4 mmol) of 1-hydroxymethylindene in 4 ml of anhydrous benzene and 2 g of dry pyridine gave, after work-up and distillation, 4.0 g (31%) of 4: bp 72–82° (0.5 mm); $n^{22}D$ 1.6016 (lit.[1] $n^{25}D$ 1.6003). The nmr spectrum of this material was identical with that reported earlier[1] for a sample of 4 obtained *via* free-radical NBS bromination of cycloprop[2,3]indene (1).

Tri-*n*-butyltin Hydride.—This was prepared in 90% yield by the reduction of tri-*n*-butyltin chloride with lithium aluminum hydride following the procedure of Kuivila:[17] bp 68–74° (0.3 mm) [lit.[17] bp 68–74° (0.3 mm)]; nmr (neat) δ 1.2 (m, 27 H) and 4.7 ppm (m, 1 H, SnH).

Triphenyltin Hydride.—This was prepared in 65% yield by the reduction of triphenyltin chloride with lithium aluminum hydride following the procedure of Kuivila:[17] bp 162–168° (0.5 mm) [lit.[17] bp 162–168° (0.5 mm)]; nmr (neat) δ *ca.* 6.9 (m, 9 H, aromatic), *ca.* 7.1 (m, 6 H, aromatic), and *ca.* 7.4 ppm (m, 1 H, SnH).

1,2-Dihydronaphthalene (8).—An impure sample of 8 was prepared *via* NBS bromination of tetralin to give 1-bromo-1,2,3,4-tetrahydronaphthalene, which upon distillation spontaneously eliminated HBr. Isolation of a pure sample of 1,2-dihydronaphthalene was accomplished by glpc techniques at 130° using a 1 m × $^3/_8$ in. column with a 20% NMPN on 80–100 mesh Chromosorb W packing: bp 65° (3.5 mm); $n^{23}D$ 1.5802 [lit.[18] bp 83–83.5° (12 mm); $n^{20}D$ 1.5817]; nmr (neat) δ 2.1 (m, 2 H), 2.65 (m, 2 H), 5.8 (sextet, 1 H, *J* = 10 and 4 Hz), 6.3 (sextet, 1 H, *J* = 10 and 1.5 Hz), and 6.9 ppm (m, 4 H).

Reductions with Tri-*n*-butyltin Hydride.—A typical reduction procedure is outlined as follows. Into a polished glass, thin-wall nmr tube was carefully weighed 0.209 g (1 mmol) of the bromide and 0.290 g (1 mmol) of tri-*n*-butyltin hydride. The mixture was then irradiated, while maintaining the temperature at 26 ± 1° by running a stream of tap water over the tube, until nmr analysis showed the complete disappearance of the tin hydride absorption (*ca.* 3–5 hr). The resulting mixture was then distilled through a short-path microdistillation apparatus to separate the hydrocarbon products from the high boiling tri-*n*-butyltin bromide. Analysis by nmr both before and after distillation showed that the relative ratios of the hydrocarbon products remained constant. The distilled hydrocarbon product was then analyzed by a combination of the glpc and nmr techniques described below.

Reductions with Triphenyltin Hydride.—The bromide (0.209 g, 1 mmol) and 0.350 g (1 mmol) of triphenyltin hydride were weighed into a 10 × 75 mm Pyrex test tube. In the case of the reductions of the *exo*- and *endo*-1-bromocycloprop[2,3]indene mixture, reaction occurred spontaneously and after about 10 min was complete. To initiate the reductions of 1-bromomethylindene, however, it was necessary to irradiate the tube at 26 ± 1° for 10–15 min. The product mixture was then extracted with three 2-ml portions of cold *n*-pentane to separate the hydrocarbon products from the triphenyltin bromide. The hydrocarbon extract was then concentrated using a stream of dry nitrogen and analyzed by a combination of the glpc and nmr techniques described below.

Hydrocarbon Analyses.—Pure samples of the various hydrocarbon products obtained from the tin hydride reductions were isolated by preparative scale glpc techniques. 1-Methylindene (9) and 3-methylindene (10) were identified by comparison of their nmr spectra with those reported by Wiedler and Bergson.[19] Cycloprop[2,3]indene (1) and 1,2-dihydronaphthalene (8) were identified by comparison of their glpc retention times and pmr spectra with those of known samples. Determination of the per cent yields of the various hydrocarbon products was done in the following manner. The yield of cycloprop[2,3]indene was obtained from the nmr spectrum of the hydrocarbon product

(14) E. Le Goff, *J. Org. Chem.*, **29**, 2048 (1964).

(15) C. Courtot, *Ann. Chim. (Paris)*, **4**, 76, 94 (1915).

(16) L. H. Smith, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 793.

(17) H. G. Kuivila and O. F. Beumel, *J. Amer. Chem. Soc.*, **83**, 1246 (1961).

(18) K. W. F. Kohlrausch and R. Seka, *Ber.*, **71**, 1551 (1938).

(19) A. Wiedler and G. Bergson, *Acta Chem. Scand.*, **18**, 1487 (1964).

mixture by integration of its quartet at δ 0.00 ppm (1 H) using the entire aromatic region (4 H) as an internal standard. The relative per cent yields of cycloprop[2,3]indene, 1,2-dihydronaphthalene, 1-methylindene, and 3-methylindene were then determined from glpc data. The actual yields of these materials were calculated by reference to the yield of cycloprop[2,3]indene obtained by nmr examination of the product mixture.

Registry No.—1, 15677-15-3; NBS, 128-08-5; Br_2, 7726-95-6; bromotrichloromethane, 75-62-7; tri-*n*-butyltin hydride, 688-73-3; triphenyltin hydride, 892-20-6.

Acknowledgment.—The authors are indebted to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Academic Senate Committee on Research of the University of California, Davis, for partial support of this research.

Azo Compounds. 1. The Synthesis and Decomposition of 3,3′-Diphenyl-5,5′-bi-1-pyrazoline[1,2]

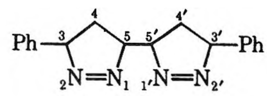
C. G. Overberger,*[3a] Richard E. Zangaro,[2] Rudolph E. K. Winter, and J.-P. Anselme[3b]

Department of Chemistry, Polytechnic Institute of Brooklyn, Brooklyn, New York 11201

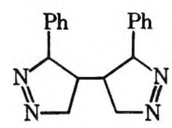
Received April 24, 1970

The only product isolated from the reaction of phenyldiazomethane with 1,3-butadiene was a mixture of three stereoisomers of 3,3′-diphenyl-5,5′-bi-1-pyrazoline (I). The thermal and photochemical decompositions of I and of one of the stereoisomers isolated in tlc homogeneous form are described.

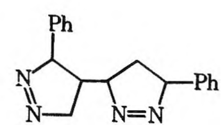
Despite a number of investigations[4-9] on the pyrolysis and photolysis of 1-pyrazolines, it has not been possible to completely generalize the mechanism of these decompositions. We report herein the formation and the decomposition of 3,3′-diphenyl-5,5′-bi-1-pyrazoline (I), obtained as a mixture of three isomers. The isolation of one of these isomers (Ia or Ib) in tlc homogeneous form, as well as its decomposition, is also described.



I



II



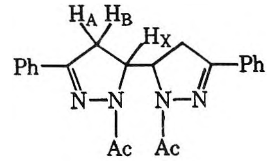
III

Results and Discussion

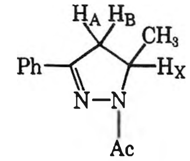
1. Synthesis and Assignment of Structure.—The reaction of diazoalkanes with olefins affords five-membered cyclic azo compounds in fair yields.[5-12] 3-Vinyl-1-pyrazoline has been prepared recently by this method.[11] Our attempts to prepare the 3-phenyl-5-vinyl-1-pyrazoline by the reaction of phenyldiazomethane with 1,3-butadiene resulted only in the formation of a 2:1 adduct, as shown by the elemental analysis. Three types of adducts (I, II, and III) are possible, depending on the direction of addition of phenyldiazomethane. Structure I was assigned to the product isolated on the basis of its spectral data.

The cis-azo linkage was confirmed by its ultraviolet absorption at 328 mμ and by a sharp band at 1540 cm^{-1} in the infrared. These values are in agreement with those previously reported for monocyclic 1-pyrazolines.[4-8,10,13-17] The lack of NH absorption in the infrared spectrum also indicated the absence of isomeric hydrazone.

The presence of several complex splitting patterns in the nmr spectrum of I did not allow unambiguous distinction between structures I, II, and III. To facilitate the nmr analysis, I was converted to the 1,1′-diacetyl-bi-2-pyrazoline derivative (IV) by acid-catalyzed isomerization and acetylation. The coupling constants J_{AB}, J_{AX}, and J_{BX} for IV agreed very well with



IV



V

(1) This is the 50th in a series of papers concerned with the preparation and decomposition of azo compounds. See previous paper in this series by C. G. Overberger and J. Stoddard, *J. Amer. Chem. Soc.*, in press.

(2) This paper comprises a portion of a dissertation submitted by R. Zangaro in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the Polytechnic Institute of Brooklyn, 1968.

(3) (a) Department of Chemistry, University of Michigan, Ann Arbor, Mich. 48104. (b) Department of Chemistry, University of Massachusetts, Boston, Mass. 02116; Fellow of the Alfred P. Sloan Foundation.

(4) C. G. Overberger and J.-P. Anselme, *J. Amer. Chem. Soc.*, **86**, 658, 5364 (1964).

(5) C. G. Overberger, R. E. Zangaro, and J.-P. Anselme, *J. Org. Chem.*, **31**, 2046 (1965).

(6) C. G. Overberger, N. Weinshenker, and J.-P. Anselme, *J. Amer. Chem. Soc.*, **87**, 4119 (1965).

(7) (a) K. L. Rinehart, Jr., and T. van Auken, *ibid.*, **82**, 5251 (1960); (b) T. van Auken and K. L. Rinehart, Jr., *ibid.*, **84**, 3736 (1962).

(8) (a) R. J. Crawford and A. Mishra, *ibid.*, **87**, 3768 (1965); (b) R. J. Crawford, A. Mishra, and R. J. Dummel, *ibid.*, **88**, 3959 (1966); (c) R. J. Crawford and A. Mishra, *ibid.*, **88**, 3963 (1966); (d) R. J. Crawford and G. L. Erickson, *ibid.*, **89**, 3907 (1967).

(9) H. M. Walborsky and C. G. Pitt, *ibid.*, **84**, 483 (1962).

(10) C. G. Overberger and J.-P. Anselme, *ibid.*, **84**, 869 (1962).

(11) R. J. Crawford and D. M. Cameron, *Can. J. Chem.*, **45**, 691 (1967); see also P. K. Kadaba, *Tetrahedron*, **25**, 3053 (1969).

(12) (a) P. Dowd, *J. Amer. Chem. Soc.*, **88**, 2587 (1966); (b) R. J. Crawford and D. M. Cameron, *ibid.*, **88**, 2589 (1966); (c) R. J. Crawford and D. M. Cameron, *Can. J. Chem.*, **45**, 691 (1967).

(13) J. A. Moore, *J. Org. Chem.*, **20**, 1607 (1955).

(14) (a) D. E. McGreer, *ibid.*, **25**, 852 (1960); (b) D. E. McGreer, N. W. K. Chiu, and M. G. Vinje, *Can. J. Chem.*, **43**, 1398 (1965); (c) D. E. McGreer, N. W. K. Chiu, M. G. Vinje, and K. C. K. Wong, *ibid.*, **43**, 1407 (1965).

(15) G. P. Mueller and B. Riegel, *J. Amer. Chem. Soc.*, **76**, 3686 (1960).

(16) R. Wiechert and E. Kaspar, *Chem. Ber.*, **93**, 1710 (1960).

(17) J. A. Moore, W. F. Holton, and E. L. Wittle, *J. Amer. Chem. Soc.*, **84**, 390 (1962).

those of *N*-acetyl-3-phenyl-5-methyl-2-pyrazoline (V).[18] These data are summarized in Table I. The ABX type

TABLE I
NMR DATA OF 2-PYRAZOLINES IV AND V[a]

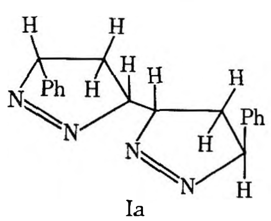
2-Pyrazoline	H_A	H_B	H_X[b]	J_{AX}	J_{BX}	J_{AB}
IV	6.52	7.00	4.80	10.5	5	18
V	6.73	7.35	5.44	10.5	5	17

[a] Peak positions determined at 60 MHz in $CDCl_3$ (at 59°) and are given in τ values (TMS internal standard); *J* values are in Hz. [b] These values are in fair agreement with those reported by Hassner and Michelson for similar compounds [*J. Org. Chem.*, **27**, 3794 (1962)].

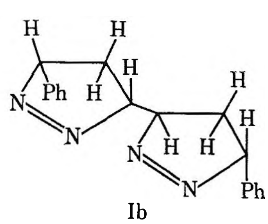
splitting pattern of V was similar to that of the 1,1′-diacetyl-bi-2-pyrazoline derivative (IV).

In contrast, the diacetyl dihydrazone pyrazoline derived from 3,3′-diphenyl-4,4′-bi-1-pyrazoline (II) would exhibit an ABX type pattern having the relative chemical shifts of the H_X and the H_A and H_B protons reversed. If IV had resulted from the other possible adduct (III), a more complex spectrum of two overlapping ABX patterns would have been anticipated.

The bi-1-pyrazoline I has four asymmetric centers (at carbon atoms 3, 3′, 5, and 5′) and, therefore, can exist as four *dl* pairs distributed as cis,cis, trans,trans, and two cis–trans geometric isomers and two meso isomers (cis,cis and trans,trans). Thin layer chromatography of analytically pure I indicated the presence of three components. The separation of the major of these as a homogeneous compound by thin layer chromatography was accomplished by repeated column chromatography over silica gel; elution with dichloromethane afforded an isomer, mp 167–168°. Although tlc homogeneity does not assure the presence of a single isomer, none of the available evidence suggested that this crystalline material was still a mixture of isomers. The structure was tentatively assigned as cis,trans, *i.e.*, as either *meso*-3,3′-diphenyl-*dl*-5,5′-bi-1-pyrazoline (Ia) or *dl*-3,3′-diphenyl-*meso*-5,5′-bi-1-pyrazoline (Ib) based on the nmr spectrum which indicated a nonequivalence of the two pyrazoline rings (in each of the other four diastereomeric choices, *i.e.*, the two isomers of *meso*-3,3′-diphenyl-*meso*-5,5′-bi-1-pyrazoline and the two isomers of *dl*-3,3′-diphenyl-*dl*-5,5′-bi-1-pyrazoline, the two pyrazoline rings are in equivalent environments). In particular, the benzylic protons are cen-



Ia

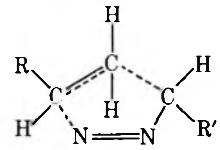


Ib

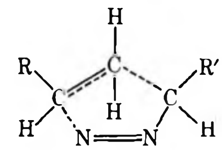
tered at τ 4.25 and consist of two overlapping "quartets" instead of a simple four-line pattern as would be expected if both rings were equivalent. Similarly, the protons at carbon atoms 5 and 5′ appear as a complex multiplet (centered at τ 4.25) apparently complicated by splitting due to H_5–$H_{5'}$ interaction which would occur only if both rings were nonequivalent.

It was not possible to further distinguish between the two possible structures Ia and Ib on the basis of the available data.

It would be difficult to apply the concerted transition states (VIa or VIb) postulated for 1,3-dipolar additions for the formation of Ia or Ib; indeed in either case (Ia or Ib), one of the two cycloaddition steps would require an unfavorable cis addition. A plausible explanation

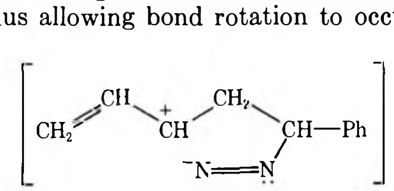


VIa



VIb

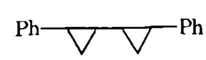
which might account for the experimental observations would involve the stepwise formation of the initial five-membered ring[6] *via* a stabilized intermediate such as VII, thus allowing bond rotation to occur prior to



VII

ring closure. This might result in the formation of both *cis*- and *trans*-3-phenyl-5-vinyl-1-pyrazoline (1:1 adduct). The addition of the sceond phenyldiazomethane to the 1:1 adduct could occur in the usual trans manner (involving a transition state such as VIa), thus leading (at least in part) to the formation of the *meso–dl* isomer of bi-1-pyrazoline. The use of lower temperatures and shorter reaction times failed to produce a 1:1 adduct 3-phenyl-5-vinyl-1-pyrazoline. The attempted addition of vinyldiazomethane[19,20] to styrene gave a high yield of pyrazole.

2. Thermal and Photolytic Decomposition.—The mixture of stereoisomers of 3,3′-diphenyl-5,5′-bi-1-pyrazoline (I) and the pure isomer (Ia,b) were each decomposed thermally and photochemically in solution. The decomposition products in each case were shown to be mixtures of isomers of 2,2′-diphenylbicyclopropane (VIII) by their infrared (1025 cm^{-1}) and nmr (τ 9.0–9.5) spectra and by their elemental analyses. No other hydrocarbon products were evident.



VIII

The per cent composition of bicyclopropyls varied slightly with conditions. The results are summarized in Table II. (The bicyclopropanes VIIIa–c are listed in order of increased vpc retention time.)

The results of the thermal and photochemical decompositions of the isomer mixture I indicated that in this case there was very little difference (essentially the same ratio for VIIIa:VIIIb:VIIIc, 5.2:1:6.2) in product selectivity between the two processes. The thermal decomposition of pure isomer Ia,b gave the same three products, but in a ratio of 6.1:1:9.4. On the other hand, photolysis of Ia,b in solution showed

(18) (a) K. von Auwers and P. Heimke, *Justus Liebigs Ann. Chem.*, **458**, 186 (1927); (b) R. C. Fuson, R. E. Christ, and G. M. Whitman, *J. Amer. Chem. Soc.*, **58**, 2450 (1936).

(19) I. Tabushi, K. Takagi, M. Okano, and R. Oda, *Tetrahedron*, **23**, 2621 (1967).

(20) C. D. Hurd and S. C. Lui, *J. Amer. Chem. Soc.*, **57**, 2656 (1935).

TABLE II
DECOMPOSITIONS OF 1-PYRAZOLINES[a]

1-Pyrazoline	Conditions	VIIIa	VIIIb	VIIIc
I (isomer mixture)	Thermal	42.2	7.3	50.5
	Photolytic	41.1	9.0	49.9
Ia,b (pure isomer)	Thermal[b]	36.9	6.1	57.0
	Photolytic[c]	12.0	0.0	88.0

[a] The thermal decompositions were carried out in *p*-xylene at the reflux temperature (145°); the photolyses were run in a Pyrex apparatus in dioxane at ~15°. [b] Very little difference (37.1:5.8:57.1) was observed at 110°. [c] Photolysis of a vigorously stirred suspension in *n*-hexane at ~15° gave essentially similar results (9.6:0.0:90.4).

enhanced product stereoselectivity affording only two of the three bicyclopropanes (VIIIa and VIIIc) in a ratio of 1:7.4. It is interesting to note that a large portion of VIIIa and all of VIIIb are apparently formed photochemically from one or both of the other two isomers present in the mixture. The data available did not allow a stereochemical assignment to these isomers.

Experimental Section

Melting points are reported as uncorrected. Microanalyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Mülheim (Ruhr), West Germany. Nmr spectra were obtained on a Varian Associates Model A-60 spectrometer using tetramethylsilane as internal standard, at room temperature except where noted otherwise. Infrared spectra were run on a Perkin-Elmer Model 521 spectrophotometer. Ultraviolet spectra were determined on a Cary Model 14 spectrophotometer. All vapor phase chromatographic analyses were performed on a Varian Aerograph Model 1520 (2 m × 0.25 in. o.d. column packed with 15% DC-710 silicone grease on firebrick) using the thermal conductivity detectors. The instrument was operated isothermally at 150° for 90 min and then programmed at 50°/min to a maximum temperature of 225° and held at this temperature until the samples eluted. All preparative vapor phase chromatography was performed on a Varian Aerograph Model A-700 (20 ft × 3/8 in. o.d. column packed with 20% SE-30 silicone gum rubber on 60–80 mesh Chromosorb W, DMCS).

3,3′-Diphenyl-5,5′-bi-1-pyrazoline (I).—One liter of a freshly prepared 0.35 *M* solution of phenyldiazomethane[21] was poured into a 3-l., three-neck, round-bottom flask, equipped with a magnetic stirring bar, gas inlet tube, and gas outlet connected to a bubble counter containing a small amount of mercury. Anhydrous ether was added to bring the total volume to 1.5 l. 1,3-Butadiene was passed slowly into the stirred solution at such a rate as to cause intermittent bubbling of the mercury in the bubble counter. The flask was then wrapped completely in aluminum foil and the reaction allowed to proceed at room temperature for 24 hr. After this time, a small amount of material began to crystallize. The flow of butadiene was stopped and the flask was cooled in a Dry Ice–trichloroethylene bath for 1 hr. The precipitate (10 g) was filtered and washed with cold pentane to remove the adhering red color. The filtrate (containing unreacted phenyldiazomethane) was returned to the 3-l. flask and the flow of 1,3-butadiene was resumed and continued for an additional 24 hr to give an additional 5 g of product. The total yield of 3,3′-diphenyl-5,5′-bi-1-pyrazoline (I) amounted to 15 g (29% based on phenyldiazomethane) of a mixture of isomers, mp 152–155°. Three recrystallizations from methanol gave a constant melting sample: mp 156–157°; ir 1540 cm^{-1} (N=N); uv λ_{max} 328 mμ (ϵ 565). This material proved stable for extended periods of time when stored in a desiccator at −20°.

Anal. Calcd for $C_{18}H_{18}N_4$: C, 74.45; H, 6.25; N, 19.30. Found: C, 74.52; H, 6.36; N, 19.31.

Chromatographic Analysis of I and Isomer Separation.—A solution of 1 mg of the freshly recrystallized 3,3′-diphenyl-5,5′-bi-1-pyrazoline mixture (I) in 0.5 ml of dichloromethane was prepared and 3 μl of this solution (equivalent to 6 μg of I) was spotted on a plate. The tlc plates consisted of a 250-μ layer of silica gel (5% $CaSO_4$ binder) on a 50 × 200 mm glass plate. The sample was eluted with a mixture of 3 parts benzene, 3 parts dichloromethane, and 1 part methanol by volume and detected by exposure of the plate to iodine vapor. Three spots were observed; the R_f values were 0.73, 0.69, and 0.66.

A column (20 mm i.d. × 400 mm length) was packed with 50 g of silica gel (particle size 0.05–0.2 mm) in a slurry of dichloromethane. Tight packing was assured by the use of an electric vibrator until the column did not appear to settle further.

A solution of 1 g of 3,3′-diphenyl-5,5′-bi-1-pyrazoline (I), in warm dichloromethane was placed on the column and eluted with 2.0–2.5 l. of dichloromethane. Tlc analysis of the fractions, mp 164–165°, indicated a predominance of the isomer with the highest R_f value and only small amounts of the other two isomers. These fractions were combined and chromatographed as before and gave the pure isomer, mp of 167–168° dec, homogeneous by thin layer chromatography (R_f 0.73). (Rechromatography or recrystallization from methanol did not raise the melting point.) The ir spectrum of this substance contained a band at 1540 cm^{-1} (N=N) and its uv spectrum exhibited an absorption at 328 mμ (ϵ 563). The nmr spectrum (DMSO-d_6, 70°) exhibited resonance as follows: τ 2.7 (10 H, C_6H_5), 4.25 (2 H, PhCH, 2 overlapping quartets), 4.75 (2 H, NCHCHN, complex multiplet), and 8.2 (4 H, CH_2, complex multiplet).

Anal. Calcd for $C_{18}H_{18}N_4$: C, 74.45; H, 6.25; N, 19.30. Found: C, 74.54; H, 6.31; N, 19.13.

1,1′-Diacetyl-3,3′-diphenyl-5,5′-bi-2-pyrazoline (IV). A. From I (Mixture of Isomers).—A mixture of 3 g (10 mmol) of freshly recrystallized I, 50 ml of acetic anhydride, and several crystals of *p*-toluenesulfonic acid was stirred at room temperature for 48 hr. The mixture was then heated to 80° for 2 hr until all solid material had dissolved. On slow cooling, the solution deposited 0.5 g of a white solid, mp 215–220°. Evaporation of the filtrate gave an additional 0.6 g of a white solid, mp 210–217°. An analytical sample of IV, mp 218–219°, was obtained by recrystallization from methanol: nmr ($CDCl_3$, 59°) τ 2.3 (10 H, C_6H_5), 4.8 (2 H, CH quartet), 6.7 (4 H, CH_2 multiplet), and 7.8 (6 H, CH_3CO, singlet).

Anal. Calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96. Found: C, 70.55; H, 5.78; N, 15.04.

B. From I (Pure Isomer).—To 100 mg (0.34 mmol) of the pure isomer of VI (mp 167–168°) was added 10 ml of acetic anhydride and a crystal of *p*-toluenesulfonic acid. The mixture was stirred and heated to about 40°, at which temperature the bi-1-pyrazoline completely dissolved. The solution was maintained at 40–50° for 3 hr. The excess acetic anhydride was then removed under vacuum. The product, obtained as a brownish-yellow powder, was taken up in hot 1:1 methanol–water. On cooling, 56 mg of a yellow powder, mp 185–190°, was obtained. A solution of this material in hot methanol, when allowed to crystallize very slowly, gave white crystals, mp 215–218°, identical (ir and mixture melting point) with that sample of IV prepared from I (isomer mixture).

Isolation and Determination of the Decomposition Products of I.—A solution of 10 g of I in *p*-xylene was heated under reflux for approximately 6 hr. After removal of the solvent by distillation, the residue was distilled at 0.2 mm and the products were collected as a liquid, bp 125–140°. Gas chromatographic analysis indicated the presence of three products. The vpc retention times were 149, 157, and 173 min, and separation was effected by preparative vpc. Repurifications by vpc and short-path distillation at 1 × 10^{-5} mm gave products of better than 99% purity. The isomer with the shortest retention time (VIIIa) exhibited a λ_{max} at 221 mμ (ϵ 23,300) and an infrared band at 1026 cm^{-1}. The nmr spectrum (CCl_4) showed peaks at τ 2.8 (10 H, C_6H_5), 8.0 (2 H, PhCH, multiplet), and 9.1 (6 H, $CHCH_2$, multiplet).

Anal. Calcd for $C_{18}H_{18}$: C, 92.25; H, 7.75. Found: C, 91.97; H, 7.80.

The isomer with intermediate vpc retention time (VIIIb) exhibited a λ_{max} at 220 mμ (ϵ 20,800) and an infrared band at 1026 cm^{-1}. The nmr spectrum (CCl_4) showed resonance at τ 2.8 (10 H, C_6H_5), 8.0 (2 H, PhCH, multiplet), and 9.1 (6 H, $CHCH_2$, unresolved multiplet). The isomer with the longest retention time (VIIIc) exhibited a uv absorption at 223 mμ (ϵ 21,200) and an ir band at 1026 cm^{-1}. The nmr (CCl_4) showed peaks at τ 2.9 (10 H, C_6H_5), 8.2 (2 H, PhCH, multiplet), and 9.1 (6 H, $CHCH_2$, multiplet).

Quantitative Determination of the Products from the Thermal Decomposition of I and VI.—The *p*-xylene (Matheson Coleman

(21) J.-P. Anselme, *Org. Prep. Proced.*, 1, 73 (1969).

and Bell, chromatographic quality) used as a solvent for the decompositions was dried by storage over activated molecular sieves and deoxygenated by bubbling purified nitrogen for 12 hr.

Samples (50–100 mg) of freshly recrystallized I or VI were weighed into a 5-ml glass ampoule kept under nitrogen and 2 ml of *p*-xylene was added. The system was then degassed by the freeze–vacuum–thaw method (3 times). The ampoule was sealed while the contents were frozen and still under high vacuum and then heated by the refluxing vapors of either xylene or toluene depending on the decomposition temperature desired. When decomposition was complete, the tube was allowed to cool and the solvent removed by freeze drying. In all cases, quantitative yields of bicyclopropyls (IX) were obtained. The ratios of products were determined by gas chromatography and results are summarized in Table II.

Quantitative Determination of the Products from the Photolytic Decomposition of I and VI in Solution.—The photolytic decompositions were carried out on approximately 50–100 mg of the freshly recrystallized I isomer mixture or pure isomer Ia,b dissolved in 30–40 ml of spectroquality dioxane. These solutions were irradiated in a Pyrex apparatus[22] (care was taken to exclude oxygen) with a Rayonet ultraviolet reactor (lamps with maximum emission at 350 nm were used). Nitrogen evolution was measured in a thermostated gas buret. Cessation of nitrogen evolution was taken as the end of the decomposition. In all cases, 95–100% of the theoretical nitrogen was evolved. After removal of the dioxane by freeze drying, the products were analyzed as before. Bicyclopropyls VIII were isolated in quantitative yields. The results are summarized in Table II.

Registry No.—*cis,trans*-I, 27694-29-7; IV, 27825-09-8; VIII, 27755-39-1.

Acknowledgment.—The authors gratefully acknowledge financial support of the National Science Foundation, Grant No. GP-7600.

(22) C. D. DeBoer, N. J. Turro, and G. S. Hammond, *Org. Syn.*, **47**, 65 (1967).

Ring Expansion of a 1,2-Dihydropyridine to an Azepine

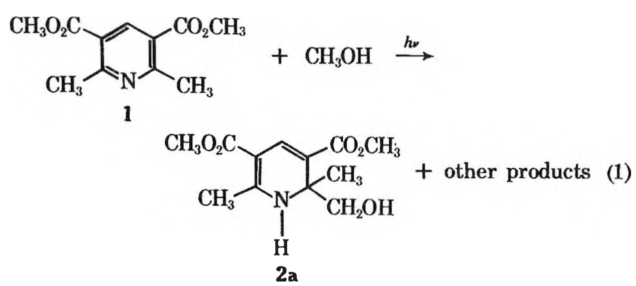
T. J. VAN BERGEN AND RICHARD M. KELLOGG*

Department of Organic Chemistry, The University Zernikelaan, Groningen, The Netherlands

Received September 11, 1970

Ring expansion of the tosylate of 3,5-dicarbomethoxy-2,6-dimethyl-2-hydroxymethyl-1,2-dihydropyridine (**2b**) is described. The product is 4,6-dicarbomethoxy-2,7-dimethyl-3*H*-azepine (**3**) which, in polar solvents, is in equilibrium with its dimer **5** formed by addition of the 2-methyl group of **3** to the N_1–C_2 double bond of another molecule of **3**. The structure of **3** is established from the nmr spectrum of its hydrogenation product. Ring expansion proceeds with the exclusive migration of a vinylic group (C_2–C_3 bond) of **2b** with no concomitant migration of the nitrogen atom. In the presence of diethylamine, **3** condenses with benzaldehyde to give 4,6-dicarbomethoxy-7-methyl-2-(*trans*-styryl)-3*H*-azepine (**8**). The nmr spectra for the methylene groups of both **3** and **8** are temperature dependent indicating ring-inversion barriers of $\Delta G^{\ddagger} = 13.7$ kcal/mol and $\Delta G^{\ddagger} = 14.2$ kcal/mol, respectively; no evidence of valence tautomerism was found. Limitations of this ring-expansion procedure are discussed.

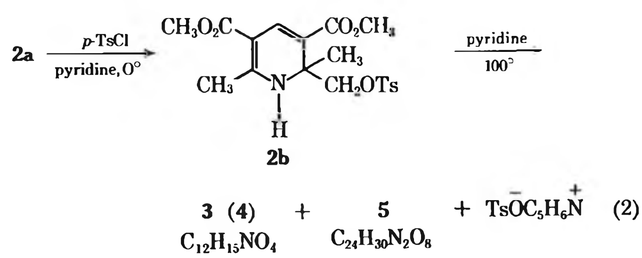
Methanol adds to the pyridine derivative **1** upon irradiation yielding 1,2-dihydropyridine **2a** (eq 1).[1] The



hydroxy methyl group of **2a** provides an obvious point at which to trigger ring expansion with either a vinylic group (C_2–C_3 bond) or the nitrogen atom (N_1–C_2 bond) being properly situated for a 1,2 shift.[2] We report here the successful ring expansion of the tosylate **2b** and subsequent transformations of the rearrangement product.

Results

Dihydropyridine **2a**, which is stable at room temperature,[3] is obtained readily from other photochemical reaction products (eq 1) by thick layer chromatography (tlc). Tosylation of **2a** in pyridine in the cold gives the tosylate **2b** (eq 2); no substitution is ob-



served at nitrogen consistent with the normal selectivity of tosyl chloride.[4] On heating at 100° in pyridine, **2b** reacts rapidly to produce *p*-toluenesulfonic acid (isolated in 85% yield as the pyridinium salt) and two neutral compounds one of which, isolated by tlc in 40–50% yield, was a rather unstable oil tentatively considered to be either 3*H*-azepine **3** or 2*H*-azepine **4**.[5] The neutral compound **5**, obtained in 18% yield, was a solid, mp 138–140°. The

(1) R. M. Kellogg, T. J. van Bergen, and H. Wynberg, *Tetrahedron Lett.*, 5211 (1969). The plethora of products which may be obtained from the photochemical reactions of pyridines are described in this article. Full details will be published in due course.

(2) For a review of ring-expansion reactions, see C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968.

(3) (a) Most 1,2-dihydropyridines are notorious for their instability. See, for example, W. Traber and P. Karrer, *Helv. Chim. Acta*, **41**, 2066 (1958). (b) See, for a review on dihydropyridines, R. A. Barnes, "Pyridine and Derivatives," part I, E. Klingsberg, Ed., Interscience, New York, N. Y., 1960.

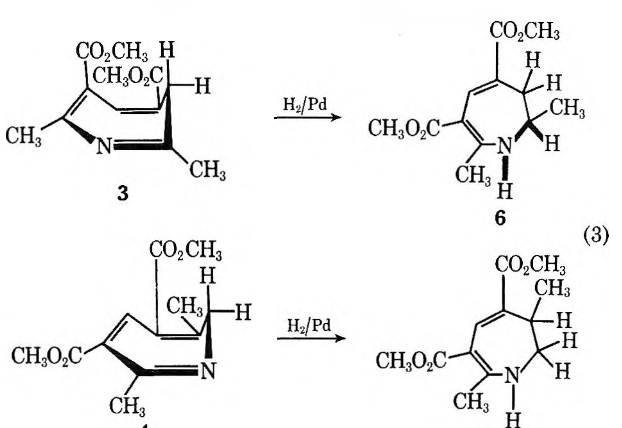
(4) L. F. Fieser and M. Fieser, "Reagents For Organic Synthesis," Wiley, New York, N. Y., 1968, p 1180.

(5) We felt it inadvisable to distil this compound in order to obtain an analytical sample; identification is based on spectral properties and chemical transformations (*vide infra*). Satisfactory elemental analyses were obtained for all of its precursors and derivatives.

molecular weight of the oil (mass spectral) accorded with the formula $C_{12}H_{15}NO_4$ consistent with the loss of the elements of *p*-toluenesulfonic acid from **2b**. Mass spectra and osmometry indicated **5** to have a dimeric composition, $C_{24}H_{30}N_2O_8$.

The ultraviolet spectrum of the oil showed major peaks at 305 mμ (log ε 3.82), 267 (3.83), and 215 (4.24) indicative of an azepine ring structure.[6] The nmr spectrum at room temperature showed nonequivalent allylic methyl groups, two nonequivalent methoxy groups, and a single vinylic proton. At temperatures below 0° a set of doublets, J = 11.0 Hz, centered at δ 0.97 and 4.15, appeared. Above 100°, these doublets were replaced by a singlet at δ 2.61. The nmr spectrum is shown in Figure 1. Measurements at various temperatures established the coalescence temperature[7] to be 25 ± 5° with $\Delta G^{\ddagger}$ = 13.7 ± 0.2 kcal/mol in either chlorobenzene or carbon tetrachloride. These data are clearly consistent with an azepine capable of ring inversion but allow no distinction between the two possible structures **3** and **4** (vinyl and nitrogen migration, respectively). An unequivocal assignment is not possible on the basis of spectral observations: simple 2*H*-azepines are unknown[8] and no 3*H*-azepine with a substitution pattern analogous to **3** has been reported. A tentative indication for structure **3** is found in the observation of homoallylic[9] coupling (J = 0.6 Hz) between the vinylic proton and the methyl group located at δ 2.56. In **4** the 2- and 7-methyl groups are equidistant from the vinylic proton, leading to the expectation that *both* methyl groups should show homoallylic coupling, whereas in **3** presumably only the 7-methyl group should be coupled.

Unambiguous evidence for the correctness of structure **3** was finally obtained by selectively reducing the imino portion of the azepine. Ample precedent exists for this type of conversion with other azepines.[6b] Low pressure hydrogenation in methylcyclohexane gave a single crystalline dihydro compound, mp 98–99°. Strong uv absorptions at 223 mμ (log ε 3.89), 280 (3.90), and 357 (3.86) point to a 1,2-dihydropyridine-like structure[10] requiring either 1,2 addition (1,2 bond) to **3** to give **6** or 1,6 addition (positions 1,3) to yield **7** (eq 3). The 100-Mc nmr spectrum of



3 → **6**; **4** → **7** (3)

the hydrogenation product in carbon tetrachloride is shown in Figure 2; J values were determined from decoupling experiments.[11] In DMSO vicinal coupling (inset, Figure 2) of the nitrogen-bound hydrogen was observed,[12] and decoupling experiments established the presence of the structural unit **HNC(CH$_3$)H** (heavy lines in **6**). These observations are consistent only with structure **6** and simultaneously *establish the ring-expansion product to be 3H-azepine* (**3**).

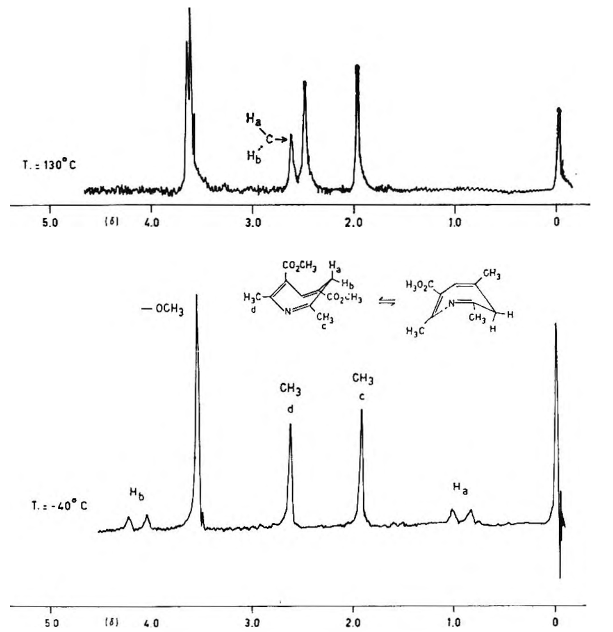


Figure 1.—Nmr spectrum of **3** at 60 Mc in C_6H_5Cl solvent. The geminal coupling constant is J = 11.0 Hz; homoallylic coupling between H-5 and the 7-methyl group (H$_d$) is J = 0.6 Hz.

The structure of dimer **5** was unraveled by consideration of the following observations: (a) only three of the expected four methyl resonances could be located in the nmr spectrum (Figure 3) [of these, one is shifted to higher field (δ 0.94) suggesting it to be attached to a sp^3 rather than sp^2 hybridized carbon atom]; (b) the ultraviolet spectrum of **5** could be duplicated closely by *adding* the spectra of **3** and **6** (a 3*H*-azepine and a dihydroazepine); (c) **3** yields **5** only slowly in nonhydroxylic solvents (benzene) and more rapidly in hydroxylic solvents (methanol); (d) above 85° **5** is visibly in equilibrium with **3** and in refluxing chlorobenzene (135°) reversion to **3** is quantitative; (e) **5** contains *one* NH proton (ir 3360 cm^{-1}) as deduced from integration of the nmr resonances; (f) one methylene resonance in the nmr spectrum (Figure 3) is not seen suggesting an azepine ring. These data, coupled with the observation of two protons of the missing methyl group as an AB system (J = 15.0 Hz, geminal coupling) at δ 2.28 and 2.48 and the third proton likely accounted for as NH suggest that

(6) (a) L. A. Paquette, D. E. Kuhla, J. H. Barrett, and R. J. Haluska, *J. Org. Chem.*, **34**, 2866 (1969); (b) M. Anderson and A. W. Johnson, *J. Chem. Soc.*, 2411 (1965); (c) R. F. Childs and A. W. Johnson, *ibid.*, *C*, 1950 (1966).

(7) R. J. Kurland, M. B. Rubin, and W. B. Wise, *J. Chem. Phys.*, **40**, 2426 (1964); M. Oki, H. Iwamura, and N. Hayakana, *Bull. Chem. Soc. Jap.*, **37**, 1865 (1964).

(8) See, for a review on azepines, L. A. Paquette in "Nonbenzenoid Aromatics," Vol. I, J. P. Synder, Ed., Academic Press, New York, N. Y., 1969.

(9) S. Sternhell, *Quart. Rev.*, **23**, 236 (1969).

(10) Compare, for example, compounds **2a,b** and ref 1. The blue shift of the long wavelength band is due to the greater ring size.

(11) We are indebted to Dr. K. Spaargaren and Mr. C. Kruk of the University of Amsterdam for measuring the 100-Mc spectra, carrying out decoupling experiments, and providing aid in interpretations.

(12) This trick has been successfully exploited with alcohols: O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).

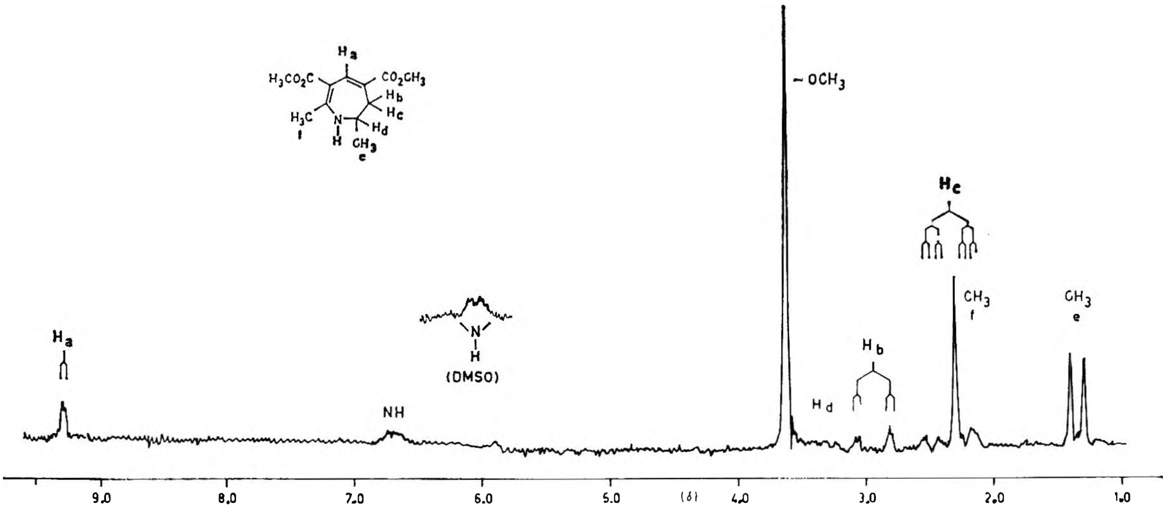


Figure 2.—Nmr spectrum of **6** at 100 Mc in CCl_4 (except for inset) taken at normal probe temperature (*ca.* 35°). Coupling constants are J_{bc} = 16.0 Hz, J_{cd} = 6.0 Hz, J_{bd} = 2.0 Hz, J_{ac} = 1.2 Hz, J_{ab} = 0 Hz, and J_{NH} = 5.0 Hz.

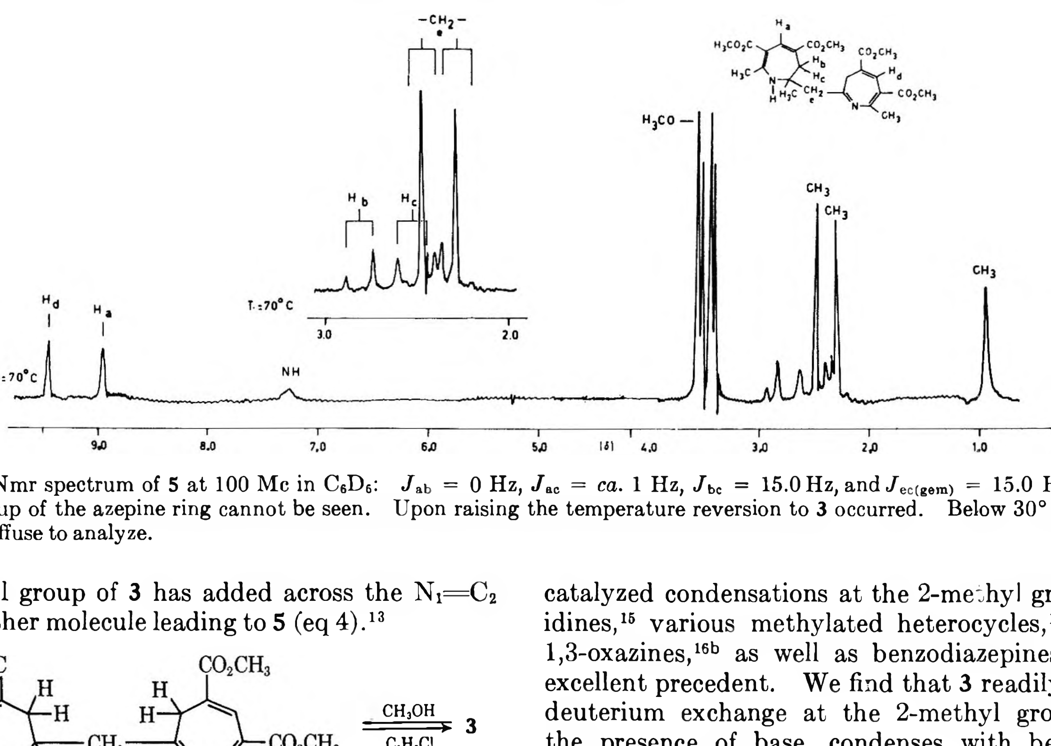
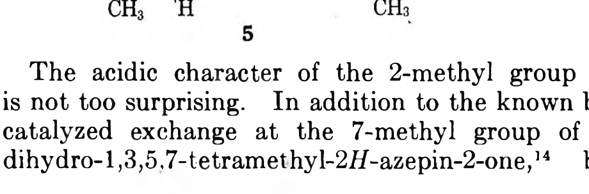


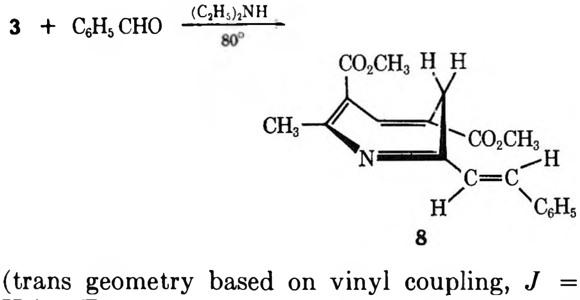
Figure 3.—Nmr spectrum of **5** at 100 Mc in C_6D_6: J_{ab} = 0 Hz, J_{ac} = *ca.* 1 Hz, J_{bc} = 15.0 Hz, and $J_{ec(gem)}$ = 15.0 Hz. The 3*H*-methylene group of the azepine ring cannot be seen. Upon raising the temperature reversion to **3** occurred. Below 30° the spectrum becomes too diffuse to analyze.

the 2-methyl group of **3** has added across the $N_1{=}C_2$ bond of another molecule leading to **5** (eq 4).[13]



5 (4)

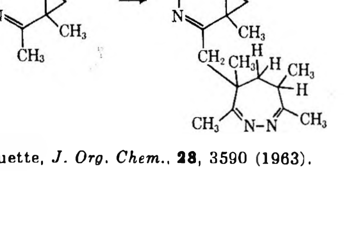
The acidic character of the 2-methyl group of **3** is not too surprising. In addition to the known base-catalyzed exchange at the 7-methyl group of 1,3-dihydro-1,3,5,7-tetramethyl-2*H*-azepin-2-one,[14] base-catalyzed condensations at the 2-methyl group of pyridines,[15] various methylated heterocycles,[16a] dihydro-1,3-oxazines,[16b] as well as benzodiazepines,[17] provide excellent precedent. We find that **3** readily undergoes deuterium exchange at the 2-methyl group and, in the presence of base, condenses with benzaldehyde to give in 32% yield (eq 5) the 2-styryl derivative **8**



8 (5)

(trans geometry based on vinyl coupling, J = 16.0 Hz). That condensation has occurred at the 2 position

(13) Most azepine dimerizations involve Diels–Alder-like cycloadditions. (a) L. A. Paquette and J. H. Barrett, *J. Amer. Chem. Soc.*, **88**, 2590 (1969). (b) A. L. Johnson and H. E. Simmons, *ibid.*, **89**, 3191 (1967). (c) K. Hafner and J. Mondt, *Angew. Chem.*, **78**, 822 (1966). (d) A most curious dimerization resembling that observed by us is shown in eq i: G. Maier, *ibid.*, **79**, 456 (1967).



(i)

(14) L. A. Paquette, *J. Org. Chem.*, **28**, 3590 (1963).

(15) For example, V. Boekelheide, H. Fritz, J. M. Ross, and H. X. Kaempfen, *Tetrahedron*, **20**, 33 (1964); S. M. McElvain and H. G. Johnson, *J. Amer. Chem. Soc.*, **63**, 2213 (1941).

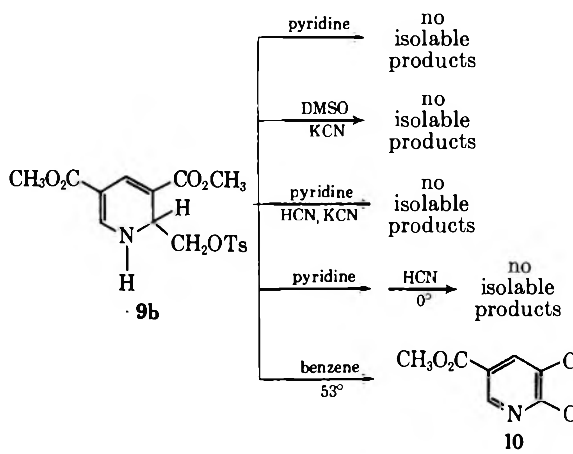
(16) (a) A. E. Siegrist and H. R. Meyer, *Helv. Chim. Acta*, **52**, 1282 (1969); (b) A. I. Meyers, A. Nabeya, H. W. Adickes, and I. R. Politzer, *J. Amer. Chem. Soc.*, **91**, 763 (1969).

(17) S. Motoki, C. Urakawa, A. Kano, Y. Fushimi, T. Hirano, and K. Murata, *Bull. Chem. Soc. Jap.*, **43**, 809 (1970); J. A. Baltrop, C. G. Richard, D. M. Russell, and G. Ryback, *J. Chem. Soc.*, 1132 (1959).

is indicated by the retention of homoallylic coupling between H-5 and the 7-methyl group. Ring inversion occurs in **8** with a coalescence temperature of 35 ± 5° ($\Delta G^{\ddagger}$ = 14.2 ± 0.2 kcal/mol) in either carbon tetrachloride or chlorobenzene.

The less than quantitative conversion of **2b** to **3** could be attributed either to work-up problems (tlc) or to formation of a second isomer, **4**, which decomposes under the reaction conditions. The ring expansion was investigated spectroscopically to resolve this question. When followed by uv the conversion of **2b** to **3** was calculated to proceed in 108% yield. No extraneous absorptions were seen and a clean isosbestic point was observed at 328 mμ. In a nmr tube the signals from **2b** were replaced exclusively by the signals from **3** (85% yield calculated using the tolylmethyl group as internal standard). The disappearance of **2b** in pyridine was cleanly first order at 53° with k = 1.8×10^{-4} l. mol^{-1} sec^{-1}.

A number of attempts were made to effect ring expansion of **9b** (eq 6) obtained by tosylation of the



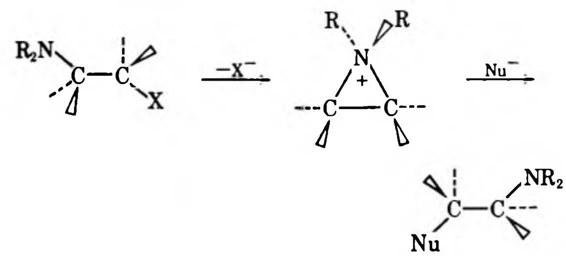
(6)

photochemically induced addition product of methanol to 3,5-dicarbomethoxypyridine **9a**. Conventional reaction in pyridine led to no isolable products. Reaction in DMSO/KCN[18] also failed. In benzene (nonsolvolytic) an 18% yield of the oxidation product 3,5-dicarbomethoxy-2-tosyloxymethylpyridine (**10**) was isolated. After a number of fruitless attempts to modify conditions or to trap an intermediate (HCN addition), we concluded that intrinsic difficulties in the system circumvent ring expansion of an azepine. Some of these problems are dealt with in the Discussion.

Descriptions of attempted Diels–Alder reactions and of photochemical experiments with **3** are given in the Experimental Section.

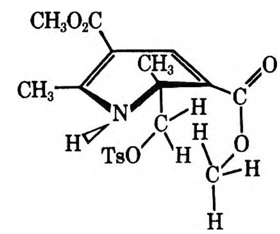
Discussion

Many of the synthetic approaches to seven-membered rings hinge on the judicious exploitation of readily available six-membered precursors suitably constituted for ring expansion. In particular, solvolyses of cyclohexadienyl tosylates provide a workable route to cycloheptatrienes.[19] Replacement of carbon by a heteroatom is also feasible as attested, for example, by the successful conversion of 4-chloromethyl-1,4-dihydropyridines to 4H-azepines.[6b,20] In dihydropyridine **2b** either the vinylic group (C_2–C_3 bond) or the nitrogen (N_1–C_2 bond) are properly disposed for a 1,2 shift. Migration of the latter leading to 2H-azepine **4** is certainly not intrinsically prohibited. Various β-amino-substituted ethyl chlorides capable of forming aziridine intermediates undergo nitrogen shifts by the route depicted in eq 7,[21,22] and, moreover, even in a



(7)

case where the nitrogen lone pair is prevented sterically from forming an aziridine, rearrangement still occurs apparently by participation of only the nitrogen–carbon σ bond.[23] In **2b** the exclusive shift of the vinylic group is likely caused by dual interplay of steric and electronic factors. As depicted in eq 8 the antiperiplanar[24] conformation for a vinylic group shift involves less steric hindrance than for a nitrogen shift where tosylate–carbomethoxy interactions may develop. Second, the carbomethoxy groups of **2b** lower the nitrogen nucleophilicity by conjugative and inductive action; these combined effects apparently overweigh the deactivating tendency of the carbomethoxy group on the migrating vinylic group.[25]



(18) This technique has been exploited by Johnson and coworkers, ref 5b.

(19) N. A. Nelson, J. H. Fassnacht, and J. U. Piper, *J. Amer. Chem. Soc.*, **81**, 5009, (1959); O. L. Chapman and P. Fitton, *ibid.*, **85**, 41 (1963).

(20) M. Anderson and A. W. Johnson, *Proc. Chem. Soc.*, 263 (1964).

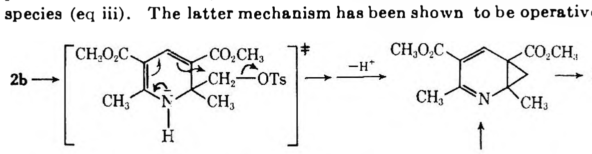
(21) See, for example, A. Streitweiser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, pp 105–108.

(22) R. C. Fuson and C. L. Zirkle, *J. Amer. Chem. Soc.*, **70**, 2760 (1948).

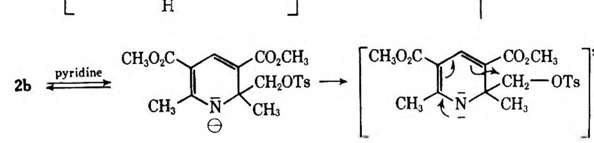
(23) R. B. Turner and R. B. Woodward, "The Alkaloids," Vol. III, R. H. F. Manske and H. L. Holmes, Ed., Academic Press, New York, N. Y., 1953, p 18.

(24) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley-Interscience, New York, N. Y., 1965, p 300.

(25) Two kinetically different processes may be imagined for the ring expansion: (a) a unimolecular process as crudely depicted in eq ii, or (b) prior ionization at *nitrogen* with the resultant anion being the rearranging species (eq iii). The latter mechanism has been shown to be operative in the



(ii)



(iii)

ring expansion of 2,6-dimethyl-4-chloromethyl-3,5-dicarbomethoxy-1,4-dihydropyridine in ethanol containing cyanide ion,[26] while the former mechanism must obtain in the ring expansion of the N-methylated derivative of the same compound where prior ionization is impossible.[6c] Ring expansion of **2b** does not lend itself to study since the reaction proceeds well only in pyridine and fails in other solvents such as acetonitrile, dioxane, and benzene (nonsolvolytic). No serious attempt to distinguish conclusively between these two mechanisms has been made.

(26) P. J. Brignell, U. Eisner, and H. Williams, *J. Chem. Soc.*, 4226 (1965).

No evidence for valence tautomerism in either **3** or **8** was obtained. The geminal coupling of the methylene hydrogens remained invariant at J = 11.0 Hz and J = 12.0 Hz, respectively, as the temperature was varied. This speaks strongly against the presence of measurable quantities of azanorcaradienes at readily reachable temperatures.[27-31] Azanorcaradienes are indicated as intermediates during ring expansion in eq ii and iii (ref 25) but a simple 1,2 shift proceeding directly to the azepine is indistinguishable. Particularly interesting are the ring-inversion barriers for **3** and **8** which are higher than ever reported for azepines not attached to condensed rings.[33] A general trend of increasing $\Delta G^{\ddagger}$ for ring inversion with increasing substitution can be discerned from the limited number of examples, but it is undoubtedly unwarranted to consider this the only causative factor.

All known 3*H*-azepines bear substituents in the 2 position.[8] Attempts to prepare an unsubstituted derivative by the solvolysis of **9b** met with failure although uv spectra (Experimental Section) suggested that an azepine may well have been formed. Most likely a 2 substituent fulfills the double role of protecting the N_1–C_2 bond from addition or dimerization reactions and, in the case of alkyl substituents, provides ylidic structures (note the acidity of the 2-methyl group of **3**) which lend further stability to the azepine. That the N_1–C_2 bond is quite sensitive to addition is shown by the replacement of a 2-ethoxy substituent in a 3*H*-azepine by a secondary amine, apparently by means of addition–elimination.[34,35]

Experimental Section

Melting points were determined with a Reichert melting point microscope and are uncorrected. Ultraviolet spectra were recorded on a Zeiss PMQ II spectrophotometer. Nmr spectra were taken on a Varian A-60 spectrometer (except where otherwise reported) with tetramethylsilane as an internal standard. An AEI MS-902 mass spectrometer equipped with an all-glass heated inlet system at 150° was used. The ionization potential and current were 70 eV and 100 μA, respectively. Microanalysis were performed by the analytical department of this laboratory under the supervision of Mr. W. M. Hazenberg.

3,5-Dicarbomethoxy-2,6-dimethylpyridine (1) was obtained by a Hantzsch pyridine synthesis as described for the corresponding diethyl ester[36] and was isolated in 30% overall yield: bp 131° (1.3 mm) and mp 100–102° (recrystallized from petroleum ether, by 40–60°); uv max (C_2H_5OH) 235 mμ (log ε 4.07), 273 (3.63), and 282 (sh, 3.54).

Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.26, 59.37; H, 5.93, 5.91; N, 6.37, 6.23.

3,5-Dicarbomethoxypyridine was prepared by adding dropwise an excess of an ethereal solution of diazomethane to a stirred and ice-cooled suspension of 17 g of pyridine-3,5-dicarboxylic acid in 100 ml of diethyl ether. Stirring was continued overnight. The unreacted acid was recovered by filtration (5.5 g) and the filtrate was evaporated. Distillation of the residue yielded 9 g (67%) of 3,5-dicarbomethoxypyridine: bp 127–132° (1.4 mm); mp 82.5–84°, recrystallized from a petroleum ether (bp 40–60°)–ethanol solvent mixture (lit.[37] mp 84–85°); uv max (CH_3OH) 220 mμ (log ε 4.02), 262 (sh, 3.18), 267 (3.21), and 276 (sh, 3.07).

3,5-Dicarbomethoxy-2,6-dimethyl-2-hydroxymethyl-1,2-dihydroxypyridine (**2a**) was obtained by irradiating a solution of 1.5 g of 3,5-dicarbomethoxy-2,6-dimethylpyridine in 650 ml of methanol for 23 hr with a Rayonet photochemical reactor equipped with 2537-Å lamps. Evaporation of the solvent and separation of the residue by preparative tlc on silica gel PF_{254} with diethyl ether as eluent afforded 1.050 g (60%) of crude **2a**. Recrystallization from ethanol gave an analytically pure sample: mp 186–188°; ir (KBr) 3520 (OH) and 3395 cm^{-1} (NH); uv max (C_2H_5OH) 216 mμ (log ε 4.10), 283 (4.34), and 385 (3.84); pmr (CD_3OD) δ 1.40 and 2.32 (s, 3, CH_3), 3.36 and 4.00 (d, 1, J = 11.5 Hz, CH_2OH), 3.67 (s, 6, ester CH_3), and 7.80 (s, 1, vinylic H).

Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.48; H, 6.70; N, 5.49. Found: C, 56.61, 56.24; H, 6.82, 6.78; N, 5.41, 5.45.

3,5-Dicarbomethoxy-2-hydroxymethyl-1,2-dihydropyridine (**9a**) was obtained from irradiation of 1.5 g of 3,5-dicarbomethoxypyridine as reported above for **2a** [1.361 g (79%) of the product **9a** was collected]: mp 139–142° (recrystallized from C_2H_5OH); ir (KBr) 3230 (NH) and 3350 cm^{-1} (OH, associated); uv max (C_2H_5OH) 218 mμ (log ε 4.11), 282 (4.26), and 383 (3.76); pmr (C_5D_5N) δ 3.56 and 3.60 (s, 3, ester CH_3), 3.50–4.20 (m, 2, CH_2OH), 5.05 (q, 1, $CHCH_2OH$), 6.00 (2, OH and NH), 7.96 (d, 1, vinylic HCNH), 8.03 (s, 1, vinylic H).

Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.17. Found: C, 52.76, 52.60; H, 5.97, 5.92; N, 6.10, 6.20.

3,5-Dicarbomethoxy-2,6-dimethyl-2-tosyloxymethyl-1,2-dihydropyridine (**2b**) was obtained by adding 1.55 g of pure *p*-toluenesulfonyl chloride[38] to an ice-cooled solution of 0.960 g of **2a** dissolved in 10 ml of dry pyridine, and the reaction mixture was stored overnight in a refrigerator. The solution was poured out into 60 g of ice-water and crystallization of the tosylate was induced by cooling for several hours. Filtration and subsequent drying afforded 1.40 g (87%) of **2b**. An analytically pure sample was obtained by recrystallization at low temperature from methanol: mp 131–133°; ir (KBr) 3320 cm^{-1} (NH); uv max (C_2H_5OH) 220 mμ (log ε 4.30), 278 (4.27), and 385 (3.79); pmr (CD_3OD) δ 1.48, 2.25, and 2.48 (s, 3, CH_3), 3.54 and 3.67 (s, 3, OCH_3), 3.54 and 3.67 (d, 1, J = 10.0 Hz, CH_2O), 7.72 (s, 1, vinylic H), 7.40 and 7.80 (d, 2, J = 7.0 Hz, aromatic hydrogens).

Anal. Calcd for $C_{19}H_{23}NO_7S$: C, 55.73; H, 5.66; N, 3.42; S, 7.83. Found: C, 55.37, 55.65; H, 5.64, 5.67; N, 3.29, 3.29; S, 8,00, 7.99.

3,5-Dicarbomethoxy-2-tosyloxymethyl-1,2-dihydropyridine (**9b**) could be obtained from **9a** in 66% yield by the same procedure as described above: mp 105–108° (recrystallized from a diethyl ether–methylene chloride solvent mixture); ir (KBr) 3290 cm^{-1} (NH); uv max (C_2H_5OH) 222 mμ (log ε 4.33), 275 (4.20), and 380 (3.16); pmr (CD_3OD) δ 2.48 (s, 3, tolyl CH_3), 3.67 and 3.69 (s, 3, OCH_3), 3.60–4.20 (m, 2, CH_2O), 4.85 (q, 1, $CHCH_2O$), 7.20–7.90 (5, aromatic and vinylic hydrogens). Owing to difficulties in crystallization an analytical sample of **9b** could not be obtained.

Solvolysis of 2b was carried out by heating a solution of 1.120 g of **2b** in 10 ml of dry pyridine for 10 min at 100°. After this time the uv-absorption band of **2b** at 385 mμ had disappeared and a new band was present at 305 mμ. The pyridine was removed by evaporation and the residue dissolved in methylene chloride. This solution was extracted three times with water, dried (Na_2SO_4), and evaporated. The aqueous layer gave upon evaporation and drying the pyridinium tosylate salt (85%), characterized by its pmr spectrum. The residue from the organic layer afforded upon separation by preparative tlc (silica gel PF_{254} and diethyl ether) 0.263 g (41%) of pure 4,6-dicarbomethoxy-2,7-dimethyl-3*H*-azepine (**3**) as an oil and 0.119 g

(27) For the oxygen ease, existence of a benzene oxide form has been demonstrated unequivocally: E. Vogel, W. A. Böll, and H. Günther, *Tetrahedron Lett.*, 609 (1965); also ref 8.

(28) Geminal coupling in cyclopropanes and related systems is usually much smaller,[29] and in norcaradienes a value of J = 4–5 Hz is found.[30] 3,4-Diazanorcaradienes are known, however.[31] Comments on the stabilization of norcaradienes have been made.[32]

(29) E. Ciganek, *J. Amer. Chem. Soc.*, **87**, 1149 (1965); **89**, 1454 (1967). F. Kaplan, C. O. Schultz, D. Weisleder, and C. Klopfenstein, *J. Org. Chem.*, **33**, 1728 (1968).

(30) E. Vogel, *Pure Appl. Chem.*, **20**, 237 (1969).

(31) G. Maier, *Angew. Chem.*, **79**, 827 (1967). The energy barrier for the conversion of 2,5-dicarbomethoxy-3,4-diazanorearadiene to its diazepine analog has recently been determined accurately: D. A. Kleiner, G. Binsch, A. Steigel, and J. Sauer, *J. Amer. Chem. Soc.*, **92**, 3787 (1970).

(32) R. Hoffmann, *Tetrahedron Lett.*, 2907 (1970).

(33) A. Mannschreck, G. Rissmann, F. Vögtle, and D. Wild, *Ber.*, **100**, 335 (1967).

(34) (a) L. A. Paquette, *J. Amer. Chem. Soc.*, **85**, 4053 (1963); (b) *ibid.*, **86**, 4096 (1964); (c) W. von E. Doering and R. A. Odum, *Tetrahedron*, **22**, 81 (1966).

(35) E. Vogel, R. Erb, G. Lenz, and A. A. Bothner-By, *Justus Liebigs Ann. Chem.*, **682**, 10 (1965).

(36) A Singer and S. M. McElvain, *Org. Syn.*, **14**, 30 (1934).

(37) A. L. Searles and R. M. Warren, *J. Org. Chem.*, **18**, 1325 (1953).

(38) S. W. Pelletier, *Chem. Ind. (London)*, 1034 (1953).

(18%) of the dimer **5**. The oily product **3** showed ir (neat) 1727 and 1712 cm^{-1} (C=O); uv max (C_6H_{12}) 215 mμ (log ε 4.24), 267 (3.83), and 305 (3.82). The dimer **5** had mp 138–140° (recrystallized from a cyclohexane–diethyl ether solvent mixture); ir (KBr) 3360 (NH), 1710 and 1680 cm^{-1} (C=O); uv max (C_2H_5OH) 219 mμ (log ε 4.49), 274 (4.35), 314 (sh, 4.06), and 354 (4.12).

Anal. Calcd for $C_{24}H_{30}N_2O_8$: C, 60.75; H, 6.38; N, 5.90. Found: C, 60.71, 60.70; H, 6.37, 6.50; N, 6.10, 6.04.

Dimerization of 3 was observed when a solution of 0.129 g in chloroform was refluxed for several hours. (Dimerization was also observed in methanol at room temperature and qualitatively proceeded more rapidly in this solvent.) A spot with the same R_f value as the above-obtained dimer appeared on the tlc plate. Separation with preparative tlc (silica gel PF_{254} and diethyl ether) yielded 0.024 g (19%) of **3** and 0.054 g (42%) of a solid, mp 130–134° (recrystallized from cyclohexane) with the same spectral properties as the earlier isolated dimer of the 3*H*-azepine **3**.

Thermal reversion of the dimer 5 to 3 was observed when 0.200 g of **5** was refluxed for 15 min in chlorobenzene. On tlc **3** appeared as the main product, while the dimer **5** was present only in a trace amount. After removal of the solvent by evaporation and column chromatography of the residue over silica gel and diethyl ether as eluent, we collected 0.120 g (60%) of an oil with the same spectral properties as **3**.

Dimerization of 3 in CH_3OD was observed when a solution of 80 mg of **3** in 5 ml of CH_3OD was refluxed for 16 hr. The solution contained at this stage almost only **5** as confirmed by tlc analysis. The methanol was removed by evaporation and the residue refluxed for 1 hr in chlorobenzene to convert the dimer **5** to monomer **3**. Evaporation of the solvent followed by column chromatography of the residue (silica gel with diethyl ether) yielded 52 mg (65%) of **3** with 53% deuterium incorporation in the 2-substituted methyl group as confirmed by pmr and mass spectral analysis.

4,6-Dicarbomethoxy-2,7-dimethyl-1,2-dihydro-3*H*-azepine (**6**) was obtained by shaking 200 mg of **3** dissolved in 50 ml of methylcyclohexane for 5 hr with 300 mg of Pt catalyst in a Parr apparatus under a hydrogen pressure of 2.5 atm. The catalyst was removed by filtration and washed carefully with methanol because of the insolubility of the reduction product in methylcyclohexane. The concentrated filtrate afforded upon preparative tlc (silica gel PF_{254} and diethyl ether) 144 mg (72%) of **6**. An analytical sample was obtained by dissolving the compound in diethyl ether and slowly evaporating the solvent until crystallization started: mp 98–99°; ir (KBr) 3360 (NH), 1660 and 1650 cm^{-1} (C=O); uv max (C_2H_5OH) 223 mμ (log ε 3.89), 280 (3.90), and 357 (3.86).

Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.23; H, 7.16; N, 5.86. Found: C, 59.86, 59.95; H, 7.34, 7.23; N, 5.92, 5.82.

4,6-Dicarbomethoxy-7-methyl-2-(*trans*-styryl)-3*H*-azepine (**8**) was formed when 260 mg of **3** was refluxed overnight with 120 mg of benzaldehyde and several drops of diethylamine in benzene. Evaporation of the solvent gave an oil that slowly solidified. Recrystallization from methanol afforded 118 mg (32%) of **8**. A second recrystallization gave an analytical sample: mp 122–123.5°; ir (KBr) 1690 and 1720 cm^{-1} (C=O); uv max (C_2H_5OH) 224 mμ (log ε 4.28), 276 (4.43), and 346 (4.25); pmr (CCl_4) δ 2.52 (s, 3, CH_3), 3.75 and 3.80 (s, 3, OCH_3), 6.67 and 7.67 (d, 1, J = 16.0 Hz, HC=CH trans), 7.20–7.60 (m, 5, aromatic hydrogens), and 7.75 (s, 1, vinylic H); pmr (C_6H_5Cl) at 10° δ 1.20 and 4.78 (d, 1, J = 12.0 Hz, CH_2), at 125° δ 2.92 (s, 2, CH_2).

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.08; H, 5.88; N, 4.31. Found: C, 69.84, 69.76; H, 5.83, 5.89; N, 4.31, 4.39.

Hydrogen cyanide addition to 3[6c] was tested by leading HCN gas through an ethereal solution of the azepine. The dimer **5** was observed as the only reaction product as confirmed by ir spectroscopy and tlc analysis.

Diels–Alder reaction of 3 with dicarbomethoxyacetylene did not take place when equimolar quantities of both reagents were refluxed in benzene.

Photolysis of 3[6a] in diethyl ether for 24 hr with a mercury high-pressure lamp with a Vycor jacket did not yield any isolable product. The course of reaction was followed by uv spectroscopy: only slow decrease in the absorption of **3** was observed and no new peaks appeared.

Solvolysis of 9b was carried out (a) at 85° in pyridine, (b) at 85° in pyridine and subsequent addition of HCN at 0° to the reaction mixture, (c) by slowly warming up a solution of **9b** in pyridine saturated with HCN and KCN to 80°, (d) in dimethyl sulfoxide solution saturated with KCN at 40°.[6b] In all cases a sharp new uv absorption was observed at 345 mμ after solvolysis but no products could be isolated despite repeated attempts.

3,5-Dicarbomethoxy-2-tosyloxymethylpyridine (**10**) was obtained when 1.1 g of **9b** were refluxed for several hours in 50 ml of benzene. **10** (177 mg, 17%) was collected after evaporation of the solvent and preparative tlc (silica gel and a diethyl ether–benzene 1:1 solvent mixture) of the residue. Recrystallization from diethyl ether afforded an analytical sample: mp 89.5–90°: uv max (C_2H_5OH) 227 mμ (log ε 4.36) and 265 (3.52); pmr (CCl_4) δ 2.40 (s, 3, CH_3), 3.95 (s, 6, OCH_3), 5.48 (s, 2, CH_2), 7.25 and 7.72 (d, 2, J = 8.0 Hz, phenyl hydrogens), 8.61 and 9.08 (d, 1, J = 2.0 Hz, pyridyl hydrogens).

Anal. Calcd for $C_{17}H_{17}NO_7S$: C, 53.83; H, 4.52; N, 3.70; S, 8.46. Found: C, 53.98, 53,80; H, 4.74, 4.57; N, 3.56, 3.48; S, 8.47, 8.40.

Determination of the yield of 3 by uv measurements was carried out by heating a solution of 1.04 g of **2b** in 10 ml of dry pyridine as described above. The solution (0.1 ml) was diluted 10^4 times and the absorptions were measured.

mμ	Before reaction, E	After reaction, E		Yield, %
385	0.154	0.006	0.015	
305	0.041	0.174	0.185	105, 112

Kinetic data were obtained from 10^{-2} *M* solutions of **2b**; 1-ml samples were diluted 50 times and the absorptions measured by uv.

Registry No.—**1**, 27525-74-2; **2a**, 27525-75-3; **2b**, 27525-76-4; **3**, 27525-77-5; **5**, 27525-78-6; **6**, 27525-79-7; **8**, 27525-80-0; **9a**, 26165-23-1; **9b**, 27525-82-2; **10**, 27525-83-3.

The Base-Promoted Rearrangements of α-Arylneopentylammonium Salts

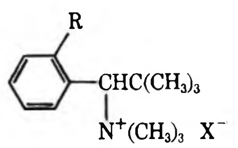
STANLEY H. PINE,* ENOCH M. MUNEMO, THOMAS R. PHILLIPS,
GIOVANNI BARTOLINI, WYATT D. COTTON, AND GLEN C. ANDREWS

Department of Chemistry, California State College, Los Angeles, California 90032

Received August 14, 1970

The base-promoted reactions of *N,N,N*-trimethyl-α-phenylneopentylammonium halides (**1a**) and *N,N,N*-trimethyl-α-*o*-tolylneopentylammonium iodide (**1b**) with numerous base-solvent systems lead to products of the Stevens **3**, ortho-Sommelet-Hauser **5**, and para-Sommelet-Hauser **6** rearrangements in addition to the demethylated tertiary amine **9**. The Stevens rearrangement is favored in nonpolar solvents and at increased temperatures, the solvent dependence being quite marked for **1a**. Increasing base concentration favors the ortho rearrangement at the expense of the Stevens and para products. The observation of nonbasic side products is considered. It is suggested that the ortho rearrangement may proceed by a mechanism different from the Stevens and para rearrangements.

As a continuation of our interest in the chemistry of quaternary ammonium salts,[1] we have investigated the base-promoted rearrangements of two series of compounds, *N,N,N*-trimethyl-α-phenylneopentylammonium iodide and chloride (**1a**) and *N,N,N*-trimethyl-α-*o*-tolylneopentylammonium iodide (**1b**). These mole-



1a, R = H
b, R = CH_3

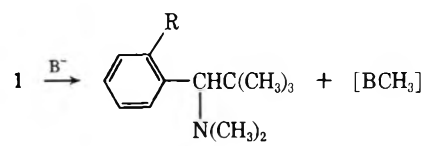
cules are the potential precursors for products of the Stevens[2] and Sommelet-Hauser[3] rearrangements with both pathways expected to occur. Scheme I illustrates the nitrogen ylides presumed to be involved and all of the potential products of these rearrangements.

Both compounds are quite hindered sterically[4] and the influence of this on possible rearrangement pathways is of interest.[5] In addition, the effect of solvent and temperature on competing Stevens and Sommelet-Hauser (ortho) rearrangements is considered along with the total question of the reaction mechanism.

Results and Discussion

Quaternary ammonium salts **1** were allowed to react with various base-solvent systems in sealed tubes under nitrogen. A reaction (*n*-butyllithium-hexane) which was carefully degassed and sealed under vacuum gave identical results with the typical runs under nitrogen. Similarly, an air purge of the reaction tube did not appreciably affect the rearrangement products. Products were analyzed by gas chromatography and positive identification of each rearrangement product was accomplished through comparison with independently synthesized material. Tables I and II indicate representative results for the two systems.

α-Phenyl System.—The influence of solvent on the course of the rearrangements of **1a** is illustrated by the results listed in Table I. It is seen that the polar "aprotic" solvents ammonia (NH_3), dimethyl sulfoxide (DMSO), and hexamethylphosphortriamide (HMPT) favor the ortho rearrangement product **5a**, while the nonpolar solvent, hexane, leads predominately to the Stevens rearrangement product **3a**. If one compares only the relative yields of the rearrangement products (Table III), this trend is quite apparent. Although the low temperature may be a factor in the ammonia solvent,[6] a similar trend has been observed with the benzyltrimethylammonium salts.[7] Interestingly, DMSO appears to favor formation of the demethylated tertiary amine **9a**, presumably through a displacement reaction. This is consistent with the well-established enhance-



9a, R = H
b, R = CH_3

ment of nucleophilic reactivity in DMSO.[8,9] Similarly, the predominant formation of **9a** with alkoxide in alcohol is consistent with the inability of the relatively weak basic species to form the requisite ylide. In the case of potassium *tert*-butoxide as base, *tert*-butyl methyl ether has been found as a product.

The Stevens rearrangement products **4** and **8** have not been detected in these reactions. The methyl-to-methyl carbanion migration required for the formation of **4** has been observed in only a few cases,[5,11] although methyl migration to a benzyl carbanion is often found.[7b,c] The absence of **8** is not surprising from a steric viewpoint. Formation of ylide **7** from **1** is sterically inhibited and **8** is considerably more crowded than the rearrangement products observed. We have found little or no analogous rearrangement product in the less crowded neopentylammonium system.[5]

(1) S. H. Pine, *Org. React.*, **18**, 403 (1970).

(2) T. S. Stevens, E. M. Creighton, A. B. Gordon, and M. McNicol, *J. Chem. Soc.*, 3139 (1928).

(3) (a) M. Sommelet, *C. R. Acad. Sci.*, **205**, 56 (1937); (b) S. W. Kantor and C. R. Hauser, *J. Amer. Chem. Soc.*, **73**, 4122 (1951); (c) S. H. Pine, *Tetrahedron Lett.*, 3393 (1967).

(4) H. C. Brown and W. H. Bonner, *J. Amer. Chem. Soc.*, **75**, 14 (1953).

(5) S. H. Pine, B. A. Catto, and F. G. Yamagishi, *J. Org. Chem.*, **35**, 3663 (1970).

(6) (a) H. E. Zimmerman in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 387; (b) C. R. Bumgardner, private communication.

(7) (a) K. P. Klein and C. R. Hauser, *J. Org. Chem.*, **31**, 4276 (1966); (b) K. P. Klein, D. N. Van Eenam, and C. R. Hauser, *ibid.*, **32**, 1155 (1967); (c) A. R. Lepley and R. H. Becker, *ibid.*, **30**, 3888 (1965).

(8) D. Martin, A. Weise, and H.-J. Niclas, *Angew. Chem., Int. Ed. Engl.*, **6**, 318 (1967).

(9) Control runs without base present provide only **9a** as product but in very low yield (<0.5%). Interestingly, the thermal decomposition of **1a** *at its melting point* leads principally to α-phenylneopentyl chloride or iodide.[10]

(10) S. H. Pine and E. M. Munemo, unpublished results.

(11) (a) H. Daniel and J. Paetsch, *Chem. Ber.*, **101**, 1445 (1968); (b) G. Wittig and D. Krauss, *Justus Liebigs Ann. Chem.*, **679**, 34 (1964); (c) W. K. Musker, *J. Org. Chem.*, **32**, 3189 (1967).

SCHEME I

POTENTIAL STEVENS AND SOMMELET–HAUSER REARRANGEMENT PATHWAYS FOR α-ARYLNEOPENTYLAMMONIUM SALTS

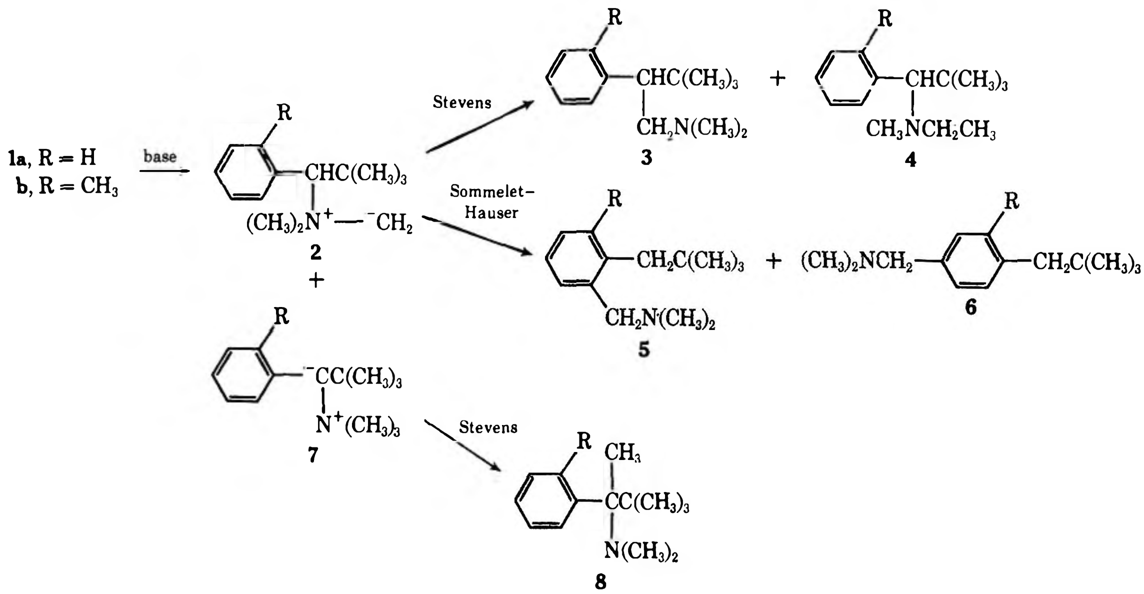


TABLE I

BASIC REACTION PRODUCTS FROM *N,N,N*-TRIMETHYL-α-PHENYLNEOPENTYLAMMONIUM CHLORIDE (**1a**)

Run	Solvent	Base[a]	T, °C	Time, hr	9a	5a	3a	6a	Yield,[b] %
1[c]	NH_3	$NaNH_2$	−33	6	6.0	81	12	0.8	75
2	DMSO	LiDMSO	51	47	49	31	18	1.2	
3	HMPT	$NaNH_2$	25	6	2.0	60	35	3.0	65
4	HMPT–hexane[d]	*n*-BuLi	25	6	1.5	63	32	3.5	
5	Hexane	*n*-BuLi	51	47	1.1	13	80	5.9	73
6	*tert*-BuOH	*tert*-BuOK	51	47	97	1.5	1.7	0.3	68
7	MeOH	MeOK	90	41	100				10

[a] Moles of base/mole of salt = 2, except run 7 (moles of base/mole of salt = 1.3). [b] Yield of total basic material assuming molecular weight of rearrangements products. [c] Iodide salt. No appreciable differences in products were observed over numerous runs in various systems with change of halide anion. [d] 85% HMPT–15% hexane.

TABLE II

BASIC REACTION PRODUCTS FROM *N,N,N*-TRIMETHYL-α-*o*-TOLYLNEOPENTYLAMMONIUM IODIDE (**1b**)

Run	Solvent	Base[a]	T, °C	Time, hr	9b	5b	3b	6b	Yield,[b] %
8	NH_3	$NaNH_2$	−33	6	1.4	32	63	3.7	70
9	DMSO	LiDMSO	80	46	74	2.0	20	4.5	32
10	DMSO–hexane[c]	LiDMSO	70	46	51	4.0	40	5.0	58
11	HMPT–hexane[d]	*n*-BuLi	71	48	5.1	31	60	3.6	79
12	Hexane	*n*-BuLi	83	43	7.5	6.6	73	13	54

[a] Moles of base/mole of salt = 2. [b] Yield of total basic material assuming molecular weight of rearrangements products. [c] 80% DMSO–20% hexane. [d] 75% HMPT–25% hexane.

TABLE III

RELATIVE YIELDS OF REARRANGEMENT PRODUCTS FROM *N,N,N*-TRIMETHYL-α-PHENYLNEOPENTYLAMMONIUM CHLORIDE (**1a**)

Run	Solvent	Base	5a	3a	6a
1	NH_3	$NaNH_2$	86	13	0.9
2	DMSO	LiDMSO	62	36	2.4
3	HMPT	$NaNH_2$	61	36	3.1
5	Hexane	*n*-BuLi	13	81	6.0

The influence of temperature is illustrated (Table IV) by a series of reactions carried out under identical conditions in hexane, but at different temperatures. As the temperature is increased, rearrangements predominate over displacement. This result is similar to the increase in elimination reactions relative to displacement with increasing reaction temperature.[12] As has been noted in other systems, the Stevens rearrangement increases markedly with temperature.[6a]

TABLE IV

INFLUENCE OF TEMPERATURE ON BASIC PRODUCT FORMATION FROM *N,N,N*-TRIMETHYL-α-PHENYLNEOPENTYLAMMONIUM IODIDE (**1a**)

Run[a]	T, °C	9a	5a	3a	6a	Yield,[b] %
13	−30	92	3.4	4.6	0.6	5
14	24	81	3.5	15	1.1	6
15	65	30	7.2	61	1.6	20

[a] All runs using *n*-BuLi in hexane with moles of base/mole of salt = 1; reaction time, 6 hr. [b] Yield of total basic materials.

(12) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 460.

α-Tolyl System.—The results shown in Table II indicate that the formation of tertiary amine **9b** is notably enhanced in the more hindered salt **1b**. Relief of strain through demethylation appears to be an important controlling factor.

In contrast to the α-phenyl salt **1a**, the rearrangements of **1b** all lead principally to the Stevens product **3b** (Table V). The decrease in Sommelet–Hauser rearrangement product **5b** cannot be accounted for by the statistical loss of one potential ortho rearrangement terminus. The data suggest that the increased crowding of the molecule inhibits the ortho rearrangement pathway, a result which may be related to the question of a concerted *vs.* a dissociation–recombination mechanism (see below).

TABLE V

RELATIVE YIELDS OF REARRANGEMENT PRODUCTS FROM *N*,*N*,*N*-TRIMETHYL-α-*o*-TOLYLNEOPENTYLAMMONIUM IODIDE (**1b**)

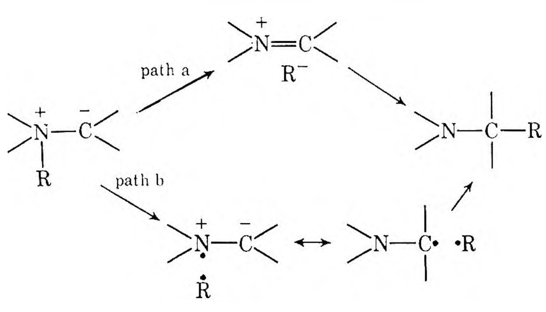
Run	Solvent	Base	5b	3b	6b
8	NH_3	$NaNH_2$	32	64	3.7
9	DMSO	LiDMSO	7.6	76	17
11	HMPT–hexane	*n*-BuLi	33	63	3.8
12	Hexane	*n*-BuLi	7.1	79	14

Although the solvent effect trend of Sommelet–Hauser *vs.* Stevens rearrangements is in the same order as found for **1a**, the variation is much less. In addition, the novel para Sommelet–Hauser rearrangement product **6b** is quite significant in most of the base–solvent systems investigated.

Reaction Mechanism.—The question of the mechanism of base-promoted rearrangements of quaternary ammonium salts has been under active investigation in recent years.[1,13] The symmetry-forbidden[14] SNi pathway[15] has been discarded for the Stevens rearrangement in favor of a dissociation–recombination mechanism involving an ion pair (Scheme II, path a) or a radical pair (Scheme II, path b). The ortho Sommelet–Hauser rearrangement could also proceed *via* pathways involving an ion pair (Scheme III, path a) or radical pair (Scheme III, path b). In addition, the allylic nature of the rearrangement provides for a symmetry-allowed [2,3]-sigmatropric rearrangement pathway (Scheme III, path c). The para rearrangement cannot be obtained by the concerted pathway.[3c]

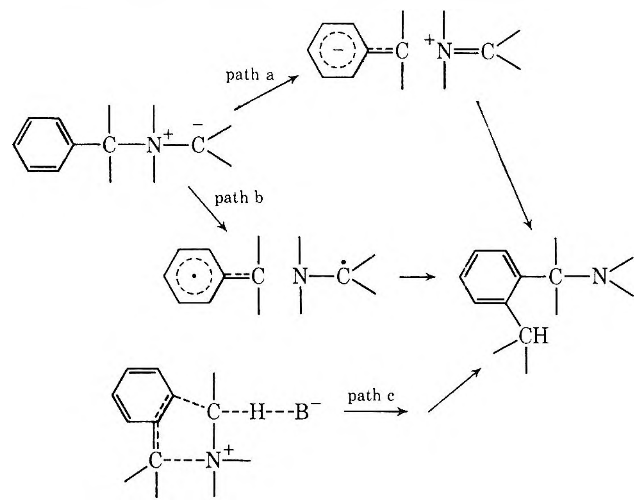
SCHEME II

ION-PAIR AND RADICAL-PAIR PATHWAYS FOR STEVENS REARRANGEMENT



SCHEME III

ION-PAIR, RADICAL-PAIR, AND CONCERTED PATHWAYS FOR SOMMELET–HAUSER REARRANGEMENT



Lepley[7c] had observed some base dependence in the ortho rearrangement and suggested that this supported the concerted pathway (Scheme III, path c), while the Stevens rearrangement might be better explained by a different mechanism. We have also observed such a base dependence in the rearrangements of **1a** using potassium *tert*-butoxide in cyclohexene (Table VI).

TABLE VI

INFLUENCE OF BASE CONCENTRATION ON PRODUCT FORMATION FROM *N*,*N*,*N*-TRIMETHYL-α-PHENYLNEOPENTYLAMMONIUM CHLORIDE (**1a**)

Run[a]	Mol of base/mol of salt	9a	5a	3a	6a
16	1.1	19	25	47	9
17	2.2	25	48	25	5

[a] Runs using *tert*-BuOK in cyclohexene at 87°.

When the base concentration is doubled, the ortho rearrangement product **5a** increases markedly at the apparent expense of the Stevens product **3a**. As expected, the displacement product **9a** also increases with base as does the *tert*-butyl methyl ether observed. Interestingly, the para rearrangement product **6a** decreases with increasing base concentration as does the Stevens product **3a**. This suggests that **3a** and **6a** may be formed through a common intermediate while the pathway to **5a** differs. Since it is unlikely that a concerted mechanism leads to the para product **6a**,[3c] a dissociation–recombination mechanism is favored. Very recently Baldwin, *et al.*,[16] have suggested that the Stevens rearrangement proceeds *via* a radical pathway (Scheme II, path b), while the ortho rearrangements involve the concerted mechanism (Scheme III, path c). They believe that this will account for the temperature dependence of the competing rearrangements.

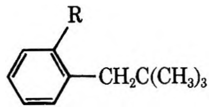
(13) (a) E. F. Jenny and J. Druey, *Angew. Chem., Int. Ed. Engl.*, **1**, 155 (1962); (b) A. R. Lepley, *J. Amer. Chem. Soc.*, **91**, 1237 (1969); (c) U. Schöllkopf, U. Ludwig, G. Ostermann, and M. Patsch, *Tetrahedron Lett.*, 3415 (1969).

(14) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academie Press, New York, N. Y., 1970, p 131.

(15) (a) C. R. Hauser and S. W. Kantor, *J. Amer. Chem. Soc.*, **73**, 1437 (1951); (b) J. H. Brewster and M. W. Kline, *ibid.*, **74**, 5179 (1952).

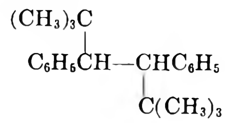
(16) J. E. Baldwin, J. E. Brown, and R. W. Cordell, *Chem. Commun.*, 31 (1970).

In the rearrangements of **1a** and **1b**, small amounts of the hydrocarbons **10** have been isolated. These products can be attributed to collapse of either the ion-pair



10a, R = H
b, R = CH_3

(Schemes II and III, path a)[3c] or the radical-pair (Schemes II and III, path b) intermediates with solvent. In the case of **1a**, another hydrocarbon has been identified as the dimer **11**.[17] This product suggests the pres-



11

ence of at least some radical intermediate. The other expected dimer from such a radical pathway, tetramethylethylenediamine **12**, has not been detected.[18]

$(CH_3)_2NCH_2CH_2N(CH_3)_2$
12

In an attempt to favor formation of the dimer **11**, **1a** was allowed to react with sodium in ammonia. No evidence for **11** was found, **10a** being the only nonbasic product. Small amounts of rearrangement products obtained in this case are presumably due to the presence of some sodium amide.[19]

The dimer **11** has been shown not to come from a secondary reaction of **10a**, although it is apparently produced in low yield from α-phenylneopentyl chloride using *n*-butyllithium in hexane under typical reaction conditions.[20]

The marked solvent dependence in the rearrangements of **1a** seems inconsistent with a radical pathway. However, the direction of the effect (Stevens rearrangement favored in less polar solvents) is opposite to what might have been expected for an ionic mechanism.

It is clear that an answer to the mechanistic questions posed is not at hand. The data presented here do suggest that the Stevens and ortho Sommelet–Hauser reactions may proceed by different mechanistic pathways. The high stereospecificity[15b] found in related systems suggests that these rearrangements may proceed *via* a tight cage intermediate[21] whether it be ion pair or radical pair. We are continuing our studies in this area.

Structural Assignments.—All of the rearrangement products detected were independently synthesized for final structure proof. Scheme IV outlines the synthetic sequences. Although the syntheses outlined in B, C, and E are relatively straight forward, A, D, and F are worthy of comment.

(17) Estimated to be formed in 2–3% yield by nmr and gc.

(18) This dimer has been used in support of a radical intermediate in another Stevens rearrangement: G. F. Hennion and M. J. Shoemaker, *J. Amer. Chem. Soc.*, **92**, 1769 (1970).

(19) E. Grovenstein, Jr., and L. C. Rogers, *ibid.*, **86**, 854 (1964).

(20) Nmr and gc analysis suggest that **11** may be formed in less than 1% yield in this reaction. Although α-phenylneopentyl chloride is the thermal decomposition product from **1a**,[10] it is unlikely to be the source of **11** in the rearrangements.[9]

(21) J. P. Lorand, R. W. Grant, P. A. Samuel, E. O'Connell, and J. Zaro, *Tetrahedron Lett.*, 4087 (1969).

The syntheses of **3a** and **3b** (Scheme IVA) through the hydroboration sequence were accomplished using either chloramine or hydroxylamine-*O*-sulfonic acid with the chloramine reagent being better. In both cases, however, yields were poor. This contrasts to the report by Brown[22] that α-methylstyrene gives greater than 60% yield of amine. We established that the hydroboration step was not at fault by forming the alcohol in greater than 90% yield. Apparently steric considerations inhibit attack by the amine precursor.

In the synthesis of **5b** (Scheme IVD) the desired 1,2,3 isomer predominated (*ca.* 3:1) in the metalation step, a result similar to analogous work by Klein and Hauser.[23] This is surprising since the product is particularly hindered as indicated by the nmr spectrum. The benzyl hydrogen atoms are nonequivalent due to hindered rotation and give rise to an AB quartet. This quartet collapses to a singlet at elevated temperatures. The data are also consistent with our structural assignment based on infrared data. Chemical evidence for crowding within the molecule was shown by the difficulty in accomplishing reduction to **5b**.

In the synthesis of **6b** (Scheme IVF) assignment of the structure of the isomeric dibromoxylenes and bromobenzylamines was important. Initial assignments were made using infrared and nmr spectral data along with model compound comparisons. The concluding evidence was based on chemical reactivity data which also served as a means of obtaining the desired isomer. Hauser, *et al.*,[23,24] had shown that ortho metalation was predominant in dimethylbenzylamines. We thus predicted that the 2-bromo-5-methyl isomer would be more reactive. By metalating the isomer mixture with *n*-butyllithium, then rapidly quenching with water, this unwanted isomer could be protonated while the desired isomer remained essentially unchanged. Recovery of the pure 4-bromo-3-methyl isomer was then easily accomplished by distillation.

Experimental Section

Analytical Data.—Nmr spectra were obtained as solutions in carbon tetrachloride, D_2O, or deuteriochloroform using a Varian A-60 spectrometer. Chemical shifts are reported as downfield from internal TMS. Infrared spectra were obtained as solutions in carbon tetrachloride or chlorofyrm using a Perkin-Elmer Infracord or for the aromatic substitution patterns on a Beckman IR-12 spectrophotometer. Ultraviolet spectra were obtained using a Cary 14 spectrophotometer. Melting points were obtained using a Hoover apparatus and are uncorrected. Gas chromatographic analysis of the amines were obtained on an F & M Model 700 or 720 instrument using a Carbowax 20M column. Peak areas were measured using a Disc integrator. Products obtained in the rearrangements were identified by separation using gas chromatography and comparison of retention times, nuclear magnetic resonance, and infrared spectral data with samples independently synthesized.

Rearrangement Reactions.—The required quaternary ammonium salt and the appropriate base–solvent system were allowed to react in sealed tubes or in closed reaction vessels under nitrogen. An oil bath was used to control the temperature to ±3° except in the case of the liquid ammonia runs where solvent reflux was the temperature control. In all cases, the reactions were quenched with water, the basic and nonbasic materials separated by acid–base extraction, and the products analyzed by gas chromatography.

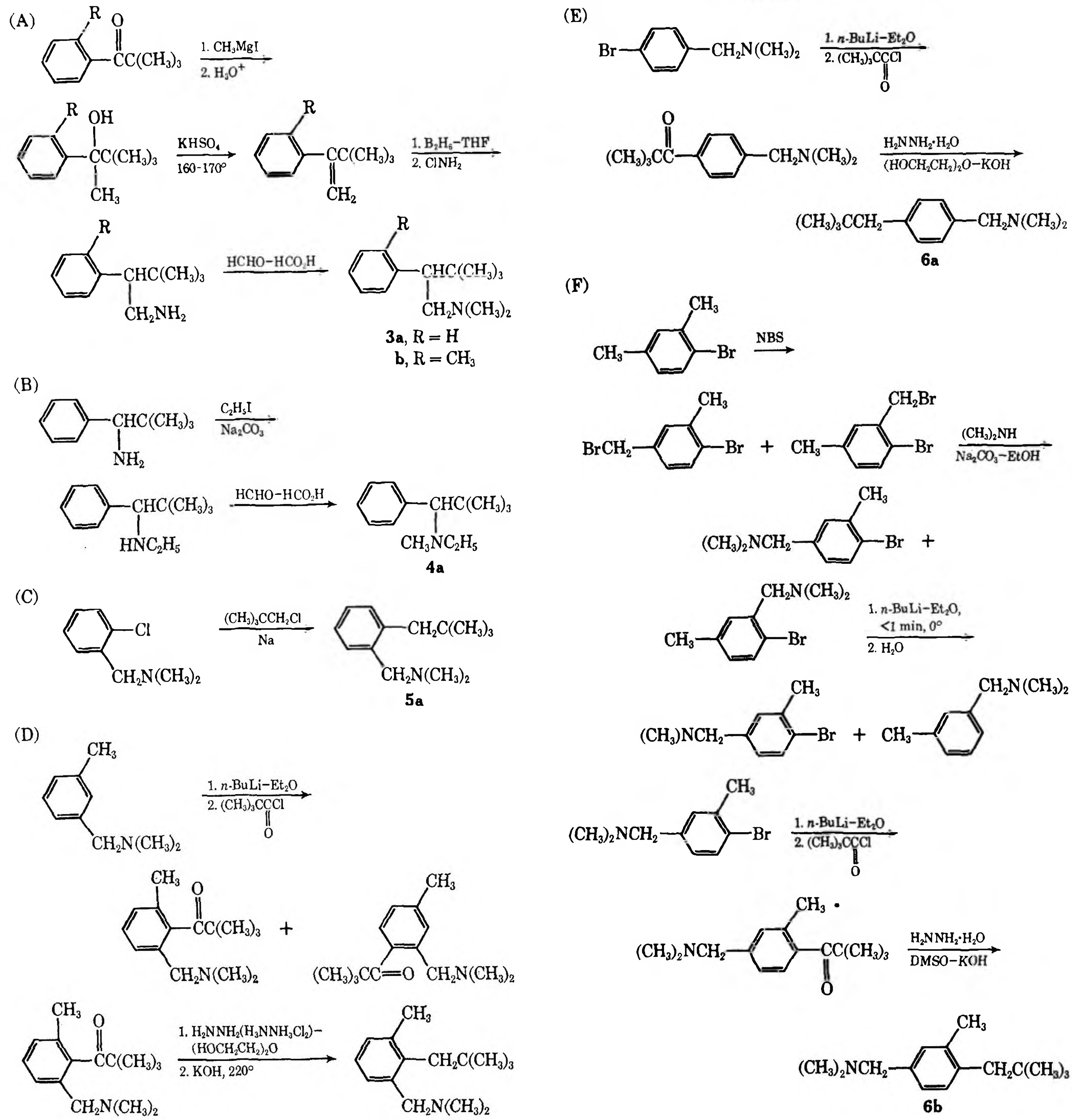
(22) H. C. Brown, W. R. Heydkamp, E. Beur, and W. S. Murphy, *J. Amer. Chem. Soc.* **86**, 3565 (1965).

(23) K. P. Klein and C. R. Hauser, *J. Org. Chem.*, **32**, 1479 (1967).

(24) F. N. Jones, R. L. Vaulx, and C. R. Hauser, *ibid.*, **28**, 3461 (1963).

SCHEME IV

SEQUENCES FOR INDEPENDENT SYNTHESES OF REARRANGEMENT PRODUCTS



Reagents.—All solvents were dried and distilled. *n*-Butyllithium was obtained commercially as a solution in hexane. In some cases, the hexane was removed *in vacuo* under nitrogen and the appropriate dry solvent carefully added, usually at low temperatures. Potassium *tert*-butoxide was obtained commercially and sublimed before use. Sodium amide was prepared as needed as was lithium dimsyl.

***N,N,N*-Trimethyl-α-phenylneopentylammonium Iodide (1a).**—α-Phenylneopentylamine was prepared by the method of Brodhog and Hauser[25] in 94% yield: nmr (CCl_4) δ 0.84 (s, 9, $C(CH_3)_3$), 1.49 (s, 2, NH_2), 3.57 (s, 1, CH), 7.13 (s, 5, C_6H_5); uv max (95% ethanol) 258 mμ (ε 246); the benzenesulfonamide, mp 152.8–153.2°. *N,N*-Dimethyl-α-phenylneopentylamine was prepared using formic acid–formaldehyde in 55% yield:[26] nmr (CCl_4) δ 1.00 (s, 9, $C(CH_3)_3$), 2.18 (s, 6, $N(CH_3)_2$), 3.06 (s, 1, CH), 7.17 (s, 5, C_6H_5); $n^{25}D$ 1.5000; ir shows no NH absorption.

Anal. Calcd $C_{13}H_{21}N$: C, 81.61; H, 11.06. Found: C, 81.78; H, 11.11.

To 3.5 g (0.05 mol) of tertiary amine in 30 ml of anhydrous acetone was added 14 ml of methyl iodide. After the mixture was stirred for 32 hr in the dark, evaporation of the solvent gave 5.6 g (92%) of white solid, mp 162–163°. Recrystallization from absolute ethanol gave mp 164.2–164.8° dec; nmr ($CDCl_3$) δ 1.35 (s, 9, $C(CH_3)_3$), 3.53 (s, 9, $N(CH_3)_3$), 5.44 (s, 1, CH), 7.2–8.0 (m, 5, C_6H_5).

Anal. Calcd for $C_{14}H_{24}NI$: C, 50.46; H, 7.26; I, 38.08; N, 4.20. Found: C, 50.50; H, 7.27; I, 38.10; N, 4.38.

***N,N,N*-Trimethyl-α-phenylneopentylammonium Chloride (1a).**—To 0.5 g (0.0015 mol) of *N,N,N*-trimethyl-α-phenylneopentylammonium iodide in 9 ml of water was added 1.0 g (0.01 mol) of silver chloride. After the mixture was stirred for 13 hr

(25) A. Brodhog and C. R. Hauser, *J. Amer. Chem. Soc.*, **77**, 3024 (1955).

(26) S. H. Pine, *J. Chem. Educ.*, **45**, 118 (1968).

at 25°, the resulting precipitate was separated and washed with water, and the total filtrates were evaporated under reduced pressure to give 0.4 g (100%) of a white solid. Recrystallization from ethanol–ethyl acetate (1:5) gave a white solid: mp 198° dec; nmr ($CDCl_3$) δ 1.31 (s, 9, $C(CH_3)_3$), 3.54 (s, 9, $N(CH_3)_3$), 5.42 (s, 1, CH), 7.2–7.9 (m, 5, C_6H_5).

Anal. Calcd for $C_{14}H_{24}NCl$: C, 69.54; H, 10.00. Found: C, 69.56; H, 10.09.

***N,N,N*-Trimethyl-α-*o*-tolylneopentylammonium Iodide (1b).**—2-Methylphenylmagnesium bromide, prepared from 50 g (0.26 mol) of 2-bromotoluene, in 125 ml of anhydrous ether was added over 1 hr to a solution of 31.8 g (0.26 mol) of pivalyl chloride in 100 ml of anhydrous ether. After an additional 1.5-hr reflux, the mixture was let stand overnight. Addition of dilute sulfuric acid, separation of the organic layer, further washing with a sodium bicarbonate solution, drying with anhydrous magnesium sulfate, and evaporation of the solvent gave 42.2 g of yellow oil. Distillation gave 31.2 g (68%) of *tert*-butyl-*o*-tolyl ketone: bp 94–95° (4 mm); nmr (CCl_4) δ 1.20 (s, 9, $C(CH_3)_3$), 2.16 (s, 3, CH_3), 7.10 (s, 4, C_6H_4); ir 1700 cm^{-1} (s).

To a 500-ml flask equipped with dropping funnel, stirrer, and reflux condenser was added 15.0 g (0.085 mol) of *tert*-butyl-*o*-tolyl ketone, 54 ml of 99% formamide, 33 ml of 88% formic acid, and 6.0 g of magnesium chloride hexahydrate. The mixture was refluxed for 30 hr and then the formic acid–water azeotrope was allowed to distil. An additional 45 ml of 99% formamide and 36 ml of 98% formic acid were added and refluxed 24 hr. The mixture was cooled and added to ice, and the resulting solid was collected by filtration. The crude product was refluxed for 24 hr with 200 ml of 7 *N* methanolic sodium hydroxide. Water (500 ml) was added and the solution extracted with four 100-ml portions of pentane. The pentane was washed with a saturated sodium chloride solution and dried over anhydrous magnesium sulfate, and the product was recovered by distillation to give 8.2 g (55%) of *o*-methyl-α-phenylneopentylamine: bp 91–92° (3 mm); nmr (CCl_4) δ 0.9 (s, 9, $C(CH_3)_3$), 1.1 (s, 2, NH_2), 1.3 (s, 3, CH_3), 4.0 (s, 1, CH), 7.2 (m, 4, C_6H_4); ir 3350 cm^{-1} (doublet).

N,N-dimethyl-α-*o*-tolylneopentylamine was prepared from the primary amine using formic acid–formaldehyde[26] over 2 hr to give an 84% yield: bp 88–89° (1 mm); nmr (CCl_4) δ 1.00 (s, 9, $C(CH_3)_3$), 2.23 (s, 6, $N(CH_3)_2$), 2.33 (s, 3, CH_3), 3.56 (s, 1, CH), 7.2 (m, 4, C_6H_4); ir shows no NH adsorption.

Anal. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 81.97; H, 11.53; N, 6.56.

To 3.0 g (0.015 mol) of *N,N*-dimethyl-α-*o*-tolylneopentylamine in 16 ml of anhydrous acetone was added 12 ml of methyl iodide. After the mixture was stirred for 24 hr, the solvent was evaporated to give 5.0 g (97%) of *N,N,N*-trimethyl-α-*o*-tolylneopentylammonium iodide as a white solid. Recrystallization from absolute ethanol–ether gave a white solid: mp 184° dec; nmr ($CDCl_3$) δ 1.31 (s, 9, $C(CH_3)_3$), 2.58 (s, 3, CH_3), 3.52 (s, 9, $N(CH_3)_3$), 4.85 (s, 1, CH), 7.3 (m, 4, C_6H_4).

Anal. Calcd for $C_{15}H_{26}NI$: C, 51.87; H, 7.55; N, 4.03. Found: C, 51.84; H, 7.63; N, 3.84.

3,3-*N,N*-Tetramethyl-2-phenyl-1-aminobutane (3a).—3,3-Dimethyl-2-phenyl-2-butanol was prepared from methylmagnesium iodide and *tert*-butyl phenyl ketone in 91% yield: bp 91–93° (4.5 mm) [lit.[27] 128° (20 mm)]; ir (CCl_4) 3450 cm^{-1}; nmr (CCl_4) δ 0.81 (s, 9, $C(CH_3)_3$), 1.45 (s, 3, CH_3COH), 1.50 (s, 1, COH), 7.2 (m, 5, C_6H_5).

The alcohol (1.53 g, 0.0086 mol) and 0.3 g of $KHSO_4$ were heated under nitrogen for 1 hr at 160–170°. The product was dissolved in ether and dried, and the solvent was removed to give 1.27 g (92%) of 3,3-dimethyl-2-phenyl-1-butene: bp 54–55° (4 mm) [lit.[27] 75° (10 mm)]; ir (CCl_4) 1620 and 905 cm^{-1}; nmr (CCl_4) δ 1.14 (s, 9, $C(CH_3)_3$), 4.75 (d, 1, J = 1.4 Hz, $C{=}CH_a$), 5.16 (d, 1, J = 1.4 Hz, $C{=}CH_b$), 7.21 (m, 5, C_6H_5).

To 2 g (0.013 mol) of the olefin in 25 ml of dry THF was added 0.013 mol of a 1 *M* solution of diborane–THF. Immediate effervescence occurred as the diborane solution was added. It was left stirring for 52 hr (24 hr would be sufficient). To the pale white solution was added 3 ml of water (considerable effervescence occurs) and 10 ml of 3 *N* NaOH solution to destroy the residual borane. Chloramine solution[28] (0.013 mol) was slowly added. The mixture was left stirring for 18 hr. It was made acid with 3 *N* HCl and extracted with ether. The ether was washed further with 3 *N* HCl solution, the washings being added to the total aqueous layer. The aqueous layer was made basic with 50% sodium hydroxide, and the basic material was extracted with pentane and dried. Evaporation of the solvent gave 0.63 g (28.5%) of 3,3-dimethyl-2-phenyl-1-aminobutane as a light yellow oil. The oil readily solidifies by CO_2 uptake if left standing in the air: nmr (CCl_4) δ 0.87 (s, 8.75, $C(CH_3)_3$), 1.15–1.53 (s, broad, 2, CH_2NH_2), 2.36 (m, 1, $CHCH_2$), 2.70–3.2 (s, broad, 2, CH_2NH_2), 7.20 (s, 5, C_6H_5).

To 0.1 g (0.0005 mol) of the primary amine was added 10 ml of 88% formic acid and 7.5 ml of 36% formaldehyde solution.[26] The stirred solution was heated to 90° and maintained at that temperature for 3 hr. The solution was cooled, 10 ml of 3 *N* HCl was added, and it was extracted with pentane. The aqueous phase was made basic with 50% sodium hydroxide and extracted with pentane, and the pentane was dried and evaporated to give 0.06 g (53%) of *N,N*-3,3-tetramethyl-2-phenyl-1-aminobutane: nmr (CCl_4) δ 0.87 (s, 9, $C(CH_3)_3$), 2.20 (s, 6, $N(CH_3)_2$), 2.5–2.6 (m, 3, $CHCH_2N$), 7.11 (s, 5, C_6H_5); uv max (absolute EtOH) 259 mμ (ε 230); ir shows monosubstitution pattern 1700–2000 cm^{-1}.[29]

Anal. Calcd for $C_{14}H_{23}N$: 81.88; H, 11.29; N, 6.82. Found: C, 82.03; H, 10.79; N, 7.19.

3,3-*N,N*-Tetramethyl-2-*o*-tolyl-1-aminobutane (3b).—3,3-Dimethyl-2-o-tolyl-2-butanol was prepared from methylmagnesium iodide and *tert*-butyl-*o*-tolyl ketone in 83% yield: bp 112–113° (5.5 mm); ir (CCl_4) 3650 cm^{-1}; nmr (CCl_4) δ 0.90 (s, 9, $C(CH_3)_3$), 1.44 (s, 1, COH), 1.57 (s, 3, CH_3COH), 2.55 (s, 3, *o*-$CH_3C_6H_4$), 7.1 (m, 4, C_6H_4).

The alcohol (10 g, 0.052 mol) and 1.5 g of $KHSO_4$ were heated at 165–170° for 2 hr. The product was dissolved in ether, dried, and recovered by distillation to give 7.5 g (83%) of 3,3-dimethyl-2-*o*-tolyl-1-butene: bp 83–84° (6 mm); ir (CCl_4) 1620 and 909 cm^{-1}; nmr (CCl_4) δ 1.10 (s, 9, $C(CH_3)_3$), 2.22 (s, 3, *o*-$CH_3C_6H_4$), 4.73 (d, 1, J = 1.5 Hz, $C{=}CH_a$), 5.26 (d, 1, J = 1.5 Hz, $C{=}CH_b$), 7.03 (m, 4, C_6H_4).

To 3.2 g (0.018 mol) of the alkene in 25 ml of dry THF was added 21 ml (0.021 mol) of a 1 *M* diborane solution. It was left stirring for 24 hr. To the solution was added 3 ml of water and 10 ml of 3 *N* sodium hydroxide. Chloramine solution[28] (0.04 mol) was slowly added. The milky white solution turned reddish purple. It was left stirring for 24 hr, made acidic with 3 *N* HCl, and extracted with ether. The aqueous acid solution was made basic with 50% sodium hydroxide and extracted with pentane. The pentane was washed with saturated sodium chloride solution, dried, and evaporated to give 0.53 g (15.4%) of 3,3-dimethyl-2-*o*-tolyl-1-aminobutane as a yellow viscous oil which readily solidifies by CO_2 uptake in the air: nmr (CCl_4) δ 0.91 (s, 9, $C(CH_3)_3$), 2.31 (s, 3, *o*-$CH_3C_6H_4$), 2.70–3.0 (s-broad, 3 $CHCH_2N$), 7.05 (s, 4, C_6H_4).

To 0.30 g (0.002 mol) of the primary amine was added 12 ml of 88% formic acid and 9 ml of 36% formaldehyde,[26] and the mixture was stirred at 90° for 22 hr. It was cooled, 10 ml of 3 *N* HCl was added, and the mixture was extracted with pentane. The aqueous solution was made basic with 50% sodium hydroxide and extracted with pentane. Drying and evaporation yielded 0.27 g (78.5%) of 3,3-*N,N*-tetramethyl-2-*o*-tolyl-1-aminobutane as a pale yellow oil: nmr (CCl_4) δ 0.81 (s, 9, $C(CH_3)_3$), 1.97 (s, 6, $N(CH_3)_2$), 2.29 (s, 3, *o*-$CH_3C_6H_4$), 2.4–2.98 (m, 3, $CHCH_2N$), 7.0 (s, 4, C_6H_4); the methiodide, mp 290–292°.

Anal. Calcd for $C_{16}H_{28}NI$: C, 53.19; H, 7.81; N, 3.88. Found: C, 53.09; H, 7.82; N, 3.63.

***N*-Ethyl-*N*-methyl-α-phenylneopentylamine (4a).**—To 1.1 g (0.007 mol) of α-phenylneopentylamine in 15 ml of absolute ethanol was added 1.0 g (0.007 mol) of ethyl iodide and 0.7 g of sodium carbonate, and the mixture was stirred for 6 hr at 40°. Filtration and then evaporation of the solvent gave 0.9 g (70%) of the *N*-ethylamine: nmr (CCl_4) δ 0.88 (s, $C(CH_3)_3$) and 1.00 (t, CH_2CH_3, J = 7 Hz) (total area 13, NH presumed to be present), 2.35 (q, 2, NCH_2, J = 7 Hz), 3.28 (s, 1, CH), 7.19 (s, 5, C_6H_5).

N-ethyl-*N*-methyl-α-phenylneopentylamine was prepared from the *N*-ethylamine using formic acid–formaldehyde at 80° for 17 hr to give a 74% yield: bp *ca.* 237°; nmr (CCl_4) δ 1.0 (s, $C(CH_3)_3$) and 1.0 (t, CH_2CH_3) (total area 12), 2.19 (s, NCH_3)

(27) B. B. Corson, H. E. Tiefenthal, G. R. Atwood, W. J. Heintzelman, and W. L. Reilly, *J. Org. Chem.*, **21**, 584 (1956).

(28) G. H. Coleman and H. L. Johnson, *Inorg. Syn.*, **1**, 59 (1939).

(29) J. R. Dyer, "Applications of Absorption Spectroscopy to Organic Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, p 52.

and 2.30 (m, NCH_2) (total area 5), 3.21 (s, 1, CH), 7.18 (s, 5, C_6H_5); the methofluoroborate salt, mp 141.5–143.5° (acetone–ether).

Anal. Calcd for $C_{15}H_{26}NBF_4$: C, 58.65; H, 8.53; N, 4.56. Found: C, 58.60; H, 8.46; N, 4.41.

N,N-Dimethyl-2-neopentylbenzylamine (5a).—2-Chloro-*N,N*-dimethylbenzylamine was prepared by the reaction of 2-chlorobenzylamine with formic acid–formaldehyde[26] in 79% yield: nmr (CCl_4) δ 2.25 (s, 6, $N(CH_3)_2$), 3.55 (s, 2, CH_2), 7.1–7.6 (m, 4, C_6H_4).

To a 50-ml flask equipped with a reflux condenser and a rapid stirrer was placed 2.1 g (0.02 mol) of neopentyl chloride, 3.4 g (0.02 mol) of 2-chloro-*N,N*-dimethylbenzylamine, and 1.0 g (0.042 g-atom) of sodium metal. After rapid stirring for 55 hr, 2 ml of methanol was added to destroy excess sodium metal, then 15 ml of water was added, and the mixture was extracted with petroleum ether (bp 30–60°). The petroleum ether was extracted with 3 *N* hydrochloric acid and then the basic materials were regenerated with dilute sodium hydroxide. Extraction with petroleum ether, drying with anhydrous magnesium sulfate, and evaporation of the solvent gave 1.35 g of dark oil. A crude distillation gave 0.5 g of colorless liquid boiling below 150° (1 mm). Preparative gas chromatography provided a pure sample of *N,N*-dimethyl-2-neopentylbenzylamine: nmr (CCl_4) δ 0.9 (s, 9, $C(CH_3)_3$), 2.15 (s, 6, $N(CH_3)_2$), 2.65 (s, 2, CH_2), 3.4 (s, 2, NCH_2), 7.0–7.4 (m, 4, C_6H_4); uv max (absolute EtOH) mμ (ε 252); ir shows ortho substitution pattern 1600–2000 cm^{-1}.[29]

Anal. Calcd for $C_{14}H_{23}N$: C, 81.88; H, 11.29; N, 6.82. Found: C, 82.16; H, 11.24; N, 6.72.

3-N,N-Trimethyl-2-neopentylbenzylamine (5b).—To 6.7 g (0.045 mol) of 3-*N,N*-trimethylbenzylamine (prepared from 3-methylbenzylamine using formic acid–formaldehyde[26]) in a 125-ml flask was added 31 ml of 1.7 *N n*-butyllithium (0.045 mol) in hexane. The flask was filled with anhydrous ether and left overnight. This solution of metalated benzylamine was then added dropwise to a solution of 8.2 g (0.07 mol) of pivalyl chloride in 30 ml of anhydrous ether. The resulting white slurry was refluxed for 3 hr and then allowed to stand overnight, 30 ml of 3 *N* HCl was added, and the nonbasic material was extracted with ether. The basic products were regenerated using 50% NaOH, extracted with ether, and dried, and the solvent was removed to give 8.1 g of liquid, shown to consist of 21% starting material and 79% of the isomeric 3-*N,N*-trimethyl-2-pivalylbenzylamine (A) and 5-*N,N*-trimethyl-2-pivalylbenzylamine (B) with A/B ≈ 3:1. The isomers were separated by chromatography on silica gel with 4–10% ether in pentane. The 1,2,4-substituted isomer B eluted first: ir shows a typical 1,2,4-aromatic substitution pattern 1600–2000 cm^{-1};[29] nmr (CCl_4) δ 1.19 (s, 9, $C(CH_3)_3$), 2.10 (s, 6, $N(CH_3)_2$), 2.30 (s, 3, CH_3), 3.25 (s, 2, CH_2), 7.0 (m, 3, C_6H_3); the methiodide, mp 202° dec (absolute ethanol).

Anal. Calcd for $C_{16}H_{26}NOI$: C, 51.21; H, 6.98; N, 3.73. Found: C, 51.37; H, 7.17; N, 3.60.

The desired 1,2,3-substituted isomer A eluted next: ir shows a typical 1,2,3-aromatic substitution pattern 1600–2000 cm^{-1};[29] nmr (CCl_4) δ 1.19 (s, 9, $C(CH_3)_3$), 2.12 (s, 6, $N(CH_3)_2$), 2.20 (s, 3, CH_3), 3.22 (AB m, 2, CH_2), 6.9–7.3 (m, 3, C_6H_3); the methiodide, mp 190° dec (acetone–ether).

Anal. Calcd for $C_{16}H_{26}NOI$: C, 51.21; H, 6.98; N, 3.73. Found: C, 51.09; H, 7.03; N, 3.60.

The 1,2,3-substituted isomer A was reduced using a modified Wolff–Kishner reaction. To 0.55 g of ketone in 33 g of diethylene glycol was added 8 g of hydrazine dihydrochloride and then 35 g of 97% hydrazine. The reaction was refluxed for 72 hr and then cooled, 10 g of KOH was added, and the temperature was raised to 220° as the hydrazine distilled. (Unreacted starting material, 0.31 g, was recovered from this distillate.) The mixture was refluxed for 3 hr, 10 ml of water added, and the product recovered by extraction with pentane. Evaporation of the solvent gave 0.1 g of oil which was further purified by preparative gas chromatography to give pure 3-*N,N*-trimethyl-2-neopentylbenzylamine: nmr (CCl_4) δ 0.94 (s, 9, $C(CH_3)_3$, 2.13 (s, 6, $N(CH_3)_2$), 2.32 (s, 3, CH_3), 2.80 (s, 2, CH_2), 3.40, (s, 2, NCH_2), 7.01 (m, 3, C_6H_3); the methiodide, mp 190° dec (ether–dichloromethane).

Anal. Calcd for $C_{16}H_{28}NI$: C, 53.19; H, 7.81; N, 3.88. Found: C, 53.08; H, 8.19; N, 3.78.

N,N-Dimethyl-4-neopentylbenzylamine (6a).—Into a 50-ml flask equipped with a reflux condenser, dropping funnel, and magnetic stirrer was placed 4.0 g (0.016 mol) of 4-bromo-*N,N*-dimethylbenzylamine and 15 ml of anhydrous ether. Then 15 ml of 1.7 *N n*-butyllithium in hexane (0.026 mol) was added over 10 min with cooling, and the mixture was allowed to stir at room temperature for 3 hr (all under nitrogen). The resulting cloudy solution was transferred to a dropping funnel and then added to a solution of 3.5 g (0.03 mol) of pivalyl chloride in 25 ml of anhydrous ether over 30 min. It was refluxed for 3 hr and then left overnight at room temperature. To the resulting white slurry was added 25 ml of 3 *N* HCl, the nonbasic organic phase removed, and the basic material regenerated with 50% sodium hydroxide. Extraction with petroleum ether (bp 30–60°), drying over magnesium sulfate, and distillation gave 1.6 g (50%) of *N,N*-dimethyl-4-pivalylbenzylamine: bp 142–155° (1.5 mm); nmr (CCl_4) δ 1.32 (s, 9, $C(CH_3)_3$), 2.20 (s, 6, $N(CH_3)_2$), 3.39 (s, 2, CH_2), 7.48 (m, AA′, BB′, 4, C_6H_4); ir 1685 cm^{-1}; the methiodide, mp 195.0–195.5°.

Anal. Calcd for $C_{14}H_{21}NO$: C, 49.87; H, 6.70; N, 3.88. Found: C, 50.10; H, 6.73; N, 3.85.

To a 35-ml flask equipped with a reflux condenser and Dean–Stark water separator was placed 1.0 g (0.005 mol) of the ketone, 15 ml of diethylene glycol, 1.0 g of potassium hydroxide, and 2 ml of 85% hydrazine hydrate. It was heated and the water was removed until the pot temperature reached 205°; then reflux was continued at this temperature for an additional 4 hr. The resulting colorless solution was cooled, and 50 ml of water was added and extracted with pentane. Drying over anhydrous magnesium sulfate and evaporation of the solvent gave 0.8 g (87%) of *N,N*-dimethyl-4-neopentylbenzylamine: bp *ca.* 70° (4 mm); nmr (CCl_4) δ 0.9 (s, 9, $C(CH_3)_3$), 2.2 (s, 6, $N(CH_3)_2$), 2.5 (s, 2, CH_2), 3.4 (s, 2, NCH_2), 7.0–7.4 (m, AA′, BB′, 4, C_6H_4); uv max (absolute EtOH) 256 mμ (ε 437); ir shows typical para substitution pattern 1600–2000 cm^{-1}.[29]

Anal. Calcd for $C_{14}H_{23}N$: C, 81.88; H, 11.29; N, 6.82. Found: C, 82.03; H, 11.23; N, 7.19.

3-N,N-Trimethyl-4-neopentylbenzylamine (6b).—To a 100-ml flask equipped with a reflux condenser and magnetic stirrer was placed 24.0 g (0.135 mol) of *N*-bromosuccinimide, 19.0 g (0.1 mol) of 4-bromo-*m*-xylene, 50 ml of carbon tetrachloride, and a trace of benzoyl peroxide. The temperature was slowly raised to *ca.* 82° where reaction initiated. After 15 min, a 5% solution of sodium sulfite was added, and the organic layer was separated and dried over anhydrous magnesium sulfate. Distillation gave 14.2 g of a mixture of 4-bromo-3-methylbenzyl bromide and 2-bromo-5-methylbenzyl bromide. Preparative gas chromatography provided pure samples of each isomer. 2-Bromo-5-methylbenzyl bromide had the following spectral properties: nmr (CCl_4) δ 2.25 (s, 3, CH_3), 4.46 (s, 2, CH_2), 7.0 (m, 3, C_6H_3). 4-Bromo-3-methylbenzyl bromide gave the following: nmr (CCl_4) δ 2.33 (s, 3, CH_3), 4.29 (s, 2, CH_2), 7.0 (m, 3, C_6H_3).

To a 100-ml flask equipped with a stirrer, dropping funnel, and Dry Ice condenser was added 60 ml of absolute ethanol, 3.5 g of anhydrous sodium carbonate, and 13.5 g (0.05 mol) of the mixed benzyl bromides (above). The mixture was cooled to 0°, then 6.0 g (0.1 mol) of dimethylamine was added rapidly, and the mixture was stirred for 1 hr. The precipitate was removed by filtration, and the filtrate evaporated. The residue was dissolved in dilute hydrochloric acid and washed with ether, and the basic products were regenerated with dilute sodium hydroxide. Extraction with ether, drying over anhydrous magnesium sulfate, and evaporation gave 6.0 g (54%) of a mixture of 4-bromo-3-*N,N*-trimethylbenzylamine and 2-bromo-5-*N,N*-trimethylbenzylamine. Preparative gas chromatography provided pure samples of each isomer. 2-Bromo-5-*N,N*-trimethylbenzylamine had the following spectral properties: nmr (CCl_4) δ 2.25 (s, 6, $N(CH_3)_2$), 2.29 (s, 3, CH_3), 3.44 (s, 2, CH_2), 7.25 (m, 3, C_6H_3). 4-Bromo-3-*N,N*-trimethylbenzylamine gave the following: nmr (CCl_4) δ 2.13 (s, 6, $N(CH_3)_2$), 2.32 (s, 3, CH_3), 3.28 (s, 2, CH_2), 7.25 (m, 3, C_6H_3). The structural assignments are based on analogy with the nmr spectra of similar systems and the following chemical reactivity difference.

The isomers were separated by the following reactivity difference. The mixed amines (3.5 g, 0.015 mol) were placed in a flask containing 60 ml of anhydrous ether and a magnetic stirrer. The solution was cooled in an ice bath, 15 ml of 1.6 *N* (0.024 mol) *n*-butyllithium in hexane was rapidly added (30 sec), and then a few drops followed by 10 ml of water were rapidly added (60 sec). Separation of the organic layer, drying over anhydrous magnesium sulfate, and evaporation of the solvent gave 3.3 g of product containing unreacted 4-bromo-3-*N,N*-trimethylbenzylamine and 3-*N*,*N*-trimethylbenzylamine. Purification was accomplished by distillation using a micro spinning-band column to give 4-bromo-3-*N*,*N*-trimethylbenzylamine: bp 105–115° (1.5 mm); the methiodide, mp 223–224° dec (absolute ethanol).

Anal. Calcd for $C_{11}H_{17}NBrI$: C, 35.90; H, 4.63; N, 3.78. Found: C, 35.90; H, 4.78; N, 3.47.

To 0.54 g (0.0024 mol) of 4-bromo-3-*N*,*N*-trimethylbenzylamine in 10 ml of anhydrous ether was added 2.0 ml of 1.6 *N* (0.0032 mol) *n*-butyllithium in hexane. After standing for 30 min (under nitrogen), the slurry was added to a solution of 0.4 g (0.0033 mol) of pivalyl chloride. It was stirred for 1.5 hr, and then 5 ml of water was added followed by 1 ml of concentrated hydrochloric acid. The ether phase was separated, the aqueous phase made basic, and the basic material extracted with ether. The ether was dried over anhydrous magnesium sulfate, and the solvent evaporated to give 0.43 g of yellow liquid, shown to be principally 4-pivalyl-3-*N*,*N*-trimethylbenzylamine by gas chromatography. A pure sample of 4-pivalyl-3-*N*,*N*-trimethylbenzylamine was obtained by preparative gas chromatography: nmr (CCl_4) δ 1.2 (s, 9, $C(CH_3)_3$), 2.18 (s, 6, $N(CH_3)_2$), 3.33 (s, 2, CH_2), 7.0 (m, 3, C_6H_3); ir 1700 cm^{-1}; the methiodide, mp 218° dec (absolute methanol–ether).

Anal. Calcd for $C_{16}H_{26}NOI$: C, 51.21; H, 6.98; N, 3.73. Found: C, 51.31; H, 7.09; N, 3.52.

To 0.4 g of 4-pivalyl-3-*N*,*N*-trimethylbenzylamine in 6 ml of dimethyl sulfoxide was added 1 ml of 85% hydrazine hydrate and 0.5 g of potassium hydroxide. It was heated at 165° for 45 hr, 10 ml of water added, the mixture extracted with 3 *N* hydrochloric acid, and then the basic material regenerated with dilute sodium hydroxide. Extraction with pentane, drying over anhydrous magnesium sulfate, and evaporation of the solvent gave 0.18 g of yellow liquid. Gas chromatography showed *ca.* 65% starting material. Preparative gas chromatography provided a sample of 3-*N*,*N*-trimethyl-4-neopentylbenzene: ir shows 1,2,4-aromatic substitution pattern 1700–2000 cm^{-1};[29] nmr (CCl_4) δ 0.92 (s, 9, $(CH_3)_3$), 2.16 (s, 6, $N(CH_3)_2$), 2.30 (s, 3, CH_3), 2.50 (s, 2, CH_2), 3.28 (s, 2, NCH_2), 6.9–7.1 (m, 3, C_6H_3); the methiodide, mp 245° dec (absolute ethanol–ether).

Anal. Calcd for $C_{16}H_{28}NI$: C, 53.19; H, 7.81; N, 3.88. Found: C, 53.45; H, 7.95; N, 3.69.

Neopentylbenzene (10a) was prepared by the method of Berliner:[30] bp 176.5–178.0°; nmr (CCl_4) δ 0.90 (s, 9, $C(CH_3)_3$), 2.85 (s, 2, CH_2), 7.13 (s, 5, C_6H_5).

***o*-Methylneopentylbenzene** (10b).—*tert*-Butyl-*o*-tolyl ketone was reduced using 85% hydrazine hydrate and potassium hydroxide in dimethyl sulfoxide at 163° for 3 hr: bp 216–218°; nmr (CCl_4) δ 0.92 (s, 9, $C(CH_3)_3$), 2.25 (s, 3, CH_3), 2.51 (s, 2, CH_2), 7.00 (m, 4, C_6H_4).

Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 88.69; H, 11.31.

3,4-Diphenyl-2,2,5,5-tetramethylhexane (11).—The dimer was collected from the nonbasic material of various rearrangement reactions. It was purified by crystallization from pentane at low temperature to give white needles: mp 180.0–181.0°; nmr (CCl_4) δ 0.53 (s, 9, $C(CH_3)_3$), 3.06 (s, 1, CH), 7.25 (m, 5, C_6H_5).

Anal. Calcd for $C_{22}H_{30}$: C, 89.73; H, 10.27. Found: C, 89.68; H, 10.32.

Registry No.—**1a** (iodide), 27617-91-0; **1a** (chloride), 18631-79-3; **1b** (iodide), 27557-79-5; **3a**, 27561-24-6; **3b**, 27561-25-7; **4a**, 27561-26-8; **4a** metho BF_4 salt, 27557-80-8; **5a**, 27561-27-9; **5b**, 27561-28-0; **5b** methiodide, 27561-29-1; **6a**, 27561-30-4; **6b**, 27561-31-5; **6b** methiodide, 27561-22-4; **10a**, 1007-26-7; **10b**, 24785-42-0; **11**, 27561-34-8; *N*,*N*-dimethyl-α-phenylneopentylamine, 27561-35-9; *tert*-butyl-*o*-tolyl ketone, 2041-37-4; *o*-methyl-α-phenylneopentylamine, 27561-36-0; *N*,*N*-dimethyl-α-*o*-tolylneopentylamine, 27561-37-1; 3,3-dimethyl-2-phenyl-2-butanol, 21811-48-3; 3,3-dimethyl-2-phenyl-1-butene, 5676-29-9; 3,3-dimethyl-2-phenyl-1-aminobutane, 27561-40-6; 3,3-dimethyl-2-*o*-tolyl-2-butanol, 27561-41-7; 3,3-dimethyl-2-*o*-tolyl-1-butene, 27561-42-8; 3,3-dimethyl-2-*o*-tolyl-1-aminobutane, 27561-43-9; *N*-ethyl-α-phenylneopentylamine, 27561-44-0; 2-chloro-*N*,*N*-dimethylbenzylamine, 10175-31-2; amine A methiodide, 27561-46-2; amine B methiodide, 27561-47-3; *N*,*N*-dimethyl-4-pivalylbenzylamine, 27561-48-4; *N*,*N*-dimethyl-4-pivalylbenzylamine methiodide, 27561-49-5; 2-bromo-5-methylbenzyl bromide, 27561-50-8; 4-bromo-3-methylbenzyl bromide, 27561-51-9; 2-bromo-5-*N*,*N*-trimethylbenzylamine, 27561-52-0; 4-bromo-3-*N*,*N*-trimethylbenzylamine, 27561-53-1, methiodide, 27561-54-2; 5-pivalyl-3-*N*,*N*-trimethylbenzylamine, 27561-23-5.

Acknowledgment is made to the National Science Foundation, to the donors of the Petroleum Research Fund administered by the American Chemical Society, and to the California State College, Los Angeles, Foundation for partial support of this work.

(30) F. Berliner and F. Berliner, *J. Amer. Chem. Soc.*, **71**, 1195 (1949).

Structural Studies of *N*-Alkyl-*N*-nitrosoanilines by Nuclear Magnetic Resonance[1a,b]

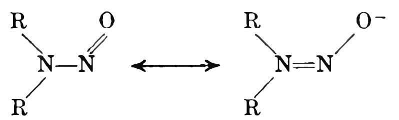
JOAN T. D'AGOSTINO[1c] AND H. H. JAFFÉ*

Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221

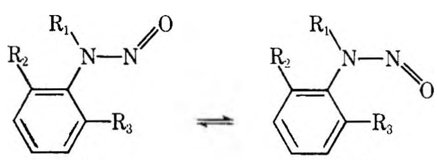
Received April 23, 1970

Configurations, and in most cases preferred conformations, were assigned to nine *N*-alkyl-*N*-nitrosoanilines from analysis of their nmr spectra. The syn:anti ratio was found to be most sensitive to the size of the *N*-alkyl substituent, although ortho substitution was also found to alter these ratios somewhat. Conformations of *N*-isopropyl groups were found to be very sensitive to ortho substitution on the ring. The enthalpy of activation for rotation about the N–N bond was determined for *N*-isopropyl-*N*-nitrosoaniline and was found to be similar to previously determined values for *N*-nitrosodimethylamine and *N*-benzyl-*N*-nitroso-2,6-xylidine, lending further support to the conclusion that the benzene ring contributes little to the partial double bond character of the N–N bond in this compound.

Nuclear magnetic resonance has been used extensively to study problems arising from restricted rotation about partial double bonds. *N*-Nitrosamines have been shown previously[2] to exhibit restricted rotation due to contributions from a polar resonance form. This barrier to rotation is readily observed in the nmr spectra of these compounds since the R groups,



located in different magnetic environments, have differing chemical shifts. In the *N*-nitrosoanilines, the partial double bond character of the N–N bond gives rise to two isomeric forms, syn and anti,[3] which are in dynamic equilibrium at room temperature.



syn anti

The nmr spectra of the nitrosoanilines give the patterns expected of molecules with partial double bonds, with the *N*-alkyl substituents of each isomer giving rise to its own set of resonances. Assignment of peaks as arising from either the syn or anti isomer has been greatly simplified by the earlier work of Karabatsos and Taller,[3] who showed that the protons usually resonate at higher fields when cis than when trans to the oxygen.

In coordination with our uv work on these compounds,[1a] we have extended the earlier work of Karabatsos and Taller[3] to a series of nine *N*-alkyl-*N*-nitrosoanilines. Configurational assignments (syn:anti) have been made in all cases; for most compounds, conformational assignments were also possible. The energy barrier restricting rotation about the N–N bond was also determined for one of the nitrosoanilines.

Experimental Section

Preparation of the nitrosoanilines has already been reported.[1a] They were either vacuum distilled or recrystallized from absolute ethanol prior to use.

All nmr spectra were obtained on a Varian Associates, Inc., Model A-60 spectrometer equipped with a V-6057 variable temperature system and a Hewlett-Packard side-band oscillator calibration. Chemical shifts were obtained on 0.1 mol-fraction solutions in CCl_4 relative to TMS as an internal standard and the τ values are accurate to ± 0.02. The neat compounds (or saturated CCl_4 solutions) were used for determination of isomer population by integration of the spectra; the reported values are accurate to $\sim 5\%$.

High temperature coalescence studies on **4** were carried out on a 0.2 mol-fraction solution, with 1-bromonaphthalene as solvent and hexamethylbenzene as the internal reference. Chemical shift separations for ethylene glycol and methanol were used to measure temperatures above and below ambient, respectively; relative temperature variation during the coalescence work was less than $\pm 1°$. Line shape measurements were run at a sweep rate of 1 cps.[2] The rf field amplitude was redetermined for each temperature and kept below the value where saturation broadening of signals occurred. All spectra were taken at least four times at each temperature to ensure no field or temperature variations during a given sweep.

The calculation of nmr line shapes was accomplished using the method of Alexander,[4] with an adaptation of a program graciously provided by Dr. J. D. Roberts, California Institute of Technology. The spectra were calculated on an IBM 7040 computer and plots of these spectra were obtained on a Calcomp plotter.

Results

The *N*-alkyl-*N*-nitrosoanilines studied in this work are listed in Table I, along with the syn:anti ratios obtained by integration of the nmr spectra. With **3** and **5**, the very low population of one isomer prevented determination by integration, and the ratios were therefore estimated. In order to verify assign-

TABLE I
ISOMER POPULATIONS OF THE *N*-NITROSOANILINES[a]

Compd	R_1	R_2	R_3	syn:anti
1[b]	CH_2	CH_2	H	100:0
2	CH_3	H	H	100:0
3	C_2H_5	H	H	96:4
4	i-C_3H_7	H	H	65:35
5	*tert*-C_4H_9	H	H	1:99
6	CH_3	CH_3	H	83:17
7	i-C_3H_7	CH_3	H	36:64
8	CH_3	CH_3	CH_3	78:22
9	i-C_3H_7	CH_3	CH_3	29:71

[a] R groups refer to syn and anti structures in the text. [b] Fused ring analog, *N*-nitrosoindoline.

(1) (a) *Cf.* J. T. D'Agostino and H. H. Jaffé, *J. Amer. Chem. Soc.*, **92**, 5160 (1970). (b) Supported in part by National Science Foundation Grant GP 7551. (c) Procter & Gamble Fellow, 1967–1968.

(2) C. E. Looney, W. D. Phillips, and E. L. Reilly, *ibid.*, **79**, 6136 (1957).

(3) G. J. Karabatsos and R. A. Taller, *ibid.*, **86**, 4373 (1964).

(4) S. Alexander, *J. Chem. Phys.*, **37**, 967 (1962).

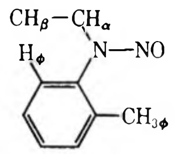
TABLE II
PROTON CHEMICAL SHIFTS (τ VALUES) OF NITROSOANILINES

Compd	α CH₃ syn	α CH₃ anti	α CH₂ syn	α CH₂ anti	α CH syn	α CH anti	β CH₃ syn	β CH₃ anti	φ CH₃ syn	φ CH₃ anti	φ H syn	φ H anti
1			6.86						5.96[a]		2.80[b]	
2	6.67										2.13–2.89[c]	
3			6.01				8.69				2.57[b]	
4					4.91	5.13	8.85	8.57			2.64	2.98–3.25[c]
5							8.68	8.46				2.69[b]
6	6.74	6.01							7.78	8.08	2.75[d]	3.17–3.33[c]
7					5.00	5.23	8.91	8.55 8.47[e]	7.81	8.07	2.79[b]	3.12–3.30[c]
8	6.80	6.09							7.89	8.06	2.86	2.97
9					5.45	5.73	8.89	8.42	7.87	8.05	2.85	2.96

[a] *o*-Methylene protons. [b] Center of multiplet pattern. [c] Region of absorbance for the ortho proton(s). [d] Position of the larger peak in a distorted doublet. [e] Two doublets appear.

ment of these weak-intensity peaks as absorption of one isomeric form, the spectra of **3** and **5** were recorded at higher temperature (<100°); the weak signals were found to collapse into the more intense isomer peak for both cases and, upon cooling, the weak signals reappeared, thus confirming their assignment as due to isomeric absorption.

The nmr chemical shift data for the nitrosoanilines were obtained from CCl_4 solutions and appear in Table II. The notation used to distinguish the various protons is shown below, with each proton tabulated as syn or anti with respect to the isomeric form in which it appears.



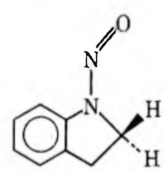
Discussion

A. Configurational Assignments.—The isomer ratios obtained for the nitrosoanilines are consistent with our knowledge of steric effects on the relative stabilities of geometric isomers.[5] The orientation of the NNO group is apparently most sensitive to the size of the R group to which it is cis; when R is methyl, the molecule exists 100% in the syn form, while changing R from ethyl to isopropyl results in an appreciable population of the anti isomer, and a *tert*-butyl group forces the molecule to exist almost completely (~99%) in the anti form.

The population of the anti isomer may also be increased by the substitution of *o*-methyl groups in the benzene ring; such substitution forces the ring to twist out of the NNO plane, thereby reducing the effective steric size of the phenyl group. This shifts the syn: anti equilibrium slightly in the direction of the anti isomer, accounting for its increased population. A second *o*-methyl group appears to be much less effective than the first in altering the syn:anti ratio.

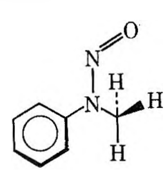
B. Conformational Analysis.—By studying the changes in chemical shift for chemically equivalent protons in the *N*-nitrosoaniline series, one can obtain information about the preferential orientation of such protons in the overall geometry of the molecule. In the case of the nitrosoanilines, this is possible because the π electron clouds of the NO and phenyl groups have anisotropic effects which may enhance (or diminish) the shielding properties in the environment of a given proton.

In the nitrosoanilines, the α protons of *N*-alkyl substituents appear to be most sensitive to these anisotropic effects. Table II reveals that the *N*-alkyl protons of **1** resonate at higher field strengths than are observed for such protons in any of the other nitrosoanilines. This is not surprising, since our knowledge of the geometry of this molecule requires that the α-methylene protons lie above and below the plane of the NNO and phenyl groups. In this configuration, these protons are relatively shielded by the anisotropy of both groups and therefore resonate at comparatively high field strengths.



syn-**1**

From a comparison of the ultraviolet absorption spectra of **1** and **2**, it has been shown[1a] that the benzene ring in **2** is not coplanar with the NNO group. The α-methyl protons (which characteristically have higher chemical shifts than methylene protons) resonate 0.19 ppm *lower* in **2** than in **1**. This can best be explained by considering that addition of a third proton to an oriented α-methylene group which staggers the oxygen requires that it be in the NNO plane and not far removed from the plane of the benzene ring. When the chemical shift of this deshielded proton is averaged with the relatively shielded values comparable to those of **1**, the result for the freely rotating methyl group is a chemical shift slightly lower than that observed for **1**.



syn-**2**

Conformational analysis of *syn*-**3** requires some information from the aliphatic nitrosamines. Table III lists the chemical shifts of α protons on methyl,

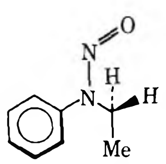
(5) R. T. Morrison and R. N. Boyd, "Organic Chemistry," Allyn and Bacon, Boston, Mass., 1962.

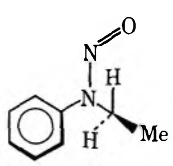
Table III
Effect of a Benzene Ring on the Chemical Shifts of α Protons

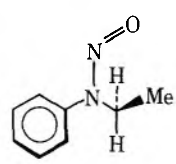
R group	RMeNNO,[a] τ	RPhNNO, τ	Δτ
$-CH_3$[b]	7.04	6.67	0.37
$-C_2H_5$[b]	6.48	6.01	0.47
$-i-C_3H_7$[b]	4.97	4.91	0.06
$-i-C_3H_7$[c]	5.15	5.13	0.02

[a] These data taken from ref 3. [b] R group is cis to the oxygen. [c] R group is trans to the oxygen.

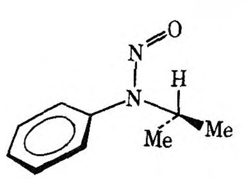
ethyl, and isopropyl groups for aliphatic and aromatic nitrosamines. The tabulation is intended to show that, for R group cis to the oxygen, the presence of the benzene ring significantly deshields the α protons in **2** and **3**, while having very little effect on the chemical shift in **4**. The similar behavior of **2** and **3** to the presence of the ring suggests that, of the three most likely conformations for the ethyl group given below, structure A contributes little, since such an orientation cannot account for the 0.47-ppm shift downfield that is observed. (This same conclusion may be reached by comparing the α-methylene chemical shifts of **3** and **1**.) While there is no evidence which allows us to conclusively distinguish between the remaining two conformations, the close similarity of the ultraviolet spectra of **2** and **3** suggests that introduction of a β-methyl group does not cause an increased twist of the benzene ring, as would be expected in B. Furthermore, the results of analysis on **4** suggest that structure B would give rise to a greater deshielding of the α protons than is actually observed. We therefore favor structure C as the preferred conformation for *syn*-**3**.[6]

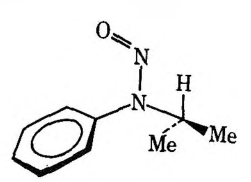

A


B


C*

The absence of significant deshielding for the α-methine protons in both *syn*- and *anti*-**4** relative to their aliphatic analogs (Table III) suggests that the α proton spends little time in the environment of the phenyl group for either isomer. For nitrosamines with an isopropyl group cis to the oxygen, Karabatsos[3] has shown that the α proton spends most of its time eclipsing the NO group, since this proton resonates at lower fields when cis than when trans to the oxygen, in contrast to α-methylene and α-methyl protons. By analogy with his observations,[3] we conclude that the α-methine proton of *syn*-**4** spends most of its time in the deshielding environment of the NNO plane. The marked similarity of α-proton chemical shifts in the *trans*-isopropyl compounds (Table III) allows the conclusion that the α proton is trans to the NO group in *anti*-**4**, by analogy to *syn*-methylisopropylnitrosamine.[3]


syn-**4**

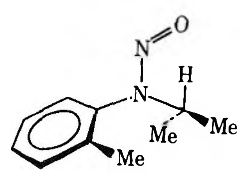

anti-**4**

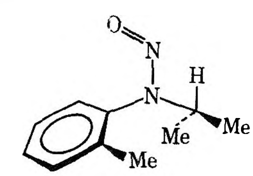
(6) Asterisks following a labeled structure indicate the preferred conformation.

An examination of the phenyl protons in **4** indicates a pleasing agreement with observations from the uv spectrum of this compound. The phenyl pattern of *syn*-**4** approximates a singlet, in contrast to the more complicated multiplet patterns of *syn*-**2** and **3**. This observation is entirely consistent with our proposal[1a] of a highly twisted (probably >60°) benzene ring where the electronic interactions between the ring and NNO group are considerably reduced so that the ortho, meta, and para protons become more equivalent magnetically and the coupling between them is minimal.

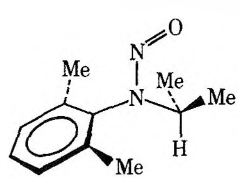
Substitution of *o*-methyl groups on the benzene ring is expected to force the ring further out of the NNO plane and the spectra of **6** and **8** support this expectation. The aromatic protons give rise to a considerably simplified pattern which allows assignments of the signals arising from the syn and anti isomers. The small but definite upfield shift of the α-methyl signals (both syn and anti) in these compounds, relative to **2**, can be attributed to shielding from the twisted benzene ring. The increased shielding of these protons in **8** relative to **6** suggests that the benzene ring is more twisted in the former. The uv spectra of these two compounds support this conclusion.[1a]

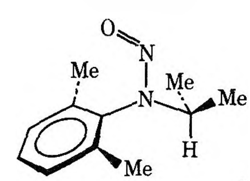
The spectrum of **7** is unique among the nitrosoanilines studied because the two β-methyl groups of the anti isomer are magnetically nonequivalent, each giving rise to its own doublet; at 80°, the spectrum shows that the two doublets have coalesced into one averaged doublet for the anti isomer. This spectral behavior is similar to that observed for other highly substituted nitrosoanilines,[7] suggesting that rotation about the aromatic C–N bond is highly restricted in this isomer; hence the two β-methyl groups find themselves in differing aromatic environments with a rate of exchange which is slow on the nmr time scale so that each gives rise to its own distinct resonance. The largest contribution to this steric barrier appears to be the oxygen atom since the syn isomer failed to demonstrate any nonequivalence as far down as −60°. Comparison of chemical shifts for the α-methine protons in **7** with those in **4** suggests that they continue to remain close to the deshielding NNO plane for both isomers.


syn-**7**


anti-**7**

Finally, the 0.54- and 0.60-ppm field shifts for the α-methine protons of *syn*- and *anti*-**9**, respectively, relative to their corresponding positions in **4**, require that the α-methine protons spend most of their time in the


syn-**9**

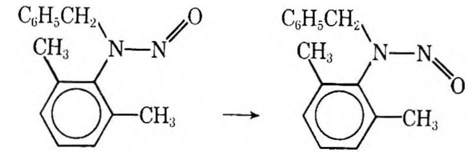

anti-**9**

(7) A. Mannschreck and H. Muensch, *Tetrahedron Lett.*, 3227 (1968).

shielding environment of the benzene ring. Furthermore, molecular models show that steric interactions between the *o*-methyl and β-methyl groups of **9** are sufficient to force the β-methyl groups to stagger the NO group.

C. Determination of the Rotational Barrier in 4.—The partial double bond character of the N–N bond has already been shown[3] to give rise to syn and anti isomeric forms in **4**. In the room temperature nmr spectrum of this compound, the magnetic nonequivalence of the isopropyl groups gives rise to two doublets for the β-methyl protons. At higher temperature, these doublets are found to broaden and, at 113°, coalesce into one very broad signal. From a line-shape study of these coalescing doublets, it was possible to determine the enthalpy of activation ($\Delta H^{\ddagger}$) for the rotation. For the process *syn*-**4** → *anti*-**4**, $\Delta H^{\ddagger} = 25.8 \pm 0.8$ kcal/mol, while, for the process *anti*-**4** → *syn*-**4**, $\Delta H^{\ddagger} = 24.1 \pm 1.1$ kcal/mol.

These enthalpies of activation are not unlike other values which have been determined for nitrosamines. Blears[8] found the $\Delta H^{\ddagger}$ for dimethylnitrosamine (mol fraction = 0.21 in 1-chloronaphthalene) to be 24 kcal/mol, while Mannschreck, *et al.*,[9] obtained a $\Delta H^{\ddagger}$ of 24.2 kcal/mol (in CCl_4) for the following process.



The close agreement between the enthalpy of activation for **4** and other such determinations suggests that there is little contribution from the phenyl group to the partial double bond character of the N–N bond. This conclusion is not surprising, however, since we know from both nmr and uv spectra[1a] of **4** that electronic interactions between the ring and NNO group have been considerably reduced because of twisting.

Registry No.—**1**, 7633-57-0; **2**, 614-00-6; **3**, 612-64-6; **4**, 24642-83-9; **5**, 24642-84-0; **6**, 10596-01-7; **7**, 24690-69-5; **8**, 24699-12-5; **9**, 24699-13-6.

Acknowledgment.—The authors would like to thank Professor F. Kaplan for many helpful discussions.

(8) D. J. Blears, *J. Chem. Soc.*, 6256 (1964).

(9) A. Manschreck, H. Muensch, and A. Mattheus, *Angew. Chem.*, **5**, 728 (1966).

Notes

Mass Spectra of Dimethyl Fumarate and Maleate

SEYMOUR MEYERSON,* P. J. IHRIG, AND T. L. HUNTER

Research and Development Department, American Oil Company, Whiting, Indiana 46394

Received August 25, 1970

A recent review of stereoisomeric effects on mass spectra,[1] coauthored by one of us, carried an introductory statement, since repeated elsewhere,[2] that "the most striking instance . . . of stereoisomers with markedly different mass spectra is that of dimethyl fumarate and maleate." We have since found the literature report that led us to make this statement to be in error.

The statement was based on a report that the most abundant ion in the spectrum of dimethyl fumarate occurs at mass 112, corresponding to the loss of CH_3OH, in contrast to 113 in the spectrum of the maleate.[3] We have located two published spectra of dimethyl fumarate but none of the maleate. The first of the fumarate spectra,[4] which presumably furnished the basis for the qualitative statement above,[3] shows the strongest peak at mass 112 and an intensity at 113 of 21.02% that at 112. The other, presented in bar-chart form, shows the strongest peak at 113, an intensity at 114 about 21% that at 113, and nothing at 112.[5] The paper in which the latter spectrum appeared stated that the authors had measured the spectra of dimethyl maleate as well as fumarate and called attention to some spectral differences between the isomers. However, they said nothing about comparative intensities at 113 or 112, and they did not report the maleate spectrum.

We have now measured the two spectra, which are shown in Table I. Intensities are expressed as $\%\Sigma_{24}$, with all values $\geq 0.5\%$ reported here. Intensity at 112 on this scale is less than 0.1% in both spectra. Evidently, the original qualitative statement contrasting the spectra was based on an error in reading the mass scale.

Nonetheless, our spectra do show significant differences. In each spectrum, the most abundant ion is $[M - CH_3O]^+$, and this species breaks down further by losing CO, as shown by a metastable peak. The

$$68.3 \quad 113^+ \longrightarrow 85^+ + 28$$

intensities of the resultant fragment ions at masses 113 and 85 in the two spectra differ substantially and these differences, coupled with the difference in geom-

* Research Department, Standard Oil Co., Naperville, Ill. 60540.

(1) S. Meyerson and A. W. Weitkamp, *Org. Mass Spectrom.*, **1**, 659 (1968).

(2) F. Benoit, J. L. Holmes, and N. S. Isaacs, *ibid.*, **2**, 591 (1969).

(3) F. W. McLafferty, "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press, New York, N. Y., 1963, Chapter 7.

(4) Uncertified Mass Spectral Data, The Dow Chemical Co., Midland, Mich., 1963, Spectrum No. 1309.

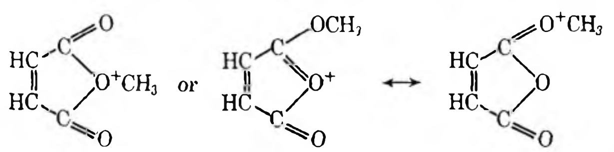
(5) J. H. Bowie, D. H. Williams, P. Madsen, G. Schroll, and S.-O. Lawesson, *Tetrahedron*, **23**, 305 (1967).

Table I
Mass Spectra of Dimethyl Maleate and Fumarate[a]

Mass	Maleate	Fumarate
26	10.2	8.9
27	2.5	2.2
28	1.2	1.6
29	5.6	4.9
30	1.2	1.1
31	1.1	1.0
39	1.2	1.7
41	0.7	1.2
42	0.7	0.6
45	0.6	0.5
53	3.1	5.7
54	4.2	4.2
55	1.7	1.1
59	11.7	9.2
81		1.0
82	1.1	1.5
85	4.8	11.9
86		0.6
99		0.6
100		1.0
113	39.5	29.5
114	3.2	5.0
144	0.2	0.6

[a] Intensities are expressed as %Σ24.

etry, suggest that the $[M - CH_3O]^+$ ion from dimethyl maleate is stabilized by participation of an oxygen atom from the second carbomethoxy group to yield



The added stabilization apparently promotes the primary decomposition step and opposes the second one.

Such participation has a direct analogy in the mass spectra of the isomeric dimethyl phthalates, shown in Table II. Here, again, the masses of prominent

Table II
Partial Spectra of the Isomeric Dimethyl Phthalates[a,b]

Mass	Ion	Ortho	Iso	Tere
135	$[M - CO_2CH_3]^+$	2.9	7.6	6.2
163	$[M - CH_3O]^+$	40.2	32.6	33.5
194	$[M]^{+\cdot}$	3.0	7.7	8.1

[a] Unpublished spectra, this laboratory, measured with 70-V electrons on a CEC Model 21-103 instrument. The spectra are qualitatively similar to those reported by F. W. McLafferty and R. S. Gohlke, *Anal. Chem.*, **31**, 2076 (1959). [b] Intensities are expressed as %Σ24.

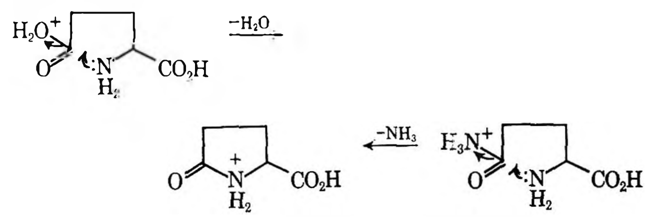
peaks and supporting metastable peaks

$$137.1 \quad 194^+ \longrightarrow 163^+ + 31$$

and

$$111.8 \quad 163^+ \longrightarrow 135^+ + 28$$

establish sequential loss of $CH_3O\cdot$ and CO in all three isomers. Dimethyl *o*-phthalate gives a sharply higher intensity for $[M - CH_3O]^+$ and lower intensities for the molecular ion and $[M - CO_2CH_3]^+$ than the iso- and terephthalates. Thus, this set of spectra also suggests that the $[M - CH_3O]^+$ ion from the *o*-phthalate is stabilized by participation of an oxygen atom from the second carbomethoxy group. Furthermore, this participation closely parallels that apparently involved in the respective loss of H_2O and NH_3 from the protonated molecules in the chemical ionization mass spectra of glutamic acid and glutamine.[6] Other



examples of participation in electron-impact mass spectra have been described recently.[7]

Experimental Section

The methyl esters were prepared by refluxing the acids with anhydrous hydrogen chloride in methanol. The fumarate was purified by recrystallization from methanol; the maleate, by water extraction. Identities and purities were checked by ir and nmr spectra as well as by melting point of the fumarate and gas chromatography on the maleate. Titration of both esters with alcoholic potassium hydroxide established the absence of free acid.

Mass spectra were measured with 70-V electrons on a CEC Model 21-103 instrument with the inlet system and source at 350 and 250°, respectively. Another 21-103 with the inlet system at 150° gave virtually identical spectra.

Registry No.—Dimethyl fumarate, 624-49-7; dimethyl maleate, 624-48-6.

(6) G. W. A. Milne, T. Axenrod, and H. M. Fales, *J. Amer. Chem. Soc.*, **92**, 5170 (1970).

(7) R. H. Shapiro and K. B. Tomer, *Org. Mass Spectrom.*, **3**, 333 (1970), and references cited therein.

Pyrolysis of 1-Nitroadamantane

Allen I. Feinstein and Ellis K. Fields*

Amoco Chemicals Corporation, Research and Development Department, Naperville, Illinois 60540

Philip J. Ihrig and Seymour Meyerson

Standard Oil Company, Research Department, Naperville, Illinois 60540

Received November 5, 1969

A recent study showed that adamantane decomposed at 550–570° when aluminum silicate and aluminum chromate were present as catalysts.[1a] In the absence of catalysts, it decomposed at 660–675°.[1b] Both reactions gave complex mixtures of products consisting primarily of benzene, mono- and dialkylbenzenes, substituted naphthalenes, and C_2–C_4 hydrocarbons. The present investigation was undertaken to learn more about the thermal decomposition of the adamantane nucleus, with particular emphasis on the thermal reactions of the adamantyl radical derived from 1-nitroadamantane.

This compound is a member of a group of 1-substituted adamantane derivatives that characteristically lose the substituent readily upon electron impact in the mass spectrometer.[2] The subsequent fragmentation of

(1) (a) B. A. Kazanskiy, E. A. Shokova, and T. V. Korosteleva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **11**, 2642 (1968); (b) *ibid.*, **11**, 2640 (1968).

(2) Z. Dolejsek, S. Hala, V. Hanus, and S. Landa, *Collect. Czech. Chem. Commun.*, **31**, 435 (1966).

the adamantyl ion formed by this process might parallel the decomposition of the adamantyl radical generated by the pyrolysis of 1-nitroadamantane. If so, the mass spectrum can give some indication of how the pyrolysis products form.

1-Nitroadamantane was pyrolyzed at 500–600° to give the products shown in Table I. No reaction occurred below 500°.

TABLE I
PYROLYSIS OF 1-NITROADAMANTANE

Conditions			
Temp, °C	500	600	600
Nitroadamantane, mol	0.027	0.030	0.030
Contact time, sec	12.9	7.1	11.1
Conversion, %	15.1	41.0	70.7
Products[a]	Yield, mol %[b]		
Benzene	0.5	0.9	2.3
Toluene	1.6	2.3	4.5
Xylenes			0.8
Phenol	6.7	16.3	18.0
Unknown, $C_{10}H_{14}$	4.4	5.1	2.4
Adamantane	18.0	13.9	12.4
Adamantanol	7.6	4.1	1.5
Gaseous products[c]	61.2	57.4	58.1

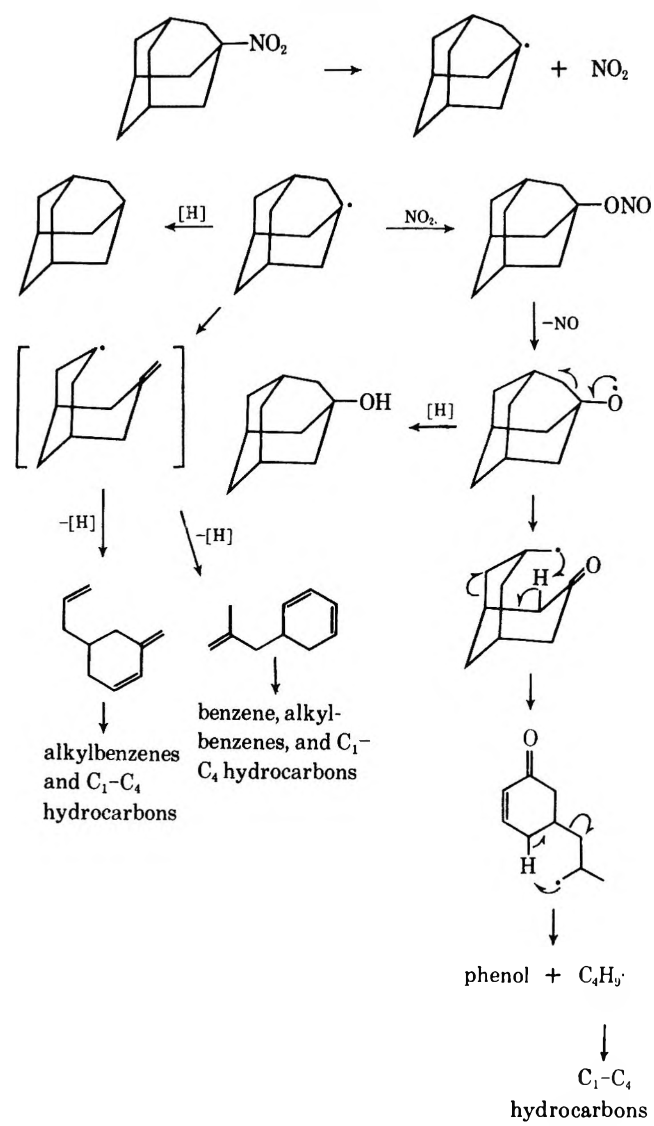
[a] Other products (combined yield less than 1%) identified by directly coupled gas chromatography–mass spectrometry were ethylbenzene, styrene, C_9 alkylbenzenes, indan, butylbenzenes, naphthalene, and cresols. These compounds were present in concentrations too low for meaningful quantitative analysis. [b] Yields were determined by gas chromatography. [c] The gaseous products consisted of methane, ethane, ethylene, propane, propylene, butane, butenes, and nitric oxide.

The data in Table I suggest the order of reactions in Scheme I. The adamantyl radical derived from the decomposition of 1-nitroadamantane appears to react *via* three paths: (1) hydrogen abstraction to give adamantane, (2) back reaction with NO_2 to form the nitrite ester, which then decomposes to NO and the adamantyloxy radical, and (3) fragmentation to alkylbenzenes and C_1–C_4 hydrocarbons. The mass spectrum of the product designated "unknown, $C_{10}H_{14}$" in Table I indicated that this product was a nonaromatic $C_{10}H_{14}$ hydrocarbon, possibly a mixture of isomers. The decrease in yield of this component at higher nitroadamantane conversions is accompanied by an increase in yield of C_6–C_8 aromatic products, suggesting that the $C_{10}H_{14}$ hydrocarbons are precursors to the alkylbenzenes as well as the C_1–C_4 hydrocarbon products.

This predominant formation of C_6 and C_7 hydrocarbons from decomposition of the adamantyl radical at higher conversions closely parallels the fragmentation of the adamantyl ion generated by electron impact on 1-nitroadamantane. The partial mass spectrum of 1-nitroadamantane is summarized in Scheme II. Reaction steps supported by metastable peaks are denoted by solid arrows; relative intensities, uncorrected for naturally occurring heavy isotopes, are expressed as percentages of total ionization above mass 25 and are enclosed in parentheses. The ions that can be identified as decomposition products of $C_{10}H_{15}^+$ (presumably formed as the adamantyl ion) consist largely of C_6 and C_7 species.

There is, of course, no mass spectral parallel for the formation of adamantane, as it involves a bimolecular hydrogen abstraction by the adamantyl radical. The decreasing yield of adamantane with increasing 1-nitro-

SCHEME I

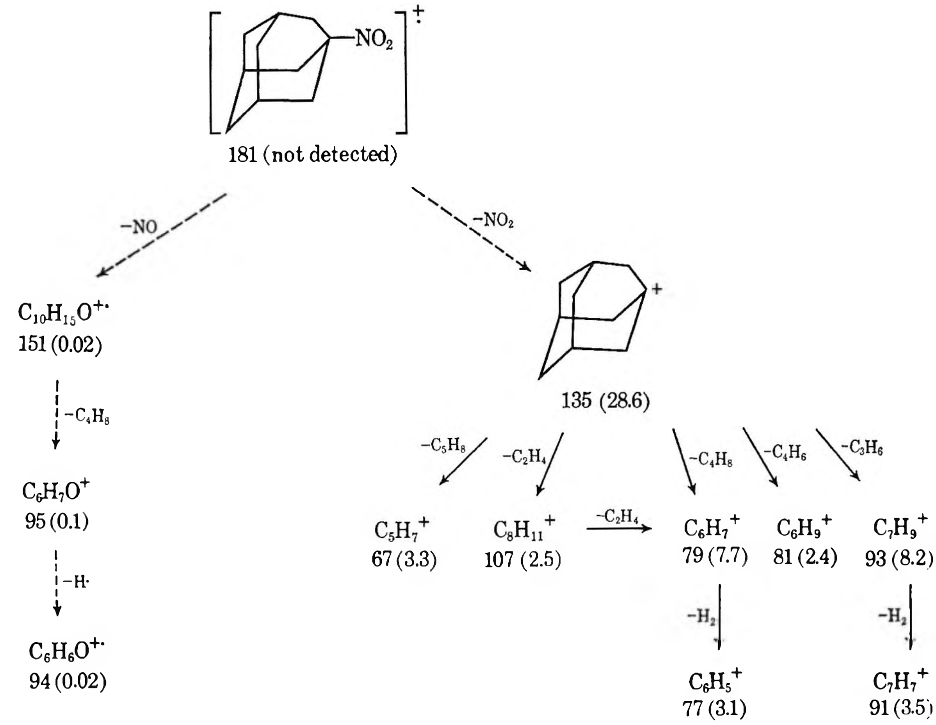


adamantane conversion in pyrolysis shows that the adamantyl radical prefers either to rearrange with loss of hydrogen to give $C_{10}H_{14}$ or to react with NO_2 to give the adamantyloxy radical at higher temperatures and/or longer contact times. The decrease in yield of adamantane cannot be attributed to its thermal decomposition since adamantane was found to be stable at the temperatures employed in this work.

The adamantyloxy radical may arise by the reaction of the adamantyl radical with NO_2 or by a nitro–nitrite rearrangement of nitroadamantane, paralleling the thermal reaction of nitrobenzene.[3] The analogous ionic product, $C_{14}H_{15}O^+$, in the mass spectrum of 1-nitroadamantane presumably arises by such a nitro–nitrite rearrangement. Hydrogen abstraction by the adamantyloxy radical gives adamantanol. The partitioning of the adamantyloxy radical between phenol and adamantanol favors phenol at higher temperatures and longer contact times as evidenced by the increase in yield of phenol and the corresponding decrease in yield of adamantanol. Phenol could also form from the reaction of NO_2 with benzene.[3] However, this would seem to be a minor reaction since toluene is formed in greater yields than benzene and only small quantities of cresols are

(3) E. K. Fields and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 3224 (1967).

Scheme II



produced. The postulate that phenol is formed by the decomposition of the adamantyloxy radical finds a parallel in the mass spectrum of 1-adamantanol, in which the most abundant ion is $C_6H_7O^+$ (mass 95) formed by loss of $C_4H_9\cdot$ from the molecular ion.[2]

The product distribution from the pyrolysis of 1-nitroadamantane differs from that of adamantane[1] in that the latter produced substantial amounts of naphthalene and alkylnaphthalenes. These products presumably stem from initial carbon–carbon bond cleavages leading to reaction intermediates other than those derived from the adamantyl radical. The gaseous products also differ in that no methane was observed from the pyrolysis of adamantane,[1] whereas methane was one of the major gaseous products from the thermal decomposition of 1-nitroadamantane. This absence of methane is surprising since methylnaphthalenes were reported as products.

We are presently studying the reactions of adamantyl radicals formed *via* hydrogen abstraction by alkyl and aryl radicals derived from nitro derivatives at elevated temperatures.

Experimental Section

1-Nitroadamantane.—To a stirred solution of 123 ml of 40% peracetic acid and 450 ml of benzene was added over a 60-min period 30 g (0.2 mol) of 1-aminoadamantane in 300 ml of benzene. The solution was then heated under reflux for 3 hr and poured into 500 ml of water. The organic layer was separated, washed twice with 200 ml of 10% aqueous sodium hydroxide and 200 ml of 10% hydrochloric acid, and then washed with 100 ml of water. The benzene solution was dried over sodium sulfate. Evaporation of the benzene gave 28 g of crude product which was recrystallized from methanol to give 24 g (67% yield) of 1-nitroadamantane, mp 157–158° (lit.[4] mp 158.5–159°).

The pyrolysis reactions were run in a Vycor tube filled with Vycor chips in an electric furnace under pure dry nitrogen with contact times of 7–13 sec. The vapors were condensed in a flask at 0° and samples of the uncondensed effluent gases were collected for mass spectral analysis. The reaction tube was washed with chloroform, which was later removed by distillation. The condensates and the residues from the chloroform washes were analyzed by gas chromatography and directly coupled gas chromatography–mass spectrometry.[5]

In a typical experiment, 1-nitroadamantane (5.45 g, 0.030 mol) was passed through a Vycor tube at 600° under a nitrogen flow of 20 cc/min with a contact time of 11.1 sec. The 1-nitroadamantane was introduced into the reaction tube by boiling it in a bulb connected to the tube and having the nitrogen sweep the vapors into the reaction zone. The vapors were condensed in a flask at 0° (2.17 g). A sample of the uncondensed effluent gases was collected for mass spectral analysis halfway through the reaction. The reaction tube was washed with chloroform which was removed by distillation to give 0.60 g of residue. The condensate and the residue were then analyzed by gas chromatography and directly coupled gas chromatography–mass spectrometry. The column used in the gas chromatography work consisted of 10% OV 17 on Chromosorb W.

Mass Spectrometry.—The mass spectrum of 1-nitroadamantane was measured with 70-V electrons on a Consolidated Model 21-103 instrument, with the source at 250° and the inlet system at 150°. At inlet temperatures above 200°, thermal degradation of the sample occurred.

Registry No.—1-Nitroadamantane, 7575-82-8.

(4) G. W. Smith and H. D. Williams, *J. Org. Chem.*, **26**, 2207 (1961).

(5) E. K. Fields and S. Meyerson, *ibid.*, **33**, 4487 (1968).

Electronic Effects of a Phosphorane Substituent[1]

Bennie C. Chang, Dorothy Z. Denney, and Donald B. Denney*[2]

Department of Chemistry, Rutgers—The State University, New Brunswick, New Jersey 08903

Received August 10, 1970

Taft and his coworkers have shown that the ^{19}F chemical shifts of *m*- and *p*-fluoro-substituted aromatics

(1) This research has been supported by the National Science Foundation, GP-12829, and by the National Institutes of Health, CA-10737.

(2) To whom inquiries should be addressed.

can be related to the substituents interaction with the π system by induction and resonance.[3] Recently this technique has been applied to various phosphorus-containing substituents.[4,5] These studies have included tri- and tetrasubstituted phosphorus compounds. Two pentasubstituted compounds, *m*- and *p*-fluorophenyltetrafluorophosphoranes, were also investigated.

The reaction of trisubstituted phosphorus compounds with diethyl peroxide provides a general route to phosphoranes.[6] This method has now been used to prepare tris-*p*-fluorophenyldiethoxyphosphorane (1) and tris-*m*-fluorophenyldiethoxyphosphorane (2). The quantities

$$\int_{\mathrm{H}}^{m\text{-X}}, \int_{\mathrm{H}}^{p\text{-X}}, \text{ and } \int_{m\text{-X}}^{p\text{-X}}$$

have been determined by recording the ^{19}F nmr spectra of 1 and 2 with fluorobenzene as an external standard. Using these data, σ_I, the inductive parameter, and σ_R, the resonance parameter, have been calculated. The values are +0.147 and +0.059, respectively. Positive values indicate that the substituent, $P(OC_2H_5)_2(C_6H_4F)_2$, is electron withdrawing both by induction and resonance. The magnitude of the parameters is so small that it is clear that the substituent has little effect on the π system. By comparison the substituent, $P(C_6H_4F)_2$ has σ_I +0.26 and σ_R −0.01 and $P(O)(C_6H_4F)_2$ has σ_I +0.45 and σ_R +0.12.[5] These values indicate that both substituents withdraw electrons by induction and the latter has some resonance interaction, although it is not strong. The σ_I value found for PF_4 (0.45) indicates that it is an inductive electron-withdrawing group and is of similar strength to PF_2 (0.39) and PCl_2 (0.44). Interestingly, the σ_R (0.35) for PF_4 was the largest observed in an extensive study of phosphorus-containing substituents. The difference between the pπ–dπ interactions in the two pentasubstituted phosphorus compounds is certainly remarkable and other systems should be studied.

Experimental Section

Preparation of 1 and 2.—The phosphines were prepared from the appropriate Grignard reagent and phosphorus trichloride. Their properties agreed well with those reported in the literature.[5] Tris-*p*-fluorophenylphosphine, 0.195 g (0.000616 mol), in 0.2 ml of methylene chloride in a cooled nmr tube was treated with 0.07 ml of diethyl peroxide. The course of the reaction was followed by ^{31}P and ^{1}H nmr spectroscopy.[7] The +9.2 absorption of the phosphine diminished and new absorptions appeared at +55 (1) and −26 (corresponding to oxide); the ratio was 6:1. Crystallization of 1 occurred and solvent was added to give a homogeneous solution. The ^{1}H nmr spectrum showed a characteristic apparent quintet for the methylene hydrogens of the ethoxy group at 2.58 ($J_{PH} = J_{HH} = 7$ Hz). The methyl protons were found at 0.77 ($J_{HH} = 7$ Hz). The ^{19}F nmr spectrum (94.1 MHz) showed an absorption at −2.18 ppm relative to fluorobenzene as external standard.

Tris-*m*-fluorophenylphosphine, 0.181 g (0.000572 mol), in 0.3 ml of methylene chloride was allowed to react with 0.07 ml of diethyl peroxide. Once again the phosphine absorption, +5, disappeared and that of 2, +55, and its corresponding oxide, +25, formed in a ratio of 5:1. The ^{1}H nmr spectrum had an apparent quintet at 2.63 ($J_{PH} = J_{HH} = 7$ Hz) and a triplet at 0.80 ($J_{HH} = 7$ Hz). The ^{19}F absorption was found at −0.44 ppm relative to external fluorobenzene.

Comparative Nmr Measurements.—In this study fluorobenzene was used as an external standard rather than as an internal standard. The change in means of measuring the chemical shifts does not have an appreciable effect on σ_I and σ_R. It was found, for example, that σ_I for *m*-fluorotriphenylphosphine, *ca.* 1.06 *M* in methylene chloride with fluorobenzene as external standard, was +0.27 (lit.[5] +0.26) and σ_R −0.01 (lit.[5] −0.01).

Registry No.—1, 27531-53-9; 2, 27570-95-2.

(3) (a) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *J. Amer. Chem. Soc.*, **85**, 709 (1963); (b) R. W. Taft, E. Price, J. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *ibid.*, **85**, 3146 (1963).

(4) J. W. Rakshys, R. W. Taft, and W. A. Sheppard, *ibid.*, **90**, 5236 (1968).

(5) A. W. Johnson and H. L. Jones, *ibid.*, **90**, 5232 (1968).

(6) (a) D. B. Denney and D. H. Jones, *ibid.*, **91**, 5821 (1969); (b) D. B. Denney, D. Z. Denney, B. C. Chang, and K. L. Marsi, *ibid.*, **91**, 5243 (1969).

(7) All ^{31}P spectra are reported in parts per million relative to 85% phosphoric acid.

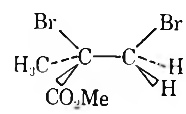
Long-Range Effects in the Proton Nuclear Magnetic Resonance Spectra of Allenes

ROGER S. MACOMBER[1]

Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221

Received June 29, 1970

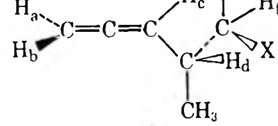
It is well known that the pmr spectrum of an acyclic compound containing both a methylene group and a neighboring asymmetrically (or pseudoasymmetrically) substituted atom can be considerably more complex than would be expected on the basis of simple spin–spin coupling rules. Thus the methylene protons in methyl 2,3-dibromo-2-methylpropionate (1) give rise to an AB



1

pattern, rather than a singlet, because the time-averaged magnetic environments of the two protons differ, and no rotational processes can occur to bring about exchange between these two environments.[2] In this case the methylene protons are said to be diastereotopically related, and as such are, in theory, distinguishable by nmr.

In connection with our study of homoallenic participation,[3] we had occasion to synthesize 2-methyl-3,4-pentadien-1-ol (2a), the derived acetate 2b, and tosylate 2c. The pmr spectra of these compounds[4] are



2

(1) Presented in part at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971.

(2) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, New York, N. Y., 1966. It is important to realize that this effect can be observed whether or not the compound has been optically resolved.

(3) (a) T. L. Jacobs and R. Macomber, *J. Amer. Chem. Soc.*, **91**, 4824 (1969). (b) The solvolytic properties of **2c** have been investigated and are reported separetely, along with synthetic details: R. S. Macomber, *ibid.*, **92**, 7101 (1970).

(4) Spectra were recorded using a Varian A-60 instrument, with samples 15% in carbon tetrachloride containing 1% TMS.

Table I

Nmr Parameters for Simulated Spectrum of **2a**[a]

ω_a	ω_b	ω_c	ω_d	J_{ab}	J_{ac}	J_{ad}	J_{bc}	J_{bd}	J_{cd}
281.57	281.57	307.90	134.79	0.0	6.57	3.19	6.57	3.19	6.06

[a] Frequencies in hertz downfield from TMS; coupling constants (absolute values) in hertz.

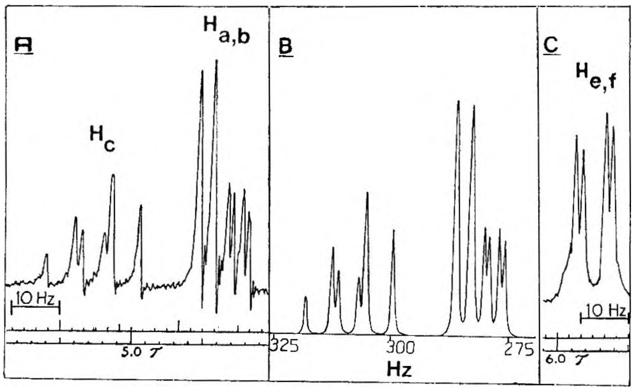


Figure 1.—A, 60-MHz pmr spectrum of the allenic protons in **2a**; B, computer-simulated spectrum of protons in A; C, 60-MHz pmr spectrum of the methylene protons in **2c**.

particularly interesting with respect to long-range proton–proton coupling and the effects of a remote asymmetric center. See Figure 1.

Owing to the asymmetric atom (C_2) in **2**, the methylene protons (H_e and H_f) are diastereotopic, giving rise to two doublets instead of one. The close similarity in chemical shift precludes observation of coupling between H_e and H_f. The two doublets are best resolved in the spectrum of **2c** ($\Delta\delta$ = 1.6 Hz; $|J_{de}| = |J_{df}|$ = 6.5 Hz) shown in Figure 1C.

More interesting, however, were the absorptions due to the allenic protons. All three compounds gave spectra in which the allenic regions were virtually superimposable, except for small differences in chemical shift. A typical spectrum is shown in Figure 1A.[5] The patterns, however, were considerably more complex than would have been anticipated from consideration of the spectra of 2,2-dimethyl-3,4-pentadienol[6] and 3,4-pentadienol,[2] which display typical A_2B and A_2BX_2 patterns, respectively.

The rigid geometry of the allenic system and the presence of the asymmetric atom render H_a and H_b diastereotopic.[5] One possible explanation for the added spectral complexity, then, could be that H_a and H_b were observably magnetically distinct. Such a long-range effect of an asymmetric center is not without precedent. It has been shown[7] that compounds of generic structure **3** give rise to diastereomers where the H* proton resonances are distinguishable.

R—O—CH*=C=CHCH(R′)OR″

3

An alternative explanation for the added complexity is the importance of second-order effects in what can be regarded as an A_2BX system (H_a *not* distinguishable from H_b), where X (H_d) is coupled to both terminal allenic protons with a coupling constant of ∼3 Hz.[8]

(5) No absolute selection between H_a and H_b is intended.

(6) R. S. Bly, A. R. Ballentine, and S. U. Knock, *J. Amer. Chem. Soc.*, **89**, 6993 (1967). We wish to thank Professor Bly for copies of the spectra of 2,2-dimethyl-3,4-pentadienol and derivatives.

(7) M. L. Martin, R. Mantione, and G. J. Martin, *Tetrahedron Lett.*, 4809 (1967).

In either of these cases coupling between H_a and H_b should *not* be observable owing to the identity (or close similarity) in chemical shift, although the magnitude of such geminal coupling ranges from 13–15 Hz.[9] Also, it should be realized that the symmetry of the system places H_c on a plane which bisects the asymmetric atom; thus the resonance for H_c must be independent of the configuration about C_2.

That the second explanation in fact accounts for the added complexity was first suggested by decoupling experiments. Both field-swept and frequency-swept decoupling of the complex pattern attributed to H_d caused the collapse of the resonances due to H_a and H_b to a slanting doublet, indicating that coupling between the terminal protons and H_d *was* important. Similarly the multiplet due to H_c collapsed to a slanting triplet, and the methyl and methylene absorptions (not shown in the figures) collapsed to broad singlets.

Final confirmation that the second explanation accounts fully for the observed spectrum was obtained from a computer-simulated spectrum[10] (Figure 1B) using values shown in Table I.

Thus we see no reason to invoke magnetic distinguishability between diastereotopic protons H_a and H_b to explain our observations. The chemical shifts of H_a and H_b can differ no more than 1 Hz. It is interesting to note that H_d has the distinction of being coupled to all eight other protons shown in **2**!

Registry No.—**2a**, 26674-94-2; **2c**, 26674-95-3.

Acknowledgments.—This work was supported by a grant from the Petroleum Research Fund of the American Chemical Society. The author also wishes to thank Professor Fred Kaplan (University of Cincinnati) and Professor Sanford Smith (University of Kentucky, Lexington) for their help in obtaining the computer-simulated spectra.

(8) Typical coupling constants are for $H_3CC\mathbf{H}=C\mathbf{H}Cl$ J = −5.8 Hz; $\mathbf{H}_3CCH=C=C\mathbf{H}_2$ J = 3.0 Hz: J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. I., Pergamon Press, London, 1967.

(9) M. L. Martin and G. J. Martin, *J. Mol. Spectrosc.*, **34**, 53 (1970).

(10) The program was LAOCOON III (used in the iterative mode) and NMRPLT, a plotting routine.

Reactions of Enamines. XI. The Reaction of Enamines with Cyanoacetic Acid[1]

G. H. Alt* and Gerlinda A. Gallegos

Research Department, Agricultural Division, Monsanto Company, St. Louis, Missouri 63166

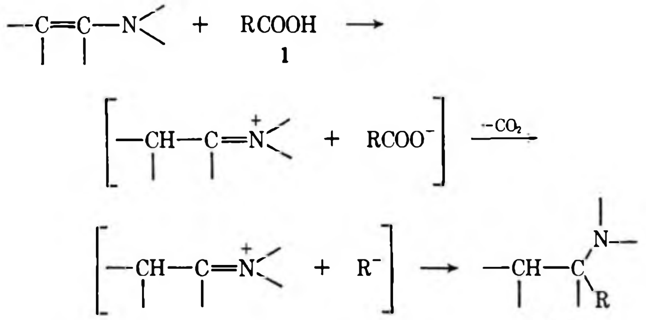
Received October 1, 1970

In previous papers in this series,[1,2] it was shown that enamines react with trichloroacetic acid (**1**, R = $-CCl_3$)

(1) Part X: G. H. Alt, *J. Org. Chem.*, **33**, 2858 (1968).

(2) G. H. Alt and A. J. Speziale, *ibid.*, **31**, 1340 (1966).

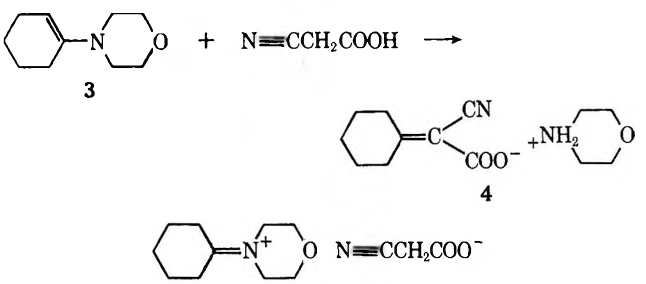
SCHEME I



2

according to Scheme I. It seemed to us that other carboxylic acids capable of facile decarboxylation such as nitroacetic acid (1, R = $-CH_2NO_2$) and cyanoacetic acid (1, R = $-CH_2CN$) should undergo similar reaction sequences. Partial confirmation for this postulate has appeared in a recent publication[3] which demonstrates that enamines react with nitroacetic acid to give the α-amino compound 2 (R = $-CH_2NO_2$) or the nitro olefin by loss of amine from 2 and prompts us to report on the somewhat different course of the reaction of cyanoacetic acid with enamines.

Treatment of 1-morpholino-1-cyclohexene (3) with 1 equiv of cyanoacetic acid in ethyl acetate solution gave an immediate exothermic reaction and a crystalline salt separated in almost quantitative yield. This proved to be the morpholine salt of α-cyanocyclohexylideneacetic acid (4) and not the iminium cyanoacetate (5) which

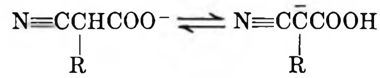


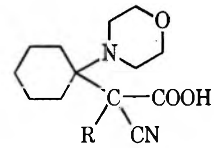
5

had been anticipated. The constitution of 4 was established by its nmr spectrum, and by its conversion to the free acid which was identical with an authentic sample.[4] Treatment of α-cyanocyclohexylideneacetic acid with 1 mol of morpholine in ethyl acetate gave a crystalline salt identical with 4.

Iminium salts have been proposed as intermediates in the Knoevenagel condensation of cyanoacetic acid with aldehydes and ketones in the presence of primary and secondary amines,[5] and it seems reasonable that the initial reaction between 3 and cyanoacetic acid would be the iminium cyanoacetate (5). The cyanoacetate anion, instead of undergoing decarboxylation and addition to the cation, is able to set up a tautomeric equilibrium with the carbanion[6] (Scheme II), and it is the latter[7] which adds to the cation to give 6 (R = H). The zwitterion of 6 (R = H) is ideally set up to lose morpholine and give the observed product 4.

SCHEME II





6

An attempt was made to isolate the intermediate 6 (R = cyclohexyl) by reacting cyclohexylcyanoacetic acid with the enamine 3. Only the iminium salt was formed as shown by the isolation of its hydrolysis products with no evidence for any addition taking place.[8] An explanation for this behavior may be the greater bulk of the cyclohexyl group which prevents addition for steric reasons. Alternatively, it might be expected that the electron-releasing properties of an alkyl group would displace the equilibrium in Scheme II toward the left and suppress formation of the carbanion. Both of these effects complement each other and probably account for the lack of addition.

Cyanoacetic acid reacted readily with the enamines of aldehydes and ketones; in each case the salt of the corresponding α-cyanoalkylideneacetic acid was isolated. The enamines of hindered ketones, however, failed to react. A similar reaction between cyanoacetic acid and the Schiff bases of aldehydes and ketones to give the corresponding primary amine salts of the α-cyanoalkylideneacetic acids has already been described.[9]

These reactions provide positive evidence for the intermediacy of iminium salts[10] in the Knoevenagel and related reactions and account for the fact that tertiary amines do not catalyze these reactions.

Experimental Section[11]

The required enamines were purchased or prepared by the standard method.[12]

α-Cyanocyclohexylideneacetic Acid Morpholinium Salt (4).—A.—To a solution of 1-morpholino-1-cyclohexene (8.35 g, 0.05 mol) in ethyl acetate (25 ml) was added with vigorous agitation a solution of cyanoacetic acid (4.25 g, 0.05 mol) in ethyl acetate (15 ml). An exothermic reaction took place and on cooling the

(3) W. L. F. Armarego, *J. Chem. Soc. C*, 986 (1969).

(4) A. C. Cope, A. A. D'Addieco, D. E. Whyte, and S. A. Glickman, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 234.

(5) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 227, and references there cited.

(6) D. J. G. Ives and K. Sames, *J. Chem. Soc.*, 513 (1943).

(7) The possibility that a dianion (formed by reaction of cyanoacetate with some external base, *e.g.*, enamine) is the reactive species is not ruled out.

(8) A β-amino acid intermediate of this type has been obtained by the reaction of *N*-benzylidenemethylamine with phenylacetic acid: see T. I. Bieber, R. Sites and Y. Chiang, *J. Org. Chem.*, **23**, 300 (1958).

(9) G. Charles, *Bull. Soc. Chim. Fr.*, 1566 (1963).

(10) N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **28**, 3021 (1963), have shown that iminium salts may be formed directly from aldehydes or ketones and secondary amine salts.

(11) Melting points were taken on a Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Infracord Model 137. Nmr spectra were taken with a Varian A-60 instrument in deuteriochloroform using tetramethylsilane as internal standard.

(12) S. Hünig, E. Lücke, and W. Brenniger, *Org. Syn.*, **41**, 65 (1961).

product crystallized. Two recrystallizations from ethyl acetate afforded the pure salt, 9.8 g (78%), as prisms: mp 89–91°; ir ($CHCl_3$) 2720, 2470 (NH_2^+), 2205 (C≡N), 1610 cm^{-1} (CO_2); nmr τ 8.33 (m, 6, CH_2), 7.4 and 7.00 (m, 4, CH_2), 6.80 (q, 4, CH_2N), 6.04 (q, 4, CH_2O), −0.3 (s, 2).

Anal. Calcd for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.60; H, 7.86; N, 11.28.

B.—To a solution of α-cyanohexylideneacetic acid[4] (1.65 g, 0.01 mol) in a minimum amount of hot ethyl acetate was added morpholine (0.9 g, 0.01 mol). On cooling the salt crystallized and had mp 88–91° not depressed in admixture with the material above.

α-Cyanocyclohexylideneacetic Acid.—To the salt 4 (2.5 g, 0.01 mol) in 50% aqueous ethanol (7 ml) was added excess concentrated hydrochloric acid. The free acid which precipitated was filtered and recrystallized from water to give 1.4 g (87%) of α-cyanocyclohexylideneacetic acid, mp 108–110°, not depressed in admixture with authentic material[4] of the same melting point.

The following compounds were prepared by similar procedures.

α-Cyanocyclopentylideneacetic acid morpholinium salt was obtained in 75% yield after recrystallization from ethyl acetate: mp 106–109° dec; ir ($CHCl_3$) 2740, 2475 (NH_2^+), 2220 (C≡N), 1625 cm^{-1} (CO_2); nmr τ 8.22 (m, 4, CH_2), 7.13 (m, 4, CH_2), 6.78 (q, 4, CH_2N), 6.07 (q, 4, CH_2O), −0.40 (s, 2).

Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.30; H, 7.85; N, 11.75.

α-Cyanocyclopentylideneacetic Acid.—The free acid had mp 131–134° (H_2O) (lit.[13] mp 130–131°).

α-Cyanocyclododecylideneacetic acid morpholinium salt was obtained in 73% yield after recrystallization from ethyl acetate: mp 115–118° dec; ir ($CHCl_3$) 2717, 2470 (NH_2^+), 2215 (C≡N), 1615 cm^{-1} (CO_2); nmr τ 8.58 (m, 18, CH_2), 7.50 and 7.12 (m, 4, CH_2), 6.78 (m, 4, CH_2N), 6.06 (m, 4, CH_2O), −0.21 (s, 2).

Anal. Calcd for $C_{19}H_{32}N_2O_3$: C, 67.82; H, 9.59; N, 8.33. Found: C, 67.80; H, 9.28; N, 8.26.

α-Cyanocyclododecylideneacetic Acid.—The free acid had mp 164–167° (H_2O containing a little ethanol); ir (Nujol) 2640 (bonded OH), 2215 (C≡N), 1690 cm^{-1} (C=O); nmr τ 8.60 (m, 18, CH_2), 7.25 (m, 4, CH_2), 0.38 (m, 1, acidic H).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.21; H, 9.28; N, 5.61.

α-Cyanoisobutylideneacetic acid dimethylammonium salt was obtained in 63% yield after recrystallization from ethyl acetate: mp 114–116° dec; ir (CHCl) 2740, 2440 (NH_2^+), 2205 (C≡N), 1630 cm^{-1} (CO_2); nmr τ 8.89 [d, 6, J = 7 Hz, $CH(CH_3)_2$], 7.28 [s, 6, N $(CH_3)_2$], 6.98 [m, 1, $CH(CH_3)_2$], 2.68 (d, 1, J = 10 Hz, vinyl H), 0.22 (m, 2).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 58.81; H, 8.66; N, 15.02.

α-Cyanoisobutylideneacetic acid.—The free acid had mp 87–89° (chloroform–methylcyclohexane) (lit.[14] mp 89°).

Attempted Preparation of 6 (R = Cyclohexyl).—1-Morpholino-1-cyclohexene (1.7 g, 0.01 mol) in benzene or ethyl acetate was treated with cyclohexylcyanoacetic acid[6] (1.7 g, 0.01 mol) at the reflux temperature for 2 hr. Evaporation of the solvent afforded an oil (*ca.* 3.4 g) which partially solidified on standing. Trituration with petroleum ether afforded a solid which on recrystallization from chloroform–petroleum ether gave 1.5 g of a solid, mp 96–98°, which from its nmr spectrum appeared to be the morpholine salt of cyclohexylcyanoacetic acid.

Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.02. Found: C, 61.84; H, 8.95; N, 10.60.

The compound dissolved in water and acidified with concentrated hydrochloric acid gave cyclohexylcyanoacetic acid, mp and mmp 79–81°. Evaporation of the petroleum ether extracts (above) gave an oil which was shown to be cyclohexanone by its ir spectrum.

Registry No.—1 (R = CH_2CN), 372-09-8; **4**, 27521-93-3; α-cyanocyclopentylideneacetic acid, 21369-42-6; α-cyanocyclododecylideneacetic acid morpholinium salt, 27521-90-0; α-cyanocyclododecylideneacetic acid, 27521-91-1; α-cyanoisobutylideneacetic acid dimethylammonium salt, 27521-92-2; cyclohexylcyanoacetic acid morpholinium salt, 27521-88-6.

(13) G. A. R. Kon and J. F. Thorpe, *J. Chem. Soc.*, **115**, 686 (1919).
(14) R. A. Letch and R. P. Linstead, *ibid.*, 443 (1932).

The Bromination of *tert*-Butylbenzene in Trifluoroacetic Acid. The Meta Partial Rate Factor

LEON M. STOCK* AND MICHAEL R. WASIELEWSKI[1]

Department of Chemistry, The University of Chicago, Chicago, Illinois 60637

Received September 8, 1970

The tritium exchange, noncatalytic bromination, and chlorination reactions of toluene, *tert*-butylbenzene, and other alkylbenzenes in trifluoroacetic acid and other mixed solvents rich in trifluoroacetic acid were examined to clarify the role of the solvent, in particular a nonnucleophilic solvent, in the determination of the substituent effects of alkyl groups.[2–6] The order of reactivity for the *p*-alkyl groups depends on the solvent. For the extreme case of the bromination reaction, $k_{p\text{-Me}}/k_{p\text{-}t\text{-Bu}}$ is 3.0 for acetic acid and 0.67 for trifluoroacetic acid.[3,4] The reversal in reactivity may be attributed, largely, to the selective increase in the free energy of solution (activity coefficient) of *tert*-butylbenzene in trifluoroacetic acid.[5] This interpretation is supported by the fact that $o_f^{t\text{-Bu}}$ and $m_f^{t\text{-Bu}}$ are unusually large for tritium exchange ($m_f^{t\text{-Bu}} = 32$)[2] and chlorination ($m_f^{t\text{-Bu}} = 39$)[5] in trifluoroacetic acid rich media. The interpretation is also supported by the finding that the partial molal enthalpy of solution of toluene and *tert*-butylbenzene in acetic acid and trifluoroacetic acid differ significantly and suggest that the activity coefficient of *tert*-butylbenzene is selectively enhanced.[5]

Unfortunately, $m_f^{t\text{-Bu}}$ values for the bromination reaction were not determined in the earlier work.[3,4] Study of the available data for the bromination reaction suggested that, if ground-state solvation effects were important, then *m*-bromo-*tert*-butylbenzene would be produced in a measurable amount. Accordingly, we carried out the bromination of *tert*-butylbenzene under the same conditions used in the prior investigations and analyzed the reaction product by capillary vpc. The bromo-*tert*-butylbenzenes were completely resolved on capillary columns with Apiezon L and Carbowax 20M. To test the procedure, we redetermined the isomer distribution for the bromination of *tert*-butylbenzene in 85% acetic acid.[7] The results obtained by vpc were in good agreement with the results obtained earlier by infrared spectroscopy.[7] The products of the bromination of *tert*-butylbenzene in three solvents rich in trifluoroacetic acid were examined. We were unable to detect *o*-bromo-*tert*-butylbenzene in these product mixtures.[8] The meta isomer, on the other hand, was evident in the chromatograms. In addition, the absorption bands for the meta isomer were apparent in the infrared spectrum of a concentrated

(1) National Science Foundation Undergraduate Research Program Participant.

(2) (a) C. Eaborn and R. Taylor, *Chem. Ind. (London)*, 949 (1959); (b) C. Eaborn and R. Taylor, *J. Chem. Soc.*, 247 (1961).
(3) H. C. Brown and R. A. Wirkkala, *J. Amer. Chem. Soc.*, **88**, 1447 (1966).
(4) W. M. Schubert and D. F. Gurka, *ibid.*, **91**, 1443 (1969).
(5) A. Himoe and L. M. Stock, *ibid.*, **91**, 1452 (1969).
(6) The problems involved in the definition of the substituent effects of alkyl groups are reviewed in ref 4 and 5.
(7) H. C. Brown and L. M. Stock, *ibid.*, **81**, 5615 (1959).
(8) The detection limit is estimated to be 0.05%.

solution of the product obtained in a preparative bromination of *tert*-butylbenzene in trifluoroacetic acid. Known mixtures (similar in composition to the product mixtures) of the isomeric bromo-*tert*-butylbenzenes were used to define the vpc response factors. Replicate analyses were obtained on each reaction product. The results are presented in Table I.

TABLE I

ISOMER DISTRIBUTIONS IN THE BROMINATION OF *tert*-BUTYLBENZENE AT 25°

Solvent,[a] %	Concentration, M: [C_6H_5-C_4H_9]	[NaBr]	[Br_2]	Isomer distribution, mol %: Ortho	Meta	Para
			Trifluoroacetic Acid			
100	0.10	0.09	0.03	0.00	0.35 ± 0.10	99.65 ± 0.10
100	0.10	0.09	0.03	0.00	0.36 ± 0.10	99.64 ± 0.10
100				Av 0.00	0.35 ± 0.01	99.65 ± 0.01
93.3	0.10	0.09	0.03	0.00	0.43 ± 0.10	99.57 ± 0.10
93.3	0.10	0.09	0.03	0.00	0.37 ± 0.10	99.63 ± 0.10
93.3	0.10	0.09	0.09	0.00	0.51 ± 0.10	99.49 ± 0.10
93.3				Av 0.00	0.44 ± 0.07	99.56 ± 0.07
78.3	0.10	0.09	0.03	0.00	0.34 ± 0.10	99.66 ± 0.10
78.3	0.05	0.045	0.015	0.00	0.34 ± 0.10	99.66 ± 0.10
78.3				Av 0.00	0.34 ± 0.00	99.66 ± 0.00
			Acetic Acid			
85	0.51	0	0.13	1.26 ± 0.20	1.72 ± 0.20	97.02 ± 0.20
85[b]	0.51	0	0.13	1.20	1.47	97.3

[a] Weight per cent of acid. [b] Analysis by infrared spectroscopy: H. C. Brown and L. M. Stock, *J. Amer. Chem. Soc.*, **81**, 5615 (1959).

The partial rate factors for the bromination reaction are presented in Table II.

TABLE II

Solvent[a]	Partial rate factor: Toluene[b] o_f^{Me}	m_f^{Me}	p_f^{Me}	*tert*-Butylbenzene[c] $m_f^{t\text{-Bu}}$	$m_f^{t\text{-Bu}}$	$p_f^{t\text{-Bu}}$
			Trifluoroacetic Acid			
100	1360	10[d]	12,700		34	19,200
93.3	4340		42,400		119	59,100
78.3[e]	2150		19,300		35	20,000
			Acetic Acid			
85.0	600	5.5	2,420	5.2	7.3	805

[a] Weight per cent of acid. [b] Factors for trifluoroacetic acid, ref 3 and 4. Factors for acetic acid: H. C. Brown and L. M. Stock, *J. Amer. Chem. Soc.*, 79, 1421 (1957). [c] Factors for trifluoroacetic acid are based on the rate data of ref 3 and 4 and the isomer distributions shown in Table I. Factors for acetic acid are based on the rate data of ref 7 and the isomer distributions shown in Table I. [d] Determined by additivity method, ref 3. [e] Note ref 9.

The isomer distributions measured in this study establish that $m_f^{t\text{-Bu}}$ is very large for the bromination reaction in the three solvents rich in trifluoroacetic acid. Indeed, $m_f^{t\text{-Bu}}$ for 93.3% acid is the largest value thus far obtained.[9] These results suggest, as discussed previously[5] for the tritium exchange and chlorination reaction, that the reversal in the relative reactivity at the para position of toluene and *tert*-butylbenzene is, in significant part, the consequence of the selective increase in the free energy of *tert*-butylbenzene in the trifluoroacetic acid solvents.

(9) It is pertinent that there is an uncertainty in the rate constant for the bromination of benzene in 78.3% trifluoroacetic acid.[4] However, there is no uncertainty in the rate data for the bromination of the alkylbenzenes in 93.3% acid.[4]

Experimental Section

tert-Butylbenzene (Phillips, research grade) was used without further purification. Trifluoroacetic acid (Matheson Co.) was used with and without fractionation. There were no discernible differences in the isomer distributions. The bromo-*tert*-butylbenzenes were prepared *via* the *tert*-butylation of acetanilide and subsequent deamination.[10] Highly purified samples were employed to standardize the analytical method. The reaction conditions adopted for the prior work[3,4] were used in this study. The products were isolated in the usual way and analyzed most effectively on either Apiezon L or Carbowax 20M columns (50 m) operated at 160° with a 0.5 ml min^{-1} He flow using a Varian Series 1200 chromatograph equipped with a flame ionization detector.

Registry No.—*tert*-Butylbenzene, 98-06-6.

(10) T. F. Crimmins, Thesis, Purdue University Library, 1966.

The Alkaline Decomposition of Organic Disulfides. IV. A Limitation on the Use of Ellman's Reagent, 2,2′-Dinitro-5,5′-dithiodibenzoic Acid

JAMES P. DANEHY,* VICTOR J. ELIA,[1] AND CHARLES J. LAVELLE[2]

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

Received August 31, 1970

About ten years ago Ellman[3] described an ingenious procedure for determining quantitatively sulfhydryl content. An excess of the reagent, 2,2′-dinitro-5,5′-dithiodibenzoic acid sodium salt, reacts by thiol–disulfide exchange to release a 2-nitro-5-mercaptobenzoate anion for each sulfhydryl group present. While the disulfide reagent has only a pale yellow color, the 2-nitro-5-mercaptobenzoate anion, like all nitrothiophenolate anions, has a deep color so that measurement of absorbance at 412 nm, as specified by Ellman, when referred to a standard, is a quantitative measure of the sulfhydryl groups originally present.

Ellman's reagent, specifically, is a 10^{-2} M solution of the disulfide in phosphate buffer (μ = 0.1) at pH 7.0. The sample to be analyzed is mixed with phosphate buffer at pH 8.0 before addition of the reagent. The reasons for the choices of pH, though not explicitly stated, are two: the dithiodicarboxylic acid is scarcely soluble in water though its sodium salt is readily so, and the mercaptide ion is much more highly colored than its conjugate acid.

Since the determination of sulfhydryl groups is a frequently employed procedure and Ellman's method is a very attractive one, it has been cited hundreds of times during the last decade. Thus, it is worthwhile to call attention to a hitherto almost unmentioned fact, the extreme sensitivity of Ellman's reagent to alkali, which could lead to erroneous results. Donovan[4] has noted that "Ellman's reagent . . . showed absorption changes in alkali [concentration not specified] very

(1) Postdoctoral Research Associate, 1969–1970.

(2) Participant in the National Science Foundation Undergraduate Research Participation Program, 1969.

(3) G. L. Ellman, *Arch. Biochem. Biophys.*, **82**, 70 (1959).

(4) J. W. Donovan, *Biochem. Biophys. Res. Commun.*, **29**, 734 (1967).

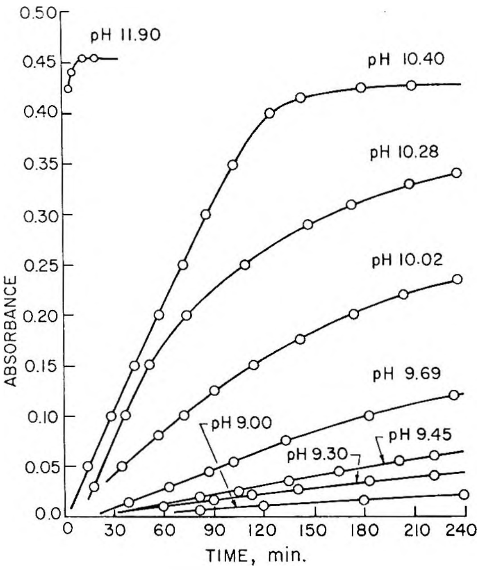
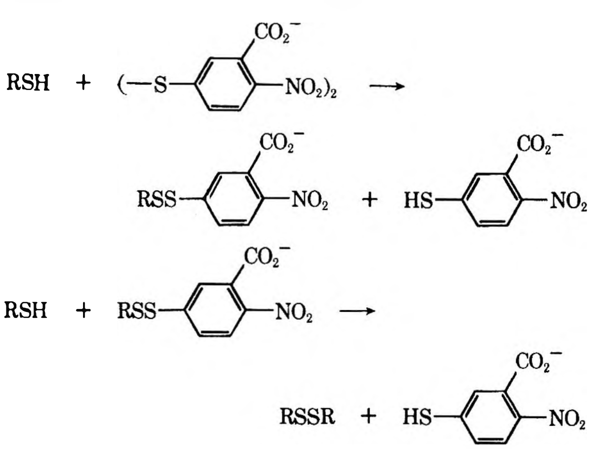


Figure 1.—In each case 0.1 ml of Ellman's reagent (10^{-2} *M* in 10^{-1} *M* phosphate at pH 7.02) was brought to 50 ml with 0.25 *M* phosphate solution at the pH value shown.

similar to those observed upon reduction. The absorption change at 412 mμ was 0.73 of that observed upon reduction, suggestive of S–S fission." It should be emphasized that the reliability of the method, when used in accord with Ellman's protocol, is not questioned. Benedict and Stedman,[5] however, have noted explicitly that a number of other nucleophiles interfere in the determination of thiol groups with Ellman's reagent: cyanide, sulfite, hydrosulfide, thiosulfate, and dithionite.

Recently, Danehy and Parameswaran[6] reported an inverse correlation between the relative sensitivity of organic disulfides to alkaline decomposition and the pK_a values of the thiols which are acids conjugate to the thiolate anions displaced by the nucleophilic attack of the hydroxide ion. The more sensitive the disulfide is to alkali, the more acidic the corresponding thiol. 4-Nitrophenyl disulfide, of which Ellman's disulfide is a derivative, was the most sensitive one examined.

While 1 mol of Ellman's disulfide, by thiol–disulfide exchange, gives 1 mol of 2-nitro-5-mercaptobenzoate, or, in the presence of excess thiol, 2 mol of the absorbing species, the action of hydroxide ion on 2 mol of the disulfide should give 3 mol of the thiol, according to the stoichiometry already established for this kind of reaction.[6]



(1)

(2)

$$2RSSR + 4OH^- \longrightarrow 3RS^- + RSO_2^- + 2H_2O \qquad (3)$$

The development of absorbance at 412 nm in aqueous solutions of 2,2′-dinitro-5,5′-dithiodibenzoate at pH values established over the range of 9–12 has now been followed at room temperature. From the results (Figure 1) it can be seen, as might have been expected from the earlier report,[6] that near pH 12 alkaline decomposition is complete within 15 min. At pH 9.30 decomposition is about 9% in 4 hr. Even as low as pH 8.00, at which sulfhydryl determinations are made, not shown on the graph, about 5% decomposition takes place within 48 hr. Ellman's reagent itself (10^{-2} *M* disulfide, pH 7.0) develops no absorbance at 412 nm in 7 weeks and may be stable for much longer periods of time.

Grassetti and Murray[7] have reported that "At pH 3.3 no reaction occurred between DTNB [2,2′-dinitro-5,5′-dithiodibenzoic acid] and cysteine; however, when the pH of the medium was increased, theoretical SH values were obtained in the range of pH between 7.8 and 10.4 . . . Absorbance (412 nm) was measured against a blank without cysteine." The time allowed for reaction was not reported by these workers. From Figure 1 it can be seen that at pH 10.4 about 11% of the disulfide has decomposed within 10 min.

In a prior publication Ellman[8] had reported that the *p*-nitrothiophenolate anion has an a_m = 13,600 at the λ_{max} 412 nm. In his definitive paper[3] (p 72), he assumes both of these values for the 2-nitro-5-mercaptobenzoate anion. Curiously, despite the extensive references to the corresponding disulfide, 2-nitro-5-mercaptobenzoic acid has never been reported.

It seemed to us worthwhile to prepare an authentic sample of 2-nitro-5-mercaptobenzoic acid and to determine its physical constants, especially the value for the molar absorptivity (a_m) of the thiolate anion at 412 nm. Samples of 2-nitro-5-mercaptobenzoic acid have been prepared by the action of aqueous alkali (reaction 3) or of aqueous sodium thioglycolate (reactions 1 and 2) on the disulfide, followed by precipitation and recovery. Elemental analyses (Table I) and absorption spectra indicate that they are essentially the same compound. Melting point ranges, low iodine titers, and the fact that the absorption spectra of aqueous solutions unprotected from the air change

Table I

Elemental Analyses

Compd	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	S, % Calcd	S, % Found
2-Nitro-5-mercaptobenzoic acid	42.41		2.53		7.03		16.09	
A[a]		42.38		2.50		7.08		15.46
B[b]		42.13		2.43		6.66		18.06

[a] Product of the action of aqueous alkali on 2,2′-dinitro-5,5′-dithiodibenzoate. [b] Product of the action of aqueous thioglycolate on 2,2′-dinitro-5,5′-dithiodibenzoate.

(5) R. C. Benedict and R. L. Stedman, *Analyst (London)*, **95**, 296 (1970).

(6) J. P. Danehy and K. N. Parameswaran, *J. Org. Chem.*, **33**, 568 (1968).

(7) D. R. Grassetti and J. F. Murray, Jr., *Arch. Biochem. Biophys.*, **119**, 41 (1967).

(8) G. L. Ellman, *ibid.*, **74**, 443 (1958).

rapidly to resemble those characteristic of the disulfide, indicate that 2-nitro-5-mercaptobenzoic acid is exceedingly sensitive to aerial oxidation.

Since it was not practical to prepare a sample of pure 2-nitro-5-mercaptobenzoic acid, its molar absorptivity was calculated from the absorbance of a solution of the disulfide in aqueous phosphate buffer to which sufficient aqueous solution of sodium thioglycolate had been added to produce maximal absorbance (Table II). A solution of exactly the same

TABLE II

ABSORPTION SPECTRAL CONSTANTS FOR CERTAIN AROMATIC DISULFIDES AND THE CORRESPONDING THIOLS

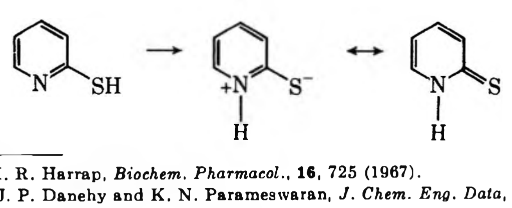
Compd	Registry no.	λ_{max}, nm	a_m
2,2′-Dinitro-5,5′-dithiodibenzoate[a]	552-24-9	325	17,500
		748	2,800
2-Nitro-5-mercaptobenzoate[b]	18430-02-9	412	13,600
		825	12,600
2,2′-Dithiodipyridine[c]	2127-03-9	233	13,900
		281	9,700
2-Mercaptopyridine[c]	2637-34-5	238	6,200
		343	8,700
		740	550
4,4′-Dithiodipyridine[d]	2645-22-9	247	16,100
4-Mercaptopyridine[d]	4556-23-4	230	9,600
		324	19,800
2,2′-Dithiodipyrimidine[c]	15718-46-4	237	19,000
2-Mercaptopyrimidine[c]	1450-85-7	278	21,000
		346	2,600
		780	795

[a] In aqueous phosphate buffer at pH 7.0. [b] The above disulfide solution to which sufficient sodium thioglycolate had been added to give maximal absorbance. [c] 0.1 N H_2SO_4. [d] Phosphate buffer at pH 7.2.

disulfide concentration, but 0.1 N in NaOH, gave exactly 0.75 of the absorbance of the previous solution, completely in agreement with reaction 3 and the observation of Donovan.[4]

The pK_a for the sulfhydryl group at 25°, determined spectrophotometrically, was found to be 4.75. Harrap[9] has reported a value of 4.8 ± 0.1 at 20°. From the recorded values[10] for 4-nitrothiophenol (4.77 at 30° in 40% aqueous ethanol) and for 3-mercaptobenzoie acid (6.15 at 28° in water) it is clear, as was expected, that the nitro group increases the acidity of thiophenol considerably more than does the carboxyl group.

An exactly parallel situation is presented by 2,2′- and 4,4′-dithiodipyridine and their nitro and carboxy derivatives, all of which have been recommended by Grassetti and Murray[7,11] as alternatives to Ellman's reagent for the determination of sulfhydryl. Albert and Barlin[12] have shown that 2- and 4-mercaptopyridine are uncommonly acidic thiols, by reason of the resonance



(9) K. R. Harrap, *Biochem. Pharmacol.*, **16**, 725 (1967).
(10) J. P. Danehy and K. N. Parameswaran, *J. Chem. Eng. Data*, **12**, 386 (1968).
(11) D. R. Grassetti and J. F. Murray, Jr., *Anal. Biochem.*, **21**, 427 (1967); D. R. Grassetti, J. F. Murray, Jr., and H. T. Ruan, *Biochem. Pharmacol.*, **18**, 603 (1969); D. R. Grassetti and J. F. Murray, *J. Chromatogr.*, **41**, 121 (1969); D. R. Grassetti and J. F. Murray, *Anal. Chim. Acta*, **46**, 139 (1969); J. N. Mehrishi and D. R. Grassetti, *Nature*, **224**, 563 (1969).
(12) A. Albert and G. B. Barlin, *J. Chem. Soc.*, 2384 (1959).

stabilization of the highly favored tautomer (pK_a values of −1.07 and +1.43, respectively). One would expect that the corresponding disulfides would be at least as susceptible to alkaline cleavage as Ellman's reagent, and such has proved to be the case (see Table III).

TABLE III

DECOMPOSITION OF SEVERAL HETEROCYCLIC DISULFIDES IN AQUEOUS SOLUTION AT 25° AS A FUNCTION OF pH

Compd	pH	Half-life, min
2,2′-Dithiodipyridine[a]	11.20	12
	10.60	58
	10.32	200
	9.92	>300
4,4′-Dithiodipyridine[b]	11.32	13
	10.52	67
	10.43	97
	9.83	>300
2,2′-Dithiodipyrimidine[c]	11.40	4
	10.40	40
	9.92	133
	9.55	>240

Decomposition followed by measurement of increase of absorbance at [a] 740 nm, [b] 324 nm, [c] 780 nm.

Experimental Section

Materials.—2,2′-Dinitro-5,5′-dithiodibenzoic acid was purchased both from Calbiochem, Los Angeles, Calif., and Aldrich Chemicals, Milwaukee, Wis. 2- and 4-Mercaptopyridine were purchased from Aldrich Chemical Co. 2-mercaptopyrimidine was obtained from Research Organic/Inorganic Chemicals, Sun City, Calif. Thioglycolic acid was a gift from Evans Chemetics, New York City. The disulfides were prepared by oxidizing aqueous solutions of the thiols with potassium triiodide: 2,2′-dithiodipyridine melted at 56–58° (lit. 57–58°); 4,4′-dithiodipyridine melted at 74–76° (lit. 74°); 2,2′-dithiodipyrimidine melted at 134–137° (lit. 139–140°).

Methods.—All melting points are uncorrected. Absorbance measurements given in Figure 1 were obtained with a Bausch & Lomb spectronic 20. Absorbance measurements required for determination of λ_{max} values, calculation of a_m values, and determination of pK_a values were obtained with a Beckman DB-G recording spectrophotometer.

Registry No.—2,2′-Dinitro-5,5′-dithiodibenzoic acid, 69-78-3.

Acknowledgment.—Grateful acknowledgment is made to National Institutes of Health (AM-13109) and to the National Science Foundation Undergraduate Research Participation Program.

Synthesis of β-Substituted Pyrroles *via* 1-(Pyrrol-2-ylmethylene)pyrrolidinium Salts

PHILIP E. SONNET

Entomology Research Division, Agricultural Research Service, U. S. Department of Agriculture, Beltsville, Maryland 20705

Received September 2, 1970

We wished to prepare 3-isoprenoid pyrroles for screening as arthropod antimaturants.[1] Such materials would be pyrrolic analogs of perillen and dendrolasin, substances isolated from the mandibular glands of an

(1) C. M. Williams, International Symposium on New Perspectives on the Control of Injurious Insects, Rome, Italy, Sept 16–18, 1968.

ant *Lasius* (*Dendrolasius*) *fuliginosus* (Latreille).[2] Dendrolasin has been reported to have juvenile hormone activity,[3] and it has been hypothesized that it acts as a defense substance.[4]

One method of preparing 3-substituted pyrroles involves synthesizing pyrroles substituted in the 2 position with a removable electron-withdrawing group. Electrophilic attack upon such a compound occurs more readily at the 4 position than at the normally more reactive 5 position. In this connection, conversion of 2-pyrrolecarboxaldehyde to a ternary iminium salt[5] seemed a useful way to protect the aldehyde group and to enhance its meta-directing influence in electrophilic substitution reactions. The free aldehyde could then be regenerated from the product salt and be removed by oxidation and decarboxylation to give a 3-substituted pyrrole.

Salt **1** was obtained quantitatively by heating 2-pyrrolecarboxaldehyde with 1 equiv of pyrrolidinium perchlorate in benzene and removing the water azeotropically. The salt was brominated in ethylene dichloride and the product could then be isolated for characterization or converted to a bromoaldehyde by treatment of the crude salt with aqueous sodium bicarbonate. The bromination of 2-pyrrolecarboxaldehyde produces primarily 4-bromo-2-pyrrolecarboxaldehyde and minor amounts of the 5 isomer and the 4,5-dibromo compound.[6] A comparison of the relative quantities of these by-products (see Table I) reveals

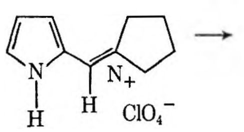
TABLE I

PRODUCT DISTRIBUTION IN MOLE PER CENT

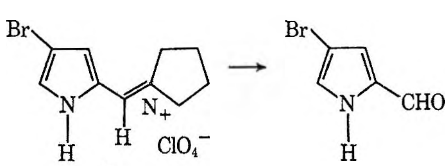
Starting material	T, °C	Products: 4-Br	5-Br	4,5-diBr
2-Pyrrolecarboxaldehyde[a]	28	83.5	14.5	2
2-Pyrrolecarboxaldehyde[a]	0	97	3	
1[b]	26–28	96.5	3.5	
1[b]	0–5	99.5	0.5	

[a] Reference 6. [b] This work.

that bromination of the iminium salt derivative is considerably more selective than bromination of the free aldehyde. Also, the yield of the brominated aldehyde from the salt (~90%) is greater than the yield which we could obtain from the free aldehyde (~55%).



1



2

The directive ability of several other α-substituted electron-withdrawing groups has been investigated. The 2-alkoxycarbonyl group was only moderately meta directing for substitution reactions on pyrrole rings;[7] the 2-formyl and 2-cyano groups were more meta selective, but the transformations required for removal of these groups from the pyrrole ring did not produce high yields.[7a,b] Also, acetylation of 2-pyrrolecarboxaldehyde gave low yields attended by considerable decomposition.[7b] Only the 2-thiolcarboxylate group appeared useful for the elaboration of 3-substituted pyrroles by the "2-meta group" approach.[8]

Acetylation of **1** followed by hydrolysis provided 4-acetyl-2-pyrrolecarboxyaldehyde in 98–98.5% purity (glpc) and 77% yield. The iminium group, therefore, provides considerable selectivity for meta substitution and also gives greater yields of 4-substituted 2-pyrrolecarboxaldehydes. In addition, 4-acetyl-2-pyrrolecarboxylic acid was obtained from the aldehyde in 86% yield compared with a reported 38%,[7b] by using a continuous extraction technique for product isolation. Therefore, this approach appears to have some utility for the preparation of 3-substituted pyrroles. The chemistry of 1-(pyrrol-2-ylmethylene)pyrrolidinium salts is being further investigated.

Experimental Section

Infrared spectra were determined on both Perkin-Elmer Model 137 and 521 infrared spectrophotometers. Nmr spectra were obtained with a Varian T-60 instrument, and chemical shifts are reported in ppm from TMS. Glpc data were obtained with an Aerograph Model A-700 instrument and an SE-30 column (5% on acid-washed Chromosorb W, 10 ft × 0.125 in.) at 180–200°. Elemental analyses were carried out by Galbraith Laboratories Inc., Knoxville, Tenn. The mention of a proprietary product in this paper does not constitute an endorsement of this product by the U. S. Department of Agriculture.

1-(Pyrrol-2-ylmethylene)pyrrolidinium Perchlorate (1).—Pyrrolidine (9.95 g) and 19.8 g of 70–72% $HClO_4$ in 50 ml each of C_6H_6 and EtOAc was heated under reflux with a Dean-Stark trap until H_2O was no longer expelled from the reaction mixture. Pyrrole-2-carboxaldehyde[9] (13.45 g) was added, and the resulting mixture was again heated under reflux to remove water (~0.5 hr). The solvent was evaporated, and the oily product was crystallized under Et_2O. The solid was filtered and air-dried to give 34.9 g (100%). Recrystallization from CH_3CN–Et_2O gave yellow needles: mp 101–102.5°; ir (mull) 3375 b, 1656 (C=N$^+$<);[1] nmr (DMSO-d_6) 2.1–2.5 (m, 4, β CH_2's), 3.8–4.4 (m, 4, α CH_2's), 6.67 (q, 1, $J_{3,4}$ = 4.1, $J_{4,5}$ = 2.5 Hz, 4 H), 7.37 (d, 1, J = 4.1 Hz, 3 H), 7.77 (bs, 1, 5 H), 8.78 (bs, 1, ArCH=N$^+$<).

Anal. Calcd for $C_9H_{13}ClN_2O_4$: C, 43.47; H, 5.27; Cl, 14.26; N, 11.27. Found: C, 43.51; H, 5.29; Cl, 14.33; N, 11.29.

1-[(4-Bromopyrrol-2-yl)methylene]pyrrolidinium Perchlorate (2) and 4-Bromo-2-pyrrolecarboxaldehyde.—Crude **1** (1.25 g) was dissolved in 25 ml of CH_2ClCH_2Cl, and 0.80 g of bromine dissolved in 10 ml of CH_2ClCH_2Cl was added dropwise to this solution (T 26–28°). After 1 hr at 28°, the mixture was concentrated to give 1.62 g (98.7%) of crude **2**. Recrystallization from CH_3CN–Et_2O gave mp 125–127.5°: ir (mull) 3340 b, 1652 (C=N$^+$<); nmr (DMSO-d_6) 2.1–2.5 (m, 4, β CH_2's), 3.8–4.4 (m, 4, α CH_2's), 7.52 (s, 1, 3 H), 7.92 (s, 1, 5 H), 8.65 (bs, 1, ArCH=N$^+$<).

Anal. Calcd for $C_9H_{12}BrClN_2O_4$: C, 33.00; H, 3.69; Br, 24.39; Cl, 10.82; N, 8.55. Found: C, 32.95; H, 3.64, Br, 24.63; Cl, 10.69; N, 8.51.

(2) (a) A. Quilico, F. Piozzi, and M. Paven, *Tetrahedron*, **1**, 177 (1957); (b) R. Bernardi, C. Cardani, D. Ghiringhelli, and A. Selva, *Tetrahedron Lett.*, 3893 (1967).

(3) V. B. Wigglesworth, *J. Insect Physiol.*, **9**, 105 (1963).

(4) M. Pavan, *Ric. Sci.*, **26**, 144 (1956).

(5) N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **28**, 3021 (1963).

(6) H. J. Anderson and S. F. Lee, *Can. J. Chem.*, **43**, 409 (1965).

(7) (a) H. J. Anderson and L. C. Hopkins, *ibid.*, **42**, 1279 (1964); **44**, 1831 (1966); (b) H. J. Anderson and C. W. Huang, *ibid.*, **45**, 897 (1967); (c) M. K. A. Khan, K. J. Morgan, and D. P. Morrey, *Tetrahedron*, **22**, 2095 (1966).

(8) C. E. Loader and H. J. Anderson, *ibid.*, **25**, 3879 (1968).

(9) R. M. Silverstein, E. E. Ryskiewicz, and C. Willard, *Org. Syn.*, **36**, 74 (1956).

The crude salt was stirred into a mixture of water, ether, and a slight excess of $NaHCO_3$ to convert it to the aldehyde. After 5 min the layers were separated, and the organic solid was isolated in the usual way. Direct conversion of 1 to 4-bromo-2-pyrrolecarboxaldehyde resulted in yields of 92% (bromination at 28°, 0.5 hr) and 89% (0°, 16 hr), mp 122.5–124.5° (C_6H_6) (lit.[6] mp 123–124°).

Minor amounts of the 5 isomer were identified by glc comparison with the bromination product from 2-pyrrolecarboxaldehyde prepared as described by Anderson and Lee.[6]

4-Acetyl-2-pyrrolecarboxaldehyde.—Acetyl chloride (0.54 ml) was injected into a violet solution of 1.25 g of 1 and 1.47 g of $AlCl_3$ in 25 ml of CH_2ClCH_2Cl at 0°. The resulting brown mixture was kept at 0° for 16 hr. The mixture was poured over crushed ice, and an aqueous solution of 2 g of NaOH was added. After the mixture had been stirred for 10 min, it was acidified (HCl) and extracted continuously with Et_2O (12 hr). The extract was dried (Na_2SO_4) and concentrated to give 0.54 g (77%), mp 139–142° (C_6H_6) (lit.[7b] 136–137°).

4-Acetyl-2-pyrrolecarboxylic Acid.—Silver nitrate (0.94 g) was dissolved in 95 ml of H_2O and added to 190 ml of 1 *N* NaOH. A solution of 0.51 g of 4-acetyl-2-pyrrolecarboxaldehyde in 38 ml of ethanol was added thereto and the resulting mixture was stirred for 0.5 hr. The mixture was filtered, acidified with HCl, and extracted continuously with ether for 6 hr. The extract was dried ($MgSO_4$) and concentrated to give 0.49 g of the acid, mp ~220° dec (lit.[7b] mp 221.5–223° dec).

Registry No.—1, 27521-94-4; 2, 27521-95-5.

Acknowledgment.—The author wishes to express his gratitude to M. Jacobson and N. Wakabayashi of this division for generously reading and commenting upon this manuscript.

Sterol Metabolism. XIV. Cholesterol 24-Hydroperoxide[1]

JOHAN E. VAN LIER AND LELAND L. SMITH*

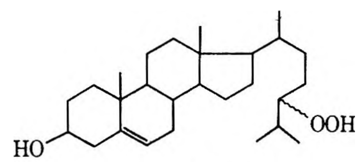
Biochemistry Laboratories, Department of Nuclear Medicine and Radiobiology, Centre Hospitalier Universitaire, Sherbrooke, P.Q., Canada, and the Department of Biochemistry, University of Texas Medical Branch, Galveston, Texas 77550

Received July 21, 1970

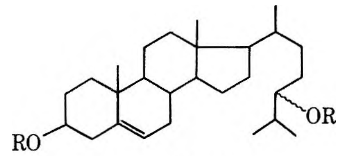
We have isolated from air-aged cholesterol the tertiary hydroperoxides, 3β-hydroxycholest-5-ene 20α-hydroperoxide and 3β-hydroxycholest-5-ene 25-hydroperoxide.[2] A third cholesterol hydroperoxide X_1, previously shown not to be the 17α-hydroperoxide, is identified herein as an epimeric mixture of the 3β-hydroxycholest-5-ene 24-hydroperoxides (I).

Sodium borohydride reduction of the hydroperoxide X_1 gave a mixture of epimeric diols from which one epimer was recovered by crystallization and identified as cholest-5-ene-3β,24ξ²-diol (IIa)[3,4] and from which both cholest-5-ene-3β,24-diol epimers were recovered and identified as their dibenzoates IIb. The 3β,24-diol structure for the cholest-5-ene-3β-24ξ²-diol epimer was suggested by its mass spectrum, which resembled in detail the mass spectra (above *m/e* 200) of the epimeric cholest-5-ene-3β-23-diols.[7] The 3β,24ξ-diols IIa (and their dibenzoates IIb) were distinguished from the known 17α-, 20α-, 22*R*-, 22*S*-, 23*R*-, 23*S*-, 25-, and 25*R*-26-monohydroxylated derivatives of cholesterol but were chromatographically similar to the 3β,24-diol cerebrosterol isolated from human and equine brain.[5] Comparison of the 3β,24ξ²-diol IIa and of the epimeric 3β,24-diol dibenzoates IIb obtained from the hydroperoxide X_1 with authentic sterols established their identity and thereby the identity of the hydroperoxide X_1 as an epimeric mixture of 3β-hydroxycholest-5-ene 24-hydroperoxides (I).

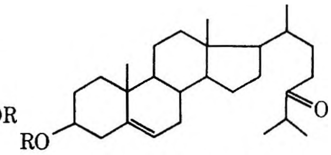
In distinction to the readily acetylated 20α- and 25-hydroperoxides of cholesterol,[2] the 24-hydroperoxides I decomposed on attempted acetylation with acetic anhydride–pyridine. Only 3β-acetoxycholest-5-en-24 one (IIIb) could be identified among the products formed.



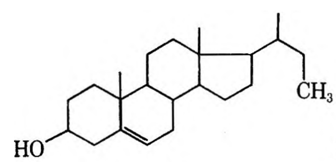
I



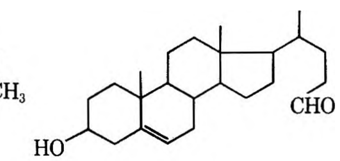
IIa, R = H
IIb, R = Bz



IIIa, R = H
IIIb, R = Ac



IV



V

The instability of the 24-hydroperoxides I to thermal and electron impact degradation was similar to that of the 20α- and 25-hydroperoxides. The three major products previously recognized[8] were identified by their chromatographic and spectral properties as 24-norchol-5-en-3β-ol (IV), 3β-hydroxychol-5-en-24-al (V), and 3β-hydroxycholest-5-en-24-one (IIa). The structure of the alcohol IV as 24-norchol-5-en-3β-ol rests on a consideration of the short gas chromatographic retention times on both 3% QF-1 and 3% SE-30 phases and the relatively high thin layer chromatographic mobility, which data imply a sterol of diminished carbon content. A magenta color with 50%

(1) Paper XIII of the series: J. E. van Lier and L. L. Smith, *J. Chromatogr.*, **49**, 555 (1970). Supported by funds from the U. S. Public Health Service (Grants NS-08106, HE-10160, and AM-13520) and from the Medical Research Council of Canada (Grant MA-4051) and the Conseil de la Recherche Médicale du Québec.

(2) J. E. van Lier and L. L. Smith, *J. Org. Chem.*, **35**, 2627 (1970).

(3) The original nomenclature for the 3β,24-diols IIa of Ercoli and de Ruggieri[4] is retained: cholest-5-ene-3β,24ξ¹-diol for the epimer named cerebrosterol occurring in human and equine brain,[5] cholest-5-ene-3β,24ξ²-diol for the epimer not found in nature. An absolute stereochemistry as the 3β,24βF (24*S*)-diol previously assigned[6] the 3β,24ξ¹-diol IIa has been questioned.[7]

(4) (a) A. Ercoli and P. de Ruggieri, *Gazz. Chim. Ital.*, **83**, 720 (1953); (b) A. Ercoli and P. de Ruggieri, *J. Amer. Chem. Soc.*, **75**, 3284 (1953).

(5) (a) A. Ercoli, S. Di Frisco, and P. de Ruggieri, *Boll. Soc. Ital. Biol. Sper.*, **29**, 494 (1953); (b) S. Di Frisco, P. de Ruggieri, and A. Ercoli, *ibid.*, **29**, 1351 (1953); (c) A. Ercoli, S. Di Frisco, and P. de Ruggieri, *Gazz. Chim. Ital.*, **83**, 78 (1953); (d) L. F. Fieser, W.-Y. Huang, and B. K. Bhattacharyya, *J. Org. Chem.*, **22**, 1380 (1957).

(6) W. Klyne and W. M. Stokes, *J. Chem. Soc.*, 1979 (1954).

(7) J. E. van Lier and L. L. Smith, *J. Pharm. Sci.*, **59**, 719 (1970).

(8) J. E. van Lier and L. L. Smith, *Steroids*, **15**, 485 (1970).

sulfuric acid and infrared absorption spectra support the Δ^5-3β-alcohol feature. The strong molecular ion at *m/e* 330 in the mass spectrum of IV together with the ion at *m/e* 273 (M − C_4H_9) representing loss of an unfunctionalized *sec*-butyl side chain complete the proof of structure. Notably no cholest-5-ene-3β,24-diols were formed thermally from the 24-hydroperoxides I.

The mass spectrum of the 24-hydroperoxides I showed a molecular ion at *m/e* 418 and an ion at *m/e* 402 representing loss of an atom of oxygen, which process also characterized the mass spectrum of 3β-hydroxycholest-5-ene 25-hydroperoxide.[8] Also significant were the molecular ions of the major thermal decomposition products including that of the 24-ketone III at *m/e* 400 (58%), the base peak ion at *m/e* 358 (100%) of the 24-aldehyde V, and an ion at *m/e* 330 (14%) corresponding to the alcohol IV.

The stereochemical composition of the 24-hydroperoxides I was checked on a sample isolated chromatographically without benefit of crystallizations. The epimeric 3β,24-diols obtained therefrom by borohydride reduction were shown by thin layer chromatographic analysis of their dibenzoates and by isolation to be a 1:2 mixture of the 3β,24ξ^1- and 3β,24ξ^2-diol epimers. On the assumption that the 24-hydroperoxides isolated were representative of those formed autoxidatively from cholesterol in the solid state, and that neither borohydride reduction nor benzoylation fractionated the epimers, the 3β,24-diol benzoate mixture recovered thus measured the composition of the 24-hydroperoxide I as a 1:2 mixture of epimers. The benzoylation and thin layer chromatographic analytical method had previously been carefully checked to show that known mixtures of the 3β,24ξ^1- and 3β,24ξ^2-diol dibenzoates in 1:1 to 1:8 ratios were correctly analyzed.[1]

Although complete stereospecificity is exhibited in the photosensitized formation in solution of steroid A- and B-ring allylic hydroperoxides,[9] competing radical attack in certain cases gave both possible epimers.[9c] In the absence of steric features of the cholesterol molecule which would provide a basis for selective approach of molecular oxygen in the formation of the 24-hydroperoxides I, we would predict formation of equal amounts of both 24-hydroperoxide epimers. The stereospecificity represented by the 1:2 ratio of epimers found implies a preference for autoxidative attack on one otherwise undistinguished face of the 24-carbon atom, which preference must derive from the orientation of the sterol side chain in the sterol crystal lattice.

Experimental Section[10]

3β-Hydroxycholest-5-ene 24-Hydroperoxides (I).—Air-aged cholesterol processed as previously described[2] gave a concentrate enriched in autoxidation products including the several hydroperoxides. By repeated alternate column chromatography on silica gel and on Sephadex LH-20, there was recovered 15 mg of I (yield 50 mg/kg of cholesterol), mp 160–165°, identical in spectral and chromatographic properties with the 24-hydroperoxide X_1 previously described.[2] The medium resolution mass spectrum of I has been published.[8] High resolution mass spectra included ions: *m/e* 418.3473 (calcd for $C_{27}H_{46}O_3$: 418.3446), 400.3370 (calcd for $C_{27}H_{44}O_2$: 400.3341), 358.2856 (calcd for $C_{24}H_{38}O_2$: 358.2872), and 330.2896 (calcd for $C_{23}H_{38}O$: 330.2923), etc.

Reduction of 3β-Hydroxycholest-5-en-24-one (IIIa).—A solution of 1.5 g of the 24-ketone IIIa[12] in methanol was reduced with an excess of sodium borohydride at 0°. After 10 min the solution was allowed to warm to room temperature, and after 12 hr the solution was treated with 0.1 *N* hydrochloric acid and the sterols were recovered by extraction with diethyl ether. The ether extract was washed with water, sodium bicarbonate solution, and brine, dried over anhydrous sodium sulfate, and evaporated under vacuum. The residue was chromatographed on a 60 × 2.5 cm column on Sephadex LH-20[11b] using methylene chloride. The fractions containing the epimeric 3β,24-diols were shown to be composed of 47% of the naturally occurring epimer cholest-5-ene-3β,24ξ^{1}diol, 53% of the unnatural epimer cholest-5-ene-3β,24ξ^2-diol by thin layer chromatography of the dibenzoates.[1] The mixed epimers were benzoylated in dry pyridine using benzoyl chloride, and the crude dibenzoates were resolved by thin layer chromatography on 20 × 40 cm chromatoplates 1- and 2-mm thick of silica gel HF_{254}, using benzene–hexane (1:1) as irrigating solvent, run for 15 hr in ascending fashion. The steryl dibenzoate zones were located under 254-nm ultraviolet light and eluted from the chromatoplate with diethyl ether, and the esters recrystallized from methanol, thus yielding the pure epimeric dibenzoates free from one another. The dibenzoates were saponified by refluxing in methanolic 5% sodium methoxide for 3 days. To the cooled solution diethyl ether was added, and the ether layer separated, washed with water three times, dried over anhydrous sodium sulfate, and evaporated under vacuum. The free sterol was recrystallized from hexane–diethyl ether.

Reduction of 3β-Hydroxycholest-5-ene 24-Hydroperoxides.—A sample of the epimeric 24-hydroperoxides I (25 mg) obtained from cholesterol air oxidation without crystallization was dissolved in methanol and reduced with an excess of sodium borohydride for 10 min at room temperature. The solution was treated with 0.1 *N* hydrochloric acid, and the sterols were isolated in exactly the same fashion as described for the reduction of the 24-ketone IIIa. The crude IIa preparation was benzoylated as described, and the crude dibenzoate was analyzed by thin layer chromatography[1] as a mixture of 35% 3β,24ξ^1-diol dibenzoate and 65% 3β,24ξ^2-diol dibenzoate. The crude dibenzoate mixture was chromatographed on a 20 × 40 cm chromatoplate 1-mm thick with benzene–hexane (1:1) for 15 hr, and the two bands of dibenzoate products were located under 254-nm ultraviolet light, the silica gel was excised, and the steryl esters were recovered by extraction with diethyl ether. Each ester was recrystallized from methanol.

Cholest-5-ene-3β,24ξ^1-diol 3β,24ξ^1-Dibenzoate (IIb). A. From the 24-Ketone IIIa.—IIb was obtained in 100-mg yield: mp 179–182° (lit. mp 179–181°,[4] 182–183°[6d]); λ_{max}^{MeOH} 228 nm (ϵ 24,400); $\bar{\nu}_{max}^{KBr}$ 1710, 1280, 1110, 710 cm^{-1}.

B. From the 24-Hydroperoxides I.—IIb was obtained in 3-mg yield, mp 179–181°, identified by mixture melting point and infrared spectral comparisons and by chromatographic behavior with authentic cholest-5-ene-3β,24ξ^1-diol dibenzoate prepared under A above.

Cholest-5-ene-3β,24ξ^2-diol 3β,24ξ^2-Dibenzoate (II). A. From the 24-Ketone IIIa.—II was obtained in 90-mg yield: mp 149–150° (lit.[4] mp 141–142°); λ_{max}^{MeOH} 228 nm (ϵ 24,000); $\bar{\nu}_{max}^{KBr}$ 1710, 1280, 1110, 710 cm^{-1}.

B. From the 24-Hydroperoxides I.—II was obtained in 7-mg yield, mp 138–141°, identified by mixture melting point and infrared spectral comparisons and by chromatographic behavior with authentic cholest-5-ene-3β,24ξ^2-diol dibenzoate prepared under A above.

The epimeric 3β,24-dibenzoates can be differentiated by their infrared absorption spectra, the fingerprint region having at least four distinguishing features: (1) a weak doublet at 668 and

(9) (a) A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, **81**, 6330 (1959); **83**, 1498 (1961); (b) A. Nickon and W. L. Mendelson, *Can. J. Chem.*, **43**, 1419 (1965); (c) A. Nickon, N. Schwartz, J. B. DiGiorgio, and D. A. Widdowson, *J. Org. Chem.*, **30**, 1711 (1965); (d) A. Nickon and W. L. Mendelson, *ibid.*, **30**, 2087 (1965).

(10) Experimental details of measurement of physical data, spectra, and chromatographic properties have been described previously in footnote 15 of ref 2. Preparative gas chromatography on 3% QF-1 columns was performed as previously described,[11a] as was preparative chromatography on Sephadex LH-20.[11b]

(11) (a) J. E. van Lier and L. L. Smith, *J. Chromatogr.*, **36**, 7 (1968); (b) *ibid.*, **41**, 37 (1969).

(12) B. Riegel and I. A. Kay, *J. Amer. Chem. Soc.*, **66**, 723 (1944).

680 cm^{-1}, the 668/680 ratio being approximately unity for the 24ξ^1 epimer, less than unity for the 24ξ^2 epimer; (2) absorption beginning below 900 cm^{-1} and a distinct band at 910 cm^{-1} for the 24ξ^1 epimer with no specific absorption at 900 cm^{-1} nor a band at 910 cm^{-1} for the 24ξ^2 epimer; (3) a complex multiplet of bands centered about 930 cm^{-1} for the 24ξ^1 epimer, around 945 cm^{-1} for the 24ξ^2 epimer; and (4) a well-formed doublet at 995 and 1005 cm^{-1}, the 995/1005 ratio being less than unity for the 24ξ^1 epimer, greater than unity for the 24ξ^2 epimer.

Cholest-5-ene-3β,24ξ^1-diol (cerebrosterol) (IIa) was obtained in 53-mg yield from its dibenzoate IIb prepared from IIIa: mp 175° (lit. mp 175–176°,[4] 170–171.5° to 173.5–175°[5d]); $\bar{\nu}_{max}^{KBr}$ 3400, 1050, 672 cm^{-1}; R_c 0.75 (red-brown color with 50% sulfuric acid); t_R 2.36 (3% QF-1), 2.20 (3% SE-30); identified by direct comparison with authentic samples of cerebrosterol obtained from equine and human brain.

Cholest-5-ene-3β,24ξ^2-diol (IIa). A. From IIIa.—IIa was obtained in 51-mg yield from its dibenzoate IIb: mp 184–186° (lit.[4] mp 182–183°); $\bar{\nu}_{max}^{KBr}$ 3400, 1050 cm^{-1} (no band at 672 cm^{-1}); R_c 0.75 (red-brown color with 50% sulfuric acid); t_R 2.36 (3% QF-1), 2.20 (3% SE-30).

B. From the 24-Hydroperoxide I.—IIa was obtained previously by borohydride reduction: mp 176–179°; R_c 0.77 (red-brown color with 50% sulfuric acid); identical in infrared and gas chromatogaphic properties with the 3β,24ξ^2-diol prepared under A above; mass spectrum m/e 402 (100), 384 (62), 369 (30), 351 (20), 317 (18), 291 (22), 273 (50), 255 (28), etc.

24-Norchol-5-en-3β-ol (IV).—Injection of 5–10 μg of I dissolved in 1–2 μl of chloroform–methanol (9:1) into the flash heater zone (250°) of a Hewlett-Packard F & M Model 402 gas chromatograph and collection of effluxing components in a glass capillary gave IV as the initially eluted component in 14% yield (unidentified component no. 1, 10% yield, in previous studies[8]). The collected sample was homogeneous by thin layer chromatography and by gas chromatography on both 3% QF-1 and 3% SE-30 phases and was characterized: R_c 1.00 (magenta color with 50% sulfuric acid); t_R 0.45 (3% QF-1), 0.38 (3% SE-30); $\bar{\nu}_{max}^{KBr}$ 3400, 1620, 1060 cm^{-1}. The pure IV was transferred in diethyl ether to a quartz probe and inserted directly into the mass spectrometer to yield the molecular ion at m/e 330 (100), 315 (34, M − H_2O), 312 (46, M − CH_3), 297 (48, M − H_2O − CH_3), 273 (28, M − C_4H_9), 255 (37, M − C_4H_9 − H_2O).

3β-Hydroxychol-5-en-24-al (V).—The second component to efflux from the thermally decomposed sample of I was collected in a capillary in 46% yield (unidentified component no. 2, 50% yield previously[8]). The component was homogeneous by thin layer and gas chromatography: R_c 0.85 (magenta-red color with 50% sulfuric acid); t_R 2.40 (3% QF-1), 0.90 (3% SE-30); $\bar{\nu}_{max}^{KBr}$ 3400, 1720, 1620, 1050 cm^{-1}, identical in these properties with an authentic sample; mass spectrum m/e 358 (100, molecular ion), 343 (23), 340 (56), 330 (10), 325 (33), 273 (40, M − C_4H_9O), 255 (20).

3β-Hydroxycholest-5-en-24-one (IIIa).—The third major thermal decomposition product of I was collected in a capillary in 27% yield (unidentified component no. 3, 40% yield previously[8]). The 24-ketone IIIa was homogeneous on thin layer and gas chromatographic analysis: R_c 0.95 (magenta-red color with 50% sulfuric acid); t_R 3.35 (3% QF-1), 1.68 (3% SE-30); $\bar{\nu}_{max}^{KBr}$ 3400, 1700, 1620, 1060, 1020, 800 cm^{-1}; identical in these properties with an authentic sample; mass spectrum m/e 400 (87%, molecular ion), 385 (27), 382 (100), 367 (57), 315 (73), 314 (92), 299 (50), 297 (44), 296 (35), 289 (45), 281 (46), 273 (30, M − $C_8H_{15}O$), 271 (60), 255 (34).

3β-Acetoxycholest-5-en-24-one (IIIb).—Attempted acetylation of I with acetic anhydride–pyridine (1:2) overnight at room temperature in the usual manner resulted in total decomposition of the sterol hydroperoxide (negative peroxide tests). The major product was isolated in 35% yield by preparative gas chromatography, yielding pure IIIb homogeneous on thin layer and gas chromatograms: R_c 1.30 (magenta-red color with 50%, sulfuric acid); t_R 5.9 (3% QF-1); $\bar{\nu}_{max}^{KBr}$ 1730, 1710, 1380, 1250, 1040 cm^{-1}; identical in these properties with an authentic sample.

Registry No.—I (24*R*), 27460-24-8; I (24*S*), 27460-25-9; IIa (24*R*), 27460-26-0; IIa (24*S*), 27460-27-1; IIb (24*R*), 27460-28-2; IIb (24*S*), 27460-29-3; IIIa, 17752-16-8; IIIb, 20981-59-3; IV, 27460-32-8; V, 27460-33-9.

Acknowledgment.—The authors thank Professor L. F. Fieser, Harvard University, for a reference sample of cerebrosterol from equine brain, and Dr. J. A. McCloskey, Baylor University School of Medicine, for mass spectra.

The Dieckmann Cyclization as a Route to *A*-Nor Steroids. Evidence Concerning Stereochemistry

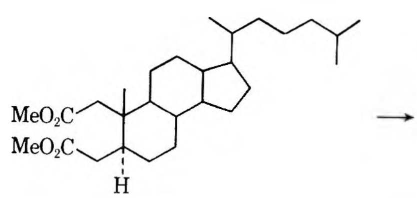
B. V. PARANJAPE[1a] AND J. L. PYLE*[1b]

Hughes Chemical Laboratories, Miami University, Oxford, Ohio 45056

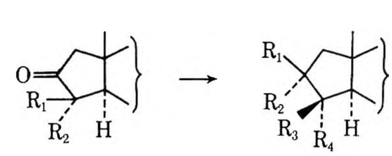
Received August 13, 1970

The successful preparation of a β-keto ester by the Dieckmann cyclization as a synthetic route to an *A*-nor steroid was first reported by Fuchs and Loewenthal in the cholestane series.[2] This synthesis was noteworthy for its specificity; of four possible isomers, with the carbomethoxyl substituted at either the 1 or 3 carbon with an α or β configuration, only one compound formed. The product was formed from the requisite diester, dimethyl 2,3-*seco*-5α-cholestan-2,3-dioate (**2**) (Scheme I), by treatment with potassium *tert*-butoxide in refluxing benzene.

SCHEME I



2



1a, $R_1 = CO_2Me$; $R_2 = H$
b, $R_1 = H$; $R_2 = CO_2Me$

3a, $R_1 = R_4 = H$; $R_3 = CO_2Me$; $R_2 = OH$
b, $R_2 = R_3 = H$; $R_4 = CO_2Me$; $R_1 = OH$

The original choice of configuration was made in favor of **1a** rather than **1b** for two reasons. It was shown that in the sodium borohydride reduction product, the hydroxy ester **3**, the hydroxyl and carbomethoxyl groups were trans with respect to one another. Then, by application of Klyne's principle of enantiomeric types,[3] the hydroxyl group was assigned as α; by inference, the carbomethoxyl group was β, and the structure was assigned as **3a**.

(1) (a) Abstracted in part from the M.S. thesis of B. V. P., Miami University, 1969. (b) Presented in part at the 2nd Central Regional Meeting of the American Chemical Society, Columbus, Ohio, June 3–5, 1970.
(2) B. Fuchs and H. Loewenthal, *Tetrahedron*, **11**, 199 (1960).
(3) W. Klyne, *J. Chem. Soc.*, 2916 (1952).

The possibility that the correct assignment for the β-keto ester is **1b** has been suggested by Smith,[4] by application of Karplus' rules to the coupling of the C-3 proton with the 5α H. The observed coupling constant is 13 cps which is consistent with the dihedral angle between the two protons such that the protons are trans, which places the carbomethoxyl group in the α configuration.

It is the purpose of this paper to examine other evidence arising particularly from the solvent effects on the C-19 proton-singlet chemical shift and from ORD studies of **1**, **3**, and other relevant compounds as it relates to the question of the stereochemistry. We also describe the preparation of the requisite compounds.

Wenkert, *et al.*,[5] have observed an empirical correlation of configuration and solvent effects on comparative chemical shifts in $CDCl_3$ and pyridine-d_5. By analysis of a large number of spectra, certain generalizations were formulated. One of these related to the interaction of a hydroxyl group 1,3 cis or trans to a methyl or hydrogen in a six-membered ring. Deshielding of the chemical shift of the latter of 0.20–0.40 ppm in pyridine relative to $CDCl_3$ was observed when a 1,3-cis diaxial orientation was present, a distinct departure from the normal shielding observed for most systems in pyridine. Less extensive evidence in their investigation suggests that the correlation also operates in five-membered rings. This represented a possible method to distinguish the configuration **3a** postulated for the hydroxy ester by Fuchs and Loewenthal and its isomer **3b**, since a substantial deshielding should be found for the C-19 singlet in the latter case but not the former. Since other orientations are precluded, one could deduce the configuration of the β-keto ester **1**.

The observed C-19 chemical shifts and Δ values ($\Delta = \delta_{CDCl_3} - \delta_{pyr}$) are given in Table I.

TABLE I

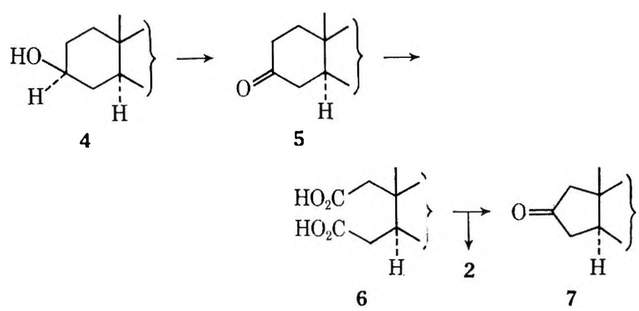
PMR C-18 AND C-19 CHEMICAL SHIFTS[a]

	C-19			C-18		
Compd	$CDCl_3$	Pyr-d_5	Δ	$CDCl_3$	Pyr-d_5	Δ
6	0.84			0.68		
2	0.81			0.65		
1	0.87	0.75	+0.12	0.67	0.63	+0.04
3	0.97	1.17	−0.20	0.68	0.68	0.00
7	0.83	0.73	+0.10	0.68	0.64	+0.04

[a] In ppm.

The Δ value of **3** supports a β configuration for the hydroxyl group. The fact that only a small change, 0.12 ppm upfield, is observed for the β-keto ester in pyridine and that this difference is similar to Δ for the ketone **7** (Scheme II) lends credence to the hypothesis that the carbomethoxyl function is α, since its presence appears not to affect solvation above the A ring. A recent example of a 1,3 methyl–carbomethoxyl group interaction reports δ 0.83 ppm (in $CDCl_3$) for the CH_3 signal when the groups are trans, and δ 0.95 ppm for the cis configuration.[6] The trans value is nearly the same as that for **1**.

SCHEME II



Further, one can compare reported chemical shifts in $CDCl_3$ observed for the hydroxyl ester **3** and the β-keto ester **1** with known *A*-norcholestan-2-ol derivatives. Conversion of the *A*-nor ketone **7** to the 2β-hydroxy compound leads to a shift downfield of 0.07 ppm in the C-19 signal; the 2α-hydroxy methyl signal is shifted upfield 0.17 ppm. Likewise in the androstane series, the effect of 16-ketone-to-alcohol conversions on the C-18 signal is 0.05 downfield for the β-OH case and 0.18 upfield in the α-OH case.[7,8] Thus, the effect of the 1,3-cis hydroxyl function appears consistently to support a deshielding of 0.05 to 0.15 ppm, for the methyl signal consistent with our assignment for the configuration of these products.

The ORD curves for **7** and the β-keto ester **1b** show positive Cotton effects centered at 300 nm. The amplitudes are, respectively, +228 and +283, so that the effect of the carbomethoxyl group is to enhance the Cotton effect observed for the ketone. This enhancement is consistent with the presence of the carbomethoxyl group in either the lower right rear octant or top right forward octant as they are structured with respect to the carbonyl nodal planes. Inspections of models of the β-keto ester show that an α configuration places the functional group in the proper lower right rear octant; however, for the β configuration the group falls in the upper right rear octant which would lead to a prediction of diminution of the magnitude of the Cotton effect as compared with the *A*-nor ketone **7**. The application of the octant rule has been used for purposes of stereochemical assignment in cases of rigid cyclopentanone systems such as **1b**.[9]

The synthetic sequence leading to the requisite compounds for this study is shown in Scheme II. The preparations in general followed methods previously reported.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are corrected. Analytical samples were recrystallized to constant melting points, and microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Ir spectra were determined on a Perkin-Elmer Model 237B spectrometer and uv spectra by a Cary Model 14 recording spectrophotometer. Nuclear magnetic resonance spectra were recorded in external lock mode on a Jeolco C-60H spectrometer at

(4) A. H. Smith, Ph.D. Thesis, 1968, Brown University, Providence, R. I.; *Diss. Abstr. B*, **30**, 139 (1969).

(5) P. V. DeMarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968).

(6) M. E. Kuehne, *J. Org. Chem.*, **35**, 171 (1970).

(7) J. Jacques, M. Minssen, and D. Varech, *Bull. Soc. Chim. Fr.*, **32**, 77 (1965).

(8) D. Williams and N. Bhacca, *Tetrahedron*, **21**, 1641, 2021 (1965).

(9) A. K. Bosey, *Tetrahedron Lett.*, 461 (1961); P. Crabbe, A. Cruz, and and J. Iriarte, *Can. J. Chem.*, **46**, 349 (1968); A. R. VanHorn and C. Djerassi, *J. Amer. Chem. Soc.*, **89**, 651 (1967).

60 MHz, using 30–35 mg of steroid per 0.6 ml of solvent, either $CDCl_3$ or pyridine-d_5, and TMS as internal standard. The methyl signals of the cholestane side chain at C-21 and C-26,27 were centered at 0.84 ± 0.02 ppm, respectively, each with J = 6–8 cps for all compounds reported in both solvents. The assignment of these bands and the C-19 signal was based on the coupling constants and the relative peak intensities. Mass spectra were determined on an Hitachi RMU-6B single-focusing mass spectrometer. ORD curves were recorded on a Jasco 5A spectropolarimeter. The authors are indebted to Dr. R. B. Treptow and to Procter and Gamble, Co., Miami Valley Laboratories, for the use of their spectropolarimeter.

Oxidation of 5α-Cholestan-3β-ol (4) to 5α-Cholestan-3-one (5) by Jones Reagent.—5α-Cholestan-3-one (5) was prepared as previously described.[10] The ketone was recrystallized from acetone: mp 128–128.5°; [α]D +44.4° (c 4.27, $CHCl_3$) (lit.[11] mp 129°; [α]D, +42–44°); ir (KBr) 1709 cm^{-1}; nmr ($CHCl_3$) δ 1.00 s (19-CH_3), 0.65 s (18-CH_3) (lit.[12] δ 1.01, 0.67).

2,3-*seco*-5α-Cholestan-2,3-dioic acid (6) was prepared according to the method of Rull and Ourisson.[13] After adding a solution of the ketone 5 (6.00 g, 13.8 mmol) in 120 ml of glacial acetic acid to CrO_3 (5.54 g, 55.4 mmol) suspended in 100 ml of HOAc at 70°, the reaction mixture was maintained at 85° for 26 hr. Subsequent work-up gave 6: 4.60 g (68%); mp 194.5–195° (EtOAc), [α]D +35.5° (c 0.013) (lit.[14] mp 195–196°; [α]D +35.7°; ir (KBr) 3700–3100 (OH), 1705 (C=O), 925 cm^{-1} (diacid); nmr ($CDCl_3$) δ 0.68 s (18-CH_3), 0.84 s(19-CH_3), 8.2–10.7 s (COOH).

Dimethyl 2,3-*seco*-5α-cholestan-2,3-dioate (2) was prepared by methylation by a method analogous to that of Ourisson[15] except that *N*-nitroso-*N*-methyl-*p*-toluenesulfonamide (Diazald, Aldrich Chemical Co., Milwaukee) was used as a CH_2N_2 precursor. The reaction gave 2 which was recrystallized (MeOH): mp 59–60°, [α]D +23.5° (lit.[16] mp 59–60°; [α]D +20°); ir (KBr) 1745 cm^{-1} (C=O ester); nmr ($CDCl_3$) δ 0.81 s (19-CH_3), 0.65 s (18-CH_3), 3.67 s ($COOCH_3$); mass spectrum (70 eV) m/e (rel intensity) 464 (1), 428 (2), 380 (24).

3α-Carbomethoxy-*A*-nor-5α-cholestan-2-one (1b) was prepared according to the method of Fuchs and Loewenthal[2] except that the solvent contained benzene and DMSO in a ratio of 5:1 by volume. The product gave the following data: mp 108–109°; [α]D +111° (c 0.10, $CHCl_3$) (lit.[2] mp 110–111°; [α]D +109°); ir 3700–3200 weak (enol OH), 1765 (cyclopentanone C=O), 1727 cm^{-1} (ester C=O); uv max (EtOH) 294 nm (ε 4.25); nmr ($CDCl_3$) 0.68 s (18-CH_3), 0.87 s (19-CH_3), 3.73 s (methyl ester), 3.08 d (C-3, J = 13 Hz); nmr (pyr) 0.75 s (19-CH_3), 0.63 s (18-CH_3); ORD (c 0.10, MeOH) $\Phi \times 10^{-3}$ (nm), +3.66 (375), +10.52 (335), +16.55 (326), +14.82 (321), +16.32 (316), +5.80 (305), 0 (300), −12.03 (278), −10.54 (255); a +283; mas spectrum (70 eV) m/e (rel intensity) 430 (62), 415 (46, M − CH_3), 399 (34, M − CH_3O), 275 (105).

3α-Carbomethoxy-*A*-nor-5α-cholestan-2β-ol (3b) was prepared by reduction of 1b as previously described.[2] The crude product recovered was chromatographed on neutral alumina and gave 3b: mp 119–122.5° (lit.[2] 121.5–122.5°); ir 3500 (broad, OH), 1728 cm^{-1} (C=O, ester); nmr ($CDCl_3$) 0.68 s (18-CH_3), 0.97 s (19-CH_3); nmr (pyr) 1.17 s (19-CH_3), 0.68 s (18-CH_3).

***A*-Nor-5α-cholestan-2-one (7)** was prepared from the diacid 6 by the method of Castells, *et al.*[17] The crude product recovered gave 7: mp 96–97° (lit.[17] 101–102°); ir (KBr) 1745 (cyclopentanone C=O); uv (MeOH) 237.5 nm (ε 253), 297.5 (97); nmr ($CDCl_3$) δ 0.65 s (18-CH_3), 0.83 s (19-CH_3); nmr (pyr) δ 0.64 (18-CH_3), 0.73 (19-CH_3); mass spectrum (70 eV) m/e (rel intensity) 372 (6.8), 357 (2.61), 202 (1.11), 214 (1.0); ORD (c 0.10, MeOH) $\Phi \times 10^{-3}$ (λ, nm) +2.64 (375), +4.38 (350), +10.69 (325), +10.57 (322), +12.20 (315), +7.85 (308), +5.00 (302), 0 (297.5), −8.53 (285), −10.57 (275), −8.53 (2.60); a +228 (lit.[18] +234).

Registry No.—**1b,** 27460-19-1; **2,** 1180-24-1; **3b,** 30157-81-4; **4,** 80-97-7; **6,** 1178-00-3; **7,** 2310-36-3.

(10) A. Bowers, T. Halsal, E. Jones, and A. Lemin, *J. Chem. Soc.*, 2548 (1953).

(11) O. Diels and E. Abderhalden, *Ber.*, **39**, 884 (1906).

(12) P. C. Cherry, R. T. Cottrell, G. D. Meakins, and E. E. Richards, *J. Chem. Soc. C*, 181 (1967).

(13) T. Rull and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1573 (1958).

(14) B. H. Brown, I. M. Heilbron, and E. R. H. Jones, *J. Chem. Soc.*, 1482 (1940).

(15) A. Giroud, A. Rassat, P. Witz, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 3240 (1964).

(16) B. B. Smith and H. R. Nace, *J. Amer. Chem. Soc.*, **76**, 6119 (1954).

(17) J. Castells, G. Fletcher, E. Jones, G. Meakins, and R. Swindells, *J. Chem. Soc.*, 2627 (1960).

(18) W. Klyne, *Tetrahedron*, **13**, 29 (1961).

The Thienylfurans

Hans Wynberg,* H. J. M. Sinnige, and H. M. J. C. Creemers

Department of Organic Chemistry, The University, Zernikelaan, Groningen, The Netherlands

Received July 14, 1970

The scope and limitations of the photochemically induced valence bond isomerization has been reasonably well defined.[1–3] Nevertheless a number of intriguing questions remain particularly in the area of heteroaromatic-substituted thiophenes.[2]

This note describes the synthesis of the four isomeric thienylfurans (1,[3a] 2,[3a] 3, and 4) and preliminary irradiation experiments (Scheme I).

2-(2-Thienyl)furan (1), a straw-colored oil, bp 46–47° (17 mm), was prepared in 20% overall yield starting with ethyl-2-thenoylacetate (5).[4] The latter (5) was condensed with α,β-dichloroethyl ethyl ether,[5] and the ester 6 thus formed could be hydrolyzed and decarboxylated to 1.

3-(2-Thienyl)furan (2), 2-(3-thienyl)furan (3), and 3-(3-thienyl)furan (4) were prepared by a route developed earlier by us for the synthesis of 2,3-diethienyl,[6] 3-phenylfuran,[7] and 3,3′-difuryl.[8] The starting materials 7, 11, and 15 have been described previously,[9–11] while the ketones 8 and 12 are also available by tested procedures.[7,12,13] Dehydration of the carbinols 9, 13, and 16 was carried out *in situ*[10,11] by distillation from dilute sulfuric acid. In each case a mixture of bond isomers, the thienyldihydrofurans 10, 14, and 17, was ob-

(1) (a) H. Wynberg, R. M. Kellogg, H. van Driel, and G. E. Beekhuis *J. Amer. Chem. Soc.*, **89**, 3501 (1967); (b) R. M. Kellogg, J. K. Dik, H. van Driel, and H. Wynberg, *J. Org. Chem.*, **35**, 2737 (1970).

(2) H. Wynberg, T. J. van Bergen, and R. M. Kellogg, *ibid.*, **34**, 3175 (1969).

(3) R. M. Kellogg, T. J. van Bergen, and H. Wynberg, *Tetrahedron Lett.*, 5211 (1069).

(3a) Note Added in Proof.—It has just come to my attention that D. J. Klinke [Dissertation Abstracts, University Microfilms, Inc., Ann Arbor, Mich., 1964; Ph.D. Thesis, University of Michigan, 1963 (thesis director Dr. R. D. Schuetz)] described the synthesis and several reactions of 1 and 2. The physical properties agree.

(4) R. Levine and C. R. Hauser, *Tetrahedron Lett.*, **66**, 1768 (1944).

(5) F. Reichstein, A. Grussner, and H. Tschokke, *Helv. Chim. Acta*, **15**, 1066 (1932).

(6) H. Wynberg, A. Logothetis, and D. Verploeg, *J. Amer. Chem. Soc.*, **79**, 1972 (1957).

(7) H. Wynberg, *ibid.*, **80**, 364 (1958).

(8) H. Wynberg and J. W. van Reijendam, *Recl. Trav. Chim. Pays-Bas*, **86**, 381 (1967).

(9) H. Gilman and D. A. Shirley, *J. Amer. Chem. Soc.*, **71**, 1870 (1949).

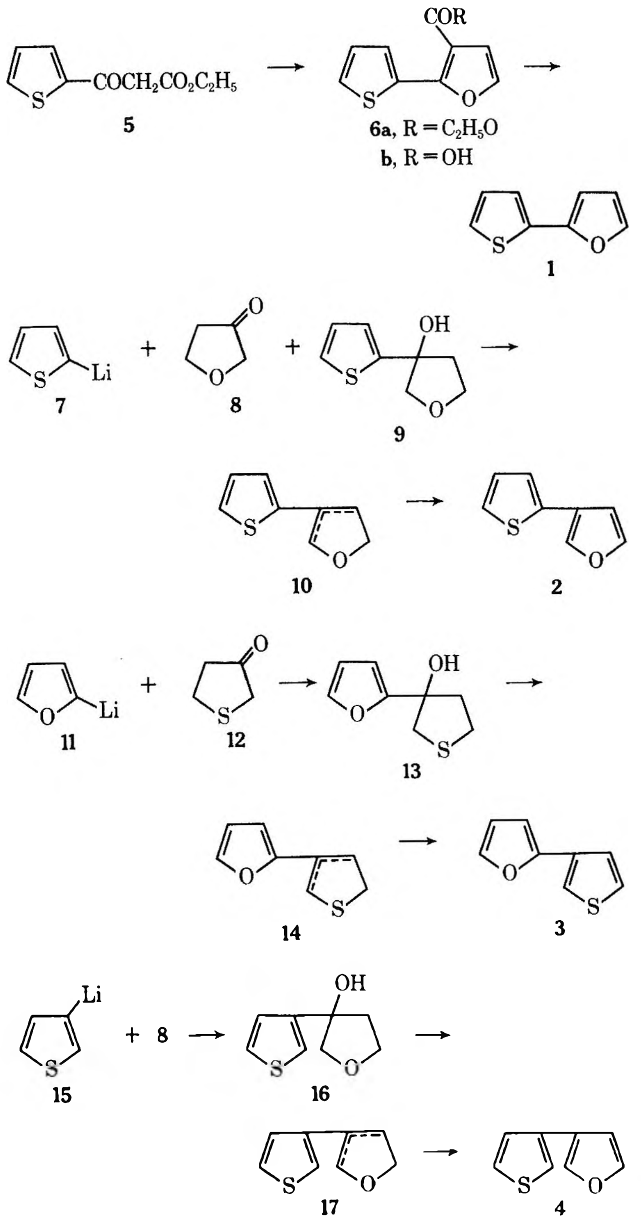
(10) S. Gronowitz, *Ark. Kemi*, **7**, 361 (1954).

(11) V. Ramananthan and R. Levine, *J. Org. Chem.*, **27**, 1216 (1962).

(12) Yu. K. Yur'ev, I. K. Korobitsyna, and L. A. Savina, *Dokl. Akad. Nauk SSSR*, **86**, 91 (1952) [*Chem. Abstr.*, **47**, 7478 (1953)]; J. H. S. Weiland, H. Dijkstra, and A. B. Pik, *Recl. Trav. Chim. Pays-Bas*, **82**, 651 (1963).

(13) P. Karrer and A. Kiese, *Helv. Chim. Acta*, **27**, 1285 (1945); R. B. Woodward and R. H. Eastman, *J. Amer. Chem. Soc.*, **68**, 2229 (1946). The most convenient preparation of ketone 12 consists of pyrolysis of the barium salt of 3-thiaadipic acid at 230° using the method developed by R. M. Acheson, J. A. Barltrop, H. Hichens, and R. F. Hichens, *J. Chem. Soc.*, 650 (1961), for alkylsubstituted thiaadipic acids. See also F. A. Buiter, *Diss.*, Groningen (Holland), 1966.

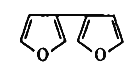
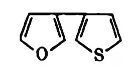
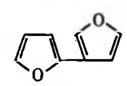
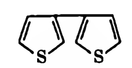
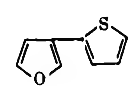
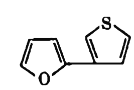
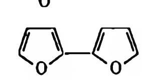
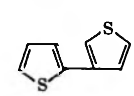
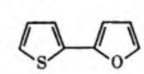
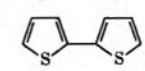
SCHEME I



tained. Gas chromatographic analysis of the ratio of one isomer to the other was relatively easy. The thienyldihydrofurans as well as the thienylfurans are quite volatile compounds. No attempts were made at this time to separate and identify each individual dihydrofuran since the mixture could be dehydrogenated smoothly using sulfur in dimethylformamide, yielding in each case one single compound (**2**, **3**, or **4**). All of the four isomers, **1**, **2**, **3**, and **4**, appeared to be sensitive to light, heat, and moisture. Even storage at $-20°$ under nitrogen and in the dark resulted in darkening after several days. The stability of a negatively substituted derivative, *viz.*, **6**, was considerably greater.[14] In principle all of the four isomers are photochemically intraconvertible. Initial attempts were made to determine whether 2-(2-thienyl)furan (**1**) would yield any of the other isomers **2**, **3**, or **4** upon irradiation under conditions similar to those described for 2-phenylthiophene.[1] Although in one experiment a 2–5% conversion to 2-(3-thienyl)furan (**3**) was detected by gas chromatography (that is, a new compound having the retention time of **3** was observed), no positive identification could be made. Longer irradiation times led to decomposition of starting material. In fact, it appears that none of the four isomers are photochemically sufficiently stable to permit preparatively useful rearrangements. This phase of our work obviously requires further study.

Spectra.—In view of the current interest[17,18] in the structure and bonding in dithienyls, Table I summarizes the ultraviolet absorption spectra of all of the ten dithienyls, difuryls, and thienylfurans. For comparison, 2,3-divinylbutadiene (**18**) and 1,3,5,7-octatetraene (**25**) are included in this chart. Note that 2,3′-difuryl (**20**) has not been reported previously.

TABLE I

Compd	No.	Uv spectrum,[a] λ_{max} (mμ) (*E*)	Ref
	18	223 (20,800)	*b*
	19	239 (sh), 231, 220 (5,420, 7,780, 7,770)	*c*
	4	242 (7,500)	*d*
	20	259, 254, 214, 270 (sh) (11,500)	*e*
	21	260, 212 (cyclohexane) (11,300, 22,300)	*f*
	2	273 (7,800)	*d*
	3	279, 270, 228 (13,500, 13,300, 12,300)	*d*
	22	281 (18,500)	*g*
	23	282, 235 (cyclohexane) (13,100, 9,400)	*f, h*
	1	296, 230 (10,950, 1,300)	*d*
	24	301, 246 (12,900, 6,100)	*h*
	25	304, 290, 278, 267	*i*

[a] Solvent 96% ethanol unless noted otherwise. [b] K. Greiner, *Diss.*, Erlangen (1960). [c] Reference 8. [d] This work. [e] Prepared in 35% overall yield from 3-furyllithium and **8** as an unstable yellow oil, n^{28}D 1.5297 (Found: C, 71.1; H, 4.50, by Mr. B. Greydanus of this laboratory). [f] H. van Driel, *Diss.*, Groningen (1967). [g] R. Grigg, J. A. Knight, and H. V. Sargent, *J. Chem. Soc. C*, 976 (1966). [h] Reference 6. [i] G. F. Woods and L. H. Schwartzman, *J. Amer. Chem. Soc.*, **71**, 1396 (1949).

(14) The purification and stability of the dithienyls have been the source of concern in ours and other laboratories. The known reactivity of dithienyls under the influence of light[1] and oxygen[15] as well as the reaction of oxygen with furans[16] are undoubtedly involved in the instability.

(15) P. Caralieri d'Oro, A. Mangini, G. F. Pedulli, P. Spagnolo, and M. Tiecco, *Tetrahedron Lett.*, 4179 (1969).

(16) G. O. Schenk, *Naturwissenschaffen*, **31**, 387 (1943).

(17) G. J. Visser, G. J. Heeres, J. Wolters, and A. Vos, *Acta Crystallogr.*, **24**, 467 (1968).

(18) H. J. S. Dewar and N. Trinajstic,[1] *J. Amer. Chem. Soc.*, **92**, 1453 (1970).

The compounds can empirically but usefully be divided into three groups: those compounds whose chromophore resembles that of 2,3-divinylbutadiene (**18**), *i.e.*, compounds **19**, **4**, and **21**; those compounds whose chromophore is similar to that of a vinylhexatriene, *i.e.*, compounds **20**, **2**, **3**, and **23**; and finally compounds **22**, **1**, and **24** whose chromophore resembles an octatriene (**25**).

As recorded earlier by others,[8,19] the resonances of the β hydrogens in five-membered heterocyclics occur at higher fields than those of the α hydrogens. This difference is most pronounced in furans,[8,19] and consequently the nmr spectra of the four diaryl **1**, **2**, **3**, and **4** are all characterized by an absorption at τ 3.6–3.7 due to the β hydrogen(s) of the furan ring and a resonance at τ 2.4–2.5 for compounds **2** and **4** due to H_2 of the furan ring. The hydrogens of the thiophene ring as well as the H_5 hydrogens of the furan ring form a complex multiplet between τ 2.67 and 3.2. The spectra, including the ir and mass spectra, are available on request.

Experimental Section

Nuclear magnetic resonance (nmr) spectra were taken on a Varian A-60 instrument using tetramethylsilane (TMS) as internal standard. Ir spectra were run on a Perkin-Elmer 257 or 137 instrument. Ultraviolet spectra were obtained with a Zeiss PHQ II spectrophotometer while mass spectra were run on an AEI MS 9. Melting points using a Reichert hot-stage are uncorrected. Microanalyses were carried out in the analytical section of our department under the direction of M. W. Hazenberg.

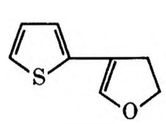
2-(2-Thienyl)furan (1).—Ethyl β-keto-β-(2-thienyl)propionate[4] (**5**) (19.8 g, 0.1 mol) and 18.0 g (0.13 mol) of 1,2-dichloroethyl ethyl ether were condensed by stirring at 30–40° in 60 ml of ether to which 11 g of sodium hydroxide in 170 ml of water was added with cooling. Following the work-up as described by Reichstein[5] for 2,2′-difuryl, we obtained 6.6 g (30%) of ethyl 2-(2-thienyl)furan-3-carboxylate (**6a**), bp 115° (0.8 mm), $n^{22}D$ 1.5765, as a pale yellow oil. Saponification with potassium hydroxide in ethanol–water for 45 min furnished a solid. Recrystallization from petroleum ether (bp 140–160°) gave 4.0 g of slightly yellow needles, mp 154.5–156°, of 2-(2-thienyl)furan-2-carboxylic acid (**6b**).

Anal. Calcd for $C_9H_6O_3S$: C, 55.66; H, 3.10; S, 16.42. Found: C, 55.7; H, 3.3; S, 16.5.

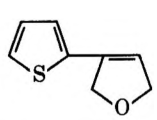
Decarboxylation of 1.5 g of the acid **6b** using 2.4 g of cupric oxide in 30 ml of quinoline at 245° for 7 min furnished 0.9 g (78%) of 2-(2-thienyl)furan (**1**) as a yellow oil which darkened upon standing. Purification was achieved by preparative gas chromatography (Carbowax SE-30 at 170°).

Anal. Calcd for C_8H_6OS: C, 63.97; H, 4.02. Found: C, 63.4; H, 5.1.

3-(2-Thienyl)furan (2).—Using an equivalent amount of *n*-butyllithium in ether, thiophene (3.7 g, 0.044 mol) in 100 ml of ether was lithiated[9] under nitrogen at −20° over a period of 1.5 hr. 3-Ketotetrahydrofuran[7,12] (**8**) (3.3 g, 0.044 mol) in 50 ml of ether was added at 0° with stirring. The reaction mixture was worked up as described in detail previously[6–8] and the mixture of dihydrofurans **10a** and **10b** was isolated as a yellow oil (3.5 g).



10a



10b

Glc analysis (diisodecyl phthalate) showed the two isomers in a ratio of 1:6. Dehydrogenation using 75 ml of dimethylformamide and 1.6 g of sulfur furnished 1.7 g (26% based on thiophene) of oil which could be purified by chromatography over alumina (benzene as eluent).

Anal. Calcd for C_8H_6OS: C, 63.97; H, 4.02; S, 21.34. Found: C, 64.1; H, 4.1; S, 21.5.

2-(3-Thienyl)furan (3).—Using 2-furyllithium[9] prepared from 16.5 g (0.24 mol) of furan and 25.2 g (0.24 mol) of 3-ketotetrahydrothiophene in 100 ml of ether at 0° yielded, after a similar work-up as above, 13.0 g (36%) of a mixture of bond isomers of 2-(3-thienyl)dihydrofuran as a yellow oil (ratio of isomers 5:4). Aromatization proceeded in 62% yield and after chromatography on alumina, 2-(3-thienyl)furan (**3**) was obtained as colorless solid, mp 24–26°.

Anal. Calcd for C_8H_6OS: C, 63.97; H, 4.02; S, 21.34. Found: C, 63.7; H, 4.4; S, 21.7.

3-(3-Thienyl)furan (4).—At −70° 3.7 g (0.05 mol) of 3-ketotetrahydrofuran (**8**) was added to a solution of 3-thienyllithium (from 7.2 g of 3-bromothiophene)[10] in 100 ml of ether. The reaction was worked up as described above to furnish, after steam distillation from dilute sulfuric acid, 4.0 g of a mixture of bond isomers of the 3-(3-thienyl)dihydrofurans (ratio 1:15) as a colorless solid. Aromatization gave 1.45 g (22% based on 3-bromothiophene) of pure 3-(3-thienyl)furan (**4**), mp 63–64°, one sublimation at 40° (0.2 mm).

Anal. Calcd for C_8H_6OS: C, 63.97; H, 4.02; S, 21.34. Found: C, 64.2; H, 4.3; S, 21.3.

Registry No.—**1**, 27521-80-8; **2**, 27521-81-9; **3**, 27521-82-0; **4**, 27521-83-1; **6a**, 27521-84-2; **6b**, 27521-85-3; **20**, 27521-86-4.

(19) E. J. Corey, G. Slomp, S. Dev, S. Tobinaga, and E. R. Glatier, *J. Amer. Chem Soc.*, **80**, 1204 (1958); R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **37**, 1056 (1959); S. Gronowitz, A. B. Hörnfeldt, B. Gestblom, and R. A. Hoffman, *Ark. Kemi*, **18**, 133 (1961).

The Reaction of Alkyl Diphenyl Phosphates with Potassium *tert*-Butoxide in Dimethyl Sulfoxide

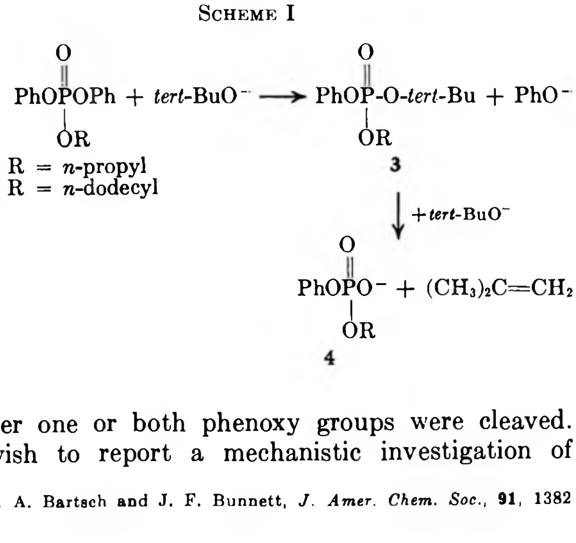
RICHARD A. BARTSCH* AND DAN G. WALLIN

Department of Chemistry, Washington State University, Pullman, Washington 99163

Received August 21, 1970

The reaction of 2-hexyl diphenyl phosphate with potassium *tert*-butoxide in dimethyl sulfoxide yields predominantly 2-methylpropene, instead of the hexene isomers anticipated from simple β elimination.[1] A two-step mechanism involving displacement of phenoxide from phosphorus by *tert*-butoxide and then β elimination in the *tert*-butyl group of the resulting ester was proposed[1] (Scheme I). It was not clear

SCHEME I



whether one or both phenoxy groups were cleaved. We wish to report a mechanistic investigation of

(1) R. A. Bartsch and J. F. Bunnett, *J. Amer. Chem. Soc.*, **91**, 1382 (1969).

TABLE I

YIELDS OF 2-METHYLPROPENE IN REACTIONS OF ALKYL DIPHENYL PHOSPHATE WITH POTASSIUM *tert*-BUTOXIDE IN DIMETHYL SULFOXIDE

Reaction no.	Alkyl diphenyl phosphate	Time, min	Temp, °C	Mmol of alkyl diphenyl phosphate	Mmol of potassium *tert*-butoxide	Yield of 2-methylpropene,[a] %
1	Dodecyl	12	50	0.73	2.6	56[b,c]
2	Dodecyl	30	50	0.71	4.9	106[d]
3	Dodecyl	30	100	0.79	4.9	105[d]
4	Dodecyl	30	50	0.78	0.78	55[c]
5	*n*-Propyl	30	50	0.91	4.6	86[d]
6	Methyl	30	50	1.32	4.9	30[c]

[a] Based upon cleavage of one phenoxy group. [b] Incomplete reaction. [c] Estimated uncertainty ±5%. [d] Estimated uncertainty ±10%.

this unusual reaction for primary alkyl diphenyl phosphates.

n-Propyl and *n*-dodecyl phosphates, **1** and **2**, respectively, were selected as representative starting materials. The yields of 2-methylpropene obtained from reactions of **1** and **2** with potassium *tert*-butoxide in dimethyl sulfoxide under various conditions are recorded in Table I. With an excess of base, approximately 1 mol of 2-methylpropene is produced per mole of **1** or **2** (reactions 2 and 5), even under forcing conditions (reaction 3). The slightly lower yield of 2-methylpropene from **1** might be due to minor incursion of a competing displacement of *tert*-butoxide upon carbon of the *n*-propyl group.[2] Support for this proposal is derived from the low yield of 2-methylpropene from methyl diphenyl phosphate (reaction 6).

Reaction of equivalent amounts of potassium *tert*-butoxide and **2** produced only a 50% yield of 2-methylpropene (reaction 4). Thus, a potassium *tert*-butoxide/alkyl diphenyl phosphate ratio of greater than 1 is required for formation of 1 mol of 2-methylpropene per mole of 2. This result, as well as those from reactions employing a severalfold excess of potassium *tert*-butoxide, is compatible with the reaction sequence depicted in Scheme I, if β elimination from the *tert*-butyl alkyl phenyl phosphate, **3** (step 2), is more rapid than the initial displacement of *tert*-butoxide upon the alkyl diphenyl phosphate (step 1).[4]

An extraction technique was employed to determine the presence and amounts of two other anticipated reaction products (after acidification), phenol and alkyl phenyl phosphate. Emulsion formation during the extraction process prevented further studies on **2**. From the reaction of **1** with 4 equiv of potassium *tert*-butoxide, 1 mol of phenol per mole of **1** was liberated.

Several attempts to isolate and purify an oil, presumably *n*-propyl phenyl phosphate, recovered from the reaction of **1** with an excess of potassium *tert*-butoxide, as the cyclohexyl amine[6] or barium salts were unsuccessful. However, the pmr spectrum of this oil was nearly identical with that observed for *n*-propyl diphenyl phosphate except for the decreased ratio of aromatic to aliphatic protons expected for *n*-propyl phenyl phosphate.

The product studies of 2-methylpropene, phenol, and alkyl phenyl phosphate are all in accord with the mechanism outlined in Scheme I. Displacement of only one phenoxy group may be attributed to the unfavorable entropy for attack of *tert*-butoxide upon the negatively charged alkyl phenyl phosphate anion 4.[7]

Another conceivable mechanism that is consistent with the observed reaction products involves a nucleophilic aromatic substitution by *tert*-butoxide upon the alkyl diphenyl phosphate producing an alkyl phenyl phosphate anion and *tert*-butyl phenyl ether. Potassium *tert*-butoxide induced β elimination from the latter would form 2-methylpropene and phenoxide ion. However, the stability of *tert*-butyl phenyl ether to the action of potassium *tert*-butoxide in dimethyl sulfoxide[8] renders this proposal untenable.

Experimental Section

Reagents.—*n*-Propyl, *n*-dodecyl, and methyl diphenyl phosphate were synthesized by literature methods.[6,9,10] Sublimed potassium *tert*-butoxide (MSA) and reagent dimethyl sulfoxide from freshly opened bottles were used directly.

Procedure for Measuring 2-Methylpropene Yields.—A special apparatus designed to sweep the evolved 2-methylpropene from the reaction solution with nitrogen was employed. The sweeping nitrogen was passed first through an empty trap to remove any high boiling materials and then through a trap containing 5 ml of chloroform which was cooled in liquid nitrogen. The alkyl diphenyl phosphate was injected into the solution of potassium *tert*-butoxide in dimethyl sulfoxide (10 ml) with a syringe. After the desired reaction time, the liquid nitrogen-cooled trap was separated and an additional 5 ml of chloroform was added. The flask was warmed in cold water until the contents were half thawed, and a measured amount of bromine in acetic acid was added. Unconsumed bromine was determined by addition of 20 ml of 15% KI and titration with standard thiosulfate using starch indicator.

Extraction Procedure for Nonvolatile Products from 1.—The solution resulting from reaction of 0.73 g of **1** (2.49 mmol) with 10 ml of 1 *N* potassium *tert*-butoxide in dimethyl sulfoxide under nitrogen for 30 min at 50° was poured into 100 ml of water. After adjusting to pH 5 with concentrated HCl, the solution was extracted with CH_2Cl_2 (five 50-ml portions). The CH_2Cl_2 was evaporated from the combined organic extracts, and a phenol yield of 2.54 mmol (102%) was determined by uv spectroscopy. The pH of the aqueous layer was adjusted to 0.1 with concentrated HCl. Extraction with CH_2Cl_2 (four 75-ml portions),

(2) Bimolecular nucleophilic displacement of phosphate diester anions is very facile.[3]

(3) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, New York, N. Y., 1967, p 209.

(4) Alkaline cleavage of *tert*-butyl groups from tertiary phosphate esters occurs readily.[5]

(5) N. A. Milas, P. Davis, and L. Chiang, *J. Amer. Chem. Soc.*, **77**, 1640 (1955). However, see H. G. Khorana, "Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest," Wiley, New York, N. Y., 1961, p 20.

(6) J. Lecocq and A. R. Todd, *J. Chem. Soc.*, 2381 (1954).

(7) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1953, p 143.

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

(9) D. A. Brown, T. Malkin, and G. K. Maliphant, *J. Chem. Soc.*, 1584 (1955).

(10) D. W. Osborne, *J. Org. Chem.*, **29**, 3570 (1964).

drying the combined extracts ($MgSO_4$), and evaporation produced an oil. The pmr spectrum of this oil exhibited $\delta_{TMS}^{CCl_4}$ 0.88 (t, 3.0), 1.62 (sextet, 2.5, J = 7 Hz), 3.95 (apparent quartet, 2.0, J = 6 Hz), 7.15 (broad singlet, 5.0), which is consistent with that expected for *n*-propyl phenyl phosphate. For *n*-propyl diphenyl phosphate, the pmr spectrum was $\delta_{TMS}^{CCl_4}$ 0.88 (t, 2.9), 1.68 (sextet, 2.2, J = 7 Hz), 4.12 (apparent quartet, resolvable into overlapping triplets centered at 4.07 and 4.20 each with J = 6 Hz, 1.9), 7.23 (multiplet, 10.0).

Registry No.—**1,** 27460-01-1; **2,** 27460-02-2; potassium *tert*-butoxide, 865-47-4; methyl diphenyl phosphate, 115-89-9.

Acknowledgment.—We wish to thank R. R. Gibson and N. L. Bartsch for technical assistance.

α-Chlorodicyclopropyl Sulfone. Its Synthesis and Behavior toward Bases[1]

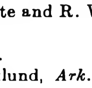
LEO A. PAQUETTE* AND ROBERT W. HOUSER[2]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received August 8, 1970

In 1940, Ramberg and Bäcklund demonstrated that exposure of acylic α-halo sulfones to the action of 2 *N* potassium hydroxide resulted in the production of alkenes with the concomitant ejection of hydrogen halide and sulfur dioxide.[3] Significantly, the new double bond unequivocally supplanted the sulfonyl group in each example studied. These findings, in conjunction with more recent mechanistic studies,[4] have resulted in broad application of the Ramberg–Bäcklund reaction to the preparation of many olefins, both cyclic and acyclic, which would be difficult to prepare by other methods.[5]

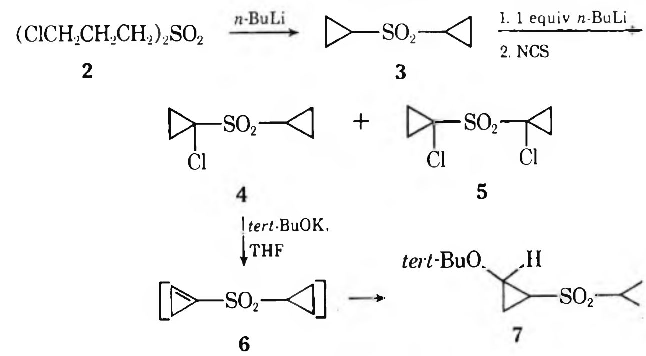
In the present instance, we felt that the α-halo sulfone rearrangement could offer an attractive opportunity for facile synthesis of bicyclopropylidene (1).



1

Hopefully, the approach would be entirely general in nature, in constrast to the limited number of highly specific methods known to date for this class of compounds.[6]

The scheme began with the *n*-butyllithium-induced cyclization of readily available γ,γ′-dichlorodipropyl sulfone (2) to give dicyclopropyl sulfone (3) in 85% yield. The nmr spectrum ($CDCl_3$) featured a multiplet of area 2 at δ 2.50 attributable to the α-sulfonyl protons and a second multiplet of area 8 centered at δ 1.08 for the remaining cyclopropyl hydrogens. Chlorination of sulfone **3** could be effected by initial treatment with slightly more than 1 equiv of *n*-butyllithium, followed by inverse addition of the α-sulfonyl carbanion



solution to excess *N*-chlorosuccinimide. Under these somewhat limiting conditions, the α,α′-dichloro derivative was produced in low (6%) yield. The nmr spectrum of this substance in deuteriochloroform was devoid of peaks in the δ 2.5–3.5 region; rather, two multiplets of equal area were displayed at approximately δ 1.97 and 1.56 for the two nonequivalent sets of ring protons. As expected, this method of chlorination also did give rise to the desired α-chloro sulfone (4) in fair (27%) yield. Its nmr spectrum in $CDCl_3$ displayed multiplets centered at δ 2.70 (1 H), 1.76 (2 H), 1.47 (2 H), and 1.18 (4 H), in full agreement with the structural assignment.

At the outset, sulfone **4** was found to be quite stable to the "normal" conditions of the α-halo sulfone rearrangement. Thus, **4** could be recovered intact from prolonged exposure to refluxing solutions of aqueous potassium hydroxide (1.2 *N*, 24 hr) and methanolic sodium methoxide (7 hr). Furthermore, it was noted that addition of *n*-butyllithium to dimethyl ether solutions of **4** at −20°, followed by controlled removal of low boiling components, afforded no volatile product other than solvent. In the presence of powdered potassium *tert*-butoxide in tetrahydrofuran at room temperature, however, **4** reacted readily to give not **1** but β-*tert*-butoxydicyclopropyl sulfone (**7**). The presence in **7** of the indicated β substituent is clearly revealed by the combination of a one-proton multiplet at δ 3.81, a two-proton multiplet at 2.20–2.70, a five-proton multiplet in the 0.80–1.70 region, and a sharp singlet (9 H) at 1.30.

It follows from these observations that **4** is particularly resistant to the α-halo sulfone rearrangement. Instead, potassium *tert*-butoxide is seen to promote dehydrochlorination to cyclopropene **6** and subsequent Michael addition of liberated *tert*-butyl alcohol to this reactive intermediate.[7] The inability of **4** to undergo

(1) This is paper XVI in the series entitled "α-Halo Sulfones." For the previous paper, see L. A. Paquette and R. W. Houser, *J. Amer. Chem. Soc.*, **93**, 944 (1971).

(2) NDEA Fellow, 1967–1970.

(3) L. Ramberg and B. Bäcklund, *Ark. Kemi, Mineral. Geol.*, **13A**, 27 (1940); *Chem. Abstr.*, **34**, 4725 (1940).

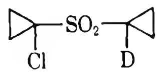
(4) For comprehensive reviews of this subject, see (a) L. A. Paquette, *Accounts Chem. Res.*, **1**, 209 (1968); (b) L. A. Paquette, *Mech. Mol. Migr.*, **1**, 121 (1968); (c) F. G. Bordwell, "Organosulfur Chemistry," M. J. Janssen, Ed., Interscience, New York, N. Y., 1967, Chapter 16.

(5) (a) L. A. Paquette, *J. Amer. Chem. Soc.*, **86**, 4383 (1964); (b) N. P. Neureiter, *J. Org. Chem.*, **30**, 1313 (1965); (c) L. A. Paquette and J. C. Philips, *Tetrahedron Lett.*, 4645 (1967); (d) E. J. Corey and E. Block, *J. Org. Chem.*, **34**, 1233 (1969); (e) L. A. Paquette and R. W. Houser, *J. Amer. Chem. Soc.*, **91**, 3870 (1969); (f) L. A. Paquette and J. C. Philips, *Chem. Commun.*, 680 (1969); (g) L. A. Paquette and J. C. Philips, *J. Amer. Chem. Soc.*, **91**, 3973 (1969); (h) R. E. Wingard and R. W. Houser, *ibid.*, in press.

(6) (a) W. R. Moore and H. Ward, *J. Org. Chem.*, **25**, 2073 (1960); (b) B. du Laurens, A. Bezaguet, G. Davidovics, M. Bertrand, and J. Chouteau, *Bull. Soc. Chim. Fr.*, 799 (1967); (c) J. K. Crandall, D. R. Paulson, and C. A. Burnel, *Tetrahedron Lett.*, 4217 (1969); (d) P. Le Perchec and J. M. Conia, *ibid.*, 1587 (1970).

(7) A number of reports have appeared in which dehydrohalogenation of halo- and dihalocyclopropanes to cyclopropene intermediates has been achieved in somewhat analogous fashion: (a) T. C. Shields and P. D. Gardner, *J. Amer. Chem. Soc.*, **89**, 5425 (1967); (b) S. W. Tobey and R. West, *ibid.*, **88**, 2478 (1966); (c) K. B. Wiberg, R. K. Barnes, and J. Albin, *ibid.*, **79**, 4994 (1957); (d) T. C. Shields, B. A. Loving, and P. D. Gardner, *Chem. Commun.*, 556 (1967).

transposition to bicyclopropylidine (**1**) cannot be rationalized on the basis of an insufficient concentration of α-sulfonyl carbanion. Evidence is available that cyclopropyl sulfones possess acidity nearly equal to that of related acyclic structures.[8] In the present work, **4** was found to undergo ready hydrogen–deuterium exchange in $NaOCH_3$–CH_3OD to give **8**.



8

This is tantamount to surmising that the energy barrier is encountered in the requisite intramolecular nucleophilic displacement of chloride ion. This conclusion would seem warranted in view of the established unreactivity of cyclopropyl halides and sulfonate esters toward displacement reactions, due to the adverse hybridization characteristics of external bonds attached to three-membered rings[9] (I strain).[10] A consequence of this conclusion is that molecules such as α-chlorocyclohexyl cyclopropyl sulfone might be expected to afford the corresponding methylenecyclopropane when treated with base because the I strain factor has now been eliminated. This point remains to be tested.

Experimental Section

Dicyclopropyl Sulfone (3).—A 1.6 *M* hexane solution of *n*-butyllithium (130 ml, 0.21 mol) was added dropwise under a nitrogen atmosphere to a solution of 20.0 g (0.092 mol) of γ,γ'-dichlorodipropyl sulfone (**2**)[11] in 250 ml of anhydrous tetrahydrofuran. After stirring the yellow solution at room temperature for 1 hr, the solvent was removed *in vacuo* and the residue was taken up in 100 ml of water and 100 ml of methylene chloride. The water phase was extracted with methylene chloride (two 50-ml portions) and the combined organic layers were dried, filtered, and evaporated. Crystallization of the residual oil from ethanol at $-10°$ afforded 11.1 g (84.5%) of **3** as white crystals: mp 69–70°; $\nu_{max}^{CHCl_3}$ 1323, 1287, and 1135 cm^{-1}.

Anal. Calcd for $C_6H_{10}O_2S$: C, 49.29; H, 6.89; S, 21.93. Found: C, 49.25; H, 6.92; S, 21.71.

Chlorination of 3.—To a solution of 2.0 g (13.7 mmol) of **3** in 150 ml of anhydrous tetrahydrofuran at room temperature under a nitrogen atmosphere was added 9.5 ml (15.0 mmol) of 1.6 *M* *n*-butyllithium in hexane. After 15 min, this solution was added dropwise to a stirred slurry of 10.0 g (75.0 mmol) of *N*-chlorosuccinimide in 250 ml of tetrahydrofuran cooled to 0° under a nitrogen atmosphere. The mixture was stirred at room temperature for 2 hr, filtered, and concentrated *in vacuo*. The resultant semisolid was triturated with 100 ml of methylene chloride and filtered. The filtrate was washed with 10% sodium hydroxide solution (three 100-ml portions) and water, dried, and evaporated to give an oil which was chromatographed on silica gel. Elution with ether–petroleum ether mixtures of increasing polarity caused **5** to be eluted first, 180 mg (6.1%). This dichloro sulfone was obtained as colorless crystals: mp 76–77°, from ether–petroleum ether; $\nu_{max}^{CHCl_3}$ 1325 and 1120 cm^{-1}.

Anal. Calcd for $C_6H_8Cl_2O_2S$: C, 33.47; H, 3.75; S, 14.91. Found: C, 33.43; H, 3.81; S, 14.83.

The less rapidly eluted product was identified as **4**, 660 mg (26.8%). Molecular distillation of the initial oil at 70° (0.05 mm) afforded a crystalline distillate, recrystallization of which from ethyl acetate–hexane afforded a white solid: mp 46–47°; $\nu_{max}^{CHCl_3}$ 1323, 1300, and 1130 cm^{-1}.

Anal. Calcd for $C_6H_9ClO_2S$: C, 39.89; H, 5.02; S, 17.75. Found: C, 39.89; H, 5.04; S, 17.25.

Continued elution afforded 330 mg (16.5%) of recovered **3**.

***β-tert*-Butoxydicyclopropyl Sulfone (7).**—To a solution of 1.13 g (6.25 mmol) of **4** in 4 ml of anhydrous tetrahydrofuran cooled to 0° under a nitrogen atmosphere was added 2.0 g (18.0 mmol) of powdered potassium *tert*-butoxide in small portions. The resulting mixture was stirred at ambient temperature for 3 hr and then concentrated by distillation with the aid of a nitrogen stream. The distillate was collected in a trap cooled in Dry Ice–acetone, analyzed by gas chromatography, and found to contain only tetrahydrofuran and *tert*-butyl alcohol. The residue was treated with 25 ml of water and 25 ml of ether. The ether layer was separated, dried, and evaporated. Molecular distillation of the resultant oil at 95–98° (0.05 mm) gave 1.12 g (82.3%) of **7** as a colorless liquid: $\nu_{max}^{CHCl_3}$ 1315, 1295, and 1140 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}O_3S$: C, 55.01; H, 8.31; S, 14.69. Found: C, 55.24; H, 8.49; S, 14.59.

Deuterium Exchange of 4.—A solution of 205 mg (1.4 mmol) of **4** and sodium methoxide (prepared from 206 mg of Na) in 5 ml of CH_3OD was heated at reflux for 6 hr, cooled, and quenched by the addition of 1 ml of deuterioacetic acid. The solvent was removed *in vacuo* and the residue was taken up in 25 ml of methylene chloride and 25 ml of water. The organic layer was dried, filtered, and evaporated to yield 150 mg of **8**: $\delta_{TMS}^{CDCl_3}$ 1.76 (m, 2 H), 1.47 (m, 2 H), 1.18 (m, 4 H), and no visible absorption at 2.70.

Registry No.—**4**, 27531-50-6; **5**, 27531-51-7; **7**, 27531-52-8.

Acknowledgment.—The authors wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their partial support of this research.

(8) (a) R. Breslow, J. Brown, and J. J. Gajewski, *J. Amer. Chem. Soc.*, **89**, 4383 (1967); (b) A. Ratajczak, F. A. L. Anet, and D. J. Cram, *ibid.*, **89**, 2072 (1967); (c) H. E. Zimmerman and B. S. Thyagarajan, *ibid.*, **82**, 2505 (1960).

(9) J. D. Roberts and V. C. Chambers, *ibid.*, **73**, 5034 (1951).

(10) H. C. Brown and M. Gerstein, *ibid.*, **72**, 2926 (1950).

(11) G. M. Bennet and A. L. Hock, *J. Chem. Soc.*, **127**, 2673 (1925).

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 preparation of ribonucleoside ketals

Bis(p-Nitrophenyl)Hydrogen Phosphate (EASTMAN 10523)

Bis(p-nitrophenyl)hydrogen phosphate is superior to p-toluenesulfonic acid as a catalyst for the preparation of acetonide—and other ketal derivatives of ribonucleosides. Superiority is partly due to the lipophilic area of bis(p-nitrophenyl)hydrogen phosphate, which is twice that of p-toluenesulfonic acid, so its nucleoside salts are correspondingly more soluble in acetone. Reaction of adenosine, the catalyst, acetone, and 2,2-dimethoxypropane (water scavenger) yields 85 to 95% adenosine-2′,3′-acetonide in 1 to 3 hours. [*J.A.C.S., 83,* 3640 (1961), *Biochem. Prepn., 10,* 91 (1963), and *J.A.C.S., 87,* 5481 (1965)].

For oxidation of alcohols

Pyridine Dichromate (EASTMAN 11269)

Pyridine dichromate as a replacement for chromium trioxide-pyridine complex in the oxidation of alcohols gives superior or comparable aldehyde yields, is stable, and safer. The reagents are compared for the oxidation of several common alcohols, and of 6β-methyl-17α-(1-propynyl)androstane-3β,5α,17β-triol to the corresponding 3-oxo steroid. [*Chem. & Ind.,* 1594 (1969)].

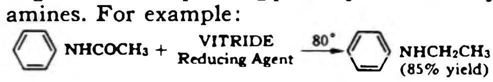
For protein synthesis and analysis

- N-tert.-Butoxycarbonyl-L-(−)-methionine Dicyclohexylamine Salt (EASTMAN 11287)
- S-Benzyl-L-(+)-cysteine (EASTMAN 11060)
- N-Acetyl-L-(+)-tyrosine Ethyl Ester (EASTMAN 11298)
- N-Acetyl-DL-tryptophan p-Nitrophenyl Ester (EASTMAN 11404)
- O-tert.-Butyl S-phenylthiocarbonate (EASTMAN 11366): Precursor for preparation of t-BOC amino acids.
- p-(Hydroxymercuri)benzoic Acid Sodium Salt (EASTMAN 5085): Sulfhydryl inhibitor.
- 4-p-Dimethylaminophenylazophenylmercuric Acetate (EASTMAN 11378): Reagent for protein sulfhydryl determination.
- Phenyl Chlorothioformate (EASTMAN 11272): N-blocking reagent for amino acids.
- Methyl Isothiocyanate (EASTMAN 13111): For protein sequenation.
- Chloromethyl Isobutyl Ether (EASTMAN 11297): S-protecting reagent for sulfhydryl amino acids and peptides.
- 2-[(p-Nitrophenyl)thio]ethanol (EASTMAN 11338): Reagent for amino acid carboxy-group protection.
- Chloromethylated Polystyrene: 2% Divinyl Benzene Copolymer Beads (EASTMAN 11264): for solid-phase peptide synthesis.

VITRIDE™ Reducing Agent [Sodium Bis(2-methoxyethoxy)aluminum Hydride (70% in Benzene)] REACTION OF THE MONTH

Reduction of amides, oximes, and nitriles

AMIDES: Nonsubstituted or monosubstituted amides react with VITRIDE Reducing Agent to give the corresponding primary or secondary amines. For example:

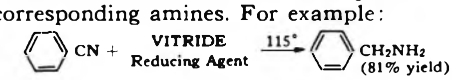


N,N-disubstituted amides such as aralkyl or diaryl amides react with cleavage of the nitrogen-carbonyl bond to give alcohols.

OXIMES: Being carbonyl-group derivatives, oximes are reduced to the corresponding amine in good yield as shown:

$$CH_3(CH_2)_2CH{=}NOH + \underset{\text{Reducing Agent}}{\text{VITRIDE}} \xrightarrow{80^\circ} CH_3(CH_2)_3NH_2 \ (79\% \text{ yield})$$

NITRILES: Aliphatic nitriles do not react with VITRIDE Reducing Agent, and arylaliphatic nitriles do so only poorly. However, nitrile groups attached directly to an aromatic nucleus are reduced in excellent yield to the corresponding amines. For example:



Details on VITRIDE Reducing Agent and its capabilities are found in Volume 43, No. 3, of the EASTMAN Organic Chemical Bulletin. *Please use the coupon below to request your copy.*

VITRIDE is a trademark of National Patent Development Corp. Manufactured by Realco Chemical Co. Available as EASTMAN 13112.

For a copy of the current EASTMAN Organic Chemicals Catalog, listing more than 6,000 reagents, and to receive periodic supplements to it automatically, simply complete and return the coupon. All of these new chemicals are available from the dealer in EASTMAN Organic Chemicals nearest you.

B&A	NORTH-STRONG	SCICHEMCO
CURTIN	PREISER	WILL/VW&R
FISHER	SARGENT-WELCH	

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"
☐ Send JJ-60-703, "EASTMAN Organic Chemical Bulletin"

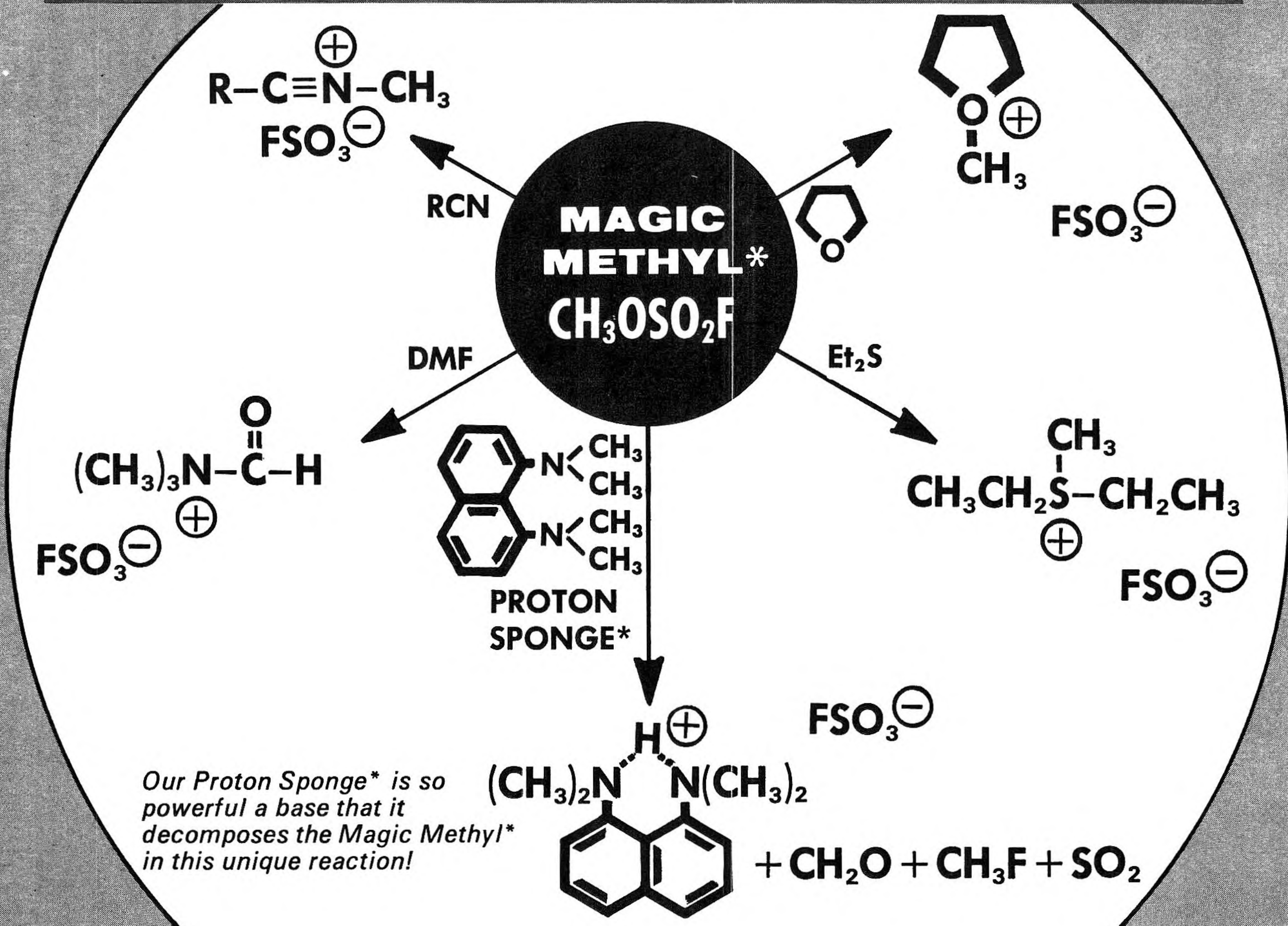
Name ______
Address ______
City ______
State ______ Zip ______ 4-86

Kodak

MAGIC METHYL*

(Methyl fluorosulfonate)

. . . an easily handled, most powerful alkylating agent



Alder, et al.[1] have shown that "Magic Methyl*" far surpasses the conventional alkylating agents in reactivity. A number of functional groups react with this reagent and the reactions are easily followed by ^{1}H and ^{19}F n.m.r.

The fact that amines[1] quaternize exothermically is not too surprising but amides[1] (eg DMF) and carbamates[2] are also readily alkylated. These compounds *instantly* undergo kinetically controlled O-methylation but can be equilibrated so that the N-methylated product is *highly favored.* Such amide salts should be easily hydrolyzed to give tertiary amines. At room temperature nitriles[1] readily yield nitrilium salts which can be reduced[3] with $NaBH_4$ to yield secondary amines. Sulfoxides[1] yield O-alkylated products and sulfides[4] give sulfonium salts which can be used synthetically[5] to form carbon-carbon bonds *via* the Stevens rearrangement. Most ethers[1] form oxonium salts but esters[1] only undergo exchange to yield methyl esters.

The physical organic chemist will find "Magic Methyl" to be an excellent probe for comparing nucleophilicity and basicity toward methyl groups. The synthetic chemist will find that "Magic Methyl" readily yields salts which, for example, can serve as leaving agents for the synthesis of olefins and acetylenes or the study of neighboring group effects.

1. M. G. Ahmed, R. W. Alder, G. H. James, M. L. Sinnott and M. C. Whiting, Chem. Comm., *1968*, 1533.
2. M. G. Ahmed and R. W. Alder, Chem. Comm., *1969*, 1389.
3. R. F. Borch, Chem. Comm., *1968*, 442.
4. R. W. Alder, private communication.
5. R. H. Mitchell and V. Boekelheide, Tetrahedron Letters, *1970*, 1197.

* *Trademark of Aldrich Chemical Co.*

#16,048-2 Magic Methyl* (methyl fluorosulfonate) 100g.-$14.00

#15,849-6 Proton Sponge* (1,8-Bis-(dimethylamino)-naphthalene) 10g.-$ 6.75 50g.-$22.50

For our new Catalog #15 write to—

ALDRICH

Aldrich Chemical Company, Inc.

CRAFTSMEN IN CHEMISTRY

940 WEST SAINT PAUL AVENUE · MILWAUKEE, WISCONSIN 53233

■ 4 5.8. 2514