VOLUME 42 DECEMBER 23, 1977 NUMBER 26 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

Published by the
AMERICAN CHEMICAL SOCIETY

BOOKS AND JOURNALS DIVISION

D. H. Michael Bowen, *Director;* Marjorie Laflin, *Assistant to the Director*

Editorial Department: Charles R. Bertsch, Head; Marianne C. Brogan, Associate Head; Mark Hackworth, Robert J. Palangio, and Kenneth E. Phillips, Editorial Assistants

Magazine and Production Department: Bacil Guiley, Head

Research and Development Department: Seldon W. Terrant, Head

Advertising Office: Centcom, Ltd., 25 Silvan Road South, Westport, Conn. 06880.

Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second class postage paid at Washington, D.C., and at additional mailing offices.

Editorial Information

Instructions for authors are printed in the first issue of each volume. Please conform to these instructions when submitting manuscripts.

Manuscripts for publication should be submitted to the Editor, Frederick D. Greene, at his Cambridge, Mass., address.

Correspondence regarding **accepted papers and proofs** should be directed to the Editorial Department at the address below.

Page charges of $70.00 per page may be paid for papers published in this journal. Payment does not affect acceptance or scheduling of papers.

Bulk reprints or photocopies of individual articles are available. For information write to Business Operations, Books and Journals Division, at the ACS Washington address.

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

Subscription and Business Information

1978 subscription prices—including surface postage:

	U.S.	Foreign
Member	$26.00	$36.00
Nonmember	104.00	114.00
Supplementary material	20.00	38.00

Air mail and Air freight rates are available from Membership & Subscription Services, at the address below.

New and renewal subscriptions should be sent with payment to the Office of the Controller at the ACS Washington address.

Changes of address must include both old and new addresses with ZIP code and a recent mailing label. Send all address changes to the Membership & Subscription Services. Please allow 6 weeks for change to become effective. **Claims for missing numbers** will not be allowed if loss was due to failure of notice of change of address to be received in the time specified; if claim is dated, (a) North America: more than 90 days beyond issue date, (b) all other foreign: more than one year beyond issue date; or if the reason given is "missing from files". Hard copy claims are handled by Membership & Subscription Services.

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

Single issues and back volumes in printed or microfiche are available at the same price for either format from Special Issues Sales. Current year single issue $5.00. Prior year single issue $5.00. Back volume $115.00. Foreign postage additional. Rates available from Special Issues Sales at the ACS Washington address or call (202) 872-4365.

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

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

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

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

Editorial Department
American Chemical Society
P.O. Box 3330
Columbus, Ohio 43210
(614) 421-6940, Ext. 2171

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

Notice to Authors printed in this issue

JOCEAH 42(26) 4173–4350 (1977)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 26 DECEMBER 23, 1977

NOTES

COMMUNICATIONS

■ Supplementary material for this paper is available separately (consult the masthead page for ordering information); it will also appear following the paper in the microfilm edition of this journal.

* In papers with more than one author, the asterisk indicates the name of the author to whom inquiries about the paper should be addressed.

AUTHOR INDEX

PUBLISHER'S NOTE

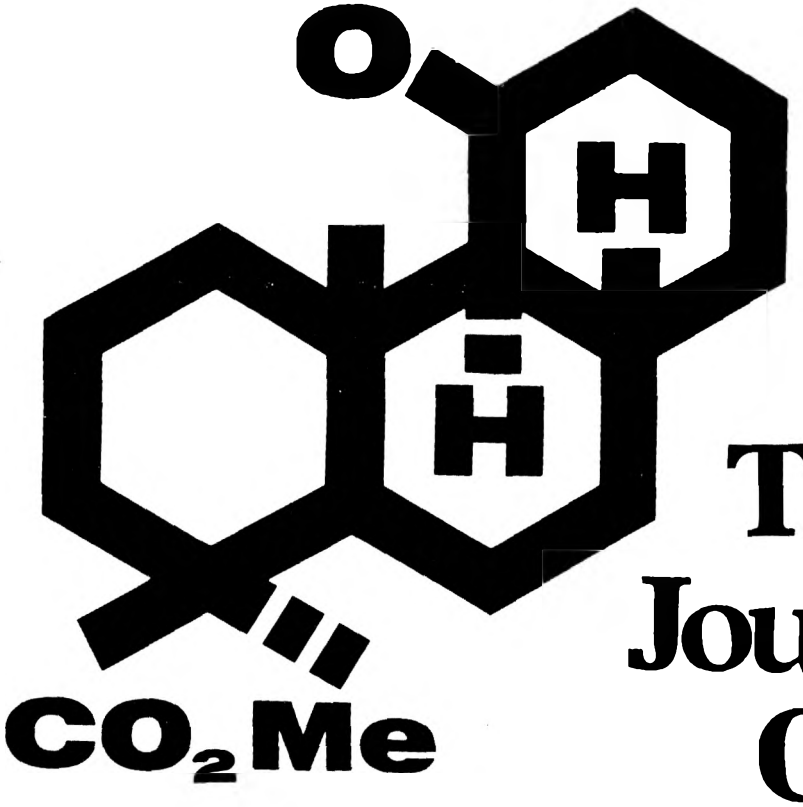
To conform to provisions of U.S. copyright law effective January 1, 1978, the American Chemical Society is instituting new procedures.

Contributors and readers will notice two changes:

(1) Authors will be required to transfer copyright to ACS by means of a simple form. The relationship between the Society and the author will remain unchanged, however, since under prior copyright law ACS has in fact been the copyright owner of individual articles.

(2) Issues published after 1/1/78 will have a multiple-digit code at the foot of the first page of most articles. This code signifies ACS participation in the not-for-profit Copyright Clearance Center. Operation of the Center will permit libraries and other institutions to reproduce legally and without delay journal articles beyond "fair use" as described in the new law and accompanying guidelines.

Questions on the new copyright law or ACS procedures may be addressed to the Office of the Director, Books and Journals Division, American Chemical Society, 1155 16th Street, N.W., Washington, D.C. 20036, or call (202) 872-4556 or -4367.



Reactions, natural products, mechanisms, theory and spectroscopy covered comprehensively in

The Journal of Organic Chemistry

Recognized by many organic chemists as the leading American journal in the field, this biweekly publication brings subscribers over 1,000 articles, notes and communications each year—over 4,000 pages including original contributions on fundamental researches in all branches of the theory and practice of organic chemistry. Improved procedures, accounts of novel observations or compounds of special interest are also noted. Complete and mail the coupon NOW to join the thousands of organic chemists who find this journal vital in keeping current in the field.

AVAILABLE IN HARD COPY OR MICROFICHE.

The Journal of Organic Chemistry
American Chemical Society **1978**
1155 Sixteenth Street, N.W.
Washington, D.C. 20036

Yes, I would like to receive THE JOURNAL OF ORGANIC CHEMISTRY at the one-year rate checked below:

	U.S.	All Other Countries
ACS Member*	☐ $26.00	☐ $36.00
Nonmember	☐ $104.00	☐ $114.00

Bill me ☐ Bill company ☐ Payment enclosed ☐

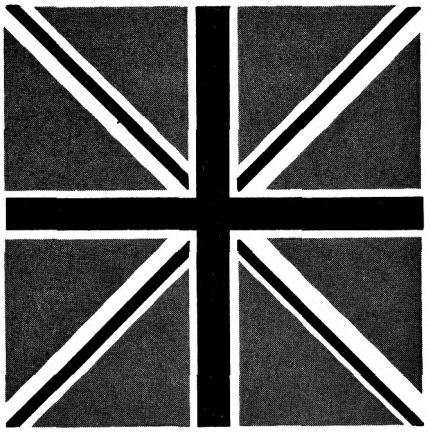
Air freight rates available on request.

Name _____

Street _____ Home ☐ Business ☐

City _____ State _____ Zip _____

Journal subscriptions start in January '78.
Allow 60 days for your first copy to be mailed.
*NOTE: Subscriptions at ACS member rates are for personal use only.



SPECIALIST PERIODICAL REPORTS published by The Chemical Society

This outstanding series provides critical and comprehensive coverage of the latest progress in major areas of chemical research. Each field is examined in depth by foremost authorities on the subject making each volume an essential resource for the specialist chemist as well as for the newcomer seeking an introduction to the state of the art.

Titles from the series currently available:

Aliphatic Chemistry, Vol. 3
Senior Reporter: A. McKillop
409 pages Cloth (1975) $37.25

Alicyclic Chemistry, Vol. 3
Senior Reporter: Prof. W. Parker
Reviews 1973 literature
581 pages Cloth (1975) $66.00

Saturated Heterocyclic Chemistry, Vol. 3
Senior Reporter: M. F. Ansell
Examines literature published during 1973
301 pages Cloth (1975) $35.75

The Alkaloids, Vol. 5
Senior Reporter: Dr. J. E. Saxton
303 pages Cloth (1975) $48.25

Amino-acids, Peptides, and Proteins, Vol. 6
Senior Reporter: Dr. R. C. Sheppard
A review of the 1973 literature on amino-acids
525 pages Cloth (1974) $45.50

Aromatic and Heteroaromatic Chemistry, Vol. 3
Senior Reporters: Dr. C. W. Bird and Dr. G. W. H. Cheeseman
July 1973 to June 1974 literature surveys ring systems
503 pages Cloth (1975) $55.00

Biosynthesis, Vol. 3
Senior Reporter: Prof. T. A. Geissman
293 pages Cloth (1975) $30.25

Carbohydrate Chemistry, Vol. 7
Senior Reporter: Prof. J. S. Brimacombe
A review of the literature published during 1973
626 pages Cloth (1975) $60.50

Chemical Thermodynamics, Vol. 1
Senior Reporter: Prof. M. L. McGlashan
362 pages Cloth (1973) $30.25

Colloid Science, Vol. 2
Senior Reporter: Prof. D. H. Everett
(1972-74 literature)
333 pages Cloth (1976) $49.50

Dielectric and Related Molecular Processes, Vol. 2
Senior Reporter: Prof. Mansel Davies
291 pages Cloth (1975) $35.75

Electrochemistry, Vol. 5
Senior Reporter: Prof. H. R. Thirsk
370 pages Cloth (1975) $46.75

Electron Spin Resonance, Vol. 2
Senior Reporter: Prof. R. O. C. Norman
349 pages Cloth (1974) $29.00

Electronic Structure and Magnetism of Inorganic Compounds, Vol. 3
Senior Reporter: Dr. P. Day
1972 and early 1973 literature
433 pages Cloth (1974) $38.50

Environmental Chemistry, Vol. 1
Senior Reporter: G. Eglinton
199 pages Cloth (1975) $22.00

Fluorocarbon and Related Chemistry, Vol. 2
Senior Reporters: Dr. R. E. Banks and Dr. M. G. Barlow
491 pages Cloth (1974) $44.00

Foreign Compound Metabolism in Mammals, Vol. 3
Senior Reporter: D. E. Hathway
727 pages Cloth (1975) $71.50

Inorganic Chemistry of the Main Group Elements, Vol. 2
Senior Reporter: Prof. C. C. Addison
September 1972 to September 1973 literature
726 pages Cloth (1974) $66.00

Inorganic Chemistry of the Transition Elements, Vol. 3
Senior Reporter: Dr. B. F. G. Johnson
(1972-73 literature)
512 pages Cloth (1974) $41.25

Inorganic Reaction Mechanisms, Vol. 3
Senior Reporter: Dr. J. Burgess
December 1971 to June 1973 literature
500 pages Cloth (1973) $38.50

Mass Spectrometry, Vol. 3
Senior Reporter: R. A. W. Johnstone
402 pages Cloth (1975) $37.25

Molecular Spectroscopy, Vol. 3
Senior Reporters: Prof. D. A. Long, Prof. D. J. Millen, Dr. R. F. Barrow
(1973-74 literature)
602 pages Cloth (1975) $66.00

Molecular Structure by Diffraction Methods, Vol. 3
Senior Reporters: Prof. G. A. Sim and Dr. L. E. Sutton
514 pages Cloth (1975) $71.50

Nuclear Magnetic Resonance, Vol. 4
Senior Reporter: Dr. R. K. Harris
340 pages Cloth (1975) $42.75

Organic Compounds of Sulphur, Selenium, and Tellurium, Vol. 3
Senior Reporter: D. H. Reid
805 pages Cloth (1975) $68.75

Organometallic Chemistry, Vol. 4
Senior Reporters: Prof. E. W. Abel and Prof. F. G. A. Stone
530 pages Cloth (1975) $74.25

Organophosphorus Chemistry, Vol. 6
Senior Reporter: Prof. S. Trippett
285 pages Cloth (1975) $30.25

Photochemistry, Vol. 6
Senior Reporter: Prof. D. Bryce-Smith
Literature published between June 1973 and June 1974.
796 pages Cloth (1975) $75.75

Radiochemistry, Vol. 2
Senior Reporter: Dr. G. W. A. Newton
248 pages Cloth (1975) $35.75

Reaction Kinetics, Vol. 1
Senior Reporter: P. G. Ashmore
396 pages Cloth (1975) $40.00

Spectroscopic Properties of Inorganic and Organometallic Compounds, Vol. 8
Senior Reporter: Prof. N. N. Greenwood
550 pages Cloth (1975) $68.75

Statistical Mechanics, Vol. 2
Senior Reporter: Prof. K. Singer
(1974 literature)
336 pages Cloth (1976) $49.50

Surface and Defect Properties of Solids, Vol. 4
Senior Reporters: Prof. M. W. Roberts and Prof. J. M. Thomas
(Recent literature up to April 1974)
255 pages Cloth (1975) $38.50

Terpenoids and Steroids, Vol. 5
Senior Reporter: Dr. K. H. Overton
A review of the literature published between September 1973 and August 1974
390 pages Cloth (1975) $57.75

Theoretical Chemistry, Vol. 2
Senior Reporter: Prof. R. N. Dixon
200 pages Cloth (1975) $27.50

For a description of contents and listing of all volumes please write the American Chemical Society, Books Department at the address listed below.

Special Issues Sales/American Chemical Society
1155 16th St., N.W./Washington, D.C. 20036

Title	No. Copies	Price
	Total	

☐ Enclosed is my check for $ _____ ☐ Bill me
Postage at 40 cents per copy if other than U.S. or Canada.

Name _____

Address _____

City _____ State _____ Zip _____

Tape Recordings for Lab Professionals

☐ **TLC—Best for Drug Abuse Screening**
Low-cost alternative to immunoassays

☐ **Microcomputers in Biochemistry Research**
New computers make possible hitherto impossible measurements

☐ **Data Analysis in the Lab**
Today and tomorrow in chem lab data analysis methods

☐ **Use of Enzymes in Immunology**
Detection of bound and free antigen without separation

☐ **Elemental Analysis of Blood: Cancer Patients & Controls**
Detailed comparisons, plus evaluation of analytical methods used

☐ **Polarographic Analysis in Drug Development**
D.P.P. assays of drugs in biological fluids

☐ **Bioanalysis with Membrane Electrode Probes**
Recent advances in electrode development

☐ **In Vivo Electrochemistry for Monitoring Drugs**
Reveals drug's chemical fate in the brain

☐ **Detection of Lipids & Amines in Biological Samples**
Chemical ionization mass spec speeds assay of closely related chemicals

☐ **Pulse Polarography Analysis in Environmental Toxicology**
Solves tough problems in human and animal poisoning

☐ **New Developments in Measurement of Proteins**
Light scattering of immune complexes provides a specific method for proteins in body fluids

☐ **Direct Determination of Drugs in Plasma & Urine**
Non-chromatographic procedure uses chemical ionization mass spec & stable isotope labeling

☐ **DSC: New Developments in Clinical Analysis**
Differential Scanning Calorimetry—a new analytical tool

☐ **Serum Electrolytes Using Vidicon Flame Spectrometry**
Fast, simultaneous determination of sodium, potassium, and calcium

☐ **Enthalpimetric Analysis of Immunological Reactions**
Thermometric enthalpy titration may revolutionize serological analysis

☐ **Clinical Application of Titration Calorimetry**
Thermochemical methods look very promising for clinical work

☐ **GC Determination of Apomorphine in Urine**
Study of apomorphine metabolism

☐ **Metals in Liver & Kidney Tissue by AA**
AA determination of copper, zinc, magnesium, and calcium

☐ **Bromazepam in Blood by Electron Capture GLC**
A sensitive, specific assay

☐ **Drug Analysis by Direct Multiple-Ion Detection**
Unique computerized system analyses drugs without use of GC

☐ **Thermochemical Analysis in Clinical Chemistry**
Total protein content in biological material can be determined with a precision of better than 0.6%

☐ **Amperometric Measurement of Enzyme Reactions**
Enzyme reactions are monitored by amperometric measurement of substrate depletion, product formation

☐ **Homovanillic Acid by GC-MS**
A simple procedure for HVA in urine

☐ **Kinetic Assay of Enzyme Activity**
Centrifugal fast analyzer provides data at output rate suitable for direct input into small computer

☐ **Automated Photochemical Analysis of Phenothiazines**
Samples were assayed by this system at the rate of 20 per hour

☐ **Automation in Clinical Medicine**
A Bureau of Standards colloquium

☐ **Analysis of Trace Elements**
Sensitive, reliable analytical methods are needed for trace elements

☐ **Electrochemical Approaches to Clinical Instrumentation**
Precise, accurate, highly specific analyses using ultramicro samples

☐ **Standardization of Protein & Enzyme Assays**
Biuret reaction as standard for measuring total serum protein

☐ **Pharmacologic Studies Using GC-MS**
Utility of GC-MS is emphasized in a report of two pharmacologic studies

☐ **Method Evaluation Studies in Clinical Analyses**
Method evaluation studies on precision and accuracy of lab methods

ORDER FROM:
American Chemical Society
1155 16th St., N.W.
Washington, D.C. 20036
ATTN: Dept. AP

PRICE: $8.95 per title, includes visual materials. CASSETTES ONLY CHECK TITLES DESIRED
(Allow 4 to 6 weeks for delivery)

Name _____

Address _____

THE JOURNAL OF Organic Chemistry

Volume 42, 1977
JOCEAH 42(1–9) 1–1670 (1977)
ISSN 0022-3263

JANUARY–APRIL

THE JOURNAL OF Organic Chemistry

Volume 42, 1977
JOCEAH 42(10–17) 1671–2952 (1977)
ISSN 0022-3263

MAY–AUGUST

THE JOURNAL OF Organic Chemistry

Volume 42, 1977
JOCEAH 42(18-36) 2953-4350 (1977)
ISSN 0022-3263

SEPTEMBER-DECEMBER

AMERICAN CHEMICAL SOCIETY, BOOKS AND JOURNALS DIVISION
D. H. Michael Bowen, *Director*

Charles R. Bertsch, *Head, Editorial Department*
Bacil Guiley, *Head, Magazine and Production Department*
Seldon W. Terrant, *Head, Research and Development Department*

Robert J. Palangio and Kenneth E. Phillips, *Editorial Assistants*

THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 26

DECEMBER 23, 1977

Host–Guest Complexation. 7. The Binaphthyl Structural Unit in Host Compounds[1,2]

Evan P. Kyba,[3a] George W. Gokel, Feike de Jong,[3b] Kenji Koga,[3c] Lynn R. Sousa,[3d] Merrell G. Siegel, Lester Kaplan, G. Dotsevi Y. Sogah,[3e] and Donald J. Cram*

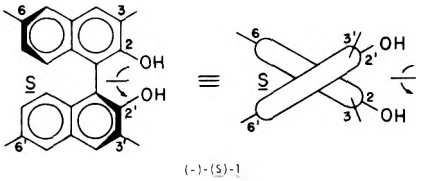
Contribution No. 3833 from the Department of Chemistry, University of California at Los Angeles, Los Angeles, California 90024

Received June 6, 1977

Reported here are the resolutions, optical stabilities, and maximum rotations of the enantiomers of 2,2′-dihydroxy-1,1′-binaphthyl (1), whose absolute configurations are known [(+)-1 is (*R*)-1]. Enantiomers, racemates, and meso forms of macrocycles have been prepared that are held together by ether linkages composed *formally* by the loss (of the elements) of water from the following units: 2,2′-dihydroxy-1,1′-binaphthyl (A); 2,2′-dihydroxy-1,1′-biphenyl (B); ethylene glycol (D); catechol (E); pentamethylenediol (F); *cis*-2,5-bis(hydroxymethyl)tetrahydrofuran (G); 1,3-bis(hydroxymethyl)benzene (J); 2,6-bis(hydroxymethyl)pyridine (K). The ring closures all involved base-catalyzed substitution by ArO^- on RCl, RBr or ROTs. In general, the larger the number of bonds made to produce a cycle in a single reaction mixture, the poorer the yield. When six bonds were made, yields were as low as 0.4%, with four, yields were usually 10–20%, with two, yields were about 45–60%. Pure enantiomers and/or diastereomers are reported that possess structures represented by the following abbreviated formulas: B–D_5; A–D; A–D_2; A–D_3; A–D_4; A–D_5; A–K; A–K–A–K; A–D_2–A–D_2; A–D_2–E–D_2; A–D–A–D_3; A–D_2–A–K; A–D_2–A–J; A–D_2–A–G; A–D_2–A–F; A–F–A–K; A–J–A–K; A–D–A–D–A–D; A–D–A–D. In several cases, the same cycles were assembled by different synthetic routes, particularly A–D_2–A–D_2 and A–D–A–D–A–D. Although optically stable at 100 °C for 24 h in dioxane–water, (−)-1 racemized 72% with HCl (~1.2 N) present. It also racemized 69% at 118 °C for 23 h in 1-butanol–0.67 M in KOH. In oxygen-free diethylene glycol, (−)-A–D_2–A–D_2 underwent 0% rotational loss in 6 h and 8.6% in 202 h. The maximum rotations and absolute configurations of all macrocycles are reported. The symmetry properties and shapes of certain of the cycles are discussed. The diastereoisomeric racemates of A–D–A–D–A–D each gave a 1:1 equilibrium mixture of the two racemates when heated at 340 °C for 7 min.

Structural recognition in molecular complexation between organic entities depends on the complementary placement of binding sites and steric barriers in hosts and guests. Paper 1[4a] of this series dealt with the general phenomenon of complexation, and parts 2–5[4b-e] dealt with the location of binding sites in disk-shaped hosts which did not extend far into a third dimension. Paper 6[4f] described the use of the [2.2]paracyclophanyl unit, which when incorporated into hosts extends rigidly into a third dimension. The [2.2]-paracyclophane unit also provides points for attachment of convergent steric barriers that might shape the environment of the binding site.

This paper describes the syntheses and properties of hosts that contain as part of their major ring systems the 1,1′-binaphthyl group. The macrorings include oxygens attached at the 2,2′ positions of the binaphthyl group, and thus, 2,2′-dihydroxy-1,1′-binaphthyl (1) is the key starting material in the syntheses. Cycles containing a 2,2′-bisoxy-1,1′-binaphthyl unit rigidly extend in three dimensions in such a way as to place one naphthalene ring above and in a plane tangent to the macrocycle, and the second naphthalene below and tangent to the macrocycle. The planes of the naphthalene rings are perpendicular to the best plane of the macroring. The dihedral angle between the two naphthalene rings of 1 in Corey–Pauling–Koltun (CPK) molecular models appears capable of varying between extremes of about 60 and 120°. With an angle of about 75°, the two oxygens are located with respect to one another about the same as they are in gauche ethylene glycol.



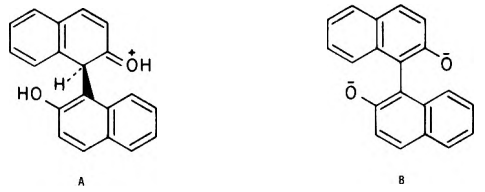
(−)-(S)-1

This binaphthyl unit possesses useful symmetry properties. It has a C_2 axis (indicated by the curved arrow with a horizontal line through it), and thus does not impart the unwanted property of "sidedness" to hosts. The unit is chiral, and the aryl rings are potential *chiral barriers* that should impart to hosts the property of *chiral recognition* toward appropriate guest compounds. The 3 and 3′ positions when substituted extend the chiral barriers, and the substituents are directed along the sides (above and below) of the macroring. The 6 and 6′ positions diverge from the binding sites of the macroring, and attached substituents can be used to manipulate solubility properties, or to bond hosts to solid supports. These structural

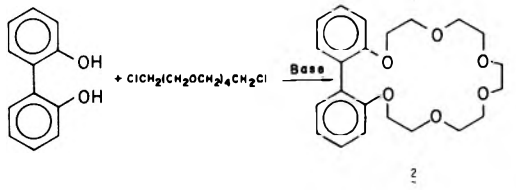
properties will be exploited in hosts described in this and subsequent papers.

Resolution, Absolute Configuration, Optical Purity, and Configurational Stability of 2,2′-Dihydroxy-1,1′-binaphthyl (1). The resolution of 1 through its mono-*l*-menthoxyacetic ester was in progress when the resolution of 1 through the cinchonine salt of its phosphate ester was reported.[5] The former method provided a maximum rotation for (−)-1 of $[\alpha]^{25}_D$ −33.6°,[6] whereas the latter and superior method gave $[\alpha]^{25}_D$ −33.9°[6] and $[\alpha]^{25}_D$ +33.8°[6] as maximum rotations for the two enantiomers. The absolute configurations of the enantiomers of 1 have been established by the x-ray method.[7] Although optically stable at 100 °C for 24 h in dioxane–water, (−)-(*S*)-1 racemized 72% under those conditions when the solution was 1.2 N in HCl. In butanol 0.67 M in KOH at 118 °C for 23 h, (−)-(*S*)-1 racemized 69%. These data set rough limits to the reaction conditions for converting (−)-(*S*)-1 or (+)-(*R*)-1 to other substances without loss of optical purity.

Molecular models (CPK) of 1 protonated or hydroxylated in either the 1 or 8 positions appear to offer less of a steric barrier to Ar–Ar rotation than that of 1 itself. Furthermore, the steric barrier is undoubtedly affected by the presence of charge that can be distributed in these positions. Possibly the acid-catalyzed racemization involves a transition state such as A, and the base-catalyzed a transition state such as B. Kinetic analyses and other mechanistic probes of the racemization should provide interesting results.

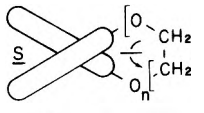


Synthesis of Systems Containing One Biaryl Unit. As a prototype reaction, 2,2′-dihydroxy-1,1′-biphenyl was treated with pentaethylene glycol ditosylate[4e,8] and sodium hydroxide in dioxane–butanol[9] to give **2** (12%). Higher yields of cycles



were obtained when (−)-(*S*)-1, (+)-(*R*)-1, or racemic 1 was treated with the various polyethylene glycol ditosylates [4e,8] in THF–*t*-BuOK under N_2 at reflux.

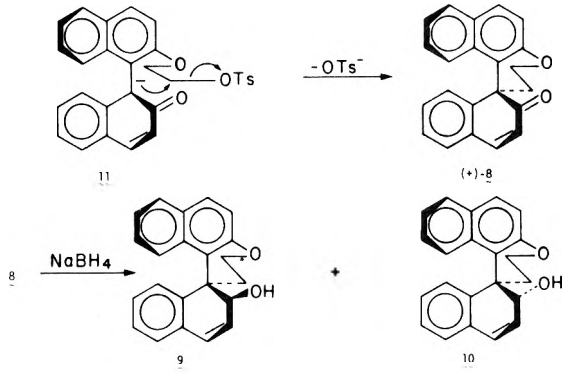
Cycles containing one binaphthyl and from one to five ethylene glycol units (**3**–**7**) were prepared from optically pure



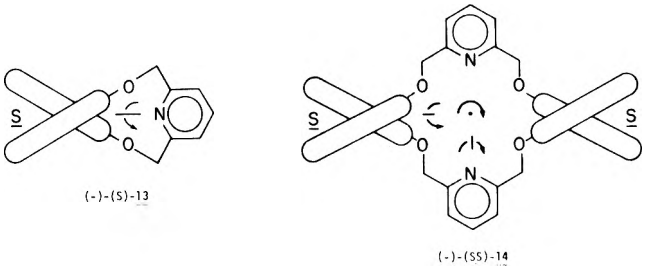
No.	n	%
(+)-(S)-3	1	23 (65)
(+)-(S)-4	2	2
(−)-(S)-5	3	65
(−)-(S)-6	4	52
(−)-(S)-7	5	64

(−)-(*S*)-1 or (+)-(*R*)-1 for studies of the ORD and CD spectra.[10] When heated in oxygen-free diethylene glycol (sealed tube) at 205 °C, (−)-(*S*)-**6** underwent 0% rotational loss in 6 h, and 9% in 202 h. Thus both starting material and product were optically stable to the reaction conditions, and the same is undoubtedly true for the other cycles reported here.

The reaction of racemic 1 with ethylene glycol ditosylate gave ketone **8** as the main product (44%, mp 198–200 °C), as well as 23% of **3** and higher oligomers. The Rast and mass spectral molecular weights of **3** differentiated it from its higher oligomers. The structure of ketone **8** was derived from its UV, IR, and ^{1}H NMR spectra.[11] When reduced with $NaBH_4$, racemic **8** gave a 20:1 ratio of the diastereomeric diols **9** and **10**, in which **9** is more likely to be the dominant isomer. Ketone **8** is the product of alkylation by ethylene glycol ditosylate of the oxygen of one ring of **1**, and of C-1′ of the other ring of **1**. Substitution of dimethylformamide (DMF) for THF as solvent in the reaction of **1** with ethylene glycol ditosylate gave a 65% yield of **3** and no detectable **8**. With (−)-(*S*)-1 as starting material, (+)-**8** was obtained (45%). The sharp melting point of (+)-**8** (187–188 °C) suggested that no racemization had occurred during formation and that the alkylation had occurred stereospecifically. Since (−)-(*S*)-1 owes its asymmetry to restricted rotation and (+)-**8** to the presence of an asymmetric carbon, the reaction represents an interesting example of conversion of torsional into atomic asymmetry. The configuration assigned to (+)-**8** arises reasonably from the configuration of (−)-(*S*)-**1**, and involves as intermediate the asymmetric carbanion **11**. Others have reported that 1-substituted 2-naphthol anions under anhydrous conditions alkylate at C-1.[12] The reactions leading to (+)-**8**, **9**, and **10** are formulated.

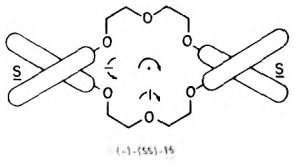


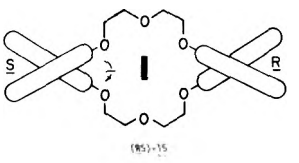
Syntheses of Systems Containing Two Binaphthyl Units. Treatment of (−)-(*S*)-1 with 2,6-bis(chloromethyl)-pyridine (**12**)[4c] in THF–*t*-BuOK produced both (−)-(*S*)-**13**



(not characterized) and (−)-(*S,S*)-**14** (26%). As CPK molecular models suggest should be the case, the two sets of β hydrogens on the pyridine rings of (−)-(*S,S*)-**14** are in different magnetic environments and have different ^{1}H NMR chemical shifts, one at δ 6.32 and the second at δ 6.40. Racemic **14** was also prepared.

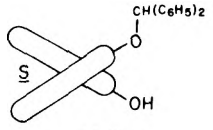
Treatment of (*R*),(*S*)-1 with diethylene glycol ditosylate (THF–*t*-BuOK) gave a mixture of products from which were isolated (*R*),(*S*)-**4** (4%, mp 226–227 °C), (*R,R*),(*S,S*)-**15** (15%, phase change at 244–251 °C), and (*R,S*)-**15** (2%, mp 283–284 °C). When (−)-(*S*)-1 was used as starting material, (+)-(*S*)-**4** (2%) and (−)-(*S,S*)-**15** (31%, mp 123–126 °C as C_6H_6–c-C_6H_{12} solvate) were obtained. The ^{1}H NMR spectrum of (−)-(*S,S*)-**15** was identical with that of (*R,R*),(*S,S*)-**15**, but different from that of (*R,S*)-**15**. Starting material (−)-(*S*)-1 can



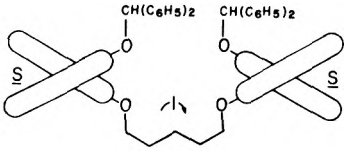


give (−)-(*S*,*S*)-**15**, but not (*R*,*S*)-**15**, whereas (*R*),(*S*)-**1** can give both (*R*,*S*)-**15** and (*R*,*R*),(*S*,*S*)-**15**. A spectral comparison identified the configurations of the latter two substances.

Compound (−)-(*S*,*S*)-**15** was also prepared by a second method which was multistep. Treatment of (−)-(*S*)-**1** with benzhydryl bromide for steric reasons gave mainly monosubstituted product (+)-(*S*)-**16** (73%). When treated with



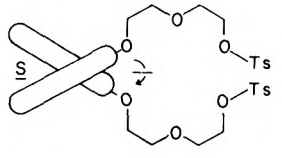
(+)-(S)-16



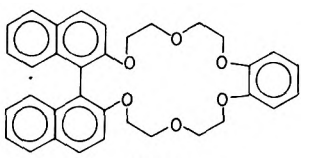
(−)-(SS)-17

diethylene glycol ditosylate (THF, KOH), (+)-(*S*)-**16** gave (−)-(*S*,*S*)-**17** (73%). The benzhydryl protecting groups were removed with acid, and the resulting diol produced was converted directly to (−)-(*S*,*S*)-**15** with diethylene glycol ditosylate (THF–KOH) in a yield of 47% for the two steps.

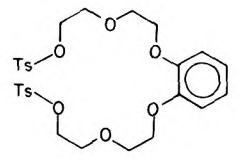
A third method of preparing (−)-(*S*,*S*)-**15** proved to be the best. Treatment of (−)-(*S*)-**1** with 2-(2′-chloroethoxy)ethyl 2″-tetrahydropyranyl ether and NaH in DMF (or NaOH in butanol) produced the bispyranyl ether, which was cleaved to diol and converted to ditosylate (−)-(*S*)-**18**. Similarly, (+)-(*R*)-**18** and (*R*),(*S*)-**18** were prepared. Treatment of (−)-(*S*)-**18** with (−)-(*S*)-**1** (THF, KOH) gave (−)-(*S*,*S*)-**15** (37%), and treatment of (+)-(*R*)-**18** with (+)-(*R*)-**1** gave (+)-(*R*,*R*)-**15** (42%). Catechol and (*R*),(*S*)-**18** in *n*-BuOH–KOH gave (*R*),(*S*)-**19** (41%), which was also obtained from (*R*),(*S*)-**1** and **20** (prepared in 47% yield similarly to **18**) in 50% yield.



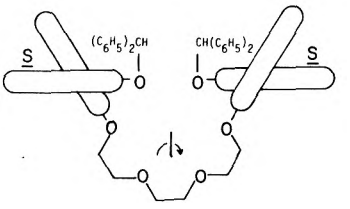
(-)-(S)-18



(R)(S)-19



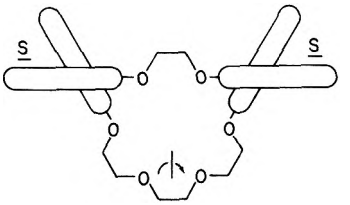
20



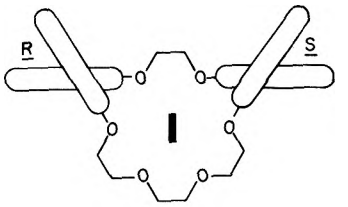
(-)-(SS)-21

The rotations of the three samples of (−)-(*S*,*S*)-**15** made by the three different methods were essentially identical and equal in magnitude with the sample of (+)-(*R*,*R*)-**15** prepared. Thus no racemization occurred during these syntheses, and the products were optically pure. The enantiomers of **15** formed a highly cyrstalline and stable solvate with CCl_4, as well as one containing 0.5 mol of benzene and 0.5 mol of cyclohexane.

Cycles isomeric to **15** were also prepared. Treatment of racemic benzhydryl derivative **16** with triethylene glycol ditosylate (THF–KOH) gave **21** as a mixture of diastereoisomers (60%), whereas (+)-(*S*)-**16** gave (−)-(*S*,*S*)-**21**. The diastereomeric mixture (**21**) was cleaved with acid, and the resulting mixture of diols without separation was converted in 50% yield with ethylene glycol ditosylate (THF–KOH) to a mixture of



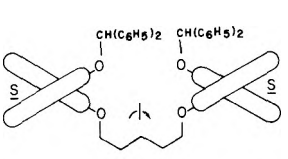
(-)-(SS)-22



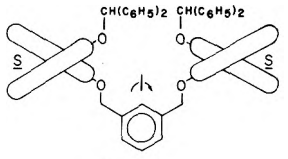
(RS)-22

(*R*,*S*)-**22** and (*R*,*R*),(*S*,*S*)-**22** (50%). These diastereoisomers were separated and characterized. Similarly (−)-(*S*,*S*)-**21** was converted to (−)-(*S*,*S*)-**22** (60%).

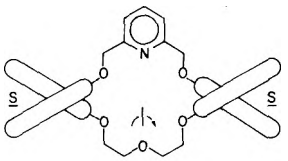
Intermediates (−)-(*S*,*S*)-**17** (see above), (−)-(*S*,*S*)-**23**, and (−)-(*S*,*S*)-**24** were used to introduce other units into cycles



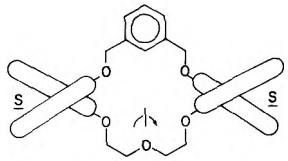
(-)-(SS)-23



(-)-(SS)-24

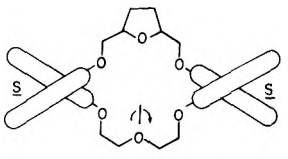


(-)-(SS)-25

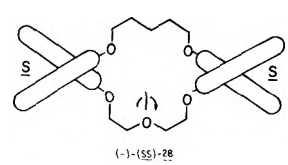


(-)-(SS)-26

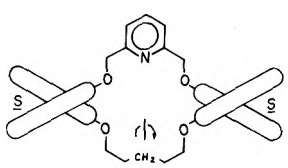
related to **15**. Treatment of (+)-(*S*)-**16** with pentamethylene glycol ditosylate (THF–KOH) provided (−)-(*S*,*S*)-**23** (54%), and with 1,3-bis(bromomethyl)benzene[4d] (−)-(*S*,*S*)-**24** (67%). These benzhydryl protected intermediates were cleaved with acid to give their respective bisphenols, which without characterization were used in their ring-closing reactions. The bisphenol from (−)-(*S*,*S*)-**17** with 2,6 bis(chloromethyl)pyridine[4c] gave (−)-(*S*,*S*)-**25** (43%), with 1,3-bis(bromomethyl)benzene[4d] gave (−)-(*S*,*S*)-**26** (13%), and with *cis*-2,5-bis(tosyloxymethyl)tetrahydrofuran[4b] gave (−)-(*S*,*S*)-**27** (26%). The bisphenol from (−)-(*S*,*S*)-**23** with diethylene glycol ditosylate gave (−)-(*S*,*S*)-**28** (41%) and with 2,6-bis(chloromethyl)pyridine[4c] gave (−)-(*S*,*S*)-**29** (29%). The bisphenol from (−)-(*S*,*S*)-**24** with 2,6-bis(chloromethyl)pyridine[4c] gave (−)-(*S*,*S*)-**30** (43%). The ring-closing reactions involved THF–*t*-BuOK or THF–KOH.



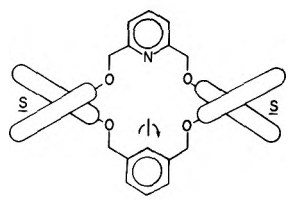
(-)-(SS)-27



(-)-(SS)-28

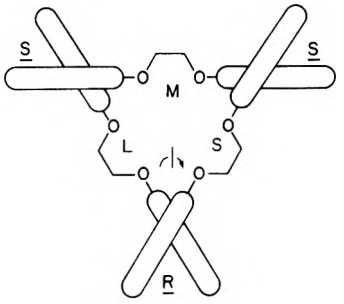


(-)-(SS)-29

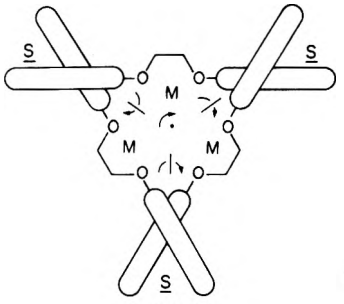


(-)-(SS)-30

Synthesis of Systems Containing Three Binaphthyl Units. When (*R*),(*S*)-**1** was treated with ethylene glycol ditosylate (THF–*t*-BuOK), besides (*R*),(*S*)-**3** and ketone (*R*),(*S*)-**8** (see above) there were produced three higher cyclic oligomers, X, Y, and Z (<1% yields). Their mass spectral molecular ions indicated their compositions, but not their configurations: X, $C_{44}H_{32}O_4$, mp 355 °C dec; Y, $C_{66}H_{48}O_6$, mp 188–190 °C; Z, $C_{66}H_{48}O_6$, mp 338–342 °C dec. The UV spectra of X and Y were very similar (five bands), but the λ_{max} in X and Y at 335–336 nm was moved to 355 nm in Z. This lowest energy band is probably associated with delocalization of the oxygen's electrons into the naphthalene rings, and is conformation dependent. The conformations in turn are dependent on the diastereomeric relationships between the binaphthyl units. The high-melting racemates (X and Z) were too insoluble for ^{1}H NMR spectral determinations. When (−)-(*S*)-**1** was used in the same reaction, in addition to (+)-(*S*)-**3** and ketone (+)-**8**, only *one* higher cyclic oligomer was produced (TLC), whose UV spectrum and TLC behavior identified it as one enantiomer of racemate Z. This evidence alone suggested X and Y must contain binaphthyl units of the *R* configuration, and that X was (*R*,*S*)-**32**, Y was (*R*,*S*,*S*),(*S*,*R*,*R*)-**31**, and Z was (*R*,*R*,*R*),(*S*,*S*,*S*)-**31**. The absence of (*R*,*R*),-



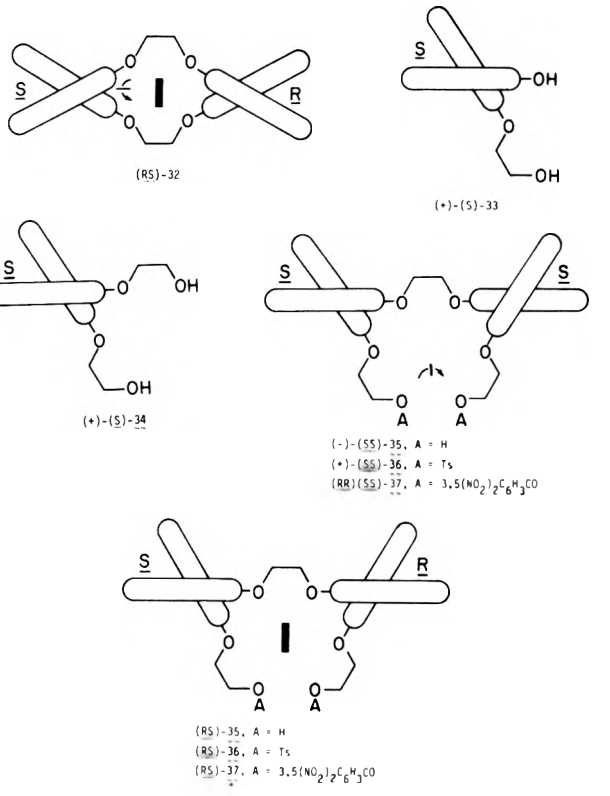
(−)-(RSS)-31



(−)-(SSS)-31

(*S*,*S*)-**32** or (*S*,*S*)-**32** in the reaction products indicates that the transition states leading to these isomers are of higher energy than those leading to (*R*,*S*)-**32** for steric–conformational reasons.

Rational, stepwise syntheses of (−)-(*R*,*S*,*S*)-**31** and (−)-(*S*,*S*,*S*)-**31** and their racemates proved more satisfactory. Treatment of (−)-(*S*)-**1** or (*R*),(*S*)-**1** with ethyl chloroacetate (THF–*t*-BuOK) gave mixtures of esters that were reduced ($LiAlH_4$) to mixtures of **33** and **34**, which were separated by distribution between ether and water–methanol–KOH mixtures. From (−)-(*S*)-**1** was produced (+)-(*S*)-**33** (43%) and (+)-(*S*)-**34** (19%), and from (*R*),(*S*)-**1**, (*R*),(*S*)-**33** (40%) and (*R*),(*S*)-**34** (15%) were produced. Treatment of (+)-(*S*)-**33** with ethylene glycol ditosylate (THF–*t*-BuOK) gave (−)-(*S*,*S*)-**35** (85%). Likewise (*R*),(*S*)-**33** gave a mixture of (*R*,*S*)-**35** and (*R*,*R*),(*S*,*S*)-**35**, which was separated through their 3,5-dinitrobenzoate esters (**37**) to give overall yields of 18% (*R*,*S*)-**35** and 25% (*R*,*R*),(*S*,*S*)-**35**. The ^{1}H NMR spectra and TLC behavior of these diastereomers were different. These properties were identical for (−)-(*S*,*S*)-**35** and for one



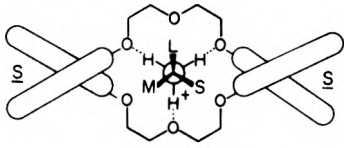
of the diastereomers, namely that of the (*R*,*R*),(*S*,*S*) configuration.

Tosylation of (−)-(*S*,*S*)-**35**, (*R*,*R*),(*S*,*S*)-**35**, and (*R*,*S*)-**35** gave (+)-(*S*,*S*)-**36**, (*R*,*R*),(*S*,*S*)-**36**, and (*R*,*S*)-**36** in 37, 50, and 52% yields, respectively. Treatment of (+)-(*S*,*S*)-**36** with (−)-(*S*)-**1** (DMF, K_2CO_3) gave (−)-(*S*,*S*,*S*)-**31** (46%), whereas (+)-(*S*,*S*)-**36** with (+)-(*R*)-**1** gave (−)-(*R*,*S*,*S*)-**31** (58%). Treatment of (*R*,*S*)-**36** with (*R*),(*S*)-**1** gave only (*R*,*S*,*S*),-(*S*,*R*,*R*,)-**31** (60%), whereas (*R*,*R*),(*S*,*S*)-**36** with (*R*),(*S*)-**1** gave (*R*,*S*,*S*),(*S*,*R*,*R*)-**31** (30%) and (*R*,*R*,*R*),(*S*,*S*,*S*)-**31** (16%). Enantiomer to racemate relationships among the stereoisomers of **31** were confirmed by the identity or nonidentity of their UV or ^{1}H NMR spectra and the TLC behavior. Diastereomers (−)-(*R*,*S*,*S*)-**31** and (−)-(*S*,*S*,*S*)-**31** possessed distinctly different ^{1}H NMR spectra, presumably due to different placements of the C-3 hydrogens of one naphthalene ring relative to the shielding or deshielding cones of a second transannular naphthalene ring in the two diastereoisomers. Two C-3 naphthalene protons were shielded and moved upfield to δ 6.58–6.78 per *S*,*S* or *R*,*R* relationship, whereas the *R*,*S* relationships provided no such shifts. Thus the doublet at δ 6.58–6.75 for (−)-(*S*,*S*,*R*)-**31** integrated to only two protons, whereas that at δ 6.62–6.78 for (−)-(*S*,*S*,*S*)-**31** integrated to six protons.

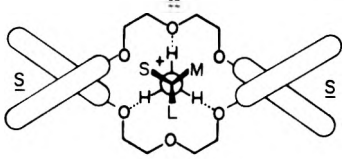
Symmetry Properties and Shapes of Host Compounds. The parent crown compounds exist in solution in all gauche conformations with the oxygens turned inward.[14] The cycles and their precursors containing the chiral binaphthyl unit possess interesting symmetry properties. Their formulas have been drawn with all oxygens turned inward. Rotation of (−)-(*S*)-**1** through 180° about the axis appended to its formula reproduces the formula, and hence the substance contains a C_2 axis. This symmetry element is carried into most of the cycles as is indicated by the curved arrow with a vertical line through it or a 180° curved arrow with a dot in it inserted into their formulas. Most of the cycles containing *both* (*R*)- and (*S*)-binaphthyl units contain mirror planes indicated in the formulas by the solid rectangular box [e.g., (*R*,*S*)-**15**, (*R*,*S*)-**22**, and (*R*,*S*)-**32**]. Interestingly, of these three meso isomers, (*R*,*S*)-**15** and (*R*,*S*)-**32** each contain a C_2 axis and are not

"sided," whereas (*R,S*)-**22** does not and is sided. Some of the cycles contain several C_2 axes. In particular, (−)-(*S,S*)-**14** and (−)-(*S,S*)-**15** contain three mutually perpendicular C_2 axes to give the molecule D_2 symmetry. Cycle (−)-(*S,S,S*)-**31** contains three C_2 axes all lying in the same plane and perpendicular to a C_3 axis (indicated in the formula by a 120° curved arrow with a dot in it), which gives the molecule overall D_3 symmetry. These symmetry properties seldomly are encountered in organic compounds and have important consequences with respect to possible host–guest complex structure.

Hosts that contain a C_2 axis in principle can complex alkylammonium ions from either face to produce the same structure (or family of structures of equilibrating conformers). Hosts that possess D_2 symmetry in principle form complexes, some of whose conformations duplicate one another. For example, if host (*S,S*)-**15** complexes LMSC*NH_3^+ (L is a large, M a medium, and S a small group), the two conformations **38** and **39** of the complex formed from one enantiomer of the



38



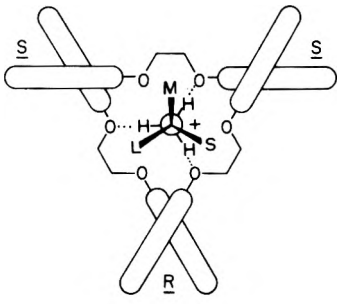
39

guest are superimposable on one another and on the two corresponding complexes formed with the guest protruding from the opposite face of the best plane of the macroring.

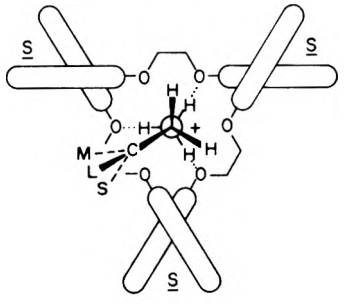
The general shape of most of the hosts described here depends on the number of binaphthyl units they contain. The central hole is designed to bind the NH_3^+ group of alkylammonium hosts, and the alkyl group in complexes protrudes approximately perpendicularly from the best plane of the oxygens. If (LMS)C is a generalized alkyl group, the substituents L, M, and S occupy the space in a complex above and around one face of the host. Since the naphthalene rings of a binaphthyl unit also extend perpendicularly above and below the face of the host, they divide the space available for L, M, and S into compartments. Hosts containing one binaphthyl unit, such as **6**, have one compartment on each face. Hosts with two binaphthyl units, such as (*S,S*)-**15** or (*S,S*)-**22**, have two compartments into which L, M, and S must fit in a complex. Hosts with three units, such as (*S,S,S*)-**31**, have three compartments. It is convenient to classify the hosts as having one, two, or three compartments on each face as monolocular, dilocular, or trilocular,[13] respectively. Hosts **2–7**, **13**, and **19** are monolocular, **14**, **15**, **22**, **25–30**, and **32** are dilocular, and the isomers of **31** are trilocular.

In CPK molecular models of these hosts, the naphthalene rings protruding from each face occupy ~65° of the 360° of the cylinder of space whose axis is perpendicular to the plane of the oxygens and is centered equidistant from all six oxygens. For the monolocular systems, this leaves ~295° of the cylinder for distribution of substituents L, M, and S in a single asymmetric cavity in host–guest complexes. For the dilocular and trilocular systems, the sizes of the compartments on each face depend both on the relative configurations and arrangements of the binaphthyl units. Dilocular hosts (*S,S*)-**15** and (*R,S*)-**15** are diastereomeric. In (*S,S*)-**15**, the two naphthalenes that extend from one face occupy roughly parallel planes that provide two spatially equivalent asymmetric cavities, each exposing ~115° of the cylinder. In (*R,S*)-**15** the planes of the two naphthalene rings converge to provide two cavities, one of ~60° and one of ~170°, each of which contains a mirror plane. Although (*S,S*)-**15** and (*S,S*)-**22** are isomeric and contain binaphthyl units of the same configuration, (*S,S*)-**15** has two equivalent cavities of ~115°, but (*S,S*)-**22** has one cavity of ~55° and one of ~175°. In (*S,S*)-**22**, an extension of the plane of one naphthalene ring would intersect the second naphthalene ring that protrudes from the same face. Isomer (*R,S*)-**22** is sided, since it contains no C_2 axis. On one side the aryls occupy planes that converge, and one cavity is ~70° and the other ~160°. On the opposite side, the aryls occupy the same plane, and one cavity is ~25° and the other ~205°.

The divisions of the cylinder of space in the trilocular systems **31** are particularly interesting. In the more symmetrical *S,S,S* isomer, the three cavities are similarly shaped, and they each expose ~55° of the cylinder. In the less symmetrical *R,S,S* isomer, the space is unevenly divided into a relatively large cavity (L) of 85°, a medium cavity (M) of ~55°, and a small cavity (S) of ~25°. In (*S,S,S*)-**31**, the cavities themselves are all *asymmetric*, whereas in (*R,S,S*)-**31**, cavity M is asymmetric, and L and S both have a mirror plane. Host (*R,S,S*)-**31** was designed to have a complementary relationship for one enantiomer of guest ions such as LMSC*NH_3^+, whereas (*S,S,S*)-**31** was designed for one enantiomer of $LMSCCH_2NH_3^+$. Complexes **40** and **41** indicate the complementary character of host and guest envisioned.



40



41

The introductions of the 2,6-pyridine, pentamethylene, benzo, 1,3-benzene, or 2,5-tetrahydrofuran units into the dilocular systems (**14**, **19**, **25–30**) do not change the cavity shapes much, since these units roughly lie in the planes of the oxygens and provide about the same space between the naphthalene walls. Of these compounds, only (*S,S*)-**14** possesses the three C_2 axes found in the parent system, (*S,S*)-**15**. The unsymmetrical distributions of some of the units of the others destroy all but one of the C_2 axes found in the parent system, (*S,S*)-**15**. These hosts are not sided, however.

Equilibration of Diastereomeric Trilocular Systems. When melted and held at 340 °C for 7 min, (*R,R,S*),(*S,S,R*)-**31** and (*R,R,R*),(*S,S,S*)-**31** each gave an approximately equal mixture of the two diastereoisomers. Thus, $\Delta\Delta G \sim 0$ for the two racemates. The symmetry number for the isomer with D_3 symmetry [(*R,R,R*)-**31** or (*S,S,S*)-**31**] is 6, and that for the isomer with C_2 symmetry is 2 [(*R,R,S*)-**31** or (*S,S,R*)-**31**]. If

the intra- and intermolecular interactions of all the units in each diastereoisomer in the melt are additive, then $\Delta\Delta G = -RT \ln (6/2) = -1340$ cal/mol for the difference in free energy for the two diastereomers, and the equilibrium mixture would be 75% (*R,R,R*),(*S,S,S*)-**31** and 25% (*R,R,S*),(*S,S,R*)-**31**. The results indicate that the interactions of the units in each diastereoisomer of **31** are not additive, and suggest that either intra- or intermolecular interactions tend to slightly destabilize the (*R,R,R*),(*S,S,S*) isomer relative to the (*R,R,S*),-(*S,S,R*) isomer. The two diastereoisomers possess different overall shapes and undoubtedly pack differently in the melt. Possibly the less symmetrical (*R,R,S*),(*S,S,R*) isomer produces a more dense melt with fewer holes and more contact points than the more symmetrical (*S,S,S*),(*R,R,R*) isomer.

The binding properties of the hosts described here will be reported in later papers of this series.

Experimental Section

General. All temperatures are in degrees Celsius. Alumina used in chromatography was MCB AX 611. Tetrahydrofuran (THF) and dioxane were distilled from sodium benzophenone ketyl immediately before use. Dimethylformamide (DMF) was distilled from CaH_2 prior to use. Magnesium sulfate was used as drying agent for organic extracts. All reactions involving NaH, *t*-BuOK, KOH, or $LiAlH_4$ were conducted under N_2. All melting points were taken on a Thomas-Hoover apparatus and are uncorrected. All ^1H NMR chemical shifts are given in δ parts per million from added Me_4Si in $CDCl_3$ and were recorded on a Varian HA-100 spectrometer. Mass spectra were taken on an AEI Model MS-9 double focusing mass spectrometer at 70 eV. Optical rotations were recorded with a Perkin-Elmer 141 polarimeter in a 1-dm thermostated cell. Gel permeation chromatographs were run on $\frac{3}{8}$ in. × 20 ft columns at flow rates of 3–4 mL/min with either THF or CH_2Cl_2 as solvent. Column A was packed with Bio-Rad CS-8 beads (1000 molecular weight exclusion limit), and column B with Styragel 100-Å beads (37–70 μm particle size, exclusion limit 1500 molecular weight). Since very similar procedures were applied to different starting materials, they will be illustrated, labeled, and then referred to by label. Systematic names will be illustrated, but are so cumbersome that semisystematic "crown" nomenclature will be more commonly used, along with compound numbers already assigned. Optically pure 2,2′-dihydroxy-1,1′-binaphthyl was used in all syntheses unless otherwise specified.

Resolution of 2,2′-Dihydroxy-1,1′-binaphthyl (1). From 2.71 g of *l*-menthoxyacetyl chloride and 2.20 g of **1** in THF–pyridine at 25 °C for 1 h was prepared the monoester, which was purified by chromatography on silica gel and crystallization from cyclohexane to give 0.40 g (9%) of product: mp 139–140.5 °C; $[\alpha]^{25}_D$ −14.4° (*c* 1.0, $(CH_3)_2CO$); M^+, 482. Anal. Calcd for $C_{32}H_{34}O_4$: C, 79.64; H, 7.10. Found: C, 79.56; H, 6.83. This material was hydrolyzed with KOH in CH_3OH to give (−)-(*S*)-**1** (70%) [mp 207–209 °C; $[\alpha]^{25}_D$ −33.4° (*c* 0.76, THF)] undepressed by admixture with diol prepared through phosphate salt (see below).

The better method is a modification of that of others,[5] and is outlined here. Racemic **1** (600 g, 2.09 mol) was slurried with 2 L of CH_2Cl_2, and under N_2 was added 450 g (2.93 mol) of $POCl_3$, followed by the slow addition with stirring of triethylamine (517 g, 5.1 mol) so as to maintain gentle reflux. After 1 h of additional stirring, the reaction mixture was washed with water, dried, and evaporated. This crude acid chloride was stirred for 1 h in 3.5 L of THF and 1 L of water at 50 °C for 1 h. Ethyl acetate (3 L) was shaken with the mixture, and the aqueous layer was washed with CH_2Cl_2. The organic layers were combined, washed with 0.5 L of water (twice) and 1 L of brine, dried, and evaporated to give 684 g (94%) of the acid phosphate of **1**. This material was mixed with 578 g (1.96 mol) of cinchonine in 8.3 L of hot CH_3OH, 3.6 L of water was added, and the mixture was filtered free of a flocculent impurity. The salt crystallized (532 g, or 84% of theory for one pure diastereomer), and its rotation did not change on recrystallization. This salt (total sample) in 1915 mL of absolute ethanol was heated to boiling, and 1915 mL of very hot 6 N HCl solution was added with vigorous stirring. After 3 days at 0 °C the white platelets were collected and digested (twice) with stirring with 1 L of hot 6 N HCl solution for 12 h, and once with 600 mL of cold water (2 h) to give after drying 222 g of the phosphate acid ester: $[\alpha]^{25}_{546}$ +722°, $[\alpha]^{25}_{436}$ +1329° (c 0.9, MeOH); yield based on enantiomer present in racemic **1** used, 59%.

The filtrate from the initial crystallization of the cinchonine salt was evaporated, the residue was dissolved in 3.1 L of refluxing absolute ethanol, and 3.1 L of hot 6 N HCl was added with stirring at a rate to aid crystallization and inhibit oiling. The product was digested, as with its enantiomer, and dried to give 115.3 g of (−)-(*R*)-acid ester: $[\alpha]^{25}_{546}$ −734°, $[\alpha]^{25}_{436}$ −1355° (c 0.9, MeOH). The filtrates were reworked to give 52.4 g of additional (redigested) material ($[\alpha]^{25}_{546}$ −714°, $[\alpha]^{25}_{436}$ −1315° (*c* 0.57, MeOH)) to give a total of 168 g of (−)-(*R*)-acid, or 46% of theory. Partially optically pure (−)-(*R*)-acid ester was brought to optical purity by one crystallization of its cinchonidine salt. The acid ester recovered (65% of theoretical maximum) gave $[\alpha]^{25}_{546}$ −728°, $[\alpha]^{25}_{436}$ −1346° (c 1.1, MeOH).

The acid phosphate ester of (+)-(*R*)-**1** was reduced to (*R*)-(+)-**1** as follows. Acid ester (115.4 g, 0.331 mol, $[\alpha]^{25}_{546}$ −734°) was mixed with 1 L of THF at 0 °C under N_2, and $LiAlH_4$ (31.4, 0.83 mol) was added in small portions during 1 h with stirring. An additional 400 mL of THF was added, and the mixture was stirred at 25 °C for 17 h, cooled to 0 °C, and cold 6 N HCl (250 mL) added slowly and cautiously. The upper phase was decanted, and the lower phase was mixed with 300 mL of 6 N HCl and 150 mL of THF. The phases were again separated and the lower phase extracted with ether. The combined organic phases were washed with brine, decolorized with Norite, and evaporated. The oil was dissolved in 1 L of benzene, which was evaporated to induce crystallization. The solid that separated (90.6 g, 96%, mp 202–207 °C) was recrystallized from benzene to give 84.5 g, 89% (mp 207.5–208.5 °C), of (+)-(*R*)-**1**: $[\alpha]^{25}_{589}$ +34.3°, $[\alpha]^{25}_{546}$ +50.9° (c 1.0, THF). The overall yield in the resolution was ~41% of theory.

Similar reduction of 198 g of (+)-(*S*)-acid phosphate ($[\alpha]^{25}_{546}$ +722°, *c* 0.9, MeOH) gave 88% of (−)-(*S*)-**1** [mp 207–208 °C; $[\alpha]^{25}_{589}$ −33.3°, $[\alpha]^{25}_{578}$ −37.8°, $[\alpha]^{25}_{546}$ −51.3°, $[\alpha]^{25}_{436}$ −228° (c 1.1, THF)], or 52% yield in the resolution. Several preparations were made by different experimentalists using a variety of procedures, but each preparation gave the same rotations and melting points for (+)- and (−)-**1**.

Racemization Experiments with 2,2′-Dihydroxy-1-binaphthyl (1). A solution of (−)-**1** (0.1 g in 12 mL of dioxane and 10 mL of H_2O) gave $[\alpha]^{25}_D$ −0.106°. After 7 and 26 h respectively at 100 °C under N_2, the solutions gave $[\alpha]^{25}_D$ −0.110° and −0.106°. A solution of 95 mg (0.331 mmol) in 10 mL of butanol containing 47 mg (0.71 mmol) of KOH gave $[\alpha]^{25}_D$ +0.734°. After 13 and 23 h respectively under N_2 at 118 °C, the solutions gave $[\alpha]^{25}_D$ +0.408 and +0.230°. A solution of 100 mg of (−)-**1** in 12 mL of dioxane and 10 mL of 20% aqueous HCl gave $[\alpha]^{25}_D$ −0.158°. After 7 and 26 h respectively at 100 °C under nitrogen, the solutions gave $[\alpha]^{25}_D$ −0.099 and −0.044°.

2,3:4,5-Dibenzo-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene [2,2′-Biphenyl-20-crown-6 (2)]. Procedure I. A mixture of 10.0 g (53.8 mmol) of 2,2′-dihydroxy-1,1′-biphenyl and 110 mL of butanol was purged with N_2 and 4.5 g (112 mmol) of NaOH was added. After the solution had refluxed for 1 h under N_2, 14.8 g (53.8 mmol) of pentaethylene glycol dichloride in 30 mL of butanol was added (0.5 h). After 17 h at reflux under N_2, the solution was shaken with 100 mL of $CHCl_3$ and 100 mL of water. The layers were separated, and the $CHCl_3$ layer was washed with water, dried, and concentrated to give 22 g of oil, which was chromatographed on 700 g of neutral alumina (activity I). Elution with 4 L of (3:2, v/v) benzene–ether gave 8.7 g of oil, which was molecularly distilled to give 2.66 g of bp 135–140 °C (20 μm) and 3.26 g of bp 177–183 °C (20 μm). The latter material crystallized and was recrystallized from heptane to give 2.5 g (12%) of **2**: mp 64–65 °C; ^1H NMR δ 3.6 (m, CH_2CH_2O, 16 H), 4.5 (m, $ArOCH_2$, 4 H), 6.9 (m, ArH, 10 H), 7.2 (m, ArH, 10 H); M^+ 388 (base peak). Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 68.01; H, 7.32.

(*R*),(*S*)-2,3:4,5-Di(1,2-naphtho)-1,6,9,12,15,18-hexaoxacycloeicosa-2,4-diene [2,2′-Binaphthyl-20-crown-6 ((*R*),(*S*)-7)]. Procedure I (without distillation of the product) applied to 4.86 g of (*R*),(*S*)-**1** gave 2.75 g (33%) of (*R*),(*S*)-**7** after recrystallization from benzene–heptane: mp 130–130.5 °C; ^1H NMR spectrum δ 3.5 (complex m, CH_2OCH_2, 16 H), 4.04 (m, $ArOCH_2$, 4 H), 7.26 (m, ArH, 8 H), 7.83 (m, ArH, 4 H); M^+ 488 (base peak). Anal. Calcd for $C_{30}H_{32}O_6$: C, 73.75; H, 6.60. Found: C, 73.88; H, 6.76.

Racemic and (−)-(*S*)-2,2′-Binaphthyl-20-crown-6 ((−)-(*S*)-7) by Procedure II. Potassium *tert*-butoxide (2.36 g, 21 mmol) was added to a stirred solution under N_2 of 3.00 g (10.5 mmol) of (−)-(*S*)-**1** dissolved in 140 mL of pure THF. To the resulting suspension was added 5.72 g (10.5 mmol) of pentaethylene glycol ditosylate. The mixture produced was heated at reflux for 5 h and evaporated under reduced pressure. The residue was shaken with water and CH_2Cl_2, and the organic layer was washed with brine and dried. Evaporation of the solvent gave 6.1 g of oil, which was absorbed on 23 g of alumina and placed on the top of a chromatograph column prepared from a slurry of alumina and ether. The (−)-(*S*)-**7** was eluted with ether, and evaporation of the eluate gave a colorless oil, which was dried as a foam for 24 h at 35 °C and 0.07 mm, yield 3.1 g, (64%). The ^1H NMR and

mass spectra were identical with racemic 7 and gave $[\alpha]^{25}_{D}$ −70.5°, $[\alpha]^{25}_{546}$ −89.8° (c 1.0, THF). Anal. Calcd for $C_{30}H_{32}O_6$: C, 73.76; H, 6.60. Found: C, 73.62; H, 6.45. When carried out at 25 °C for 16 h, procedure II gave a 52% yield of (−)-(S)-7 of identical properties. When applied to racemic 1, racemic 7 resulted: 60%; mp 130–130.5 °C.

Optical Stability of (−)-(S)-2,2′-Binaphthyl-20-crown-6 ((−)-(S)-7). When a solution (1 M) of optically pure (−)-(S)-7 in oxygen-free diethylene glycol in a tube sealed under vacuum was heated at 205 °C for 6 h, the compound underwent no rotational loss. In 202 h at 205 °C, 9% rotational loss was observed. In a second experiment, two samples (0.50 g each) of (−)-(S)-7 of $[\alpha]^{25}_{578}$ −74.5° (c 1.0, THF) were sealed in ampules under vacuum as solutions in 10 mL of diphenyl ether. One tube was heated at 226 °C for 6 days and the other was held at 25 °C. The cycles were recovered by chromatography. The heated sample gave $[\alpha]^{25}_{578}$ −41.9° and the unheated gave $[\alpha]^{25}_{578}$ −74.2° (c 1, THF).

Applications of Procedure II to the Preparation of (−)-(S)-2,2′-Binaphthyl-14-crown-4 ((−)-(S)-5) and (−)-(S)-2,2′-Binaphthyl-17-crown-5 ((−)-(S)-6). From (−)-(S)-1 and triethylene glycol ditosylate was obtained (−)-(S)-5 (65%) as a gum: M^+ 400; $[\alpha]^{25}_{589}$ −127° (c 0.91, $CHCl_3$). Anal. Calcd for $C_{26}H_{24}O_4$: C, 78.00; H, 6.00. Found: C, 78.04; H, 5.96. From (−)-(S)-1 and tetraethylene glycol ditosylate was obtained (−)-(S)-6 (52%) as a gum: $[\alpha]^{25}_{589}$ −63°, $[\alpha]^{25}_{578}$ −67° (c 1.89, $CHCl_3$). Anal. Calcd for $C_{28}H_{28}O_5$: C, 75.68; H, 6.31. Found: C, 75.75; H, 6.31.

(R),(S)-2,3:4,5-Di(1,2-naphtho)-1,6,9-trioxacycloundeca-2,4-diene ((R),(S)-4) and (R,S)- and (R,R),(S,S)-2,3:4,5:13,14:15,16-Tetra(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene ((R,R),(S,S)-15 and (R,S)-15). By procedure I, 10.9 g of (±)-1, 5.5 g of diethylene glycol dichloride, and 1.6 g of NaOH were converted to a mixture of the three title products, which were separated on 500 g of neutral alumina with benzene and 4:1 (v/v) benzene–ether as eluting agents. Benzene eluted 2,2′-binaphthyl-11-crown-3 ((R),(S)-4), which was sublimed [195 °C (50 μm)] to give 0.50 g (4%) of material: mp 226–227 °C; ^{1}H NMR spectrum, δ 3.5 (m, 4 H, CH_2), 4.01 (8 lines, 2 H, CH_2), 4.32 (8 lines, 2 H, CH_2) as a whole ABX_2 pattern, 7.2 (complex m, ArH, 8 H), 7.8 (m, ArH, 4 H); M^+ 356 (base peak). Anal. Calcd for $C_{24}H_{20}O_3$: C, 80.88; H, 5.66. Found: C, 81.01; H, 5.77.

Benzene–ether eluted a mixture of (R,S)- and (R,R),(S,S)-15, which was crystallized and recrystallized from 1:1 (v/v) benzene–cyclohexane to give 0.22 g (2%) of (R,S)-15; mp 283–284 °C. It proved necessary to heat the sample to 165 °C (50 μm) to completely rid the sample of solvent. The material gave: ^{1}H NMR δ 3.29 (m, CH_2OCH_2, 8 H), 3.90 (m, $ArOCH_2$, 8 H), 7.20 (complex m, ArH, 16 H), 7.76 (m, ArH, 8 H); M^+ 712 (base peak). Anal. Calcd for $C_{48}H_{40}O_6$: C, 80.88; H, 5.66. Found: C, 80.88; H, 5.84.

From the filtrates was crystallized by fractional crystallization from benzene–cyclohexane (R,R),(S,S)-15, 2.0 g (15%), phase change at mp 244–251 °C. This isomer was much more soluble in $CDCl_3$ than (R,S)-15, and gave a different ^{1}H NMR fine structure: ^{1}H NMR δ 3.18 (m, CH_2OCH_2, 8 H), 3.81 (m, $ArOCH_2$, 8 H), 7.2 (complex m, ArH, 16 H), 7.83 (m, ArH, 8 H); M^+ 712 (base peak). Anal. Calcd for $C_{48}H_{40}O_6$: C, 80.88; H, 5.66. Found: C, 81.05; H, 5.92.

(+)-(S)-2,2′-Dinaphthyl-11-crown-3 ((+)-(S)-4), (−)-(S,S)--Bis(binaphtho)-22-crown-6 ((−)-(S,S)-15), and (+)-(R,R)-15. By procedure II, 14 g of diethylene glycol ditosylate, 10.0 g of (−)-(S)-1, and 8 g of t-BuOK produced a mixture of (+)-(S)-4 and (−)-(S,S)-15. Separation of these oligomers by chromatography on 1 kg of neutral alumina gave 4.3 g of (−)-(S,S)-15 as white needles containing 0.5 mol each of benzene and cyclohexane (^{1}H NMR integration): mp 123–126 °C. Anal. Calcd for $C_{48}H_{40}O_6 \cdot {}^1/_2C_6H_{12} \cdot {}^1/_2C_6H_6$: C, 81.69; H, 6.22. Found: C, 81.71; H, 6.06. The material also formed a solvate with CCl_4 (needles). The initial solvate when heated 17 h at 170 °C (50 μm) gave 3.9 g (31%) of (−)-(S,S)-15 as a foam: ^{1}H NMR identical with (+)-15; M^+ 712 (base peak); $[\alpha]^{25}_{578}$ −220°, $[\alpha]^{25}_{546}$ −262°, $[\alpha]^{25}_{436}$ −599°, $[\alpha]^{25}_{365}$ −1620° (c 1.1, CH_2Cl_2).

From the mother liquors from the crystallization of (−)-(S,S)-15 was obtained by sublimation and resublimation 0.24 g (2%) of (+)-(S)-4, mp 231–232 °C, whose ^{1}H NMR spectrum was identical with (±)-4: M^+ 356 (base peak); $[\alpha]^{25}_{578}$ +72.0°, $[\alpha]^{25}_{546}$ +78.0°, $[\alpha]^{25}_{436}$ +40.0°, $[\alpha]^{25}_{365}$ −672° (c 0.88, CH_2Cl_2). Anal. Calcd for $C_{24}H_{20}O_3$: C, 80.88; H, 5.66. Found: C, 80.81; H, 5.55.

Similarly, (+)-(R,R)-15 was prepared in 22% yield: $[\alpha]^{25}_{578}$ +221°, $[\alpha]^{25}_{546}$ +262°, $[\alpha]^{25}_{436}$ +600°, $[\alpha]^{26}_{365}$ +1630° (c 0.87, CH_2Cl_2).

(+)-2,2′-Bis(5-tosyloxy-3-oxa-1-pentyloxy)-1,1′-binaphthyl ((R),(S)-18), (−)-(S)-18, and (+)-(R)-18. The required intermediate 2-(2′-chloroethoxy)ethyl 2″-tetrahydropyranyl ether was reported previously.[4a]

A solution of 120 g (575 mmol) of 2-(2′-chloroethoxy)ethyl 2″-tetrahydropyranyl ether in 700 mL of butanol was added (15 min) to a stirred, boiling mixture of 60 g (0.217 mol) of (±)-1 and 20 g (0.500 mol) of NaOH in 700 mL of butanol. The resulting mixture was stirred and refluxed for 10 h (pH 7–8), and then 6.0 g (0.15 mol) more of NaOH and 60 g (0.278 mol) of the chloro ether in 100 mL of butanol was added. The mixture was stirred at reflux for an additional 10 h. The procedure was repeated with 6.0 g (0.15 mol) of NaOH and 20 g (0.096 mol) of the chloro ether in 50 mL of butanol and a 15-h reflux period. The reaction mixture was cooled and filtered, and the filtrate was concentrated under vacuum, ultimately at 150 °C (50 μm) to remove the excess chloro ether. The residue (140 g) was heated at 100 °C and 5 g (0.044 mol) of pyridine hydrochloride was added. The resulting mixture was heated at 190 °C (50 μm) *with stirring* for 2 h to give, upon cooling, 98.3 g of a light brown glass (diol precursor to (±)-18). A solution of 104 g (0.545 mol) of tosyl chloride in 300 mL of dry pyridine at 0 °C was added to 98.3 g (0.210 mol) of this diol dissolved in 400 mL of dry pyridine at 0 °C. The reaction mixture was allowed to stand at 0 °C for 24 h, poured onto 2 kg of ice water, and stirred for 2 h. The mixture was extracted with 2-L portions of CH_2Cl_2. The extracts were combined, washed with two 1-L portions of cold 6 N hydrochloric acid and 100 mL of brine, and dried. The solvent was evaporated to give 138 g of a brown glass which was chromatographed on 2 kg of silica gel with chloroform as eluent. Elution with 4 L of solvent brought 6 g of material off the column which was discarded. Elution with an additional 16 L of solvent gave upon evaporation ditosylate (R),(S)-18, which was pure by TLC. The material was film dried at 105 °C (50 μm) for 24 h to give 101 g (63%): ^{1}H NMR δ 2.35 (s, CH_3, 6 H), 2.95 (m, CH_2, 4 H), 3.30 (m, CH_2, 4 H), 3.61 (m, CH_2, 4 H), 3.95 (m, CH_2, 4 H), 7.2 (m, ArH, 12 H), 7.7 (m, ArH, 8 H). The material crystallized from CH_3CN–CH_3OH gave mp 69–71 °C. Anal. Calcd for $C_{42}H_{42}O_{10}S_2$: C, 65.44; H, 5.49. Found: C, 65.64; H, 5.36.

A different procedure was applied to (−)-(S)-18. To a solution of 50.0 g of (−)-(S)-1 in 1 L of dry DMF was added 19.5 g of NaH (50% oil dispersion). The mixture was heated to 70 °C with stirring under N_2. After 1 h, 2-(2′-chloroethoxy)ethyl 2″-tetrahydropyranyl ether (83.2 g) was added. The reaction mixture was stirred at 70 °C for 48 h under N_2, cooled, and shaken with 2 L of water. The mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with water, dried, and evaporated. The residue in 1:1 pentane–CH_2Cl_2 was filtered through 250 g of basic alumina, which was washed with additional solvent. The eluent was concentrated, and the oil was dissolved in 300 ml of CH_2Cl_2 to which was added 150 mL of methanol and 10 mL of concentrated hydrochloric acid. The solution was stirred for 1 h at 25 °C and neutralized with aqueous $NaHCO_3$, and the organic layer was separated and combined with CH_2Cl_2 washes of the aqueous layer. The organic layer was dried and evaporated, and the oil was washed with pentane to remove the mineral oil. The oil was dried at 90 °C (0.1 mm) to give 57.4 g (70%) of diol as a gum. This material, 31.7 g, in 300 mL of dry pyridine was cooled to −20 °C, and 30.0 g of tosyl chloride was added in small portions during 15 min, during which time and for an additional 1.5 h the mixture was cooled and stirred. After standing at −20 °C for 24 h, the mixture was stirred into 1000 g of ice. The water was decanted, and the residual oil was shaken with CH_2Cl_2 and 10% aqueous hydrochloric acid. The organic layer was washed with the same acid, then with 10% aqueous $NaHCO_3$ and water. The solution was dried, evaporated at 25 °C under vacuum, and dried at 0.01 mm (25 °C) to give 41.5 g (80%) of (−)-(S)-18 as a gum. This material possessed a ^{1}H NMR spectrum identical with racemic 18: $[\alpha]^{25}_{578}$ −30.7° (c 1.0, THF). Anal. Calcd for $C_{42}H_{42}O_{10}S_2$: C, 65.44; H, 5.49. Found: C, 65.40; H, 5.30.

Similarly, (+)-(R)-18 was prepared (68%): $[\alpha]^{25}_{578}$ +31.0° (c 1.0, THF).

(−)-(S,S)-Bis(binaphtho)-22-crown-6 ((−)-(S,S)-15) from (−)-(S)-2,2′-Bis-(5-tosyloxy-3-oxa-1-pentyloxy)-1,1′-binaphthyl ((−)-(S)-18), and (+)-(R,R)-15 from (+)-(R)-18. Procedure III. To a solution of 15.4 g (0.54 mol) of (−)-(S)-1 in 1 L of THF was added under N_2 7.15 g (0.108 mol) of KOH (85%) in 50 mL of water. The solution was refluxed under N_2 for 1 h and 41.5 g (0.54 mol) of (−)-(S)-18 was added. The solution was refluxed for 50 h, evaporated at 25 mm to 150 mL, and shaken with 150 mL of CH_2Cl_2 and 150 mL of water. The phases were separated, the aqueous phase was extracted with two 150-mL portions of CH_2Cl_2, and the combined organic phases were washed successively with 10% aqueous KOH and water. The solution was dried and evaporated under vacuum to give 40.0 g of oil, which was chromatographed on 850 g of silica gel with CH_2Cl_2 as eluting agent to give (−)-(S,S)-15, which was crystallized from benzene–cyclohexane to give 16.2 g of the solvate: mp 123–124 °C. When heated to 170 °C (0.06 mm) for 10 h, this material gave 14.0 g (37%) of (−)-(S,S)-15 as a glass: $[\alpha]^{25}_{578}$ −220° (c 1.0, CH_2Cl_2).

Similarly prepared (+)-(*R,R*)-**15** (from (+)-(*R*)-**18**, 42%) gave $[\alpha]^{25}_{578}$ +221° (*c* 1.0, CH_2Cl_2).

(*R*),(*S*)-2-Benzhydryloxy-2'-hydroxy-1,1'-binaphthyl ((*R*),(*S*)-16) and (+)-(*S*)-16. A mixture of 28.6 g (0.10 mol) of 1,300 mL of THF, and 12.0 g (0.11 mol) of *t*-BuOK was stirred under N_2 (5 min), and benzyhydryl bromide (27.1 g or 0.11 mol) in 200 mL of THF was added. The mixture was heated at reflux for 24 h, cooled, and evaporated under vacuum. The residue was partitioned between CH_2Cl_2 and 10% NaOH solution. The aqueous layer on acidification gave 4 g of recovered **1**. The organic layer was washed with brine, dried, and evaporated (vacuum) to give an oil that crystallized as a solvate of diethyl ether from that solvent: weight 31.6 g (60%); mp 103–105 °C (bubbles). Anal. Calcd for $C_{33}H_{24}O_2 \cdot C_4H_{10}O$: C, 84.38; H, 6.51. Found: C, 84.27; H, 6.35. This material crystallized from pentane gave: melting behavior, translucent at 62 °C, cloudy at 84 °C, liquid at 138–140 °C; M^+ 452. Anal. Calcd for $C_{33}H_{24}O_2$: C, 87.58; H, 5.35. Found C, 87.73; H, 5.37.

From (−)-(*S*)-**1** (28.6 g) by the same procedure was obtained 33 g (73%) of (+)-(*S*)-**16**, except the material was purified by chromatography on 700 g of alumina (CH_2Cl_2–pentane eluting agent). The material was a foam: $[\alpha]^{25}_{589}$ +18.7°, $[\alpha]^{25}_{578}$ +19.6°, $[\alpha]^{25}_{546}$ +21.3° (*c* 0.55, THF). Anal. Calcd. for $C_{33}H_{24}O_2$: C, 87.58; H, 5.35. Found: C, 87.49; H. 5.57.

(−)-(*S,S*)-1,17-Bisbenzyhydryl-2,3:4,5:13,14:15,16-tetra-(1,2-naphtho)-1,6,9,12,17-pentaoxaheptadecyl-2,4,13,15-tetraene ((−)-(*S,S*)-17). From 9.05 g of (+)-(*S*)-**16**, 6.14 g of diethylene glycol ditosylate, and 2.45 g of KOH by procedure III (THF–H_2O, reflux, 48 h) was obtained an oil that was chromatographed on 500 g of alumina developed with CH_2Cl_2 in pentane. The product came off with 40% CH_2Cl_2–60% pentane (by volume) to give 7.15 g (73%) of (−)-(*S,S*)-**17** as a white foam: $[\alpha]^{25}_{578}$ −3.04°, $[\alpha]^{25}_{546}$ −5.18°, $[\alpha]^{25}_{436}$ −30.25° (c 1.0, $CHCl_3$); M^+ 974. Anal. Calcd for $C_{70}H_{54}O_5$: C, 86.21; H, 5.58. Found: C, 86.08; H, 5.69.

(−)-(*S,S*)-Bis(binaphtho)-22-crown-6 ((−)-(*S,S*)-15) from (−)-(*S,S*)-17, Procedure IV. A solution of 4.35 g of bisbenzhydryl ether (−)-(*S,S*)-**17** in 50 mL of CH_2Cl_2, 50 mL of methanol, and 5 mL of concentrated hydrochloric acid was stirred for 20 h at 25 °C. The mixture was shaken with 200 mL of ice water and 200 mL of CH_2Cl_2, and the organic phase was water washed, dried, and evaporated under vacuum. The resulting mixture of diphenylmethoxymethane and the bisphenol was mixed with 200 mL of THF, 1.85 g of diethylene glycol ditosylate, and 0.65 g of KOH in 1 mL of water. The solution was heated at reflux under N_2 for 24 h, and the impure product isolated as usual and chromatographed on 200 g of alumina. Elution of the column with 1:9 CH_2Cl_2–pentane (v/v) gave 1.51 g (85%) of diphenylmethoxymethane. Elution with 1:1 CH_2Cl_2–pentane (v/v) gave (−)-(*S,S*)-**15**, which was purified through crystallization of its benzene–cyclohexane solvate and dried: weight 1.48 g (47%); $[\alpha]^{25}_{578}$ −215°, $[\alpha]^{25}_{546}$ −255° (*c* 0.31, CH_2Cl_2). Its ^1H NMR was superimposable on authentic material.

(−)-(*S,S*)-2,3:4,5:13,14:15,16-Tetra(1,2-naphtho)-8,9,10:19,20,21-bis(1,3-benzo)-9,20-diaza-1,6,12,17-tetraoxacyclodocosa-2,4,8,13,15,19-hexaene ((−)-(*S,S*)-14). To a solution of 14.3 g (0.050 mol) of (−)-(*S*)-**1** in 500 mL of THF was added under N_2 12.3 g (0.11 mol) of *t*-BuOK along with 350 mL of additional THF. The initial solution became a slurry during 15 min of stirring at 25 °C. In one portion, 8.8 g (0.050 mol) of 2,6-bis(chloromethyl)pyridine was added with 1 L of THF. The reaction mixture was stirred and heated at reflux under N_2 for 96 h and cooled, and the THF was evaporated under vacuum. The residue was shaken with CH_2Cl_2 and water, and the organic layer was washed with water, dried, and evaporated. The residue was dissolved in hot THF and cooled, and the THF disolvate that crystallized was collected to give, after drying in vacuo at 25 °C for 48 h, 7.2 g (31%) of (−)-(*S,S*)-**14**·2$(CH_2)_4O$: mp 295–298 °C dec; ^1H NMR δ 1.76 (m, 8 H, $(CH_2)_4$), 3.66 (m, 8 H, $(CH_2)_4$), 4.82 (s, 8 H, pyrCH_2), 6.32, 6.40 (portion of A_2B, 4 H, pyr-H-3), 6.8–7.9 (m, 26 H, naphthyl-H); M^+ 778 (solvate lost); $[\alpha]^{25}_{589}$ −250°, $[\alpha]^{25}_{578}$ −264°, $[\alpha]^{25}_{546}$ −319°, $[\alpha]^{25}_{436}$ −772° (c 1.1, $CHCl_3$, rotation adjusted for solvate). Material obtained by evaporation of a solution of (−)-(*S,S*)-**14** in CH_2Cl_2 was free of solvate. Anal. Calcd for $C_{54}H_{38}N_2O_4$: C, 83.27; H, 4.92. Found: C, 83.20; H, 5.03.

The filtrates from the crystallizations were evaporated and chromatographed on silica gel (350 g). Elution of the products with CH_2Cl_2 gave first (−)-(*S,S*)-**14**, then mixtures, and finally the oligomer composed of one binaphthyl and one pyrido unit ((−)-(*S*)-**13**), whose ^1H NMR py-CH_2O protons came at δ 5.07. This material was not characterized.

1,2-Bis(5-tosyloxy-3-oxa-1-pentyloxy)benzene (20). A solution of 68.0 g (0.326 mol) of 2-(2-chloroethoxy)ethyl 2-tetrahydrofuranyl ether in 150 mL of butanol was added dropwise under N_2 to a mixture of 11.0 g (0.100 mol) of catechol and 8.2 g (0.200 mol) of NaOH in 300 mL of boiling butanol. The mixture was stirred under N_2 for 15 h, and an additional 2.9 g (0.07 mol) of NaOH was added. The mixture was refluxed for an additional 16 h. The mixture was cooled and filtered from 14.9 g (94%) of NaCl, the filtrate was evaporated to an oil at 20 mm, and the oil was heated to 120 °C (50 μm) to give 47 g of residue. This material was stirred with 1 g of pyridine hydrochloride for 1 h at 155–160 °C (50 μm). The product was distilled, and the 1,1-bis(5-hydroxy-3-oxa-1-pentyloxy)benzene was collected as a colorless oil (19.5 g or 68%) at 185–187 °C (50 μm). Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 59.03; H, 7.87.

To 5.7 g (20 mmol) of this diol in 130 mL of dry pyridine at 0 °C was added 15.2 g (60 mmol) of tosyl chloride. The mixture was stirred at 0 °C until homogeneous, and stored at 0 °C for 24 h. The usual extraction procedure gave 9.8 g of a brown oil, which was dissolved in 400 mL of 49:1 (v/v) $CHCl_3$–ether and run through a column of 20 g of silica gel. The column eluate was concentrated and the residue dried at 50 °C (20 μm) for 15 h to give 8.2 g (69%) of **20** as a viscous oil: ^1H NMR δ 2.40 (s, CH_3, 6 H), 3.75 (m, $CH_2CH_2OCH_2$, 8 H), 4.10 (m, $ArOCH_2$ and CH_2OTs, 8 H), 6.89 (m, benzo Ar-H, 4 H), 7.29–7.79 (m, ArH, 4 H). Anal. Calcd for $C_{28}H_{34}O_{10}S_2$: C, 56.55; H, 5.75. Found: C, 56.24; H, 5.90.

2,3-Benzo-11,12:13,14-di(1,2-naphtho)-1,4,7,10,15,18-hexaoxacycloeicosa-2,11,13-triene or Benzo-2,2'-binaphtho-20-crown-6 (19). A solution of 20.8 g (35.0 mmol) of ditosylate **20** in 40 mL of butanol was added to a mixture of 10.0 g (35.0 mmol) of (±)-**1** and 2.88 g (70 mmol) of NaOH in 70 mL of boiling butanol stirred under N_2. The mixture was refluxed for 20 h. The crude product was isolated in the usual way and chromatographed on 800 g of neutral alumina with benzene–ether as eluting agent to give crystalline (±)-**19**, which was recrystallized from cyclohexane–benzene to give 9.3 g (50%) of needles: mp 147–148 °C; ^1H NMR δ 3.6 (m, $CH_2CH_2OCH_2$, 8 H), 4.0 (complex m, $ArOCH_2$, 8 H), 6.84 (narrow m, benzo ArH, 4 H), 7.20 (complex m, naphthyl ArH, 8 H), 7.80 (m, naphthyl ArH, 4 H); M^+ 536 (base peak). Anal. Calcd for $C_{34}H_{32}O_6$: C, 76.10; H, 6.01. Found: C, 75.78; H, 5.99.

Cycle **20** was also prepared by procedure I from ditosylate (±)-**18** and catechol in 41% yield. mp 147–148 °C, undepressed by admixture with authentic material.

Mixture of (*R,S*)- and (*R,R*),(*S,S*)-1,20-Bis(benzhydryl)-2,3:4,5:16,17:18,19-tetra(1,2-naphtho)-1,6,9,12,15,20-hexaoxaeicosa-2,4,16,18-tetraene ((*R,S*)-21 and (*R,R*),(*S,S*)-21) and (−)-(*S,S*)-21. From 10.5 g (0.020 mol) of (*R*),(*S*)-**16** as its etherate (monobenzhydryl ether of **1**), potassium hydroxide, and triethylene glycol ditosylate (4.6 g, 0.010 mol) was prepared crude **21** (12.3 g) by procedure III which was chromatographed on 400 g of alumina with CH_2Cl_2–pentane (1:5, v/v) as eluting agent to remove impurities, and 1:1 to bring off 6 g (60%) of the diastereomeric mixture **21**: white foam; M^+ 1018. Anal. Calcd for $C_{72}H_{58}O_6$: C, 84.84; H, 5.73. Found: C, 84.88; H, 5.84.

Similarly from (+)-(*S*)-**16** (29.3 g or 0.0647 mol), KOH (4.70 g or 0.0712 mol), and triethylene glycol ditosylate (14.82 g or 0.0324 mol) was obtained 24.0 g (73%) of (−)-(*S,S*)-**21**: M^+ 1018; ^1H NMR δ 2.67 (s, central CH_2OCH_2, 4 H), 3.15 (pseudo t, $ArOCH_2CH_2$, 4 H), 3.84 (m, $ArOCH_2$, 4 H), 6.04 (s, Ar_2CH, 2 H), 6.8–7.9 (complex m, ArH, 44 H); $[\alpha]^{25}_{589}$ −3.04°, $[\alpha]^{25}_{578}$ −3.40°, $[\alpha]^{25}_{546}$ −5.25°, $[\alpha]^{25}_{436}$ −28.7° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{72}H_{58}O_6$: C, 84.84; H, 5.73. Found: C, 85.01; H, 5.67.

(*R,R*),(*S,S*)-, (*R,S*)-, and (−)-(*S,S*)-2,3:4,5:10,11:12,13-Tetra(1,2-naphtho)-1,6,9,14,17,20-hexaoxacyclodocosa-2,4,10,12-tetraene ((*R,R*),(*S,S*)-22, (*R,S*)-22, and (−)-(*S,S*)-22). A solution of 4.9 g of the above mixture of racemic and *meso*-**21** in 300 mL of THF and 100 mL of concentrated hydrochloric acid was allowed to stand at 25 °C for 16 h. The solution was evaporated under vacuum until it became turbid, at which point it was shaken with 200 mL of water and 200 mL of CH_2Cl_2. The aqueous phase was extracted with additional CH_2Cl_2, and the combined organic layers were washed with water and evaporated. Toluene (150 mL) and enough concentrated ammonium hydroxide to neutralize the residue were added, and the solution was evaporated under vacuum. The toluene–ammonium hydroxide–evaporative treatment was repeated, and the phenolic oil produced was used directly in the next step. This material was dissolved in 100 mL of THF, and 3 g of potassium hydroxide dissolved in 15 mL of water was added. To the resulting mixture was added 3.7 g of ethylene glycol ditosylate in 75 mL of tetrahydrofuran. The solution was refluxed for 36 h, and an additional 1.5 g of potassium hydroxide and 1.5 g of ethylene glycol ditosylate were added. The resulting mixture was refluxed for an additional 12 h, filtered, and shaken with 200 mL of CH_2Cl_2 and 200 mL of water. The organic phase was washed with 10% sodium hydroxide solution, water, and

brine. The solution was dried and evaporated, and the resulting oil was chromatographed on neutral alumina (500 g) made up in 1:1 CH_2Cl_2–pentane. The column was washed with the same solvent mixture, and 75-mL fractions were cut. Cycle **22** was eluted in fractions 5–14, 1.7 g (50%), as a 3:7 mixture of (*R,S*) and (*R,R*),(*S,S*) isomers. A sample of this material was molecularly distilled at 250 °C (10 μm) to give material for analysis: M^+ 712. Anal. Calcd for $C_{48}H_{40}O_6$: C, 80.87; H, 5.66. Found: C, 80.59; H, 5.94.

A solution of 100 mg of (*R,S*)- and (*R,R*),(*S,S*)-**21** mixture was submitted to thick-layer chromatography on silica gel (1-mm thick plate) with $CHCl_3$–cyclohexane as developer (six times). The bands were scraped from the plate, and the products were recovered by repeated washing of the silica gel with 1:3 methanol–chloroform. The *R,S* isomer (R_f 0.13, SiO_2–$CHCl_3$) was crystallized from ethanol: mp 118–121 °C (bubbles at 180 °C). The (*R,R*),(*S,S*) isomer (R_f 0.28, SiO_2–$CHCl_3$) was crystallized and recrystallized from ethanol: mp 132–135 °C after recrystallization (bubbles at 180 °C).

The ^1H NMR spectrum of dried (*R,R*),(*S,S*)-**22** gave δ 2.9–4.0 (m, OCH_2CH_2O, 16 H), 6.75 and 6.86 (d, Ar^3-H, 2 H), 7.03–8.0 (complex m, ArH, 22 H). The ^1H NMR spectrum of the dried (*R,S*)-**22** gave δ 3.0–4.0 (m, OCH_2CH_2O, 16 H), 6.9–7.9 (complex m, ArH, 24 H). The spectra of other cycles containing two binaphthyl units *of the same configuration* separated by a single ethylenedioxy unit exhibit signals at ca. δ 6.76 and 6.86, and are assigned to those protons at the 3 positions of the naphthalene rings that thrust into the face of a naphthalene ring of the attached binaphthyl unit, and are thus moved upfield by the shielding cone of the aromatic system.

By a similar procedure, (−)-(*S,S*)-**21** was converted (60%) to (−)-(*S,S*)-**22**: foam; M^+ 712; ^1H NMR spectrum identical with (*S,S*),(*R,R*)-**22**; $[\alpha]^{25}_{589}$ −212°, $[\alpha]^{25}_{578}$ −223°, $[\alpha]^{25}_{546}$ −265° (*c* 4.5, $CHCl_3$). Anal. Calcd for $C_{48}H_{40}O_6$: C, 80.88; H, 5.66. Found: C, 80.96; H, 5.95.

(−)-(*S,S*)-1,1,19,19-Tetraphenyl-3,4:5,6:14,15:16,17-tetra(1,2-naphtho)-2,7,13,18-tetraoxanonadeea-3,5,14,16-tetraene ((−)-(*S,S*)-23). A solution of (+)-(*S*)-2′-benzhydryloxy-2-hydroxy-1,1′-binaphthyl ((+)-(*S*)-**16**) (17.7 g or 0.0391 mol), 1,5-pentanediol ditosylate (8.06 g or 0.0196 mol), and KOH (2.84 g, 85% pellets, 0.043 mol in 10 mL of H_2O) in 400 mL of THF was refluxed for 24 h. The precipitated KOTs was filtered, the filtrate was evaporated in vacuo, and the residual oil was chromatograpned on 500 g of alumina. The desired product was eluted with CH_2Cl_2–pentane (3:7, v/v): weight 10.35 g (54%); white foam; ^1H NMR δ 0.92 (m, $OCH_2(CH_2)_3$, 6 H), 3.44 (t, $ArOCH_2$, 4 H), 6.00 (s, Ar_2CH, 2 H), 7.0, 7.7 (m, m, ArH, 48 H); M^+ 972; $[\alpha]^{25}_{578}$ −20.8°, $[\alpha]^{25}_{546}$ −25.5°, $[\alpha]^{25}_{436}$ −69.3° (*c* 0.8, $CHCl_3$). Anal. Calcd for $C_{71}H_{56}O_4$: C, 87.62; H, 5.80. Found: C, 87.32; H, 5.58.

(−)-(*S,S*)-1,1,19,19-Tetraphenyl-3,4:5,6:14,15:16,17-tetra(1,2-naphtho)-9,10,11-(1,3-benzo)-2,7,13,18-tetraoxanonadeca-3,5,9,14,16-pentaene ((−)-(*S,S*)-24). To a solution of 19.9 g (0.044 mol) of (+)-(*S*)-**16** in 400 mL of THF was added 4.93 g (0.044 mol) of *t*-BuOK. The solution was stirred under nitrogen for 10 min, and a solution of 5.80 g (0.022 mol) of 2,6-bis(bromomethyl)benzene in 100 mL of THF was added. The mixture was heated at reflux for 36 h, the solvent was evaporated *in vacuo*, and the residue was chromatographed on 700 g of alumina. The desired product eluted with CH_2Cl_2–pentane (1:3, v/v) to give 14.9 g (67%) of white foam: M^+ 1006; $[\alpha]^{25}_{578}$ −8.9°, $[\alpha]^{25}_{546}$ −11.7°, $[\alpha]^{25}_{436}$ −34.7° (*c* 0.6, $CHCl_3$). Anal. Calcd for $C_{74}H_{54}O_4$: C, 88.24; H, 5.40. Found: C, 88.02; H, 5.40.

(−)-(*S,S*)-2,3:4,5:13,14:15,16-Tetra(1,2-naphtho)-8,9,10-(1,3-benzo)-9-aza-1,6,12,17,20-pentaoxacyclodocosa-2,4,8,13,15-pentaene ((−)-(*S,S*)-25). Procedure IV was used except as follows. The benzhydryl groups were removed from 7.65 g (0.784 mmol) of (−)-(*S,S*)-**17**, and the derived bisphenol was mixed with *t*-BuOK (1.93 g, 1.725 mmol) and 2,6-bis(chloromethyl)pyridine (1.40 g, 7.84 mmol) in 200 mL of THF. The product was chromatographed on 250 g of alumina, and the desired product was eluted with from 2:3 to 1:1 CH_2Cl_2–pentane (v/v) to give 2.54 g (43%) of (−)-(*S,S*)-**25** as a foam dried at 110 °C for 20 h at 50 μm: ^1H NMR δ 2.9 (m, CH_2OCH_2, 4 H), 3.62 (pseudo-t, $ArOCH_2$, 4 H), 4.89 (s, $pyCH_2$, 4 H), 6.68, 6.76 (s, s, py-H-3, 2 H), 7.0–7.4, 7.7–7.9 (m, m, ArH, 27 H); $[\alpha]^{25}_{578}$ −241.9°, $[\alpha]^{25}_{546}$ −288.2°, $[\alpha]^{25}_{436}$ −664.9° (*c* 0.7, $CHCl_3$). Anal. Calcd for $C_{51}H_{39}NO_5$: C, 82.12; H, 5.27. Found: C, 82.33; H, 5.43.

(−)-(*S,S*)-2,3:4,5:13,14:15,16-Tetra(1,2-naphtho)-8,9,10-(1,3-benzo)-1,6,12,17,20-pentaoxacyclodocosa-2,4,8,13,15-pentaene ((−)-(*S,S*)-26). Proceudre IV was used except as follows. The benzhydryl groups were removed from 9.15 g (9.34 mmol) of (−)-(*S,S*)-**17**, and the bisphenol was mixed with 2.30 g (0.020 mol) of *t*-BuOK and 2.47g (9.34 mmol) of 1,3-bis(bromomethyl)benzene in 200 mL of THF. After 69 h of reflux under N_2, the products were isolated and chromatographed on 400 g of alumina, the desired product being eluted with 2:3 (v/v) CH_2Cl_2–pentane, which dried to a white foam: weight 0.9 g (13%); M^+ 744; ^1H NMR δ 2.78 (m, CH_2OCH_2, 4 H), 3.52 (t, $ArOCH_2$, 4 H), 4.80 (s, $ArOCH_2$, 4 H), 6.7–7.9 (complex m, ArH, 28 H); $[\alpha]^{25}_{589}$ −214.9°, $[\alpha]^{25}_{578}$ −230.5°, $[\alpha]^{25}_{546}$ −274.9°, $[\alpha]^{25}_{436}$ −629.9° (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{52}H_{40}O_5$: C, 83.85; H, 5.41. Found: C, 83.92; H, 5.57.

(−)-(*S,S*)-2,3:4,5:13,14:15,16-Tetra(1,2-naphtho)-8,9,10-(1,3-cyclopentano)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene ((−)-(*S,S*)-27). Proceudre IV was used except as follows. The benzhydryl groups were removed from 3.31 g (3.4 mmol) of (−)-(*S,S*)-**17**, and the derived bisphenol in 100 mL of THF was mixed with 0.60 g (9.00 mmol) of KOH in 5 mL of water and 3.96 g (9.00 mmol) of *cis*-2,5-bis(tosyloxymethyl)tetrahydrofuran[4b] in 20 mL of THF. After the mixture had refluxed under N_2 for 100 h, another 2.0 g (4.5 mmol) of the ditosylate and 0.30 g (4.5 mmol) of KOH was added, and the refluxing was continued for 100 h. The isolated mixed products were chromatographed on 200 g of alumina, and the desired product was eluted with CH_2Cl_2–pentane (1:1, v/v) to give after drying 0.65 g (26%) of (−)-(*S,S*)-**27** as a white glass: ^1H NMR δ 1.1–1.4 (m, $C(CH_2)_2C$, 4 H), 2.9–4.2 (m, 14 H, all other aliphatic H), 6.8–7.4 (m, ArH-3,6,7,8, 16 H), 7.6–8.1 (m, ArH-4,5, 8 H); M^+ 738; $[\alpha]^{25}_{589}$ −218°, $[\alpha]^{25}_{578}$ −229°, $[\alpha]^{25}_{546}$ 270°, $[\alpha]^{25}_{436}$ −599° (*c* 0.56, $CHCl_3$). Anal. Calcd for $C_{50}H_{42}O_6$: C, 81.28; H, 5.73. Found: C, 81.09; H, 5.67.

(−)-(*S,S*)-2,3:4,5:13,14:15,16-Tetra(1,2-naphtho)-1,6,9,12,17-pentaoxacyclodocosa-2,3,13,15-tetraene ((−)-(*S,S*)-28). Procedure IV was used except as follows. The benzhydryl groups were removed from 4.51 g (4.64 mmol) of (−)-(*S,S*)-**23**, and the bisphenol was mixed in 200 mL of THF with 1.14 g (10 mmol) of *t*-BuOK and diethylene glycol ditosylate (2.02 g, 4.9 mmol). The solution was refluxed for 48 h, and the product mixture was chromatographed on 200 g of alumina. The desired product was eluted with 3:7 (v/v) CH_2Cl_2–pentane to give after drying 1.36 g (41%) of (−)-(*S,S*)-**28** as a white foam: ^1H NMR δ 1.18 (m, $C(CH_2)_3C$, 6 H), 3.06 (m, CH_2OCH_2, 4 H), 3.70 (m, $ArOCH_2$, 8 H), 7.14, 7.80 (m, m, ArH, 24 H); M^+ 710 (base peak); $[\alpha]^{25}_{589}$ −193°, $[\alpha]^{25}_{578}$ −203°, $[\alpha]^{25}_{546}$ −241°, $[\alpha]^{25}_{436}$ −553° (*c* 0.15, $CHCl_3$). Anal. Calcd for $C_{49}H_{42}O_5$: C, 82.79; H, 5.96. Found: C, 82.80; H, 5.88.

(−)-(*S,S*)-2,3:4,5:13,14:15,16-Tetra(1,2-naphtho)-8,9,10-(1,3-benzo)-9-aza-1,6,12,17-tetraoxacyclodocosa-2,4,8,13,15-pentaene ((−)-(*S,S*)-29). Procedure IV was used except as follows. The benzhydryl groups were removed from 4.51 g (4.64 mmol) of (−)-(*S,S*)-**23** to give the bisphenol, which in 200 mL of THF was mixed with 1.14 g (10.21 mmol) of *t*-BuOK and 0.86 g (4.87 mmol) of 2,6-bis(chloromethyl)pyridine[4c] and refluxed for 48 h. The crude reaction product was chromatographed on 300 g of alumina, and the desired product was eluted with 2:3 (v/v) CH_2Cl_2–pentane to give after drying a white foam: weight 1.5 g (29%); ^1H NMR δ 0.80 (br s, $C(CH_2)_3C$, 6 H), 3.52 (br s, $ArOCH_2$, 4 H), 4.88 (s, py-CH_2, 4 H), 6.62, 6.73 (s, s, py-H-3,5, 2 H), 7.0–7.9 (complex m, ArH and py-H-4, 25 H); M^+ 743; $[\alpha]^{25}_{589}$ −240°, $[\alpha]^{25}_{578}$ −250°, $[\alpha]^{25}_{546}$ −301°, $[\alpha]^{25}_{436}$ −702° (*c* 0.50, $CHCl_3$). Anal. Calcd for $C_{52}H_{41}NO_4$: C, 83.96; H, 5.56. Found: C, 83.98; H, 5.69.

(−)-(*S,S*)-2,3:4,5:13,14:15,16-Tetra(1,2-naphtho)-8,9,10:19,20,21-di(1,3-benzo)-9-aza-1,6,12,17-tetraoxacyclodocosa-2,4,8,13,15,20-hexaene ((−)-(*S,S*)-30). Procedure IV was used except as follows. The benzhydryl groups were removed from 15.8 g (0.016 mol) of (−)-(*S,S*)-**24** to give the bisphenol, which in 300 mL of THF was mixed with 3.86 g (0.0345 mol) of *t*-BuOK and 2.76 g (0.016 mol) of 2,6-bis(chloromethyl)pyridine[4c] in 100 mL of THF. The mixture was refluxed for 42 h, an additional 1.0 g of 2,6-bis(chloro)-pyridine and 1.5 g of *t*-BuOK were added, and refluxing was continued for an additional 24 h. The product mixture was chromatographed on 500 g of alumina, and the desired product was eluted with from 1:1 CH_2Cl_2–pentane (v/v) to pure CH_2Cl_2 to give after drying (−)-(*S,S*)-**30** as a white foam: weight 5.3 g (43%); ^1H NMR δ 4.57 (s, $ArOCH_2$, 4 H), 4.82 (AB, J = 4 Hz, $ArOCH_2$, 4 H), 6.40–7.90 (complex m, ArH, 31 H); M^+ 777; $[\alpha]^{25}_{589}$ −269°, $[\alpha]^{25}_{578}$ −283°, $[\alpha]^{25}_{546}$ −339°, $[\alpha]^{25}_{436}$ −798° (*c* 0.54, $CHCl_3$). Anal. Calcd for $C_{55}H_{39}O_4N$: C, 84.92; H, 5.05. Found: C, 84.83; H, 5.18.

Syntheses of (*R*),(*S*)- or (+)-(*S*)-2,3:4,5-Di(1,2-naphtho)-1,6-dioxacycloocta-2,4-diene ((*R*),(*S*)-3 and (+)-(*S*)-3), (*R,S*)-2,3:4,5:10,11:12,13-Tetra(1,2-naphtho)-1,6,9,14-tetraoxacyclohexadeca-2,4,10,12-tetraene ((*R,S*)-32), (*R,R,R*),(*S,S,S*)-, (*R,S,S*),(*S,R,R*)-, and (−)-(*S,S,S*)-2,3:4,5:10,11:12,13:18,19:20,21-hexaene ((*R,R,R*),(*S,S,S*)-31, (*R,S,S*),(*S,R,R*)-31, and (−)-(*S,S,S*)-31), and of Anomalous Ketone 8 and (+)-8 from Diethylene Glycol Ditosylate and (*R*),(*S*)- or (−)-(*S*)-2,2′-Dihydroxy-1,1′-binaphthyl ((±)-1 and (−)-(*S*)-1). A mixture of (±)-1 (10.0 g, 34.9 mmol), *t*-BuOK (7.83 g, 69.8 mmol), and ethylene glycol ditosylate (12.93 g, 34.9 mmol) in 600 ml of THF was prepared. The

mixture was stirred under N_2 for 20 h at 25 °C, refluxed for 44 h, and cooled, and the product mixture was isolated as 11.2 g of tan solid. This material in CH_2Cl_2 was filtered through 100 g of neutral alumina to give 10.1 g of light yellow solid. This material was rechromatographed on 150 g of silica gel. Pentane–ether (94:6, v/v) eluted cycle **3**, then a mixture of **3** and ketone **8**, and finally **8** itself. Pentane–benzene (1:1, v/v) and then benzene eluted, in this order, **8**, cycle (*R,S*)-**32**, (*R,S,S*),(*S,R,R*)-**31**, and (*R,R,R*),(*S,S,S*)-**31**. The combined latter fractions were rechromatographed on 300 g of silica gel with benzene as eluting agent. Preparative thick-layer chromatography on silica gel plates with CH_2Cl_2–pentane (4:6 v/v) as developer applied to the appropriate fractions provided samples of the last three compounds. Cycle (±)-**3**, after recrystallization from pentane–ether, weighed 2.46 g (23%): mp 222–223 °C; UV spectrum in $CHCl_3$ gave λ_{max} at 325 (log ϵ 3.76) and 298 (log ϵ 4.07) with shoulders at 317 and 291 nm; M^+ 312; Rast molecular weight in camphor, 391; ^1H NMR δ 4.00–4.36 (m, $ArOCH_2$, 4 H), 7.40 (m, ArH, 8 H), 7.76–7.92 (m, ArH, 4 H). Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.52; H, 5.33. Recrystallization of ketone **8** from pentane–ether gave 4.80 g (44%) of light yellow crystals: mp 196.5–198 °C, sublimation of which at 200 °C (10 μm) gave mp 198–200 °C; M^+ 312; Rast molecular weight in camphor, 338; UV spectrum ($CHCl_3$) gave λ_{max} at 289 (log ϵ 4.10) and 278 (log ϵ 4.00) and shoulders at 331 and 268 nm; IR spectrum (KBr), strong band at 1660 cm^{-1} (C=O); ^1H NMR δ 2.22 (symmetric m, CCH_2, 2 H), 4.18 (symmetric m, OCH_2, 2 H), 6.22–6.50 (m, CH=CH, 2 H) 6.68–7.70 (m, ArH, 10 H). Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.61; H, 5.30. The smaller cycle (*R,S*)-**32** was separated from the larger (*R,S,S*),(*S,R,R*)-**31** by fractional sublimation at 250 °C (10 μm) to give 0.085 g (1%) of (*R,S*)-**32** as white crystals: mp 355 °C dec; M^+ 624; UV spectrum λ_{max} 336 (log ϵ 4.06), 323 (log ϵ 4.02), 292 (log ϵ 4.26), 282 (log ϵ 4.06), with a shoulder at 273 nm. Anal. Calcd for $C_{44}H_{32}O_4$: C, 84.59; H, 5.16. Found: C, 84.54; H, 5.03. Preparative thick-layer chromatography of the mixture of (*R,S*)-**32** and (*R,S,S*),(*S,R,R*)-**31** gave the latter, which was recrystallized from ether to give 52 mg (0.5%) of fine crystals: mp 188–190 °C; UV spectrum ($CHCl_3$) λ_{max} 355 (log ϵ 4.15), 324 (log ϵ 4.14), 292 (log ϵ 4.38) and 282 (log ϵ 4.44) with a shoulder at 273 nm; M^+ 937; ^1H NMR spectrum δ 3.62–4.02 (m, $ArOCH_2$, 12 H), 6.52–7.96 (br m, ArH, 36 H). Anal. Calcd for $C_{66}H_{48}O_6$: C, 84.59; H, 5.16. Found: C, 84.49; H, 5.08. Preparative thick-layer chromatography of the mixture of (*R,S,S*),(*S,R,R*)-**31** and (*S,S,S*),(*R,R,R*)-**31** led to pure (*S,S,S*),(*R,R,R*)-**31**, which was recrystallized from a large volume of ether to give 30 mg of white crystals: mp 338–342 °C dec; UV spectrum λ_{max} 335 (log ϵ 4.12), 325 (log ϵ 4.17), 293 (log ϵ 4.41), and 282 (log ϵ 4.46) with a shoulder at 273 nm; M^+ 937. This material was too insoluble for a ^1H NMR spectrum. Anal. Calcd for $C_{66}H_{48}O_6$: C, 84.59; H, 5.16. Found: C, 84.47; H, 5.45.

When 8.6 g of (*R*),(*S*)-**1**, 6.75 g of *t*-BuOK, and 11.1 g of ethylene glycol ditosylate in 100 mL of DMF were stirred under nitrogen at 70 °C for 70 h, product was obtained which was chromatographed on alumina to give, after crystallization from ether–CH_2Cl_2, 6.1 g (65%) of (*R*),(*S*)-**3**: mp 221–223 °C, undepressed by admixture with authentic material.

Treatment of 0.50 g of (−)-(*S*)-**1** by the first procedure (THF–*t*-BuOK) gave (+)-(*S*)-**3**: weight 0.113 g (21%); mp 216.5–217 °C; UV and ^1H NMR spectra and TLC behavior identical with (±)-**3**; $[\alpha]^{25}_{578}$ +546°, $[\alpha]^{25}_{546}$ +628°, $[\alpha]^{25}_{436}$ +1116°, $[\alpha]^{25}_{365}$ +1427° (*c* 0.93, CH_2Cl_2). Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.49; H, 5.10. Also produced was 0.221 g (40%) of ketone (+)-**8**: mp 187–188 °C; UV and ^1H NMR spectra and TLC behavior identical with (±)-**8**; $[\alpha]^{25}_{578}$ +247°, $[\alpha]^{25}_{546}$ +314°, $[\alpha]^{25}_{436}$ +1324° (c 0.97, CH_2Cl_2). Also obtained was 9 mg (1.7%) of (−)-(*S,S,S*)-**31**: glass; phase transition, 185–200 °C; M^+ 937; UV spectrum and TLC behavior identical with (*R,R,R*),(*S,S,S*)-**31**; analysis and ^1H NMR spectrum are recorded for the sample whose preparation is described in the next section.

Ketone (±)-**8**, 200 mg, was reduced in 15 mL of methanol containing 1 drop of 6 N NaOH solution with 200 mg of $NaBH_4$. The mixture was stirred at 25 °C for 0.5 h, then refluxed for an additional 0.5 h. The solvent was evaporated, and the residue was distributed between water and CH_2Cl_2. The organic phase was washed with water and dried, the solvent was evaporated, and the residual oil was submitted to thick layer chromatographic separation on a silica gel plate with CH_2Cl_2–pentane (4:6, v/v) as developer. The faster moving spot, probably **9**, gave 174 mg (87%) of crystalline material: mp 136–138 °C; IR spectrum, no C=O absorption, but O–H bonds at 3590 and 3400 cm^{-1}. Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.82; H, 6.05. The slower moving isomer, probably **10**, was obtained as 9 mg of crystalline material, mp 156–157 °C, and was not further characterized.

(*R*),(*S*)- and (−)-(*S*)-1,7-Dihydroxy-4,5:6,7-di(1,2-naphtho)-3-oxahepta-4,6-diene ((*R*),(*S*)-33 and (−)-(*S*)-33) and (*R*),(*S*)- and (−)-(*S*)-1,10-Dihydroxy-4,5:6,7-di(1,2-naphtho)-3,8-dioxadeca-4,6-diene ((*R*),(*S*)-34 and (−)-(*S*)-34). To a stirred solution of (*R*),(*S*)-**1** (50.0 g, 0.175 mol) in 1.8 L of THF was added 23.5 g (0.21 mol) of *t*-BuOK, and the mixture was heated to reflux under N_2. A solution of ethyl chloroacetate (25.8 g, 0.21 mol) in 30 mL of THF was added (30 min), and the reflux was continued for 14 h. The solvent was evaporated and the residue was distributed between 600 mL of ether and 400 mL of water. The ether layer was washed with water, dried, evaporated to 300 mL volume, and added dropwise to a slurry of 7.0 g (0.184 mol) of $LiAlH_4$ in 1.5 L of anhydrous ether. The mixture was stirred at 25 °C for 12 h, and 3 mL of ethyl acetate was added, followed by 400 mL of 6 N HCl solution. The mixture was stirred for 4 h, the **33** that separated was filtered, and the ether layer of the filtrate was extracted with three 80-mL portions of 2 N KOH in water–methanol (2:1, v/v). The ether layer was washed with water, dried, and evaporated, and the residue was crystallized from benzene–hexane to give 9.8 g (15%) of (*R*),(*S*)-**34**: mp 112–113 °C. Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 76.81; H, 5.76. The basic combined aqueous extracts were acidified with concentrated aqueous HCl, and the precipitate was filtered. This material was dissolved in a minimum amount of hot THF, and the solution was added to a threefold volume of ether. The precipitate (**33**) was collected, the filtrates were evaporated, and the process was repeated to give more **33**. From the final filtrates was recovered 10.0 g (20%) of **1**. The combined samples of **33** were recrystallized from ethanol–THF to give 23.2 g (40%) of fine crystals of (*R*),(*S*)-**33**: mp 209–211 °C; ^1H NMR (CD_3SOCD_3) δ 3.32 (m, OCH_2, 2 H), 3.92 (m, OCH_2, 2 H), 3.9 (s, OH, 2 H), 6.7–7.9 (m, ArH, 12 H). Anal. Calcd for $C_{22}H_{18}O_3$: C, 79.98; H, 5.49. Found: C, 79.77; H, 5.49.

A similar procedure applied to (−)-(*S*)-**1** gave (+)-(*S*)-**33** (43%) as an oil, $[\alpha]^{25}_{546}$ +12.9° (c 1.2, THF), whose spectral and TLC properties were the same as (*R*),(*S*)-**33**. Also obtained was (+)-(*S*)-**34** [19%, mp 133–134 °C, $[\alpha]^{25}_{546}$ +23.2° (*c* 1.05, THF)], whose spectral and TLC properties were the same as (*R*),(*S*)-**34**. The two compounds were easily separated by silica gel chromatography. The crude recovered (−)-(*S*)-**1** exhibited 98% of its original optical rotation.

(−)-(*S,S*)-, (*R,R*),(*S,S*)-, and (*R,S*)-1,18-Dihydroxy-4,5:6,7:12,13:14,15-tetra(1,2-naphtho)-3,8,11,16-tetraoxadeca-4,6,12,14-tetraene ((−)-(*S,S*)-35, (*R,R*),(*S,S*)-35, and (*R,S*)-35). A mixture of 6.5 g (0.058 mol) of *t*-BuOK was added to a stirred solution under N_2 of 18.9 g (0.057 mol) of (*R*),(*S*)-**33** in 600 mL of THF, followed by 10.7 g (0.029 mol) of ethylene glycol ditosylate in 100 mL of THF. The mixture was refluxed for 28 h, the solvent was evaporated (vacuum), and the oily residue was dissolved in a 4:1 (v/v) mixture of ether–CH_2Cl_2. This solution was washed three times with a 2 N KOH solution in 2:1 (v/v) water–methanol, then water, and was then dried. Evaporation of the solvent in small portions yielded, after drying under vacuum, 18.3 g (93%) of crude **35** (diastereomeric mixture) as a solid foam.

A solution of 8.5 g (0.012 mol) of this mixture in 30 mL of benzene was added to a solution of freshly prepared 3,5-dinitrobenzoyl chloride (8.5 g, 0.037 mol) in 100 mL of benzene. The mixture was refluxed for 12 h, the solvent was evaporated (vacuum), and the residual oil was chromatographed on 800 g of silica gel in CH_2Cl_2 to give first (*R,S*)-**37** and then (*R,R*),(*S,S*)-**37**. Each isomer was recrystallized from acetone–ether to produce 2.8 g (21%) of (*R,S*)-**37**, mp 124–126 °C, and 4.0 g (30%) of (*R,R*),(*S,S*)-**37**, mp 174–176 °C. The *R,S* isomer gave a ^1H NMR spectrum δ 4.05 (m, CH_2CH_2, 12 H), 6.80–8.0 (m, ArH, 24 H), 8.6 (d, ArH, 4 H), 9.10 (t, ArH, 2 H). Anal. Calcd for $C_{60}H_{42}O_{16}N_4$: C, 67.03; H, 3.94. Found: C, 66.78; H, 4.01. The (*R,R*),(*S,S*) isomer gave an ^1H NMR spectrum δ 3.95 (s, OCH_2, 4 H), 4.28 (m, OCH_2, 8 H), 6.82–8.0 (m, ArH, 24 H), 9.10 (t, ArH, 2 H). Anal. Calcd for $C_{60}H_{42}O_{16}N_4$: C, 67.03; H, 3.94. Found: C, 67.01; H, 3.80.

To a solution of (*R,R*),(*S,S*)-**37** (2.4 g, 2.23 mmol) in 60 mL of THF and 30 mL of water was added 0.350 g (6.2 mmol) of KOH. The mixture was stirred at 25 °C for 12 h, the solvent was evaporated, and the residue was dissolved in CH_2Cl_2. This solution was washed with water, dried, and evaporated under vacuum to give 1.4 g (91%) of (*R,R*),-(*S,S*)-**35** as a foam: transition point 95–105 °C; ^1H NMR δ 2.08 (s, OH, 2 H), 3.45 (m, OCH_2, 4 H), 3.82 (s, OCH_2, 4 H), 3.94 (m, OCH_2, 4 H), 6.78–8.00 (m, ArH, 24 H). Anal. Calcd for $C_{46}H_{38}O_6$: C, 80.44; H, 5.58. Found: C, 79.78; H, 5.50. By a similar procedure, (R,S)-**37** was converted to (*R,S*)-**35** (92%), which was a foam: transition point 95–105 °C; ^1H NMR δ 1.80 (s, OH, 2 H), 3.32 (m, OCH_2, 4 H), 3.81 (m, OCH_2, 8 H), 6.80–8.00 (m, ArH, 24 H). Anal. Calcd for $C_{46}H_{38}O_6$: C, 80.44; H, 5.58. Found: C, 80.30; H, 5.60.

By a procedure similar to that applied to the conversion of (*R*),-(*S*)-**33** to the mixture of (*R,R*)(*S,S*)-**35** and (*R,S*)-**35**, (−)-(*S*)-**33** was converted to (−)-(*S,S*)-**35** (85%, $[\alpha]^{25}_{546}$ −55.8° (c 1.0, THF)), which

was purified by chromatography on silica gel. The material gave the same NMR spectrum and TLC behavior as (*R,R*),(*S,S*)-**35**.

(−)-(*S,S*)-, (*R,R*),(*S,S*)-, and (*R,S*)-1,18-Ditosyloxy-4,5:6,7:12,13:14,15-tetra(1,2-naphtho)-3,8,11,16-tetraoxaoctadeca-4,6,12,14-tetraene ((−)-(*S,S*)-36, (*R,R*),(*S,S*)-36, and (*R,S*)-36). The procedure is illustrated as follows. The mixture of (*R,R*),(*S,S*)-**35** and (*R,S*)-**35** (see above), 10.0 g (14.6 mmol) in 80 mL of dry pure pyridine, was cooled to −3 °C, and 8.3 g (43 mmol) of tosyl chloride was added in one portion. The mixture was stirred for 30 min at 0 °C, and held at 0 °C for 7 days. The mixture was stirred in 500 mL of ice water for 45 min, and the precipitate was filtered, washed with water, and dried in vacuum over solid KOH. The crude material (12.5 g) was dissolved in 450 mL of CH_2Cl_2 and rapidly chromatographed on 70 g of silica gel to give 7.6 g (52%) of a mixture of (*R,R*),(*S,S*)-**36** and (*R,S*)-**36** as a white powder: mp 175–190 °C; ^1H NMR δ 2.30 (s, $ArCH_3$, 6 H), 3.9 (m, OCH_2, 12 H), 6.8–8.0 (m, ArH, 32 H).

Similarly (*R,R*),(*S,S*)-**35** was converted to (*R,R*),(*S,S*)-**36** (50%): mp 204–205.5 °C; ^1H NMR δ 2.30 (s, $ArCH_3$, 6 H), 3.90 (m, OCH_2, 12 H), 6.8–8.0 (m, ArH, 32 H). Anal. Calcd for $C_{60}H_{50}O_{10}S_2$: C, 72.42; H, 5.06. Found: C, 72.38; H, 4.97. Similarly (*R,S*)-**35** was converted to (*R,S*)-**36** (52%): mp 217–219 °C (too insoluble for an ^1H NMR spectrum). Anal. Calcd for $C_{60}H_{50}O_{10}S_2$: C, 72.42; H, 5.06. Found: C, 72.25; H, 5.03. Similarly (−)-(*S,S*)-**35** was converted to (+)-(*S,S*)-**36** (37%, mp 172–174 °C), whose ^1H NMR and TLC properties were identical with those of (*R,R*),(*S,S*)-**36**: $[\alpha]^{25}_{546}$ +68.2° (*c* 1.00, THF).

(*R,R,R*),(*S,S,S*)-, (*R,S,S*),(*S,R,R*)-, (−)-(*S,S,S*)-, and (−)-(*R,S,S*)-2,3:4,5:10,11:12,13:18,19:20,21-hexa(1,2-naphtho)-1,6,9,14,17,22-hexaoxacyclotetracosa-2,4,10,12,18,20-hexaene ((*R,R,R*),(*S,S,S*)-, (*R,S,S*),(*S,R,R*)-, (−)-(*S,S,S*)-, and (−)-(*R,S,S*)-31). A mixture of (*R*),(*S*)-**1** (1.5 g, 5.25 mmol) and K_2CO_3 (0.75 g, 5.5 mmol) was heated for 2 h at 80 °C in 50 mL of DMF under N_2 with stirring. This mixture was added in one portion to a warm solution of 5 g (5.0 mmol) of the diastereomeric mixture of ditosylates (*R,R*),(*S,S*)- and (*R,S*)-**36** in 350 mL of DMF. The resulting mixture was stirred under N_2 for 30 h at 80 °C, the solvent was evaporated under vacuum, and the residue in 400 mL of CH_2Cl_2 was filtered through 150 g of silica gel to give 3.4 g (68%) of a mixture of diastereomeric cycles as a white solid. Extraction of this material with three 20-mL portions of CH_2Cl_2 left 0.6 g of (*R,R,R*),(*S,S,S*)-**31** undissolved. The extract was concentrated and chromatographed on 300 g of silica gel. The first fractions of CH_2Cl_2 eluate contained 2.0 g of pure (*R,S,S*),(*S,R,R*)-**31**, and the middle fractions contained 0.2 g of additional (*R,R,R*),(*S,S,S*)-**31**, which was combined with the first sample. The 0.8 g of (*R,R,R*),(*S,S,S*)-**31** was dissolved in 140 mL of hot dioxane, the solution was cooled, and 120 mL of ether was added. The pure (*R,R,R*),(*S,S,S*)-**31** crystallized: weight 0.72 g (14%); mp 335–340 °C (decomposition by isomerization); M^+ 936; ^1H NMR δ 3.49–3.94 (m, CH_2CH_2, 12 H), 6.62, 6.78 (d, ArH-3, 6 H), 6.85, 8.12 (m, ArH, 36 H). Anal. Calcd for $C_{66}H_{48}O_6$: C, 84.59; H, 5.16. Found: C, 84.47; H, 5.45. The (*R,S,S*),(*S,R,R*)-**31** was recrystallized from benzene–cyclohexane to give 1.8 g (36%) of pure isomer: mp 185–187 °C; M^+ 936; ^1H NMR δ 3.41–3.94 (m, $ArOCH_2$, 12 H), 6.58, 6.75 (d, ArH-3, 2 H), 6.85–8.13 (m, ArH, 36 H). Anal. Calcd for $C_{66}H_{48}O_6$: C, 84.59; H, 5.16. Found: C, 84.43; H, 5.25. Values for R_f were 0.65 and 0.75 on silica gel in CH_2Cl_2 for (*R,R,R*),(*S,S,S*)-**31** and (*R,S,S*),(*S,R,R*)-**31**, respectively.

In similar experiments, pure ditosylate (*R,S*)-**36** was treated with (*R*),(*S*)-**1** to give *only* (*R,S,S*),(*S,R,R*)-**31** (mp 185–187 °C; 60%) whereas pure ditosylate (*R,R*),(*S,S*)-**36** treated with (*R*),(*S*)-**1** gave 30% (*R,S,S*),(*S,R,R*)-**31**, mp 185–187 °C, and 16% (*R,R,R*),(*S,S,S*)-**31**, mp 345–350 °C dec. Similarly, from ditosylate (+)-(*S,S*)-**36** and (−)-(*S*)-**1** was obtained (−)-(*S,S,S*)-**31** (46%): white solid with a phase transition at 185–200 °C (solid → foam) and ~250 °C (foam to liquid); M^+ 936; $[\alpha]^{25}_{546}$ −175° (*c* 1.0, THF). Anal. Calcd for $C_{66}H_{48}O_6$: C, 84.59; H, 5.16. Found: C, 84.43; H, 5.31. Similarly, from ditosylate (+)-(*S,S*)-**36** and (+)-(*R*)-**1** was obtained (−)-(*S,S,R*)-**31** (58%): M^+ 936; mp 247–249 °C; $[\alpha]^{25}_{546}$ −141° (*c* 1.0, THF). Anal. Calcd for $C_{66}H_{48}O_6$: C, 84.59; H, 5.16. Found: C, 84.49; H, 5.20.

Comparisons of the ^1H NMR spectra of (−)-(*S,S,S*)-**31** and (−)-(*S,R,R*)-**31** showed differences in the ArH chemical shift region. Both compounds gave a high-field doublet (part of an AX system) at about δ 6.6–6.8 due to the H-3 protons of the binaphthyl system. Integration of the spectrum of (−)-(*S,S,S*)-**31** indicated the presence of six protons, whereas that of (−)-(*R,S,S*)-**31** gave only two such protons. Examination of CPK molecular models of the diastereomers indicates that when two binaphthyl units are connected by an ethylene glycol bridge, each *S,S* configurational relationship between binaphthyls places two naphthalene H-3 protons in the shielding cone of a transannular naphthyl group, whereas each *R,S* configurational relationship places two naphthalene H-3 protons in the deshielding cone of a transannular naphthyl group. Thus (−)-(*S,S,S*)-**31** has three *S,S*-binaphthyl relationships and should have six upfield shifted C-3 protons, and (−)-(*R,S,S*)-**31** has one *S,S* relationship and should have two upfield shifted C-3 protons, as was observed.

Thermal Equilibration of (*R,S,S*),(*S,R,R*)-31 and (*R,R,R*),-(*S,S,S*)-31. Vials of about 10 mg of each of the above diastereoisomers were sealed under vacuum and placed in a Woods metal bath at a temperature of 340 °C for 7 min. The vials were opened, and the material was dissolved in CH_2Cl_2 and the isomers separated by TLC on silica gel. The separate spots were eluted, and the relative amounts of each isomer were estimated to be about equal (±5%) from the intensities of their UV spectra compared to standards.

Registry No.—(±)-**1**, 41024-90-2; (+)-(*R*)-**1**, 18531-94-7; (−)-(*S*)-**1**, 18531-99-2; (−)-(*S*)-**1** *l*-menthoxyacetyl chloride monoester, 63731-41-9; **2**, 41051-91-6; (±)-**3**, 55442-18-7; (+)-(*S*)-**3**, 55515-85-0; (±)-**4**, 41024-96-8; (+)-(*S*)-**4**, 41051-92-7; (−)-(*S*)-**5**, 55442-00-7; (−)-(*S*)-**6**, 55442-01-8; (±)-**7**, 53783-48-2; (−)-(*S*)-**7**, 41024-92-4; **8**, 55442-19-8; (+)-**8**, 55515-86-1; **9**, 63731-42-0; (−)-(*S,S*)-**14**, 54108-54-2; (*R,S*)-**15**, 41024-94-6; (*R,R*),(*S,S*)-**15**, 41024-97-9; (−)-(*S,S*)-**15**, 41024-93-5; (+)-(*R,R*)-**15**, 41024-95-7; (±)-**16**, 55515-79-2; (+)-(*S*)-**16**, 55442-12-1; (−)-(*S,S*)-**17**, 55442-13-2; (−)-(*S,S*)-**17** free alcohol, 57244-65-2; (±)-**18** free alcohol, 55441-93-5; (±)-**18**, 55441-94-6; (−)-(*S*)-**18**, 55515-77-0; (+)-(*R*)-**18**, 55821-78-8; (±)-**19**, 55442-86-9; **20**, 41024-87-7; **20** free alcohol, 41757-99-7; (*R,S*)-**21**, 55442-14-3; (*R,R*),(*S,S*)-**21**, 55515-80-5; (−)-(*S,S*)-**21**, 55515-83-8; (*R,S*)-**22**, 55442-15-4; (*R,R*),(*S,S*)-**22**, 55515-81-6; (−)-(*S,S*)-**22**, 55515-84-9; (−)-(*S,S*)-**23**, 57244-63-0; (−)-(*S,S*)-**23** free alcohol, 57244-66-3; (−)-(*S,S*)-**24**, 57244-64-1; (−)-(*S,S*)-**24** free alcohol, 57244-67-4; (−)-(*S,S*)-**25**, 59346-20-2; (−)-(*S,S*)-**26**, 59346-25-7; (−)-(*S,S*)-**27**, 63731-43-1; (−)-(*S,S*)-**28**, 57244-68-5; (−)-(*S,S*)-**29**, 59346-21-3; (−)-(*S,S*)-**30**, 59346-26-8; (*R,S,S*),(*S,R,R*)-**31**, 55528-99-9; (*S,S,S*),(*R,R,R*)-**31**, 55442-21-2; (−)-(*S,S,S*)-**31**, 55515-87-2; (−)-(*S,S,R*)-**31**, 55515-94-1; (±)-**32**, 55442-20-1; (±)-**33**, 55442-22-3; (+)-(*S*)-**33**, 55515-89-4; (±)-**34**, 55441-95-7; (+)-(*S*)-**34**, 55515-88-3; (*R,R*),(*S,S*)-**35**, 55442-24-5; (*R,S*)-**35**, 63731-44-2; (−)-(*S,S*)-**35**, 55515-93-0; (*R,S*)-**36**, 55515-92-9; (*R,R*),(*S,S*)-**36**, 55442-25-6; (+)-(*S,S*)-**36**, 55529-00-5; (*R,S*)-**37**, 63731-45-3; (*R,R*),(*S,S*)-**37**, 55442-23-4; *l*-menthoxyacetyl chloride, 15356-62-4; pentaethylene glycol dichloride, 5197-65-9; pentaethylene glycol ditosylate, 41024-91-3; triethylene glycol ditosylate, 19249-03-7; diethylene glycol dichloride, 111-44-4; 2-(2′-chloroethoxy)ethyl 2″-tetrahydropyranyl ether, 54533-84-5; tosyl chloride, 98-59-9; benzhydryl bromide, 776-74-9; diethylene glycol ditosylate, 7460-82-4; 2,6-bis(chloromethyl)pyridine, 3099-28-3; 2-(2-chloroethoxy)ethyl 2-tetrahydrofuranyl ether, 63731-46-4; catechol, 120-80-9; ethylene glycol ditosylate, 6315-52-2; 1,3-bis(bromomethyl)benzene, 626-15-3; *cis*-2,5-bis(tosyloxymethyl)tetrahydrofuran, 1472-00-0; ethyl chloroacetate, 105-39-5; 3,5-dinitrobenzoyl chloride, 99-33-2; 1,5-pentanediol ditosylate, 24293-28-5; tetraethylene glycol ditosylate, 37860-51-8.

References and Notes

(1) This work was supported by the U.S. Public Health Service, Research Grant No. GM 12640-11, from the Department of Health, Education and Welfare, and by a grant from the National Science Foundation, GP 33533X.

2) Some of these results were outlined in communications: (a) E. P. Kyba, M. G. Siegel, L. R. Sousa, G. D. Y. Sogah, and D. J. Cram, *J. Am. Chem. Soc.*, **95**, 2691 (1973); (b) E. P. Kyba, K. Koga, L. R. Sousa, M. G. Siegel, and D. J. Cram, *ibid.*, **95**, 2692 (1973); (c) G. W. Gokel, J. M. Timko, and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, **444** (1975); (d) F. de Jong, M. G. Siegel, and D. J. Cram, *ibid.*, 551 (1975); (e) M. Newcomb, G. W. Gokel, and D. J. Cram, *J. Am. Chem. Soc.*, **96**, 6810 (1974).

(3) (a) National Research Council of Canada Postdoctoral Fellow, 1971–1972. (b) Grants are gratefully acknowledged from the Netherlands American Commission for Educational Exchange under Sponsorship of the Fulbright–Hayes program, and the Netherlands Organization for the Advancement of Pure Research (Z.W.O.). (c) Public Health Service International Postdoctoral Research Fellow, 1971–1972. (d) National Institutes of Health Postdoctoral Fellow, 1971–1972. (e) African–American Institute, AFGRAD Fellow.

(4) (a) E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, T. L. Tarnowski, S. S. Moore, and D. J. Cram, *J. Am. Chem. Soc.*, **99**, 2564 (1977); (b) J. M. Timko, S. S. Moore, D. M. Walba, P. Hiberty, and D. J. Cram, *ibid.*, **99**, 4207 (1977); (c) M. Newcomb, J. M. Timko, D. M. Walba, and D. J. Cram, *ibid.*, **99**, 6392 (1977); (d) S. S. Moore, T. L. Tarnowski, M. Newcomb, and D. J. Cram, *ibid.*, **99**, 6398 (1977); (e) M. Newcomb, S. S. Moore, and D. J. Cram, *ibid.*, **99**, 6405 (1977); (f) R. C. Helgeson, T. L. Tarnowski, J. M. Timko, and D. J. Cram, *ibid.*, **99**, 6411 (1977).

(5) J. Jacques and C. Fouquay, *Tetrahedron Lett.*, 4617 (1971).

(6) *c* 0.87–1.0, THF.

(7) (a) H. Akimoto, T. Shioiri, Y. Iitaka, and S. Yamada, Tetrahedron Lett., 97 (1968); (b) H. Akimoto and Y. Iitaka, *Acta Crystallogr., Sect. B*, **25**, 1491 (1969); (c) I. Hanazaki and H. Akimoto, *J. Am. Chem. Soc.*, **94**, 4102 (1972); (d) H. Akimoto and S. Yamada, *Tetrahedron*, **27**, 5999 (1971).

(8) (a) J. Dale and P. O. Kristianson, *Acta Chem. Scand.*, **26**, 1471 (1972); (b) S. Z. Perry and H. Hibbert, *Can. J. Res., Sect. B*, **14**, 77 (1936).
(9) C. J. Pedersen's conditions, *J. Am. Chem. Soc.*, **89**, 2495, 7017 (1967).
(10) G. D. Y. Sogah and D. J. Cram, unpublished work.
(11) J. E. Simpson, H. G. Daub, and F. N. Hayes, *J. Org. Chem.*, **38**, 1771 (1973), describe a synthesis of **3**, but report mp 197–198.5 °C similar to our **8** (mp 198–200 °C), but dissimilar to our **3** (mp 222–223 °C).
(12) E. Wenkert, R. D. Youssefyeh, and R. G. Lewis, *J. Am. Chem. Soc.*, **82**, 4675 (1960).
(13) Webster's New Collegiate Dictionary, 1973 edition, defines *loculus* as "a small chamber or cavity," and *locular* as the adjactival form "having or composed of loculi."
(14) D. Live and S. I. Chan, *J. Am. Chem. Soc.*, **98**, 3769 (1976).

Application of the Salicylidenimino Chirality Rule to Chiral 1-Alkyl-2-propynylamines and 1-Alkyl-2-propenylamines[1]

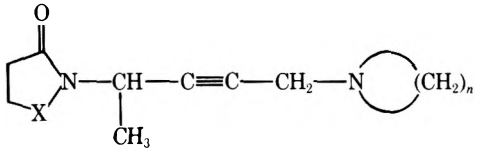
Björn Ringdahl,[2a] Howard E. Smith,*[2b] and Fu-Ming Chen[2c]

Department of Organic Pharmaceutical Chemistry, Biomedical Center, University of Uppsala, S-751 23 Uppsala, Sweden, and Departments of Chemistry, Vanderbilt University, Nashville, Tennessee 37235, and Tennessee State University, Nashville, Tennessee 37203

Received May 3, 1977

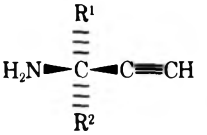
The sign of the Cotton effects near 255 and 315 nm in the circular dichroism (CD) spectra of the *N*-salicylidene derivatives of chiral 1-alkyl-2-propynylamines and 1-alkyl-2-propenylamines correlates with their absolute configurations. The Cotton effects are generated by the coupled oscillator mechanism and their sign is the same as the chirality (right-handed screw for positive chirality) of the triple and the double bond with the phenyl group–methine bond of the salicylidenimino chromophore. The chirality is determined by both the absolute configuration and the preferred conformation of the respective *N*-salicylidene derivatives. Thus those derivatives with the *R* configuration display negative Cotton effects near 255 and 315 nm, and those with the *S* configuration, positive.

In connection with the study of the stereospecific blockade of the motor effects of the muscarinic agent oxotremorine, *N*-(4-pyrrolidino-2-butynyl)-2-pyrrolidone, by *N*-(4-*tert*-amino-1-methyl-2-butynyl)-substituted succinimides (**1**) and 2-pyrrolidones (**2**),[3] the respective enantiomers of **1** and **2** were

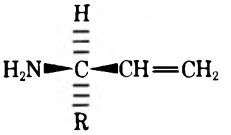


1a, X = CO; *n* = 4
b, X = CO; *n* = 6
2, X = CH_2; *n* = 4

prepared from the enantiomers of 1-methyl-2-propynylamine (**3a**),[3] the absolute configurations of the latter being rigorously

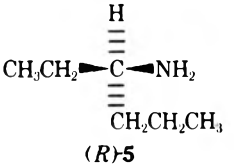


(*R*)-**3a**, R^1 = H; R^2 = CH_3
b, R^1 = H; R^2 = CH_3CH_2
c, R^1 = H; R^2 = $CH_3CH_2CH_2$
d, R^1 = CH_3; R^2 = CH_3CH_2



(*R*)-**4a**, R = CH_3
b, R = CH_3CH_2
c, R = $CH_3CH_2CH_2$

established in two ways.[3,4] For the possible synthesis of chiral analogues of **1** and **2**, the enantiomers of 1-ethyl-2-propynylamine (**3b**), 1-propyl-2-propynylamine (**3c**) and 1-ethyl-1-methyl-2-propynylamine (**3d**) were also prepared and their absolute configurations were also established by chemical transformations.[5,6] Partial reduction of (*R*)-**3a** and of the enantiomers of **3b** and **3c** with hydrogen over Lindlar's catalyst afforded (*R*)-1-methyl-2-propenylamine [(*R*)-**4a**] and the enantiomers of 1-ethyl-2-propenylamine (**4b**) and 1-propyl-2-propenylamine (**4c**).[7] Reduction of (*S*)-**3c** with hydrogen over Raney nickel gave (*R*)-1-ethylbutylamine [(*R*)-**5**].[7] Thus a group of chiral 1-alkyl-2-propynylamines (**3**) and 1-alkyl-2-propenylamines (**4**) of established configuration became available for a rigorous test of the salicylidenimino chirality rule[8] for the deduction of the absolute configurations of amines of this type.

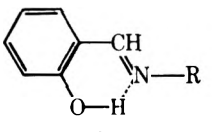


(*R*)-**5**

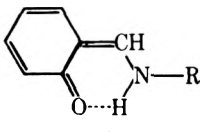
We now report the preparation of the *N*-salicylidene derivatives (**6**) of an enantiomer of each of these amines and the interpretation of the circular dichroism (CD) spectra of these derivatives.

Results and Discussion

Electronic Absorption Spectra. The electronic (isotropic) absorption (EA) spectra of the *N*-salicylidene derivatives of the 1-alkyl-2-propynylamines (**3**), of the 1-alkyl-2-propenylamines (**4**), and of 1-ethylbutylamine (**5**) in hexane exhibit three absorption bands with maxima at 318–320 (log ϵ 3.69–3.71), 254–255 (log ϵ 4.11–4.15), and 216 nm (log ϵ 4.40–4.42), designated as bands I, II, and III, respectively. These bands are assigned to transitions of the intramolecularly hydrogen-bonded salicylidenimino chromophore (**6a**).[8]



6a



6b

As is frequently the case,[9] band II also shows a shoulder at 260–261 nm (log ϵ 4.07–4.09) and at a slightly longer wavelength than the absorption maximum. In methanol, a broad band with maximum at 400–403 nm (log ϵ 2.03–2.19 for the derivatives of **3a–3d**, 2.97–2.99 for those of **4a–4c**, and 3.23 for that of **5**) becomes evident, and bands I, II, and III show a slight decrease in intensity. A shoulder near 260 nm is no

Table I. Circular Dichroism Data for the *N*-Salicylidene Derivatives of Some Chiral Amines

Registry no.	Amine	Solvent	CD max, λ, nm ([θ][a]) Quinoid	I		II	III
54139-78-5	(*R*)-**3a**	Hexane		322 (−4400)	268 (+3700)	250 (−4 300)	220 (+9 000)
		MeOH	400 (−120)[b]	316 (−4900)	269 (+6100)	251 (−5 900)	219 (+7 800)
50285-35-3	(*S*)-**3b**	Hexane		319 (+5700)	267 (−4100)	251 (+4 700)	220 (−11 000)
		MeOH	400 (+130)[b]	316 (+5600)	268 (−6800)	250 (+6 500)	221 (−11 000)
62227-54-7	(*S*)-**3c**	Hexane		318 (+6200)	268 (−4000)	250 (+5 400)	221 (−13 000)
		MeOH	400 (+140)[b]	317 (+5400)	271 (−7000)	252 (+5 900)	219 (−11 000)
62141-59-7	(*R*)-**3d**	Hexane		320 (−2700)		255 (−4 300)	224 (+3 200)
		MeOH	400 (−60)[b]	316 (−3000)		254 (−4 9000)	221 (+2 500)
63731-07-7	(*R*)-**4a**	Hexane		320 (−8200)	272 (+4200)	255 (−17 000)	213 (−14 000)
		MeOH	400 (−790)	316 (−6000)	271 (+3500)	251 (−15 000)	210 (−9 400)
63731-08-8	(*R*)-**4b**	Hexane		320 (−7300)	272 (+5900)	254 (−19 000)	214 (−15 000)
		MeOH	400 (−800)	316 (−5300)	272 (+5300)	252 (−16 000)	212 (−11 000)
63731-09-9	(*S*)-**4c**	Hexane		320 (+5100)	272 (−7200)	254 (+16 000)	214 (+15 000)
		MeOH	400 (+580)	315 (+3900)	272 (−5800)	251 (+14 000)	213 (+11 000)
63731-10-2	(*R*)-**5**	Hexane		320 (−2400)		255 (−2 400)	224 (+3 000)
		MeOH	400 (−590)	316 (−1800)		252 (−2 000)	220 (+2 400)

[a] Molecular ellipticity. [b] Shoulder.

longer evident in any of the spectra, but the derivatives of **3–5** now show a shoulder at 277–278 nm (log ε 3.43–3.61). The absorption bands at 400 and 278 nm are assigned to a quinoid tautomer (**6b**), stabilized by and in greater concentration in the more polar solvent.[10,11]

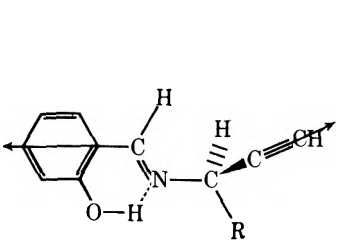
Circular Dichroism Spectra. The *N*-salicylidene derivatives show circular dichroism (CD) spectra with multiple Cotton effects (Table I) which in general correspond to the EA maxima and which are generated by the coupled oscillator mechanism.[12] Thus in the ethynyl (**3**) and ethenyl (**4**) derivatives, the dominant contribution to the circular dichroism arises from the interaction of the salicylidenimino chromophore with the lowest energy $\pi \rightarrow \pi^*$ transition of the ethynyl ($^1A_{1u} \leftarrow {}^1A_{1g}$ of acetylene at ca. 152 nm[13]) and the ethenyl group [$^1B_{1u} \leftarrow {}^1A_{1g}$ (N-V) of ethylene at ca. 175 nm[13]], both red-shifted by alkyl substitution.

The assignment of the Cotton effects near 400, 320, 252, and 220 nm as shown in Table I is straightforward, but that for the 270-nm Cotton effect is somewhat more difficult. The latter cannot be attributed to an electronic transition of the quinoid tautomer since it is observed in hexane. Since a carbon–carbon triple bond has no electronic transition in this spectral region and a carbon–carbon double bond has only a weak singlet → triplet transition above 200 nm,[13] the CD maximum near 270 nm in the *N*-salicylidene derivatives of **3a–3c** and **4a–4c** must be assigned to some transition of the salicylidenimino chromophore. One possibility is a weak $n \rightarrow \pi^*$ transition of the azomethine group, similar to that at 240 nm in nonconjugated azomethines[14] but shifted to longer wavelength by conjugation with the phenyl ring. Another is a weak $\pi \rightarrow \pi^*$ transition of the intramolecularly hydrogen-bonded salicylidenimino chromophore. Dynamic coupling of this transition with the ethynyl and ethenyl transitions results in a large enhancement of the CD band near 270 nm.

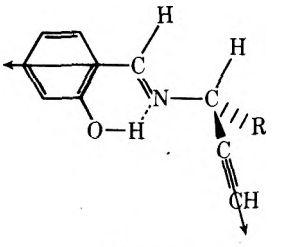
A similar CD maximum near 270 nm, opposite in sign to band I, was found in the spectra of a number of the *N*-salicylidene derivatives of α- and β-arylalkylamines,[1,8,15-18] acyclic β-hydroxyalkylamines,[19] steroidal amines,[20] and α-amino acids and esters.[1] In most of these spectra, band II had the same sign as band I and was easily identified. Since the 270-nm band was observed for the α-(1-naphthyl)- and α-phenylalkylamine derivatives in nonpolar solvents, it was assigned to the aryl group of the amine moiety, both the naphthyl and phenyl groups showing absorption bands near 270 nm.[8,15] For the α- and β-(2-thienyl)alkylamine and β-hydroxyalkylamine derivatives, also showing the CD maximum near 270 nm in hexane, the band was unassigned.[1,19] In the spectra of some of the steroidal amine derivatives and the α-amino acid derivatives, examined only in polar solvents, the maximum was assigned to the quinoid tautomer.[1,21] For a few other steroidal amine and the α-amino ester derivatives, the band was assigned to band II of the hydrogen bonded salicylidenimino chromophore.[1,21] Some of these earlier assignments of this band may require revision in view of the present results.

Since the CD maxima associated with bands I and II in the *N*-salicylidene-1-alkyl-2-propynylamines and *N*-salicylidene-1-alkyl-2-propenylamines are easily identified, the sign of these maxima can be correlated with the absolute configurations of the respective amines, much the same as is done for *N*-salicylidene derivatives of chiral α- and β-arylalkyl amines[1,8,15-18] and α-amino acids.[1] In propynes and propenes, the electric transition moment of the lowest energy $\pi \rightarrow \pi^*$ transition is directed along the multiple bond.[13] The transition moments of bands I and II in the salicylidenimino chromophore are approximately aligned with the phenyl group–methine carbon bond.[8] Thus the sign of the circular dichroism associated with bands I (315 nm) and II (255 nm) in the *N*-salicylidene derivatives of **3** and **4** should be the same as the chirality of the triple and double bond with the phenyl group–methine bond.[8] This chirality is determined by both the absolute configuration and the preferred conformation of the respective derivatives.

For the intramolecularly hydrogen-bonded (*R*)-*N*-salicylidene-1-alkyl-2-propynylamines [(*R*)-**7**], the proton magnetic resonance (^{1}H NMR) spectra (Table II) in which the methine proton of the salicylidenimino group is seen as a doublet (J = 1.6 Hz) suggest a perferred conformation depicted as (*R*)-**7a**.[22] This conformation is somewhat different from an alternate one [(*R*)-**7b**] analogous to that deduced for an *N*-salicylidene-α-phenylalkylamine[8] in which the hydrogen atom



(*R*)-**7a**



(*R*)-**7b**

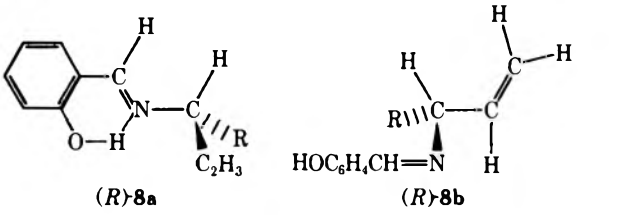
Table II. Proton Magnetic Resonance Data for the *N*-Salicylidene Derivatives of Some Chiral Amines

Amine	Solvent	δ,[a] ppm (*J*,[b] Hz) N=C*H*[c]	N—C*H*[d]
(*R*)-**3a**	CCl_4	8.61 (1.6)	4.51
	CD_3OD	8.65 (1.5)	4.50
(*S*)-**3b**	CCl_4	8.62 (1.6)	4.40
(*S*)-**3c**	CCl_4	8.62 (1.6)	4.48
(*R*)-**3d**	CCl_4	8.68	
(*R*)-**4a**	CCl_4	8.30	3.89
	CD_3OD	8.40	3.94
(*R*)-**4b**	CCl_4	8.30	3.60
(*S*)-**4c**	CCl_4	8.30	3.72
(*R*)-**5**	CCl_4	8.23	2.97
	CD_3OD	8.36	3.10

[a] Chemical shift downfield from Me_4Si = 0. [b] Coupling constant. [c] Doublet or if no coupling constant given, singlet. [d] Multiplet.

at the chiral center eclipses the carbon–nitrogen double bond of the salicylidenimino group. The chirality of the relevant bonds as shown in both (*R*)-**7a** and (*R*)-**7b**, however, is negative, and the *N*-salicylidene derivative of (*R*)-**3a** shows negative Cotton effects for bands I and II. Derivatives of those amines [(*S*)-**3b** and (*S*)-**3c**] with the enantiomeric configuration give rise to positive Cotton effects. Since an ethyl group is larger in effective bulk size than a methyl group, the *N*-salicylidene derivative of (*R*)-**3d** should have a preferred conformation analogous to (*R*)-**7a** or (*R*)-**7b**, the methyl and ethyl groups replacing the hydrogen atom and the R group, respectively, with negative chirality for the coupled oscillators. Thus negative Cotton effects for bands I and II are observed. The reduced molecular ellipticity for these maxima can be explained on the basis of a reduced preference for the conformer of lowest energy since a methyl group is more nearly the same size as an ethyl group than is a hydrogen atom compared to a methyl group. The absence of a 270-nm CD maximum in the spectrum of the derivative of (*R*)-**3d** may also be a consequence of this same reduced preference for the conformer of lowest energy.

In the ^1H NMR spectra of the intramolecularly hydrogen-bonded (*R*)-*N*-salicylidene-1-alkyl-2-propenylamines [(*R*)-**8**], the methine proton of the salicylidenimino group appears as a singlet, indicating a preferred conformation [(*R*)-**8a** and (*R*)-**8b**] such that the hydrogen atom at the chiral center is eclipsed by both the carbon–nitrogen [(*R*)-**8a**] and carbon–carbon double bonds [(*R*)-**8b**].[22] For this conformation, the chirality of the relevant transition moments is negative and negative Cotton effects are observed for the derivatives of



(*R*)-**4a** and (*R*)-**4b**. Positive Cotton effects are observed for the derivative of (*S*)-**4c**.

In both the ethynyl and ethenyl derivatives the sign of the Cotton effects associated with band III may be understood if this band is the bathochromically shifted ^1B benzenoid transition.[23] Thus there are two electric transition moments, one approximately parallel and the other perpendicular to the methine carbon–phenyl group bond. Both transitions give Cotton effects with opposite signs resulting in partial cancellation. This may explain the observation that the intensity of band III is not much greater than and is sometimes less than the intensity of band II. The opposite signs for bands II and III for the 1-alkyl-2-propynylamine (**3**) derivatives indicate that in their preferred conformation the orientation of the interacting chromophores is such that the perpendicular component of the ^1B transition dominates. On the other hand, with the 1-alkyl-2-propenylamine (**4**) derivatives, the parallel component of the ^1B transition, apparently at a shorter wavelength than the perpendicular one, wins out, and these derivatives show Cotton effects for bands II and III of the same sign.

The negative Cotton effects for bands I and II of the *N*-salicylidene derivative of (*R*)-1-ethylbutylamine [(*R*)-**5**] are also most likely generated by a coupled oscillator mechanism,[12,24] but because of the many conformational possibilities for (*R*)-**5**, no simple prediction concerning the sign of the observed Cotton effects is possible. It is to be noted, however, that (*S*)-*N*-salicylidene-*sec*-butylamine displays positive Cotton effects, near 315 and 255 nm, while those of (*R*)-*N*-salicylidene-2,2-dimethyl-3-aminobutane are negative, and neither shows a CD maximum near 270 nm.[19]

Experimental Section

Optical rotations at the sodium D line were measured in a 1-dm tube with a Perkin-Elmer 141 spectropolarimeter. Electronic (isotropic) absorption (EA) spectra were obtained with a Zeiss Spektralfotomer Pm QII. Circular dichroism (CD) spectra were recorded on a Jasco J-41 spectropolarimeter at 20 °C with a cell length of 2 mm. Proton magnetic resonance (^1H NMR) spectra were recorded with a Perkin-Elmer R 12 B spectrometer at 37 °C. Elemental analyses were done at the Microanalytical Laboratory, Royal Agricultural College, Uppsala, Sweden.

Table III. *N*-Salicylidene Derivatives of Chiral Amines

		N-Salicylidene derivative									
						Elemental analysis					
						Calcd			Found		
Registry no.	Amine	Bp, °C (mmHg)	Yield, %	$n^{22}D$	$[\alpha]^{22}D$, deg (*c* EtOH)	C	H	N	C	H	N
63731-13-5	(*R*)-**3a**	80 (0.3)	70	1.5682	+14 (1.2)	76.27	6.40	8.09	75.11	6.28	8.06
63731-14-6	(*S*)-**3b**	105 (0.6)	86	1.5614	+8 (1.3)	76.98	7.00	7.48	76.88	6.94	7.56
63731-15-7	(*S*)-**3c**	112 (0.6)	88	1.5534	+5 (1.5)	77.58	7.51	6.96	77.36	7.55	6.91
63731-16-8	(*R*)-**3d**	105 (0.6)	90	1.5480	−66 (1.2)	77.58	7.51	6.96	76.92	7.60	7.10
63731-17-9	(*R*)-**4a**	90 (0.5)	72	1.5575	−170 (1.4)	75.40	7.48	7.99	75.28	7.52	7.83
63731-18-0	(*R*)-**4b**	95 (0.7)	74	1.5513	−154 (1.4)	76.16	7.99	7.40	76.31	8.07	7.34
63731-19-1	(*S*)-**4c**	100 (0.5)	84	1.5450	+111 (1.3)	76.81	8.43	6.89	76.70	8.47	6.80
63765-60-6	(*R*)-**5**	95 (0.5)	86	1.5338	−37 (1.2)	76.06	9.33	6.82	75.94	9.18	6.85

N-Salicylidene derivatives were prepared from the respective amines[4-7] by the usual procedure.[25] Yields and physical properties are given in Table III.

References and Notes

(1) This is part 23 in the Vanderbilt University series, "Optically Active Amines". Part 22: H. E. Smith, E. P. Burrows, M. J. Marks, R. D. Lynch, and F.-M. Chen, *J. Am. Chem. Soc.*, **99**, 707 (1977).
(2) (a) University of Uppsala; (b) Vanderbilt University; (c) Tennessee State University.
(3) R. Dahlbom, A. Lindquist, S. Lindgren, U. Svensson, B. Ringdahl, and M. R. Blair, Jr., *Experientia*, **30**, 1165 (1974).
(4) A. Lindquist, B. Ringdahl, U. Svensson, and R. Dahlbom, *Acta Chem. Scand. B*, **30**, 517 (1976).
(5) B. Ringdahl and R. Dahlbom, *Acta Chem. Scand. B*, **30**, 812 (1976).
(6) B. Ringdahl and R. Dahlbom, *Acta Chem. Scand. B*, **30**, 993 (1976).
(7) B. Ringdahl and R. Dahlbom, to be published.
(8) H. E. Smith, J. R. Neergaard, E. P. Burrows, and F.-M. Chen, *J. Am. Chem. Soc.*, **96**, 2908 (1974).
(9) H. E. Smith, E. P. Burrows, E. H. Massey, and F.-M. Chen, *J. Org. Chem.*, **40**, 2897 (1975).
(10) D. Heinert and A. E. Martell, *J. Am. Chem. Soc.*, **85**, 183, 188 (1963).
(11) P. W. Alexander and R. J. Sleet, *Aust. J. Chem.*, **23**, 1183 (1970).
(12) J. A. Schellman, *Acc. Chem. Res.*, **1**, 144 (1968).
(13) C. Sandorfy, "Electronic Spectra and Quantum Chemistry", Prentice-Hall, Englewood Cliffs, N.J., 1964, pp 341 and 342.
(14) R. Bonnet in "Chemistry of the Carbon–Nitrogen Double Bond", S. Patai, Ed., Interscience, New York, N.Y., 1970, Chapter 4.
(15) H. E. Smith and R. Records, *Tetrahedron*, **22**, 813 (1966).
(16) H. E. Smith and T. C. Willis, *Tetrahedron*, **26**, 107 (1970).
(17) H. E. Smith, L. J. Schaad, R. B. Banks, C. J. Wiant, and C. F. Jordan, *J. Am. Chem. Soc.*, **95**, 811 (1973).
(18) H. E. Smith, E. P. Burrows, J. D. Miano, C. D. Mount, E. Sanders-Bush, and F. Sulser, *J. Med. Chem.*, **17**, 416 (1974).
(19) H. E. Smith and H. E. Ensley, Can. *J. Chem.*, **49**, 2902 (1971).
(20) H. Ripperger, K. Schreiber, G. Snatzke, and K. Ponsold, *Tetrahedron*, **25**, 827 (1969).
(21) H. E. Smith, E. P. Burrows, and F.-M. Chen, *J. Org. Chem.*, **41**, 704 (1976).
(22) K. A. W. Parry, P. J. Robinson, P. J. Sainsbury, and M. J. Waller, *J. Chem. Soc. B*, 700 (1970).
(23) B. Katz, M. Brith, B. Shart, and J. Jortner, *J. Chem. Phys.*, **54**, 3924 (1971).
(24) H. E. Smith, E. P. Burrows, E. H. Massey, and F.-M. Chen, *J. Org. Chem.*, **40**, 2897 (1975).
(25) H. E. Smith, S. L. Cook, and M. E. Warren, Jr., *J. Org. Chem.*, **29**, 2265 (1964).

Heterogeneous Catalysis by Solid Superacids. 3.[1a] Alkylation of Benzene and Transalkylation of Alkylbenzenes over Graphite-Intercalated Lewis Acid Halide and Perfluorinated Resin-Sulfonic Acid (Nafion-H) Catalysts

George A. Olah,* Joseph Kaspi,[1b] and Josef Bukala[1c]

The Institute of Hydrocarbon Chemistry, Department of Chemistry, University of Southern California, Los Angeles, California 90007, and The Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

Received May 31, 1977

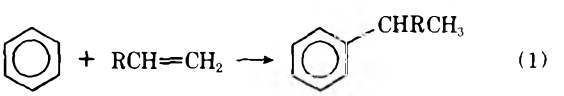
The use of superacidic solid catalysts in heterogeneous gas-phase alkylation reactions, such as the ethylation of benzene by ethene and the transethylation of benzene with diethylbenzene, was studied. Such catalysts enable us to conduct the reactions under relatively mild conditions and to obtain clean reaction products. Reactions were carried out in a flow system, in the gas phase, in the temperature range of 125–210 °C at atmospheric pressure. Intercalated $AlCl_3$ and $AlBr_3$ gave good initial yields of alkylated products. The lifetime of the catalyst was, however, limited as the active Lewis acid is leached out from the catalyst, causing a sharp decline in the catalytic activity with on-stream time. Other possible reasons of the deactivation of the catalyst are also discussed. A perfluorinated sulfonic acid resin catalyst (Nafion-H) was found to have a much better stability, while showing good catalytic activity. Alcohols were also found to dehydrate in the gas phase efficiently over this catalyst and could be used as alkylating agents for benzene.

Friedel–Crafts alkylation and transalkylation reactions are traditionally carried out in the liquid phase. Catalysts are generally based on aluminum chloride and related Lewis acid halides. The ethylation of benzene with ethylene to form ethylbenzene using aluminum chloride as catalyst is one of the largest chemical processes carried out in industry. Application of solid supported catalysts in heterogeneous vapor phase ethylation started to gain importance only recently. One of the major difficulties is the sluggishness of the ethylation reaction. Ethene is far less readily protonated than, for example, the more polar propene, and its equilibrium with the ethyl cation is rather unfavorable. Few (if any) of the known solid acid catalysts are able to catalyze efficiently the ethylation of benzene or the transethylating benzene with polyethylbenzenes (which are inevitably formed as by-products in the ethylation of benzene). This is not the case with the isopropylation of benzene to cumene. Cumene has been industrially produced for decades over supported acid catalysts such as supported phosphoric acid. Obviously, the more polar propene is protonated much more readily than ethene and polyisopropylbenzenes also transalkylate benzene with greater ease.

In continuation of our studies of Friedel–Crafts and superacid chemistry, our interest was directed to the possibility of applying solid superacidic catalysts to heterogeneous reactions.[1-3] These catalysts can be based either on Lewis acid halides bound or intercalated to suitable supports or solid (polymeric) protic acid, such as perfluorinated resin sulfonic acids.

Results and Discussion

The alkylation of benzene with ethene and propene (eq 1)



(1)

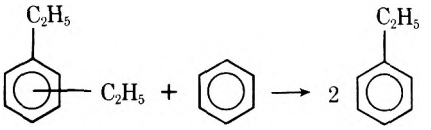
R = H, CH_3

and the transethylation of benzene with diethylbenzenes (eq 2) was studied over several solid superacidic catalysts. Reac-

* Address correspondence to this author at the University of Southern California.

Table I. Ethylation of Benzene with Ethene over Graphite-Intercalated Metal Halides

Metal halide	$AlCl_3$	$AlCl_3$	$AlCl_3$	$AlCl_3$	$AlBr_3$	SbF_5	$FeCl_3$
% intercalated	16.6	16.6	16.6	28.4	4.5	26.1	50.5
Temp, °C	125	160	200	160	160	160	185
$[C_6H_6]/[C_2H_4]$ ratio	3.3	3.4	3.2	3.5	3.3	3.6	3.2
Onstream time, h	% conversion (based on ethene)						
1	61.7	41.7	15.1	60.4	31.7	4.8	
2	10.3	12.0	5.7	62.9	15.1		
3	5.4	7.3	2.4	43.8			
4	4.3	5.3	1.7	33.7			
5	2.9	5.7	1.9	26.5			
6	1.9	1.4	0.7	6.8			
7				2.6			
8				2.2			
9				1.7			
10				1.5			



(2)

tions were carried out in the gas phase in the temperature range of 125–210 °C.

A. Reactions over Graphite-Intercalated Metal Halides. Many metal halides when heated with graphite are capable of inserting themselves between the graphite layers thus forming intercalates.[4] As a result the distance between the graphite layers is increased from 3.35 to 9–10 Å depending on the intercalated halides. Some chlorides such as aluminum chloride are intercalated only in the presence of chlorine gas and it was shown[5] that the intercalated $AlCl_3$ contains more than 3 Cl atoms per Al atom. Lately,[6] intercalation of $AlCl_3$ and other halides was also achieved by treating graphite with solutions of the metal halides. Higher valency metal fluorides such as SbF_5[7] and AsF_5[8] were also shown to intercalate easily into graphite. Wide-line NMR studies showed that intercalated SbF_5 behaves as a liquid well below the freezing point of SbF_5.[9]

The possibility of intercalating metal halides into graphite suggested their use as Friedel–Crafts catalysts.[10] Lalancette[11] reported the catalytic activity of intercalated $AlCl_3$ for aromatic alkylations of liquid hydrocarbons with alkyl halides or alkenes as alkylating agents. In his experiments the intercalate was stirred in the solution as a heterogeneous catalyst. It was found that intercalated $AlCl_3$ is a milder catalyst than neat $AlCl_3$. The rate of the reaction was somewhat lower but the tendency to form polyalkylbenzenes was reduced. It was, however, observed that under these conditions $AlCl_3$ is leached out from the intercalate into the reaction medium and reactions thus may be to a significant degree catalyzed in the conventional fashion with the intercalate serving only as a reservoir for the $AlCl_3$ catalyst.

We have studied graphite intercalated aluminum chloride and bromide, as well as antimony pentafluoride and ferric chloride, as solid heterogeneous catalysts for the gas-phase ethylation of benzene with ethene. A flow system with a fixed bed catalyst was used in our experiments. Products were collected, periodically sampled, and analyzed by gas–liquid chromatography. Results obtained are summarized in Table I.

As seen from data in Table I intercalated $AlCl_3$ and $AlBr_3$ are efficient ethylation catalysts. High initial conversions were observed at temperatures as low as 125 °C. Of the two additional acidic haldies investigated SbF_5 gave lower initial conversions and rapidly lost activity, indicating the extreme sensitivity of this catalyst to hydrolysis and other impurities. The weaker Lewis acid $FeCl_3$ was, on the other hand, inactive. However, both the $AlCl_3$ and $AlBr_3$ intercalates were efficient only for 3 to 6 h under the continuous experimental conditions. Reactivity declined with onstream time and the catalyst became deactivated after 6 to 8 h.

Transethylation of benzene with diethylbenzenes was also studied over the same catalysts at 180 °C. Results are shown in Table II. Good initial catalytic reactivity was again observed which decreased sharply with onstream time.

Several factors can contribute to the loss of the catalytic activity. Upon following the course of the $AlCl_3$-graphite-catalyzed reaction aluminum chloride was found (analyzed as hydrolyzed chloride) in the liquid products and HCl was found in the effluent gases. The amount of the eluted chloride in each fraction was measured. Figure 1 shows the amount of the eluted chloride against the conversions obtained in the ethylation of benzene.[12] As seen from the figure the elution of $AlCl_3$ and the loss of catalytic reactivity are related to each other. In the ethylation reaction loss of 30% of the overall aluminum chloride content caused complete deactivation of the catalyst. Similar results were also obtained in the transethylation reaction of benzene with diethylbenzenes.

There may be two reasons for the loss of the catalytic halides. The first is the possible hydrolysis of $AlCl_3$ by small amounts of moisture in the feed. It is known[4b] that intercalated $FeCl_3$ which is more stable to hydrolysis by aqueous HCl[4b] also showed loss of chloride ion during attempted transethylation reaction. This is in accord with the desorption of metal halide from the catalyst. Intercalation into graphite is a reversible process and there is always a certain vapor pressure of the free metal halide at the reaction temperatures studied. The conditions in a fixed bed flow reactor favor desorption because the desorbed aluminum halide is readily complexed by the organic reagents and thus can be continuously carried away by the fresh feed. This is also sustained by the observation that the completely deactivated catalyst kept further loss of $AlCl_3$ at approximately the same rate (Figure 1). These observations are in accord with Lalancette's observations concerning intercalation of metal halides from their solutions in CCl_4.[6] Intercalation took place only for halides which are slightly soluble in CCl_4. Those which showed better solubility stayed in the solution and did not intercalate (or were desorbed to the extend that no intercalation was observed).

The relation between the catalytic activity and the overall amount of intercalated $AlCl_3$ is not a simple one. The actual catalytic sites of intercalated metal halides are not well known. Considering the layer structure and steric requirements of the intercalate it is reasonable to assume that catalysis can take

Table II. Transethylation of Benzene with Diethylbenzene over Graphite-Intercalated Metal Halides

Metal halide	$AlCl_3$	$AlBr_3$	SbF_5
% intercalated	28.4	4.5	26.1
Temp, °C	180	180	180
$[C_6H_6]/[C_6H_4Et_2]$ ratio	4	4	4
Onstream time, h	% conversion (based on diethylbenzene)		
1	45.0	66.2	2.4
2	70.4	51.8	
3	66.9	41.4	
4	70.3	3.1	
5	56.9		
6	16.2		
7	13.8		
8	15.2		
9	12.7		
10	10.4		

place only on the exposed surface areas or edges but not in the deeper layers of the catalyst. For steric reasons alone the reactants cannot be expected to penetrate well into the deeper layers containing metal halides. Diminished reactivity thus may involve desorption of the metal halide from the catalytically active exposed areas which, however, account only for a fraction of the overall amount of intercalated halide. One must further consider the probable migration of halide intercalated into the deeper inside layers of the surface areas. Comparative elementary analysis of fresh catalyst and samples of the same catalyst taken from the reactor after prolonged reaction time showed that 56% of the chlorine and 34% of the aluminum were lost in the spent catalyst. ESCA spectral study, which is detecting the upper 30 Å of the catalyst's surface, showed at the same time chlorine loss of 66 and 32% loss of aluminum. These results indicate that the bulk of the graphite-intercalated catalyst loses $AlCl_3$ at a different rate than the catalytically active exposed surface areas. In a typical ethylation reaction it was observed that complete deactivation of the catalyst took place after ca. 30% of the chloride was lost (Figure 1). Such an amount of $AlCl_3$ is much too large to be present on the surface alone. Furthermore, even after the catalytic activity is completely lost, chlorine continues to be eluted at about the same rate. This shows that at the reaction temperature (160 °C) there is some equilibration between the $AlCl_3$ in the deeper lattice areas and that of the surface.

We had already mentioned the possible hydrolysis of the metal halide by traces of moisture in the feed. Analytical data of the deactivated catalysts indeed clearly show that more chloride than aluminum is lost from the catalyst, i.e., the ratio Cl/Al in the spent caltalyst decreases, in good agreement with partial hydrolysis of exposed $AlCl_3$. As the result of hydrolysis chloride is lost as HCl, while the aluminum remains as a nonvolatile hydroxide (or oxide).

Finally, there must be considered another source of catalyst deactivation, not connected with loss of the metal halide. Ethene and other alkenes are well-known poisons for many solid acidic catalysts as they have the tendency to polymerize on the catalyst surface. Higher pressure reactions and high dilution of ethene by the alkylated compound give partial relief from this problem. The transalkylation reaction which does not involve ethene shows much lesser tendency for deactivation.

B. Reactions over Perfluorinated Resin-Sulfonic Acid (Nafion-H). Sulfonated ion exchange resins, of the cross-linked polystyrene type (Dowex, Amberlyst) in which the sulfonic acid group is bound to the polymeric framework, are frequently used as acid catalysts of moderate strength. The

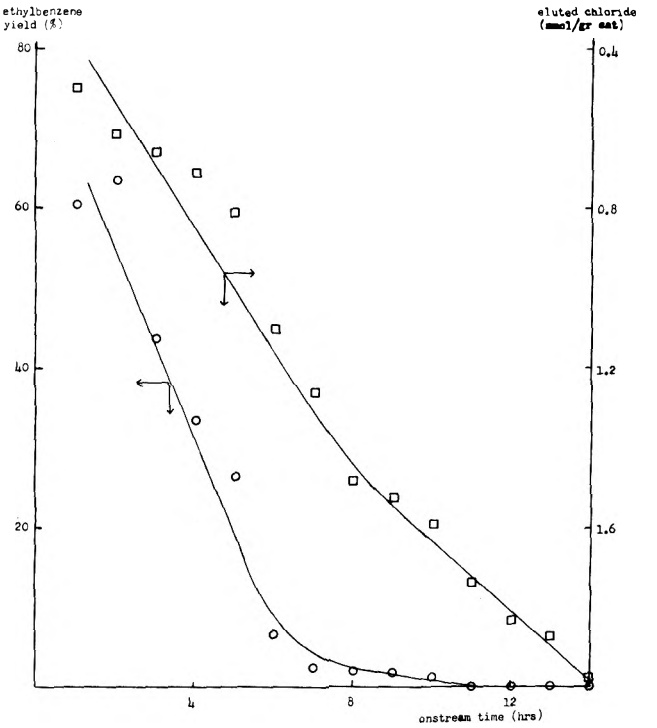


Figure 1. Yield of ethylbenzene and loss of chloride from intercalated $AlCl_3$ against onstream time in the ethylation of benzene by ethene.

Table III. Alkylation of Benzene over Nafion-H Catalyst

Alkene	Temp, °C	$[C_6H_6]$/[alkene]	Contact time, s	Alkene conversion, %
Ethene	110	4	7	10
	150	4	6	24
	180	4	6	36
	190	3.4	3.5	44
Propene	110	1.5	7	9
	150	1.5	6	16
	180	1.5	6	19
	180	3	4	21
	180	6	4	29

use of such sulfonic acid resins in acid catalysis was reviewed.[13] The acidity of these catalysts can be enhanced by complexing with Lewis acid halides such as $AlCl_3$,[14] SbF_5, or TaF_5 and the like. However, by increasing the acidity to the superacidic range, protolytic cleavage (degradation) of the hydrocarbon polymer backbone can take place. We therefore searched for strong resin sulfonic acids which at the same time are stable under highly acidic conditions. The commercially available copolymer of a perfluorinated ether and perfluoroalkanesulfonic acid, Du Pont's Nafion resin,[15] used as its K salt in dielectric membranes material, in its activated free acid form (Nafion-H) was found to fulfill best these requirements.

(1) Alkylation with Alkenes and Transalkylation with Dialkylbenzenes. When ethene or propene were reacted with benzene over Nafion-H at temperatures between 125 and 190 °C, alkylated benzenes were obtained with yields significantly increasing at higher temperatures. The results are summarized in Table III. Transalkylation of benzene with diethylbenzene (as well as diisopropylbenzene) was also found to be efficiently catalyzed by Nafion-H. Using a typical ratio of benzene:diethylbenzene of 4.5:1 the yield of ethylbenzene (based on diethylbenzene) was 45% at 130 °C and 76% at 190 °C. At 130 °C there was no decline in the reactivity of the catalyst after

Table IV. Dehydration of Alcohols over Nafion-H Catalyst

Alcohol	Temp, °C	Contact time, s	% dehydration	Product % alkene	Product % ether
i-PrOH	100	10	9		100
	130	9	28	45	55
	160	8	>97	100	
n-PrOH	130	4.5	8	47	53
	160	8	96	100	
t-BuOH	120	5	100	100	

Table V. Alkylation of Benzene with Alcohols over Nafion-H Catalyst

Alcohol	$[C_6H_6]/[ROH]$	Temp, °C	Contact time, s	% alcohol conversion
EtOH	2.6	180	9	3.5
	2.6	210	8	6
n-PrOH	0.85	110	10	0
	0.85	175	9	5
	2	175	9	17
i-PrOH	2	170	9	11
	2	210	8	16

15 h onstream time (the longest experiments carried out) and at 190 °C after 8 h. This contrasts sharply with the rapid deactivation of intercalated metal halides. However, the thermal stability of Nafion-H rapidly decreases at the region of 220 °C. Extended exposure to such temperatures results in loss of sulfonic groups and of activity which is substantiated by observed loss of sulfur as found by ESCA spectroscopy in the thermally deactivated catalyst.

The selectivity of Nafion-H in effecting polyalkylation is relatively low. About 20% of the alkylated products at 190 °C are diethylbenzenes. The isomeric composition of the diethylbenzenes is 9% ortho, 75% meta, and 34% para. Venuto[16] studied the ethylation of benzene over a rare earth exchanged Zeolite X catalyst. He found that with a feed composition of benzene/ethene of 5:1 the ratio of diethylbenzene/ethylbenzene was 1:4.65. Similar results were obtained with a silica–alumina catalyst.[17] Ten percent diethylated products were obtained using a feed ratio benzene/ethene of 10:1. The large amount of *m*-diethylbenzene formed shows significant thermodynamically influenced isomerization (probably in the arenium ion intermediates). Electrophilic attack on ethylbenzene is prone to occur initially at the ortho and para positions. Isomerization is, however, incomplete as higher amounts of *m*-diethylbenzene were obtained in the isomerization of diethylbenzenes using $AlCl_3$,[17,18] Nafion-H,[19] or Zeolite Y type[20] catalysts. Formation of substantial amounts of *m*-diethylbenzene is common for all acidic catalysts. The strong complexing ability of $AlCl_3$ (or its conjugate acid) helps to form increased amounts of the meta isomer, whereas silica–alumina gives amounts similar to those obtained with Nafion-H. The less acidic zeolite Y is reported to give mostly the ortho and para isomers.[20] Formation of *sec*-butylbenzene, expected by possible ipso attack of ethene on ethylbenzene, was detected with some catalysts such as supported phosphoric acid,[17] ferric phosphate,[17] or $AlCl_3$–NiO–SiO_2.[21] In some cases *sec*-butylbenzene is indeed an important alkylation product. No *sec*-butylbenzene was found, however, with $AlCl_3$ (maybe due to the ready dealkylation of *sec*-butylbenzene with such a strong catalyst). Similarly there was no evidence for the formation of *sec*-butylbenzene using Nafion-H catalyst.

(2) Alkylation with Alcohols. Perfluoro resin sulfonic acids of the Nafion-H type also allow the use of alcohols as the alkylating agents. Water formed as by-product in the reactions does not affect the acidic groups of the catalyst by hydrolysis. The use of alcohols instead of alkenes indeed improves the lifetime of the catalyst. With alcohols no ready polymerization side reactions take place whereas alkenes, such as ethene, can poison the catalyst by polymer formation on its surface. To avoid polymer formation it was recommended to use higher pressures and to introduce first the benzene into the reactor followed by the ethene–benzene mixture. The use of alcohols which form water as a by-product thus inhibits polymerization and helps to minimize poisoning of the catalyst.

The behavior of several neat alcohols over Nafion-H catalyst in the gas phase was studied. The results, summarized in Table IV, show that the alcohols are efficiently dehydrated under these conditions. There is no evidence for other side reactions such as dehydrogenation[22a] or decomposition[22b] often found over other solid acid catalysts. The ease of dehydration is in the order tertiary > secondary > primary alcohols. At higher temperatures the alcohols are dehydrated in nearly quantitative yield and the appropriate alkenes are formed. At lower temperatures ether formation predominates. The ease of the dehydration of alcohols over Nafion-H prompted us to study their alkylating ability of benzene under similar conditions.

The alkylation of benzene was studied with ethanol, 1-propanol, and 2-propanol. The results of these alkylations are summarized in Table V. 1-Proponal gave only cumene as the alkylation product. Propylbenzene could not be detected. This indicates the intermediacy of the 2-propyl cation in the alkylation process. The initial formation of *O*-protonated 1-propanol is assumed as the first step of the reaction. This species was indeed shown to be formed from 1-propanol in FSO_3H–SbF_5 at low temperatures[23a] and to cleave to water and propyl cation above 0 °C.[23b] But the sole formation of cumene as the reaction product rules out the possibility of alkylation by it through an S_N2 type process. Hydration of the 2-propyl cation to give 2-propanol is not a favored reaction under the reaction conditions. The only alcohol recovered from an incomplete conversion of the feed was 1-propanol. The 2-propyl cation either alkylates benzene or reforms (via proton elimination) propene. In control experiments under the same conditions propene was found to hardly react with water over Nafion-H to give 2-propanol. Alkylation of benzene by alcohols gave lower yields than with alkenes. Possible reasons may be the difference in the catalytic activity as a consequence of water formed[24] or the shorter contact time for the alkylation reaction as dehydration clearly precedes alkylation and thus decreases the de facto contact time for the alkylation step.

Conclusions

The alkylation of benzene and the transalkylation of alkylbenzenes were studied in the gas phase over highly acidic solid catalysts. The high activity of these catalysts permitted the use of relatively low temperatures and atmospheric pressure, instead of the higher temperatures and pressures usually employed in such reactions, without significantly affecting the yields. The major difficulties encountered with these catalysts are their relatively short lifetime and ease of deactivation. Perflorinated resin-sulfonic acids such as Nafion-H were found to give significant improvement in this regard. They offer the possibility to extend the application of acid-catalyzed Friedel–Crafts reactions to "clean" heterogeneous gas-phase reactions without complex formation and many of the side reactions observed in solution chemistry.

Experimental Section

Materials. Ethene and propene were at least 99.5% pure. Aromatics used were highest purity commercial products (>99%). Diethylben-

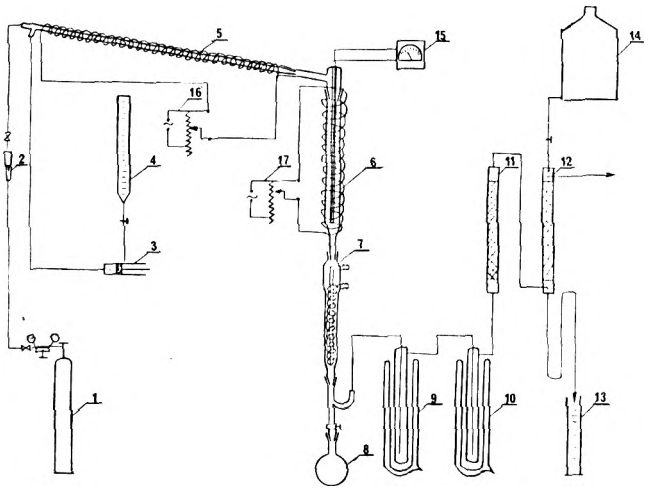


Figure 2. Scheme of the catalytic reactor: (1) alkene supply; (2) flow controller; (3) syringe pump; (4) reservoir for liquid feed; (5) evaporator; (6) reactor; (7) condenser; (8) liquid product receiver; (9, 10) traps; (11) $CaCl_2$ drying tube; (12) water absorber; (13) receiver for water; (14) water reservoir; (15) pyrometer; (16, 17) heater powerstat.

zenes used were a commercial mixture containing 8% ortho, 66% meta, and 26% para isomer.

Catalytic Reactor. We used a single pass, fixed bed flow reactor which is schematically depicted in Figure 2. When Nafion-H was used as a catalyst the HCl absorption system (No. 11–14 in Figure 2) could be omitted.

Catalysts. Graphite intercalated metal halides were either prepared according to known procedures[7,25] or were commercially available (Alfa Products). Nafion 501 as the potassium salt was obtained from the Du Pont Co. The acidic form (Nafion-H) was prepared by treatment with 20% aqueous nitric acid followed by that with fluorosulfuric acid.

Procedure for Catalytic Alkylations. Reactions were carried out in a 170 × 12 mm glass tube reactor in which the catalyst was supported by a sintered glass disk. The reactor was charged with 1 g of the activated dry catalyst, while dry N_2 was passed through generally at the rate of 5 mL/min. The reactor was electrically heated. The reactions were introduced with a syringe pump at a constant liquid rate of 0.02 mL/min. Products emerging from the catalytic reactor were condensed and analyzed at time intervals by gas–liquid chromatography. During individual experiments the reactor temperature did not deviate by more than ±1 °C. The maximal variation of the temperature in all the experiments was less than 4 °C. Under the used experimental conditions the space velocity was in the range of 1.6–2.2 × 10^{-6} mol/s·g catalyst and the contact time over the catalyst (if otherwise not indicated) was 4–5 s. Variations are mainly due to the different molecular weights and densities of the liquid reactants, as they were introduced on a fixed volume basis.

Analysis of Products. Products were analyzed by gas–liquid chromatography using a Perkin-Elmer Model 226 gas chromatograph equipped with flame ionization detector. A 150 ft × 0.1 in. capillary column coated with *m*-bis(*m*-phenoxyphenoxy)benzene + Apiezon L at 120 °C separated the products very efficiently.

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged. Dr. G. D. Mateescu is thanked for the ESCA measurement.

Registry No.—Benzene, 71-43-2; ethene, 74-85-1; graphite aluminum chloride, 39383-90-9; graphite aluminum bromido, 11129-35-4; graphite antimony floride, 56093-42-6; graphite iron chloride, 11115-86-9; diethylbenzene, 25340-17-4; Nafion-H, 63937-00-8; propene, 115-07-1; 2-propanol, 67-63-0; 1-propanol, 71-23-8; 1-butanol, 71-36-3; ethanol, 64-17-5.

References and Notes

(1) (a) Part 2: G. A. Olah and J. Kaspi, *J. Org. Chem.*, **42**, 3046 (1977); (b) postdoctoral fellow; (c) visiting scientist from the Technical University of Szczecin, Poland.
(2) Presented in part: J. Kaspi, J. Bukala, J. A. Olah, and G. A. Olah, Abstracts, 173rd National Meeting of the American Chemical Society, New Orleans, La., March 1977, No ORGN-186.
(3) G. A. Olah, G. Messina, J. Bukala, J. A. Olah, and G. D. Matesscu, Abstract of papers PHSC 153, 1st North American Chemical Conference, Mexico City, December 1975.
(4) (a) R. C. Croft, *Q. Rev., Chem. Soc.*, **14**, 1 (1960); (b) W. Rüdorff, *Adv. Inorg. Chem. Radiochem.*, **1**, 223 (1959); (c) W. Rüdorff, *Angew. Chem., Int. Ed. Engl.*, **2**, 67 (1963).
(5) M. Dzurus and G. R. Hennig, J. Am. Chem. Soc., **79**, 1051 (1957).
(6) J. M. Lalancette, L. Roy, and J. Lafontaine, *Can. J. Chem.*, **54**, 2505 (1976).
(7) J. M. Lalancette and J. Lafontaine, Chem. Commun., 815 (1973).
(8) L. C. Hsu, H. Selig, M. Rabinovitz, I. Agranat, and S. Sarig, *Inorg. Nucl. Chem. Lett.*, **11**, 601 (1975).
(9) L. B. Ebert, R. A. Huggins, and J. I. Brauman, *Chem. Commun.*, 924 (1974).
(10) P. G. Rodewald, U.S. Patent 3 925 495.
(11) J. M. Lalancette, M. J. Fournier-Breault, and R. Thiffault, Can. J. Chem., **52**, 589 (1974).
(12) Figure 1 relates to entry No. 4 in Table I.
(13) G. A. Olah, "Friedel-Crafts Chemistry", Wiley, New York, N.Y., 1973, pp 356–358.
(14) (a) V. L. Magnotta, B. C. Gates, and G. C. A. Schuit, *Chem. Commun.*, 342 (1976); (b) V. L. Magnotta and B. C. Gates, *J. Catal*, **46**, 266 (1977).
(15) (a) Nafion is a registered trademark of the Du Pont Co. whom we thank for samples of the potassium salt of Nafion. (b) P. R. Resnick, 2nd Winter Fluorine Conference, St. Petersburg, Fl., February 1974.
(16) P. B. Venuto, C. A. Hamilton, P. S. Landis, and J. J. Wise, *J. Catal.*, **4**, 81 (1966).
(17) W. M. Kurz, J. E. Nickels, J. J. McGovern, and B. B. Corson, *J. Org. Chem.*, **16**, 699 (1951).
(18) G. A. Olah, M. W. Meyer, and N. A. Overchuk, *J. Org. Chem.*, **29**, 2313 (1964).
(19) J. Kaspi and G. A. Olah, to be published.
(20) A. P. Bolton, M. A. Lanawela, and P. E. Pickert, *J. Org. Chem.*, **33**, 1513 (1968).
(21) G. C. Bailey and J. A. Reid, U.S. Patent 2 519 099.
(22) (a) T. Yashima, H. Suzuki, and N. Hara, *J. Catal.*, **33**, 486 (1974); (b) T. Kotaniyawa, *Bull. Chem. Soc. Jpn.* **47**, 2466 (1974).
(23) (a) G. A. Olah and E. Namanworth, *J. Am. Chem. Soc.*, **88**, 5327 (1966); (b) G. A. Olah, J. Sommer, and E. Namanworth, *ibid.*, **89**, 3576 (1967).
(24) R. B. Wesley and B. C. Gates, *J. Catal.*, **34**, 288 (1974).
(25) (a) W. Rüdorff and R. Zeller, *Z. Anorg. Allg. Chem.*, **279**, 182 (1955); (b) R. C. Croft, *Aust. J. Chem.*, **9**, 184 (1956).

N-*tert*-Butylanilino Radicals. 3. X-Ray Crystallographic Structure Determination of 1,4-Di-*tert*-butyl-1,4-diaryl-2-tetrazenes and a Single-Crystal Electron Spin Resonance Study of *N*-*tert*-Butylanilino Radical Pairs

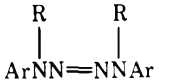
S. F. Nelsen,* R. T. Landis II, and J. C. Calabrese

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received March 25, 1977

The structures, determined by x-ray crystallography, are reported for 1,4-di-*tert*-butyl-1,4-bis(4-chlorophenyl)-2-tetrazene (**2A**) and 1,4-di-*tert*-butyl-1,4-bis(2,4,6-trideuteriophenyl)-2-tetrazene (**2B**). Crystals of **2A** are triclinic, $P\bar{1}$, with a = 8.654 (3), b = 6.648 (1), c = 9.666 (2) Å, α = 86.34 (1), β = 104.15 (2), γ = 98.60 (2)°, V = 533.1 (2) Å^3, and Z = 1. The structure was solved by heavy-atom methods, and refined to R_1 = 4.9 and R_2 = 5.2% for 847 independent observed reflections. Crystals of **2B** are monoclinic, $P2_1/n$, with a = 10.7082 (6), b = 8.697 (1), c = 11.479 (1) Å, α = 90.0, β = 109.647 (9), γ = 90.0°, V = 1006.8 (2) Å^3, Z = 2. The structure was solved by direct methods, and refined to R_1 = 4.3, R_2 = 6.5% for 1118 independent observed reflections. An ESR study of triplet radical pairs formed by photolysis of **2B** determined D = −0.0110, E = 0.0004 cm^{-1}. Nitrogen hyperfine splittings were observed in some orientations, but not analyzed.

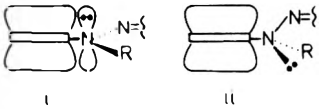
From studies of the effect of aromatic ring substituents on the thermal decomposition rates of aralkyltetrazenes **1**[2] and **2**,[1,3] we concluded that the sensitivity of the decomposition



1, R = CH_3

2, R = $(CH_3)_3$

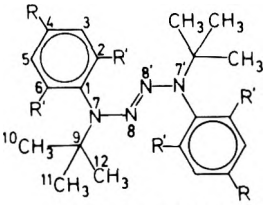
rate of **1** to substituent [rate ratio for **1** (4-OCH_3)/**1** (4-CO_2Et) of about 200 at 110 °C] was principally a conformational effect. We suggested that **1** exists in a conformation in which nitrogen lone pair, aromatic π-cloud overlap is maximized (i), but that the transition state for decomposition resembles ii,



i ii

such that the breaking N–N bond is positioned for maximum delocalization of the odd electron in the anilino radical being formed.[2] The substituent effect on the rate for **1** decomposition, we proposed, largely reflects the ease of deconjugation of the nitrogen lone pair from the aromatic π system. The rate of decomposition of **2** is far less sensitive to substituent[1] (relative rates for **2** (4-OCH_3)/**2** (4-H)/**2** (4-CN) 4.5:1:1.1 at 90 °C), which we postulated was caused by the steric bulk of the *tert*-butyl group forcing **2** to assume conformation ii, in which the nitrogen lone pair is not strongly interacting with the aromatic ring.

We report here the solid-state structures of two *N*-*tert*-butylaryltetrazenes, **2A** and **2B**, and a brief ESR study of the triplet radical pairs produced by photolysis of **2B**.



2A R=Cl, R'=H

2B R=R'=D

Experimental Section

Single-Crystal X-Ray Structure of 1,4-Di-*tert*-butyl-1,4-bis(4-chlorophenyl)-2-tetrazene (2A). A parallelepiped-shaped crystal (0.10 × 0.14 × 0.24 mm) prepared by the published method[3] and grown from pentane was attached to a glass fiber with Elmer's Glue. Preliminary oscillation, Weissenberg, and precession photographs indicated the crystal symmetry to be triclinic. The crystal was mounted on a Syntex $P\bar{1}$ four-circle computer-controlled diffractometer. Graphite-monochromated Cu Kα (λ 1.5418 Å) radiation was used throughout the alignment and data collection procedure. Lattice constants were obtained from 15 diffraction maxima well distributed in 2θ, χ, and ω. The Syntex routines[4] indicated a triclinic unit cell, with the cell parameters listed in Table I. Data were collected in the usual θ–2θ scan mode from 5° ≤ 2θ ≤ 100°. Two standard reflections monitored every 50 reflections indicated no significant drift in intensity. The data were corrected for Lorentz polarization effects with the polarization term including a correction for the graphite monochromator.[5] Absorption corrections were not applied because of the symmetrical shape of the crystal and the small value of the linear absorption coefficient.[6] The data were reduced in the usual manner[7] with $\sigma(F)$, including a term of 0.0025$(I)^2$ to avoid overweighting the strong reflections in least squares. Of the 1183 total independent measurements, the 847 with $I > 2\sigma(I)$ were used in the structural analysis.[8]

The structure was solved by the heavy-atom method.[9] The orientation of eight atoms of the *p*-chloroanilino fragment was observed as intramolecular Cl–C and Cl–N vectors comprising the three-dimensional Patterson function. Those eight atoms were included in a structure factor Fourier calculation[10] assuming the acentric space group $P1$, which then yielded the orientation of the other Cl and 17 nonhydrogen atoms. Since derived coordinates appeared to possess $\bar{1}$ site symmetry, the position of the molecule was shifted to place this point (midway between the nitrogens comprising the azo linkage) in coincidence with the center of symmetry at the origin (0,0,0). Refinement was then begun assuming the centric space group $P\bar{1}$. Nine cycles of full-matrix least-squares refinement,[11] ultimately including anisotropic temperature factors for all nonhydrogen atoms and idealized positions for hydrogen atoms using C–H distances set to 0.95 Å and B_{iso} = 5.0 Å yielded R_1 and R_2[12] of 4.9 and 5.2%. The atomic scattering factors for nonhydrogen atoms are those compiled by Hanson and co-workers,[13] and those for hydrogen atoms from Stewart and co-workers.[14] Interatomic distances and bond angles were calculated with the Busing-Martin-Levy function and error program.[15]

Aniline-*2,4,6-d*$_3$. A mixture of 31 g (0.33 mol) of freshly distilled aniline, 5 g of concentrated sulfuric acid, and 25 mL (0.13 mol) of D_2O (99.8%) was heated for 36 h at 100 °C, and then contaminated heavy water was distilled from the mixture at 1 mm. After three repetitions with 25 mL of fresh D_2O, the product was added to an ice-cold sodium carbonate solution, extracted into ether, dried with sodium sulfate, and distilled, giving aniline-d_3 appearing to have about 98% incorporation of three deuteriums by NMR: ^{1}H NMR (CCl_4) δ 6.96 (s, 2 H), 3.1 (br s, 2 H).

1,4-Di-*tert*-butyl-1,4-bis(2,4,6-trideuteriophenyl)-2-tetrazene (2B). The deuterated aniline was *tert*-butylated in methylene chloride by the method employed for the protio material[3] in 90% yield, bp 42 °C (0.45 mm). Nitrosation, reduction to the hydrazine, and

Table I. Unit Cell Parameters of 2A and 2B

	2A	2B
a, Å	8.654 (3)	10.7082 (6)
b, Å	6.648 (1)	8.697 (1)
c, Å	9.666 (2)	11.479 (1)
α, deg	86.34 (1)	90.0
β, deg	104.15 (2)	109.647 (9)
γ, deg	98.60 (2)	90.0
Volume, Å^3	533.1 (2)	1006.8 (2)
Density (calcd), g cm^{-3}	1.22	1.01
Density (obsd), g cm^{-3}	1.12	1.02
Mol/cell	1	2
Space group symmetry	$P\bar{1}$	$P2_1/n$

quinone oxidation[3] gave the tetrazene, mp 114.5–115 °C dec. Spectral data: ^{1}H NMR ($CDCl_3$) δ 7.27 (s, 4 H), 1.02 (s, 18 H); UV (EtOH) 297 (6200), 238 (9900) nm.

Single-Crystal X-Ray Structure of 1,4-Di-*tert*-butyl-1,4-bis(2,4,6-trideuteriophenyl)-2-tetrazene (2B). A single crystal of **2B** of appropriate size was cut from a large single crystal grown by slow evaporation from pentane; this compound tends to crystallize in leaves. Alignment and obtainment of cell parameters were performed as for **2A**. The Syntex autoindexing procedure indicated a monoclinic unit cell. Data were collected from $5° \leq 2\theta \leq 110°$. Standard reflection intensity data indicated no significant drift in intensity. Nine reflections exceeded the rate limits of the x-ray counter and were manually scaled to fit the remaining data by comparison with several other reflections. The data were reduced as described for **2A** to yield 1118 independent reflections significantly above background [$I > 2\sigma(I)$], which were used in the solution and refinement of the structure. Inspection of systematic absences in the merged data confirmed the choice of space group as $P2_1/n$. Since the observed density indicated the presence of two molecules per cell, this required that the molecules lie on the inversion center.

Solution of the structure was completed by direct methods. The independent data were first converted to the normalized structure factors (E values) by the program FAME.[16] The program MULTAN then generated 16 sets of possible solutions by the symbolic addition method, two of which indicated significantly greater phase angle consistency than the others. One of these gave a Fourier map which could not be interpreted in terms of a meaningful physical structure, but the second solution allowed recognition of all 12 nonhydrogen atoms. After several cycles of full-matrix isotropic least-squares refinement, idealized positions of the hydrogen atoms were included in fixed atom contributions based on C–H bond distances of 1.0 Å and $B_0 = 4.0$ Å^2, and the values of R_1 and R_2 converged to 13.6 and 22.0%, respectively. The 12 nonhydrogen atoms were then allowed anisotropic thermal motion and R_1 dropped to 5.2%. A Fourier difference map based on the 12 nonhydrogen atoms then revealed the true positions of all 14 hydrogen atoms, and these coordinates were allowed to refine isotropically in the full-matrix procedure, yielding final values of R_1 and R_2 of 4.3 and 6.5%.

ESR spectra were determined using a Varian E.3 spectrometer. A crystal of **2B** was attached with silicone grease to the horizontal face of a brass cylinder with a horizontal cut to the axis and a vertical cut along the axis. The brass fitting was then attached to a stainless steel rod which extended into the ESR cavity, inside a liquid nitrogen Dewar. After cooling, irradiation, and collection of spectra, the sample was allowed to slowly return to room temperature and the crystal checked for cracks or shifts of positions, and then moved to the vertical face, where spectra were recorded with the crystal attached in two mutually perpendicular directions.

Results and Discussion

X-Ray Structure Determination. The *p*-chloro compound **2A** was chosen for study because of the ease of analysis by heavy-atom methods. The deuterated compound **2B** was chosen for simplification of the triplet radical pair ESR spectrum (see following section). When it was shown that, although the solid-state conformations of **2A** and **2B** were similar their crystal packing was considerably different, the refinement of **2A** was not carried out to as great a degree as that of **2B**, which was used for the ESR study. The positional and thermal parameters for **2A** and **2B** appear in Tables II and III, and the heavy-atom bond distances and bond angles in Tables IV and V. Thermal ellipsoid plots appear in Figures 1 and 2. The agreement in intramolecular structure between **2A** and **2B** is seen to be excellent, although the distortion suggested in the C–C distances of the *tert*-butyl group of **2A**

Table II. Positional and Thermal Parameters for 2A [a,b]

Atom	x	y	z	$10^4\beta_{11}$	$10^4\beta_{22}$	$10^4\beta_{33}$	$10^4\beta_{12}$	$10^4\beta_{13}$	$10^4\beta_{23}$
Cl(4)	0.2525 (2)	−0.5776 (2)	−0.3777 (2)	184 (3)	314 (5)	231 (3)	37 (3)	94 (2)	−89 (3)
C(4)	0.1361 (6)	−0.4280 (9)	−0.3145 (6)	122 (9)	249 (18)	139 (9)	24 (10)	33 (7)	−57 (10)
C(3)	0.0445 (6)	−0.5151 (8)	−0.2234 (6)	236 (12)	226 (16)	189 (11)	57 (12)	101 (10)	23 (11)
C(2)	−0.0455 (7)	−0.3957 (9)	−0.1713 (6)	233 (12)	250 (18)	149 (9)	63 (12)	111 (9)	51 (10)
C(1)	−0.0465 (6)	−0.1938 (8)	−0.2137 (5)	120 (9)	220 (16)	100 (8)	18 (10)	24 (7)	−21 (9)
C(6)	0.0455 (6)	−0.1106 (8)	−0.3074 (6)	158 (10)	210 (16)	159 (9)	17 (10)	65 (9)	3 (10)
C(5)	0.1365 (6)	−0.2292 (9)	−0.3588 (6)	159 (10)	262 (19)	159 (9)	14 (11)	82 (8)	4 (10)
N(7)	−0.1355 (5)	−0.0619 (6)	−0.1600 (5)	129 (8)	249 (13)	117 (7)	37 (8)	31 (6)	−32 (7)
N(8)	−0.0723 (4)	0.0094 (6)	−0.0238 (5)	133 (7)	209 (11)	112 (6)	19 (9)	31 (7)	−25 (7)
C(9)	−0.3155 (6)	−0.0923 (8)	−0.1975 (6)	122 (10)	302 (18)	128 (9)	32 (10)	33 (7)	−14 (10)
C(10)	−0.3694 (7)	0.1117 (11)	−0.1916 (8)	183 (12)	418 (24)	286 (14)	121 (14)	28 (11)	−60 (14)
C(11)	−0.3735 (7)	−0.1667 (10)	−0.3493 (7)	137 (11)	518 (25)	146 (10)	34 (13)	14 (8)	−31 (13)
C(12)	−0.3845 (7)	−0.2467 (11)	−0.0969 (7)	178 (12)	517 (26)	173 (11)	−23 (14)	70 (9)	−2 (13)
H(2)	0.0441	−0.6648	−0.1951	5.0[c]					
H(3)	−0.1101	−0.4550	−0.1017	5.0[c]					
H(5)	0.0384	0.0315	−0.3405	5.0[c]					
H(6)	0.2068	−0.1706	−0.4235	5.0[c]					
H(10A)	−0.2996	0.2255	−0.2346	5.0[c]					
H(10B)	−0.3603	0.1487	−0.0905	5.0[c]					
H(10C)	−0.4851	0.1201	−0.2468	5.0[c]					
H(11A)	−0.3191	−0.0793	−0.4184	5.0[c]					
H(11B)	−0.3492	−0.3109	−0.3540	5.0[c]					
H(11C)	−0.4946	−0.1711	−0.3896	5.0[c]					
H(12A)	−0.3391	−0.3786	−0.0971	5.0[c]					
H(12B)	−0.5040	−0.2756	−0.1233	5.0[c]					
H(12C)	−0.3483	−0.1946	0.0032	5.0[c]					

[a] The form of the anisotropic temperature factor which is used is $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$. [b] The standard deviations in the last significant figure are given in parentheses in this and succeeding tables. [c] Isotropic thermal parameters.

Table III. Positional and Thermal Parameters for 2B [a,b]

Atom	x	y	z	$10^4\beta_{11}$	$10^4\beta_{22}$	$10^4\beta_{33}$	$10^4\beta_{12}$	$10^4\beta_{13}$	$10^4\beta_{23}$
C(1)	0.2705 (1)	0.5705 (2)	0.4601 (1)	75	153	85	−1	33	15
C(2)	0.2386 (2)	0.7156 (2)	0.4883 (2)	123	165	124	12	31	1
C(3)	0.1469 (2)	0.8034 (3)	0.4007 (2)	145	186	171	38	29	24
C(4)	0.0872 (2)	0.7477 (3)	0.2850 (2)	106	220	154	13	27	70
C(5)	0.1170 (2)	0.6038 (3)	0.2544 (2)	123	279	96	−32	22	25
C(6)	0.2111 (2)	0.5140 (3)	0.3426 (2)	118	187	99	2	38	6
N(7)	0.3684 (1)	0.4851 (2)	0.5550 (1)	83	147	94	0	39	18
N(8)	0.4883 (1)	0.4551 (1)	0.5373 (1)	82	130	87	−3	34	8
C(9)	0.3280 (2)	0.3537 (2)	0.6183 (1)	106	157	90	−23	45	12
C(10)	0.3068 (4)	0.2077 (3)	0.5425 (2)	296	181	142	−93	87	−3
C(11)	0.2021 (3)	0.3997 (4)	0.6421 (3)	169	335	220	31	131	105
C(12)	0.4374 (3)	0.3283 (3)	0.7412 (2)	165	248	116	−42	27	63
D(6)	0.2377 (18)	0.4196 (23)	0.3209 (16)	5.325[c]					
H(5)	0.0809 (22)	0.5603 (23)	0.1710 (19)	6.729[c]					
D(4)	0.0261 (21)	0.8107 (22)	0.2250 (19)	6.175[c]					
H(3)	0.1193 (28)	0.9075 (34)	0.4159 (24)	10.144[c]					
D(3)	0.2819 (23)	0.7532 (24)	0.5713 (22)	7.025[c]					
H(10A)	0.2898 (24)	0.1251 (27)	0.5878 (21)	7.931[c]					
H(10B)	0.2267 (29)	0.2312 (24)	0.4630 (27)	9.317[c]					
H(10C)	0.3977 (32)	0.1835 (35)	0.5213 (27)	11.970[c]					
H(11A)	0.1244 (29)	0.4104 (33)	0.5620 (25)	9.861[c]					
H(11B)	0.2221 (39)	0.5042 (45)	0.6898 (33)	14.592[c]					
H(11C)	0.1794 (24)	0.3183 (31)	0.6893 (24)	8.712[c]					
H(12A)	0.5217 (31)	0.3122 (30)	0.7286 (25)	9.632[c]					
H(12B)	0.4392 (25)	0.4326 (30)	0.7895 (22)	9.236[c]					
H(12C)	0.4140 (20)	0.2489 (25)	0.7855 (20)	6.694[c]					

[a] The form of the anisotropic temperature factor which is used is $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$. [b] The standard deviations in the last significant figure are given in parentheses in this and succeeding tables. [c] Isotropic thermal parameters.

Table IV. Heavy-Atom Intramolecular Distances for 2A and 2B (Å)

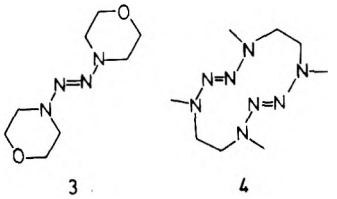
	2A	2B
C(1)-C(2)	1.379 (7)	1.374 (3)
C(2)-C(3)	1.387 (8)	1.376 (3)
C(3)-C(4)	1.367 (7)	1.356 (3)
C(4)-C(5)	1.363 (7)	1.366 (3)
C(5)-C(6)	1.384 (7)	1.401 (3)
C(1)-C(6)	1.384 (7)	1.374 (3)
C(1)-N(7)	1.445 (6)	1.439 (2)
N(7)-N(8)	1.381 (5)	1.390 (2)
N(8)-N(8′)	1.246 (7)	1.246 (2)
N(7)-C(9)	1.496 (6)	1.494 (2)
C(9)-C(10)	1.507 (8)	1.513 (3)
C(9)-C(11)	1.519 (8)	1.516 (3)
C(9)-C(12)	1.527 (8)	1.516 (3)
N(7)-N(7′)	3.456 (11)	3.464 (4)
C(4)-Cl	1.748 (5)	

Table V. Heavy-Atom Bond Angles for 2A and 2B (deg)

	2A	2B
C(2)-C(1)-C(6)	119.28 (47)	119.36 (17)
C(3)-C(2)-C(1)	120.35 (50)	120.67 (20)
C(4)-C(3)-C(2)	119.05 (51)	120.21 (22)
C(5)-C(4)-C(3)	121.75 (48)	120.33 (19)
C(6)-C(5)-C(4)	119.15 (50)	119.92 (20)
C(1)-C(6)-C(5)	120.37 (50)	119.50 (20)
C(2)-C(1)-N(7)	122.55 (46)	118.10 (15)
C(6)-C(1)-N(7)	118.13 (47)	122.52 (16)
C(1)-N(7)-N(8)	117.71 (39)	117.39 (11)
N(7)-N(8)-N(8′)	113.71 (49)	113.07 (12)
C(1)-N(7)-C(9)	121.16 (41)	120.42 (12)
N(8)-N(7)-C(9)	112.09 (37)	111.12 (12)
N(7)-C(9)-C(10)	107.63 (45)	111.97 (15)
N(7)-C(9)-C(11)	108.25 (43)	107.87 (16)
N(7)-C(9)-C(12)	111.99 (46)	107.70 (14)
C(10)-C(9)-C(11)	108.90 (52)	110.76 (22)
C(11)-C(9)-C(12)	109.41 (49)	109.41 (20)
C(10)-C(9)-C(12)	110.57 (50)	109.05 (20)
C(3)-C(4)-Cl	118.93 (41)	
C(5)-C(4)-Cl	119.31 (44)	

is not borne out in the more refined structure for **2B**. The hydrogens refined to reasonable positions for **2B**, the aliphatic hydrogens giving final C–H distances of 0.940 (25)–1.101 (28) Å and the aromatic C–D distances obtained were 0.966 (22), 0.948 (21), and 0.930 (19) Å at C(2), C(4), and C(6), marginally shorter than the 0.986 (29) and 0.980 (20) Å obtained for the C(3) and C(5) C–H bonds.

The geometries found at the planar tetrazene linkages are compared in Figure 3. Some preliminary structural data have been reported for two aliphatic *trans*-2-tetrazenes, azomorpholine (**3**) and the bistetrazene 1,4,7,10-tetramethyl-1,2,3,4,7,8,9,10-octaazacyclododeca-2,8-diene (**4**),[17] which have N–N distances of 1.393 (1) and 1.385 (2, av, max dev 7) Å and N=N distances of 1.251 (2) and 1.253 (2, av, max dev 1) Å, respectively, and N—N=N angles averaging 113.0 (2, max dev 4)°; the geometry at the tetrazine linkage of **2** closely resembles that of **3** and **4**.



3 4

Information on the dihedral angles between planes containing several atoms in **2B** appears in Table VI. The aryl ring and N(7) lie in plane, and the two aryl rings of each molecule are in parallel planes, separated by 2.98 Å. The planes of the aryl rings have a dihedral angle of 57° with respect to the tetrazene nitrogen plane. The trisubstituted nitrogen is nonplanar, N(7) lying 0.28 Å from the plane through the three

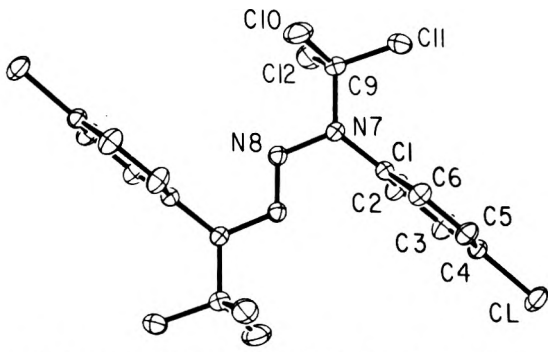


Figure 1. Thermal ellipsoid plot of **2A**, hydrogens omitted.

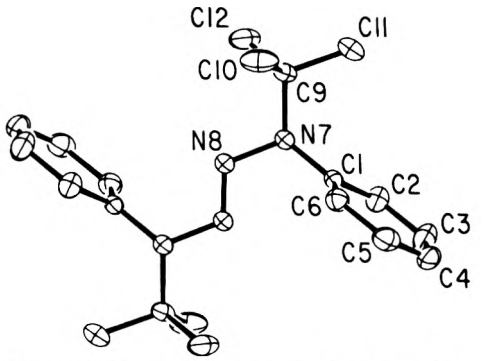
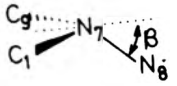
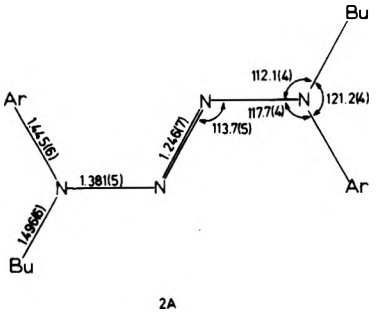


Figure 2. Thermal ellipsoid plot of **2B**, hydrogens omitted.



atoms attached to it [plane 4, C(1)–N(8)–C(9)], $\beta = 34.1°$. The lone pair of N(7) was not observed by x-ray analysis, but its axis should lie approximately perpendicular to plane 4. The lone-pair orbital axis is thus inferred to lie nearly in the plane of the aryl ring, so that **2** does indeed have the "deconjugated" conformation suggested previously.[1,3] The flattening at N(7) must be largely steric, because the N(7) lone pair is twisted out of conjugation with both the aryl ring and the azo linkage. For the single-crystal ESR study, the relationship between the symmetry-related molecules and the crystal faces are important. A packing diagram appears in Figure 4, and intermolecular closest heavy-atom approaches are shown in Table VII. Table VIII contains information on the relationship of the aryl ring planes in the symmetry-related pairs of molecules, and the orientation of these planes with respect to the crystal faces. The aryl rings of the two types of symmetry-related **2B** molecules within the crystal make an angle of 45° with each other, and the aryl rings are nearly perpendicular (97° angle) with the A face of the crystal.

Triplet Radical Pairs from 2. Since the pioneering study by Bartlett and McBride[18] of α-phenylethyl triplet radical pairs trapped in a matrix of the azo compound, several other triplet radical pairs have been studied. Radical precursors have included azo compounds,[18,19] tetraphenylhydrazine,[20] and diacyl peroxides;[21,22] especially detailed studies of the triplet pairs from benzoylacetyl peroxide have been carried out.[23] It was expected from this work that *N*-*tert*-butylanilino triplet radical pairs would be observed upon photolysis of **2**, as proved to be the case. When powdered samples of **2** are photolyzed at liquid nitrogen temperature, powder spectra of a triplet with D of about 100 G, as well as a weak half-field absorption, are observed. Single crystals of variously substituted **2** molecules gave strongly anisotropic ESR spectra,



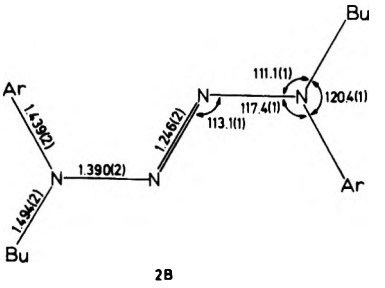


Figure 3. Comparison of geometries at the 2-tetrazene linkage for **2A** and **2B**.

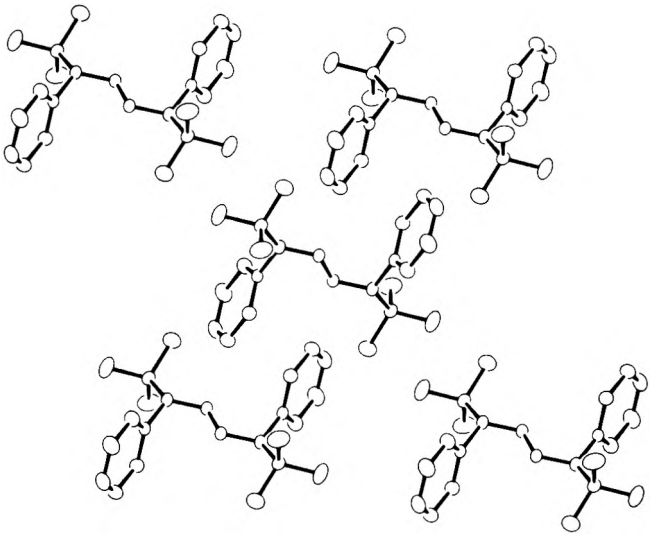


Figure 4. Packing diagram for **2B**, showing four molecules of one orientation surrounding one of the other orientations.

Table VI. Planes and Dihedral Angles in 2B

Atoms in place	Plane no.	Atoms out of plane (distance, Å)
C(1)–C(2)–C(3)–C(4)–C(5)–C(6)	1	N(7) (+0.01), N(8) (+1.15)
C(1′)–C(2′)–C(3′)–C(4′)–C(5′)–C(6′)	2	N(7′) (−0.01), N(8) (−1.15)
N(7)–N(8)–N(8′)–N(7′)	3	C(1) (+1.15), C(6) (+1.49)
C(1)–N(8)–C(9)	4	N(7) (−0.28), C(4) (+0.40)

Angles (deg) between Plane n and the Other Planes			
Planes	2	3	4
1	0.01	57.16	94.18
2		57.16	94.18
3			96.19

Table VII. Intramolecular Aryl Group Closest Approaches for 2B

Atoms[a]	Distance, Å
C(2)–C(4″)	4.133 (4)
C(3)–C(6″)	4.040 (4)
C(3)–C(12″)	3.985 (4)
C(4)–C(6‴)	3.781 (3)
C(4)–N(8‴)	3.948 (4)
C(4)–N(7″)	3.701 (3)
C(4)–N(8″)	3.723 (3)

[a] The ″ designation refers to the half-molecule fragment related by the symmetry operation $\frac{1}{2} + x, \frac{1}{2} - y, \frac{1}{2} + z$, and the ‴ to the half-molecule fragment related by $\frac{1}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z$.

Table VIII. Intermolecular and Crystal Face Planes in 2B

Atoms in plane	Plane no.
C(1)–C(2)–C(3)–C(4)–C(5)–C(6)	1
C(1″)–C(2″)–C(3″)–C(4″)–C(5″)–C(6″)	5
Crystal face A	6
Crystal face B	7
Crystal face C	8

Angles (deg) between Plane n and the Other Planes				
Planes	5	6	7	8
1	45.47	97.04	26.69	61.34
5		61.34	26.69	97.04
6			70.40	102.37
7				70.40

which showed very complex patterns in some orientations. We concluded that hyperfine splittings were being observed in the dipolar splitting lines. The isotropic ESR spectrum of *N*-phenylanilino radical in solution shows several splittings of comparable magnitude; $a(N) = 9.70$ $a(H_p) = 7.09$, $a(2H_o) = 5.74$, $a(2H_m) = 1.99$ G, $g = 2.0033$.[3] To simplify the spectra of the triplet radical pairs, we prepared the deuterated compound **2B.** Irradiation of **2B** in pentane gave the expected *N*-*tert*-butylanilino-d_3 radical isotropic ESR spectrum, $a(N) = 9.70$, $a(2H_m) = 1.97$, $a(3D) \approx 1.0$ g, $g = 2.0033$. The isotropic nitrogen splitting is five times larger than any of the other splittings in the deuterated material. Since spectral lines attributable to less highly deuterated *N*-*tert*-butylanilino radicals were not observed, a usefully high degree of deuterium incorporation in **2B** had been achieved.

A single crystal of **2B** was mounted to a brass fitting attached to a rod which could be rotated inside a liquid nitrogen Dewar in the cavity of the ESR spectrometer. The brass fitting had faces perpendicular and parallel to the axis of rotation, so that by mounting the same face of the crystal to these faces, rotations about three mutually perpendicular axes could be achieved. ESR spectra were recorded at 10–15° rotation intervals about each of these three mutually perpendicular axes, after irradiation at liquid nitrogen temperature. In addition to a large central peak about 50 G wide, attributed to the monoradical, four peaks (which were split further in some orientations) were found to have positions very sensitive to rotation angle. Because of the two orientations of **2B** known to be present in the crystal, this is expected; loss of nitrogen from the symmetry-related tetrazene molecules should give radical pairs in two different orientations, and each radical pair will give rise to an anisotropic doublet ESR spectrum, because of its dipolar splitting. The orientation of the crystal employed (large face parallel and perpendicular to the axis of rotation) nearly coincided with the principal axes of one dipolar doublet (hereafter called species I), and the anisotropy

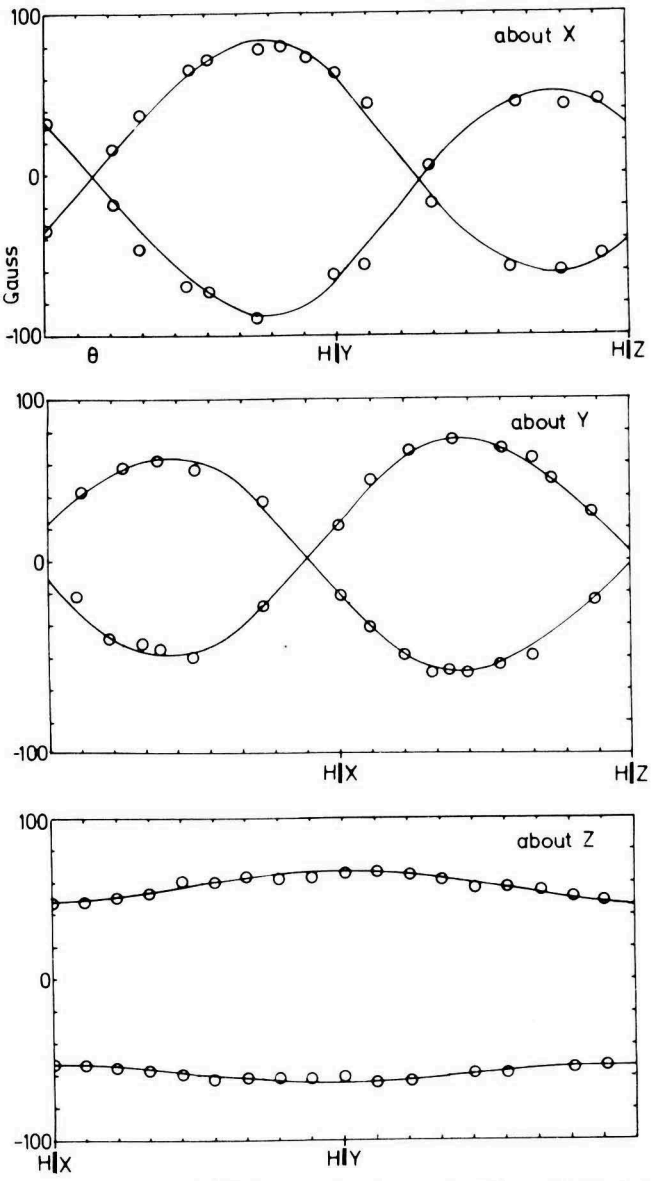


Figure 5. Observed ESR line positions for species II from **2B** (circles), compared with the positions calculated from the positions of species I and the relative orientation of the two types of **2B** molecules in the crystal (Table VIII).

of the line positions was analyzed by the method described in Wertz and Bolton,[24] giving a D matrix which was diagonalized, allowing calculation of the zero-field splitting parameters $D' = (-)117$ G, $E' = (+)4$ G ($D = (-)0.0110$, $E = (+)0.0004$ cm^{-1}). In a further check on our analysis, the line separations for species I were plotted vs. $\sin^2\theta$, giving straight lines for which D and E can be estimated using the equations of Vincent and Maki[25] for rotation about the principal axes, giving $D' = 0.0110, 0.0108, 0.0112$, and $E' = 0.00018, 0.00065, 0.0004$, respectively, for the three axes of rotation used, in good agreement with the matrix diagonalization analysis. Species II clearly did not have its principal axes aligned in the directions for rotation chosen, as expected from the crystal structure. The expected spectrum was calculated, again using the equations of Vincent and Maki, from the relative orientation of the two molecules in the crystal lattice of **2B** (see Figure 4 for a packing diagram, and Table VIII for the relative orientation of the molecules in the crystal), resulting in fairly good agreement to the observed line positions for species II, as shown in Figure 5.

The D value for the *N*-*tert*-butylanilino radicals from **2B** corresponds to an average odd electron separation of over 5

Å. Great motion of the radicals with respect to each other upon loss of nitrogen is not expected, because of the good alignment of the C(1)–N(7) bond with the aryl π cloud in the tetrazene. Our ESR data is not good enough to measure the actual amount of motion of the radicals from their positions in the tetrazene precursor, as McBride and co-workers[19,23] have done for several crystals. As a qualitative way of gauging motion, we calculated the D' and E' expected using the spin densities estimated from the doublet ESR spectrum ($\rho_N = 0.489$, $\rho_o = 0.234$, $\rho_m = -0.080$, $\rho_p = -0.284$; these are only estimates, and ignore spin density in the *tert*-butyl group) and the atom positions of the tetrazene, obtaining $D' = -146$, $E' = 10$ G, both rather higher than the observed values.

The axes for the anisotropic g tensor coincided, with our rather wide experimental error, with those for the D tensor, and the observed values were $g_{zz} = 2.0058$, $g_{yy} = 2.0003$, $g_{xx} = 2.0044$, $g_{iso} = 2.0035$, close to the 2.0033 observed for the doublet in solution.

Hyperfine splittings caused by the nitrogen atoms were observed in some orientations of the triplet, but we have not been able to analyze them. No splittings were observed in the dipolar lines for orientation about the axis nearly coincident with the z axis of the triplet, although the line width varied from about 6.5 to 15 G, but in rotations about the other axes, each half of the doublet for species I varied from appearing as a singlet (splitting under 2 G) to appearing as a five to nine line pattern with apparent line separation of up to 12 G.

Quantitative study of these triplets was hampered by the presence of species I and II, which frequently merged with each other, disrupting our ability to accurately measure the line positions of either one. Preparation of deuterated **2A** would allow study of the nitrogen hyperfine splittings without this difficulty, but such a study has not been carried out.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for partial financial support of this research. The funds used for purchasing the diffractometer came partly from the Major Instrument Program of the NSF. We thank Professor J. M. McBride for extensive discussions and the program used for calculation of D' and E', and W. C. Hollinsed for assistance in calculations from the x-ray data.

Registry No.—**2A,** 63641-20-3; **2B,** 63641-21-4; aniline-2,4,6-d_3, 7291-08-9; aniline, 62-53-3; D_2O, 7789-20-0.

References and Notes

(1) For Part 2, see S. F. Nelsen and R. T. Landis II, *J. Am. Chem. Soc.*, **95,** 8707 (1973).
(2) S. F. Nelsen and D. H. Heath, *J. Am. Chem. Soc.*, **91,** 6452 (1969).
(3) S. F. Nelsen, R. T. Landis II, L. H. Kiehle, and T. H. Leung, *J. Am. Chem. Soc.*, **94,** 1610 (1972).
(4) R. A. Sparks, "Operations Manual, Syntex $P\bar{1}$ Diffractometer", Syntex Analytical Instruments, Cupertino, Calif., 1970.
(5) G. H. Stout and L. H. Jensen, "X-ray Structure Determination", Macmilian, New York, N.Y., 1968, p 411.
(6) "International Tables for X-ray Crystallography", Vol. I., The Kynoch Press, Birmingham, England, 1965.
(7) Cf., V. A. Uchtman and L. F. Dahl, *J. Am. Chem. Soc.*, **91,** 3756 (1969).
(8) Computer programs used for data reduction were FOBS and SORTMERGE, written ty the author (J.C.C.).
(9) A. L. Patterson, *Z. Kristallogr.*, **A90,** 517 (1935).
(10) J. C. Calabrese, "A Three-Dimensional Fourier Summation Program—Fourier", unpublished.
(11) ORFLSD, a local modification of the program by W. R. Busing, K. O. Martin, and H. A. Levy, "ORFLS, A Fortram Crystallographic Least Squares Program", Oak Ridge National Laboratory, Oak Ridge, Tenn. 1964, N, ORNL-TM-305.
(12) $R_1 = [\Sigma||F_o| - |F_c||/\Sigma|F_o|] \times 100$ and $R_2 = [\Sigma W_i||F_o| - |F_c||^2/\Sigma W_i|F_o|^2]^{1/2} \times 100$. All least-squares refinements were based on the mimimunation of $\Sigma W_i||F_o| - |F_c||^2$ with the individual weights $W_i = 1/\sigma(F_o)^2$.
(13) H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Crystallogr.*, **17,** 1040 (1964).
(14) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42,** 3175 (1965).
(15) W. R. Busing, K. O. Martin, and H. A. Levy, "ORFFE, A Fortram Crystallographic Function and Error Program", Oak Ridge National Laboratory, Oak Ridge, Tenn., 1964, No. ORNL-TM-306.
(16) R. B. K. Dewar and A. L. Stone, "FAME", University of Chicago, 1966.
(17) V. W. Day, D. H. Campbell, and C. J. Michejda, *J. Chem. Soc., Chem. Commun.*, 118 (1975).
(18) P. D. Partlett and J. M. McBride, *Pure Appl. Chem.*, **15,** 89 (1967).
(19) Detailed study of azoisobutyronitrile decomposition has been carried out by the group of McBride, but their ESR studies remain largely unpublished. For earlier studies of radical pairs from this compound, see A. S. Lebedev, *Dokl. Akad. Nauk. SSSR*, **171,** 378 (1966); M. C. R. Symons, *Nature-(London)*, **213,** 1226 (1967).
(20) (a) D. A. Wiersma and J. Kommandeur, *Mol. Phys.*, **13,** 241 (1967); (b) D. A. Wiersma, J. H. Lichtenbott, and J. Kommandeur, *J. Chem. Phys.*, **50,** 2974 (1968).
(21) A. V. Zubkov, A. T. Koritskii, and Ya. S. Lebedev, *Dokl. Akad. Nauk. SSSR*, **180,** 1150 (1968).
(22) (a) H. C. Box, *J. Phys. Chem.*, **75,** 3426 (1971); (b) H. C. Box, E. E. Budzaski, and H. G. Freund, *J. Am. Chem. Soc.*, **92,** 5305 (1970).
(23) (a) N. J. Karch and J. M. McBride, *J. Am. Chem. Soc.*, **94,** 5092 (1972); (b) N. J. Karch, E. T. Koh, B. L. Whitsel, and J. M. McBride, *ibid.*, **97,** 6729 (1975).
(24) J. E. Wertz and J. R. Bolton, "Electron Spin Resonance", McGraw-Hill, New York, N.Y., 1972, p 125.
(25) J. S. Vincent and A. H. Maki, *J. Chem. Phys.*, **39,** 3088 (1963).

Telesubstitution and Other Transformations of Imidazo[1,2-a]- and s-Triazolo[4,3-a]pyrazines[1]

Jernej Bradač, Zdenka Furek, Daša Janežič, Stana Molan, Igor Smerkolj, Branko Stanovnik, Miha Tišler,* and Bojan Verček

Department of Chemistry, University of Ljubljana, 61000 Ljubljana, Yugoslavia

Received May 23, 1977

Imidazo[1,2-a]pyrazine is brominated to give either the 3-bromo- or the 3,5-dibromo derivative. The 6,8-dibromo compound, prepared from 2-amino-3,5-dibromopyrazine, is brominated to 3,6,8-tribromoimidazo[1,2-a]pyrazine. With sodium methylate only the bromine atom at position 8 is substituted, and from the 6,8-dibromo compound 6-bromo-8-methoxyimidazo[1,2-a]pyrazine is prepared. Quaternization of imidazo[1,2-a]pyrazine gives a mixture of the 1-methyl and 7-methyl derivatives. s-Triazolo[4,3-a]pyrazine afforded upon bromination the 5-bromo derivative. This and other 5-halo compounds reacted with nucleophiles to give either the anticipated 5-substituted derivative or at position 8 telesubstituted product, or both. Mechanistic aspects of telesubstitution are outlined.

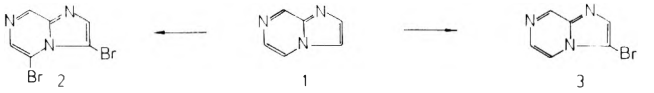
As part of our interest in the chemistry of azolopyrazines we would like to report some new transformations of imidazo[1,2-a]- and s-triazolo[4,3-a]pyrazines.

A general method for the synthesis of imidazo[1,2-x]azines consists of the reaction between the corresponding 2-aminoazines and α-halocarbonyl compounds. In the pyrazine

series this method gives less satisfactory results and only a few 2- or 3-substituted imidazo[1,2-*a*]pyrazines were synthesized.[2,3] In connection with the isolation of luciferins, new and better synthetic approaches have been devised. Imidazo[1,2-*a*]pyrazines were prepared from aminopyrazines and α-keto aldehydes or formaldehyde and hydrogen cyanide.[4-10] In another method 2-formylimidazoles were used as starting material and at position 1 quaternized derivatives were thus accessible.[11] Although the first derivative of this bicyclic system was reported in 1957,[12] the parent system has so far not been described in the free form but was obtained as the perchlorate[13] in low yield.

We have recently reported the synthesis of imidazo[1,2-*a*]pyrazine[14] and have examined its reaction with hydrazine to give a mixture of 2-methylimidazole and 1-ethyl-2-methylimidazole. It was established that these compounds arise from an initial attack of hydrazine on the pyrazine part of the bicycle, either at position 5 or at position 8.

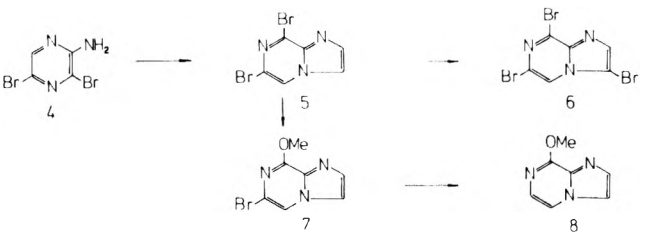
The ready availability of the parent heterocycle (**1**)[14] prompted us to investigate in more detail the reactivity of this system, in particular, electrophilic and nucleophilic substitutions. Bromination of **1** with bromine in glacial acetic acid



afforded the 3,5-dibromo compound **2**, whereas with *N*-bromosuccinimide the 3-bromo derivative **3** was obtained. The structure of this monobromo derivative follows from the following observations. The compound was resistant to nucleophilic substitution and no reaction with either sodium alcoholate, or sodium thiophenolate, hydrazine hydrate, or liquid ammonia could be observed. Such unreactivity toward nucleophiles is incompatible with structure of a 5-bromo compound, since because of theoretical considerations[15] as well as practical experience[16] a halogen atom at position 5 should be easily replaced. The NMR parameters of this monobromo compound did not allow unambiguous assignment of the peaks. However, when the spectrum was recorded after addition of a shift reagent, assignment became possible. In the normal NMR spectrum a broad singlet at δ 8.19 was observed, assignable to H_5 and H_6 protons. After addition of some-Eu(fod)$_3$ a doublet for H_6 at δ 9.43 and a doublet of doublets at δ 8.79 for H_5 were clearly separated. Moreover, coupling constants, $J_{5,6}$ = 5.5 and $J_{5,8}$ = 2.0 Hz, could be observed. This excludes other possible structures with the bromide atom either at positions 5, 6, or 8. The structure as a 2-bromo derivative is also excluded if we compare chemical shifts for H_2 and H_3 in the unsubstituted compound[14] and the monobromo derivative, since the signal for H_3 appears at lower field. Such spectral characteristics were observed also with pyrroloazines or imidazo[1,2-*b*]pyridazines.[17-21] All this evidence favors the structure of 3-bromoimidazo[1,2-*a*]pyrazine (**3**).

The structure of the dibromo compound **2** is also in agreement with NMR data. The signal for H_2 appears as a singlet at δ 7.73 and is almost at the same position as that of the unsubstituted compound[14] or the 3-bromo derivative **3**. Moreover, two other singlets at δ 7.95 and 8.96 appear in the NMR spectrum of **2**, and this excludes substitution at position 8. In this case a $J_{5,6}$ should be observable. Substitution at position 6 is also excluded, since in this case one should observe a $J_{5,8}$, observed so far in all 5,8-unsubstituted imidazo[1,2-*a*]pyrazines, such as the parent compound[14] or compounds **3**, **9**, and **10**.

Other bromo derivatives were prepared as follows. 6,8-Dibromoimidazo[1,2-*a*]pyrazine (**5**) was synthesized from 2-amino-3,5-dibromopyrazine (**4**) and bromoacetaldehyde, and after bromination with *N*-bromosuccinimide a tribromo derivative was obtained. Because of the NMR spectral evi-

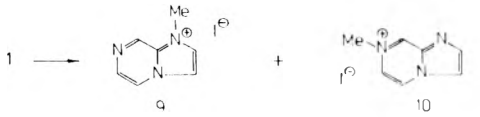


dence for this compound the structure of 3,6,8-tribromoimidazo[1,2-*a*]pyrazine (**6**) could be assigned. These findings agree with theoretical predictions of reactivity of imidazo[1,2-*a*]pyrazine, based on calculated electron densities.[15] These indicate that the most reactive position for electrophilic attack should be position 3, followed by position 5, whereas nucleophilic substitutions should take place predominantly at positions 5 and 8.

In a nucleophilic substitution, 6,8-dibromoimidazo[1,2-*a*]pyrazine (**5**) exchanged only one bromine atom with a methoxy group. For the purpose of structural assignment the obtained compound was catalytically dehalogenated to give the monomethoxy derivative. Since this compound revealed in its NMR spectrum a coupling constant of 5.0 Hz, corresponding to two ortho protons, its structure can be only 8-methoxyimidazo[1,2-*a*]pyrazine (**8**) and the precursor is 6-bromo-8-methoxy compound **7**.

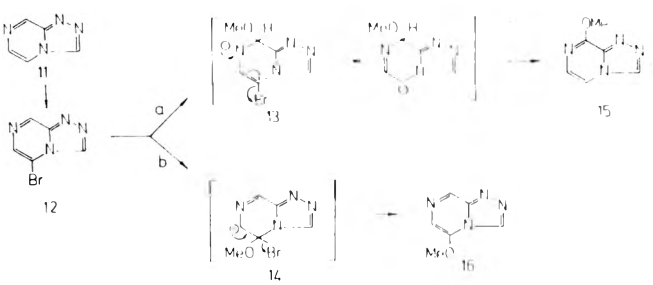
Imidazo[1,2-*a*]pyrazine does not undergo hydrogen–deuterium exchange under neutral or acid conditions. In an alkaline solution of aqueous NaOD in dimethyl sulfoxide exchange of protons 3 and 5 was complete in 19 min at room temperature (50% of H_5 is exchanged in <2 min, whereas 50% of H_3 is exchanged in 2 min). Other protons were not exchanged even at 100 °C after 75 min. This contrasts the more reactive *s*-triazolo[1,2-*a*]pyrazine system.[16]

Quaternization of imidazo[1,2-*a*]pyrazine with methyl iodide at room temperature afforded after 5 days a mixture of 7-methyl (**10**) and 1-methyl quaternary compounds (**9**) in a

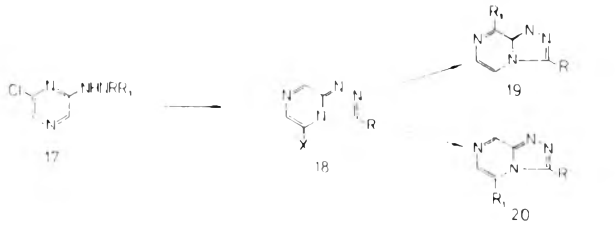


ratio of 1:1.6, as determined from NMR evidence. The structure assignment to both quaternary compounds follows from the following observations. The most important feature which allows the structure assignment to **10** is the appearance of $J_{6,8}$ = 1 Hz, this coupling constant being otherwise not observable with all azolopyrazines.[14,19] In the last case the quadrupole effect of N_7 is responsible for the fact that $J_{6,8}$ does not appear or is very small. The same effect, when blocking the free electron pair on the ring nitrogen, has been observed also with some azine *N*-oxides.[22] In addition, the signals for H_6 and H_8 in **10** are sharper in comparison to those of **9** or all other azolopyrazines, again because of the absence of the quadrupole effect of N_7.

As a continuation of our investigations on *s*-triazolo[1,5-*a*]- and *s*-triazolo[4,3-*a*]pyrazine,[14,16,23-25] we now report some new findings. 5-Bromo-*s*-triazolo[4,3-*a*]pyrazine (**12**) was



obtained from the parent compound **11** upon bromination with bromine in acetic acid. Its structure follows from the following considerations. In the NMR spectrum appear three singlets and this excludes substitution at either position 3 or 8, since in these cases a $J_{5,6}$ would be observed. Substitution at position 6 is also excluded, since in this case a $J_{5,8}$ would be observed. Moreover, the NMR spectrum of **12** is very similar to that of the analogous 5-chloro compound (**18**, R = H, X = Cl, three singlets for protons H_3, H_6, and H_8), whose structure follows unequivocally from its synthesis from the corresponding chloropyrazine (**17**, R = R_1 = H).



Compound **12** reacted with sodium methylate at room temperature to give a mixture of 5-methoxy (**16**) and 8-methoxy compounds (**15**). The structure assignment follows from NMR spectroscopic data. One of the isomers showed a $J_{5,6}$ = 5 Hz, which is characteristic for two ortho protons and therefore only structure **15** is acceptable. To the other compound the structure of the 5-methoxy isomer **16** was assigned, since its NMR spectrum revealed three singlets for ring protons. The possibility of a 6-methoxy derivative is excluded because of reasoning which is presented above for the related 5-bromo compound **12**. The formation of the 8-methoxy isomer is another example of telesubstitution which we have observed previously.[16] On the other hand, 5-bromo-*s*-triazolo[4,3-*a*]pyrazine (**12**) or its 3-phenyl analogue (**18**, R = Ph, X = Br) reacted with hot sodium thiophenolate to give only the corresponding 5-phenylthio derivatives (**20**, R_1 = SPh, R = H or Ph). So far, we have no adequate explanation for the specific reactivity of sodium thiophenolate; yet it should be mentioned that we have observed similar specificity also with *s*-triazolo[1,5-*a*]triazine.[16]

From 2-hydrazino-6-chloropyrazine (**17**, R = R_1 = H) and diethoxymethyl acetate 5-chloro-*s*-triazolo[4,3-*a*]pyrazine (**18**, R = H, X = Cl) was obtained in low yield. Cyclization was attempted also with triethyl orthoformate or a mixture of the latter and acetic anhydride, but without success. However, the 3-phenyl analogue (**18**, R = Ph, X = Cl) could be prepared in good yield from the benzylidene derivative of 2-hydrazino-6-chloropyrazine (**17**, RR_1 = CHPh) by oxidative cyclization with lead tetraacetate. We have attempted also another approach for the synthesis of *s*-triazolo[4,3-*a*]pyrazines, which proved to be successful in the pyridazine series.[26] From hydrazinopyrazines and *N*,*N*-dimethylformamide dimethyl acetal the corresponding *N*,*N*-dimethylaminomethylenehydrazine derivatives were prepared, but attempts to cyclize these were unsuccessful.

3-Phenyl-5-chloro-*s*-triazolo[4,3-*a*]pyrazine (**18**, R = Ph, X = Cl) reacted with sodium methoxide either at room temperature or under reflux to give only the telesubstituted product, the 8-methoxy derivative (**19**, R = Ph, R_1 = OMe). With sodium ethoxide under reflux the same chloro compound afforded again only the 8-ethoxy derivative (**19**, R = Ph, R_1 = OEt) in moderate yield. On the other hand, this compound is obtainable also from the 8-methoxy derivative (**19**, R = Ph, R_1 = OMe) with hot sodium ethoxide. Telesubstitution occurred also when **18** (R = Ph, X = Cl) reacted at room temperature with methanolic ammonia to give the 3-phenyl-8-amino derivative (**19**, R = Ph, R_1 = NH_2), formed also from the corresponding 8-methoxy compound (**19**, R = Ph, R_1 = OMe).

For telesubstitution one can postulate the following reaction mechanism. In view of the electron-withdrawing property of the 7-aza group, position 8 of imidazo[1,2-*a*]- or *s*-triazolo[4,3-*a*]pyrazines is activated for nucleophilic attack. Accordingly, besides the normal addition–elimination process at position 5 (**14**) (path b), a competitive addition of the nucleophile at position 8 (**13**) can take place (path a). These and previous results[14] appear to be consistent with this mechanism, although by monitoring the reaction in a NMR probe the anticipated σ complex could not be detected. To the best of our knowledge, there are no previous examples of telesubstitution in the azoloazine series with a bridgehead nitrogen atom.

Experimental Section

Melting points were determined on a Kofler hot plate melting point apparatus. The NMR spectral measurements were performed on a JOEL JNM C-60 HL spectrometer with Me_4Si as internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6L spectrometer.

Materials. 2-Chloropyrazine was prepared from glyoxal and formamide according to the described procedure[27] and was transformed further into 2-hydrazinopyrazine.[28] *s*-Triazolo[4,3-*a*]pyrazine[29] (^{1}H NMR (Me_2SO-d_6) δ 9.55 (s, H_3), 8.71 (dd, H_5), 8.01 (d, H_6), 9.55 (d, H_8), $J_{5,6}$ = 5.0, $J_{5,8}$ = 2.0 Hz), 2-amino-3,5-dibromopyrazine,[30] and imidazo[1,2-*a*]pyrazine[14] were reported previously.

3,5-Dibromoimidazo[1,2-*a*]pyrazine (2). A solution of **1** (0.2 g) in glacial acetic acid (4 mL) was cooled on ice, and a solution of bromine (0.5 mL) in glacial acetic acid (2 mL) was added dropwise with stirring. The separated orange-colored product was filtered and crystallized from water: mp 150–151 °C (yield 75 mg, 16%); MS *m/e* 273 (M); ^{1}H NMR ($CDCl_3$) δ 7.73 (s, H_2), 7.95 (s, H_6), 8.96 (s, H_8).

Anal. Calcd for $C_6H_3Br_2N_3$: C, 26.02; H, 1.09; N, 15.17. Found: C, 26.33; H, 1.35; N, 15.07.

3-Bromoimidazo[1,2-*a*]pyrazine (3). A mixture of **1** (2.0 g), *N*-bromosuccinimide (2.94 g), and chloroform (100 mL) was heated under reflux for 2 h. Upon cooling, the solution was treated with a saturated aqueous solution of sodium carbonate (200 mL) and shaken. The chloroform layer was separated and upon evaporation of the solvent the residue was crystallized from chloroform–petroleum ether: mp 193–194 °C (1.9 g, 58% yield); MS *m/e* 197 (M); ^{1}H NMR ($CDCl_3$) δ 7.84 (s, H_2), 8.19 (br s, H_5 and H_6), 9.15 (s, H_8); ^{1}NMR (after addition of 15 mg of Eu(fod)$_3$ in 0.5 mL of $CDCl_3$) δ 10.6 (s, H_2), 9.82 (dd, H_5), 11.0 (d, H_6), 13.2 (d, H_8), $J_{5,8}$ = 2.0, $J_{5,6}$ = 5.5 Hz.

Anal. Calcd for $C_6H_4BrN_3$: C, 36.39; H, 2.04; N, 21.22. Found: C, 36.72; H, 2.14; N, 21.45.

6,8-Dibromoimidazo[1,2-*a*]pyrazine (5). A mixture of bromoacetaldehyde diethyl acetal (1.4 g), concentrated hydrobromic acid (0.38 mL), and water (0.38 mL) was heated under reflux for 1 h. Upon cooling the reaction mixture was poured into ethanol (15 mL) and neutralized with solid sodium bicarbonate. To the filtrate 2-amino-3,5-dibromopyrazine (1 g) was added and the reaction mixture was stirred for 3 days at room temperature. The separated product was filtered and crystallized from water: mp 165–166 °C (yield 0.40 g, 33%); MS *m/e* 275 (M); ^{1}H NMR ($CDCl_3$) δ 8.26 (s, H_5), 7.80 (m, H_3 and H_2).

Anal. Calcd for $C_6H_3Br_2N_3$: C, 26.02; H, 1.09; N, 15.17. Found: C, 26.44; H, 1.33; N, 14.99.

The hydrobromide salt, prepared with concentrated hydrobromic acid, revealed the following: ^{1}H NMR (Me_2SO-d_6) δ 8.00 (d, H_2), 8.37 (d, H_3), 9.17 (s, H_5), $J_{2,3}$ = 1.2 Hz.

3,6,8-Tribromoimidazo[1,2-*a*]pyrazine (6). A mixture of 6,8-dibromoimidazo[1,2-*a*]pyrazine (0.24 g), NBS (151 mg), and chloroform (10 mL) was heated under reflux for 1 h and a white precipitate was formed. The reaction mixture was shaken with a saturated aqueous solution of sodium carbonate (15 mL), and the chloroform layer was separated and evaporated to dryness. The residue was sublimed in vacuo to give the pure product: mp 161–165 °C (yield 0.135 g, 44%); ^{1}H NMR ($CDCl_3$) δ 7.83 (s, H_2), 8.23 (s, H_5).

Anal. Calcd for $C_6H_2Br_3N_3$: C, 20.25; H, 0.57; N, 11.81. Found: C, 20.39; H, 1.06; N, 11.50.

6-Bromo-8-methoxyimidazo[1,2-*a*]pyrazine (7). A methanolic solution of sodium methylate was prepared from sodium (20 mg) and methanol (15 mL) and to this 6,8-dibromo compound **5** (0.25 g) was added. The reaction mixture was heated under reflux for 2 h and evaporated to dryness, and the residue was crystallized from water: mp 208–210 °C (yield 0.147 g, 72%); MS *m/e* 228 (M); ^{1}H NMR

($CDCl_3$) δ 7.50 (d, H_2), 7.56 (d, H_3), 7.83 (s, H_5), 4.14 (s, OMe), $J_{2,3}$ = 1.0 Hz.

Anal. Calcd for $C_7H_6BrN_3O$: C, 36.86; H, 2.65. Found: C, 37.06; H, 2.77.

8-Methoxyimidazo[1,2-*a*]pyrazine (8). To a solution of the above compound (7) (0.265 g) in methanol (40 mL) palladized carbon (60 mg of 10%) was added and the mixture was shaken in an atmosphere of hydrogen for 15 h. Upon filtration the filtrate was evaporated to dryness and the hydrobromide salt was crystallized from methanol–ether: mp 244–245 °C (yield 92%); MS *m/e* 149 (M − HBr); ^1H NMR (Me_2SO-d_6) δ 7.89 (d, H_6), 8.25 (d, H_2), 8.53 (d, H_3), 8.60 (d, H_5), 4.17 (s, OMe), $J_{5,6}$ = 5.0, $J_{2,3}$ = 2 Hz.

Anal. Calcd for $C_7H_8N_3OBr$: C, 36.54; H, 3.51. Found: C, 36.45; H, 3.41.

5-Chloroimidazo[1,2-*a*]pyrazine. A mixture of bromoacetaldehyde diethyl acetal (0.4 g), hydrobromic acid (0.12 mL of 48%), and water (0.12 mL) was heated under reflux for 1 h. Upon cooling the reaction mixture was diluted with ethanol (5 mL), neutralized with sodium bicarbonate, and filtered. The filtrate was treated with 2-amino-6-chloropyrazine (0.3 g) and the mixture was stirred at 40 °C for 30 h. The solvent was evaporated in vacuo and the residue was dissolved in water (1 mL). The solution was neutralized with sodium bicarbonate, and the aqueous layer was separated and extracted with chloroform. Upon evaporation of the solvent the residue was crystallized from cyclohexane (yield 14 mg, 4%) and had mp 88–95 °C; ^1H NMR ($CDCl_3$) δ 7.99 (s, H_2 and H_3), 8.06 (s, H_6), 9.20 (s, H_8).

Anal. Calcd for $C_6H_4ClN_3$: C, 46.93; H, 2.63. Found: C, 47.02; H, 2.90.

Methylation of Imidazo[1,2-*a*]pyrazine. A solution of imidazo[1,2-*a*]pyrazine (0.24 g) in methanol (4 mL) was treated with methyl iodide (0.48 g), and the reaction mixture was left in a sealed tube in the dark at room temperature for 5 days. The separated crystals (0.181 g, 35%) were filtered and dissolved in hot methanol, and upon cooling the separated crystals of the 7-methyl derivative **10** were filtered: mp 270–280 °C dec (55 mg, yield 11%); ^1H NMR δ 4.36 (s, Me), 8.25 (dd, H_5), 8.43 (d, H_2), 8.77 (d, H_3), 9.25 (dd, H_6), 9.98 (dd, H_8), $J_{5,8}$ = 1.5, $J_{2,3}$ = 1.0, $J_{6,8}$ = 1.0, $J_{5,6}$ = 5.6 Hz.

Anal. Calcd for $C_7H_8IN_3$: C, 32.20; H, 3.09. Found: C, 32.61; H, 3.28.

The filtrate, when evaporated to dryness, afforded the 1-methyl isomer **9**: mp 199–200 °C (from methanol) (0.107 g, 21%); ^1H NMR (Me_2SO-d_6) δ 8.50 (d, H_2), 8.55 (d, H_3), 8.50 (dd, H_5), 9.05 (d, H_6), 9.55 (d, H_8), 4.28 (s, Me), $J_{2,3}$ = 1.0, $J_{5,6}$ = 5.6, $J_{5,8}$ = 1.5 Hz. (In the literature, however, 1-methylimidazo[1,2-*a*]pyrazinium bromide, mp >330 °C, has been reported.[11])

2-Hydrazino-6-chloropyrazine (17, R = R_1 = H). A solution of 2,6-dichloropyrazine (10 g) in ethanol (30 mL) was treated with hydrazine hydrate (15 mL of 98%) and the reaction mixture was heated under reflux for 3 h. The solvent was evaporated in vacuo and the residue was crystallized from water and toluene: mp 136–139 °C (yield 6.7 g, 69%); MS *m/e* 144 (M); ^1H NMR (Me_2SO-d_6) δ 8.10 (s, H_3 or H_5), 7.74 (s, H_3 or H_5), 8.45 (br s, NH), 4.40 (hr s, NH_2).

Anal. Calcd for $C_4H_5ClN_4$: C, 33.23; H, 3.48; N, 38.76. Found: C, 33.34; H, 3.50; N, 39.18.

The compound formed the benzylidene derivative in the usual manner: mp 223 °C; MS *m/e* 232 (M).

Anal. Calcd for $C_{11}H_9ClN_4$: C, 56.78; H, 3.90; N, 24.08. Found: C, 56.97; H, 3.75; N, 23.94.

If 2-hydrazino-6-chloropyrazine (1 g), *N,N*-dimethylformamide dimethyl acetal (1.5 mL), and absolute ethanol (7 mL) were heated under reflux for 30 min, upon cooling the corresponding *N,N*-dimethylaminomethylenehydrazino derivative (**17**, R, R_1 = $CHNMe_2$) was separated (0.5 g, 36%): mp 168–170 °C (from ethanol); MS *m/e* 199 (M).

Anal. Calcd for $C_7H_{10}ClN_5$: C, 42.11; H, 5.05; N, 35.08. Found: C, 42.17; H, 5.25; N, 35.10.

In a similar manner 2-*N,N*-dimethylaminomethylenehydrazinopyrazine was prepared, mp 141 °C (from cyclohexane), in 67% yield: MS *m/e* 165 (M).

Anal. Calcd for $C_7H_{11}N_5$: C, 50.89; H, 6.71; N, 42.40. Found: C, 50.90; H, 6.90; N, 42.72.

5-Bromo-*s*-triazolo[4,3-*a*]pyrazine (12). A solution of **11** (3.0 g) in glacial acetic acid (90 mL) was treated with bromine (4.0 g in 25 mL of glacial acetic acid) at room temperature. The separated product was filtered and crystallized from ethanol: mp 214–217 °C (yield 1.70 g, 34%); MS *m/e* 198 (M); ^1H NMR (Me_2SO-d_6) δ 8.24 (s, H_6), 9.67 (s, H_3 or H_8), 9.49 (s, H_3 or H_8).

Anal. Calcd for $C_5H_3BrN_4$: C, 30.17; H, 1.52; N, 28.15. Found: C, 30.40; H, 2.02; N, 28.02.

5-Chloro-*s*-triazolo[4,3-*a*]pyrazine (18, R = H, X = Cl). A mixture of 2-hydrazino-6-chloropyrazine (1 g) and diethoxymethyl acetate (3 mL) was heated under reflux for 10 h. The solvent was evaporated in vacuo to dryness and the residue was sublimed. The compound had mp 167–172 °C (yield 0.125 g, 12%); MS *m/e* 154 (M); ^1H NMR ($CDCl_3$) δ 7.94 (s, H_6), 9.06 (s, H_3 or H_8), 9.27 (s, H_3 or H_8).

Anal. Calcd for $C_5H_3ClN_4$: C, 38.85; H, 1.96. Found: C, 38.89; H, 2.30.

3-Phenyl-5-chloro-*s*-triazolo[4,3-*a*]pyrazine (18, R = Ph, X = Cl). A suspension of 2-benzylidenehydrazino-6-chloropyrazine (1.1 g) in benzene (15 mL) was treated with lead tetraacetate (2.5 g, washed with benzene before use) with stirring. The reaction mixture was left at room temperature for 6 h, the solid was filtered, and the filtrate was evaporated in vacuo to dryness. The residue was crystallized from ethanol: mp 176 °C (yield 0.7 g, 64%); MS *m/e* 230 (M); ^1H NMR (Me_2SO-d_6) δ 7.65 (m, Ph), 8.10 (s, H_6), 9.52 (s, H_8).

Anal. Calcd for $C_{11}H_7ClN_4$: C, 57.28; H, 3.06; N, 24.29. Found: C, 57.50; H, 3.21; N, 24.31.

5-Phenylthio-*s*-triazolo[4,3-*a*]pyrazine (20, R = H, R_1 = SPh). To a solution of sodium thiophenolate in ethanol, prepared from 12 mg of sodium, 55 mg of thiophenol, and 5 mL of absolute ethanol, the 5-bromo compound **12** (0.1 g) was added. The reaction mixture was heated under reflux for 1 h and upon cooling poured on ice. The product which separated (14 mg) was filtered and the filtrate was evaporated in vacuo to dryness. Some water was added and the residue was filtered (65 mg). Both products were found to be identical, and they were combined and crystallized from water: mp 95–96 °C (yield 26 mg, 23%); MS *m/e* 228 (M); ^1H NMR (Me_2SO-d_6) δ 8.26 (s, H_6), 10.57, 10.47 (s, H_3 and H_8), 7.5 (m, Ph).

Anal. Calcd for $C_{11}H_8N_4S$: C, 57.89; H, 3.53; N, 24.55. Found: C, 58.08; H, 3.80; N, 24.50.

3-Phenyl-5-phenylthio-*s*-triazolo[4,3-*a*]pyrazine (20, R = Ph, R_1 = SPh) was prepared in a similar manner in 52% yield: mp 194–198 °C; MS *m/e* 304 (M); ^1H NMR (Me_2SO-d_6) δ 7.9 (s, H_6), 9.25 (s, H_8), 7.43 (m, Ph), 6.8, 7.23 (m, 3-Ph).

Anal. Calcd for $C_{17}H_{12}N_4S$: C, 67.09; H, 3.98; N, 18.41. Found: C, 66.79; H, 4.28; N, 18.69.

Reaction between 5-Bromo-*s*-triazolo[4,3-*a*]pyrazine and Sodium Methylate. A methanolic solution of sodium methylate (prepared from 8 mL of ethanol and 25 mg of sodium) was treated with **12** (0.2 g) and the reaction mixture was left at room temperature overnight. The solvent was evaporated in vacuo and the residue was extracted with chloroform. Upon evaporation of the solvent the product was crystallized from chloroform and petroleum ether. There were obtained 40 mg of a mixture of 8-methoxy- (**15**) and 5-methoxy-*s*-triazolo[4,3-*a*]pyrazine (**16**): mp 131–134 °C; MS *m/e* 150 (M); ^1H NMR (Me_2SO-d_6) 8-methoxy isomer δ 4.15 (s, 8-OMe), 7.49 (d, H_6), 9.17 (s, H_3), 8.17 (d, H_5), $J_{5,6}$ = 5 Hz; 5-methoxy isomer δ 4.25 (s, 5-OMe), 7.66 (s, H_6), 9.55 (s, H_3), 9.49 (s, H_8).

Anal. Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.03. Found: C, 47.69; H, 3.70.

3-Phenyl-8-methoxy-*s*-triazolo[4,3-*a*]pyrazine (19, R = Ph, R_1 = OMe). Compound **18** (R = Ph, X = Cl) (231 mg) was dissolved in methanol (14 mL) and a solution of sodium methylate (23 mg of sodium in 3 mL of methanol) was added. The progression of the reaction was followed by TLC and when reaction was complete, the solvent was evaporated and the residue crystallized from aqueous methanol: mp 190–193 °C (yield 89 mg, 39%). However, if the reaction was conducted under reflux for 30 min the product was obtained in 17% yield: MS *m/e* 226 (M); ^1H NMR (Me_2SO-d_6) δ 4.25 (s, OMe), 7.45 (d, H_5), 7.90 (d, H_6), 8.0-7.5 (m, Ph), $J_{5,6}$ = 4.5 Hz.

Anal. Calcd for $C_{12}H_{10}N_4O$: C, 63.70; H, 4.46; N, 24.77. Found: C, 63.42; H, 4.90; N, 24.66.

3-Phenyl-8-ethoxy-*s*-triazolo[4,3-*a*]pyrazine (19, R = Ph, R_1 = OEt). (A) The compound was prepared in an analogous manner as the 8-methoxy compound from **18** (R = Ph, X = Cl), but under reflux: mp 172–173.5 °C (yield 76 mg, 31%); MS *m/e* 240 (M); ^1H NMR (Me_2SO-d_6) δ 7.37 (d, H_5), 7.82 (d, H_6), 7.95–7.46 (m, Ph), 1.55 (t, CH_2CH_3), 4.70 (CH_2CH_3), $J_{5,6}$ = 4.5, J_{EI} = 7.2 Hz.

Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.03; N, 23.32. Found: C, 64.71; H, 5.29; N, 23.15.

(B) A solution of the 8-methoxy compound **19** (R = Ph, R_1 = OMe) (10 mg) in 50% aqueous ethanol was treated with ethanolic sodium ethylate (prepared from 2.9 mg of sodium in 1 mL of ethanol). The reaction mixture was heated under reflux for 30 min, the solvent was evaporated in vacuo to dryness, and the residue was treated with some water. The product was filtered (yield 1.5 mg, 14%) and had mp 171 °C. The compound has been identified by its IR spectrum and mixture melting point as the above 8-methoxy compound, prepared as described under A.

3-Phenyl-8-amino-*s*-triazolo[4,3-*a*]pyrazine (19, R = Ph, R_1 = NH_2). (A) Compound **18** (R = Ph, X = Cl) (231 mg) was added to

a saturated methanolic solution of ammonia (30 mL) and the reaction mixture was left to stand at room temperature for 20 h. The separated product was filtered off, the filtrate was evaporated to dryness and treated with water (5 mL), and the residue was filtered. The combined products were crystallized from ethanol: mp 247–248.5 °C (yield 53.5 mg, 30%); MS *m/e* 211 (M); ^{1}H NMR (Me_2SO-d_6) δ 7.26 (d, H_5), 7.74 (d, H_6), 8.0–7.4 (m, Ph), 3.33 (s, NH_2), $J_{5,6}$ = 4.5 Hz.

Anal. Calcd for $C_{11}H_9N_5$: C, 62.55; H, 4.30; N, 33.16. Found: C, 62.77; H, 4.55; N, 33.36.

(B) Compound **19** (R = Ph, R_1 = OMe) (50 mg) was added to a saturated methanolic solution of ammonia (10 mL) and the reaction mixture was heated in an autoclave at 100 °C for 5 h. Upon evaporation of the solvent, the residue was crystallized from ethanol. The compound was found to be identical in all respects with product obtained as described under A.

Acknowledgment. We thank the Boris Kidrič Fund for partial support of the research.

Registry No.—**1**, 274-79-3; **2**, 63744-21-8; **3**, 57948-41-1; **4**, 24241-18-7; **5**, 63744-22-9; **5** HBr, 63744-23-0; **6**, 63744-24-1; **7**, 63744-25-2; **8** HBr, 63744-26-3; **9**, 63744-27-4; **10**, 63744-28-5; **11**, 274-82-8; **12**, 63744-29-6; **15**, 63744-30-9; **16**, 63744-31-0; **17** (R = R_1 = H), 63286-29-3; **17** (RR_1 = PhCH=), 63744-32-1; **17** (RR_1 = =CHNMe$_2$), 63744-33-2; **18** (R = H, X = Cl), 63744-34-3; **18** (R = Ph, X = Cl), 63744-35-4; **19** (R = Ph, R_1 = OMe), 63744-36-5; **19** (R = Ph, R_1 = OEt), 63744-37-6; **19** (R = Ph, R_1 = NH_2), 63744-38-7; **20** (R = H, R_1 = SPh), 63744-39-8; **20** (R = Ph, R_1 = SPh), 63744-40-1; 5-chloroimidazo[1,2-*a*]pyrazine, 63744-41-2; 2-amino-6-chloropyrazine, 33332-28-4; 2,6-dichloropyrazine, 4774-14-5; 2-*N*,*N*-dimethylaminomethylenehydrazinopyrazine, 63744-42-3; sodium thiophenolate, 930-69-8; ammonia, 7664-41-7; *N*,*N*-dimethylformamide dimethyl acetal, 4637-24-5; hydrazinopyrazine, 54608-52-5.

References and Notes

(1) Heterocycles. Part 167. Presented in part at the 6th International Congress of Heterocyclic Chemistry, Tehran, Iran, 1977.
(2) L. M. Werbel and M. L. Zamora, *J. Heterocycl. Chem.*, **2**, 287 (1965).
(3) P. Guerret, R. Jacquier, and G. Maury, *J. Heterocycl. Chem.*, **8**, 643 (1971).
(4) S. Inoue, S. Sugiura, H. Kakoi, and T. Goto, *Tetrahedron Lett.*, 1609 (1969).
(5) T. Goto, S. Inoue, and S. Sugiura, *Tetrahedron Lett.*, 3873 (1968).
(6) S. Sugiura, S. Inoue, and T. Goto, *Yakugaku Zasshi*, **90**, 431 (1970); *Chem. Abstr.*, **73**, 45460 (1970).
(7) S. Inoue, S. Sugiura, H. Kakoi, K. Hasizume, T. Goto, and H. Iio, *Chem. Lett.*, 141 (1975); *Chem. Abstr.*, **83**, 28185 (1975).
(8) S. Sugiura, S. Inoue, Y. Kishi, and T. Goto, *Yakugaku Zasshi*, **89**, 1646 (1969); *Chem. Abstr.*, **72**, 90404 (1970).
(9) S. Sugiura, S. Inoue, and T. Goto, *Yakugaku Zasshi*, **90**, 423 (1970); *Chem. Abstr.*, **73**, 45459 (1970).
(10) S. Sugiura, H. Kakoi, S. Inoue, and T. Goto, *Yakugaku Zasshi*, **90**, 441 (1970); *Chem. Abstr.*, **73**, 45462 (1970).
(11) J. Adamson and E. E. Glover, *J. Chem. Soc. C*, 2748 (1971).
(12) R. H. Martin and Z. Tarasiejska, *Bull. Soc. Chim. Belg.*, **66**, 136 (1957).
(13) W. F. F. Amarego, *J. Chem. Soc.*, 2778 (1965).
(14) B. Verček, B. Stanovnik, and M. Tišler, *Heterocycles*, **4**, 943 (1976).
(15) J. Arriau, O. Chalvet, A. Dargelos, and G. Maury, *J. Heterocycl. Chem.*, **11**, 1013 (1974).
(16) B. Verček, B. Stanovnik, and M. Tišler, *Tetrahedron Lett.*, 4539 (1974).
(17) W. Flitsch and U. Krämer, *Tetrahedron Lett.*, 1479 (1968).
(18) J. L. Long, M. S. Brown, and H. Rapoport, *J. Org. Chem.*, **30**, 2398 (1965).
(19) W. W. Paudler and D. E. Dunham, *J. Heterocycl. Chem.*, **2**, 410 (1965).
(20) J. P. Cress and D. M. Fokkey, *J. Chem. Soc., Chem. Commun.*, 35 (1973).
(21) J. Kobe, B. Stanovnik, and M. Tišler, *Tetrahedron*, **24**, 239 (1968).
(22) A. Poliak, B. Stanovnik, and M. Tišler, *J. Org. Chem.*, **35**, 2478 (1970).
(23) S. Polanc, B. Verček, B. Šek, B. Stanovnik, and M. Tišler, *J. Org. Chem.*, **39**, 2143 (1974).
(24) K. Babič, S. Molan, S. Polanc, B. Stanovnik, J. Stres-Bratoš, M. Tišler, and B. Verček, *J. Heterocycl. Chem.*, **13**, 487 (1976).
(25) S. Polanc, B. Verček, B. Stanovnik, and M. Tišler, *Tetrahedron Lett.*, 1677 (1973).
(26) J. Faganeli, S. Polanc, B. Stanovnik, and M. Tišler, *Croat. Chem. Acta*, **48**, 161 (1976).
(27) A. C. Currie, A. H. Dinwoodie, G. Fort, and J. M. C. Thompson, *J. Chem. Soc. C*, 491 (1967).
(28) S. E. Mailett and F. L. Rose, *J. Chem. Soc C*, 2038 (1966).
(29) P. Y. Nelson and K. T. Potts, *J. Org. Chem.*, **27**, 3243 (1962).
(30) B. Camerino and G. Palamidessi, British Patent 928 152 (1963); *Chem. Abstr.*, **60**, 2971 (1964).

Deuterium Isotope Effects in the Thermochemical Decomposition of Liquid 2,4,6-Trinitrotoluene: Application to Mechanistic Studies Using Isothermal Differential Scanning Calorimetry Analysis

S. A. Shackelford,*[1] J. W. Beckmann, and J. S. Wilkes

Directorate of Chemical Sciences, Frank J. Seiler Research Laboratory (AFSC), USAF Academy, Colorado 80840

Received April 22, 1977

The thermochemical decomposition of liquid 2,4,6-trinitrotoluene (TNT) produces a primary kinetic deuterium isotope effect when its methyl moiety is deuterium labeled. The novel integration of the deuterium isotope effect with isothermal differential scanning calorimetry analysis provides the first directly measured mechanistic evidence that carbon–hydrogen bond rupture in the TNT methyl group constitutes the rate-determining step of the thermochemical decomposition reaction. This thermochemical reaction possesses an induction period during which a single species forms from TNT and catalyzes a sustained exothermic decomposition. An expression was derived that correlated deuterium/hydrogen induction time ratios with inaccessible hydrogen/deuterium rate constant ratios during this induction period. Direct induction time measurement allowed deuterium isotope effect evaluation before interfering side reactions diluted the magnitude of the isotope effect during the latter stages of exothermic decomposition. Hydrogen donor effects suggest that the rate-determining carbon–hydrogen bond rupture proceeds homolytically. A large negative entropy of activation reveals a high degree of orderliness during the decomposition.

The kinetic deuterium isotope effect has proved to be a powerful tool in mechanistic elucidations of gaseous and solvolyzed chemical reactions. Recently, isothermal differential scanning calorimetry (isothermal DSC) proved its value as a rapid and elegant technique for determining kinetic parameters (e.g., reaction rate, rate constant, reaction order, activation energy) in thermochemical decomposition reactions of liquified nitrated organic compounds.[2-4] Because liquid organic compounds constitute a homogeneous phase, and because an isothermal DSC curve is directly proportional to a reaction rate that is easily converted into a rate constant, we felt the deuterium isotope effect concept could be integrated

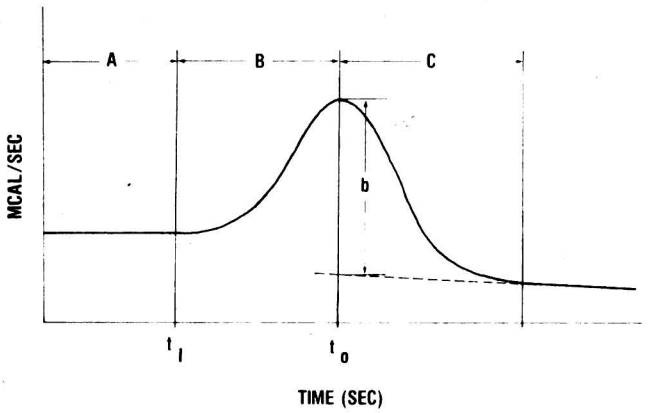
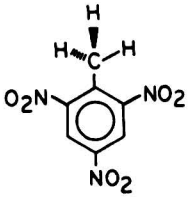


Figure 1. Generalized isothermal DSC trace for TNT comprised of an induction period (A), exothermic acceleratory phase (B), and decay phase (C). Note that mcal/s is directly proportional to reaction rate.[2]

with isothermal DSC analysis to provide novel mechanistic information previously unobtainable in thermochemical decomposition studies.

This paper describes the integration of deuterium isotope effect studies with the isothermal DSC analysis technique to elucidate the rate-determining step in the thermochemical decomposition reaction of liquid 2,4,6-trinitrotoluene (TNT).



This study represents the first direct mechanistic conformation that carbon–hydrogen bond rupture in the benzylic methyl moiety is the rate-determining step that initiates the exothermic decomposition of liquid TNT.

Results and Discussion

Isothermal DSC is an excellent method to conveniently determine the kinetic parameters in the thermochemical decomposition reaction of liquid polynitro organic compounds. Direct kinetic data is rapidly obtained that allows the determination of reaction rates (r), rate constants (k), reaction orders (n), preexponential factors (Z), and activation energies (E_a).[2,3] Secondly, isothermal DSC analyzes thermochemical decomposition reactions in a homogeneous liquid phase where crystal-lattice stabilization effects are not a complicating factor and where the process is likely to be first order.[2,5] The direct measurement of pure molten solutions also negates the presence of potential solvent[6] and/or dilution effects that could interfere with the true mode of bulk thermochemical decomposition. Finally, liquid 2,4,6-trinitrophenyl compounds generate only small amounts of gaseous products during thermochemical decomposition and convert instead mainly to molecular, self-condensing derivatives.[7-9] Thus, isothermal DSC provides an attractive alternative to gas-evolution techniques which often produce conflicting kinetic results in low gas-evolving compounds like 2,4,6-trinitrotoluene (TNT).[9,10]

Polynitro aromatic compounds possessing benzylic hydrogen atoms adjacent to an o-nitro group show a higher sensitivity toward thermochemical decomposition than other structural isomers. An oxidation–reduction mechanism that involves chemical interaction between the benzylic substituent and the neighboring o-nitro group is one reason postulated

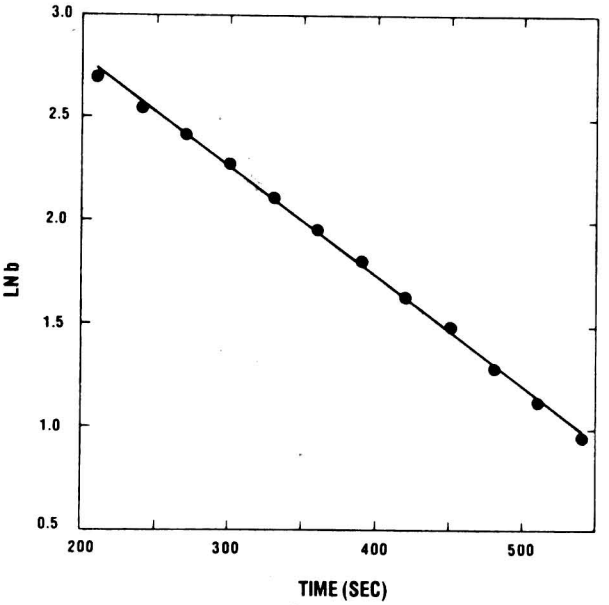


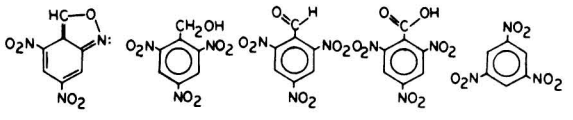
Figure 2. First-order rate constant graph for TNT-d_3 at 263 °C.

Table I. Decay Phase Rate Constants (s^{-1})

Temp, °C	TNT	TNT-d_3
245	3.38×10^{-3} [b]	2.18×10^{-3} [a]
251	4.09×10^{-3} [c]	3.46×10^{-3} [a]
257	5.92×10^{-3} [b]	4.32×10^{-3} [a]
263	8.36×10^{-3} [b]	5.61×10^{-3} [b]
269	11.4×10^{-3} [a]	8.58×10^{-3} [a]

[a] Average value for three runs. [b] Average value for four runs. [c] Average value for five runs.

to explain this thermally reactive behavior.[8,9,11-13] Past analyses of thermochemically decomposed TNT at temperatures ranging between 195 and 330 °C revealed the following products which necessitate rupture of the methyl carbon–hydrogen bond at some point during the decomposition reaction:[8,9] 4,6-dinitroanthranil (1), 2,4,6-trinitrobenzyl alcohol



(2), 2,4,6-triintrobenzaldehyde (3), 2,4,6-trinitrobenzoic acid (4), and 1,3,5-trinitrobenzene (5). Recently, isothermal DSC analysis was employed to follow liquid TNT's thermochemical decomposition reaction within a 245–269 °C range. The study was conducted at 6 °C increments, and kinetic parameters, including the rate constant, were determined.[10] The homogeneous nature of the liquid TNT, the ability to conveniently determine rate-constant data by isothermal DSC, plus the thermochemical decomposition product analyses that revealed carbon-hydrogen bond rupture occurring in TNT's methyl moiety[8,9] represented all the conditions necessary to allow the study of potential kinetic deuterium isotope effects during TNT's thermochemical decomposition reaction. Detection of a deuterium isotope effect from rate-constant ratios (k_H/k_D) between TNT and its α,α,α-trideuterio analogue (TNT-d_3) would confirm the potential importance of the carbon–hydrogen bond rupture in this thermochemical decomposition mechanism.

Decay Phase Analysis. Isothermal DSC analysis of liquid TNT (mp 81–82 °C) was taken at 6 °C increments from 245

Table II. Decay Phase Kinetic Data

Compd	n (order)	E_a, kcal mol^{-1}	ΔH^*, kcal mol^{-1}	ΔS^*, eu	k_H/k_D
TNT	0.97 ± 0.07	29.4 ± 1.4	28.35 ± 0.01	−16.4 ± 0.1	1.35 ± 0.02[a]
TNT-d_3	0.86 ± 0.06	29.9 ± 1.6	28.85 ± 0.01	−16.1 ± 0.1	

[a] Average deuterium isotope effect for all five temperatures (Table I).

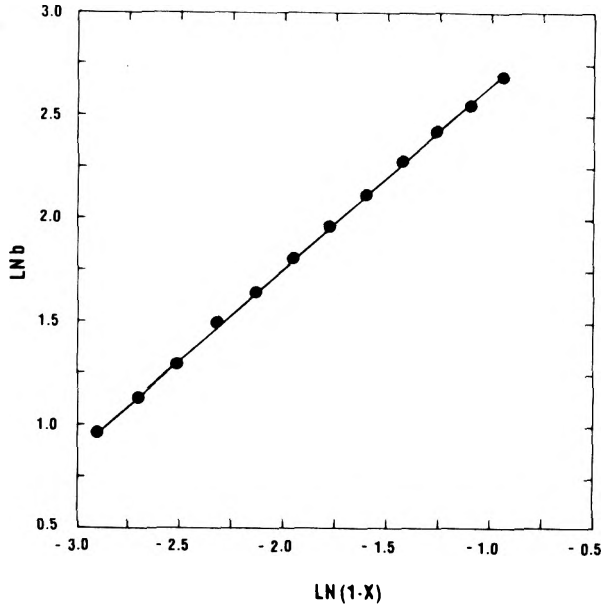


Figure 3. Order plot (slope = 0.89) for TNT-d_3 at 263 °C. Analogous TNT order plot (slope = 1.01).

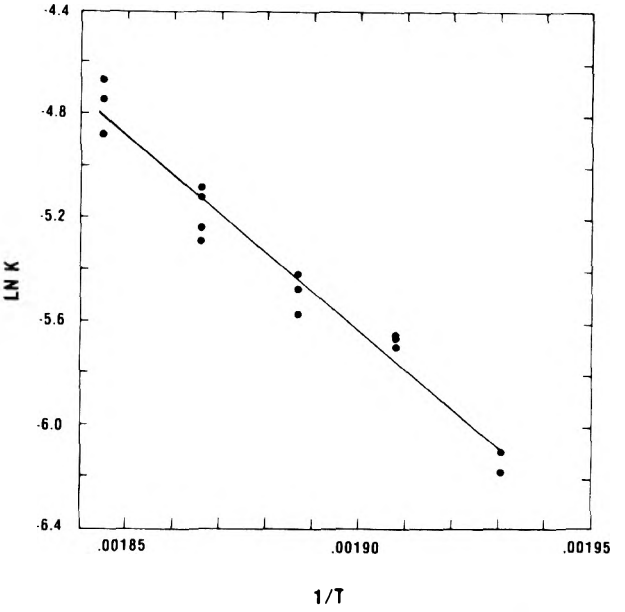


Figure 4. Decay phase Arrhenius plot for activation energy (E_a) of TNT-d_3.

to 269 °C. A slightly skewed bell-shaped curve was produced. This curve was comprised of an induction period A, an exothermic acceleratory phase B, and a decay phase C, where the decomposition reaction dissipates to completion (Figure 1). During the decay phase C, the deflection of the isothermal DSC curve (b) is measured as the difference between the curve and baseline at specific time intervals. Simpson's rule is then employed to integrate these closely spaced deflection measurements to easily obtain the desired kinetic parameters previously discussed.[2,3,10] Kinetic parameters obtained in the isothermal DSC analysis of TNT and TNT-d_3 from the decay phase are illustrated in Tables I and II. Figure 2 is a first-order plot of ln b vs. time for TNT-d_3 at 263 °C, from which the rate constant k was obtained as the slope ($-k$). Figure 3 illustrates the order plot obtained for this compound, and Figure 4, in which ln k is graphed against reciprocal temperature, provides the activation energy cited in Table II for TNT-d_3 (see paragraph at the end of paper about supplementary material). The change in enthalpy of activation (ΔH^*) and entropy of activation (ΔS^*) in this thermochemical decomposition reaction was readily calculated (eq 1 and 2) from the rate constant (k) and activation energy (E_a) values obtained in the isothermal DSC analysis at the temperatures listed in Tables I and II.

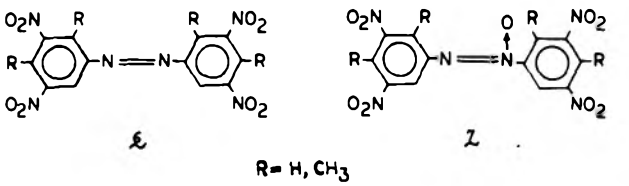
$$\Delta H^* = E_a - RT \quad (1)$$

$$\Delta S^* = 2.303R\left(\log k - \log\left(\frac{k}{h}\right) - \log T\right) + \frac{\Delta H^*}{T} \quad (2)$$

The magnitude and sign of ΔS^* reflects a very high degree of orderliness once the self-sustained, exothermic decomposition is initiated and could suggest a cyclic structural interaction.[14] A cyclic interaction reasonably could result in a transition-state species formed by an intramolecular reaction between the o-nitro group and methyl moiety of TNT.[7,8,11,13]

A significant deuterium isotope effect is found for TNT (Table II). Carbon–hydrogen bond rupture in the methyl moiety during the rate-determining step would produce a deuterium isotope effect ratio equal to or greater than 1.41.[15] However, the magnitude of the observed isotope effect during the decay phase (Table II) of TNT's thermochemical decomposition reaction is not definitive for a primary isotope effect. This 1.35 value is slightly lower than most ratios cited. However, TNT's inherent chemical structure ruled out a secondary isotope effect and suggested the low 1.35 value to be a dilution of the primary isotope process.

The isothermal DSC technique measures the total reaction rate during the decay phase C. Competing side reactions can produce decomposition products in which no carbon–hydrogen rupture occurs.[9] These reactions would have different rate-determining steps that contribute to the total reaction-rate measurement revealed by isothermal DSC during the decay phase. These competing side reactions, not involving carbon–hydrogen bond rupture, would dilute the magnitude of the actual deuterium isotope effect, since they comprise a portion of the total reaction-rate measurement. Previous product isolation of dimeric TNT reduction products that contained azo-6 and/or azoxy-7 linkages with undisturbed



methyl groups strongly suggests this to be the case.[9] Analysis of the induction period A of the isothermal DSC curve offered an answer to this dilemma.

Induction Period Analysis. High-pressure liquid chromatographic analysis was performed on TNT samples that were thermochemically decomposed only during the induction period A. Analysis revealed an apparent single, unidentified

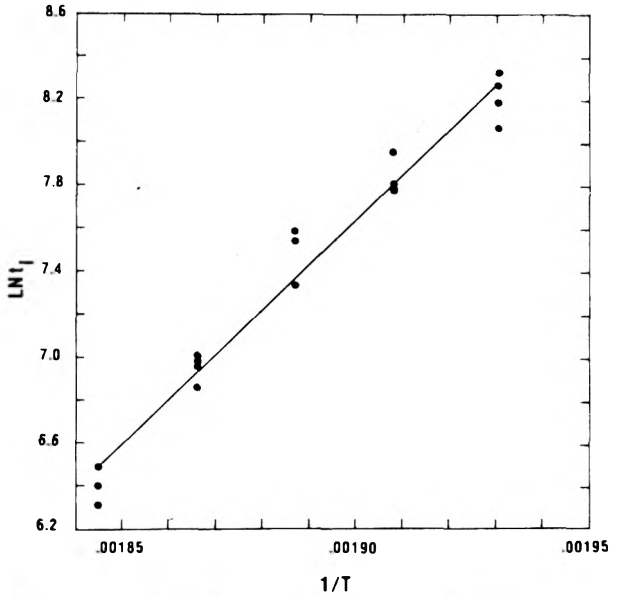


Figure 5. Induction period Arrhenius plot for activation energy (E_a^I) of TNT-d_3.

compound I formed from TNT during the induction period A and prior to the thermochemical decomposition reaching its exothermic acceleratory phase B. A trace amount of compound I was isolated and was added to a pure TNT sample. Isothermal DSC analyses of this sample (263 °C) showed a significant rate enhancement; the induction period was decreased by a factor of nearly 2.5. Thus, compound I appears responsible for catalyzing the thermochemical decomposition of *TNT* during the induction period. If the apparent catalytic precursor species I forms from TNT by carbon–hydrogen bond rupture in the methyl moiety, a pure, undiluted deuterium isotope effect could be operating during the induction period A. The problem of obtaining data that defined this potential deuterium isotope effect was addressed next.

Evaluation of the k_H and k_D rate constants during the thermochemical decomposition's decay phase C depends upon the isothermal DSC curve's deflection from the baseline *b*. The horizontal induction period A generates no such deflection; however, the induction time (t_I) can he used to obtain deuterium isotope effects and is conveniently measured from the isothermal DSC curve.

The induction time (t_I) of a catalytic decomposition curve is defined as the time elapsed from sample pan placement into the DSC instrument until the initial deflection of the exothermic acceleratory phase B from the horizontal baseline comprising the induction period A (Figure 1). The t_I value for TNT has been used to calculate the induction period reaction's activation energy (E_a^I) for compound I formation.[10] Two mathematical approximations were invoked to arrive at eq 3 where k is the decomposition reaction's rate constant and i_I the small mole fraction of compound I formed at a given induction time, t_I.

$$k = i_I/t_I \tag{3}$$

Equation 4 was obtained by taking the natural logarithm of the Arrhenius equation. Equation 5 resulted by setting eq 4 equal to eq 3 in logarithmic form.

$$\ln k = E_a^I/RT + \ln Z \tag{4}$$

$$\ln k = \ln i_I - \ln t_I = E_a^I/RT + \ln Z \tag{5}$$

A graphical plot of $\ln t_I$ vs. the reciprocal temperature ($1/T$) afforded a slope that when multiplied by the ideal gas constant produced E_a^I.[10] Figure 5 displays the graphical data obtained for TNT-d_3. Equation 5 serves as the starting point for determining deuterium isotope effects using t_I data.

Table III. Induction Period Kinetic Parameters

Compd	E_a, kcal mol^{-1}	t_{ID}/t_{IH}
TNT	46.5 ± 1.5	1.66 ± 0.2
TNT-d_3	41.6 ± 1.8	

Equation 5 may be rearranged to yield eq 6.

$$\ln i_I = \ln k + \ln t_I \tag{6}$$

Assuming the mole fraction (i_I) of compound I, generated during the induction period, must reach a specific threshold concentration to catalyze TNT's thermochemical decomposition into the acceleratory phase B,[16] only t_I and k may vary between the deuterated and nondeuterated TNT reactions. Assuming i_I to be a constant threshold concentration, the following equations are derived:

$$\ln k_H + \ln t_{IH} = \ln i_I = \ln k_D + \ln t_{ID} \tag{7}$$

$$\ln k_H + \ln t_{IH} = \ln k_D + \ln t_{ID} \tag{8}$$

and finally

$$\frac{k_H}{k_D} = \frac{t_{ID}}{t_{IH}} \tag{9}$$

Equation 9 establishes the necessary relationship between nondeuterated/deuterated rate constants and deuterated/nondeuterated induction times to determine deuterium isotope effects that operate during thermochemical decomposition induction periods. Direct measurement of t_I values from isothermal DSC curves for deuterated and nondeuterated liquid-phase TNT allows deuterium isotope effects to be evaluated by t_{ID}/t_{IH}, where t_{ID} represents the deuterated compound's induction time and t_{IH} the nondeuterated analogue. Results showing the t_{ID}/t_{IH} values obtained are given in Table III, as is E_a^I for each compound.

A primary deuterium isotope effect is revealed during the thermochemical decomposition reaction's induction period A. The 1.66 value clearly represents a primary kinetic isotope effect.[17] The minimum value expected for the primary hydrogen/deuterium isotope effect would equal 1.41. This minimum value could be expected when a high-temperature limit is reached where the isotope effect depends solely upon the vibrational frequencies of each bond.[15] Indeed, if the primary deuterium isotope effect for molten TNT was normalized from the very high 245–269 °C temperature range into the 25–100 °C range generally employed for deuterium isotope effect studies in solvolyzed reactions, the 1.66 value of TNT would be more profound. This data (Table III) represents the first direct experimental verification that benzylic carbon–hydrogen bond rupture is the critical rate-determining step in the thermochemical degradation of liquid TNT. Apparently, this rate-determining carbon–hydrogen bond rupture results in the accumulation of a threshold concentration of compound I which then catalytically initiates the self-sustained, exothermic thermochemical reaction. The deuterium isotope effect data obtained from the induction period provides a clearer picture of the *initiation mechanism before other* interferring side reactions dilute kinetic data and complicate mechanistic elucidation.

Hydrogen Donor Effects. Hydroquinone (HQ) is an effective scavenger for reactions that proceed by a radical mechanism. One then might expect hydroquinone to rapidly react with the products obtained from TNT's benzylic carbon–hydrogen bond rupture if radical species are produced. When a 3.7 mol % HQ/TNT mixture was thermochemically decomposed by isothermal DSC at 263 °C, molten TNT's

decomposition reaction greatly accelerated.[18] The decomposition reaction accelerates so markedly that the induction period A totally disappears. With pure TNT samples, approximately 2 min were required for thermal equilibration to be achieved, and an induction period followed as part of the normal isothermal DSC curve (Figure 1). However, the 3.7% HQ/TNT samples displayed no induction period, and following the 2-min thermal equilibration a steep exothermic slope characterized the 3.7% HQ/TNT reaction as being well advanced into the self-sustained exothermic acceleration phase B. This rapid exothermic reaction suggests that any measurable induction period A in the 3.7% HQ/TNT reaction is considerably less than 2-min long and that a bimolecular reaction occurs between TNT and hydroquinone.

Formation of compound I during the induction period apparently is initiated from a hydrogen species being generated by the rate-determining carbon–hydrogen bond cleavage in pure TNT. Hydroquinone possesses a labile hydroxyl hydrogen which could be introduced to the TNT molecule more readily than by a methyl group's carbon–hydrogen bond rupture. Thus, very rapid catalysis of the molten TNT thermochemical decomposition reaction likely results from hydroquinone providing a more labile hydrogen species to a TNT molecule than can pure TNT in hydroquinone's absence. While hydroquinone is usually a hydrogen-atom donor, the possibility that it acted as a proton donor under our reaction conditions had to be addressed. To determine which type of hydrogen species was catalyzing TNT's molten thermochemical decomposition reaction, 3.7 mol % benzoic acid (BA), a proton donor, was mixed with TNT. Isothermal DSC analysis of the 3.7% BA/TNT samples (263 °C) produced a normal decomposition curve like that exhibited by pure TNT.[19] While the 3.7% BA/TNT[20] samples yielded an induction time only 8% less than that of pure TNT (Table IV), the relative acceleratory effect of hydroquinone is exceptionally dramatic. Assuming the 3.7% HQ/TNT thermochemical decomposition reaction possessed a maximum induction period A equal to the instrumental temperature equilibration time (ca. 120 s), hydroquinone represents a 60% reduction in pure TNT's induction period. Interestingly, hydroquinone accelerates the thermochemical decomposition of TNT mainly during the early induction period (60% a minimum value) as opposed to the exothermic acceleratory phase (45% a maximum value),[21] while benzoic acid shows its largest acceleration during the exothermic acceleratory phase (32%) vs. the induction period (8%).[21]

The tremendous induction period acceleration in the 3.7% HQ/TNT reactions leads to the conclusion that hydroquinone provides a hydrogen atom which rapidly catalyzes the thermochemical decomposition of liquid TNT. TNT's rapid decomposition in the presence of a hydrogen-atom donor strongly suggests that the rate-determining carbon–hydrogen bond rupture found to occur in pure TNT proceeds by a homolytic cleavage during the induction period.[22] This homolytic carbon–hydrogen bond rupture generates a chain-initiating hydrogen atom that leads to the production of compound I, which in turn must catalyze the exothermic decomposition reaction of TNT.

Conclusion

A deuterium isotope effect study was successfully integrated with isothermal DSC kinetic analysis to elucidate by direct experiment the rate-determining step in liquid TNT's thermochemical decomposition reaction. This application of the deuterium isotope effect to isothermal DSC analysis provided mechanistic information, heretofore unobtainable, which is important in elucidating thermochemical reaction pathways of compounds in a homogeneous liquid phase. Crystal lattice stabilization effects and the influences of solvent or dilution were eliminated as factors that complicate the kinetic evaluation of thermochemical reactions. A primary deuterium isotope effect was obtained that directly revealed the critical bond rupture responsible for initiating TNT's sustained exothermic decomposition reaction.

Table IV. Hydrogen Donor Effect upon Molten TNT Decomposition (263 °C)

	TNT	3.7% BA/TNT	3.7% HQ/TNT
Induction time, s	297	272	0[a]
Time to max reaction, s	644	436	356[b]

[a] Not detectable below 120 s due to temperature equilibration time required for molten TNT. [b] This is a maximum value assuming a 120-s induction period.

A significant deuterium isotope effect (1.35) was observed during the decay phase C (Figure 1) of TNT's thermochemical decomposition reaction where sustained exothermic degradation occurs. But, competing, simultaneous reactions proceed during this latter decay phase C and dilute the observed k_H/k_D isotope ratio. The decay phase C represents a total reaction rate and includes the reaction rates of compounds that form from TNT without carbon–hydrogen bond rupture occurring in the methyl moiety. The previous isolation of 6- and 7-type compounds from TNT thermochemical decomposition reactions supports this.[8,9] This work has shown that induction time ratios, obtained directly from isothermal DSC curves, can be used in lieu of undeterminable rate-constant ratios to determine the deuterium isotope effect during the initial induction period A. High-pressure liquid-chromatography studies at this laboratory revealed a singular catalytic species, compound I, formed from TNT during the induction period; thus, reactions found in the decay phase C that dilute the isotope effect are likely absent in the induction period A. Direct measurement of TNT and TNT-d_3 induction times provided a t_{ID}/t_{IH} ratio indicative of a primary isotope effect equal to 1.66 over the range 245–269 °C. This rate-determining carbon–hydrogen bond rupture in the TNT methyl group ultimately must be responsible for initiating the exothermic decomposition process.

Mixing 3.7 mol % hydroquinone with TNT resulted in a substantially accelerated thermochemical decomposition, as evidenced by the disappearance of the induction period. This behavior is best explained by hydroquinone donating its more labile hydrogen atom to a TNT molecule. This strongly suggests that the rate-determining carbon–hydrogen rupture in pure TNT proceeds homolytically with transfer of a benzylic hydrogen probably to an oxygen in a nitro group. The reaction between hydroquinone would be expected to be an oxidation–reduction which is also characteristic of pure TNT thermochemical decomposition reactions. Mixing 3.7 mol % benzoic acid, a proton donor, with TNT failed to accelerate the decomposition reaction significantly. This further supports the proposed homolytic carbon–hydrogen bond rupture in the TNT methyl group.

Calculations from decay phase C data produced a large negative entropy of activation (−16.4 eu) that is consistent with the formation of a highly ordered cyclic transition species. Such a species might be generated during the degradation by a cyclic interaction between the methyl group and adjacent *o*-nitro group during either an intra- or intermolecular reaction pathway. But cyclic interactions resulting from subsequent oxidation reactions, known to proceed during this latter decay phase C, could be responsible in part or whole for the entropy of activation found.

This study successfully integrated the deuterium isotope effect concept with isothermal DSC analysis. It represents the first direct experimental evidence that homolytic carbon–hydrogen bond rupture in the methyl moiety constitutes the initial rate-determining step for exothermic thermochemical decomposition of liquid TNT. The mechanism of this reaction is quite complex, and additional investigation is required for a total mechanistic elucidation of neat TNT thermochemical decomposition. Studies are continuing to determine the chemical identity of the catalytic compound I and to elucidate this complex decomposition mechanism. Further investigations using isothermal DSC measured deuterium isotope effects are in progress to relate the nature of polynitro aromatic structure and bonding to a compound's stability/instability toward thermochemical decomposition processes. This successful use of deuterium isotope effects with the convenient isothermal DSC kinetic analysis technique paves the way for the direct experimental study of thermochemical mechanistic phenomena, that to date have eluded detection by other investigative techniques. Application of deuterium isotope effects to isothermal DSC analyses is limited only to the imaginative approach and insight of future investigations.

Experimental Section

General Procedures. All isothermal DSC measurements were obtained with a Perkin-Elmer Model DSC-1 instrument. The average and differential temperature settings on the DSC-1 were calibrated with a tin standard (mp 222 °C). The instrument was preheated to the desired reaction temperature for each analysis. A sealed but empty aluminum cell, Perkin-Elmer part no. 219-0062, always remained upon the reference thermal support. While the instrument thermally equilibrated, the weighed TNT samples (4.05 ± 0.05 mg) were sealed in an aluminum cell using a Perkin-Elmer sealer assembly, part no. 219-0061, that provided a cold weld of the cell lid to the pan. The loaded cell was placed upon the sample thermal support, and immediately the chart recorder scan was activated. The thermochemical decomposition reaction then proceeded to completion, and the isothermal DSC curve was evaluated for the desired data.[2-4,10] Analyses of TNT and TNT-d_3 were conducted isothermally for each compound at 245, 251, 257, 263 and 269 °C. The TNT used was synthesized by a previously developed procedure[23] and was purified by recrystallization from 95% ethanol (mp 80.0–81.2 °C). Sublimed samples afforded isothermal DSC induction times no different from the recrystallized material.

Synthesis of α,α,α-Trideuterio-2,4,6-trinitrotoluene (TNT-d_3). Into 35 mL of acetone was dissolved 5 g of TNT. Next, 10 mL of 98% D_2O was added to the solution followed by less than 1 mL of triethylamine (catalytic amount). The solution instantaneously became dark red. After stirring for 15 min at room temperature, D_2SO_4 was added dropwise until the solution was acidic (pH 3 by wide-range pH paper). The solution was extracted with $CHCl_3$ and dried over anhydrous $MgSO_4$. In vacuo solvent removal of the $CHCl_3$ afforded 4.5 g of solid product. The product was purified by sublimation to yield an off-white solid (mp 80.2–81.6 °C). Analysis by NMR indicated deuterium exchange had occurred at the methyl moiety, and mass spectrometry (M^+ 230) revealed the TNT-d_3 to be 96% isotopically pure by analysis of the m/e 212 and 210 fragments (base peak: TNT-d_3 212; TNT 210).

Preparation of the Mixed 3.7% Hydroquinone/2,4,6-Trinitrotoluene Sample. To ensure sample homogeneity, the 3.7 mol % HQ/TNT sample was prepared as follows. Into a 4 dr. glass vial was weighed 1.80 mg of Mallinckrodt "photo purified" hydroquinone and 100.00 mg of TNT. The mixture was dissolved in about 2 mL of Burdick–Jackson "Distilled-in-Glass" acetone, and the acetone was air evaporated. The remaining solid was thoroughly dried in a vacuum oven before being triturated into a fine powder. A pure TNT sample was also dissolved in acetone, dried, and triturated into a fine powder. Isothermal DSC analysis of this "blank" TNT sample revealed no significant difference in its thermochemical decomposition behavior compared to the untreated TNT.

Preparation of the Mixed 3.7% Benzoic Acid/2,4,6-Trinitrotoluene Sample. Preparation of the 3.7 mol % BA/TNT sample was accomplished as described for the 3.7 mol % HQ/TNT sample using 2.00 mg of benzoic acid (Eastman Organic Chemicals) and 100.14 mg of TNT.

Acknowledgments. The authors express their appreciation to B. A. Loving (FJSRL) for constructive discussions, helpful comments, and managerial support concerning this work. R. N. Rogers, J. K. Erbacher, E. E. Gilbert, R. M. Guidry, L. P. Davis, R. R. McGuire, M. J. Kamlet, G. U. Yuen, R. E. Cochoy, L. B. Sims, and W. D. Closson are acknowledged for their informative discussions and comments. R. P. Davenport synthesized the TNT-d_3.

Registry No.—TNT, 118-96-7; TNT-d_3, 52886-05-2.

Supplementary Material Available. Figures 6–9 which are the hydrogen-substituted TNT kinetic plots analogous to Figures 2–5, respectively (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Address correspondence to this author.
(2) R. N. Rogers and L. C. Smith, *Thermochim. Acta*, **1**, 1 (1970).
(3) R. N. Rogers, *Anal. Chem.*, **44**, 1336 (1972).
(4) R. N. Rogers, *Thermochim. Acta*, **3**, 437 (1972).
(5) R. N. Rogers and G. W. Daub, *Anal. Chem.*, **45**, 596 (1973).
(6) For example, the thermochemical decomposition products of TNT in benzene solvent are markedly different from those isolated from molten TNT (no solvent). Compare the results of E. K. Fields and S. Meyerson, *J. Org. Chem.*, **33**, 4487 (1968), with those of ref 8 and 9.
(7) L. A. Wiseman, Bistrol Research Report No. 51, A.C. 2670, Ministry of Supply, Great Britain, 1942.
(8) R. N. Rogers, *Anal. Chem.*, **39**, 730 (1967).
(9) J. C. Dacons, H. G. Adolph, and M. J. Kamlet, *J. Phys. Chem.*, **74**, 3035 (1970).
(10) J. W. Beckmann, J. S. Wilkes, and R. R. McGuire, *Thermochim. Acta*, **19**, 111 (1977).
(11) E. K. Fields, *Tetrahedron Lett.*, 1201 (1968).
(12) J. M. Rosen and J. C. Dacons, *Explosivstoffe*, **16**, 250 (1968).
(13) Y. Y. Maksimov, *Zh. Fiz. Khim.*, **46**, 990 (1972).
(14) J. W. A. Janssen, C. L. Habraken, and R. Louw, *J. Org. Chem.*, **41**, 1758 (1976).
(15) (a) J. Bigeleisen and M. Wolfsberg, "Advances in Chemical Physics", Vol. I, I. Prigogine, Ed., Interscience, New York, N.Y., 1958, pp 15–31; (b) K. B. Wiberg, *Chem. Rev.*, **55**, 717–8 (1955).
(16) E. Swinborn, "Analysis of Kinetic Data", Appleton-Century-Crofts, New York, N.Y., 1971, p 47.
(17) (a) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure", McGraw-Hill, New York, N.Y., 1968, pp 213–6; (b) R. D. Gilliom, "Introduction to Physical Organic Chemistry", Addison-Wesley, London, 1970, pp 136–7, and references cited therein; (c) ref 15b, pp 718, 727, and 731.
(18) Pure hydroquinone did not thermochemically decompose at 263 °C during isothermal DSC analysis conducted over a period of time greater than that required to effect a total thermochemical decomposition of pure TNT.
(19) Pure benzoic acid was thermally stable to isothermal DSC analysis at 263 °C.
(20) Many additives to TNT result in an acceleration of its thermochemical decomposition. T. B. Joyner, private discussion, and A. J. B. Robertson, *Trans. Faraday Soc.*, **44**, 677 (1948).
(21) Acceleration percentages, during the exothermic acceleratory phase B, were determined from the "time to max reaction" values in Table IV. These values represent the time required for a thermochemical decomposition reaction to reach the peak of the isothermal DSC curve where the exothermic reaction is at a maximum once the induction period is terminated.
(22) The conclusion of homolytic bond rupture is further supported by previously reported EPR data showing a 10^{-4} M concentration of radicals being formed in liquid TNT at 240 °C: E. G. Janzen, *J. Am. Chem. Soc.*, **87**, 3531 (1965).
(23) U.S. Army Materiel Command, "Engineering Design Handbook, Explosive Series, Properties of Explosives of Military Interest", 1967, p 356.

Chemical Transformations of Abundant Natural Products. 3.[1a] Modifications of Eremanthin Leading to Other Naturally Occurring Guaianolides[1b]

Lélio A. Maçaira, Marcos Garcia, and Jaime A. Rabi*

Núcleo de Pesquisas de Produtos Naturais, Instituto de Ciências Biomédicas, Bloco H, Universidade Federal do Rio de Janeiro, Ilha do Fundão, Rio de Janeiro ZC-32-Brasil

Received May 16, 1977

Several selective modifications of eremanthin (**1**) were achieved. Reaction of the epoxide **2** with equimolar amounts of BF_3-Et_2O gave mainly the aldehyde **4**. On the other hand, treatment of **2** with HCl gave a mixture of chlorohydrins **5** (55%) and **6** (45%). Dehydration of **5**, followed by dechlorination of the resulting product **7**, gave **8**. This latter compound was shown to be identical with dehydrocostus lactone. In addition, reaction of **1** with excess BF_3-Et_2O yielded isoeremanthin (**9**), which upon treatment with *N*-bromosuccinimide in dioxane–water gave the dibromo ether **10**.

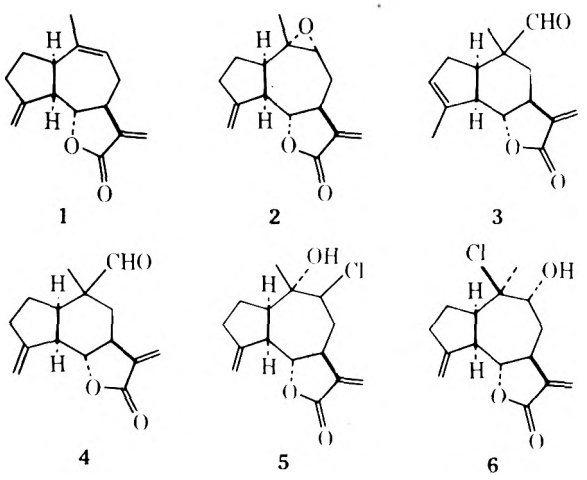
The interesting biological properties of sesquiterpene lactones[2] and the possibility that they could represent a lead in the search for new tumor inhibitors has stimulated many research groups to develop total syntheses for some of the most promising members of this group of compounds.[3]

In this Center the search for plant-derived inhibitors against infection by cercariae of *Schistosoma mansoni* led to the isolation and characterization of eremanthin (**1**) from *Eremanthus elaeagnus*.[4,5] The relative abundance of this latter compound made it possible to start a program of chemical modifications of **1** as an alternative route to the synthetic approach for the obtention of other biologically active derivatives. In addition, selective transformations of **1** could also provide an entry to the partial synthesis of less abundant, and sometimes not well characterized, naturally occurring lactones.

In this paper we report the synthesis of several derivatives of **1**, including dehydrocostus lactone.

Results and Discussion

We have briefly reported that treatment of the epoxide **2** with excess BF_3-Et_2O gives the aldehyde **3**.[5] We have now found that isomerization of the exocyclic double bond at the five-membered ring can be prevented by using equimolar amounts of BF_3-Et_2O. In this manner compound **4** could be obtained selectively.



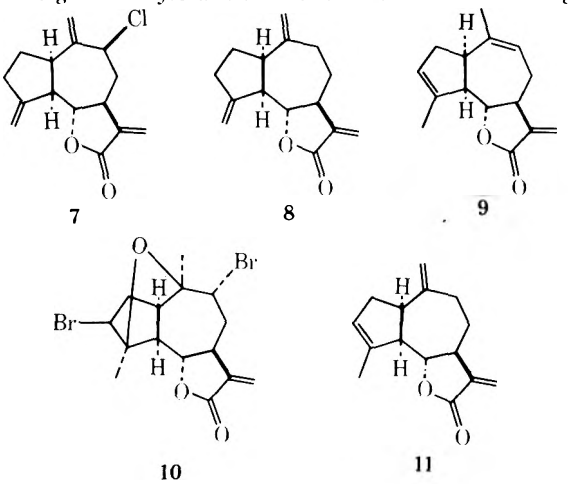
1 **2** **3**

4 **5** **6**

Ring contraction to give **4** without double bond migration could be easily determined by ^1H NMR spectroscopy. A sharp singlet at δ 9.45 could be attributed to the aldehyde function, consistent with the presence of a three-proton singlet at δ 1.13 assigned to the quaternary C_{10}–CH_3. Two typical broad singlets at δ 5.03 and 5.17 assured the presence of the exocyclic nonconjugated double bond whereas the unmistakable doublets at δ 5.44 and 6.10 (J = 3.5 Hz) demonstrated the presence of the conjugated α-methylene group. These features were also corroborated by the IR spectrum which showed characteristic bands at 2740 and 1724 cm^{-1} attributed to the aldehyde function. A strong band at 890 cm^{-1} further supported the exocyclic nonconjugated double bond. The molecular formula was supported by the mass spectrum which showed besides the parent peak at *m/e* 246 fragments at *m/e* 218 ($M^+ - 28$) and *m/e* 217 ($M^+ - 29$) characteristic of the aldehyde group.

On the other hand when **2** was treated with HCl in THF at room temperature, two chlorohydrins could be isolated. These were identified as **5** (55%) and **6** (45%). Both isomers showed spectral properties in complete agreement with the proposed structures. In particular, the ^1H NMR spectrum of **5** showed the C_{10}–CH_3 at δ 1.12 while H-9 appeared as a double doublet centered at δ ~4.10. The corresponding signals in **6** appeared at δ 1.69 and 4.09. Further comparison between the ^1H NMR spectrum of **5** and **6** showed their H-6 at δ 4.22 and 4.70, respectively. This difference in chemical shift in H-6 is attributed to field effects caused by a β-oriented electronegative substituent at C_{10} and has been found to be of great value in determining the stereochemistry of addition reactions at the 9,10 double bond.[6] Additional support for the trans nature of the halohydrins **5** and **6** was obtained by transforming a mixture of them into **2** by reaction with Na_2CO_3 in MeOH.

The facile conversion of **2** into **5** provided an entry toward the syntheses of other naturally occurring guaianolides. Thus, treatment of **5** with a mixture of thionyl chloride and pyridine[7] at −8 °C gave 85% yield of **7**. The structure of **7** was strongly



7 **8** **9**

10 **11**

supported by physical methods. In the IR spectrum a band at ~890 cm^{-1} appeared much stronger than the corresponding band in any of the previously discussed compounds. The ^1H NMR spectrum clearly indicated the dehydration reaction as proposed. Thus, the methyl group at δ 1.12 disappeared and a new pair of well-separated signals associated with the newly formed exocyclic methylene group appeared at δ 5.08 and 5.60. Dechlorination of **7** by treatment with Zn in MeOH gave **8** in about 80% yield. The absence of C_9–Cl was easily determined by inspection of the ^1H NMR spectrum which showed the signals associated to the C_{10}=CH_2 group at δ 4.83 and 4.91, 0.25 and 0.69 ppm upfield from the corresponding signals in **7**.

The structure of **8** as depicted is the same as that proposed for dehydrocostus lactone.[8] Comparison of our data with those for this latter compound[8,9] (optical rotation and ^1H NMR spectrum) confirms that both compounds are identical.[10] Since the sequence of reactions leading to **8** from **1** would hardly result in epimerization at the chiral centers, the absolute configuration at C_1, C_5, C_6, and C_7 in dehydrocostus lactone would thus be established as being identical to those found for **1**.[5]

It was shown at the beginning that ring contraction of **2** with 4,14 double-bond isomerization depended on using an excess of BF_3·Et_2O. This finding suggested that **1** and **8** could be isomerized to their corresponding $\Delta^{3,4}$ isomers. In fact, when **1** was allowed to react with excess of BF_3·Et_2O in dry benzene ar room temperature, a smooth conversion to isoeremanthin (**9**) took place.[11,12] Spectral data strongly support the double-bond migration as indicated. In the IR spectrum, the characteristic exocyclic double-bond absorption at ~890 cm^{-1} was absent whereas the band at ~811 cm^{-1}, typical of trisubstituted double bond, increased in intensity. The absorptions at 1754 and 1661 cm^{-1} typical of the α-methylene-γ-lactone group were intact. The mass spectrum of **9** was almost identical to that of **1** and the molecular ion at *m/e* 230 supported its molecular formula. In the ^1H NMR spectrum the signals at δ 5.08 and 5.25, attributed to the exocyclic double bond at C_4 in **1**, were substituted by a new methyl at δ 1.95 long-range coupled with an additional vinylic proton located at δ 5.50. That isomerization of **1** to **9** did not result in change of the configuration at C_1 or C_5 was firmly demonstrated by the formation of the dibromo ether **10** when **9** was allowed to react with NBS in a mixture of dioxane–H_2O. Here again, the structure of **10** was easily determined by ^1H NMR spectroscopy. The ether linkage between C_4 and C_{10} determined both methyl groups to appear at δ 1.59 whereas the signals corresponding to H-3 and H-9 appeared at δ 4.10 and 4.24, respectively.

The utilization of **9** in the partial synthesis of eregoyazin and eregoyazidin, two new guaianolides isolated from *Eremanthus goyazensis*, is described in a following paper.

Initial evaluation of the cercaricidal activities of some of the compounds under study showed that **9** is the most active of the derivatives of **1** so far studied.[13]

Experimental Section

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. IR spectra were run as KBr pellets on a Perkin-Elmer 137-B spectrophotometer. ^1H NMR spectra of $CDCl_3$ solutions using Me_4Si as internal standard were recorded on a Varian XL-100 instrument. Mass spectra were obtained at 70 eV on a Varian-Mat CH-5 spectrometer. Silica gel GF_{254}, PF_{254}, and Kieselgel 60 were used for TLC, preparative TLC, and column chromatography, respectively. Microanalyses were performed by Alfred Bernhardt, West Germany.

Reaction of Eremanthin 9,10-α-Epoxide (2) with BF_3·Et_2O. Epoxide **2** (0.100 g, 0.408 mmol) was dissolved in benzene (6 mL) and the solution was frozen at −5 °C. Recently distilled BF_3·Et_2O (0.1 mL, 0.408 mmol) was added and the mixture was allowed to reach 10 °C slowly (~3 h). The mixture was then diluted with EtOAc (25 mL), washed with 5% aqueous $NaHCO_3$ (3 × 20 mL) and H_2O (3 × 20 mL), and concentrated in vacuo to give an oily residue which was purified by preparative TLC using hexane–EtOAc (7:3) as eluent. The main product (R_f 0.32) was eluted giving 0.050 g (50%) of **4**: mp 102–104 °C; IR 2740, 1754, 1724, 1667, 890 cm^{-1}; ^1H NMR δ 1.13 (s, 3, C_{10}–CH_3), 3.56 (t, 1, J = 10 Hz, H-6), 5.03 and 5.17 (narrow m, 1 each, C_4=CH_2), 5.44 and 6.10 (d, 1 each, J = 3.5 Hz, C_{11}=CH_2), 9.45 (s, 1, C_{10}–CHO); mass spectrum *m/e* (rel intensity) 246 (M^+, 15), 228 (10), 218 (30), 217 (17), 80 (100). Anal. Calcd for $C_{15}H_{18}O_3$: M^+, 246.1255. Found: M^+, 246.1293. A small amount of **3**[5] (R_f 0.38, <10%) could also be detected on the preparative TLC.

Reaction of Eremanthin 9,10-α-Epoxide (2) with HCl. Epoxide **2** (1.878 g, 7.634 mmol) was dissolved in THF (10 mL) and the solution was stirred and cooled at ~0 °C. Concentrated HCl was then added (37%, 0.7 mL, 8 mmol) and the stirring was continued for 30 min. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (3 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue (2.0 g, 88%) was purified by column chromatography using a gradient of CH_2Cl_2 in hexane as eluant to give 1.031 g (48%) of **5** and 0.852 g (39.7%) of **6**. **5**: mp 152–154 °C; IR 3540, 1755, 1650, 1250, 890 cm^{-1}; ^1H NMR δ 1.12 (s, 3, C_{10}–CH_3), 4.10 (dd, 1, J = 5 and 12 Hz, H-9), 4.22 (t, 1, J = 9.5 Hz, H-6), 5.00 and 5.16 (narrow m, 1 each, C_4=CH_2), 5.60 and 6.30 (d, 1 each, J = 3 Hz, C_{11}=CH_2); mass spectrum *m/e* (rel intensity) 284 (M^+, 2), 282 (M^+, 6), 266 (2), 264 (6), 229 (14), 131 (16), 107 (30), 93 (33), 81 (37), 43 (100). Anal. Calcd for $C_{15}H_{19}{}^{35}ClO_3$: M^+, 282.1022. Found: M^+, 282.0996. **6**: mp 142–144 °C; IR 3450, 1760, 1660, 1265, 885 cm^{-1}; ^1H NMR δ 1.69 (s, 3, C_{10}–CH_3), 4.09 (broad t, 1, H-9), 4.70 (t, 1, J = 9 Hz, H-6), 4.95 and 5.15 (narrow m, 1 each, C_4=CH_2), 5.50 and 6.22 (d, 1 each, J = 3 Hz, C_{11}=CH_2); mass spectrum *m/e* (rel intensity) 284 (M^+, 5), 282 (M^+, 15), 246 (5), 230 (14), 133 (24), 107 (64), 51 (58), 80 (64), 53 (100). Anal. Calcd for $C_{15}H_{19}{}^{35}ClO_3$: M^+, 282.1022. Found: M^+, 282.0949. A mixture of **5** and **6** (0.04 g) was dissolved in MeOH (5 mL) and Na_2CO_3 (~0.050 g) was added. After ~10 h at room temperature with vigorous stirring, the product was isolated and shown to be identical (TLC, ^1H NMR) with **2**.

Reaction of 9-β-chloro-10-α-hydroxyl Eremanthin (5) with $SOCl_2$/Pyridine. A solution of compound **5** (1.072 g, 3.78 mmol) in pyridine (~1 ml) was cooled to ~8 °C and a mixture of $SOCl_2$/pyridine (6 mL of a mixture prepared by mixing 9.5 mL of pyridine and 0.5 mL of $SOCl_2$) was added. After 5 min, CH_2Cl_2 (~50 mL) was added and the resulting mixture was washed with water (3 × 30 mL). The organic phase was dried ($MgSO_4$) and concentrated to give a residue (~1.030 g) which was purified by column chromatography to give 0.842 g (85%) of **7**: mp 128–130 °C; IR 1755, 1645, 1242, 890 cm^{-1}; ^1H NMR δ 3.97 (t, 1, J = 9.5 Hz, H-6), 4.44 (dd, 1, J = 4.5 and 12 Hz, H-9), 5.08 and 5.60 (broad s, 1 each, C_{10}=CH_2), 5.10 and 5.27 (narrow m, 1 each, C_4=CH_2), 5.56 and 6.28 (d, 1 each, J = 3.5 Hz, C_{11}=CH_2); mass spectrum *m/e* (rel intensity) 266 (M^+, 6), 264 (M^+, 21), 230 (16), 229 (16), 149 (25), 105 (31), 91 (76), 80 (100), 53 (70), 39 (73). Anal. Calcd for $C_{15}H_{17}{}^{35}ClO_2$: M^+, 264.0917. Found: M^+, 264.0896.

Reaction of 7 with Zn. Compound **7** (0.8 g, 3.03 mmol) was dissolved in MeOH (15 mL) containing AcOH (0.1 mL) and Zn dust was added (2.0 g). The mixture was vigorously stirred at room temperature for 72 h. It was then filtered and the precipitate was washed with AcOEt (25 mL). The solvent was removed in vacuo and the residue (0.625 g) was purified by column chromatography to give 0.56 g (80%) of **8** as an oil which did not crystallize: $[\alpha]^{30}_D$ −12.2 (*c*, 0.33, $CHCl_3$); IR (film) 1760, 1640, 1250, 890 cm^{-1}; ^1H NMR δ 3.96 (t, 1, J = 9 Hz, H-6), 4.83 and 4.91 (broad s, 1 each, J = 3 Hz, C_{11}=CH_2); mass spectrum *m/e* (rel intensity) 230 (M^+, 48), 150 (50), 105 (65), 81 (53), 80 (100), 77 (66), 53 (57), 44 (75), 41 (78), 39 (85). Anal. Calcd for $C_{15}H_{18}O_2$: M^+, 230.1306. Found: M^+, 230.1342

Reaction of Eremanthin (1) with BF_3·Et_2O. Synthesis of Isoeremanthin (9). A solution of **1** (0.50 g, 0.218 mmol) was dissolved in benzene (4 mL) and recently distilled BF_3·Et_2O (0.1 mL, 0.408 mmol) was added. The mixture was stirred for 4 h at room temperature, diluted with AcOEt (20 mL), washed with 5% aqueous $NaHCO_3$ (2 × 20 mL) and H_2O (3 × 20 mL), dried (Na_2SO_4), and concentrated. The residue was purified by preparative TLC to give 0.026 g (52%) of **9**: mp 71–73 °C; IR 1754, 1661, 811 cm^{-1}; ^1H NMR δ 1.81 (broad s, 3, C_{10}–CH_3) 1.95 (broad s, 3, C_4–CH_3), 4.03 (dd, 1, J = 9 and 11 Hz, H-6), 5.50 (m, 2, H-3 + H-9), 5.48 and 6.17 (d, 1 each, J = 3.5 Hz, C_{11}=CH_2); mass spectrum *m/e* (rel intensity) 230 (M^+, 16), 215 (3), 150 (100), 122 (22), 119 (20), 91 (30), 80 (25). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.30; H, 7.80. Found: C, 78.12; H, 7.65. We have repeated this reaction many times in up to 5 g scale obtaining yields ranging from 65 to 80%. When the reaction is run in more than 0.5 g scale better yields

have been obtained using a 4-mol excess of BF_3·Et_2O and allowing the reaction to proceed for ~30 h at room temperature.

Reaction of 9 with *N*-Bromosuccinimide. A solution of **9** (0.09 g, 0.38 mmol) in dioxane-H_2O (8/2) was frozen at −30 °C and NBS (0.14 g, 0.76 mmol) was added. The temperature was then allowed to reach room temperature (4 h) and the mixture was diluted with AcOEt and washed with H_2O (2 × 50 mL), the resulting organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by preparative TLC to give 0.014 g (9.1%) of **10**: IR 1754, 1653 cm^{-1}; ^1H NMR δ 1.59 (s, 6, C_{10}-CH_3 + C_4-CH_3), 4.01 to 4.10 (m, 2, H-3 + H-6), 4.24 (t, 1, J = 3 Hz, H-9), 5.49 and 6.18 (d, 1 each, J = 3.5 Hz, C_{11}=CH_2); mass spectrum *m/e* (rel intensity) 404 (M^+, 1) 406 (M^+, 2), 408 (M^+, 1), 387 (1), 389 (3), 391 (1), 325 (6), 327 (8), 57 (100). Anal. Calcd for $C_{15}H_{18}{}^{79}BrO_3$: M^+ − Br, 325.0439. Found: M^+ − Br, 325.0483. Anal. Calcd for $C_{15}H_{18}{}^{81}BrO_3$: M^+ − Br, 327.0419. Found: M^+ − Br, 327.0492.

Acknowledgment. We are grateful to Dr. P. M. Baker, J. Joia, and T. Müller for ^1H NMR and mass spectra and to G. Magela for assistance during part of the work. Financial support was provided by the Ministry of Planning (FINEP), the National Research Council of Brazil (CNPq), and the Research Council of this University (CEPG).

Registry No.—**1**, 37936-58-6; **2**, 38963-61-0; **4**, 63832-99-5; **5**, 63833-00-1; **6**, 63833-01-2; **7**, 63833-02-3; **8**, 477-43-0; **9**, 63569-76-6; **10**, 63833-03-4.

References and Notes

(1) (a) Part 2 is *Tetrahedron Lett.*, 4535 (1975); (b) Taken in part from the M. S. Theses of Marcos Garcia, NPPN-UFRJ, 1975, and Lélio A. Maçaira, NPPN-UFRJ, in preparation.
(2) For a recent review covering some of the most important biological activities shown by sesquiterpene lactones, see: E. Rodriguez, G. H. N. Towers, and J. C. Mitchell, *Phytochemistry*, **15**, 1573 (1976).
(3) (a) For a review of α-methylenelactone syntheses, see (a) P. A. Grieco, *Synthesis*, 67 (1975); (b) S. Danishefsky, T. Kitahara, P. F. Schuda, and S. J. Etheredge, *J. Am. Chem. Soc.*, **98**, 3028 (1976); (c) P. A. Grieco, J. A. Noguez, and Y. Masaki, *J. Org. Chem.*, **42**, 495 (1977); (d) P. A. Grieco, J. A. Noguez, Y. Masaki, K. Hiroi, M. Nishizawa, A. Rosowsky, S. Oppenheim, and H. Lazarus, *J. Med. Chem.*, **20**, 71 (1977), and references cited therein.
(4) W. Vichnewski and B. Gilbert, *Phytochemistry*, **11**, 2563 (1972).
(5) M. Garcia, A. J. R. da Silva, P. M. Baker, B. Gilbert, and J. A. Rabi, *Phytochemistry*, **15**, 331 (1976).
(6) In addition, we have found that for a given pair of α- and β-oriented electronegative groups at C_4 and/or C_{10}, only the β-oriented isomer causes a marked downfield shift for H-6. These include: hydroxyl groups, epoxides, halohydrins, and dibromides. M. Garcia, F. Welbaneide L. Machado, L. A. Maçaira, and J. A. Rabi, unpublished observations. The following paper in this series includes δ values of H-6 for a number of bromo derivatives showing the utility of this effect in determining the stereochemistry of bromine addition to **9**.
(7) A. Corbella, P. Gariboldi, G. Jommi, and G. Ferrari, *Phytochemistry*, **13**, 459 (1974).
(8) S. B. Mathur, S. V. Hiremath, G. H. Kulkarni, G. R. Kelkar, S. C. Bhattacharyya, D. Simonovic, and A. S. Rao, *Tetrahedron*, **21**, 3575 (1965).
(9) M. Romanuk, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **21**, 894 (1976); *Chem. Abstr.*, **50**, 9344f (1956).
(10) There are a few minor differences between our rotation and NMR data and those reported for dehydrocostus lactone in ref 8 and 9. However, direct comparison of our TLC, IR, and ^1H NMR data with those obtained on an authentic sample of dehydrocostus lactone kindly supplied by Dr. S. C. Bhattacharyya (Bombay) establishes that the two samples are identical.
(11) Isoeremanthin (**9**) seems to be a powerful allergen having caused allergic contact dermatitis in some workers of this laboratory.
(12) In a similar manner **8** has been isomerized to **11** which has been converted to a compound showing similar properties with estafiatin [J. Romo, and F. Sanchez-Viesca, *Tetrahedron*, **19**, 1285 (1963)]. Estafiatin possess a 1,5-cis-fused guaiane skeleton. J. Romo, private communication.
(13) J. C. Holanda, M. Garcia, and J. A. Rabi, unpublished observations.

Syntheses of Nitrogen-Containing Heterocyclic Compounds. 26.[1] Reaction of Benzo[*f* or *h*]quinolines and Their *N*-Oxides with Methylsulfinyl Carbanion

Yoshiki Hamada* and Isao Takeuchi

Faculty of Pharmacy, Meijo University, Tenpaku-ku, Nagoya 468, Japan

Received March 31, 1977

Benzo[*h*]quinoline (**1**) and its methyl derivatives were synthesized by the modified Skraup reaction of 1-naphthylamines with glycerol, crotonaldehyde, or methyl vinyl ketone, in the presence of Sulfo-mix, ferrous sulfate, and boric acid. **1** or benzo[*f*]quinoline (**8**) was treated with dimethyl sulfoxide in the presence of sodium hydride at 70 °C to give methylated products. When benzo[*h* or *f*]quinoline *N*-oxide (**6** or **11**) was treated with methylsulfinyl carbanion in the usual procedure, a new reaction took place to produce phenanthrene (**7**) in excellent yield, whereas in the presence of potassium *tert*-butoxide only the methylated product was obtained. Reaction conditions of **6** with methylsulfinyl carbanion or deuterated methylsulfinyl carbanion and substituent effects were examined.

Reaction of quinolines, isoquinolines,[2] and their *N*-oxides[3] with methylsulfinyl carbanion has already been reported, and the products were all methylated compounds. We have also carried out methylation of 1,*X*-naphthyridines (*X* = 5, 6, 7, and 8) with methylsulfinyl carbanion.[4] In the present work, reaction of benzo[*h*]quinoline and its *N*-oxide with methylsulfinyl carbanion was carried out in order to examine the difference, if any, in reactivity between the parent ring and the *N*-oxide. We have found that the *N*-oxide and methylsulfinyl carbanion undergo an entirely different reaction.

Results and Discussion

To identify the methylated derivatives expected from methylation of benzo[*h*]quinoline, syntheses of the starting benzo[*h*]quinoline and its methylated derivatives were carried out by a modified Skraup reaction.[5] Glycerol, crotonaldehyde, and methyl vinyl ketone were reacted with 1-naphthylamine, in the presence of Sulfo-mix,[6] ferrous sulfate, and boric acid; and benzo[*h*]quinoline[7] (**1**), 2-methylbenzo[*h*]quinoline[8] (**2**), and 4-methylbenzo[*h*]quinoline[9] (**3**) were obtained in a respective yield of 50, 36, and 36%. 6-Methylbenzo[*h*]quinoline[10] (**4**) was obtained in a low yield of 15% by the application of glycerol to 4-methyl-1-naphthylamine[11] by the modified Skraup reaction. Compound **1** has been obtained by the usual Skraup reaction in 45% yield. There are several methods for the synthesis of **2**, such as the Doebner–Miller reaction of 1-naphthylamine[8a] and from acetylene and ethanol.[8b] Compound **3** has been synthesized using 1-naphthylamine and 1,3-dichloro-2,3-butene[9a] or 1-naphthylamine and ethyl acetoacetate.[9b] These synthetic methods for **2** and **3** are all complicated, and our procedure provides a better method.

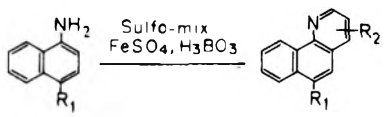
The compounds synthesized were identified by mixture melting point determination with the samples obtained by the method in the literature[7,8a,9a,10] for **1**–**4**, by comparison of IR

Table I. *S* Values[a] and the Ratios in the Lanthanide-Induced Shift of Compounds 8–10 (in $CDCl_3$)

Compd	Registry no.	Protons	H-1	H-2	H-3	H-5	H-6	H-10	5-Me	6-Me
8	85-02-9	*S* value	7.39	6.69	20.12	23.86	4.05	5.12		
		Ratio	0.31	0.28	0.84	1	0.17	0.21		
9	31486-01-8	*S* value	8.97		24.71	28.81		6.26		2.01
		Ratio	0.31		0.86	1		0.22		0.07
10	6237-04-3	*S* value	0.77		4.51		0.82	0.42	2.98	
		Ratio	0.17		1		0.18	0.09	0.66	

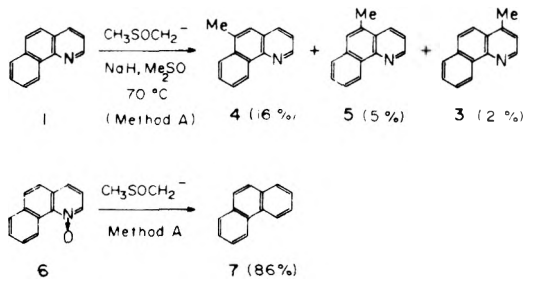
[a] *S* value = chemical shift (ppm) × [substrate]/[Eu(fod)$_3$].

Scheme I



R_1 = H, $HOCH_2CHOHCH_2OH$ 1, R_1 = H; R_2 = H (50%)
R_1 = H, $CH_3CH{=}CHCHO$ 2, R_1 = H; R_2 = 2-Me (36%)
R_1 = H, $CH_2{=}CHC(=O)CH_3$ 3, R_1 = H; R_2 = 4-Me (36%)
R_1 = Me, $HOCH_2CHOHCH_2OH$ 4, R_1 = Me; R_2 = H (15%)

Scheme II



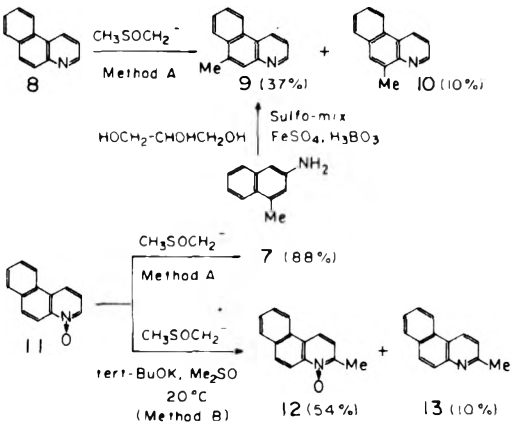
and NMR spectra. Details of these synthetic procedures are illustrated in Scheme I.

Reaction of **1** with methylsulfinyl carbanion was carried out in dimethyl sulfoxide at 70 °C for 4 h, by using sodium hydride as the base (method A), and three products were obtained: compound **4**, mp 55–57 °C; **5**, mp 54–56 °C; and **3**, mp 76–78 °C. The position of the methyl groups in these compounds was deduced from their NMR spectra, and **3** and **4** were identified by mixture melting point determination with authentic samples prepared from the Skraup reaction of 1-naphthylamine.

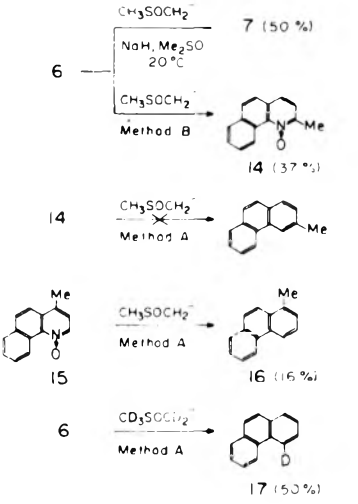
Application of methylsulfinyl carbanion to benzo[*h*]quinoline 1-oxide[12] (**6**) in dimethyl sulfoxide, by method A, gave phenanthrene (**7**) in 86% yield. Details of these reactions are illustrated Scheme II.

Kobayashi and others[3] have already carried out the reaction of benzo[*f*]quinoline and its *N*-oxide with methylsulfinyl carbanion, with sodium hydride at 20 °C for 2 h, and obtained the 5-methyl derivative from the parent compound and the 3-methyl derivative from its *N*-oxide. In order to compare benzo[*f*]quinoline (**8**) and this reaction with that of **1**, we carried out the reaction of **8** and methylsulfinyl carbanion by method A and obtained the 5-methyl compound **10** and the 6-methyl compound **9** in ca. 1:4 ratio. Compound **9** was identified by mixture melting point determination with authentic samples prepared from the Skraup reaction of 4-methyl-2-naphthylamine.[11] Compound **10** was deduced from the NMR spectra by the use of the shift reagent. The proton signals in the NMR spectrum of the 5 and 6 positions of **8** appear at around δ 7.9, there being almost no difference between them, but the addition of a shift reagent [Eu(fod)$_3$] results in lanthanide-induced shift and a difference appears between them.

Scheme III



Scheme IV



This relationship is expressed by the *S* value[13] in Table I, showing that the *S* value in **8** is greater in the proton at the 5 than at the 6 position. The *S* value of the 6 position in **10** is less than that of the 5 position in **9** and, therefore, **10** is presumed to be the 5-methylated compound.[4]

The reaction of benzo[*f*]quinoline 4-oxide[15] (**11**) with methylsulfinyl carbanion by method A gave phenanthrene in 88% yield.

The same reaction with methylsulfinyl carbanion, using potassium *tert*-butoxide as a base, at 20 °C for 4 h (method B), gave 3-methylbenzo[*f*]quinoline 4-oxide[3] (**12**), mp 123–125 °C, and a deoxygenated product, 3-methylbenzo[*f*]quinoline[16] (**13**), mp 81–82 °C. The structure of **12** and **13** was confirmed by the agreement of their melting point with those reported in literature[3,16] and from their NMR spectra. Details of these reactions are illustrated in Scheme III and their data are given in Table I.

Examination of the reaction conditions for the reaction of **6** and methylsulfinyl carbanion, as shown in Scheme IV, in-

dicated that an equal mole concentration of sodium hydride and a lower reaction temperature did not favor the formation of **7**. The use of potassium *tert*-butoxide of method B was found to inhibit liberation of the *N*-oxide group, and a product formed by methylation of the position ortho to the *N*-oxide group, 2-methylbenzo[*h*]quinoline 1-oxide (**14**), mp 128–129 °C, was obtained. This difference in reactivity of **1** and **6** with potassium *tert*-butoxide is explained by some kind of coordination of potassium ion to *N*-oxide, as reported by Kobayashi et al.[3] When the base is sodium hydride, the reaction proceeds to the formation of **7** by liberation of *N*-oxide from **6**, and we had already assumed and reported the process.[17]

An attempt to synthesize the starting **14**[18] by the N-oxidation of **2** gave the desired product in a very low yield of 5%. Therefore, **14** was prepared by the methylation of **6** with methylsulfinyl carbanion by method B. 4-Methylbenzo[*h*]quinoline 1-oxide (**15**), mp 126–128 °C, was obtained by oxygenation of **3** with hydrogen peroxide in acetic acid. Reaction of **14** with methylsulfinyl carbanion by method A ended in recovery (50%) of the starting material, but the reaction of **15** with methylsulfinyl carbanion by method A resulted in the liberation of the *N*-oxide group, and 1-methylphenanthrene (**16**), mp 120–122 °C, was obtained.

In order to prove that the carbon from methylsulfinyl carbanion was introduced into the position vacated by liberation of the *N*-oxide group, **6** was reacted with deuterated methylsulfinyl carbanion in deuteriodimethyl sulfoxide by method A, and the reaction was stopped by the addition of water. The product **17** of mp 99–101 °C thereby obtained corresponded to formula $C_{14}H_9D$ from its elemental analytical values and mass spectrum with *m/e* 179 (M^+). It is known that the NMR spectrum of **7** exhibits the signals of equivalent C-4 H and C-5 H in a lower magnetic field than those of C-1–3 H and C-6–10 H, and their integral ratio is 2:8. In comparison of the NMR spectra of **17** and **7**, the coupling of C-4 H and C-5 H of the low-field proton signal in **17** has been unchanged, but the high-field proton signal of C-1–3 or C-6–8 in **17** has been changed. The integral ratio in the NMR spectrum of **17** for (C-4 H or C-5 H):(C-1–3 H and C-6–10 H) was 1:8.09; that is to say, one proton in the low-field proton signal has disappeared. The foregoing results indicate that **17** was to be **7** deuterated at the 4 position. Details of these reaction schemes are summarized in Scheme IV.

Conclusion

The foregoing experimental results indicate that the nucleophilic activity of **1** is the 4, 5, and 6 position from the yield of methylated products. Comparison of the nucleophilic activity of **1** and quinoline or phenanthrene indicates that the effect of the phenanthrene ring seems to be stronger than that of the ring-nitrogen atom, because of the yield of the 5- and 6-methylated products which is phenanthrene's active position more than the 4-methylated product which is quinoline's active position. Compound **8** was not methylated in 1 position, possibly due to steric hindrance, and 5- and 6-methylated compounds were obtained, indicating the activity of the phenanthrene ring.

In the reaction of **6** or **11** and methylsulfinyl carbanion, the anion was found to add to the position ortho to the *N*-oxide group, then the carbon from dimethyl sulfoxide entered the position vacated by nitrogen, followed by cyclization, and the *N*-oxide group was liberated to form **7**. This reaction is now being examined with other heterocycles.

Experimental Section

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Proton NMR spectra were recorded using a PS-100 (Joel) spectrometer with tetramethylsilane as an internal standard. The IR spectra were taken on a IR-A-1 (Jasco) spectrometer. Mass spectra were obtained with a RMU-6 (Hitachi) spectrometer operating at an ionization potential of 70 eV.

Benzo[*h*]quinoline (1). To a chilled (5–10 °C), homogeneous mixture of 117 g of Sulfo-mix[6] [prepared from 96 g of $H_2SO_4 \cdot SO_3$ (20%) and 21 g of nitrogenzene], 1.4 g of $FeSO_4 \cdot 7H_2O$, 2.4 g of H_3BO_3, and 25 g of anhydrous glycerol were added, followed by 11.44 g (0.08 mol) of 1-naphthylamine and 40 mL of warmed water (50 °C). The mixture was vigorously stirred in an oil bath at 130 °C for 5 h and cooled in an ice bath, and the reaction mixture was neutralized with aqueous 20% NaOH. This solution was extracted with four 100-ml portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed with water, dried over $MgSO_4$, and evaporated to dryness. The solid residue was chromatographed on 100 g of alumina. The elution with C_6H_6 was recrystallized from petroleum ether to give colorless needles, mp 51–52 °C, 7.17 g (50%), of **1**, which was undepressed on admixture with an authentic sample, prepared by an earlier method,[7] and its IR spectrum was identical with that of an authentic sample.

Anal. Calcd for $C_{13}H_9N$: C, 87.12; H, 5.06; N, 7.82. Found: C, 87.41; H, 5.35; N, 7.48.

2-Methylbenzo[*h*]quinoline (2). To a solution of 58.5 g of Sulfo-mix, 1.4 g of $FeSO_4 \cdot 7H_2O$, 2.4 g of H_3BO_3, 25 mL of water, and 5.72 g (0.04 mol) of 1-naphthylamine, warmed to 110 °C, was added dropwise over 30 min 3.5 g (0.05 mol) of crotonaldehyde. The bath temperature was raised to 130 °C, and the reaction mixture was stirred for 5 h. The cooled solution was made basic with aqueous 20% NaOH and extracted with four 100-mL portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed with water, dried over $MgSO_4$, and evaporated to dryness. The brown liquid residue was chromatographed on 100 g of alumina. The elution with C_6H_6 was evaporated to give a yellow oil. Distillation gave 2.8 g (36%) of **2** as a pale-yellow liquid: bp 322–324 °C; picrate mp 224–226 °C (lit.[8a] bp 324–326 °C, picrate mp 226 °C); NMR ($CDCl_3$) δ 2.69 (s, 3, C-2 CH_3), 7.06 (d, 1, J = 8.4 Hz, C-3 H), 7.35–7.70 (m, 5, C-5 and C-9 aromatic H), 7.70 (d, 1, J = 8.4 Hz, C-4 H), 9.15 (m, 1, C-10 H); MS *m/e* 193 (M^+).

Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.23; H, 5.92; N, 7.06.

4-Methylbenzo[*h*]quinoline (3). The same procedure was used as for the preparation of **2**, except that 3.5 g (0.05 mol) of methyl vinyl ketone was substituted for the crotonaldehyde. Three crystallizations from cyclohexane gave colorless needles, mp 76–78 °C (lit.[9b] mp 77–78 °C), 2.8 g (36%), of **3**: NMR ($CDCl_3$) δ 2.58 (s, 3, C-4 CH_3), 7.12 (d, 1, J = 4.4 Hz, C-3 H), 7.47–7.83 (m, 5, C-5 and C-9 aromatic H), 8.64 (d, 1, J = 4.4 Hz, C-2 H), 9.14 (m, 1, C-10 H); MS *m/e* 192 (M^+).

Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.14; H, 5.65; N, 7.31.

6-Methylbenzo[*h*]quinoline (4). The same procedure was used as for the preparation of **1**, except that 0.63 g (0.004 mol) of 4-methyl-1-naphthylamine was substituted for the 1-naphthylamine. Three crystallizations from cyclohexane gave colorless plates, mp 55–57 °C, picrate mp 204–206 °C (lit.[11] mp 57 °C, picrate mp 206 °C), 0.12 g (15%), of **4**: NMR ($CDCl_3$) δ 2.68 (s, 3, C-6 CH_3), 7.24–7.97 (m, 5, C-5 and C-9 aromatic H), 7.33 (dd, 1, J = 8.0 Hz, C-3 H), 7.90 (dd, 1, J = 8.0 Hz, C-4 H), 8.75 (dd, 1, J = 4.4 Hz, C-2 H), 9.18 (m, 1, C-10 H); MS *m/e* 193 (M^+).

Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.37; H, 5.75; N, 7.18.

General Procedure of Methylsulfinyl Carbanion ($CH_3SOCH_2^-$). (A) Method A. The methylsulfinyl carbanion was prepared in a nitrogen atmosphere by dissolving sodium hydride in Me_2SO. The sodium hydride (50% mineral oil dispersion) was washed three times with absolute petroleum ether (bp 40–50 °C). The sodium hydride–Me_2SO mixture was stirred vigorously at 70 °C until the sodium hydride dissolved. The reaction mixture of methylsulfinyl carbanion was stirred for 4 h at 70 °C.

(B) Method B. The methylsulfinyl carbanion was prepared in a nitrogen atmosphere by dissolving potassium *tert*-butoxide in Me_2SO. The potassium *tert*-butoxide–Me_2SO mixture was stirred at 70 °C until the potassium *tert*-butoxide dissolved. The reaction mixture of methylsulfinyl carbanion was stirred for 4 h at 20 °C.

Reaction of 1 with Methylsulfinyl Carbanion (Method A). To a solution of 2.64 g (0.11 mol) of sodium hydride in 100 mL of Me_2SO at 70 °C was added 3.58 g (0.02 mol) of **1** in 100 mL of Me_2SO. The reaction mixture was stirred for 4 h at 70 °C under a nitrogen atmosphere followed by the addition of 100 mL of water. The reaction mixture was neutralized with aqueous 10% HCl which was extracted with four 100-mL portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed with three 100-mL portions of water, dried over $MgSO_4$, and evaporated to dryness. The brown liquid residue was chromatographed three times on 200 g of silica gel. Elution with cyclohexane–benzene (10:2) gave the three kinds of products. The first elution was

recrystallized from cyclohexane to give colorless plates, mp 55–57 °C, picrate mp 204–206 °C, 0.6 g (16%), of **4**: MS *m/e* 193 (M^+).

Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.33; H, 5.72; N, 7.31.

The second elution was recrystallized from cyclohexane to give colorless needles, mp 54–56 °C, 0.2 g (5%), of **5**: NMR ($CDCl_3$) δ 2.62 (s, 3, C-5 CH_3), 7.41 (dd, 1, J = 8.4 Hz, C-3 H), 7.50–8.02 (m, 5, C-5 and C-9 aromatic H), 8.18 (dd, 1, J = 8.4 Hz, C-4 H), 8.93 (dd, 1, J = 4.4 Hz, C-2 H), 9.30 (m, 1, C-10 H); MS *m/e* 193 (M^+).

Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.12; H, 5.73; N, 7.14.

The third elution was recrystallized from cyclohexane to give colorless needles, mp 76–78 °C, 0.066 g (2%), of **3**: MS *m/e* 193 (M^+).

Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.19; H, 5.54; N, 7.05.

The position of the methyl group in these compounds was presumed from their NMR spectra, **5** as 5-methylbenzo[*h*]quinoline and **3** and **4**, respectively, from no depression of the melting point on mixed fusion with authentic samples prepared from the Skraup reaction of 1-naphthylamine, and by comparison of their IR and NMR spectra.

Reaction of 6 with Methylsulfinyl Carbanion. (A) Method A. To a solution of 1.06 g (0.044 mol) of sodium hydride in 40 mL of Me_2SO at 70 °C was added 1.56 g (0.008 mol) of **6** in 40 mL of Me_2SO. The reaction mixture was stirred for 4 h at 70 °C under a nitrogen atmosphere followed by the addition of 40 mL of water. The reaction mixture was neutralized with aqueous 10% HCl which was extracted with four 100-mL portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed with three 100-mL portions of water, dried over $MgSO_4$, and evaporated to dryness. The residue was chromatographed on 100 g of silica gel. The eluate with cyclohexane was recrystallized from petroleum ether to give colorless plates, mp 98–100 °C, 1.22 g (86%), of **8**, which was undepressed on admixture with commercial phenanthrene,[19] and its IR and NMR spectra were identical with that of phenanthrene: MS *m/e* 178 (M^+).

Anal. Calcd for $C_{14}H_{10}$: C, 94.34; H, 5.66. Found: C, 94.56; H, 5.53.

(B) The same procedure was used as for the preparation by method A, except that reaction temperature was 20 °C. **7** was prepared in 50% yield.

(C) Method B. A solution of 1.6 g (0.0143 mol) of potassium *tert*-butoxide dissolved in 25 mL of Me_2SO at 70 °C under a nitrogen atmosphere was cooled to 20 °C, and 0.5 g (0.0026 mol) of **6** was added in 25 mL of Me_2SO. The reaction mixture was stirred for 4 h at 70 °C under a nitrogen atmosphere followed by the addition 50 mL of water. The reaction mixture was neutralized with aqueous 10% HCl which was extracted with four 100-mL portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed with three 100-mL portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed with three 100-mL portions of water, dried over $MgSO_4$, and evaporated to dryness. The residue was chromatographed on 100 g of sillica gel. The elution with $CHCl_3$ was recrystallized from C_6H_6 to give colorless needles, mp 68–70 °C, 0.2 g (37%), of **14**, which was undepressed on admixture with 2-methylbenzo[*h*]quinoline 1-oxide,[18] prepared by N-oxidation of **2**, and its IR spectrum was identical with that of an authentic sample: NMR ($CDCl_3$) δ 2.72 (s, 3, C-2 CH_3), 7.27 (d, 1, J = 8.4 Hz, C-3 H), 7.45–8.03 (m, 5, C-5 and C-9 aromatic H), 7.70 (d, 1, J = 8.4 Hz, C-4 H), 10.75 (m, 1, C-10 H); MS *m/e* 209 (M^+), 193 ($M^+ - 0$).

Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.55; H, 5.17; N, 6.31.

4-Methylbenzo[*h*]quinoline 1-Oxide (15). To a solution of 3.5 mL of acetic acid and 2.5 g of **3**, 0.7 mL of 30% H_2O_2 was added, the reaction mixture was stirred for 3 h at 110 °C and poured into 10 mL of water, and powdered MnO_2 was added. After decomposition of H_2O_2, the MnO_2 was filtered off and the filtrate was neutralized with aqueous 10% K_2CO_3, which was extracted with four 100-mL portions of $CHCl_3$. The combined $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed on 100 g of sillica gel and eluted with C_6H_6. The first elution gave 0.3 g of starting material. The second elution was recrystallized from C_6H_6 to give colorless needles, mp 142–144 °C, 0.2 g (8%), of **15**: NMR ($CDCl_3$) δ 2.51 (s, 3, C-4 CH_3), 6.97 (d, 1, J = 6.4 Hz, C-3 H), 7.50–7.80 (m, 5, C-5 and C-9 aromatic H), 8.33 (d, 1, J = 6.4 Hz, C-2 H), 10.75 (m, 1, C-10 H); MS *m/e* 209 (M^+), 193 ($M^+ - 0$).

Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.47; H, 5.52; N, 6.58.

Reaction of 15 with Methylsulfinyl Carbanion (Method A). The same procedure was used as for the reaction of **6** with methylsulfinyl carbanion, except that 0.84 g (0.0043 mol) of **15** was substituted for **6**. The elution with cyclohexane was recyrstallized from petroleum ether to give colorelss plates, mp 120–122 °C, picrate mp 135–136 °C, 0.13 g (16%), of **16**, which was presumed from its melting point (lit.[20] mp 118 °C; picrate mp 135–136 °C) and NMR spectra to be 1-methylphenanthrene: NMR ($CDCl_3$) δ 2.64 (s, 3, C-1 CH_3), 7.20–7.85 (m, 7, C-2,3 and C-6 and C-10 aromatic H), 8.33–8.64 (m, 2, C-4 and C-5 aromatic H); MS *m/e* 192 (M^+).

Anal. Calcd for $C_{15}H_{12}$: C, 93.71; H, 6.29. Found: C, 94.10; H, 6.12.

Reaction of 6 with Deuterated Methylsulfinyl Carbanion. The same procedure was used as for the preparation by method A, except that use of 0.2 g (0.001 mol) of **6** and Me_2SO-d_6 was substituted for the Me_2SO. The elution with cyclohexane was recrystallized from petroleum ether to give colorless plates, mp 99–101 °C, 0.09 g (50%), of **17**, which was presumed from its NMR spectrum as 4-deuteriophenanthrene: NMR ($CDCl_3$) δ 7.40–7.80 (m, 8, C-1 and C-3 and C-6 and C-10 aromatic H), 8.50 (m, 1, C-5 H); MS *m/e* (rel intensity) 180 ($M^+ + 1$, 24), 179 (M^+, 100), 178 (12), 177 (17).

Anal. Calcd for $C_{14}H_9D$: C, 93.81; H, 5.63. Found: C, 93.83; H, 5.60.

Reaction of 8 with Methylsulfinyl Carbanion (Method A). The same procedure was used as for the reaction of **1** with methylsulfinyl carbanion by method A, except that 3.4 g (0.019 mol) of **8** was substituted for **1**. The first elution was recrystallized from cyclohexane to give colorless needles, mp 81–83 °C, 0.35 g (10%), of **10**, which was presumed from its NMR spectra as 5-methylbenzo[*f*]quinoline. This melting point differs from that reported by Loader[21] (mp 100–101 °C): NMR ($CDCl_3$) δ 2.83 (s, 3, C-5 CH_3), 7.48 (dd, 1, J = 8.4 Hz, C-2 H), 7.52–7.87 (m, 3, C-7 and C-9 aromatic H), 7.77 (s, 1, C-6 H), 8.48 (m, 1, C-10 H), 8.83 (dd, 1, J = 8.4 Hz, C-1 H), 9.00 (dd, 1, J = 4.4 Hz, C-3 H); MS *m/e* 193 (M^+).

Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 86.84; H, 5.96; N, 7.02.

The second elution was recrystallized from cyclohexane to give colorless needles, mp 77–79 °C, 1.34 g (37%), of **9**, which was undepressed on admixture with 6-methylbenzo[*f*]quinoline prepared from the Skraup reaction of 4-methyl-2-naphthylamine and identified by comparison its IR and NMR spectra: NMR ($CHCl_3$) δ 2.65 (s, 3, C-6 CH_3), 7.34 (dd, 1, J = 8.4 Hz, C-2 H), 7.80 (s, 1, C-5 H), 8.03–8.52 (m, 3, C-7 and C-9 aromatic H), 8.43 (m, 1, C-10 H), 8.65 (dd, 1, J = 8.4 Hz, C-3 H); MS *m/e* 193 (M^+).

Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 86.88; H, 5.84; N, 7.10.

6-Methylbenzo[*f*]quinoline (9). The same procedure was used as for the preparation of **1**, except that 0.2 g (0.001 mol) of 4-methyl-2-naphthylamine was substituted for the 1-naphthylamine. Three crystallizations from cyclohexane gave colorless needles, mp 77–79 °C, 0.13 g (53%), of **9**: MS *m/e* 193 (M^+).

Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.78; H, 5.95; N, 7.06.

Reaction of 11 with Methylsulfinyl Carbanion. (A) Method A. The same procedure was used as for the reaction of **6** with methylsulfinyl carbanion by method A, except that 2.1 g (0.011 mol) of **11** was substituted for **6**. The elution was recrystallized from petroleum ether to give colorless plates, mp 98–100 °C, 1.72 g (88%), of **7**, which was undepressed on admixture with commercial phenanthrene,[19] and its IR and NMR spectra were identical with that of phenanthrene: MS *m/e* 178 (M^+).

Anal. Calcd for $C_{14}H_{10}$: C, 94.34; H, 5.66. Found: C, 94.14; H, 5.80.

(B) Method B. The same procedure was used as for the reaction of **6** with methylsulfinyl carbanion by method B, except that 1.1 g (0.0055 mol) of **11** was substituted for **6**. The first elution with C_6H_6 was recrystallized from cyclohexane to give colorless needles, mp 80–82 °C, 0.1 g (10%), of **13**, which was presumed from its melting point (lit.[21] mp 81–82 °C) and NMR spectra to be 3-methylbenzo[*f*]-quinoline: NMR ($CDCl_3$) δ 2.68 (s, 3, C-3 CH_3), 7.18 (d, 1, J = 8.4 Hz, C-2 H), 7.47–8.00 (m, 3, C-7 and C-9 aromatic H), 7.86 (s, 1, C-6 H), 7.88 (s, 1, C-5 H), 8.35 (m, 1, C-10 H), 8.55 (d, 1, J = 8.4 Hz, C-1 H); MS *m/e* 193 (M^+).

Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.18; H, 5.64; N, 7.40.

The second elution with $CHCl_3$–C_6H_6 (8:2) was recrystallized from cyclohexane to give pale yellow needles, mp 128–129 °C, 0.55 g (54%), of **12**, which was undepressed on admixture with 3-methylbenzo[*f*]-quinoline 4-oxide,[22] prepared by earlier method, and its IR spectrum was identical with that of an authentic sample: NMR ($CDCl_3$) δ 2.76 (s, 3, C-3 CH_3), 7.47 (d, 1, J = 9.0 Hz, C-2 H), 7.66–8.03 (m, 3, C-7 and C-9 aromatic H), 8.05 (d, 1, J = 9.4 Hz, C-6 H), 8.40 (d, 1, J = 9.0 Hz, C-1 H), 8.57 (m, 1, C-10 H), 8.82 (d, 1, J = 9.4 Hz, C-5 H); MS *m/e* 209 (M^+), 193 ($M^+ - 0$).

Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: c, 80.62; H, 5.24; N, 6.40.

Acknowledgments. The authors are grateful to Professor Minoru Hirota, Yokohama National University, for his NMR spectral data of the lantanide-induced shift and to the staff of the Analysis Center of this University for elemental analyses.

Registry No.—**1**, 230-27-3; **2**, 605-88-9; **2** picrate, 63783-90-4; **3**, 40174-37-6; **4**, 31485-96-8; **4** picrate, 63783-91-5; **5**, 59181-25-8; **6**, 17104-70-0; **7**, 85-01-8; **11**, 17104-69-7; **12**, 50697-49-9; **13**, 85-06-3; **14**, 3900-23-0; **15**, 59181-26-9; **16**, 832-69-9; **16** picrate, 63783-92-6; **17**, 62163-01-3; glycerol, 56-81-5; 1-naphthylamine, 134-32-7; crotonaldehyde, 4170-30-3; methyl vinyl ketone, 78-94-4; 4-methyl-1-naphthylamine, 4523-45-9; methylsulfinyl carbanion, 13810-16-7; dimethyl sulfoxide, 67-68-5; 4-methyl-2-naphthylamine, 4523-46-0.

References and Notes

(1) Part 25 of this series: Y. Hamada and I. Takeuchi, *Chem. Pharm. Bull.*, **24**, 2769 (1976).
(2) G. A. Russell and S. A. Weiner, *J. Org. Chem.*, **31**, 248 (1966).
(3) Y. Kobayashi, I. Kumadaki, H. Sato, C. Yokoo, and T. Mimura, *Chem. Pharm. Bull.*, **21**, 2066 (1973).
(4) (a) Y. Hamada, I. Takeuchi, and M.Hirota, *Chem. Pharm. Bull.*, **19**, 1751 (1971); (b) I. Takeuchi and Y. Hamada, *ibid.*, **24**, 1813 (1976).
(5) (a) Y. Hamada and I. Takeuchi, *Chem. Pharm. Bull.*, **19**, 1857 (1971); (b) Y. Hamada, I. Takeuchi, and M. Hirota, *ibid.*, **22**, 485 (1974); (c) Y. Hamada, I. Takeuchi, and M. Sato, *Yakugaku Zasshi*, **94**, 1328 (1974); (d) Y. Hamada, M. Sato, and I. Takeuchi, *ibid.*, **95**, 1492 (1975).
(6) W. P. Utermohlen, Jr., *J. Org. Chem.*, **8**, 544 (1943).
(7) A. Purenas and J. Zdanavičius, *Resp. Chem. Konf., [Pranesimai], 1st, 1958*, 175 (1959).
(8) (a) O. Doebner and W. v. Miller, *Chem. Ber.*, **17**, 1698 (1884); (b) N. S. Kozlov, *Zh. Obshch. Khim.*, **8**, 419 (1938).
(9) (a) I. Vavrečka, *Collect. Czech. Chem. Commun.*, **14**, 399 (1949); (b) R. J. Gobeil and C. S. Hamilton, *J. Am. Chem. Soc.*, **67**, 511 (1945).
(10) Buu-Hoi and D. Guettier, *C. R. Hebd. Seances Acad. Sci.*, **222**, 665 (1946).
(11) M. G. Barclay, A. Burawoy, and G. H. Thomson, *J. Chem. Soc.*, 109 (1944).
(12) I. Iwai, *Yakugaku Zasshi*, **71**, 1288 (1951).
(13) A. F. Cockerill and D. M. Rackham, *Tetrahedron Lett.*, 5149, 5153 (1970).
(14) A. Fisher, G. J. Sutherland, and R. D. Topson, *J. Chem. Soc.*, 5948 (1965).
(15) E. Ochiai and S. Tamura, *Yakugaku Zasshi*, **72**, 985 (1952).
(16) W. Mathes and W. Sauermilch, *Chem. Ber.*, **89**, 1183 (1956).
(17) Y. Hamada, I. Takeuchi, and M. Hirota, *Tetrahedron Lett.*, 495 (1974).
(18) N. N. Zatsepina, I. F. Tupitsyn, and L. S. Efros., *Zh. Obshch. Khim.*, **34**, 4072 (1964).
(19) Phenanthrene of Yoneyama Chemical Industries, Ltd., Osaka, Japan.
(20) R. D. Haworth, *J. Chem. Soc.*, 1125 (1932).
(21) C. E. Loador and C. J. Timmons, *J. Chem. Soc. C*, 1078 (1966).
(22) P. Mamalis and V. Petrow, *J. Chem. Soc.*, 703 (1950).

Synthesis with 1,2-Oxazines. 3.[1] Reactions of α-Chloro Aldonitrones with Enol Ethers: a Synthetic Route to Medium-Ring Lactones

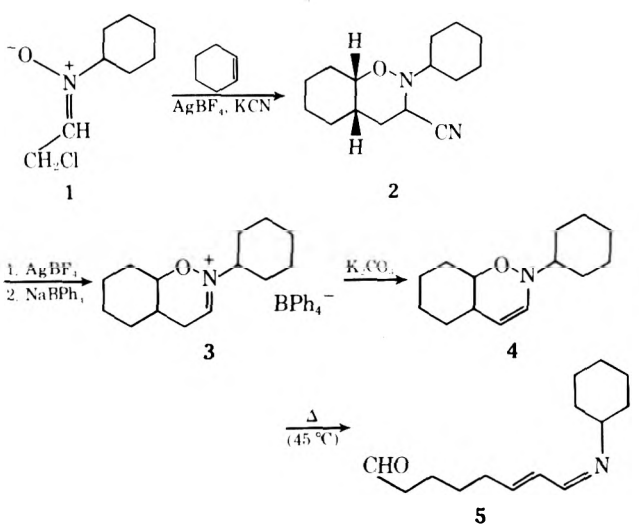
Eitan Shalom, Jean-Louis Zenou, and Shimon Shatzmiller*

Department of Chemistry, Tel-Aviv University, Tel Aviv, Israel

Received March 21, 1977

Cyclic enol ethers can undergo a Ag^+-induced cycloaddition with α-chloro nitrones. The corresponding polycyclic adducts were converted to enamoid structures of type **17b** via the immonium tetraphenylborate salts. The existence of an intramolecular ketal and the *N*-alkyl-5,6-dihydro-2*H*-1,2-oxazine ring as moieties in **17b** and **21a–c** allowed a thermolysis to the 10–12-membered lactones through cleavage of a central C–C bond in the polycyclic system. Structural effects on the thermolysis have been noted.

The usefulness of 1,4 dipolar cycloaddition for the construction of heterocyclic systems using positively charged heterodienes has been noted by some research groups.[2,3] α-Chloro nitrones were introduced by Eschenmoser as a new class of potent reagents of broad synthetic capability.[4–9] One major synthetic application of α-chloro nitrone chemistry was a new general way to construct the *N*-alkyl-5,6-dihydro-4*H*-oxazinium ion **3** in a Ag^+-induced cycloaddition reaction with isolated olefinic double bonds.[4] Imminium salts like **3** lead to a "carboxolytic" bond cleavage, occurring as a result of a retro-Diels–Alder reaction of the deprotonated enamoid derivative **4**, and end with the open-chain aldehyde **5**.



The object of this work was to examine if an analogous series of reactions could be applied to simple bicyclic enol ether **6** and **10a–c** (Scheme I). These were chosen as models for a possible synthesis of medium- and large-ring lactones in the α-chloro nitrone method. This involved (a) determining the generality of the cycloaddition reaction with enol ethers, (b) looking for "side" reactions and examining their influence on the cycloaddition, and (c) checking whether the carboxolytic bond cleavage procedure could also be applied in this case.

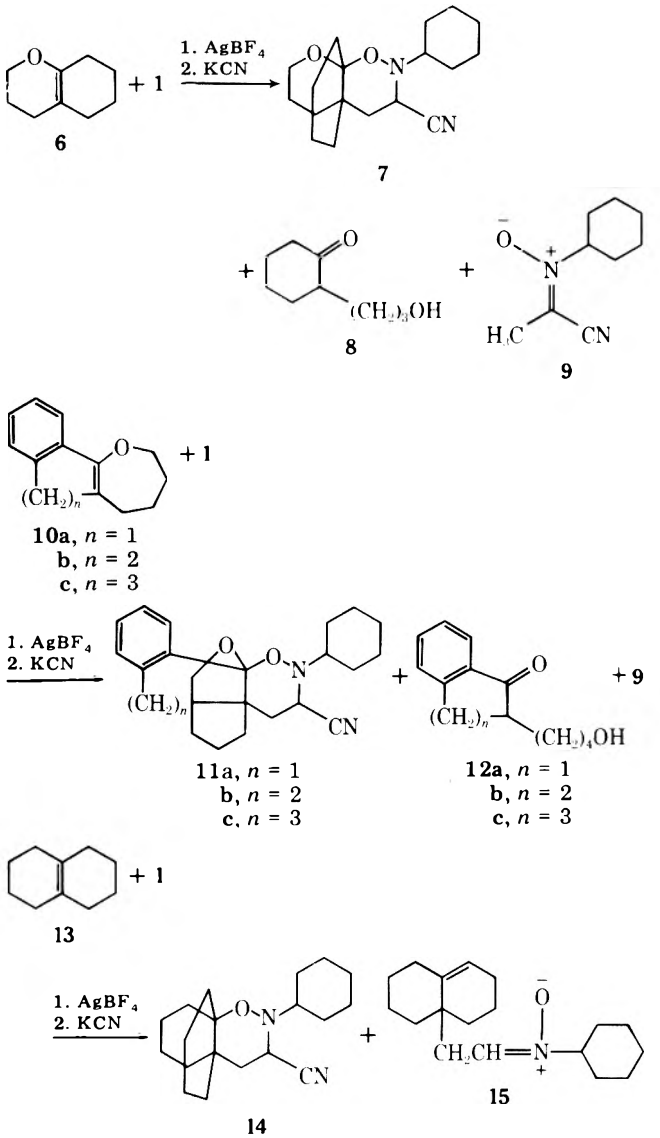
Starting enol ethers were prepared according to Obara (compound **6**)[10] and Immer (compounds **10a–c**).[11] Work on enol ethers was carried out in parallel with similar experiments on octalin (**13**) for possible special behavior in propellanes.[12] The reaction products obtained as a result of reaction with α-chloro nitrone **1** and the olefin were analyzed quantitatively and isolated by column chromatography. Results and yields are given in Table I.

The reaction products from enol ethers were mixtures of three main components: (1) cycloaddition products, (2) hydroxy ketones, and (3) a by-product having the structure **9**. Cycloaddition products were propellanes **7** and **11a–c**. It was

Table I. Products and Yields in the Ag^+-Induced Reaction of 1 with Enol Ethers

Registry no.	Enol ether (equiv)	1, equiv	Cycloaddition product (equiv)	Keto alcohol (equiv)	9, equiv	Enol ether recovered, equiv: From reaction	Enol ether recovered, equiv: Recycled keto alcohol	Net yield of cycloaddition based on enol ether consumed, %
7106-07-2	**6** (2.72)	1.0	**7** (0.26)	8 (0.30)	0.02	1.12	0.28	26
63689-21-4	**10a** (1.20)	1.0	**11a** (0.19)	**11a** (0.52)	0.21	0.02	0.42	25
16425-91-5	**10b** (1.0)	1.02	**11b** (0.14)	**12b** (0.77)	0.22	0.01	0.52	29
	10b (1.0)	1.58	**11b** (0.21)	**12b** (0.68)	0.08		0.50	42
63689-22-5	**10c** (1.16)	1.0	**11c** (0.11)	**12c** (0.86)	0.20	0.30	0.69	64

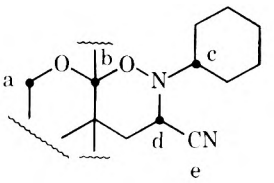
Scheme I



assumed that these CN^- addition products are a quantitative representation of the actual cycloaddition products, taking into account a very efficient CN^- addition reaction.[4] It was clear at that stage that cycloaddition to enol ethers **6** and **10a–c** is *regioselective*. However, the *direction* of α-chloro nitrone addition had to be determined. Structure assignment and proof for the existence of an intramolecular ketal in compounds **7** and **11a–c** were done mainly by ^{13}C NMR spectroscopy (see Table II). Signals at 101.7, 112.5, 103.8 and 108.4 ppm (remain as singlets in the "off-resonance" technique) gave proof for the structures in Scheme II, although these compounds were resistant to dilute HCl.[13]

The hydroxy ketones **8** and **12a–c** could be recycled to increase the yields of cycloaddition products. They could result from a relatively stable oxonium intermediate formed during the reaction to give the hydroxy ketones under the hydrolytic conditions present in the workup of the reaction.

Table II. ^{13}C NMR Signals in Cycloadducts 7 and 11a–c[a]



e

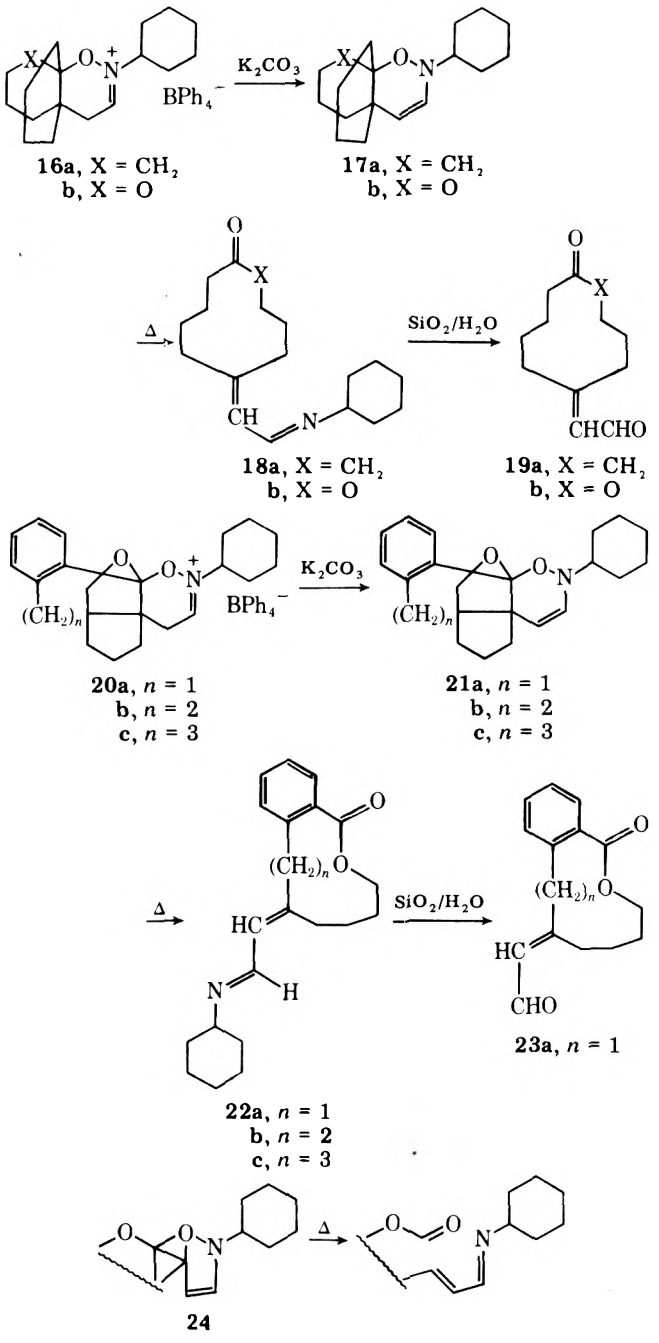
Registry no.	Cycloadduct	^{13}C resonance (ppm): a	b	c	d	e
63689-23-6	**7**	61.9	101.7	47.7	61.2	118.4
63714-00-1	**11a**	65.2	112.5	47.8	61.1	118.4
63689-24-7	**11b**	64.9	103.8	48.0	61.9	118.2
63689-25-8	**11c**	66.3	108.4	48.7	62.5	118.6

[a] In $CDCl_3$. Compare Scheme II.

Nitrone **9** was isolated also in the reaction with **13** and other olefins and was presumably overlooked in previous work. Its yield varies, however, and the mechanism by which it is formed is still obscure.

After achieving the first objectives—construction of propellanes **14**,[12] **7**, and **11a–c**—we came to the last aspect of this work: synthesis and thermal cycloreversion of enamines **17a,b** and **21a–c** applying reaction conditions already worked out by Eschenmoser et al.[5] to the solid tetraphenylborate immonium salts **16a,b** and **20a–c**, respectively. On treating these salts with solid K_2CO_3 in dichloromethane at 0 °C, deprotonation to the corresponding enamines took place. Differences in thermal stability of the enamines were observed as follows: compounds **17b** and **21a** were extremely unstable and could not be isolated even in solution at 0 °C. Instead, they were converted in good (76 and 81% overall) yields to the ten-membered lactones **18b** and **22a**, respectively. It was possible to trap **20b** at 0 °C and to take the IR and ^1H NMR spectra and determine thereby its structure. However, rapid decomposition ($t_{1/2}$ at 45 °C ~ 10 min) gave the corresponding lactone **22b** in 82% yield. **20c** was converted at **21c** in 78% yield. This material was far more stable ($t_{1/2}$ at 80 °C ~ 1.5 h) than the analogous compounds **21a** and **21b** and decomposed to the 12-membered lactone **22c** in only 56% yield. In comparison, the carbocyclic analogue **16a** gave an extraordinarily stable enamine **17a** in 87% yield. This was stable enough to allow recrystallization (mp 128–135 °C dec), making this material one of the most unusual members of the *N*-alkyl-6,6-dihydro-2*H*-1,2-oxazine series. Fortunately, this material still underwent thermolysis to the ten-membered ketone in 35% ($t_{1/2}$ at 80 °C ~ 3.5 h) yield. The differences in stability are evidently dependent on ring size (compare **21a** and **21c**) and the presence of the oxygen ring B as a part of the internal ketal. Comparison of **17a** and **17b** brought us to consider a possible anomeric effect leading to a higher energy content of the fragmenting system[14] **24** which is released by cleaving the long and relatively weak neopentyl bond. The effect re-

Scheme II



sulting from lone-pair interactions existing in **17a** and **21a–c** does not exist in **17b**. Steric hindrance in achieving a suitable conformation for cycloreversion was considered here as a possible reason for a thermal stability of **17a**. Different conformations of the cycloreverting intermediates can explain the appearance of 1:1 *E*/*Z* aldimines in **18b** and **22a–c**.[5] The aldimines were converted to the unsaturated aldehydo lactones in 76% (**18b** → **19b**) and 65% (**22a** → **23**) yield using the SiO_2/H_2O hydrolysis used previously.[5] Similarly, **18a** was converted to **19a** in 70% yield.

Enol ethers are very susceptible to cleavage under the reaction conditions and yield cycloaddition in low yields (18–25%). The resulting intramolecular ketals formed in the cycloaddition reaction serve as good models for a synthesis of medium- and large-ring lactones. The cleavage of the central bond in a polycyclic system, having an internal ketal and the *N*-alkyl-5,6-dihydro-2*H*-1,2-oxazine ring as moieties, allow such a thermolytic process. In this process, formation of the lactone ring and lactone carbonyl grouping is achieved simultaneously using as a tool the special properties of the 1,2-oxazine derivative. It looks, however, as if electronegative atoms could cause difficulties in the α-chloro nitrone cycloaddition to double bonds. Ring size was added to the list of steric effects governing the delicate cycloreversion process.[2] The anomeric effect resulting from the oxygen function on C-6 in **17a** and **21a–c** is still under investigation.

Experimental Section[15]

Ag^+-Induced Reaction of *N*-Cyclohexyl-2-chloroacetaldehyde Nitrone 1 with Enol Ethers. A solution of the α-chloro nitrone **1** in dry 1,2-dichloroethane (20 mL) was added under dry nitrogen with stirring to a solution of $AgBF_4$ in dry 1,2-dichloroethane (40 mL) and the enol ether at 0 °C during 2 h. After an additional 1 h at 0 °C, the mixture was shaken with 5 g of KCN in 20 mL of water during 5 min. The aqueous solution was then extracted twice with dichloromethane, and the combined organic layers were dried over Na_2SO_4. The residue obtained after removal of the solvents in vacuo was chromatographed over Al_2O_3[16] (using ligroine–benzene mixtures).

Products were obtained after reactions involving the following compounds.

(1) 3,4,5,6,7,8-Hexahydrobenzopyran (6)[10]. The enol ether **6** (1.5 g, 10.85 mmol), $AgBF_4$ (700 mg, 3.60 mmol), and **1** (700 mg, 3.98 mmol) gave 1.2 g of crude product. After chromatography, the following were obtained. (a) Propellane **7** (316 mg, 1.04 mmol): mp 138 °C (from hexane); 28% yield; IR 2225 and 1180 cm^{-1}; ^1H NMR δ 0.9–2.0 and 2.0–3.0 (two m, 25 H), 3.5–4.2 (m, 2 H); MS *m/e* (304.435) 304 (12%), 148 (100%), 136 (12%). Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 70.72; H, 9.25; N, 9.36. (b) **9** (47 mg) obtained from the mother liquor of **7** (0.28 mmol, 7.86%): mp 113–114 °C; IR 2210 and 1530 cm^{-1}; UV λ_{max} 254 nm (ε 9500); ^1H NMR 1.9 (m, 10 H), 2.12 (s, 3 H), and 4.75 (m, 1 H); MS *m/e* (166.223) 166 (3%). Anal. Calcd for $C_9H_{14}N_2O$: C, 65.00; H, 8.71; N, 16.51. (c) Hydroxy ketone **8** (190 mg, 1.2 mmol). This was recycled to give 152 mg of **6**.

(2) 2,3,4,5,6-Pentahydroindano[1,2-*b*]oxepin (10a).[11] The enol ether **10a** (2.3 g, 12.35 mmol), α-chloro nitrone (1.8 g, 10.24 mmol), and $AgBF_4$ (2.0 g, 10.27 mmol) gave 4.0 g of crude product. After chromatography the following were obtained. (a) Starting ether **10a** (50 mg, 0.27 mmol). (b) Cycloaddition product **11a** (703 mg): mp 112 °C (from hexane); 19.35% yield; IR 3080, 3040, 2240, 1620 and 1100 cm^{-1}; ^1H NMR δ 0.9–3.0 (m, 21 H), 3.7–4.5 (m, 3 H), and 7.0–7.5 (m, 4 H); MS *m/e* (352.431) 352 (9%), 186 (100%). Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.71; H, 7.97; N, 7.95. (c) **9** (410 mg, 2.27 mmol), mp 113 °C, obtained from the mother liquor of **10a**. (d) Keto alcohol **12a** (1.09 g, 5.3 mmol). This was recycled to give 0.84 g of **10a**.

(3) 2,3,4,5,6,7-Hexahydronaphth[1,2-*b*]oxepin (10b).[11] The enol ether (4.0 g, 19.97 mmol), α-chloro nitrone (3.6 g, 20.49 mmol), and $AgBF_4$ (3.40 g, 20.55 mmol) gave 7.3 g of crude product. After chromatography the following were obtained. (a) Starting ether **10b** (50 mg). (b) Propellane **11b** (1 g, 2.720 mmol): mp 141 °C; 13.62% yield; IR 2240, 1600 and 1080 cm^{-1}; ^1H NMR δ 0.9–1.9 (m, 18 H), 2.80 (d, *J* = 2 Hz, 4 H), 2.6–2.8 (m, 4 H), 3.90 (t, *J* = 2 Hz, 1 H), 4.20 (t, *J* = 5 Hz, 2 H), and 7.30–7.60 (m, 4 H). Anal. Calcd for $C_{23}H_{30}N_2O_2$: C, 75.37; N, 7.64. (c) **9** (100 mg), mp 113 °C, obtained from the mother liquor of the **11b** cycloaddition product (22.01% yield). (d) Keto alcohol **12b** (2.7 g, 12.37 mmol). This was recycled to give 2.1 g of **10b**.

(4) 2,3,4,5,6,7,8-Heptahydrobenzo[6,7]cyclohept[1,2-*b*]oxepin (10c).[11] The enol ether **10c** (5.4 g, 25.19 mmol), chloro nitrone (3.7 g, 20.06 mmol), and $AgBF_4$ (4.0 g, 20.54 mmol) gave 8.5 g of crude product. After chromatography the following were obtained. (a) Starting enol ether **10c** (1.4 g). (b) Cycloaddition product **11c** (980 mg): mp 161–162 °C (from hexane–dichloromethane); 11.86% yield; IR (KBr) 2230 and 1070 cm^{-1}; ^1H NMR δ 0.9–3.5 (m, 23 H), 4.0–4.5 (m, 2 H), 4.8 (t, *J* = 7 Hz, 1 H), and 7.0–7.8 (m, 4 H); MS *m/e* (380.533) 380 (18%), 353 (18%), 214 (100%). Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 75.53; H, 8.34; N, 6.98. (c) **9** (750 mg), mp 112–113 °C, isolated from the mother liquor of **11c** (4.51 mmol, 20.83% yield from **1**). (d) Hydroxy ketone **12c** (3.7 g, 18.7 mmol). This was recycled to give 3.2 g of starting ether **10c**.

(5) 1,2,3,4,5,6,7,8-Octahydronaphthalene (13).[12] The olefin (500 mg, 3.67 mmol), α-chloro nitrone (800 mg, 4.5 mmol), and $AgBF_4$ (800 mg) gave 1.2 g of crude product. After chromatography the following were obtained: (a) Propellane **14** (475 mg, 1.58 mmol; 43% yield): mp 93–94 °C (lit.[12] 95–96 °C); from dichloromethane–hexane. (b) **9** (20 mg), mp 111–113 °C isolated from the mother liquor. (c) Nitrone **15** (200 mg, 0.98 mmol; 26% yield): mp 137 °C; IR 1600 and 1530 cm^{-1}; ^1H NMR δ 1.0–2.8 (m, 24 H), 2.6 (d, *J* = 6 Hz, 2 H), 3.5 (m, 1 H), 5.38 (m, 1 H), and 6.46 (t, *J* = 6 Hz, 1 H); MS *m/e* (275.436) 275 (4%). Anal. Calcd for $C_{18}H_{29}NO$: C, 78.90; H, 11.61; N, 5.08.

Preparation of the Imminium Tetraphenylborate Salts. Note: All operations were carried out under dry nitrogen. A solution of 1 mmol of nitrile in 1,2-dichloromethane (15 mL) was added dropwise with stirring to a solution of $AgBF_4$ (1.08 mmol) in 1,2-dichloroethane (30 mL) at room temperature during 5 min. After an additional 15 min at room temperature, the mixture was filtered to a solution of 2.5 g of $NaBPh_4$ in 20 mL of water. After shaking for 20 min, the resulting emulsion was filtered. The aqueous layer was extracted with dichloromethane, and the combined organic layers were dried (Na_2SO_4). Removal of the solvents in vacuo left a residue which was treated with ether and solidified. This was crystallized from ether–dichloromethane. The following were thus obtained.

(1) *N*-Cyclohexyl-7-oxa-8-ammonium[4.4.4]propell-8-ene Tetraphenylborate (16a): from **14** in 93% yield; mp 135–157 °C (dec); IR 1660 and 1590 cm^{-1}; ^1H NMR δ 0.9–2.0 (m, 26 H), 3.0 (m, 1 H), 3.8 (s, 1 H), 5.12 (t, J = 2 Hz, 1 H), 6.8–7.8 (m, 20 H). Anal. Calcd for $C_{42}H_{50}NOB$: C, 84.68; H, 8.46; N, 2.35.

(2) *N*-Cyclohexyl-7,11-dioxa-12-ammonium[4.4.4]propell-12-ene Tetraphenylborate (16b): from **7** in 97% yield; mp 141–163 °C (dec); IR 1665 cm^{-1}; ^1H NMR δ 0.9–2.0 (m, 22 H), 3.2 (m, 1 H), 5.05 (t, 1 H), and 6.9–8.0 (m, 20 H). Anal. Calcd for $C_{41}H_{48}NO_2B$: C, 82.40; H, 8.03; N, 2.34.

(3) *N*-Cyclohexyl-2,3-benz-6,11-dioxa-12-ammonium[5.4.3]-propellene Tetraphenylborate (20a): from **11a** in 97% yield; mp 138–162 °C (dec); IR 1643 and 1600 cm^{-1}; ^1H NMR δ 0.9–2.3 (m, 17 H), 2.8 (m, 2 H), 3.4 (m, 4 H), 5.25 (t, 1 H), 7.2–7.8 (m, 24 H). Anal. Calcd for $C_{45}H_{48}NO_2B$: C, 83.39; H, 7.63; N, 2.21.

(4) *N*-Cyclohexyl-2,3-benz-7,12-dioxa-13-ammonium[5.4.4]-propell-13-ene Tetraphenylborate (20b): from **11b** in 92% yield; mp 145–170 °C (dec); IR 1670 and 1600 cm^{-1}; ^1H NMR δ 0.9–2.0 (m, 20 H), 3.0 (m, 3 H), 3.75 (m, 2 H), 5.30 (t, J = 1 Hz, 1 H), 6.7–7.8 (m, 24 H). Anal. Calcd for $C_{46}H_{50}NO_2B$: C, 83.45; H, 7.78; N, 2.16.

(5) *N*-Cyclohexyl-2,3-benz-8,13-dioxa-14-ammonium[5.5.4]-propell-14-ene Tetraphenylborate (20c): from **11c** in 81% yield; mp 143–182 °C (dec); IR 1665 and 1600 cm^{-1}; ^1H NMR δ 0.9–2.0 (m, 22 H), 2.5–2.8 (m, 3 H), 3.6 (m, 2 H), 6.4 (m, 1 H), 6.8–7.5 (m, 24 H). Anal. Calcd for $C_{47}H_{52}NO_2B$: C, 83.49; H, 7.92; N, 2.11.

Deprotonation of the Tetraphenylborate Salts. The tetraphenylborate imminium salt (1 mmol) was dissolved in dichloromethane (20 mL) and stirred vigorously under nitrogen with K_2CO_3 (Merck analyzed, powdered) at 0 °C during 1 h. After removal of the solvent, in vacuo at 0 °C, the following were obtained.

(1) *N*-Cyclohexyl-7-oxa-8-aza [4.4.4] propell-9-ene (17a): from **16a** in 71% yield; mp 128–135 °C (dec); IR 1640 cm^{-1}; ^1H NMR δ 0.9–2.2 (m, 26 H), 2.9 (m 1 H), 4.40 and 5.90 (two d, J = 8 Hz, each 1 H); MS m/e (275.436) 275 (2%). Anal. Calcd for $C_{18}H_{29}NO$: C, 78.41; H, 10.32; N, 5.90. This was refluxed in chloroform (5 mL) under dry nitrogen. Samples were taken at 10-min intervals and IR and ^1H NMR spectra were taken to follow the reaction. After 1.5 h, signals at δ 6.10 and 8.15 were of equal intensity as those at 4.40 and 5.90. An absorption at 1720 cm^{-1} indicated formation of a carbonyl function. The thermolysis proceeded for 5 h more, and solvents were removed in vacuo. Chromatography of the resulting oil yields 72 mg (0.26 mmol; 36% yield) of **18a:** mp 137–139 °C; IR 1720 and 1670 cm^{-1}; ^1H NMR δ 0.9–2.2 (m, 28 H), 3.0 (m, 1 H), 6.10 (d, J = 8 Hz, 1 H), and 8.15 (d, J = 8 Hz, 1 H); MS m/e (275.436) 275 (3%). Anal. Calcd for $C_{18}H_{29}NO$: C, 78.24; H, 10.30; N, 5.10.

(2) *N*-Cyclohexylimino-$\Delta^{6,\beta}$-ethano-2-oxocyclodecan-1-one (18b): from **16b;** after workup, no enamine was detected. Instead, lactone **18b** was isolated in 78% yield as an oil: IR (neat) 1730, 1640, and 1605 cm^{-1}; ^1H NMR δ 0.9–2.5 (m, 22 H), 3.0 (m, 1 H), 4.12 and 4.20 (two t, J = 7 and 6 Hz, together 2 H), 5.80 and 5.86 (two d, J = 9 Hz, together 1 H, 1:1), and 8.21 (d, J = 9 Hz, 1 H); MS m/e (277.408) 277 (4%). Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.54; H, 9.45; N, 4.73.

(3) *N*-Cyclohexylimino-$\Delta^{7,\beta}$-ethano-3,4,5,6-tetrahydro-8*H*-2-benzoxacin-1-one (22a): from **20a** in 81% yield. After removal of the solvent, no enamine was detected. Instead, lactone **22a** was isolated as an oil and was distilled at 150 °C (0.03 mmHg): IR 1720, 1645, and 1605 cm^{-1}; ^1H NMR δ 0.9–2.5 (m, 14 H), 3.0 (m, 1 H), 3.65 and 3.78 (two s, 1:1, together 2 H), 4.32 (m, 2 H), 5.88 (d, J = 9 Hz, 1 H), 6.8–7.5 (m, 3 H), 7.82 (m, 1 H), and 8.16 (d, J = 9 Hz, 1 H); signals at δ 3.65 and 3.78 indicated a E:Z = 1:1 in **22a;** MS m/e (340.488) 340 (4%). Anal. Calcd for $C_{22}H_{30}NO_2$: C, 77.62; H, 8.84; N, 4.10.

(4) *N*-Cyclohexylimino-$\Delta^{7,\beta}$-ethano-3,4,5,6,8,9-hexahydro-2-benzoxacycloundecan-1-one (22b): from **20b.** Propellane **21b** (290 mg) was isolated as an oil at 0 °C: IR (neat) 1660 and 1600 cm^{-1}; ^1H NMR δ 0.9–2.2 (m, 18 H), 2.80 (t, J = 7 Hz, 2 H), 2.0 (m, 1 H), 4.18 (m, 2 H), 4.50 and 6.10 (two d, each 1 H), 6.6–7.8 (m, 4 H). On taking the ^1H NMR spectrum at 45 °C cycloreversion took place. After 10 min, a new signal at 8.10 and the old at δ 4.10 were of the same intensity. The reaction continued for another 30 min at 45 °C, and the solvent was evaporated in vacuo. **22b** was obtained in this way in quantitative yield: IR (neat) 1710, 1640, and 1600 cm^{-1}; ^1H NMR δ 0.9–3.5 (m, 21 H), 4.42 (m, 2 H), 5.9 and 6.08 (two d, J = 9 Hz, together 1 H), 7.0–7.65 (m, 3 H), and 8.10 (d, J = 9 Hz, 1 H); signals at 5.9 and 6.08 refer to E and Z isomers of **22b;** MS m/e (354.514) 354 (4%). Anal. Calcd for $C_{23}H_{32}NO_2$: C, 77.80; H, 9.22; N, 8.87.

(5) *N*-Cyclohexylimino-$\Delta^{7,\beta}$-ethano-3,4,5,6,7,9,10-hexahydro-8*H*-2-benzoxacyclododecan-1-one (22c): from **20c.** Propellane **21c** (290 mg) (0.78 mmol; 78% yield) was isolated: IR (neat) 1670 and 1590 cm^{-1}. On boiling the material in chloroform for 5 h, decomposition to the lactone **22c** took place. The ^1H NMR experiment indicated that the signals at δ 8.25 and 6.10 were of same intensity after ca. 1.5 h. Heating was stopped after 5 h, since products other than the lactone were formed. After distillation (0.02 mmHg) at 160 °C, 152 mg of **22c** was isolated as a 1:1 E:Z isomer mixture: IR 1710 and 1600 cm^{-1}; ^1H NMR δ 0.9–3.5 (m, 23 H) 4.50 (m, 2 H), 6.0 and 6.10 (two d, J = 8 Hz, together 1 H, 1:1), 7.0–7.5 (m, 3 H). 8.0 (m, 1 h), and 8.25 (d, J = 8 Hz, 1 H); MS m/e 368 (368.540).

Procedure for Hydrolysis of Aldimino Lactones to Aldehydo Lactones. Aldimino lactone was filtered on a 100-fold SiO_2 + 10% water column at 0 °C using a 1:1 chloroform–benzene mixture as eluent. Filtration was done in a rate of 3 mL/min and fractions of 3 mL were collected and analyzed on TLC. Those having product were evaporated to give the following compounds.

$\Delta^{6,\alpha}$-Cyclodecanoneacetaldehyde (19a). **18a** (32 mg, 0.11 mmol) yielded 15 mg of **19a** (0.07 mmol; 70%), mp 167–169 °C, which was collected: IR (KBr) 2850, 1725 1670, and 1620 cm^{-1}; ^1H NMR δ 0.9–3 (m, 10 H), 4.05 and 6.05 (two d, J = 9 Hz, each 1 H), and 10.0 (d, J = 1 Hz, 1 H); MS m/e (104.274). Anal. Calcd for $C_{12}H_{18}O_2$: C, 73.97; H, 5.10.

$\Delta^{6,\alpha}$-Oxacyclodecanoneacetaldehyde (19b). **18b** (100 mg) distilled (0.05 mm, 120 °C) lactone **19b** (0.27 mmol; 76% yield): IR (neat) 1725, 1670, and 1620 cm^{-1}; ^1H NMR 0.93–3 (m, 8 H), 4.18 (t, J = 6 Hz, 2 H), 5.90 (d, J = 8 Hz, 1 H), and 10.1 (d, J = 8 Hz, 1 H); MS m/e 106 (196.247). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.57; H, 8.04.

$\Delta^{7,\alpha}$-3,4,5,6-Tetrahydro-8*H*-benzoxacin-1-oneacetaldehyde (23a). **22a** (E + Z) (150 mg, 0.44 mmol) was hydrolyzed to give 68 mg (0.28 mmol; 65% yield) of **23a** (E + Z): IR (neat) 2850, 1710, 1670 and 1595 cm^{-1}; ^1H NMR δ 0.9–2.0 (m, 6 H), 2.60 and 2.92 (two, each 2 H), 3.72 and 4.00 (two, together 2 H in 1:1 ratio), 4.46 (q, J = 5 Hz, 2 H), 5.30 and 5.70 (two d, J = 9 and 7 Hz, respectively, together 1 H); this is a 1:1 mixture of (E + Z)-**23a;** MS m/e 196 (196.247). Anal. Calcd for $C_{15}H_{16}O_3$: C, 67.54; H, 8.24.

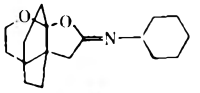
Acknowledgment. This work was supported by the Israel Academy of Sciences, Jerusalem, and by the Friends of the Tel-Aviv University in France. The authors express their appreciation to the donors of these funds.

Registry No.—**1,** 37898-41-2; **8,** 62456-11-5; **9,** 63689-26-9; **12a,** 63689-27-0; **12b,** 16425-84-6; **12c,** 63689-28-1; **13,** 493-03-8; **14,** 58598-27-9; **15,** 63689-29-2; **16a,** 63689-31-6; **16b,** 63689-33-8; **17a,** 63689-34-9; **18a,** 63689-35-0; *E*-**18b,** 63689-36-1; *Z*-**18b,** 63689-37-2; **19a,** 63689-38-3; **19a,** 63689-39-4; **20a,** 63689-41-8; **20b,** 63689-43-0; **20c,** 63689-45-2; **21b,** 63689-46-3; **21c,** 63689-47-4; *E*-**22a,** 63689-48-5; *Z*-**22a,** 63689-49-6; *E*-**22b,** 63689-50-9; *Z*-**22b,** 63689-51-0; *E*-**22c,** 63689-52-1; *Z*-**22c,** 63689-53-2; *E*-**23a,** 63689-54-3; *Z*-**23a,** 63689-55-4.

References and Notes

(1) Part 2: B. Hardegger and S. Shatzmiller, *Helv. Chim. Acta*, **59**, 2765 (1976).
(2) R. R. Schmidt, *Angew. Chem.*, **85**, 235 (1973).
(3) C. K. Bradsher, N. A. Porter, and T. G. Wallis, *J. Org. Chem.*, **39**, 1172 (1974).
(4) U. M. Kempe, T. K. Das-Gupta, K. Blatt, P. Gygax, D. Felix, and A. Eschenmoser, *Helv. Chim. Acta*, **55**, 2187 (1972).
(5) T. K. Das-Gupta, D. Felix, U. M. Kempe, and A. Eschenmoser, *Helv. Chim. Acta*, **55**, 2198 (1972).
(6) P. Gygax, T. K. Das-Gupta, and A. Eschenmoser, *Helv. Chim. Acta*, **55**, 2205 (1972).
(7) M. Petrzilka, D. Felix, and A. Eschenmoser, *Helv. Chim. Acta*, **56**, 2970 (1973).
(8) S. Shatzmiller, P. Gygax, D. Hall, and A. Eschenmoser, *Helv. Chim. Acta*, **56**, 2961 (1973).
(9) S. Shatzmiller and A. Eschenmoser, *Helv. Chim. Acta*, **56**, 2975 (1973).
(10) H. Obara, *Nippon Kagaku Zasshi*, **82**, 60 (1961); *Chem. Abstr.*, **57**, 16426 (1962).
(11) H. Immer and J. F. Bagli, *J. Org. Chem.*, **33**, 2457 (1968).
(12) A. Ruttimann and D. Ginsburg, *Helv. Chim. Acta*, **58**, 2237 (1975).

(13) Reaction with *t*-BuOK in *t*-BuOH gave imino lactone I in 76% yield. Compare ref 12.



I

(14) C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Top. Stereochem.*, **4**, 39 (1969).

(15) Melting points are uncorrected. Ultraviolet spectra were measured on a Cary 14 instrument. Infrared spectra were taken on Perkin-Elmer 251 instrument. ^{1}H NMR spectra were taken in CCl_4 solutions for neutral materials or in deuteriochloroform for salts and are in δ values.

(16) Olefins and ethers are purified on distillation over Na. Merck Art 1097 activity II–III Al_2O_3 was used for the column chromotography. Dry solvent was obtained by distillation over P_2O_5 and filtration over a 100-fold amount of basic Al_2O_3 (activity I, Merck).

(17) The formation of a mass M − 166 as base peak in propellanes **42** and **48–50** was noted.

Reactions of Phthalaldehyde with Ammonia and Amines

T. DoMinh, A. L. Johnson, J. E. Jones,* and P. P. Senise, Jr.

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

Received August 5, 1976

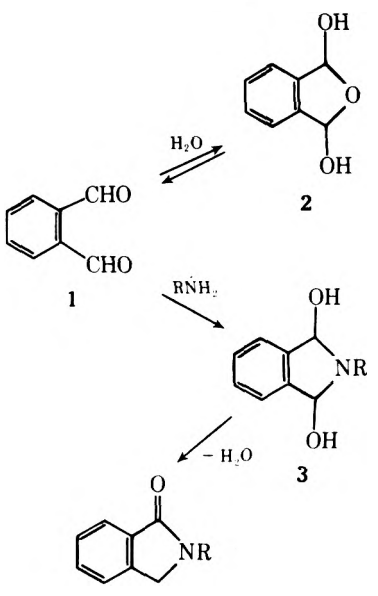
Reactions of phthalaldehyde with ammonia and amines are described. Major products from ammonia were phthalimidine and 3-(2-cyanophenyl)isoquinoline. Primary amines reacted with 2 mol of aldehyde to produce N-substituted adducts whose steric requirements lead to unusual NMR spectra. At elevated temperatures unidentified colored materials were formed. 1-Hydroxyisoindoles are proposed intermediates.

The reaction between phthalaldehyde and ammonia produces colored polymeric[1-3] products. These reactions have served as a basis for polarographic methods for the determination of ammonia[3] and for the location of sweat pores in the skin.[4] Similar reactions of phthalaldehyde with various primary amines, amino acids, and indoles also produce dark-colored products. Qualitative and semiquantitative methods for the detection of these nitrogen-containing materials depend on the fluorescence of their condensation products with phthalaldehyde.[5-7]

Preliminary to an investigation of the colored products, a study of these reactions under carefully controlled conditions was made.

Results

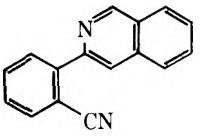
At room temperature water reacts reversibly with phthalaldehyde (**1**) to produce a hydrate[8] which was shown by NMR to have the structure **2**; phthalaldehyde was recovered unchanged by evaporating the solution to dryness. By contrast, the reaction with ammonia is not reversible. In cold dilute dimethyl sulfoxide (Me_2SO) an adduct formed which had an NMR spectrum consistent with **3a**. The initially formed product dehydrated and rearranged to phthalimidine (**4a**), identified by comparison to an authentic sample.[9] The diol **3a**, precipitated from dry ether at −70 °C, was very unstable and resinified rapidly when warmed to room temperature.



4

a, R = H
b, R = Me
c, R = Ph
d, R = 2,6-Me_2Ph

The products from the reaction of phthalaldehyde and ammonia in Me_2SO depended on the initial concentration of aldehyde. While phthalimidine (**4a**) was produced in high yield in dilute Me_2SO solutions, more concentrated solutions yielded 3-(2-cyanophenyl)isoquinoline (**5**) and a dark polymer



5

with a consequent decrease in the yield of **4a**. The structure of **5** was inferred from the following considerations: (1) IR showed a -CN; (2) NMR showed nine aromatic protons and a tenth at 9.29 ppm, characteristic of the proton in the 1 position of isoquinoline; and (3) its mass spectrum.

The reaction between phthalaldehyde and ammonia is strongly exothermic. The rate of ammonia addition had to be controlled carefully to maintain a low reaction temperature. Warming after the reaction had been completed did not affect the product composition, but at higher reaction temperatures greater amounts of polymer were formed at the expense of **4a** and **5**.

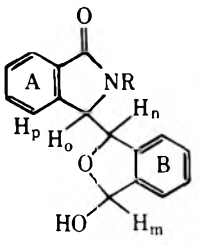
Reactions of excess aldehyde with primary amines in cold solutions (ether, acetone, benzene) produced **6** and N-substituted phthalimidines **4** as the major isolable products.

Elemental analyses of the products (**6**) from the primary amines showed that they were made up of 2 mol of aldehyde and 1 mol of amine with the loss of 1 mol of water. Mass spectra established their molecular weights and IR showed the presence of amide and hydroxyl groups, the latter of which was proved to be secondary by oxidation. In addition, the mass spectra indicated cleavage into two major fragments, each

Table I. The Effect of N Substituent on Proton Chemical Shifts (ppm) in 6

Substituent (R)	H_m	$\Delta\delta H_m$[a]	H_p	$\Delta\delta H_p$	H_n	$\Delta\delta H_n$	H_o	$\Delta\delta H_o$
-Me	5.86		6.60		6.06		5.11	
$-CHMe_2$	5.66	−0.20	6.31	−0.29	6.02	−0.04	5.15	+0.14
$-CMe_3$	5.13	−0.73	5.85	−0.75	6.08	+0.02	5.32	+0.21
-Ph	5.28	−0.58	6.58	−0.02	6.03	−0.03	5.78	+0.67
$-2,6\text{-}Me_2Ph$	5.63	−0.23	6.25	−0.35	5.63	−0.43	5.30	+0.19

[a] Referred to the Me compounds.



6a, R = Me
b, R = *i*-Pr
c, R = *n*-Bu
d, R = *t*-Bu
e, R = Ph
f, R = $2,6\text{-}Me_2Ph$

containing a phenyl group and one of which was identifiable as coming from a phthalimidine-like structure.

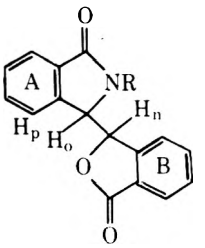
The NMR of the *tert*-butylamine product (**6d**) showed only seven protons in the aromatic region and a doublet at 5.85 ppm (J = 9 Hz), the coupling of which showed it to be aromatic and adjacent to a bridgehead. Furthermore, the aliphatic hydrogen of the secondary alcoholic group was found upfield (5.18 ppm) from the region usually associated with such a proton. ^{13}C NMR showed the *tert*-butyl group attached to the N atom.

Construction of the proposed structure (**6d**) from Catalin molecular models[10] showed crowding so severe that of the eight possible stereoisomers (four enantiomorphic pairs) only four would be expected to be formed. The NMR spectra indicate that one enantiomorphic pair is formed predominantly.

In the preferred conformation the aromatic hydrogen (H_p) is situated closely above the center of the aromatic ring B. This accounts for the upfield shift of the aromatic proton. Similarly, when H_m and H_n are trans, H_m is centered over the aromatic ring A, accounting for its comparable upfield shift. The *o*-methyl groups in **6f** prevent free rotation of the *N*-aryl group as indicated by models and by the nonequivalent absorptions of the two methyl groups. As a consequence H_n lies just above the *N*-aryl group and its absorption is shifted upfield to coincide with that of H_m.

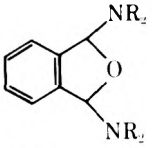
Further evidence supporting the proposed structure is found in the NMR spectra of the lower homologues of **6d**. The *N*-methyl derivative is much less crowded, allowing movement of H_m and H_p away from the phenyl rings, as compared to the *tert*-butyl derivative, and the chemical shifts are closer to the normal values for such protons. Chemical shifts of H_m and H_p in the isopropyl derivative **6b** are intermediate between those of the methyl and *tert*-butyl derivatives (Table I). Models show that the freedom of rotation between the two benzylic nuclei increases in the order *tert*-butyl < isopropyl < Me. The absorption due to H_n is relatively unaffected by the substituent on the N atom, but that due to H_o is shifted downfield as the bulkiness of the group on the N atom increases.

These compounds were readily oxidized in good yields to lactam lactones (**7**), for which the chemical shifts of H_n, H_o, and H_p are not appreciably different from those of the parent compounds.



7a, R = Me
b, R = *t*-Bu
c, R = Ph

Secondary amines reacted rapidly with equal moles of phthalaldehyde in Me_2SO to form intermediates whose structures were not determined. The reaction continued slowly, forming **8** and regenerating 0.5 mol of phthalaldehyde.

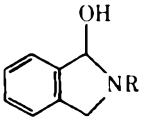


8a, R = Me
b, R = Et
c, R = $-(CH_2)_5-$
d, R = $-(CH_2)_2O(CH_2)_2-$

In the presence of excess amine the initial product underwent conversion to **8** quantitatively as inferred from NMR spectra. The structure of **8b** was established by NMR and mass spectrometry.

Discussion

The reactions between phthalaldehyde and ammonia or amines may be rationalized best by a 1-hydroxyisoindole intermediate (**9**) from transannular dehydration of the adducts (**3a–d**).[11] Under conditions of low temperature and high dilution, hydroxyisoindoles could rearrange to phthalimidines (**4**) by two 1,3-hydrogen shifts.

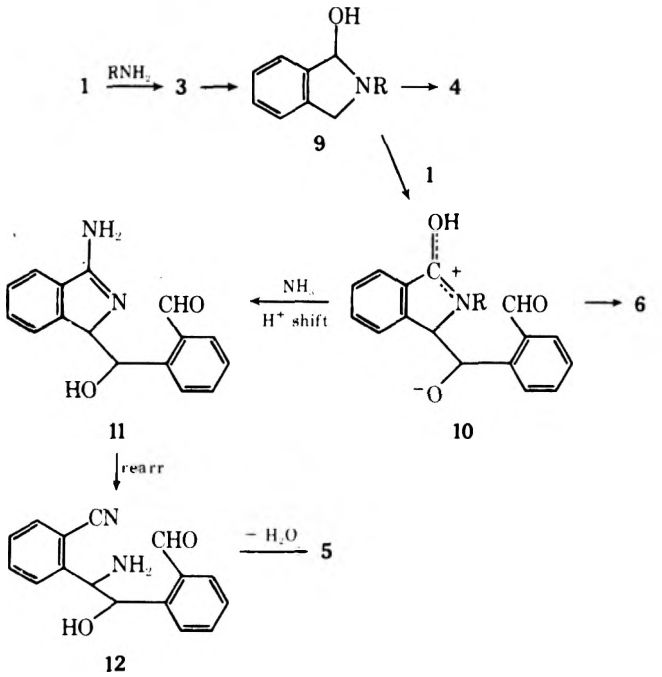


9a, R = H
b, R = alkyl, aryl

Higher concentrations and temperatures favor the formation of colored polymers. Isoindole is known to be highly reactive, readily forming dark tars under mild conditions.[12] Isoindole and its derivatives are most reactive in the 1 and 3 positions toward dienophiles.[13-17] The 1-phenyl derivative also resinifies readily, and it can be dimerized oxidatively through the 3 position by refluxing in benzene.[18]

The formation of cyanophenylisoquinoline (**5**) can be rationalized by rapid dehydration of **3a** as it is formed, producing the isoindole **9a** which, by polar addition to unreacted phthalaldehyde present in the early stages of the reaction, would produce **10a** (Scheme I). Subsequent attack on **10a** by

Scheme I



a, R = H
b, R = alkyl or aryl

ammonia (in excess as the addition continues) followed by a proton shift would form the amidine **11**.[19] The latter may tautomerize to the unstable iminoamide which opens to the isomeric benzonitrile **12**, and ring closure followed by dehydration would produce cyanophenylisoquinoline (**5**).

A similar sequence of reactions can explain the products **6** from primary amines via the similar intermediate **10b**. The reaction is amine limited so that the replacement of the -OH of **10b** would not occur. Since N substitution would prevent rearrangement to an amidine, cyclization via the alkoxy anion would be favored and **6** would be produced.

Experimental Section

Water Adduct of Phthalaldehyde (2). A water (or D_2O) slurry of phthalaldehyde was stirred for 2 days, during which time the aldehyde dissolved. The mixture was filtered and the filtrate was analyzed by NMR: NMR (D_2O) δ 6.14, 6.45 (s, s, 2, *cis*- and *trans*-OCHOH), 7.35 (s, 4, aromatic). The assignments of the absorptions for cis and trans isomers are based on those reported for the 1,3-dialkoxyphthalans and the polymer of phthalaldehyde.[20]

Ammonia Adduct of Phthalaldehyde (3a). A solution of 0.2 g of phthalaldehyde in 50 mL of anhydrous ether was cooled to 0 °C, and dry NH_3 was bubbled into the solution. A white solid formed immediately. The solution was centrifuged and the white precipitate was dried at −70 °C in vacuo: mass spectrum (70 eV) *m/e* 230, 134 (molecular ion minus H_2O), 133, 105, 77, 51, 50; after silation (*N,O*-bis(trimethylsilyl)trifluoroacetamide) 205 (molecular ion minus H_2O), 190, 147, 133, 116, 105, 104, 77, 75, 74, 73. This result suggests monosilation and loss of 1 mol of water.

Anal. Calcd for $C_8H_9NO_2$: C, 63.6; H, 6.0; N, 9.3. Found: C, 62.8; H, 5.8; N, 8.9.

The solid was very unstable, accounting for the poor elemental analysis and the trace material of mass 230 in the mass spectrum. Upon being warmed to room temperature, it darkened and formed a tarry polymer from which was extracted phthalimidine as the only identifiable product.

A solution of phthalaldehyde in Me_2SO (5%) was cooled to 18–20 °C and dry ammonia was bubbled into the solution. The solution contained **3a**: NMR (Me_2SO) δ 5.00, 5.36 (s, s, 2, *cis*- and *trans*-CHOH), 7.27 (s, 4, aromatic).

After standing for several hours at room temperature the initial product was converted quantitatively to phthalimidine (**4a**), identified by comparison of UV, NMR, and mass spectra to those of an authentic sample:[9] UV (CH_3CN) 220 (ϵ 1.09 × 10^4), 262 (ϵ 1.31 × 10^3), 268 (ϵ 1.55 × 10^3), 275 nm (ϵ 1.38 × 10^3); NMR (Me_2SO) δ 4.41 (s, 2, $-CH_2-$), 7.60 (m, 4, aromatic), 8.54 (s, 1, >NH); mass spectrum (70 eV) *m/e* 133 (molecular ion), 132, 105, 104, 77.

3-(2-Cyanophenyl)isoquinoline (5). A solution of phthalaldehyde in Me_2SO (20%) was cooled to 15 °C and dry ammonia was bubbled into the solution at a rate such that the temperature did not rise above 18 °C. After the reaction was complete, the yellow solution was allowed to stand overnight, during which time it darkened. The solution was added to ten times its volume of water and the solid was filtered. The filtrate contained mainly phthalimidine and traces of the cyanophenylisoquinoline.

The dried residue was extracted in a Soxhlet apparatus with hexane. The hexane solution rapidly assumed a blue fluorescence from the dissolved cyanophenylisoquinoline. Removal of solvent gave crude **5** in 30% yield. Repeated crystallization from hexane gave pale yellow silky needles: mp 104–105 °C; UV max (CH_3CN) 222 (ϵ 4.42 × 10^4), 295 (ϵ 9.52 × 10^3), 320 nm (ϵ 4.4 × 10^3); IR (KBr) 2220 cm^{-1} (CN); NMR δ 8.00 (m, 9, aromatic), 9.29 (s, 1, H_1 of isoquinoline); mass spectrum (70 eV) *m/e* (major peaks italicized) *230* (molecular ion), *229*, 203, 202, 201, 176, 175, 102, 101, 77, 76, 75. Elemental analyses consistently were low for no apparent reason.

Anal. Calcd for $C_{16}H_{10}N_2$: C, 83.5; H, 4.4; N, 12.15. Found: C, 82.3; H, 4.1; N, 11.9.

Reactions Involving Excess Primary Amine. (1) Methylamine. Dry CH_3NH_2 was bubbled into a Me_2SO solution of phthalaldehyde (10%) maintained at a temperature below 20 °C. The solution contained **3b**: NMR (Me_2SO) δ 5.08, 5.47 (s, s, 2, *cis*- and *trans*-CHOH), 7.37 (m, 4, aromatic).

After a few hours these absorptions disappeared and the spectrum became identical with that of *N*-methylphthalimidine (**4b**):[21] NMR (Me_2SO) δ 4.37 (s, 2, $-CH_2-$), 7.50, 8.1 (m, 4, aromatic).

(2) Aniline. To a stirred solution of 4.0 g (0.03 mol) of phthalaldehyde in 75 mL of ether was added 3.0 g (0.032 mol) of aniline in 75 mL of ether, whereupon **3c** precipitated at once as a colorless solid, 5.2 g (77%). It was filtered and dried in vacuo: IR (KBr) 3280 (OH), 1680 (C=O), 1600, 1500 cm^{-1}; NMR (Me_2SO) δ 5.51, 5.93 (d, d, 4, AB pair, J = 18 Hz, -CHOH), 7.14 (m, 4, aromatic), 7.40 (s, 5, aromatic); NMR (Me_2SO–D_2O) δ 6.03 (s, 2, -OCHNPh-), 7.22 (m, 4, aromatic), 7.49 (s, 5, aromatic); mass spectrum (70 eV) *m/e* 209 (molecular ion minus H_2O), 208, 181, 160, minor components (a) 284, 283, (b) 298, 297, (c) 400, 399, 371.

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.7; N, 6.2. Found: C, 73.6; H, 5.7; N, 6.1.

The compound **3d** decomposed while the IR spectrum was being recorded; the hydroxyl absorption disappeared and the carbonyl absorption was enhanced.

From the filtrate was isolated a small amount of a yellow solid, which consisted of a mixture of 2-phenylphthalimidine[22] and 2-phenyl-1-phenyliminoisoindoline.[23] Recrystallization from benzene produced colorless prisms (0.25 g) of impure 2-phenylphthalimidine (**4c**), mp 157–160 °C, identified by IR, NMR, and mass spectra in comparison to an authentic sample.

Reactions Involving Excess Phthalaldehyde. (1) Methylamine. To a stirred solution of 12.0 g (0.09 mol) of phthalaldehyde in 200 mL of acetone was added 4.5 g (0.06 mol) of 40% aqueous methylamine in 100 mL of acetone. The solution turned pale yellow immediately and then darkened gradually to a reddish color as the product crystallized from the solution. The mixture was chilled in the refrigerator and filtered to give 6 g (35%) of **6a**. Recrystallization twice from acetone or methanol gave colorless needles: mp 220–222 °C dec; UV max (CH_3CN) 228 (ϵ 892), 248 (ϵ 506), 269 (ϵ 333), 276 nm (ϵ 213); IR 3380 (OH), 1680 cm^{-1} (-C(=O)N-); NMR (Me_2SO) δ 3.05, 3.07 (s, s, 3, >NCH_3), 5.11 (m, 1, $-OCH_nN-$), 5.83, 5.90 (d, d, 1, J = 2 Hz, -O-CH_mOH), 6.06 (m, 1, $-OCH_nO-$), 6.60 (d, 1, J = 9 Hz, H_p), 6.82 (d, 1, J = 8 Hz, -OH), 7.4 (m, 7, aromatic); NMR (Me_2SO, silated) δ 3.03, 3.05 (s, 3, >NCH_3), 5.10 (m, 1, $-OCH_nN-$), 6.07 (m, 2, $-OCHOSiMe_3$, $-OCH_nO-$), 7.3 (m, 7, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 282 (molecular ion), 264, 247, 165, *117*, *116*, 135, 118, 117, 91, 77; after silation (*N,O*-bis(trimethylsilyl)trifluoroacetamide), 425 (molecular ion), 338, 337, 322, *219*, *207*, *146*, *118*, *73*.

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.6; H, 5.4; N, 5.0. Found: C, 72.3; H, 5.6; N, 4.9.

The NMR spectrum shows two different -NMe absorptions indicative of at least two isomeric compounds, one of which is present to a minor extent.

(2) Isopropylamine. To a stirred solution of 5.0 g (0.037 mol) of phthalaldehyde in 75 mL of dry ether was added 1.24 g (0.021 mol) of isopropylamine in 75 mL of dry ether. The product **6b** crystallized from the solution as fine colorless prisms: mp 186–188 °C dec; UV max (CH_3CN) 229 (ϵ 820), 248 (ϵ 470), 268 (ϵ 341), 276 nm (ϵ 222); IR (KBr) 3400 (OH), 1680 cm^{-1} (-C(=O)N); NMR (Me_2SO) δ 1.38 (d, 6, J =

8 Hz, -CH(CH_3)$_2$), 4.20 (septet, 1, J = 8 Hz, -CH(CH_3)$_2$), 5.15 (m, 1, -OCH_oN<), 5.62, 5.70 (d, d, 1, J = 4 Hz, -OCH_mOH), 6.02 (m, 1, -OCH_nO-), 6.31 (d, 1, J = 8 Hz, H_p), 6.78 (d, 1, J = 8 Hz, -OCHOH), 7.5 (m, 7 aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 310 (molecular ion), 309, *175*, 174, 135, 133, 132, 104, 77.

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.8; H, 6.2; N, 4.5. Found: C, 73.8; H, 6.4; N, 4.6.

(3) *n*-Butylamine. A reaction similar to that with isopropylamine was run with *n*-butylamine. The product (**6c**) crystallized from the solution as fine colorless prisms: mp 177–179 °C dec; mass spectrum (70 eV) *m/e* (major peaks italicized) 324 (molecular ion), 305, *189*, *147*, *146*, 135, *132*, 119, 104, 90, 77.

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.3; H, 6.5; N, 4.3. Found: C, 74.0; H, 6.8; N, 4.3.

(4) *tert*-Butylamine. The reaction was run as that with *n*-butylamine. The product **6d**, 3.0 g (50%), crystallized from the solution as fine colorless prisms: mp 218–220 °C dec; UV max (CH_3CN) 229 (ϵ 810), 253 (ϵ 453), 269 (ϵ 364), 276 nm (ϵ 225); IR (KBr) 3380 (OH), 1680 cm^{-1} (-C(=O)N-); NMR (Me_2SO) δ 1.60, 1.64 (s, s, 9, >NC(CH_3)$_3$), 5.10 5.18 (d, d, 1, J = 2 Hz, -OCH_mOH), 5.32 (m, 1, -OCH_oN<), 5.85 (d, 1, J = 9 Hz, H_p), 6.08 (m, 1, -OCH_nO-), 6.83 (d, 1, J = 10 Hz, OH), 7.4 (m, 7, aromatic); NMR (Me_2SO-D_2O) δ 1.62, 1.64 (s, s, 9, >NC(CH_3)$_3$), 5.15 (d, 1, J = 2 Hz, -OCH_mOH), 5.32 (m, 1, -OCH_oN<), 5.79 (d, 1, J = 9 Hz, H_p), 6.08 (m, 1, -CH_nO-), 7.4 (m, 7, aromatic); ^{13}C NMR (Me_2SO) δ 28.2 (-C(CH_3)$_3$), 54.3 (>NCMe_3), 63.9 (-CH-), 81.7 (-CH-), 100.7 (-CH-), 121.8, 122.9, 127.7, 128.8, 129.5, 135.1, 139.1, 140.9, 141.0 (12 aromatic), 168.0 (C=O); mass spectrum (70 eV) *m/e* (major peaks italicized) 324 (molecular ion), 305, *189*, 144, *135*, *133*, *132*, 105, 104, *77*; after silation (*N*,*O*-bis(trimethylsilyl)trifluoroacetamide), 467 (molecular ion), 395, 394, 380, 324, *261*, *207*, 188, 132, 130, 77, 75, 73.

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.3; H, 6.5; N, 4.3. Found: C, 74.0; H, 6.7; N, 4.2.

The NMR spectrum shows two *tert*-butyl absorptions indicative of at least two isomers being present, one of which is in a relatively small proportion.

(5) Aniline. To a stirred solution of 5.0 g (0.037 mol) of phthalaldehyde in 75 mL of acetone was added dropwise 2.3 g (0.025 mol) of aniline in 75 mL of acetone. The solution gradually turned yellow and then deep red. The solution was heated and stirred at the boiling point for 1 h and then evaporated to dryness. To the red tar was added 25 mL of benzene and the slurry was filtered to obtain 2.5 g (39%) of crude product, which crystallized from acetone as colorless prisms (**6e**): mp 196–198 °C dec; IR (KBr) 3280 (OH), 1670 cm^{-1} (-C(=O)-N-); NMR (Me_2SO) δ 5.28 (m, 1, -OCH_oN<), 5.78 (m, 1, -OCH_mOH), 6.03 (d, 1, J = 2 Hz, -OCH_nO-), 6.58 (d, 1, J = 9 Hz, H_p), 6.65 (m, 1, -OH), 7.5 (m, 12, aromatic); NMR (Me_2SO-D_2O) δ 5.28 (d, 1, J = 2 Hz, -OCH_mOH), 5.78 (m, 1, -OCH_oN<), 6.02 (d, 1, J = 2 Hz, -OCH_nO-), 6.58 (d, 1, J = 9 Hz, H_p), 7.5 (m, 12, aromatic); NMR (pyridine) δ 5.86, 5.95, 6.05 (m, 3, -OCHO-), 6.70 (d, 1, J = 9 Hz, aromatic), 7.35 (m, 9, aromatic), 7.98, 8.06 (m, 3, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 341 (molecular ion), *208*, 180, 179, 152, 133, 77.

Anal. Calcd for $C_{22}H_{17}NO_3$: C, 77.0; H, 5.0; N, 4.1. Found: C, 76.9; H, 5.2; N, 4.0.

The filtrate contained 2-phenylphthalimidine.

(6) 2,6-Dimethylaniline. The reaction was run as that with isopropylamine. The product, 0.6 g (8.7%), crystallized slowly from the solution as colorless needles (**6f**), which were recrystallized from ethanol: mp 248–250 °C dec, with prior discoloration at 235–240 °C; IR (KBr) 3300 (OH), 1675 cm^{-1} (C=O); NMR ($CDCl_3$-Me_2SO) δ 2.20 (s, 1, -CH_3), 2.25, 2.30 (s, s, 6, -CH_3), 5.30 (s, 1, -OCH_oN<), 5.64 (m, 2, -OCH_nO-, -OCH_mOH), 6.25 (d, 1, J = 9 Hz, H_p), 6.65 (d, 1, J = 8 Hz, OH), 7.20 (s, 3, aromatic), 7.35–8.00 (m, 7, aromatic); NMR ($CDCl_3$-Me_2SO-D_2O) δ 2.20 (s, 1, -CH_3), 2.25, 2.30 (s, s, 6, -CH_3), 5.29 (m, 1, -OCH_oN<), 5.64 (m, 2, -OCH_nO-, -OCH_mOH), 6.25 (d, 1, J = 9 Hz, H_p), 7.26 (s, 3, aromatic), 7.30–8.00 (m, 7, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 372 (molecular ion), 354, 237, 236, 220, 218, 135, 132, 106, 105.

Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.6; H, 5.7; N, 3.8. Found: C, 77.4; H, 5.6; N, 3.6.

From the filtrate was isolated 4.0 g of 2-(2,6-dimethylphenyl)-phthalimidine (**4d**), which crystallized from ligroine in colorless prisms: mp 139–141 °C; IR 1675 cm^{-1} (C=O); NMR (Me_2SO) 2.2 (s, 6, -CH_3), 4.73 (s, 2, -CH_2-), 7.23 (s, 3, aromatic), 7.5–8.0 (m, 4, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 237 (molecular ion), 222, 220, 165, *132*, 106.

Anal. Calcd for $C_{16}H_{15}NO$: C, 81.0; H, 6.3; N, 5.9. Found: C, 81.0; H, 6.3; N, 5.9.

Oxidation of Dimeric Products. (1) Oxidation of 6a. To a stirred suspension of 2.0 g (0.007 mol) of **6a** in 50 mL of pyridine was added 2.0 g (0.02 mol) of CrO_3 in small portions over 15 min. Stirring was continued for 48 h. The mixture was poured into water and extracted with ether. Removal of the ether and crystallization of the colorless residue from methanol gave 1.6 g (80%) of colorless prisms of **7a**: mp 212–215 °C dec; UV (CH_3CN) 222 (ϵ 1.81 × 10^4), 228 (ϵ 1.47 × 10^4), 268 (ϵ 351), 275 nm (ϵ 314); IR (KBr) 1680 (-C(=O)N-), 1760 cm^{-1} (-C(=O)O); NMR ($CDCl_3$, Me_2SO) δ 3.12 (m, 3, >NCH_3), 5.28 (d, 1, J = 3 Hz, -OCH_oN<), 6.28 (d, 1, J = 3 Hz, -OCH_nO-), 6.78 (m, 1), 6.96 (m, 1, aromatic), 7.6 (m, 6, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 279 (molecular ion), 165, 162, *146*, 133, 118, 117, 105, 91, 77, 42.

Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.1; H, 4.7; N, 5.0. Found: C, 72.8; H, 5.1; N, 4.9.

(2) Oxidation of 6d. The oxidation was carried out as described for the methyl derivative. The product (**7b**) crystallized from methanol as colorless prisms (70%): mp 236–248 °C dec; IR (KBr) 1680 (-C(=O)N-), 1760 cm^{-1} (-C(=O)O); NMR (Me_2SO) δ 1.58, 1.62 (s, 9, -C(CH_3)$_3$), 5.65 (d, 1, J = 2 Hz, -OCH_oN<), 5.70 (d, 1, J = 9 Hz, H_p), 6.38 (d, 1, J = 2 Hz, -OCH_nO-), 6.95–8.0 (m, 7, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 322 (molecular ion), 321, 306, 266, 248, *188*, *132*, 104, 77, 57.

Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.8; H, 5.9; N, 4.4. Found: C, 75.2; H, 6.1; N, 4.5.

(3) Oxidation of 6e. The oxidation was carried out as described for the methyl derivative. The product (**7c**) crystallized from methanol as colorless prisms (83%): mp 227–229 °C; IR (KBr) 1680 (-C(=O)-N-), 1760 cm^{-1} (-C(=O)O); NMR (Me_2SO) δ 6.09 (d, 1, J = 2 Hz, -OCH_oN<), 6.39 (d, 1, J = 2 Hz, -OCH_nO-), 6.55 (d, 1, J = 9 Hz, H_p), 7.6 (m, 12, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 341 (molecular ion), *208*, 180, 179, 152, 133, 77.

Anal. Calcd for $C_{22}H_{15}NO_3$: C, 77.4; H, 4.4; N, 4.1. Found: C, 77.2; H, 4.5; N, 3.8.

Reactions with Secondary Amines. The amine (0.2 g) was added to 0.41 g of a 15% solution of phthalaldehyde in dimethyl sulfoxide, and the solution was allowed to stand at room temperature. The reaction was followed by NMR.

Immediately after addition of the amine, absorptions were observed in the regions 5.75–5.90 (s, 1), 6.02–6.20 (d, 1, J = 4 Hz), 6.23–6.29 (s, 1), 6.33–6.38 ppm (d, 1, J = 4 Hz). Upon being warmed to 45 °C or standing at room temperature for 2 weeks, the product was converted to the isobenzofurans **8** as show by NMR. Absorptions of the products contained two singlets associated with the *cis*- and *trans*-OC**H**NR_2 as follows: **8a** (5.67, 5.92); **8b** (5.77, 6.03); **8c** (5.64, 5.84); **8d** (5.70, 5.90).

A 10% solution of phthalaldehyde in diethylamine was warmed to the boiling point. Removal of the excess amine and distillation of the residue produced **8b** as a colorless oil (80%): bp 58–59 °C (15 μm); NMR (neat) δ 1.0 (m, 12, -CH_2CH_3), 2.65 (m, 8, -CH_2CH_3), 5.82, 5.96 (s, s, 2, *cis*- and *trans*-OC**H**NEt_2), 7.23 (s, 4, aromatic); mass spectrum (70 eV) *m/e* (major peaks italicized) 262 (molecular ion), 233, 191, *190*, 162, *160*, 134, 132, 199, 118, 116, 91, 77.

Anal. Calcd for $C_{16}H_{26}N_2O$: C, 73.2; H, 10.0; N, 10.7. Found: C, 73.2; H, 10.0; N, 10.5

Acknowledgment. It is a pleasure to acknowledge the valuable contributions of Tom Regan, Robert Young, and David Maier of these laboratories for their help in obtaining and interpreting the NMR and mass spectra.

Registry No.—**1**, 643-79-8; *cis*-**2**, 63883-89-6; *trans*-**2**, 63883-90-9; *cis*-**3a**, 63883-91-0; *trans*-**3a**, 63883-92-1; *cis*-**3b**, 63883-93-2; *trans*-**3b**, 63883-94-3; **3c**, 63883-95-4; **4a**, 480-91-1; **4b**, 5342-91-6; **4c**, 5388-42-1; **4d**, 63883-96-5; **5**, 63883-97-6; **6a**, 63883-98-7; **6b**, 63883-99-8; **6c**, 63884-00-4; **6d**, 63884-01-5; **6e**, 63884-02-6; **6f**, 63884-03-7; **7a**, 63904-77-8; **7b**, 63884-04-8; **7c**, 63884-05-9; *cis*-**8a**, 63884-06-0; *trans*-**8a**, 63884-07-1; *cis*-**8b**, 63884-08-2; *trans*-**8b**, 63884-09-3; *cis*-**8c**, 63884-10-6; *trans*-**8c**, 63884-11-7; *cis*-**8d**, 63884-12-8; *trans*-**8d**, 63884-13-9; water, 7732-18-5; ammonia, 7664-41-7; methylamine, 74-89-5; aniline, 62-53-3; isopropylamine, 75-31-0; *n*-butylamine, 109-73-9; *tert*-butylamine, 75-64-9; 2,6-dimethylaniline, 87-62-7; diethylamine, 109-89-7; dimethylamine, 124-40-3; piperidine, 110-89-4; morpholine, 110-91-8.

References and Notes

(1) L. Thiele and E. Winter, *Justus Liebigs Ann. Chem.*, **311**, 360 (1900).
(2) L. Seekles, *Recl. Trav. Chim. Pays-Bas*, **43**, 93 (1924).
(3) D. R. Norton and C. K. Mann, *Anal. Chem.*, **26**, 1180 (1954).
(4) L. Juhlin and W. B. Shelley, *Nature (London)*, **213**, 408 (1967).
(5) N. H. Furman and D. R. Norton, *Anal. Chem.*, **26**, 1111 (1954).

(6) T. D. Turner and S. L. Wightman, *J. Chromatogr.*, **32**, 315 (1968), and references cited therein.
(7) R. Hakanson and A. L. Ronnberg, *Anal. Biochem.*, **54**, 353 (1973); *Chem. Abstr.*, **79**, 63336r (1973).
(8) L. Seekles, *Recl. Trav. Chim. Pays.-Bas*, **42**, 706 (1923).
(9) W. Treibs, H. M. Barchet, G. Bach, and W. Kirchhof, *Justus Leibigs Ann. Chem.*, **574**, 54 (1951).
(10) Catalin Covalent Models obtained from Catalin, Ltd., Waltham Abbey, Essex, England.
(11) After this paper was submitted for publication an isoindole intermediate was also suggested to account for the products from phthalaldehyde, *n*-propylamine, and 2-mercaptoethanol: S. Simons, Jr., and D. F. Johnson, *J. Am. Chem. Soc.*, **98**, 7098 (1976).
(12) R. Bonnett and R. F. C. Brown, *J. Chem. Soc., Chem. Commun.*, 393 (1972).
(13) G. M. Priestly and R. N. Warrener, *Tetrahedron Lett.*, 4295 (1972).
(14) R. Kreher and J. Seubet, *Z. Naturforsch. B*, **20**, 75 (1965).
(15) J. Bornstein, D. E. Remy, and J. E. Shields, *J. Chem. Soc., Chem. Commun.*, 1149 (1972).
(16) J. Bornstein, D. E. Remy, and J. E. Shields, *Tetrahedron Lett.*, 4247 (1974).
(17) D. F. Veber and W. Lwowski, *J. Am. Chem. Soc.*, **86**, 4152 (1964).
(18) R. I. Fryer, B. Brust, J. V. Early, and L. H. Sternbach, *J. Chem. Soc. C*, 366 (1967).
(19) A precedent for this reaction is found in the preparation of benzamidine hydrochloride by the reaction of alcoholic ammonia on the imino ester hydrochloride obtained from the reaction of benzonitrile, hydrogen chloride, and ethanol: see A. W. Dox in "Organic Syntheses", Collect. Vol. I, 2nd ed, Wiley, New York, N.Y., 1958, p 6; see also A. Pinner, *Ber.*, **16**, 1643 (1883); **17**, 178 (1884).
(20) C. Aso and S. Tagami, *Am. Chem. Soc., Div. Polym. Chem., Prepr.*, **8**, 906 (1967); *Macromolecules*, **2**, 414 (1969).
(21) C. Graebe and P. Pictet, *Justus Liebigs Ann. Chem.*, **247**, 303 (1888).
(22) R. E. Ludt and C. R. Hauser, *J. Org. Chem.*, **36**, 1607 (1971); A. Rosenthal and M. R. S. Weir, *J. Org. Chem.*, **28**, 3025 (1963).
(23) J. Thiele and J. Schneider, *Justus Liebigs Ann. Chem.*, **369**, 287 (1909).

Isolation of Potent New Antileukemic Trichothecenes from *Baccharis megapotamica*[1,2]

S. Morris Kupchan,[16] David R. Streelman, Bruce B. Jarvis,[3]
Richard G. Dailey, Jr., and Albert T. Sneden*

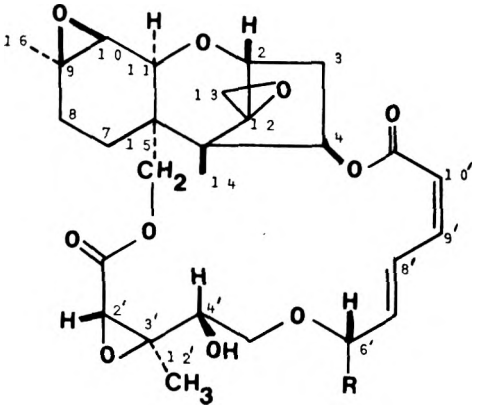
Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

Received June 14, 1977.

The isolation and structural elucidation of the new potent antileukemic trichothecenes baccharin (1), baccharinol (2), isobaccharinol (3), and isobaccharin (4) are reported. Baccharinol (2) and isobaccharinol (3) were shown to be esters of 8β-hydroxyverrucarol (9) by hydrolysis to 9 and the dimethyl esters 5 and 11. Hydrolysis of baccharin (1) and isobaccharin (4) gave 6 and esters 5 and 11. Conversion of 2 and 3 to the common intermediate 13 demonstrated that 4 and 3 were the C-13′ epimers of 1 and 2, respectively.

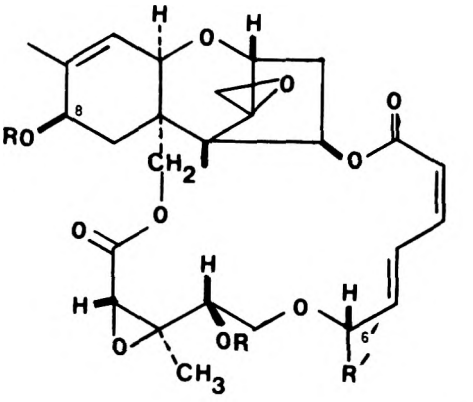
In the course of a continuing search for tumor inhibitors of plant origin, an alcoholic extract of *Baccharis megapotamica* Spreng (Asteraceae)[4] was found to show significant activity in vivo against P-388 leukemia in mice (PS)[5] and in vitro against cells derived from human carcinoma of the nasopharynx (KB). A preliminary communication[6] described the structural elucidation of the potent antileukemic trichothecene triepoxide baccharin (1). It is the purpose of this paper to present in detail the isolation and structural elucidation of baccharin (1), as well as the new potent antileukemic principles baccharinol (2), isobaccharinol (3), and isobaccharin (4).[7]

Fractionation of the alcohol extract, guided by a combination of P-388 in vivo assay in mice and KB testing in vitro, revealed that the inhibitory activity was concentrated, suc-



1, R = –C(CH3)(H)–OH

4, R = –C(CH3)(H)–OH



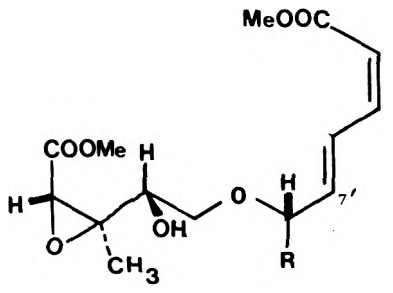
2, R = H ; R′ = –C(CH3)(H)–OH

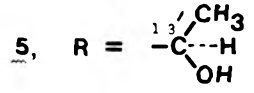
3, R = H ; R′ = –C(CH3)(H)–OH

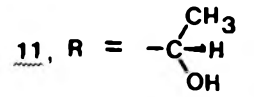
7, R = Ac ; R′ = –C(CH3)(H)–OAc

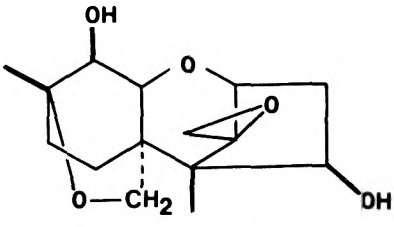
cessively, in the ethyl acetate layer of an ethyl acetate–water partition and in the aqueous methanol layer of a 10% aqueous methanol–petroleum ether partition. The aqueous methanol-soluble material, following filtration through alumina, was submitted to column chromatography on alumina. Elution with 10% methanol in ether gave a fraction containing baccharin (1) and isobaccharin (4), as well as other related trichothecene epoxides. Further column chromatography on silica gel, with methanol in chloroform as eluent, yielded pure baccharin (1), followed by a fraction which, after purification by preparative TLC, gave isobaccharin (4). Elution of the alumina column with methanol gave a residue containing baccharinol (2) and isobaccharinol (3). Rechromatography on silica gel with methanol–ether as eluent, followed by preparative TLC on silica gel, afforded the closely related compounds baccharinol (2) and isobaccharinol (3).

Elemental analysis and high-resolution mass spectrometry established that all four compounds were isomeric, with molecular formula of $C_{29}H_{38}O_{11}$. The ^1H NMR spectrum of each compound contained a pair of doublets (J = 4 Hz) centered at ca. 3.0 ppm corresponding to an exocyclic epoxide, as well as signals characteristic of a dienoate ester. Methanolysis of 1 gave a dimethyl ester, later identified as **5**, and a 15-carbon fragment which was later shown to be **6**, a known compound[8] resulting from intramolecular opening of the 9,10-epoxide by the C-15 hydroxyl.





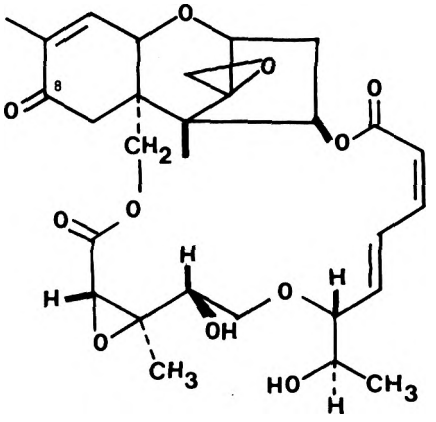




6

Consideration of the above data suggested that these compounds were structurally related to the roridins, a class of macrocyclic diesters of the 12,13-epoxytrichothecene, verrucarol. Confirmation was obtained by the determination of the structure and stereochemistry of baccharin (1) via a direct single-crystal x-ray analysis, the results of which were described in our preliminary communication.[6]

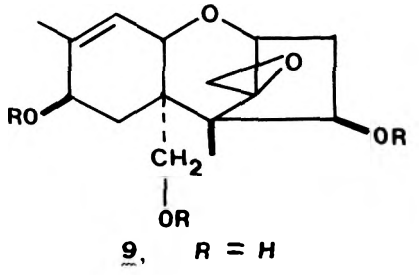
The ^1H NMR spectrum of baccharinol (2) was similar to that of baccharin (1) except that the C-16 methyl at δ 1.37 in 1 was shifted to δ 1.83 in 2 and the C-10 H at δ 3.11 had shifted to δ 5.46, changes which indicated that the 9,10-epoxide in 1



8

was replaced with a carbon–carbon double bond. The last oxygen atom was shown to be present as a hydroxyl group in baccharinol (2), since acetylation of 2 *in pyridine–acetic anhydride* gave triacetate **7**. The allylic nature of the hydroxyl was demonstrated by oxidation of 2 to give the unsaturated ketone **8**. The shift of the C-10 hydrogen resonance from δ 5.46 in 2 to δ 6.63 in the ^1H NMR spectrum of 8 confirmed the α,β-unsaturated ketone functionality of 8 and therefore showed that the hydroxyl was allylic to the C-9,10 double bond.

Methanolysis of 2 yielded dimethyl ester **5**, identical to that obtained from baccharin (1), and the trihydroxytrichothecene **9**. Acetylation of **9** produced triacetate **10**, the ^1H NMR



9, R = H

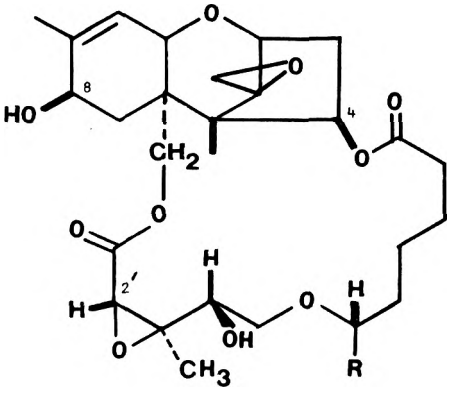
10, R = Ac

spectrum of which contained a doublet of doublets (J = 8 and 4 Hz) at δ 5.24 assigned to the C-8 hydrogen. Examination of molecular models showed that the observed coupling was more readily accommodated by the postulated stereochemistry with the C-8 oxygen function β. Furthermore, trichothecenes with an α C-8 ester function are known,[9] and the proton in question shows coupling constants of 5.5 and 0.2 Hz in these compounds.[10]

The spectral data of isobaccharinol (3) was nearly identical to that of baccharinol (2), suggesting the possibility that the two differed only in stereochemistry. Methanolysis of 3 gave 8β-hydroxyverrucarol (**9**), identical to that obtained from 2, and the dimethyl ester **11**. The ^1H NMR spectrum of 11 differed substantially from that of 5 only in the chemical shift of the C-7 hydrogen, which was shifted from δ 5.83 in 5 to δ 5.96 in 11, indicating the site of the postulated stereochemical change was probably at C-6′ or C-13′. Further evidence for a stereochemical change in the vicinity of C-6′ or C-13′ was obtained by a comparison of the ^{13}C NMR spectra of baccharinol (2) and isobaccharinol (3) (Table I). Careful assignment of the carbon spectra, utilizing broad-band and off-resonance decoupling techniques, and the relative wealth of published ^{13}C NMR spectra of related compounds,[11] revealed that all of the corresponding carbon resonances of the two

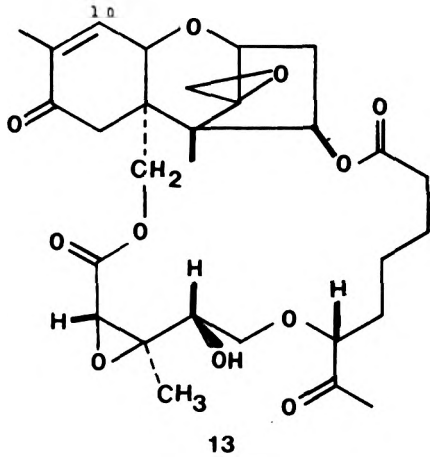
compounds had chemical shifts within a few tenths of 1 ppm of each other with only three exceptions. The exceptions were carbons 6′, 13′, and 14′ which appeared at 86.7, 71.0, and 17.8 ppm, respectively, in **2**, and at 85.2, 69.0, and 15.8 ppm in **3**.

The structure of isobaccharinol (**3**) was finally determined by chemical transformations. Catalytic hydrogenation of **3** gave the tetrahydro derivative **12**. Oxidation of **12** with pyridinium chlorochromate in dichloromethane yielded the diketo compound **13**. The ^{1}H NMR spectrum of **13** showed resonances for a vinyl methyl (δ 1.85, br s) and a vinyl proton (δ 6.52, dq, J = 4 and 1.5 Hz) as in **8**, and, in addition, contained a low-field methyl signal at δ 2.17, characteristic of methyl ketones. The infrared spectrum of **13** contained new carbonyl absorptions at 1720 and 1690 cm^{-1}. Hydrogenation of baccharinol (**2**) gave **14** which was oxidized to **13**, identical in all respects to that derived from **3**. The structure of isobaccharinol (**3**), then, was established to be the C-13′ epimer of baccharinol (**2**).



12, R = 13′-CH$_3$, -H, -OH

14, R = 13′-CH$_3$, -H, -OH



13

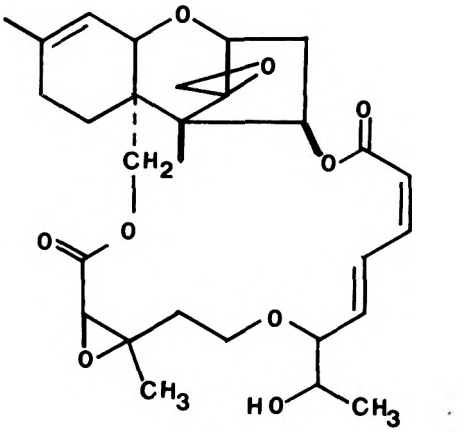
The spectral data of isobaccharin (**4**) suggested that it had the same relationship to baccharin (**1**) as isobaccharinol (**3**) to baccharinol (**2**). Particularly enlightening was the ^{13}C NMR spectra of **4** (Table I), in which the chemical shifts of C-6′, C-13′, and C-14′ were nearly identical to those of **3**, but differed from those of **1** and **2**. Methanolysis of **4** gave **6** and dimethyl ester **11**, the same ester that was obtained from **3**, confirming the structure of isobaccharin (**4**) as the C-13′ epimer of baccharin (**1**).

Table I. ^{13}C NMR Spectra (δ in ppm from Me$_4$Si)[a]

	Baccharinol (2)	Isobaccharinol (3)	Baccharin (1)	Isobaccharin (4)
C-2	78.6	78.8	78.1	78.2
C-3	34.5	34.5	34.0	34.0
C-4	73.8	73.9	73.8	73.9
C-5	48.9	49.1	48.5	48.5
C-6	44.7	44.8	42.3	42.4
C-7	29.6	29.7	16.7	16.7
C-8	66.7	67.0	25.7	25.8
C-9	143.2	143.3	57.7	57.7
C-10	119.4	119.6	56.9	57.0
C-11	66.4	66.7	66.6	66.7
C-12	65.0	65.4	65.2	65.4
C-13	47.2	47.5	47.1	47.2
C-14	6.5	6.7	6.5	6.6
C-15	64.4	64.6	63.1	63.1
C-16	18.3	18.5	21.6	21.6
C-1′	167.3	167.4	167.4	167.4
C-2′	55.9	56.3	56.0	56.1
C-3′	64.8	65.0	64.4	64.4
C-4′	74.9	75.5	75.3	75.6
C-5′	72.0	72.3	72.1	72.1
C-6′	86.7	85.2	86.8	85.3
C-7′	138.1	138.4	138.2	138.7
C-8′	125.3	125.3	125.1	125.0
C-9′	142.2	142.5	142.6	142.7
C-10′	117.7	117.5	117.4	117.1
C-11′	166.2	166.4	166.3	166.3
C-12′	11.8	11.9	11.6	11.6
C-13′	71.0	69.0	71.0	68.8
C-14′	17.8	15.8	17.7	15.6

[a] Spectra measured in $CDCl_3$ solution containing from 5 to 30% CD_3OD.

Trichothecenes, prior to now, have been observed only as secondary metabolites of imperfect fungi,[12] and have never been found in higher plants. It is noteworthy, then, that we found trichothecenes in large amounts (ca. 0.02% w/w of dried plant material) in two separate collections of *B. megapotamica*, especially in view of their high cyto- and phytotoxicity.[12-14] An examination of the dried plant material revealed no obvious fungal contamination; however, it is possible that the compounds we isolated represent plant-altered fungal products. It also should be noted that, while baccharin (**1**), baccharinol (**2**), isobaccharinol (**3**), and isobaccharin (**4**) all show potent in vivo antileukemic activity against P-388 leukemia in mice,[7] very similar compounds, e.g., roridin D (**15**),[15]



15

show no in vivo activity. The key difference seems to be the presence of an oxygen substitutent in the A ring of the trichothecene nucleus in the baccharinoids. Work is presently in progress in these laboratories to determine more fully the

structural features which are necessary for high in vivo activity.

Experimental Section

General. Melting points were determined on a Mettler Model FP2 hot stage and are uncorrected. Ultraviolet absorption spectra were determined on a Beckman Model DK-2A recording spectrophotometer. Infrared spectra were determined on Perkin-Elmer Model 257 and Model 337 recording spectrophotometers. Nuclear magnetic resonance spectra were determined on a Varian HA-100 spectrometer or a JEOL PS-100 p FT NMR spectrometer interfaced to a Texas Instrument JEOL 980A computer, with tetramethylsilane as an internal standard. Mass spectra were determined on Hitachi Perkin-Elmer Model RMU-6E and AEI Model MS-902 spectrometers. Values of $[\alpha]_D$ were determined on a Perkin-Elmer Model 141 automatic polarimeter. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Atlantic Microlab, Inc., Atlanta, Georgia. Petroleum ether refers to the fraction of bp 60–68 °C. All thin-layer chromatography was carried out on prepared plates (E. Merck). Visualization of TLC was effected with short-wavelength UV and concentrated sulfuric acid–vanillin–ethanol (20:1:3) spray.

Extraction and Preliminary Fractionation of *Baccharis megapotamica*. The dried ground twigs and leaves (54 kg) were extracted in 18-kg batches in a Soxhlet extractor with 96 L of 95% ethanol per batch, for successive periods of 6, 15, and 24 h. The combined ethanol extracts were concentrated in vacuo and partitioned between water (15 L) and ethyl acetate (four 12-L portions). Concentration of the ethyl acetate layer gave a residue which was partitioned between 10% aqueous methanol (12 L) and petroleum ether (three 12-L portions). The aqueous methanol-soluble material was taken up in 3 L of methanol–ethyl acetate (1:4) and filtered through a column of alumina (4.5 kg; activity II–III). The alumina was washed with an additional 6 L of methanol–ethyl acetate, and the combined filtrates were evaporated to give a residue which was subjected to column chromatography on alumina (6.5 kg, activity II–III) with ether followed by ether containing increasing amounts of methanol as eluent. Elution with 10% methanol–ether gave fraction A (10 g), and elution with methanol gave fraction B (48 g).

Isolation of Baccharin (1). Fraction A was further fractionated by column chromatography on silica gel 60 (1 kg). Elution with 2% methanol–chloroform gave fraction C (3 g) which was crystallized from methanol–chloroform. Recrystallization from acetone–hexane gave baccharin (**1**, 1.1 g, 0.002%): mp 238–240 °C; $[\alpha]^{24}_D$ +41.5° (*c* 2.2, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 259 nm (18 700); IR ($CHCl_3$) 3600, 3450, 1760, 1720, 1650, 1605 cm^{-1}; NMR ($CDCl_3$) δ 0.75 (3 H, s, 14-H), 1.20 (3 H, d, J = 5.6 Hz, 14′-H), 1.37 (3 H, s, 16-H), 1.65 (3 H, s, 12′-H), 2.48 (1 H, dd, J = 16 and 8.8 Hz, 3α-H), 2.75, 3.16 (each 1 H, d, J = 4 Hz, 13-H), 3.11 (1 H, d, J = 5.8 Hz, 10-H), 3.37 (1 H, s, 2′-H), 4.24, 4.42 (2 H, AB q, J = 12.2 Hz, 15-H), 5.8 (1 H, m, 4-H), 5.82 (1 H, d, J = 11 Hz, 10′-H), 5.98 (1 H, dd, J = 15.5 and 2 Hz, 7′-H), 6.60 (1 H, dd, J = 11 and 11 Hz, 9′-H), 7.48 (1 H, dd, J = 15.5 and 11 Hz, 8′-H); mass spectrum (chemical ionization: methane reagent gas) *m/e* 563.2476 (M^+ + H, calcd for $C_{29}H_{39}O_{11}$, 563.2492).

Anal. Calcd for $C_{29}H_{38}O_{11}$: C, 61.91; H, 6.81. Found: C, 61.78; H, 6.81.

Isolation of Isobaccharin (4). *Continued* elution of the fraction A column with 2% methanol in chloroform gave fraction D (0.37 g). Fraction D was purified by preparative TLC, first on silica gel with 8% methanol in chloroform as eluent, then on alumina with 25% 2-propanol in benzene as eluent, to give a residue which was crystallized from methanol–chloroform. Recrystallization from acetone–hexane gave isobaccharin (**4**, 0.10 g, 0.00018%): mp 228–230 °C; $[\alpha]^{24}_D$ +42° (c 0.36, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 260 nm (21 300); IR (KBr) 3470, 1755, 1710, 1650, 1605 cm^{-1}; NMR ($CDCl_3$) δ 0.76 (3 H, s, 14-H), 1.17 (3 H, d, J = 6.6 Hz, 14′-H), 1.34 (3 H, s, 16-H), 1.68 (3 H, s, 12′-H), 2.47 (1 H, dd, J = 16 and 8 Hz, 3α-H), 2.75, 3.16 (each 1 H, d, J = 4 Hz, 13-H), 3.09 (1 H, d, J = 6 Hz, 10-H), 3.35 (1 H, s, 2′-H), 4.22, 4.47 (2 H, AB q, J = 12.2 Hz, 15-H), 5.8 (1 H, m, 4-H), 5.80 (1 H, d, J = 11 Hz, 10′-H), 5.93 (1 H, dd, J = 16 and 3 Hz, 7′-H), 6.60 (1 H, dd, J = 11 and 11 Hz, 9′-H), 7.44 (1 H, dd, J = 16 and 11 Hz, 8′-H); mass spectrum (chemical ionization: methane reagent gas) *m/e* 563.2493 (M^+ + H, calcd for $C_{29}H_{39}O_{11}$, 563.2492).

Anal. Calcd for $C_{29}H_{38}O_{11}\cdot H_2O$: C, 59.99; H, 6.94. Found: C, 59.79; H, 6.94.

Isolation of Baccharinol (2). Fraction B was subjected to column chromography on silica gel 60 (1 kg). Elution with 10% methanol in ether yielded fractions E and F. Fraction E was combined with similar material obtained from column chromatography or preparative TLC of adjacent fractions and crystallized from methanol–chloroform. Recrystallization from acetone–hexane gave baccharinol (**2**, 3.5 g, 0.0065%): mp 259–263 °C from methanol–chloroform–ether; $[\alpha]^{24}_D$ +165° (c 0.50, MeOH); UV (EtOH) λ_{max} (ϵ) 260 nm (20 400); IR (KBr) 3360, 1750, 1715, 1640, 1600 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (3 H, s, 14-H), 1.18 (3 H, d, J = 6 Hz, 14′-H), 1.59 (3 H, s, 12′-H), 1.83 (3 H, s, 16-H), 2.50 (1 H, dd, J = 15 and 8 Hz, 3α-H), 2.88, 3.13 (each 1 H, d, J = 4 Hz, 13-H), 3.44 (1 H, s, 2′-H), 4.24, 4.44 (2 H, AB q, J = 12 Hz, 15-H), 5.46 (1 H, d, J = 5 Hz, 10-H), 5.8 (1 H, m, 4-H), 5.83 (1 H, d, J = 11 Hz, 10′-H), 6.02 (1 H, dd, J = 15 and 3 Hz, 7′-H), 6.63 (1 H, dd, J = 11 and 11 Hz, 9′-H), 7.42 (1 H, dd, J = 15 and 11 Hz, 8′-H); mass spectrum (chemical ionization: methane reagent gas) *m/e* 563.2465 (M^+ + H, calcd for $C_{29}H_{39}O_{11}$, 563.2492).

Anal. Calcd for $C_{29}H_{38}O_{11}$: C, 61.91; H, 6.81. Found: C, 61.69; H, 6.87.

Isolation of Isobaccharinol (3). Preparative TLC of fraction F on silica gel with 10% methanol in chloroform as eluent gave baccharin (**2**) which was combined with fraction E and a residue which was crystallized from methanol–chloroform–ether. Recrystallization from acetone–hexane gave isobaccharinol (**3**, 0.20 g, 0.00037%): mp 249–251 °C; $[\alpha]^{24}_D$ + 149° (*c* 0.66, MeOH); UV (EtOH) λ_{max} (ϵ) 260 nm (20 400); IR (KBr) 3420, 1750, 1720, 1650, 1605 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (3 H, s, 14-H), 1.16 (3 H, d, J = 6 Hz, 14′-H), 1.65 (3 H, s, 12′-H), 1.83 (3 H, s, 16-H), 2.84, 3.13 (each 1 H, d, J = 4 Hz, 13-H), 3.38 (1 H, s, 2′-H), 4.24, 4.46 (2 H, AB q, J = 12 Hz, 15-H), 5.52 (1 H, d, J = 5 Hz, 10-H), 5.8 (1 H, m, 4-H), 5.81 (1 H, d, J = 11 Hz, 10′-H), 5.92 (1 H, dd, J = 15 and 3 Hz, 7′-H), 6.59 (1 H, dd, J = 11 and 11 Hz, 9′-H), 7.40 (1 H, dd, J = 15 and 11 Hz, 8′-H); mass spectrum (chemical ionization: methane reagent gas) *m/e* 563.2493 (M^+ + H, calcd for $C_{29}H_{39}O_{11}$, 563.2492).

Anal. Calcd for $C_{29}H_{38}O_{11}$: C, 61.91; H, 6.81. Found: C, 61.86; H, 6.85.

Baccharinol Triacetate (7). A solution of 50 mg of baccharinol (**2**) in 2 mL of pyridine and 1 mL of acetic anhydride was allowed to stand at room temperature for 18 h. The solvent was removed *in vacuo* and the residue was crystallized from dichloromethane–hexane to give 47 mg of baccharinol triacetate (**7**): mp 255–257 °C; $[\alpha]^{28}_D$ +145° (*c* 0.39, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 257 nm (18 700); IR (KBr) 1750 (sh), 1735, 1715 (sh), 1640, 1600 cm^{-1}; NMR ($CDCl_3$) δ 0.80 (3 H, s, 14-H), 1.22 (3 H, d, J = 6.3 Hz, 14′-H), 1.71 (6 H, s, 16-H and 12′-H), 2.03, 2.09, 2.16 (each 3 H, s, -OAc), 2.81, 3.13 (each 1 H, d, J = 4 Hz, 13-H), 3.50 (1 H, s, 2′-H), 4.29, 4.53 (2 H, AB q, J = 12 Hz, 15-H), 5.57 (1 H, d, J = 5 Hz, 10-H), 5.8 (1 H, m, 4-H), 5.81 (1 H, d, J = 11 Hz, 10′-H), 5.90 (1 H, dd, J = 15.5 and 3 Hz, 7′-H), 6.60 (1 H, dd, J = 11 and 11 Hz, 9′-H), 7.41 (1 H, dd, J = 15.5 and 11 Hz, 8′-H); mass spectrum (chemical ionization: methane reagent gas) *m/e* 689.2830 (M^+ + H, calcd for $C_{35}H_{45}O_{14}$, 689.2809).

Anal. Calcd for $C_{35}H_{44}O_{14}$: C, 61.04; H, 6.44. Found: C, 61.21; H, 6.42.

8-Ketobaccharinol (8). Baccharinol (**2**, 56 mg, 0.1 mmol), pyridinium chlorochromate (34 mg, 0.15 mmol), and anhydrous sodium acetate (3 mg, 0.3 mmol) were stirred in 4 mL of dichloromethane for 1.5 h. The reaction mixture was filtered, the solids were washed with 10 mL of additional dichloromethane, and the combined filtrate was evaporated in vacuo. Preparative TLC on silica gel with 10% methanol in chloroform as eluent followed by crystallization from 1,2-dichloroethane–ether yielded 8-ketobaccharinol (**8**, 27 mg): mp 265–266 °C; $[\alpha]^{26}_D$ +127° (*c* 0.39, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 259 nm (19 300), 235 (sh) (14 300); IR (KBr) 3450, 1760, 1715, 1680, 1645, 1605 cm^{-1}; NMR ($CDCl_3$) δ 0.81 (3 H, s, 14-H), 1.19 (3 H, d, J = 5.5 Hz, 14′-H), 1.49 (3 H, s, 12′-H), 1.85 (3 H, s, 16-H), 2.86, 3.16 (each 1 H, d, J = 4 Hz, 13-H), 3.53 (1 H, s, 2′-H), 4.15, 4.45 (2 H, AB q, J = 12.5 Hz, 15-H), 5.8 (1 H, m, 4-H), 5.85 (1 H, d, J = 11 Hz, 10′-H), 6.05 (1 H, dd, J = 15.5 and 3 Hz, 7′-H), 6.62 (1 H, dd, J = 11 and 11 Hz, 9′-H), 6.63 (1 H, br d, J = 5 Hz, 10-H), 7.52 (1 H, dd, J = 15.5 and 11 Hz, 8′-H); mass spectrum (chemical ionization: methane reagent gas) *m/e* 561.2320 (M^+ + H, calcd for $C_{29}H_{37}O_{11}$, 561.2336).

Anal. Calcd for $C_{29}H_{36}O_{11}$: C, 62.13; H, 6.47. Found: C, 61.89; H, 6.49.

Hydrolysis of Baccharin (1). A solution of 25 mg of baccharin (**1**) and 20 mg of lithium hydroxide monohydrate in methanol was stirred at room temperature for 3 h. The reaction mixture was passed through a small column (ca. 5 g) of Dowex 50W-X8 ion-exchange resin and the methanol was evaporated. The residue was treated with excess ethereal diazomethane for 30 min. Evaporation of the solvent followed by preparative TLC on silica gel, developed with 6% methanol in chloroform, gave trichothecene **6** (9.2 mg), a compound previously described,[8] and dimethyl ester **5** (7.9 mg), as a colorless glass: $[\alpha]^{19}_D$ +60° (*c* 1.19, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 256 nm (20 000); IR ($CHCl_3$) 3500, 1745, 1710, 1640, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.14 (3 H, d, J = 6 Hz, 14-H), 1.37 (3 H, s, 12-H), 3.74, 3.81 (each 3 H, s,

$-COOCH_3$), 5.74 (1 H, d, J = 11 Hz, 10′-H), 5.83 (1 H, dd, J = 15 and 7 Hz, 7′-H), 6.59 (1 H, dd, J = 11 and 11 Hz, 9′-H), 7.59 (1 H, dd, J = 15 and 11 Hz, 8′-H); mass spectrum m/e 300, 285, 268, 211, 193, 187, 161, 159, 141, 137, 109.

Methanolysis of Baccharinol (2). To a solution of 25 mg of baccharinol (**2**) in 2 mL of dry methanol at room temperature under argon was added slowly 0.4 mL of 1.4 M n-butyllithium in hexane. The mixture was stirred for 2 h, poured onto a small column of silica gel, and washed with 20% methanol in ethyl acetate. The filtrate was evaporated and the residue subjected to preparative TLC on silica gel, developed with 10% methanol in chloroform, to give dimethyl ester **5** (9.7 mg) identical to that obtained from baccharin (**1**) and the trihydroxytrichothecene **9** (11.1 mg), which was crystallized from acetone–hexane: mp 185–186 °C; $[\alpha]^{20}_D$ + 14.5° (c 0.38, MeOH); NMR ($CDCl_3$–CD_3OD, 9:1) δ 0.80 (3 H, s, 14-H), 1.70 (3 H, s, 16-H), 2.38 (1 H, dd, J = 16 and 8 Hz, 3α-H), 2.73, 2.97 (each 1 H, d, J = 4 Hz, 13-H), 3.69 (2 H, s, 15-H), 3.96 (1 H, dd, J = 8 and 4 Hz, 8-H), 4.49 (1 H, dd, J = 8 and 3.4 Hz, 4-H), 5.32 (1 H, d, J = 5.4 Hz, 10-H); mass spectrum m/e 282.14659 (M^+, calcd for $C_{15}H_{22}O_5$, 282.14671).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.86. Found: C, 63.95; H, 7.82.

Acetylation of 4β,8β,15-Trihydroxy-12,13-epoxytrichothecene (9). A solution of 29 mg of **9** in 1 mL each of pyridine and acetic anhydride was allowed to stand at room temperature for 18 h. The solvent was removed in vacuo and the residue crystallized from benzene–hexane to give **10**, 20 mg: mp 124–126 °C; $[\alpha]_D$ +26° (c 0.55, $CHCl_3$); IR ($CHCl_3$) 1735 cm^{-1}; NMR ($CDCl_3$) δ 0.80 (3 H, s, 14-H), 1.70 (3 H, s, 16-H), 2.0 (3 H, m, 3β-H, 7-H), 2.07, 2.08, 2.11 (each 3 H, s, –OAc), 2.52 (1 H, dd, J = 15.5 and 7.5 Hz, 3α-H), 2.85 (1 H, d, J = 5.1 Hz, 2-H), 2.82, 3.14 (each 1 H, d, J = 4 Hz, 13-H), 3.70 (1 H, d, J = 5.8 Hz, 11-H), 4.06, 4.23 (2 H, AB q, J = 12.5 Hz, 15-H), 5.24 (1 H, dd, J = 8 and 4 Hz, 8-H), 5.6 (2 H, m, 4-H and 10-H); mass spectrum m/e 408.17939 (M^+, calcd for $C_{21}H_{28}O_8$, 408.17840).

Anal. Calcd for $C_{21}H_{28}O_8$: C, 61.75; H, 6.91. Found: C, 61.66; H, 7.02.

Methanolysis of Isobaccharinol (3). By a procedure similar to that described for **2**, isobaccharinol gave the trihydroxytrichothecene **9**, identical to that obtained from **2**, and the dimethyl ester **11**: $[\alpha]^{27}_D$ +38° (c 0.14, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 257 nm (19 100); IR ($CHCl_3$) 3500, 1750, 1720, 1645, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.13 (3 H, d, J = 6 Hz, 14-H), 1.36 (3 H, s, 12-H), 3.74, 3.81 (each 3 H, s, $-COOCH_3$), 5.73 (1 H, d, J = 11 Hz, 10′-H), 5.96 (1 H, dd, J = 15.5 and 8 Hz, 7′-H), 6.60 (1 H, dd, J = 11 and 11 Hz, 9′-H), 7.56 (1 H, dd, J = 15.5 and 11 Hz, 8′-H); mass spectrum m/e 300, 285, 268, 211, 193, 187, 161, 159, 141, 137, 109.

Methanolysis of Isobaccharin (4). By a procedure similar to that described for **2**, isobaccharin (**4**) gave **6** and **11**, identical to those described above.

Catalytic Hydrogenation of Baccharinol (2). A solution of baccharinol (**2**, 25 mg) in 25 mL of absolute ethanol was hydrogenated at atmospheric pressure using 10% palladium on charcoal (9 mg) as catalyst. After 2 equiv of hydrogen was taken up, the catalyst was removed by filtration and the solvent evaporated to afford a colorless glass. Crystallization from acetone–hexane gave tetrahydrobaccharinol (**14**): mp 245–246 °C; $[\alpha]^{22}_D$ +32° (c 0.53, $CHCl_3$); IR (KBr) 3430, 1745, 1735 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (3 H, s, 14-H), 1.13 (3 H, d, J = 6 Hz, 14′-H), 1.51 (3 H, s, 12′-H), 1.83 (3 H, s, 16-H), 2.85, 3.16 (each 1 H, d, J = 4 Hz, 13-H), 3.36 (1 H, s, 2′-H), 4.16, 4.31 (2 H, AB q, J = 12 Hz, 15-H), 5.47 (1 H, d, J = 5 Hz, 10-H), 5.70 (1 H, dd, J = 7.5 and 3.5 Hz, 4-H); mass spectrum (chemical ionization: methane reagent gas) 567.2811 (M^+ + H, calcd for $C_{29}H_{43}O_{11}$, 567.2805).

Anal. Calcd for $C_{29}H_{42}O_{11}$: C, 61.47; H, 7.47. Found: C, 61.49; H, 7.48.

Catalytic Hydrogenation of Isobaccharinol (3). By the same procedure as that described above, isobaccharinol (**3**) afforded tetrahydroisobaccharinol (**12**): mp 248–250 °C; $[\alpha]^{22}_D$ +35° (c 0.27, $CHCl_3$); IR (KBr) 3400, 1755, 1735 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (3 H, s, 14-H), 1.15 (3 H, d, J = 6.5 Hz, 14′-H), 1.51 (3 H, s, 12′-H), 1.83 (3 H, s, 16-H), 2.85, 3.16 (each 1 H, d, J = 4 Hz, 13-H), 3.40 (1 H, s, 2′-H), 4.12, 4.38 (2 H, AB q, J = 12 Hz, 15-H), 5.50 (1 H, br d, J = 5 Hz, 10-H), 5.71 (1 H, dd, J = 8 and 4 Hz, 4-H); mass spectrum (chemical ionization: methane reagent gas) 567.2811 (M^+ + H, calcd for $C_{29}H_{43}O_{11}$, 567.2805).

Anal. Calcd for $C_{29}H_{42}O_{11}$: C, 61.47; H, 7.47. Found: C, 61.47; H, 7.50.

Oxidation of Tetrahydrobaccharinol (14). Tetrahydrobaccharinol (**14**, 22 mg, 0.04 mmol), pyridinium chlorochromate (45 mg, 0.21 mmol), and anhydrous sodium acetate (5 mg, 0.06 mmol) were stirred in 2 mL of dichloromethane for 2 h. The reaction was filtered and the solids were washed twice with 2 mL of dichloromethane. The combined filtrates were extracted with 10 mL of water, and the solvent was evaporated. Preparative TLC on silica gel, developed with 6% methanol in chloroform, gave a colorless glass (17 mg). Crystallization from acetone–hexane afforded **13**: mp 260–262 °C; $[\alpha]^{24}_D$ +49° (c 0.34, $CHCl_3$); UV (EtOH) λ_{max} (ϵ) 227 nm (8450); IR (KBr) 3400, 1760, 1730, 1720, 1690 cm^{-1}; NMR δ 0.82 (3 H, s, 14-H), 1.44 (3 H, s, 12′-H), 1.85 (3 H, br s, 16-H), 2.17 (3 H, s, 14′-H), 2.85, 3.17 (each 1 H, d, J = 4 Hz, 13-H), 3.51 (1 H, s, 2′-H), 4.05, 4.47 (2 H, AB q, J = 12.5 Hz, 15-H), 5.80 (1 H, dd, J = 7.5 and 4 Hz, 4-H), 6.52 (1 H, dq, J = 4 and 1.5 Hz, 10-H); mass spectrum (chemical ionization: methane reagent gas) 563.2482 (M^+ + H, calcd for $C_{29}H_{39}O_{11}$, 563.2492).

Anal. Calcd for $C_{29}H_{38}O_{11}$: C, 61.91; H, 6.81. Found: C, 61.67; H, 6.88.

Oxidation of Tetrahydroisobaccharinol (12). By the same procedure as that described for **14**, tetrahydroisobaccharinol (**12**) gave **13**, identical to that obtained from **14**.

Registry No.—**1**, 61251-97-6; **2**, 63783-94-8; **3**, 63814-57-3; **4**, 63814-58-4; **5**, 63783-95-9; **6**, 63783-96-0; **7**, 63783-97-1; **8**, 63783-98-2; **9**, 63783-99-3; **10**, 63784-00-9; **11**, 63814-59-5; **12**, 63784-01-0; **13**, 63784-02-1; **14**, 63814-60-8.

References and Notes

(1) Tumor Inhibitors 125. Part 124: S. M. Kupchan, A. T. Sneden, A. R. Branfman, G. A. Howie, L. I. Rebhun, W. E. McIvor, R. W. Wang, and T. C. Schnaitman, *J. Med. Chem.*, submitted for publication.

(2) This investigation was supported by grants from the National Cancer Institute (CA-11718) and American Cancer Society (CH-42L and CH-42M), and by a contract with the Division of Cancer Treatment, National Cancer Institute (N01-CM-67002). One of us (B.B.J.) wishes to thank the National Institutes of Health for a National Research Service Award (1F32 CA05368-01).

(3) Visiting Scholar, 1975–1976; on sabbatical leave, University of Maryland, College Park, Md.

(4) Leaves, twigs, and flowers were collected in Brazil in May 1975. The authors acknowledge with thanks receipt of the dried plant material from Dr. R. E. Perdue, Jr., United States Department of Agriculture, Baltimore, Md., in accordance with the program developed by the National Cancer Institute.

(5) Antileukemic activity was assayed under the auspices of the National Cancer Institute by the procedures described by R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep., Part 3*, **3**, 1 (1972).

(6) S. Morris Kupchan, Bruce B. Jarvis, Richard G. Dailey, Jr., William Bright, Robert F. Bryan, and Yoshikazu Shizuri, *J. Am. Chem. Soc.*, **98**, 7092 (1976).

(7) Baccharin (**1**) and isobaccharin (**4**) gave typical *T/C* values in the range of 180–230 at dose levels of 0.5 to 8 mg/kg against PS. Baccharinol (**2**) and isobaccharinol (**3**) showed *T/C* values of 160–220 in the dosage range of 0.5 to 4 mg/kg. All four compounds showed cytotoxicity (ED_{50}) against KB cell culture at 10^{-3}–10^{-4} μg/mL.

(8) W. Zürcher, J. Gutzwiller, and Ch. Tamm, *Helv. Chim. Acta*, **48**, 840 (1965).

(9) J. R. Bamburg, N. V. Riggs, and F. M. Strong, *Tetrahedron*, **24**, 3329 (1968).

(10) A single crystal x-ray analysis of a related compound from *B. megapotamica* proves conclusively the β stereochemistry of the C-8 hydroxyl. Details will be presented in a forthcoming publication.

(11) (a) W. Breitenstein and Ch. Tamm, *Helv. Chim. Acta*, **58**, 1172 (1975). (b) J. R. Hanson, T. Marten, and M. Siverns, *J. Chem. Soc., Perkin Trans. 1*, 1033 (1974). (c) R. A. Ellison and F. N. Kotsonis, *J. Org. Chem.*, **41**, 576 (1976).

(12) J. R. Bamburg and F. M. Strong, *Microbial Toxins*, **7**, 207 (1971).

(13) J. R. Bamburg, *Adv. Chem. Ser.*, **149**, 144 (1976).

(14) Ch. Tamm, *Fortschr. Chem. Org. Naturst.*, **31**, 63 (1974).

(15) B. Böhner and Ch. Tamm, *Helv. Chim. Acta*, **49**, 2547 (1966). Roridin D was also isolated from *B. megapotamica* and found to be inactive against the P-388 leukemia in mice.

(16) Deceased Oct. 19, 1976.

Reaction of α-Keto Triflates with Sodium Methoxide

Xavier Creary* and Anthony J. Rollin

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

Received May 17, 1977

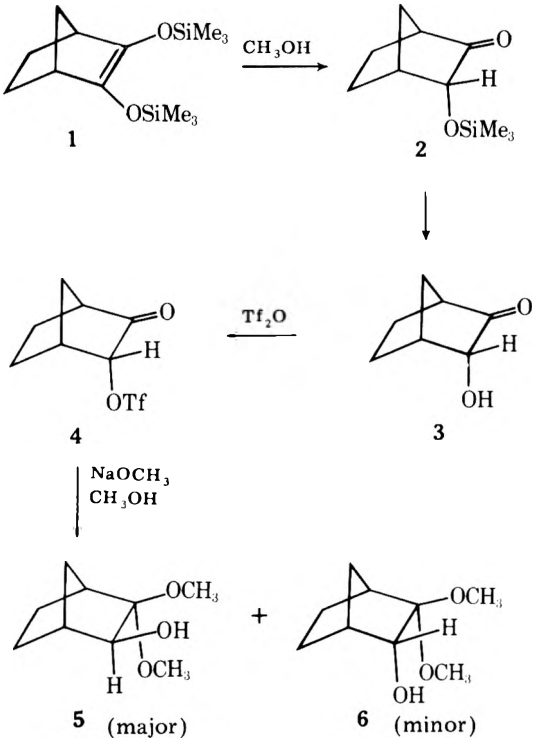
2-Oxo-*endo*-bicyclo[2.2.1]hept-3-yl triflate (**4**) reacts with sodium methoxide in methanol to give *exo*-2,2-dimethoxybicyclo[2.2.1]heptan-3-ol (**5**) as the major product along with smaller amounts of the endo epimer **6**. Complete deuterium incorporation was observed in the carbinyl position of these ketal alcohols when the reaction was carried out in the presence of methanol-d_1. These results were interpreted in terms of the intermediacy of an alkoxy epoxide intermediate which results from endo attack at the carbonyl center and intramolecular displacement of triflate. The epoxide intermediate could be independently generated, in situ, by epoxidation of 2-methoxybicyclo[2.2.1]hept-2-ene (**17**), but opened to give **5**. The reaction appears to be quite general for α-keto triflates. Opening of the methoxy epoxides derived from 2-oxo-*exo*-bicyclo[2.2.1]hept-3-yl triflate (**12**) and oxocyclohex-2-yl triflate (**32**) gave α-methoxy ketone products in addition to the ketal alcohols. Hydride migration in a zwitterionic intermediate is the suggested origin instead of direct S_N2 displacement of triflate. Triflate **32** gave no Favorskii ring contraction or deuterium incorporation in methanol-d_1, suggesting that epoxide formation is much more rapid than potential enolization processes.

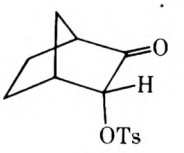
α-Hydroxy ketones are easily prepared via the Ruhlmann and Schrapler modification of the acyloin condensation[1] or epoxidation of silyl enol ethers.[2] The carbonyl function next to the hydroxyl group, in principle, should allow the preparation of secondary trifluoromethanesulfonate (triflate) esters without the problem of in situ solvolysis. It was also anticipated that the extreme lability of this leaving group could lead to unusual transformations of the α-keto triflates. We have prepared some of these triflate esters and have undertaken a study of their reaction with sodium methoxide with the goal of understanding the diverse mechanistic processes which can occur.

Results and Discussion

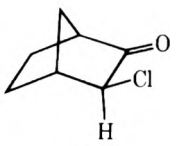
2-Oxo-*endo*-bicyclo[2.2.1]hept-3-yl Triflate. α-Hydroxy ketone **3** could be readily prepared from bis(trimethylsilyl) ether **1** in a methanolysis procedure. The intermediate keto silyl ether **2** can be isolated without significant amounts of the α-hydroxy ketone **3** if triethylamine is added. Conversion of **3** to 2-oxo-*endo*-bicyclo[2.2.1]hept-3-yl triflate (**4**) was straightforward. Treatment of triflate **4** with excess sodium methoxide in methanol at 0 °C led to formation of 3,3-dimethoxy-*exo*-bicyclo[2.2.1]heptan-2-ol (**5**) in 68% yield and 12% of 3,3-dimethoxy-*endo*-bicyclo[2.2.1]heptan-2-ol (**6**). Even under more strenuous conditions, keto tosylate **7** failed to undergo the analogous reaction. Chloro ketone **8** was epimerized under the attempted reaction conditions to a 1:1.6 mixture of exo and endo isomers,[3] while tosylate **7** gave none of the ketal alcohol. This is in line with the approximately 10^5 greater reactivity of triflates relative to tosylates.[5]

Scheme I





7



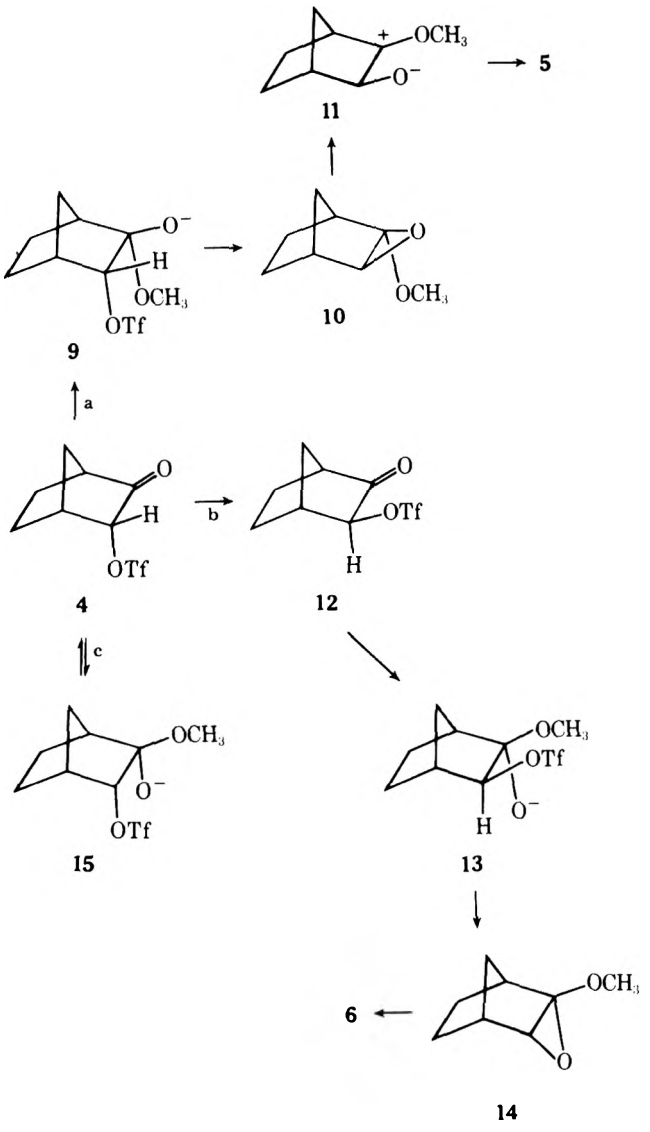
8

A mechanistic scheme to account for the formation of **5** is given in Scheme II. We envisage three competing reactions of triflate **4** with methoxide. Process a involves endo attack of methoxide at the carbonyl center leading to tetrahedral intermediate **9**. Collapse of **9** would lead to the exo epoxide **10**. Opening of epoxide **10** under the reaction conditions[4] via zwitterion **11** would lead to the observed 3,3-dimethoxy-*exo*-bicyclo[2.2.1]heptan-2-ol (**5**). This opening of epoxide **10** followed by methanol capture is preferred over a bimolecular process involving methoxide attack on epoxide **10**. That such processes can occur has been shown in the uncatalyzed opening of allylic epoxides via allylically stabilized cationic intermediates.[6]

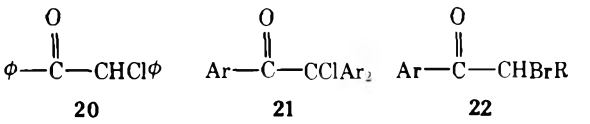
The viability of the suggested mechanism has been supported by the in situ generation of epoxide **10** as shown in Scheme III. Ketalization of 3-chloronorcamphor (**8**) gave **16**. Attempted dechloromethoxylation with sodium in liquid ammonia gave norcamphor dimethyl ketal **18** and only traces of **17**. Treatment of **16** with magnesium–ethylene dibromide in refluxing tetrahydrofuran gave the desired, extremely acid sensitive, enol ether **17**. Reaction with *m*-chloroperbenzoic acid in methanol containing sodium carbonate gave none of epoxide **10**. The product of methanol addition, ketal alcohol **5**, along with norcamphor dimethyl ketal **18** were produced. This observation strongly supports the intermediacy of exo epoxide **10** in the reaction of keto triflate **4** with sodium methoxide.

The formation of alkoxy epoxides by such a mechanism is not unprecidented. Alkoxy epoxides intervene in the reaction of certain aromatic halo ketones, namely, **20**,[7] **21**,[7,8] and **22**,[9] with sodium methoxide. The reactions are overall second

Scheme II



order. With care, in certain cases the epoxide intermediates can be isolated.[10] The present example is of special interest in that the system is purely aliphatic and involves endo attack on a norbornyl system. The highly reactive triflate leaving group is necessary to achieve the epoxide-forming reaction in this system, since direct rearward displacement of a leaving group in the intermediate methoxide complex in this rigid system is precluded.

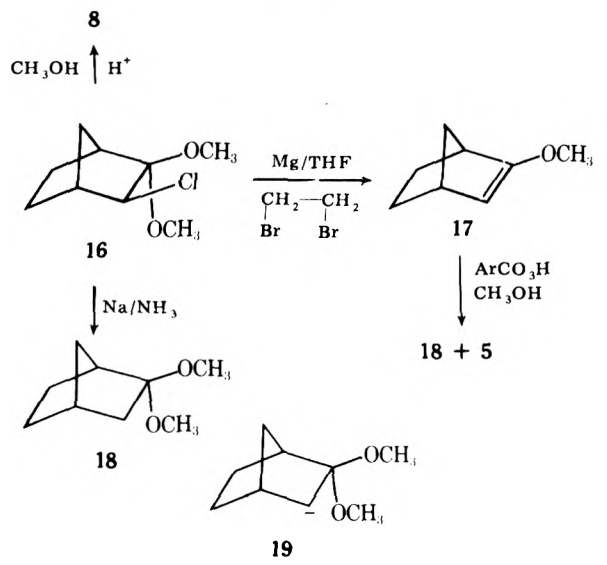


20 21 22

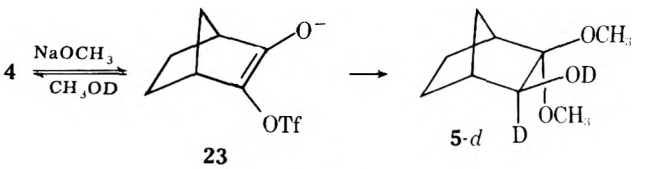
An alternate reaction pathway for triflate 4 (path b) involves isomerization to the exo epimer 12. Addition of methoxide from the exo side of 12 would lead to the 3,3-dimethoxy-*endo*-bicyclo[2.2.1]heptan-2-ol (6) as shown in Scheme II. We believe that this process must be included to account for the small amount of 6 seen in this reaction. Process c, which involves exo attack of methoxide at the carbonyl center of 4, is, no doubt, a more rapid process than the endo attack route. It is suggested that this process is nonproductive and reversible with the two products arising via paths a and b. The overall conversion of 4 to 5 represents a rare case of the major product of a reaction resulting from endo attack on an unencumbered bicyclo[2.2.1]heptyl system. In methanol-d_1, the ketal alcohol product **5d** was completely deuterated in the α position. Apparently, rapid reversible deprotonation of 4 giving enolate ion 23 occurs faster than the endo attack of methoxide at the carbonyl center.

2-Oxo-*exo*-bicyclo[2.2.1]hept-3-yl Triflate. The suggested origin of *endo*-3,3-dimethoxybicyclo[2.2.1]heptan-2-ol (6) in the reaction of triflate 4 with sodium methoxide involved the intermediacy of *exo*-triflate 12. The independent preparation of 12 was accomplished by epoxidation–hydrolysis of silyl enol ether 24 which gave the dimer of 25. Subsequent conversion to the triflate derivative 12 and treatment of 12 with sodium methoxide in methanol gave the endo ketal alcohol 6 and a small amount of *endo*-3-methoxybicyclo[2.2.1]-heptan-2-one (27). The inverted stereochemistry of 27 (relative to 12) initially suggests an S_N2 type displacement as its origin. While we have not ruled out this possibility, we prefer the hydride shift mechanism shown in Scheme VI to account for the formation of 27. This mechanism, in addition to accounting for the stereochemistry of 27, also accounts for the fact that *endo*-triflate 4 gives none of the analogous *exo*-3-methoxybicyclo[2.2.1]heptan-2-one. Such a product would require an endo hydride migration in a norbornyl system. Such processes are quite unfavorable.[11] An S_N2 mechanism for the

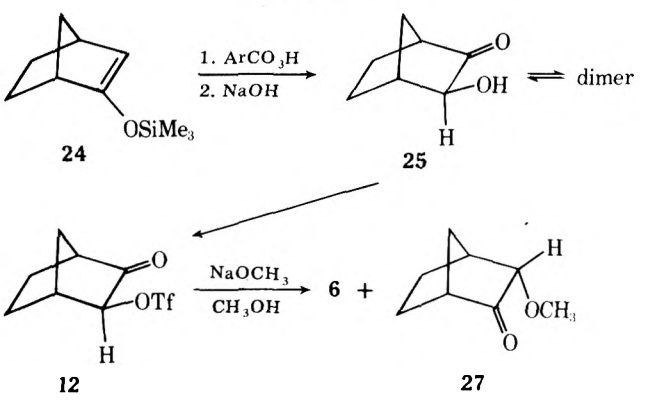
Scheme III



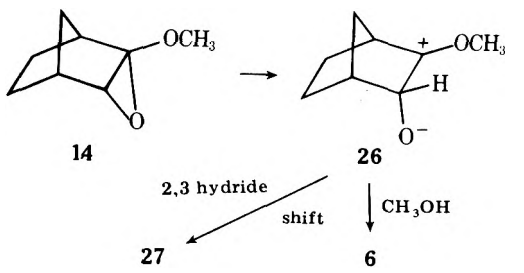
Scheme IV



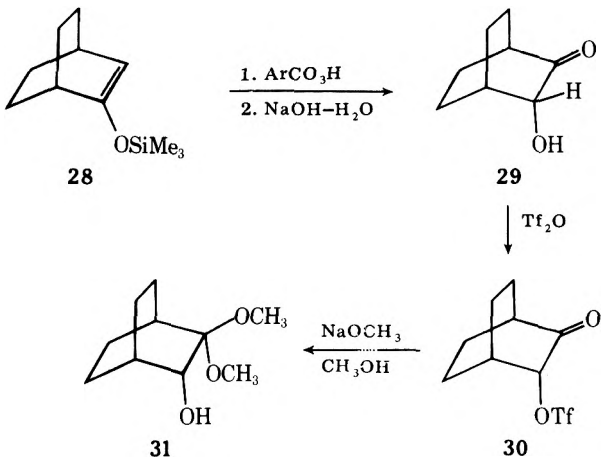
Scheme V



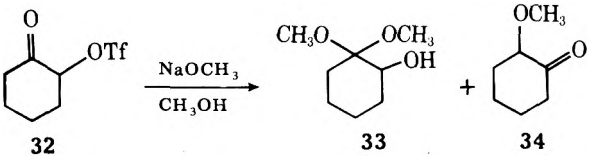
Scheme VI



Scheme VII



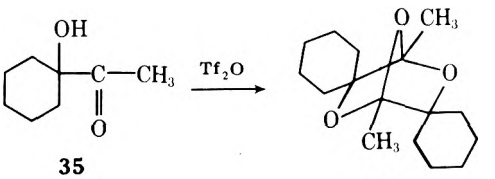
Scheme VIII



formation of **27** would also require an endo approach of methoxide on **12**. This process should be less favorable than an exo approach to triflate **4**. The relative amounts of keto ethers formed in reaction of triflates **4** and **12** with sodium methoxide are therefore not consistent with an S_N2 process.[12]

Generality of the Reaction. Attention was next turned to an evaluation of the generality of the reaction of α-keto triflates with sodium methoxide. Hydroxy ketone **29** could be prepared by epoxidation–hydrolysis of silyl enol ether **28**. Reaction of the triflate derivative **30** with sodium methoxide gave ketal alcohol **31**. The triflate derivative **32** of 2-hydroxycyclohexanone also gave a ketal alcohol product **33** along with 2-methoxycyclohexanone (**34**). It is interesting to note that *none* of the Favorskii product, methyl cyclopentanecarboxylate, is formed under the reaction conditions. The reaction of **32** truely contrasts with the reaction of 2-chlorocyclohexanone with methoxide[13] and demonstrates the generality of the alkoxy epoxide forming reaction even when the Favorskii ring contraction is a mechanistic alternative. The triflate leaving group is undoubtedly the key which allows rapid epoxide formation while bypassing the Favorskii product. The keto ether product could arise by a direct displacement of triflate by methoxide as well as by a variety of processes involving the alkoxy epoxide intermediate. In contrast to triflate **4**, reaction of **32** with sodium methoxide in methanol-d_1 gave *no* deuterium incorporation in the carbinyl position of ketal alcohol product **33**. This attests to the rapidity of the epoxide-forming reaction to the complete exclusion of enolate-forming reactions of **32**.

Although the preparation of certain triflate derivatives of α-hydroxy ketones was quite straightforward, all attempted preparations were not uniformly successful. Attempted conversion of 2-hydroxycyclopentanone to the triflate derivative by usual procedures gave no isolable products. The triflate derivative of 2-hydroxycyclohexanone (**32**) decomposed readily when inpure. Also attempts to prepare **32** in pyridine as solvent were unsuccessful. Also unsuccessful was an attempt to prepare the triflate derivative of **35**. In addition to recovered starting alcohol, only a product of dehydration, **36**, was isolated.[14]



Experimental Section

NMR spectra were recorded on a Varian A-60A or XL-100 spectrometer. Mass spectra were recorded on an AEI Scientific Apparatus MS902 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 455 or Infracord spectrometer.

Methanolysis of 1. Bis(trimethylsilyl) ether **1** (5.0 g), prepared as previously described,[15] was dissolved in 25 mL of dry methanol under nitrogen. After refluxing for 15 min, the solvent was removed under vacuum leaving 2.2 g of crude **3**. The residue was slurried with pentane and 1.66 g (71%) of crystalline **3** was collected: mp 137–143 °C (lit.[16] mp 143–151 °C); IR (neat) ν_{O-H} 2.88 μm, $\nu_{C=O}$ 5.71 μm; NMR (CCl_4) δ 4.0–4.2 (1 H, br s, exchanges with D_2O), 3.88 (1 H, d of d, J = 1.5 and 5 Hz), 2.25–2.85 (2 H, m), 1.1–2.3 (6 H, m).

Methanolysis of 1 with Triethylamine Present. Bis(trimethylsilyl) ether **1** (10 g) was dissolved in 50 mL of dry methanol containing five drops of triethylamine. After a 2-h reflux, the solvent was removed under vacuum, and the infrared and NMR spectra of the residue were recorded: IR (neat) no OH, $\nu_{C=O}$ 5.68 μm, ν_{C-C} 5.95 μm (m, unreacted **1**); NMR (CCl_4) δ 3.78, (d of d, J = 1.3 and 4.5 Hz, C-3 H of **2**), and multiplets at 2.4–2.65, 0.75–2.3, 0.05–0.25 consistent with a mixture of **2** and **1**. After addition of 50 mL of dry methanol and another 2-h reflux, the solvent was again removed by vacuum. The residue had an infrared spectrum consistent with a mixture of **1**, **2**, and **3**. Even longer reflux times with more methanol consumed **1** and gave mixture of **2** and **3**.

Preparation of 4. Pyridine (30 mL) was cooled in an ice–water bath and 8.46 g of trifluoromethanesulfonic anhydride was added slowly dropwise with stirring. The ice bath was removed until the white precipitate dissolved completely and the solution was recooled in the ice bath. Keto alcohol **3** (3.15 g) was added slowly in small portions, and the resulting solution was stored at −15 °C for 2.5 h. The solution was then diluted with 30 mL of ether and extracted with water. The water layer was separated and extracted with ether, and the combined ether extracts were washed with water, cold dilute hydrochloric acid until acidic, and brine. After standing over sodium sulfate, the solvent was removed through a Vigreux column on a steam bath and the residue was distilled to give 5.31 g (82%) of **4**: bp 62–64 °C (0.05 mm); IR (neat) C=O 5.64 μm; NMR (CCl_4) δ 4.89 (1 H, d, J = 5 Hz), 2.87–3.15 (1 H, m), 2.65–2.87 (1 H, m), 1.0–2.5 (6 H, m); mass spectroscopic molecular weight, 258.0191 (calcd for $C_8H_9F_3O_4S$, 258.0173).

Reaction of 4 with Sodium Methoxide in Methanol. Sodium (0.96 g) was dissolved in 25 mL of dry methanol under nitrogen and the solution was cooled to 0 °C. Triflate **4** (1.88 g) was added dropwise and the solution was refluxed for 1.8 h. After diluting with ether, the solution was extracted with water. The water layer was extracted with another portion of ether. The combined ether extracts were washed with water and brine, and dried over sodium sulfate. The solvents were removed through a Vigreux column and the residue was distilled to give 0.85 g (80%) of a 5.7 to 1 mixture of **5** and **6**,[11c] bp 67–69 °C (1.5 mm). In a separate run, gas chromatographic analysis on 5 ft, 5% SE30 on chromsorb G (column A), showed immediate consumption of **4** when added to sodium methoxide in methanol at 0 °C. Ketal alcohol **5** had the following spectral properties: NMR (CCl_4) δ 3.1–3.4 (7 H, m with sharp s at 3.18 and 3.29), 2.7–3.0 (1 H, br s, exchanges with D_2O), 1.87–2.40 (8 H, m); mass spectroscopic molecular weight 172.1076 (calcd for $C_9H_{16}O_3$, 172.1099).

Reaction of 4 with Sodium Methoxide in Methanol-d_1. The procedure was the same as that above, except the reaction time was 10 min at 25 °C after addition of **4**. Sodium (0.16 g), 7 mL of methanol-d_1, and 0.79 g of **4** gave 0.42 g (79%) of **5**-*d*: bp 69 °C (2 mm). Complete deuteration at C-3 was confirmed by conversion of **5**-*d* to its acetate[11c] followed by NMR analysis. The NMR of the acetate of **5** shows the C-3 H cleanly separated from all other absorptions.[11c]

Preparation of 7. Keto alcohol **3** (1.34 g) was dissolved in 15 mL of pyridine and cooled to 0 °C in an ice-water bath. *p*-Toluenesulfonyl chloride (2.13 g) was added in small portions and the solution was stored at −5 °C for 24 h. The reaction mixture was diluted with 50 mL of ether and extracted with water, dilute hydrochloric acid until acidic, brine, and dried over sodium sulfate. The solvent was removed by a rotary evaporator, leaving 2.36 g (79%) of **7** which was recrystallized from methanol: mp 102.5–103.5 °C; IR (neat) $\nu_{C=O}$ 5.69 μm; NMR ($CDCl_3$) δ 7.75–8.0 (2 H, m), 4.58 (1 H, d, J = 5 Hz), 2.55–3.05 (2 H, m), 2.45 (3 H, s), 1.2–2.2 (6 H, m).

Anal. Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75. Found: C, 60.09; H, 5.77.

Preparation of 16. Chloro ketone **8**[17] (8.0 g) was dissolved in 40 mL of dry methanol and 7.4 g of trimethyl orthoformate. *p*-Toluenesulfonic acid monohydrate (250 mg) was added and the solution was refluxed for 10.5 h. After cooling, the acid was neutralized with sodium methoxide and the solvents were removed at 140 mm. The residue was distilled to give 10.12 g (96%) of **16**: bp 73–75 °C (0.85 mm); NMR (100 MHz, $CDCl_3$) δ 3.69 (1 H, d, J = 2.5 Hz), 3.34 (3 H, s), 3.25 (3 H, s), 2.25–2.55 (2 H, m), 1.1–2.25 (6 H, m); mass spectroscopic molecular weight 190.0752 (calcd for $C_9H_{15}O_2Cl$, 190.0760).

Preparation of 17. Chloro ketal **16** (2.02 g) was dissolved in 15 mL of dry tetrahydrofuran (THF) and 0.84 g of magnesium was added. After refluxing for 1.5 h under nitrogen, 4 g of 1,2-dibromoethane in 5 mL of THF was added dropwise over 3 h to the refluxing mixture. The mixture was cooled, filtered, and diluted with ether. The organic phase was extracted with dilute sodium carbonate and brine, and dried over sodium sulfate. Two drops of triethylamine were added and the solvents were removed through a Vigreux column. The residue was distilled to give 0.34 g of a mixture of three products containing 60% of **17** or 15% overall yield of **17** from **16**. Enol ether **17** had spectra consistent with those previously reported.[18]

Reaction of 17 with *m*-Chloroperbenzoic Acid in Methanol. Sodium acetate (94 mg) and sodium carbonate (122 mg) were suspended in 3 mL of dry methanol. *m*-Chloroperbenzoic acid (284 mg) was added. The enol ether **17** (170 mg, 60% of the mixture as prepared above) was added in 1 mL of methanol at 0 °C. After the addition of **17**, the reaction was warmed to 25 °C and stirred for 1 h. Ether and water were added, and the phases were separated. The ether layer was washed with dilute sodium thiosulfate and brine, and dried over sodium sulfate. The solvents were removed through a Vigreux column and the residue was distilled (1–2 mm) to give 70.3 mg of a mixture of **5** (60%) and **18**[18] (40%).

Reaction of 16 with Sodium in Liquid Ammonia. Liquid ammonia (10 mL) was condensed into a mixture of 1 g of **16** in 2 mL of dry ether. Sodium was then added in small pieces under nitrogen until a blue color persisted, and the solution was stirred for another 15 min. Water was carefully added. After the ammonia had evaporated, the aqueous phase was extracted with two portions of ether. The combined ether extracts were washed with brine and dried over sodium sulfate. The solvent was removed through a Vigreux column and the residue was distilled to give 0.56 g of a 4 to 1 mixture of **18**[18] and **17**.

Preparation of 24. Methyl lithium (138 mL of 1.84 M) was added slowly dropwise to 27.6 g of diisopropylamine dissolved in an equal volume of dry ether under nitrogen. The resulting solution was cooled to −78 °C in a dry ice-acetone bath and 19.7 g of norcamphor in 20 mL of ether was slowly added dropwise. After stirring for 10 min, the solution was warmed to 0 °C and 46 mL of chlorotrimethylsilane was added all at once. The solution was warmed to 25 °C and stirred for 30 min. The mixture was then extracted with cold dilute sodium bicarbonate and brine, and dried over sodium sulfate. The solvents were removed through a Vigreux column and the residue was distilled to give 26.08 g (80%) of **24**: bp 58–63 °C (14 mm); IR (neat) $\nu_{C=C}$ 6.20 μm; NMR (CCl_4) δ 4.50 (1 H, d, J = 3 Hz), 2.3–2.8 (2 H, m), 0.7–1.9 (6 H, m), 0.07 (9 H, s); mass spectroscopic molecular weight 182.1109 (calcd for $C_{10}H_{18}OSi$, 182.1127).

Reaction of 24 with *m*-Chloroperbenzoic Acid. *m*-Chloroperbenzoic acid (6.12 g of Aldrich 85% peracid) was suspended in 130 mL of dry hexane and the mixture was cooled in an ice-methanol bath. Silyl ether **24** (5 g) was dissolved in 50 mL of hexane and was added dropwise over 15 min. After stirring for another hour, the *m*-chlorobenzoic acid was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 60 mL of ether and 50 mL of 15% aqueous sodium hydroxide was added. After vigorously stirring the system for 11.5 h, the phases were separated and the aqueous phase was extracted with a 20-mL portion of ether. The combined ether phases were washed with a small portion of water and brine, and dried over sodium sulfate. The solvent was removed by a rotary evaporator, leaving an oil which consisted mostly of noncamphor and **25**. Upon standing, the dimer crystallized from the oil and was collected in several crops. The yield was 0.28 g (8%) which could be cleaved to monomer **25** by heating to its melting point or by sublimation at 1–2 mm. The dimer of **25** melted at 139–145 °C. Previously reported **25**[19] had the following properties: IR (neat) ν_{O-H} 2.84 μm, $\nu_{C=O}$ 5.79 μm; NMR ($CDCl_3$) δ 3.52 (1 H, d, J = 2.8 Hz), 2.98 (1 H, br s, exchanges with D_2O), 2.5–2.7 (2 H, m), 1.1–2.4 (6 H, m).

Preparation of 12. Pyridine (3 mL) was cooled in an ice-water bath and 0.29 g of triflic anhydride was added dropwise. Monomer **25** (0.100 g), prepared by heating the dimer to the melting point, was added rapidly using a small amount of methylene chloride as solvent. The resulting solution was stored at −15 °C for 55 min. Ether (10 mL) was added, and the mixture was extracted with water, cold dilute hydrochloric acid until acidic, and brine, and dried over sodium sulfate. The solvent was removed through a Vigreux column, the last traces by rotary evaporator. Pentane (5 mL) was added to the residue and the solution was stored at −15 °C overnight. The solid which had formed was separated by decantation of the solvent and washing with another portion of fresh pentane. The solid was unreacted dimer (0.04 g). The pentane solution was concentrated by rotary evaporator and the residue was distilled to give 0.076 g (62% based on unrecovered **25**) of **12**: bp 65–72 °C (0.07 mm); IR (neat) $\nu_{C=O}$ 5.64 μm; NMR (CCl_4) δ 4.43 (1 H, d, J = 2.8 Hz), 2.6–3.0 (2 H, m), 1.4–2.4 (6 H, m); mass spectroscopic molecular weight, 258.0198 (calcd for $C_8H_9F_3O_4S$, 258.0173).

Reaction of 12 with Sodium Methoxide in Methanol. Triflate **12** (0.0511 g) was dissolved in 0.4 mL of dry methanol at 25 °C, and 0.3 mL of 1 M sodium methoxide in methanol was immediately added all at once. After stirring for 1 h, the solution was diluted with 7 mL of ether. The ether phase was extracted with water and brine, and dried over sodium sulfate. Gas chromatographic analysis on column A indicated two products, **6** and **27**, which were identified by spectral comparison with authentic samples[11c] after separation by preparative gas chromatography on 6 ft, 5% SE30 on chromosorb G (column B). The yields of **6** and **27** were 70 and 22% as determined by gas chromatography using napthalene as an internal standard.

Preparation of 28 The procedure was identical to that used for the preparation of **24**. Diisopropylamine (1.80 g), 1.84 M methyllithium (9.2 mL), bicyclo[2.2.2]octan-2-one (2.00 g), and chlorotrimethylsilane (3.5 g) gave 2.87 g (88%) of **28**: bp 85–87 °C (12 mm); IR (neat) $\nu_{C=C}$ 6.08 μm; NMR (CCl_4) δ 4.98 (1 H, d of d, J = 2 and 7 Hz), 2.0–2.3 (2 H, m), 1.1–1.9 (8 H, m), 0.14 (9 H, s); mass spectroscopic molecular weight, 196.1277 (calcd for $C_{11}H_{20}OSi$, 196.1283).

Reaction of 28 with *m*-Chloroperbenzoic Acid in Hexane. The procedure was identical to that used for the reaction of **24** with with *m*-chloroperbenzoic acid. Silyl ether **28** (1.70 g) dissolved in 12 mL of hexane was added to a cooled suspension of 1.57 g of *m*-chloroperbenzoic acid in 35 mL of hexane. After filtration and solvent removal, the residue was partitioned between 13 mL of ether and 25 mL of 10% aqueous sodium hydroxide for 12 h. Workup gave a mixture of bicyclo[2.2.2]octan-2-one and the desired hydroxy ketone **29** in a ratio of about 2 to 1 as determined by gas chromatographic analysis (column A). The hydroxy ketone dimer was separated by slurrying the mixture with petroleum ether and filtering off the insoluble dimer. The yield of dimer was 0.33 g (27%). The monomeric **29** could be obtained by heating the dimer to the melting point as previously described.[20]

Preparation of 30. Pyridine (2.5 mL) was cooled in an ice-water bath and 0.33 g of triflic anhydride was added slowly dropwise. The dimer of **29** (0.13 g) was melted (sealed tube) and transferred to the cooled solution with 1.5 mL of pyridine. After storing at −15 °C for 2 h, 10 mL of ether was added, and the organic phase was extracted with cold water, cold dilute hydrochloric acid until acidic, cold water, and brine, and dried over sodium sulfate. The solvents were removed through a Vigreux column on a steam bath, with the last traces being removed by a rotary evaporator, leaving 0.21 g (87%) of offwhite unstable solid triflate **30**, mp 48–51 °C; IR (KBr pellet) $\nu_{C=O}$ 5.73 μm; NMR (CCl_4) δ 4.88 (1 H, d, J = 2.7 Hz) 2.3–2.6 (2 H, m), 1.5–2.3 (8 H, m); mass spectroscopic molecular weight, 272.0340 (calcd for $C_9H_{11}F_3O_4S$, 272.0330).

Reaction of 30 with Sodium Methoxide in Methanol. Sodium (0.10 g) was dissolved in 4 mL of dry methanol and the solution was cooled in an ice-water bath. Keto triflate **30** (0.13 g) was dissolved in

dry ether and added dropwise. The solution was refluxed for 30 min, cooled, and diluted with 20 mL of ether. The organic phase was extracted with water and brine, and dried over sodium sulfate. The solvent was removed through a Vigreux column and the residue was distilled to give 0.05 g (56%) of **31**, contaminated with traces of two lower boiling unidentified components: bp 80–83 °C (2.0 mm); IR (neat) ν_{O-H} 2.73 μm; NMR (CCl_4) δ 3.50–3.65 (1 H, m), 3.26 (3 H, s), 3.20 (3 H, s), 2.8–3.1 (1 H, br s, exchanges with D_2O), 1.0–2.0 (10 H, m); mass spectroscopic molecular weight, 186.1252 (calcd for $C_{10}H_{18}O_3$, 186.1256).

Preparation of 32. Pyridine (0.68 g) was dissolved in 22 mL of methylene chloride and the solution was cooled in an ice–water bath. 2-Hydroxycyclohexanone dimer (0.70 g) was heated to its melting point (sealed tube) and quickly transferred to the cooled solution. Triflic anhydride (2.25 g) was added dropwise and the solution was stored at −15 °C for 1 h. A cold, rapid workup was necessary to prevent decomposition of **22**. The solution was diluted with 50 mL of ether, extracted with cold water, cold dilute hydrochloric acid until acidic, and cold saturated sodium chloride (brine), and dried over sodium sulfate. The organic phase was decanted from the drying agent into a flask containing a small amount of sodium bicarbonate, and the solvent was removed on a rotary evaporator. The crude residue crystallized to give 1.76 g (118%) of **32** as an unstable offwhite solid: mp 59–62 °C dec; IR (neat) $\nu_{C=O}$ 5.81 μm; NMR (CCl_4) δ 4.9–5.3 (1 H, m), 1.3–2.8 (8 H, m).

Reaction of 32 with Sodium Methoxide in Methanol. Keto triflate **32** (0.50 g) was dissolved with stirring in 3 mL of 1 M sodium methoxide in methanol. After stirring at room temperature for 30 min, the solution was diluted with ether and extracted with water and brine, and dried over sodium sulfate. The solvent was removed on a steam bath through a Vigreux column and the residue distilled to give 0.10 g of a 3.5 to 1 mixture of **33** and **34**, identified by spectral comparison with authentic samples. Gas chromatographic analysis confirmed the absence of both 2-cyclohexen-1-one and methyl cyclopentanecarboxylate. In a duplicate reaction, crude triflate **32**, prepared from 0.56 g of 2-hydroxycyclohexanone, gave 0.24 g of **33** and **34**.

Reaction of 35 with Triflic Anhydride. Pyridine (0.80 g) and 1 g of **35** were dissolved in 10 mL of methylene chloride. The solution was cooled in an ice–water bath and 2.6 g of triflic anhydride was slowly added dropwise. Precipitation of a white solid was observed. After standing at −15 °C for 30 min, the mixture was diluted with ether and extracted with water and brine, and dried over sodium sulfate. The solvents were removed on a steam bath through a Vigreux column, leaving an unstable residue which discolored rapidly upon standing. Addition of 10 mL of 1 M sodium methoxide in methanol followed by a standard aqueous workup and removal of solvent gave a residue which was distilled in two fractions. Fraction one contained 0.37 g (37%) of **35**, bp 35 °C (0.06 mm). Fraction two contained 0.34 g (36%) of **36**,[14] bp 80–82 °C (0.07 mm). When pyridine was used as solvent for this reaction, only unreacted **35** and 1-acetylcyclohexene was recovered in 1 to 2.2 ratio.

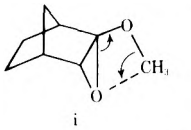
Acknowledgment. Financial support from the Research Corp. is gratefully acknowledged.

Note Added in Proof. Epoxidation of 1-methoxycyclohexene in methanol has recently been found to also give 33.[21]

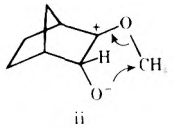
Registry No.—**1**, 63715-72-0; **2**, 63715-73-1; **3**, 5164-68-1; **4**, 63715-74-2; **5**, 63703-36-6; **6**, 63703-35-5; **7**, 10464-71-8; **12**, 63715-76-4; **16**, 63715-77-5; **24**, 57722-40-4; **25**, 5164-67-0; **28**, 63715-78-6; **29** dimer, 63715-71-9; **30**, 63715-79-7; **31**, 63715-80-0; **32**, 63715-81-1; trifluoromethanesulfonic anhydride, 358-23-6; sodium methoxide, 124-41-4; *p*-toluenesulfonyl chloride, 98-59-9; norcamphor, 497-38-1; chlorotrimethylsilane, 75-77-4; bicyclo[2.2.2]octan-2-one, 2716-23-6; 2-hydroxycyclohexanone dimer, 30282-14-5.

References and Notes

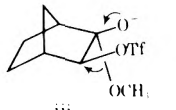
(1) (a) U. Schrapler and K. Ruhlmann, *Chem. Ber.*, **96**, 2780 (1963); (b) U. Schrapler and K. Rulhmann, *ibid.*, **97**, 1383 (1964); (c) J. J. Bloomfield, *Tetrahedran Lett.*, 587 (1968); (d) J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, *Org. React.*, **23**, 259 (1976).
(2) G. M. Rubottom, M. A. Vazquez, and D. Pelegrina, *Tetrahedron Lett.*, 4319 (1974).
(3) A similar epimerization has been observed using aqueous potassium carbonate. See: J. Meinwald, Y. C. Meinwald, and T. N. Baker, III, *J. Am. Chem. Soc.*, **86**, 4074 (1964).
(4) A similar opening of an alkoxy epoxide has been observed under neutral conditions. See: P. G. Gassman and X. Creary, *Tetrahedron Lett.*, 4411 (1972).
(5) T. M. Su, W. F. Sliwinski, and P. R. Schleyer, *J. Am. Chem. Soc.*, **91**, 5386 (1969).
(6) (a) G. J. Kaspereck, T. C. Bruice, H. Yagi, and D. M. Jerina, *Chem. Commun.*, 784 (1972); (b) G. J. Kaspereck and T. C. Bruice, *J. Am. Chem. Soc.*, **94**, 198 (1972); (c) D. L. Whalen, *ibid.*, **95**, 3432 (1973); (d) D. L. Whalen and A. M. Ross, *ibid.*, **96**, 3678 (1974); (e) D. L. Whalen and A. M. Ross, *ibid.*, **98**, 7859 (1976).
(7) T. I. Temnikova and V. S. Karavan, *Zh. Obshch. Khim.*, **34**, 3157 (1964).
(8) (a) C. L. Stevens and J. J. DeYoung, *J. Am. Chem. Soc.*, **76**, 718 (1954); (b) V. S. Karavan and T. I. Temnikova, *J. Org. Chem. USSR (Engl. Transl.)*, **2**, 1410 (1966).
(9) T. I. Temnikova and O. A. Kaurov, *Zh. Obshch. Khim.*, **34**, 3165 (1964).
(10) Attack at the carbonyl position of chloro ketones by cyanide also yields isolable epoxides. For a review and leading references, see: R. N. McDonald in "Mechanisms of Molecular Migrations", B. S. Thyagarajan, Ed., Wiley, New York, N.Y., 1971, p 67.
(11) (a) G. D. Sargent in "Carbonium Ions", Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley, New York, N.Y., 1972, p 1110; (b) X. Creary, F. Hudock, M. Keller, J. F. Kerwin, and J. P. Dinnocenzo, *J. Org. Chem.*, **42**, 409 (1977); (c) X. Creary and A. J. Rollin, *J. Org. Chem.*, **42**, following paper in this issue.
(12) Other mechanistic possibilities for the formation of **27** involve processes i, ii, and iii. Although not considered likely, these processes cannot be ruled out with the available data.



i



ii



iii

(13) D. W. Goheen and W. R. Vaughan, Organic Syntheses, Collect. Vol. IV, 594 (1963).
(14) G. F. Hennion and E. J. Watson, *J. Org. Chem.*, **23**, 658 (1958).
(15) X. Creary, Ph.D. Thesis, The Ohio State University, 1973.
(16) P. Yates and R. J. Crawford, *J. Am. Chem. Soc.*, **88**, 1561 (1966).
(17) R. N. McDonald and T. E. Tabor, *J. Org. Chem.*, **33**, 2934 (1968).
(18) J. S. McConaghy and J. J. Bloomfield, *J. Org. Chem.*, **33**, 3425 (1968).
(19) M. Hanack and J. Dolde, *Tetrahedron Lett.*, 321 (1966).
(20) R. N. McDonald and R. N. Steppel, *J. Org. Chem.*, **35**, 1250 (1970).
(21) A. A. Frimer, *Synthesis*, 578 (1977).

Rearrangements of α-Hydroxy Ketals and Derivatives of α-Hydroxy Ketals

Xavier Creary* and Anthony J. Rollin

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

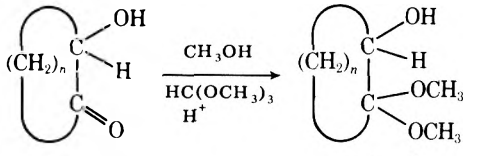
Received May 17, 1977

α-Hydroxy ketals are found to rearrange when treated with acid to give alkoxy ketones. The k_H/k_D value of 3.1–3.5 for *endo*-2,2-dimethoxybicyclo[2.2.1]heptan-3-ol (**4**) suggests a mechanism involving rate-limiting hydride migration to an α-alkoxy cation. *exo*-2,2-Dimethoxybicyclo[2.2.1]heptan-3-ol (**5**) gives a dimeric product consistent with the low propensity for *endo*-hydride migration in the norbornyl system. Solvolysis of tosylate and triflate derivatives of α-hydroxy ketals gives rates largely inductively retarded by the dimethoxy grouping. Hydrolysis or acetolysis of 2,2-dimethoxycyclobutyl tosylate (**23**) gave methyl cyclopropanecarboxylate (**32**) via a ring-contraction process. 2,2-Dimethycyclopentyl triflate (**26**) gave 2,3-dimethoxycyclopentene (**38**) on acetolysis and 1,1,2-trimethoxycyclopentane on methanolysis. These products arise from methoxy participation. *endo*-2,2-Dimethoxybicyclo[2.2.1]hept-3-yl triflate (**28**) gave products arising from a k_s process and from methoxy participation. Additionally, methyl cyclohex-3-enecarboxylate (**41**) was produced. A deuterium-labeling study showed that **41** was produced from the rarely observed C_1–C_7 participation in the norbornyl system. The migration is suggested to arise from the increased demand for participation as a result of the inductively destabilizing dimethoxy substituents.

α-Hydroxy ketals are readily available from the corresponding acyloins, which are in turn prepared using the Ruhlmann and Schrapler modification of the acyloin condensation.[1] Complimenting this route is the recently developed procedure involving epoxidation, hydrolysis of silyl enol ethers.[2] The presence of both the alcohol and masked keto functionality makes the hydroxy ketal potentially interesting from a synthetic viewpoint and additionally with respect to potential rearrangement processes. We have undertaken a study of some of the reactions which these acyloin derivatives undergo with the goal of elucidating mechanistic processes. Reported here are the results of these studies.

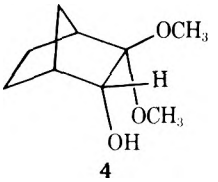
Results and Discussion

Acid-Catalyzed Rearrangements of α-Hydroxy Ketals. α-Hydroxy ketals **1**–**4** were prepared by ketalization of the appropriate α-hydroxy ketone produced in the acyloin condensation. The *exo*-hydroxy ketal **5** was produced in the unusual reaction of *endo*-keto triflate **6** with sodium methoxide in methanol.[3]

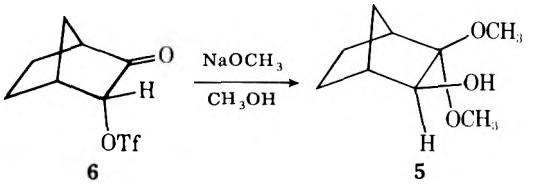


n = 2,3,4

1, *n* = 2
2, *n* = 3
3, *n* = 4



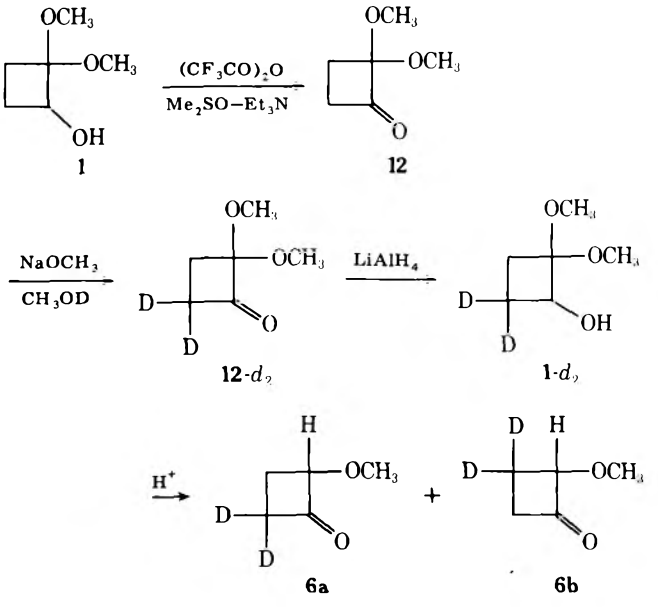
4



6 **5**

Ketal alcohols **1**–**5** undergo rearrangement when treated with hydrochloric acid vapors. Table I gives the products and reaction conditions employed for these transformations. Conia has previously reported rearrangement of **1** under thermal conditions at temperatures greater than 200 °C and has suggested mechanisms ranging from entirely concerted to acid catalyzed.[4] We have found that **1** is thermally stable in base-washed glassware and that the reaction of **1** is truely acid catalyzed. The mechanism of rearrangement of **1** remains open to question and we therefore sought to shed further light on this process.

Scheme I



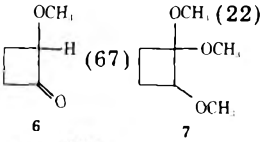
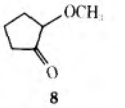
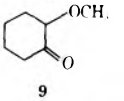
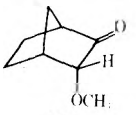
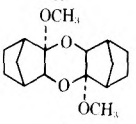
1 **12** **12-d_2** **1-d_2** **6a** **6b**

Among other mechanisms, Conia has suggested that aldehyde **16** is involved in formation of **7**. Aldehyde **16** was shown to rapidly rearrange to **7** on treatment with acid.[4c,d] We therefore prepared deuterated alcohol **1**-d_2 by the route shown in Scheme I to evaluate the importance of the rearrangement processes shown in Scheme II.

After many attempted alternate oxidations, 2,2-dimethoxycyclobutanone (**12**) was prepared in 83% yield by oxidation of **1** with the trifluoroacetic anhydride–dimethyl sulfoxide–triethylamine reagent.[5] Exchange of **12** in methanol-d_1 with sodium methoxide followed by lithium aluminum hydride reduction gave **1**-d_2.

Acid-catalyzed rearrangement of **1**-d_2 gave, by NMR determination, equal amounts of **6a** and **6b**. This observation suggests the complete involvement of a symmetrical intermediate **16** in the rearrangement of **1**. The mechanism most consistent with this and Conia's observed acid-catalyzed re-

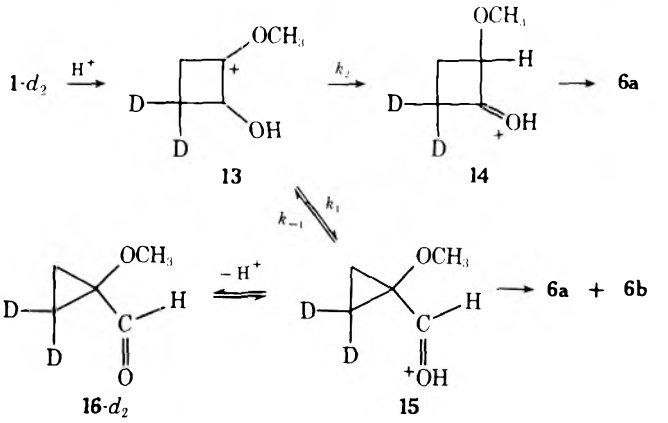
Table I. Acid-Catalyzed Rearrangement of α-Hydroxy Ketals

Alcohol	Registry no.	Temp, °C	Reaction time, min	Products (% yield)
1	42082-99-5	100	50	 (67) (22) 6 7
2	63703-33-3	120	18	 (89) 8
3	63703-34-4	100	18	 (87) 9
4	63703-35-5	110	20	 (89) 10
5	63703-36-6	120	45	 (95) 11

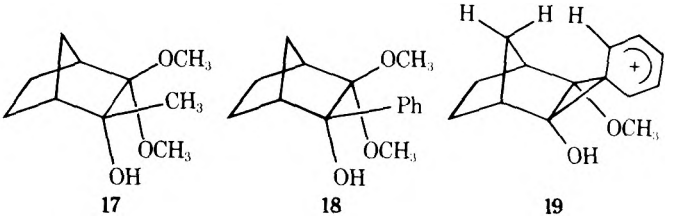
arrangement of **16** involves ring contraction of **13** (k_1) occurring at a rate much *faster* than hydride migration (k_2). The acid-catalyzed conversion of **16** to **6** probably proceeds via reprotonation of **16** leading to **13** and subsequent hydride migration. Concerted thermal rearrangements of **1** and **16** now appear improbable under the current reaction conditions.

Hydroxy ketals **2**, **3**, and **4** also rearrange to give analogous methoxy ketone products. No evidence is seen for ring-contraction processes. This general type of reaction has some precedent.[6] Certain α-hydroxy ketones produce methoxy ketones when treated with methanolic hydrochloric acid.[6a] Ainsworth has produced a methoxy ketone directly from a bis(trimethylsilyl) enol ether under similar conditions.[6b] However, we are unaware of any studies designed to elucidate mechanistic details of this transformation. Table II gives rate data for rearrangement of **4** and the deuterated analogue **4-*d***. The deuterium isotope effect k_H/k_D is large (3.1 to 3.5) and consistent with carbon–hydrogen bond fragmentation in the rate-controlling step. In view of this isotope effect, we suggest hydride migration to a cationic center generated by acid-catalyzed loss of methoxide is rate determining. The overall mechanistic scheme is reminescent of the pinacol rearrangement in which deuterium isotope effects are also analogous[7] (primary). The rearrangement reaction of α-hydroxy ketals provides a novel route for the preparation of certain α-keto

Scheme II



ethers. However, attempts to rearrange ketals **17** and **18** under more strenous conditions than those in Table I were unsuccessful. Reasons for these failures may lie in the decreased migratory aptitude of the methyl group and steric strain in the transition state **19** necessary for phenyl migration.[8]



Treatment of *exo*-3-hydroxynorcamphor dimethyl ketal **5** with acid gave only **11**.[10] Undoubtedly, the low propensity for *endo*-hydride migration in the norbornyl system[9] accounts for this product, which is suggested to arise as shown in Scheme III. Intermolecular capture of **20** by **5** occurs in pref-

Scheme III

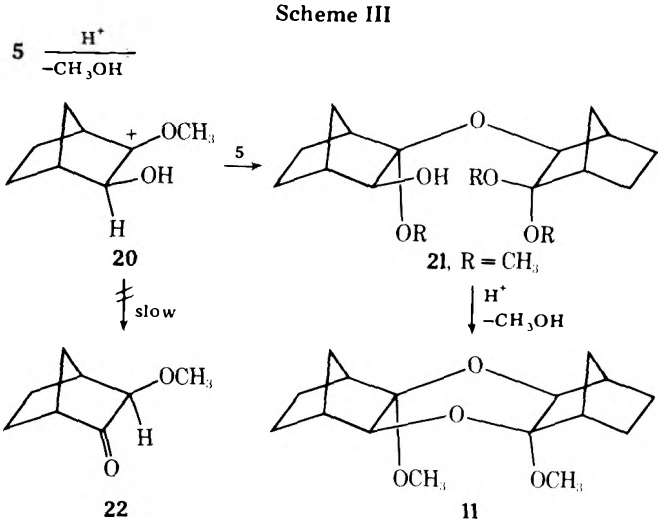


Table II. Rearrangement Rates of **4** and **4-*d*** in 0.057 M HCl in Di-*n*-propyl Ether

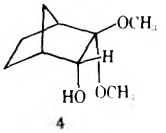
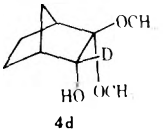
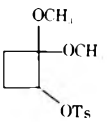
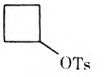
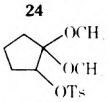
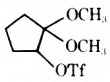
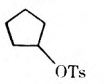
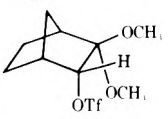
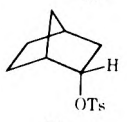
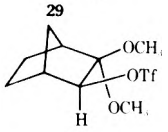
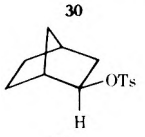
Compound	Temp, °C	k, s^{-1}	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, eu	k_H/k_D
 4	35.0	$(1.05 \pm 0.03) \times 10^{-4}$			3.5 ± 0.2
	50.0	$(4.68 \pm 0.11) \times 10^{-4}$	19.1 ± 0.8	-15 ± 2	3.1 ± 0.2
 4d	35.0	$(3.05 \pm 0.07) \times 10^{-5}$			
	50.0	$(1.53 \pm 0.03) \times 10^{-4}$	20.6 ± 0.5	-12 ± 2	

Table III. Solvolysis Rates of α-Hydroxy Ketal Derivatives

Compound	Registry no.	Solvent	Temp, °C	k, s^{-1}	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, eu	$k_{rel}^{25°C}$ (HOAc)[b]	$k_{rel}^{60°C}$ (70% acetone)
 23	63703-37-7	HOAc	25.0[a]	3.15×10^{-9}			1.5×10^{4}	
			100.0	$(7.33 \pm 0.05) \times 10^{-5}$	29.1	0.2		
			120.0	$(5.71 \pm 0.10) \times 10^{-4}$				
		70% acetone	60.0[a]	1.53×10^{-6}				
			90.0	4.39×10^{-5}	26.5	−5.8		2.7
			100.0	$(1.19 \pm 0.02) \times 10^{-4}$				
			110.0	3.18×10^{-4}				
 24	10437-85-1	HOAc	25.0[a,c]	6.97×10^{-7}			3.4×10^{6}	
		70% acetone	60.0	$(6.58 \pm 0.03) \times 10^{-4}$				1140
 25	63703-38-8	70% acetone	60.0[a]	5.78×10^{-7}				
			100.0	$(5.80 \pm 0.01) \times 10^{-5}$	27.5	−4.7		1.0
			120.0	$(4.03 \pm 0.01) \times 10^{-4}$				
 26	63703-39-9	HOAc	25.0	$(2.37 \pm 0.05) \times 10^{-4}$			1.2×10^{4} [b]	
 27	3558-06-3	HOAc	25.0[a,d]	1.68×10^{-6}			8.2×10^{6}	
			25.0[a]	2.06×10^{-8}			1.0[b]	
 28	63703-40-2	HOAc	100.0	$(2.21 \pm 0.08) \times 10^{-4}$	26.8	−3.8		
			120.0	$(1.47 \pm 0.08) \times 10^{-4}$				
 29	840-90-4	HOAc	25.0[a,e]	8.3×10^{-8}			3.9×10^{5}	
 30	63703-41-3	HOAc	25.0	$(3.06 \pm 0.05) \times 10^{-5}$	22.8	−2.6	1.5×10^{3} [b]	
			60.0	$(1.97 \pm 0.02) \times 10^{-3}$				
 31	959-42-2	HOAc	25.0[a,e]	2.3×10^{-5}			1.1×10^{8}	

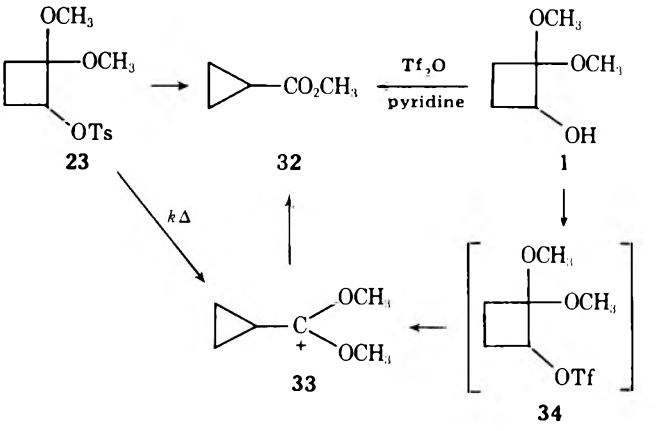
[a] Extrapolated value. [b] For the tosylate derivative assuming $k_{ROTf}/k_{ROTs} = 10^{5}$. [c] Reference 18. [d] Reference 19. [e] Reference 20.

erence to *endo*-hydride migration, leading ultimately to **11** rather than **22.** This reaction provides yet another example of the avoidance of *endo*-2,3-hydride migration in a norbornyl system.

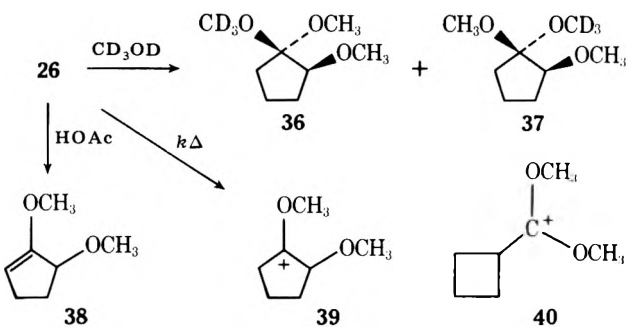
Solvolysis of α-Hydroxy Ketal Derivatives. Hydroxy alcohols **1** and **2** were converted to the tosylate derivatives **23** and **25,** respectively, and **2, 4** and **5** were converted to the corresponding triflates. Solvolytic rate data are given in Table III. Immediately apparent are the decreased rates (10^{2} to 10^{5}) of solvolysis of the α-ketal derivatives relative to their unsubstituted analogues. This rate retardation is a result of the electron-withdrawing α-dimethoxy grouping adjacent to the ionization center. Product analyses were therefore carried out to evaluate the effect of increasing inductive destabilization on neighboring-group participation as reflected by rearranged products.

Solvolysis of 2,2-dimethoxycyclobutyl tosylate (**23**) in 70% aqueous acetone gave only methyl cyclopropanecarboxylate (**32**). The same product was observed in the pyrolysis of 1-bromo-2,2-dimethoxycyclobutane[4a] and was suggested to arise via a concerted process.[4b] In the solvolytic reaction, the rearranged ester **32** suggests an assisted ionization leading to **33.** Attempts to prepare the triflate derivative of **1** by reaction with trifluoromethanesulfonic anhydride in pyridine gave only ester **32** apparently by the in situ ionization of **34.** No products

Scheme IV



Scheme V



of retained cyclobutyl structure or homoallylic rearrangement products were produced.

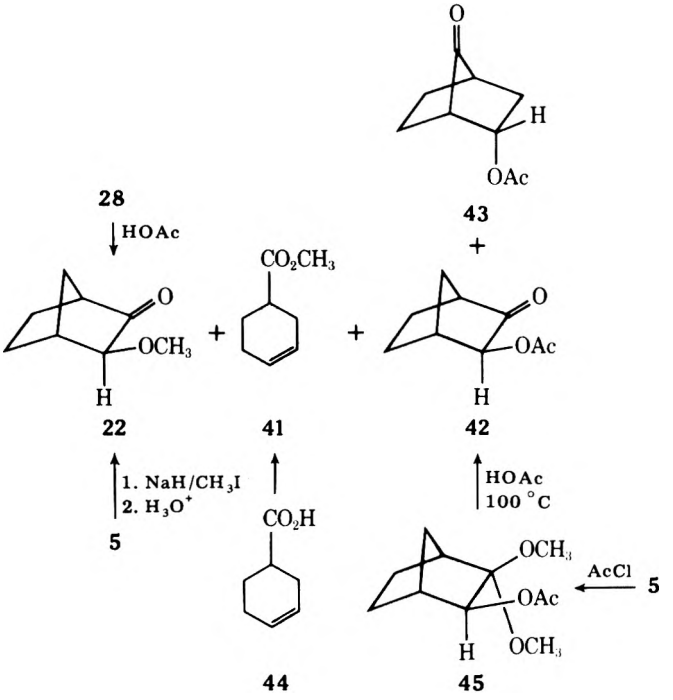
Despite the expected stability of cation **33**, the rate of solvolysis of **23** is less than cyclobutyl tosylate **24**. Apparently, the transition state for ionization of **23** still reflects some of the inductive effect of the dimethoxy grouping. The relative stability of **33** vs. that of the much debated intermediate in the solvolysis of cyclobutyl tosylate **24**[11] is not the only factor influencing the rate of solvolysis of **23**. However, by any method of estimation, there is still substantial anchimeric assistance in the ionization of **23**.

In order to determine whether an analogous ring contraction could occur in a cyclopentyl system, the tosylate and triflate derivatives **25** and **26** of alcohol **2** were prepared. Methanolysis of **25** gave 1,1,2-trimethoxycyclopentane (**35**) which could be prepared independently by treatment of **2** with sodium hydride followed by methyl iodide. However, the origin of the methoxy groups in **35** was uncertain due to the high temperature necessary to methanolize **25**. Triflate **26** was therefore prepared. Methanolysis in methanol-d_4 gave **36** and **37** with the deuterium incorporated in the ketal function (Scheme V). The structural assignments on **36** and **37** were based on NMR. A mixture of **36** and **37** showed a three-proton methoxy signal at δ 3.29, as well as signals at δ 3.14 and 3.21, having a combined integral of three protons. The signal at δ 3.29 is assigned to the ether methoxy group. The signals at δ 3.14 and 3.21 (ketal protons) exchange rapidly when 1,1,2-trimethoxycyclopentane is treated with methanol-d_4 and a trace of toluenesulfonic acid, while the signal at δ 3.29 does not exchange.

The isolation of **36** and **37** shows that methoxy group migration giving **39** must have occurred. The k_s process does not appear to be important in this system. A similar methoxy participation process is suggested to occur in the acetolysis of **26** which gave exclusively enol ether **38**. Apparently, the driving force for ring contraction is insufficient in **26** to produce **40**, despite its expected stability. The increased demand for stabilization in the solvolysis of **26** results in methoxyl participation giving **39** rather than σ participation giving **40**.

Attention was next turned to the bicyclo[2.2.1]heptyl system. Solvolysis of triflate **28** gave *exo*-2-methoxynorcamphor (**22**), 4-carbomethoxycyclohexene (**41**), and keto acetates **42** and **43**. The structure of **22** was based on its spectral properties as well as its independent synthesis, as shown in Scheme VI. Methylation of alcohol **5** followed by hydrolysis gave authentic **22**. Ester **41** could be prepared independently from the acid **44**. The structure of keto acetate **42** was inferred from its spectral properties and proven by its alternate preparation from **5**. Conversion of **5** to the corresponding acetate **45** followed by treatment of **45** under the reaction conditions resulted in its complete conversion to **42**. The structure of **43** was inferred from its spectral properties. Spectral comparison with *exo*-2-acetoxy-7-ketonorbornane showed the solvolysis

Scheme VI

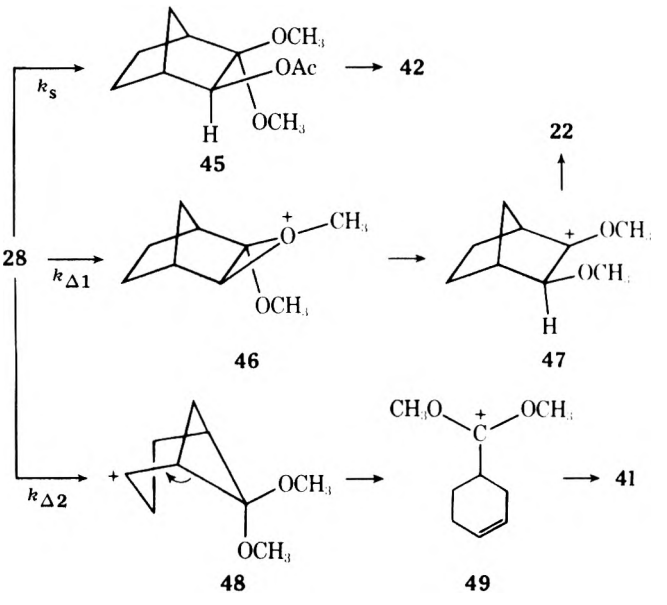


product to be different and therefore, in all probability, the endo epimer.

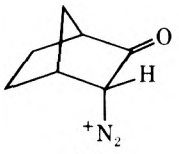
Keto acetate **42** is suggested to arise via ketal acetate **45** which has been shown to deketalize under the reaction conditions. The source of **45** may be a solvent-assisted process or may involve a classical 2-norbornyl cation, which captures solvent from the exo side. The *endo*-2-acetoxy-7-ketonorbornane (**43**) would be a Wagner–Meerwein rearrangement product of such a cation. Such products have been seen in the solvolysis of 7,7-dimethoxy-2-norbornyl tosylate.[12]

A second process is a methoxy-assisted pathway ($k_{\Delta 1}$) which leads to **47**[13] and ultimately to **22**. This 1,2 type of methoxy participation in solvolytic displacement reactions is a well-documented phenomenon.[14] However, such participation usually leads to onium-type ions.[14b,c] The fact that complete migration occurs to give **47** as an intermediate can be attributed to the cationic stabilizing influence of the second methoxy group.

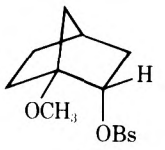
Scheme VII



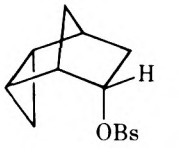
Perhaps the most unusual process which **28** undergoes involves the rare case of C_1–C_7 bond participation ($k_{\Delta 2}$) and resultant migration of C_7. Such processes are quite infrequent in the norbornyl system and occur usually when the intermediate is greatly stabilized or the demand for stabilization in the cationic intermediate is enormous. Examples of such participation include the acid-catalyzed decomposition of diazonorcamphor via **50**,[15] and the solvolyses of **51**[16] and **52**.[17] The deamination of **53** also results in some C_1–C_7 migration.[8]



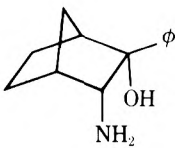
50



51



52

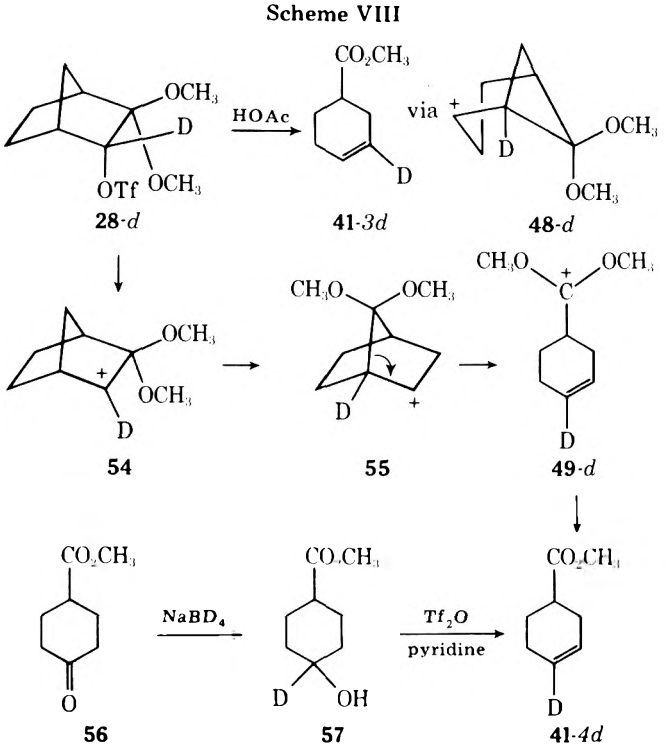


53

The C_1–C_7 bond participation in the solvolysis of **28** probably reflects the enormous demand for stabilization induced by the dimethoxy grouping. Such C_1–C_7 participation is consistent with increased participation as a function of increased electron demand. Fragmentation of the indicated bond in **48** (which may be in concert with C_1–C_7 participation) leads to **49** and ultimately to the monocyclic ester, methyl cyclohex-3-enecarboxylate (**41**).

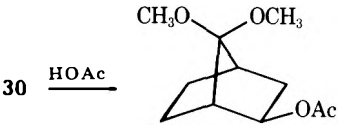
An alternative mechanism that must also be considered for the formation of methyl cyclohex-3-enecarboxylate (**41**) is shown in Scheme VIII. Wagner–Meerwein rearrangement of a classical ion generated from **28** followed by fragmentation of the C_1–C_7 bond of such a rearranged cation could lead in principle to **41**. This mechanism has been *ruled out* as a source of **41**. Solvolysis of **28**-*d* gave exclusively **41**-*3d*, which is *consistent* with the $k_{\Delta 2}$ process. The Wagner–Meerwein rearrangement–fragmentation mechanism predicts formation of **41**-*4d*.

Scheme VIII



The assignment of the position of the deuterium in the solvolysis product of **28**-*d* was made by ^{13}C NMR spectroscopy. Ester **41** showed olefinic ^{13}C signals at δ 124.9 and 126.4 (vs. Me_4Si). The solvolysis product showed only a signal at δ 126.4. An authentic sample of **41**-*4d* was prepared by sodium borodeuteride reduction of ketone **56**. Elimination with triflic anhydride in pyridine gave **41**-*4d*. The ^{13}C spectrum of **41**-*4d* showed only the C_3 olefinic signal at δ 124.9. (The unenhanced C_4 triplet does not appear under the spectral conditions.) The infrared spectrum of **41**-*4d* is also significantly different from that of the solvolysis product. Hence, the structure of the solvolysis product must be **41**-*3d*. Ester **41** therefore cannot arise by the Wagner–Meerwein rearrangement–fragmentation mechanism of Scheme VIII.

Solvolysis of triflate **30** gave, as expected, a product of Wagner–Meerwein rearrangement, ketal acetate **58**. The



58

similarity of this product with those observed in the solvolysis of 7,7-dimethoxy-*exo*-2-norbornyl tosylate[12] suggests a similar cationic intermediate. The chemistry of this intermediate has been discussed. The major effect of the dimethoxy grouping in **30** is a large inductive rate retardation with no resultant new or unusual processes.

Experimental Section

NMR spectra were recorded on a Varian A-60A or XL-100 spectrometer. Mass spectra were recorded on an AEI Scientific Apparatus MS902 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 455 or Infracord spectrometer.

2,2-Dimethoxycyclobutanol (1). Dry methanol (76 mL) was added to 50 g of 1,2-bis(trimethylsiloxy)cyclobutene, which was prepared by the procedure of Bloomfield.[1c] After refluxing under nitrogen for 6.5 h, 50 mL of solvent was removed at reduced pressure. More dry methanol (50 mL), 30.9 g of trimethyl orthoformate, and 50 mg of *p*-toluenesulfonic acid monohydrate were added, and the solution was stirred for 4 h. Acid was neutralized with 14 mg of sodium methoxide and the solvents were removed at 140 mm through a Vigreux column. The residue was distilled to give 22.5 g (79%) of **1**, previously prepared in a similar manner.[4c] Hydroxy ketal **1** had the following properties: bp 43–45 °C (1.4 mm); NMR (CCl_4) δ 3.8–4.2 (1 H, m), 2.9–3.4 (7 H, m with sharp s at 3.18 and 3.26, 1 H exchanges with D_2O), 1.0–2.3 (4 H, m).

2,2-Dimethoxycyclopentanol (2). 1,2-Bis(trimethylsiloxy)cyclopentene (107 g), prepared by the method of Ruhlmann,[16] was dissolved in 570 mL of dry methanol, and the solution was refluxed for 6 h. Solvents were removed under vacuum and the residue was distilled to give a mixture of acyloin and ketal (about 60% ketal). To complete ketalization, 5 g of this mixture was dissolved in 10 mL of dry methanol and 2.2 mL of trimethyl orthoformate and 4 mg of *p*-toluenesulfonic acid monohydrate was added. After stirring at 25 °C for 30 min, the acid was neutralized with sodium methoxide and the solvents were removed by vacuum distillation. The residue was distilled to give 5 g of **2**: bp 64–66 °C (4.5 mm); NMR (CCl_4) ν 3.7–4.0 (1 H, m), 3.28 (3 H, s), 3.19 (3 H, s), 2.21 (1 H, s exchanges with D_2O), 1.3–2.2 (6 H, m); mass spectroscopic molecular weight, 146.0908 (calcd for $C_7H_{14}O_3$, 146.0943).

2,2-Dimethoxycyclohexanol (3). 2-Hydroxycyclohexanone dimer (Aldrich Chemical Co.) (0.50 g) was heated to the melting point in a sealed tube and the liquid monomer was added to 0.58 g of trimethyl orthoformate and 5 mL of dry methanol. A small crystal of *p*-toluenesulfonic acid monohydrate was added and the solution was stirred for 2 h at 25 °C. Neutralization of the acid with sodium methoxide followed by distillation of solvents at 140 mm left a residue which distilled to give 0.51 g (73%) of **3**: bp 66–68 °C (2 mm); NMR (CCl_4) δ 3.57–3.82 (1 H, m), 3.16 (6 H, s), 1.0–2.1 (9 H, m, 1 H exchanges with D_2O); mass spectroscopic molecular weight, 160.1096 (calcd for $C_8H_{16}O_3$, 160.1099).

2,3-Bis(trimethylsiloxy)bicyclo[2.2.1]hept-2-ene. Sodium (29.0 g) was dispersed in 1.5 L of refluxing toluene and 137 g of chlorotrimethylsilane was added. *cis*-1,3-Dicarbomethoxycyclopentane (42.6

g), prepared by Fisher esterification of the acid,[21] dissolved in 500 mL of toluene was added dropwise over 10 h. Refluxing was continued for an additional 12 h and the mixture was cooled. After filtering through celite, the toluene was removed under reduced pressure and the residue was distilled to give 50.3 g (81%) of the bis(trimethylsilyl) ether: bp 60–65 °C (0.05 mm) lit.[22] bp 65–68 °C (0.1 mm).

***endo*-2,2-Dimethoxybicyclo[2.2.1]heptan-3-ol (4).** Hydroxy ketal **4** was prepared from 1,2-bis(trimethylsiloxy)bicyclo[2.2.1]-hept-2-ene as previously described.[22]

***exo*-2,2-Dimethoxybicyclo[2.2.1]heptan-3-ol (5).** Hydroxy ketal **5** was prepared from 2-oxo-*endo*-bicyclo[2.2.1]hept-3-yl triflate as previously described.[3]

Acid-Catalyzed Rearrangements of Hydroxy Ketals. General Procedure. A known amount of hydroxy ketal was placed in a glass tube. An HCl atmosphere (vapors from 12 N HCl) was introduced and the tube was sealed. After heating in an oil bath, the tube was broken open and the products were transferred to a distillation flask with a minimum amount of anhydrous ether. The residue was distilled to give the indicated products. Products **8**, **9**, and **10** contained traces of the corresponding ketal derivatives.

Rearrangement of 1. Hydroxy ketal **1** (0.45 g) gave 0.33 g of a 3 to 1 mixture of **6** and **7**. Ketone **6** had spectra consistent with those reported[4a] and **7** had the following properties: bp 50–52 °C (15 mm); NMR (CCl_4) δ 3.5–3.8 (1 H, m), 3.26 (3 H, s), 3.20 (3 H, s), 3.11 (3 H, s), 1.2–2.2 (4 H, m); mass spectrum exhibited no parent ion.

Rearrangement of 2. Hydroxy ketal **2** (0.46 g) gave 0.32 g (89%) of **8**: bp 67–70 °C (15 mm), lit.[23] bp 68–70 °C (15 mm). Ketone **8** had spectra identical to that previously reported for 2-methoxycyclopentanone.[23]

Rearrangement of 3. Hydroxy ketal **3** (0.179 g) gave 0.124 g (87%) of **9**: bp 72–75 °C (15 mm), lit.[10] bp 72–75 °C (14 mm); IR $\nu_{C=O}$ 5.78 μm; NMR (CCl_4) δ 3.2–3.7 (4 H, m with sharp singlet at 3.30), 1.1–2.7 (8 H, m).

Rearrangement of 4. Hydroxy ketal **4** (0.454 g) gave 0.329 g (89%) of **10**: bp 71–74 °C (3.5 mm). All spectra of ketone **10** were identical to those of independently syntbesized *endo*-3-methoxybicyclo-[2.2.1]heptan-2-one.

Rearrangement of 5. Hydroxy ketal **5** (0.550 g) gave 0.425 g (95%) of **11**: bp 103–108 °C (0.15 mm); NMR (CCl_4) δ 3.11 (3 H, s), 3.03 (1 H, d, J = 2.3 Hz), 0.9–2.3 (8 H, m); mass spectroscopic molecular weight, 280.1597 (calcd for $C_{16}H_{24}O_4$, 280.1674).

2,2-Dimethoxycyclobutanone (12). Methylene chloride (200 mL) was added to 25 mL of dimethyl sulfoxide (ME_2SO) under dry nitrogen and the solution was cooled to −60 °C in a dry ice–chloroform bath. Trifluoroacetic anhydride (35.8 g) was slowly added dropwise and precipitation of a white complex was observed. Ketal-alcohol **1** (15.0 g) dissolved in 15 mL of Me_2SO and 15 mL of methylene chloride was slowly added dropwise. After stirring 10 min more, 34.5 of triethylamine was added dropwise and the solution was warmed to room temperature. Water was added and the aqueous phase was extracted with three portions of ether. The combined ether extracts were washed with a minimum of water to remove the Me_2SO, dilute sodium carbonate, and brine, and dried over sodium sulfate. The solvents were removed through a Vigreux column and the residue was distilled to give 12.47 g (83%) of the desired ketone: bp 55–60 °C (20 mm); IR (neat) $\nu_{C=O}$ 5.56 μm; NMR (CCl_4) δ 3.29 (6 H, s), 2.5–3.0 (2 H, m), 1.9–2.4 (2 H, m); mass spectroscopic molecular weight, 130.0588 (calcd for $C_6H_{10}O_3$, 130.0630).

Preparation of 12-*d*$_2$. A small piece of sodium (1 mm^3) was dissolved in 12 mL of methanol-d_1. Ketone **12** (2 g) was added and the solution was heated (sealed tube) for 14 min at 87 °C. The tube was opened and the solvent was removed at 140 mm. The residue distilled only at a high pot temperature (130–150 °C) to give 1 g of partially deuterated ketone, bp 55–65 °C (14 mm). This ketone was recycled with another piece of sodium dissolved in 6 mL of methanol-d_1. After heating at 83 °C for 30 min, workup gave 0.69 g of the fully deuterated ketone. The deuterated ketone had the following spectral properties: NMR (CCl_4) δ 3.33 (3 H, s), 2.15 (1 H, br s).

Preparation of 1-*d*$_2$. Lithium aluminum hydride (0.4 g) was suspended in 4 mL of anhydrous ether, and 0.65 g of **12**-d_2 dissolved in 3 mL of anhydrous ether was slowly added dropwise. After stirring at an ambient temperature for 10 min, 0.4 mL of water, 0.4 mL of 15% aqueous sodium hydroxide, and 1.2 mL of water were added in that order. The mixture was filtered and the ether phase was dried over sodium sulfate. Solvents were removed through a Vigreux column and the residue was distilled to give 0.54 g (82%) of 1-d_2: bp 65–68 °C (14 mm); NMR (CCl_4) δ 4.04 (1 H, br s), 3.28 (3 H, s), 3.20 (3 H, s), 2.7–3.1 (1 H, m, exchanges with D_2O), 1.85–2.20 (1 H, m), 1.30–1.70 (1 H, m).

Rearrangement of 1-*d*$_2$. The deuterated hydroxy ketal 1-d_2 (0.239 g) was sealed in a glass tube containing HCl vapors as previously described. After heating at 110 °C for 15 min, the residue was distilled giving 0.128 g of a mixture of deuterated **6** and **7** which were separated by preparative gas chromatography on 6 ft, 5% SE 30 on chromosorb G (column A). Deuterated **6** showed equal integrations for protons at C-3 and C-4 by using 100-MHz NMR which cleanly separated the two methylene multiplets: 100-MHz NMR (CCl_4) δ 1.3–2.0 (2 H, m, C-3), 2.0–2.5 (2 H, m, C-4), 3.21 (3 H, s), 4.0–4.25 (1 H, m).

Preparation of 4-*d*. 2,3-Bis(trimethylsiloxy)bicyclo[2.2.1]hept-2-ene (1.88 g) was refluxed in 8 mL of methanol-d_1 for 2.5 h. The solvent was removed by aspirator and the residue was dissolved in 5 mL of methanol-d_1 and 4 mL of trimethyl orthoformate, and 3 mg of *p*-toluenesulfonic acid monohydrate was added. After stirring at room temperature for 35 min, the acid was neutralized with sodium methoxide and the solvents were removed at reduced pressure. The residue was dissolved in 7 mL of methanol and after 5 min the solvent was again removed. After repeating the same procedure with another 7 mL of methanol, the residue was distilled to give 1.13 g (94%) of 4-*d*: bp 64 °C (1.1 mm); NMR (CCl_4) δ 3.25 (3 H, s), 3.10 (3 H, s), 2.1–2.5 (3 H, m, 1 H exchanges with D_2O), 0.9–1.9 (6 H, m).

Kinetics of Acid-Catalyzed Rearrangement of 4 and 4-*d*. Di-*n*-propyl ether was dried by distillation from lithium aluminum hydride. Dry hydrochloric acid gas was bubbled through the solvent and the resulting solution was diluted to approximately 0.05 M in hydrochloric acid. The exact concentration of hydrochloric acid was determined by pipetting 1 mL of the solution into 2 mL of water and titrating the aqueous phase to pH 7 with standard sodium hydroxide while vigorously stirring the system. The rate of disappearance of **4** (or **4**-*d*) was monitored by gas chromatography using naphthalene as internal standard. In a typical run, 48.4 mg of **4** and 8.1 mg of naphthalene were diluted to 1 mL with 0.057 M hydrochloric acid in di-*n*-propyl ether. Nine aliquots were sealed in glass tubes and withdrawn at appropriate times. Analysis consisted of breaking open the tubes, addition of 20 μL of triethylamine followed by vigorous shaking, and addition of 100 μL of 0.3 M sodium carbonate. The organic phase was separated and dried over anhydrous sodium sulfate and immediately analyzed on 5 ft, 5% SE 30 on chromosorb G (column B).

3,3-Dimethoxybicyclo[2.2.1]heptan-2-one. This ketone was prepared by Sarett oxidation of **4** as previously reported.[22]

Preparation of 17. 3,3-Dimethoxyhicyclo[2.2.1]heptan-2-one (1.5 g) was dissolved in 10 mL of anhydrous ether and cooled to 0 °C under dry nitrogen. Methyl lithium (6.3 mL of 1.84 M) was slowly added dropwise. After warming to 25 °C, water was carefully added and the phases were separated. The ether phase was washed with brine and dried over sodium sulfate. Removal of solvents and distillation of the residue gave 1.58 g (96%) of **17**: bp 75–80 °C (1.6 mm); NMR ($CDCl_3$) δ 3.32 (3 H, s), 3.28 (3 H, s), 1.0–2.5 (11 H, m with sharp s at 1.31); mass spectroscopic molecular weight, 186.1268 (calcd for $C_{10}H_{18}O_3$, 186.1256).

Preparation of 18. 3,3-Dimethoxybicyclo[2.2.1]heptan-2-one (0.54 g) was dissolved in 2 mL of anhydrous ether, and phenyllithium (5.3 mL of 1.8 M) was added dropwise at 0 °C. After stirring at 25 °C for 10 min, a workup procedure identical to that used for the preparation of **17** gave 0.69 g (86%) of **18**: bp 105–110 °C (0.1 mm); NMR (CCl_4) δ 7.0–7.8 (5 H, m), 3.23–3.40 (4 H, overlapping singlets at 3.29 (3 H) and 3.33, 1H (at 3.33) exchanges with D_2O), 0.7–2.7 (11H, m with sharp s at 2.56); mass spectroscopic molecular weight, 248.1413 (calcd for $C_{15}H_{20}O_3$, 248.1412).

Preparation of 23. Pyridine (10 mL) was cooled to 0 °C and 1.5 g of **1** was added. *p*-Toluenesulfonyl chloride (2.6 g) was dissolved with stirring and the solution was stored at −5 °C for 48 h. Ether (40 mL) and ice-cold water (20 mL) were added, and the phases were separated. The ether extract was washed consecutively with cold water, cold dilute hydrochloric acid until acidic to litmus, and brine, and dried over sodium sulfate. Solvent was removed on a rotary evaporator leaving a white solid (3.09 g) (95%) of **23**. A pure sample was obtained by recrystallization from hexane: mp 61.5–62.5 °C; NMR ($CDCl_3$) δ 7.2–8.1 (4 H, m), 4.6–5.0 (1 H, m), 3.27 (3 H, s), 3.15 (3 H, s), 1.4–2.6 (7 H, m with sharp s at 2.48).

Preparation of 25. The preparation of **25** was analogous to the preparation of **23**. Ten milliliters of pyridine, 1.57 g of *p*-toluenesulfonyl chloride, and 1.0 g of **2** were used. After storing at −5 °C for 12 h, workup gave a clear viscous oil which crystallized after several days at −5 °C but was unstable neat at 25 °C. Yield of crude **25** was 1.23 g (60%): NMR ($CDCl_3$) δ 7.2–8.0 (4 H, m), 4.4–4.6 (1 H, m), 3.16 (6 H, s), 2.43 (3 H, s), 1.3–2.1 (6 H, m).

Preparation of Triflates. General Procedure. A given amount of pyridine was cooled to 0 °C and 1.5–2.0 equiv of trifluoromethanesulfonic (triflic) anhydride was added slowly dropwise with stir-

ring. A white solid precipitate formed and was dissolved by warming the mixture to near 20 °C. After recooling the solution to 0 °C, 1 equiv of the alcohol was added slowly dropwise with stirring and the resulting solution was stored at −5 °C for the noted times. Workup consisted of a threefold dilution with ether, extraction with ice-cold water, ice-cold dilute hydrochloric acid until the aqueous phase was acidic, and brine, and drying over sodium sulfate. After removal of the solvent, distillation under high vacuum gave the triflate products, which were unstable at room temperature in air.

Attempted Preparation of 2,2-Dimethoxycyclobut-1-yl Triflate. Nine grams of pyridine, 2.8 g of triflic anhydride, and 1.09 g of 1 gave, after 12 h at −5 °C, no triflate, and the only product present was identified as methylcyclopropane carboxylate by comparison of its infrared spectrum with an authentic sample.

Preparation of 26. Ten milliliters of pyridine, 2.24 g of triflic anhydride, and 0.6 g of **2**, after 1.5 h at −5 °C, rapid workup and rotary evaporation of the solvent gave 0.84 g of **26** which was stable at 0 °C only for about 1 day: NMR (CCl_4) δ 4.9–5.1 (1 H, m), 3.32 (3 H, s), 3.23 (3 H, s), 1.4–2.6 (6 H, m).

Preparation of 28. Eleven milliliters of pyridine, 2.6 g of triflic anhydride, and 1.0 g of **4** after reaction for 1 h and distillation give 1.54 g (87%) of **28**: bp 67–69 °C (0.15 mm); NMR (CCl_4) δ 4.78 (1 H, d, J = 5 Hz), 3.25 (3 H, s), 3.19 (3 H, s), 2.3–2.8 (3 H, m), 1.1–2.0 (6 H, m).

Preparation of 30. Ten milliliters of pyridine, 1.7 g of triflic anhydride, and 0.71 g of **5** gave after distillation at less than 0.07 mm 1.16 g (92%) of **30**: NMR (CCl_4) δ 4.47 (1 H, d, J = 2.5 Hz), 3.31 (3 H, s), 3.23 (3 H, s), 2.3–2.6 (2 H, m), 1.1–2.25 (6 H, m).

Kinetics Procedure. The kinetics procedure for runs in acetic acid is described elsewhere,[24] as is the kinetics procedure in 70% aqueous acetone.[25]

Solvolysis of 23. Product Analysis. Tosylate **23** (0.497 g) and 0.43 g of triethylamine were dissolved in 12 mL of 70% aqueous acetone and heated (sealed tube) at 100 °C for 18 h. A standard workup and distillation gave one product homogeneous by gas chromatographic analysis at 60 °C on 6 ft, 10% XE 60 on Chromosorb P which was identical by infrared and NMR spectral comparison to methylcyclopropane carboxylate. An authentic sample was prepared by esterification of the acid by standard techniques. The yield of methylcyclopropane carboxylate was 86% as determined in a separate run by gas chromatography, using di-*n*-butyl ether as an internal standard.

Solvolysis of 26 in Methanol-d_4. Product Analysis. Crude triflate **26** (0.2 g) and 0.15 g of triethylamine were dissolved in 2 mL of methanol-d_4 and the solution was heated (sealed tube) at 30 °C for 50 min. A standard workup and distillation gave 0.03 g of **36** and **37**: bp 60–70 °C (14 mm); NMR (CCl_4) δ 3.1–3.5 (7 H, m with 3 sharp s at 3.14, 3.21, 3.29; relative areas 0.61:0.39:1), 1.2–2.1 (6 H, m).

Solvolysis of 26 in Acetic Acid. Product Analysis. Crude triflate **26** (0.29 g) and 0.14 g of sodium acetate were dissolved in 7 mL of acetic acid and the solution was heated (sealed tube) at 55 °C for 30 min. Workup consisted of dilution with ether and extraction with water, dilute sodium carbonate until basic, and brine, and drying over sodium sulfate. Solvents were distilled through a Vigreux column and the residue was distilled and analyzed by gas chromatography which showed one major (~80%) product and two minor unidentified products. For the major product **38**: IR (neat) $\nu_{C=C}$ 6.04 μm; NMR (CCl_4) δ 4.5–4.7 (1 H, m), 3.95–4.25 (1 H, m), 3.59 (3 H, s), 3.30 (3 H, s), 1.4–2.5 (4 H, m); mass spectroscopic molecular weight, 128.0853 (calcd for $C_7H_{12}O_2$, 128.0837).

Hydrolysis of 38. Enol ether **38** (30 mg) was dissolved in 0.5 mL of dilute hydrochloric acid, and methanol was added to cause complete solution. After heating at 50 °C for 5 min, the solution was saturated with salt and extracted with ether. The ether extract was dried over sodium sulfate and solvents were removed by aspirator. The infrared spectrum of the residue indicated methanol and **8** to be present.

Solvolysis of 28. Product Analysis. The procedure was identical to that used for **26**. Acetic acid (31 mL), 0.71 g of **28**, 0.31 mL of acetic anhydride, and 0.28 g of sodium acetate, after heating at 120 °C for 1.75 h and distillation, gave 270 mg of a mixture of **22**, **41**, **42**, and **43** which were separated by preparative gas chromatography on column A. Structural assignments of **22**, **41**, and **43** were confirmed by independent syntheses. Product **43** showed a carbonyl band at 5.57 μm, but did not exhibit other spectral properties consistent with authentic *exo*-2-acetoxybicyclo[2.2.1]heptan-7-one and was assigned the endo structure **43**. Cyclohex-3-enecarboxaldehyde was oxidized to cyclohex-3-enecarboxylic acid as previously described.[26] An acid-catalyzed esterification gave authentic **41**. Yields of **22**, **41**, **42**, and **43** were 18, 23, 31, and 18%, respectively, as determined in a separate run by gas chromatography using column B and naphthalene as an internal standard.

Methylation of 5. Sodium hydride (0.1 g) was suspended in 5 mL of tetrahydrofuran and 0.5 g of **5** was added at 25 °C. The mixture was refluxed under nitrogen for 15 min. After cooling, an excess of methyl iodide was added and the mixture was refluxed for 1 h. The mixture was again cooled and 3 mL of water was added slowly. Ether was added and the phases were separated. The ether layer was washed with brine and dried over sodium sulfate. The solvent was removed through a Vigreux column, with the last traces by aspirator. The residue was distilled to give 0.44 g of 2,2,3-trimethoxybicyclo[2.2.1]heptane: bp 63 °C (1.7 mm); NMR (CCl_4) δ 3.30 (3 H, s), 3.24 (3 H, s), 3.13 (3 H, s), 2.90 (1 H, d, J = 2.5 Hz), 0.9–2.4 (8 H, m).

Preparation of 22. Three milliliters of 5% aqueous sulfuric acid was added to 0.32 g of 2,2,3-trimethoxybicyclo[2.2.1]heptane. The heterogeneous mixture was stirred at 25 °C for 12 h. Ether was added and the phases were separated. The ether phase was washed with saturated sodium carbonate and brine, and dried over sodium sulfate. Solvent was removed through a Vigreux column and the residue was distilled to give 170 mg (71%) of **22**: bp 53–55 °C (4.7 mm); IR (neat) $\nu_{C=O}$ 5.69 μm; NMR (CCl_4) δ 3.41 (3 H, s), 2.89 (1 H, d, J = 2.5 Hz), 1.1–2.6 (8 H, m); mass spectroscopic molecular weight, 140.0815 (calcd for $C_8H_{12}O_2$, 140.0837).

Preparation of 45. A solution of 0.48 g of **5** in 7 mL of pyridine was cooled to 0 °C and 0.42 g of acetyl chloride was added slowly dropwise. After stirring at 25 °C for 35 min, the solution was diluted with ether and extracted with water, dilute hydrochloric acid until acidic, and brine, and dried over sodium sulfate. Removal of solvents and distillation of the residue gave 0.48 g (84%) of **45**: bp 79–81 °C (1.9 mm); IR (neat) $\nu_{C=O}$ 5.74 μm; NMR (CCl_4) δ 4.40 (1 H, d, J = 2.5 Hz), 3.18 (6 H, s), 0.9–2.5 (11 H, m with sharp s at 1.99).

Acetolysis of 45. Eleven milliliters of 0.1 M sodium acetate–acetic acid was added to 0.364 g of **45** and after heating (sealed tube) at 100 °C for 15.75 h the contents were diluted with ether, and water was added. The aqueous phase was extracted with another portion of ether and the combined ether extracts were washed with dilute sodium carbonate and brine and dried over sodium sulfate. Removal of solvent afforded a residue which was distilled to give **42**, 0.253 g (88%): bp 57–59 °C (0.08 mm); IR (neat) $\nu_{C=O}$ 5.65 and 5.74 μm; NMR (CCl_4) δ 4.44 (1 H, d, J = 2.5 Hz), 2.4–2.7 (2 H, m), 1.2–2.3 (9 H, m with sharp s at 2.04); mass spectroscopic molecular weight, 168.0818 (calcd for $C_9H_{12}O_3$, 168.0786).

Solvolysis of 30. Product Analysis. The procedure was identical to that used for **26** and **28**. Triflate **30** (0.0776 g), 0.03 mL of acetic anhydride (0.03 mL), and 0.2 M sodium acetate–acetic acid (3 mL) at 100 °C for 10 min gave 28.3 mg (52%) of the previously reported **58**.[12] Longer reaction times (15 h) lead to formation of nortricyclanone and *exo*-2-acetoxybicyclo[2.2.1]heptan-7-one.

Solvolysis of 28-*d*. Deuterated **28**-*d* (prepared in a manner analogous to **28** from 4-d) was solvolyzed in acetic acid using the procedure for product analysis of **28**. Preparative gas chromatographic separation of the products gave pure **41**-*3d*: ^{13}C NMR ($CDCl_3$) δ 176.0, 126.4 (C-4), 51.5, 39.2, 27.4, 25.1, 24.3, C-3 was not observable; IR (neat) $\nu_{C=O}$ 5.73 μm, $\nu_{C=C}$ 16.9 μm, ν_{C-D} 4.41 μm; mass spectroscopic molecular weight, 141.0895 (calcd for $C_8H_{11}DO_2$ 141.0900).

Preparation of 57. Methyl 4-cyclohexanonecarboxylate (**56**) (0.897 g) was dissolved in 5 mL of dry methanol containing one drop of triethylamine. Sodium borodeuteride (0.124 g) was added slowly to the solution at 5 °C and the reaction was allowed to warm to 25 °C. After stirring for 2 h, the solution was added to 0.8 g of acetic acid in 3 mL of water cooled in an ice bath. After 2 min, the aqueous phase was extracted with 2–10-mL portions of ether, and the combined ether extracts were washed with dilute sodium carbonate and brine and dried over sodium sulfate. The solvent was removed through a Vigreux column and the residue was distilled to give 0.710 g (78%) of **57**: bp 71–76 °C (0.08 mm); IR (neat) ν_{OH} 2.85 μm, $\nu_{C=O}$ 5.75 μm; NMR (CCl_4) δ 3.58–3.75 (3 H, overlapping sharp s at 3.29 and 3.31), 2.75 (1 H, s, exchanges with D_2O), 0.9–2.6 (9 H, m); mass spectroscopic molecular weight, 159.1032 (calcd for $C_8H_{13}DO_3$, 159.1004).

Preparation of 41-*4d*. Deuterated alcohol **57** (0.600 g) was dissolved in 6 mL of pyridine and the solution was cooled to 0 °C in an ice–water bath. Triflic anhydride (1.27 g) was added slowly dropwise, the reaction was stored, at −5 °C for 35 min. The solution was diluted with 10 mL of ether and extracted with water. The water extract was extracted with one more portion of ether and the combined ether extracts were washed with dilute hydrochloric acid until acidic and brine, and dried over sodium sulfate. The solvent was removed through a Vigreux column, and the residue was distilled to give 0.300 g (56%) of **41**–*4d*: bp 72–73 °C (12 mm); IR (neat) $\nu_{C=O}$ 5.73 μm, ν_{C-D} 4.41 μm, $\nu_{C=C}$ 17.0 μm; NMR ($CDCl_3$) δ 5.6–5.9 (1 H, m), 3.70 (3 H, s), 1.4–2.8 (7 H, m); fully decoupled ^{13}C NMR ($CDCl_3$) δ 176.0, 124.9

(C-3), 51.5, 39.2, 27.4, 25.1, 24.3; C-4 was not observable; mass spectroscopic molecular weight, 141.0891 (calcd for $C_8H_{11}DO_2$, 141.0900). Ester **41** showed ^{13}C NMR ($CDCl_3$) δ 176.0, 126.4 (C-4), 124.9 (C-3), 51.5, 39.2, 27.4, 25.1, 24.3; IR (neat) $\nu_{C=O}$ 5.73 μm, $\nu_{C=C}$ 15.1 μm.

Acknowledgment. Financial support from the Research Corp. is gratefully acknowledged.

Registry No.—**1**-d_2, 63703-42-4; **4**-*d*, 63703-43-5; **6a**, 63703-44-6; **6b**, 63703-45-7; **7**, 63703-46-8; **9**, 7429-44-9; **11**, 63703-47-9; **12**, 63703-48-0; **12**-d_2, 63703-49-1; **17**, 63703-50-4; **18**, 63703-51-5; **22**, 63329-06-9; **28**-*d*, 63703-52-6; **36**, 63703-53-7; **37**, 63703-54-8; **38**, 61860-73-9; **41**, 6493-77-2; **41**-*3d*, 63703-55-9; **41**-*4d*, 63703-56-0; **42**, 63703-57-1; **45**, 63703-58-2; **56**, 6297-22-9; **57**, 63703-59-3; 1,2-bis(trimethylsiloxy)cyclobutene, 17082-61-0; 1,2-bis(trimethylsiloxy)cyclopentene, 6838-66-0; 2-hydroxycyclohexanone dimer, 30282-14-5; 2-hydroxycyclohexanone, 533-60-8; 2,3-bis(trimethylsiloxy)bicyclo[2.2.1]hept-2-ene, 63715-72-0; 3,3-dimethoxybicyclo[2.2.1]heptan-2-one, 35611-45-1; *p*-toluenesulfonyl chloride, 98-59-9; triflic anhydride, 358-23-6; 2,2,3-trimethoxybicyclo[2.2.1]heptane, 63703-60-6.

References and Notes

(1) (a) U. Schrapler and K. Ruhlmann, *Chem. Ber.*, **96**, 2780 (1963); (b) U. Schrapler and K. Ruhlmann, *ibid.*, **97**, 1383 (1964); (c) J. J. Bloomfield, *Tetrahedron Lett.*, 587 (1968); (d) J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, *Org. React.*, **23**, 259 (1976).
(2) G. M. Rubottom, M. A. Vanzquez, and D. Pelegrina, *Tetrahedron Lett.*, 4319 (1974).
(3) X. Creary and A. J. Rollin, *J. Org. Chem.* **42**, preceding paper in this issue.
(4) (A(J. Salaun and J. M. Conia, *Chem. Commun.*, 1358 (1970); (b) J. M. Conia and J. R. Salaun, *Acc. Chem. Res.*, **5**, 33 (1972); (c) J. P. Barnier, J. M. Denis, J. Salaun, and J. M. Conia, *Tetrahedron*, 1405 (1974); (d) J. M. Conia and M. J. Robson, *Angew. Chem., Int. Ed. Engl.*, **14**, 473 (1975).
(5) (a) J. Omura, A. K. Sherma, and D. Swern, *J. Org. Chem.*, **41**, 957 (1976); (b) L. Huang, K. Omura, and D. Swern, *ibid.*, **41**, 3329 (1976).
(6) (a) J. C. Irvine and D. McNicoll, *J. Chem. Soc.*, **93**, 1601 (1908); (b) F. Chen, R. E. Robertson, and C. Ainsworth, *J. Chem. Eng. Data*, **16**, 121 (1971).
(7) (a) C. J. Collins, W. T. Rainey, W. B. Smith, and J. A. Kaye, *J. Am. Chem. Soc.*, **81**, 460 (1959); (b) W. B. Smith, R. E. Bowman, and T. J. Kmet, *ibid.*, **81**, 997 (1959).
(8) C. J. Collins, V. F. Raaen, B. M. Benjamin, and I. T. Glover, *J. Am. Chem. Soc.*, **89**, 3940 (1967).
(9) (a) G. D. Sargent in "Carbonium Ions", Vol III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley, New York, N.Y., 1972, p 1110; (b) X. Creary, F. Hudock, M. Keller, J. F. Kerwin, and J. P. Dinnocenzo, *J. Org. Chem.*, **42**, 409 (1977).
(10) An analogous dimeric product has been observed in the acid-catalyzed treatment of α-hydroxycyclohexanone with alcohols. See: H. W. Durbeck, C. G. B. Frischkorn, and K. Hilpert, *Tetrahedron*, 2927 (1971).
(11) For a review and leading references, see: (a) H. G. Rickey, Jr., In "Carbonium Ions", Vol III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley, New York, N.Y., 1972, p 1201; (b) K. B. Wiberg, B. A. Hess, Jr., and A. J. Ashe, III, *ibid.*, p 1295.
(12) P. G. Gassman, J. L. Marshall, and J. G. Macmillan, *J. Am. Chem. Soc.*, **95**, 6319 (1973).
(13) Ion **46** may be involved as a discrete intermediate which rearranges to **47**. If the rearrangement of **28** to **47** is a concerted process, the transition state should resemble **46**.
(14) (a) B. Capon, *Q. Rev., Chem. Soc.*, **18**, 45 (1964); (b) S. Winstein and R. B. Henderson, *J. Am. Chem. Soc.*, **65**, 2196 (1943); (c) S. Winstein and L. L. Ingraham, *ibid.*, **74**, 1160 (1952).
(15) P. Yates and R. J. Crawford, *J. Am. Chem. Soc.*, **88**, 1561 (1966).
(16) Y. Lin and Alex Nickon, *J. Am. Chem. Soc.*, **92**, 3496 (1970).
(17) G. R. Wenzinger and P. Benz, *Tetrahedron Lett.*, 727 (1976).
(18) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034 (1951).
(19) S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan, and H. Marshall, *J. Am. Chem. Soc.*, **74**, 1127 (1952).
(20) P. v. R. Schleyer, M. M. Donaldson, and W. E. Watts, *J. Am. Chem. Soc.*, **87**, 375 (1965).
(21) R. H. Perry, *J. Org. Chem.*, **24**, 829 (1959).
(22) X. Creary, Ph.D. Thesis, The Ohio State University, 1973.
(23) A. Barco, G. DeGiuli, and G. P. Pollini, *Synthesis*, **11**, 626 (1972).
(24) X. Creary, *J. Org. Chem.*, **40**, 3326 (1975).
(25) X. Creary, *J. Am. Chem. Soc.*, **98**, 6608 (1976).
(26) H. Fiesselmann, *Chem. Ber.*, **75**, 881 (1942).

Photochemical Cycloadditions of Benzonitrile to Alkenes. Factors Controlling the Site of Addition

Thomas S. Cantrell

Department of Chemistry, The American University, Washington, D.C. 20016

Received July 12, 1977

The photochemical cycloaddition of benzonitrile to a diverse array of alkenes has been studied in order to determine the factors controlling the site of addition to the nitrile. The reaction course depends critically on the number and type of electron-donating groups on the alkene. Alkenes having four alkyl substituents, or two alkoxyls, or two alkyl and one alkoxyl, undergo addition to the C≡N triple bond, furnishing mainly 2-azabutadienes, together with varying amounts of their azetine precursors. With less electron-rich alkenes, i.e., those containing two or three alkyl groups, addition occurs at the 1,2 positions of the ring, furnishing 1-cyanobicyclo[4.2.0]octadienes. Both types of alkenes strongly quench benzonitrile fluorescence, indicating intermediacy of excited nitrile singlets. It is speculated that the difference in reaction sites for the two classes is the result of different sites of complexation at benzonitrile in singlet exciplexes.

Much of the vast amount of research performed during the past 15 years on the photochemical behavior of organic molecules has centered on carbonyl compounds, particularly ketones.[1] A wide array of interesting transformations have been observed, the reaction course depending on the exact structure of the ketone and upon the presence or absence of substrates or reactive solvents. In contrast, there have been very few reports on the photochemistry of nitriles and other carboxylic acid derivatives. In an early study, Buchi and colleagues showed that benzonitrile undergoes a [2 + 2] cycloaddition at the 1,2 positions of the benzene ring to certain alkenes, including 2-methyl-2-butene and ethoxyethylene, to yield 1-cyanobicyclo[4.2.0]octadienes.[2] Certain α,β-unsaturated nitriles, such as acrylonitrile,[3a] 2-cyanobutadiene,[3b] and 1-cyanocyclohexene,[3c] are reported to add alkenes across the C=C double bond and/or dimerize. Naphthonitriles have been observed to add certain alkenes at the 1,2 positions,[4a] as does naphthalene itself to acrylonitrile,[4b-d] via intermediate exciplexes. Two groups have observed [2 + 2] cycloaddition of 9-phenanthronitrile to alkenes at the 9,10 positions.[5] Since the publication of some of the present results, Yang and coworkers have very recently reported both 2-azabutadienes and azetines to be formed from benzonitrile and naphthonitriles with 2,3-dimethyl-2-butene.[6]

In a preliminary communication, it was reported that photochemically excited benzonitrile adds to certain electron-rich alkenes, such as 2,3-dimethyl-2-butene and 1,1-dimethoxy-2,2-dimethylethylene, across the cyano group to

Table I

Registry no.	Alkene	% yield of 2-azabutadienes and azetine[a]	% yield of bicyclo[4.2.0]-octadienes[a]	Ionization potentials, eV
5634-54-8	1,1-Dimethoxy-2,2-dimethylethylene (2)	45		
922-69-0	1,1-Dimethoxyethylene (3)	28		
931-57-7	1-Methoxycyclohexene (4)	46		
764-13-6	2,5-Dimethyl-2,4-hexadiene (5)	54		8.1
1674-10-8	1,2-Dimethylcyclohexene (6)	67[b]		8.5
563-79-1	2,3-Dimethyl-2-butene (7)	74		8.5
513-35-9	2-Methyl-2-butene (8)	6	65	8.80
142-29-0	Cyclopentene (9)		35	9.03
115-11-7	Isobutene (10)		46	9.3
121-46-0	Norbornadiene (11)		41	8.4
108-05-4	Vinyl acetate (12)		60	
116-11-0	2-Methoxypropene (13)		43	
156-60-5	*trans*-1,2-Dichloroethylene (14)		27	

[a] Yields given are of isolated products. [b] Includes product from hydrogen abstraction by CN.

Table II. Reaction of Benzonitrile with Alkenes of Type B

Alkene	Adduct(s)	Φ_{254}	Φ_{254} + diene	% isolated yield	Mp of NPM adduct, °C
8	**29, 30**	0.18	0.13	63	247–248
9	**36**	0.11	0.07	27	214–215
10	**33**	0.02		40	184–185
11	**38**			36	
12	**35**	0.15	0.11	61	211–212
13	**34**	0.16		52	163–164
14	**37**	0.08		35	

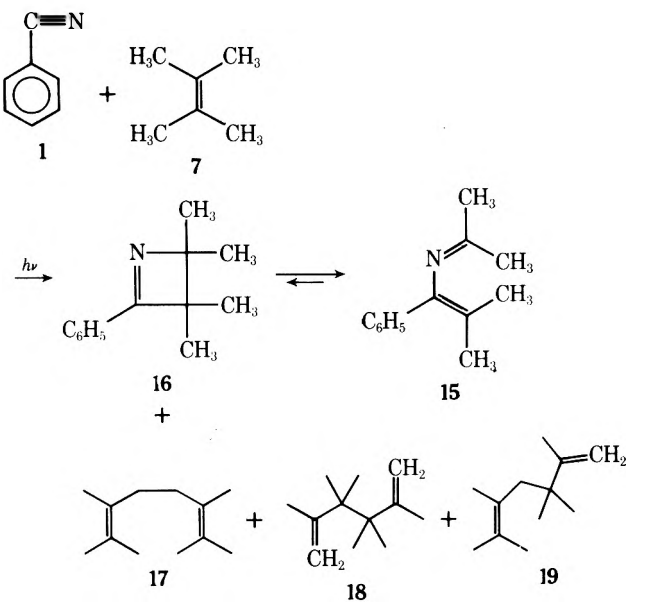
afford 2-azabutadienes, the products of electrocyclic ring opening of azetines produced by an initial [2 + 2] cycloaddition across the CN function.[7] Addition to alkenes of lower π-electron density, such as isobutene and cyclohexene, occurred at C(1)–C(2) of the aromatic ring to give substituted bicyclo[4.2.0]octadienes, in agreement with the results of Buchi et al.[2] Since the initial report, the author has extended the study to numerous other alkenes and has characterized some products not identified earlier, including the azetines in certain cases. Furthermore, additional information concerning the mechanism has now been obtained which requires a modification of the hypothesis presented in ref 7. There follows herewith the results of the detailed study.

Results

The addition of photoexcited benzonitrile to carbon–carbon double bonds may proceed either across the cyano group or at the 1,2 positions of the benzene ring. The more electron-rich alkenes, such as 2,3-dimethyl-2-butene, react at the nitrile function to give varying amounts of 2-azabutadienes and their valence tautomers, the 1-azetines. Less electron-rich alkenes, including those with one to three alkyl substituents on the double bond, add to the benzene ring to give bicyclo[4.2.0]-octadienes. In all cases except those of alkenes possessing no allylic hydrogens, there are also formed products resulting from coupling of radicals produced by allylic hydrogen abstraction from the alkene, e.g., 2,3,6,7-tetramethylocta-2,6-diene from 2,3-dimethyl-2-butene. The chemical yields of the products obtained are given in Tables I and II. The results in some cases were previously noted,[7] for example, the formation of the major product with 2,3-dimethyl-2-butene. However, the earlier report did not metnion the minor product, azetine **16**, which had at that time escaped our notice. Since then we have conducted a thorough examination of the reaction mixtures for products of this type, and have examined the reactions of **1** with a number of other alkenes in order to delineate precisely the combination of structural features necessary to result in reaction at the cyano group. The first six alkenes (**2–7**) belong in the former category, group A, whereas the remainder (8–14) belong in the latter, group B. Brief inspection reveals that, in order for reaction at the cyano group to predominate, either four alkyl groups, or two alkyl and one alkoxy group, must be located on the doubly bonded carbons. The dramatic difference caused by a single methyl group is illustrated by the divergent results obtained with 2,3-dimethyl-2-butene (**7**), with which reaction of **1** occurs exclusively at the cyano group, and 2-methyl-2-butene (**8**), in which over 90% of the products result from addition to the benzene ring. The reaction of **1** with alkenes **4** and **13** illustrates the same striking difference caused by one alkyl group.

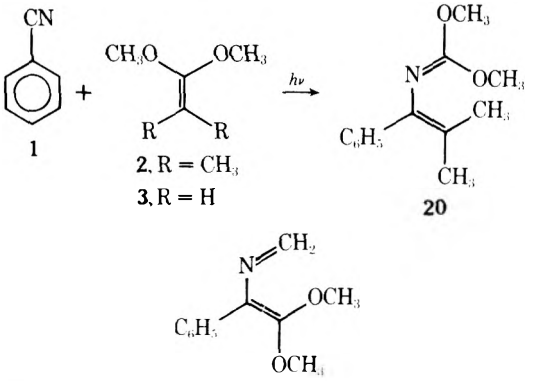
2,3-Dimethyl-2-butene. Irradiation through Vycor of hexane solutions of **1** with a two- to tenfold excess of 2,3-dimethyl-2-butene (**7**) until 50% of **1** was consumed gave two products (Scheme I): 2,5-dimethyl-3-phenyl-4-azahexa-2,4-diene (**15**; 66% based on unrecovered **1**), and its valence isomer, 2-phenyl-3,3,4,4-tetramethyl-1-azetine (**16**; 8%). The structure of azadiene **15** was deduced from its spectral properties, which include NMR singlets at τ 7.84, 8.08, 8.15, and 8.32, indicative of methyls on vinyl carbons, and was established conclusively by its rapid hydrolysis by cold aqueous acid

Scheme I



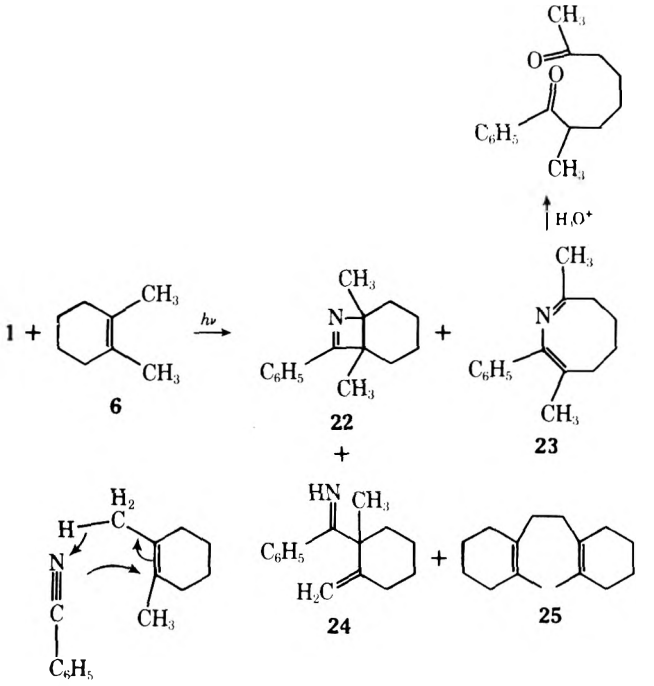
to isobutyrophenone and acetone. The quantum yield for **15** at 254 nm was 0.23. Photoproduct **16** escaped detection in the early experiments and hence was not mentioned in the preliminary communication. Its identity followed from its spectral features. Of particular help were two three-hydrogen singlets in the NMR spectrum at τ 8.62 and 8.66, a region characteristic of methyl groups on saturated carbon, and an infrared C=N band at 1580 cm^{-1}, which coincides exactly with that reported for 2-phenyl-1-azetine.[8] The manifest thermal stability of **16**, which allows it to survive gas chromatograpby at 170 °C, suggests that **15** is formed from it in a photochemical, rather than a thermal, ring opening. Indeed, direct reirradiation of purified **16** produces appreciable quantities of **15**; evidently the ratio of the two products, as isolated, reflects the equilibrium composition.[6] Also isolated from irradiation of mixtures of **1** and **7** was a mixture of hydrocarbons **17**–**19** in 62% yield. It proved to be possible to isolate **17** and **18** in pure form by GC; their identity was apparent from their NMR and mass spectra. These hydrocarbons evidently result from coupling of the allylic radical produced by abstraction of a hydrogen atom from alkene **7** by photoexcited benzonitrile. Coupling of two radicals in the head-to-bead, tail-to-tail, or head-to-tail manner produces **17**–**19**, respectively.

Irradiation of **1** with excess 1,1-dimethoxy-2,2-dimethylethylene (**2**, the dimethyl acetal of dimethylketene)[9] until 40% of **1** was destroyed, followed by evaporation of the solvent and excess **2**, gave 45% of a single photoproduct, assigned structure **20** on the basis of its spectra properties and hydrolysis products. Compound **20** is an imidocarbonate ester, rather than a simple imine as was **15**, and proved to be more resistant to hydrolysis, in keeping with its chemical nature. Warming of 20–50 °C in acetic acid containing hydrochloric acid gave a fair yield of isobutyrophenone; long reaction times gave only products of aldolization of isobutyrophenone. In the reaction mixture with **20** were also detected small amounts of a mixture of incompletely characterized compounds produced hy the coupling of radicals formed by hydrogen abstraction from **2**. Use of unsubstituted ketene dimethyl acetal gave 28% of the unstable imine **21**, not obtained analytically pure, but identifiable from its NMR and mass spectra.



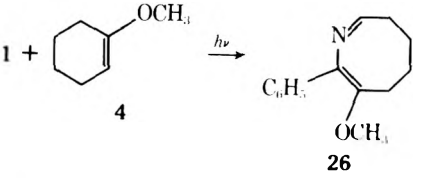
1,2-Dimethylcyclohexene. Irradiation of hexane solutions of **1** with excess 1,2-dimethylcyclohexene (**6**) afforded products **22** (17%), **23** (26%), **24** (24%), and **25** (16%) (Scheme II). Azacyclooctadiene **23** was identified by spectral data and by its hydrolysis to 1-phenyloctane-1,7-dione, whose spectral data and analytical data were in exact accord with expectation. Azetine **22**, identified from its NMR and mass spectral properties and an infrared band at 1568 cm^{-1}, constituted a significantly larger portion of the product mixture than did azetine **16**, derived from alkene **7**, also a tetraalkylalkene. Evidently azetine **22** is somewhat more stable with respect to isomerization to its azadiene isomer **23**, because of the reduced repulsion between the methyls and the α-methylene groups of **22** as compared with the two *gem*-dimethyl moieties of **16**.

Scheme II



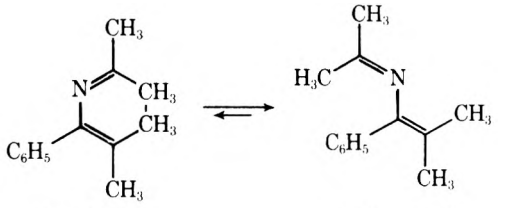
Hydrocarbon **25** is analogous to **17**, formed from **1** and 2,3-dimethyl-2-butene; it is not clear why coupling products analogous to **18** and **19** were not observed. Interestingly, in the present case there was found, however, a significant quantity of **24**, possibly the product of cross-coupling of the two radicals produced via hydrogen abstraction from **6** by photoexcited **1**. The structure of imine **24** was deduced from spectral data, including, inter alia, an infrared C=N band at 1681 cm^{-1}, and NMR signals at τ 4.6 and 5.2 (1 H each, $=CH_2$), 6.1 (1 H, br, NH), 7.4–8.4 (8 H, m, CH_2), and 8.66 (3 H, d, J = 7.1 Hz, $-C-CH_3$); *m/e* 213. The formation of **24** was surprising, both because of the absence of an analogous product in the reaction of **1** and alkene **7**, and because it is the result of coupling of a benzimidyl radical to the tertiary more hindered site of the allylic radical derived from **6**. Imine **24** could also result from an ene reaction, as shown in Scheme II.

1-Methoxycyclohexene. Irradiation of mixtures of **1** and excess 1-methoxycyclohexene (**4**) produced 46% of azahutadiene **26**, identified by its spectral properties (see Experimental Section). There was also isolated 17% of a mixture which was not completely characterized but which, on the basis of spectral evidence, appeared to be composed of compounds derived from the combination of methoxycyclohexenyl radicals formed by hydrogen abstraction from alkene **4**. Thus, two alkyl groups and one alkoxyl attached to a carbon–carbon double bond provide sufficient electron density to cause photoexcited benzonitrile to react at the cyano group.

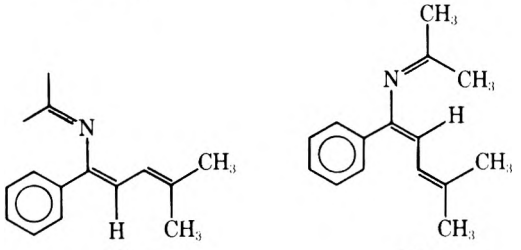


2,5-Dimethyl-2,4-hexadiene (5). Photolysis of **1** with excess **5** gave ~54% of a mixture of the geometric isomers **27a** and **27b** (ratio 57:43) in addition to small amounts of C_{16} hydrocarbons formed via coupling of radicals derived from **5**. The *E* and *Z* isomers **27a** and **27b** could not be separated by

the gas and thin-layer chromatographic techniques available, but were identified by the NMR signals in the spectrum of the mixture. Isomer **27a**, which exhibits an AB pattern at τ 3.78 and 4.30 (J = 11.4 Hz), is assigned the E geometry, since it shows four well-separated methyl singlets, whereas isomer **27b** shows a narrow six-hydrogen doublet at τ 8.18 and a six-hydrogen singlet at τ 8.27. Geometric isomer **27a** bears an alkyl group (isobutenyl) on C-4 of the 2-azahexatriene chain which is cis to the imine function. The same is true in azadiene **15**, whose NMR spectrum shows four well-separated methyl signals, the alkyl group which corresponds to the iso butenyl of **15** being one of those methyls. The fact that the methyls of the imine moiety of **15** exhibit different chemical shifts may



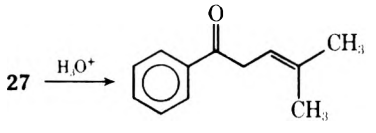
15-cisoid **15**-transoid



27a **27b**

be attributed to the existence of the compound predominantly in the transoid conformation, in which the methyl syn to the benzene ring will experience an environment different from the other, a consequence of the nearby phenyl group. It therefore seems likely that the transoid conformation of **27a** will be considerably more populated than in the case of **27b**, since in the cisoid form of **27b** (shown) only a hydrogen atom, rather than an alkyl, is syn to the imine proximate methyl group. On this basis, it seems more likely that **27a** will have its transoid conformer more highly populated than will **27b**, and consequently its imine methyls will exhibit significantly different chemical shifts.

Acid hydrolysis of the **27a–b** mixture gave 2-methyl-5-phenyl-2-hexen-1-one (**28**), whose spectral properties were in agreement with expectation, thus further securing the gross structural assignment of **27**. It seems worth noting that the double bond of **28** shows no inclination to shift into conjuga-

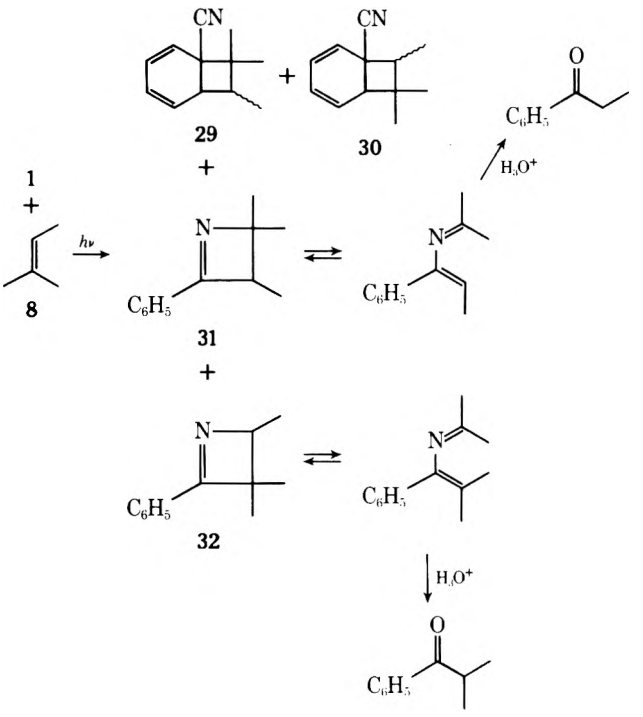


28

tion with the ketonic carbonyl group; evidently the stabilizing effect of a trialkyl substitution vs. dialkyl outweighs the stability to be gained via conjugation with carbonyl.

2-Methyl-2-butene. Irradiation of **1** with either an equimolar amount or a tenfold excess of 2-methyl-2-butene (**8**) gave an identical mixture of adducts (Scheme III); the yield was 62% under the latter conditions (Φ = 0.17). The major (70% of the mixture) component has been shown by earlier workers[2] to be the 1-cyanobicyclo[4.2.0]octadiene **29**. Treatment of the mixture with N-phenylmaleimide (NPM) gave one pure product whose spectral properties were in accord with those expected of a Diels–Alder adduct of **29** and NPM.

Scheme III

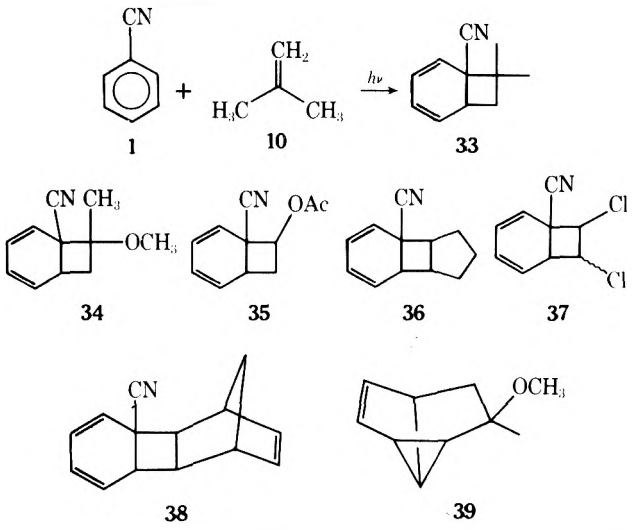


A small amount of a second adduct, possibly derived from the regioisomer **30**, was also observed.

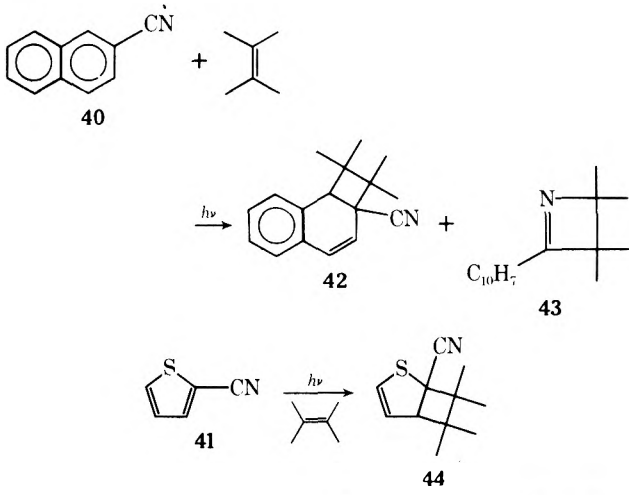
Because of the fishy amine-like odor of the distilled product mixture from **1** and alkene **8**, it was suspected that azetines and/or azadienes might be present therein. Extraction of a cold ether solution of the product mixture with ice-cold 10% hydrochloric acid, followed by immediate basification and reextraction, led to the isolation of an acid-soluble organic fraction, amounting to ~9% of the total product. By preparative GC one pure component, azetine **31**, was isolated in pure form (yield, 4%) and identified by spectral means. Allowing the acid extracts to stand at room temperature, followed by reextraction with ether, resulted in the isolation of propiophenone as its 2,4-dinitrophenylhydrazone. In the course of work described in part in ref 2, Ayer isolated from the acid-soluble fraction of the product mixture propiophenone, isobutyrophenone, and α,β-dimethyl-β-aminobutyrophenone, all in the form of derivatives.[10] The formation of all the products mentioned can reasonably be accounted for by the transformations shown in Scheme III, involving hydrolysis of azetines **31** or **32**, or of the ring-opened 2-azadiene valence isomers derived therefrom.

Isobutene. The photochemical addition of **1** to isobutene proceeded at a considerably slower rate than to the more highly alkylated alkenes; after 30 h of irradiation, only 25% of **1** had been destroyed. Workup gave a 42% chemical yield of a mixture of one major and two minor isomers. A pure sample of the major isomer, compound **33**, was obtained by repeated gas chromatography. It was additionally characterized by its Diels–Alder adduct with NPM.

2-Methyoxypropene, Vinyl Acetate, Cyclopentene, 1,2-Dichloroethylene, and Bicyclo[2.2.1]heptadiene. Irradiation of mixtures of **1** with all of these monoalkenes led to mixtures which, on the basis of their NMR and mass spectral properties, are formed by attachment of the substrate to the aromatic ring of **1**. The major isomer in each case must be a bicyclo[4.2.0]octadiene, since adducts with NPM could be obtained in the yields listed in Table II. It is likely that regio- and stereoisomers of the same gross structure (**34–38**) make up a large portion of the remainder of each mixture. In the case of the mixture obtained with 2-methoxypropene,



however, it appears that adducts from 1,3 addition across the benzene ring may comprise a major portion of the material remaining after treatment of the product mixture with NPM. The ratio of vinyl to saturated hydrogen in its NMR spectrum is too low to reconcile with a cyclohexadiene structure but is reasonable if some 1,3 addition to the benzene ring of **1** has occurred to give adducts of type **39**. The exact structure of the minor adducts from **1** and alkene **13** is still under investigation.



The photolyses of β-naphthonitrile (**40**) and 2-thienonitrile [2-cyanothiophene (**41**)] with alkene **7** were briefly examined in order to determine the preference for cycloaddition site. In our hands, irradiation of **40** with excess **7**, followed by chromatography on silica gel, gave a 52% isolated yield of **42**, the product of ring addition. However, short-path distillation of the crude reaction mixture gave an oil whose NMR spectrum exhibited signals, besides those of **42**, at τ 8.68 and 8.79, which are ascribable to the methyls of azetine **43**. The distilled oil displayed an infrared band at 1585 cm^{-1}, similar to azetines **16** and **22**. The intensity of the NMR signals indicates a yield of ~20% of **43**.[11]

Discussion

The most remarkable feature of the present investigation is the dramatic dependence of the site of addition to **1** upon alkene structure. This is perhaps best illustrated by the divergence in reaction course caused by the presence or absence of one methyl group, as in the pair of alkenes 2,3-dimethyl-2-butene (**7**) and 2-methyl-2-butene (**8**). The preference shown by benzonitrile to add the latter alkene at C(1)–C(2) of the aromatic ring of **1** vs. addition at the nitrile function is

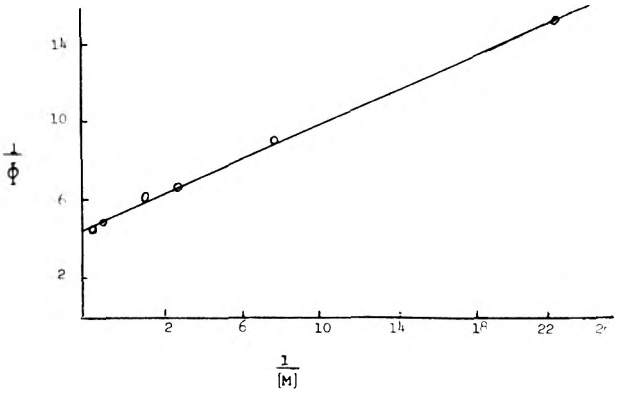


Figure 1.

Table III.

	$k_q\tau$	$k_q \times 10^{-9}$ [a]	$k_q \times 10^{-9}$ [b]
Benzonitrile + **7**	10.2	1.06	1.3
Benzonitrile + **8**	6.1	0.63	

[a] From fluorescence lifetime quenching. [b] From quantum yields.

~12:1. Addition of **1** to alkene **7**, however, occurs exclusively at the nitrile group. A similar pair of alkenes are 2-methoxypropene (**13**) and 1-methoxycyclohexene (**4**). The latter bears one more alkyl group than **13**. Addition of **4** occurs exclusively to the cyano group of **1**, whereas reaction with **13** takes place only across the benzene ring.

In the preliminary communication[7] reporting some of the present results, the statement was made that addition of the less highly substituted alkenes to **1** apparently occurred via excited triplet benzonitrile, since addition to these alkenes could be partially quenched by added 1,3-dienes. However, subsequent experiments showed that this effect is smaller than originally thought. While there is a definite quenching observed with added 1,3-pentadiene, the maximum observed at larger quencher concentrations is a reduction in reaction efficiency to about 0.6–0.7 of that observed in the absence of added diene. This and other information is collected in Table II.

Studies subsequent to the earlier report have shown that 1,3-dienes of a low degree of alkyl substitution, such as 1,3-butadiene and *cis*-1,3-pentadiene (the latter was the quenching agent used earlier), do in fact add slowly to **1** to give adducts of bicyclo[4.2.0]octadiene type. When a correction is made for the reaction of **1** with the quencher, it is apparent that little if any triplet quenching is observed. In fact, we have now found that alkenes of both groups A and B, as well as simple dienes, quench benzonitrile fluorescence effectively. Benzonitrile exhibited a fluorescence lifetime in fluid solution at 25 °C of 9.6 ns. The k_q's for alkenes **7** and **8**, representatives of groups A and B, respectively, are given in Table III. The dependence of quantum yield of **15** and **16** (the products from **7**) on the concentration of alkene **7** was measured; the results are shown in Figure 1. The value of k_q obtained from these experiments via the equation

$$\frac{1}{\Phi_a} = \frac{1}{\Phi_I}\left[1 + \frac{1}{k_q\tau[A]}\right] \quad (1)$$

where Φ_a is the quantum yield for addition and Φ_I is the quantum yield at infinite alkene concentration, is in reasonable agreement with the value obtained by fluorescence, indicating that the same excited state of **1** is involved in both emission and photochemical reactions. This value is probably the diffusion-controlled rate.

Figure 2.

This evidence, together with the observed photochemistry of 1 and alkenes, supports the formation of exciplexes from excited singlet 1 and ground-state alkenes and dienes. Aryl nitriles such as naphthonitriles form fluorescent exciplexes with alkenes.[12] Exciplexes have been implicated as intermediates in numerous photochemical cycloaddition reactions of aromatic compounds.[4,5,13-15] Firm evidence for their intermediacy has been presented in some cases.[5,15] It appears, therefore, that singlet exciplexes are involved in the formation of both types of products observed in the present study.

An alternate explanation of the present observations involves charge-transfer complexes of ground-state 1 with various alkenes. Such a charge-transfer complex is believed to be an intermediate in the photochemical cycloaddition of benzene and maleic anhydride.[16] The most direct evidence for formation of charge-transfer complexes is nonadditivity in the UV–visible spectrum of mixtures of the two components. There does appear to be a slightly enhanced absorption area on the tail of the UV spectrum of benzonitrile when alkene 7 is added. However, this effect is small, and does not seem sufficient to justify invoking the intermediacy of charge-transfer complexes here.

There remains to be considered the reason for the great dependence on the site of addition to benzonitrile on alkene structure. It can be seen from the quantum yields for addition of 1 to alkenes 7 (Φ = 0.24 at infinite alkene concentration), 8, 9, and 10 (Table II) that the rates of conversion of the exciplexes to adducts vs. the rate of collapse to starting components is also a sensitive function of alkene structure. However, the differences in efficiencies of addition to 8–10 are of minor interest. Our concern here is in the difference in behavior of alkenes of categories A and B. One possibility is that the exciplexes formed with the two types of alkenes differ in the site of complexation with excited singlet 1, i.e., in exciplex geometry. The more electron-rich alkenes, of category A, lie directly over the cyano group of excited 1, as shown in Figure 2, whereas the less electron-rich alkenes, of category B, in the exciplex are located over the face of the benzene ring of 1, the site of higher electron density. One piece of evidence which is consistent with this hypothesis is the observation of distinctly different exciplex emissions from mixtures of 1 with the two alkenes, 7 and 8. Addition of either alkene results in enhanced emission in the 320–360-nm range, distinct from the fluorescence of 1. While the effect is moderate in the case of 8 (a type of B alkene), the enhancement is enormous for alkene 7 (a type A alkene). Since the only gross structural difference of the components is one methyl group, the most likely explanation for the difference in exciplex emission is a considerably different geometry in the two exciplexes.

Since the behavior of various alkenic substrates toward excited singlet 1 depends on the π-electron density of the substrate, as determined by the number and kind of electron-donating substituents on the double bond, we should be able to predict whether still other alkenes will behave as a member of group A or B. One measure of π-electron density of alkenes is the ionization potential. Inspection of the ionization potentials of several of the alkenes used here (Table I) reveals those of IP of 8.6 eV or below add to the cyano group of 1 (group A), whereas those of IP 8.7 eV or above belong to group B. The exception to this is norbornadiene. Attempts have been made to correlate k_q with ionization potential, but with limited success.[18]

Studies are in progress on the behavior of substituted benzonitriles and related compounds.

Experimental Section

Irradiations were conducted in an annular apparatus using light from a Hanovia 450-W medium-pressure mercury arc lamp, filtered through Vycor (transmits >220 nm) and cooled by ice water in an immersion well. All photochemical reaction solutions were flushed with argon for 1 h prior to irradiation and an argon atmosphere was maintained during irradiation. NMR spectra were obtained on Varian A-60 and HR-220 instruments. Mass spectra were obtained on a Hitachi Perkin-Elmer Model RMU-6E. Gas chromatography was performed on the following columns: column A, 2 ft × 0.25 in., 10% SE-30 on Chromosorb W; column B, 2 ft × 0.25 in., 15% Carbowax 20M on Chromosorb W; column C, 6 ft × 0.25 in., 10% SE-30 column D, 6 ft × 0.25 in., 15% Carbowax 20M; column E, 6 ft × 0.375 in., 25% SE-30; and column F, 6 ft × 0.25 in., 15% Carbowax 20M on Chromosorb W + 2% KOH. Emission spectral data were obtained on a TRW Instruments Nanosecond Fluorescence Apparatus of Dr. Raymond Chen of the National Institutes of Health. Some of the quenching experiments were performed by Dr. Paul Engel at Rice University on an Aminco-Bowman Apparatus.

Irradiation of Benzonitrile with 2,3-Dimethyl-2-butene. A solution of 1 (4.0 g, 0.04 mol) and 2,3-dimethyl-2-butene (7, 20 g, 0.24 mol) in spectrograde hexane (80 mL) was irradiated through a Vycor filter for 4 h. Following evaporation of the solvent and excess alkene 7 from the yellow solution, the residue was fractionally distilled to give: (a) 1.4 g of recovered 1, bp 35–38 °C (4 mm); (b) 1.8 g, bp 38–45 °C (0.2 mm); (c) a product mixture, bp 70–74 °C (0.1 mm) (3.3 g, 78%). Separation of fraction c on column F at 170 °C afforded pure 15 [retention time 5.2 min, 90% of total, 66% yield; IR (film) 1656 cm^{-1}; NMR τ 2.70 (5 H, s, br), 7.84 (3 H, s), 8.08 (3 H, s), 8.15 (3 H, s), 8.32 (3 H, s); *m/e* 187 (13, P), 172 (18), 148 (29), 131 (25), 105 (100), 77 (74). Anal. $C_{13}H_{17}N$: C, H, N] and 16 [retention time, 7.0 min, 10% of total, 8% yield; IR 1580 cm^{-1}; NMR τ 2.2 (2 H, m), 2.5–2.7 (3 H, m), 8.62 (6 H, m), 8.68 (6 H, m); *m/e* 187 (13, P), 172 (15), 131 (12), 104 (100), 103 (76), 91 (60), 84 (39). Anal. $C_{13}H_{17}N$: C, H]. There was present a third peak, of retention time 8.8 min (3% of total), which was not identified. Fraction b showed three peaks on column D at 120 °C, of retention times 4.5, 4.9, and 6.1 min, with relative areas of 28:15:57. The first and third peaks were sufficiently well separated to allow collection of pure samples. The third peak showed two slightly broadened NMR singlets at τ 7.8 and 8.3 in the ratio 2:9, and a mass spectral parent ion at *m/e* 166 with the major peak at 83, indicating structure 17. The first peak showed a very similar mass spectrum, and NMR signals at τ 5.2 (4 H, s br), 8.2 (6 H, s br), and 8.7 (12 H, s), and hence is 18.

Hydrolysis of 15. A mixture of imine 15 (0.97 g, 5.0 mmol), 15 mL of tetrahydrofuran, and 5 mL of 3% aqueous hydrochloric acid was allowed to stand at 10–15 °C for 2 h. Solid sodium bicarbonate was added until the solution was approximately neutral. The solution was distilled at 80 mm (bath temperature 35 °C) until the volume was reduced by two-thirds. Treatment of the distillate with 2,4-dinitrophenylhydrazine solution in the usual manner and recrystallization of the orange precipitate from ethanol gave the acetone 2,4-DNPH derivative (0.23 g), mp 126 °C, identical with an authentic sample. Extraction of the pot residue twice with ether, drying and evaporation of the combined extracts, and short-path distillation gave isobutyrophenone (0.42 g, 60%), identical in all respects with an authentic sample (IR, melting point, and mixture melting point of 2,4-DNPH).

Irradiation of 1 with 1,1-Dimethoxy-2,2-dimethylethylene (2). A solution of 1 (3.0 g, 0.03 mol) and ketene acetal 2 (20 g, 0.17 mol) in spectrograde hexane (110 mL) was irradiated for 7 h. The solvent was evaporated and the excess 2 was recovered by distillation under reduced pressure, bp 40–44 °C (12 mm). Fractional distillation of the residue gave two fractions. The first, bp 56–59 °C (0.1 mm), further purified by GC on column C, was dimethyl tetramethylsuccinate: IR (film) 1734 cm^{-1}; NMR τ 6.2 (6 H, s), 8.6 (12 H, s); *m/e* 202 (P, CI), 143 (58), 102 (100). The second fraction, bp 86–88 °C (0.08 mm), was almost pure imido carbonate 20: IR (film) 1686 cm^{-1}; NMR τ 2.8 (5 H, s), 6.30, 6.34 (3 H each, s), 8.36 (6 H, s); *m/e* 219 (P, 92), 204 (32), 129 (100), 115 (78). Anal. $C_{13}H_{17}NO_2$: C, H.

Irradiation of 1 with 1,1-Dimethoxyethylene. Irradiation of 2 g of 1 with 10 g of ketene dimethyl acetal in 80 mL of spectrograde hexane at 2537 Å for 3 h gave a yellow solution. After evaporation of the solvent and excess reactants, short-path distillation gave 0.42 g of a yellow, unstable oil, bp 45–50 °C (bath, (0.06 mm) (21): IR (film) 1680, 1740 cm^{-1}; NMR τ 2.8 (5 H), 5.3 (2 H, br); *m/e* 191 (30), 176 (21),

103 (46). A satisfactory analysis was not obtained, owing to the compound's instability.

Photochemical Reaction of 1 with 1,2-Dimethylcyclohexene (6). Irradiation of a solution of 1 (3.0 g, 0.03 mol) and 6 (22 g, 0.20 mol) for 6 h and workup in the usual manner gave 1.6 g of recovered 1 and 1.9 g of a product mixture, bp 102–105 °C (0.08 mm). Separation was readily accomplished by GC on column F at 190 °C. The first peak, of retention time 2.6 min, was hydrocarbon **25** (19% of total): NMR τ 7.5–8.4 (20 H, m, br), 8.3 (6 H, s); *m/e* 218 (CI), 110 (100), 109 (38). Anal. $C_{16}H_{26}$: C, H.

Peak 2, retention time 6.8 min, was imine **24:** IR 1650 cm^{-1}; NMR τ 2.1 (2 H, m), 2.6 (3 H, m), 4.61 (1 H, br), 5.12 (1 H, m), 6.1 (1 H, m, v br), 7.0–8.4 (8 H, m), 8.66 (3 H, s); *m/e* 213 (P, 8), 120 (18), 134 (43), 105 (100). Anal. $C_{15}H_{19}N$: C, H, N.

Peak 3, rentention time 8.7 min, was azetine **22:** IR 1568 cm^{-1}; NMR τ 2.2 (2 H, m, br), 2.6 (3 H, m), 7.9–8.7 (8 H, m), 8.70 (6 H, s); *m/e* 213 (P, 45), 198 (62), 189 (26), 120 (34), 104 (27), 84 (100). Anal. $C_{15}H_{19}N$: C, H, N.

Peak 4, retention time 11.5 min, was enamine **23:** IR 1647 cm^{-1}; NMR τ 2.73 (5 H, s), 7.6–8.9 (8 H, m), 7.83 (3 H, s), 8.21 (3 H, s); *m/e* 213 (P, 9), 170 (18), 134 (44), 105 (100), 91 (16). Anal. $C_{15}H_{19}N$: C, H.

Hydrolysis of Azadiene 23. A mixture of **23** (0.22 g, 1.0 mmol), tetrahydrofuran (15 mL), water (3 mL), and 2 drops of concentrated hydrochloric acid was stirred at 10 °C for 4 h. Concentration by rotary evaporation, dilution with water, and extraction with ether (2 × 15 mL), followed by drying of the combined extracts, evaporation of solvents, and short-path distillation gave 2-methyl-1-phenyloctane-1,7-dione (0.146 g, 62%): bp 110 °C (bath, 0.08 mm); IR 1680 cm^{-1}; NMR τ 2.3 (2 H, m), 2.7 (3 H, m), 7.1–8.4 (12 H, m), 7.78 (3 H, s); *m/e* 232 (P, 1.2), 134 (37), 105 (100). Anal. $C_{15}H_{20}O_2$: C, H.

Photochemical Reaction of 1 with 1-Methoxycyclohexene. A solution of 1 (3.0 g) and 1-methoxycyclohexene (**4**) (30 g) in spectrograde pentane (80 mL) was irradiated in the usual manner for 10 h. Workup gave 1.1 g of recovered **1**, a low-boiling fraction [bp 64–76 °C (0.08 mm)] which appeared to consist of compounds formed by combination of radicals derived from hydrogen abstraction from alkene **4** (mass spectral parent ion at *m/e* 214; no C=N or C≡N bands in IR; methoxyls in NMR at τ 6.20–6.24) and a product fraction from which one pure compound (**26**) was isolated by GC (~85% of total, 1.8 g, 42%): bp 104–108 °C (0.08 mm); IR 1682 cm^{-1}; NMR τ 2.5–2.9 (5 H, m), 4.7 (1 H, t, J = 8 Hz), 6.1 (3 H, s), 7.6–8.5 (8 H, m); *m/e* 215 (36, P), 200 (52), 184 (50), 112 (49), 111 (60), 84 (100). Anal. $C_{14}H_{17}ON$: C, H.

Photochemical Reaction of Benzonitrile with 2,5-Dimethyl-2,4-hexadiene. A solution of 1 (3.0 g) and diene **5** (20 g) was irradiated through Vycor for 10 h. Workup in the usual manner gave, besides 1.5 g of recovered **1**, 1.7 g of a mixture of geometric isomers **27a** and **27b;** bp 118–120 °C (0.08 mm) after a second fractional distillation; IR 1655 cm^{-1}; NMR τ 2.5–2.7 (5 H, m), 3.78, 4.30 (2 H, AB, J = 11.4 Hz, $\Delta\nu$ = 32, isomer A), 3.93, 4.22 (2 H, AB of isomer B further split by allylic coupling to CH_3), for isomer A, 3-H singlets at 7.78, 7.91, 8.10, 8.23; for isomer B, 6-H doublets (J ~1 Hz) at 8.18, 8.27; *m/e* 213 (P, 40), 198 (31), 157 (100), 104 (61). Anal. $C_{15}H_{19}N$: C, H, N.

Hydrolysis of 27a and 27b. A solution of **27a–b** (0.8 g) and 4 drops of concentrated hydrochloric acid in THF was allowed to stand at room temperature for 6 h. Dilution with water, extraction with ether (2 × 10 mL), drying and concentration of the extracts, and distillation of the residue gave 0.45 g (73%) of 1-phenyl-4-methyl-3-penten-1-one (**28**): bp 120 °C (bath, 0.08 mm); IR 1682 cm^{-1}; NMR τ 2.0 (2 H, m), 2.5 (3 H, m), 4.50 (1 H, 3q, J = 7.5, J' = 1.6 Hz), 6.38 (2 H, d, br, J = 7.5 Hz), 8.24, 8.72 (3 H each, s); *m/e* 162 (P, 2), 105 (100). Anal. $C_{12}H_{14}O$: C, H.

Photochemical Reaction of Benzonitrile with 2-Methyl-2-butene. A solution of 1 (3.0 g, 0.03 mol) and 2-methyl-2-butene (22 g, 0.3 mol) and spectrograde pentane (150 mL) was irradiated for 8 h. The usual workup gave a product fraction, bp 62–70 °C (0.1 mm) (1.8 g, 70%), in addition to recovered 1 (1.3 g). The combined product fractions from four such reactions were dissolved in 60 mL of ether, cooled in ice, and rapidly extracted with three 15-mL portions of ice-cold 10% hydrochloric acid.

The combined extracts were made basic with 20% NaOH, keeping the temperature below 5 °C by cooling with an ice–salt bath. Reextraction with ether (3 × 10 mL) gave 0.51 g of acid-soluble material which was short-path distilled to afford 0.26 g of colorless oil. Purification by GC on column F gave azetine **31:** IR 1576 cm^{-1}; NMR τ 2.3–2.8 (5 H, m), 7.1 (1 H, q, J ~7 Hz), 8.6 (3 H, d, J ~7 Hz), 8.8 (6 H, s); *m/e* 173 (P, 4), 158 (13), 103 (100), 70 (38).

The neutral material remaining in the ether layer after acid extraction was a mixture of three major components in the ratio 7:2:1. The NMR spectrum of the mixture exhibited peaks in agreement with the assignment of **29** as the major product. Warming of the nitrile mixture (0.30 g) with *N*-phenylmaleimide in benzene at 40 °C for 4 h, followed by addition of half a volume of hexane and cooling overnight at 5 °C, led to formation of a yellowish solid. Filtration and recrystallization from chloroform–hexane gave colorless needles (0.18 g): mp 247–248 °C; IR 1705 cm^{-1}; NMR τ 2.7 (5 H, s, br), 3.5–3.9 (2 H, br), 6.4–7.9 (H, m), 8.71 (3 H, d, J = 6 Hz), 9.00 (6 H, s). Anal. $C_{22}H_{22}N_2O_2$: C, H, N.

Photochemical Reaction of Benzonitrile with Isobutene. A solution of 1 (3.0 g) and isobutene (30 mL) in spectrograde pentane was cooled externally with a dry ice–acetone bath while a glycol–water mixture at −30 °C was circulated through the immersion well. The solution was irradiated through Vycor for a total of 62 h, interrupting the irradiation three times to allow the apparatus to cool off overnight. Evaporation of solvent and fractional distillation of the residue gave 0.94 g of almost colorless oil **33:** bp 60–62 °C (0.2 mm); IR (film) 2242 cm^{-1}; NMR τ 3.8–4.3 (4 H, *m*), 6.7–8.2 (3 H, *m*), 8.85 (3 H, s), 8.97 (3 H, s); *m/e* 159 (P, 31), 144 (70), 117 (48), 104 (71), 103 (100), 77 (49). Anal. Calcd for $C_{11}H_{13}N$: C, 83.04; H, 8.27. Found: C, 82.74; H, 8.01. Analysis on column G at 160 °C shows one major component with ~4% of a second.

Warming of a solution of **33** (0.20 g) and *N*-phenylmaleimide (0.22 g) in benzene at 40 °C for 3 h, followed by cooling at 0 °C overnight gave a precipitate which was recrystallized from benzene–hexane to give colorless blades (0.23 g): mp 184–185 °C; IR (KBr) 1705, 2238 cm^{-1}; NMR τ 2.7–2.8 (5 H), 4.1–4.3 (2 H, m), 6.1–8.2 (5 H, m), 8.72, 8.80 (3 H each, s); *m/e* 334 (P). Anal. $C_{21}H_{20}N_2O_2$: C, H.

Photochemical Reaction of Benzonitrile with 2-Methoxypropene (13), Vinyl Acetate (12), Cyclopentene (9), 1,2-Dichloroethylene (14), and Norbornadiene (11). Solutions of 3.0 g of 1 (0.03 mol) and a tenfold excess of each alkene were irradiated and worked up in the usual fashion. Listed below are the irradiation times, yields of products (**33–38**), and pertinent spectral features of the mixture. All gave satisfactory C and H analyses unless so designated.

2-Methoxypropene: 30 h; 52%; bp 82–85 °C (0.1 mm); IR 2238 cm^{-1}; NMR τ 3.9–4.5 (4 H, m), 6.70 and 6.78 (singlets, total 3 H), 7.9 (2 H, AB, J = 13 Hz), 8.41 and 8.53 (singlets, total 3 H); *m/e* 175 (21), 160 (11), 104 (100), 103 (44). *N*-Phenylmaleimide adduct of major component (**34**): mp 163–164 °C; IR (KBr) 2240 (m), 1698 (s) cm^{-1}; NMR τ 2.6–2.8 (5 H, m), 3.9 (2 H, m), 6.8–7.5 (3 H, m), 6.83 (3 H, s), 8.07 (2 H, AB, J = Hz), 8.41 (3 H, s); *m/e* 348 (P)

Vinyl acetate: 12 h, with cleaning of polymer from apparatus after 6 h; 61% bp 96–99 °C (0.08 mm); IR (film) 2237 (m), 1732 (s) cm^{-1}; NMR τ 3.8–4.3 (4 H, m), 5.1 (1 H, m), 6.5–7.7 (3 H, m), 7.90, 8.04, 8.07 (all s, total, 3 H); *m/e* 189 (74), 129 (100); 104 (23), 103 (26). *N*-Phenylmaleimide adduct of major component (**35**): mp 211–212 °C; IR 2236 (m), 1736, 1700 (s) cm^{-1}; NMR τ 2.8 (5 H), 4.1 (2 H, m), 5.1 (1 H, m), 6.6–7.9 (4 H, m), 7.88 (3 H, s); *m/e* 362.

Cyclopentene: 24 h; 35%; bp 94–96 °C (0.1 mm); IR (film) 2240 cm^{-1}; NMR τ 4.1–4.5 (~2.6 H), 6.4–8.7 (9 H, m, br); *m/e* 171 (P, 45), 170 (26), 143 (29), 142 (36), 104 (41), 103 (87), 81 (100). *N*-Phenylmaleimide adduct of major component (**36**): mp 214–215 °C; IR 1700, 2240 cm^{-1}; NMR τ 2.8 (5 H), 3.9–4.1 (2 H, m), 6.7–6.8 (2 H, m), 7.2–8.4 (10 H, m); *m/e* 344.

1,2-Dichloroethylene: 30 h, with cleaning of polymer from the surfaces of the immersion well on three occasions during that time; 27%; bp 93–96 °C (bath, 0.06 mm); IR 2242 cm^{-1}; NMR τ 3.9–4.3 (~4 H, m, br), 5.8–6.9 (3 H, m, br); *m/e* 203, 201, 199 (parent, dichloro compound isotope distribution), 164 (100), 103 (22). A satisfactory analysis could not be obtained for this material (**37**).

Norbornadiene: 20 h; 42%; bp 108–110 °C (0.08 mm); IR (film) 2240 cm^{-1}; NMR τ 3.6–4.2 (6 H, m), 6.4–8.7 (7 H, m); *m/e* 195 (P, 17), 103 (40), 92 (26), 91 (100). Anal. $C_{14}H_{13}N$: C, H.

Irradiation of 2-Cyanothiophene (41) and Alkene 7. A solution of 2-cyanothiophene (1.1 g, 0.01 mol) and tetramethylethylene **7** (20 g) made up to 120 mL in spectrograde pentane was irradiated through Vycor for 6 h. Workup in the usual manner gave, besides 0.4 g of recovered **41**, adduct **44** (0.28 g, 24%): bp 76–79 °C (0.1 mm); IR 2230 cm^{-1}; NMR τ 3.70 (1 H, 2d, J' ~1 Hz), 4.52 (1 H, 2d, J = 6, J' ~3 Hz), 6.42 (1 H, m), 8.63, 8.68, 8.80, 8.95 (3 H each, s); *m/e* 193 (P, 0.6), 178 (14), 109 (61), 84 (100). Anal. $C_{11}H_{15}NS$: C, H.

Photolysis of 2-Cyanonaphthalene (40) with 2,3-Dimethyl-2-butene. A solution of **40** (1.2 g) and alkene **7** (20 g) in 80 mL of spectrograde pentane was irradiated through Corex for 10 h. Evaporation of excess alkene, followed by short-path distillation, gave almost pure adduct **42** (0.56 g): bp 120 °C (0.06 mm); IR 2235 cm^{-1}; NMR τ 2.7–3.1 (4 H, m), 3.49, 4.28 (2 H, AB, J = 9.6 Hz), 6.30 (1 H, s, br), 8.52 (3 H, s), 8.90 (6 H, s), 9.21 (3 H, s); *m/e* 237 (P, 0.4), 153 (60), 105

(100), 84 (73). Anal. $C_{17}H_{19}N$: C, H. When the crude oil remaining after evaporation of excess alkene was chromatographed on silica gel, elution with mixtures of benzene and ethyl acetate gave fractions containing first 0.3 g of **42**, followed by fractions which on evaporation gave 0.16 g of an oil which appears to be azetine **43**: IR 1660 cm^{-1}; NMR τ 2.2–2.7 (7 H, m), 8.62 (6 H, s), 8.69 (6 H, s); *m/e* 237 (Parent).

Acknowledgments. The author is grateful to William Landis of the National Institutes of Health for the mass spectra of the compounds described herein. Special thanks are due Professor Paul Engel for many helpful discussions and for reading the manuscript.

Registry No.—**1**, 100-47-0; **15**, 37771-71-4; **16**, 61838-76-4; **17**, 18495-18-6; **18**, 62816-34-6; **20**, 37771-72-5; **21**, 63704-25-6; **22**, 63704-26-7; **23**, 63704-27-8; **24**, 63704-28-9; **25**, 63704-29-0; **26**, 63704-30-3; **27a**, 63704-31-4; **27b**, 63704-32-5; **28**, 36597-09-8; **29**, 37771-73-6; **29** NPM adduct, 63704-33-6; **31**, 63704-34-7; **33**, 37771-74-7; **33** NPM adduct, 63704-35-8; **34**, 37771-77-0; **34** NPM adduct, 63704-36-9; **35**, 37771-76-9; **35** NPM adduct, 63704-37-0; **36**, 37771-75-8; **36** NPM adduct, 63704-38-1; **37**, 63704-39-2; **38**, 63704-40-5; **40**, 613-46-7; **41**, 1003-31-2; **42**, 37771-79-2; **43**, 63765-57-1; **44**, 63704-41-6; NPM, 941-69-5; dimethyl tetramethylsuccinate, 17072-58-1; 2-methyl-1-phenyloctane-1,7-dione, 63704-42-7; acetone 2,4-DNPH, 1567-89-1.

References and Notes

(1) (a) N. J. Turro in "Energy Transfer and Organic Photochemistry," A. A. Lamola and N. J. Turro, Ed., Wiley- Interscience, New York, N.Y., 1969, Chapter 3; (b) W. M. Horspool, "Organic Photochemistry", Academic Press, New York, N.Y., 1976, Chapter 6.
(2) G. Buchi, J. G. Atkinson, D. E. Ayer, and E. W. Robb, *J. Am. Chem. Soc.*, **85**, 2257 (1963).
(3) (a) S. Hosaka and S. Wakamatsu, *Tetradedron Lett.*, **219** (1968); (b) D. M. Gale, *J. Org. Chem.*, **35**, 970 (1970); (c) T. S. Cantrell, *ibid.*, **40**, 1447 (1975).
(4) (a) J. J. McCullough, R. C. Miller, D. Fung, and W. S. Wu, *J. Am. Chem. Soc.*, **97**, 5942 (1975); (b) R. M. Bowman, C. Calvo, J. J. McCullough, R. C. Miller, and I. Singh, *Can. J. Chem.*, **51**, 1060 (1973); (c) T. R. Chamberlain and J. J. McCullough, *ibid.*, **51**, 2578 (1973); (d) R. M. Bowman, T. R. Chamberlain, C. W. Huang, and J. J. McCullough, *J. Am. Chem. Soc.*, **96**, 692 (1974).
(5) (a) K. Mizumo, C. Pac, and H. Sakurai, *J. Am. Chem. Soc.*, **96**, 2993 (1974); (b) R. A. Caldwell and L. Smith, *ibid.*, **96**, 2994 (1974).
(6) N. C. Yang, B. Kim, W. Chiang, and T. Hamada, *J. Chem. Soc., Chem. Commun.*, 729 (1976). We are grateful to Professor Yang for informing us of these results prior to publication.
(7) T. S. Cantrell, *J. Am. Chem. Soc.*, **94**, 5929 (1972).
(8) G. Sziemies, U. Siefkin, and R. Rinck, *Angew. Chem., Int. Ed. Engl.*, **12**, 161 (1973).
(9) S. M. McElvain and W. R. Davie, *J. Am. Chem. Soc.*, **73**, 1400 (1951).
(10) (a) D. E. Ayer, Ph.D. Dissertation, Massachusetts Institute of Technology, 1958; (b) we are grateful to Professor Buchi for communicating these results to us.
(11) See, however, ref 6.
(12) (a) W. R. Ware, D. Watt, and J. D. Holmes, *J. Am. Chem. Soc.*, **96**, 7853 (1974); (b) W. R. Ware, J. D. Holmes, and D. R. Arnold, *ibid.*, **96**, 7861 (1974).
(13) (a) C. Pac, T. Sugioka, and H. Sakurai, *Chem. Lett.*, 39 (1972); (b) *ibid.*, 667 (1973); (c) C. Pac, T. Sugioka, K. Mizuno, and H. Sakurai, *Bull. Chem. Soc. Jpn.*, **46**, 238 (1973).
(14) N. C. Yang, K. Srinavaschar, B. Kim, and J. Libman, *J. Am. Chem. Soc.*, **97**, 5006 (1975).
(15) F. D. Lewis and R. H. Hirsch, *J. Am. Chem. Soc.*, **98**, 5914 (1976).
(16) W. H. Hardham and G. S. Hammond, *J. Am. Chem. Soc.*, **89**, 3200 (1967).
(17) D. A. Deneo and M. A. El-Sayed, *J. Chem. Phys.*, **52**, 2622 (1970).
(18) D. A. Labianca, G. N. Taylor, and G. S. Hammond, *J. Am. Chem. Soc.*, **94**, 3679 (1972).

α- and β-Rearrangement Products, Benzoylpyridyltriphenylphosphonium Methylides and Phenylethynylpyridines, from Pyridine *N*-Oxides and Phenylethynyltriphenylphosphonium Bromide

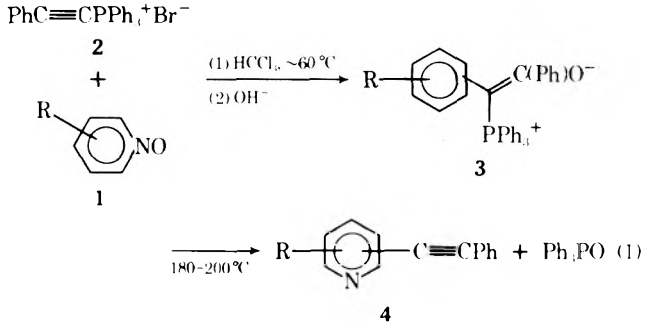
Noboru Morita and Sidney I. Miller*

Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois 60616

Received June 7, 1977

Pyridine *N*-oxides and phenylethynyltriphenylphosphonium bromide react in chloroform to produce α- and β-benzoylpyridyltriphenylphosphonium methylides. When sublimed at ca. 200 °C, these enol phosphoranes yield triphenylphosphine oxide and α- and β-phenylethynylpyridines.

Recently we have been exploring the chemistry of ethynylphosphonium salts (**2**).[1] Here we report on process 1 which juxtaposes steps which have separately become familiar. By bringing together pyridine *N*-oxides (**1**) with **2** (eq 1), we have



obtained some new enol phosphoranes (**3**) and pyridylacetylenes (**4**) which are collected in Table I.

Michael additions of ylides, e.g., $\equiv N^+-N^-$—, $=S^+-N^-$—, $\equiv N^+-O^-$, to alkynes are known and have been reviewed both generally[2a] and in the context of specialized topics, e.g., nitrone,[2b] azomethine ylide[2c] and other dipolar cycloadditions,[2d] indolizine synthesis,[2e] and nuclear substitution in heteroaromatic *N*-oxides.[3,4] Pertinent here is the specific area of *N*-oxide attacks on activated alkynes. Although apparent rearrangements in pyridine *N*-oxide chemistry yield numerous α-substituted pyridines, those which give β-pyridines have few precedents but are not unknown.[3-5] Indeed, the recent elucidation of possible mechanisms and products of the reaction of pyridine (or quinoline) with phenylpropionitrile, described by Abramovitch's group, stimulated our interest in this area (eq 2).[3]

Now there are other syntheses which appear to be related to those of eq 1, at least in overall effect. Pyridine *N*-oxides and pyridines, usually as salts, and metal acetylides give 2- and occasionally 4-ethynylpyridines;[6a-d] pyridine, benzoyl chloride, and silver phenylacetylide yield *N*-benzoyl-2-phenylethynyl-1,2-dihydropyridine.[6e] The thermal conversion of the phosphorane enolate, **3** to **4**, has ample precedent in other alkyne syntheses.[7]

Table I. Products of the Reaction of RC_5H_4NO (1) and $PhC{\equiv}CPPH_3^+Br^-$ (2)

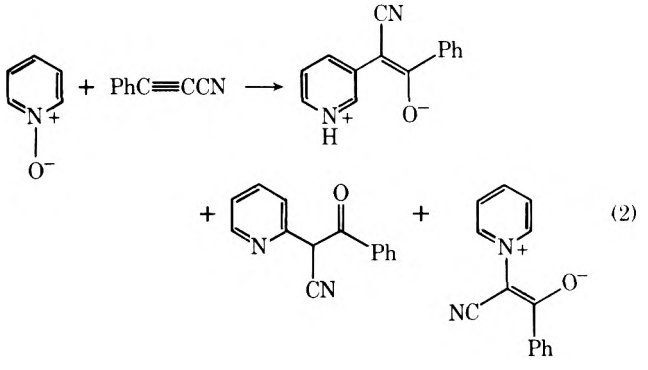
(RC_5H_3N)-*n*-$Ph_3P^+C{=}C(Ph)O^-$ (3)

3	R	n	Registry no.	Yield %	Mp, °C	Formula	C Calcd	C Found	H Calcd	H Found	NMR ($CDCl_3$), δ H2	H3	H4	H5	H6	IR (KBr), cm^{-1} ν_{CO}	ν_{PC}
a	H	2	63731-21-5	55.7[a]													
b		3	63731-22-6		203–204	$C_{31}H_{24}NOP$	81.38	81.15	5.28	5.33						1500	1101
c	2-Me	5	63731-23-7	45.5	222–223	$C_{32}H_{26}NOP$	81.51	81.88	5.56	5.54		6.61	6.97		7.93	1480	1100
d	3-Me	2	63731-24-8	61.7	189–190	$C_{32}H_{26}NOP$	81.51	81.89	5.56	5.55				6.51		1500	1100
e		5	63731-25-9	1.1	209.5–210.5			81.03		5.29	7.88		6.83		7.88	1502	1100
f	4-Me	2	63731-26-0	~13	178.5–179.5	$C_{32}H_{26}NOP$	81.51	81.98	5.56	5.46	6.75			6.53		1495	1100
g		3	63731-27-1	~27	230–231			81.94		5.56	8.05			6.80	8.05	1495	1097
h	4-Cl	2	63731-28-2	29	206–207	$C_{31}H_{23}NOP$-Cl	75.68	76.02	4.71	4.74		6.91		6.63		1507	1105
i	4-MeO	2	63731-29-3	~13	169.5–171	$C_{32}H_{26}NO_2P$	78.83	79.03	5.38	5.35		6.45		6.25		1510	1100
j		3	63731-30-6	~13	221.5–222			78.86		5.32	8.1			6.30	8.1	1480	1100

(RC_5H_3N)-*n* C≡CPh (4)

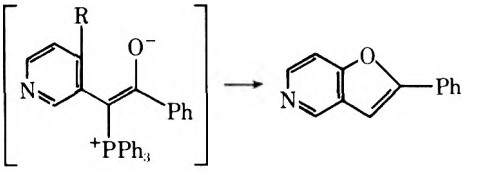
4	R	n	Registry no.	Yield, %	Mp or bp (mm), °C	Formula	C Calcd	C Found	H Calcd	H Found	NMR (CCl_4) δ H2	H3	H4	H5	H6	IR, cm^{-1}, $\nu_{C\equiv C}$
a	H	2	13141-42-9			$C_{13}H_9N$										2215 (m)
b	H	3	13238-38-5	95	50–51	$C_{13}H_9N$					8.77				8.51	2210 (w)
c	2-Me	5	63731-31-7	85	60.5–61	$C_{14}H_{11}N$	87.01	87.13	5.74	5.76		7.03	7.59		8.67	2200 (w)
d	3-Me	2	63731-32-8	94	105 (0.1)	$C_{14}H_{11}N$	87.01	86.88	5.74	5.60				7.00	8.35	2210 (s)
f	4-Me	2	63731-33-9	~100	105 (0.1)	$C_{14}H_{11}N$	87.01	86.65	5.74	5.67				6.9	8.35	2200 (w)
g	4-Me	3	63731-34-0	~100	105 (0.1)	$C_{14}H_{11}N$	87.01	86.82	5.74	5.70	8.45			7.03	8.45	2205 (w)
h	4Cl	2	63731-35-1	84	105 (0.1)	$C_{13}H_8N$-Cl[b]									8.45	2220 (s)

[a] Isomer mixture. [b] Analyzed as picrate.



(2)

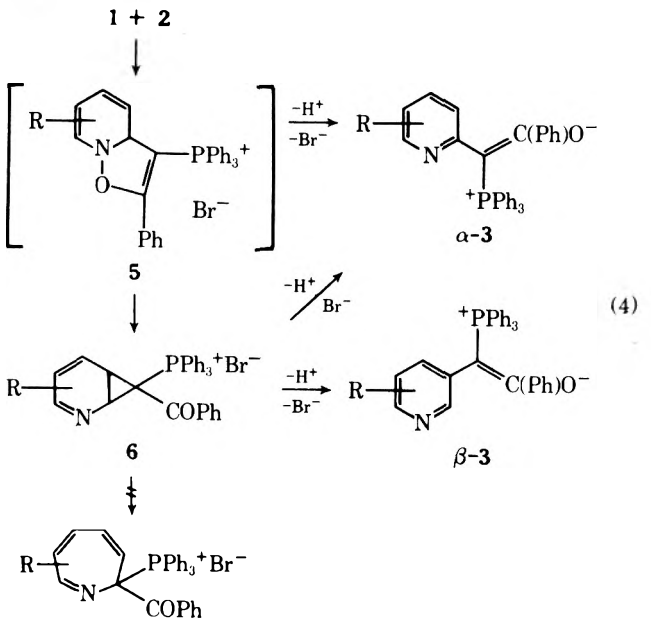
With respect to process 1, we found that 4-methoxy and 4-nitropyridine *N*-oxides produced at least some **3**; the subsequent conversion of **3** to **4** led to complex mixtures. Guided by the work on process 2 in which γ-Cl, NO_2 and MeO of **1** could be replaced,[3a,c] we also found another route whereby β-**3** could be consumed (eq 3). This constitutes a possible obstacle to β-**4** products. Although we did not isolate other plausible products of reaction of **3** with **2**, e.g., divinyl ethers,[3] the involvement of **2** in such reactions has precedent and would not be unexpected.[1] At this stage, therefore, we believe that speculations on extensions of process 1 or rationalizations of the orientation, α-**3** vs. β-**3**, are unwarranted. What does emerge is that we do have a practical route to some α- and β-ethynylpyridines.



β-**3**, R = Cl; R = NO_2

(3)

We apply the mechanism which Abramovitch used to account for the products of eq 2 to the formation of **3** in eq 4.[3] It is not clear whether **5** is formed in one or two steps but "dipolar" adducts of the type **5** have actually been isolated by others.[2,3] Elimination at the 1,2 positions of **5** yields α-**2** or α-**3**; the corresponding step in eq 2 is favored by added triethylamine.[3b]



Although the azanorcaradiene (**6**) appears to be the most plausible precursor of β-**3**, it is not obvious why this route competes so well. (Another postulated addition–rearrangement is on record: with mercaptans in acetic anhydride pyridine, *N*-oxides yield both 2- and 3-pyridyl sulfides, the latter presumably forming via a 2,3-episulfonium species analogous to **6**.[5]) An interesting option for **6** is that it may isomerize to the azepine. The literature does in fact indicate that *some* azepines are thermodynamically favored over isomeric azanorcaradienes and that the barrier is low, e.g., $\Delta G^{\ddagger} \leq 11$ kcal/mol at ≤ -40 °C.[8] On the other hand, pyrolysis of several 3-acyl-3*H*-azepines at 150 °C effected ring contraction to 3-acylmethylpyridines, presumably by way of an intermediate like **6**.[9] It would appear that the energetics favor the pyridine structure. Moreover, the presence of base, i.e., excess **1**, bromide ion, or pyridine products, may facilitate the formation of β-**3**. Clearly, the diversion of **6** in some way, e.g., to azepine, Diels–Alder adduct, etc., would provide additional support for the proposed route to β-**3**.

Several prominent spectral characteristics of **3** and **4** have been included in Table I. These correspond to literature correlations of IR and ^{1}H NMR data for pyridines[4a,10] and were invaluable aids in assigning isomeric structures.

Experimental Section

Melting points are uncorrected. Infrared spectra were measured on Perkin-Elmer 237 and Beckman IR8 spectrophotometers: solids were taken in KBr pellets while liquids were taken as films. NMR spectra were measured on a Varian T-60 instrument: compounds **3** were taken in $CDCl_3$ and **4** in CCl_4 solution, except as noted below. Mass spectra were measured on a Varian MAT CH-7 spectrograph.

The unsubstituted **1** was distilled before use; the other *N*-oxides were used directly. Compound **2** was prepared in the standard way.[11] Many of the properties of **3** and **4** are given in Table I. After a description of our standard methods of synthesis and purification, additional data for **3** and **4** will be listed in abbreviated form. IR absorptions are strong(s), unless otherwise indicated.

Reactions of Pyridine *N*-Oxides (1) with Phenylethynyltriphenylphosphonium Bromide (2). The *standard* procedure was to add **1** (7–10 mmol) to a solution of **2** (5 mmol) in chloroform (ca. 30 mL) under nitrogen and heat at reflux temperature for ca. 24 h. After the solvent was evaporated, the residue was taken up in methanol (30–40 mL) and heated with 10% aqueous potassium hydroxide (15–20 mL) at ca. 75 °C for 2–3 h. The methanol was evaporated and the aqueous mixture was extracted, usually with chloroform–ether, and occasionally with ether, then dried over magnesium sulfate and filtered. A few milliliters of ether was added to this filtrate, whereupon the bulk of the product(s), mainly β-**3** compound(s), precipitated. The solid was filtered off. At this point a purification *cycle* was started. The filtrate was treated with hydrochloric acid (3 M) and ether. The ether layer which was washed with aqueous base and dried usually yielded some triphenylphosphine oxide. The hydrochloric acid layer was treated with chloroform several times; this chloroform extract, which was washed with aqueous base and dried, yielded mainly α-**3**. The hydrochloric acid layer was treated with a slight excess of potassium hydroxide and extracted with chloroform. On workup the chloroform solution yielded mainly β-**3**.

To purify α-**3**, it was dissolved in chloroform and extracted with 3 M hydrochloric acid. This tended to remove β-**3**.

To purify the β-**3**, it was dissolved in 3 M hydrochloric acid and extracted with chloroform. This tended to remove the α-**3**.

Occasionally, samples of impure **3** were purified by recrystallization from ethyl acetate or by column chromatography on alumina with chloroform as a solvent. The β-substituted compounds usually have the higher melting point and are easier to crystallize.

Conversion of Benzoylpyridyltriphenylphosphonium Methylides (3) to Phenylethynylpyridines (4). In the standard procedure, **3** was heated under nitrogen in a sublimation apparatus at 180–200 °C for 4–5 h. The product was then collected by sublimation at ca. 1 mm. The sublimate was further separated by column chromatography on alumina. Triphenylphosphine was eluted in high yields (88–100%) by chloroform.

Some picrates of **4**, e.g., **4a** and **4b**, are readily prepared in ethanol. Since these compounds may dissociate readily when heated in solution or treated with base, a picrate may be a useful form in which to store **4**.

Reaction of Pyridine *N*-Oxide (1a) and 2. Compound **3b** was (**3a** was not) separated from the mixture of **3a** and **3b**. For **3b**: NMR δ 7.0–8.27 (m); IR 3050 (w), 1449, 1357, 1213, 970 (m), 763, 752, 739, 732 cm^{-1}. Compound **4b**: lit.[12] mp 47–48.5 °C; NMR δ 7.0–7.8 (m), 8.51 (d, 1 H, J = 4 Hz); IR (KBr) 3030 ± 35 (b, w), 1488, 1411, 1018, 811, 755, 685 cm^{-1}; MS (*m/e*) 179 (parent).

The picrate of **4b** had mp 157–159 °C dec from ethanol.

Compound **4a**, prepared by another route,[6c] was shown to be essentially pure by GC. It is a low-melting solid (lit.[13] mp 29–32 °C; lit.[6e] bp 116 °C (0.1 mm)) whose picrate had mp 147–150 °C dec (lit.[13] mp 152–153 °C dec).

Since **3a** and **4a** were not separated free from their isomers **3b** and **4b** respectively, in eq 1, their presence was established in two ways. The mixture of **3a** and **3b** was pyrolyzed to give **4a** and **4b** which was oxidized with potassium permanganate according to a literature procedure.[14] Benzoic acid (66% yield) and pyridine carboxylic acids (39% yield) were formed. The latter were esterified with 1-butanol and analyzed by GC on an SE column kept at 145 °C. The retention times of the two esters were identical with those of authentic samples made from α-picolinic and nicotinic acids.

Another experiment was designed to estimate the product ratios **3a/3b** and **4a/4b**. Accordingly, **1a** (286 mg, 3 mmol) and **2** (887 mg) were combined in the standard way. Compounds **3** (510 mg, 55.7% yield) were carefully separated from triphenylphosphine oxide (108 mg) by the standard workup and sublimed under nitrogen at 180–200 °C for 5 h. The components of the sublimate were obtained by chromatography on alumina, **4a** and **4b** (142 mg, 71% yield) being eluted by benzene and triphenylphosphine oxide (185 mg, 60% yield) by chloroform. The ratio **4a/4b** = 1/3 was established by GC using an SE column at 180 °C. The retention times of **4a** and **4b** in the mixture were identical with those of the individual compounds.

Reaction of α-Picoline *N*-Oxide (1c) and 2. For **3c**: NMR δ 2.33 (d, 3 H, J = 2 Hz), 6.61 (d, 1 H, J = 8 Hz), 7.0–7.9 (m); IR 3010 ± 40 (b, w) 1480, 1370, 1260, 1170 (w), 1024 (m), 959 (m), 745, 690 cm^{-1}. For **4c**: NMR δ (CCl_4/$CDCl_3$) 2.53 (s, 3 H), 7.03 (d, 1 H, J = 8 Hz), 7.2–7.5 (m), 7.59 (dd, 1 H, J = 8 and 2 Hz); IR (KBr) 3025 (w), 2920 (w), 1593, 1493, 1020 (m), 823 (m), 745, 680 (m) cm^{-1}; MS (*m/e*) 193 (parent).

Reaction of β-Picoline *N*-Oxide (1d) and 2. For **3d**: NMR δ 2.10 (s, 3 H), 6.51 (ddm, 1 H, J = 7.5 Hz), 7–8 (m); IR (KBr) 3023 (w), 1473, 1463, 1367, 743 (m), 716 (m), 688 cm^{-1}. For **3e**: NMR δ 1.78 (s, 3 H), 7.0–7.8 (m); IR (KBr) 3000 (w), 1433 (m), 1363 (m), 1277 (m), 760 (w), 745 (w), 715 (m), 691 cm^{-1}. For **4d**: NMR (CCl_4) 2.45 (s, 3 H), 7.00 (dd, 1 H, J = 8 Hz, J = 5 Hz), 7.2–7.6 (m), 8.35 (dm, 1 H, J = 5 Hz); IR (neat) 3050 (m), 1580 (m), 1490, 1441, 1105 (m), 785 (m), 755, 685 cm^{-1}; MS (*m/e*) 193 (parent).

Reaction of γ-Picoline *N*-Oxide (1f) with 2. For **3f**: NMR δ 1.97 (s, 3 H), 6.53 (dm, 1 H, J = 5 Hz), 7.0–7.9 (m), 7.97 (d, 1 H, J = 5 Hz); IR 3041 (w), 1594, 1495, 1436, 1358, 1270 (m) 1100, 1021 (m), 780 (m), 750, 719, 675 cm^{-1}. For **3g**: NMR δ 2.07 (s, 3 H), 6.80 (dm, 1 H, J = 5 Hz), 7.0–7.8 (m); IR 3040 ± 40 (w) 1495, 1437 (m), 1375 (m), 1124 (m), 1095, 957 (m), 760 (m), 721, 685 cm^{-1}. For **4f**: NMR δ 2.28 (s, 3 H), 6.9 (d, 1 H, J = 5 Hz), 7.1–7.7 (m) 8.35 (d, 1 H, J = 5 Hz); IR (neat) 3050

(w), 2915 (w), 1599, 1492 (m), 920 (w), 820 (m), 751, 684 cm^{-1}; MS (*m/e*) 193 (parent). For **4g**: NMR δ 2.47 (s, 3 H), 7.2–7.7 (m); IR (neat) 3050 (b, w), 2920 (b, w), 1588, 1492, 1440, 1400, 1216 (w), 1117 (w), 823 (m), 750, 685 cm^{-1}; MS (*m/e*) 193 (parent).

Reaction of 4-Chloropyridine *N*-Oxide (1h) with 2. For **3h**: NMR δ 6.63 (dm, 1 H, J = 5 Hz), 7–8 (m); IR 3050 (b, w), 1563 (m), 1540 (m), 1476 (m), 1430, 1392, 1340, 1127 (m), 1013 (m), 755 (m), 739 (m), 720, 686 cm^{-1}. For **4h**: NMR δ 7.1–7.7 (m), 8.45 (d, 1 H, J = 5 Hz); IR (neat) 3050 (m), 1597 (w), 1567, 1545, 1491 (m), 1453 (m), 1381 (m), 1095 (m), 890 (m), 823 (m), 755, 685 cm^{-1}; MS (*m/e*) 213 (parent).

A picrate of **4h** had mp 165–167 °C dec from ethanol: IR (KBr) 2205 (m) 1640 cm^{-1}. Anal. Calcd for $C_{19}H_{11}N_4O_7Cl$: C, 51.53; H, 2.50. Found: C, 51.54; H, 2.74.

2-Phenylfuro[3,2-c]pyridine. This compound was obtained both from the aqueous and chloroform portions in the preparation of **3h**. Column chromatography yielded the furopyridine (27% yield), from the benzene eluate: mp 123.5–124 °C; NMR ($CDCl_3$) 7.0 (d, H_3, J = 1 Hz), 7.43 (m, 4 H), 7.83 (m, 2 H), 8.45 (d, H_6, J = 6 Hz), 8.90 (d, H_4, J = 1 Hz); IR (KBr) 1462 (m), 1456 (m), 1260 (m), 1011 (m), 883, 826, 752, 680 (m) cm^{-1}; MS (*m/e*) 195 (parent). Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65. Found: C, 80.52; H, 4.67.

Reaction of 4-Methoxypyridine *N*-Oxide (1i) with 2. For **3i**: NMR δ 3.4 (s, 3 H), 6.25 (dm, 1 H, J = 6 Hz), 7–8 (m); IR 3050 (w), 1580, 1475, 1437, 1365, 1207 (m), 742 (m), 718 (m), 687 (m) cm^{-1}. For **3j**: NMR δ 3.33 (s, 3 H), 6.30 (d, 1 H, J = 6 Hz), 7–7.8 (m), 8.1 (2 H); IR 3021 (b, w), 1573, 1430, 1368, 1272, 1020, 960 (m), 850 (m), 800 (m), 743, 705 ± 20 (b) cm^{-1}.

Reaction of 4-Nitropyridine *N*-Oxide (1k) with 2. In this system, the "standard" conditions were altered: The reaction was carried out in DMF as solvent at 110 °C for **3d**. The solvent was then evaporated under reduced pressure and the residue was treated with methanol and 10% aqueous potassium hydroxide at reflux temperature for 3 h. The solid was filtered and purified by chromatography; the filtrate was extracted with chloroform and subjected to the standard purification cycle yielding 2-phenylfuro[3,2-c]pyridine (4% yield), mp 118.5–119 °C, by column chromatography and sublimation.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—**1a**, 694-59-7; **1c**, 931-19-1; **1d**, 1003-73-2; **1f**, 1003-67-4; **1h**, 1121-76-2; **1i**, 1122-96-9; **1k**, 1124-33-0; **2**, 34387-64-9; **4b** picrate, 63731-36-2; **4h** picrate, 63731-37-3; 2-phenylfuro[3,2-c]-pyridine, 63731-38-4.

References and Notes

(1) N. Morita, J. I. Dickstein, K. Imafuku, and S. I. Miller, in preparation.
(2) (a) J. I. Dickstein and S. I. Miller, "Chemistry of the Carbon Carbon Triple Bond", S. Patai, Ed., Wiley, New York, N.Y., in press; (b) D. St. C. Black, R. F. Crozier, and V. C. Davis, *Synthesis*, 205 (1975); (c) C. G. Stuckwisch, *ibid.*, 469 (1973); (d) J. Bastide, J. Hamelin, F. Texier, and Y. Vo Quang, *Bull. Soc. Chim. Fr.*, 2555, 2871 (1973); (e) T. Uchida and K. Matsumoto, *Synthesis*, 209 (1976).
(3) (a) R. A. Abramovitch and I. Shinkai, *Acc. Chem. Res.*, **9**, 192 (1976); (b) R. A. Abramovitch, G. Grins, R. B. Rogers, and I. Shinkai, *J. Am. Chem. Soc.*, **98**, 5671 (1976); (c) R. A. Abramovitch and I. Shinkai, *ibid.*, **97**, 3227 (1975).
(4) (a) R. A. Abramovitch and G. M. Singer, "Pyridine and Its Derivatives: A Supplement", Part I, R. A. Abramovitch, Ed., Wiley, New York, N.Y., 1974, Chapter 1A; (b) E. Ochiai, "Aromatic Amine Oxides", Elsevier, Amsterdam, 1967.
(5) F. M. Hershenson and L. Bauer, *J. Org. Chem.*, **34**, 655 (1969). A referee "pointed out that there is a plausible alternative to the episulfonium ion mechanism", namely, one which proceeds via 2,3-dithioalkyl-2,3-dihydropyridine (R. A. Abramovitch and P. Tomasik, *J. Heterocycl. Chem.*, **12**, 501 (1975)).
(6) (a) C. K. McGill, U.S. Patent 3 045 022; *Chem. Abstr.*, **57**, 15077 (1962); (b) J. H. Blumenthal, U.S. Patent 2 874 162; *Chem. Abstr.*, **53**, 12311 (1959); (c) N. Morita, unpublished results; (d) Ch. Kaneko and T. Miyasaka, *Shika Zairyo Kenkyusho Hokoku, Tokyo Ika Shika Daigaku*, **2**, 269 (1963), cited in ref 4b, p 253; (e) T. Agawa and S. I. Miller, *J. Am. Chem. Soc.*, **83**, 449 (1961).
(7) J. C. Craig, M. D. Bergenthal, I. Fleming, and J. Harley-Mason, *Angew. Chem.*, **8**, 429 (1969).
(8) A. Steigel, J. Sauer, D. A. Kleier, and G. Binsch, *J. Am. Chem. Soc.*, **94**, 2770 (1972).
(9) M. Ogata, H. Matsumoto, and H. Kanō, *Tetrahedron*, **25**, 5217 (1969).
(10) A. R. Katritzky and A. P. Ambler, "Physical Methods in Heterocyclic Chemistry", Vol. II, A. R. Katritzky, Ed., Academic Press, New York, N.Y., 1963, Chapter 10.
(11) J. I. Dickstein and S. I. Miller, *J. Org. Chem.*, **37**, 2175 (1972).
(12) C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.*, **31**, 4070 (1969).
(13) A. R. Katritzky, D. J. Short, and A. J. Boulton, *J. Chem. Soc.*, 1516 (1960).
(14) A. W. Singer and S. M. McElvain, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 740.

The Vilsmeier–Haack Aroylation of Pyrroles Reexamined

Julian White and George McGillivray*

Department of Chemistry, University of South Africa, Pretoria, South Africa

Received April 6, 1977

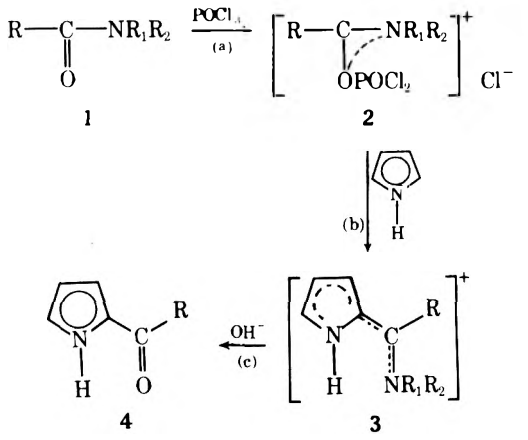
Vilsmeier–Haack formylation of pyrroles is well established, but its extension to aroylation, despite offering advantages over other methods, has not been properly exploited as no systematic study of the reaction has been reported. The latter reaction has been reexamined and a method for the aroylation of certian pyrroles on a 5–200-mmol scale in yields of 85–96% is given together with a brief discussion of the reactivity of pyrroles and carboxamides, the preparation of the amide–phosphoryl chloride complex, azafulvene formation, and general experimental conditions necessary for efficient reaction. The preparation of 2-benzoylpyrrole is described to illustrate the improvements, and several new aroylpyrroles are reported.

The Vilsmeier–Haack reaction[1] (Scheme I[2]) is well established[3] as a means of formylating pyrroles (Scheme I, R = H) and the experimental procedure widely used is that of Silverstein et al.[4] The reaction offers the advantages of monoformylation,[5] virtually exclusive attack[6] at the α position of unsubstituted pyrroles lacking bulky N substituents[7] and consistently high yields.

The reaction was later extended to include the acylation[8] (Scheme I, R = alkyl) and aroylation[9] (Scheme I, R = aryl) of pyrroles. While retaining the other advantages of the formylation reaction, the extended processes usually gave poorer yields. Consequently, aroylation by the Vilsmeier–Haack method, notwithstanding occasional reported yields of 80% or more,[10,11] appears to have fallen into disfavor and to have been supplanted by other procedures,[12] themselves often severely limited in their application to pyrrolic substrates.

Despite recognition[13] that "the conditions employed in the Vilsmeier–Haack condensation can be critical", no systematic investigation of the experimental conditions necessary for efficient aroylation by this procedure has yet been reported. Consequently, the conditions commonly employed are those reported for the formylation of pyrrole,[4] which are, in fact, unnecessarily harsh and unsuitable for the aroylation of pyrroles.

Scheme I



Accordingly, we undertook a thorough investigation[14] of the aroylation of pyrroles by the Vilsmeier-Haack procedure and wish to report those results which bear directly on the use of the reaction as an efficient method for the preparation of aroyl pyrroles.

The Amide. Despite the widespread use of *N,N*-dimethylamides (**1**, R_1, R_2 = CH_3) in reported Vilsmeier-Haack procedures, it was found that morpholides (**1**, R_1R_2 = $-CH_2CH_2OCH_2CH_2-$) were better reagents except when the phenyl nucleus carried a strongly electron withdrawing group such as a nitro group which rendered reaction with phosphoryl chloride incomplete. In such cases, the dimethylamide analogues gave better results.

Morpholides formed complexes (**2**, R_1R_2 = $-CH_2CH_2OCH_2CH_2-$) with phosphoryl chloride which were eight to ten times more reactive than the corresponding *N,N*-dimethylamide complexes. This may be ascribed to enhancement of the activating effect of the morpholine oxygen atom by coordination of that atom with the excess phosphoryl chloride used in the present procedure.

Thiobenzamide-phosphoryl chloride complexes,[15] although readily formed, are unreactive toward pyrrole and appear to be of little synthetic utility.

Formation of the Vilsmeier-Haack Reagent (Scheme I, Step a). A report that amide-phosphoryl chloride complex formation (**2**, R = aryl) is best carried out in the absence of solvent[10] was confirmed and it was further shown that such reaction could readily be followed by NMR spectrometry using the neat complex. The progress of the reaction was apparent from the relative intensity of new signals 0.7 to 1 ppm downfield of the original signals due to the nitrogen-substituent protons and ca. 0.3 ppm downfield of the original aromatic proton resonances. Following complex formation was necessary, as complete reaction prior to admixture with the pyrrole proved essential.

By custom, complex formation is carried out by treating the amide with no more than 1 equiv of phosphoryl chloride, often in the presence of halogenated hydrocarbons.[4,11] In fact, an excess of 1 to 10 equiv of phosphoryl chloride had no adverse effect on the Vilsmeier-Haack reaction itself and was beneficial during complex formation not only because of a reduction in viscosity which assisted monitoring by NMR spectrometry but also because the rate of complex formation was increased thereby.[16] The optimum quantity of phosphoryl chloride was found to be 2 to 2.5 equiv, and the presence of halogenated solvents during complex formation was avoided as these solvents promoted dissociation of the complex.

The rate of complex formation was found to be dependent on the electron density at the carbonyl oxygen of the amide, the reaction being retarded by the presence of groups that are electron withdrawing in the presence of phosphoryl chloride. When morpholides formed complexes very slowly or incompletely, the use of *N,N*-dimethylamides was satisfactory.

Although complex formation could be accelerated by gentle warming, temperatures above 40 °C were best avoided because of partial dissociation of the complex. Subsequently, cooling did, however, permit the reaction to go to completion. This effect was most marked in the case of slowly formed amide-phosphoryl chloride complexes for which the temperature range of 25 to 35 °C was found to be satisfactory.

The Vilsmeier-Haack Reaction (Scheme I, Step b). Azafulvenes (**3**, R = aryl) were formed by treating the amide-phosphoryl chloride complex with the pyrrole in anhydrous 1,2-dichloroethane within the temperature range of 20 to 35 °C. The reaction was followed by UV spectrophotometry by measuring the increase in absorption in the 350- to 400-nm region.

The presence of 1,2-dichloroethane at this stage had no adverse effect, as dissociation of the amide complex was considerably slower than azafulvene formation. The use of *strictly* anhydrous 1,2-dichloroethane was essential, however, as traces of water not only led to lower yields and products of poorer quality, but also retarded the reaction appreciably.[17] Although slightly higher reaction temperatures could be used, both yield and product quality suffered at temperatures above 40 °C. Reactions carried out under the conditions described were clean, and notwithstanding the presence of excess phosphoryl chloride the reaction mixtures could be allowed to stand for long periods without side reactions occurring. Consequently, sluggish reactions such as those involving *N*-methylpyrrole (reaction time ca. 28 days) also proceeded in high yield.

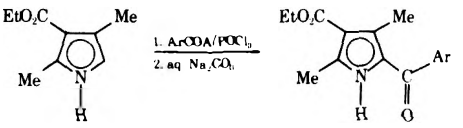
The Pyrrole. Pyrrole and a number of substituted pyrroles were investigated. In no case, where both α and β positions were vacant, was evidence of attack in the β position found. The reaction proved effective in the presence of C-alkyl substituents and a 4-alkoxycarbonyl group (relative to attack in the 2 position), but not so when a 4-acetyl group was present.

Steric retardation of the reaction due to an adjacent C-methyl group was more than offset by its activating electronic effect. An *N*-methyl substituent, however, markedly reduced the rate of aroylation. Thus, *N*-methyl pyrrole reacted at approximately one hundredth of the rate of pyrrole itself. The inference that this was due to a steric factor arising from a specific orientation in the transition state is supported by the fact that *N*-methylpyrrole undergoes formylation by the Vilsmeier-Haack procedure more rapidly than pyrrole.[18] *N*-methyl-2-aroylpyrroles are therefore best prepared by introducing the *N*-methyl group after aroylation. Such alkylation was performed to good effect by way of the thallium(I) intermediate.[19]

Hydrolysis (Scheme I, Step c). Hydrolysis of the azafulvene was carried out using aqueous sodium carbonate solution at room temperature followed by heating for 45 min. This period of heating was often far in excess of requirement for full hydrolysis but was convenient and did not lead to a reduction in yield. Monitoring of the hydrolysis was not attempted because the reaction mixtures were heterogeneous. The products were isolated by conventional means and were obtained in satisfactory purity after one recrystallization.

Yields. Yields, physical constants, and some reaction times are given in Tables I and II and are reproducible for preparations on the scale of 5 to 200 mmol (ca. 1 to 34 g of 2-benzoylpyrrole). Ethyl 2,4-dimethylpyrrole-3-carboxylate was chosen as the principal substrate for studying changes in experimental procedures aimed at improving yields as it was also suitable as a reference compound for the rate studies which were concurrently under way.[14] For the same reason most of the reactions were carried out at 35 °C. However, in those

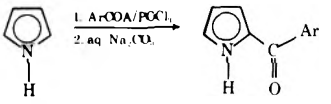
Table I



Registry no.	Ar	A	Complex formation[a]	Azafulvene formation,[b] h (λ_{max}, nm)	% Yield[c]	Mp °C[d,e]
63833-34-1	4-Methoxyphenyl	Morpholide	60 min	10.8 (376)	90 (96)	148.5–149.5
63833-35-2	4-Tolyl	Morpholide	120 min	7.0 (379)	85 (92)	133–134
63833-46-5	Phenyl	Morpholide	160 min	3.1 (379)	92 (99)	109–110[f]
63833-36-3	4-Chlorophenyl	Morpholide	10 h	2.3 (386)	87 (95)	174–174.5
	4-Chlorophenyl	Dimethylamide	55 min	18.2 (374)	90 (93)	174–174.5
63833-37-4	3-Chlorophenyl	Dimethylamide	85 min	7.8 (374)	88 (94)	135–136
63833-38-5	4-Nitrophenyl	Dimethylamide	4 h	1.9 (388)	96 (*g*)	173–175
63833-39-6	3-Nitrophenyl	Dimethylamide	7 h	3.2 (381)	87 (90)	180–181
63833-40-9	3,5-Dinitrophenyl	Dimethylamide	None			
63833-41-0	2-Pyrrolyl	Dimethylamide	<4 min	178 (~374)	86 (*g*)	188–189
63833-42-1	2-Furyl	Dimethylamide	50 min	1.8 (391)	80 (87)	110–111
63833-43-2	2-Thienyl	Dimethylamide	90 min	2.7 (385)	86 (88)	107.5–108.5
63833-45-4	3-Pyridyl	Diethylamide	120 min	8.7 (388)	85 (97)	155–156.5[h]

[a] At 35 °C using 2.16 equiv of $POCl_3$, minimum time for full formation. [b] At 35 °C, 0.2 M in 1,2-dichloroethane, 10-mmol scale. [c] First crop only from petroleum ether (60–65 °C) or toluene/petroleum ether. Second figure gives yield by spectrophotometric assay. [d] Satisfactory analyses (±0.2% for C, H and N) were reported for all new compounds listed. [e] All compounds gave satisfactory NMR and IR spectra. Keto carbonyl absorptions were all in the region 1590–1621 cm^{-1}. [f] In agreement with literature value, ref 9. [g] Product crystallized before assay could be performed. [h] In agreement with literature value, ref 20.

Table II



Registry no.	Ar	A	% yield[a]	Mp, °C
63833-47-6	4-Nitrophenyl	Dimethylamide	91	160–162 (160–161[b])
13169-71-6	4-Chlorophenyl	Morpholide	87	118.5–119.5 (114–115[b])
	Phenyl	Morpholide	86	77.5–78 (79[c])
55895-62-0	4-Tolyl	Morpholide	86	118–119 (119[b])
11963-43-5	4-Methoxyphenyl	Morpholide	88	112.5–113.5 (110–112[b])

[a] First crop only. Prepared on a 20-mmol scale at 25 °C using a 0.2 M solution in 1,2-dichloroethane. Pyrrole reacted at approximately half the rate of ethyl 2,4-dimethylpyrrole-3-carboxylate. [b] Reference 21. [c] Reference 22.

cases where reactions were repeated at 25 °C the yields rose by 2–3%.

To estahlish that the improved procedure was appropriate to an acid-sensitive substrate, several of the aroylations were repeated using pyrrole. These reactions also went in good yield, indicating that the experimental procedure here reported is not limited to very stable pyrroles only.

Experimental Section

Pyrrole was redistilled and stored, under argon, at 0 °C. Ethyl 2,4-dimethylpyrrole-3-carboxylate[23] was sublimed[24] before use. Phosphoryl chloride was twice redistilled at atmospheric pressure and stored, under argon, in sealed ampules. Anhydrous 1,2-dichloroethane was obtained by distillation from phosphorus pentoxide. All other solvents and reagents were of good commercial quality and were used without further purification.

Dimethylamides were prepared in high yield by treatment of the appropriate acid chloride (0.5 M in toluene) with anhydrous dimethylamine and were recrystallized from petroleum ether (60–65 °C) or toluene/petroleum ether. Morpholides were prepared in the same way using an equimolecular mixture of morpholine and triethylamine which facilitated the removal of the amine salt.

Melting points (Kofler hot stage) are uncorrected.

General Prodedure. The appropriate amide was dissolved in phosphoryl chloride (0.2 mL/mmol of amide), and the solution, protected from moisture, was allowed to stand until NMR spectrometry showed complex formation to he complete. A solution (0.2 M) of the pyrrole (1 equiv relative to amide) in anhydrous 1,2-dichloroethane was added in one batch to the syrupy complex. After thorough mixing, the homogeneous solution, protected from moisture, was allowed to stand until azafulvene formation was complete as shown by UV spectrophotometry using 1,2-dichloroethane for dilution of the samples drawn. The reaction mixture was poured, with stirring, into 10% aqueous sodium carhonate solution (25 mL/mL of $POCl_3$), stirred at room temperature for 15 min, and then for 45 min at reflux temperature. After cooling, the product was isolated from the dichloroethane layer and recrystallized from petroleum ether (60–65 °C) or toluene/petroleum ether.

2-Benzoylpyrrole (Representative Example). A mixture of *N*-benzoylmorpholine (2.96 g, 20 mmol) and phosphoryl chloride (4.0 mL, 43.2 mmol) was kept at 25 °C for 6 h. A solution of pyrrole (1.38 mL, 20 mmol) in anhydrous 1,2-dichloroethane (100 mL) was added and, after swirling, the reaction mixture was left at ca. 25 °C for 14 h. After hydrolysis with 10% aqueous sodium carhonate solution (100 mL), the organic layer was separated and the aqueous layer was washed with 1,2-dichloroethane (two 20-mL portions). The combined organic layers were dried (Na_2CO_3), the solvent was removed, and the residue was recrystallized (charcoal) from petroleum ether (60–65 °C) to give the desired ketone as colorless needles (2.95 g, 86%), mp 77.5–78 °C (lit.[22] mp 79 °C).

Acknowledgments. Financial assistance from the University of South Africa (Research Grants Committee) and the CSIR, Pretoria, South Africa, is gratefully acknowledged.

Registry No.—$ArCONMe_2$ (Ar = 4-ClC_6H_4), 14062-80-7; $ArCONMe_2$ (Ar = 3-ClC_6H_4), 24167-52-0; $ArCONMe_2$ (Ar = 4-$O_2NC_6H_4$), 7291-01-2; $ArCONMe_2$ (Ar = 3-$O_2NC_6H_4$), 7291-02-3; $ArCONMe_2$ (Ar = 3,5-di$O_2NC_6H_3$), 2782-45-8; $ArCONMe_2$ (Ar = 2-pyrrolyl), 7126-47-8; $ArCONMe_2$ (Ar = 2-furyl), 13156-75-7; $ArCONMe_2$ (Ar = 2-thienyl), 30717-57-8; *N*-(4-methoxybenzoyl)morpholine, 7504-58-7; *N*-(4-methylbenzoyl)morpholine, 63833-44-3; *N*-(4-chlorobenzoyl)morpholine, 19202-04-1; ethyl 2,4-dimethylpyrrole-3-carboxylate, 2199-51-1; phosphoryl chloride, 10025-87-3; 2-benzoylpyrrole, 7697-46-3; *N*-benzoylmorpholine, 1468-28-6; *N,N*-diethyl-3-pyridinecarboxamide, 59-26-7; pyrrole, 109-97-7; 4-nitro-*N,N*-dimethylbenzamide, 7291-01-2.

References and Notes

(1) A. Vilsmeier and A. Haack, *Chem. Ber.*, **60**, 119 (1927).
(2) The exact structure of the amide–$POCl_3$ complex (**2**) is uncertain; see, for example, G. Jugie, J. A. Smith, and G. J. Martin, *J. Chem. Soc., Perkin Trans. 2*, 925 (1975), and references cited therein. For complexes generated and used in situ we favor the structure shown.
(3) Early reports include M. A. T. Rogers, *J. Chem. Soc.*, 596 (1943); A. H. Cook and J. R. Majer, *J. Chem. Soc.*, 482 (1944).
(4) R. M. Silverstein, E. E. Ryskiewicz, and C. Willard, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1967, p 831.
(5) P. E. Sonnett, *J. Org. Chem.*, **37**, 925 (1972), has shown that the intermediate azafulvene (**3**, R = H) does not react further with Vilsmeier–Haack reagents.
(6) H. J. Anderson and H. Nagy, *Can. J. Chem.*, **50**, 1961 (1972), in a footnote report a 0.5% yield of the 3-aldehyde in a large-scale preparation of 2-formylpyrrole.
(7) C. F. Candy, R. A. Jones, and P. H. Wright, *J. Chem. Soc. C*, 2563 (1970); however, J. K. Chakrabarti and D. E. Turner, *J. Heterocycl. Chem.*, **11**, 417 (1974), report formation of 5% of the 3-aldehyde on formylation of *N*-methylpyrrole.
(8) E. Ghigi and A. Drusiani, *Atti Accad. Sci. Ist. Bologna, Cl. Sci. Fis., Rend.*, **5**, 56 (1957–1958); *Chem. Abstr.*, **54**, 5613i (1960). See also W. C. Anthony, *J. Org. Chem.*, **25**, 2049 (1960).
(9) G. G. Kleinspehn and A. E. Briod, *J. Org. Chem.*, **26**, 1652 (1961).
(10) J. A. Ballantine, A. H. Jackson, G. W. Kenner, and G. McGillivray, *Tetrahedron, Suppl.* **7**, 241 (1966).
(11) L. J. Dolby, S. J. Nelson, and D. Senkovich, *J. Org. Chem.*, **37**, 3691 (1972).
(12) See, for example, J. M. Patterson, *Synthesis*, 281 (1976).
(13) A. Ermili, A. J. Castro, and P. A. Westfall, *J. Org. Chem.*, **30**, 339 (1965).
(14) Results dealing with the effect of substituents and reaction conditions on the rate of reaction will be published in the appropriate journal.
(15) J. G. Dingwall, D. H. Reid, and K. Wade, *J. Chem. Soc. C*, 913 (1969), reported that *N,N*-dimethylthioformamide is more effective than *N,N*-dimethylformamide in the formylation of certain compounds.
(16) S. Alunni, P. Linda, G. Marino, S. Santini, and G. Savelli, *J. Chem. Soc., Perkin Trans. 2*, 2070 (1972).
(17) The presence of 0.05% water in the reaction mixture approximately halved the rate and reduced the yield by one seventh.
(18) S. Clementi, P. Linda, and G. Marino, *J. Chem. Soc., Chem. Commun.*, 427 (1972).
(19) M. Beyers, J. White, and G. McGillivray, unpublished results. The method is a modification of that of C. F. Candy and R. A. Jones, *J. Org. Chem.*, **36**, 3993 (1971).
(20) M. Strell and E. Kopp, *Chem. Ber.*, **91**, 1621 (1958).
(21) M. K. A. Khan and K. J. Morgan, *J. Chem. Soc.*, 2579 (1964).
(22) H. Fischer and H. Orth, "Die Chemie de Pyrroles", Vol. I, Johnson Reprint Corp., New York, N.Y., 1968, p 204.
(23) Reference 22, p 247.
(24) Strictly speaking, the purification was by low-pressure distillation onto a cold-finger condenser. When quite pure, this compound is stable indefinitely at room temperature. See, however, A. H. Corwin and K. W. Doak, *J. Am. Chem. Soc.*, **77**, 464 (1955).

N-Nitroaziridines: Synthesis, Thermal Stability, and Solvolytic Reactivity

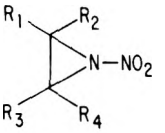
Michael J. Haire* and George A. Boswell, Jr.

Contribution No. 2497 from the Central Research and Development Department, E. I. du Pont de Nemours & Co. Wilmington, Delaware 19898

Received June 29, 1977

The syntheses of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestane (**5**) and 10-methyl-1,9-(*N*-nitroaziridino)decalin (**6**), the first known *N*-nitroaziridines, are described. Their thermal rearrangements and their reactivity in the presence of protic solvents are also examined.

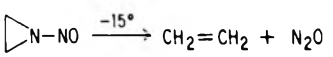
Synthetic and naturally occurring aziridines and nitro-substituted heterocycles are rich sources of important pharmaceuticals, veterinary medicines, and agrichemicals.[1] *N*-Nitroaziridines (**1**) are representative of both classes, but until



1

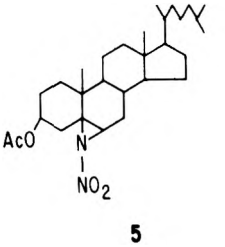
R_1, R_2, R_3, R_4 = H or ALKYL

now were unknown. Research in this area may have been inhibited by the impression that these aziridines would be too unstable to isolate, since *N*-nitrosoaziridines are known to decompose spontaneously at −15 °C, giving nitrous oxide and olefin.[2]

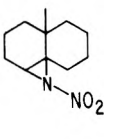


2 **3** **4**

We now wish to report the synthesis of two stable *N*-nitroaziridines (**5** and **6**) by a novel route. Both compounds are



5



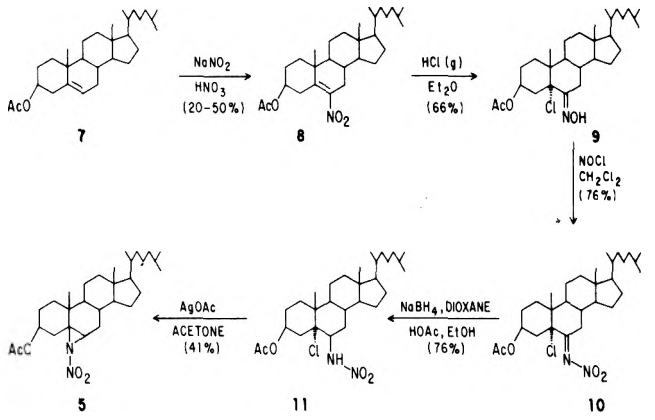
6

stable at room temperature, but undergo unique thermal rearrangements at elevated temperatures.

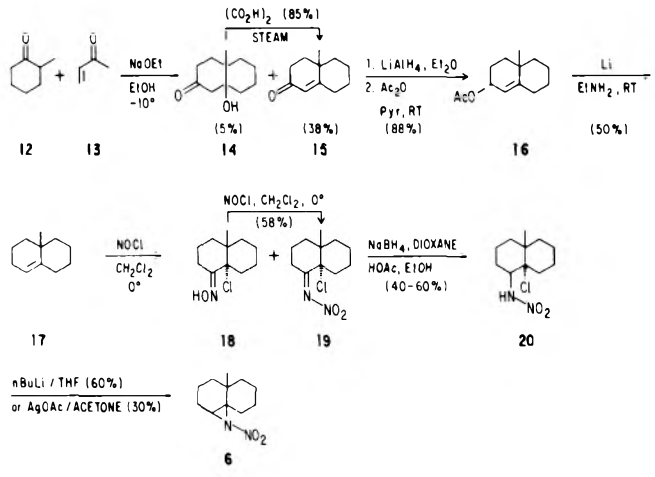
Synthesis

The synthesis of *N*-nitroaziridine **5** began with nitration of cholesteryl acetate (**7**) to give 6-nitrocholesteryl acetate (**8**) (Scheme I). This reaction proved quite capricious with yields from 20 to 50% even under identical conditions, probably because of variations in quality of the sodium nitrite and nitric acid. Conversion to the chlorooxime **9** was effected with dry hydrogen chloride in ether.[3] Direct addition of nitrosyl chloride to cholesteryl acetate, followed by acidic isomerization to chlorooxime **9**, was an unacceptable alternative because steroidal olefins give chloronitro derivatives rather than the

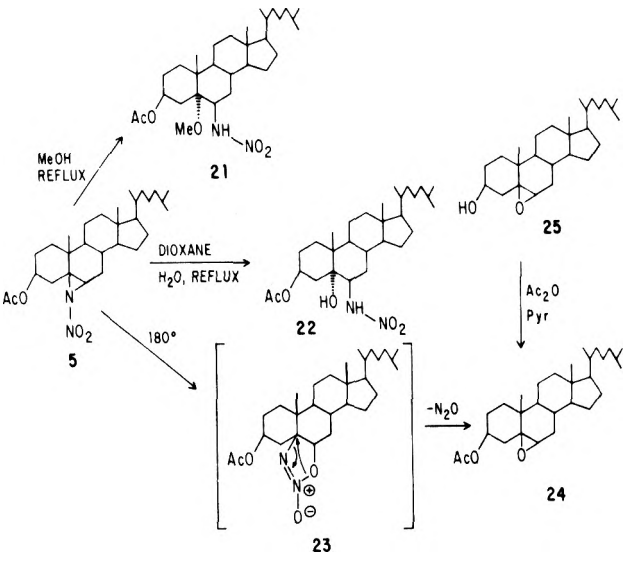
Scheme I



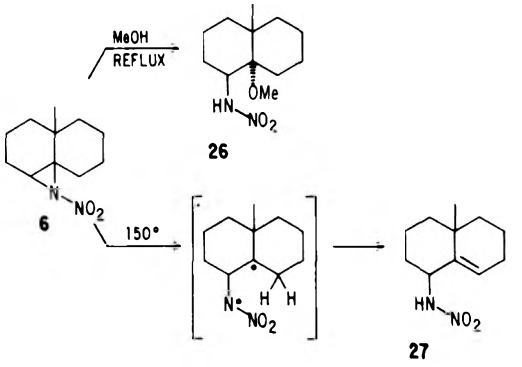
Scheme II



Scheme III



Scheme IV



desired chloronitroso compounds upon addition of nitrosyl chloride.[4-6]

Nitrosyl chloride was used[3,7] to convert 3β-acetoxy-5α-chloro-6-oximinocholestane (**9**) to 3β-acetoxy-5α-chloro-6-nitriminocholestane (**10**). The nitrimino moiety in **10** was reduced to the nitramine **11** in 15% yield with sodium borohydride in dioxane and ethanol. However, yields of 76% could be obtained by adding glacial acetic acid to the reaction mixture.[8]

Ring closure to the *N*-nitroaziridine **5** was obtained by the novel reaction of the chloronitramine **11** with silver acetate in acetone. Although silver acetate appears insoluble in acetone, there is sufficient solubility to allow the reaction to proceed. Silver chloride is precipitated as a purple solid. Periodic filtering and addition of fresh silver acetate[9] are required for acceptable yields. *n*-Butyllithium treatment of **11** afforded only trace amounts of *N*-nitroaziridine. By comparison, treatment of 5α-fluoro-6β-nitraminocholestan-3β-ol acetate with base gave no *N*-nitroaziridine.[10] 3β-Acetoxy-5β,6β-*N*-nitroaziridinylcholestane (**5**) was a stable, crystalline solid melting at 134–135 °C.

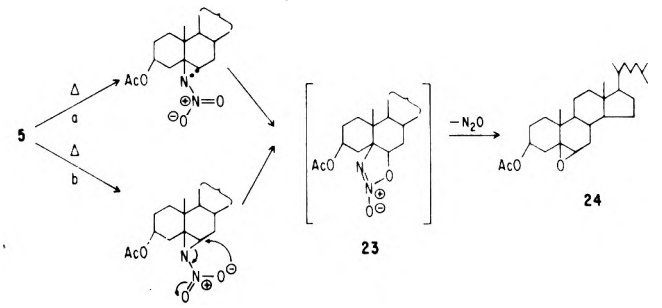
10-Methyl-1,9-(*N*-nitroaziridino)decalin (**6**) was prepared in more direct fashion from the known[11,12] 10-methyl-$\Delta^{1,9}$-octalin (**17**) (Scheme II). Nitrosyl chloride addition to **17** gave a 50:50 mixture of 1-oximino-9-chloro-10-methyldecalin (**18**) and 1-nitrimino-9-chloro-10-methyldecalin (**19**). The oxime **18** could be isolated and treated again with nitrosyl chloride to give the nitramine **19** in 58% yield. Reduction of **19** with sodium borohydride afforded 1-nitramino-9-chloro-10-methyldecalin (**20**); again glacial acetic acid was added to facilitate reduction of the C=N bond. Ring closure to the *N*-nitroaziridine **6** was accomplished with either silver acetate in acetone or *n*-butyllithium in tetrahydrofuran. In contrast to the steroidal system, the best results were obtained with *n*-butyllithium rather than silver acetate because traces of silver acetate remain in solution during filtration of the reaction mixture. This impurity proved difficult to remove from this *N*-nitroaziridine because it is an oil. Distillation afforded pure *N*-nitroaziridine, but decomposition during distillation considerably lowered the yield. The *n*-butyllithium route, on the other hand, afforded pure *N*-nitroaziridine without further purification. 10-Methyl-1,9-(*N*-nitroaziridino)decalin (**6**) is a clear oil boiling at 63–75 °C (0–1 mm).

Discussion

The syntheses of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestane (**5**) and 10-methyl-1,9-(*N*-nitroaziridino)decalin (**6**) have shown *N*-nitroaziridines to be stable, isolable compounds. They undergo characteristic solvolytic opening of the aziridine ring in the presence of protic solvents (Schemes III and IV). When either **5** or **6** is heated to reflux in methanol, the corresponding methoxynitramines **21** and **26**, respectively, are obtained; and, when **5** is heated in a dioxane/water mixture, the alcoholic nitramine **22** is produced. However, this reactivity does not extend to all protic solvents, since the steroidal *N*-nitroaziridine **5** can be recrystallized without change from isopropyl alcohol.

Thermal transformations of *N*-nitroaziridines appear unique to each system. When *N*-nitroaziridine **6** is heated to 150 °C under vacuum, the allylic nitramine **27** is produced. Presumably the mechanism involves thermal homolytic

Scheme V

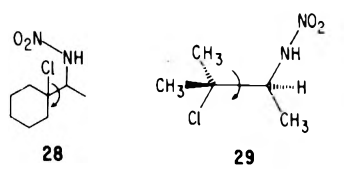


opening of the aziridine ring followed by hydrogen transfer to give an allylic nitramine. In contrast, when the steroidal *N*-nitroaziridine **5** is heated in neat solution to 180 °C, only traces of olefinic material are seen. The primary product isolated is the β-epoxide **24** (Scheme V), whose structure was established by independent synthesis from the known 5β,6β-oxocholesterol.[10,13] This is supported by mass spectrometric analysis of **5**, which shows no molecular ion, but instead exhibits a strong peak at *m/e* 444 corresponding to loss of $\cdot N_2O$ to give the epoxide **23**. The formation of the epoxide can best be attributed to intramolecular opening of the aziridine ring to give a nonisolable intermediate **23**, which promptly loses N_2O.

The intermediate **23** can be thought to arise from a vinylcyclopropane–cyclopentene type rearrangement of the *N*-nitroaziridine. Alternatively, attack on the aziridinyl carbon by the negatively polarized oxygen would also lead to **23**. Although **6** is also capable of undergoing such a rearrangement, formation of the allylic nitramine (**27**) appears more facile. No epoxide was isolated from the thermolysis of **6** or seen in the crude thermolysis mixture. Since both epoxide formation routes appear available equally to **5** and **6**, the fact that **6** does not form an epoxide thermally does not eliminate either route from consideration. Reasons for the diverse thermolysis pathways of **5** and **6** remain unclear, particularly in view of their structural similarities.

Although **6** displays notable thermal and solvolytic activity, it is remarkably unreactive under various conditions. When treated in ether solution with either dry hydrogen chloride, acetic anhydride, methyl iodide, or sodium borohydride, the *N*-nitroaziridine was recovered unchanged. Treatment with lithium aluminum hydride gave unidentified complex reaction products.

There are distinct structural limitations to ring closure of chloronitramine precursors. Ring closure of 1-chloro-1-(α-nitraminoethyl)cyclohexane (**28**) to its corresponding *N*-



nitroaziridine could not be forced using either base or Ag^+ under a variety of conditions: silver acetate/acetone; silver tetrafluoroborate/ether; silver tetrafluoroborate/ether, triethylamine; silver hexafluorophosphate/acetone; triethylamine/ether; silver oxide/acetone; sodium hydride/ether; potassium *tert*-butoxide/dimethyl sulfoxide; and *n*-butyllithium/tetrahydrofuran. To determine if aziridine formation was inhibited by strain introduced by the incipient spiro system, ring closure of 3-chloro-3-methyl-2-nitraminobutane (**29**) was attempted. Again, the *N*-nitroaziridine did not form with either Ag^+ or base (NaH or *n*-BuLi). The optimal configuration for aziridine formation is a trans-diaxial alignment of the chloro and nitramino groups. Both **11** and **20** are held rigidly in this configuration and the aziridine forms readily. Although chloronitramines **27** and **28** can achieve a trans-diaxial configuration, relatively free rotation about the central C–C bond does not make this preferred, and there is less chance of ring closure.

N-Nitroaziridines are relatively stable compounds which are easily synthesized provided certain structural limitations are considered. They possess unique thermal properties that make them interesting compounds for future study.

Experimental Section

6-Nitrocholesteryl Acetate (8). To a vigorously stirred suspension of 100 g (0.23 mol) of cholesteryl acetate in 1700 mL of concentrated nitric acid with a water bath for cooling was added 100 g of sodium nitrite in small portions over 30 min. The pink solution turned yellow and brown fumes evolved. After stirring overnight at room temperature, the mixture was filtered and the precipitate washed well with water to give a yellow solid, which was recrystallized from methanol/ether to give 52.49 g (0.11 mol, 47%) of 6-nitrocholesteryl acetate, mp 102–104 °C.

The spectral data were: IR ($CHCl_3$) 3.38 (s), 3.48, 5.80 (s), 6.59 (s), 6.82, 6.96, 7.30, 7.99, 9.62 μm; NMR ($CDCl_3$) τ 5.37 (m, 1 H –COOCH<), 7.70–9.25 (m, 28 H, aliphatic), 7.98 (s, 3 H, CH_3CO–), 8.87 (s, 3 H, C-19 methyl), 9.10 (br s, 6 H, C-26 and C-27 methyls), 9.19 (br s, 3 H, C-21 methyl), 9.31 (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{47}NO_4$: C, 73.53; H, 10.00; N, 2.96. Found: C, 73.81; H, 9.74; N, 2.65.

3β-Acetoxy-5α-chloro-6-oximinocholestane (9). The procedure of Komeichi et al. was used.[3] A stream of anhydrous hydrogen chloride was bubbled into a stirred solution of 6-nitrocholesteryl acetate (47.74 g, 0.101 mol) in 1300 mL of ether for 3 h at 0 °C. The reaction mixture was allowed to stand at 0 °C for 2 days, followed by 2 days at room temperature. The ether and hydrogen chloride were then removed in vacuo, and the residue was taken up in ether, washed with water, dried, filtered, and concentrated in vacuo to give a red oil, which was taken up in 50 mL of ether and 100 mL of acetone. The ether was boiled off and crystallization occurred on cooling to room temperature. Recrystallization from acetone gave 33.11 g (0.0672 mol, 66%) of 3β-acetoxy-5α-chloro-6-oximinocholestane, mp 153.5–155 °C dec.

The spectral data were: IR ($CHCl_3$) 2.92, 3.36, 5.76 (s), 5.82 (s), 6.80, 6.92, 7.32, 8.02, 8.57, 8.70, 9.58, 9.76, 10.22, 10.47, 10.82, 10.92, 11.12, 12.12 μm; NMR ($CDCl_3$) τ 1.0–2.0 (br s, 1 H, NOH), 4.40–5.00 (m, 1 H, COOCH<), 7.98 (s, 3 H, CH_3CO–), 8.00–9.25 (m, 28 H, aliphatic), 9.03 (s, 3 H, C-19 methyl), 9.07 (br s, 6 H, C-26 and C-27 methyls), 9.18 (br s, 3 H, C-21 methyl), 9.33 (s, 3 H, C-18 methyl).

3β-Acetoxy-5α-chloro-6-nitriminocholestane (10). The procedure of Komeichi et al. was used.[3] A solution of 3.5 g (7.1 mmol) of 3β-acetoxy-5α-chloro-6-oximinocholestane in 300 mL of methylene chloride was stirred at 0 °C, while nitrosyl chloride was slowly bubbled into the solution for ca. 10 min until a deep brownish red color appeared. The stoppered flask was allowed to stand at 10 °C overnight, and then the contents was poured into water. The organic layer was washed with water and brine, dried, filtered, and concentrated in vacuo to give a clear oil which crystallized upon addition of ether/methanol. Recrystallization from ether/methanol yielded 2.8 g (5.4 mmol, 76%) of 3β-acetoxy-5α-chloro-6-nitriminocholestane, mp 121–123 °C.

The spectral data were: IR ($CHCl_3$) 3.38, 3.48, 5.82 (s), 6.15, 6.36, 6.80, 6.92, 7.22, 7.30, 7.55, 8.02, 8.60, 9.57, 9.80, 10.20, 10.80, 11.40 μm; NMR ($CDCl_3$) τ 4.50–5.00 (m, 1 H, –COOCH<), 7.80–9.25 (m, 28 H, aliphatic), 7.98 (s, 3 H, CH_3CO–), 8.95 (s, 3 H, C-19 methyl), 9.10 (br s, 6 H, C-26 and C-27 methyls), 9.18 (br s, 3 H, C-21 methyl), 9.35 (s, 3 H, C-18 methyl).

3β-Acetoxy-5α-chloro-6β-nitraminocholestane (11). The acidification technique of Meyers and Nabeya[8] was modified for this imine reduction. To a stirred solution of 1.00 g (1.91 mmol) of 3β-acetoxy-5α-chloro-6-nitriminocholestane in 25 mL of dioxane, 25 mL of absolute ethanol, and 5 drops of glacial acetic acid with an ice/acetone bath for cooling was added 1.22 g (32.2 mmol) of sodium borohydride in small portions to control frothing. The mixture was allowed to stir for 30 min at reduced temperature, 15 drops of glacial acetic acid were added, and stirring was continued for 60 min at reduced temperature, followed by 30 min at room temperature. The reaction was then carefully diluted with 100 mL of 3% aqueous acetic acid and extracted thoroughly with methylene chloride. The combined organic extracts were dried, filtered, and concentrated in vacuo to give a white solid, which was recrystallized from acetone to give 760 mg (1.45 mmol, 76%) of 3β-acetoxy-5α-chloro-6β-nitraminocholestane,

mp 206–206.5 °C dec.

The spectral data were: IR (Nujol) 2.90, 3.00, 3.30, 5.85 (s), 6.20 (s), 6.88, 7.10, 7.40, 7.60, 7.71, 7.95, 8.12, 8.19, 8.33, 8.70, 9.30, 9.41, 9.60, 9.81, 10.08, 10.40, 10.55, 10.77, 10.88, 11.09, 11.39, 11.80, 12.15, 12.94, 13.19 μm; NMR [$(CD_3)_2SO$] τ 4.50–5.10 (m, 1 H, –COOCH<), 7.72–9.28 (m, 30 H, aliphatic), 8.01 (s, 3 H, CH_3CO–), 8.81 (s, 3 H, C-19 methyl), 9.10 (br s, 6 H, C-26 and C-27 methyls), 9.20 (br s, 3 H, C-21 methyl), 9.31 (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{49}N_2O_4Cl$: C, 66.32; H, 9.50; N, 5.33; Cl, 6.75. Found: C, 66.40; H, 9.29; N, 5.16; Cl, 6.83.

3β-Acetoxy-5β,6β-*N*-Nitroaziridinylcholestane (5). A suspension of 2.61 g (4.98 mmol) of 3β-acetoxy-5α-chloro-6β-nitraminocholestane and 5.00 g of silver acetate in 150 mL of acetone was stirred under nitrogen for 1 day and 5.22 g of silver acetate was added. After stirring for another day, the mixture was filtered and the precipitate washed with acetone. The acetone was removed in vacuo, the solid residue was taken up in 150 mL of acetone, and 6.95 g of fresh silver acetate was added. The suspension was stirred for 1 day and 6.46 g of silver acetate was added. After stirring for an additional day (4 days total), the mixture was filtered and the filtrate concentrated in vacuo to give a white solid. Recrystallization from isopropyl alcohol gave 1.00 g (2.05 mmol, 41%) of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestane, mp 134.5–135 °C.

The spectral data were: IR ($CHCl_3$) 3.35, 5.84 (s), 6.45 (s), 6.81, 6.93, 7.34, 7.74, 7.79, 7.99, 8.51, 9.63, 10.19, 11.14 μm; NMR ($CDCl_3$) τ 4.86–5.44 (m, 1 H, COOCH<), 6.72 (m, 1 H, >CHN), 7.55–9.25 (m, 28 H, aliphatic), 7.99 (s, 3 H, CH_3CO–), 8.83 (s, 3 H, C-19 methyl), 9.09 (br s, 6 H, C-26 and C-27 methyls), 9.18 (br s, 3 H, C-21 methyl), 9.35 (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{48}N_2O_4$: C, 71.27; H, 9.90; N, 5.73. Found: C, 71.32; H, 9.54; N, 5.40. MS shows no molecular ion; only a large M − 44 peak. Calcd for $C_{29}H_{48}O_3$: 444.3601. Found 444.3601.

3β-Acetoxy-5β,6β-oxocholestane (24) from Thermolysis of 3β-Acetoxy-5β,6β-*N*-nitroaziridinylcholestane (5). A sample of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestane (590 mg) was heated under vacuum to 190–193 °C for 30 min until bubbling ceased. After cooling to room temperature, the darkened product was chromatographed on two 20 cm × 20 cm × 2 mm plates of silica gel (E. Merck, according to Stahl). After one development with chloroform, the plate was divided into three bands. The second band from the top contained 70 mg of 3β-acetoxy-5β,6β-oxocholestane, whose NMR and IR were identical with authentic material obtained in the following experiment.

The spectral data were: IR ($CHCl_3$) 3.40, 5.71, 5.96, 6.81, 7.31, 8.12, 8.90, 9.00, 9.81 μm; NMR ($CDCl_3$) τ 4.25–4.80 (m, 1 H, COOCH<), 7.70–9.20 (m, 29 H, aliphatic), 7.82–7.95 (m, 3 H, CH_3CO–), 8.78 (br s, 3 H, C-19 methyl), 9.08 (br s, 6 H, C-26 and C-27 methyls), 9.18 (s, 3 H, C-21 methyl), 9.28 (s, 3 H, C-18 methyl).

Anal. MS Calcd for $C_{29}H_{48}O_3$: 444.3601. Found: 444.3588.

3β-Acetoxy-5β,6β-oxocholestane (24). A mixture of 20 mg of 5β,6β-oxocholesterol,[12] 0.1 mL of pyridine, and 5 mL of acetic anhydride was heated to gentle reflux for 1 h under nitrogen followed by stirring overnight at room temperature. The mixture was concentrated in vacuo to give 20 mg of 3β-acetoxy-5β,6β-oxocholestane, whose spectral data were identical with those of the thermolysis product of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestane.

Methanolysis of 3β-Acetoxy-5β,6β-*N*-nitroaziridinylcholestane (5). A solution of 500 mg (1.02 mmol) of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestane in 40 mL of methanol was refluxed for 4 h, and the methanol was removed under a stream of nitrogen, giving a white solid. The solid was recrystallized from methanol, giving 340 mg (0.65 mmol, 64%) of 3β-acetoxy-5α-methoxy-6β-nitraminocholestane, mp 209–210 °C.

The spectral data were: IR ($CHCl_3$) 2.90, 3.39, 3.48, 5.77 (s), 6.30 (s), 6.80, 7.31, 7.51, 7.97, 8.55, 9.29, 9.69, 10.36 μm; NMR ($CDCl_3$) τ 4.24–4.76 (m, 1 H, –COOCH<), 6.67 (s, 3 H, CH_3O–), 7.70–9.25 (m, 30 H, aliphatic), 7.98 (s, 3 H, CH_3CO–), 8.88 (s, 3 H, C-19 methyl), 9.08 (br s, 6 H, C-26 and C-27 methyls), 9.17 (br s, 3 H, C-21 methyl), 9.30 (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{30}H_{52}N_2O_5$: C, 69.19; H, 10.06; N, 5.38. Found: C, 69.08; H, 10.13; N, 5.35.

3β-Acetoxy-5α-hydroxy-6β-nitraminocholestane (22). A 1.00-g (2.04 mmol) sample of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestane in 25 mL of dioxane and 10 mL of water was refluxed for 1 h, diluted with methylene chloride and water, extracted with methylene chloride (3×), dried, filtered, and concentrated in vacuo to give 1.16 g of white solid. The solid was recrystallized from acetone, giving 460 mg (0.908 mmol, 44%) of 3β-acetoxy-5α-hydroxy-6β-nitraminocholestane, mp 241–242 °C.

The spectral data were: NMR (Me_2SO-d_6) τ 7.70–9.70 (m); IR (Nujol) 2.84, 3.10, 3.20, 3.40 (s), 5.84 (s), 6.30, 6.84, 7.05, 7.26, 7.37, 7.50, 7.66, 7.90, 8.05, 8.25, 8.58, 8.90, 9.23, 9.71, 10.39, 10.88, 11.49 μm.

Anal. Calcd for $C_{29}H_{50}N_2O_5$: C, 68.74; H, 9.95; N, 5.53. Found: C, 69.02; H, 9.59; N, 5.65.

10β-Methyl-Δ^{1,9}-octal-2-one (15). The procedure of Marshall and Fanta was followed.[11] A mixture of 28.17 g (0.154 mol) of *cis*-10-methyl-2-decalon-9-ol and 300 mL of 10% aqueous oxalic acid was steam-distilled. The distillate was saturated with sodium chloride and ether-extracted. The combined ether extracts were dried, filtered, and concentrated in vacuo to give 19.03 g (0.116 mol, 75%) of 10β-methyl-Δ^{1,9}-octal-2-one.

***cis*-10-Methyl-2-decalon-9-ol (14) and 10β-Methyl-Δ^{1,9}-octal-2-one (15)** The procedure of Marshall and Fanta[11] was followed. To a stirred mixture of 4.90 g (72 mmol) of sodium ethoxide in 25 mL of absolute ethanol and 400 g (3.57 mol) of 2-methylcyclohexanone at −10 to 0 °C was added dropwise 250 g (3.57 mol) of methyl vinyl ketone over 1.5 h under nitrogen. The thick mixture was stirred for 5 h at −10 to 0 °C, diluted with ether and brine, and extracted with ether. The combined ether extracts were washed with brine, dried, filtered, and concentrated in vacuo to ca. 900 mL. The ether was boiled off while volume was maintained with hexane. Cooling to room temperature overnight gave 32.08 g (0.176 mol, 5%) of cis-10-methyl-2-decalon-9-ol, mp 120–121 °C (lit.[11] mp 120–121 °C). Hexane was removed from the mother liquors in vacuo, and the residue was distilled giving: fraction 1, 75 °C (30 mm), 144.52 g of 2-methylcyclohexanone; and fraction 2, 135 °C (0.1 mm), 171.55 g of 10β-methyl-Δ^{1,9}-octal-2-one. Steam distillation of the pot residue with 300 mL of 10% aqueous oxalic acid followed by ether extraction, drying, and concentration in vacuo gave an additional 49.21 g of enone. The total yield of 10β-methyl-Δ^{1,9}-octal-2-one was 220.76 g (1.34 mol, 38%).

10-Methyl-Δ^{1,9}-octal-2-ol Acetate (16). The procedure of Marshall and Hochstetler was followed.[12] To a stirred solution of 50.00 g of lithium aluminum hydride in 2 L of ether was added 204.0 g (1.24 mol) of 10β-methyl-Δ^{1,9}-octal-2-one in 200 mL of ether over 45 min. A ice bath was used for cooling during the addition and then removed. After stirring for 3 h at room temperature, the mixture was cautiously treated with a mixture of 100 mL of water and 80 mL of 10% aqueous sodium hydroxide. An ice bath was used for cooling during the addition and then removed. After stirring for an additonal 2 h, the mixture was filtered and concentrated in vacuo to give a yellow liquid (204.5 g) whose NMR and IR were consistent with an allylic alcohol.

The crude alcohol was dissolved in 1300 mL of pyridine and 355 mL of acetic anhydride was added. The clear solution was stirred under nitrogen at room temperature for 23 h, 5 L of brine was added, and the mixture was extracted with ether. The combined ether extracts were washed with water, 2% aqueous sulfuric acid, and brine. The ether layer was then dried, filtered, and concentrated in vacuo to give a light yellow liquid which was distilled, giving 228.58 g (1.10 mol, 88%) of 10-methyl-Δ^{1,9}-octal-2-ol acetate, bp 117 °C (2.5 mm) [lit.[12] bp 62–63 °C (0.08 mm)].

10-Methyl-Δ^{1,9}-octalin (17) and 2-Hydroxy-10-methyldecalin. The procedure of Marshall and Hochstetler was followed.[12] To a stirred solution of 60.0 g (0.288 mol) of 10-methyl-Δ^{1,9}-octal-3-ol acetate in 75 mL of ethylamine was added 20.0 g (225 cm, 2.88 mol) of lithium cut in small pieces. After ca. 15 min, a deep blue color appeared and the mixture was stirred at room temperature for 40 min more. Solid ammonium chloride was added carefully to neutralize the lithium salts and destroy any excess lithium metal. Ether was added to maintain volume and an ice bath was used to control the reaction. When most of the lithium had been destroyed, a small amount of water was added to speed the hydrolysis. When all the lithium had been destroyed, the mixture was diluted with 2 L of brine and extracted with ether. The combined ether extracts were washed with water, 2% aqueous sulfuric acid, and brine, and then dried, filtered, and concentrated in vacuo to give a yellow liquid which was vacuum distilled to give 21.25 g (0.141 mol, 49%) of 10-methyl-Δ^{1,9}-octalin, bp 70 °C (0.7 mm) [lit.[12] bp 86–88 °C (26 mm)], and 16.13 g (0.096 mol, 29%) of 2-hydroxy-10-methyldecalin, bp 90–95 °C (0.8 mm).

The spectral data for 10-methyl-Δ^{1,9}-octalin were identical with those reported in the literature.[12] The spectral data for 2-hydroxy-10-methyldecalin were: NMR ($CDCl_3$) τ 6.1–6.7 (br m, 1 H, –OH), 7.9–9.0 (br m, 16 H, aliphatic), 9.15 (s, 3 H, methyl); IR ($CHCl_3$) 2.74, 2.91, 3.42, 3.50, 6.88, 7.26, 7.34, 8.06, 8.53, 9.19, 9.49, 9.74, 9.16, 10.56 μm.

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.90; H, 12.08. MS calcd for $C_{11}H_{18}$: 150.1408. Found: 150.1407. Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.44; H, 11.84. MS calcd for $C_{11}H_{20}O$: 168.1514. Found: 168.1526.

1-Oximino-9-chloro-10-methyldecalin (18) and 1-Nitri-

mino-9-chloro-10-methyldecalin (19). A solution of 58.0 g of 10-methyl-$\Delta^{1,9}$-octalin in 1 L of methylene chloride at 0 °C was stirred while nitrosyl chloride was slowly bubbled in for 20 min. The reddish brown solution was stirred at 0 °C for 3 h and concentrated in vacuo to give a light green solid which was washed with cold hexane and filtered, giving 22.72 g (0.105 mol, 27%) of 1-oximino-9-chloro-10-methyldecalin, mp 128–132 °C dec. The filtrate was concentrated in vacuo to give a dark oil, which was chromatographed on a 6.5 cm × 34.5 cm column of silicic acid (Mallinckrodt, Silic AR, CC-7) slurry packed in 10% chloroform in hexane. Elution in 500-mL fractions gave: fraction 1, 1.38 g of unidentified oil; fractions 2–4, 25.05 g (0.102 mol, 26%) of 1-nitrimino-9-chloro-10-methyldecalin; and fraction 5, 2.13 g.

The spectral data for 1-oximino-9-chloro-10-methyldecalin were: NMR (CCl_3) τ 1.30 (s, 1 H, =NOH), 6.50–8.90 (m, 14 H, aliphatic), 9.00 (s, 3 H, methyl); IR ($CHCl_3$) 2.68, 3.01, 3.36, 6.86, 6.99, 7.26, 7.36, 7.61, 8.33, 8.70, 9.86, 10.26, 10.58, 11.30, 11.37, 11.65, 12.15, 12.32 μm.

The spectral data for 1-nitrimino-9-chloro-10-methyldecalin were: NMR ($CDCl_3$) τ 6.70–9.00 (m, 14 H, aliphatic), 8.89 (s, 3 H, methyl); IR ($CHCl_3$) 3.45, 3.52, 6.19, 6.38, 6.90, 6.96, 7.30, 7.65, 7.76, 7.90, 8.10, 8.70, 9.05, 9.50, 9.62, 9.96, 10.24, 10.33, 11.04, 11.21, 11.80, 12.20 μm.

Anal. Calcd for $C_{11}H_{18}NOCl$: C, 61.25; H, 8.41; N, 6.49; Cl, 16.43. Found: C, 61.41; H, 8.30; N, 6.35; Cl, 16.12. MS Calcd for $C_{11}H_{18}NOCl$: 215.1077. Found: 215.1075. Anal. Calcd for $C_{11}H_{17}N_2O_2Cl$: C, 53.99; H, 7.00; N, 11.45. Found: C, 54.22; H, 7.16; N, 11.11.

1-Nitrimino-9-chloro-10-methyldecalin (19). A solution of 22.73 g (0.105 mol) of 1-oximino-9-chloro-10-methyldecalin in 1.5 L of methylene chloride at 0 °C was stirred while nitrosyl chloride was slowly bubbled in for 30 min. The reddish brown solution was stirred at 0 °C for 5.5 h, poured into water, washed with water and brine, dried, filtered, and concentrated in vacuo to give a yellow oil which was chromatographed on a 3.5 cm × 39.5 cm column of silicic acid (Mallinckrodt, Silic-AR, CC-7) slurry packed in 10% chloroform in hexane. Elution in 200 mL fractions gave: fraction 1, nil; fractions 2–5, 14.49 g (0.059 mol, 56%) of 1-nitrimino-9-chloro-10-methyldecalin; and fraction 6, 160 mg.

A small sample of 1-nitrimino-9-chloro-10-methyldecalin was recrystallized from ethanol, yielding white crystals which melted at 61–62 °C.

1-Nitramino-9-chloro-10-methyldecalin (20). The acidification technique of Meyers and Nabeya[8] was modified for the imine reduction. To a stirred solution of 14.49 g (59.2 mmol) of 1-nitrimino-9-chloro-10-methyldecalin in 420 mL of dioxane, 420 mL of absolute ethanol, and 107 drops of glacial acetic acid at 0 °C was added 22.00 g (0.579 mol) of sodium borohydride as fast as possible while still controlling frothing. The mixture was stirred at 0 °C for 30 min, and 3.8 mL (306 drops) of glacial acetic acid was added. Stirring was continued for 1 h at 0 °C followed by 1 h at room temperature. The mixture was then diluted with 1700 mL of 3% aqueous acetic acid and extracted with methylene chloride. The organic extracts were washed with water, dried, filtered, and concentrated in vacuo to give a white solid which was washed with hexane, filtered, and vacuum dried to give 10.24 g (41.5 mmol, 70%) of 1-nitramino-9-chloro-10-methyldecalin, mp 136 °C dec.

The spectral data were: NMR ($CDCl_3$) τ 0.90–1.50 (br m, 1 H, >NH), 5.28–5.51 (br m, 1 H, $-CHNHNO_2$), 7.32–9.16 (m, 14 H, aliphatic), 8.80 (s, 3 H, methyl); IR ($CHCl_3$) 2.96, 3.09, 3.42, 3.49, 6.24, 6.38, 6.74, 6.84, 7.09, 7.29, 7.44, 7.53, 7.75, 7.88, 8.14, 8.44, 8.58, 8.85, 9.16, 9.31, 9.84, 10.99, 11.20, 11.43, 11.79 μm.

Anal. Calcd for $C_{11}H_{19}N_2O_2Cl$: C, 53.55; H, 7.76; N, 11.35; Cl, 12.97. Found: C, 53.52; H, 7.62; N, 11.30; Cl, 12.99.

10-Methyl-1,9-(*N*-nitroaziridino)decalin (6) by the Silver Acetate Route. A mixture of 1.03 g (4.17 mmol) of 1-nitramino-9-chloro-10-methyldecalin and 2.13 g of silver acetate in 200 mL of acetone was stirred at room temperature under nitrogen for 8 h and 2.18 g of fresh silver acetate was added. Stirring was continued for 89 h more. The mixture was filtered and the filtrate was concentrated in vacuo to give a dark oil which was taken up in methylene chloride, washed with water, dried, filtered, and concentrated in vacuo to give a dark oil, which was vacuum distilled on a Kugelrohr distillation apparatus at 73–75 °C (0.1 mm), giving 260 mg (1.24 mmol, 30%) of 10-methyl-1,9-(*N*-nitroaziridino)decalin.

The spectral data were: NMR ($CDCl_3$) τ 6.89 (br d, 1 H, J = 5.6 Hz, >CHN<), 7.50–9.50 (m, 14 H, aliphatic), 8.78 (s, 3 H, methyl); IR ($CHCl_3$) 3.39, 3.47, 6.43, 6.83, 6.93, 7.27, 7.78, 7.96, 8.19, 8.71, 8.88, 9.23, 9.51, 10.07, 10.18, 10.45, 11.23, 11.92, 12.03, 12.38, 12.59 μm.

Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 63.39; H, 8.84; N, 13.17. No molecular ion was found in MS; however, a strong peak from the loss of $\cdot NO_2$ was found. Calcd for $C_{11}H_{18}N$: 164.1438. Found: 164.1433.

10-Methyl-1,9-(*N*-nitroaziridino)decalin (6) by the *n*-Butyllithium Route. To a solution of 4.76 g (19.3 mmol) of 1-nitramino-9-chloro-10-methyldecalin in 475 mL of dry tetrahydrofuran at room temperature under nitrogen was added 23.2 mmol of *n*-butyllithium. The solution was stirred and refluxed for 1 h and then stirred at room temperature for 24 h. The mixture was diluted with 1.5 L of methylene chloride, washed with water, dried, filtered, and concentrated in vacuo to give 2.42 g (11.5 mmol, 60%) of 10-methyl-1,9-(*N*-nitroaziridino)decalin.

Thermolysis of 10-Methyl-1,9-(*N*-nitroaziridino)decalin (6). A neat sample of 10-methyl-1,9-(*N*-nitroaziridino)decalin (500 mg, 2.38 mmol) was heated to 149 °C under nitrogen for 5 min. After sitting at room temperature for several days, the oil crystallized and was chromatographed on a 20 cm × 20 cm × 2 mm plate of silica gel (E. Merck, according to Stahl). After one development with chloroform, the plate was divided into four bands: the second band from the bottom contained 170 mg (0.81 mmol, 34%) of 1-nitramino-10-methyl-Δ^8-decalin, which was recrystallized from hexane to give white crystals, mp 97.5–98.5 °C; the third band contained 5 mg of starting *N*-nitroaziridine; and the first and fourth bands contained a total of 10 mg of unidentified material.

The spectral data were: NMR ($CDCl_3$) τ 1.28–1.68 (br m, 1 H, >NH), 4.18 (t, 1 H, J = 3.5 Hz, vinyl), 5.35–5.64 (br m, 1 H, $>CHNHNO_2$), 7.65–8.80 (m, 12 H, aliphatic), 8.87 (s, 3 H, methyl); IR ($CHCl_3$) 2.90, 3.03, 3.38, 6.35, 6.86, 6.93, 7.23, 7.38, 7.47, 7.65, 7.77, 8.53, 9.27, 9.51, 9.88, 11.02 μm.

Anal. Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.75; H, 8.88; N, 13.52.

Methanol Solvolysis of 10-Methyl-1,9-(*N*-nitroaziridino)-decalin (6). A solution of 500 mg (2.38 mmol) of 10-methyl-1,9-(*N*-nitroaziridino)decalin in 100 mL of methanol was stirred and refluxed under nitrogen for 16 h. The methanol was removed in vacuo to give an oil which crystallized. The solid was washed with hexane, filtered, and vacuum dried to give 160 mg (0.66 mmol, 28%) of 1-nitramino-9-methoxy-10-methyldecalin as a cream-colored solid, mp 120–125 °C.

NMR analysis of the crude reaction mixture showed it to also contain trace amounts of 1-nitramino-10-methyl-Δ^8-decalin.

The spectral data were: NMR ($CDCl_3$) τ 1.16–1.70 (br m, 1 H, >NH), 5.40–5.75 (br m, 1 H, $>CHNHNO_2$), 6.80 (s, 3 H, OCH_3), 7.75–9.35 (m, 14 H, aliphatic), 8.87 (s, 3 H, aliphatic methyl); IR ($CHCl_3$) 2.92, 3.40, 6.32, 6.68, 6.93, 7.14, 7.34, 7.49, 8.55, 9.24, 10.46, 11.44, 11.79, 14.34 μm.

Anal. Calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15. Found: C, 59.84; H, 9.25. No molecular ion was found in MS; however, a strong peak due to loss of $\cdot NO_2$ was found. Calcd for $C_{12}H_{22}NO$: 196.1700. Found: 196.1695.

1-Chloro-1α-nitrosoethylcyclohexane.[14] A solution of 50.0 g (0.454 mol) of ethylidenecyclohexane in 250 mL of ether at −78 °C was stirred while nitrosyl chloride was bubbled in for ca. 20 min. The solution rapidly turned dark brown, and a precipitate began to form after ca. 10 min. The mixture was stirred for 1 h, and the precipitate was filtered, washed with ice-cold ether, and vacuum dried to give 52.98 g (0.302 mol, 66%) of 1-chloro-1α-nitrosoethylcyclohexane, mp 130–131.5 °C (lit.[14] mp 134–135 °C). Both NMR and IR were in agreement with the reported spectra.[14]

Methyl 1-Chlorocyclohexylketoxime.[14] A suspension of 20.00 g (113.9 mmol) of 1-chloro-1α-nitrosoethylcyclohexane was stirred in 600 mL of ether at room temperature, while anhydrous hydrogen chloride was bubbled in for 45 min. The suspension was allowed to stir overnight at room temperature, was filtered, and the ether and hydrogen chloride were removed in vacuo. The resultant white solid was recrystallized from hexane to give 13.71 g (78.0 mmol, 68%) of methyl 1-chlorocyclohexylketoxime, mp 80.0–80.5 °C (lit.[14] mp 70–71 °C). Both NMR and IR were in agreement with the reported spectra.[14]

Methyl 1-Chlorocyclohexylnitroketimine.[14] A solution of 11.02 g (62.7 mmol) of methyl 1-chlorocyclohexylketoxime in 800 mL of chloroform at 0 °C was stirred while nitrosyl chloride was slowly bubbled in for ca. 15 min until the solution became reddish brown. The mixture was allowed to return to room temperature while stirring for 1 h. Solid sodium carbonate (15.0 g) was added and stirring was continued for 2.5 h. The mixture was filtered and concentrated in vacuo to give a blue liquid which was taken up in methylene chloride, washed with water and brine, dried, filtered, and concentrated in vacuo to give a blue liquid which was distilled, giving 4.83 g (23.6 mmol, 38%) of methyl 1-chlorocyclohexylnitroketimine, bp 52 °C (0.2 mm). Both NMR and IR were in agreement with the reported spec-

tra.[14]

1-Chloro-1-(α-nitraminoethyl)cyclohexane (28). The acidification technique of Meyers and Nabeya[8] was modified for this imine reduction. To a stirred solution of 4.00 g (19.5 mmol) of methyl 1-chlorocyclohexylnitroketimine in 100 mL of dioxane, 100 mL of absolute ethanol, and 24 drops of glacial acetic acid with an ice/acetone bath for cooling was added 12.8 g of sodium borohydride in small portions to control frothing. The mixture was allowed to stir for 30 min at reduced temperature, 60 drops of glacial acetic acid was added, and stirring was continued for 60 min at reduced temperature, followed by 30 min at room temperature. The mixture was carefully diluted with 400 mL of ca. 3% aqueous acetic acid and extracted with methylene chloride. The organic extracts were dried, filtered, and concentrated in vacuo to give a yellow oil which crystallized from hexane. Recrystallization from hexane yielded 1.66 g (8.03 mmol, 41%) of 1-chloro-1-(α-nitraminoethyl)cyclohexane, mp 84–85 °C (lit.[14] mp 91–92.5 °C). Both NMR and IR were in agreement with the reported spectra.[14]

3-Chloro-3-methyl-2-nitroiminobutane. A solution of 200 g (2.85 mol) of 2-methyl-2-butene in 1200 mL of methylene chloride was stirred at 0 °C while nitrosyl chloride was slowly bubbled into the solution for 1.3 h. The resultant blue solution was stirred for 1.5 h at 0 °C and concentrated in vacuo without heating to give ca. 200 g of 3-chloro-3-methyl-2-butanone oxime as an oily blue-green solid. Further purification was not attempted.

The 200 g of 3-chloro-3-methyl-2-butanone oxime in 1600 mL of methylene chloride was stirred at 0 °C while nitrosyl fluoride was slowly bubbled into the solution for 1.25 h. The green solution was stirred at 0 °C for 3.5 h, followed by 1.5 h at room temperature. The mixture was slowly poured into saturated aqueous sodium carbonate and washed with saturated aqueous sodium carbonate, water, and brine. The organic layer was dried, filtered, and concentrated in vacuo to give a blue oil which was distilled giving 21.00 g (0.128 mol, 4% overall) of 3-chloro-3-methyl-2-nitroiminobutane, bp 48–50 °C (0.5 mm).

The spectral data for the oxime were: IR ($CHCl_3$) 3.01, 3.32, 3.81 (br), 6.36, 6.96, 7.24, 7.32, 7.76, 8.13, 8.71, 9.01, 9.86, 10.06, 10.56, 11.11 μm; NMR ($CDCl_3$) τ 0.56 (s, 1 H, C=NOH), 7.95 (s, 3 H, CH_3C=NOH), 8.23 (s, 6 H, $(CH_3)_2CCl$).

The spectral data for the nitrimine were: IR (neat) 3.40, 3.47, 6.17, 6.36 (s), 6.92, 7.34, 7.65, 7.85, 8.12, 8.72, 9.01, 9.82, 10.12, 10.52, 10.94, 11.52, 11.87, 13.32 μm; NMR ($CDCl_3$) τ 7.76 (s, 3 H, $-C(CH_3)$=N–), 8.17 (s, 6 H, $(CH_3)_2CCl$).

Anal. Calcd for $C_5H_9N_2O_2Cl$: C, 36.49; H, 5.51; N, 17.02; Cl, 21.54. Found: C, 36.30; H, 5.59; N, 17.27; Cl, 21.51.

3-Chloro-3-methyl-2-nitraminobutane (29). The acidification technique of Meyers and Nabeya[8] was modified for this imine reduction. To a stirred solution of 4.04 g (24.6 mmol) of 3-chloro-3-methyl-2-nitroiminobutane in 100 mL of dioxane, 100 mL of absolute ethanol, and 24 drops of acetic acid at 0 °C was added 5.18 g (136 mmol) of sodium borohydride as fast as possible while still controlling frothing. The mixture was allowed to stir for 20 min at 0 °C, 60 drops of glacial acetic acid were added, and stirring was continued for 1 h at 0 °C, followed by 15 min at room temperature. The mixture was carefully diluted with 400 mL of ca. 3% aqueous acetic acid and extracted with methylene chloride. The combined organic extracts were dried, filtered, and concentrated in vacuo to give a light yellow liquid which was taken up in ether, washed with water (to remove dioxane), dried, filtered, and concentrated in vacuo to give a light yellow liquid which was distilled, giving 1.73 g (10.4 mmol, 42%) of 3-chloro-3-methyl-2-nitraminobutane as a clear liquid, bp 60 °C (0.1 mm).

The spectral data were: IR ($CHCl_3$) 2.90, 3.30, 6.35, 6.88, 7.25, 7.45, 7.74, 8.23, 8.75, 8.85, 9.17, 9.68, 11.00, 12.15 μm; NMR ($CDCl_3$) τ 1.45 (br m, 1 H, >NH), 5.56 (br q, 1 H, J = 6.5 Hz, $>CHNHNO_2$), 8.33 (s, 3 H, $CH_3C(Cl)<$), 8.36 (s, 3 H, $CH_3C(Cl)<$), 8.61 (d, 3 H, J = 6.5 Hz, $>C(CH_3)NH-$).

Anal. Calcd for $C_5H_{11}N_2O_2Cl$: C, 36.05; H, 6.66; N, 16.81; Cl, 21.28. Found: C, 36.09; H, 6.52; N, 16.28; Cl, 21.49.

***Registry No.*—5,** 63866-33-1; **6,** 63866-34-2; **7,** 604-35-3; **8,** 1912-54-5; **9,** 31239-32-4; **10,** 31239-36-8; **11,** 63215-89-4; **17,** 13943-77-6; **18,** 63866-35-3; **19,** 63866-36-4; **20,** 63866-37-5; **21,** 63866-38-6; **22,** 63866-39-7; **24,** 1256-31-1; **25,** 4025-59-6; **26,** 63866-40-0; **27,** 63866-41-1; **29,** 63215-91-8; nitric acid, 7697-37-2; 2-hydroxy-10-methyldecalin, 2547-28-6; 2-methyl-2-butene, 513-35-9; 3-chloro-3-methyl-2-nitriminobutane, 63215-90-7; 3-chloro-3-methyl-2-butanone oxime, 3238-16-2.

References and Notes

(1) (a) G. A. M. Butchart, M. F. G. Stevens, and B. C. Gunn, *J. Chem. Soc., Perkin Trans. 1*, **10**, 956 (1975); (b) W. G. Taylor and W. A. Remers, *J. Med. Chem.*, **18**, 307 (1975).
(2) (a) W. Rundel and E. Muller, *Chem. Ber.*, **96**, 2528 (1963); (b) R. D. Clark and G. K. Hemkamp, *J. Org. Chem.*, **29**, 1316 (1964).
(3) Y. Komeichi, S. Tomioka, T. Iwasaki, and K. Watunabe, *Tetrahedron Lett.*, **No. 53**, 4677 (1970).
(4) K. Tanabe and R. Hayashi, *Chem. Pharm. Bull.*, **10**, 1177 (1962).
(5) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964).
(6) W. A. Harison, E. R. Jones, S. D. Meakins, and P. A. Wilkinson, *J. Chem. Soc.*, 3210 (1964).
(7) J. H. Kyung and L. B. Clapp, *J. Org. Chem.*, **41**, 2024 (1976).
(8) A. I. Meyers and A. Nabeya, *Chem. Commun.*, 1163 (1967).
(9) The authors found the quality of the silver acetate to be an important factor. Best results were obtained with silver acetate purchased from Fisher Scientific Company, Fair Lawn, N.J. 07410. Poor quality silver acetate afforded only traces of *N*-nitroaziridine. In general, yields varied from 28 to 82% depending on reaction time and silver acetate quality.
(10) G. A. Boswell, Jr., *J. Org. Chem.*, **33**, 3699 (1968).
(11) J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2503 (1964).
(12) J. A. Marshall and A. R. Hochstetler, *J. Org. Chem.*, **31**, 1020 (1966).
(13) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4765 (1957).
(14) C.-Y. Shiue and L. B. Clapp, *J. Org. Chem.*, **36**, 1169 (1971).

Chirality of Nucleophilic Reactions of Axial Aldehydes and Methyl Ketones in the Diterpene Series

Gerard Aranda, Jean-Marie Bernassau, and Marcel Fetizon*

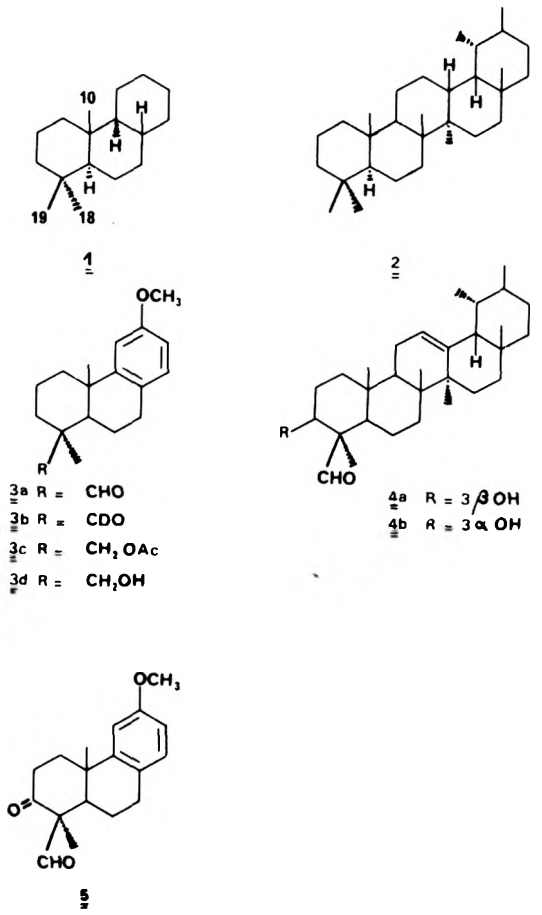
Laboratoire de Synthèse Organique, Ecole Polytechnique Plateau de Palaiseau, 91128, Cedex, France

Received January 28, 1977

The conformation of the 4β aldehyde and methyl ketone groups in the podocarpane series has been reinvestigated. Felkin's hypothesis on the geometry of the most favored transition state for a nucleophilic reaction on these aldehydes and ketones combined with a calculation of the energy profile for the rotation around the C_α—C=O bond gives explanations for both chemical results and NMR data.

I. Introduction

The determination of the most stable conformation of the axial aldehyde group (4β) in the podocarpane **1** or ursane **2** series relies upon the following arguments.[1] (a) In the ^1H NMR spectra the signal associated with the aldehyde proton in a compound such as **3a** appears as a doublet (J = 1.6 Hz)[2] which has been shown to be due to long-range ^4J coupling with the 3α proton. The conformation of 3β-hydroxyaldehyde **4a**

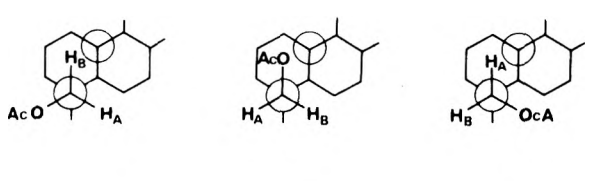


is frozen owing to strong hydrogen bonding (no "free" OH vibration in the IR spectrum). Upon irradiation of the 3α proton the aldehyde doublet merges into a singlet. No such coupling can be detected in the NMR spectra of the 3α-hydroxyaldehyde **4b** or the 3-ketoaldehyde **5**. (b) Reduction of aldehyde **3a** with $LiAlD_4$ is highly stereoselective. It gives an alcohol whose acetate A exhibits a singlet at δ 3.95 in the NMR spectrum instead of the classical quartet found in its nondeuterated counterpart (Figure 1).

Likewise, reduction of the deuterated aldehyde **3b** is nearly stereospecific. The corresponding acetate B gives rise to a singlet at δ 4.26 (Figure 1). In order to get a deeper knowledge of the reduction mechanism, a careful study of the chirality of acetates A and B was undertaken.

II. Nuclear Overhauser Effect in the Acetates

In the NMR spectrum of acetate **3c** the two protons bonded to C-19[3] are expected to appear as an AB quartet.[4,5] In fact, each of the two A lines is split into two parts of equal intensity (J = 0.5 Hz).[6] No modification of the shape of this multiplet was observed between −40 and 110 °C. Thus one of the conformations must be highly favored. A reasonable assumption is that the *most stable conformation can be represented by* **6a**.[7] Rotamer **6b** is ruled out, since the acetate moiety is too



6a 6b 6c

bulky for its having any tendency to rest close to the angular methyl group. Rotamer **6c** cannot be accepted either without violating the present status of ^4J σ coupling, i.e., upon irradiation of any of the two methyl groups no simplification of the A part of the signal taking place.

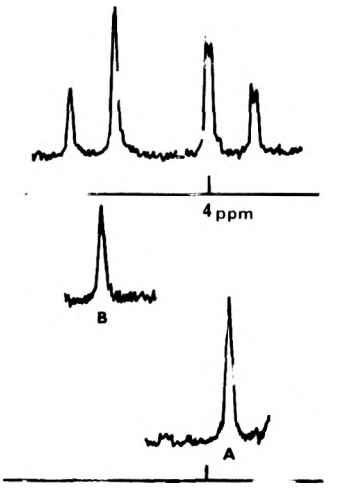


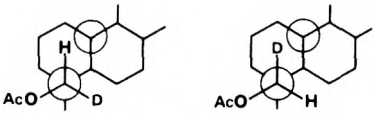
Figure 1.

Table I. Chemical Shifts of the Two CCH_3 Groups of Podocarpinol *O*-Methyl Ether 3d in Various Solvents[a]

Solvent	δ Me-18, ppm	δMe-20, ppm
CCl_4	1.18	1.02
$CDCl_3$	1.19	1.04
$CCl_2{=}CCl_2$	1.15	1.01
Pyridine	1.21	1.22

[a] Me_4Si as internal reference.

If the assumption is correct, it should be easy to determine the chirality of the two previously mentioned deuterated acetates A and B, either **7** or **8**, by NMR spectroscopy. Upon



7 8

irradiation of the angular methyl groups the nuclear Overhauser effect (NOE) on the italicized proton of the $CH_3COOCHD$ group should be higher in **7** than in **8**. It is therefore necessary to make sure that the designation of the two CCH_3 signals is correct.

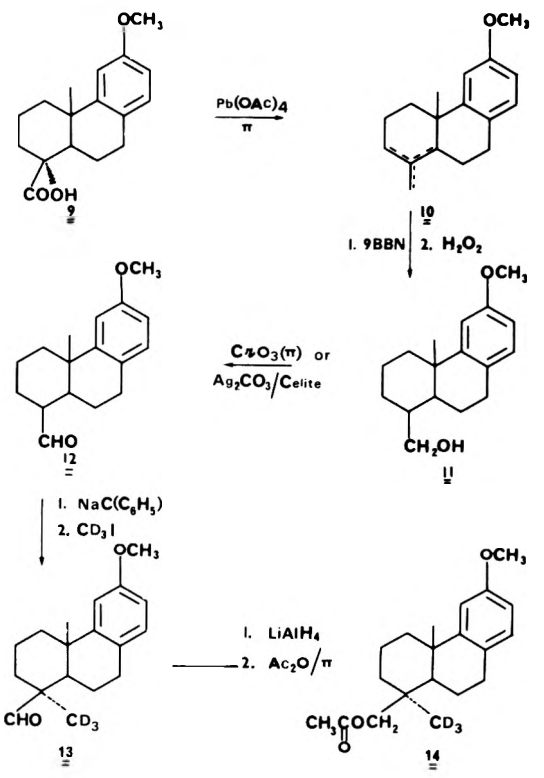
According to Wenkert[8] the peak observed at 1.20 ppm is due to the angular methyl group. However, NOE experiments, carried out on the basis of this assignment and the previously accepted reaction mechanism of aldehyde reduction, led to results inconsistent with the hypothesis of rotamer **6a** being the most stable conformer. Thus it was necessary to check Wenkert's assignment, however sound it seems to be.[9] Thus a synthesis of the deuterated acetate **14** (Scheme I) was undertaken. Decarboxylation of podocarpic acid *O*-methyl ether **9** by lead tetraacetate in pyridine[10] gives a mixture of three olefins which without separation was converted to the noralcohol **11** by hydroboration (9-BBN)[11] and then to the noraldehyde **12** on oxidation with Collins reagent or silver carbonate on Celite. The crude aldehyde was alkylated with trideuteriomethyl iodide in the presence of triphenylmethyl sodium in a mixture of diethyl ether and dimethylformamide.[12] The resulting aldehyde **13**, which has the same melting point as *O*-methylpodocarpinal,[13] exhibits in its NMR spectrum a doublet at 9.70 ppm (J = 1.5 Hz) indicative of an axial

Table II. Chemical Shifts of Podocarpane and Podocarpane-*18*-d_3 derivatives[a]

Registry no.			
16826-83-8	Podocarpinal *O*-methyl ether **3a**	1.05	1.07
63533-65-3	Podocarpinal-*18*-d_3 *O*-methyl ether **13**		1.07
16826-86-1	Podocarpinol *O*-methyl ether **3d**	1.04	1.19
63533-66-4	Podocarpinol-*18*-d_3 *O*-methyl ether		1.20
16826-82-7	Podocarpinol *O*-methyl ether acetate **3c**	1.04	1.20
63533-67-5	Podocarpinol-*18*-d_3 *O*-methyl ether acetate **14**		1.21

[a] In parts per million in $CDCl_3$ with Me_4Si as internal standard.

Scheme I



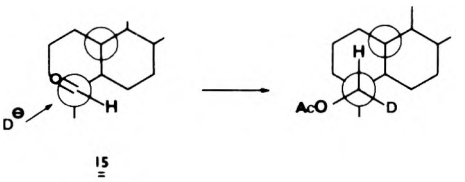
aldehyde group[1,14] and a CCH_3 singlet at 1.06 ppm, in agreement with the published data. Lithium aluminium hydride reduction of the aldehyde gave a carbinol which was converted ultimately into its acetate **14**. A comparison between the NMR spectra of the deuterated and nondeuterated acetates **4** and **3c**, respectively, shows that the signal at 1.20 ppm assigned by Wenkert to the angular methyl group had been assigned correctly (Table II). This point settled firmly, the NOE of acetates A and B was measured (Table II) and showed them to have structures **8** and **7**, respectively.

Discussion of the Experimental Results

The NOE result raises a question, since the earlier interpretation of the experimental data[1] had led to opposite chiralities for the two deuterated acetates.[1] Were aldehyde **3a** to react in its most stable conformation **15** and the reducing agent to arrive from the less hindered side, acetate A (from lithium aluminium deuteride reduction of the aldehyde group, followed by acetylation) should be **7**, i.e., 19*S*.

Similarly acetate B (from lithium aluminium hydride reduction of the deuterioaldehyde group followed by acetylation) should be **8**, i.e., 19*R*.

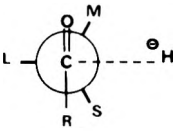
Therefore, either the basic assumption on which the interpretation of the NOE data relies is wrong or the reduction mechanism is more subtle than interpreted. In order to check



15

16

our hypothesis on the most stable acetate rotamer we have calculated the energy profile for the rotation of the C-4-axial substituent around the C-4β bond with the molecular mechanics method developed by Allinger.[15-17] The calculated rotational profile[18] is shown in Figure 2 and indicates the most stable conformation to be the predicted one. Hence the chirality of the deuterated acetates, deduced from NOE, is established. Various geometries of the transition state for the $LiAlH_4$ reduction of a carbonyl group have been proposed.[19-23] Recently the validity of Felkin's model has been established as a result of ab initio calculations.[24] The lithium aluminium hydride reagent, however, always has been considered as a bare H^- ion, neither the lithium cation nor any solvent being taken into account. The transition state has been represented by **17** (L = large, M = medium, S = small), the incipient car-

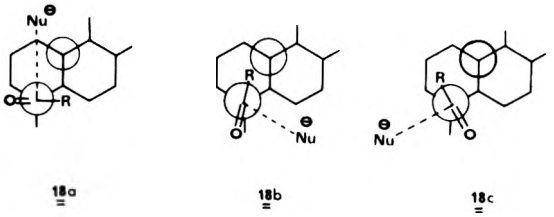


17

bon–hydrogen bond being antiperiplanar with respect to the bond between the α carbon and the bulkier (L) group attached to it.

In the case of aldehydes **3a** or **3b** six such transition states must be considered (**18a-f**; R = H or D, Nu = D or H, respectively). The stability of the required conformation of the aldehyde group was estimated with the "force field" program (Figure 3).[25]

Transition states **18b** and **18e** are ruled out on the basis of the high interaction energy between the angular methyl group and the oxygen or hydrogen (deuterium) of the aldehyde



18a 18b 18c

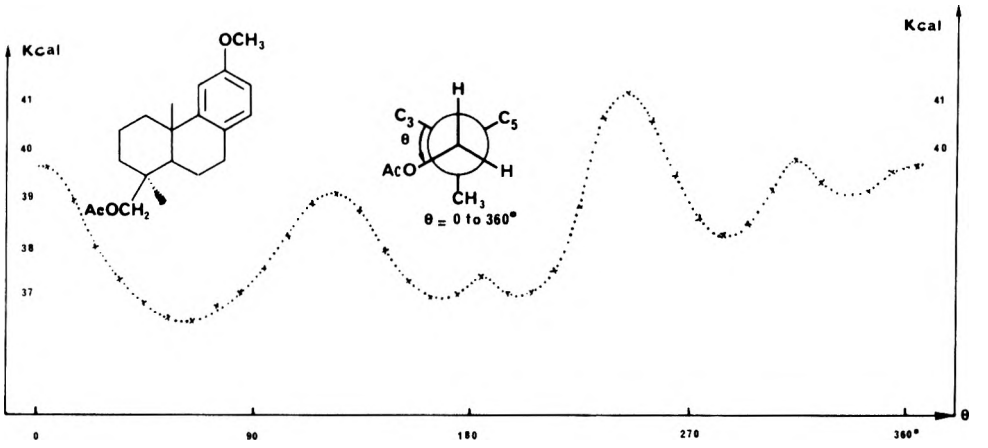


Figure 2.

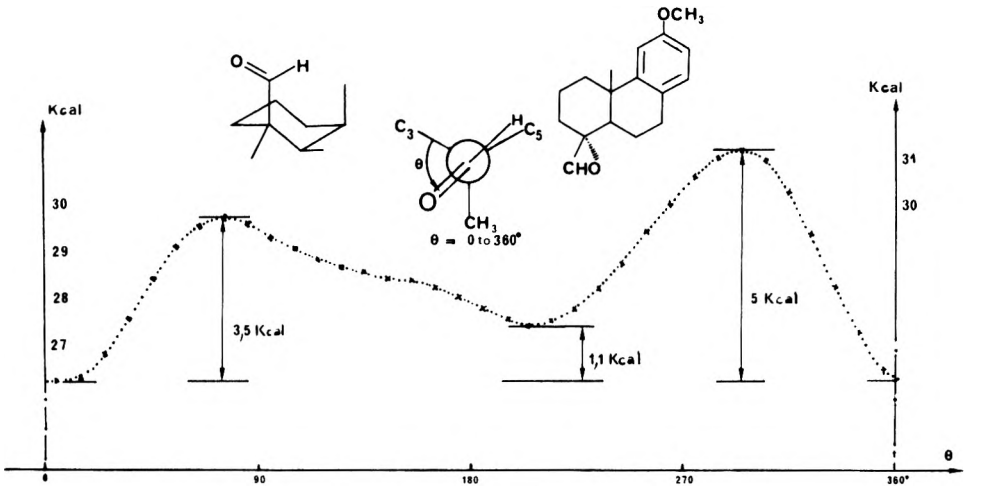
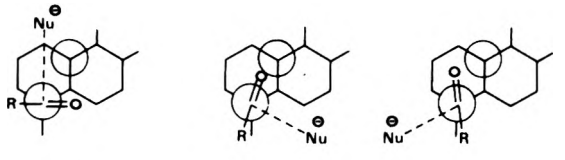


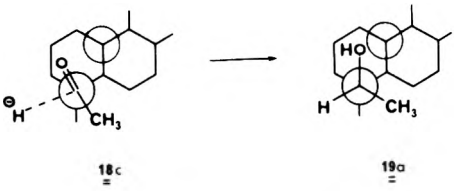
Figure 3.

(deuterioaldehyde) group. Transition states **18a** and **18d** may be excluded also, since steric hindrance impedes the required antiperiplanar attack of the deuteride (hydride) ion. The energies of the aldehyde conformations in the last two transition states **18c** and **18b** are approximately the same (although **18c** seems to be slightly more stable than **18b**).



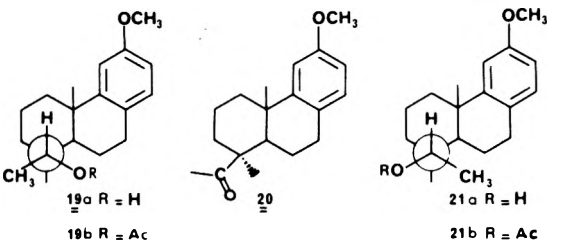
18d **18e** **18f**

Unfortunately the program cannot accommodate the presence of a solvated lithium cation in the neighborhood of the oxygen, the increase of electron density on this oxygen, and the elongation of the carbon–oxygen bond. All these factors destabilize transition state **18f**[26] and suggest the aldehyde reduction to proceed via transition state **18c**. This conclusion, the opposite of the one previously accepted, is substantiated fully by the NOE results. Similarly, a reaction of methyllithium with the aldehyde **3a** (R = H, Nu = CH_3) should give the secondary alcohol **19a** through transition state **18c**. The alcohol thus is expected to he the 19*R* isomer. Indeed this reaction has been found to be highly stereoselective.[27] Moreover, the same alcohol is the major component of the 94:6 mixture of carbinols obtained by $LiAlH_4$ reduction of the parent



18c **19a**

methyl ketone **20**. The energy profile for the internal rotation around the C-4β bond of this ketone has been calculated (Figure 4). Among the six transition states (**18a–f**; R = CH_3, Nu = H) five may be disregarded either on the basis of the high energy of the required conformation (**18b**, **18c**, and **18e**) or because of steric hindrance in the approach of the nucleophile (**18a** and **18d**). The remaining transition state **18f** is expected to lead to the 19*R* isomer **19a**, in agreement with the experimental findings. Horeau's analysis of the chirality of carbon centers shows the stereochemistry of both the major and minor secondary alcohols **19a** and **21a** to be correct.[28,29]



19a R = H **20** **21a** R = H

19b R = Ac **21b** R = Ac

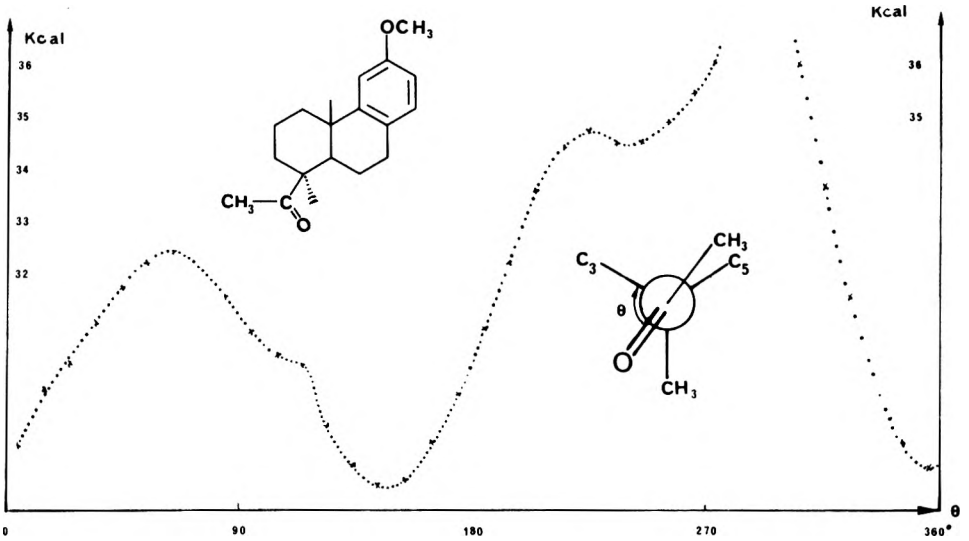


Figure 4.

It is noteworthy that NOE gives approximately the same values for the acetates **19a** and **7**, thereby confirming the chirality of the latter compound (*regardless of the stereochemistry of* **19b**). The most stable conformation of 19*S*-acetate is represented by **21b**. In both 19*R* and 19*S* isomers the C-19 proton is located the same distance from the angular methyl group.

Conclusion

Felkin's hypothesis on the geometry of the most favored transition state for the nucleophilic attack on an aldehyde or methyl ketone proved to be reliable. Therefore a combination of this assumption and of a calculation of the energy profile for the rotation around the C_α—C=O bond appears to be extremely valuable for the prediction of the course of such reactions.

Experimental Section

General. Melting points (Köfler microscope) were not corrected. The IR spectra were recorded on a Perkin-Elmer 577 spectrophotometer. Unless stated otherwise, the NMR spectra were obtained either on a Varian T60 or NV14 in CCl_4 or $CDCl_3$ with tetramethylsilane as internal standard. Nuclear Overhauser effects were measured on a Varian XL-100, in sealed tubes, the solution being carefully degassed.

Podocarpic Acid *O*-Methyl Ether. It was prepared from methyl podocarpate *O*-methyl ether according to a published procedure:[31] mp 154–156 °C.

Oxidative Decarboxylation of Podocarpic Acid *O*-Methyl Ether. It was carried out according to Bennett and Cambie's method:[10] 8.55 g of the acid gave 3.85 g of a mixture of the three expected olefins, which could not be separated and was used as such for the next step.

18-Nor-19-hydroxy-12-methoxypodocarpa-8,11,13-triene (11). To 3.85 g of the preceding mixture in 30 mL of dry THF, 30 mL of a 0.50 M solution of 9-BBN in THF was added dropwise at 0 °C under a dry nitrogen atmosphere. After 48 h at room temperature, the clear solution is treated with 5 mL of 6 N NaOH and 4 mL of H_2O_2 (110 vol). After the usual workup, the oily substance is separated by chromatography on silica gel. A mixture of Δ^3 and Δ^4 olefins is eluted first, followed by the expected primary alcohol **11** (2.02 g).

A careful analysis (TLC) indicated that two isomers (roughly 3:1) (R_f 0.55 and 0.58, hexane/diethyl ether, 7:3) are formed. However, they could not be separated in a preparative scale. NMR (CCl_4): 1.13 and 3.66 (minor compound), 1.01 and 3.66 ppm (major compound).

Aldehyde 12. (**a**) The preceding alcohol mixture (0.476 g) and 15 g of Ag_2CO_3/Celite in 100 mL of benzene are refluxed under argon for 24 h. After filtration of the solid, evaporation of benzene, and chromatography of the resulting oil, 0.242 g of aldehyde **12** (a mixture of axial and equatorial isomers) is obtained.

(**B**) The alcohol mixture (0.473 g) is oxidized by Collins reagent (from 1.2 g of CrO_3 and 1.9 g of pyridine in 30 mL of CH_2Cl_2) for 15 min at room temperature. After the usual workup, the mixture of the axial and equatorial aldehydes is separated by preparative thin-layer chromatography; 0.115 g are thus obtained: IR 1710 cm^{-1} (ν C=O); NMR 0.98 (s, 10-CH_3), 3.68 (OCH_3), 9.89 ppm (br s, -CHO) (major compound); NMR 1.06 (s, 10-CH_3), 3.68 (OCH_3), 9.68 ppm (d, J = 1.0 Hz, -CHO) (minor compound).

***O*-Methylpodocarpinal-*18-d*$_3$ (13).** A mixture of the preceding aldehydes (0.158 g) in 22 mL of dry DMF was added dropwise, under argon, to 22 mL of a solution of 0.028 M of triphenylmethyl sodium in diethyl ether.[30] Freshly distilled methyl-d_3 iodide (3 mL) was added. The reaction mixture was refluxed for 15 h, and then poured in 120 mL of 3 N hydrochloric acid. After the usual workup and chromatography on silica gel, 0.088 g of the crystalline aldehyde was isolated. It was recrystallized twice in hexane/diethyl ether: mp 135–137 °C (nondeuterated podocarpinal, mp 135–136 °C[1]); IR (CCl_4) 2214 (ν -CD_3) and 1713 cm^{-1} (ν C=O); NMR (CCl_4) 1.04 (10-CH_3), 9.70 ppm (CHO, d, J = 1.25 Hz); NMR ($CDCl_3$) 1.06 (10-CH_3), 9.65 ppm (d, J = 1.25 Hz, CHO).

Podocarpinol-*18-d*$_3$ *O*-Methyl Ether. Podocarpinol-*18-d*$_3$ (0.042 g) in 6 mL of diethyl ether was reduced at 0 °C by 0.05 g of $LiAlH_4$ in 8 mL of diethyl ether. The resulting alcohol (oil, 0.042 g) was purified by TLC and crystallized as white needles: mp 88.5–90 °C (hexane); IR (CCl_4) 3608 cm^{-1}; NMR (CCl_4) 1.19 (10-CH_3), 3.78 ppm (s, OCH_3); NMR ($CDCl_3$) 1.20 (s, 10-CH_3), 3.78 ppm (s, OCH_3).

NOE Measurements. Nuclear Overhauser effect measurements have been carried out in the CW or FT modes either on a Varian HA 100 or a Varian XL-100. The concentrations of the samples were 0.25 × 10^{-4} mol/L (FT mode) and 1 × 10^{-4} mol/L (CW mode). The solutions were degassed three times and the tubes were sealed.

Acknowledgments. We thank Professor N. L. Allinger for kindly sending the "force field" program, Professor R. Bell, in whose laboratory most of the NOE experiments have been carried out, and the C.N.R.S. for generous financial support.

Registry No.—**9**, 10037-26-0; Δ^3-**10**, 54168-28-4; Δ^4-**10**, 13740-16-4; **11** isomer 1, 63533-68-6; **11** isomer 2, 63533-69-7; **12** isomer 1, 63597-43-3; **12** isomer 2, 23962-85-8.

References and Notes

(1) M. Fetizon, G. Moreau, and N. Moreau, *Bull. Soc. Chim. Fr.*, 3295 (1968).
(2) Contrastingly the same proton of an equatorial aldehyde gives rise to a sharp singlet.[1]
(3) The Rowe nomenclature and numbering has been used throughout the text: J. W. Rowe, "The Common and Systematic Nomenclature of Cyclic Diterpenes", Forest Products Laboratories, USDA, 1968.
(4) A. Gaudemer, J. Polonsky, and E. Wenkert, *Bull. Soc. Chim. Fr.*, 407 (1964).
(5) By convention, in an AB quartet part A appears at higher field than part B.
(6) Such small coupling is difficult to observe. In particular, it is necessary to strip the molecular oxygen from solution.
(7) If this assumption is correct, proton H_A should be coupled with the 3α-

proton. It therefore would be associated with the A part of the observed spectrum.
(8) E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, J. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965).
(9) Interpretation of the solvent effect on the chemical shifts of the two CCH_3 groups of podocarpinol *O*-methyl ether **3d** is questionable (Table I).
(10) C. R. Bennet and R. C. Cambie, *Tetrahedron*, **23**, 927 (1967).
(11) E. F. Knights and H. C. Brown, *J. Am. Chem. Soc.*, **90**, 5280 (1968).
(12) S. W. Pelletier and D. L. Herald, *Chem. Commun.*, 11 (1971).
(13) No depression of the melting point was observed when the latter aldehyde was mixed with authentic *O*-methylpodocarpinal. The crude alkylation product contains about 50% of the enol ether of **12**.
(14) The occurrence of such a doublet in the deuterated aldehyde confirms the previously described spin decoupling experiments, there being no coupling between the aldehyde proton and the 4α-methyl group.
(15) N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Am. Chem. Soc.*, **93**, 1637 (1971).
(16) D. H. Wertz and N. L. Allinger, *Tetrahedron*, **30**, 1579 (1974).
(17) N. L. Allinger and J. T. Sprague, *J. Am. Chem. Soc.*, **95**, 3893 (1973).
(18) The computation of the energy of a given conformation of the acetate **3c** takes about 3 min with the IBM 370/168 computer. Thirty seven points (every 10°) were calculated.
(19) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).
(20) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959).
(21) G. J. Karabatsos, *J. Am. Chem. Soc.*, **89**, 1367 (1967).
(22) M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2201 (1968).
(23) M. Cherest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968).
(24) N. T. Anh and O. Eisenstein, *Tetrahedron Lett.*, 155 (1976).
(25) As expected in the most stable conformation the carbonyl group and the C(3)–C(4) bond are eclipsed.
(26) They all contribute to increasing the bulk of the oxygen of the carbonyl dipole.
(27) M. Fétizon, G. Moreau, and N. Moreau, *Bull. Soc. Chim. Fr.*, 1614 (1969).
(28) By the use of Karabatsos's transition state for the prediction of the reaction course we once believed[27] that the lithium aluminium hydride reduction of **20** would give 19*S* secondary alcohol. Hence we thought that the major compound, now known to be 19*R*, represented an exception to Horeau's rule, now shown to be an erroneous assumption.
(29) A. Horeau and H. B. Kagan, *Tetrahedron*, **20**, 2431 (1964).
(30) "Organic Syntheses", Collect. Vol. 2, Wiley, New York, N.Y., 1963, p 607.
(31) G. Aranda and M. Fetizon, *Synthesis*, 330 (1975).

Notes

Kinetics and Mechanism of Ynamine–Isocyanate Additions[1]

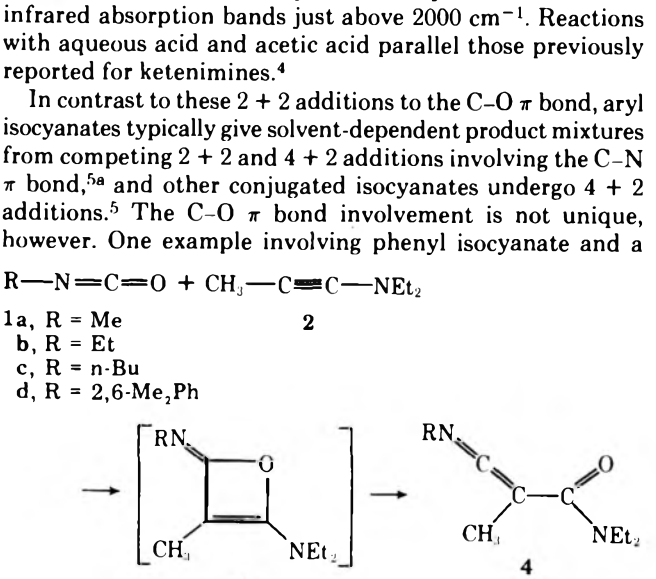
James U. Piper,* Maryanne Allard, Maureen Faye, Lisa Hamel,[2] and Virginia Chow

Department of Chemistry, Simmons College, Boston, Massachusetts 02115

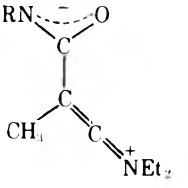
Received May 18, 1976

Alkyl isocyanates **1a–c** and the ortho-blocked aryl isocyanate **1d** react with 1-diethylaminopropyne to give ketenimines.[3] The products are easily identified by their characteristic infrared absorption bands just above 2000 cm^{-1}. Reactions with aqueous acid and acetic acid parallel those previously reported for ketenimines.[4]

In contrast to these 2 + 2 additions to the C–O π bond, aryl isocyanates typically give solvent-dependent product mixtures from competing 2 + 2 and 4 + 2 additions involving the C–N π bond,[5a] and other conjugated isocyanates undergo 4 + 2 additions.[5] The C–O π bond involvement is not unique, however. One example involving phenyl isocyanate and a cyanoynamine has been reported,[6] and a reexamination of the reaction of phenyl isocyanate with **2** indicates that in CCl_4 a ketenimine (IR 2010 cm^{-1}; NMR δ 1.92 (s)) forms and disappears in the reaction mixture. We have not been able to determine the fate of the ketenimine.



These reactions are very solvent dependent. In acetonitrile, phenyl isocyanate and **2** react rapidly to produce the 4 + 2 adduct. No intermediates are detectable by IR or NMR. Ketenimine **4d** also forms rapidly and in high yield in acetonitrile but slowly and in poor yield in CCl_4. Solvent effects are expected to be significant for reactions which proceed through zwitterionic intermediates such as **7**,[7] and ynamine reactions



7

are characteristically solvent sensitive.[8] For that reason it was surprising to find that the alkyl isocyanate reactions did not show either product or significant rate dependence on solvents. The rate of the reaction of **2** with methyl isocyanate was followed by NMR and found to be first order in each reactant with rate constants as shown in Table I. The factor of 8 difference between rate constants in benzene and acetonitrile at 34 °C can be compared to factors of 10^3–10^4 for tetracyanoethylene/enol ether additions for which a zwitterionic intermediate has been established.[7] From the temperature dependence of the rate constant in benzene, values of 13 ± 2 kcal/mol and −31.5 ± 5 eu can be derived for the activation

Table I. Solvent and Temperature Dependence of Rate Constants for Formation of 4a

Solvent	T, °C	$k \times 10^4$, M^{-1} s^{-1}
C_6H_6	16	0.45 ± 0.05
C_6H_6	34	1.8 ± 0.1
C_6H_6	56	8.8 ± 0.5
$C_6H_5NO_2$	34	9.5 ± 1.0
C_6H_5CN	34	8.0 ± 0.5
CD_3CN	34	15.3 ± 1.6

enthalpy and entropy, respectively. The negative activation entropy indicates that the rate-determining step involves formation of either **3** or **7**.

Uncertainties in the interpretation of solvent effects make it impossihle to rule out **7** as an intermediate in the alkyl isocyanate reactions. At least two cases exist in which the formation of a polar intermediate from less polar reactants will not be reflected in solvent effects. A reaction which proceeds through an electronically early transition state which does not reflect the character of the intermediate will be solvent insensitive.[9] A more likely consideration for the alkyl isocyanate reactions is the possibility of offsetting solvent effects in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$,[10] a point which is difficult to probe because of the stringent requirements on the precision of the rate constants.[11] The probability that the measured rate constants contain contributions from partitioning of **7** between starting materials and **3** has heen discussed by Huisgen.[12]

Experimental Section

Spectra were obtained from the following instruments: IR, Beckman IR20; NMR, Hitachi Perkin-Elmer R-20; MS, DuPont Instruments 21-491. Melting points and boiling points are uncorrected.

***N,N*-Diethyl-2-methyl-3-(alkylimino)-2-propenamides 4a–c.** A solution of 0.03 mol of isocyanate and 0.03 mol of dietbylamino-1-propyne in 50 mL of dry carbon tetrachloride or benzene was allowed to stand 3–5 days under nitrogen at room temperature. After concentration under reduced pressure, tbe residue was distilled.

From methyl isocyanate **4a** was obtained in 78% yield: bp 73–6 °C (0.3 mm) [lit.[3b] bp 70 °C (0.2 mm)]; IR (CCl_4) 2010, 1615 cm^{-1}; NMR (CCl_4) δ 1.10 (t, 6 H), 1.73 (s, 3 H), 3.21 and 3.31 (overlapping s and q, 7 H).

From ethyl isocyanate **4b** was obtained in 67% yield: bp 67–9 °C (0.3 mm); IR (CCl_4) 2010, 1615 cm^{-1}; NMR (CCl_4) δ 1.09 and 1.27 (overlapping triplets, 9 H), 1.73 (s, 3 H), 3.30 and 3.47 (overlapping quartets, 6 H); mass spectrum, *m/e* 81 (B), 109, 167, 182. Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.90; H, 9.95; N, 15.37. Found: C, 65.67; H, 9.90; N, 15.39.

From *n*-butyl isocyanate **4c** was ohtained in 51% yield: bp 89–91 °C (0.3 mm); IR (CCl_4) 2010, 1615 cm^{-1}; NMR (CCl_4) δ 1.10 (t, 3 H), 0.9–1.7 (m, 10 H), 1.72 (s, 3 H), 3.29 and 3.42 (overlapping q and t, 6 H). Anal. Calcd for $C_{12}H_{22}N_2O$: N, 13.32. Found: N, 13.25.

***N,N*-Diethyl-2-methyl-3-(2,6-dimethylphenylimino)-2-propenamide (4d).** To a solution of 2.94 g (0.02 mol) of 2,6-dimethylphenyl isocyanate in 10 mL of acetonitrile under nitrogen and in a room-temperature water bath was added a solution of 2.72 g (0.02 mol) of diethylamino-1-propyne in 10 mL of acetonitrile dropwise with stirring over 20 min. The resulting solution was concentrated under reduced pressure at 50 °C. The residue showed only product NMR absorptions. Distillation gave a small forerun of unchanged isocyanate and 1.8 g (35%) of the ketenimine: bp 144–9 °C (0.4 mm); IR (CCl_4) 2015, 1610 cm^{-1}; NMR (CCl_4) δ 1.08 (t, 6 H), 1.90 (s, 3 H), 2.34 (s, 6 H, 3.36 (q, 4 H), 6.93 (s, 3 H). A large pot residue appeared to be polymeric material. Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.17; H, 8.65; N, 11.02.

***N*-Alkyl-*N',N'*-diethyl-2-methylpropanediamides 5b and 5c.** The addition of 1.0 g of the ketenimine to 15 mL of cold, 6 M hydrochloric acid resulted in a clear solution which was extracted several times with chloroform. The extracts were dried over anhydrous sodium sulfate and concentrated, and the residue was distilled.

The amide **5b** was obtained in 50% yield: bp 85–90 °C (0.3 mm); IR (CCl_4) 3340, 1675, 1635, 1530 cm^{-1}; NMR (CCl_4) δ 1.07 (t), 1.16 (t), 1.31 (d) all overlapping (12 H), 3.0–3.5 (m, 6 H), 6.9 (hroad s, 1 H).

The amide **5c** was obtained in 75% yield as a waxy solid: bp 90–95 °C (0.3 mm); mp 43–5 °C; IR (CCl_4) 3340, 1675, 1632, 1530 cm^{-1}; NMR (CCl_4) δ 0.8–1.6 (m, 16 H), 2.9–3.6 (m, 7 H), 7.2 (broad s, 1 H). Anal. Calcd for $C_{12}H_{24}N_2O_2$: C, 63.12; H, 10.59; N, 12.27. Found: C, 63.32; H, 10.80; N, 12.48.

***N*-(1-Butyl)-*N*-acetyl-*N',N'*-diethyl-2-methylpropanediamide (6c).** To a solution of 1.6 g (9.5 mmole) of ketenimine **4c** in 10 mL of CCl_4 under nitrogen was added a solution of 0.57 g (9.5 mmol) of anhydrous acetic acid in 5 mL of CCl_4. An exothermic reaction occurred which was complete within an hour. The solution was concentrated and the residue was distilled giving 1.0 g of **4c**: bp 58–60 °C (0.3 mm); IR (CCl_4) 1660 cm^{-1}, unresolved band; NMR (CCl_4) δ 1.03 (t, 6 H), 1.50 (d, 3 H), 1.87 (s, 3H), 2.85 and 2.92 (overlapping s and q, 7 H), 4.13 (q, 1 H). Anal. Calcd for $C_{11}H_{26}N_2O_3$: C, 57.87; H, 8.83; N, 12.27. Found: C, 57.75; H, 8.80; N, 12.38.

Kinetics. Diethylamino-1-propyne was obtained from Columbia Organic Chemicals and redistilled under nitrogen. Methyl isocyanate was redistilled immediately before use. Solvents were reagent grade, redried, and distilled. For 34 °C runs (ambient probe temperature for the thermostated permanent magnet) 0.5 to 1 M solutions of the two reactants were mixed at 34 °C and an aliquot in a NMR sample tube was kept in the prohe throughout the entire run. For high- or low-temperature runs, the reaction was carried out in a constant temperature bath (± 0.2 °C) and aliquots were withdrawn periodically. The probe was maintained at the same temperature (± 1 °C) as determined by ethylene glycol or methanol calibration spectra. Integrals were recorded as the average of four sweeps at 60 or 120 Hz sweep widths and 1 Hz/s sweep times. The rf level was kept well helow saturation, generally 500 μV. The integrals were reproducible within ±4% and tbe instrument stability was such as to necessitate no rebalancing of the integration circuit throughout the course of a run. The peaks monitored were those of the C-methyl singlets of the ynamine, ketenimine, and isocyanate. Trial runs indicated that the ketenimine did not react with either the ynamine or the isocyanate under the reaction conditions.

The rate constants reported in Table I are averages of three independent runs. Second-order plots for the reactions in benzene were linear through 75% completion. In other solvents, curvature was noticeable after 50% completion.

Registry No.—**1a**, 624-83-9; **1b**, 109-90-0; **1c**, 111-36-4; **1d**, 28556-81-2; **2**, 4231-35-0; **4a**, 36277-29-9; **4b**, 63815-28-1; **4c**, 63797-98-8; **4d**, 63797-99-9; **5b**, 63798-00-5; **5c**, 63798-01-6; **6c**, 63798-02-7.

References and Notes

(1) Supported by grants from the Research Corporation and the Simmons College Fund for Research.
(2) Deceased.
(3) (a) J. U. Piper, M. B. Allard, and V. Lee, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D.C., September 1971, ORGN 103; (b) J. Ficini and J. Pouliquen, *Tetrahedron Lett.*, 1139 (1972).
(4) C. L. Stevens and M. E. Munk, *J. Am. Chem. Soc.*, **80**, 4065 (1958).
(5) (a) M. E. Kuehne and P. J. Sheeran, *J. Org. Chem.*, **33**, 4407 (1968); M. E. Kuehne and H. Linde, *ibid.*, **37**, 1846 (1972); (b) H. J. Gais and K. Hafner, *Tetrahedron Lett.*, 5101 (1970); (c) G. J. Mikol, Abstracts, 166th National Meeting of the American Chemical Society, Chicago, Ill., August 1973, ORGN 102.
(6) M. E. Kuehne and H. Linde, *J. Org. Chem.*, **37**, 1846 (1972).
(7) R. Huisgen, *Acc. Chem. Res.*, **10**, 117 (1977).
(8) J. Ficini, *Tetrahedron*, **32**, 1449 (1976).
(9) D. C. Wigfield and B. Lem, *Tetrahedron*, **31**, 9 (1975).
(10) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, N.Y., 1963, p 324.
(11) R. C. Petersen, J. H. Markgraf, and S. D. Ross, *J. Am. Chem. Soc.*, **83**, 3819 (1961).
(12) R. Huisgen and G. Steiner, *Tetrahedron Lett.*, 3769 (1973).

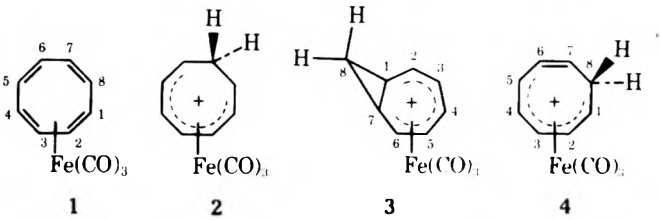
Organometallic Chemistry. 16.[1a] Carbon-13 Nuclear Magnetic Resonance Spectroscopic Structural Investigation of Protonated Cyclooctatetraeneiron Tricarbonyl in Superacid Solution

George A. Olah,* [1b] Gao Liang, and Simon Yu

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

Received February 8, 1977

Cyclooctatetraeneiron tricarbonyl **1**[2] has been extensively studied as one of the earliest examples of the fluxional behavior of organometallic compounds.[3] Both proton[4] and carbon-13[5] NMR spectroscopic studies have unequivocally



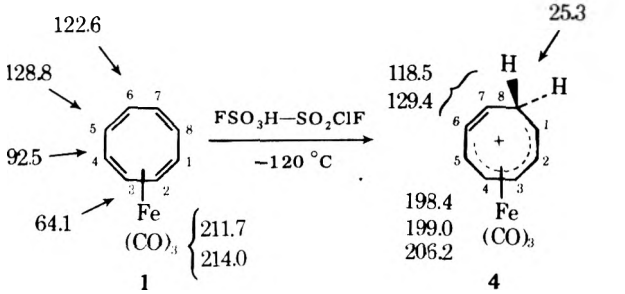
1 **2** **3** **4**

shown that simple 1,2″ shifts are responsible for the fluxional behavior of **1** and its analogues.[5] Complex **1** was first converted, via protonation in etheral solution of fluoroboric acid, into a tetrafluoroborate salt by Schrauzer and thought to be cyclooctatrienyliron tricarbonyl cation **2**.[6] A year later, Davison, McFarlane, Pratt, and Wilkinson refuted structure **2** and unequivocally presented structure **3** to be the actual cation formed.[7] At even lower temperature (−120 °C), Brookhart and co-workers were able to obtained the monocyclic cyclooctatrienyliron tricarbonyl cation **4** initially formed from **1** by protonation in FSO_3H–SO_2F_2 solution.[8] Structure **4** was confirmed by their proton NMR spectroscopic study. Furthermore, upon warming the solution of **4** to −60 °C, cation **3** was quantitatively formed via a first-order electrocyclic ring-closure reaction.

Our recent report of the ^{13}C NMR study of σ–π complex formation in strong acid solution[9] prompts us to describe the ^{13}C NMR study of protonated cyclooctatetraeneiron tricarbonyl **1** under stable ion conditions.

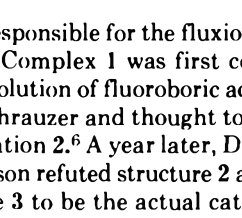
Results and Discussion

^{13}C NMR Spectroscopy Study of Protonated Cyclooctatetraeneiron Tricarbonyl at −120 °C. Cotton[5a] and Giacometti[5c] separately reported the ^{13}C NMR spectra of cyclooctatetraeneiron tricarbonyl **1** at various temperatures. **1** shows only a doublet at δ 102.1 (J_{CH} = 160 Hz) and a carbonyl singlet at δ 213.5 at 0 °C. The doublet splits into four doublets at δ 128.8, 122.6, 92.5, and 63.7 at −120 °C, while the carbonyl splits into two singlets at δ 214.0 and 211.7 in a ratio of 2:1. Addition of the solution of **1** in SO_2ClF to FSO_3H–SO_2ClF at −120 °C results in a light-yellow solution which gives an ^1H NMR spectrum identical with that reported by Brookhart.[8]



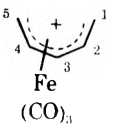
1 **4**

The proton-decoupled ^{13}C NMR spectrum of **4** in FSO_3H–SO_2ClF solution at −90 °C consists of eight carbon resonances in the organic region and three in the carbonyl region. According to the off-resonance ^{13}C NMR spectrum, the signal at δ 25.3 is a triplet which naturally can be assigned to the methylene carbon C_8. The two lowest field shifts δ 118.5 and 129.4 (both are doublets) in the olefinic region can be attributed to C_6 and C_7 since they resemble the olefinic carbon (uncomplexed) atoms (C_5–C_8) of **1**. C_6 should experience inductive deshielding from the neighboring positive charge more than C_7 does. The lower field shift at δ 129.4 is thus assigned to C_6. The other five carbon shifts at higher field are divided into three groups: δ 94.1 and 98.1 (both show $J_{CH} \sim 174$ Hz), 70.9 and 73.4 ($J_{CH} \sim 160$ Hz), and 105.7 (J_{CH} = 184.0 Hz). These shifts are assigned to the five pentadienyl carbon atoms (C_1–C_5) since they are apparently complexing with $Fe(CO)_3$ which induces substantial shielding toward these carbon atoms. This is clearly seen in the case of the open-chain analogue **5** previously reported by us.[9] The terminal positions (C_1 and C_5) in ion **5** show the smallest magnitude of J_{CH} (in Hz), and the central position (C_3) shows the largest value of J_{CH}. According to this order, chemical shifts are assigned to ion **4** as shown. The ^{13}C NMR thus confirms **4** as the initially formed ion from **1** and the former contains a methylene group and an olefinic bond remaining intact by the iron tricarbonyl group. Other structures such as **6** or **7** can be excluded.



4

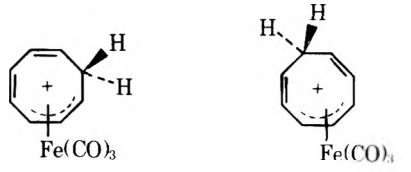
positions	$\delta^{13}C$
1,5	70.9 (d, 159.7 Hz) 73.4 (d, 158.2 Hz)
2,4	94.1 (d, 174.5 Hz) 98.1 (d, 173.0 Hz)
3	105.7 (d, 184.0 Hz)
6	129.4 (d, 161.0 Hz)
7	118.5 (d, 170.7 Hz)
8	25.3 (t)



5

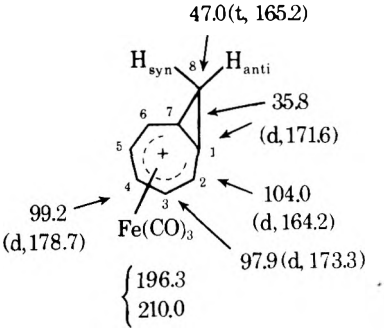
$\delta^{13}C$

65.4 (d d, 165, 4, 164.4)
104.6 (d m, 170.8)
98.6 (d t, 180.3)

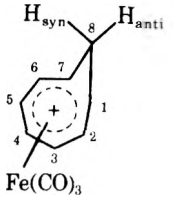


6 **7**

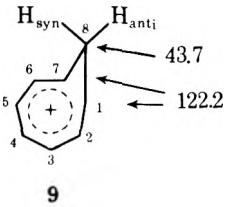
Thermal Rearrangement of the Protonated Cyclooctatetraeneiron Tricarbonyl. When the solution of protonated cyclooctatetraeneiron tricarbonyl **4** was allowed to stand at −60 °C, a clean transformation of the ion took place giving the bicyclo[5.1.0]octadienyliron tricarbonyl cation **3**.[8] The eight carbon resonances in the organic and three in the carbonyl region originally present in the ^{13}C NMR spectrum of **4** are now replaced by five and three carbon resonances, respectively. In the proton-coupled ^{13}C NMR spectrum the two



3



8



9

Table I. ^{13}C Chemical Shifts of Carbonyl Groups of Olefiniron Tricarbonyls and Their Related Ions

δ ^{13}C CO, ppm	3	4	5	10	11	12	13	14	15	16	17	18
Apical or axial	210.0	206.2	206.0	209.0[a]	218.3[a]	207.5	208.1	207.9	203.1	205.9[b]	202.7	205.6
Basal or equatorial	196.3	198.4 199.0	197.3	209.0[a]	218.3[a]	198.1 198.5	198.4	198.2	196.0 199.2	204.6[b] 205.5[b]	200.0	191.3

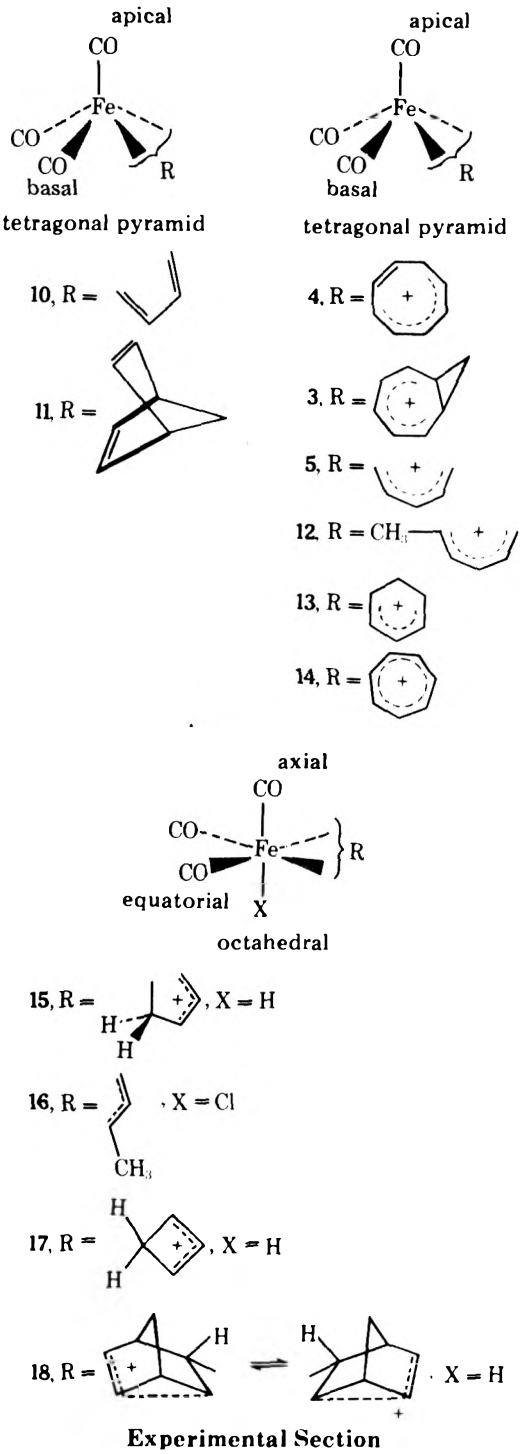
[a] Averaged shift at −90 °C in SO_2 solution. [b] Interchangeable values.

high-field signals at $\delta_{^{13}C}$ 35.8 and 47.0 are a doublet and a triplet, respectively. These are assigned to the cyclopropane ring carbons formed via a first-order electrocyclic ring closure reaction.[8] They are substantially deshielded from other neutral cyclopropane-ring carbons, obviously due to charge delocalization into the three-membered ring. They do, however, show chemical shifts in the aliphatic region which confirm the assigned structure **3** for the observed ion. Otherwise in a complexed homotropylium ion **8** both C_1 and C_7 should have chemical shifts of about $\delta_{^{13}C}$ 100 (olefinic region). The NMR data thus exclude the homotropyliumiron tricarbonyl ion **8** structure. Using **5** as the model ion, the chemical shifts for ion **3** are summarized as shown.

Study of the Carbonyl Absorptions. In recent carbon-13 NMR studies of the fluxional behavior of 1,3-dieneiron tricarbonyl complexes, only two resonances were observed in the carbonyl region, even at temperatures below −90 °C, usually in a ratio of 2:1, corresponding to the basal and apical carbonyl groups, respectively.[11] 1,3-Butadiene **10** and norbornadiene **11**–iron tricarbonyls both undergo fast fluxional exchange and even at −90 °C they only show a single averaged carbonyl shift at $\delta_{^{13}C}$ 209.0 and 218.3, respectively.[9a] Upon protonation, i.e., **15** from **10** in excess acid, **16** (the neutral HCl adduct) from HCl solution, and **18** from **11**, the octahedral organoiron tricarbonyl cations show either two or three carbonyl absorptions depending whether they are symmetrical or unsymmetrical. For example, **15** and **16** are unsymmetrical and thus they show one axial and two equatorial carbonyl resonances. The former is found more deshielded than the latter. On the other hand, the symmetrical ion **18** which undergoes fast equilibration shows only one axial and one equatorial carbonyl absorption in a ratio of 1:2.[9a] The symmetrical σ–π complex ion **17** derived from cyclobutadieneiron tricarbonyl via protonation also shows two carbonyl resonances[9b] (Table I).

For organoiron tricarbonyl complex ions **3**–**5** and **12**–**14** which adopt tetragonal-pyramidal configuration, the possibility arises of observing apical and both of the basal carbonyl absorptions, which indeed was the case. This depends, however, on whether the complexed ions are symmetrical or unsymmetrical. The carbonyl shifts of these ions are summarized in Table I.

Chemical shifts of the carbonyl carbons in transition-metal carbonyls are sensitive to the electron density on the metal atom.[12] The less the positive charge on the metal atom, the more carbonyl groups become shielded. The shieldings found for the basal (tetragonal-pyramidal configuration) and equatorial (octahedral configuration) carbonyl groups thus indicate significant positive charge density on iron. Contribution to the total shielding due to other factors (i.e., anisotropic shielding from organic moiety) should also be considered. However, the neutral species **10**, **11**, and **16** which do not bear formal positive charge on iron only display unchanged carbonyl absorptions (relative to their parent neutral iron carbonyl complexes). This indicates that the development of positive charge density on iron arising from strong complexation between the olefinic and iron tricarbonyl groups may be the key factor toward the total shielding of the carbonyl absorptions for organoiron tricarbonyl complexed ions.



Experimental Section

Cyclooctatetraeneiron Tricarbonyl (**1**) was prepared according to the literature procedure.[5a]

Protonation of Cyclooctatetraeneiron Tricarbonyl (1) in FSO_3H–SO_2ClF Solution at −120 °C. Ion **4** was prepared by addition of **1** in SO_2ClF solution to excess FSO_3H–SO_2ClF solution with vigorous stirring at ethanol–liquid nitrogen bath temperature (ca. −120 °C) under dry-nitrogen atmosphere to give an approximately 5% so-

lution of **4**. The yellow solution formed this way was then transferred under dry nitrogen into a precooled NMR tube.

The Thermal Rearrangement of 4 to Bicyclo[5.1.0]octadienyliron Tricarbonyl Cation 3. When a solution of **4** was allowed to warm up to −60 °C, ^{1}H NMR signals due to ion **4** completely disappeared and were replaced by those of **3** formed quantitatively.

^{13}C NMR Spectroscopic Study. The ^{13}C NMR spectra were obtained using a Varian XL-100-15 NMR spectrometer equipped with FT accessory, spin decoupler, and a variable temperature probe. A Varian 620L computer was used to accumulate data. An external lock (fluorobenzene) was used and all chemical shifts are referred to the ^{13}C signal of the enriched (5) Me_4Si capillary.

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

Registry No.—**1**, 12093-05-9; **3**, 41853-19-4; **4**, 41370-96-1; **5**, 45977-75-1; **10**, 12078-32-9; **11**, 12307-07-2; **12**, 46134-85-4; **13**, 49654-90-2; **14**, 46236-85-1; **15**, 63765-50-4; **16**, 61216-90-8; **17**, 63765-51-5; **18**, 63765-52-6.

References and Notes

(1) (a) Organometallic Chemistry, 15: G. A. Olah, G. K. Prakash, G. Liang, K. L. Henold, and G. B. Haigh, *Proc. Natl. Acad. Sci. U.S.A.*, in press. Address correspondence to this author at the Institute of Hydrocarbon Chemistry, Department of Chemistry, University of Southern California, Los Angeles, Calif.

(2) (a) T. A. Manuel and F. G. A. Stone, *Proc. Chem. Soc., London*, 90 (1959); *J. Am. Chem. Soc.*, **82**, 366 (1960); (b) M. D. Rausch and B. N. Schrauzer, *Chem. Ind. (London)*, 957 (1959); (c) K. Nakamura and N. Hagihara, *Bull. Chem. Soc. Jpn.* **2**, 880 (1959); (d) B. Dicken and W. N. Lipscomb, *J. Am. Chem. Soc.*, **83**, 4862 (1961); *J. Chem. Phys.*, **37**, 2084 (1962); (e) C. E. Keller, G. F. Emerson, and R. Pettit, *J. Am. Chem. Soc.*, **87**, 1388 (1965).

(3) (a) F. A. Cotton, *Acc. Chem. Res.*, **1**, 257 (1968); *J. Chem. Soc.*, 400 (1960); (b) F. A. Cotton, "Dynamic NMR Spectroscopy", L. M. Jackman and F. A. Cotton, Ed., Academic Press, New York, N.Y., 1975; (c) D. A. Brown, *J. Inorg. Nucl. Chem.*, **10**, 39 49 (1959).

(4) (a) C. G. Kreiter, A. Maasbol, F. A. L. Anet, H. D. Kaesz, and S. Winstein, *J. Am. Chem. Soc.*, **88**, 3444 (1966); (b) F. A. Cotton, A. Davison, and J. W. Faller, *ibid.*, **88**, 4507 (1966); (c) C. E. Keller, B. A. Shoulders, and R. Pettit, *ibid.*, **88**, 4760 (1966); (d) F. A. Cotton, J. N. Faller, and A. Musco, *ibid.*, **90**, 1438 (1968); (e) S. Winstein, H. D. Kaesz, C. G. Kreiter, and E. C. Friedrich, *ibid.*, **87**, 5267 (1965); (f) F. A. L. Anet, *ibid.*, **89**, 2491 (1967); (g) A. Carbonaro, A. Greco, and G. Dall'Aota, *Tetrahedron Lett.*, 2037 (1967); (h) W. K. Bratton, F. A. Cotton, A. Davison, J. W. Faller, and A. Musco, *Proc. Natl. Acad. Sci. U.S.A.*, **58**, 1324 (1967); (i) M. I. Bruce, M. Cooke, M. Green, and F. G. A. Stone, *Chem. Commun.*, 523 (1967); (j) R. Grubbs, R. Breslow, R. Herber, and S. J. Lippard, *J. Am. Chem. Soc.*, **89**, 6864 (1967).

(5) (a) F. A. Cotton and D. L. Hunter, *J. Am. Chem. Soc.*, **98**, 1413 (1976); (b) F. A. Cotton, D. L. Hunter, and P. LaLuerta, *ibid.*, **96**, 7926 (1974); (c) G. Rigatti, G. Boccalon, A. Accon, and G. Giacometti, *Chem. Commun.*, 1165 (1972).

(6) G. N. Schrauzer, *J. Am. Chem. Soc.*, **83**, 2966 (1961).

(7) A. Davison, W. McFarlane, L. Pratt, and G. Wilkinson, *Chem. Ind. (London)*, 555 (1961); *J. Chem. Soc.*, 482 (1962).

(8) (a) M. Brookhart and E. R. Davis, *J. Am. Chem. Soc.*, **92**, 7622 (1970); (b) M. Brookhart, E. R. Davis, and D. L. Harris, *ibid.*, **94**, 7853 (1972).

(9) (a) G. A. Olah, S. H. Yu, and G. Liang, *J. Org. Chem.*, **41**, 2227, 2383 (1976); (b) G. A. Olah and G. Liang, *ibid.*, **41**, 2659 (1976).

(10) G. A. Olah, G. Liang, L. A. Paquette, M. J. Broadhurst, and P. Warner, *J. Am. Chem. Soc.*, **95**, 3386 (1973).

(11) (a) L. Kruczynski and J. Takats, *J. Am. Chem. Soc.*, **96**, 932 (1974); (b) F. A. Cotton, V. W. Days, B. A. Frenz, K. I. Hardcastle, and J. M Troup, *ibid.*, **95**, 4522 (1973).

(12) (a) G. M. Bodner and L. J. Todd, *Inorg. Chem.*, **13**, 360, 1335 (1974); (b) L. Vancea, R. K. Pomeroy, and W. A. G. Graham, *J. Am. Chem. Soc.*, **98**, 1407 (1976); (c) L. F. Farnell, E. W. Randall, and E. Rosenberg, *Chem. Commun.*, 1078 (1971); (d) H. L. Retcofsky, E. N. Frankel, and H. S. Gutowsky, *J. Am. Chem. Soc.*, **88**, 2710 (1966); (e) C. G. Kreiter, M. Lang, and H. Strack, *Chem. Ber.*, **108**, 1502 (1975); (f) J. Evans and J. R. Norton, *Inorg. Chem.*, **13**, 3042 (1974).

A Synthesis of 6-Hydroxy-1-benzoxepin-3,5(2*H*,4*H*)-dione

B. K. Wasson,* P. Hamel, and C. S. Rooney

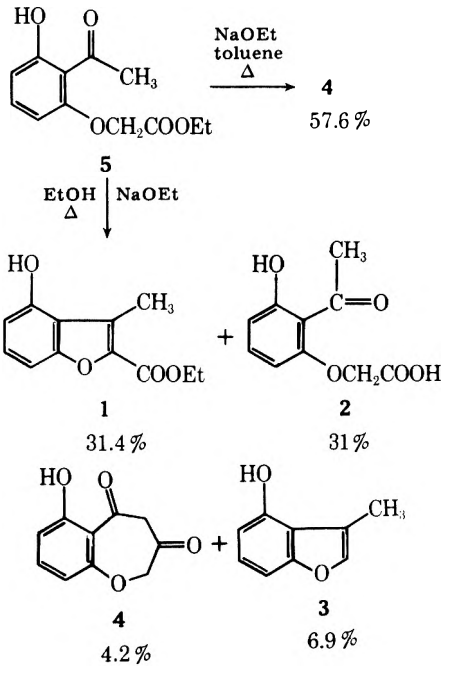
Medicinal Chemistry Department, Merck Frosst Laboratories, Pointe Claire/Dorval, Quebec H9R 4P8, Canada.

Received June 2, 1977

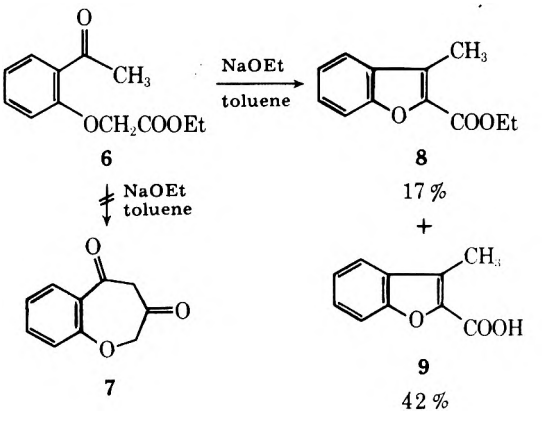
Recently, a relatively large quantity of the known ethyl 4-hydroxy-3-methyl-2-benzofurancarboxylate (**1**) was required. Repetition of Whalley's[1] procedure in a modified form afforded not only **1** in 31.4% yield, but three additional products (see Scheme I). Two of these, (2-acetyl-3-hydroxyphenoxy)acetic acid (**2**) and 4-hydroxy-3-methylbenzofuran (**3**) isolated in 31 and 6.9% yields, respectively, had been reported by Whalley.[1] Compound **3** could also be formed from **2** when the latter was heated with acetic anhydride.[1] The fourth product, identified as the hitherto unknown 6-hydroxy-1-benzoxepin-3,5(2*H*,4*H*)-dione (**4**), was isolated along with **2** and **3** after silica gel column chromatography in 4.2% yield. The assignment of structure to **4** was based on microanalysis, NMR, IR, UV, and mass spectrometry. Spectral evidence supports the diketo form rather than the enolic in both the solid state and in solution. Thus, the NMR spectrum exhibits two $-CH_2-$ peaks at δ 4.32 and 4.50 and one exchangeable proton at δ 12.31. Similar conclusions have been reported for the structure of 1-benzoxepin-3,5(2*H*,4*H*)-diones.[2-5] The pK_a of **4** is 4.83—presumably representing dissociation of the diketone function.

When ester **5** was allowed to react with sodium ethoxide in dry toluene, **4** was obtained in 57.6% yield. However, similar treatment of ethyl 2-(2-acetylphenoxy)acetate (**6**) gave only the benzofurans **8** and **9**, and no 1-benzoxepin-3,5(2*H*,4*H*)-dione (**7**) was observed. It thus appears that the phenolic hydroxyl plays an essential role in the formation of the benzoxepin **4**. Compound **4** remained unchanged after heating at 65 °C in sodium ethoxide–ethanol. Thus, **4** is not an intermediate

Scheme I



Scheme II



which in the ethanolic medium can serve as a precursor of **1**, **2**, and/or **3**.

Tyman and Pickles[2] have reported the preparation of 1-benzoxepin-3,5(2*H*,4*H*)-diones by treatment of 2-acetylphenoxyacetic esters with either ethanolic sodium ethoxide or phosphorous oxychloride in benzene. However, yields apparently were low. The high yield of **4** obtained in our work using sodium ethoxide in toluene is therefore unique, and is dependent on the acidic group ortho to the ketone combined with the aprotic solvent medium (toluene).[6] We attribute the facilitation of benzoxepin formation to the presence of an unsolvated phenolate anion which will deactivate the adjacent ketone to nucleophilic attack. Interaction of the anion formed from the methyl group, adjacent to the ketone, on the ester carbonyl can then predominate.

Experimental Section

Melting points were taken on a Thomas-Hoover Uni-melt apparatus and are uncorrected. Ultraviolet spectra were recorded on a Perkin-Elmer 202 spectrophotometer. Infrared spectra were determined on a Perkin-Elmer 257 spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian EM 360 spectrometer with Me_4Si as an internal reference. Mass spectral analyses were provided by Morgan-Schaffer Corp., and elemental microanalyses were carried out by Dr. C. Daessle. The pK_a determination was performed by Mr. S.-C. Ho in these Laboratories.

Cyclization of Ethyl 2-(2-Acetyl-3-hydroxyphenoxy)acetate (5) with Sodium Ethoxide in Ethanol. The compound **5**[1] (23.8 g, 0.1 mol), dissolved in 600 mL of ethanol containing 2.3 g of reacted sodium, was stirred overnight at room temperature. The solution was heated at 80 °C for 3 h and then evaporated. The residue was partitioned between ethyl ether and water. The aqueous fraction was acidified and extracted with diethyl ether, and the ethereal extract was evaporated to give 10.4 g of a brown solid. The solid was triturated with benzene to afford 6.52 g (31%) of semipure 2-acetyl-3-hydroxyphenoxyacetic acid (**2**), mp 183–188 °C. A recrystallization raised the melting point to 193–195 °C (H_2O) (lit.[7] mp 193–194.5 °C): IR (KBr) 1785, 1630, 1605, 1480, 1262, 1213 and 1120 cm^{-1}; NMR (Me_2SO-d_6) δ 2.62 (3 H, s), 4.75 (2 H, s), 6.53 (2 H, m), and 7.4 (1 H, t). Evaporation of the combined benzene and the first ethereal extracts gave 12.2 g of a solid which was chromatographed on silica gel (60–200 mesh). Elution with benzene–ethyl acetate (changing from a ratio of 1:99 to 1:1) afforded three major fractions. The first fraction of 1.02 g (6.9%) was crude 4-hydroxy-3-methylbenzofuran (**3**), which afforded needles: mp 110–112 °C (lit.[1] mp 111 °C) (C_6H_6–petroleum ether); IR (KBr) 3300 (br), 1640, 1620, 1600, 1480, 1470, 1332, 1260, 1220, 1109, 1040, 790, 746; NMR ($CDCl_3$) δ 2.34 (3 H, s), 5.03 (1 H, s) (exchanged with D_2O), 6.52 (1 H, m), 7.03 (1 H, s), and 7.2 (2 D, m). The second fraction afforded 340 mg (2.3%) of 6-hydroxy-1-benzoxepin-3,5(2*H*,4*H*)-dione (**4**); mp 139–141 °C (C_6H_6–petroleum ether); UV (EtOH) λ_{max} 217 nm (ϵ 15 100), 226 (ϵ 14 800), 266 (ϵ 10 235), and 341 (ϵ 4100); IR (KBr) 1740, 1630, 1603, 1555, 1538, 1455, 1232, 1058, 970, 790, and 740 cm^{-1}; NMR ($CDCl_3$) δ 4.32 (2 H, s), 4.50 (2 H, s), 6.78 (2 H, m), 7.45 (1 H, m), and 12.31 (1 H, s) (exchanged with D_2O); mass spectrum *m/e* 192 (M^+), 150 ($M^+ - C_2H_2O$), 121 ($M^+ - C_3H_3O_2$).

Anal. Calcd for $C_{10}H_8O_4$ (192.17): C, 62.50; H, 4.20. Found: C, 62.43; H, 4.33. pK_a = 4.83. A second crop of **4** was obtained in a 280-mg (1.9%) yield, mp 136–139 °C.

The third fraction gave 6.91 g (31.4%) of ethyl 4-hydroxy-3-methyl-2-benzofurancarboxylate (**1**): mp 157–159 °C (lit.[1] mp 155 °C) (C_6H_6–petroleum ether); IR (KBr) 3290, 1690, 1622, 1592, 1460, 1392, 1283, 1190, 1065 and 752 cm^{-1}; NMR (Me_2SO-d_6) δ 1.33 (3 H, t), 2.68 (3 H, s), 4.32 (2 H, q), 6.72 (1 H, m), 7.2 (2 H, m), and 10.28 (1 H, br) (exchanged with D_2O).

The compound **4** (19.2 mg, 0.1 mmol) dissolved in 2 mL of absolute ethanol containing 2.3 mg (0.1 mmol) of sodium was stirred at room temperature for 60 h and then heated at 65 °C for 3 h. Monitoring by TLC indicated no change. The product, isolated by acidification and evaporation, was shown by NMR analysis to be unchanged **4**.

Cyclization of Ethyl 2-(2-Acetyl-3-hydroxyphenoxy)acetate (5) with Sodium Ethoxide in Toluene. The compound **5** (476.4 mg, 2 mmol) was refluxed for 24 h in a suspension of sodium ethoxide (56.5 mg, 2.3 mmol) in 10 mL of toluene. The reaction mixture was evaporated and acidified, and the chloroform extract was washed with 5% sodium bicarbonate solution and then with water, dried (Na_2SO_4), and evaporated to give 300 mg of solid product. The solid gave 221 mg (57.6%) of **4** (C_6H_6–petroleum ether), identical to the sample described in the preceding experiment.

Cyclization of Ethyl 2-(2-Acetylphenoxy)acetate (6) with Sodium Ethoxide in Toluene. Similarly, a mixture of 11.10 g (50 mmol) of **6**,[8] sodium ethoxide (from 1.26 g of sodium), and 50 mL of toluene was refluxed for 1.5 h. The solvent was removed in vacuo and the residue partitioned between water and chloroform. The dried chloroform extract afforded 1.96 g (17.5%) of ethyl 3-methyl-2-benzofurancarboxylate (**8**), mp 48–50 °C (lit.[9] mp 49–51 °C). The aqueous extract was acidified, and the resulting solids were collected and crystallized to give 4.12 g (42.6%) of 3-methyl-2-benzofurancarboxylic acid (**9**), mp 187–190 °C (lit.[9] mp 192–194 °C).

Registry No.—**1**, 3781-69-9; **2**, 3361-22-6; **3**, 3610-15-9; **4**, 63815-26-9; **5**, 6769-65-9; **6**, 63615-27-0; **8**, 22367-82-4; **9**, 24673-56-1.

References and Notes

(1) W. B. Whalley, *J. Chem. Soc.*, 3229 (1951).
(2) J. H. P. Tyman and R. Pickles, *Tetrahedron Lett.*, 4993 (1966).
(3) (a) H. Hofmann, *Angew. Chem.*, **77**, 864 (1965). (b) H. Hofmann and H. Westernacher, *Chem. Ber.*, **102**, 205 (1969).
(4) J. R. Doherty, D. D. Keane, W. I. O'Sullivan, and E. M. Philbin, *Chem. Ind. (London)*, 586 (1969).
(5) S. Klutchko and M. Von Strandtmann, *Synthesis*, 61 (1977).
(6) An alternate route to 1-benzoxepin-3,5(2*H*,4*H*)-diones from flavanone epoxides through 3-hydroxyflavanones has been described.[3,4] Also, 1-benzoxepin-3,5(2*H*,4*H*)-dione has been prepared from 3-(bromoacetyl)chromone.[5]
(7) W. G. Scharpt (FMC Corp.), Belgium 670 764 (Jan. 31, 1966); *Chem. Abstr.*, **65**, 8876c (1966).
(8) S. K. V. Kulkarni, P. B. Sattur, and K. S. Nargund, *J. Karnatak Univ.* **2**, 69–78 (1957); *Chem. Abstr.*, **53**, 14986b (1959).
(9) B. Sila, *Rocz. Chem.* **43**, 1413–1418 (1969).

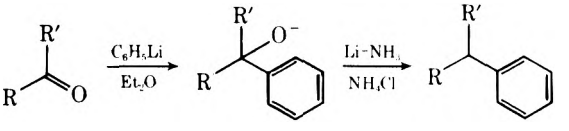
Synthesis of Aromatic Hydrocarbons and Alcohols by Tandem Phenylation–Reduction of Esters and Lactones[1]

Srisamorn T. Srisethnil[2] and Stan S. Hall*

Carl A. Olson Chemistry Laboratories, Rutgers University, Newark, New Jersey 07102

Received June 10, 1977

This laboratory has been exploring the potential applications of tandem alkylation–reduction of aromatic carbonyl systems[3] and phenylation–reduction of aldehydes and ketones[1,4] as a convenient method of preparing aromatic hydrocarbons. The method involves the lithium–ammonia–ammonium chloride reduction of a benzyl alkoxide generated in situ by alkylation. Since the entire sequence is performed in the same reaction vessel without the isolation or purification of intermediates, the total synthesis consumes only a few hours and the isolated yield of the product is usually good. Herein we extend the application of this tandem phenylation–reduction procedure to esters and lactones.



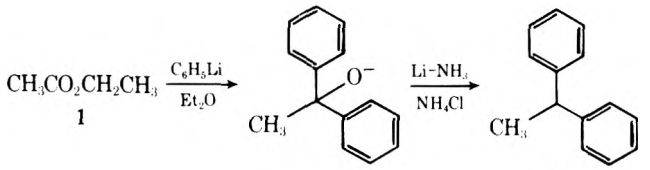
Since subjecting esters and lactones to an excess of phenyllithium results in the formation of a benzyl alkoxide (a 1,1-diphenyl 1-alkoxide), these carbonyl systems seemed appropriate starting materials for the synthesis of 1,1-diphenyl hydrocarbons and alcohols using this tandem sequence. The results are listed in Table I. Esters yield the corresponding 1,1-diphenyl hydrocarbons. Two examples are given. Phenylation–reduction of ethyl acetate (**1**) yielded 1,1-diphenylethane (**9**) and methyl benzoate (**2**) yielded triphenylmethane (**10**).

Phenylation–reduction of lactones, on the other hand, yields the corresponding diphenyl alcohols. For example, γ-butyrolactone (**3**) yielded 4,4-diphenyl-1-butanol (**11**). Related

Table I. Phenylation–Reduction of Esters and Lactones[a]

Ester or lactone	Registry no.	Product[b]	Registry no.	Yield c	Yield d
Ethyl acetate (1)	141-78-6	1,1-Diphenylethane (9)	612-00-0	80	70[e]
Methyl benzoate (2)	93-58-3	Triphenylmethane (10)	519-73-3	89	84[f]
γ-Butyrolactone (3)	96-48-0	4,4-Diphenyl-1-butanol (11)	56740-71-7	92	69[g]
γ-Valerolactone (4)	108-29-2	5,5-Diphenyl-2-pentanol (12)	63797-58-0	70	55[h]
α-Methyl-γ-butyrolactone (5)	1679-47-6	3-Methyl-4,4-diphenyl-1-butanol (13)	63797-59-1	95	45[i]
γ-Phenyl-γ-butyrolactone (6)	1008-76-0	1,1,4-Triphenylbutane (14)	33885-06-2	90	65
Dihydrocoumarin (7)	119-84-6	o-(3,3-Diphenylpropyl)phenol (15)	63797-60-4	95	86
Coumarin (8)	91-64-5	o-(3,3-Diphenylpropyl)phenol (15)		98	78[f]

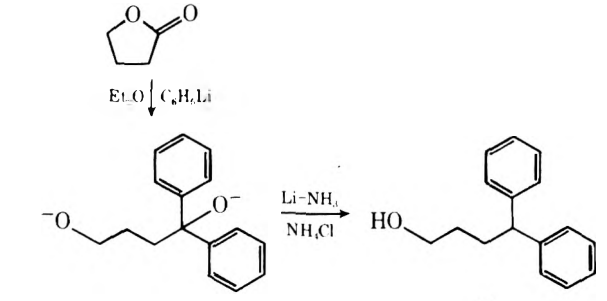
[a] See Experimental Section for details. [b] Products 9, 10, 14, and 15 gave satisfactory composition analyses (±0.4% for C, H). [c] Analyzed by GLC (% of volatiles). [d] Isolated by column chromatography unless stated otherwise. [e] Isolated after column chromatography followed by evaporative distillation. [f] Isolated after recrystallization. [g] An inseparable mixture of 11 (98%) and the overreduced dihydro and tetrahydro compounds (ca. 1% each). [h] An inseparable mixture of 12 (90%) and the overreduced dihydro (3%) and tetrahydro (7%) compounds. [i] An inseparable mixture of 13 (96%) and the overreduced dihydro and tetrahydro compounds (ca. 2% each).



9

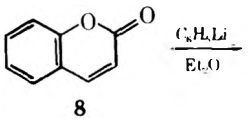
examples appear in Table I. γ-Phenyl-γ-butyrolactone (6) yielded the aromatic hydrocarbon 1,1,4-triphenylbutane (14) since both alkoxides are benzylic and reduce during the reduction sequence. Only one lactone, α,α-diphenyl-γ-butyrolactone (not shown in Table I), was found not amenable to this procedure. This was evidently because of its resilience to phenylation during the first step for steric reasons. The products from a few of the lactones, notably alcohols 12 and 13, were contaminated (NMR and GC–MS analyses) with small amounts of overreduction products (see footnotes to Table I).

Phenylation–reduction of the phenolic lactones dihydrocoumarin (7) and coumarin (8) both resulted in the formation

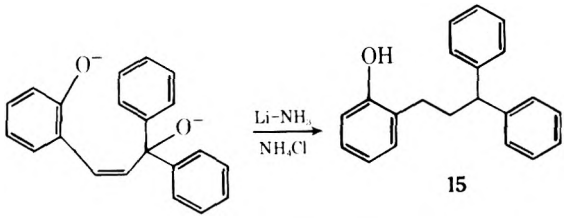


11

of o-(3,3-diphenylpropyl)phenol (15). This result is expected since the intermediate from coumarin is a styrene system that will reduce rapidly[5] to the saturated phenol derivative 15.



8



15

Although some of the isolated yields of the alcohols and hydrocarbons listed in Table I are only moderate, the availability of the starting materials and efficiency (time, energy, cost) of this one-pot synthesis make this tandem sequence a very useful method for the synthesis of these structural types.

Experimental Section[6]

General Comments. See ref 4 for general experimental comments. Compounds 1–5 were distilled just prior to use. Gas chromatography (GLC) analyses were performed on 120 × 0.2 cm (i.d.) glass columns packed either with 3% silicon gum rubber OV-17 (methylphenyl) or 3% silicon gum rubber SE-30 (methyl) supported on 100–120 mesh HP Chromosorb W (AW, DMCS). Purification of each product by column chromatography was accomplished on chromatographic grade activated alumina (80–325 mesh, Matheson Coleman and Bell) grade I (for the hydrocarbons) and grade III (6% H_2O, for the alcohols) by elution with petroleum ether and petroleum ether–Et_2O. Evaporative distillations, sometimes necessary for microanalyses, were performed in a Kügelrohr oven. The assigned structure of each product was consistent with the spectral data and some were compared with authentic samples. The phenylation–reduction of coumarin (8) is described, in detail, to illustrate the procedure.

Phenylation–Reduction of Coumarin (8). o-(3,3-Diphenylpropyl)phenol (15). To a metal–ammonia reaction vessel containing a stirred mixture of 350 mg (50.0 mg-atoms, ca. 25 pieces) of lithium foil in 10 mL of anhydrous ether was slowly added (ca. 10 min)[7] a solution of 1.962 g (12.50 mmol) of bromobenzene in 10 mL of ether. After 50 min, the reaction mixture was diluted with 10 mL of ether and then cooled to ca. −70 °C (dry ice–acetone bath). A solution of 730 mg (5.00 mmol) of coumarin (8) in 20 mL of ether was slowly added (ca. 15 min) and after 10 min the cooling bath was removed and the mixture was stirred for 50 min. After a further dilution with 25 mL of ether, ca. 75 mL of ammonia was carefully distilled[8] (15–20 min) into the mixture and after 30 min the dark blue color of the reaction mixture was discharged by the addition[9] (5–10 min) of excess ammonium chloride (ca. 1.8 g). After the ammonia had evaporated the residue was partitioned between ether and brine. The organic phase was dried ($MgSO_4$), filtered, concentrated at water aspirator pressure, and then analyzed (GLC). The crude yellow viscous oil (1.440 g) crystallized as white needles (1.123 g, 78%) from benzene–petroleum ether: mp 65–66 °C; IR (film) 3550, 3440 (br), 1600, 1500, 1460, 750, 700 cm^{-1}; NMR (100 MHz, $CDCl_3$, 25 transients) δ 7.24 (10 H, apparent s), 7.1–6.6 (4 H, complex m), 4.84 (1 H, broad s, exchangeable with D_2O), 3.93 (1 H, t, J = 7.5 Hz), 2.6–2.3 (4 H, complex m); MS m/e (rel intensity) 288 (M^+, 3), 167 (95), 121 (100), 77 (81). Anal. Calcd for $C_{21}H_{20}O$: C, 87.46; H, 6.99. Found: C, 87.57; H, 7.10.

Acknowledgment. The authors are grateful to Dr. F. Scheidl, Hoffmann-La Roche Inc., Nutley, N.J., for the microanalyses, and the Charles and Johanna Busch Memorial Fund, the Research Council (Rutgers), and N.I.H. (Biomedical Sciences Support Grant) for supporting grants.

References and Notes

(1) Part 9 in the series, "Alkylation-Reduction of Carbonyl Systems". For part 8, see F. J. McEnroe, C.-K. Sha, and S. S. Hall, *J. Org. Chem.*, **41**, 3465 (1976).
(2) Taken in part from the M.S. Thesis of S.T.S., Rugers University, Dec 1976.

(3) (a) S. S. Hall and S. D. Lipsky, *J. Org. Chem.*, **38**, 1735 (1973); (b) S. D. Lipsky and S. S. Hall, *Org. Synth.*, **55**, 7 (1976).
(4) S. S. Hall and F. J. McEnroe, *J. Org. Chem.*, **40**, 271 (1975).
(5) (a) S. S. Hall, *J. Org. Chem.*, **38**, 1738 (1973); (b) M. Smith, "Reduction", R. L. Augustine, Ed., Marcel Dekker, New York, N.Y., 1968, pp 98–105.
(6) GLC analyses were determined on a Hewlett-Packard Model 7610A (flame detector) chromatograph. The IR spectra were determined with a Beckman Model AccuLab 6 infrared recording spectrophotometer. The ^{1}H NMR spectra were determined at 100 MHz with a JEOL Model JNM-PS-FT-100 fast Fourier Transform NMR spectrometer. The chemical shifts are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were determined with a Finnigan Model 3100D mass spectrometer (70 eV) to which was interfaced a Varian Associates Model 1400 gas chromatograph.
(7) During the addition the exothermic reaction was moderated (18–25 °C, internal thermometer) with a water bath.
(8) To increase the efficiency of the condensation process, the reaction vessel was cooled (dry ice–acetone bath), and to prevent splattering, the apparatus was tilted slightly to allow the condensing ammonia to run down the walls of the flask.
(9) The NH_4Cl is most conveniently introduced by attaching a glass bulb filled with the salt to a side arm by means of tygon tubing. When the salt is to be added, the bulb is raised and tapped gently to smoothly introduce the quenching agent. Should this step start to become violent, the addition and sometimes even the vigorous stirring should be momentarily stopped to avoid an eruption.

Oxidation of Olefins with Silver Chromate–Iodine. A New and Facile Synthesis of α-Iodo Ketones

Giuliana Cardillo* and Makoto Shimizu[1]

Istituto Chimico "G.Ciamician", Università di Bologna Via Selmi 2,40126 Bologna, Italy

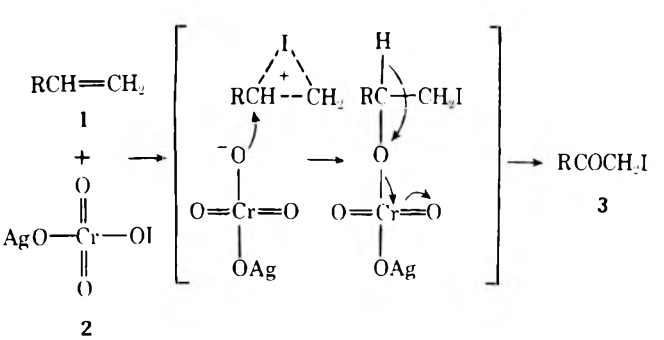
Received April 22, 1977

Our interest in the nucleophilic properties of chromate anion coupled with the recent attention accorded to the oxidation of activated alkyl halides to the corresponding aldehydes[2] prompts this report on the capahility of the silver chromate–iodine system for the facile oxidation of douhle bonds to the corresponding α-iodo ketones.

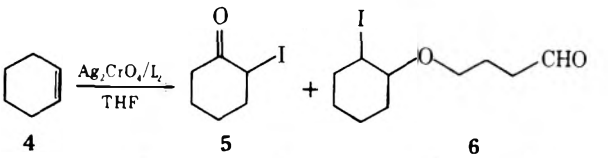
α-Halo ketones have been regarded as synthetically useful materials and several general methods for their syntheses have been established.[3] In contrast to their chloro or hromo analogues, α-iodo ketones, however, have not heen sufficiently studied. This is partly because of their relative instahility and that there are only a few satisfactory synthetic methods available, e.g., halogen–iodide interchange[4] and treatment of enol acetates with *N*-iodosuccinimide.[5] Furthermore, both methods appeared to need relatively high reaction temperatures which might cause decomposition of the products. It is, therefore, of value to develop an easy and mild synthetic route to α-iodo ketones.

Until now, for one-step oxidations of olefins to α-chloro ketones only two methods have been known, one utilizing nitrosyl chloride[6a,b] and the other chromyl chloride.[6c] On the other hand, oxidation of alkenes with acyl hypoiodite provides an easy way to introduce α-iodo alcohols to douhle honds.[7] In an analogy to the well-known Prevost reaction, we considered

Scheme I



Scheme II



that the generation of a hypoiodous–chromic acid mixed anhydride (**2**) under mild conditions would lead to a one-step oxidation of olefins to α-iodo ketones. Scheme I reports a possible mechanism.

We have now found that the treatment of cyclohexene with silver chromate[8] and iodine leads to 2-iodocyclohexanone. A series of experiments was carried out in an effort to find the optimum conditions for the oxidation of cyclohexene. Table I lists the results obtained.

When THF was used as a solvent, a small amount of ether **6**[9] arising from THF was always recovered together with 2-iodocyclohexanone (**5**).

As shown in Table I, the best yield was ohtained when dichloromethane was used as a solvent in the presence of 0.5 to 1.0 equiv of pyridine.[10] The reactions summarized in Table II (vide infra) were performed under the optimum conditions found for cyclohexene.

This reaction seemed to have wide applicability. In general, electron-rich olefins gave better results, while electron-deficient ones such as crotononitrile resulted in the recovery of the starting olefins. Aliphatic, alicyclic, and aromatic olefins gave satisfactory yields in the majority of cases. The lower yields observed in the cases of allyl benzoate and 2,3-dihydro-4*H*-pyran are due to the formation of the unidentified by-products which decomposed despite several attempts for isolation. Further, terminal olefins were converted exclusively to the corresponding α-iodo ketones.

Thus, the above results as well as mild reaction conditions make the present method highly useful for the synthesis of α-iodo ketones from olefins.

Further studies utilizing other metal chromates are currently in progress.

Experimental Section

General. All reactions were run under a positive pressure of dry argon. Infrared spectra (IR) were recorded on a Perkin-Elmer 710B spectrometer and are given in cm^{-1}. Nuclear magnetic resonance spectra (NMR) were determined on a Perkin-Elmer R12B spectrometer. Chemical shifts are given in ppm from internal tetramethylsilane. Mass spectra (MS) were taken on a Varian MAT 111 (70 eV). Melting points (mp) which were determined in glass capillaries and boiling points (bp) were uncorrected. Preparative thin-layer chromatography (TLC) was carried out on a glass plate (20 × 20 cm) coated with Merck silica gel HF_{254} (1-mm thick). Columun chromatography was performed on Merck silica gel (0.05–0.20 mesh).

Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from sodium benzophenone ketyl immediately before use. Benzene was distilled from sodium and stored over it. Dichloromethane was distilled from phosphorus pentoxide and stored over 4-Å molecular sieves. Pyridine was distilled from calcium hydride and stored under argon.

Silver Chromate.[8] A solution of silver nitrate (17.0 g, 100 mmol) in 200 mL of water was added with stirring to a solution of potassium chromate (9.7 g, 50 mmol) in 200 mL of water. Promptly and quantitatively reddish-brown silver chromate precipitated. The precipitate was filtered, washed successively with water, dried in vacuo, finely pulverized, and dried again in vacuo at 90 °C for 5 h.

Unless otherwise indicated, the following α-iodo ketones were prepared according to the general procedure.

Phenacyl Iodide (General Procedure). To a suspension of silver chromate (1.10 g, 3.3 mmol) and 4-Å molecular sieves[11] (1.5 g) in 15 mL of dichloromethane were added iodine (1.14 g, 4.5 mmol) and a solution of pyridine (118 mg, 1.5 mmol) in 0.75 mL of dichloromethane at 0 °C and stirred for 5 min.

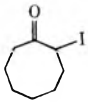
A solution of styrene (312 mg, 3.0 mmol) in 5 mL of dichloromethane was added dropwise during 5 min to the ice-cooled suspen-

Table I. Oxidation of Cyclohexene: Comparison of Reaction Conditions[a]

Entry	Ag_2CrO_4, equiv	I_2, equiv	Solvent	React. condns, °C (period, min)	Yield,[b] % 5	6
1	2.0[c]	1.0	THF	0 (30), rt (30)	35	10
2	3.0	1.0	THF	−10 (10), 0 (50)	41	18
3	3.0	1.0	THF	0 (5), rt (90)	52	26
4	6.0	1.0	THF	0 (10), rt (60)	61[d]	15[d]
5	3.0	1.0	DME	0 (180), rt (240)	40	
6	3.0[c,e]	1.0	C_6H_6	rt (60)	46	
7	1.1[c,e]	1.1	CH_2Cl_2	0 (20), rt (40)	51	
8	2.0[c,e]	1.1	CH_2Cl_2	0 (5), rt (60)	65	
9	1.1[c,f]	1.5	CH_2Cl_2	0 (15), rt (45)	63	
10	1.1[c,f]	1.5	CH_2Cl_2	0 (30), rt (60)	60[d]	

[a] Reactions were carried out in 1-mmol scale. [b] Yield determined by NMR using pyrazine or 1,1,2,2-tetrachloroethane as internal standard. [c] Molecular sieves (0.5 g) were used. [d] Isolated yield. [e] In the presence of pyridine (1.0 equiv). [f] In the presence of pyridine (0.5 equiv).

Table II. Oxidation of Olefins with Silver Chromate–Iodine[a]

Entry	Olefin	Registry no.	α-Iodo ketone,[b]	Registry no.	Yield,[c] %
11	Cyclohexene	110-83-8		35365-19-6	60
12	Cyclooctene	931-88-4		63641-49-6	65
13	1-Octene	111-66-0	$C_6H_{13}CCH_2I$ (O)	63641-50-9	74
14	1-Octadecene	112-88-9	$C_{16}H_{33}CCH_2I$ (O)	63641-51-0	65
15	Styrene	100-42-5	$PhCCH_2I$ (O)	4636-16-2	86
16	Cinnamyl acetate	103-54-8	$PhCCHICH_2OAc$ (O)	63641-52-1	82
17	Allyl benzoate	583-04-0	$BzOCH_2CCH_2I$ (O)	27933-28-4	49
18	2,3-Dihydro-4*H*-pyran	110-87-2		63641-53-2	39

[a] Reactions were carried out in 2–3-mmol scale. [b] All products were characterized by IR, NMR, and mass spectra. [c] Isolated yield.

sion, which was stirred for 20 min at 0 °C. Then, the cooling bath was removed and the reaction mixture was stirred for an additional hour at room temperature.

The dark-brown mixture was filtered through a pad of Celite. The filtrate was washed with 5% aqueous $Na_2S_2O_3$ and saturated aqueous NaCl, and dried ($MgSO_4$). The crude product (668 mg) obtained after concentration was purified on column chromatography (ca. 20 g of silica gel: elutant, hexane/ether 90/10)[12] to give the title compound (636 mg, 86%) as a slightly yellow oil, which on cooling crystallized: mp (hexane) 34.0–34.5 °C;[13] IR (neat) 1685 cm^{-1} (vs, C=O); NMR (CCl_4) 4.25 (s, 2 H, CH_2ICO–), 7.28–7.65 (m, 3 H, aromatic), 7.87–8.10 ppm (m, 2 H, aromatic); MS *m/e* (rel intensity) 246 (M^+·, 18), 119 (M^+· –I, 13), 105 (M^+· $-CH_2I$, 20), 77 (Ph^+, 100), 51 (M^+· $-C_2H_2COH_2I$, 40).

2-Iodocyclohexanone. The reaction was carried out in a 2-mmol scale, and the title compound (268 mg, 60%) was obtained: bp 54 °C/1 mm;[14] IR (neat) 1710 cm^{-1} (vs, C=O); NMR (CCl_4) 1.50–2.55 (m, 8 H, $-CH_2$–, $-CH_2CO$–), 4.45–4.70 ppm (m, 1 H, –CHICO–); MS *m/e* (rel intensity) 224 (M^+· 67), 97 (M^+· –I, 100), 55 (M^+· $-C_3H_6I$, 100), 42 (M^+· $-C_3H_3OI$, 36).

2-Iodocyclooctanone. The reaction was carried out in 3-mmol scale, and the title compound (429 mg, 65%) was obtained: bp 58 °C/1.5 mm; IR (neat) 1700 cm^{-1} (vs, C=O); NMR (CCl_4) 1.15–2.60 (m, 12 H, $-CH_2$–, $-CH_2CO$–), 4.50 ppm (dd, 1 H, J = 13 and 5.5 Hz, –CHICO–); MS *m/e* (rel intensity) 252 (M^+· 11), 125 (M^+· –I, 22), 70 (M^+· $-C_3H_3OI$, 8), 55 (M^+· $-C_5H_5I$, 100).

1-Iodo-2-octanone. The reaction was carried out in 3-mmol scale, and the title compound (566 mg, 74%) was obtained: bp 63 °C/1 mm; IR (neat) 1715 cm^{-1} (vs, C=O); NMR (CCl_4) 0.75–1.75 (m, 13 H, $-CH_2$–, $-CH_3$), 2.67 (t, 2 H, J = 7 Hz, $-CH_2CO$–), 3.70 ppm (s, 2 H, CH_2ICO–); MS *m/e* (rel intensity) 254 (M^+· 9), 184 (M^+· $-C_5H_{10}$, 20), 169 (M^+· $-C_6H_{13}$, 8), 127 (M^+· –I, 23), 113 (M^+· $-CH_2I$, 100), 85 (M^+· $-COCH_2I$, 59).

1-Iodo-2-octadecanone. The reaction was carried out in 3-mmol scale, and unreacted 1-octadecene (20 mg, 3%) and the title compound (765 mg, 65%) was obtained: mp 66–66.5 °C (hexane); IR (nujol) 1715 cm^{-1} (vs, C=O); NMR ($CDCl_3$) 0.75–1.75 (m, 31 H, $-CH_2$–, $-CH_3$), 2.72 (t, 2 H J = 7 Hz, $-CH_2CO$–), 3.78 ppm (s, 2 H, CHICO–); MS *m/e* (rel intensity) 267 (M^+· –I, 100), 253 (M^+· $-CH_2I$, 67), 225 (M^+· $-COCH_2I$, 3), 184 (M^+· $-C_{15}H_{30}$, 66), 169 (M^+· $-C_{16}H_{33}$, 20).

2-Iodo-3-oxo-3-phenylpropyl Acetate. The reaction was carried out on a 2-mmol scale, and the title compound (520 mg, 82%) was obtained: mp 56–57 °C (CCl_4) dec; IR (nujol) 1740 (vs, –O–C=O), 1670 cm^{-1} (vs, C=O); NMR (CCl_4) 1.93 (s, 3 H, $-CH_3CO$–), 4.55 (d, 2 H, J = 7.5 Hz, –CHO–), 5.53 (t, 1 H, J = 7.5 Hz, –CHICO–), 7.20–7.65 (m, 3 H, aromatic), 7.90–8.12 ppm (m, 2 H, aromatic); MS *m/e*

(rel intensity) 191 (M^+ -I, 14), 105 ($PhCO^+$, 100), 106 ($PhCHO^+$, 9), 60 (CH_3COOH^+, 9), 43 (CH_3CO^+, 9).

3-Iodo-2-oxopropyl Benzoate. The reaction was carried out in 2-mmol scale. The crude product was purified on TLC to give unreacted allyl benzoate (55 mg, 17%), and the title compound was obtained (229 mg, 49%): mp 77–77.5 °C (hexane); IR (nujol) 1735 (vs, -O-C=O), 1715 cm^{-1} (vs, C=O); NMR ($CDCl_3$) 3.96 (s, 2 H, CH_2ICO-), 5.20 (s, 2 H, $-OCH_2CO-$), 7.50–7.80 (m, 3 H, aromatic), 8.21–8.35 ppm (m, 2 H, aromatic); MS *m/e* (rel intensity) 304 (M^+· 2), 177 (M^+· -I, 16), 169 (CH_2ICO^+, 1), 135 (M^+· $-COCH_2I$, 4), 106 ($PhCHO^+$, 11), 105 ($PhCO^+$, 100), 77 (Ph^+, 46).

α-Iodo-δ-valerolactone. The reaction was carried out in 2-mmol scale using 1.2 equiv of iodine, and the crude product was purified on TLC to give the title compound (175 mg, 39%): bp 80–82 °C/1.5 mm; IR (neat) 1730 cm^{-1} (vs, C=O); NMR (CCl_4) 1.70–2.45 (m, 4 H, $-CH_2-$), 4.37–4.64 (m, 2 H, $-OCH_2-$), 4.86 ppm (t, 1 H, J = 5 Hz, -CHICO-); MS *m/e* (rel intensity) 226 (M^+· 28), 196 (M^+· $-CH_2O$), 11), 127 (I^+, 32), 99 (M^+· -I, 20), 55 ($COCHCH_2^+$, 100).

Registry No.—**2**, 63641-54-3; **6**, 63641-55-4; silver chromate, 19247-15-5; iodine, 7553-56-2.

References and Notes

(1) Graduate research student on a grant (1021H) from the Italian Government (1976–1977).
(2) (a) G. Cardillo, M. Orena, and S. Sandri, *J. Chem. Soc., Chem. Commun.*, 190 (1976); (b) *Tetrahedron Lett.*, 3985 (1976).
(3) R. H. Reuss and A. Hassner, *J. Org. Chem.*, **39**, 1785 (1974), and references cited therein.
(4) P. C. Julian and W. J. Karpel, *J. Am. Chem. Soc.*, **72**, 362 (1950).
(5) C. Djerassi and C. T. Lenk, *J. Am. Chem. Soc.*, **75**, 3493 (1953).
(6) (a) M. Ohono, N. Naruse, and I. Terasawa, *Org. Synth.*, **49**, 27 (1969). (b) B. W. Ponder and D. R. Walker, *J. Org. Chem.*, **32**, 4136 (1967). (c) K. B. Sharpless and A. Y. Teranishi, *J. Org. Chem.*, **38**, 185 (1973).
(7) For reviews: (a) C. V. Wilson, *Org. React.*, **9**, 332 (1957); (b) H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, New York, N.Y., 1972, pp 436–441.
(8) R. B. Turne, V. R. Mattox, L. L. Engel, R. F. Mckonzie, and E. C. Kendall, *J. Biol. Chem.*, **166**, 345 (1946).
(9) The structure of **6** was inferred on the basis of its spectral properties: IR (neat) 1725 cm^{-1} (vs, C=O); NMR (CCl_4) 0.80–2.30 (m, 10 H), 2.55 (t, 2 H, J = 6 Hz), 3.20–3.70 (m, 3 H), 3.75–4.30 (m, 1 H), 9.80 ppm (br s, 1 H); MS *m/e* (rel intensity) 296 (M^+· 1), 267 (1), 252 (2), 209 (4), 169 (3), 87 (24), 71 (100), 57 (9), 43 (56), 29 (17).
(10) The role of pyridine is presumably that of facilitating the formation of the supposed hypoiodous-chromic acid mixed anhydride: In fact, an addition of pyridine to the silver chromate-iodine mixture caused an immediate change of color.
(11) To ensure dryness of silver chromate, the use of molecular sieves is preferable.
(12) Because of the less stable nature of the product, both a short column and rapid elution are recommendable.
(13) D. J. Pasto and K. Garves, *J. Org. Chem.*, 32, 778 (1967).
(14) J. Cantacuzene, R. Jantzene, and D. Ricard, *Tetrahedron*, **28**, 717 (1972).

Photochemistry of a Ketone with a Reportedly High Circular Dichroism Using Circularly Polarized Light

J. F. Nicoud, C. Eskenazi, and H. B. Kagan*

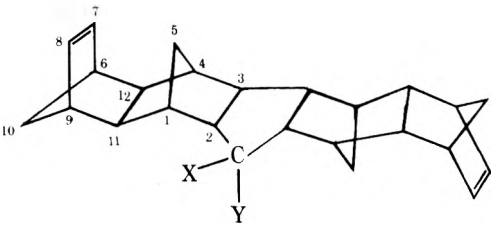
Laboratoire de Synthèse Asymétrique, LA CNRS No. 040255, Université de Paris-Sud, 91405-Orsay, France

Received June 13, 1977

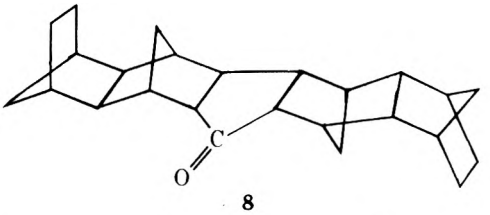
Partial photoresolution with circularly polarized light (CPL) is useful in the determination of the anisotropy factor (g factor = $\Delta\epsilon/\epsilon$) of chiral compounds. This easily available test led us to reinvestigate the previously described[1] chiroptical properties of ketone **1**.

Partial photodecomposition of a racemic mixture with CPL was first realized by Kuhn.[2] We reinvestigated this field in 1974 and gave a kinetic treatment permitting the prediction of the optical purity of the remaining material (characterized by its g factor) for a given fraction of destruction.[3] With *dl*-camphor (g = 0.09, λ 310 nm) 99% destruction allowed us to recover optically active camphor with 20% enantiomeric excess (e.e.).

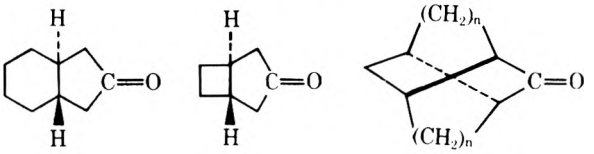
Scheme I



1, X = Y = O
6, X = H, Y = OH
7, X = H, Y = OCO_2(−)Menthyl



8



2 3 4, n = 1; 5, n = 2

This method can be useful for obtaining, for the first time, a chiral compound if classical resolution methods fail but, of course, either a high g factor or a high degree of photodestruction is necessary if reasonable optical purities are needed. Therefore, very little of the unphotolyzed starting material is obtained, and it must be separated and purified from a huge mass of photodecomposition products. In addition, we pointed out[3] that with a few independent experiments it should be possible to calculate the g factor and specific rotation of the optically pure compound.[4]

Our attention was drawn by a report[1] describing the resolution and chiroptical properties of ketone **1**. From the published data, g factor values can be calculated at several wavelengths: g = 0.77 (322 nm), g = 0.70 (312 nm), and g = 0.65 (301 nm). These values can be compared with those of all known polycyclic ketones and even with other organic compounds.[5] For example, some of the highest known g factor values are 0.24 (313 nm), 0.20 (311 nm), 0.12 (286 nm), and 0.30 (288 nm) for the chiral twisted ketones **2**–**5**,[6-9] respectively.

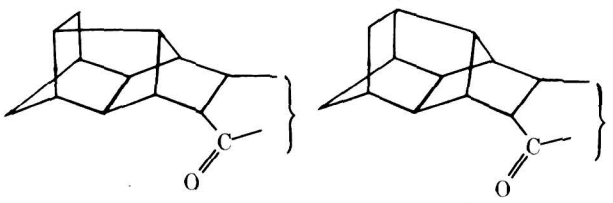
It thus appears that for **1** the CD and g values are exceptionally high. This might be the consequence of high twist of the cyclopentanone unit, as shown by a recent report about ketones **2** and **3**.[10]

These considerations led us to investigate the promising photochemistry of ketone **1** with CPL. Computations with g = 0.80 showed that 90% and 99% decomposition should allow the recovery of **1** in 81% and 99% e.e.,[3] respectively, making this method very competitive with the previously described resolution involving formation of diastereomers.[1]

Results and Discussion

The partial photoresolution with CPL of ketone **1** is very disappointing; enantiomeric enrichment is smaller than expected and is in agreement with an average g factor of 0.10. Photoproducts[11] could possibly arise from an energy transfer mechanism which would change the basis of our previous calculations (Scheme II).[3] Before considering this hypothesis, we reinvestigated the chiroptical properties of ketone **1**. LAH reduction of *dl*-**1** quantitatively gave *dl*-**6**. Treatment by

Scheme II



9a 9b

(−)-menthyl chloroformate in the presence of pyridine in benzene yielded the mixture of diastereomeric carbonates **7**. Two crystallizations of the crude material in hexane afforded a pure diastereomer in excellent yield (as shown by GLC analysis on a 4% OV1 column which permitted a nice separation of the two diastereomers). LAH treatment of the latter diastereomer in THF and purification gave alcohol (−)-**6**: $[\alpha]_D$ −12 ± 1° (*c* 0.40, cyclohexane) which was optically pure. Oxidation[12] of (−)-**6** gave (−)-**1**, purified by chromatography on silica and crystallized from hexane. Optically pure **1** (as shown by GLC analysis on **7**) has the following properties: $[\alpha]_D$ −270 ± 10° (*c* 0.104, cyclohexane; *c* 0.066, ether), $[\alpha]_D$ −244 ± 10° (*c* 0.390, benzene).

These optical rotations are in good agreement with the previous $[\alpha]_D$ value of −261° (solvent not specified).[1] The UV spectrum is identical with that described, while strong disagreement exists concerning the CD spectrum. Our value of $\Delta\epsilon$ (Figure 1) is always much smaller than the published data.[1] From the curves of Figure 1, *g* values could be calculated for several wavelengths. An average *g* value of 0.15 between 290 and 330 nm was obtained, close to that deduced from our partial photoresolution experiment. In addition, reduction of the double bonds in (+)-**1** (53% e.e.) and chromatographic purification yielded the partially resolved ketone **8**. From its rotation and circular dichroism, the optical rotation of the pure ketone **8** was calculated to be $[\alpha]_D$ +250 ± 10° (*c* 0.171, cyclohexane). From the CD and UV spectra, an average *g* factor of 0.16, of the same magnitude as for **1**, was calculated. It is clear that contrary to previous reports[1,13] ketone **1** has no unusual chiroptical properties; its behavior is very similar to that of ketones **2** and **3** which were recently described. Tricyclo[4.4.0.0^{3,8}]decan-2-one (**5**) and *trans*-2-hydrindanone (**2**) remain, to our knowledge, the ketones with the highest anisotropy factor.[14]

Experimental Section

Melting points, uncorrected, were determined on a Reichert apparatus using a microscope hot stage. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer and ultraviolet spectra on a Unicam SP 1800 spectrometer. ^{1}H NMR spectra were determined on a Perkin-Elmer R-32 instrument (90 MHz) (δ, parts per million from Me_4Si), the optical rotations on a Perkin-Elmer 141 polarimeter, and the circular dichroism (CD) on a Roussel-Jouan dichrograph. A Carlo Erba GI chromatograph was used for the GLC experiments (N_2 as carrier gas). Mass spectra were recorded on an AEI MS30 mass spectrometer.

Irradiation of Ketone 1 with Natural Light. A solution of 240 mg (0.7 mmol) of (±)-ketone **1** in 900 mL of cyclohexane was irradiated in a classical photochemical apparatus (Hanovia 450 W) with a Pyrex filter. The progress of the reaction was monitored by GLC analysis using an OV17 4% 2-m column (oven 260 °C). Two photoproducts were detected, the second one coming from a photochemical rearrangement of the first one. At the end of the reaction, a single photoproduct was isolated.[11] Purification by chromatography on silica gel (95:5 hexane–ether) and crystallization from cyclohexane gave 140 mg of white plates (60%): mp 241–242 °C; IR 1715 cm^{-1} (Nujol); NMR ($CDCl_3$) δ 0.4–2.4 (m); UV (cyclohexane) λ_{max} (*c*) 290, 298, 308 (55), 319, 331 nm; mass spectrum *m/e* 344 (P). Anal. Calcd for $C_{25}H_{28}O$: C, 87.19; H, 8.19. Found: C, 86.95; H, 8.34.

Irradiation of Ketone 1 with Circularly Polarized Light (CPL). A solution of 615 mg (1.8 mmol) of (±)-ketone **1** in 760 mL of cyclohexane was irradiated with right CPL (313 nm) using the apparatus previously described.[3] The progress and the extent of the reaction were measured by GLC analysis using an internal standard (OV 17 4% 2 m, 260 °C). The irradiation was stopped before the disappearance of all of the ketone. The more accurate determination of percent destruction of **1** by GLC is 60 ± 5%. An NMR study by analysis of the H vinylic signals showed a destruction of 65 ± 5%. A first purification by chromatography on silica gel–$AgNO_3$ (10%) followed by two others on silica gel (97:3 hexane–ether) gave a sample of pure ketone **1** $[\alpha]^{25}_D$ +8.20° (*c* 0.3, cyclohexane) e.e. 3%, whereas computation with $g = 0.80$ shows that 60% photodestruction would allow the recovery of **1** in 38% e.e.

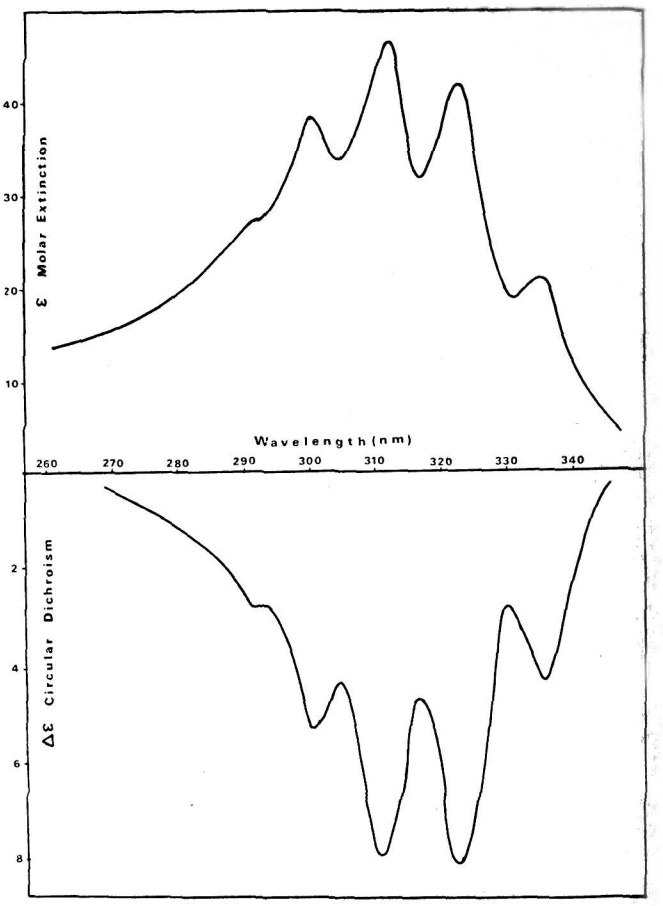


Figure 1. UV and CD spectra of ketone **1** in cyclohexane.

Diastereomeric Carbonates 7. (−)-Menthyl chloroformate (0.7 g (3.2 mmol)) was added to a solution of 1.07 g (3.1 mmol) of (±)-alcohol **6**[15] in 30 mL of benzene with a few drops of pyridine. The mixture was stirred at room temperature for 24 h. Then 20 mL of chloroform was added and the solution was washed once with 1 N NaOH and twice with NaCl saturated solution. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The solid residue was recrystallized from 45 mL of hexane to give 430 mg of (−)-carbonate **7** (81% e.e.): mp 212 °C. A new recrystallization in hexane gave 320 mg of (−)-carbonate **7** optically pure (checked by GLC analysis on a OV 1 4% 1.70-m column): mp 217–218 °C; $[\alpha]^{25}_D$ −76° (*c* 1.24, $CHCl_3$), $[\alpha]^{25}_D$ −65° (*c* 0.89, C_6H_6); IR (Nujol) 3040 (=CH), 1725 (C=O), 1285 (CO), 775, 755 cm^{-1}; NMR ($CDCl_3$) δ 0.30–2.10 (m, 28, CH menthyl + cycle), 2.80 (s, 4 H, allylic), 4.50 (m, –CHOCOOCH–), 5.88 (s, 4, –HC=CH–). Column chromatography of the residue obtained from the mother liquor on 100 g of silica gel with hexane as eluent gave 1.15 g of (+)-carbonate **7** (53% e.e.). The enantiomeric excess was determined by GLC (column OV1 4%, 250 °C).

(−)-Alcohol 6 from (−)-Carbonate 7. To a magnetically stirred mixture of 40 mg (1 mmol) of LAH in 20 mL of dry THF was added slowly a solution of 300 mg (0.57 mmol) of (−)-carbonate **7** in 20 mL of THF. The mixture was boiled under reflux for 1 h. After hydrolysis by 1 M H_2SO_4, the organic layer was washed (5% $NaHCO_3$ and NaCl saturated solutions). After drying (Na_2SO_4) and evaporation of the solvent, the menthol was removed by sublimation (120 °C (0.1 mm), 3 h). A sample of (−)-alcohol **6** was obtained, 170 mg (87%): mp 208 °C; $[\alpha]^{25}_D$ −12° (*c* 0.39, cyclohexane) (lit.[1] $[\alpha]_D$ −14°, solvent not specified).

(−)-Ketone 1 from (−)-Alcohol 6. A solution of 160 mg of optically pure (−)-alcohol **6** in 2 mL of benzene was added to a mixture of 2 drops of CH_3COOH, 4 drops of H_2SO_4, 30 mg of $Na_2Cr_2O_7$, and 0.5 mL of water. The mixture was stirred for 1 h at room temperature and then washed ($NaHCO_3$ and water). The organic layer was dried (Na_2SO_4) and evaporated. A recrystallization in hexane gave 140 mg (87%) of optically pure (−)-ketone **1**: mp 266–267 °C; $[\alpha]^{25}_D$ −270° (*c* 0.104, cyclohexane), $[\alpha]^{25}_D$ −244° (*c* 0.39, benzene); CD λ_{max} ($\Delta\epsilon_{max}$) 300.5 (−5.33), 311.5 (−7.91), 323 (−8.17), 336 nm (−4.37) (*c* 3.02 mmol/L, cyclohexane); UV (cyclohexane) λ_{max} (ϵ_{max}) 301 (37.2), 312 (45.8), 323 (41.0), 335 nm (20.6).

(+)-Ketone 8 from (+)-Ketone 1. The (+)-ketone **1** (53% e.e.) was prepared from (+)-carbonate **7** (53% e.e.) according to the method previously described. A catalytic hydrogenation of ketone **1**[15] on Pd/C gave the saturated ketone **8** (53% e.e.): mp 281–282 °C, $[\alpha]^{25}_D$ +32° (*c* 0.17, cyclohexane) which gives $[\alpha]^{25}_D$ max calcd +250°; CD (corrected for 100% e.e.) λ_{max} ($\Delta\epsilon_{max}$) 301 (4.14), 311.5 (6.13), 324 (6.39), 336.5 (3.37); UV (cyclohexane) λ_{max} (ϵ_{max}) 302 (40.8), 312 (49), 324 (44.2), 337 (24.3) nm.

Acknowledgment. We thank CNRS for financial support.

Registry No.—(±)-**1**, 63864-540-; **1** isomer 1, 63864-55-1; **1** isomer 2, 54383-73-2; (±)-**6**, 63864-56-2; (−)-**6**, 63864-57-3; **7** isomer 1, 63784-77-0; **7** isomer 2, 63814-62-0; (+)-**8**, 63864-58-4; **9a**, 63784-78-1; **9b**, 63784-79-2; (−)-menthyl chloroformate, 14602-86-9.

References and Notes

(1) E. Weissberger, *J. Am. Chem. Soc.*, **96**, 7219 (1974).
(2) W. Kuhn and E. Knopf, *Z. Phys. Chem., Abt. B*, **7**, 292 (1930).
(3) G. Balavoine, A. Moradpour, and H. B. Kagan, *J. Am. Chem. Soc.*, **96**, 5152 (1974).
(4) Recently an accurate kinetic treatment of a photoresolution allowed Rau et al.[4a] to calculate the *g* factor, and molar ellipticity of a tetraazaspirane. A special case of photoresolution was developed by Nelander and Norden[4b] by working in an iced matrix. Thus the dithiane itself (which is a stable racemic mixture at 77 K) was resolved for the first time and its chiroptical properties studied at 77 K; (a) R. Blume, H. Rau, and O. Schuster, *J. Am. Chem. Soc.*, **98**, 6583 (1976); (b) B. Nelander and B. Norden, *Chem. Phys. Lett.*, **28**, 384 (1974).
(5) There has been no recent tabulation of *g* factors since that of S. F. Mason, *Q. Rev., Chem. Soc.*, **17**, 20 (1963).
(6) C. A. Emeis, L. J. Oosterhoff, and G. de Vries, *Proc. R. Soc. London, Ser. A*, **297**, 54 (1967).
(7) J. C. A. Windhorst, *J. Chem. Soc., Chem. Commun.*, 331 (1976).
(8) M. Nakazaki, N. Naemura, and N. Arashiba, *J. Chem. Soc., Chem. Commun.*, 678 (1976).
(9) K. Adachi, K. Naemura, and M. Nakazaki, *Tetrahedron Lett.*, 5467 (1968).
(10) T. D. Bouman, *J. Chem. Soc., Chem. Commun.*, 665 (1976).
(11) Two photoproducts were detected during photolysis of **1** and their structures were investigated by spectrometric methods (IR, MS, NMR). One and two double bonds disappear, the cyclopentanone ring is not cleaved, and the molecular weight remains unchanged. These data led us to consider two possible internal hydrogen abstractions (cyclization C_5–C_8 or C_5–C_7). Two structures, **9a** and **9b**, satisfy these data. Further work is needed to decide between the two possibilities. For a previously described similar photoreaction see (a) W. Herz and M. G. Nair, *J. Am. Chem. Soc.*, **89**, 5474 (1967); (b) W. Herz, V. S. Iyer, M. G. Nair, and J. Saltiel, *ibid.*, **99**, 2704 (1977).
(12) W. S. Johnson, C. D. Gutsche, and D. K. Banerjee, *J. Am. Chem. Soc.*, **73**, 5464 (1951).
(13) P. Laszlo and E. Weisseberger, *Acc. Chem. Res.*, **9**, 209 (1976).
(14) We investigated the photochemistry of *dl-trans*-2-hydrindanone with CPL. Observed optical purities were higher than what was observed with *dl*-camphor[3] and were in agreement with predictions from computations.
(15) J. Mantzaris and E. Weissberger, *J. Am. Chem. Soc.*, **96**, 1873 (1974).

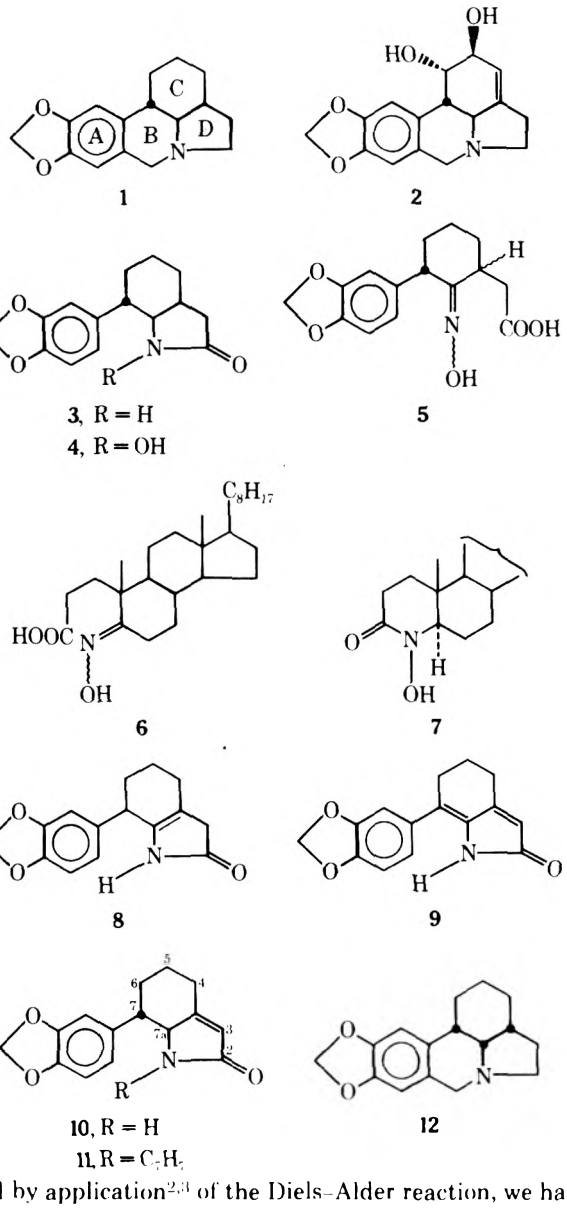
An Alternative Synthesis of (±)-α- and (±)-γ-Lycoranes

Bunsuke Umezawa,* Osamu Hoshino, Shohei Sawaki, Seiichi Sato, and Naganori Numao

Faculty of Pharmaceutical Sciences, Science University of Tokyo, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan

Received April 26, 1977

Although an important stereochemical requirement to build up the skeleton of α-lycorane (**1**)[1,2] and lycorine (**2**)[3,4] centers around the construction of the C ring and is successfully fulfilled by application[2,3] of the Diels–Alder reaction, we have searched for another route starting from a cyclohexanone to prepare a lactam (**3**),[2a] which is already converted into **1**. Thus, a cyclic hydroxamic acid (**4**) is considered as an equivalent synthon for **3** and reaction of an oxime (**5**) with zinc dust in boiling acetic acid was carried out in view of the fact[5] that the similar reaction of an oxime (**6**) gives a cyclic hydroxamic acid (**7**) of a six-membered ring. However, we found that reaction of the oxime (**5**) gave unsaturated lactams instead of **4**. Here, we wish to report on the structures of unsaturated lactams **8**, **9**, and **10** and on an alternative synthesis of (±)-α-lycorane (**1**) via unsaturated lactams **10** and **11** and (±)-γ-lycorane (**12**)[2b,c,6] via **9**.



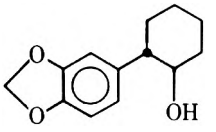
Grignard reaction of cyclohexanone with 3,4-methylenedioxyphenylmagnesium bromide[7] in tetrahydrofuran followed by dehydration and hydroboration oxidation produced a cyclohexanol (**13**) whose Jones oxidation gave a cyclohexanone (**14**).[8] Alkylation of **14** via an enamine and successive alkaline hydrolysis furnished a 2-oxocyclohexylacetic acid (**15**).

Refluxing with zinc dust in glacial acetic acid of the oxime **5** afforded a mixture of lactams A, B, and C. Mass spectra of the lactams A and C showed the same molecular peak at *m/e* 257, which was two mass units less than that of **3**, while that of the lactam B was at *m/e* 255.

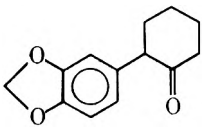
From the spectral data (NMR, IR, and MS), structures of the lactams A, B, and C proved to be **8**, **9**, and **10**, respectively.

It was notable that unsaturated lactams instead of the cyclic hydoxamic acid (4) were obtained in the reaction.

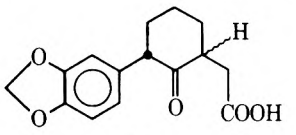
Although two stereoisomers (10 and 16) were possible for the lactam C, the former was favored by the NMR spectrum, which showed a doublet peak (1 H, J = 10 Hz) at δ 3.81 for C-7a hydrogen. Namely, referring to a modified Karplus equation,[9] the observed value of J indicated that the dispositions of C-7 and C-7a hydrogens were trans diaxial.[10] Accordingly, the stereoisomer (16) was ruled out.



13



14



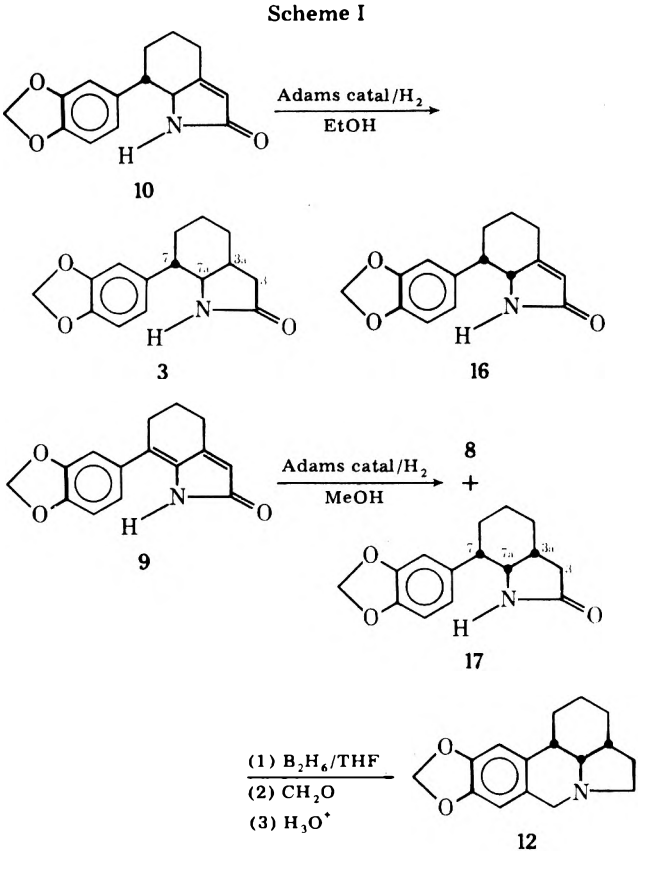
15

Catalytic hydrogenation of 10 gave the lactam 3[2a] whose NMR spectrum exhibited double doublet peaks (1 H, J = 7 and 10 Hz) at δ 3.41 for C-7a hydrogen. Since the lactam is already converted into (±)-α-lycorane (1),[2a] formation of the former constituted the formal synthesis of the latter.

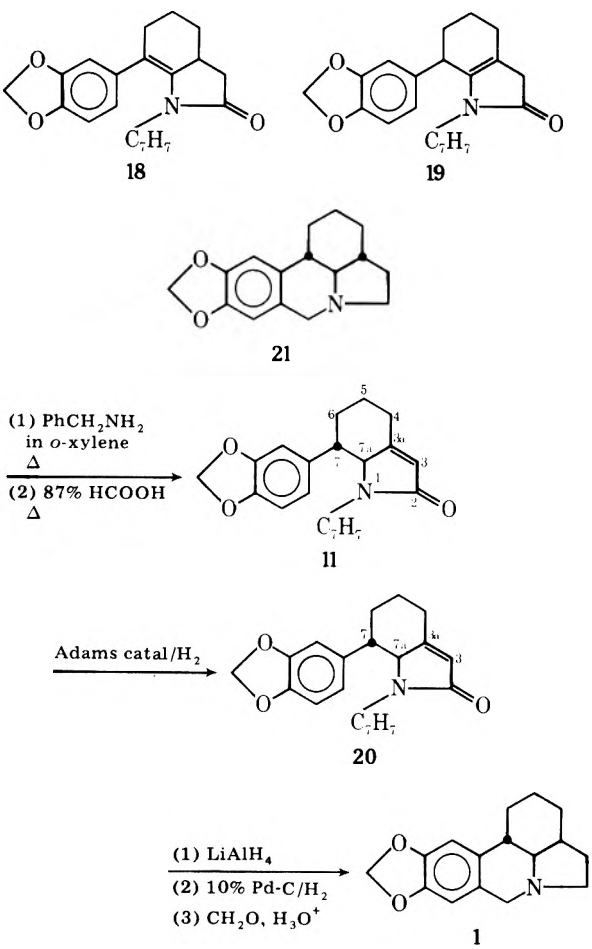
In sharp contrast, the similar reaction of 9 led to a new lactam 17, whose NMR spectrum indicated a triplet peak (1 H, J = 4 Hz) at δ 3.88 for C-7a hydrogen, besides the lactam 8. Reduction of 17 followed by the Pictet–Spengler reaction gave (±)-γ-lycorane (12). The finding[11] revealed that three substituents of the C ring in 17 were all cis oriented.

Formation of 10 in the reaction suggested that if an unsaturated lactam such as 18[12] or 19 could be produced its acid treatment would lead to a lactam 11 predominantly by isomerization of the double bond to the α,β-unsaturated system. Thus, refluxing of 15 with benzylamine in o-xylene

Scheme I



Scheme II



followed by 87% formic acid yielded an amorphous unsaturated lactam 11 whose mass spectrum showed a molecular peak at m/e 347 ($C_{22}H_{21}NO_2$) and a base peak at m/e 91 ($C_7H_7^+$). IR and NMR spectra of 11 exhibited an absorption band at 1680 cm^{-1} for a lactam carbonyl, a doublet peak (1 H, J = 10 Hz) at δ 3.78 for C-7a hydrogen, and a singlet (1 H) at δ 5.91 for C-3 hydrogen, respectively. It was supported by the NMR spectrum that stereochemistry of 11 was the same as that of 10.

Catalytic hydrogenation of 11 afforded a saturated lactam 20 as a sole product. The NMR spectrum of 20 showed diffuse double doublet peaks[14] (1 H, J = 6.25 and 10 Hz) at δ 3.37 for C-7a hydrogen, suggesting that stereochemical features of 20 were similar to those of the lactam 3. Furthermore, the suggestion was substantiated by the result that 20 was not converted into β-lycorane (21)[1c,2a,d] but α-lycorane (1).

As expected, reduction of 20 followed by debenzylation and the Pictet–Spengler reaction gave exclusively (±)-α-lycorane (1) in a moderate yield.

Experimental Section[15]

***trans*-2-(3′,4′-Methylenedioxyphenyl)cyclohexanol (13).** To an ice-cooled, stirred solution of Grignard reagent[7] in anhydrous THF [prepared from 5-bromobenzo-1,3-dioxole[16] (45 g), magnesium turnings (6.6 g), and iodine (catalytic amount) in anhydrous THF (200 mL)] was added dropwise at 0–5 °C a solution of cyclohexanone (22.5 g) in anhydrous THF (40 mL) under nitrogen over a period of 1 h. To the stirred solution was added at 0 °C 10% HCl (100 mL) and the whole was heated at 50–60 °C with stirring for 1 h. After cooling, the organic layer was separated and the aqueous solution was extracted with ether. The combined organic layer was washed with brine and dried ($MgSO_4$). Removal of the solvent gave 43.4 g of an oil, which was distilled fractionally furnishing 40.1 g (88.7%) of a pale yellow oil, bp 120–160 °C (40 mm). To a stirred mixture of the oil (20.5 g) and $NaBH_4$ (3.53 g) in anhydrous THF (100 mL) was added dropwise at 20–25 °C a solution of BF_3-etherate (17 g) in anhydrous THF (50 mL)

under nitrogen over a period of 45 min. Excess of the hydride was decomposed under ice cooling with H_2O (50 mL) and 10% NaOH (153 mL). To the stirred mixture was added dropwise at 20–25 °C 30% H_2O_2 (92 mL) over a period of 45 min. After 1 h of agitation, the same workup as noted above gave 20.1 g of a pale yellow oil, which was distilled to afford 17.5 g (82.5%) of a colorless viscous oil (**13**), bp 150–175 °C (4 mm). The oil was triturated in *n*-hexane to lead to a solid, which was recrystallized from *n*-hexane–petroleum ether furnishing 16.8 g (75%) of colorless prisms: mp 63 °C; IR ($CHCl_3$) 3580 (OH) cm^{-1}; NMR δ 3.60 (m, 1, C(1)H), 5.95 (s, 2, OCH_2O), 6.67–6.87 (m, 3, aromatic H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.49; H, 7.35.

2-(3′,4′-Methylenedioxyphenyl)cyclohexanone (14). Jones reagent[17] (114 mL) was added dropwise to an ice-cooled, stirred solution of **13** (51.3 g) in acetone (1200 mL) over a period of 1.5 h and stirring was continued at room temperature for 1 h. The condensed mixture at reduced pressure (below 30 °C) was poured into ice-cooled brine (1000 mL) and the product was taken up in ether. The ether extract was washed with 5% aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). Evaporation of the solvent gave 45.2 g of a brown oil, which was extracted with hot *n*-hexane. Condensation of the solvent gave 23 g of pale yellow needles, mp 93–94 °C. Distillation of the residue obtained from the mother liquor gave 10.5 g of a pale yellow oil, bp 160–190 °C (4 mm), which was crystallized from acetone–*n*-hexane to afford 9.1 g of pale yellow needles, mp 92–93 °C. Total yield of **14** was 32.1 g (62.6%). Recrystallization from the same solvent furnished colorless needles: mp 92.5 °C (lit.[8] mp 93–94 °C); IR ($CHCl_3$) 1708 (C=O) cm^{-1}; NMR δ 3.50 (m, 1, C(2)H), 5.93 (s, 2, OCH_2O), 6.52–6.82 (m, 3, aromatic H).

3-(3′,4′-Methylenedioxyphenyl)-2-oxocyclohexylacetic Acid (15). An enamine was prepared in the usual manner refluxing **14** (5.45 g) and pyrrolidine (4 g) in anhydrous benzene (150 mL) for 16 h and used after complete evaporation of the solvent at reduced pressure. To a stirred solution of the above enamine in freshly distilled dioxane–benzene (1:1) (100 mL) was added a solution of $BrCH_2COOCH_3$ (7.65 g) in the same solvent (100 mL) during 2 h and refluxing was continued for 15 h. H_2O (50 mL) was added to the mixture and the whole was refluxed for 1 h. To the residue obtained on removal of the solvent at reduced pressure was added CH_3OH (20 mL) and 10% aqueous KOH (20 mL) and the mixture was refluxed for 2 h. The mixture was condensed at reduced pressure, diluted with H_2O, and washed with ether. The usual workup of the ether extract gave 2.4 g of unchanged **14**, mp 80–85 °C. The alkaline solution was acidified with concentrated HCl and the product was taken up in $CHCl_3$. The usual workup of the $CHCl_3$ extract gave 4 g of a solid, which was recrystallized from benzene–*n*-hexane to give 3.1 g (80.7%) of colorless prisms (**15**): mp 124–128 °C; an analytical sample had mp 129–130 °C; IR ($CHCl_3$), 1710 (C=O,COOH) cm^{-1}; NMR δ 2.75 (d, J = 7.5 Hz, 2, $CHCH_2COOH$), 3.60 (m, 1, C(3)H), 5.95 (s, 2, OCH_2O), 6.65–6.90 (m, 3, aromatic H). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 64.96; H, 5.82.

Oxime 5 of 15. A mixture of **15** (2.1 g) and NH_2OH·HCl (2.9 g) in 2 N NaOH (100 mL) was refluxed for 3 h. The mixture was adjusted to pH 2–3 under ice cooling by careful addition of concentrated HCl over a period of 30 min. A resulting precipitate was collected by filtration, washed with cold H_2O, and dried. Recrystallization from aqueous CH_3OH gave 1.66 g (75.4%) of light brown prisms (**5**): mp 137 °C dec; an analytical sample had mp 139–142 °C dec; IR (KBr) 3320 (OH), 1713 (COOH), 1668 (C=N) cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.67; H, 5.85; N, 4.89.

Treatment of 5 with Zinc Dust in Acetic Acid. A mixture of **5** (1.02 g) and zinc dust (1 g) in glacial AcOH (40 mL) was stirred at reflux for 3 h. After cooling, the mixture was filtered and the filtrate was condensed at reduced pressure leading to an amorphous mass, which was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 5% aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). Evaporation of the solvent gave 450 mg of an amorphous mass, which was chromatographed over silica gel (10 g). Elution with benzene–$CHCl_3$ (4:1) led to 70.5 mg (7.8%) of **8**, mp 162–165 °C, which was recrystallized from benzene–*n*-hexane yielding colorless prisms: mp 168–171.5 °C; IR (KBr) 3210 (NH), 1670 (CONH) cm^{-1}; NMR δ 2.68–3.10 (m, 1, C(7)H), 5.88 (s, 2, OCH_2O), 6.55–6.88 (m, 3, aromatic H); MS *m/e* 257 (M^+). Anal. Calcd for $C_{15}H_{15}NO_5$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.88; H, 5.72; N, 5.67.

Elution with benzene–$CHCl_3$ (4:2) afforded 138 mg (15%) of **9**, mp 187–189 °C, which was recrystallized from benzene–*n*-hexane producing pale yellow needles: mp 191–192 °C; IR (KBr) 3190 (NH), 1667 (CONH) cm^{-1}; NMR δ 1.92 (quintet, J = 6.3 Hz, 1, C(5)H), 2.57 (t, J = 6.3 Hz, 2, C(6)H), 2.65 (t, J = 6.3 Hz, 2, C(4)H), 5.74 (brs, 1, C(3)H), 5.92 (s, 2, OCH_2O), 6.80 (s, 3, aromatic H); MS *m/e* 255 (M^+). Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found; C, 70.73; H, 5.20; N, 5.59.

Elution with benzene–$CHCl_3$ (1:1) and $CHCl_3$ furnished 94 mg (10.5%) of **10**, mp 192–197 °C, whose recrystallization from CH_3OH yielded colorless prisms: mp 193–198 °C; IR (KBr) 3170 (NH), 1668 (CONH) cm^{-1}; NMR δ 3.81 (d, J = 10 Hz, C(7a)H), 5.67 (m, 1, NH), 5.73 (brs, 1, C(3)H), 5.90 (s, 2, OCH_2O), 6.60–6.78 (m, 3, aromatic H); MS *m/e* 257 (M^+). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.14; H, 5.75; N, 5.54.

The alkaline solution was acidified with concentrated HCl and the product was taken up in $CHCl_3$. Usual workup of the $CHCl_3$ extract gave 500 mg of **15**, which was characterized by the IR spectrum.

Catalytic Hydrogenation of 9 and 10. (1) A mixture of **9** (90.2 mg) and Adams catalyst (70 mg) in CH_3OH (18 mL) was shaken at room temperature in hydrogen atmosphere. After filtration of the catalyst, the solvent was removed at reduced pressure to give 89 mg of a solid, which was subjected to preparative TLC[18] over a silica gel GF_{254} plate affording 6.6 mg (7.3%) of **8** (from the faster moving band), whose IR spectrum was identical with that of a sample obtained above, and 76.6 mg (84.8%) of **17** (from the slower moving band). Recrystallization of the latter from benzene–*n*-hexane led to 41.8 mg (46%) of colorless prisms: mp 193–195.5 °C; an analytical sample had mp 194–196 °C; IR ($CHCl_3$) 3420 (NH), 1692 (CONH) cm^{-1}; NMR δ 2.80 (m, 1, C(7)H), 3.88 (t, J = 4 Hz, 1, C(7a)H), 5.04 (brs, 1, NH), 5.96 (s, 2, OCH_2O), 6.62–6.83 (m, 3, aromatic H). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.43; H, 6.74; N, 5.17.

A mixture melting point of this and Hill's lactam[2a] (mp 191–192 °C) showed appearant depression (mp 160–180 °C).

(2) A mixture of **10** (26.6 mg) and Adams catalyst (13 mg) in CH_3OH (5 mL) was treated in the same manner as noted above to give 27 mg (quantitative yield) of **3**, whose recrystallization from ether furnished colorless needles: mp 191.5–192.5 °C; NMR δ 3.41 (dd, J = 7 and 10 Hz, 1, C(7a)H), 5.88 (brs, 1, NH), 5.96 (s, 2, OCH_2O), 6.60–6.90 (m, 3, aromatic H). This was identical in all respects with Hill's lactam.[2a]

(±)-γ-Lycorane (12). To an ice-cooled solution of **17** (39.4 mg) in anhydrous THF (6 mL) was added 0.92 M diborane–THF (1.5 mL) and the mixture was refluxed for 2.5 h. Excess of diborane was decomposed with 6 N HCl (0.75 mL). The solvent was removed at reduced pressure and the residue was dissolved in H_2O. The mixture was washed with ether and basified with K_2CO_3 (powder). The product was taken up in ether and the usual workup afforded a pale yellow oil (37.2 mg). A mixture of the amine (37.2 mg) and 37% formaline (1.2 mL) in CH_3OH (1.2 mL) was stirred at room temperature for 10 min. To the stirred mixture were added CH_3OH (0.3 mL) and 6 N HCl (3.7 mL) and stirring was continued at room temperature for 3 h. The same workup as noted above gave a pale yellow oil (37.6 mg), which was chromatographed over alumina (Merck Co., Ltd.) to yield 22.1 mg (56.6%) of (±)-γ-lycorane (**12**), mp 66–77 °C. Recrystallization from petroleum ether led to 5.8 mg (14.8%) of colorless prisms, mp 105–106 °C, which were identical in all respects with an authentic specimen.[6a]

(±)-1-Benzyl-*trans*-7,7a*H*-4,5,6,7,7a-pentahydro-7-(3′,4′-methylenedioxyphenyl)-3,3a-dehydroindolin-2-one (11). A mixture of **15** (2.76 g) and benzylamine (1.57 g) in *o*-xylene (60 mL) was refluxed in a flask equipped with a Dean–Stark apparatus for 8 h. The solvent was removed at reduced pressure and the residue was refluxed with 87% HCOOH (20 mL) for 1 h. Evaporation of the solvent at reduced pressure gave a brown oil, which was dissolved in $CHCl_3$. Usual workup of the $CHCl_3$ solution afforded a brown amorphous mass (4.08 g), which was subjected to column chromatography over silica gel (120 g). Elution with benzene–$CHCl_3$ (1:1) and $CHCl_3$ furnished 2.35 g (67.8%) of a pale yellow amorphous product (**11**). All attempts to crystallize failed: IR[19] (film) 1680 cm^{-1} (CON=); NMR δ 3.32 (d, J = 15 Hz, 1, NCHHAr), 3.78 (d, J = 10 Hz, 1, C(7a)H), 4.93 (d, J = 15 Hz, 1, NCHHAr), 5.91 (s, 1, C(3)H), 5.97 (s, 2, OCH_2O), 6.54–6.81 (m, 5, aromatic H), 7.10–7.23 (m, 3, aromatic H); MS *m/e* 347 (M^+), 91 (base peak).

(±)-1-Benzyl-*trans*-7,7a*H*-*cis*-3,3a*H*-3a,4,5,6,7,7a-hexahydro-7-(3′,4′-methylenedioxyphenyl)indolin-2-one (20). A mixture of **11** (500 mg) and Adams catalyst (50 mg) in C_2H_5OH (50 mL) was shaken at room temperature with hydrogen until uptake of hydrogen ceased. Usual workup of the mixture gave 443 mg (88.6%) of a solid (**20**), mp 132–136 °C, which was recrystallized from *n*-hexane to produce 400 mg (80%) of colorless prisms: mp 137–138 °C; IR (KBr) 1672 (CON=) cm^{-1}; NMR δ 2.96 (d, J = 15 Hz, 1, NCHHAr), 3.37 (diffuse dd, J = 6.25 and 10 Hz, 1, C(7a)H), 4.95 (d, J = 15 Hz, 1, NCHHAr), 5.97 (s, 2, OCH_2O), 6.58–6.88 (m, 5, aromatic H), 7.15–7.30 (m, 3, aromatic H). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.68; H, 6.52; N, 4.09.

(±)-α-Lycorane (1). A mixture of **20** (349 mg) and $LiAlH_4$ (157 mg) in anhydrous ether–THF (1:1) (66 mL) (freshly distilled from $LiAlH_4$) was refluxed with stirring for 40 min. Excess of $LiAlH_4$ was decomposed at 0–5 °C with saturated aqueous Na_2SO_4 (4 mL) and a precipitate was filtered. The precipitate was washed well with ether and the combined organic layer was dried ($MgSO_4$). Evaporation of the solvent gave an oily residue. A mixture of the residue, 2% aqueous $PdCl_2$ (6.8 mL), concentrated HCl (1 mL), and active carbon (320 mg) in C_2H_5OH (20 mL) was shaken in a Parr hydrogenation apparatus (hydrogen pressure of 80 psi) at room temperature for 87 h. Usual workup of the mixture gave 219.1 mg of an oil, whose NMR spectrum showed no signals due to the benzyl group. A mixture of the crude residue, $KHCO_3$ (163 mg)–H_2O (2.3 mL), 37% formalin (3.5 ml), and concentrated HCl (1.6 mL) in CH_3OH (11.6 mL) was refluxed for 45 min. To the mixture was added concentrated HCl (1.6 mL) and refluxing was continued for 45 min. The same treatment as noted above gave 208.9 mg of an oil, which was chromatographed over Al_2O_3 (Grade II–III) (Merck Co., Ltd.) (12 g). Elution with benzene–*n*-hexane (24:1) gave 128 mg (50%) of (±)-α-lycorane (**1**), mp 85–92.5 °C, which was recrystallized from petroleum ether to yield 30 mg (11.7%) of colorless prisms, mp 95.5–97 °C. This was identical in all respects with an authentic sample[2b] (mp 96–97.5 °C), which was kindly provided by Drs. K. Kotera and Y. Hamada.

Acknowledgments. We wish to express our sincere thanks to Drs. K. Kotera and Y. Hamada, Central Research Laboratory of Shionogi Co., Ltd., and Professor R. K. Hill, University of Georgia, for their kind gifts of (±)-α- and (±)-γ-lycorane with their spectral data and of the lactam **3**. We are indebted to Dr. H. Yoshitake, Ube Kosan Co., Ltd., for his kind supply of a starting material. We are grateful to Dr. H. Hara for his useful discussion and to Misses Y. Arigaya and T. Umemura for their technical assistance. Thanks are also due to Misses T. Kawana and S. Komatsu of this Faculty for spectral measurements and to Sankyo Co., Ltd., for elemental analysis.

Registry No.—**1**, 63814-02-8; **3**, 63797-13-7; **5**, 63784-87-2; **8**, 63765-06-0; **9**, 63765-07-1; **10**, 63765-08-2; **11**, 63765-09-3; **12**, 63814-03-9; **13**, 63765-10-6; **14**, 63765-11-7; **14** pyrrolidine enamine, 63765-12-8; **15**, 63765-13-9; **17**, 63765-14-0; **20**, 63765-15-1; cyclohexanone, 108-94-1; 5-bromobenzo-1,2-dioxole, 2635-13-4; pyrrolidine, 123-75-1; benzylamine, 100-46-9.

References and Notes

(1) (a) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 4395 (1958); (b) K. Takeda, K. Kotera, S. Mizukami, and M. Kobayashi, *Chem. Pharm. Bull.*, **8**, 483 (1960); (c) K. Kotera, *Tetrahedron*, **12**, 240 (1961).
(2) (a) R. K. Hill, J. A. Joule, and L. J. Loeffler, *J. Am. Chem. Soc.*, **84**, 4951 (1962); (b) K. Kotera, Y. Hamada, and K. Fujimoto, Abstracts of Papers at the 90th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, Hokkaido, II-79, 1970; (c) H. Irie, Y. Nishitani, M. Sugita, and S. Uyeo, *Chem. Commun.*, 1313 (1970); *Yakugaku Zasshi*, **96**, 631 (1976); (d) H. Irie, Y. Nagai, K. Tamoto, and H. Tanaka, *J. Chem. Soc., Chem. Commun.*, 302 (1973).
(3) Y. Tsuda, T. Sano, J. Taga, K. Isobe, J. Toda, H. Irie, H. Tanaka, S. Takagi, M. Yamaki, and M. Murata, *J. Chem. Soc., Chem. Commun.*, 933 (1975).
(4) Synthetic endeavors toward **2** have been reported by several groups of chemists: J. B. Hendrickson, R. W. Alder, D. R. Dalton, and D. G. Hey, *J. Org. Chem.*, **34**, 2667 (1969); S. F. Dyke, M. Sainsbury, and I. R. Evans, *Tetrahedron*, **29**, 213 (1973); H. Muxfeldt, J. P. Bell, J. A. Baker, and U. Cuntze, *Tetrahedron Lett.*, 4587 (1973); K. Torssell, *ibid.*, 623 (1973).
(5) J. T. Edward and P. F. Morand, *Can. J. Chem.*, **38**, 1316 (1960).
(6) (a) K. Kotera, *Tetrahedron*, **12**, 248 (1961); (b) N. Ueda, T. Tokuyama, and T. Sakan, *Bull. Chem. Soc. Jpn.* **39**, 2012 (1966); (c) B. Ganem, *Tetrahedron Lett.*, 4105 (1971); (d) H. Hara, O. Hoshino, and B. Umezawa, *ibid.*, 5031 (1972); (e) H. Iida, S. Aoyagi, and C. Kibayashi, *J. Chem. Soc., Chem. Commun.*, 499 (1974); *J. Chem. Soc., Perkin Trans. 1*, 2502 (1975).
(7) C. Feugeas, *Bull. Soc. Chim. Fr.*, 1892 (1964).
(8) W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2567 (1958).
(9) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, p 50.
(10) The values of $J_{a,e}$ and $J_{a,a}$ corresponding to $\Phi \sim 45°$ and $\Phi \sim 170°$ as measured on a Dreiding model for **16** and **10** were 4.9 and 15.5 Hz, respectively.
(11) An exception where catalytic hydrogenation of 3a,4,5,6-tetrahydro-7-phenyloxindole gave *trans*-hexahydro-7-phenyloxindole is reported: A. N. Kost and I. P. Rudakova, *J. Gen. Chem. USSR (Engl. Transl.)*, **35**, 140 (1965).
(12) Considering the $A^{1,3}$ strain[13] by interaction of the aryl and benzyl group in **18**, the unsaturated lactam (**19**) would have been formed predominantly at the initial stage.
(13) Cf. F. Johnson, *Chem. Rev.*, **68**, 375 (1968).
(14) Long-range coupling was likely responsible, though unchecked experimentally.
(15) Melting and boiling points are uncorrected. IR spectra were taken with a Hitachi Perkin-Elmer Model 225 grating spectrometer, unless otherwise noted. NMR spectra were recorded on a JEOL JNM-4H-100 spectrometer at 100 MHz in $CDCl_3$ solution (5–10%) using $(CH_3)_4Si$ as an internal standard. Mass spectra were measured with a Hitachi RMU-7M double-focusing mass spectrometer at 70 eV by direct insertion.
(16) W. J. Gensler and J. E. Stouffer, *J. Org. Chem.*, **23**, 908 (1958).
(17) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).
(18) 5% CH_3OH–$CHCl_3$ solution was used as a developing solvent.
(19) A 215 Hitachi grating infrared spectrometer was used.

Behavior and Stability of Catalysts in Bi- and Triphase Transfer Catalysis

Henri J.-M. Dou,*[1a] Roger Gallo,[1b] Parina Hassanaly,[1a] and Jacques Metzger

Department of Organic Chemistry and I.P.S.O.I, Faculté des Sciences, Centre Universitaire Saint Jérôme, 13013 Marseille, France

Received July 15, 1977

Phase-transfer catalysis is becoming an increasingly important technique in organic synthesis.[2-7] However, very little is known about the behavior of the catalysts under biphase[2-6] and triphase conditions.[7]

Recently we observed that alkylation of thio reagents, by alkyl halides of low reactivity, gave poor yields (<20%) under biphasic conditions. Furthermore, with triphase systems, the repeatability of the reaction with the same catalyst (anion exchange resin) was not maintained after three runs.[8]

These facts prompted us to examine the chemical behavior, in classical PTC media, of various catalysts and anions (obtained from phenylacetonitrile, imidazole, phenol, thiophenol, and octylmercaptan) in the absence of alkylating reagent.

Under biphase catalysis conditions the catalysts used were: TEBA-Cl, TBAB, and CTAB.[9] The results, presented in Table I, show that the catalyst may be decomposed by alkylating the anion. This decomposition depends upon the nature of the anion and the structure of the ammonium catalyst. With TEBA-Cl and thiophenoxide this corresponds to 93% of the concentration of the catalyst. The results obtained are consistent with a nucleophilic substitution where the anion is the nucleophile and the tertiary amine is the leaving group (Scheme I). This is analogous to the dealkylation reactions of quaternary ammonium salts by nucleophilic sulfur reagents[11] or soft nucleophiles.[12,19]

Under triphase catalysis, the catalysts used were Dowex 1 × 8 and Dowex 11 anion exchange resins. Both resins are of the trimethylbenzylammonium type (Scheme II). During the reaction the gas evolved (a volatile amine if dequaternization occurred according to Scheme I) was trapped in a saturated solution of picric acid in ethanol. The results obtained show that without anion and for a reaction time of 6 h no picrate was formed, but with the anions of thiophenol and phenylacetonitrile a picrate did form.[10]

Although the decomposition of the quaternary ammonium catalyst (Scheme I) is in most cases only a secondary reaction, it can become more important for soft nucleophiles (RS^- >

Scheme I

$$Nu^- + RCH_2N^+R'_3\ X^- \xrightarrow{PTC} NuCH_2R + NR'_3 + X^-$$

Scheme II

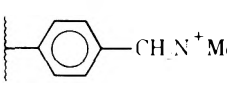


Table I. Alkylation (%) of Anions by Quaternary Ammonium Catalysts Under PTC Conditions

Anions	Catalysts[g] TEBA-Cl[a]	TBAB	CTAB[b]
$C_6H_5CH^-CN$	85[c]	Traces[c]	
$C_3H_3N_2^-$ [i]	0.5[c]	0.6[e]	
$C_6H_5O^-$	0[e]	0[d]	0[c]
$C_6H_5S^-$	93[d]	90[d]	33[g]
	17[f]		
$C_8H_{17}S^-$	93[h]	90[e]	

[a] Only benzylation of the anion was detected. [b] Only methylation of the anion was detected. [c] 6 h at 60 °C. [d] 7 h at 70 °C. [e] 7 h at 60 °C. [f] 11 h at 30 °C, with 1.5 g of TEBA-Cl. [g] 7 h at 60 °C with 1.5 g of CTAB. [h] 7 h at 45 °C with 20% by weight sodium hydroxide. [i] Imidazole.

$R_3C^- > R_2N^- > RO^-$) and for substituents of the quaternary ammonium salt R_4N^+ which are easily displaced (R = CH_2Ph > Me > alkyl). This, in turn, will have a dramatic effect on the yields of the phase transfer catalyzed reaction itself.

Since normal PTC reaction conditions necessitate a 5% molar concentration of the catalyst, the side products obtained by dealkylation of the catalyst will never exceed 5% yield; e.g., the alkylation of thiophenol by 1-bromooctane has been studied, using several ammonium catalysts, without evidence of decomposition of the catalyst.[13] On the other hand, when reagents of low reactivity are used the effect is more pronounced; e.g., when thiophenol is reacted with 2-bromothiophene or 2-bromothiazole the yield of the reaction with the bromide is 0–4% while the alkylation by the ammonium salt corresponds to 55–85% of the concentration of the catalyst (see Experimental Section).

Furthermore, one must note that for continuous processes, where the catalyst is recycled, even a slow quaternary ammonium salt decomposition will lead to the disappearance of the catalyst and to an eventual termination of the phase transfer catalysis process.

One way to circumvent this inconvenience is the use of more stable catalysts such as crown ethers,[13,14] but their use for large scale synthetic purposes is still difficult.[15] One other possibility is the use of polyglymes, which can be considered as noncyclic crown ethers. They are stable, easily available, and could be used both under bi-[17] and triphase conditions.[18] We are presently studying these possibilities further.

In summary, the results reported in this study can be used to explain the origin of side products, low yields, and nonconstancy of the performances of supported catalysts in phase-transfer catalysis.

Experimental Section

The phase-transfer catalysts and nucleophiles are commercial products. They have been used without further purification. The quantitative determinations of alkylated compounds have been made by GLC with a IGC 120FB Intersmat instrument or with a coupled GLC-mass spectrometer Varian Mat111.

Procedure for Biphase Conditions (Table I). The general experimental procedure was as follows: 3 g of the anion precursor, 1 g of catalyst, and 40 mL of sodium hydroxide (50% by weight) were stirred for 6–11 h at 30–70 °C. The organic layer was directly analyzed by GLC.

Procedure for Triphase Conditions. The general experimental procedure was as follows: 1.5 g of resin, 4 mL of sodium hydroxide (50% by weight), and 0.5 g of anion precursor were stirred at 80 °C for 3 h. The gas evolved was trapped in a solution of picric acid in ethanol. The picrate was filtered. The melting point was measured with a Koffler apparatus.

Procedure for 2-Bromothiazole: 5.5 g of thiophenol (0.05 mol), 8.2 g of 2-bromothiazole (0.05 mol), 1.09 g of CTAB, 100 mL of NaOH (50% by weight), and 150 mL of benzene were reacted with stirring for 24 h at 70 °C. The analysis of the organic layer by GLC showed 4% of 2-thiazolyl phenyl thioether and 55% of methyl phenyl thioether (from the catalyst CTAB). The above reaction with the same compounds, except NaOH (25% by weight), TBAB as catalyst, and a reaction time of 10 h at 80 °C gave 0% of 2-thiazolyl phenyl thioether and 84% of butyl phenyl thioether.

Procedure with 2-Bromothiophene: 5.5 g of thiophenol (0.05 mol), 8.2 g of 2-bromothiophene (0.05 mol), 0.7 g of TBAB, and 100 mL of NaOH (50% by weight) were reacted for 10 h at 80 °C. Less than 1% of 2-thiophenyl phenyl thioether and 85% of butyl phenyl thioether was detected from the catalyst.

Registry No.—Phenylacetonitrile, 140-29-4; imidazol, 288-32-4; phenol, 108-95-2; thiophenol, 108-98-5; octanethiol, 111-88-6; TEBA-Cl, 56-37-1; TBAB, 1643-19-2; CTAB, 57-09-0; Dowex 1 × 8, 12627-85-9; Dowex 11, 9049-12-1; 2-bromothiazole, 3034-53-5; 2-thiazolyl phenyl thioether, 33342-67-5; methyl phenyl thioether, 100-68-5; butyl phenyl thioether, 1126-80-3; 2-bromothiophene, 1003-09-4; 2-thiophenyl phenyl thioether, 16718-12-0.

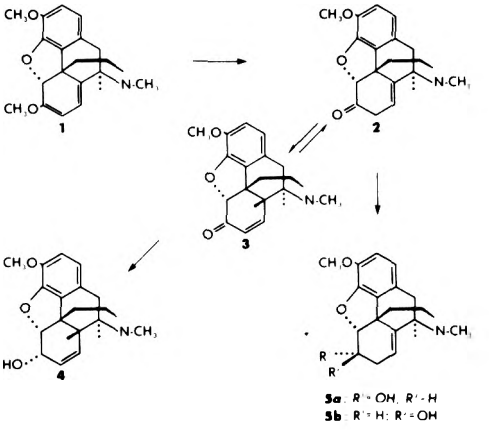
References and Notes

(1) (a) Department of Organic Chemistry; (b) I.P.S.O.I.
(2) (a) C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971); (b) M. Makosza, *Pure Appl. Chem.*, **43**, 439 (1975).
(3) E. V. Dehmlow, *Angew. Chem., Int. Ed. Engl.*, **13**, 170 (1974).
(4) H. J.-M. Dou, *Chim. Actual.*, 41 (1974).
(5) J. Dockx, *Synthesis*, 441 (1973).
(6) A. Brändström, "Preparative Ion Pair Extraction", Apotekarsocieteten/Lakemedel, Stockholm, 1974.
(7) S. L. Regen, *J. Am. Chem. Soc.*, **97**, 5956 (1975); S. L. Regen, *ibid.*, **98**, 6260 (1976).
(8) H. J.-M. Dou, P. Hassanaly, J. Kister, G. Assef, and J. Metzger, *Synthesis*, 253 (1977); H. J.-M. Dou, P. Hassanaly, J. Kister, and J. Metzger, *"Phosphorous and Sulfur"*, **3**,355 (1977) H. J.-M. Dou, H. Komeilei-zadeh, and J. Metzger, *J. Org. Chem.*, submitted for publication.
(9) TEBA-Cl, triethylbenzylammonium chloride; TBAB, tetrabutylammonium bromide; CTAB, hexadecyltrimethylammonium bromide.
(10) Unfortunately, this result which indicates a dequaternization of the resin is not fully understood because the melting point of the picrate ranges from 145 to 155 °C, a value different from that of the picrate of the trimethylamine.
(11) K. C. Westaway and R. A. Poirier, *Can. J. Chem.*, **53**, 3216 (1975), and references cited; N. Shamma, N. C. Deno, and J. F. Remar, *Tetrahedron Lett.*, 1375 (1966); T. Kametani, K. Kigasawa, M. Hiiragi, and K. Wakisawa, *ibid.*, 635 (1969); G. H. Posner and J. S. Ting, *Synth. Commun.*, **4**, 355 (1974); R. O. Hutchins and F. J. Dux, *J. Org. Chem.*, **38**, 196 (1973).
(12) U. Berg, R. Gallo, and J. Metzger, *J. Org. Chem.*, **41**, 2621 (1976); T. H. Lane and J. L. Spier, *ibid.*, **41**, 2714 (1976); H. J.-M. Dou, R. Gassend, and J. C. Maire, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **281**, 945 (1975).
(13) A. W. Herriott and D. Picker, *J. Am. Chem. Soc.*, **97**, 2345 (1975).
(14) D. Landini, F. Montanari, and F. Parisi, *J. Chem. Soc., Chem Commun.*, 879 (1974); M. Cinquini and P. Tundo, *Synthesis*, 316 (1976).
(15) Preparation and purification of crown ether is still a tedious task.[16]
(16) G. W. Gokel and H. D. Durst, *Synthesis.*, 168 (1976).
(17) H. Lehmkuhl, F. Rabet, and K. Hanschild, *Synthesis*, 184 (1977).
(18) S. L. Regen and L. Dulak, *J. Am. Chem. Soc.*, **99**, 624 (1977).
(19) J. B. Bapat et al. *Tetrahedron Lett.*, 2694 (1976); N. F. Eweiss, A. R. Katritzry, R. L. Nie, and C. A. Ramsden, *Synthesis*, 634 (1977).

Selective Reductions of Neopinone to Neopine and Isoneopine

Summary: Reduction of neopinone (**2**) with sodium borohydride in alcoholic solvents is not stereoselective because of a balance between steric interference caused by the hydrofuran ring and by the axial hydrogens at C-5 and C-7. When bulky reducing agents are used, the blocking effect of the hydrofuran ring becomes the dominant factor, and stereoselective reduction to neopine (**5a**) is achieved; with a small reducing agent, such as sodium borohydride in an aqueous alkaline medium, the main directing force is represented by the axial hydrogens, leading to a predominance of isoneopine (**5b**).

Sir: Conroy[1] reported that reduction of neopinone (**2**) with sodium borohydride gave neopine (**5a**) as the only product observed and isolated. This was analogous to the report of Gates[2] that codeinone (**3**) is stereospecifically reduced to codeine (**4**). However, more recent studies by Okuda et al.[3,4]



showed that the reduction of neopine is not stereospecific and gives a mixture of neopine (**5a**) and isoneopine (**5b**) in approximately equal amounts. This greatly limits the efficiency of the syntheses of neopine and isoneopine, both of which are of interest, neopine as a natural opium alkaloid[5] and isoneopine as an intermediate in the synthesis of B/C trans-fused morphine analogues.[6]

We would like to report the stereoselective reduction of neopinone to either neopine or isoneopine in nearly quantitative yields under carefully controlled reaction conditions.

The stereochemistry of metal hydride–ketone reductions is determined by a combination of steric interference, torsional strain, and electrostatic effects.[7] Examination of a molecular model of neopinone indicates that the plane of ring A makes an angle of about 110° with the plane of ring C, as illustrated in Figure 1. This implies that the α face of the carbonyl group of neopinone is partially blocked by the hydrofuran ring. Bulky borohydride reducing agents, such as those developed by Brown and Krishnamurthy,[8] are very sensitive to steric influence around the carbonyl group and should, therefore, approach neopinone from the less hindered β face to give the α-alcohol, neopine. This proved to be the case. When neopinone, produced from thebaine (**1**),[9] was treated with either lithium triethylborohydride[10] or lithium tri-*sec*-butylborohydride[11] in tetrahydrofuran, neopine was the sole reduction product detected by TLC and NMR and isolated in 95% yield on a column of neutral alumina (Table I).

Small reducing agents such as the borohydride anion or the aluminum hydride anion appear to have an intrinsic preference for "axial" attack in substituted cyclohexanones.[7] "Product development control"[12] and "torsional strain"[13] are rationalizations that have been offered to explain this preference, although recent work[14,15] seems to indicate that "product development control" is not a viable hypothesis for this reaction. Torsional strain in cyclohexanone systems is the interaction between axial hydrogens α to the carbonyl group and the incoming reducing agent.

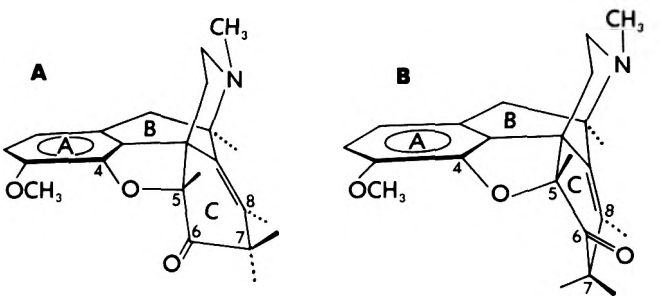


Figure 1. Conformations of neopinone.

Molecular models of neopinone indicate that there are two possible conformations for ring C (Figure 1, A and B). In conformation A the oxygen of the carbonyl group is resting below the plane of the ring, and the C(5) hydrogen and one hydrogen at C(7) are in an axial configuration extending above the plane of the ring. Thus, "axial" attack of a reducing agent would lead to isoneopine. In conformation B the oxygen of the carbonyl group extends above the plane of ring C, and the hydrogen at C(5) assumes a pseudoequatorial orientation. "Axial" attack by borohydride on the carbonyl group in this conformation would give neopine. It is, therefore, necessary to establish the correct conformation of neopinone before considering the effect of torsional strain.

In conformation A (Figure 1) the dihedral angle between the C(7) axial hydrogen and the olefinic hydrogen at C(8) was measured from the molecular model to be about 95°. The dihedral angle between the C(7) equatorial hydrogen and the C(8) hydrogen was found to be about 27°. Calculation of the coupling constants from the Karplus equation, as modified by Conroy,[16] between C(7)–H_{ax} and C(8)–H and between C(7)–H_{eq} and C(8)–H are 0.4 and 6.4 Hz, respectively. In conformation B the dihedral angle was measured from the molecular model to be about 55° between C(7)–H_β and C(8)–H and about 65° between C(7)–H_α and C(8)–H. Calculation of the coupling constants from the modified Karplus

Table I. Effect of Solvent and Bulkiness of Reducing Agent on Reduction of Neopinone

Reducing agent/solvent	Neopinone solvent	Neopine–isoneopine	Total yield **5a** + **5b**, %
$LiEt_3BH$/THF	THF	100:0	95
$Li(s\text{-}Bu)_3BH$/THF	THF	100:0	95
$NaBH_4$/no solvent	CH_3OH	58:42	96
$NaBH_4/C_2H_5OH$	C_2H_5OH	60:40	77
$NaBH_4/i$-PrOH	i-PrOH	63:37	80
$NaBH_4$/diglyme	diglyme + Et_3N	27:73	35
$NaBH_4/H_2O/OH^-$	CH_3OH	42:58	86
$NaBH_4/H_2O/OH^-$	H_2O	11:89	98

equation gave values of 2.4 and 1.2 Hz, respectively. The observed coupling constants were 1.8 and 6.3 Hz. Consequently, the conformation of neopinone corresponds most closely to that illustrated in Figure 1A.

According to the torsional strain concept "axial" attack by sodium borohydride in the reduction of neopinone should lead to a predominance of isoneopine. However, since the reduction of neopinone is very sensitive to the bulkiness of the reducing agent, as shown by the fact that neopine was the only product of reduction with lithium triethylborohydride which is not usually so highly selective, the nature of the solvent must also be considered. In alcoholic solvents the alcohol acts as a catalyst[17] and enters into the transition state, from which a series of alkoxyborohydrides is formed, $R_nBH_{4-n}^-$, where R is the alkoxy group of the solvent.[18] The alkoxyborohydrides reduce the carbonyl group more rapidly than does the borohydride ion.[19] This can result in a change in the ratio of isomers during the course of the reduction,[20-22] presumably because of the added bulkiness of the alkoxyborohydrides formed in the reaction.

When neopinone was reduced with an excess of sodium borohydride in alcoholic solvents, neopine and isoneopine were produced in ratios of approximately 6:4 (Table I). There appeared to be a trend toward a greater proportion of isoneopine with a decrease in the molecular weight of the alcohol, although the difference may be too small to be considered significant. Apparently, the bulkiness of the alkoxyborohydrides formed in any alcoholic solvent is such that steric interference from the hydrofuran ring plays a greater role than torsional strain in directing the borohydride attack.

When sodium borohydride reductions are performed in diglyme in the presence of an excess of triethylamine, the borohydride anion alone is the reducing agent.[22] Subsequent borane is trapped as the aminoborane, which is incapable of further reductions in this system. When neopinone was reduced under these conditions, the ratio of isoneopine to neopine was greatly increased. However, the overall yield of alcohols was poor (35%). Finally, a method was devised for reduction of neopinone in aqueous solution. Neopinone was generated from 400 mg of thebaine in aqueous acetic acid as described by Barber and Rapoport.[9] The neopinone solution was cooled in an ice bath to 0 °C and neutralized slowly with potassium hydroxide to about pH 6.5. A solution of 1 g of sodium borohydride in potassium hydroxide solution (pH ≥13) was added over 5 min and the mixture immediately extracted with chloroform. Evaporation of the solvent left a residue which was chromatographed on neutral alumina, first with 25% chloroform in benzene which eluted neopine (11% yield), then with 60% chloroform in benzene which gave isoneopine (88% yield). The identity of both compounds was confirmed by melting point, TLC, and NMR spectroscopy.[23]

There may be several reasons why this selectivity is achieved when the reduction is carried out in an aqueous alkaline medium. Perhaps the bulkiness of the hydroxyborohydrides formed after the initial step is insufficient to be adversely affected by the steric hindrance posed by the hydrofuran ring. It is also possible that the hydroxyborohydrides are unstable and disproportionate rapidly to boric acid and sodium borohydride. In either case, the major directing influence would be torsional strain resulting in a predominance of the β-alcohol, isoneopine.

Acknowledgment. This work was supported by a grant from the National Institute on Drug Abuse (DA 0014-17) and the NIH Division of Research Resources (RR 00892-1A1).

References and Notes

(1) H. Conroy, *J. Am. Chem. Soc.*, **77**, 5960 (1955).
(2) M. D. Gates, *J. Am. Chem. Soc.*, **75**, 4340 (1953).
(3) S. Okuda, S. Yamaguchi, and K. Tsuda, *Chem. Pharm. Bull.*, **13**, 1092 (1965).
(4) K. Abe, M. Onda, and S. Okuda, *Chem. Pharm. Bull.*, **17**, 1847 (1969).
(5) A. H. Hohmeyer and W. L. Shilling, *J. Org. Chem.*, **12**, 356 (1947).
(6) H. Kugita, M. Takeda, and H. Inoue, *J. Med. Chem.*, **13**, 973 (1969).
(7) H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 54-64.
(8) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972).
(9) R. B. Barber and H. Rapoport, *J. Med. Chem.*, **19**, 1175 (1976).
(10) "Superhydride", Aldrich Chemical Co., Inc.
(11) "L-Selectride", Aldrich Chemical Co., Inc.
(12) W. G. Dauben, G. F. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).
(13) M. Cherest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968).
(14) D. C. Wigfield and D. J. Phelps, *Can. J. Chem.*, **50**, 388 (1972).
(15) E. C. Ashby and S. A. Noding, *J. Am. Chem. Soc.*, **98**, 2010 (1976).
(16) H. Conroy, *Adv. Org. Chem.*, **2**, 311 (1960).
(17) D. C. Wigfield and F. W. Gowland, *J. Org. Chem.*, **42**, 1108 (1977).
(18) D. C. Wigfield and F. W. Gowland, *Tetrahedron Lett.*, 3373 (1976).
(19) E. R. Garrett and D. A. Lyttle, *J. Am. Chem. Soc.*, **75**, 6051 (1953); H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6902 (1955).
(20) R. E. Davis and J. A. Gottbrath, *J. Am. Chem. Soc.*, **84**, 895 (1962).
(21) B. Rickborn and M. R. T. Wuesthoff, *J. Am. Chem. Soc.*, **92**, 6894 (1970).
(22) W. M. Jones and H. E. Wise, *J. Am. Chem. Soc.*, **84**, 997 (1962).
(23) Mixture melting point of neopine with an authentic sample[24] showed no depression. The melting point of isoneopine was 158–159 °C (lit.[3] 155–156 °C). The R_f values on alumina with chloroform–methanol (99:1) were 0.54 for neopine and 0.27 for isoneopine, in good agreement with reported values.[4] The most significant difference in the NMR spectra was the chemical shift of C(6)-H observed at 4.23 ppm for neopine (lit.[25] 4.22) and 3.80 ppm for isoneopine (lit.[25] 3.62). The C(5)-H of neopine resonated at 4.63 ppm (d, J = 4.3 Hz) [lit.[25] 4.62 (J = 4.2 Hz)] and of isoneopine at 4.48 ppm (d, J = 8.5 Hz) [lit.[25] 4.54 (J = 8.6 Hz)]. The methoxy protons of neopine showed a chemical shift at 3.86 ppm (lit.[26] 3.86) and of isoneopine at 3.82 ppm (lit.[4] 3.82).
(24) Mallinckrodt Chemical Works.
(25) T. J. Batterham, K. H. Bell, and A. Weiss, *Aust. J. Chem.*, **18**, 1799 (1965).
(26) K. Abe, Y. Nakamura, and M. Onda, *Tetrahedron*, **27**, 4495 (1971).

Stephen W. Wunderly, Einar Brochmann-Hanssen*
Department of Pharmaceutical Chemistry
School of Pharmacy, University of California
San Francisco, California 94143

Received June 7, 1977

Additions and Corrections

Vol. 40, 1975

Baldev K. Bandlish, A. Greg Padilla, and Henry J. Shine*: Ion Radicals. 33. Reactions of 10-Methyl- and 10-Phenylphenothiazine Cation Radicals with Ammonia and Amines. Preparation and Reactions of 5-(*N*-Alkyl)sulfilimines and 5-(*N*,*N*-Dialkylamino)sulfonium Salts.

Page 2592. Column 1, Table IV and line 2, paragraph 1: for **9m** read **9f**.

Page 2595. Column 1, line 12. Line 12 should read: ". . . (**17**) from **9f**. To a solution of 125 mg (0.26 mmol) of **9f** in 20 mL . . .".

Vol. 41, 1976

Earl Doomes,* Patricia A. Thiel, and Mark L. Nelson: Rearrangement–Substitution Reactions of a 2-(Arylsulfonyl)allyl System.

Page 251. References 3b and 9 should read as follows: (3) (b) R. H. Dewolfe and W. G. Young, *Chem. Rev.*, **56**, 753 (1956). (9) F. G. Bordwell and T. G. Mecca, *J. Am. Chem. Soc.*, **94**, 5229 (1972). An exception to this generalization was reported recently: F. G. Bordwell and G. A. Pagui, *ibid.*, **97**, 118 (1975).

Oswald S. Tee* and Ghanshyam V. Patil: The Mechanism of Bromination of 4(3*H*)-Quinazolinone, Its 3-Methyl and Its 1,3-Dimethyl Derivatives in Aqueous Acidic Solutions.

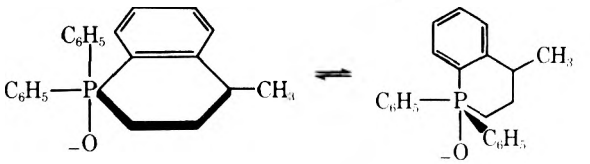
Page 842. Column 2, line 47 should read ". . . $k_2 = 0.8 \times 10^7$ M^{-1} min^{-1} (1.3×10^5 M^{-1} s^{-1}).[29]"

Page 844. Column 2, ref 7a should read ". . . *J. Chem. Soc. B*, 1484 (1968); . . ."

Page 844, Column 2, ref 29 should read ". . . 1.5×10^5 M^{-1} s^{-1}."

M. El-Deek, G. D. Macdonell, S. D. Venkataramu, and K. Darrell Berlin*: Carbon–Phosphorus Heterocycles. A One-Step Synthesis of Phosphindolines and Phosphinolines. Cyclization of Diphenylalkenylphosphine Oxides with Polyphosphoric Acid.

Page 1404. Structures **6a** and **6b**.



6a **6b**

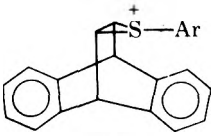
other rotamers

Tadashi Sasaki,* Shoji Eguchi, and Osamu Hiroaki: Synthesis of Adamantane Derivatives. 32. The Beckmann Rearrangement and Fragmentation Aptitude of Noradamantan-2-one Oxime.

Page 1803. Formula **17** in Scheme I should read: 6-*endo*-bicyclo[3.2.1]octanecarbonitrile.

Stanley J. Cristol,* John S. Perry, Jr., and Ronald S. Beckley: Bridged Polycyclic Compounds. 82. Multiple Mechanisms for Oxymercuration of Some Dibenzobicyclo[2.2.2]octatrienes.

Page 1912. Structure **2**.



2

Edwin D. Stevens, James D. Kramer, and Leo A. Paquette*: X-Ray Crystal Structure Analysis of Triquinacene at 90 K.

Page 2267. The third sentence of the Experimental Section, which describes the ^{13}C NMR spectrum (in $CDCl_3$) of triquinacene, contains an erroneous chemical shift value. The three peaks which characterize this molecule appear at 132.89, 57.68, and 47.96 ppm.

D. P. Bauer and R. S. Macomber*: Tricyclic Dimers from Cyclic α-Diketones.

Page 3059. Professor George M. Whitesides (MIT) has called to our attention a publication by R. A. Raphael and A. I. Scott [*J. Chem. Soc.*, 4566 (1952)], where the preparation of the compounds we designated **2a** and **7-OH** was reported. The assigned structures and physical properties (mp, IR, UV) corresponded very closely to the data we reported. Professor Whitesides also described his group's related work in the area, which he intends to publish in another connection. We are grateful for his communication.

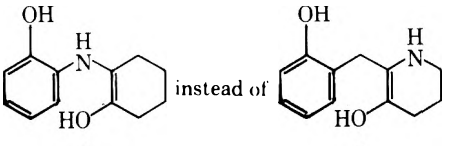
David C. Baker, Jacques Defaye, Andrée Gadelle, and Derek Horton*: Reduction of Ketones with Incorporation of Deuterium at the α Position. Anomalous Reduction of Keto Sugar Derivatives.

Page 3836. Table I. The data for compound **9** should read: **9**, $CDCl_3$[e] 4.95 d (H-1), 4.79 dd (H-2), 4.15 t (H-3), 3.52 t (H-4), 3.84 s (H-5), 4.29 q (H-6), 3.74 t (H-6′), 5.53 s (PhCH), 2.12 s (OAc), 3.39 s (OMe), 7.40 m (aryl).

Page 3837. Table II. The data for compound **9** should read: **9** $CDCl_3$[f] 3.7 ($J_{1,2}$), 9.5 ($J_{2,3}$), 9.5 ($J_{3,4}$), 9.5 ($J_{4,5}$), 4.0 ($J_{5,6}$), 10 ($J_{5,6'}$), 9.5 ($J_{6,6'}$).

Samuel G. Levine,* Charles Gragg, and Jon Bordner: Structure of the *o*-Aminophenol–Adipoin Condensation Product.

Page 4026. Column 1. Structure **5** should be given as

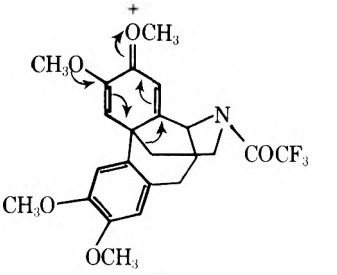


5 instead of **5**

Page 4026. Column 2. "ABC" should read "ABX" and, five lines from the bottom, "fb6" should read "**6**".

S. M. Kupchan,* Om P. Dhingra, Chang-Kyu Kim, and Venkataraman Kameswaran: Novel Nonphenol Oxidative Coupling of Phenethylisoquinolines.

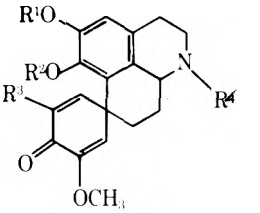
Page 4048. The structure **7** should appear as:



7

S. M. Kupchan,* Om P. Dhingra, and Chang-Kyu Kim: Efficient Intramolecular Monophenol Oxidative Coupling.

Page 4049. The structures of compounds **2c–f** should appear as:



2c-f

John F. Blount, Ru-Jen L. Han, Beverly A. Pawson,* Ross G. Pitcher, and Thomas H. Williams: (*E*)- and (*Z*)-4-Methyl-5-[5-(2,6,6-trimethylcyclohexen-1-yl)-3-methyl-2(*E*),4(*E*)-pentadienylidene]-2(5*H*)furanone. Synthesis and Spectral Properties.

Page 4110. Table II. The δc for C-14 of **2** should read 115.1, not 155.1. The assignment of chemical shift to C-19 and C-20 in **2** should be reversed, based upon a reexamination of the residual *J*'s in the SFOR spectra in conjunction with the proton spectra. (We thank Professor G. P. Moss, Queen Mary College, London, for this suggestion.)

Vol. 42, 1977

Milton L. Honig* and Edward D. Weil: A Convenient Synthesis of Diaryl Methylphosphonates and Transesterification Products Therefrom.

Page 379. The procedure of Laughlin (ref 5) has been used effec-

tively with butyl, propyl, ethyl, and methyl alcohols, obtaining yields of the corresponding diaryl alkylphosphonates in excess of 70% yield of theory (private communication, I. Hechenbleikner).

Timothy B. Patrick* and Philip A. Egan: An Improved Preparation of Phenolic [1.1.1.1]Metacyclophanes.

Page 382. This work had its inception as the result of contacts with the Washington University group, and it was intended that it he published with a paper from that laboratory. It should be considered as a companion piece to a forthcoming article from the research group of C. D. Gutsche.

J. B. Hobbs and F. Eckstein*: A General Method for the Synthesis of 2′-Azido-2′-deoxy- and 2′-Amino-2′-deoxyribofuranosyl Purines.

Page 714. Summary, line 9. **2b** should read **12b.**

Page 715. Scheme I. The figures **11a,b** and **10a,b** should be interchanged.

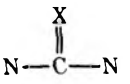
Page 718. Column 1, line 77 and 78. The figures **10b** and **11b** should be interchanged.

William G. Dauben* and David J. Hart: A Synthesis of the Ophinoholin Nucleus.

Page 922. Column 1. Structure **3** is incorrectly shown with an extra double bond. The correct representation is as shown for **3** on p 923, column 1.

Harold Kohn,* Melanie J. Cravey, Janice H. Arceneaux, Rodney L. Cravey, and M. R. Willcott III*: Syntheses and Spectral Properties of Substituted Imidazolidones and Imidazolines.

Page 942. Column 7, Table I.



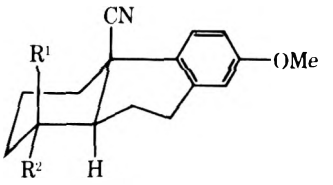
John F. Evans, Jerome R. Lenhard, and Henry N. Blount*: The Pyridination of 10-Phenylphenothiazine: Heteroatom Effects on Rates and Mechanisms of Pyridinations.

Page 986. Column 1, text line 16. "$k_{16}k_{17}/k_{-17}$" should be "$k_{16}k_{17}/k_{-16}$."

Page 986. Column 1, text lines 17–18. "2.94 (± 0.60) × 10^{-1} M^{-2} s^{-1}" should be "2.94 (± 0.60) × 10^{1} M^{-2} s^{-1}."

Tetsuji Kametani,* Yasuyuki Kato, Fumio Satoh, and Keiichiro Fukumoto: Studies on the Syntheses of Heterocyclic Compounds. 696. Stereochemistry of Four Isomeric 4a-Cyano-1,2,3,4,4a,9,10,10a-octahydro-7-methoxy-1-methoxycarbonyl-1-methylphenanthrenes.

Page 1178. Column 1. Structures B and D in Scheme II should be as follows:



Page 1178. Column 2, line 20 from bottom. "Wenkert[12] had proposed that podocarpic acid. . ." should read "On the basis of the experiment using podocarpic acid, Wenkert[12] had proposed that. . .".

Robert E. Ireland,* Pierre Beslin, Rudolf Giger, Urs Hengartner, Herbert A. Kirst, and Hans Maag: Studies on the Total Synthesis of Steroidal Antibiotics. 2. Two Convergent Schemes for the Synthesis of Tetracyclic Intermediates.

Page 1267. Substituent at positions 4, 8, 10, and 14 (steroid numbering) in all formulas, 1 through **34,** unless otherwise specified, should he taken to represent methyl groups. Angular substituents at other positions should he taken to represent hydrogens.

Robert E. Ireland,* Rudolf Giger, and Susumu Kamata: Studies on the Total Synthesis of Steroidal Antibiotics. 3. Generation and Correlation of Tetracyclic Derivatives from the Degradation of Fusidic Acid and Total Synthesis.

Page 1276. Substituents at positions 4, 8, 10, and 14 (steroid numbering) in all formulas, 1 through **34,** unless otherwise specified, should be taken to represent methyl groups. Angular substituents at other positions should be taken to represent hydrogens.

Paul G. Gassman,* Berkeley W. Cue, Jr., and Tien-Yau Luh: A General Method for the Synthesis of Isatins.

Page 1344. The ^{13}C chemical shift assignments for atoms 4, 5, and 6 in Table II are in error. The correct assignments, plus the data on additional compounds which pointed out this error, are presented in a corrected version of Table II.

Table II. ^{13}C Chemical Shifts for Substituted Isatins

Registry no.	Compd		2	3	3a	4	5	6	7	7a	Substituent
91-56-5	Isatin	Obsd	159.5	184.6	117.9	124.8	122.9	138.5	112.4	150.9	
39755-95-8	5-OCH_3	Obsd	159.6	184.1	118.1	108.8	155.4	124.9	113.3	144.7	55.8
		Calcd			119.3	110.0	155.7	123.7	113.8	143.9	
608-05-9	5-CH_3	Obsd	159.5	184.6	117.8	124.8	132.0	138.8	112.1	148.5	20.1
		Calcd			117.8	125.7	132.3	139.4	112.3	148.4	
1127-59-9	7-CH_3	Obsd	159.6	184.3	117.3	121.6[a]	122.3[a]	139.2	121.1	149.0	15.9
		Calcd			117.8	122.3	122.8	139.4	121.8	151.8	
	4-Cl	Obsd	158.6	181.2	114.8	131.1	123.6	139.0	111.0	152.1	
		Calcd			118.0	129.9	123.0	140.1	111.3	152.5	
17630-76-1	5-Cl	Obsd	159.1	183.4	119.1	124.2	126.9	137.3	113.9	149.2	
		Calcd			119.5	124.9	128.0	138.6	114.0	149.8	
	6-Cl	Obsd	159.4	183.0	116.8	126.2	122.8	142.4	112.3	151.9	
		Calcd			116.8	126.4	123.0	143.6	112.5	152.5	
25128-38-5	5-$CO_2C_2H_5$	Obsd	159.4	183.4	117.8	125.0	124.6	139.0	112.3	154.1	164.6, 60.9, 14.2
		Calcd			118.1	124.1	124.6	139.8	112.6	155.4	
	4-CF_3[b]	Obsd	158.2	180.5	115.5	126.2[c]	119.2[d]	138.3	116.8	152.5	123.0[e]
		Calcd			114.7	127.3	119.7	138.8	115.7	151.2	
345-32-4	5-CF_3[b]	Obsd	159.4	183.1	118.2	121.4[f]	123.2[g]	134.7[h]	112.8	153.4	124.0[i]
		Calcd			118.2	121.6	125.4	135.3	112.7	154.2	
	6-CF_3[b]	Obsd	159.0	184.6	121.0	125.3	119.5[j]	136.2[k]	108.4[l]	150.7	123.5[m]
		Calcd			121.2	125.1	119.7	141.0	109.2	151.2	
61394-92-1	5-CN	Obsd	159.4	182.6	118.6[a]	128.5	104.9	141.7	113.1	153.7	118.3[a]
		Calcd			119.0	129.1	105.5	142.8	113.5	155.4	
	4-NO_2	Obsd	158.1	178.1	109.3	144.4	116.8[a]	138.8	117.1[a]	151.8	
		Calcd			113.6	144.9	118.6	139.4	118.7	151.8	
611-09-6	5-NO_2	Obsd			118.2	119.6	142.7	133.2	112.6	155.3	
		Calcd			118.8	120.5	143.0	134.2	113.3	157.2	

[a] Values may be interchanged for this compound. [b] Contrary to the literature values[21,22] for the ^{13}C substituent effect of substituted benzenes, we found that a study of α,α,α-trifluorotoluene vs. benzene indicated that the shifts should be: C-1, +2.5; C_{ortho}, −3.2; C_{meta}, +0.3; and C_{para}, +3.3. [c] J_{CCF} = 35 Hz. [d] J_{CCCF} = 5.6 Hz. [e] J_{CF} = 277 Hz. [f] J_{CCCF} = 3.6 Hz. [g] J_{CCF} = 33 Hz. [h] J_{CCCF} = 3.4 Hz. [i] J_{CF} = 272 Hz. [j] J_{CCCF} = 3.9 Hz. [k] J_{CCF} = 32 Hz. [l] J_{CCCF} = 3.3 Hz. [m] J_{CF} = 276 Hz.

Samuel P. McManus* and J. Milton Harris: A Method for the Evaluation of Steric Contributions to ρ^+ Based on Aryl/Methyl Rate Ratios. Application to the Gassman–Brown Tool of Increasing Electron Demand.

Page 1422. The second sentence of the abstract should read: The factors are steric and electronic effects.

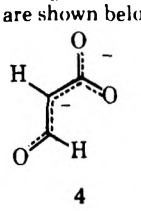
Page 1427. In ref 33, replace ρ^+ by γ^+.

Stanley H. Pine* and Eric Fujita: Ylide Autoxidation during the Stevens Rearrangement.

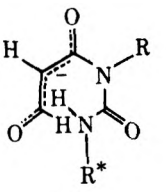
Page 1460. The structure of eq 1 should have been C_6H_5COOH rather than C_6H_5H.

Eva G. Lovett and David Lipkin*: Base-Catalyzed Reactions of 1,3-Disubstituted Uracils.

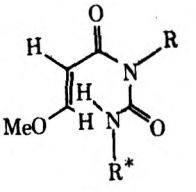
Page 2575. Structures **4**, **5**, and **14** are incorrect. Correct structures are shown below.



4



5



14

AUTHOR INDEX

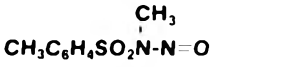
Note: In this Author Index, titles of papers are listed after the name of each author of the paper. Multiple authorship is not indicated. Complete authorship may be ascertained by consulting the original paper.

KEYWORD INDEX

Diazomethane Precursors

Diazomethane is an exceedingly useful reagent in organic synthesis.[1] The mild and quantitative esterification of carboxylic acids, sulfonic acids and phosphonic acids by diazomethane proceeds rapidly with evolution of nitrogen. It methylates mineral acids, phenols and phthalimide as well as alcohols in the presence of a Lewis acid (*e.g.*, $BF_3 \cdot Et_2O$). Diazomethane may be used for the ring enlargement of cyclic ketones and enamines. Its use in the Arndt-Eistert reaction extends the chain of a carboxylic acid by one methylene unit.

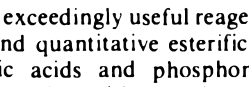
Unfortunately, this useful reagent does not lend itself to storage, much less to shipping. Diazomethane is an explosive and toxic gas[2] which should be freshly prepared (usually as an ethereal solution) when needed. All preparations and reactions using diazomethane, regardless of how it is produced, should be carried out behind a safety shield in an efficient hood.[3,4] We know of no diazomethane precursor which is clearly superior for all applications so we offer a variety of reagents, each with a particular advantage.



Diazald, *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, is the reagent most commonly used for preparing ethereal solutions of diazomethane by distillation. We recommend the use of our Diazald Kit distillation apparatus* which features Clear-Seal® joints for this process. An advantage of using **Diazald** is that at no time is a large amount of diazomethane present in the distilling flask. **Diazald** is relatively inexpensive and has a good shelf life (*ca.* one year). A disadvantage is the need for a nonaqueous solvent.

This new reagent recently described by Sekiya *et al.*[5] has an excellent storage life and may be used in our Diazald Kit to produce ethereal solutions of diazomethane. We expect this reagent to take the place of *N,N'*-dimethyl-*N,N'*-dinitrosoterephthalamide (EXR-101) which has been discontinued due to the explosive character of the unstabilized product.[6] ***N*-['-Methyl-*N'*-nitroso(aminomethyl)]benzamide** appears to have a somewhat better shelf life than **Diazald**, but is more expensive, and also requires a nonaqueous solvent.

Clear Seal® license, Ronor SA, Berne, Switzerland.
*See pp 978-980 of the Aldrich Catalog Handbook for a description.



MNNG, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, has been used to prepare diazomethane by distillation with ether; however, millimole quantities may be quickly and conveniently prepared without distillation using our MNNG-Diazomethane apparatus.* The apparatus is available in millimole and micromole sizes with either "O" ring or Clear-Seal® joints. The procedure[7] involves the *slow* dropwise addition of aqueous sodium hydroxide *via* a syringe into the closed apparatus. The diazomethane produced collects in an outer tube containing chilled ether. This solution is sufficient for small-scale reactions or the preparation of methyl esters for gc analysis.

When only small quantities of diazomethane are needed, **MNNG** is the reagent of choice. It is the only reagent from which diazomethane can be generated with aqueous alkali, thus avoiding alcoholic contamination. It has an excellent shelf life. The disadvantages of **MNNG** are its relatively high cost and its powerful mutagenic activity.[8]

All precursors to diazomethane are nitroso compounds and therefore should be handled with great care.

References:

1) J.S. Pizey, *Synthetic Reagents*, Vol. 2, John Wiley and Sons, Inc., New York, N.Y., 1974, Chapter 2; H. Hopps *Aldrichimica Acta*, 3, 9 (1970).
2) F.W. Sunderman, *Laboratory Diagnosis of Diseases Caused by Toxic Agents*, Warren H. Green, Inc., St. Louis, Mo., 1970.
3) T.J. de Boer and J.J. Backer, *Org. Syn.*, Coll. Vol. 4, John Wiley and Sons, Inc., New York, N.Y., 1963, p 250.
4) J.A. Moore and D.E. Reed, *Org. Syn.*, Coll. Vol. 5, John Wiley and Sons, Inc., New York, N.Y., 1973, p 351.
5) M. Sekiya, Y. Ohahi, Y. Terao, and K. Ito, *Chem. Pharm. Bull.*, 24, 369 (1976).
6) E.I. du Pont de Nemours and Co., private communication, 1977.
7) H.M. Fales, T.M. Jaouni, and J.F. Babashak, *Anal. Chem.*, 45, 2302 (1973).
8) J.D. Mandell and J. Greenberg, *Biochem. Biophy. Res. Commun.*, 3, 575 (1960); E.A. Adelberg, M. Mandel, and G.C.C. Chen, *ibid.*, 18, 788 (1965).

D2800-0 Diazald® 100g $7.50; 1kg $49.00; 10kg $350.00
19,738-6 *N*-[*N'*-Methyl-*N'*-nitroso(aminomethyl)]benzamide 25g $8.00; 100g $22.00
12,994-1 *N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine 10g $10.00; 25g $22.00
Z10,025-0 Diazald Kit $114.00ea.
Z10,100-1 MNNG-Diazomethane Kit, millimole size with "O" ring **$19.66ea.**
Z10,102-8 MNNG-Diazomethane Kit, micromole size with "O" ring **$17.86ea.**
Z10,159-1 MNNG-Diazomethane Kit, millimole size with Clear-Seal® joint **$22.94ea.**
Z10,161-3 MNNG-Diazomethane Kit, micromole size with Clear-Seal® joint **$20.85ea.**

Craftsmen in Chemistry

Corporate Offices:
Aldrich Chemical Co., Inc.
940 W. Saint Paul Ave.
Milwaukee, Wisconsin 53233
U. S. A.

Great Britain:
Aldrich Chemical Co., Ltd.
The Old Brickyard, New Road
Gillingham, Dorset SP8 4JL
England

Belgium/
Continental Europe
Aldrich-Europe
B-2340 Beerse
Belgium

West Germany/
Continental Europe
EGA-Chemie KG
7924 Steinheim am Albuch
West Germany