VOLUME 41 MARCH 19, 1976 NUMBER 6 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*

Editorial Department: Charles R. Bertsch, Head; Marianne C. Brogan, Associate Head; Eileen B. Segal, Production Editor; Fern S. Jackson, Assistant Editor; Andrew J. D'Amelio, Editorial Assistant; Jane U. Lutick, Production Assistant.

Graphics and Production Department: Bacil Guiley, Head

Research and Development Department: Seldon W. Terrant, Head

Advertising Office: Centcom, Ltd., 50 W. State St., 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 ACS Easton address.

Page charges of $70.00 per page are assessed for papers published in this journal. Ability to pay 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. Requests for **permission to reprint** should be directed to Permissions, 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

1976 subscription rates—including surface postage:

	Domestic	PUAS	Canada, Foreign
Member	$26.00	$33.25	$34.25
Nonmember	104.00	111.25	112.25
Supplementary material	15.00	19.00	20.00

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

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 ACS Columbus address. 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 at the ACS Columbus address.

Microfiche subscriptions are available at the same rates but are mailed first class to U.S. subscribers, air mail to the rest of the world. Direct all inquiries to Business Operations, Books and Journals Division, at the ACS Washington address or call (202) 872-4444.

Single issues in hard copy and/or microfiche are available from Special Issues Sales at the ACS Washington address. Current year $5.00. Back issue rates available from Special Issues Sales. **Back volumes** are available in hard copy and/or microform. Write to Special Issues Sales at the ACS Washington address for further information. **Microfilm** editions of ACS periodical publications are available from volume 1 to the present. For further information, contact Special Issues Sales at the ACS Washington address.

Supplementary material must be ordered directly from Business Operations, Books and Journals Division, at the ACS Washington address. Orders over 20 pages

	U.S.	PUAS, Canada	Other Foreign
Microfiche	$2.50	$3.00	$3.50
Photocopy			
1–7 pages	4.00	5.50	7.00
8–20 pages	5.00	6.50	8.00

are available only on microfiche, 4 × 6 in., 24×, negative, silver halide. Orders must state photocopy or microfiche if both are available. Full bibliographic citation including names of all authors and prepayment are required. Prices are subject to change.

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

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

Editorial Department
American Chemical Society
20th and Northampton Sts.
Easton, Pa. 18042
(215) 258-9111

Notice to Authors last printed in the issue of January 9, 1976

JOCEAH 41(6) 899-1080 (1976)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry®

VOLUME 41, NUMBER 6 MARCH 19, 1976

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

The textbook integrates pertinent biological, biochemical, and medical examples into a "major's level" coverage of organic chemistry—

Ternay: Contemporary Organic Chemistry

If your organic chemistry class includes biology majors, pre-medicine students, and pharmacy majors as well as chemistry majors—then Ternay's **Contemporary Organic Chemistry** is the perfect text for your course.

Why?

- **Ternay** has succeeded in interweaving biological, biochemical, and medical applications throughout a "major's level" coverage of organic chemistry, providing a fascinating, well balanced presentation of what organic chemistry is and its relevance to other disciplines.
- The author's early introduction of functional groups and the coverage of *alkanes, stereoisomerism in aliphatic compounds, nucleophilic substitution reactions and elimination reactions* gives the student an early start on significant laboratory experimentation.
- Pertinent examples of medical and biological applications of organic chemistry include: *the relationship between sulfa drugs and mental retardation in children, the Krebs cycle, fatty acid biosynthesis, enolization, the structure of terpenes and discussion of their odor,* and many other discussions.
- The text provides clear, explicit definitions of terms, *and most chapters include their own glossary.*
- Modern synthetic methods are clearly described—and there's particularly extensive material on *polymers* and *polymerization, the role of organometallic compounds in organic synthesis, prochirality,* **E, Z-** *nomenclature, ylid reactions, diimide reduction,* and other significant aspects of organic chemistry.
- Almost 1,000 individual problems are provided, both within individual sections and at the conclusion of each chapter. Some are drill exercises—others are thought problems. An appendix provides answers to selected problems.
- Virtually a 2nd edition, this text has been extensively class tested since 1973. Discussions, examples, and problems have all been thoroughly scrutinized and "debugged."
- *Chapter 28*—**Infrared, Ultraviolet and Mass Spectroscopy,** and *Chapter 29*—**Nuclear Magnetic Resonance Spectroscopy** have been written as independent free-standing treatments that you can introduce at any appropriate time in your lecture sequence.
- Particular care has been paid to discussion of nuclear magnetic resonance spectroscopy to lead the student to a better understanding of the relationship between stereochemistry, symmetry, and nmr spectroscopy.
- **Contemporary Organic Chemistry** devotes its first chapter to a brief review of atomic structure: *atomic orbitals, quantum numbers,* and *electronegativity.* Although this chapter may be eliminated from classroom discussion, it provides the student with a frame of reference and sufficient refresher instruction to "get started" in organic chemistry.

By **Andrew L. Ternay, Jr.** The University of Texas at Arlington and Health Sciences Center at Dallas. 993 pages. 244 illustrations. $20.75. Published Jan. 1976.

Table of Contents:

Atoms and Things • From Bonds to Small Molecules • Alkanes • Stereoisomerism in Aliphatic Compounds • Alkyl Halides—Nucleophilic Substitution Reactions • Alkyl Halides—Elimination Reactions and Grignard Reagents • The Stereochemistry of Ring Systems • Alkenes • Alkynes • Alcohols • Ethers, Epoxides and Diols • Dienes and Terpenes • Electrocyclic and Cycloaddition Reactions • Aromaticity • Electrophilic Aromatic Substitution • Synthesis and Simple Addition Reactions of Aldehydes and Ketones • Aldehydes and Ketones—Their Carbanions and Spectra • Carboxylic Acids and Their Derivatives • Synthesis of Carbon-Carbon Bonds Employing Esters and Other Acid Derivatives • Amines • Aryl Nitrogen Compounds • Aryl Oxygen Compounds • Organic Compounds of Sulfur and Phosphorus • Amino Acids, Peptides and Proteins • Carbohydrates and Monosaccharides • Oligosaccharides and Polysaccharides • Nucleic Acids • The Catalyst and the Container—A Saga of the Cell • Infrared, Ultraviolet and Mass Spectroscopy • Nuclear Magnetic Resonance Spectroscopy • Appendix

---

Francis: Student Guide and Solutions Manual to Ternay's Contemporary Organic Chemistry

These detailed answers to the problems in **Ternay's Contemporary Organic Chemistry** allow the student to gain a better understanding of the rationale behind each solution.

Professor Francis specifies the section within the text which provides the theoretical basis for the solution, and offers helpful hints about working the problems. In addition, if the student feels he needs more practice on a particular concept, similar problems are referenced by chapter and problem number.

By **Robert F. Francis,** University of Texas at Arlington. 441 pp. Soft cover. $5.95. Published Jan. 1976.

SAUNDERS COMPLETE PACKAGE FOR

A unique lab manual which describes the interpretation of carbon-13 nmr spectra—

Moore & Dalrymple: Experimental Methods in Organic Chemistry, *New 2nd Edition*

Saunders Golden Sunburst Series in Chemistry

The new 2nd edition of this hardcover manual introduces the techniques and instrumental methods in actual use throughout the world. It's ideally suited for the laboratory portion of a two-semester organic course for chemistry, chemical engineering, pre-medicine, and other science majors. *And this is the first organic laboratory manual to describe the interpretation of carbon-13 nmr spectra,* thus allowing ^{13}C nmr spectra to be used profitably in the identification of unknowns.

You'll discover that this 2nd edition:

- Continues to achieve a balance between the constraints imposed by time, space, and equipment;
- Provides experiments from which individuals at each end of the spectrum of ability can profit;
- Includes new experiments on carbohydrates, amino acids, drugs, a plant bioregulator, and enzymatic reactions—a major expansion of material geared to the needs of students in biologically oriented curricula;
- Adds polarimetry, chemiluminescence, and synthetic polymers and dyes to the list of topics;
- Reaffirms the authors' commitment to the use of chromatographic methods and spectroscopic data;
- Has enlarged many experiments retained from the first edition to allow additional options in the material you assign to your students and;
- Instructs your students in crystallization; extraction; distillation; vapor phase, thin layer, and column chromatography; quantitative studies of reaction rates and product mixtures; physical constants; solubility products; *and much more.*

An 83 page **Instructor's Manual** discusses each individual experiment and lists the required chemicals and equipment. Answers to all questions are given in full detail.

By **James A. Moore** and **David L. Dalrymple,** both of the University of Delaware. 334 pages. 103 ill. $10.95. Published January 1976.

Five sets of unknowns (Kits A thru E described in the Instructor's Manual) are offered by Aldrich Chemical Company at a discount of 20% off their normal list price. Each kit contains 100 grams each of 50 compounds selected by the authors for suitability as unknowns. Infrared and proton nmr spectra of each unknown are included gratis with the kits. The spectra can also be purchased separately. Instructors may reproduce the spectra as often as desired for distribution along with samples of unknowns. The spectra are large enough to permit measurement of integral steps and coupling constants. Expanded-scale tracings and offsets are added when appropriate; exchangeable proton peaks are designated by shading. The spectra for two of the five sets—D and E—include C nmr data.

The ancillary guide to nomenclature—

Banks: Naming Organic Compounds: A Programed Introduction to Organic Chemistry, *New 2nd Edition*

Learning to write chemical formulas and to give those formulas accurate systematic names is essential to students beginning to study organic chemistry. Although the skills are not difficult to develop, explanations can use up a lot of your limited lecture time. This outstanding self-teaching tool will allow your students to instruct themselves in chemical nomenclature.

- **Naming Organic Compounds** employs a programed format which provides both the incentive and the reinforcement necessary for successful study.
- Each section explains a fundamental rule, then asks a question providing a choice of plausible answers.
- For each answer, the text offers a short discussion of why it is either correct or incorrect.
- The system of nomenclature follows the most current IUPAC-Chemical Abstract rules.
- Coverage includes: *Classification of organic compounds, cyclic hydrocarbons and substituted hydrocarbons, functional groups, heterocyclic compounds,* and *natural products.*
- The book's appendix includes a valuable section, the Wiswesser Line-Formula Notation.

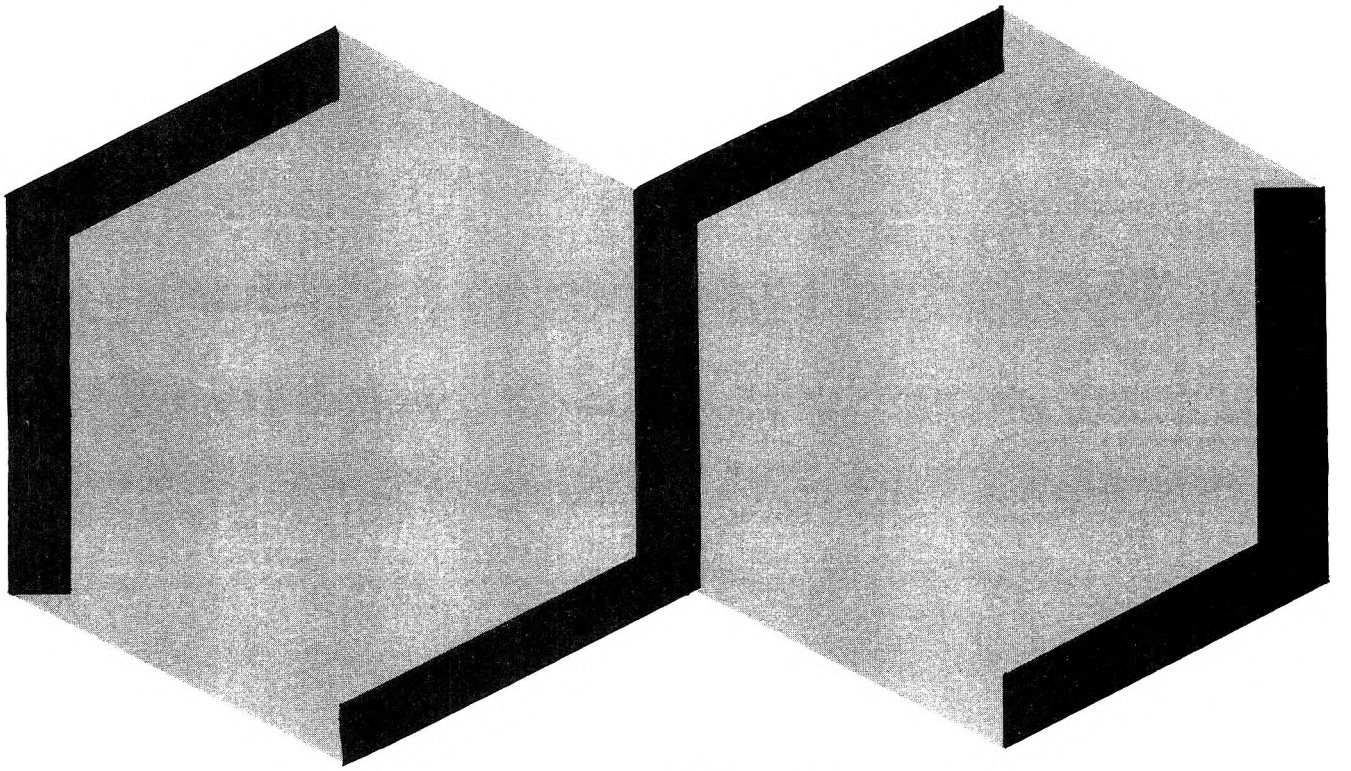
By **James E. Banks,** Montana State University. 309 pp. Illustd. Soft cover. $5.95. Published Jan. 1976

For more information or examination copies, write Textbook Marketing Division

W. B. Saunders Company
West Washington Square
Philadelphia, Pa. 19105

TEACHING ORGANIC CHEMISTRY (Continued)

The leading American journal devoted to general organic chemistry:



The Journal of Organic Chemistry

The career wise way to keep up with current thinking in the field. You get the *total picture* presented through forty some papers per biweekly issue. Areas of emphasis include:

- Organic reactions
- Natural products
- Studies of mechanism
- Theoretical organic chemistry
- Various aspects of spectroscopy related to organic chemistry

You get all of this, in the 1100 articles and NOTES (brief, concise accounts of studies of smaller scope) and over 4000 pages a year from your big informative issues of THE JOURNAL.

You owe it to your career to find out for yourself why The Journal of Organic Chemistry is the leader in its field.

Send your order today.

. . . *another ACS service*

The Journal of Organic Chemistry
American Chemical Society **1976**
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.	*Canada***	*Latin America***	*Other Nations***
ACS Member One-Year Rate*	☐ $26.00	☐ $34.25	☐ $33.25	☐ $34.25
Nonmember	☐ $104.00	☐ $112.25	☐ $111.25	☐ $112.25

Bill me ☐ Bill company ☐ Payment enclosed ☐

Air freight rates available on request.

Name _____

Street _____ Home ☐ Business ☐

City _____ State _____ Zip _____

Journal subscriptions start January '76

*NOTE: Subscriptions at ACS member rates are for personal use only. **Payment must be made in U.S. currency, by international money order, UNESCO coupons, U.S. bank draft, or order through your book dealer.

THE JOURNAL OF Organic Chemistry®

VOLUME 41, NUMBER 6

MARCH 19, 1976

Chemistry of Singlet Oxygen. XXIII.[1,2] Low Temperature Photooxygenation of Indenes in Aprotic Solvent

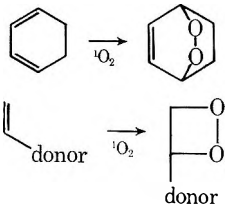
Paul A. Burns, Christopher S. Foote,* and S. Mazur

Contribution No. 3501 from the Department of Chemistry, University of California, Los Angeles, California 90024

Received November 17, 1975

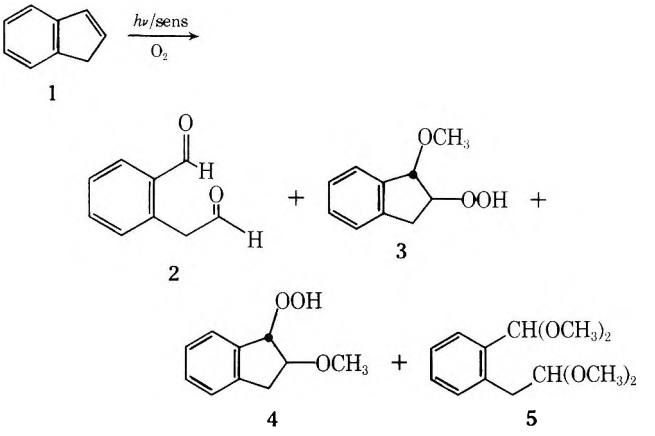
Indenes undergo dye-sensitized photooxygenation at −78 °C in acetone to yield unusual dioxygenated products **9** (2,3:7,9-diepoxy-6,9-peroxy-$\Delta^{4,5}$-hexahydroindenes). These compounds undergo thermal rearrangement to form indene tetraepoxides (benzene trioxides), react with trimethyl phosphite to form 2,3:4,9:7,8-triepoxy-$\Delta^{5,6}$-hexahydroindenes, and with triethylamine to form 2,3:7,8-diepoxy-6-keto-9-hydroxy-$\Delta^{4,5}$-hexahydroindenes. The probable mode of formation of the adducts **9** involves initial 1,4 addition of singlet oxygen to the indene, followed by rearrangement of the initial endoperoxide to a diepoxide and addition of a second mole of singlet oxygen.

The photosensitized 1,4 cycloaddition of oxygen to dienes is believed to involve singlet ($^1\Delta_g$) oxygen as an intermediate,[3] and 1,2 cycloadditions of singlet oxygen to electron-rich olefins have also been recognized.[4,5] The products of those 1,2 cycloadditions, dioxetanes, have been characterized from enamines,[6] vinyl ethers,[5] and a few less electron-rich olefins[7] such as adamantylideneadamantane.[7a] Dioxetanes have also been suggested as the reactive intermediates in certain other cases of oxidative double bond cleavage.[8]



Recent work has shown that the photooxygenation of certain substituted styrenes can lead to 1,4 cycloadducts in which the aromatic ring acts as part of the diene systems, in an unusual type of Diels–Alder reaction with singlet oxygen.[9] Although many examples of 1,4 cycloadditions of dienophiles to styrene derivatives are known,[10,11] these were the first examples involving singlet oxygen.

Consideration of the above results suggested that the photooxygenation of indene (**1**) should be reinvestigated. The original observations were that in methylene chloride, the product was homophthalaldehyde **2**,[12] while, in methanol, the products were (after reduction) **2–5**.[8c] These results were confirmed by Mazur,[9b] who found reaction to be extremely slow in aprotic solvents and accompanied by dye bleaching. In protic solvents, the reaction is much faster. The product proportions vary with the conditions, and other products are formed, such as indene oxide.



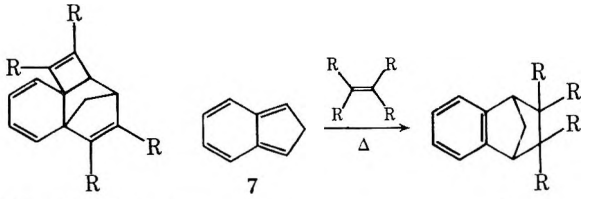
These products were suggested by Kearns et al.[8c] to derive from an initial 1,2 cycloaddition of singlet oxygen; no products were isolated that suggested a 1,4-cycloaddition reaction. (In fact, corresponding dioxetanes have subsequently been shown to be formed in good yield when the reaction of substituted indenes is carried out in methanol[13]). However, reactive dienophiles such as dicyanoacetylene and dimethyl acetylenedicarboxylate form Diels–Alder adducts with indene, although the yields are low.[11,14] These adducts were assigned the structure **6** (R = CO_2CH_3 or CN). At elevated temperatures (~200 °C) indene also forms cycloadducts such as **8** which are derived from an isoindene (2*H*-indene) intermediate (**7**).[15]

In an attempt to clarify the mechanism, Mazur photooxygenated indene at low temperature in an aprotic solvent (acetone, −78 °C); under these conditions the reaction proved to be much faster than at room temperature, and an unexpected product was formed in good yield.[9a,b] This paper describes in detail these results, and those obtained by pursuing this initial observation.

Table I. ^{1}H Chemical Shifts (δ, Me_4Si, $CDCl_3$, 60 MHz) of the Ring Protons of 9a–g[a]

	9a	9b[b]	9c[b]	9d	9e	9f	9g
H_A[c]	6.50	6.46	6.62	6.53	6.53	6.62	6.47
H_B[c]	6.27	6.29	6.27	6.31	6.27	6.19	6.24
H_C	5.15	5.06	5.03	5.07	5.04	4.97	4.63
H_D	3.7	3.81	3.65	3.73	3.72	3.73	
H_E	3.7				3.70		
H_F	3.62		3.60			3.38	3.56
H_G[d]	2.10	2.55	2.20	2.45	2.45	2.42	2.06
H_H	2.73	3.43	2.75	3.20	3.27		2.58

[a] Substituent resonances omitted for clarity. [b] 100-MHz spectra. [c] Chemical shifts determined by analysis of the ABX system of protons A–C.[18] [d] The lower field of G, H was assigned as H because phenyl substituents at E and F have larger effect on this resonance.

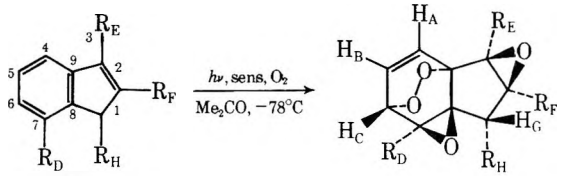


6 (R = CO_2CH_3, CN)

Results and Structure Assignments

Photooxygenation of the Indenes. Indene (**1a**) was photooxygenated at −78 °C in acetone containing rose bengal; the oxygen uptake was 1.5 equiv. Both the NMR spectrum and TLC showed mainly starting material and a single product (**9a**) which was isolated in 38% yield.[16]

Similarly, acetone solutions of **1b–g** were photooxygenated at −78 °C. These compounds took up oxygen at a faster rate than the parent indene and without dye bleaching (or with dye bleaching only at the end of the reaction). In all cases, 1.6–2.0 mol of O_2/mol of indene were taken up, and products **9b–g** were isolated in yields which varied from 40 to 93%.



1a–g **9a–g**

a, $R_D = R_E = R_F = R_H = H$
b, $R_D = R_H = H$; $R_E = R_F = C_6H_5$
c, $R_D = R_F = R_H = H$; $R_E = i\text{-}C_3H_7$
d, $R_D = R_H = H$; $R_E = CH_3$; $R_F = C_6H_5$
e, $R_D = R_E = R_H = H$; $R_F = C_6H_5$
f, $R_D = R_F = H$; $R_E = t\text{-}C_4H_9$; $R_H = CH_3$
g, $R_D = CH_3$; $R_E = i\text{-}C_3H_7$; $R_F = R_H = H$

All these compounds gave analyses and mass spectra consistent with formulation as starting material plus two molecules of oxygen. The mass spectra have significant peaks at P − 32 (loss of oxygen).

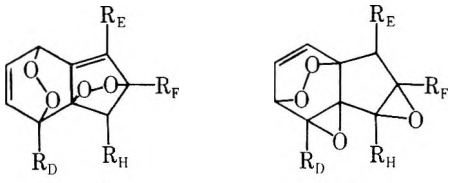
The compounds give a positive test for peroxide with acidified KI. The ir spectra show no carbonyl, hydroxyl, or hydroperoxyl bands, but there are many strong bands between 750 and 1280 cm^{-1}. This region contains the three substituted epoxide ring vibration bands.[17] The ^{1}H NMR chemical shifts of products **9a–g** are summarized in Table I; the couplings of these spectra (checked by double resonance) are summarized in Table II.

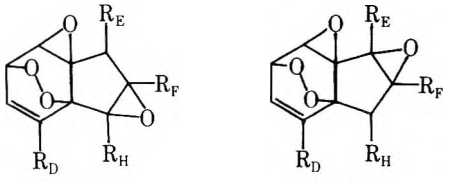
Since these compounds contain an O–O group but no OOH, they must contain an endoperoxide (also consistent with the loss of molecular oxygen in the mass spectra). The presence of only one proton with a resonance of δ ~5.0 in the NMR spectra, which is the region expected for an allylic proton α to an endoperoxide, eliminates structure **10** (or other structures containing more than one peroxide) as a possibility.

Table II. Couplings (Hz) Derived from Peaks of Table I

J	9a	9b	9c	9d	9e	9f	9g
AB[a]	8.6	8.6	8.8	8.6	8.6	8.8	8.9
AC[a]	1.4	1.3	1.4	1.5	1.4	1.4	1.6
BC[a]	6.1	6.1	6.2	6.1	6.2	6.2	6.3
BD	~0.8	~0.6	~0.8	~0.6	~0.8	~0.9	
CD	4.0	4.0	4.0	4.2	4.2	4.4	
GH	16	16	16	16	16		16
FH[b]	1.3		1.1				1.3
FG	c		c			~0.8	~0.7
EF	c						
EG	c				~0.7		

[a] Couplings obtained from analysis of the ABX system of protons A–C.[18] [b] Proton F to lower field of G, H. [c] Coupling is either obscured by other resonances or not resolved.





Since there is only one peroxide, one O–O bond must be broken to give the observed products. Since neither carbonyl nor hydroxyl groups are present in the ir, the remaining oxygens must be ethers, and the NMR spectra show resonances between δ 3.6 and 3.8 which are assigned to protons α to epoxide groups in a system heavily substituted by electronegative groups. The NMR spectra also show two olefinic protons forming the AB part of an ABXY system with $J_{AD} \sim 0$ and the proton α to the endoperoxide and one epoxide proton forming the XY part. These four protons must be on the original six-membered ring of the indene, assuming no skeletal rearrangement. These spectra confirm the exclusion of **10** as a possibility. Possible structures with one endoperoxide and two epoxide groups are then limited to **9** and **11–13**. The latter three are ruled out by the spectra of the substituted compounds **9b–f**. The presence of a methylene group in **9b–d** excludes **11** and **12**, and the presence of both olefinic protons in **9g** rules out structure **13**, which has a methyl group at position D.

Strong further support has been obtained for these structures by the ^{13}C spectra, which were obtained using single-frequency and off-resonance proton decoupling, and have been published.[19] In addition, the chemistry of these substances, reported below, and an x-ray structure of a compound in the analogous dihydronaphthalene series[2] leave no doubt that structures **9a–f** are correct. The stereochemical assignments will be discussed in the Discussion.

Thermolysis of the Photooxygenation Products. On melting, **9d** and **9e** resolidified and then remelted at a higher temperature. Refluxing toluene or heptane solutions of

Table III. ^{1}H Chemical Shifts (δ, Me_4Si, $CDCl_3$, 100 MHz) of the Ring Protons of Thermolysis Products 14 and 15[a]

Proton	14a	14b	14c	14d	14f	14g	15d[b]	15f	15g
H_A	3.86	3.35	3.84	3.77	3.89	3.82	3.56	3.78	3.71
H_B	3.26	3.18	3.27	3.29	3.24	3.25[c]	2.74[e]	2.67[e]	2.75
H_C	3.43	3.44	3.42	3.43	3.41	3.25[c]	3.14	3.11	3.13
H_D	3.57	3.67	3.54	3.63	3.46		3.50	3.34	
H_E	3.31								
H_F	3.79		3.66		3.46	3.65		3.50	3.74
H_G[d]	1.92	2.19	1.83	2.05	2.00	1.86	2.19	2.00	1.98
H_H	2.52	3.31	2.51	3.05		2.40	3.24		2.40

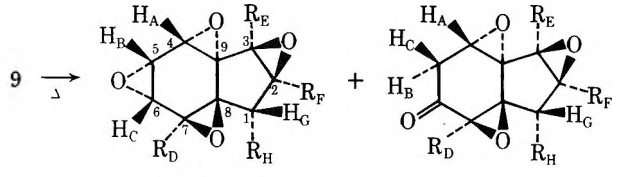
[a] Substituent resonances omitted for clarity; shifts are approximate multiplet centers. [b] 60-MHz spectrum. [c] Multiplet center of the AB portion of a degenerate ABX system. [d] Lower field of G, H assigned as H because of larger coupling to H and because the phenyl substituent has a larger effect on this resonance. [e] Lower field of B, C assigned to B owing to W coupling with D.

Table IV. Couplings (Hz) Derived from the Peaks of Table III

J	14a	14b	14c	14d	14f	14g	15d	15f	15g
AB	3.1	3.0	3.2	3.0	3.1	c	2.8	3.0	3.0
AC	b	b	b	b	b	c	1.4	1.2	1.1
BC	3.7	3.6	3.8	3.5	3.7	c	16.5	16.1	16.0
BD	1.0	1.0	1.0	1.0	1.0		0.8	1.0	
CD	1.7	1.7	1.7	1.7	1.7		b	b	
GH	15.1	14.8	14.8	14.8		14.9	16.0		16.0
FH[a]	1.2		1.1			1.1			1.0
FG	0.7		d		0.9	d		0.9	d
EF	2.6								
EG	d								

[a] Proton F to lower field of G, H; assignment as H consistent with observed coupling as shown by models. [b] No observed coupling. [c] Protons A, B, and C comprise a degenerate ABX system with the chemical shift of B and C nearly identical. [d] Coupling is not observed although peak broadening is present.

the photooxygenation products (**9**) led to the formation of two new compounds in the ratio of ~4:1. The major products (**14**) were isolated in 38–60% yield by chromatography on silica gel and/or crystallization. The analyses and mass



14 **15**

spectra of these compounds showed them to be isomeric with compounds **9**. Their ir spectra showed neither carbonyl nor hydroxyl bands, and the NMR spectra (Tables III and IV) showed no resonances below 3.9 ppm (except phenyl when present as a substituent) and several resonances in the region associated with epoxides were present. These compounds were assigned the tetraepoxide (benzene trioxide) structure **14** on the basis of their NMR spectra (discussed below), their ^{13}C spectra,[19] and analogy with compounds in the dihydronaphthalene series[2] for which an x-ray structure is available. The minor products all showed a carbonyl band at 1720–1727 cm^{-1} (saturated ketone) and no hydroxyl absorption; these compounds could not be isolated in pure form, but the NMR spectra of several of them were determined (Tables III and IV) and are consistent with structure **15**. They isomerized during chromatography to the unsaturated ketones (**16**) discussed below.

The coupling pattern of the ring protons A–D is identical in all the tetraepoxides; they form a system in which J_{AD} and J_{AC} are too small to resolve (≤0.5 Hz). The only difficulty in unequivocal assignment was the determination of which proton is A and which is D. The ^{1}H NMR of **14g** did not solve the problem because the ring protons form a degenerate (deceptively simple) ABX system.[18] The marked upfield shift of 0.5 ppm for proton A in **14b** (R_E = R_F = C_6H_5), due to shielding by the 3-phenyl substituent, supported this assignment, which was later conclusively confirmed by ^{13}C NMR spectroscopy.[19]

Models of the minor products, β-epoxy ketones (**15**), show that proton B, but not C, has the planar configuration with proton D required for W coupling.[20] This coupling is also lost in **15g**, in which proton D is replaced by a methyl group. The larger value of J_{AB} compared to J_{AC} is also in agreement with this, since the dihedral angle between A and B is the smaller. The low-field proton in both **15d** and **15f**, therefore, must be A. This is unusual since proton D is α to a carbonyl group and would thus be expected to be at lowest field. The 7-methyl group of **15g** also appears at higher field than the methyl of **14g**; it appears that this shift is an effect similar to the inverted axial–equatorial chemical shift relationship experienced by the α protons of α-halocyclohexanones.[20]

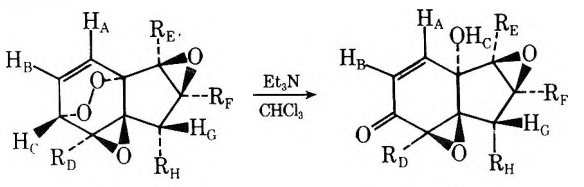
Table V. ^{1}H Chemical Shifts (δ, Me_4Si, $CDCl_3$, 60 MHz) of Ring Protons of Compounds 16a[a]

Proton	16a[b]	16b	16c	16d	16f	16g[c]
H_A[d]	6.95	6.66	7.02	6.90	7.18	6.93
H_B[e]	5.97	5.97	5.91	5.97	5.81	5.83
H_C[f]	g	2.77	3.00	3.42	2.74	4.82
H_D	3.54	3.68	3.46	3.60	3.42	
H_E	3.65[h]					
H_F	3.76[h]		3.62		3.40	3.60
H_G[i]	2.02	2.28	1.90	2.12	2.19	1.83
H_H[j]	2.83	3.66	2.80	3.36		2.68

[a] Substituent resonances omitted for clarity. [b] Impure compound obtained during chromatography of **15a**. [c] In $CDCl_3$–$(CD_3)_2CO$. [d] J_{AB}: 10.5 (**16a**, **16c**, and **16d**), 10.6 (**16f** and **16g**), and 10.0 Hz (**16b**). [e] J_{BD} = 2.0 Hz. [f] Chemical shift variable. [g] Obscured. [h] Relative assignment of E, F uncertain; J_{EF} = 3 Hz. [i] J_{GH} = 14 Hz. [j] J_{FH} = 1 Hz for **16c** and **16g**; obscured in **16a**; proton H assigned as lower field of G, H owing to its absence in **16f** and the large effect of phenyl substituent on this proton.

The rates of thermolysis of **9c** (R_E = i-C_3H_7) and **9d** (R_E = CH_3; R_F = C_6H_5) in $CDCl_3$ at 69.0 °C were determined by NMR spectroscopy by following the disappearance of the starting compounds. The thermolyses followed first-order kinetics; the rates were determined to be 8.2 × 10^{-5} s^{-1} for **9c** and 8.0 × 10^{-5} s^{-1} for **9d**.

Reaction with Base. Compounds **9b–g** react exothermically with triethylamine in $CHCl_3$ to give γ-hydroxy-α,β-unsaturated ketones (**16**) in 37–96% yield. The reaction of



9 **16**

9a (R_E = R_F = H) gave only a black, tarry residue, even with a milder base, *N*,*N*-dimethylaniline. The ir spectra (KBr) of these compounds had carbonyl bands at 1680–1700 cm^{-1} and a strong OH band at 3535–3580 cm^{-1} (**16b** showed a broad band at 3460 cm^{-1}). The NMR spectra are tabulated in Table V. Proton B is coupled with proton D

Table VI. ^{1}H Chemical Shifts (δ, Me_4Si, $CDCl_3$, 60 MHz) of the Ring Protons of 17[a]

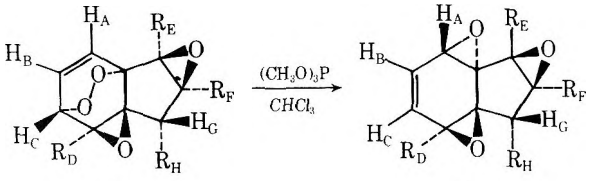
Proton	17a[b]	17b[b]	17c	17d	17f	17g[d]
H_A[c]	3.74[d]	3.42[e]	3.69[d]	3.60[d]	3.72[d]	3.67[f]
H_B	6.11	6.15[g]	6.12	6.12	6.07	6.02[h]
H_C	6.11	5.97	6.12	6.12	6.07	5.93
H_D	3.35	3.20	3.30	3.38	3.24	
H_E	3.36[i]					
H_F[j,k]	3.75		3.63		3.41	3.64
H_G[l]	2.02	2.29	1.95	2.14	2.10	1.95
H_H	2.64	3.42	2.64	3.21		2.55

[a] Substituent resonances omitted for clarity. [b] 100-MHz spectra. [c] Assignment based on presence of this proton in 17g. [d] $J_{A(BC)} = J_{D(BC)}$: 2.7 (17a), 2.5 (17c and 17d), and 2.8 Hz (17f). [e] $J_{AC} = J_{BD} = 2.0$ and $J_{AB} = J_{CD} = 3.4$ Hz. [f] An ABX system with $J_{AB} = 3.9$ and $J_{AC} = 1.7$ Hz. [g] $J_{BC} = 10.0$ Hz; relative assignment of protons B, C uncertain. [h] $J_{BC} = 10.0$ Hz. [i] $J_{EF} = 2.7$ Hz. [j] J_{FH}: 1.4 (17a), ~1 (17c), and 1.2 Hz (17g). [k] J_{FG}: 0.9 (17f) and <1 Hz (17g). [l] $J_{GH} = 15$ Hz; lower field of G, H assigned as H based on its absence in 17f and the larger effect of the phenyl groups on this proton in 17b and 17d.

(J_{BD} = 2.0 Hz). This W coupling across the carbonyl group agrees with the value of 2.1 Hz found for 3,4-diphenyl-2,3-cyclopentenone oxide,[21] and it is absent in **16g**, in which proton D has been replaced by a methyl group.

These rearrangements are common with diene endoperoxides with a proton α to the peroxy group,[22,23] but, in those cases, the reactions require basic alumina or methanolic sodium hydroxide solution, indicating that endoperoxides **9** are more reactive.

Reaction with Trimethyl Phosphite. Compounds **9a–f** react exothermically with trimethyl phosphite in $CHCl_3$ solution to give benzene dioxides (**17**, 28–96% yield) with removal of one oxygen atom. Structure assignments are



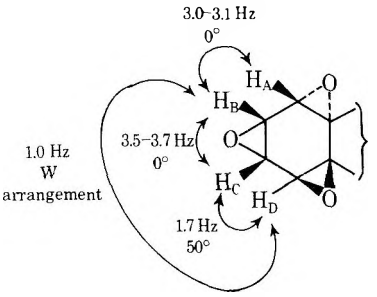
9 **17**

based on infrared (no carbonyl or OH) and NMR spectra (see Table VI) and analogy with simpler diene endoperoxides, for which the corresponding reaction is well known.[22c,d,24]

In **17a** and **17c–f** the olefinic protons have the same chemical shift, resulting in virtual coupling with protons A and D; thus, protons B and C together and protons A and B each appear as a triplet with splitting = $(J_{AB} + J_{AC})/2 = (J_{BD} + J_{CD})/2$ = 2.5–2.8 Hz. In **17b**, the olefinic protons have slightly different chemical shifts, and protons A–D form a four-spin system with $J_{AB} = J_{CD} = 3.4$, $J_{AC} = J_{BD} = 2.0$, $J_{BC} = 10$, and $J_{AD} \simeq 0$ Hz (not resolved). The substitution of a methyl group at the 7 position in **17g** reduces protons A–C to an ABX system, with $J_{AB} = 3.9$, $J_{AC} = 1.7$, and $J_{BC} = 10$ Hz.

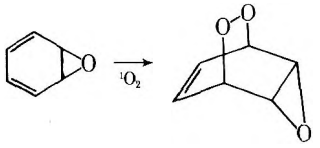
Discussion

Stereochemical Assignments. The magnitude of the couplings in Table IV allows stereochemical assignments in the six-membered ring of compounds **14**, and, by extension, to compounds **9**. Consider the four-spin system formed by protons ABCD. Proton D is assigned by the absence of this resonance in compound **14g**; proton C is coupled to it with a 1.7-Hz coupling, while proton B is coupled to D (four-bond coupling, presumably requiring the W arrangement) by 1.0 Hz. Proton B is coupled to C by 3.5–3.7 Hz, and to A by 3.0–3.1 Hz. Inspection of models shows that the *anti*-benzene trioxide geometry is the only one which permits appropriate dihedral angles (0° for the AB and BC pair, and 50° for the CD pair). These coupling constants compare well with those of other diepoxide compounds with similar stereochemistries.[2]

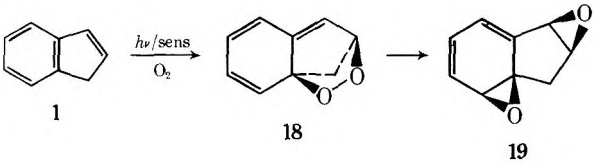


The proton assignments are confirmed by single frequency double resonance experiments in the ^{13}C spectrum.[19] In addition, the *anti*-benzene trioxide structure is the same one found by an x-ray structure of one of the corresponding tetraepoxides in the dihydronaphthalene series,[2] where the NMR coupling patterns are the same as with compound **14**.

The stereochemistry of the six-membered ring in endoperoxide compounds **9** is then that which would be expected on singlet oxygen addition to a benzene oxide from the less hindered anti side, which is the stereochemistry found in the parent system.[25,26]

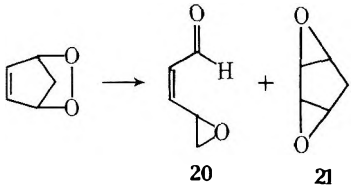


Mechanism of the Formation of 9. The mode of formation of compounds **9** can be readily understood if the first step is a Diels–Alder addition of singlet oxygen to the indene to give **18**. Rearrangement of this endoperoxide would give the bisepoxide **19**. Addition of another molecule of sin-



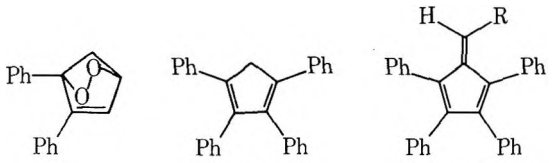
1 **18** **19**

glet oxygen to **19** would give the observed products **9**, and should be more rapid than the initial addition to **1**. All attempts to detect either **18** or **19** as intermediates by running the photooxidation to partial conversion or in the presence of dienophiles have failed so far. The rearrangement of **18** to **19** at −78° is somewhat surprising, although cyclopentadiene endoperoxide undergoes a related reaction at higher temperatures; the product is mainly **20** along with some **21**.[27] The reaction proceeds explosively even in solution above 0 °C.



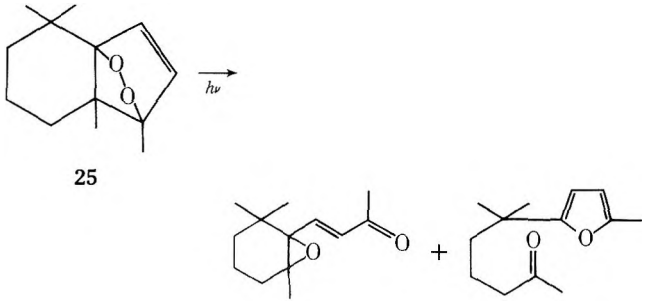
20 **21**

The endoperoxide **22**, derived from 1,2-diphenyl-1,3-cyclopentadiene, is also unstable above −20 °C.[28]



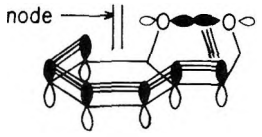
22 23 24 (R = H, Ph)

Diene endoperoxides can be rearranged photochemically as well as thermally, as they have tail absorptions which extend beyond 360 nm.[29] For example, the self-sensitized photooxygenation of **23** and **24** at −50 °C leads to the corresponding bisepoxides instead of the endoperoxide compounds (although dye-sensitized photooxygenation leads mainly to the endoperoxides owing to the greatly increased rate of photooxygenation relative to the rate of the subsequent rearrangement).[30] Direct photochemical rearrangement of **18**, however, does not account for the present results, since the photooxygenation of **1b** with light >525 nm led to exactly the same product. A rearrangement photosensitized by rose bengal is still possible, however. Ohloff et al. found that peroxide **25** rearranged in a reaction photosensitized by rose bengal, but not by methylene blue (which has a lower triplet energy).[31] The same products are

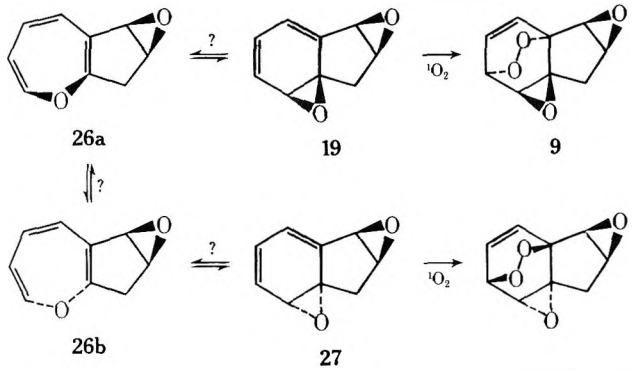


25

formed in this system by both rose bengal and methylene blue, however. The rearrangement in this case may be more facile than usual because the triene system in **18** is well set up to attack the ends of the peroxide bond in an eight-electron "Möbius" arrangement, which would be thermally allowed as a concerted process.[32] Whether concerted or not,



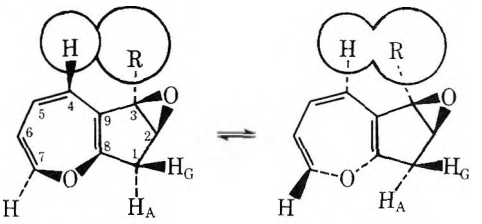
if the diepoxide is formed from the endoperoxide, the epoxide groups in **19** should be cis. However, the benzene oxide–oxepin equilibrium is facile and allows a mechanism for isomerization at this point; in fact, the tetraepoxide in the dihydronaphthalene series subjected to x-ray crystal structure determination actually has these two epoxide groups trans.[2]



26a 19 9

26b 27

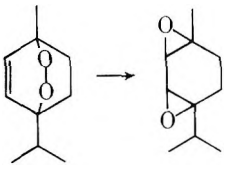
For this reason, and because the NMR is unhelpful, relative stereochemistry of the two epoxide groups in **9** or any of the transformation products cannot be assigned with confidence at present. It is significant that, in contrast to the situation in the dihydronaphthalenes, only a single isomer of **9** is actually formed. It is probably important that models of the two oxepins show **26b** to have a severe peri



26a 26b

interaction which is not present in the oxepins in the dihydronaphthalene series. If this interaction governs the equilibrium constant or rate of isomerization 19 ⇌ 27, then the cis isomer **19** should predominate in the indene series.

The rearrangement of peroxides **9** to the tetraepoxides **14** is a reaction exactly analogous to that of **18** to **19** and is well precedented in cyclohexane endoperoxide systems.[22] It is, however, much more facile than in simpler systems, for instance, for ascaridole (**28**). The data of Boche and Runquist[22a] allow calculation of the rate to be 6×10^{-8} s^{-1} at 69°, compared to 8×10^{-5} at this temperature for **9c** and **9d.** This surprising reactivity toward this rearrangement is also shown in the parent benzene oxide endoperoxide–benzene trioxide rearrangement.[25,26,33]



28

It is remarkable that in all of the indenes studied here, no "ene" product, or at most only traces, is formed, especially since Fenical, Kearns, and Radlick found that in 2,3-dimethylindene, photooxygenation at room temperature in CH_2Cl_2 gave 65% of the ene product;[8c] also, in the closely related dihydronaphthalene series, substantial amounts of ene product are formed in some cases under conditions very similar to the present ones. The balance of products seems very sensitive to structure and conditions.

The remarkable solvent and temperature effects on this reaction (slow reaction, complex product mixture at room temperature in aprotic solvents, fast reaction giving **9** at low temperature in aprotic solvents, and fast reaction giving dioxetanes at low temperature in methanol) are the subject of a current investigation.

Experimental Section

Boiling points and melting points are uncorrected. NMR spectra were taken on a Varian T-60 or HA-100 spectrometer; chemical shifts are relative to tetramethylsilane. Ir spectra were taken on a Perkin-Elmer Model 137 spectrophotometer calibrated with the 1603-cm^{-1} band of polystyrene. Mass spectra were obtained on an AEI MS-9 operated by Elizabeth Irwin. Elemental analyses were by Heather King. NMR spectral details listed in the tables are not repeated here.

Photooxygenations were carried out using a Sylvania DWY 650W tungsten–halogen lamp at 90 V. The reaction solutions were cooled with a dry ice–acetone bath contained in a half-silvered Dewar; oxygen was circulated through a capillary bubbler immersed in the solution using a Neptune diaphragm pump; the oxygen uptake was measured by a gas buret.

Starting Materials. 3-Isopropylindene (**1c**) was prepared by the method of Makosza:[34,35] bp 100–101 °C (12 mm) [lit.[36] bp 99–100 °C (9.5 mm)]; NMR (CCl_4) δ 1.23 (d, 6 H, J = 7 Hz), 2.85 (septet, 1 H), 3.15 (m, 2 H), 6.00 (m, 1 H) and 7.15 (broad m, 4 H); ir (KBr) 1389, 1377, 763, 717 cm^{-1}. 2,3-Diphenylindene [**1b**, mp 110–111 °C (lit.[37] 108.5–109.5 °C)] was prepared from 2-phenyl-1-indanone,[38] which was made from 2,3-diphenylpropionic acid.[38] 2-Phenyl-3-methylindene (**1d**), mp (ethanol) 76.7–77.4 °C (lit.[39] 75 °C), was prepared from 2-phenyl-1-indanone. 2-Phenylindene (**1e**), mp 167–169 ° (lit.[40] 167.5 °C), was made from 2-phenyl-1-indanone. 1-Methyl-3-*tert*-butylindene[41,42] (**1f**) was made from 3-methyl-1-indanone[41] (prepared in turn from β-phenylbutyric acid[43]) and had bp 70–71 °C (0.5 mm) [lit.[41] bp 70 °C (0.3 mm)] and was chromatographed on silica gel to remove unreacted starting material.

3-Isopropyl-7-methylindene (1g). 4-Methyl-1-indanone, mp 96–98 °C (lit.[44] 98–101 °C), was prepared by the method of Koo[45] from 3-(o-methylphenyl)propionic acid[46] prepared in turn from *trans*-o-methylcinnamic acid.[46,47] To a Grignard solution prepared from Mg (3.04 g) and isopropyl bromide (15.4 g, 0.125 mol) in 200 ml of anhydrous ether was added dropwise during 15 min 4-methyl-1-indanone (15.0 g, 0.103 mol) in 100 ml of anhydrous ether. After the solution was refluxed for 30 min, saturated NH_4Cl (25 °C) was added.[48] The solution was decanted and the residue washed with ether. The combined ether solutions were evaporated, and the residue was dissolved in 220 ml of benzene with 0.5 g of *p*-toluenesulfonic acid and refluxed (water trap) until the distillate was free of water. The solution was extracted with water and saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated. The residue was distilled to give 5.2 g of a partially solidified oil, bp 87–105 °C (3 mm), which was chromatographed on a 2.5 × 15 cm silica gel column with petroleum ether (bp 30–60 °C) to remove the starting material. Evaporation of the filtrate gave 3.0 g of **1g** (17%) as a colorless oil: NMR ($CDCl_3$) δ 1.25 [d, 6 H, $C(CH_3)_2$, J = 7 Hz], 2.28 (s, 3 H, CH_3), ca. 2.87 (symmetrical m, 1 H, CH), 3.10 (m, 2 H, CH_2), 6.12 (m, 1 H, C=CH), and 7.02 (m, 4 H, aromatic).

2,3:7,8-Diepoxy-6,9-peroxy-Δ^{4,5}-hexahydroindene (9a). Freshly distilled indene (**1a**,[16] 0.56 g, 4.8 mmol) in 5 ml of acetone containing 0.1 mg of rose bengal took up 165 ml of oxygen (1.5 equiv) during 80 min. The solution was warmed to room temperature and evaporated without heating to give a semicrystalline oil. Addition of methanol and filtration gave 311 mg (38%). The filtrate contained mostly indene (by NMR). Crystallization from methanol gave colorless crystals, mp 105.0–105.5 °C dec. **9a** gives a positive test for peroxide with acidified starch–iodide paper: mass spectrum (70 eV, source temperature 90 °C) *m/e* (rel intensity) 148 (M − 32, 26), 91 (15), 68 (15), 55 (13), 39 (15), 32 (17), 29 (14), 28 (100), 27 (15), 18 (87), and 17 (16); ir (KBr) 1370, 1281, 1260, 1219, 1028, 953, 919, 907, 860, 845, 811, 758, 734, and 708 cm^{-1}.

Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 60.19; H, 4.45.

2,3-Diphenyl-2,3:7,8-diepoxy-6,9-peroxy-Δ^{4,5}-hexahydroindene (9b). 2,3-Diphenylindene (**1b**, 0.573 g, 2.00 mmol) in 5 ml of acetone containing 0.1 mg of rose bengal took up 92 ml of oxygen (2.0 equiv) in 50 min. The solution was warmed to room temperature and evaporated to give a glass, which was passed through a 1 × 14 cm silica gel column with $CHCl_3$ to remove the rose bengal. Evaporation of the filtrate and trituration of the residue with ether gave 615 mg of **9b** (93%). Recrystallization by slow evaporation of a petroleum ether–CH_2Cl_2 solution gave colorless crystals, mp 107–108 °C dec. **9b** gives a positive test for peroxide with acidified starch–iodide paper: NMR (100 MHz) δ 7.18 (broad m, 10 H, aromatic); mass spectrum (70 eV, source temperature 105 °C) *m/e* (rel intensity) 300 (M − 32, 4), 105 (52), 86 (15), 84 (26), 77 (18), 72 (19), 57 (29), 49 (30), 43 (100), 42 (84), 41 (41), 39 (11), 29 (20), 28 (33), 27 (21), and 18 (87); ir (KBr) 1605, 1267, 1252, 957, 938, 903, 860, 834, 777, 762, 746, 733, 693, and 675 cm^{-1}.

Anal. Calcd for $C_{21}H_{16}O_4$: C, 75.89; H, 4.85. Found: C, 75.61; H, 4.71.

The reaction was repeated, irradiating the solution through a 0.11 M $K_2Cr_2O_7$ filter solution with a path length of 0.3 cm (cutoff 520 nm). The solution took up 2.0 equiv of oxygen, and an NMR ($CDCl_3$) of the reaction mixture showed only **9b**.

3-Isopropyl-2,3:7,8-diepoxy-6,9-peroxy-Δ^{4,5}-hexahydroindene (9c). 3-Isopropylindene (**1c**, 2.00 g, 12.7 mmol) in 45 ml of acetone containing ~1 mg of rose bengal took up 589 ml of oxygen (1.9 equiv) during 4.5 h with dye bleaching at the end of the reaction. The solution was warmed to room temperature and evaporated to give an oil, which crystallized on trituration with methanol to give 2.07 g of 9c (74%). Recrystallization from methanol gave colorless needles, mp 95.3–96.5 °C dec. **9c** gives a positive test for peroxide with acidified starch–iodide paper: NMR ($CDCl_3$, 100 MHz) δ 0.97 and 1.07 [two d, 6 H, $C(CH_3)_2$, J = 7 Hz] and 2.26 (septet, 1 H, isopropyl CH); mass spectrum (70 eV, source temperature 98 °C) *m/e* (rel intensity) 190 (M − 32, 32), 173 (23), 147 (53), 119 (10), 71 (12), 55 (11), 43 (40), 41 (13), 39 (11), 32 (10), 28 (51), 27 (13), 18 (100), and 17 (18); ir (KBr) 1606, 1370, 1351, 1283, 1270, 1237, 1225, 1000, 978, 942, 932, 917, 899, 878, 850, 827, 813, 756, and 701 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.95; H, 6.27.

2-Phenyl-3-methyl-2,3:7,8-diepoxy-6,9-peroxy-Δ^{4,5}-hexahydroindene (9d). 2-Phenyl-3-methylindene (**1d**, 2.48 g, 12.0 mmol) in 200 ml of acetone containing 2 mg of rose bengal took up 585 ml (2.00 equiv) of O_2 in 5 h. The solution was warmed to room temperature and evaporated to give a yellow solid. Addition of methanol and filtration gave 2.52 g of **9d** (78%) which crystallized from methanol–$CHCl_3$ to give pale yellow needles, mp 135 °C dec, with resolidification and remelting at 183–189 °C. **9d** gives a positive test for peroxide with acidified starch–iodide paper: NMR ($CDCl_3$) δ 1.21 (s, 3H, CH_3) and 7.38 (s, 5 H, C_6H_5); mass spectrum (70 eV, source temperature 115 °C) *m/e* (rel intensity) 241 (21), 238 (M − 32, 44), 237 (10), 227 (16), 195 (11), 105 (100), 103 (31), 77 (49), 51 (12), 43 (59), 28 (18), and 18 (24); ir (KBr) 1603, 1278, 1255, 1001, 949, 937, 905, 877, 850, 833, 822, 760, 736, 707, 693, and 681 cm^{-1}.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.24; H, 5.29.

2-Phenyl-2,3:7,8-diepoxy-6,9-peroxy-Δ^{4,5}-hexahydroindene (9e). 2-Phenylindene (**1e**, 200 mg, 1.04 mmol) in 200 ml of 1:1 acetone–CH_2Cl_2 containing 3 mg of rose bengal took up 41 ml (1.6 equiv) of oxygen in 3 h. Most of the **1e** crystallized from the solution and slowly redissolved as the reaction proceeded. The solution was warmed to room temperature and evaporated to give a solid which was chromatographed on a 2.5 × 18 cm silica gel column with benzene to give 42 mg of **1e** (21%) and 125 mg of **9e** (49%). **9e** was recrystallized from methanol to give colorless needles, mp ~100 °C dec, with resolidification and remelting at 180–183 °C. **9e** gives a positive test for peroxide with acidified starch–iodide paper: NMR ($CDCl_3$) δ 7.33 (s, 5 H, C_6H_5); ir (KBr) 1603, 1263, 1245, 953, 939, 915, 891, 802, 753, 710, and 687 cm^{-1}.

Anal. Calcd for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72. Found: C, 70.22; H, 4.86.

1-Methyl-3-*tert*-butyl-2,3:7,8-diepoxy-6,9-peroxy-Δ^{4,5}-hexahydroindene (9f). 1-Methyl-3-*tert*-butylindene (**1f**, 1.23 g, 6.59 mmol) in 25 ml of acetone containing ~1 ml of rose bengal took up 313 ml of oxygen (1.9 equiv) in 2.5 h. The solution was warmed to room temperature and filtered through charcoal. Evaporation of the filtrate and trituration with methanol gave 1.02 g of **9f** (62%). Recrystallization from ether–petroleum ether gave colorless crystals, mp 99–100 °C dec. **9f** gives a positive test for peroxide with acidified starch–iodide paper: NMR ($CDCl_3$) δ 1.07 [s, 9 H, $C(CH_3)_3$] and 1.26 (d, 3 H, CH_3, J_{HCCH_3} = 7 Hz); mass spectrum (70 eV, source temperature 150 °C) *m/e* (rel intensity) 218 (M − 32, 20), 161 (51), 69 (11), 57 (50), 43 (16), 41 (34), 39 (12), 29 (20), 28 (32), 27 (11), and 18 (100); ir (KBr) 1363, 1268, 1243, 1228, 983, 961, 935, 909, 902, 867, 841, 781, 737, 706, and 685 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.00: H, 7.22.

3-Isopropyl-7-methyl-2,3:7,8-diepoxy-6,9-peroxy-Δ^{4,5}-hexahydroindene (9g). 3-Isopropyl-7-methylindene (**1g**, 1.00 g, 5.82 mmol) in 50 ml of acetone containing ~2 mg of rose bengal took up 279 ml of oxygen (2.0 equiv) during 1.5 h. The solution was warmed to room temperature and evaporated without warming to give an oil. Trituration with methanol gave 560 mg of **9g** (40%), mp 88–89 °C dec. (A reaction carried out in an NMR tube with acetone-d_6 as solvent showed, by NMR, no starting material and >75% **9g**.) Recrystallization from methanol gave colorless crystals, mp 87–89 °C dec. **9g** gives a positive test for peroxide with acidified starch–iodide paper: NMR ($CDCl_3$) δ 0.97 and 1.08 [two d, 6 H, $C(CH_3)_2$, J_{CHCH_3} = 7 Hz], 1.53 (s, 3 H, CH_3), and 2.24 (septet, 1 H, isopropyl CH); mass spectrum (70 eV, source temperature 95 °C) *m/e* (rel intensity) 204 (M − 32, 63), 161 (33), 121 (11), 119 (13), 94 (22), 91 (13), 77 (13), 71 (22), 67 (11), 55 (29), 53 (12), 43 (100), 41 (25), 39 (23), 28 (55), 27 (30), and 18 (22); ir (KBr) 1475, 1289, 1270, 1250, 967, 955, 940, 926, 904, 891, 856, 829, 778, 714, and 701 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.83; H, 6.88.

Thermolysis of 9a. 9a (400 mg) was refluxed in 15 ml of toluene

for 1 h and evaporated. TLC (silica gel–$CHCl_3$) showed only two compounds, with R_f 0.44 (**15a**) and 0.30 (**14a**). The material was chromatographed on a 2.5 × 93 cm nylon dry column containing silica gel with $CHCl_3$ as solvent. The first fraction (63 mg) contained **14a** and a new compound **16a** with R_f 0.07. One fraction contained 217 mg of **14a** and the last fraction (~5 mg) was mostly **16a,** which could not be isolated, but the NMR is satisfactory for 9-hydroxy-2,3:7,8-diepoxy-6-keto-$\Delta^{4,5}$-hexahydroindene: NMR (100 MHz), Table V. **14a** was recrystallized from toluene to give 203 mg of 2,3:4,9:5,6:7,8-tetraepoxyoctahydroindene (**14a,** 51%) as colorless needles: mp 178.5–180.5 °C; mass spectrum (70 eV, source temperature 200 °C) *m/e* (rel intensity) 125 (23), 95 (23), 81 (38), 71 (49), 68 (100), 67 (28), 65 (26), 55 (67), 53 (44), 52 (28), 51 (43), 50 (24), 43 (36), 42 (29), 41 (50), 40 (22), 39 (75), 29 (77), 28 (59), 27 (74), 26 (34), 18 (21) and 15 (23); ir (KBr) 1415, 1270, 1255, 1233, 933, 978, 964, 925, 891, 838, 805, 778, 765, 737, and 711 cm^{-1}.

Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48 Found: C, 60.10; H, 4.53.

Thermolysis of 9b. 9b (500 mg) in 15 ml of toluene was refluxed for 1 h and the solution evaporated. TLC (silica gel–benzene) showed only two compounds, with R_f 0.32 (**15b**) and 0.12 (**14b**). The material was chromatographed on a 2.5 × 93 cm nylon dry column containing silica gel with benzene as solvent. The first fraction contained **15b** and a new compound (**16b**) with R_f 0.02. One fraction, containing 300 mg of almost pure **14b** (60%), was recrystallized three times by the slow evaporation of an ether–hexane solution to give 2,3-diphenyl-2,3:4,9:5,6:7,8-tetraepoxyoctahydroindene (**14b**): mp 149.0–150.5 °C; NMR ($CDCl_3$, 100 MHz) δ 7.16 (broad m, 10 H, aromatic); mass spectrum (70 eV, source temperature 195 °C) *m/e* (rel intensity) 331 (M − 1, 7), 303 (9), 227 (6), 212 (6), 105 (100), 103 (13), 77 (60), 51 (9), 28 (5), and 18 (6); ir (KBr) 1605, 1282, 1248, 997, 972, 930, 913, 883, 868, 843, 808, 757, 747, 737, 710, and 693 cm^{-1}.

Anal. Calcd for $C_{21}H_{16}O_4$: C, 75.89; H, 4.85. Found: C, 75.97; H, 4.85.

Thermolysis of 9c. 9c (500 mg) in 10 ml of heptane was refluxed for 1 h, and the solution evaporated. TLC (silica gel–$CHCl_3$) showed only two compounds, with R_f 0.42 (**15c**) and 0.24 (**14c**). The mixture was chromatographed on a 2.5 × 94 cm nylon dry column containing silica gel using $CHCl_3$ as solvent. The first fraction (25 mg) contained **15c** and a new compound, **16c,** with R_f 0.07. One fraction (260 mg) containing mostly **14c** was recrystallized from ether–hexane to give 220 mg of 3-isopropyl-2,3:4,9:5,6:7,8-tetraepoxyoctahydroindene (**14c,** 44%) as colorless needles: mp 123–124 °C; NMR ($CDCl_3$, 100 MHz) δ 0.88 and 0.98 [two d, 6 H, $C(CH_3)_2$, J_{CHCH_3} = 7 Hz] and 2.10 (septet, 1 H, isopropyl CH); mass spectrum (70 eV, source temperature 145 °C) *m/e* (rel intensity) 95 (23), 94 (53), 91 (38), 79 (37), 77 (50), 71 (29), 67 (30), 53 (23), 43 (100), 41 (62), 39 (43), 28 (51), and 27 (50); ir (KBr) 1373, 1359, 1263, 1218, 985, 929, 896, 872, 829, 790, 768, and 727 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.13: H, 6.44.

9c (400 mg) in 10 ml of heptane was refluxed for 5 min, and the solution evaporated. The residue was chromatographed as noted above. One fraction (220 mg) containing starting material and **15c** was rechromatographed; one fraction, an oil which crystallized on trituration with petroleum ether, was mainly **16c.** It was recrystallized three times from ether–hexane to give 3-isopropyl-9-hydroxy-2,3:7,8-diepoxy-6-keto-$\Delta^{4,5}$-hexahydroindene (**16c**): mp 122–124 °C; NMR ($CDCl_3$) δ 1.00 and 1.07 [two d, 6 H, $C(CH_3)_2$, J_{CHCH_3} = 7 Hz] and 2.58 (septet, 1 H, isopropyl CH); mass spectrum (70 eV, source temperature 210 °C) *m/e* (rel intensity) 151 (12), 123 (30), 95 (14), 77 (11), 71 (25), 67 (14), 55 (26), 51 (10), 43 (100), 41 (24), 39 (22), 28 (15), 27 (26), and 18 (10); ir (KBr) 3580, 1680, 1381, 1331, 1286, 1253, 1230, 1150, 1105, 1027, 963, 887, 826, 799, and 744 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.80; H, 6.23.

Thermolysis of 9d. 9d (2.00 g) in 20 ml of xylene was refluxed for 3 h, and the solution evaporated. TLC (silica gel–6% ethyl acetate in benzene) showed only two compounds, with R_f 0.52 (**15d**) and 0.31 (**14d**). NMR showed that the reaction mixture contained ~30% **15d** and ~70% **14d.** The reaction mixture was chromatographed on a 2.5 × 68 cm nylon dry column containing silica gel using 6% ethyl acetate in benzene as solvent One fraction was recrystallized twice from ether–hexane to give 1.0 g of 2-phenyl-3-methyl-2,3:4,9:5,6:7,8-tetraepoxyoctahydroindene (**14d,** 50%) as colorless needles: mp 184.5–186 °C; NMR ($CDCl_3$ 100 MHz) δ 1.04 (s, 3 H, CH_3) and 7.33 (s, 5 H, C_6H_5); mass spectrum (70 eV, source temperature 200 °C) *m/e* (rel intensity) 269 (16), 241 (42), 139 (14), 105 (100), 103 (42), 77 (56), 51 (15), 43 (55), 39 (10), and 28 (37); ir (KBr) 1603, 1238, 1222, 1006, 974, 956, 930, 914, 903, 858, 827, 776, 753, 743, 718, and 693 cm^{-1}.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.94; H, 5.37.

Another fraction containing a new compound (**16d**) with R_f 0.12 was recrystallized from methanol–$CHCl_3$ to give 45 mg of 2-phenyl-3-methyl-9-hydroxy-2,3:7,8-diepoxy-6-keto-$\Delta^{4,5}$-hexahydroindene (**16d**) as colorless crystals: mp 183–184.5 °C dec; NMR ($CDCl_3$) δ 1.33 (s, 1 H, CH_3) and 7.38 (s, 5 H, C_6H_5); mass spectrum (70 eV, source temperature 220 °C) *m/e* (rel intensity) 225 (6), 165 (7), 137 (11), 105 (100), 103 (8), 77 (22), 55 (5), 51 (7), 43 (43), 39 (5), 28 (24), 18 (86), and 17 (18); ir (KBr) 3535, 1693, 1603, 1368, 1330, 1253, 1025, 982, 965, 908, 867, 832, 809, 768, 758, and 699 cm^{-1}.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.20; H, 5.24.

One fraction contained ~65% **16d** and ~35% 2-phenyl-3-methyl-2,3:4,9:7,8:triepoxy-6-ketooctahydroindene (**15d**), enabling an NMR of **15d** to be obtained: NMR ($CDCl_3$) δ 1.06 (s, 3 H, CH_3) and 7.38 (s, 5 H, C_6H_5); ir (KBr) 1724 cm^{-1}.

Thermolysis of 9f. 9f (836 mg) was refluxed in 25 ml of heptane for 2 h. While still hot, 1 ml of the solution was removed and evaporated, and the residue (~40 mg) was dissolved in 1 ml of $CHCl_3$ and treated with several drops of triethylamine. After 10 min the solution was evaporated; NMR ($CDCl_3$) showed ~80% **14f** and ~20% **15f.** On cooling, the remaining solution gave 640 mg of a mixture of **14f** and **15f.** Three recrystallizations from heptane gave 300 mg of 1-methyl-3-*tert*-butyl-2,3:4,9:5,6:7,8-tetraepoxyoctahydroindene (**14f,** 38%) as colorless crystals: mp 155.0–156.5 °C; NMR ($CDCl_3$, 100 MHz) δ 1.01 [s, 9 H, $C(CH_3)_3$] and 1.14 (d, 3 H, CH_3, J_{CHCH_3} = 7.2 Hz); mass spectrum (70 eV, source temperature 190 °C) *m/e* (rel intensity) 57 (6), 43 (4), 41 (6), 39 (4), 32 (8), 28 (100), 18 (85), and 17 (10); ir (KBr) 1375, 1357, 1242, 1227, 969, 948, 913, 887, 847, 831, 817, 806, 786, and 770 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.16; H, 7.25. Found: C, 67.27; H, 7.33.

Concentration of the first filtrate, followed by filtration and evaporation of the filtrate, gave 68 mg of material containing ~30% **14f** and ~70% 1-methyl-3-*tert*-butyl-2,3:4,9:7,8-triepoxy-6-ketooctahydroindene (**15f**): NMR ($CDCl_3$, 100 MHz) δ 1.02 [s, 9 H, $C(CH_3)_3$] and 1.17 (d, 3 H, CH_3, J_{CHCH_3} = 7.1 Hz); ir (KBr) 1727 cm^{-1}.

Thermolysis of 9g. 9g (580 mg) was refluxed for 6 h in a benzene–heptane solution. Crystallization of the reaction solution gave 538 mg of a mixture of **14g** and **15g.** (A reaction carried out in a sealed NMR tube using $CDCl_3$ as solvent showed, by NMR, ~85% **14g** and ~15% **15g.**) Seven recrystallizations from heptane–benzene gave 300 mg of 3-isopropyl-7-methyl-2,3:4,9:5,6:7,8-tetraepoxyoctahydroindene (**14g,** 52%) as colorless crystals: mp 161–162 °C; NMR ($CDCl_3$, 100 MHz) δ 0.87 and 0.96 [two d, 6 H, $C(CH_3)_2$, J_{CHCH_3} = 7.0 Hz), 1.47 (s, 3 H, CH_3), and 2.08 (septet, 1 H, isopropyl CH); mass spectrum (70 eV, source temperature 225 °C) *m/e* (rel intensity) 149 (5), 95 (6), 94 (21), 93 (6), 91 (7), 79 (7), 77 (9), 67 (5), 55 (8), 43 (38), 41 (14), 39 (8), 28 (26), 27 (10), 18 (100), and 17 (21); ir (KBr) 1372, 1356, 1281, 1272, 1246, 985, 980, 931, 877, 863, 852, 837, 767, 749, and 696 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.07; H, 6.73.

Concentration of the mother liquor from the first two crystallizations gave 50 mg of material containing ~55% **14g** and ~45% 3-isopropyl-7-methyl-2,3:4,9:7,8-triepoxy-6-ketooctahydroindene (**15g**): NMR ($CDCl_3$, 100 MHz) δ 0.92 and 0.95 [two d, 6 H, $C(CH_3)_2$, J_{CHCH_3} = 7.0 Hz], 1.33 (s, 3 H, CH_3), and 2.08 (septet, 1 H, isopropyl CH); ir (KBr) 1720 cm^{-1}.

9-Hydroxy-2,3:7,8-diepoxy-6-keto-$\Delta^{4,5}$-hexahydroindene (16a). All attempts to isolate **16a** from the base-catalyzed rearrangement of **9a** using triethylamine or *N,N*-dimethylaniline were unsuccessful, giving only black tars.

2,3-Diphenyl-9-hydroxy-2,3:7,8-diepoxy-6-keto-$\Delta^{4,5}$-hexahydroindene (16b). Triethylamine (0.5 ml) was added to a solution of **9b** (200 mg, 0.603 mmol) in 4 ml of $CHCl_3$. An exothermic reaction took place. After cooling, the solution was evaporated to give an oil which crystallized on trituration with ether–petroleum ether. Recrystallization by slow evaporation of an ether–hexane solution (the product tends to oil out of solution) gave 100 mg of **16b** (50%) as colorless needles: mp 156–158 °C dec; NMR ($CDCl_3$) δ 7.22 (s, 5 H, C_6H_5) and 7.35 (m, 5 H, C_6H_5); mass spectrum (70 eV, source temperature 200 °C) *m/e* (rel intensity) 227 (8), 199 (17), 116 (9), 115 (8), 105 (100), 77 (28), 57 (6), 56 (7), 43

(6), 41 (5), 28 (8), 18 (25), and 17 (5); ir (KBr) 3460, 1675, 1603, 1268, 1245, 1023, 1006, 895, 834, 814, 782, 757, 741, and 692 cm^{-1}.

Anal. Calcd for $C_{21}H_{16}O_4$: C, 75.89; H, 4.85. Found: C, 76.07; H, 5.08.

3-Isopropyl-9-hydroxy-2,3:7,8-diepoxy-6-keto-$\Delta^{4,5}$-hexahydroindene (16c). Triethylamine (0.5 ml) was added to a solution of **9c** (250 mg, 1.13 mmol) in 3 ml of $CHCl_3$. An exothermic reaction took place. After cooling, the solution was evaporated, and trituration of the residue with ether gave a yellow-brown precipitate. The material was passed through a 1 × 19 cm silica gel column with $CHCl_3$ to remove the colored impurities. Evaporation of the filtrate gave 224 mg of **16c** (96%). Recrystallization from hexane–CH_2Cl_2 gave colorless crystals, mp 122.5–124.0 °C, with properties identical with those of material obtained on chromatography of the product of thermolysis of **9c**.

2-Phenyl-3-methyl-9-hydroxy-2,3:7,8-diepoxy-6-keto-$\Delta^{4,5}$-hexahydroindene (16d). Triethylamine (0.25 ml) was added to a solution of **9d** (200 mg, 0.742 mmol) in 3 ml of $CHCl_3$. An exothermic reaction took place. After cooling, the solution was evaporated, and the crystalline residue was washed with hexane to give 192 mg of **16d** (96%), with properties identical with those of material obtained in chromatography of the product of thermolysis of **9d**.

1-Methyl-3-*tert*-butyl-2,3:7,8-diepoxy-6-keto-9-hydroxy-$\Delta^{4,5}$-hexahydroindene (16f). Triethylamine (0.25 ml) was added to a solution of **9f** (64 mg, 0.25 mmol) in 3 ml of $CHCl_3$. After 10 min, the solution was evaporated, and the residue passed through a 1 × 18 cm silica gel column with $CHCl_3$. Evaporation of the filtrate gave a semicrystalline oil which gave 53 mg of **16f** (83%) from ether–petroleum ether. Crystallization from heptane gave colorless needles: mp 162–163 °C; NMR ($CDCl_3$) δ 1.18 [s, 9 H, $C(CH_3)_3$] and 1.34 (d, 3 H, CH_3, J_{CHCH_3} = 7 Hz); mass spectrum (70 eV, source temperature 200°) *m/e* (rel intensity) 193 (5), 166 (5), 165 (10), 147 (5), 137 (14), 123 (8), 109 (5), 105 (24), 91 (7), 77 (9), 69 (8), 57 (66), 55 (8), 43 (19), 41 (23), 39 (11), 32 (16), 29 (13), 28 (100), 27 (7), 18 (55), and 17 (13); ir (KBr) 3577, 1700, 1381, 1359, 1281, 1245, 1171, 1060, 1028, 1020, 919, 901, 844, 830, 815, 802, and 775 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.16; H, 7.25. Found: C, 67.04; H, 7.22.

3-Isopropyl-7-methyl-2,3:7,8-diepoxy-6-keto-9-hydroxy-$\Delta^{4,5}$-hexahydroindene (16g). 3-Isopropyl-7-methylindene (**1g**, 400 mg, 2.32 mmol) in 25 ml of acetone with ~1 mg of rose bengal took up 115 ml of oxygen (2.0 equiv). To the cold solution was added 0.5 ml of triethylamine, and the solution was warmed to room temperature for 1 hr. The solution was heated briefly to boiling and evaporated. The residue was passed through a 2.5 × 20 cm silica gel column with $CHCl_3$. Evaporation of the filtrate gave 205 mg of **16g** (37%). Recrystallization from benzene–heptane gave colorless crystals: mp 185–186.5 °C; NMR ($CDCl_3$, Me_2CO-d_6) δ 0.94 and 1.06 [two d, 6 H, $C(CH_3)_2$, J_{CHCH_3} = 7 Hz], 1.36 (s, 3 H, CH_3), and 2.60 (septet, 1 H, isopropyl CH); mass spectrum (70 eV, source temperature 225 °C) *m/e* (rel intensity) 193 (12), 166 (10), 165 (29), 137 (21), 123 (23), 105 (30), 77 (14), 71 (36), 55 (28), 43 (100), 41 (22), 39 (17), 28 (27), 27 (24), and 18 (27); ir (KBr) 3350, 1675, 1605, 1370, 1356, 1335, 1285, 1260, 1232, 1017, 982, 951, 921, 902, 873, 857, 811, 777, 763, and 702 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C. 66.27; H, 6.68.

Reaction of the Photooxygenation Products with Trimethyl Phosphite. To solutions of 0.250–1.00 g of the photooxygenation products **9a–d** and **9f** in 5 ml of $CHCl_3$ was slowly added ~1.25 equiv of trimethyl phosphite. Exothermic reactions took place, causing the solutions to boil. After cooling, the solutions were evaporated, and the residues filtered through 1 × 20 cm silica gel columns with $CHCl_3$. Evaporation of the filtrates and trituration of the residues with ether–petroleum ether gave crystalline products. Recrystallizations gave the following compounds.

2,3:4,9:7,8-Triepoxy-$\Delta^{5,6}$-hexahydroindene (**17a**, 79%): mp 94–95 °C (methanol); mass spectrum (70 eV, source temperature 160 °C) *m/e* (rel intensity) 135 (6), 109 (5), 107 (7), 77 (6), 52 (8), 51 (5), 39 (6), 32 (18), 28 (100), 27 (5), 18 (80), and 17 (17); ir (KBr) 1387, 1357, 1267, 1234, 1014, 968, 936, 915, 864, 838, 826, 812, 803, 765, 713, and 706 cm^{-1}.

Anal. Calcd for $C_9H_8O_3$: C, 65.83; H, 4.91. Found: C, 65.91; H, 4.96.

2,3-Diphenyl-2,3:4,9:7,8-triepoxy-$\Delta^{5,6}$-hexahydroindene (**17b**): mp 150–153 °C after three crystallizations from benzene–cyclohexane (tends to oil out); NMR ($CDCl_3$, 100 MHz) δ 7.14 (m, 10 H, aromatic); ir (KBr) 1603, 1224, 983, 929, 908, 866, 843, 776, 758, 729, 699, and 685 cm^{-1}.

Anal. Calcd for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10. Found: C, 79.41; H, 5.11.

3-Isopropyl-2,3:4,9:7,8-triepoxy-$\Delta^{5,6}$-hexahydroindene (**17c**, 96%): mp 92–93 °C after three crystallizations from hexane–CH_2Cl_2; NMR ($CDCl_3$) δ 0.90 and 0.99 [two d, 6 H, $C(CH_3)_2$, J_{CHCH_3} = 7 Hz] and 2.17 (septet, 1 H, isopropyl CH); mass spectrum (70 eV, source temperature 200 °C) *m/e* (rel intensity) 191 (11), 177 (43), 163 (35), 135 (52), 107 (35), 91 (20), 79 (26), 77 (33), 55 (34), 52 (22), 43 (89), 41 (28), 39 (24), 28 (68), 27 (28), 18 (100), and 17 (20); ir (KBr) 1383, 1357, 1270, 1248, 1221, 985, 911, 876, 857, 833, 794, 767, 723, and 708 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.97; H, 7.09.

2-Phenyl-3-methyl-2,3:4,9:7,8-triepoxy-$\Delta^{5,6}$-hexahydroindene (**17d**, 77%): mp 161.5–163 °C (hexane–CH_2Cl_2); NMR ($CDCl_3$) δ 1.05 (s, 3 H, CH_3) and 7.50 (s, 5 H, C_6H_5); mass spectrum (70 eV, source temperature 200 °C) *m/e* (rel intensity) 253 (10), 225 (62), 105 (69), 103 (45), 85 (34), 77 (36), 51 (12), 43 (30), 41 (5), 39 (6), 28 (26), 18 (100), and 17 (22); ir (KBr) 1609, 1390, 1238, 1165, 1077, 1029, 1007, 921, 897, 867, 848, 802, 778, 769, 737, 722, and 706 cm^{-1}.

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C. 75.43; H, 5.36.

1-Methyl-3-*tert*-butyl-2,3:4,9:7,8-triepoxy-$\Delta^{5,6}$-hexahydroindene (**17f**, 55%): mp 148–150 °C (hexane); NMR ($CDCl_3$) δ 1.02 [s, 9 H, $C(CH_3)_3$] and 1.16 (d, 3 H, CH_3, $J_{HC(}CH_3$ = 7 Hz); mass spectrum (70 eV, source temperature 200 °C) *m/e* (rel intensity) 219 (14), 205 (28), 177 (48), 149 (56), 121 (28), 91 (24), 77 (21), 69 (32), 57 (86), 52 (19), 43 (19), 41 (62), 32 (11), 29 (33), 28 (100), and 18 30); ir (KBr) 1380, 1355, 1282, 1240, 1224, 1106, 991, 948, 902, 880, 834, 822, 804, 788, 743, and 721 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.75; H, 7.75. Found: C, 71.84; H, 7.68.

3-Isopropyl-7-methyl-2,3:4,9:7,8-triepoxy-$\Delta^{5,6}$-hexahydroindene (17g). 3-Isopropyl-7-methylindene (**1g**, 800 mg, 4.65 mmol) in 30 ml of acetone with ~1 mg of rose bengal took up 230 ml of oxygen (2.0 equiv) during 90 min. To the cold solution was added 1.25 ml of trimethyl phosphite, and the solution was warmed to room temperature for 1 h. The solution was briefly heated to boiling and evaporated to give a red oil. The oil was chromatographed on a 2.5 × 15 cm silica gel column with $CHCl_3$ to remove the trimethyl phosphate. Evaporation of the filtrate gave a mixture of product and trimethyl phosphite, which was removed under high vacuum at 60 °C. The residue was rechromatographed on a 2.5 × 19 cm silica gel column with $CHCl_3$. Evaporation of the filtrate and trituration of the residue with ether gave 289 mg of **17g** (28%). Recrystallization from heptane gave colorless crystals: mp 109.5–110.5 °C; NMR ($CDCl_3$) δ 0.90 and 0.98 [two d, 6 H, $C(CH_3)_2$, J_{CHCH_3} = 7 Hz], 1.38 (s, 3 H, CH_3), and 2.16 (septet, 1 H, isopropyl CH); mass spectrum (70 eV, source temperature 190 °C) *m/e* (rel intensity) 205 (32), 191 (51), 177 (57), 149 (55), 135 (20), 121 (26), 95 (24), 91 (22), 79 (20), 77 (28), 71 (22), 66 (26), 43 (100), 41 (31), 39 (36), 28 (79), 27 (32), and 18 (77); ir (KBr) 1381, 1357, 1276, 1239, 1075, 980, 962, 913, 867, 856, 842, 827, and 743 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.81; H, 7.10.

Rate of Thermolysis of 9c. A solution of **9c** and $CHCl_3$ in $CDCl_3$ was sealed in an NMR tube. The solution was heated at 69.0 °C by placing the NMR tube in a silicone oil filled finger well protruding into a flask containing refluxing hexane. NMR spectra were taken at 1-h intervals, and the amount of **9c** was measured by the ratio of the average of the area of protons A, B, and C of **9c** to that of $CHCl_3$. After completion of the reaction, the NMR showed 85% **14c** and 15% **15c**. The following data were obtained [h (% **9c** remaining)]: 0 (100), 1 (79), 2 (56), 3 (43), 4 (32), and 5 (23). Fitting the equation for ln [**9c**] vs. time by least squares gave a straight line with slope −0.295, intercept 4.631, and a correlation coefficient 0.9990.

Rate of Thermolysis of 9d. The rate study was done as described for **9c**, but without the $CHCl_3$ as an internal standard. The loss of **9d** was determined by the ratio of the area of the CH_3 group of **9d** to the total CH_3 group areas. The following data were obtained [h (% **9d** remaining)]: 0 (96), 1 (74), 2 (54), 3 (41), and 5 (23). The NMR after completion of the reaction showed 80% **14d** and 20% **15d**. Least-squares treatment gave a straight line with slope −0.287, intercept 4.573, and correlation coefficient 0.9998.

Registry No.—**1a**, 95-13-6; **1b**, 5324,00-5; **1c**, 57653-14-2; **1d**, 10425-96-4; **1e**, 4505-48-0; **1f**, 944-98-9; **1g**, 57653-15-3; **9a**, 40237-80-7; **9b**, 40237-81-8; **9c**, 40237-82-9; **9d**, 40237-83-0; **9e**, 57694-16-

3; **9f,** 57694-17-4; **9g,** 57653-16-4; **14a,** 57694-18-5; **14b,** 57694-19-6; **14c,** 57694-20-9; **14d,** 40237-84-1; **14f,** 57694-21-0; **14g,** 57694-22-1; **15d,** 57653-17-5; **15f,** 57653-18-6; **15g,** 57653-19-7; **16a,** 57653-20-0; **16b,** 57653-21-1; **16c,** 57653-22-2; **16d,** 57653-23-3; **16f,** 57653-24-4; **16g,** 57653-25-5; **17a,** 57694-23-2; **17b,** 57760-11-9; **17c,** 57694-24-3; **17d,** 57760-12-0; **17f,** 57694-25-4; **17g,** 57694-26-5; 2-phenyl-1-indanone, 16619-12-8; 3-methyl-1-indanone, 6072-57-7; 4-methyl-1-indanone, 24644-78-8; isopropyl bromide, 75-26-3; oxygen, 7782-44-7; trimethyl phosphite, 121-45-9.

References and Notes

(1) Part XXII: C. S. Foote and T.-Y. Ching, *Tetrahedron Lett.*, 3771 (1975). Taken in part from P. Burns, Dissertation, University of California, Los Angeles, 1975; supported by National Science Foundation Grants GP 37165X and GP 25790 and Public Health Service Grants AP-00681 and GM 20080.

(2) P. A. Burns and C. S. Foote, *J. Org. Chem.*, following paper in this issue.

(3) (a) K. Gollnick and G. O. Schenck in "1,4-Cycloaddition Reactions", J. Hamer, Ed., Academic Press, New York, N.Y., 1967, p 255; (b) C. S. Foote, *Acc. Chem. Res.*, **1,** 104 (1968); (c) K. Gollnick, *Adv. Photochem.*, **6,** 1 (1968).

(4) (a) C. S. Foote and J. W.-P. Lin *Tetrahedron Lett.*, 3267 (1968); (b) J. E. Huber, *ibid.*, 3271 (1968).

(5) (a) P. D. Bartlett and A. P. S[illegible]ap, *J. Am. Chem. Soc.*, **92,** 3223 (1970); (b) S. Mazur and C. S. Foote, *ibid.*, **92,** 3225 (1970); (c) G. Rio and J. Berthelot, *Bull. Soc. Chim. Fr.*, 3555 (1971); (d) A. P. Schaap, *Tetrahedron Lett.*, 1757 (1971); (e) A. P. Schaap and N. Tontapanish, *J. Chem. Soc., Chem. Commun.*, 490 (1972); (f) A. P. Schaap and P. D. Bartlett, *J. Am. Chem. Soc.*, **92,** 6055 (1970).

(6) C. S. Foote, A. A. Dzakpasu, and J. W.-P. Lin, *Tetrahedron Lett.*, 1247 (1975).

(7) (a) J. H. Wieringa, J. Strating, H. Wynberg, and W. Adam, *Tetrahedron Lett.*, 167 (1972); (b) A. P. Schaap and G. R. Faler, *J. Am. Chem. Soc.*, **95,** 3381 (1973); (c) P. D. Bartlett and M. S. Ho, *ibid.*, **96,** 627 (1974); (d) N. C. Yang and R. V. Carr, *Tetrahedron Lett.*, 5143 (1972); (e) N. M. Hasty and D. R. Kearns, *J. Am. Chem. Soc.*, **95,** 3380 (1973).

(8) (a) G. Rio and J. Berthelot, *Bull. Soc. Chim. Fr.*, 3609 (1969); (b) W. H. Richardson and V. Hodge, *J. Org. Chem.*, **35,** 1216 (1970); (c) W. Fenical, D. R. Kearns, and P. Radlick, *J. Am. Chem. Soc.*, **91,** 3396 (1969); (d) D. R. Kearns, *Ann. N.Y. Acad. Sci.*, **171,** 34 (1970); (e) W. Adam and J.-C. Liu, *J. Am. Chem. Soc.*, **94,** 1206 (1972); (f) L. J. Bollyky, *ibid.*, **92,** 3231 (1970).

(9) (a) C. S. Foote, S. Mazur, P. A. Burns, and D. LERDAL= *J. Am. Chem. Soc.*, **95,** 586 (1973); (b) S. Mazur, Dissertation, University of California, Los Angeles, 1970; (c) G. Rio, D. Bricout and L. Lacombe, *Tetrahedron Lett.*, 3583 (1972).

(10) A. S. Onishchenko, "Diene Synthesis", translated by L. Mandel, Israel Program of Scientific Translation, Jerusalem, 1964.

(11) E. Ciganek, *J. Org. Chem.*, **34,** 1923 (1969).

(12) (a) E. Koch, *Tetrahedron*, **24,** 6295 (1968); (b) W. Schänzer, Dissertation, University of Gottingen, 1952; *Jahresverzeichnis der Deutschen Hochschulschriften*, **69,** 281 (1953).

(13) P. A. Burns and C. S. Foote, *J. Am. Chem. Soc.*, **96,** 4339 (1974).

(14) K. W. Muir, G. A. Sim, P. Stracham, and C. F. Huebner, *Chem. Ind. (London)*, 1581 (1964); (b) C. F. Huebner, P. L. Strachan, E. M. Donogue, N. Cahoon, L. Dorfman, R. Margerison, and E. Wenkert, *J. Org. Chem.*, **32,** 1126 (1967); (c) K. W. Muir and G. A. Sim, *J. Chem. Soc. B*, 667 (1968).

(15) (a) K. Alder, F. Pascher and H. Vogt, *Ber. Dtsch. Chem. Ges.*, **75,** 1501 (1942); (b) W. R. Roth, *Tetrahedron Lett.*, 1009 (1964); (c) J. A. Berson and G. B. Aspelln, *Tetrahedron*, 2697, (1964); (d) J. A. Berson and M. Pomerantz, *J. Am. Chem. Soc.*, **86,** 3896 (1964).

(16) Indene polymerizes and autoxidizes readily even on storage below 0 °C, forming a white solid insoluble in methanol. Its photooxygenation is accompanied by dye bleaching, even when vacuum distilled at low temperature immediately prior to use. The oxygen uptake and dye bleaching vary markedly from one reaction to another, O_2 uptake being least and dye bleaching most on aged samples. The **9a** yield reported here is an average; that reported previously[9a] was the maximum obtained.

(17) (a) M. Avram and G. D. Mateescu, "Infrared Spectroscopy, Applications in Organic Chemistry", translated by L. Birladenau, Wiley-Interscience, New York, N.Y., 1972, p 283; (b) K. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day, San Francisco, Calif., 1962, p 36.

(18) E. D. Becker, "High Resolution NMR, Theory and Chemical Applications", Academic Press, New York, N.Y., 1969, p 149.

(19) N. R. Easton, Jr., F. A. L. Anet, P. A. Burns, and C. S. Foote, *J. Am. Chem. Soc.*, **96,** 3945 (1974). The initial assignment of protons A and D was reversed in ref 9a.

(20) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Vol. 5, 2nd ed, International Series of Monographs in Organic Chemistry, D. H. R. Barton and W. Doering, Ed., Pergamon Press, Elmsford, N.Y., 1969.

(21) A. Padwa, *Tetrahedron Lett.*, 813 (1964).

(22) (a) J. Boche and O. Runquist, *J. Org. Chem.*, **33,** 4285 (1968); (b) J.-P. Le Roux and J.-J. Basselier, *C. R. Acad. Sci.*, **271,** 461 (1970); (c) M. Mousseron-Canet, J.-P. Dalle, and J.-C. Mani, *Tetrahedron Lett.*, 6037 (1968); (d) M. Mousseron-Canet, J.-P. Dalle, and J.-C. Mani, *Bull. Soc. Chim. Fr.*, 1561 (1968); (e) E. J. Agnello, R. Pinson, and G. D. Loubach, *J. Am. Chem. Soc.*, **78,** 4756 (1956).

(23) M. Mousseron-Canet, J.-C. Mani, and J.-P. Dalle, *Bull. Soc. Chim. Fr.*, 603 (1967).

(24) G. O. Pierson and O. A. Runquist, *J. Org. Chem.*, **34,** 3659 (1969).

(25) C. H. Foster and G. A. Berchtold, *J. Am. Chem. Soc.*, **94,** 7939 (1972).

(26) E. Vogel, H.-J. Altenbach, and C. D. Sommerfeld, *Angew. Chem.*, **84,** 986 (1972).

(27) (a) G. O. Schenck, *Angew. Chem.*, **64,** 12 (1952); (b) G. O. Schenck and D. E. Dunlap, *ibid.*, **68,** 248 (1956); (c) G. O. Schenck, *ibid.*, **69,** 579 (1957); (d) K.-H. Schulte-Elte, B. Wilhalm, and G. Ohloff, *Angew. Chem., Int. Ed. Engl.*, **8,** 985 (1969); (e) W. R. Adams and D. J. Trecker, *Tetrahedron*, **27,** 2631 (1971).

(28) (a) G. Rio and M. Charifi, *C. R. Acad. Sci.*, **268,** 1960 (1969); (b) *Bull. Soc. Chim. Fr.*, 3585 (1970).

(29) K. K. Maheshwari, P. de Mayo, and D. Wiegand, *Can. J. Chem.*, **48,** 3265 (1970).

(30) (a) C. Dufraisse, G. Rio, and J.-J. Basselier, *C. R. Acad. Sci.*, **246,** 1640 (1958); (b) J.-J. Basselier, *ibid.*, **258,** 2851 (1964).

(31) W. Skorianetz and G. Ohloff, *Helv. Chim. Acta*, **56,** 2151 (1973).

(32) H. E. Zimmerman, *Acc. Chem. Res.*, **5,** 393 (1972).

(33) *syn*-Benzene trioxide[26] and *anti*-benzene trioxide[25,26] were prepared at the same time as the indene tetraepoxides,[9a] the anti compound by the analogous thermal rearrangement of the epoxy endoperoxide.

(34) M. Makosza, *Tetrahedron Lett.*, 4621 (1966).

(35) (a) M. Makosza and B. Serafin, *Rocz. Chem.*, **39,** 1223 (1965); *Chem. Abstr.*, **64,** 12595*h*; (1966); (b) *Rocz. Chem.*, **39,** 1401 (1965); *Chem. Abstr.*, **64,** 17474*g* (1966); (c) *Rocz. Chem.*, **39,** 1805 (1965); *Chem. Abstr.*, **64,** 17475*g* (1966).

(36) A.-M. Weidler, *Acta Chem. Scand.*, **17,** 2724 (1963).

(37) C. F. Koelsch and P. R. Johnson, *J. Org. Chem.*, **6,** 540 (1941).

(38) N. Campbell and E. Ciganek, *J. Chem. Soc.*, 3834 (1956).

(39) J. Buddrus, *Chem. Ber.*, **101,** 4152 (1968).

(40) D. G. Markees and A. Burger, *J. Am. Chem. Soc.*, **71,** 2031 (1949).

(41) A.-M. Weidler and G. Bergson, *Acta Chem. Scand.*, **18,** 1483 (1964).

(42) J. Almy and D. J. Cram, *J. Am. Chem. Soc.*, **91,** 4459 (1969).

(43) C. S. Marvel, J. Dec, and H. G. Cooke, Jr., *J. Am. Chem. Soc.*, **62,** 3499 (1940).

(44) T. Money, R. A. Raphael, A. I. Scott, and D. W. Young, *J. Chem. Soc.*, 3958 (1961).

(45) J. Koo, *J. Am. Chem. Soc.*, **75,** 1891 (1953).

(46) J. Cymerman-Craig, B. Moore, and E. Ritchie, *Aust. J. Chem.*, **12,** 447 (1959).

(47) J. Koo, M. S. Fish, G. N. Walker, and J. Blake, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 327.

(48) E. R. Coburn, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 696.

Chemistry of Singlet Oxygen. XXIV. Low Temperature Photooxygenation of 1,2-Dihydronaphthalenes[1]

Paul A. Burns and Christopher S. Foote*

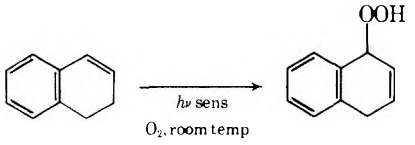
Contribution No. 3502 from the Department of Chemistry, University of California, Los Angeles, California 90024

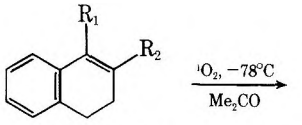
Received November 17, 1975

1,2-Dihydronaphthalenes react with singlet oxygen at −78 °C in acetone to yield products derived from both ene reaction and 1,4 cycloaddition; substitution of a phenyl group on the double bond strongly influences the course of the photooxygenation. The presumed initial 1,4 cycloadducts rearrange and react further to form two isomeric endoperoxide-bisepoxide compounds (**2** and **3**). The structures of these isomers have been determined; their formation suggests a benzene oxide–oxepin equilibrium at an intermediate stage of the photooxygenation. The dioxygenated products react smoothly with trimethyl phosphite to form triepoxides and with triethylamine to form γ-hydroxy-α,β-unsaturated ketones, and thermolyze to form dihydronaphthalene tetraepoxides.

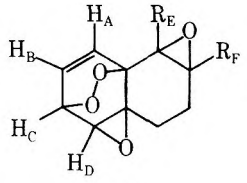
In the accompanying paper,[1a] it was shown that substituted indenes can be photooxygenated at −78 °C in acetone to give dioxygenated products in good yields. This reaction proved to be so novel and preparatively interesting that its extension to other areas appeared worthwhile, and, for this purpose, a series of dihydronaphthalenes seemed to offer interesting possibilities.

Previously, only 1,2-dihydronaphthalene itself had been photooxygenated; at room temperature, the expected ene product was reported.[2] 1,2-dihydronaphthalene also gives Diels–Alder adducts with both dicyanoacetylene and dimethyl acetylenedicarboxylate, but these reactions require elevated temperatures, and the adducts lose ethylene to form the corresponding substituted naphthalenes under these conditions.[3] The results reported in this paper show a varied and interesting chemistry of photooxygenation which depends markedly on the substitution of the dihydronaphthalene.

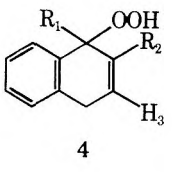




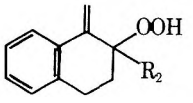
1a, R_1 = H; R_2 = C_6H_5
b, R_1 = C_6H_5; R_2 = H
c, R_1 = R_2 = C_6H_5
d, R_1 = CH_3; R_2 = C_6H_5
e, R_1 = CH_3; R_2 = H
f, R_1 = R_2 = H



2,3



4



5

Results

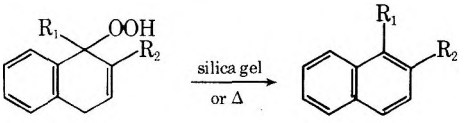
Low Temperature Photooxygenation. An acetone solution of 1-phenyl- 3,4-dihydronaphthalene (**1b**) was photooxygenated at −78 °C using rose bengal as sensitizer. As with the indenes,[1a] the solution took up 2.0 equiv of oxygen, and an NMR spectrum showed only dioxygenated products. However, two sets of olefinic protons appeared, indicating the formation of isomeric compounds (**2b** and **3b**) with very similar structures whose spectra were closely analogous to those of diepoxy endoperoxides formed in the indene series.[1a]

Under the same conditions, however, 2-phenyl-3,4-dihydronaphthalene (**1a**) reacted with only 1 equiv of singlet oxygen, and NMR showed the ene product (**4a**) to be the only product. Other dihydronaphthalenes (**1c–f**) gave mixtures of products **2** and **3** with **4** and/or **5**; Table I shows the product composition determined by NMR for all the compounds photooxygenated, along with yields of each compound as isolated.

Isolation of the Products. When the reaction solutions were evaporated and redissolved in ether–petroleum ether, one of the two dioxygenated products crystallized preferentially.[4] This product is designated isomer **2**. The other isomer, **3**, would not crystallize in the presence of significant amounts of compound **4**, the ene product, unless the solution was seeded with crystals previously isolated by column chromatography. This was not possible for compounds **3e,f**, as both products had R_f values close to those of the ene products. In addition, the dioxygenated compounds slowly decompose on chromatography, further limiting their purity.

The products derived from ene reaction, **4**, could not be isolated pure enough for analysis. As might be expected, they tend to lose hydrogen peroxide readily; indeed, fractions of this product isolated by chromatography on silica gel were almost invariably contaminated by the corresponding naphthalene. Thus, identification of these compounds was based on their NMR and ir spectra and on their conversion to the naphthalenes.

Authentic samples of naphthalenes **6a**,[5] **6c**,[6,7] and **6d**[7] were prepared by the procedure of Campbell and Kidd[5] by



4 **6**

refluxing a xylene solution containing chloranil and the corresponding 3,4-dihydronaphthalene. These compounds, and purchased samples of **6e** and **6f**, had NMR and ir spectra identical with those of naphthalenes from compounds **4**.

Treating **4a** and **4e** with excess $NaBH_4$ led to the isolation of small amounts of the corresponding alcohols; how-

Table I. Products of Photooxygenation of 1,2-Dihydronaphthalenes[a]

			Products of			
			[2 + 4] attack		"Ene" reaction	
Compd	R_1	R_2	2, %	3, %	4, %[b]	5, %
1a	H	C_6H_5	0	0	100	c
1b	C_6H_5	H	40 (33)	60 (34)	0	c
1c	C_6H_5	C_6H_5	25 (20)	40 (32)	35	c
1d	CH_3	C_6H_5	4[d]	6[d]	85	5
1e	CH_3	H	25 (13)	35	40	e
1f	H	H	37.5 (17)	37.5	25	c

[a] Determined by NMR; numbers in parentheses are isolated yields. [b] Not isolated in pure form because of ready loss of H_2O_2. [c] Not applicable. [d] Compounds 2d and 3d were not isolated; the assignment is based on analogies to the chemical shifts of the products of the other reactions. [e] Presence uncertain; if present, the yield is included in the yield of compound 4e.

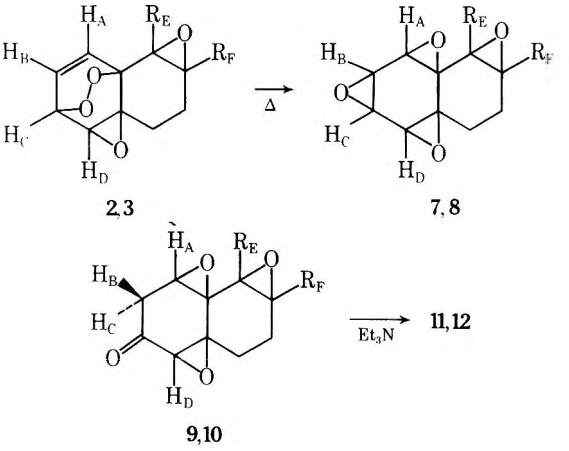
ever, on drying under high vacuum, the alcohols lost water to form the naphthalenes.

Characterization of the Dioxygenated Products. The analyses and mass spectra of the photooxygenation products were consistent with starting material plus two molecules of oxygen, although, unlike the analogous indene products,[1a] the peaks for P − 32 (loss of oxygen) were not significant. The ir spectra showed neither carbonyl nor hydroxyl absorptions, but there were many strong bands between 750 and 1280 cm^{-1}, the region containing substituted epoxide ring vibrations.[8] The compounds give a positive test for peroxide with acidified starch–iodide paper. The NMR spectra of these compounds are tabulated in Table II.

The NMR spectra all show two olefinic protons, an endoperoxy CH proton, and an epoxide proton that form an ABXY system (protons A–D). There are also one or two additional epoxide protons, depending on the substitution at positions E and F, and two methylene groups. The spectra are exactly analogous to the spectra of the dioxygenated indenes;[1a] the only difference is that, with the exception of **2b**, the ABXY system is degenerate (or simplified) because the difference in the chemical shift of the olefinic protons, A and B, is small (<~10 Hz) and the coupling pattern approaches that of an A_2XY system.[9]

The above data show that, for the same reasons advanced for the dioxygenated indenes,[1a] the general structure of these products must be diepoxy endoperoxides **2** and **3**. Discussion of the stereochemical assignments will be deferred until the Discussion.

1,2-Dihydronaphthalene Tetraepoxides. As did the dioxygenated indenes,[1] the dioxygenated dihydronaphthalenes undergo thermal rearrangement. Refluxing benzene or xylene solutions of **2** or **3** gave tetraepoxides **7** or **8** in ~75% yield. In the two cases where the endoperoxides were not



isolated (**3e** and **3f**), the photooxygenated solutions, after crystallization of the other isomers (**2e** and **2f**), were evaporated and heated under vacuum at ~90 °C for several hours. In this manner, the ene products were converted to their corresponding naphthalenes, which did not interfere with the isolation of the tetraepoxides. The isomeric tetraepoxides (**7** and **8b,c,e,f**) were isolated and purified in 26–58% yield by repeated crystallization from benzene–heptane solution. The minor products of the thermolysis are β-epoxy ketones (**9** or **10**); an ir spectrum taken after each reaction showed a carbonyl band at ~1725 cm^{-1} and no hydroxyl band. These ketones are very sensitive to base, and readily isomerize to the corresponding γ-hydroxy-α,β-unsaturated ketones (**11** or **12**). However, it was possible to isolate and characterize **9e.**

The NMR spectra of the tetraepoxides are summarized in Tables III and IV. In contrast to the indene tetraepoxides,[1a] the relative chemical shifts o protons A–D show no general trends. In fact **8b, 7e,** and **7f** have almost equivalent chemical shifts for protons B–D. The assignment as A–D (and not the reverse, with A = D, etc.) was based on the following arguments. (1) As in the indenes, there is an upfield shift of δ 0.6–0.8 for proton A owing to the shielding of phenyl substituents; proton D shows only a small upfield shift. (2) This assignment gives the protons with the 0° dihedral angle the larger coupling constants (see Discussion). (3) This assignment then agrees with that of the indene tetraepoxides,[1a] which was confirmed by ^{13}C NMR;[10] the

Table II. ^1H Chemical Shifts (δ, Me_4Si, $CDCl_3$, 60 MHz) of the Ring Protons of the Dioxygenated Products

Proton	2b[a,b]	3b[a]	2c	3c	2e[a]	3e	2f	3f
H_A	5.90	6.13[c]	6.05[c]	6.09[c]	6.34[c]	6.33[c]	6.29[c]	6.30[c]
H_B	6.09							
H_C	4.96	4.92	4.97	4.96	5.02	4.98	5.03	4.98
H_D[d]	3.54	3.38	3.62	3.48	3.51	3.38	3.55[e]	3.45[e]
H_E[f]							3.24	3.21
H_F	3.72	3.25			3.21	3.24	3.44	3.45
$(CH_2)_2$	1.32 (1)	2.2 (4)	1.50 (1)	2.6 (4)	1.22 (1)	2.0 (4)	1.25 (1)	2.1 (4)
	2.29 (2)		2.6 (3)		2.16 (2)		2.4 (3)	
	2.71 (1)				2.57 (1)			

[a] 100-MHz spectra. [b] Protons A–C form an ABX system with J_{AB} = 8.9, J_{AC} = 2.9, and J_{BC} = 5.1 Hz. [c] Center of the AB portion of a degenerate ABX system. [d] J_{CD} = 4.2–4.5, J_{BD} < 1 Hz. [e] Proton D of D and E was assigned by decoupling proton C. [f] J_{EF} = 4.0 Hz.

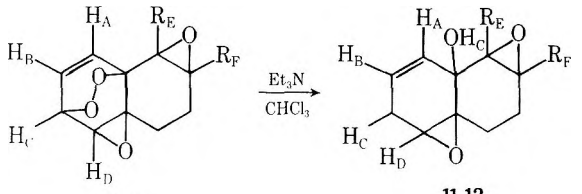
Table III. ^{1}H Chemical Shifts (δ, Me_4Si, $CDCl_3$, 100 MHz) of the Ring Protons of the Dihydronaphthalene Tetraepoxides

Proton	7b	8b	7c	8c	7e[a]	8e	7f	8f
H_A	3.02	2.92	2.83	2.80	3.65	3.66	3.60	3.56
H_B	3.19	3.19	3.13	3.14	3.36	3.40	3.37	3.37
H_C	3.35	3.19	3.36	3.30	3.36	3.31	3.37	3.32
H_D	3.43	3.19	3.49	3.27	3.36	3.17	3.37	3.18
H_E							3.02	2.74
H_F	3.28	3.19			3.23	3.21	3.47	3.33
$(CH_2)_2$	1.09 (1)	1.19 (1)	1.24 (1)	1.46 (1)	0.97 (1)	1.10 (1)	1.02 (1)	1.11 (1)
	2.30 (3)	2.30 (3)	2.50 (3)	2.60 (3)	2.20 (3)	2.20 (3)	2.20 (3)	2.20 (3)

[a] 60-MHz spectrum.

presence of an additional methylene group would not be expected to cause a complete reversal of the assignment.

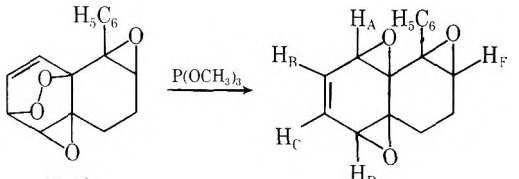
Base-Catalyzed Rearrangement. Compounds **2** and **3** rearrange readily with triethylamine, as did the analogous indene compounds.[1a] The resulting α,β-unsaturated ketones (**11** and **12**) are formed in 83–97% yield. The ir spec-



2,3 11,12

tra all show a strong hydroxyl band at ~3550 cm^{-1} and an α,β-unsaturated carbonyl band at 1680–1690 cm^{-1}.

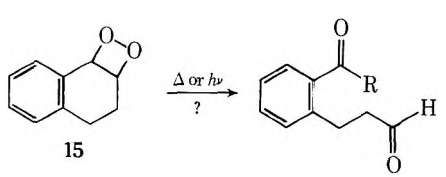
Reaction of 2 and 3 with Trimethyl Phosphite. As with the analogous indene products,[1a] compounds **2** and **3** also react with trimethyl phosphite. This was shown by the reaction of both isomers **2b** and **3b** to give the corresponding benzene dioxide compounds **13** and **14** in about 70% yield. The NMR spectra of **13** and **14** have an AA'XX' sys-



2b,3b 13,14

tem, with the olefinic protons appearing as a complex multiplet.

Photooxygenations in Methanol. It was previously shown that, with indenes, carrying out the photooxygenations in methanol instead of acetone led to the isolation of dioxetanes in good yield.[11] This is not the case with the dihydronaphthalenes. The photooxygenation of **1b** and **1e** in methanol at −78 °C gave a product distribution almost identical with that of the reactions in acetone. There were very small triplet resonances at 9.64 ppm consistent with the aldehydes **16b** and **16e** (the expected thermolysis products of dioxetanes **15b** and **15e**), but integration showed them to be present in <1% of the total product. The solutions also did not show any fluorescence when heated in the presence of 9,10-diphenylanthracene. Thus, dioxetanes were formed in only trace amounts at most in these reactions.



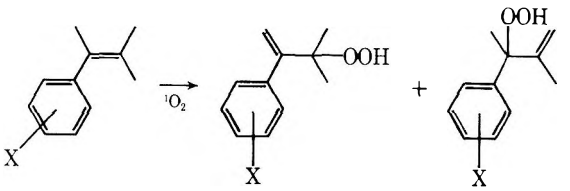
15 16

When the same reactions were carried out at room temperature, **1b** gave 23% **16b** (by NMR), and no fluorescence was observed on adding diphenylanthracene to reaction solutions and heating. The reaction of **1e** gave ~12% **16e** by NMR, and a very weak fluorescence was observed under the above conditions. Since potential routes which do not pass through **15** are conceivable for formation of **16**, the evidence is not conclusive for formation of any dioxetane.

Discussion

A directing effect of the phenyl group on the attack of singlet oxygen is clearly shown by Table I. The parent compound, 1,2-dihydronaphthalene (**1f**), gives 25% ene product. However, substitution of a phenyl group at the α position of the double bond (**1b**) eliminates the formation of this product, while substitution of a phenyl group at the β position (**1a**) causes the exclusive formation of ene product and no dioxygenated products (from [2 + 4] attack). With **1c** (phenyl substitution at both positions) the effect of the two phenyls are both felt, the β-phenyl perhaps more strongly since 35% of the ene product is formed compared to 25% in the unsubstituted compound. The phenyl group seems to direct the attack of singlet oxygen on the dihydronaphthalene ring, in one case to give an ene reaction, and in the other to give a 1,4 cycloaddition.

The reaction appears to form products with conjugated olefin preferentially; in **1b**, the ene product, which would have an unconjugated double bond, is not formed and the initial cycloadduct is further conjugated with the phenyl substituent; the ene product from **1a** is conjugated while the Diels–Alder product retains the same conjugation as the unsubstituted compound; both the ene product and the presumed initial Diels–Alder product from **1c** are conjugated.[12] This effect is reminiscent of the preferential formation of the conjugated ene product from the α,β,β-trimethylstyrenes,[13] and probably reflects productlike character in the transition state for the product-determining step.



2,7 1

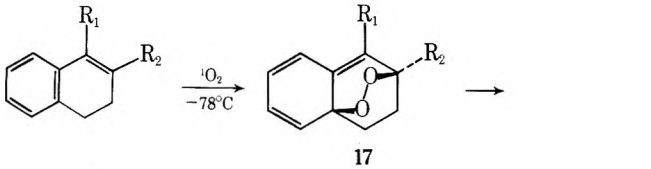
Stereochemistry of the Isomeric Dioxygenated Products. The physical and chemical properties of the two isomeric dioxygenated products formed in these photooxygenations show that they both must have the same general structure as those of the indene-derived products.[1a] That the less soluble isomers **2** all belong to the same stereochemical series is shown by the fact that their NMR spectra (Table II) all have one very high-field CH_2 proton (~1 ppm upfield from the other methylene protons), whereas all four CH_2 protons in the **3** series occur within a narrow

Table IV. Coupling Constants (Hz) for the Tetraepoxide Protons[a]

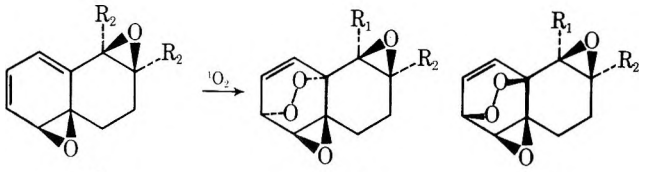
J	7b	8b[b]	7c	8c[c]	7e[c]	8e	7f[c]	8f
AB	3.3	3.3	3.3	3.3	3.3	3.3	3.0	3.2
BC	3.7		3.7	3.7	3.7	3.6		3.5
BD	1.1		1.2	1.4	1.0	1.1	1.3	1.1
CD	1.7		1.5	1.7	1.6	1.5	1.8	1.7
EF							3.7	3.5

[a] J_{AC} not resolved. [b] Protons B–D could not be separated with Eu(fod)$_3$. [c] Eu(fod)$_3$ was used to separate overlapping proton resonances; this technique was only partially successful with 7f.

range. Similar regularities occur with protons C and D, all members of a series having resonances for a given proton either higher or lower field than in the other series. Also, the amount of **2** is always ≤3. Analogy with the indene case[1a] suggested that one isomer should be **19**. The rearrangement of an initial endoperoxide (**17**) would lead to a bisepoxide (**18**) in which the two epoxide groups must be cis. The second 1,4 cycloaddition of singlet oxygen would occur on the less hindered side, leading to **19**, in which the endoperoxide group is trans to the two epoxide groups.

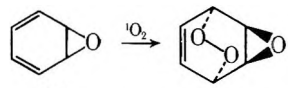


17



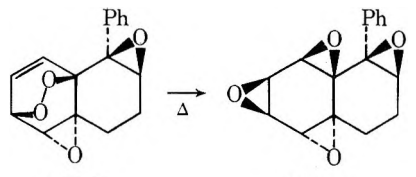
18 **19** **20**

However, if the two epoxide groups in **18** must be cis, then the only possible structure for the second isomer would be **20**, in which the second addition of singlet oxygen occurs cis to the epoxide group. However, this conclusion did not seem reasonable since models showed that the diene system of both **18** and the analogous indene compounds should both favor the attack of singlet oxygen trans to the epoxide group. Furthermore, the analogous reaction of benzene oxide **21** with singlet oxygen leads to the formation of **22** with high stereospecificity.[14,15]



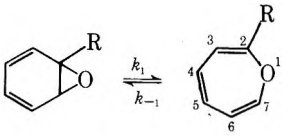
21 **22**

An x-ray crystal structure determination has been carried out on tetraepoxide **7b**;[16] this compound was chosen since it is more stable than the endoperoxide **2b**, and the two structures are directly related. The structure was unexpectedly found to be **24**; thus the structure of **2b** must be **23**, in which the two epoxide groups are trans!



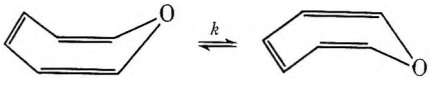
23 (**2b**) **24** (**7b**)

The formation of this isomer can be easily rationalized by the benzene oxide–oxepin chemistry observed by Vogel et al.[17] Benzene oxide was shown to equilibrate with its tautomer, oxepin (**25**, R = H).[17,18] Temperature-dependent



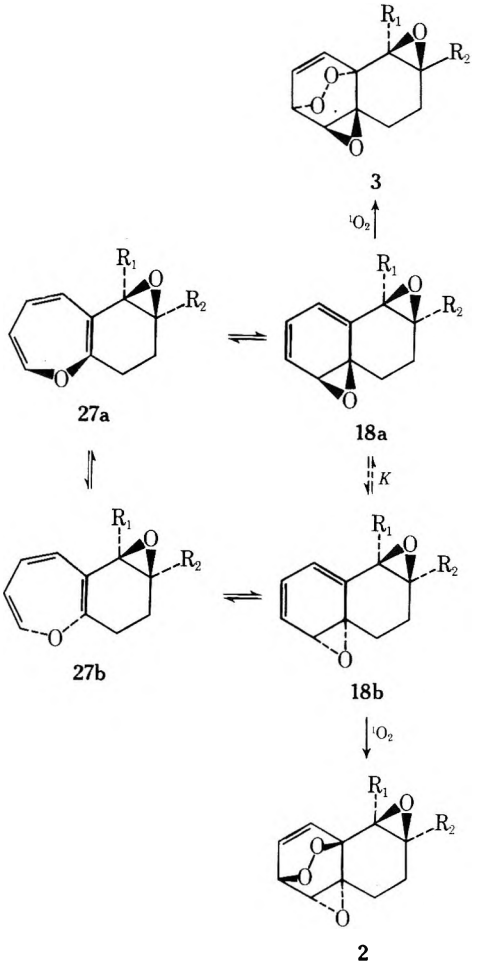
25

NMR studies of the equilibrium were carried out on both oxepin and 2-methyloxepin (**25**, R = CH_3).[19,20] At −78 °C, $k_1 = 2 \times 10^4$ s^{-1} and $K = 3.2$ for oxepin and $k_1 = 9.5 \times 10^3$ s^{-1} and $K = 4.0$ for 2-methyloxepin ($K = k_1/k_{-1}$). Thus, there are substantial amounts of both oxepins present. Substitution favors the oxepin form; however, even when the oxepin form is strongly favored, as in 2,7-dimethyloxepin (which shows no benzene oxide by spectroscopic methods),[17,20] a Diels–Alder reaction occurs readily with maleic anhydride[20] and proceeds via the benzene oxide form. Oxepin exists in a boat conformation with a very rapid interconversion between the two conformers (**26a** ⇄ **26b**).[20,21] One might expect the barrier to inversion to be comparable to that of cycloheptatriene, where Anet found $k = 180$ s^{-1} at −143 °C, $\Delta F^{\ddagger} = 6.1$ kcal mol^{-1}, and $\Delta S^{\ddagger} = 0$;[22] the calculated rate of inversion at −78 °C would be $k = 6.5 \times 10^5$ s^{-1}.



26a **26b**

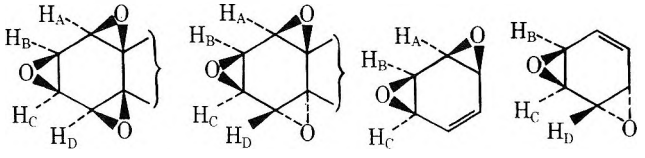
Thus, it seems likely that the benzene oxide intermediate **18a** can equilibrate readily with its isomer **18b** via the intermediate oxepin **27**. The stereospecific attack of singlet



3 **27a** **18a** **27b** **18b** **2**

oxygen on **18a** and **18b** would then give the two isomeric dioxygenated products, **2** and **3**.

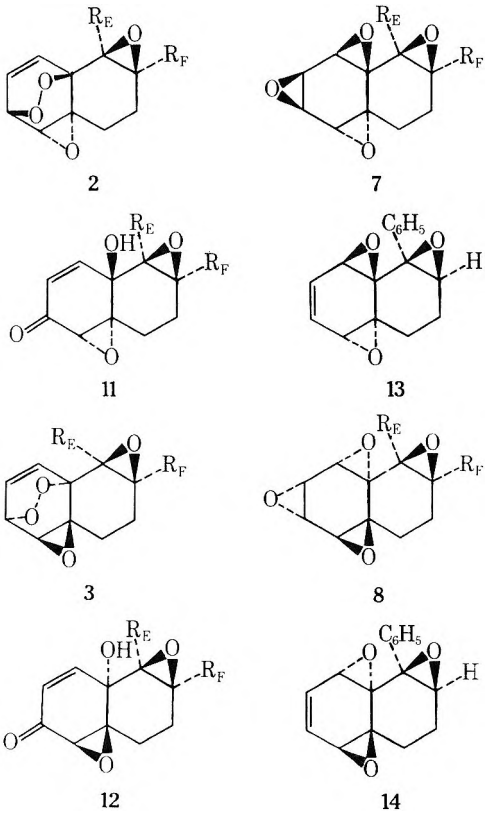
By this mode of formation, isomers **2** and **3** should have the same relative geometry for the ring containing the endoperoxide group (the A ring). That this is true can be shown by the NMR spectra of the corresponding tetraepoxide isomers (**7** and **8**). There are only two possible configurations, **28** and **29** for the A ring, and these can be compared with *syn*-benzene dioxide (**30**)[23] and *anti*-benzene dioxide (**31**),[23b,24] prepared by Vogel et al.[25] (see Table V).



28 **29** **30** **31**

Both **7** and **8** in the entire series of tetraepoxides have essentially the same coupling constants for the A ring. Moreover, Table V shows that J_{CD} for the tetraepoxides is only consistent with the *anti*-benzene oxide structure **29,** which has these protons on adjacent trans epoxide groups, with a dihedral angle of 50°.[27] Protons A and B must be on adjacent cis epoxide groups, with a dihedral angle of 0°, since the J_{AB} values are much larger than the J_{CD} value for **31.** The J_{BD} value for the tetraepoxides (J_{BD} ~1.0 Hz) is also closer to the value observed for **31** (J_{BD} = 0.8 Hz) for the long-range coupling of protons on trans epoxide groups. Since J_{AC} = 0.4 Hz for **30,** the corresponding AC coupling was probably not resolved in **7** and **8**. J_{BC} for **7** and **8** is approximately midway between the values of J_{BC} for the benzene dioxides.

We conclude from these data that both tetraepoxide isomers **7** and **8**, and, thus, the isomeric photooxygenation products **2** and **3**, have the same geometry for the A ring.[30] Therefore, the only possible structure for **3** is the one in which two cis epoxide groups are trans to the endoperoxide groups. The assignments of each series are then as shown below.



2 **7**

11 **13**

3 **8**

12 **14**

Table V. Coupling Constants (Hz) for the Tetraepoxide A Ring Protons and *syn*- and *anti*-Benzene Dioxide

J	Dihedral angle, deg	7, 8[a]	30	31
BC	0	3.7	3.5	4.2
AB	0	3.3	2.8	
CD	50	1.6		1.7
BD		1.1	0.4	0.8

[a] Average values of all compounds.

That two isomeric products should be formed here but only one in the indene series appears to be well accounted for by the absence of the severe peri interaction in the intermediate oxepins **27a,b,** which appears to inhibit the formation of one conformational isomer in the indene series.[1a] With a six-membered ring instead of a five-membered ring, the puckering of the ring decreases the interaction; the six-membered ring is also considerably less rigid than the cyclopentadiene epoxide ring in the intermediate, which should allow the ring to distort more to relieve peri interactions. (See ref 1a for further discussion of these points).

The ready rearrangement of the intermediate endoperoxide to the diepoxide is even more surprising than in the indene series, since ordinary cyclohexadiene endoperoxides are stable well above room temperature. The same arguments as in the case of the indene[1a,12] concerning the nature of this rearrangement must apply here, with even greater force.

Experimental Section

General conditions, including photooxygenation conditions, are as in the accompanying paper.[1a] Details of NMR spectra which occur in the tables are not repeated in this section.

Starting Materials. 2-Phenyl-3,4-dihydronaphthalene (**1a**) was prepared from 2-phenyl-1-tetralone[5] and had mp 61–62 °C (lit.[5] 64–66 °C). 1,2-Diphenyl-3,4-dihydronaphthalene (**1e**)[6] was prepared from 2-phenyl-1-tetralone and had mp 89.5–91 °C (hexane) (lit.[6] 76.5–77 °C, EtOH–EtOAc). 1-Methyl-2-phenyl-3,4-dihydronaphthalene (**1d**) was prepared from the 2-phenyl-1-tetralone with methyl Grignard and dehydration, and had mp 75–77 °C (lit.[31] 76 °C). 1-Methyl-3,4-dihydronaphthalene[31,32] (**1e**) was similarly prepared from α-tetralone and had bp 80–81 °C (5 mm) [lit.[32] bp 105 °C (14 mm)]. 1,2-Dihydronaphthalene (**1f**) was prepared by $LiAlH_4$ reduction of α-tetralone followed by dehydration and had bp 74–77 °C (7 mm) [lit.[33] bp 78 °C (6 mm)]. 1-Phenyl-3,4-dihydronaphthalene, purchased from Aldrich, was used as received.

Photooxygenation of 2-Phenyl-3,4-dihydronaphthalene (1a). A solution of 1.00 g (4.86 mmol) of **1a** in 175 ml of acetone containing ~2 mg of rose bengal took up 110 ml (0.92 equiv) of O_2 during 2.5 h. The solution was warmed to room temperature and evaporated; NMR showed **1a** (~10%), 2-phenylnaphthalene (**6a,** ~15%), and the ene product (**4a,** ~75%); NMR ($CDCl_3$) δ 3.37 (m, 2 H, CH_2), 5.65 (br t, 1 H, H_1, J = 2 Hz), 6.45 (d of d, 1 H, H_3, J = 4.6 and 3.4 Hz), 7.33 (m, 9 H, aromatic), and 7.75 (s, 1 H, OOH). The reaction mixture was dissolved in methanol and treated with excess $NaBH_4$; ether was added and the solution was extracted with water, dried over $MgSO_4$, and evaporated; NMR ($CDCl_3$) showed 1-hydroxy-2-phenyl-1,4-dihydronaphthalene (40%), **6a** (50%), and **1a** (10%). The material was chromatographed on a 2.5 × 20 cm silica gel column with $CHCl_3$. The forerun contained 500 mg of **1a** (25%) and **6a** (75%), colorless plates, (CH_3OH), mp 102–103 °C (lit.[5] 101–102 °C), not depressed by mixture with an authentic sample, and with NMR and ir spectra superimposable with those of an authentic sample. Other fractions gave 350 mg of crystalline 1-hydroxy-2-phenyl-1,4-dihydronaphthalene: NMR ($CDCl_3$) δ 2.0 (broad s, 1 H, OH, chemical shift variable, exchangeable with D_2O), 3.47 (m, 2 H, CH_2), 5.52 (broad t, 1 H, HOCH), 6.11 (t, 1 H, olefinic CH), and 7.35 (m, 9 H, aromatic); ir (KBr) 3490, 1487, 1436, 745, and 680 cm^{-1}. On drying under high vacuum, the alcohol dehydrated to form 2-phenylnaphthalene, identical with an authentic sample.

Photooxygenation of 1-Phenyl-3,4-dihydronaphthalene (1b). A solution of 3.00 g (14.5 mmol) of **1b** in 150 ml of acetone containing ~4 mg of rose bengal took up 666 ml (1.88 equiv) of

oxygen during 3.5 h. The solution was warmed to room temperature and evaporated; NMR ($CDCl_3$) showed two compounds, **2b** (40%) and **3b** (60%). Crystallization from ether gave 1.04 g of **2b.** The filtrate was evaporated, and the residue chromatographed on a 2.5 × 19 cm silica gel column with $CHCl_3$. The forerun contained ~75 mg (3%) of starting material (R_f 0.72). The fractions containing **3b** (R_f 0.42) were evaporated; crystallization from ether–pentane gave 1.32 g of **3b** (34%), mp 80–83 °C. The fraction containing **2b** (R_f 0.30) yielded a further 250 mg of **2b;** total recovered was 1.29 g (33%), mp 115.5–116.5 °C. The remaining material contained ~10% rearrangement products (**7b** and **8b**), ~10% **2** and **3b,** and other unidentified material. Both **2b** and **3b** free iodine from acidified KI. Recrystallization of **2b** from ether–petroleum ether gave colorless crystals: mp 115.5–116.5 °C dec; NMR ($CDCl_3$) δ 7.37 (s, 5 H, C_6H_5); ir (KBr) 1443, 1362, 1263, 1247, 962, 912, 887, 845, 758, 739, 700, and 694 cm^{-1}; mass spectrum (70 eV, source temperature 132 °C) *m/e* (rel intensity) 270 (4), 209 (5), 141 (6), 128 (6), 115 (4), 105 (28), 77 (10), 32 (15), 28 (100), and 18 (7).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.96; H, 5.15.

Recrystallization of **3b** from ether–petroleum ether gave colorless crystals: mp 80.0–80.5 °C dec; NMR ($CDCl_3$) δ 7.36 (m, 5 H, C_6H_5); ir (KBr) 1603, 1491, 1256, 1239, 968, 950, 916, 891, 838, 811, 798, 752, and 695 cm^{-1}; mass spectrum (70 eV, source temperature 140 °C) *m/e* (rel intensity) 270 (2), 241 (3), 209 (3), 128 (5), 115 (3), 105 (21), 77 (7), 32 (16), 28 (100), 18 (33), and 17 (6).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.90; H, 5.12.

Photooxygenation of 1,2-Diphenyl-3,4-dihydronaphthalene (1c). **1c** (1.00 g, 3.55 mmol) in 75 ml of acetone containing ~2 mg of rose bengal took up 151 ml (1.75 equiv) of oxygen during 5 h. The solution was warmed to room temperature and evaporated; NMR ($CDCl_3$) showed the diepoxy endoperoxides **2c** (25%) and **3c** (40%), and the ene product **4c** (35%). The addition of ether gave 280 mg of **2c** (containing 15% **3c,** by NMR). Seeding the concentrated filtrate with **3c** (from chromatography of a previous reaction mixture) gave 400 mg of **3c.** The filtrate was evaporated and chromatographed on a 2 × 25 cm silica gel column with $CHCl_3$. The first fractions contained 1,2-diphenylnaphthalene (**6c**) and **4c:** NMR ($CDCl_3$) δ 3.58 (d, 2 H, CH_2, $J_{H_3CH_2}$ = 2 Hz), 6.38 (t, 1 H, H_3), 7.14 (m, 14 H, aromatic), and 7.33 (s, 1 H, OOH). The residue from one fraction gave a further 35 mg of **3c.** The fractions containing **6c** and **4c** were combined and evaporated. The residue was treated with 10 ml of 4% ethanolic KOH solution; 50 ml of ether was added, and the solution was extracted with water and saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated to give 350 mg of **6c** (31%). Recrystallization gave 168 mg, mp 109 °C (ethanol), not depressed by mixture with an authentic sample, and with ir and NMR superimposable with those of an authentic sample.

Recrystallization of **2c** from methylene chloride–heptane gave 240 mg (20%): mp 130–131 °C dec; NMR ($CDCl_3$) δ 7.04 (s, 5 H, C_6H_5) and 7.10 (s, 5 H, C_6H_5); ir (KBr) 1603, 1241, 1232, 965, 923, 908, 900, 876, 868, 848, 763, 759, 703, and 697 cm^{-1}; mass spectrum (70 eV, source temperature 165 °C) *m/e* (rel intensity) 241 (8), 225 (4), 213 (4), 121 (5), 115 (5), 106 (9), 105 (100), 103 (5), 77 (25), 69 (6), 49 (5), 28 (7), and 18 (11).

Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.28; H, 5.24. Found: C, 76.10; H, 5.42.

Recrystallization of **3c** from ether–chloroform solution gave 395 mg (32%): mp 112 °C dec (with resolidification and remelting at 205–215 °C dec); NMR ($CDCl_3$) δ 7.17 (m, 10 H, C_6H_5); ir (KBr) 1604, 1244, 1233, 937, 913, 902, 889, 876, 757, 748, 717, and 687 cm^{-1}; mass spectrum (70 eV, source temperature 180 °C) *m/e* (rel intensity) 105 (30), 77 (8), 32 (24), 28 (100), and 18 (11). Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.28; H, 5.24. Found: C, 76.33; H, 5.33.

Photooxygenation of 1-Methyl-2-Phenyl-3,4-dihydronaphthalene (1d). A solution of 500 mg (2.77 mmol) of **1d** in 45 ml of acetone containing ~1 mg of rose bengal took up 61 ml (1.10 equiv) of oxygen during 70 min. The solution was warmed to room temperature and evaporated; NMR showed the diepoxy endoperoxides **2d** (4%, methyl singlet at δ 1.07) and **3d** (6%, methyl singlet at δ 1.00), the ene product **4d** (85%), NMR ($CDCl_3$) δ 1.42 (s, 3 H, CH_3), 3.44 (d, 2 H, CH_2, J_{3,CH_2} = 4 Hz), 6.08 (t, 1 H, H_3), 7.20 (s, 1 H, OOH), and 7.30 (m, 9 H, aromatic), and **5d** (~5%, olefinic protons as singlets at δ 5.13 and 5.67). The material was treated with 4% ethanolic KOH. After 10 min, 50 ml of ether was added, and the solution was extracted with water and saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated. Addition of ethanol gave 275 mg of **6d** (48%); recrystallization gave **6d,** mp 85–86 °C (lit.[7] 85 °C); the melting point was not depressed by mixture with an authentic sample (see below), and the ir and NMR spectra were superimposable.

Photooxygenation of 1-Methyl-3,4-dihydronaphthalene (1e). A solution of 3.00 g (20.8 mmol) of **1e** in 70 ml of acetone containing ~2 mg of rose bengal took up 752 ml (1.50 equiv) of oxygen during 3.3 h. The solution was evaporated at room temperature; NMR ($CDCl_3$) showed the diepoxy endoperoxides **2e** (25%) and **3e** (35%), and the ene product **4e** (40%). Trituration with ether–petroleum ether gave 555 mg (13%) of **2e,** mp 119–120 °C (hexane–CCl_4). **2e** freed iodine from acidified KI: NMR ($CDCl_3$) δ 1.49 (s, 3 H, CH_3); ir (KBr) 1366, 1260, 1206, 950, 914, 891, 855, 817, 799, 760, 745, and 704 cm^{-1}; mass spectrum (70 eV, source temperature 140 °C) *m/e* (rel intensity) 147 (2), 137 2), 79 (2), 55 (3), 44 (4), 43 (11), 41 (2), 39 (3), 32 (18), and 28 (100).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.35, H, 5.91.

The filtrate was evaporated and the residue chromatographed on a 2.5 × 25 cm silica gel column with CCl_4. The first fractions contained 1-methylnaphthalene (**6e**) and **4e**: NMR ($CDCl_3$) δ 1.41 (s, 3 H, CH_3), 3.28 (d of d, 2 H, CH_2, J_{2,CH_2} = 2, J_{3,CH_2} = 3 Hz), 5.82 (t of d, 1 H, H_2, $J_{2,3}$ = 11 Hz), 6.06 (t of d, 1 H, H_3), 7.30 (m, 4 H, C_6H_4), and 7.64 (s, 1 H, OOH). Rechromatography of this material gave only **6e** (800 mg, 27%), a colorless oil: NMR ($CDCl_3$) δ 2.44 (s, 3 H, CH_3); NMR and ir spectra were superimposable with those of a purchased sample (Aldrich); picrate, mp 240–241 °C (lit.[34] 241 °C). Trituration of the residue from another fraction with ether–petroleum gave 290 mg of impure **3e** (60% by NMR), which could not be purified for analysis, NMR δ 1.37 (s, 3 H, CH_3).

The photooxygenation was repeated with a solution of 300 mg (2.08 mmol) of **1e** in 10 ml of acetone. The solution was evaporated, redissolved in ethanol, and treated with excess $NaBH_4$. After 10 min, 50 ml of ether was added, and the solution was extracted with water, dried over $MgSO_4$, filtered, and evaporated. Crystallization from pentane gave 73 mg of 1-hydroxy-1-methyl-1,4-dihydronaphthalene: mp 87–90 °C; ir (KBr) 3350 cm^{-1}; NMR ($CDCl_3$) δ 1.48 (s, 3 H, CH_3), 2.14 (broad s, 1 H, OH), 3.33 (m, 2 H, CH_2), 5.90 (m, 2 H, olefinic protons), 7.18 (m, 3 H, aromatic), and 7.67 (m, 1 H, aromatic); on drying under high vacuum, the alcohol was dehydrated to 1-methylnaphthalene (**6e**).

Photooxygenation of 1,2-Dihydronaphthalene (1f). A solution of 2.00 g (15.4 mmol) of **1f** in 50 ml of acetone containing ~1 mg of rose bengal took up 610 ml (1.60 equiv) of oxygen during 8.5 h; the dye was replenished after 4.5 and 7 h. The solution was warmed to room temperature and evaporated; NMR ($CDCl_3$) showed the diepoxy endoperoxides **2f** (33.5%) and **3f** (33.5%), the ene product **4f** (23%), and unreacted **1f** (10%). The product was precipitated with ether and a small amount of methanol and recrystallized from heptane–methylene chloride to give 500 mg (17%) of **2f:** mp 118–120 °C dec; ir (KBr) 1257, 1229, 938, 923, 898, 875, 834, 815, 787, 746, and 701 cm^{-1}; mass spectrum (70 eV, source temperature 155 °C) *m/e* (rel intensity) 162 (7), 149 (10), 133 (11), 94 (10), 81 (13), 77 (11), 71 (10), 68 (28), 65 (11), 57 (16), 55 (19), 53 (11), 43 (13), 41 (25), 39 (27), 32 (16), 29 (16), 28 (100), 27 (20), 18 (86), and 17 (21).

Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.85, H, 5.35.

The filtrate was evaporated and the residue chromatographed on a 2.0 × 12 cm silica gel column with 1:1 $CHCl_3$–petroleum ether to remove unreacted **1f** and with $CHCl_3$ containing 1% methanol to collect **3f** and **4f:** NMR ($CDCl_3$) δ 3.40 (m. 2 H, CH_2), 5.35 (m, 1 H, H_1), 6.17 (m, 2 H, H_2 and H_3), 7.22 (s, 1 H, OOH), and 7.28 (m, 4 H, C_6H_5). Repeated attempts to isolate **3f** by chromatography and/or crystallization were unsuccessful.

Naphthalenes. 6a, 6c, and **6d** were prepared by the method of Campbell and Kidd[5] by refluxing 250–500 mg of the dihydronaphthalene with 1.0 equiv of chloranil in 20 ml of xylene for 2 days (for **1a**), 3 days (for **1c**), and 4 days (for **1d**). After work-up the products were crystallized from ethanol to give **6a** (85%), mp 101–103 ° (lit.[5] 101–102 °C), **6c** (67%), mp 108–109 °C (lit.[6] 109.5–110 °C), and **6d** (53%), mp 83–84 °C (lit.[7] 85 °C).

Thermolysis of the Dioxygenated Products. The dioxygenated dihydronaphthalene products (200–600 mg) were dissolved in 15 ml of toluene and the solutions refluxed for 2.5 h. On cooling, 1.5-ml aliquots were removed and treated with 0.25 ml of triethylamine; the solutions were warmed for several minutes and evaporated. NMR spectra ($CDCl_3$) of the residues showed 75% tetraepoxide and 25% γ-hydroxy-α,β-unsaturated ketone for each reaction. The remaining solutions were evaporated. Trituration with ether–petroleum ether gave crystals of the impure tetraepoxides;

they were purified by repeated crystallization from benzene–heptane, following the purity by TLC (silica gel–$CHCl_3$). Ir (KBr) spectra of further material collected from the first filtrates of each reaction showed a carbonyl band for the β-epoxy ketones: compound (carbonyl band) **9b** (1727 cm^{-1}), **10b** (1723 cm^{-1}), **9c** (1727 cm^{-1}), **10c** (1723 cm^{-1}), **9f** (1725 cm^{-1}). In one case (the reaction of **2e**), several recrystallizations of this further material gave 45 mg (8%) of the pure β-epoxy ketone **9e**: mp 111–113 °C; NMR ($CDCl_3$) δ 1.04 (m, 1 H, one methylene proton), 1.24 (s, 3 H, CH_3), 2.20 (m, 2 H, two methylene protons), 2.49 (m, 1 H, one methylene proton), 2.80 (one part of ABX, 1 H, H_B, J_{AB} = 2.7, J_{BC} = 16.5, J_{BD} = 0.8 Hz), 3.02 (ABX, 1 H, H_C, J_{AC} = 1.8 Hz), 3.16 (d, 1 H, H_D), 3.33 (m, 1 H, H_F), and 3.45 (ABX, 1 H, H_A); ir (KBr) 1727, 1244, 968, 947, 923, 888, 872, 844, 782, and 734 cm^{-1}; mass spectrum (70 eV, source temperature 180 °C) *m/e* (rel intensity) 137 (11), 123 (6), 110 (5), 109 (7), 79 (7), 55 (7), 43 (37), 41 (6), 39 (8), 28 (20), 27 (8), 18 (100), and 17 (19).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.58; H, 6.09.

The following tetraepoxides were prepared.

7b (57%): mp 195.0–195.5 °C; NMR ($CDCl_3$) δ 7.29 (s, 5 H, C_6H_5); ir (KBr) 1252, 950, 923, 872, 842, 835, 800, 764, 743, 711, and 689 cm^{-1}; mass spectrum (70 eV, source temperature 220 °C) *m/e* (rel intensity) 270 (4), 241 (9), 183 (6), 169 (6), 142 (7), 141 (30), 129 (10), 128 (25), 127 (6), 115 (18), 106 (8), 105 (100), 91 (6), 85 (6), 77 (35), 55 (11), 51 (11), 39 (8), 29 (6), 28 (12), 27 (8), and 18 (20).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.03; H, 5.24.

8b (53%): mp 122–123 °C; NMR ($CDCl_3$) δ 7.31 (m, 5 H, C_6H_5); ir (KBr) 1279, 1254, 948, 919, 892, 866, 840, 819, 788, 755, 712, and 693 cm^{-1}; mass spectrum (70 eV, source temperature 210 °C) *m/e* (rel intensity) 270 (6), 241 (10), 197 (6), 183 (6), 169 (6), 142 (7), 141 (29), 129 (10), 128 (26), 127 (8), 115 (16), 106 (8), 105 (100), 91 (8), 85 (6), 77 (38), 55 (9), 51 (13), 39 (10), 32 (9), 29 (9), 28 (46), 27 (9), 18 (72), and 17 (16).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.09; H, 5.39.

7c (37%): mp 163.5–164.5 °C; NMR ($CDCl_3$) δ 7.06 (m, 10 H, aromatic); ir (KBr) 1268, 1250, 1230, 948, 926, 917, 903, 862, 855, 741, and 709 cm^{-1}; mass spectrum (70 eV, source temperature 200 °C) *m/e* (rel intensity) 241 (8), 213 (4), 115 (6), 105 (100), 103 (5), 78 (4), 77 (31), 51 (5), and 28 (8).

Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.28; H, 5.24. Found: C, 76.27; H, 5.32.

8c (35%): mp 223–224 °C dec; NMR ($CDCl_3$) δ 7.07 (m, 10 H, aromatic); ir (KBr) 1272, 1251, 965, 957, 898, 859, 855, 840, 797, 769, 714, and 698 cm^{-1}; mass spectrum (70 eV, source temperature 205 °C) *m/e* (rel intensity) 241 (2), 213 (3), 144 (5), 129 (6), 105 (20), 97 (7), 85 (7), 83 (10), 81 (11), 73 (16), 71 (11), 70 (8), 69 (24), 60 (1)), 57 (23), 56 (8), 55 (22), 43 (28), 41 (25), 32 (21), 29 (10), 28 (100), and 18 (16).

Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.28; H, 5.24. Found: C, 76.28; H, 5.23.

7e (58%): mp 150–152 °C NMR ($CDCl_3$) δ 1.25 (s, 3 H, CH_3); ir (KBr) 1271, 1246, 960, 934, 918, 886, 871, 845, 769, 747, and 717 cm^{-1}; mass spectrum (70 eV, source temperature 190 °C) *m/e* (rel intensity) 137 (6), 107 (6), 105 (5), 95 (7), 91 (5), 85 (7), 81 (6), 79 (12), 77 (10), 71 (5), 68 (7), 67 (6), 65 (6), 55 (11), 53 (8), 43 (48), 41 (9), 39 (11), 29 (6), 28 (22), 27 (9), 18 (100). and 17 (21).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.33; H, 5.90.

7f (46%): mp 157–158 °C; ir (KBr) 1278, 947, 907, 872, 850, 828, 784, 776, 759, and 741 cm^{-1}; mass spectrum (70 eV, source temperature 215 °C) *m/e* (rel intensity) 121 (17), 110 (14), 109 (16), 107 (15), 95 (15), 94 (18), 91 (16), 84 (15), 82 (13), 81 (42), 79 (20), 77 (22), 71 (35), 69 (16), 68 (100), 67 (17), 66 (12), 65 (30), 56 (13), 55 (45), 53 (34), 51 (23), 43 (21), 42 (20), 41 (56), 40 (17), 39 (69), 29 (46), 28 (23), 27 (54), and 26 (11).

Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 62.07; H, 5.32.

Preparation of Tetraepoxide 8e. A solution of 3.00 g (20.8 mmol) of **1e** in 100 ml of acetone containing ~2 mg of rose bengal as sensitizer was photooxygenated at −78 °C for 2 h (at 120 V); the solution took up 783 ml (1.54 equiv) of oxygen. The solution was warmed to room temperature and evaporated. The addition of ether–pentane gave 503 mg of the diepoxy endoperoxide **2e**. The filtrate was evaporated and the resulting oil, containing **3e** and the ene product (**4e**), was heated on a rotary evaporator under vacuum (0.1 Torr) at 85 °C for 4.5 h [1-methylnaphthalene (**6e**) was slowly given off]. Addition of ether to the resulting oil gave 867 mg of pale-yellow crystals (~90% **8e** by NMR). The crystals were dissolved in CH_2Cl_2 and filtered through silica gel. The filtrate was evaporated and the residue purified by repeated crystallizations from benzene–heptane to give 387 mg of **8e**: mp 156–158.5 °C; NMR ($CDCl_3$) δ 1.17 (s, 3 H, CH_3); ir (KBr) 1277, 1263, 1259, 955, 933, 911, 883, 842, 815, 776, 767, 750, and 705 cm^{-1}; mass spectrum (70 eV, source temperature 208 °C) *m/e* (rel intensity) 151 (6), 137 (12), 123 (10), 107 (10), 95 (12), 85 (13), 81 (10), 79 (24), 77 (19), 71 (10), 68 (11), 67 (11), 65 (11), 55 (19), 53 (16), 43 (100), 41 (21), 39 (25), 29 (14), 28 (17), 27 (22), and 18 (11).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.62; H, 5.69.

Preparation of Tetraepoxide 8f. A solution of 2.00 g (15.4 mmol) of **1f** in 50 ml of acetone containing ~1 mg of rose bengal was photooxygenated at −78 °C for 4.5 h (at 120 V); the solution took up 647 ml (1.72 equiv) of oxygen. The solution was warmed to room temperature and evaporated. The addition of ether to the resulting oil gave 622 mg of the diepoxy endoperoxide **2f**, mp 110–113 °C dec. The filtrate was evaporated, and the resulting oil, containing **3f** and the ene product (**4f**), was heated on a rotary evaporator under vacuum (0.1 Torr) at ~90 °C for 3.5 h. The resulting oil was chromatographed on a 2 × 24 cm silica gel column with $CHCl_3$. Evaporation of the forerun and addition of methanol gave 110 mg of naphthalene (**6f**); the NMR and ir spectra are superimposable with those of an authentic sample (Aldrich). Evaporation of the remaining fractions and addition of ether gave 537 mg of colorless crystals (20% **7f** and 80% **8f** by NMR). Repeated crystallizations from benzene–heptane finally gave 287 mg of **8f**: mp 151–152 °C; ir (KBr) 1268, 994, 944, 871, 835, 804, 779, 757, and 689 cm^{-1}; mass spectrum (70 eV, source temperature 205 °C) *m/e* (rel intensity) 121 (17), 110 (12), 109 (13), 107 (15), 95 (12), 94 (21), 91 (14), 84 (14), 82 (13), 81 (37), 79 (17), 77 (18), 71 (36), 69 (14), 68 (100), 67 (14), 66 (12), 65 (26), 56 (12), 55 (40), 53 (21), 51 (16), 43 (18), 42 (18), 41 (49), 40 (16), 39 (59), 29 (39), 28 (27), 27 (44), 26 (11), and 18 (14).

Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 62.04; H, 5.19.

General Procedure for the Preparation of the γ-Hydroxy-α,β-Unsaturated Ketones 11, 12. Triethylamine (0.25 ml) was added to solutions of 95–300 mg of **2** or **3** in 10 ml of $CHCl_3$, causing exothermic reactions. After cooling, the solutions were evaporated, and $CHCl_3$ solutions of the residues were filtered through silica gel. The filtrates were evaporated and crystallized by addition of ether; the products were then recrystallized from benzene–heptane. The following compounds were prepared.

11b (97%): mp 140–143 °C; NMR ($CDCl_3$, 100 MHz) δ 1.21 (m, 1 H, one methylene proton), 1.49 (m, 3 H, three methylene protons), 3.46 (d, 1 H, H_D, J_{BD} = 1.9 Hz), 3.47 (m, 1 H, H_F), 3.90 (s, 1 H, OH), 5.70 (half of AB q, 1 H, H_B, J_{AB} = 10.8 Hz), 5.95 (half of AB q, 1 H, H_A), and 7.31 (s, 5 H, C_6H_5); ir (KBr) 3530, 1683, 1266, 1241, 1229, 989, 927, 919, 902, 824, 813, 737, 711, 691 cm^{-1}; mass spectrum (70 eV, source temperature 190 °C) *m/e* (rel intensity) 165 (20), 146 (8), 145 (5), 138 (5), 133 (31), 115 (5), 110 (5), 106 (9), 105 (100), 77 (29), 51 (7), 39 (6), 28 (7), and 27 (6).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.01; H, 5.22.

12b (97%): mp 162.5–163.5 °C; NMR ($CDCl_3$, 100 MHz) δ 1.17 (m, 1 H, one methylene proton), 2.26 (m, 2 H, two methylene protons), 2.84 (m, 1 H, one methylene proton), 3.08 (d, 1 H, H_D, J_{BD} = 2.1 Hz), 3.20 (m, 1 H, H_F), 3.87 (s, 1 H, OH), 5.71 (half of AB q, 1 H, H_B, J_{AB} = 10.7 Hz), 6.48 (half of AB q, 1 H, H_A), 7.28 (m, 3 H, aromatic), and 7.58 (m, 2 H, aromatic); ir (KBr) 3580, 3410, 1680, 1276, 1250, 1239, 949, 898, 824, 814, 785, 751, and 691 cm^{-1}; mass spectrum (source temperature 200 °C) *m/e* (rel intensity) 165 (16), 146 (4), 133 (16), 115 (4), 105 (100), 77 (24), 55 (14), 51 (6), 39 (5), 28 (9), and 27 (5).

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.88; H, 5.47.

11c (90%): mp 193–194.5 °C dec; NMR ($CDCl_3$) δ 1.36 (m, 1 H, one methylene proton), 2.67 (m, 3 H, three methylene protons), 3.54 (d, 1 H, H_D, J_{BD} = 1.7 Hz), 4.03 (s, 1 H, OH), 5.75 (half of AB q, 1 H, H_A, J_{AB} = 10.7 Hz), 5.84 (half of AB q, 1 H, H_B), and 7.07 (m, 10 H, aromatic); ir (KBr) 3510, 1693, 1270, 940, 856, 818, 741, and 685 cm^{-1}; mass spectrum (source temperature 225 °C) *m/e* (rel intensity) 214 (7), 105 (31), 77 (10), 69 (6), 57 (7), 55 (6), 43 (6), 41 (5), 32 (19), 28 (100), and 18 (15).

Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.28; H, 5.24. Found: C, 76.16; H, 5.43.

12c (83%): mp 172–173.5 °C dec; NMR ($CDCl_3$) δ 1.39 (m, 1 H,

one methylene proton), 2.58 (m, 2 H, two methylene proton), 3.04 (m, 1 H, methylene proton), 3.21 (d, 1 H, H_D, J_{BD} = 2.0 Hz), 3.64 (s, 1 H, OH), 5.76 (half of AB q, 1 H, H_B, J_{AB} = 10.7 Hz), 6.43 (half of AB q, 1 H, H_A), and 7.20 (m, 10 H, aromatic); ir (KBr) 3540, 3470, 1681, 1275, 1229, 949, 886, 748, 733, and 682 cm^{-1}; mass spectrum (70 eV, source temperature 210 °C) *m/e* (rel intensity) 71 (5), 69 (9), 57 (12), 55 (10), 43 (10), 41 (8), 32 (23), 28 (100), and 18 (34).

Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.28, H, 5.24. Found: C, 76.20; H, 5.47.

11e (88%): mp 102–103 °C; NMR ($CDCl_3$) δ 1.07 (m, 1 H, one methylene proton), 1.48 (s, 3 H, CH_3), 2.28 (m, 3 H, three methylene protons), 3.36 (m, 1 H, H_F), 3.37 (d, 1 H, H_D, J_{BD} = 2.0 Hz), 3.66 (s, 1 H, OH), 5.95 (half of AB q, 1 H, H_B, J_{AB} = 10.8 Hz), and 6.72 (half of AB q, 1 H, H_A); ir (KBr) 3550, 1687, 1271, 1237, 983, 968, 920, 878, 863, 829, 784, 743, and 709 cm^{-1}; mass spectrum (source temperature 180 °C) *m/e* (rel intensity) 165 (29), 137 (11), 123 (11), 109 (9), 91 (10), 84 (12), 77 (10), 71 (28), 69 (9), 65 (10), 55 (42), 53 (11), 51 (9), 43 (100), 41 (15), 39 (22), 32 (16), 28 (94), 18 (91), and 17 (18).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.45; H, 5.96.

11f (84%): mp 135.5–137°; NMR ($CDCl_3$) δ 1.21 (m, 1 H, one methylene proton), 2.31 (m, 3 H, three methylene protons), 3.35 (d, 1 H, H_E, J_{EF} = 3.9 Hz), 3.40 (s, 1 H, OH), 3.44 (d, 1 H, H_D, J_{BD} = 1.9 Hz), 3.59 (m, 1 H, H_F), 6.01 (half of AB q, 1 H, H_B, J_B = 10.4 Hz), and 6.56 (half of AB q, 1 H, H_A); ir (KBr) 3540, 1692, 1250, 1231, 980, 974, 944, 919, 860, 837, 820, and 788 cm^{-1}; mass spectrum (source temperature 195 °C) *m/e* (rel intensity) 165 (85), 149 (31), 138 (30), 137 (22), 123 (24), 122 (31), 121 (28), 120 (22), 119 (24), 110 (53), 109 (23), 97 (32), 96 (22), 91 (50), 82 (34), 81 (32), 79 (23), 77 (31), 70 (28), 69 (30), 68 (20), 67 (24), 57 (33), 55 (100), 53 (37), 51 (29), 43 (29), 41 (69), 39 (77), 29 (34), 28 (56), 27 (60), and 18 (26).

Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 62.01; H, 5.24.

Reaction of 2b and 3b with Trimethyl Phosphite. Trimethyl phosphite (100 mg, 0.80 mmol) was added to a solution of 200 mg (0.742 mmol) of **2b** in 2 ml of $CHCl_3$. An exothermic reaction occurred; after cooling, the solution was heated briefly and evaporated. The residue was passed through a 2.5 × 20 cm silica gel column with $CHCl_3$. Evaporation of the filtrate, crystallization from ether-pentane, and recrystallization gave 135 mg (68%) of triepoxide **13b**: mp 136–137.5 °C; NMR ($CDCl_3$, 100 MHz) δ 1.11 (m, 1 H, methylene proton), 2.45 (m, 3 H, three methylene protons), 2.83 (part of ABXY, 1 H, H_D[35], J_{CD} = 3.2, J_{BD} = 1.5 Hz), 3.10 (part of ABXY, 1 H, H_A, J_{AB} = 3.2, J_{AC} = 1.5 Hz), 3.22 (m, 1 H, H_F), 5.93 (part of ABXY, 1 H, H_C, J_{BC} = 9.8 Hz), 6.10 (part of ABXY, 1 H, H_B), and 7.29 (s, 5 H, C_6H_5); ir (KBr) 1608, 1276, 1234, 966, 939, 917, 875, 800, 769, 750, and 709 cm^{-1}; mass spectrum (70 eV, source temperature 250°C) *m/e* (rel intensity) 149 (9), 141 (10), 129 (5), 128 (6), 115 (10), 106 (8), 105 (100), 77 (28), 55 (5), 52 (6), 51 (7), 39 (8), 32 (6), 28 (53), 27 (5), and 18 (8).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.57; H, 5.74.

In the same manner, the addition of 87 mg (0.70 mmol) of trimethyl phosphite to a solution of 170 mg (0.630 mmol) of **3b** gave 116 mg of **14b** (73%), recrystallized to give pure **14b**: mp 132.5–134.5 °C; NMR ($CDCl_3$, 100 MHz) δ 1.24 (m, 1 H, one methylene proton), 2.45 (m 3 H, three methylene protons), 2.71 (part of ABXY, 1 H, H_D,[35] J_{CD} = 3.2, J_{BD} = 1.5 Hz), 2.88 (part of ABXY, 1 H, H_A, J_{AB} = 3.2, J_{AC} = 1.5 Hz), 3.28 (m, 1 H, H_F), 5.92 (part of ABXY, 1 H, H_C, J_{BC} = 9.8 Hz), 6.02 (part of ABXY, 1 H, H_B), 7.30 (m, 5 H, C_6H_5); ir (KBr) 1264, 1234, 944, 884, 867, 816, 788, 761, 729, and 700 cm^{-1}; mass spectrum (source temperature 200 °C) *m/e* (rel intensity) 197 (12), 170 (5), 149 (10), 141 (11), 129 (5), 128 (7), 115 (11), 106 (7), 105 (83), 77 (28), 55 (6), 52 (6), 51 (10), 41 (6), 39 (8), 32 (17), 28 (100), 27 (5), 18 (52), and 17 (10).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.47; H, 5.82.

Photooxygenation of 1b and 1e in Methanol at −78 °C. A solution of 100 mg (0.486 mmol) of **1b** in 10 ml of 9.1 methanol–acetone solution containing 0.1 mg of rose bengal took up 22 ml (2.0 equiv) of oxygen during 3 h. The solution was warmed to room temperature and evaporated; the NMR ($CDCl_3$) spectrum was almost identical with that taken after the photooxygenation in acetone. A small resonance at 9.64 ppm (presumably due to **16b**) was observed (<1%). No fluorescence was observed in the dark on heating the solution in the presence of 9,10-diphenylanthracene.

A similar photooxygenation of 100 mg (0.695 mmol) of **1e** in 10 ml of methanol took up 25.5 ml (1.50 equiv) of oxygen during 2 h. The NMR ($CDCl_3$) spectrum of the evaporated solution gave similar results.

Photooxygenation of 1b and 1e in Methanol at Room Temperature. The above photooxygenations were repeated at room temperature. **1e** took up 16.8 ml (1.0 equiv) of oxygen during 30 min; the NMR ($CDCl_3$) spectrum showed a resonance near 9.6 ppm attributable to ~12% **16e**. When the NMR solution was saturated with 9,10-diphenylanthracene and heated to ~80°C, only a very weak fluorescence was observed in the dark. **1b** took up 16.4 ml (1.38 equiv) of oxygen during 35 min; the NMR ($CDCl_3$) spectrum showed a resonance near 9.6 ppm (~23% **16e**), and no fluorescence was observed on the addition of 9,10-diphenylanthracene. The NMR spectra did show the presence of the endoperoxides **2b** and **3b**.

Registry No.—**1a**, 20669-52-7; **1b**, 7469-40-1; **1c**, 57652-90-1; **1d**, 1022-15-7; **1e**, 4373-13-1; **1f**, 447-53-0; **2b**, 57652-91-2; **2c**, 57652-92-3; **2e**, 57652-93-4; **2f**, 57652-94-5; **3b**, 57694-05-0; **3c**, 57694-06-1; **3e**, 57694-07-2; **3f**, 57694-08-3; **4a**, 57652-95-6; **4c**, 57652-96-7; **4d**, 57652-97-8; **4e**, 57652-98-9; **4f**, 57652-99-0; **5d**, 57653-00-6; **6a**, 612-94-2; **6c**, 30877-08-8; **6e**, 90-12-0; **7b**, 57653-01-7; **7c**, 57653-02-8; **7e**, 57653-03-9; **7f**, 57653-04-0; **8b**, 57694-09-4; **8c**, 57694-10-7; **8e**, 57694-11-8; **8f**, 57694-12-9; **9e**, 57653-05-1; **11b**, 57653-06-2; **11c**, 57653-07-3; **11e**, 57653-08-4; **11f**, 57653-09-5; **12b**, 57694-13-0; **12c**, 57694-14-1; **13b**, 57653-10-8; **14b**, 57694-15-2; **30**, 39078-08-5; **31**, 51153-58-3; 2-phenyl-1-tetralone, 7498-87-5; α-tetralone, 529-34-0; oxygen, 7782-44-7; 1-hydroxy-2-phenyl-1,4-dihydronaphthalene, 57653-11-9; 1-hydroxy-1-methyl-1,4-dihydronaphthalene, 2042-22-0; trimethyl phosphite, 121-45-9.

References and Notes

(1) (a) Part XXIII: P. A. Burns, C. S. Foote, and S. Mazur, *J. Org. Chem.*, preceding paper in this issue. (b) Supported by National Science Foundation Grants GP 37165X and GP 25790 and Public Health Service Grants AP-00681 and GM 20080. (c) Taken in part from P. A. Burns, Dissertation, University of California, Los Angeles, 1975.

(2) (a) K. Gollnick, *Adv. Photochem.*, **6**, 1 (1968); (b) G. O. Schenck, *Angew. Chem.*, **64**, 12 (1952).

(3) (a) E. Ciganek, *J. Org. Chem.*, **34**, 1923 (1969); (b) F. Pascher, Ph.D. Thesis, University of Cologne, 1944.

(4) The isolation of the dioxygenated products (**2d, 3d**) from the photooxygenation of 1-methyl-2-phenyl-3,4-dihydronaphthalene (**1d**) was not attempted since their combined yield was only 10%.

(5) N. Campbell and D. Kidd, *J. Chem. Soc.*, 2154 (1954).

(6) H. M. Crawford, *J. Am. Chem. Soc.*, **61**, 608 (1939).

(7) E. A. Baude, L. M. Jackman, R. P. Linstead, and G. Love, *J. Chem. Soc.*, 3123 (1960).

(8) (a) M. Avram and G. D. Mateescu, "Infrared Spectroscopy Applications in Organic Chemistry", translated by L. Birladeanu, Wiley-Interscience, New York, N.Y., 1972, p 283; (b) K. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day, San Francisco, Calif., 1962, p. 36; (c) R. Conley, Infrared Spectroscopy, Allyn and Bacon, Boston, Mass., 1966, p 130.

(9) E. D. Becker, "High Resolution NMR, Theory and Chemical Applications", Academic Press, New York, N.Y., 1969, pp 149–170.

(10) N. R. Easton, Jr., F. A. L. Anet, P. A. Burns, and C. S. Foote, *J. Am. Chem. Soc.*, **96**, 3945 (1974).

(11) P. A. Burns and C. S. Foote, *J. Am. Chem. Soc.*, **96**, 4339 (1974).

(12) We thank Professor Orville Chapman for discussions of this point.

(13) C. S. Foote and R. W. Denny, J. Am. Chem. Soc., **93**, 5162 (1971).

(14) C. H. Foster and G. A. Berchtold, *J. Am. Chem. Soc.*, **94**, 7939 (1972).

(15) E. Vogel, H.-J. Altenbach, and C. D. Sommerfeld, *Angew. Chem.*, **84**, 986 (1972); *Angew. Chem., Int. Ed. Engl.*, **11**, 939 (1972).

(16) P. A. Burns, H. S. Brown, and C. S. Foote, to be published.

(17) (a) E. Vogel, R. Schubart, and W. A. Böll, *Angew. Chem.*, **76**, 535 (1964); (b) E. Vogel, R. Schubart, and W. A. Böll, *Chem. Eng. News*, **42**, 40 (1964). We thank Professor J. Rebek for helpful discussions of this chemistry.

(18) E. Vogel, W. A. Böll, and H. Günther, *Tetrahedron Lett.*, 609 (1965).

(19) H. Günther, *Tetrahedron Lett.*, 4085 (1965).

(20) H. Günther, R. Schubart, and E. Vogel, *Z. Naturforsch. B*, **22**, 25 (1967).

(21) Reviews: (a) E. Vogel and H. Günther, *Angew Chem.*, **79**, 429 (1967); (b) G. Maier, *Angew. Chem., Int. Ed. Engl.*, **6**, 408 (1967).

(22) F. A. L. Anet, *J. Am. Chem. Soc.*, **86**, 458 (1964).

(23) (a) E. Vogel, H.-J. Altenbach, and D. Cremer, *Angew. Chem.*, **84**, 983 (1972); (b) H.-J. Altenbach and E. Vogel, *ibid.*, **84**, 985 (1972).

(24) E. Vogel, H.-J. Altenbach, and E. Schmidbauer, *Angew. Chem.*, **85**, 862 (1973).

(25) Both *anti-benzene trioxide*[14,15] and *syn-benzene trioxide*[15,26] have been prepared, but give simple NMR spectra because of their high symmetry.

(26) R. Schwesinger and H. Prinzbach, *Angew. Chem.*, **84**, 990 (1972).

(27) The coupling values are all smaller than would be expected from the Karplus equation,[28] which predicts J_{AB} = 8.5 and J_{CD} = 3 Hz. The observed values retain the $J_{cis} > J_{trans}$ relationship, and agree with the observation of Tori[29] that in 1,2-epoxycyclopropane the couplings between the epoxide and methylene protons are smaller than predicted for dihedral angles between 0 and 50°.

(28) M. Karplus, J. Am. Chem. Soc., 85, 2870 (1963).
(29) K. Tori, T. Komeno, and T. Nakagawa, J. Org. Chem., 29, 1136 (1964).
(30) The analogous indene compounds also have this geometry.[1a]
(31) J. P. Quillet, A. Duperrier, and J. Dreux, Bull. Soc. Chim. Fr., 255 (1967).
(32) J. Jacques and H. B. Kagan, Bull. Soc. Chim. Fr., 128 (1956).
(33) "Handbook of Chemistry and Physics", R. C. Weast, Ed., 4th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1964.
(34) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", Wiley, New York, N.Y., 1960, p 241.
(35) The lower field of protons A and D was assigned as A based on the analogous indene triepoxides.[1a]

Thermal and Photochemical Decomposition of Silver Carboxylates

Ellis K. Fields*

Amoco Chemicals Corporation, Naperville, Illinois 60540

Seymour Meyerson

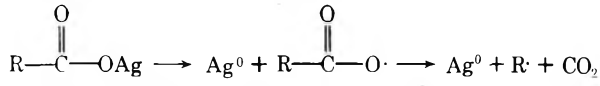
Standard Oil Company (Indiana), Naperville, Illinois 60540

Received September 19, 1975

Silver salts of carboxylic acids decompose at 200–350 °C to silver, carbon dioxide, and radicals. Silver benzoate at 276 °C gives polyphenyls containing two to five benzene rings, as well as benzene, benzoic acid, and 3,4-benzocoumarin. Arylation of benzophenone was effected by silver benzoate at 300 °C, along with formation of biphenyl and benzophenone dimer. An intimate mixture of silver isonicotinate and silver benzoate at 275 °C gave coupling products of phenyl and pyridyl radicals with themselves and with each other. Silver trifluoroacetate decomposes thermally above 260 °C or irradiated with ultraviolet light in solution at 25 °C, to silver, carbon dioxide, and trifluoromethyl radicals. As silver trifluoroacetate, unlike most silver salts, is relatively soluble in organic solvents, it may be used as a convenient source of trifluoromethyl radicals. With benzene at 325 °C it gave 38 mol % of benzotrifluoride; 57 mol % of benzotrifluoride resulted from the photochemical reaction. Benzonitrile gave a good yield of the three isomeric trifluoromethyl benzonitriles, mainly ortho. With 4-benzoylpyridine at 300 °C silver trifluoroacetate gave derivatives formed predominantly by addition of trifluoromethyl radicals to the benzene ring. Silver salts of polycarboxylic acids decompose at 200–425 °C to silver, carbon dioxide, and products apparently formed from polyradicals. Silver isophthalate, pyrolyzed under nitrogen at 375 °C and cooled under hydrogen, gives silver imbedded in a black, carbonlike polymer that ignites at 25 °C when exposed to air. Different silver salts give a wide variety of different shapes upon being pyrolyzed. Heteroatoms are retained; silver pyridine-3,5-dicarboxylate at 310 °C yielded carbon dioxide, silver, and black polymer with the theoretical amount of nitrogen. Considerable control of pore-size distribution and surface area for silver imbedded in carbonlike polymers has been achieved by pyrolyzing the appropriate silver polycarboxylate. Silver carboxylates represent a new class of stable radical precursors of great variety, ready availability, and easy preparation.

As organic chemistry developed in the middle and late 19th century, silver salts of carboxylic acids were among the first derivatives prepared, primarily because they were easy to make and to purify. Surprisingly, except for a few scattered references in the literature dealing with explosives,[1] the behavior of silver carboxylates at elevated temperatures has been wholly ignored.

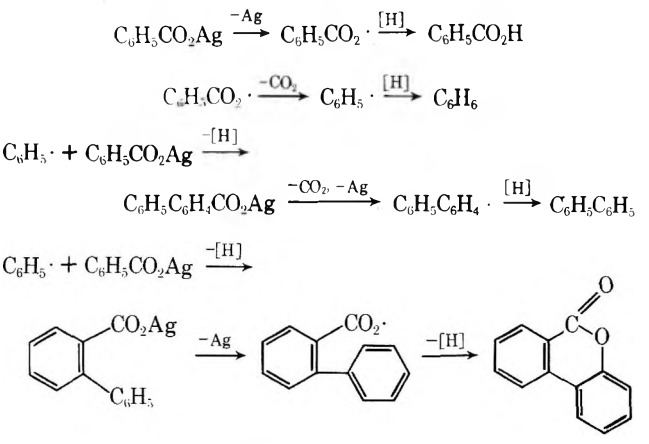
We have discovered that silver carboxylates decompose, when heated, according to the scheme



As an example, 45.8 g (200 mmol) of silver benzoate (276 °C dec), heated in a Pyrex tube under a stream of nitrogen to 280 °C for 1 min, gave the products shown in Table I. The gas evolved, together with benzoic acid and benzocoumarin, accounted for 196 mmol (98%) of CO_2; the products listed in Table I accounted for 197.4 mmol (98.7%) of phenyl radicals.

Silver benzoate was pyrolyzed under a variety of conditions: diluted with twice its weight of silica; in a bomb under 300 psi autogenous pressure; and in a pellet formed under 10 000 psi. In all cases the identical products were formed and in about the same proportions.

Benzene and benzoic acid are the products of hydrogen abstraction by phenyl and benzoyloxy radicals, respectively.[2] Biphenyl and higher polyphenyls may form by phenylation of silver benzoate and subsequent decomposition; ortho phenylation gives 3,4-benzocoumarin. Some biphenyl may result from dimerization of phenyl radicals trapped in a solid matrix, although dimerization is not favored in liquid or gas phase reactions of phenyl radicals.[3]



Silver salts of substituted benzoic acids behave similarly to silver benzoate. Silver *p*-fluorobenzoate and silver pentafluorobenzoate, each decomposed at 300 °C under nitrogen, gave the products shown in Tables II and III, respectively.

Among the heterocyclic compounds, silver thiophene-2-carboxylate at 275 °C gave thiophene and bithiophene in a weight ratio of 3:1. Silver salts of pyridinecarboxylic acids at 280–320 °C gave bipyridyls and terpyridyls with varying amounts of pyridine, as shown in Table IV. Hydrogen ab-

straction by radicals from thermal decomposition of silver salts, a minor reaction in the aromatic series, becomes more pronounced in some heterocyclic radicals, and is the major reaction of aliphatic radicals.

Although silver arenecarboxylates have little, if any, solubility in most organic solvents, arylation could be effected in high-boiling liquids. A mixture of benzophenone and silver benzoate, 2:1 molar, stirred and refluxed for 30 min, gave phenylbenzophenone and diphenylbenzophenone, as well as some biphenyl and benzophenone dimer.

Mixtures of silver salts give products derived from mixed, as well as like, radicals. Equimolar amounts of silver benzoate and silver isonicotinate, milled together and heated to 275 °C under nitrogen, gave the major products shown in Table V. There were formed additionally benzocoumarin and the mono- and dipyridyl analogues of benzocoumarin in concentrations of 2.2, 2.6, and 0.7 respectively, on the same scale.

Table I. Products from Silver Benzoate at 280 °C

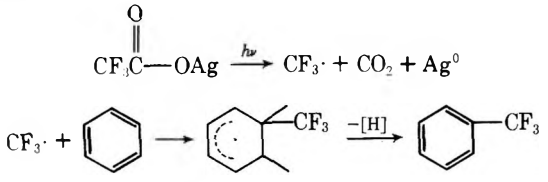
Product	mmol[a]	Product	mmol[a]
CO_2	189.9	Terphenyl	12.4
Benzene	10	Quaterphenyl	3
Benzoic acid	1.5	Quinquephenyl	0.5
Biphenyl	61.5	Silver	200
3,4-Benzocoumarin	5.6		

[a] Analysis by gas chromatography and low voltage (7.5 eV nominal) mass spectrometry.

Silver trifluoroacetate differs from most silver salts in being relatively soluble in organic solvents. Silver trifluoroacetate decomposes when heated above 260 °C or irradiated with ultraviolet light in solution at 25 °C to give silver, carbon dioxide, and trifluoromethyl radical, and thus may be used as a convenient source of this radical.

For example, a solution of 4.4 g (20 mmol) of silver trifluoroacetate in 600 ml of benzene was added dropwise to a vertical Vycor tube containing Vycor chips at 325 °C; contact time was 5 s. The benzene condensate, analyzed by gas chromatography, contained 7.6 mmol of benzotrifluoride, a yield of 38 mol %.

The same solution was rotated in a 1-l. quartz flask 2 in. from a 500-W Hanovia high-pressure mercury lamp for 6 h at 25 °C. Irradiation was interrupted every hour to remove with nitric acid the silver mirror that deposited on the inner surface of the flask. The filtered benzene solution contained 11.4 mmol (57 mol % yield) of benzotrifluoride, formed evidently by these reactions:



A mixture of 50 mmol of silver trifluoroacetate and 150 mmol of chlorobenzene was heated in a bomb at 300 °C for 5 min. Chlorobenzotrifluoride isomers, 5.9 mol % yield, consisted of 83% ortho and 17% para; no *m*-chlorobenzotrifluoride was detected. The accuracy of the analysis was somewhat impaired by interference from other components of the mixture. Nonetheless, trifluoromethylation evidently is mainly ortho, as has been found for other radical additions to aromatic compounds such as arylation of chlorobenzene by phenyl radicals.[4]

A better yield of products was obtained from benzonitrile. A mixture of 100 mmol of benzonitrile and 50 mmol of silver trifluoroacetate in a bomb at 300 °C for 10 min gave a 70 mol % yield of trifluoromethylbenzonitrile of isomer composition 50.7% ortho, 14.1% meta, and 35.2% para. The three isomers gave qualitatively similar mass spectra, the most pronounced difference occurring at *M/z* 170, corresponding to $(M - H)^+$. Intensity at *M/z* 170 relative to that of the molecular ion, the most abundant ion in each of the spectra, is 28% for the meta isomer and 22% for the ortho and para. The difference may well be a reflection of the fact that only the meta isomer contains a ring hydrogen not deactivated by one or both electron-withdrawing substituents.

The products other than trifluoromethylbenzonitrile consisted mainly of bis(trifluoromethyl)benzonitrile, with

Table II. Products from Silver *p*-Fluorobenzoate at 300 °C

Product[a]	Concn[b]	Product[a]	Concn[b]
Fluorobenzene	2.1	Trifluoroterphenyl	13.8
Difluorobiphenyl	27.4	Fluorophenylfluorobenzocoumarin	9.0
Fluorobenzocoumarin	13.8	Fluorophenyldifluorobenzocoumarin	4.7
Difluorobenzocoumarin	22.9	Tetrafluoroquaterphenyl	4.0

[a] Isomers are included. [b] Percent of total ions in the low-voltage mass spectrum.

Table III. Products from Silver Pentafluorobenzoate at 300 °C

Product	Concn[a]
Perfluorobiphenyl	86
Perfluoroterphenyl	10
Perfluoroquaterphenyl	4

[a] Percent of total ions in the low-voltage mass spectrum.

Table IV. Products from Silver Pyridinecarboxylates at 280–320 °C

Pyridinecarboxylate isomer Product[a]	2-	3- Concn[b]	4-
Pyridine	53.2	46.0	2.4
Bipyridyl	36.6	36.7	80.9
Terpyridyl	8.6	14.8	14.2
Quaterpyridyl	1.6	2.5	2.3

[a] Isomers are included. [b] Percent of total ions in the low-voltage mass spectrum.

Table V. Products from Silver Benzoate and Silver Nicotinate at 275 °C

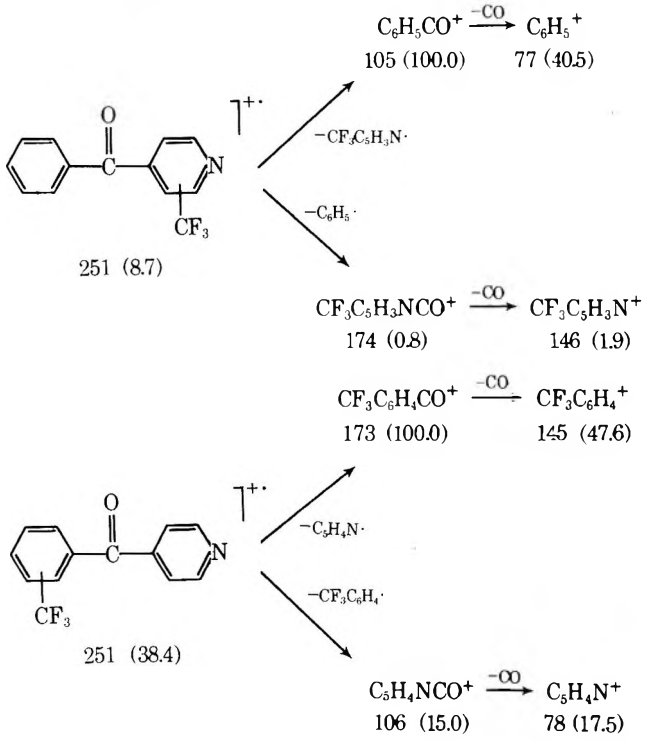
Product[a]	Concn[b]	Product[a]	Concn[b]
Benzoic acid	11.8	Phenylbipyridyl	7.1
Biphenyl	9.6	Terpyridyl	0.9
Phenylpyridine	16.5	Quaterphenyl	2.6
Bipyridyl	4.1	Pyridylterphenyl	3.8
Terphenyl	7.7	Diphenylbipyridyl	2.0
Diphenylpyridine	14.2	Phenylterpyridyl	0.5

[a] Isomers are included. [b] Percent of total ions in the low-voltage mass spectrum.

traces of benzoyl fluoride, biphenyl, and trifluoromethylbiphenyl.

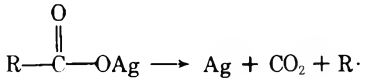
Reagents boiling above 260 °C could be trifluoromethylated at atmospheric pressure. A stirred mixture of 50 mmol of silver trifluoroacetate and 100 mmol of benzophenone at 290 °C for 10 min gave 26 mol % of trifluoromethylbenzophenone isomers. Coumarin and 4-benzoylbiphenyl, under the same conditions, gave 18 and 32 mol %, respectively, of the corresponding trifluoromethyl derivatives. In all these reactions small amounts of bis(trifluoromethyl) derivatives and dehydro dimers of the reagent also formed.

A mixture of 50 mmol each of 4-benzoylpyridine and silver trifluoroacetate, heated at 300 °C for 10 min, yielded 14 mol % trifluoromethylbenzoylpyridine isomers. To find the distribution of trifluoromethyl radicals between the benzene and pyridine rings, we analyzed the products by directly coupled gas chromatography–mass spectrometry. The analysis showed that a considerably greater portion of the product was trifluoromethylphenyl pyridyl ketone than phenyl trifluoromethylpyridyl ketone. The CF_3 radical added to the phenyl group in preference to the pyridyl. The mass spectra of individual gas chromatographic fractions judged to comprise chiefly the ketones shown below indicated decompostion of the molecular ions to RCO^+ and R^+ according to the scheme (initial numbers are masses, those in parentheses are relative intensities):

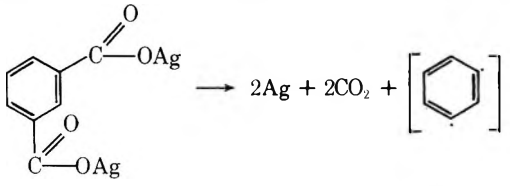


Relative intensities of the various ions show that, in these decompositions to ions and neutral products, the molecules preferentially yield benzoyl and thence phenyl ions rather than pyridoyl and pyridyl, regardless of which group carries the CF_3 substituent. The same preference for primary loss of the pyridyl radical over that of phenyl is observed in the mass spectra of the isomeric unsubstituted benzoylpyridines.[5] The difference suggests a preference for charge localization in the phenyl ring of the molecular ions,[6] in accord with the difference between the ionization potentials of the $C_6H_5CO\cdot$ and $C_5H_3NCO\cdot$ radicals, the former an estimated 0.6 eV lower than the latter (para isomer).[7] The ionization potential difference is increased by CF_3 substitution in the pyridyl ring; it is decreased by CF_3 substitution in the phenyl ring, but not enough to change the algebraic sign. The implied greater electron-releasing ability of the benzoyl radical, in turn, offers a plausible rationale for the addition of the electrophilic $CF_3\cdot$ radical to the phenyl ring in preference to the pyridyl.[8]

As silver salts of monocarboxylic acids decompose at 200–300 °C to metallic silver, carbon dioxide, and free radicals

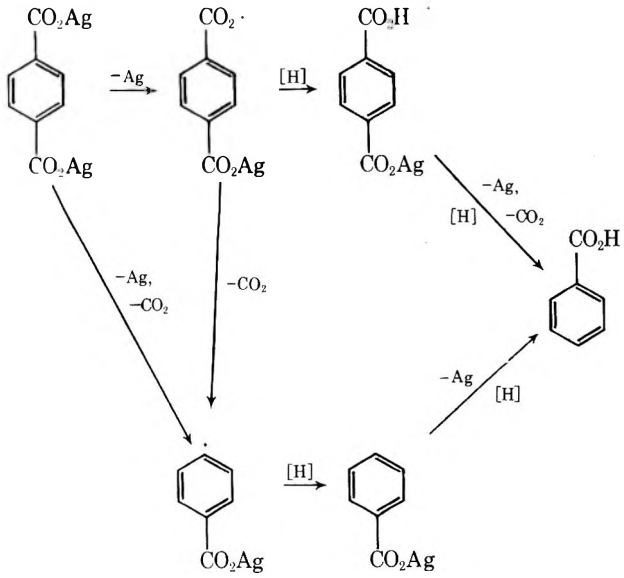


silver salts of dicarboxylic acids should decompose to give diradicals and products derived from diradicals. To investigate this intriguing possibility we heated silver isophthalate to 375 °C under nitrogen. At this temperature the solid expanded rapidly and voluminously, gave off carbon dioxide, and left a black residue that analyzed 74% Ag, 24% C, and 1.3% H. Calculated for $[2Ag\cdot C_6H_4]_n$ from the reaction



Ag, 73.9%; C, 24.7%; H, 1.4%.

Losses of weight of silver polycarboxylates at their decomposition temperatures were determined. In separate experiments, the amounts of carbon dioxide evolved were measured. Results are shown in Table VI. In all cases the thermogravimetric curves had smooth, single inflections, indicating concerted, rather than stepwise, decompositions. Evidence for some stepwise decomposition was obtained by compressing the silver salts at 10 000 psi in a tabletting machine and pyrolyzing the tablet. Silver isophthalate (10 mmol), thus tabletted and pyrolyzed at 375 °C, gave 0.1 g of acetone-soluble products consisting mainly of benzoic acid, biphenyl, terphenyl, and benzocoumarin. Silver terephthalate (30 mmol) gave 0.18 g of acetone-soluble products identical with those from silver isophthalate although differing somewhat in relative amounts. The products from both silver salts are similar to those from pyrolyzed silver benzoate, Table I, and evidently formed by hydrogen abstraction by radical intermediates.



Silver isophthalate decomposed at 375 °C in air, giving silver imbedded in a black, carbonlike polymer[9] that rapidly ignited and burned, leaving a web of silver metal. The

Table VI. Weight Loss and Carbon Dioxide Evolved from Silver Polycarboxylates upon Pyrolysis

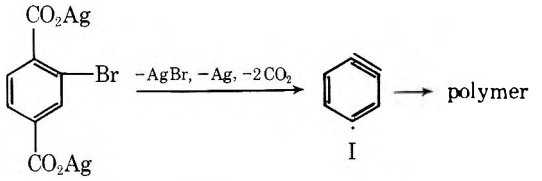
Registry no.	Silver salt	Dec temp, °C	Calcd wt loss as CO_2, %[a]	Found	
				Wt loss, %	CO_2 evolved, %
29327-92-2	Ag_2 terephthalate	425	23.2	23.6	22.8
57664-97-8	Ag_2 isophthalate	375	23.2	23.5	22.7
57664-98-9	Ag_3 trimellitate	305	24.9	26.2	24.0
57664-99-0	Ag_3 trimesate	325	24.9	25.8	24.4
57665-00-6	Ag_4 pyromellitate	332	25.8	26.8	24.7
57665-01-7	Ag_5 benzenepentacarboxylate	330	26.4	28.0	24.7
19403-20-4	Ag_6 mellitate	280	26.8	*b*	24.0
23417-03-0	Ag_2 naphthalene-2,6-dicarboxylate	430	20.5	20.7	20.1
57665-02-8	Ag_2 pyridine-3,5-dicarboxylate	302	23.2	23.8	23.5
57665-03-9	Ag_2 thiophene-2,5-dicarboxylate	315	22.9	23.8	22.8

[a] Calculated on the basis $R(CO_2Ag)_n \rightarrow R(Ag)_n + nCO_2$. [b] Rapid runaway reaction, which was reproducible. Approximate weight loss, 70%.

polymer first formed may contain radicals that react readily with oxygen; if formed under nitrogen and exposed to air at 80 °C or higher, the polymer ignites readily. Silver isophthalate, pyrolyzed under nitrogen and cooled under hydrogen, gives a product that ignites spontaneously at 25 °C when exposed to air.

The silver polycarboxylates listed in Table VI give a variety of curious shapes when pyrolyzed under nitrogen; pyrolyzed silver trimesate, silver thiophene-2,5-dicarboxylate, silver terephthalate (Ag_2TA), and silver isophthalate (Ag_2IA) are shown in the photomicrographs (Figure 1), all at 50× magnification.

X-Ray photoelectron spectroscopy (ESCA) revealed sharp lines in all pyrolyzed salts for silver absorption at binding energies of 368–369 eV; these were of relatively low intensity, 70–80 Hz, consistent for Ag imbedded in carbonlike polymer, with only a small amount lying on the surface. Two species of silver were shown clearly by broad peaks in the ESCA spectrum for pyrolyzed silver bromoterephthalate, as called for by the equation



The benzynyl free radical I has been suggested previously to explain the products from 4-nitrophthalic anhydride in the gas phase at 600 °C.[10]

A strong nitrogen line at 402.7 eV appeared in both silver pyridine-3,5-dicarboxylate as prepared and the salt pyrolyzed at 310 °C under helium, as evidence that the heteroatom was retained in the carbonlike polymer. Additional evidence came from elemental analysis. Anal. Calcd for $[2Ag \cdot C_5H_3N]_n$: N, 4.8. Found: N, 4.4.

Surface areas and pore-size distributions for some of the pyrolyzed silver salts in Table VI were determined. These physical characteristics varied widely depending on the silver salt pyrolyzed. The surface area of pyrolyzed silver terephthalate was 0.57 m^2/g; that for silver trimesate, 549 m^2/g. Silver mellitate pyrolyzed under N_2 contained pores from 15 to 600 Å in diameter, uniformly distributed; pyrolyzed silver trimesate under the same conditions had pores 80% of which were 15–20 Å in diameter. Evidently we have achieved considerable control of pore-size distribution and surface area for silver imbedded in carbonlike polymer matrices by pyrolyzing the appropriate silver polycarboxylate.

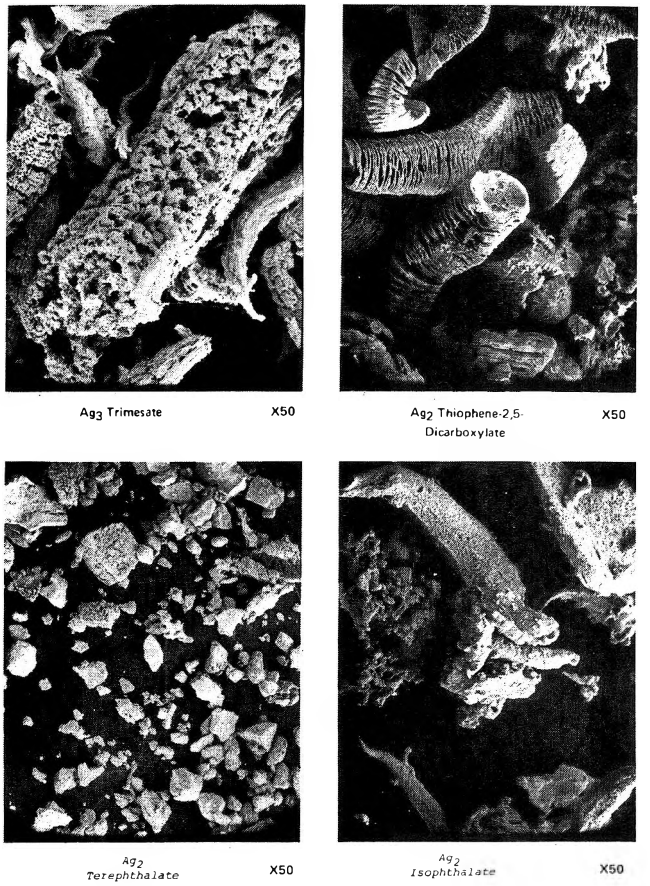


Figure 1.

Experimental Section

Silver salts of the carboxylic acids were prepared by adding the sodium salts in aqueous solution to aqueous silver nitrate in 5% molar excess at 20 °C with rapid stirring. The precipitated silver salts were collected on a filter, washed thoroughly with water, and dried in vacuo at 90 °C.

Thermal decompositions were run in Pyrex or Vycor tubes, heated in a tube furnace with the dry silver salt spread evenly in shallow layers. Weight losses were determined in a Du Pont Model 950 thermogravimetric attachment for the Model 900 thermal analyzer. Surface areas and pore-size distributions were determined by the Digisorb 2500 computerized analyzer (Micromeritics, Norcross, Ga.). Mass spectra were measured on a Du Pont Model 21-

104 instrument using electrical scanning, with normal and low-voltage electron energies set at 70 and 7.5 eV nominal, and with inlet and source temperatures of 350 and 250 °C, respectively. Directly coupled gas chromatography–mass spectrometry utilized a 5 ft × 0.125 in. stainless steel column packed with 10% SE-30 on Chromosorb W, coupled via a jet-orifice separator to a Du Pont Model 21-491 mass spectrometer; electron energy was 70 eV and ion source temperature was 250 °C.

Acknowledgment. The authors are greatly indebted to Drs. A. P. Yu of Amoco Oil Co., J. B. Hall and B. L. Meyers of Standard Oil Co. (Indiana), and C. A. Lucchesi of Northwestern University for much of the data on products from silver polycarboxylates.

Registry No.—Silver benzoate, 532-31-0; sodium benzoate, 532-32-1; silver *p*-fluorobenzoate, 57665-04-0; sodium *p*-fluorobenzoate, 499-90-1; silver pentafluorobenzoate, 3796-31-4; sodium pentafluorobenzoate, 4830-57-3; silver 2-pyridinecarboxylate, 27876-60-4; sodium 2-pyridinecarboxylate, 57665-05-1; silver 3-pyridinecarboxylate, 57665-06-2; sodium 3-pyridinecarboxylate, 54-86-4; silver 4-pyridinecarboxylate, 57665-07-3; sodium 4-pyridinecarboxylate, 16887-79-9; Na_2 terephthalate, 10028-70-3; Na_2 isophthalate, 10027-33-5; Na_3 trimellitate, 50976-34-6; Na_3 trimesate, 17274-08-7; Na_4 pyromellitate, 148-04-9; Na_5 benzenepentacarboxylate, 145-45-9; Na_6 mellitate, 145-44-8; Na_2 napthalene-2,6-dicarboxylate, 16303-32-5; Na_2 pyridine-3,5-dicarboxylate, 57665-08-4; Na_2 thiophene-2,5-dicarboxylate, 57665-09-5; silver nitrate, 7761-88-8.

References and Notes

(1) E.g., J. Y. MacDonald and C. N. Hinshelwood, *J. Chem. Soc.*, **127**, 2764 (1925), on the explosive decomposition of silver oxalate at 140 °C.
(2) D. C. Nonhebel and J. C. Walton, "Free-Radical Chemistry", Cambridge University Press, New York, N.Y., 1974, pp 426–432.
(3) E. K. Fields and S. Meyerson, *Acc. Chem. Res.*, **2**, 273 (1969); *Adv. Free-Radical Chem.*, **5**, 101 (1975).
(4) D. H. Hey and G. H. Williams, *Discuss. Faraday Soc.*, **14**, 216 (1953); R. L. Dannley and E. C. Gregg, Jr., *J. Am. Chem. Soc.*, **76**, 2997 (1954).
(5) E. V. Brown and M. B. Shambhu, *Org. Mass Spectrom.*, **6**, 479 (1972).
(6) Cf. S. Meyerson, H. Hart, and L. C. Leitch, *J. Am. Chem. Soc.*, **90**, 3419 (1968).
(7) Estimate based on ionization potentials of related species from R. W. Kiser, "Introduction to Mass Spectrometry and Its Applications", Prentice-Hall, Englewood Cliffs, N.J., 1965, Appendix IV.
(8) For a somewhat different electronic interpretation with essentially the same chemical effects, see S. A. Holmes and T. D. Thomas, *J. Am. Chem. Soc.*, **97**, 2337 (1975).
(9) We use the term "carbonlike polymer" to distinguish our products from nondescript carbons of varying elemental compositions. The structures of the antecedent silver salts appear to set the structures of the polymerized radicals formed by loss of silver and carbon dioxide.
(10) E. K. Fields and S. Meyerson, *Tetrahedron Lett.*, 719 (1971).

Studies on Catalytic Hydrogenation. I. The Influence on Reaction Rates of the Metal–Carrier Ratio of Solvents and Acidity[1]

Richard Baltzly

Memorial Sloan-Kettering Cancer Center, New York, New York 10021, and the Wellcome Research Laboratories, Research Triangle Park, North Carolina 27709

Received June 3, 1975

It is shown that in aqueous methanolic and aqueous acetic acid solutions catalytic hydrogenations of a variety of substrates can be conducted at rates independent of hydrogen pressure and substrate concentration. The pressure above which hydrogen availability ceases to be limiting is about 3 atm. Substrate adsorption is a function of the activity (and an inverse function of the solubility) of the substrate in the solvent. Platinum, palladium, and rhodium adsorbed on carbon (charcoal and powdered graphite) were examined. Platinized carbon is highly sensitive to acidity, palladized carbon only in the reduction of C–O functions. Rhodium on carbon is somewhat inhibited by acidity in reductions of benzene and acetophenone and indifferent to acidity in the reduction of cyclohexene. The efficiency of various metal–carrier ratios varies somewhat with the substrate, especially with rhodium. Metallized graphites resemble closely the corresponding metallized charcoals but require 10–20 times as much carrier.

This investigation had a dual purpose: to provide a basis of standard catalyst activity for poisoning studies and to relate the behaviors of metallized charcoals and graphites.[2] For both projects it was necessary to have more knowledge of the reaction kinetics and the effect thereon of the solvent medium.

The kinetics of catalytic hydrogenation of nitro compounds in aqueous alcoholic solutions have been studied by Yao and Emmett[3] and of cycloalkenes in cyclohexane by Hussey and his co-workers.[4] Both groups gave extended discussions of theoretical and experimental kinetics. For the present purpose eq 1

$$\text{rate} = \frac{\text{mmol}}{\text{min}} H_2 = Akw\theta_H\theta_S \qquad (1)$$

is proposed as valid when small amounts of catalyst are used. Here A is a constant containing factors dependent on the solubility of hydrogen in the solvent, the viscosity and surface tension of the solvent, and the efficiency of mixing.[5] w and k are the weight of catalyst (in default of the unknown surface area) and the real constant of hydrogenation and θ_H and θ_S are adsorption terms for hydrogen and substrate.[6]

In extended form, the substrate adsorption term

$$\theta_S = \frac{\alpha_s C_s}{\beta + \alpha_s C_s + \alpha_{SH} C_{SH} + \Sigma\alpha_{sv} C_{sv} + \alpha_i C_i}$$

where β is a constant,[7] the C symbols refer to concentrations of substrate, reduced substrate, solvents, and inhibitor, if any, and the α symbols are the appropriate adsorption coefficients. The term $\alpha_{SH}C_{SH}$, if sizable, corresponds to product inhibition, frequently observed with enzymes. It is probably not significant in the present work except in the reduction of nitrobenzene. Consideration of $\alpha_i C_i$ is to be taken up later. In the absence of poison or product inhibition

$$\theta_S = \frac{\alpha_s C_s}{\beta + \alpha_s C_s + \Sigma\alpha_{sv} C_{sv}}$$

and two simple methods of treatment are available.

Yao and Emmett chose to regard the denominator as

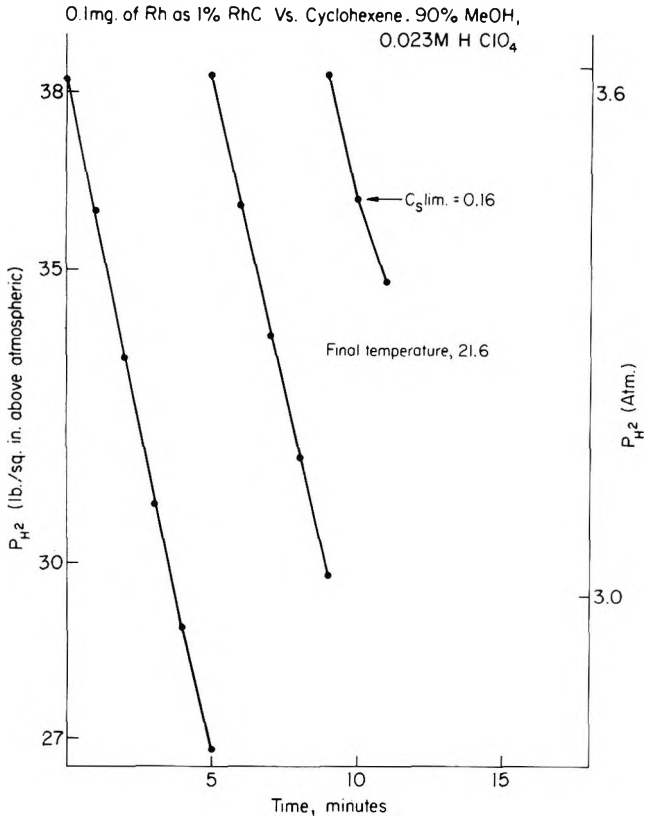


Figure 1.

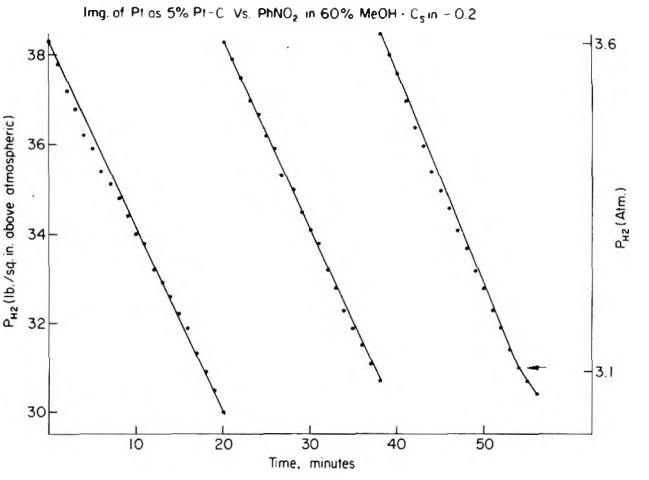


Figure 2.

large in proportion to $\alpha_s C_s$ leading to a rate first order in substrate concentration. They achieved this in part by operating in rather dilute solutions but reported that increase in the water content of the solvent favored lower order kinetics. The alternative is to regard $\alpha_s C_s$ as large in relation to β and the solvent-adsorption term, in which case θ_s approaches 1 and may be experimentally indistinguishable from 1 over a convenient portion of the reduction. This treatment leads to the function C_s lim, defined as that concentration of substrate above which zero-order kinetics are observed. For this, the solvent adsorption terms need not be zero. In the work of Hussey and coworkers, using cyclohexane as solvent, $\Sigma\alpha_{sv}C_{sv}$ could well have been zero. They reported that platinum on alumina reduced cycloalkenes with zero-order kinetics almost throughout. This was not the case with palladized alumina: Figure 1 of ref 4b suggests C_s lim around 0.35 (not far from the figure given in Table IIb of the present communication). In the present work, cyclohexene appeared more strongly adsorbed by platinized charcoal than by palladized charcoal (and more strongly on Rh/C than on the other catalysts). The differences, however, are not sufficient to account for the large variations reported by Hussey, with, of course, markedly different catalysts. In the present studies operations were feasible above C_s lim with the possible exceptions of the reduction of benzyl alcohol by Pd/C and of benzene and acetophenone by Rh/C.

The hydrogen adsorption term

$$\theta_H = \frac{\alpha_H P_{H_2}}{\beta + \alpha_H P_{H_2}}$$

The denominator may contain further adsorption terms corresponding to those of θ_s. Similar simplifying assumptions can be applied leading to kinetics of first order in hydrogen or to kinetics of lower order. Most accurate work has been done with constant-pressure apparatus which does not accommodate large pressure variations. As a consequence, most experiments were at atmospheric pressure with a very few explorations of the effect of lower hydrogen pressures and of higher pressures up to 1.5 atm.[4a] Within this range, Yao and Emmett found their rates proportional to hydrogen pressure, as did Hussey et al. with platinized alumina. However, Hussey and Nowack reported lower orders of hydrogen dependence with palladized alumina.

Since, in principle, hydrogen pressure is capable of very large variations, one may postulate some hydrogen pressure, P_{H_2} lim, above which θ_H should be experimentally equal to 1. Whether this pressure would be accessible with the available apparatus was not a priori predictable. In the present work, above about 3 atm of hydrogen pressure, it was found that pressure drop was linear with time so that work was possible above both P_{H_2} lim and C_s lim. This is especially advantageous when dealing with poisoning phenomena.[8]

With Pd/C and Rh/C, P_{H_2} lim appeared appreciably lower than with Pt/C. The value of this function is probably dependent on the solvent, the apparatus, and the hydrogen demand, although in the present work no correlation with this last factor was noted. No attempt was made to study its variation further after finding that a P_{H_2} lim exists and is accessible. Figures 1 and 2 give plots of two reductions illustrating the determinations of C_s lim and the constancy of the pressure drop above P_{H_2} lim.

The value of C_s lim depends heavily on that of α_s, which is, in general, unknown. However, α_s should be dependent on the thermodynamic activity of the substrate (equated to 1 as a pure substance). Since most organic substrates are sparingly soluble in water, α_s should increase with the water content of the solvent mixture and C_s lim for such substrates should diminish. Figure 3 shows the plot of the concentrations of nitrobenzene in saturated solution and C_s lim of nitrobenzene in 60–75% methanolic solutions. The general similarity of the two curves is obvious.

Choice of Substrates. It was desired to have substrates typifying a number of the functions of major interest. Stability of the substrate was also advisable; however, cyclohexene was selected for study despite the difficulties in dealing with it because of the studies of Hussey.[4] Some olefene was desired, and there was no reason to prefer another of this class. Nitrobenzene and acetophenone were also used with all the metallized charcoals.[9] The reduction of benzene was examined with rhodium on charcoal and hydrogenolysis of benzyl alcohol with palladized charcoal. The results of poisoning studies with benzyl alcohol led to the examination of benzaldehyde with the same catalyst. A limited amount of work was done with benzyl methyl and benzyl isopropyl ethers in order to correlate the benzyl alcohol results with other substrates for debenzylation.[10]

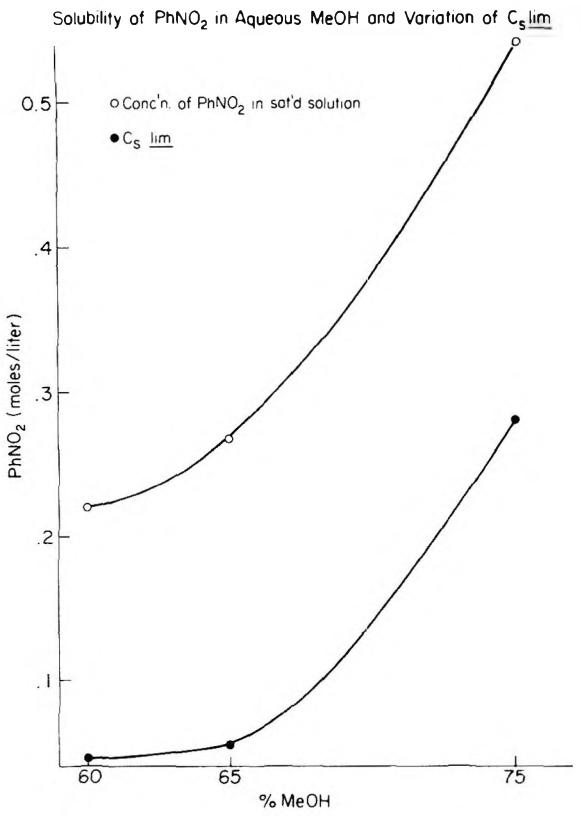


Figure 3.

Experimental Section

Apparatus. Reductions were performed in an Adams-Burgess-Parr reducer having a pressure gauge registering the pressure in the isolated shaking bottle (volume 400 ml). This gauge was marked at intervals for 1 psi and could be read with fair accuracy to 0.1 lb. A pressure drop of 1 psi corresponds very closely to 1 mmol of hydrogen when the volume of solution is 50 ml, as in all kinetic runs here reported. The rate of shaking was 170 ± 10 strokes/min.

Temperature Control. Initially this was one of the major problems since considerable amounts of heat were liberated in a moving, thick-walled glass vessel. No method of thermostating by a circulated fluid at the desired temperature was likely to be adequate. Fortunately, the heat produced must be proportional to the rate of hydrogen consumption. The heats of hydrogenation of benzene and cyclohexene are known accurately.[11] Those for the hydrogenation of nitrobenzene to aniline, benzyl alcohol to toluene, and C=O to CHOH can be deduced less certainly from combustion data. From these it appears that the heat liberated per H_2 *absorbed* in these reductions varies in the proportion cyclohexene, 1; nitrobenzene, 1.5; acetophenone and benzaldehyde, 0.5; benzene, 0.6; and benzyl alcohol, 0.9.

Cooling was accomplished by placing a strip of wet paper toweling around the shaking bottle under the protective wire screen. The strip could be varied in size and cooling increased (up to about a third) by projecting a variable air stream upon the shaking bottle. Before beginning a day's run, a bottle containing 50 ml of water initially at 22 °C was shaken for 5 min while cooled by a standard strip (13 cm in width), and the fall in temperature was recorded. With this as a guide, the cooling requirement for an expected rate of hydrogen absorption could be selected. The temperature of the solution was set at 22 °C immediately before hydrogenation[12] and redetermined at the end. Runs in which the deviation was more than 1 °C were discarded.[13]

At the start of a run, after evacuation, shaking was started and hydrogen admitted rapidly to the desired level (ca. 3.5 atm). The first reading was made about 10 s after full pressure had been attained. When more hydrogen was introduced, this was done without stopping the motor, and the first reading of the new series was made after a 10-s interval. Pressure readings were made 1 min apart, and a record was made of the variable air stream (for cooling) when it was used. In general, a run was terminated soon after the rate of pressure drop had departed significantly from linearity, and the temperature of the reduction mixture was redetermined.

Substrates. Benzyl alcohol and benzaldehyde were commercial grades (the latter freed of benzoic acid). It was not certain that the benzyl alcohol was completely free of poison since the available solvent conditions were limited, and it was not certain that a true C_s lim had been determined. The amount of contamination could not have been large. A commercial sample of benzyl methyl ether, on the other hand, was obviously poisoned as was the same material prepared in this laboratory and benzyl isopropyl ether,[14] when prepared from commercial benzyl chloride. These ethers could be obtained in satisfactory condition by recovery from partial reductions with larger amounts of catalyst or by synthesis using benzyl chloride prepared by chloromethylation of pure benzene.

Commercial nitrobenzene and acetophenone were quite unusable. Both were generally prepared by synthesis from pure benzene. For this purpose a small Friedel–Crafts reaction (ca. 0.5 mol of acetyl chloride) was run in about 1 l. of "thiophene-free" benzene. The acetophenone from this reaction was discarded, and the recovered benzene was suitable for nitration and acetylation reactions and as a substrate for Rh/C reductions. The nitrobenzene and acetophenone so prepared were distilled thrice in vacuo through a 25-cm Vigreux column. Both were stable without special precautions.[15,16]

Cyclohexene is a troublesome substrate: Hussey and co-workers[4] have described the extreme precautions necessary (but not always sufficient) for their very precise operations. The possible accuracy in the present work being less, it was found generally sufficient to distill under nitrogen each day a sample sufficient for the runs to be attempted. The distillate was kept under nitrogen until used. The first run on each sample was always a control. Batches were not always satisfactory: inferior material was often usable in orienting runs for locating half-poisoning concentrations. A few bottles of cyclohexene were of good quality when first opened. In such cases, the contents were protected as well as possible with nitrogen and used as long as satisfactory controls could be obtained.

The precautions for operations on cyclohexene with platinum and palladium were less frequently adequate with rhodium. In part, this is a function of the high activity of Rh/C in this reduction. Whereas 1 mg of Pt and 0.5 mg of Pd were the standard amounts for cyclohexene reductions, only 0.1 mg of Rh was used. Thus, an amount of poison capable of depressing the reduction rate of Pt or Pd by 5% would be expected to lower the Rh rate by 25%.

On the Nature of the Contaminants in Cyclohexene. On long standing a considerable amount of thickish and presumably polymeric material accumulates in bottles of cyclohexene. This can be removed by distillation, but such purification is not enough. It is clear that rapidly forming poisons of low molecular weight are present, owing their origin to traces of oxygen and (probably) light.

Some further information was obtained fortuitously. An inferior sample of cyclohexene was used in orienting experiments on poisoning by manganous ion. As small, but increasing amounts of manganous chloride were employed in successive runs the rate *increased* to, but not above, the best standard rate. Still larger amounts of manganese resulted only in poisoning. It was found that as a rule when the control run on a newly distilled sample of cyclohexene was not depressed more than a third below the standard rate, it was possible to regain the normal rate by use of manganous chloride, which seemed to operate at least roughly in a stoichiometric fashion. The concentrations of Mn^{2+} required were in the order of 10^{-4}, which is twice the half-inhibitory concentration of Mn^{2+} with pure cyclohexene.

It thus appeared likely that the manganous ion was acting as a scavenger, being itself oxidized to a higher valence not reducible under the conditions. This effect was not manifested by zinc and cadmium, which have only one ionic valence. A further indication about the toxic contaminants is that this manganese effect is not manifested when the manganese is added *after* the reduction has begun. The manganese must be present at the start and the evacuated reduction bottle shaken for 2 or 3 min before admission of hydrogen (the usual procedure in poisoning experiments).

Thus it appears that cyclohexene can contain at least two toxic contaminants not readily separated by fractional distillation, both presumably derived from the attack of oxygen on the substrate. The one can be decomposed by shaking with catalyst and manganous ion and is reducible to a poison not so decomposed. Since not all distilled samples could be so restored, at least one other poison is probable. Some at least of the poisons tend to be adsorbed on activated alumina.

The manganese effect was prominent with Pt/C, much less so with Pd/C, and absent with Rh/C. Manganous ion is a moderately

strong poison against cyclohexene with Pt/C ($C_{i\,1/2} = 5 \times 10^{-5}$),[17] very much weaker with Pd/C ($C_{i\,1/2} > 6 \times 10^{-3}$), and substantially nontoxic with Rh/C. It is thus probable that the scavenging action takes place on the catalyst.

Preparation of Catalysts. Platinum and palladium were portions of rather large stocks in the author's possession. Platinum was purified by precipitation as $(NH_4)_2PtCl_6$ and recrystallization of that salt from water containing a little NH_4Cl. Palladium was purified by alternate precipitation as $Pd(NH_3)_2Cl_2$ and $(NH_4)_2PdCl_6$.

When needed, the appropriate amounts of $(NH_4)_2PtCl_6$ and $(NH_4)_2PdCl_6$ were weighed into a porcelain crucible, ignited, and converted via HBr–aqua regia and HCl treatments to chloroplatinic acid and palladous chloride. These residues were dissolved in water containing a little excess hydrochloric acid and made up to volume so that 1 ml contained 1 mg of metal.

Rhodium was in the form of a commercial sample of $RhCl_3 \cdot 3H_2O$. A solution was made up to 250 ml containing 639.8 mg of this salt and 1 ml of 1 N HCl, thus containing 1 mg of Rh/ml. A more dilute solution was prepared containing 0.2 mg of Rh/ml. In order to have a substantially chloride-free solution, 25 ml of the 1 mg/ml solution plus 0.1 ml of 70% $HClO_4$ was evaporated to a syrup in a rotary evaporator and made up to 25 ml.

Palladized charcoal was prepared by shaking an aqueous solution containing the desired amount of palladous chloride with a weighed quantity of charcoal[18] under hydrogen.[19]

Platinized charcoal was prepared by two methods. One, in which a trace (1 atom:500) of palladium is present in the chloroplatinic acid solution to initiate deposition of metal,[20] gave a preparation referred to here as Pt/C (B). Later, an alternative preparation, Pt/C(Z), was studied. This was based on the work of Zeliger.[21] The difference is that no palladium initiator was present. The two preparations were equivalent in most respects.[22]

In the course of the present work, it was found that both platinum and palladium are strongly adsorbed on charcoal in equilibrium with the solutions used. If this was also the case with the carriers used by Zeliger, it is probable that reduction of the chloroplatinate ion occurs only on the surface of the carrier and that the metal is not picked up by the carrier from a colloidal state. Some support to this hypothesis may be drawn from the deposition of metal on the inside of the glass reaction vessel. This was very rare with platinum, infrequent with palladium, and almost invariable with rhodium. Experiments on the adsorption of the metal ions by the carrier indicate that under the conditions of the preparation, about 90% of the palladium, 75% of the platinum, but only 25% of the rhodium is resident on the charcoal before hydrogen is admitted.

Rhodium on charcoal was prepared by the same method as with palladium. That prepared in this laboratory is symbolized as Rh/C. Catalyst E was a "5%" Rh/C obtained from Engelhard (lot 14 269).

The metallized graphites were prepared in the same fashion as the corresponding metallized charcoals. The powdered graphite used was "special spectrographic graphite powder" grade SP-2 (lot 302) obtained from the National Carbon Co. Some preparations employing very large amounts of carrier were made using some methanol in the solution. These preparations were apparently satisfactory, but were regarded with some suspicion since catalyst preparation is not feasible from high (ca. 75%) concentrations of methanol.

All the catalysts prepared here were shaken under hydrogen at least 30 min. This is probably an excessive time. One suspects that Pt/C(Z) may be formed more slowly than the B variety, but an attempt to determine the time involved by preparing the catalyst in 75% methanol with nitrobenzene present failed; virtually no catalytic activity resulted.

For nitrobenzene reductions an extra step was required for consistent results. After the catalyst had been prepared, the shaking vessel was evacuated, air was admitted, and shaking was resumed for 15 min (again, probably an excessive time) to remove traces of hydrogen. In the absence of this step, rates were erratic. The probable point is that when some hydrogen is on the catalyst when nitrobenzene is added, there is some reduction while oxygen is still present and oxidation of the reduction products produces poison. If strong acid is to be added in the reduction, this should be done after this aeration step.

Solvents. A few reductions of benzaldehyde were done in 2-propanol, the others in methanol or acetic acid and their mixtures with water. The water was distilled in glass. Commercial methanol, 2-propanol, and acetic acid were found satisfactory.[23] Since the catalysts were prepared in aqueous solution (5–10 ml), direct addition of solvent sufficed to give up to 90% solutions (v/v). For higher concentrations, the initial preparation was diluted to ca. 350 ml with solvent, equilibrated, and allowed to settle. The supernatant was then removed (to 10 ml) through an upturned capillary. Addition of the required amount of solvent gave the desired composition for the reduction mixture. This operation was used mainly with platinum catalysts since the stability of palladium and rhodium under the conditions was doubtful. When used with these metals, the settling out process was carried out under hydrogen.

Solubilities and Choice of Substrate Concentrations. Substrate concentrations were chosen with the aim of having a reasonable range showing a zero-order rate. The upper limit of substrate concentration was taken as 20% (10 ml in 50 ml). Solubilities of the substrates used and of some reduced substrates were determined by placing a known volume of the substrate in a graduated cylinder and adding solvent in portions until all dissolved. The charge was chosen so that there should be only one liquid phase. Thus, in reductions of nitrobenzene in 75–99% methanol, the starting substrate concentration (C_s in) was 0.39 M, 0.23 in 65% methanol, 0.2 in 60% methanol, and 0.18 in 60% methanol 1 M in NaCl.

There are certain practical limitations in solvent composition. While all the substrates used are more soluble in methanol and acetic acid than in water, and, in principle, it should be possible to lower C_s lim to any desired level by using a more aqueous solvent, the properties of the reduced substrate must also be considered. This complication does not arise with aniline or α-phenethyl alcohol, but cyclohexane is much less soluble in aqueous solvents than cyclohexene and benzene. Similarly, toluene is less soluble than benzyl alcohol and the two benzyl ethers studied. Benzyl alcohol was examined in 80 and 90% methanol and in 75% acetic acid. Second liquid layers could be avoided by not carrying the reductions too far, but it is not certain that C_s in exceeded C_s lim. The benzyl ethers gave satisfactory zero-order rates in 75% acetic acid, but C_s lim was doubtful in 80% methanol. Reductions of benzene in 80% methanol gave indications of a second phase and 85% methanol was the solvent of choice, even though C_s lim was very close to C_s in.

Purity of Substrates. Hussey and co-workers[4] imposed very rigid criteria: that three successive charges of substrate could be hydrogenated over the same catalyst and in the same solution and give the same rate within the limit of other experimental errors. This was feasible in their experiments since their substrates, on reduction, became identical or substantially identical with the solvent. When this would not be the case, this criterion cannot be applied.

A second criterion proposed originally was that one should be able to reduce a charge of substrate, dilute with solvent, draw off the supernatant after the catalyst had settled, restore the original conditions, and obtain the same rate with a fresh charge. This operation is, in fact, feasible with Pt/C and cyclohexene provided that the first charge of substrate is completely reduced. However, since the cyclohexene was redistilled each day and not all samples were acceptable, this criterion was at best inconvenient. This criterion was never regarded as applicable to nitrobenzene since traces of oxygen produce toxic substances very rapidly from aniline in the presence of catalyst. The test was tried with varying but not complete success for awhile with acetophenone. It was never possible to match the second rate with the first, and the attempt was abandoned when it was found that the discrepancy *increased* when the first charge had been completely reduced. This suggests that the deterioration is due to some reaction of α-phenethyl alcohol.

No attempt was made to apply this test with palladium and rhodium catalysts since it was doubtful whether one could expect the integrity of the catalyst surfaces to be maintained in the presence of even traces of acid.

The third test requires that the rate should be proportional to the amount of catalyst with small amounts of the latter. Thus, for nitrobenzene and cyclohexene, runs were compared with 0.5, 1, and 1.5 mg of Pt, with acetophenone runs with 5, 10, and 20 mg of metal. Having found such proportionality, standard zero-order rates under various conditions were established, and later samples of substrate were required to meet the standards of these rates.

Amounts of Catalysts. Throughout this communication the amount of catalyst is given as the amount of metal, and the percentage refers to the (wt of metal × 100)/wt of carrier. Thus, 1 mg of 5% Pt/C means 1 mg of Pt on 20 mg of charcoal; 5 mg of 3% Pd/C means of 5 mg of Pd on 165–170 mg of charcoal, etc.

It has already been shown abundantly (cf., among others, ref 3, 4) that significant rates are obtainable only with small amounts of

Table I. Standard Zero-Order Rates of Hydrogenation with 5% Pt/C ("Old" Darco)

Solvent	Acidity (or electrolyte)	Rate, mmol H_2/min	C_S lim
A. Substrate Nitrobenzene, 1 mg of Pt: C_S in = 0.39			
99% MeOH	Residual (res)	2.14	0.31
95% MeOH	Res	2.15	0.26
75% MeOH	Res	1.4	0.28
65% MeOH[a]	Res	0.67	0.05–0.06
60% MeOH[b]	Res	0.42	0.045
95% MeOH	0.72 M H_2SO_4	2.35	0.22
95% MeOH	0.72 M HCl	1.37	0.2
75% MeOH	0.72 M H_2SO_4	1.7	0.14
75% MeOH	0.46 M $HClO_4$	1.6	0.16
75% MeOH	0.6 M HCl	0.93	0.14
75% MeOH	0.38 M NaCl	1.0	0.20
65% MeOH[a]	0.36 M H_2SO_4	1.02	0.09
65% MeOH[a]	0.38 M HCl	0.67	0.075
65% MeOH[a]	0.38 M NaCl	0.54	0.05–0.06
60% MeOH[b]	0.72 M H_2SO_4	0.8	0.05
60% MeOH[b]	1.0 M HCl	0.57	0.07
60% MeOH[c]	1.0 M NaCl	0.43	0.04
99% MeOH	Neutral	1.4	0.32
75% MeOH	Neutral	0.7	0.32
65% MeOH[a]	Neutral	0.6	0.07
99% HAc	Res	0.54	0.34
75% HAc	Res	0.74	0.26
60% HAc	Res	0.64	0.21
50% HAc	Res	0.44	0.21
89% HAc	0.46 M $HClO_4$	0.73	0.37
75% HAc	0.46 M $HClO_4$	0.93	0.3
75% HAc	0.48 M HCl	0.57	0.31
B. Substrate Acetophenone, 10 mg Pt: C_S in = 1.7			
99% MeOH	Res	1.9	1.5
99% MeOH	Neutral	0.7	1.6
75% MeOH	Res	1.86	1.12
75% MeOH	0.36 M HCl	1.46	1.46
75% MeOH	0.36 M $HClO_4$	2.0	1.3
75% MeOH	Neutral	0.6	1.45
65% MeOH	Res	1.7	1.2
60% MeOH	Res	1.12	1.1
75% HAc	Res	1.0	1.5
60% HAc	Res	1.1	1.2
C. Substrate Cyclohexene, 1 mg Pt [3% Pt/C (B)]			
99% MeOH (C_S in 2.0)	0.01 M HCl	1.55	1.8
90% MeOH	Res	1.2	0.3
(C_S in 0.6)	0.115 M $HClO_4$	1.4	0.3
	Neutral	0.6	0.3–0.4

[a] C_S in = 0.23. [b] C_S in = 0.2. [c] C_S in = 0.18.

Table II. Standard Zero-Order Rates of Hydrogenation with 3% Pd/C

Solvent	Acidity	Rate, mmol H_2/min	C_S lim
A. Substrate Nitrobenzene, 0.5 mg Pd: C_S in = 0.39			
90% MeOH	0.46 M $HClO_4$	1.0	0.32
75% MeOH	0.46 M $HClO_4$	0.99	0.06
75% MeOH	Neutral	0.8	0.26
65% MeOH	Res	0.35	0.05
B. Substrate Acetophenone, 5 mg of 3% Pd/C, C_S in = 1.3			
99% MeOH	Res	1.66	0.85
90% MeOH	0.23 M $HClO_4$	1.6	0.96
90% MeOH	Neutral	1.1	
75% MeOH	0.23 M $HClO_4$	1.07	0.76
75% MeOH	Res	1.09	0.94
75% MeOH	Neutral	0.6	
C. Substrate Benzaldehyde, 3 mg of 3% Pd/C, C_S in = 2.0			
90% MeOH	0.23 M $HClO_4$	1.63	1.5
90% MeOH	Neutral	0.6	
85% Me_2CHOH	Res	1.77	1.45
80% MeOH	0.23 M $HClO_4$	1.64	<1.0
D. Substrate Benzyl Alcohol, 5 mg of 3% Pd/C, C_S in = 1.94			
90% MeOH	0.46 M $HClO_4$	2.8	1.6
90% MeOH	0.23 M $HClO_4$	2.2	1.8
90% MeOH	0.115 M $HClO_4$	2.1	1.8
90% MeOH	0.046 M $HClO_4$	1.7	1.8
90% MeOH	Res	1.07	1.8
90% MeOH	Neutral	0.05?	
80% MeOH	0.23 M $HClO_4$	1.7	1.75
75% HAc	0.23 M $HClO_4$	2.1	1.7
75% HAc	Res	1.01	1.75
E. Substrate Benzyl Methyl Ether, 5 mg of 3% Pd/C, C_S in = 1.58			
80% MeOH	0.46 M $HClO_4$	0.55	?
80% MeOH	0.23 M $HClO_4$	0.45	?
80% MeOH	Neutral	0.1	?
75% HAc	0.46 M $HClO_4$	1.4	1.4
75% HAc	0.23 M $HClO_4$	1.4	1.4
75% HAc	0.115 M $HClO_4$	1.3	1.4
75% HAc	Res	0.63	1.4
F. Substrate Benzyl Isopropyl Ether, 5 mg of 3% Pd/C, C_S in = 0.86			
80% MeOH	0.23 M $HClO_4$	0.53	?
80% MeOH	Neutral	~0.1	?
75% HAc	0.46 M $HClO_4$	1.5	0.7
75% HAc	0.23 M $HClO_4$	1.3	0.7
75% HAc	0.115 M $HClO_4$	1.3	0.7
75% HAc	Res	0.7	0.7
G. Substrate Cyclohexene, 0.5 mg of 3% Pd/C in 90% MeOH, C_S in = 0.6			
	0.23 M $HClO_4$	0.7	~0.4
	0.023 M $HClO_4$	0.73	~0.4
	Res	0.78	~0.4
	Neutral	0.6	~0.4

catalyst (in Emmett's case 5 mg or less as a rule). Actually the amount of catalyst consistent with useful rates depends on the substrate and is presumably a function of the hydrogen demand. A more rigid limitation applies to the present work, that the rate must be such as not to exceed the capacity of the cooling system. In practice, it was desirable that hydrogen absorption should not exceed 2.5 mmol/min or, in a standard run, be less than 0.5–0.6 mmol/min (this level was such that a half-poisoning rate could be determined without excessive error). After exploratory experiments, 1 mg of Pt (ca. 5×10^{-6} atom) was chosen as the standard quantity for reductions of nitrobenzene and cyclohexene and 10 mg for acetophenone. The corresponding amounts of Pd were 0.5 and 5 mg. The latter quantity was also used with benzyl alcohol and 3 mg with benzaldehyde. With rhodium 5 mg was convenient for reductions of benzene, nitrobenzene, and acetophenone, 0.1 mg for cyclohexene.

Results and Discussion

Data on the effects of acidity and variation of solvents with the various substrates and catalysts are shown in Tables I–III. Data on the effects of carrier metal ratios, mainly with standard solvent and acidity, are presented in Tables V–VII. Metallized graphites were studied chiefly in the faster reductions because the high ratio of carrier to metal required becomes inconvenient with larger amounts of metal. The operations with rhodium were less extensive than would be desirable. This work was done last, and the time available to the author was limited.

The notation Res in the acidity columns indicates that the acid present was that resultant from the preparation of the catalyst. This amounted to an initial acid concentration in batches of 10 mg of platinum of 0.016 M and $\frac{1}{10}$ that in 1-mg batches. A 5-mg batch of palladium catalyst would have a res acidity of 6.8×10^{-3} whereas res for a 0.1-mg batch of rhodium was 0.003. These quantities, while small,

Table III. Standard Zero-Order Rates for Hydrogenation by Rh/C

Catalyst	Solvent	Acidity	Rate, mmol H_2/min	C_S lim
	A. Substrate Cyclohexene, 0.1 mg Rh/C (1%), C_S in = 0.6			
	90% MeOH	Res	2.29	0.28
	90% MeOH	0.023 M $HClO_4$	2.16 ± 0.08	0.16
	90% MeOH	2.2×10^{-3} OH	2.4	0.41
	90% MeOH	10^{-2} OH	1.83	0.48
	B. Substrate Acetophenone, 5 mg of Rh, C_S in = 1.7			
E	90% MeOH	Neutral	0.97	1.6?
E	90% MeOH	0.03 M HCl	0.73	1.6?
E	75% MeOH	Neutral	0.77	1.58
5% Rh/C	90% MeOH	Res	0.5	1.6?
5% Rh/C	90% MeOH	0.23 M $HClO_4$	0.42	?
1% Rh/C	90% MeOH	0.23 M $HClO_4$	0.22	?
	C. Substrate Benzene, C_S in = 1.97			
E	90% MeOH	None	2.05	~1.9
E	85% MeOH	None	1.8	~1.9
E	80% MeOH	None	1.45	~1.5
E	80% MeOH	0.23 M $HClO_4$	1.33	~1.8
E	90% HAc	None	1.1	~1.9
E	85% MeOH	0.003 M HCl	1.06	~1.9
E	85% MeOH	0.02 M NaCl	1.075	~1.9
5% Rh/C	85% MeOH	Res	1.05	~1.9
5% Rh/C	85% MeOH (Cl free)	0.4 M $HClO_4$	1.1	~1.9
5% Rh/C	85% MeOH (Cl free)	0.4 M $NaClO_4$	0.98	~1.9
	D. Substrate Nitrobenzene, 5 mg of Rh, 75% MeOH, C_S in = 0.39			
1% Rh/C		0.46 M $HClO_4$	0.84	0.32
3% Rh/C		0.46 M $HClO_4$	0.76	0.34
5% Rh/C		0.46 M $HClO_4$	0.79	0.31
3% Rh/C		Neutral	0.39	?
3% Rh/C		0.01 M OH	0.7 (1.1-0.5)[a]	
E		0.46 M $HClO_4$	0.99 (1.5–0.7)[b]	
E		Neutral	0.98 (1.4–0.7)[c]	
E		0.01 M OH	1.8	0.31

[a] Average of standing 6 min. [b] Average of two nearly identical runs. The figures given are for the first 5 min. The average of the next 6 min was 0.55. [c] Average of first 5 min. Average of next 6 min was 0.53.

are in excess of the amounts strongly adsorbed by the catalysts.

With platinum, the presence or absence of this adsorbed acid is the dominant factor in the influence of acidity on the reduction rate. In the study of nitrobenzene reductions, this factor was ignored initially since it was supposed that the aniline formed would remove adsorbed acid within the first minute or two. Anomalous poisoning results with anions led to the realization that this assumption was unsound, and it is to be noted that there is a large difference between neutral and residual acid rates in the less aqueous solutions (Table IA).

The quantitative aspects of this adsorption of acid were examined with 10-mg batches of Pt/C in the reduction of acetophenone, data being presented in Table IV. In these experiments, after preparation of the catalyst, the quantities of sodium acetate or of alkali given in the first column were added. The solution was then diluted with methanol to 350 ml, equilibrated, and allowed to settle. After removal of supernatant to 10 ml, 30 ml of methanol and 10 ml of acetophenone were added after which the reductions were run. Immediate titration in situ after preparation of catalyst required 0.78 ml of 1 M NaOH, but titration of the supernatant removed in the first experiment required only 0.45 ml. In a parallel experiment with the same amount of acid but only carrier present, there was no significant retention of acid.[24] The amount of acid retained by Pd/C is about half of that held by Pt/C while Rh/C adsorbs still less. Probably corresponding to this, the effect of acidity on rate with Pd/C is marked only with acetophenone, benzaldehyde, and the benzyl–oxygen substrates while with Rh/C acidity is usually inhibitory.

Further increase in acidity through the addition of perchloric or sulfuric acid[25] accelerated the reduction of nitrobenzene moderately but had a more marked effect on C_S lim. Presumably this identifies a case of product inhibition. In 75% methanol with 0.46 M acid, all the aniline that can be formed is protonated, and the zero-order rate continues until more than half of the charge has been reduced. In the absence of added acid, the zero-order rate begins to fade when the reduction is a little more than a quarter done. In other words, when the aniline is 0.11 M, it *begins* to compete for the catalyst surface with 0.28 M nitrobenzene. The effect of added HCl on C_S lim is essentially the same as that of the preferred acids, but the rate is lowered, apparently through toxic action by chloride ion.[26] This subject is discussed further in the following communication. The inhibitory effect of sodium chloride is comparable to that of chloride from HCl but is not compensated by increased acidity. Thus, in 65% methanol sodium chloride inhibited hydrogenation, but HCl did not. The neutral salt also lowered C_S lim presumably by increasing the activity of nitrobenzene more than that of aniline.[27]

In the more aqueous solutions, product inhibition was imperceptible; aniline being relatively soluble in water, the increase in water content raises the activity of nitrobenzene

Table IV. 10 ml of PhCOMe, 40 ml of 99% MeOH, 10 mg of Pt on 200 mg of Charcoal

NaAc added before washout, mmol	HCl remaining before washout, mmol	Rate, mmol H_2/min
None	0.77	1.9
0.4	0.37	1.83
0.48	0.29	1.1
0.56	0.21	0.95
0.64	0.13	0.7
0.68	0.09	0.7
0.77 (NaOH)	Zero	0.7

Table V. Carrier–Metal Ratios for Reduction by Pt, Nitrobenzene in 75% MeOH, 0.46 M $HClO_4$

(Metal × 100)/ carrier	Pt/C "Old" Darco rate	"New" Darco rate	(Metal × 100)/ carrier	Graphite rate
10	0.92			
5	1.6	1.35	0.5	1.15
4		1.47		
3		1.55		
2	1.85	1.65		
1	2.0	1.75	0.1	1.4
0.5	2.2	1.7	0.05	1.72
0.33	2.0	1.73		
0.2		1.6	0.02	1.9
0.1	0.76 Pt/C (Z)			
10		0.83		
5		1.33	0.5	0.3
3		1.49	0.2	0.95
1		1.74	0.1	2.29
0.5		1.67	0.05	1.67

Substrate: Cyclohexene in 90% MeOH, 1 mg of Pt (Pt/C B)

	"New" Darco 0.115 M $HClO_4$	Res Acid
5	1.34	1.13
3	1.4	1.2
2	1.45	1.15
1	1.6	1.15
0.5	1.6	

Table VI. Carrier–Metal Ratios for Reduction by Pd

Pd/C Metal × 100/ carrier	Rate	Pd/graphite Metal × 100/ carrier	Rate
Nitrobenzene: 0.5 mg Pd in 75% MeOH, 0.46 M $HClO_4$			
9	0.85	0.02–0.05	2.1
1–5	1.0	0.01	1.4
Benzyl Alcohol: 5 mg of Pd in 90% MeOH, 0.23 M $HClO_4$			
10	1.8	0.5	1.9
1–5	2.1	0.2	1.5

Table VII. Carrier–Metal Ratios with Rh/C

"New" Darco Metal × 100/carrier	Rate	Graphite[d] Metal × 100/ carrier	Rate
6	(0.3)[a]		
4	(0.8)[a]		
2	(1.2)[a]		
5 (cat. E)	2.36[b]		
1	2.16[c]		
0.6	2.4		
0.33	2.3		
0.16	1.0		
Benzene, 5.0 mg of Rh in 85% MeOH			
5 (cat. E, neutral)	1.8		
5	1.05[d]	0.5	1.1
1	0.5[d]	0.3	1.45
5 (E, neutral)	1.45[e]	0.25	1.5
5	0.7[d,e]	0.1	0.5
3	0.53[d,e]		
1	0.4[d,e]		

[a] Run on inferior cyclohexene. Result should be multiplied by ~3/2. [b] 0.25 mg of Rh. [c] Average of five runs varying between 2.08 and 2.24. [d] Res acid present = 0.03 M HCl. [e] In 80% MeOH.

selectively. In agreement with this, added acid had no effect on C_s lim in 65 and 60% methanol, though it increased the rate.

Whereas in methanolic solutions throughout this study, the rate increased with increasing methanol content (up to 95%) in acetic acid solutions maximal rates were in the neighborhood of 75% acetic acid (or of a hypothetical hydrate). In these acetic acid solutions the effects of added perchloric and hydrochloric acids on the rate were similar to their effects in methanol, but the C_s lim was unaffected. The solvent itself sufficed to bind the aniline formed.

These studies with nitrobenzene appear to support rather thoroughly the arguments on the effect of solvents stated in the introduction. Beyond checks on the validity of these principles, it was not felt necessary to make further examinations in detail. Solvent variation in reductions of cyclohexene, benzene, and benzyl alcohol was, in any case, restricted by the properties of the reduction products.

With acetophenone and cyclohexene (Tables IB and IC) as substrates, the effect of acid on the activity of platinized charcoal was much the same as above if we take into account the point that acid is now irrelevant to product inhibition (probably not significant anyway).

The palladized charcoal reductions of nitrobenzene and cyclohexene (Tables IIA and IIG) were relatively insensitive to acid in respect to rate, whereas the substrates possessing a C–O bond are highly sensitive. The extreme case is benzyl alcohol whose hydrogenation rate is almost entirely acid dependent leading to the hypothesis that it is the protonated species that is being reduced.[28] The benzyl ethers were also highly sensitive to the *presence* but were less so to the concentration of acid. Their reduction rates in neutral solution were low but appreciably higher than that of benzyl alcohol and clearly distinguishable from zero. The reduction rates of these ethers were lower than that of benzyl alcohol (except in neutral solution) but did not differ significantly from each other. The less water soluble ether had a lower value of C_s lim as would be expected.

The function C_s lim was appreciably lower in acetophenone reductions catalyzed by Pd/C than with Pt/C, permitting use of a smaller charge. On the other hand, cyclohexene was adsorbed less strongly on Pd.

The reductions of cyclohexene, acetophenone, benzene, and nitrobenzene by rhodium on carbon were examined. Benzaldehyde, as reported by Dunworth and Nord,[29] is reduced slowly, in fact, very much more slowly than by palladized charcoal. The neutral rate with acetophenone is not far below that with palladium, but acid inhibits this catalyst with acetophenone as with benzene. The reduction of cyclohexene was little affected by acid and that of nitrobenzene was promoted, as also by alkali.[28] The reduction of nitrobenzene by Rh/C is very slow as compared to that by palladium or platinum while the ability of Rh/C to reduce aromatic rings is one of its special recommendations. It is not clear to what extent this is a matter of adsorption. Ni-

trobenzene is clearly rather poorly adsorbed on rhodium, as shown by the high value of C_s lim. Benzene is not very strongly adsorbed but may be more strongly than on platinum. (Since Pt/C does not reduce benzene, comparison by C_s lim is impossible.)

Dunworth and Nord[29] had remarked on the exceptional activity of Rh/C in the reduction of unsaturated fatty acids with isolated double bonds. They reported activity about twice that of Pd/C but studied only a 5% catalyst that may have resembled catalyst E. The activities presented in Tables IIIA and VII are the highest observed in this study, and the turnover rate compares favorably with those reported for enzymes.[30] This reduction is also peculiar in that, while the rate is little affected by acid and is slightly promoted by alkali in low concentration (but inhibited in higher), the C_s lim is markedly dependent on the acidity.

These disparate effects of acidity and alkalinity between these three catalytic metals and among the various substrates suggest that the fine details of catalytic hydrogenation may vary markedly from case to case.

The Metal–Carrier Ratio. Two samples of charcoal (Darco) were used which were not quite equivalent as carriers. Roughly a 3% Pt/C with the newer charcoal was considered comparable to a 5% with the older. Two methods of preparation were used, differing in that one (B) employed a trace of Pd to initiate deposition of metal while the other (Z) did not. With the new charcoal, the two methods gave very similar preparations, maximal activity being at about the 1% catalyst. The "old" charcoal gave a somewhat higher maximal activity in the range of 100–300 parts of carrier to 1 of metal. The platinized graphites required much more carrier with some variation according to the method of preparation. Pt/graphite (B) was not pushed to a point of diminishing activity with increased amount of carrier. The difficulty of handling the rather large amounts of solid in the small amount of aqueous solution desired imposed a limit of convenient operation. (This was still more forcing when larger amounts of metal would be needed.)

With palladium, the carrier–metal ratio was less critical; no significant differences were observed in the reduction of nitrobenzene from 1% catalyst to 5% catalyst. Curiously, the palladized graphite was markedly more active for this purpose than palladized charcoal.

Against benzyl alcohol as substrate, palladized charcoal was almost as efficient as 10% catalyst as in the range 1–5%. The palladized graphites were slightly less active, but the range of composition was not thoroughly explored.

The situation with rhodium is complicated by unknown facts as the manufacturers of catalyst E have consistently refused to divulge any information as to the preparation of their catalysts.[31] Consequently, it is impossible to correlate the properties with the method of formation. As compared to the Rh/C prepared in this laboratory, catalyst E was clearly superior for reduction of benzene and acetophenone, clearly inferior against cyclohexene, and extremely erratic against nitrobenzene.

Against cyclohexene, maximal efficiency lay in the range of 0.3–1% catalysts. Against benzene a higher ratio of metal to carrier (ca. 5%) was more effective. Catalyst E was more effective than the Rh/C prepared immediately before reductions. The difference appeared to be due in part to the inhibitory effect of acidity and chloride ion; however, the data in Table IIIB did not reconcile the disparities entirely. Rhodium on graphite was very nearly as effective as catalyst E and maximal activity here lay in the region of 0.25–0.3% catalysts.

Catalyst E was also superior to those prepared in this laboratory in the reduction of acetophenone. A 5% catalyst was more effective than a 1% preparation.

In the reduction of nitrobenzene, there was little variation in the catalysts prepared here from 1% to 5%. Catalyst E gave a high rate in the presence of alkali, but in acid and neutral conditions started out with a high activity which was halved within 5 min. The function C_s lim is rather high in this reduction (corresponding to relatively poor adsorption of nitrobenzene on rhodium), but that alone cannot account for this behavior which was observed in the catalysts prepared here *only* in the presence of alkali. The results suggest that the rhodium deposits are subject to alteration in the early stages of the reduction of nitrobenzene.

While the original hypothesis as to the graphitic nature of the charcoal surface seems to be tolerably borne out, it is evident that quite minor variations in the charcoal may be responsible for considerable variation.

Acknowledgment. The hospitality afforded the author by Dr. George Bosworth Brown and his department in the Walker Laboratory of the Sloan-Kettering Institute was indispensable to the accomplishment of this work and is gratefully acknowledged.

Registry No.—Platinum, 7440-06-4; palladium, 7440-05-3; rhodium, 7440-16-6; nitrobenzene, 98-95-3; acetophenone, 98-86-2; cyclohexene, 110-83-8; benzaldehyde, 100-52-7; benzyl alcohol, 100-51-6; benzyl methyl ether, 538-86-3; benzyl isopropyl ether, 937-54-2; benzene, 71-43-2.

References and Notes

(1) This investigation was supported in part by funds from the Public Health Service Research Grant CA-08748 from the National Cancer Institute.
(2) Some years ago, at the suggestion of Mr. Emil Lorz, palladized and platinized graphites were prepared. These catalysts resembled qualitatively the corresponding metallized charcoals. Since ordinary charcoals are known to be extensively graphitic in structure, it seemed probable that metallized charcoals are essentially metallized graphites. A nongraphitic charcoal prepared by the reaction of sodium with hexachlorobenzene [J. Gibson, M. Holohan, and H. L. Riley, *J. Chem. Soc.*, 456 (1956)] afforded catalysts of minimal activity.
(3) (a) H. C. Yao and P. H. Emmett, *J. Am. Chem. Soc.*, **81**, 4125 (1959); (b) *ibid.*, **83**, 796 (1961).
(4) (a) A. S. Hussey, G. W. Keulks, G. P. Nowack, and R. H. Baker, *J. Org. Chem.*, **33**, 610 (1968); (b) A. S. Hussey and G. P. Nowack, *ibid.*, **34**, 439 (1969).
(5) Equation 1 is equivalent to eq 1 of Yao and Emmett.[3a] Most of the real differences in the kinetic treatment of the present and the above-cited papers are in the evaluation of the θ factors.
(6) A further question which is not readily answered is whether hydrogen and substrate are adsorbed independently or competitively. For palladium on alumina, Hussey and Nowack[4b] incline toward independent adsorption, and the data of the present work are consistent with this. For indications that, taken together, suggest the contrary, cf. E. B. Maxted and H. C. Evans, *J. Chem. Soc.*, 1750 (1939); E. B. Maxted and G. T. Ball, *ibid.*, 2778 (1954).
(7) Yao and Emmett[3] take β as 1. The actual value of β is irrelevant to the present discussion as long as it is small.
(8) In the presence of poison, the term $\alpha_i C_i$ is relatively large and θ_s must diminish with C_s. However, by operating above the C_s lim in unpoisoned situations, it is possible to observe a reasonably linear reduction rate for a long enough period to render extrapolation to zero time unnecessary.
(9) A considerable amount of exploratory work was done with dimethyl maleate, maleic acid, and cinnamic acid. These substrates were abandoned when it was found that acetic ion was a weak inhibitor and probably other anions of carboxylic acids. There was also some concern that in alcoholic–aqueous solutions the nature of the substrate could change, especially if esterifications should be catalyzed on the active surface.
(10) Dr. Robert Klein of this Institute had experienced difficulty in completing the debenzylation of some methylpentoside 3,5-dibenzyl ethers. It later became apparent that poisoning (presumably originating in the benzyl chloride used in synthesis) was involved. The rates of hydrogenolysis of the mono- and dibenzyl sugars appear to have been in a ratio of about 1:3 which could be a function of adsorption coefficients. If only the ring, the methylene, and the O need lie on the catalyst surface, it would seem that the other O-bound structure must be very bulky to interfere, unless it bears another point of attachment.
(11) G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith, and W. E. Vaughan, *J. Am. Chem. Soc.*, **58**, 137, 146 (1936), give 28.6 and 49.8 kcal/mol for the reduction of cyclohexene and benzene at 80 °C.
(12) The small samples (2 and 3 ml, respectively) of nitrobenzene and cyclohexene were added after the temperature had been set.
(13) The effect of a 1 °C variation in temperature on rate varies from substrate to substrate. For cyclohexene, Hussey et al.[4a] give a rather low energy of activation, 6–7 kcal/mol. This leads to a temperature effect

for 1 °C less than other uncertainties. Yao and Emmett[3a] give 13–14 kcal/mol for the energy of activation in the reduction of nitrobenzene. According to that figure, an increase in temperature of 1 °C should produce a rate increase of about 8%. No figures are available for the other substrates used. One suspects that the energy of activation for hydrogenation of benzene may be relatively high.

(14) W. T. Olson, H. F. Hipscher, C. F. Buess, I. A. Goodman, I. Hart, J. M. Lamneck, Jr., and L. C. Gibbons, *J. Am. Chem. Soc.*, **69**, 2451 (1947).

(15) Since the acetophenone reductions were not run near to completion, it was possible and convenient to recover substrate after filtration from catalyst, a number of batches being combined. Control runs were made on all batches, recovered or new, before use.

(16) Commercial acetophenone could also be purified by repeated passages through Raney nickel columns, followed by distillation. This process had no advantage over synthesis. Aside from the complications of handling very large amounts of substrate in solutions, the adsorption is not very efficient. E. B. Maxted [*J. Chem. Soc.*, 624 (1947)] considered thiophene a relatively weak poison which acts mainly through reduction to tetrahydrothiophene. Under nonreducing conditions, the inhibitor competes poorly with the much larger amount of substrate. An attempt at a similar column purification of benzyl methyl ether was unsuccessful.

(17) $C_{i\ 1/2}$ is the concentration of poison that lowers the reduction rate to half the standard value.

(18) Darco G-60 was used. In the earlier part of this work, the sample was a special one obtained from the manufacturer (Darco Department, Atlas Powder Co.) and prepared by the method in use when the author first employed this method (ca. 1940). A later sample, here called "New Darco," was the usual commercial grade of the present time.

(19) The method of E. Ott and R. Schröter, *Ber.*, **60**, 624 (1927).

(20) R. Baltzly, *J. Am. Chem. Soc.*, **74**, 4586 (1952).

(21) H. I. Zeliger, *J. Catal.*, **7**, 198 (1967).

(22) Zeliger reported that chloroplatinic acid was reduced by hydrogen and platinum deposited on finely divided carriers *wetted* by the solution. This does not appear to have been investigated previously since it was "known" that hydrogen did not precipitate metal from chloroplatinic acid solutions.

(23) Hussey and co-workers[4a] reported acetic acid to have been unusable in their studies. This may correspond to the greater precision of their operations or the acetic acid modifying the nature of their support (activated alumina).

(24) That such an adsorption of acid exists has been suspected but not demonstrated previously. Cf. ref 20.

(25) Perchloric acid was preferred. The sulfuric acid available gave consistently *lower* rates for about the first 5 min of reductions. It is suspected that traces of nitrous or nitric acid were present which acted initially as poisons but were then reduced to ammonia which would have been nontoxic under the conditions.

(26) Cf. M. Freifelder, "Practical Catalytic Hydrogenation", Wiley-Interscience, New York, N.Y., 1971, p 26. Freifelder appears to be the first to suspect this inhibitory action, which, however, he believed confined to nonaqueous solutions.

(27) Phosphoric and oxalic acids were intermediate between perchloric and hydrochloric. The oxalic acid may have produced some inhibition as its anion.

(28) That a significant amount of $BzOH_2^+$ is present is suggested by the observation that when the charge of benzyl alcohol was added to the solvent containing perchloric acid the temperature of the solution rose about 2 °C. When acid was absent, a fall in temperature of about the same size was noted. These temperature effects were not observed with the benzyl ethers.

(29) W. P. Dunworth and F. F. Nord, *J. Am. Chem. Soc.*, **74**, 1459 (1952).

(30) The rates of 2–2.4 mmol/min per 0.1 mg of Rh give turnover rates of about 2×10^3 mol atom^{-1} min^{-1}: reported for invertase, 4×10^3, carboxylase, 10^3, choline esterase and catalase, ca. 10^6. The figure of 2×10^3 is, of course, based on the number of Rh atoms on the catalyst sample, whereas the enzyme figures are per active site, usually one to a molecule. If one assumes that the metal plaques average five atoms thick and that an adsorbed molecule of cyclohexene obscures the surface of four atoms of Rh, the turnover rate becomes 4×10^4.

(31) Specifically they were asked whether they employed (a) reduction by hydrogen, (b) chemical reduction, or (c) ignition of carrier impregnated with metal salt. (All these methods have been employed in the past for one catalyst or another.) They were also asked what charcoal they use.

Studies on Catalytic Hydrogenation. II. Poisoning by Nucleophiles[1]

Richard Baltzly[2]

Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Received June 3, 1975

A selected group of nucleophilic inhibitors has been studied in the reduction of different types of substrates and with platinum, palladium, and rhodium on carbon catalysts. Variation of solvent affects the adsorption of inhibitors along the same lines as with substrates. Higher molecular inhibitors, having high intrinsic toxicity through obstructing access to an extended surface, also show diminished adsorption coefficients. Certain irregularities in poisoning tendencies may be due to differing details of hydrogenation of different substrates.

The extensive investigations of catalyst poisoning by Maxted[3] permit a division of poisons into two main classes,[4] those attaching themselves to the catalyst through an unshared electron pair, and a second group of metallic cations—the subject of the third communication of this series.

Poisons of the first class are acting as nucleophiles and a logical extension of the original concept led to the recognition of bases and of iodide ion as poisons. Weaker nucleophiles such as chloride,[5] bromide, and acetate (or carboxylate ions, generally) have not usually been recognized as inhibitors in default of specific investigation. Two major questions left unanswered by Maxted's work were:

1. To what extent are his generalizations, based mainly on the study of Willstätter platinum and, to a lesser degree, of a supported nickel catalyst, valid for hydrogenation catalysts in general?

2. To what extent are toxicities altered by comparison with different substrates and by changes in solvent?

It seemed worthwhile, therefore, to attempt a study using several metallized charcoals with some variation of substrates and of solvent conditions and a representative group of poisons, though not the very large selection examined by Maxted.

In the preceding communication, the effect of solvent conditions on reaction rate has been considered, and it has been shown that under suitable conditions the rate may be of zero order in respect to hydrogen pressure and substrate concentration: i.e., the adsorption terms approximate the value of 1. Under such conditions, presence of poison should modify the substrate adsorption term (θ_s) so that

$$\theta_s = \frac{\alpha_s C_s}{\alpha_s C_s + \alpha_i C_i} \qquad (1)^6$$

and at half-poisoning, $\theta_s = \frac{1}{2}$ and $\alpha_i C_i = \alpha_s C_s$.

Plots of rate against poison concentration according to eq 1 with $C_{i\ 1/2}$ as the unit of poison concentration give theoretical poisoning curves such as curve A of Figure 1. The characteristic feature of such a curve is that at $C_i = 2C_{i\ 1/2}$ the rate should be one-third of the standard and at $C_i = \frac{1}{2}C_{i\ 1/2}$, two-thirds. (Obviously, other simple relationships are also deducible.) On this basis in a poisoning study, one

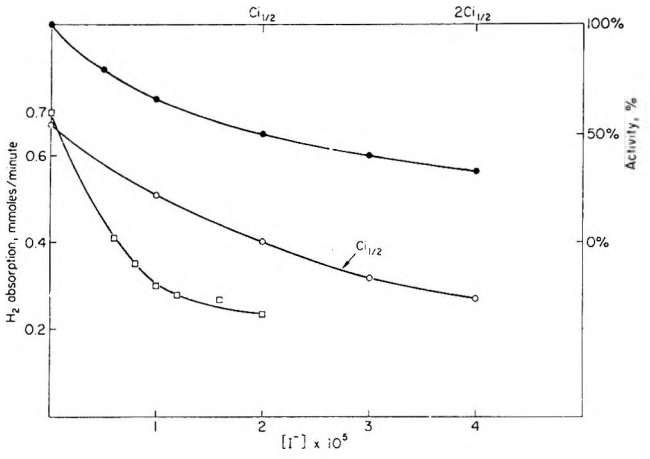


Figure 1. A, ●—●, theoretical poisoning curves; B, ○—○, I^- vs. PhCOMe in 75% MeOH; C, □—□, I^- vs. PhCOMe in 99% MeOH.

can easily discern if eq 1 is being approximated. Three main conditions became apparent that produced major deviations.

1. With quite weak poisons, such as chloride and bromide, increasing concentrations so modify the medium that half-poisoning is not attainable. An example is shown in Figure 2 for the reduction of nitrobenzene in 75% methanol over platinum (and by the data of Table IA of the preceding communication). If HCl is the source of Cl^-, the anion concentration cannot be increased without increasing acidity. The acidity tends to increase the rate, and beyond about 0.6 M the rate increases. If NaCl is the source of chloride, increasing salt concentration also increases the activity, and presumably the adsorption coefficient of the substrate.

2. With very strong poisons, a large part of the inhibitor may be resident on the catalyst, and the real concentration in solution may be much less than the apparent concentration. This situation can be dealt with by cross-over experiments (vide infra). Whether this situation can possibly exist is deducible by consideration of the quantities present. A 1-mg batch of platinum contains approximately 5×10^{-6} g-atom, not all of which are on the surface.[7] When $C_{i\,1/2} = 10^{-4}$, the amount of inhibitor in 50 ml is 5×10^{-6} *mol*—capable of covering all the atoms of metal wherever situated. At such or higher concentrations of inhibitor, the true and apparent C_i values must be very close.

3. There is evidence of competing interaction of inhibitor and substrate. This applies principally to the cationic inhibitors to be taken up in the following communication. Because of anticipation of such interaction, however, it was felt inadvisable to examine some poisoning situations; e.g., the inhibition of the reduction of benzaldehyde by cyanide or butyl mercaptan.

The considerations advanced in the preceding communication as to the effect of solvent changes on the adsorption coefficient of the substrate should apply also to an inhibitor. Thus, an inorganic poison such as the anion of a neutral salt should be more toxic in a less aqueous solvent. This is usually the case: curve B of Figure 1 is a poisoning curve of iodide ion vs. acetophenone in 75% methanol with platinized charcoal. It closely resembles the theoretical curve A. Curve C is for iodide poisoning in 99% methanol and is clearly quite different.[8] Not only is the toxicity of iodide greater in the less aqueous solvent, but the curve appears discontinuous. Crossover experiments showed that at half-poisoning, the iodide was about evenly divided between catalyst and solution and that $C_{i\,1/2}$ was in fact 3×10^{-6} rather than 8×10^{-6}, as suggested by curve C.

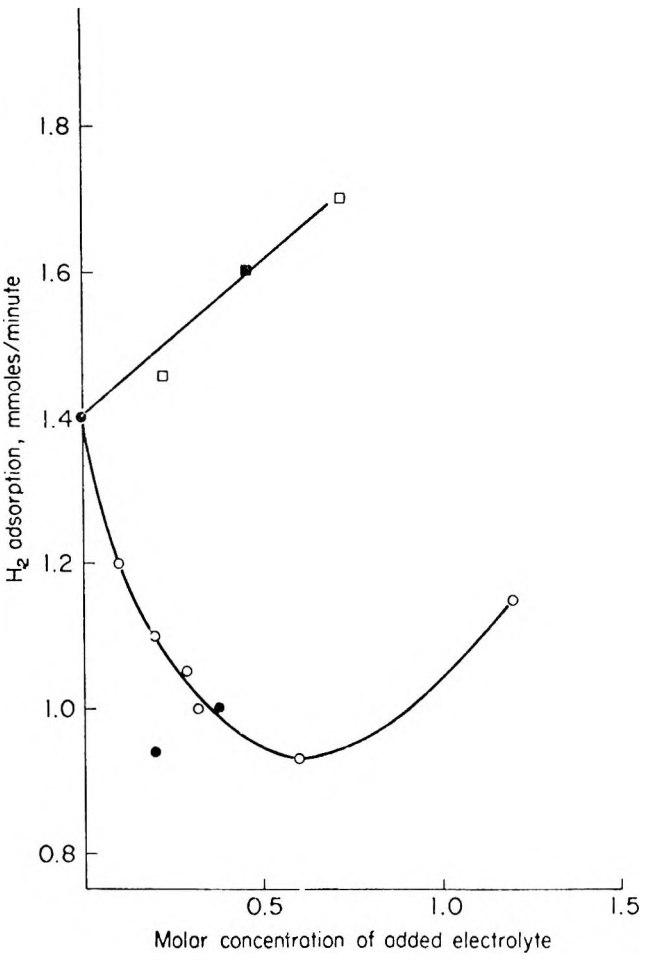


Figure 2. Effect of electrolytes on rate of reduction of $PhNO_2$ in 75% MeOH, 1 mg of Pt as 5% Pt/C: □, H_2SO_4; ■, $HClO_4$; ○, HCl; ●, NaCl.

Choice of Poisons. Butyl mercaptan and dibutyl sulfide were selected from the much larger list studied by Maxted and Evans,[9] in part because of relative ease in handling, in part to investigate a particular point. These authors observed that toxicity in their series of sulfur compounds increased with size (the relative toxicities of these two compounds being 6 and 15 referred to hydrogen sulfide as 1). Their interpretation was that the poison, being bound by the sulfur to one platinum atom, shielded also a number of neighboring atoms. Calculations suggested that dimethyl sulfide could block the surface of nine platinum atoms. In fact, the relative toxicity of dimethyl sulfide to hydrogen sulfide was 9 when corrected for the amounts of the two poisons *on the catalyst*. Based on the amounts of poison in the reduction mixtures, however, the relative toxicity was only 7.1. The dimethyl sulfide was less completely adsorbed.

It would seem that a corollary of Maxted's interpretation would require that the bulkier molecule, while occluding a greater surface area, should be exposed to stronger forces tending to its removal, wherefore it should have a smaller adsorption coefficient. Unfortunately, Maxted and Evans did not examine the distribution of their higher molecular poisons. In the present investigation it was expected that the relative toxicities of dibutyl sulfide and butyl mercaptan in competition with differently absorbed substrates might elucidate this point.

Cyanide and iodide were taken as typical strong poisons and ammonia, acetate, and alkalinity as relatively weak ones. Alkali (indicated as OH^-–OMe^-) is somewhat indefinite under the conditions, the actual concentrations of the

Table I. Half-Poisoning Concentrations. Substrate Nitrobenzene

	C_s in = 0.39					
	Pt/C (1 mg Pt)		Pd/C (0.5 mg Pd)		Rh/C (5 mg Rh)	
Inhibitor	Solvent	$C_{i\,1/2}$	Solvent	$C_{i\,1/2}$	Solvent	$C_{i\,1/2}$
OH^-–OMe^-	99% MeOH	$\sim 7 \times 10^{-2}$	n.i.[e]		Pr[e]	
N_3^-	95% MeOH	$> 8 \times 10^{-3}$	75% MeOH	$\sim 5 \times 10^{-3}$		
I^-	90% MeOH	$\sim 4 \times 10^{-3}$ [a]	90% MeOH	1.8×10^{-6} [b]		
			75% MeOH	1.8×10^{-6} [b]		
CN^-	75% MeOH	4×10^{-5}	75% MeOH	4×10^{-5}		
	65% MeOH	6×10^{-4} [b]	90% MeOH	2×10^{-5}		
Bu_2S	75% MeOH	2×10^{-6} [b,c]	75% MeOH	2×10^{-6} [b]	75% MeOH	10^{-5}
BuSH	75% MeOH	1.7×10^{-6} [d]	75% MeOH	1.2×10^{-6} [b]	75% MeOH	1.5×10^{-5}

[a] Done with Pt/C (Z). [b] Poisoning data in fair agreement with theoretical curves. [c] From crossover experiments. Apparent $C_{i\,1/2} = 2.6 \times 10^{-6}$. [d] From crossover experiments. Apparent $C_{i\,1/2} = 5 \times 10^{-6}$. [e] n.i. = no inhibition; Pr = promotion.

Table II. Half-Poisoning Concentrations. Substrate Acetophenone

	Pt/C (10 mg Pt) C_s in = 1.7		Pd/C (5 mg Pd) C_s in = 1.38		Rh/C (5 mg Rh) C_s in = 1.7	
Inhibitor	Solvent	$C_{i\,1/2}$	Solvent	$C_{i\,1/2}$	Solvent	$C_{i\,1/2}$
OH^-–OMe^-	99% MeOH	10^{-4} [a]	90% MeOH	$\sim 10^{-4}$	75% MeOH	6×10^{-3}
Acetate	99% MeOH	10^{-4} [a]			75% MeOH	$\sim 2 \times 10^{-2}$
NH_3	99% MeOH	5×10^{-4} [a]	90% MeOH	7×10^{-4}	75% MeOH	$\sim 10^{-2}$
I^-	99% MeOH	3×10^{-6} [b]	90% MeOH	5×10^{-6} [a]	75% MeOH	4×10^{-5} [a]
	75% MeOH	2.8×10^{-5} [a]				
CN^-	99% MeOH	2×10^{-6} [a]				
	75% MeOH	4×10^{-5} [a]				
Bu_2S	75% MeOH	2.5×10^{-6} [c,e]	90% MeOH	3×10^{-5} [a,e]	75% MeOH	1.6×10^{-5} [a]
BuSH	75% MeOH	3×10^{-6} [d,e]	90% MeOH	1.4×10^{-5} [a,e]	75% MeOH	8×10^{-5} [a]

[a] Poisoning data in fair agreement with theoretical curve. [b] From crossover experiments. Apparent $C_{i\,1/2} = 8 \times 10^{-6}$. [c] From crossover experiments. Apparent value about the same. [d] From crossover experiments. Apparent $C_{i\,1/2} = 8 \times 10^{-6}$. [e] Run in 0.115 M $HClO_4$.

two anions being unknown. Since, however, these other anions and ammonia were to be examined in previously neutralized solution, it was essential to know what effect small amounts of OH^-–OMe^- would have on the rate. Inhibition with chloride and bromide was readily demonstrated, but half-poisoning could seldom be attained. Later, attempts were made in the reduction of benzene and acetophenone on Rh/C where the substrates seemed weakly absorbed. Azide ion was examined in several reductions because of possible inhibition from it when azide is used to introduce the amino group into nucleosides and a noncrystalline intermediate is hydrogenated.[10]

Experimental Section

Materials. The preparation of catalysts and purification of substrates have been discussed in the preceding communication. Standard solutions of NaCl, KI, NaBr, KCN, and NaCN, NaN_3, K and Na acetate, and NH_4Cl were prepared in methanol, usually M/10 in concentration and diluted further when required. Alkali was 1 M NaOH diluted 1:10 in methanol. Dibutyl sulfide (Aldrich) and butyl mercaptan (E.K.) were prepared as M/10 solutions in methanol, which were diluted further as needed. The more dilute solutions of butyl mercaptan were prepared shortly before use.

Methods. The procedure for poisoned reductions was mainly the same as in the kinetic runs described in the previous communication except that when the poison concentration was low (below 10^{-3}), it was necessary to shake in vacuo before admitting hydrogen. This shaking period was 2 or 3 min with very low poison concentrations.[11]

Somewhat greater tolerance of temperature deviations was possible. In exploratory runs when the rate was not close to the critical half-poisoned value, an informative result could be obtained without concern for the temperature. When the rate was in the vicinity of half that of the standard, an approximately constant range covering the consumption of 5–10 mmol of hydrogen (and lasting 5–20 min) was the best that could be expected.[12] The hydrogenation was usually stopped 3–5 min after a significant drop in rate had been observed. As cooling was generally excessive in this period, it was considered normal for the final temperature to be about 1 °C low.

Standards. These are given in the preceding communication. Since it was desired to avoid uncertainty as to the nature of the poison, all these inhibitors except the sulfur compounds were added to neutralized solutions, and poisoning was referred to the *neutral* reduction rate. Two methods were employed with ammonia. The first, used with platinized charcoal, was to add to the catalyst preparation sufficient of a standard solution of ammonia in methanol to neutralize the residual HCl and produce the desired concentration of ammonia. The second procedure, regarded as preferable, was to add NH_4Cl solution to give an M/100 solution and, thereafter, to add M/10 alkali (in methanol) to neutralize the residual HCl and liberate the amount of ammonia desired. With this procedure, the reference standard was the rate in a neutralized solution M/100 in NH_4Cl (generally about 10% lower than the neutral rate).

Under the above conditions, inhibition by ammonia could be differentiated clearly from hydroxide (or alkoxide) poisoning. This was not the case with the stronger base pyrrolidine. Assuming that the dissociation constants known for aqueous solutions were approximately valid in the partly methanolic solutions employed, it could not be determined whether toxicity was due to pyrrolidine base or to hydroxide and alkoxide predictably present.[13]

The sulfur compounds were studied in acid solution, and the poisoned runs referred to acid rates except for the reductions of benzene and acetophenone by Rh/C, which were in neutral solution.

Crossover Experiments. This procedure is a variant of that devised by Maxted and Evans[9c] to determine the distribution of poison between catalyst and solution. The essential difference is due to the physical properties of the catalysts used. Maxted and Evans operated with Willstätter platinum, a relatively dense powder, from which almost all of the solution could be drawn off. While platinized charcoal, the only one of the present catalysts regarded as stable enough for this type of experiment, settles fairly well, clearly not all the solution could be removed.

Accordingly, two identical batches of catalyst were prepared. To the first (A) methanol was added to give 50 ml of the desired composition. The solution was mixed and allowed to stand overnight stoppered. To the second batch of catalyst (B) was added solvent,

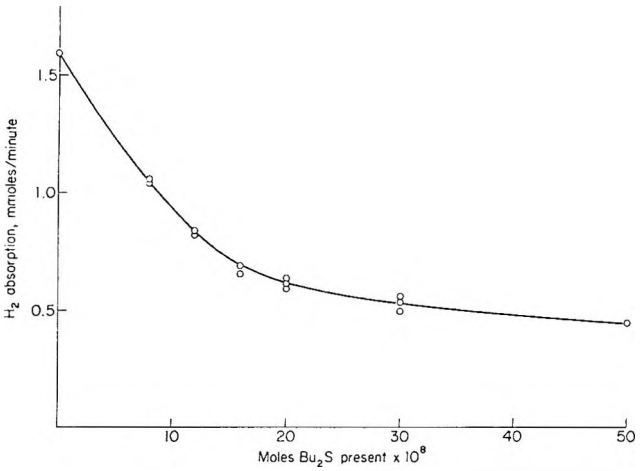


Figure 3. Poisoning curve: Bu_2S vs. $PhNO_2$ in 75% MeOH, 0.46 M $HClO_4$, 1 mg of Pt as Pt/C (5%).

substrate, and a quantity of poison sufficient to produce a known degree of inhibition, conveniently with about one-third of standard activity. (With reference to a previously determined poisoning curve such as that shown in Figure 3.) The mixture, now with a volume of 50 ml, was placed on the reducing apparatus, evacuated, and shaken for 5 min. It was then allowed to settle overnight in vacuo. In the morning, 40 ml of the supernatant of bottle A was removed and discarded. Forty milliliters of the supernatant of bottle B was transferred to A plus one-fifth of the standard charge of substrate (and of $HClO_4$ if used). To bottle B was added $\frac{4}{5}$ of the standard charge of substrate (and acid) plus solvent to 50 ml. The two batches were then reduced and the rates determined. By reference to the poisoning curve, it was then possible to determine how much poison was in each reduction mixture. The sum of these quantities should equal the amount initially placed in B (a deviation of ±10% was considered acceptable). The container A had, during reduction, $\frac{4}{5}$ of the poison present in solution. Container B held $\frac{1}{5}$ of the poison in solution plus that adsorbed on the catalyst. The distribution, of course, applied to the poisoning level of B as originally equilibrated. From this, assuming the validity of the theoretical curve, the half-poisoning concentration was deduced.

It is, of course, obvious that this operation must be futile unless a considerable proportion of the poison is present in both solutions. It is, therefore, of no use with weak poisons (if, for example, one should wish to learn if an apparent inhibitor is really being adsorbed).

Results and Discussion

Tables I–IV show the half-poisoning concentrations obtained. The azide data are given as tentative. This inhibitor was relatively weak, and there was some question as to its stability under the conditions.[14]

In nitrobenzene reductions with Pt/C, iodide behaved rather irregularly. Speculations are possible as to reversible involvement in the reduction process whereby part of the poison could have a different valence state temporarily. All that can be said on this definitely is that at the end of one such reduction, the iodide introduced could be quantitatively recovered as silver iodide.

Cyanide seemed to be stable in the presence of platinum but to be vulnerable to the larger amount (5 mg) of palladium used in acetophenone reductions. With the rhodium catalysts all inhibition was gone after 2 min of hydrogenation.[15]

With the sulfur compounds, especially dibutyl sulfide, there was a tendency with the lower concentrations of poison for the rate to *increase* after about 10 min. This is interpretable as due to rupture of the R–S bond to liberate a compound of lower toxicity.[16] In such cases the level rate *before* the increase was regarded as valid.

The difficulties encountered in cyclohexene reductions with the enormously active rhodium catalyst have been mentioned in the previous communication. The data in the last column of Table III are tentative, except for the case of NH_3 poisoning, since obtained on substrate giving inferior ($\frac{2}{3}$–$\frac{3}{4}$ of standard) control values. They are probably correct within a factor of 2.

Only a few poisoning data are given here for the Pd/C reductions of benzaldehyde, benzyl alcohol, and benzyl methyl ether. With the benzyl compounds, the neutral rate was not usefully above zero. With benzaldehyde, most of these poisons could be expected to react with the substrate.

Table III. Half-Poisoning Concentrations. Substrate Cyclohexene[d]

Inhibitor	Pt/C (1 mg Pt) 3% catalyst	Pd/C (0.5 mg Pd) 3% catalyst	Rh/C (0.1 mg Rh) 1% catalyst
$\bar{O}H$–$\bar{O}Me$	5×10^{-5} [a]	Pr	Pr
Acetate	8×10^{-5}	$4\text{-}5 \times 10^{-2}$	(3×10^{-3})[b]
NH_3	10^{-3}	1.2×10^{-3}	1.5×10^{-3}
N_3^-		$\sim 6 \times 10^{-3}$	
I^-		1.5×10^{-4} [a]	(1.6×10^{-6})[b]
CN^-	8×10^{-7}	8×10^{-5}	
Bu_2S	7×10^{-7} [a,c]	3×10^{-6} [c]	(6.4×10^{-7})[b,c]
BuSH	4×10^{-6} [a,c]	3.2×10^{-6} [c]	(1.6×10^{-6})[b,c]

[a] Poisoning data in fair agreement with theoretical curves. [b] Tentative values obtained with relatively poor substrate. [c] 0.023 M $HClO_4$ present. [d] 90% MeOH, C_s in = 0.6.

Table IV. Miscellaneous Poisoning Data

Catalyst	Substrate	Solvent	Inhibitor	$C_{i\,1/2}$
Rh/C (E)[a]	Benzene	85% MeOH	Cl^-	$\sim 2 \times 10^{-2}$
	(C_s in = 2.0)		Br^- [b]	8×10^{-3}
Rh/C (E)[a]	(C_s in = 2.0)		I^- [b]	5×10^{-5}
Rh/C (E)[a]	(C_s in = 2.0)		$\bar{O}H$–$\bar{O}Me$	8×10^{-3}
Rh/C (E)[a]	(C_s in = 2.0)		NH_3[b]	5.5×10^{-3}
Rh/C (E)[a]	(C_s in = 2.0)		Bu_2S[b]	1.5×10^{-5}
Rh/C (E)[a]	(C_s in = 2.0)		BuSH	10^{-4}
Rh/C (E)[a]	Acetophenone	75% MeOH	Cl^-	$>2 \times 10^{-2}$
	(C_s in = 1.7)	75% MeOH	Br^-	10^{-2}
Pd/C	Ph CHO	90% MeOH	I^- [b]	10^{-5}
	(C_s in = 2.08)	(Neutral)		
Pd/C	(C_s in = 2.08)	(0.23 M $HClO_4$)	Bu_2S[b]	3×10^{-5}
	Ph CH_2 OH	90% MeOH		
	(C_s in = 1.95)	0.23 M $HClO_4$	Bu_2S[b]	1.2×10^{-5}
	(C_s in = 1.95)	0.23 M $HClO_4$	BuSH[b]	2.4×10^{-5}
	Ph CH_2 OMe	75% HAc	Bu_2S[b]	2.5×10^{-5}
	(C_s in = 1.58)	0.23 M $HClO_4$	BuSH	3.5×10^{-5}

[a] All rhodium reductions done in neutral solution. [b] Poisoning data in fair agreement with theoretical curve.

Table V. Analysis of Crossover Experiments

Substrate	Inhibitor	C_s in/$C_{i\,1/2} = \alpha_i/\alpha_s$	Activity at equilibration level, %	Inhibitor on catalyst, mol	M[a]/i
$PhNO_2$	Bu_2S	2×10^5	33	10^{-7}	50
(75% MeOH)	BuSH	2.3×10^5	40	2×10^{-7}	25
(75% MeOH)	Cd^{2+}	6.6×10^4	25	2×10^{-7}	25
PhCOMe					
(75% MeOH)	Bu_2S	6.7×10^5	33	1.5×10^7	330
(75% MeOH)	BuSH	5.7×10^5	33	5.5×10^7	90
(75% MeOH)	Cd^{2+}	1.1×10^5	33	4×10^7	125
(99% MeOH)	I^-	5.7×10^5	33	2.8×10^7	200

[a] g-atoms of Pt in catalyst/mol of inhibitor adsorbed.

General Aspects. Inspection of Tables I–IV shows two major classes of inhibitors: strong poisons—cyanide, iodide, and the sulfur compounds—and weak inhibitors—ammonia, azide, acetate, and alkali. The half-poisoning concentrations of the strong poisons are low, and it is probably not justified to attempt fine analysis except for the crossover experiments.

The half-poisoning concentrations of the weak poisons cannot be seriously in error because of extensive adsorption. Consideration of these and of a few of the situations with stronger poisons reveals certain anomalies (conditions in which an inhibitor, certainly adsorbed because of the result with one substrate, has no effect or very much less effect in the reduction of another substrate by the same catalyst). Particularly marked is the behavior of alkali in the reduction of nitrobenzene on all three metals and in the reduction of cyclohexene over Pd and Rh. The reductions of acetophenone on all three metals and of cyclohexene on Pt are clearly inhibited; also, the behavior of the iodide in the platinum-catalyzed reduction of nitrobenzene. It seems possible that these anomalies are related to the existence of alternative reduction schemes (differing in fine detail) for some of which the initial adsorption and first attachment of hydrogen may not be uniquely rate determining. Nitrobenzene is almost certainly reduced stepwise. Reduction of olefins at low hydrogen pressure has frequently been observed to be accompanied by bond migration and occasionally aromatization.[17] Thus, residence of substrate on the catalyst surface is of finite though small duration and interference by other adsorbed substances may at times affect the overall rate.

It had been anticipated that inorganic poisons would be less potent in more aqueous solutions. This is borne out by comparisons of the $C_{i\,1/2}$ data for cyanide poisoning against nitrobenzene and acetophenone and for iodide poisoning against acetophenone with platinum. With the weaker poisons variation of solvent was not always attempted. The choice of high methanol percentages in the platinum reductions generally came from inability to obtain half-poisoning in more aqueous solutions.

The further hypothesis offered earlier as to the binding forces of higher molecular sulfur compounds is also well borne out. Against the strongly adsorbed nitrobenzene it is evident that butyl mercaptan is a better competitor than dibutyl sulfide though inherently less toxic. (The *inherent* toxicities of Maxted based on adsorbed quantities are in good agreement with those calculated from the crossover experiments.[18]) All of the substrates of the present work are probably better adsorbed than that of Maxted and Evans, who started with molar solutions of crotonic acid in glacial acetic acid. If Maxted was generally operating below the C_s lim of his substrate, the toxicities he would have observed should have been generally higher than in the present work, and a greater proportion of his poisons should have been on the catalysts. This seems to have been the case for the instances investigated.

Table V shows a further analysis of the crossover results, in which are included data on cadmium poisoning from the succeeding communication.[19] The last two columns give the amounts of poison *on* the catalyst corresponding to the poisoning level of the equilibrated solutions and the ratio of total platinum atoms to moles (or atoms) of adsorbed poison.[20]

Beyond the expected evidence that nitrobenzene competes more successfully with inhibitors than acetophenone, a curious relationship emerges: *A much larger fraction of the catalyst surface has to be occupied by inhibitor to suppress the reduction of nitrobenzene comparably.* There appear to be two simple interpretations of this, not necessarily mutually exclusive.

1. Reduction of acetophenone requires complete planar adsorption, whereas with nitrobenzene, approach of the oxygen atoms to the surface suffices for primary attachment.

2. The more strongly adsorbed substrate may be able to nudge aside single particles of inhibitor.

If the first interpretation is valid, experiments of this sort could provide means of studying the mode of attachment of other substrates.

Acknowledgment. The author wishes to express his gratitude to Dr. George B. Brown and his department for their hospitality, which was indispensable for the accomplishment of this work.

Registry No.—Cl^-, 16887-00-6; Br^-, 24959-67-9; I^-, 20461-54-5; MeO^-, 3315-60-4; HO^-, 14280-30-9; Cd^{2+}, 22537-48-0; N_3^-, 14343-69-2; CN^-, 57-12-5; NH_3, 7664-41-7; Bu_2S, 544-40-1; BuSH, 109-79-5; rhodium, 7440-16-6; palladium, 7440-05-3; platinum, 7440-06-4; acetate, 71-50-1; cyclohexene, 110-83-8; acetophenone, 98-86-2; benzene, 71-43-2; nitrobenzene, 98-95-3.

References and Notes

(1) Part I: R. Baltzly, *J. Org. Chem.*, preceding paper in this issue.
(2) The author wishes to express his gratitude to the Wellcome Research Laboratories and to the Public Health Service Grant CA-08748 from the National Cancer Institute for partial financial support of this investigation.
(3) For a review, cf. R. Baltzly, *Ann. N.Y. Acad. Sci.*, **145**, 31–45 (1967).
(4) This omits substances the toxicity of which may be due to reduction to a primary poison. For example, a sulfoxide may be a poison *per se* but is almost certainly reduced to a sulfide. A number of such poisons were examined by V. Horner, H. Reuter and E. Herrmann, *Justus Liebigs Ann. Chem.*, **660**, 1 (1962). Except when the ostensible poison is more potent than its presumptive reduction product (e.g., Mexted's mercaptans and dialkyl sulfides which are more toxic than hydrogen sulfide), it is not a simple matter to identify the true inhibitor in such cases.
(5) Cf. ref 26 of part I of this series.
(6) The α symbols are adsorption coefficients of substrate and inhibitor; the C symbols are concentrations corresponding. The relationship between this equation and that used by Maxted is discussed in ref 3. $C_{i\,1/2}$ is the concentration of poison that produces a rate half that of the unpoisoned standard.
(7) E. B. Maxted and S. Akhtar [*J. Chem. Soc.*, 1995 (1960)] showed that on metal oxide supports catalytic metals were in patches. A more gen-

eral argument is that the metal layer on a charcoal such as Darco cannot be continuous since a monatomic layer covering the reported surface of this charcoal would require more metal (30% of the weight of the carrier) than corresponds to high efficiency. Further, since too high a carrier–metal ratio results in *less* active catalysts, it must be possible for the metal to be spread too thin. It, therefore, seems likely that active surfaces are supported by several layers of underlying metal.

(8) Curve C resembles some of those shown in the earlier Maxted papers, in which he proposed the existence of two types of active sites. An alternative interpretation is offered in ref 2, p 38.

(9) (a) E. B. Maxted and H. C. Evans, *J. Chem. Soc.*, 1004 (1937); (b) *ibid.*, 455 (1937); (c) *ibid.*, 2071 (1938).

(10) In various instances (e.g., G. B. Elion, private communication), protective benzyl groups elsewhere in the molecule were removed poorly by the Pd/C hydrogenation employed to convert N_3 to $NH_2 + N_2$. The author is of the opinion that poisoning through sulfur analogues present in commercial benzyl chloride is probably responsible. The shape of nucleosides, with ring systems at a sharp angle to each other, also presents a possibility for self-poisoning, should the nitrogen-containing heterocycle be adsorbed preferentially.

(11) In low concentration the poison does not attain the catalyst surface immediately. Without such a period of equilibration, the reduction data resemble those often observed in preparative reductions with poison present: the initial rate is almost normal and diminishes after 1 or 2 min to a low or zero level.

(12) As mentioned in the previous communication, a true C_s lim cannot exist in the presence of serious concentrations of inhibitor. However, deviations from constancy do not become notable during the first 10–20% of reaction.

(13) E. B. Maxted and M. S. Biggs, *J. Chem. Soc.*, 3844 (1957), reported on the toxicity of ammonia, butylamine, cyclohexylamine, and dicyclohexylamine in the reduction of cyclohexene over platinum. To avoid inhibition by solvent anions, they employed cyclohexane as solvent. This, in turn, raises questions as to the influence of the solvent on the activity of the poisons. (All were considerably more toxic than in the present study, but there was about a twofold variation among the first three with dicyclohexylamine much less toxic. Maxted suggested that this might be a case of hindrance, ignoring solubility effects.) In the present study it had been planned to examine ammonia, pyrrolidine, piperidine, and morpholine, whose activities should not vary much because of solubility. This plan was abandoned when it was found impossible to deal with the stronger bases under comparable conditions.

(14) Regarding N_3^- as a nucleophile, its adsorbed condition has some resemblance to hydrazoic acid.

(15) Rhodium has been especially recommended for the reduction of nitriles. Cf. M. Freifelder, *J. Am. Chem. Soc.*, **82**, 3286 (1960).

(16) While this phenomenon does not appear to have been observed previously with noble metals, preparative dethiation with Raney nickel is, of course, a familiar process.

(17) E.g., the occurrence of β-naphthol as a by-product in the reduction of octalone. Cf. R. L. Augustine, D. C. Migliorini, R. F. Fusante, C. S. Sudano, and M. J. Sisbarro, *J. Org. Chem.*, **34**, 1075 (1969).

(18) Maxted's ratio was 2.5:1 relating to the reduction of crotonic acid. From Table V we see that 2×10^{-7} mol of BuSH permitted 40% activity vs. nitrobenzene, whereas 10^{-7} of Bu_2S permitted 33%. Against acetophenone at 33% activity, the ratio is 3.7:1.

(19) R. Baltzly, *J. Org. Chem.*, following paper in this issue.

(20) Maxted preferred not to work with supported catalysts since he feared that adsorption of poison on the carrier would complicate the situation unduly. Consideration of the data of this table in light of the fact that in the acetophenone reductions ten times as much carrier was used as well as ten times as much metal shows that adsorption on the carrier cannot be significant. Comparing lines 1 and 4 of Table V (Bu_2S poisoning), if the carrier per se in the former case held 10% of the adsorbed poison, the carrier per se in the latter case should have held two-thirds. This seems unlikely.

Studies on Catalytic Hydrogenation. III. Poisoning and Promotion by Cations[1]

Richard Baltzly[2]

Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Received June 3, 1975

The toxicities of zinc, cadmium, and manganese as bivalent cations earlier reported as equipotent poisons toward platinum have been examined with platinum, palladium, and rhodium on carbon and against a variety of substrates. Zinc and manganese are essentially nontoxic toward palladium and rhodium and, in fact, act as promoters in the palladium-catalyzed hydrogenolysis of benzyl alcohol. The observed promotion and certain variations in toxicity from substrate to substrate are interpreted as due to complex formation between cation and substrate and preferential adsorption of the complex in certain situations.

Maxted and Marsden[3,4] investigated the toxic action of a number of metallic cations in the reduction of crotonic acid in alcohol by Willstätter platinum. It was desired to reexamine a representative group of these against metallized charcoals, and zinc, cadmium, and manganese were selected for study. Of the 12 metallic elements identified by Maxted and Marsden as toxic, these have certain advantages. They are unlikely to be reduced to the metals under the conditions (as are Cu^{2+}, Ag^+, and Hg^{2+} or perhaps Pb^{2+} and Sn^{2+}). They were among the most toxic agents of this type, and their solutions are stable (whereas Fe^{2+} tends to pass to Fe^{3+}). It was anticipated that by using substrates having varying adsorption tendencies, further variation in the toxicities might be revealed, taking into account the arguments of the preceding communications of this series as to reaction kinetics and toxicity.

Since the variation in behavior far exceeded anticipation, it may be in point to outline the chronological course of this investigation. At the start of the program platinized charcoal was studied and the necessary conditions and techniques were worked out with it, using nitrobenzene and acetophenone as substrates. Toxicity studies were interspersed with standard runs as was convenient. The troublesome substrate, cyclohexene, was taken up later after which palladized charcoal was examined and finally (though somewhat incompletely) rhodium on charcoal.

The first data on cationic poisons that became available were, therefore, those of the left half of Table II followed by those of the first section of Table III. While poisoning by nucleophiles (the subject of the preceding communication) showed few unanticipated peculiarities of major importance, the nitrobenzene reductions exhibited far greater variation between Maxted's equitoxic ions than had been felt to be possible. The data with cyclohexene, when obtained, did, however, display the sort of behavior anticipated.

When the study of palladized charcoal was begun, there was special interest in the hydrogenation of benzyl alcohol (taken as an example of debenzylation for which this catalyst is especially preferred). When poisoning by zinc was studied, it was found that increasing concentrations of zinc ion had at first little effect on the reduction rate, but eventually produced a clear *increase* in rate. The prospect then presented itself that some or all of the anomalous results might be the result of concurrent poisoning and promotion.

Major interest in promotion arose from the work of Carothers and Adams[5] and of Faillebin.[6] Carothers and Adams studied promotion in the reduction of aldehydes by Adams'

Table I. Inhibition by Cations of Reductions of Nonpolar Substrates

	Substrate cyclohexene in 90% MeOH, 0.023 M $HClO_4$, C_s in = 0.6						Substrate benzene 5 mg of Rh/C (E) neutral in 85% MeOH, C_s in = 2.05	
	3% Pt/C, 1 mg Pt		3% Pd/C, 0.5 mg Pd		1% Rh/C, 0.1 mg Rh[a]			
Cation	$C_{i½}$	α_i/α_s	$C_{i½}$	α_i/α_s	$C_{i½}$	α_i/α_s	$C_{i½}$	α_i/α_s
Zn^{2+}	1.6×10^{-6}	3.75×10^5	$>8 \times 10^{-3}$	$<10^{-2}$	$(2 \times 10^{-4}$	$3 \times 10^3)$	1.5×10^{-4}	1.4×10^4
Mn^{2+}	$\sim 5 \times 10^{-5}$	1.2×10^4	$>6 \times 10^{-3}$	$<10^2$	$(1.5 \times 10^{-3}$	$4 \times 10^2)$	$>10^{-2}$ [b]	$<2 \times 10^2$
Cd^{2+}	2×10^{-6}	3×10^5	3×10^{-6}	2×10^5	$(2 \times 10^{-6}$	$3 \times 10^5)$	7×10^{-5}	2.9×10^4
Fe^{2+}			$\sim 5 \times 10^{-5}$	1.2×10^4				

[a] Tentative values obtained with substrate samples giving control rates $^2/_3$–$^3/_4$ of standard. [b] 25% inhibited at 10^{-2}.

catalyst, Faillebin by Willstätter platinum. In their work, Carothers and Adams examined the effect of a number of metallic salts among which those of iron were preferred. Promotion was also observed with Zn^{2+}, Mn^{2+}, Ni^{2+}, Co^{2+}, and chromium. All of these except the last are on Maxted's list of poisons.[7] These authors reported further that their promoters acted as poisons as their concentration was raised beyond the optimum for aldehyde reduction. They also observed that with higher than optimal amounts of iron (but not obstructive quantities) reduction to toluene was extensive. This amounts to promotion of the hydrogenolysis of benzyl alcohol by concentrations of Fe^{2+} higher than optimal for benzaldehyde reduction.

Maxted and Akhtar[8] reexamined the problem of promotion and found Sn^{2+} to be even more effective than Fe^{2+} as a promoter. They also observed promotion in the reduction of acetone and of ethyl cinnamate. Of these, the former was unreduced in the absence of promoter; with the latter, promotion increased an already considerable reduction rate. (It is doubtful if this sort of effect could have been observed with the apparatus employed by Carothers and Adams.)

Tin salts, while poisons in the Maxted studies, were relatively weak and chromium is perhaps not toxic. The possibility arises, therefore, that the promotion phenomena may not be intimately connected with catalyst poisoning.

Experimental Section

The methods used have been described in the earlier communications of this series. Zinc and manganous chlorides were CP commercial materials. They were weighed out and made up to M/10 concentrations, further dilutions being made into methanol. Cadmium was available as the carbonate which was converted to the chloride after weighing. Iron was made up as ferrous sulfate. All the poisoning runs were made under acid conditions except those with Rh/C on benzene and acetophenone, which were neutral. The appropriate standard rates (cf. first communication) were taken as the basis for comparison. The amounts of chloride introduced with the poison were too small to influence the rate significantly.[9]

Results and Discussion

The poisoning data are shown in Tables I–IV. The first of these gives results with cyclohexene and benzene. Since promotion or other interaction between substrate and poison should be minimal in these situations, these data are believed to be indicative of the inherent tendencies of the cations to be adsorbed on the three catalysts. The calculated ratios α_i/α_s are also given for comparison. While none of the data of this table can be supported by crossover experiments, those conducted with $CdCl_2$ against nitrobenzene and acetophenone showed the bulk of the inhibitor to be in solution and that the true and apparent half-inhibitory concentrations were not far apart.

With platinized charcoal, cadmium and zinc are adsorbed about equally while manganous ion is bound less strongly. Using a less strongly adsorbed substrate below its C_s lim, this difference might not be apparent. Zinc is weakly adsorbed on rhodium and not appreciably on palladium,

Table II. Inhibition of Nitrobenzene Reductions by Cations

	C_s in = 0.39 Pt/C, 1 mg Pt		$HClO_4$ = 0.46 Pd/C, 0.5 mg Pd	
Cation	Solvent	$C_{i½}$	Solvent	$C_{i½}$
Zn^{2+}	75% MeOH	$>1.5 \times 10^{-2}$	75% MeOH	$>4 \times 10^{-2}$
	89% HAc	9×10^{-3}	90% MeOH	$>4 \times 10^{-3}$
Mn^{2+}	89% HAc	8×10^{-3}	75% MeOH	$>1.6 \times 10^{-2}$
			90% MeOH	$>4 \times 10^{-3}$
Cd^{2+}	75% MeOH	6×10^{-6} [a]	75% MeOH	$>10^{-3}$ [b]
	89% HAc	8×10^{-6}	90% MeOH	4×10^{-4}

[a] From crossover experiment. The apparent value is the same. Two runs with 0.05% Pt/graphite gave ca. 3×10^{-6} as apparent $C_{i½}$. [b] Rate nearly constant 1.6×10^{-4}–10^{-3}.

while manganous ion is minimally toxic to both these catalysts. Cadmium is highly toxic to all three catalysts; in fact, the α_i/α_s values are remarkably constant. Ferrous ion was moderately toxic toward palladized charcoal (it was examined mainly with respect to benzaldehyde and benzyl alcohol reductions, for which Pt/C and Rh/C are ineffective).

Table II shows results against nitrobenzene for Pt/C and Pd/C. [The Rh-catalyzed reductions of nitrobenzene are rather erratic (cf. part I), and no toxicities were run therewith in this series.] The toxic activity of cadmium on Pt is reasonably in line here, but it proved impossible to get half-poisoning concentrations of zinc and manganese in 75% methanol. Satisfactory data could be obtained in 89% acetic acid where these two ions had about equal low toxicities, $C_{i1/2}$ being almost 1000 times that with cadmium. The results with Pd/C and Zn^{2+} and Mn^{2+} are what might be expected from the above, but cadmium also was markedly less active. Its $C_{i1/2}$ had to be obtained in 90% methanol. The resultant value for α_i/α_s is 10^3 while that for reduction of cyclohexene by the same catalyst and in the same solvent is 2×10^5. The α_s figures cannot differ to that extent so this result is clearly anomalous.

The acetophenone data shown in Table III are fairly well in line: cadmium ion continues to be a strong poison; zinc and manganese are relatively weak except with platinum. It is to be noted, however, that even with platinum, manganese poisoning did not follow the theoretical curves, and with palladized charcoal, zinc and manganese inhibition was largely independent of concentration as though compensating forces were at work. At first sight, one might be surprised that $C_{i1/2}$ for Cd^{2+} vs. acetophenone with Pt/C is higher than the figure for nitrobenzene (1.5×10^{-5} and 6×10^{-6}). If, however, the substrate concentrations are considered, the relationship is revised: α_i/α_s for nitrobenzene is 6.6×10^4 and for acetophenone, 1.1×10^5.

When we examine the palladized-charcoal reductions of benzaldehyde, benzyl alcohol, and benzyl methyl ether, presented in Table IV, we again encounter standard behavior from cadmium. Zinc and manganese have little effect on the reduction of benzaldehyde but clearly promote the reduction of benzyl alcohol and benzyl methyl ether. Ferrous

Table III. Inhibition of Acetophenone Reductions by Cations

Catalyst	Solvent and acidity	Inhibitor	$C_{i1/2}$	Remarks
Pt/C (3%) C_s in = 1.7 10 mg Pt	75% MeOH Res	Zn^{2+}	2×10^{-5}	
Pt/C (3%) C_s in = 1.7 10 mg Pt	99% MeOH Res	Mn^{2+}	4×10^{-5}	Does not follow poisoning curve
Pt/C (3%) C_s in = 1.7 10 mg Pt	75% MeOH 0.023 M $HClO_4$	Cd^{2+}	1.5×10^{-5}	From crossover[a]
Pd/C (3%) C_s in = 1.33 5 mg Pd	90% MeOH 0.23 M $HClO_4$	Zn^{2+}	$>10^{-3}$	Fairly constant 2×10^{-5}–10^{-3}
Pd/C (3%) C_s in = 1.33 5 mg Pd	0.23 M $HClO_4$	Mn^{2+}	$>10^{-3}$	Fairly constant 2×10^{-4}–10^{-3}
Pd/C (3%) C_s in = 1.33 5 mg Pd	0.23 M $HClO_4$	Cd^{2+}	2×10^{-5}	
Rh/C (5%, cat. E) C_s in = 1.7 5 mg Rh	75% MeOH Neutral	Zn^{2+}	3×10^{-4}	
Rh/C (5%, cat. E) C_s in = 1.7 5 mg Rh	Neutral	Mn^{2+}	$>10^{-2}$	Rate $^2/_3$ of standard at 10^{-2}
Rh/C (5%, cat. E) C_s in = 1.7 5 mg Rh	Neutral	Cd^{2+}	6×10^{-5}	

[a] Apparent $C_{i1/2} = 2 \times 10^{-5}$.

ion, which is adsorbed on palladium, had little effect on the reduction of benzyl alcohol and promoted the reduction of benzaldehyde only slightly. It is reasonable to view this finding as due to compensating poisoning and promotion.

On the Nature of Promotion. The work of Carothers and Adams can be discussed only in general terms since they employed platinum and particularly because this was in the form of Adams' catalyst. This catalyst is of the highest practical use, and its introduction was a landmark in organic chemistry, but it is unsuited to kinetic studies. Aside from the variability of batches, its state of subdivision is not constant. When first formed and engaged in a rapid reduction, it is highly colloidal and extremely active. When reduction stops or slows, it coagulates and does not thereafter recover *full* activity. Thus, inherently slow reductions are depressed out of reasonable comparison. Whether qualitative as well as quantitative changes in activity occur is uncertain. This point was considered by Adams, who thought that the activity of his promoters might be due in part to effect on the subdivision of the catalyst. This may have contributed, but it seems unlikely to be the major influence. Promotion was observed with *lower* concentrations of promoter than required for poisoning. We may assume that as *poisons* these ions were adsorbed on the catalyst. It is hard to see how they could prevent coagulation when less adsorbed or not adsorbed. Therefore, it is more likely that the promoters prevented coagulation merely by increasing the hydrogenation rate.

In the present studies, zinc and manganese are poorly adsorbed on palladium but function as promoters while iron, which is moderately well adsorbed, seems to have a dual role.

It is pertinent to ask a question that seems hitherto to have been avoided. Why should aldehydes, generally not noted for inactivity, be resistant to reduction in the first place? A possible answer is that in hydroxylic solvents they are present mainly or entirely as solvates. To the catalyst, a solvated aldehyde is simply a substituted alcohol, in the case of benzaldehyde a benzyl alcohol. Platinized charcoal, which does not reduce benzyl alcohol appreciably, also does not reduce benzaldehyde (and the usual promoters are here of no assistance). Adams' catalyst has some debenzylative abilities but is not superior in this respect. Palladized charcoal is superior for debenzylations and reduces benzyl alcohol rapidly, benzaldehyde even more rapidly.

If one imagines benzaldehyde hydrate or alcoholate adsorbed on a planar surface, the phenyl, α-carbon, and one C–O bond can lie on the surface. The other C–O bond cannot but will alter the electronic environment. Accordingly, the palladized charcoal reduction of benzaldehyde is less sensitive to acid than that of benzyl alcohol. One might also suppose that the coordinated metal could take the place of acid to which these debenzylations are so sensitive. That is not so, at least in any dramatic fashion. Runs in neutral solutions containing zinc chloride were only marginally faster than the neutral rate, both in the reduction of benzyl alcohol and that of benzyl methyl ether. In the latter case the difference may have been significant. This point might be settled by use of larger amounts of catalyst. Under the conditions of these reductions, formation of hemiacetal and hydrate would probably be instantaneous. Formation of full acetal would be much slower.

It is suggested that in the presence of polar substrates, zinc, manganese, and iron are extensively coordinated with substrate, while cadmium, as would be expected on general principles, is less so (or not at all). With nitrobenzene and platinized charcoal, the principal result is to diminish the availability of the inhibitor so that a larger amount is necessary to poison the catalyst. Coordination could also be expected with acetophenone. The data of Table III do not reveal any major influence of this sort, but this could be the result of compensating interactions. With the benzyl compounds, the metal coordinate constitutes a second and probably preferred substrate.[10] The effect is not dramatic in these palladium-catalyzed reductions since the unpromoted rate is very considerable. A quantitatively comparable promotion starting from a low or zero rate could easily account for the promotion with Adams' catalyst. Iron is not superior as a promoter in the present experiments because it is simultaneously an effective poison while zinc and man-

Table IV. Inhibition and Promotion in Palladium-Catalyzed Reductions

Cation	Solvent	$C_{i1/2}$	Remarks
	A. Substrate Benzyl Alcohol: C_s in = 2.1, $HClO_4$ = 0.23 M 5 mg of Pd as 3% Pd/C		
Zn^{2+}	90% MeOH		10% promotion at 10^{-3}
	80% MeOH		10% promotion at 8×10^{-3}
	75% HAc		25% promotion at 10^{-2}
Mn^{2+}	90% MeOH		10% promotion at 4×10^{-3}
	80% MeOH		10% promotion at 8×10^{-3}
	75% HAc		20% promotion at 10^{-2}
Cd^{2+}	90% MeOH	2×10^{-5}	
	80% MeOH	2×10^{-5}	
	75% HAc	3×10^{-5}	
Fe^{2+}	90% MeOH	?	Rate fairly constant 5×10^{-5}–2×10^{-4} marginal inhibition at 10^{-3}
	B. Substrate Benzyl Methyl Ether: C_s in = 1.4, $HClO_4$ = 0.23 M 5 mg of Pd as 3% Pd/C		
Zn^{2+}	75% HAc		30% promotion at 8×10^{-3}
Cd^{2+}	75% HAc	$\sim 5 \times 10^{-5}$	
	C. Substrate Benzaldehyde: C_s in = 2.08, $HClO_4$ = 0.23 M 3 mg of Pd as 3% Pd/C		
Zn^{2+}	90% MeOH		Rate fairly constant 2×10^{-5}–8×10^{-3}
	80% MeOH		Rate fairly constant 4×10^{-3}–2×10^{-2}
Mn^{2+}	90% MeOH		No inhibition at 4×10^{-3}
	80% MeOH		No inhibition at 2×10^{-3}–10^{-2}
Cd^{2+}	90% MeOH	3.5×10^{-5}	
Fe^{2+}	90% MeOH		Fairly constant 0–2×10^{-4} Slight promotion at 10^{-4}
			With no added acid (res) 25% promotion at 2×10^{-5}

ganese are not. Assuming that the toxicities to Adams' catalyst are comparable to those with other platinum catalysts (Maxted's and platinized charcoal), these three metals were on a comparable basis as poisons, and the superiority of iron as a promoter was manifested. Maxted and Akhtar's observation with stannous ion also falls into line since this was a poison of lower potency.

The only useful data on rhodium in the present work are with benzene and acetophenone (and, with reservations, cyclohexene). The pattern is intermediate between those of platinum and palladium. Cadmium ion is a strong poison, zinc considerably weaker, and Mn^{2+} is barely toxic.

Maxted[11] proposed a rule as to the metal ions that are toxic to hydrogenation catalysts. This rule depends on electron disposition in the incompletely filled shell below the valence electrons. It appeared to be valid for the catalysts he examined. It clearly is not of general validity. In the present investigation cations Maxted considered nontoxic were not tested, but in view of the failure of this rule, a reexamination of other ions is distinctly indicated.

Acknowledgment. The author wishes to express his gratitude to Dr. George B. Brown and his department for their hospitality, which was indispensable for the accomplishment of this work.

Registry No.—Zn^{2+}, 23713-49-7; Mn^{2+}, 16397-91-4; Cd^{2+}, 22537-48-0; Fe^{2+}, 15438-31-0; platinum, 7440-06-4; palladium, 7440-05-3; rhodium, 7440-16-6; cyclohexene, 110-83-8; benzene, 71-43-2; nitrobenzene, 98-95-3; acetophenone, 98-86-2; benzyl alcohol, 100-51-6; benzyl methyl ether, 538-86-3; benzaldehyde, 100-52-7.

References and Notes

(1) Parts I and II: R. Baltzly, *J. Org. Chem.*, preceding papers in this issue.
(2) The author wishes to express his gratitude to the Wellcome Research Laboratories and to the Public Health Service Grant CA-08748 from the National Cancer Institute for partial financial support of this investigation.
(3) E. B. Maxted and A. Marsden, *J. Chem. Soc.*, 469 (1940).
(4) For a review of catalyst poisoning cf. R. Baltzly, *Ann. N.Y. Acad. Sci.*, **145**, 31–45 (1967).
(5) W. H. Carothers and R. Adams, *J. Am. Chem. Soc.*, **45**, 1071 (1923); **47**, 1047 (1925). Some further references, mainly of doubtful relevance, are cited in these papers. It is of interest to note that the second of these Adams papers contains what may well be the first observation of poisoning by iodide ion.
(6) Faillebin, *C. R. Acad. Sci.*, **175**, 1077, 1118 (1922).
(7) Actually, Carothers and Adams introduced chromium as CrO_4^{2-}, Maxted as Cr^{3+}. In both laboratories, it seems to have been tacitly assumed that the metal would end up in the same state. This would doubtless be the case if all the ions possibly involved should be adsorbed on the catalyst. It is, however, perfectly possible for any particle thermodynamically reducible to remain unaltered because not adsorbed. The equivalence of Fe^{2+} and Fe^{3+} was established.
(8) E. B. Maxted and S. Akhtar, *J. Chem. Soc.*, 3130 (1959). Relevant to footnote 7, stannous and stannic tin *were not equivalent*.
(9) This is also true of Maxted's experiments in which metals were introduced as chlorides and acetates.
(10) It was observable in the zinc and manganese runs of Table IV with benzyl alcohol that the linear portion of the reduction plot was appreciably prolonged (lower value for C'_s lim).
(11) E. B. Maxted, *J. Chem. Soc.*, 1987 (1949).

Cross-Cyclizations of Alkylacetylenes to Cyclobutane Compounds via Vinyl Cations as Intermediates

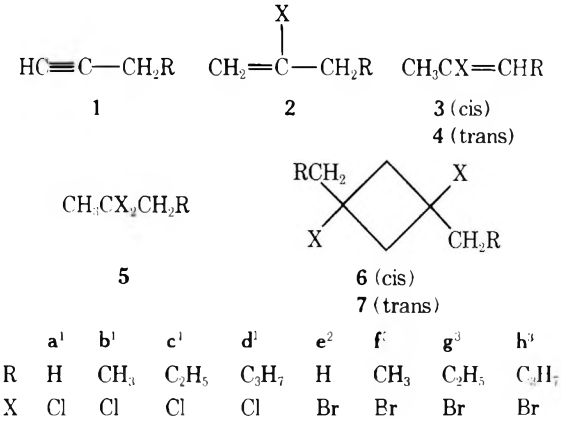
Karl Griesbaum* and Wolfgang Seiter

Engler-Bunte-Institut, Bereich Petrochemie, Universität Karlsruhe, D-75 Karlsruhe, Germany

Received September 22, 1975

Reactions of anhydrous hydrogen chloride with mixtures of propyne and 1-butyne, of propyne and 1-pentyne, and of 1-butyne and 1-pentyne produced the corresponding 1,3-dialkyl-1,3-dichlorocyclobutane cross-cyclization products along with the addition and cyclodimerization products of the individual acetylenes.

In previous work we have shown that liquid-phase reactions of anhydrous hydrogen chloride[1] or hydrogen bromide[2,3] with the alkylacetylenes **1a–d** produce the corresponding cyclodimerization products **6** and **7**, along with the respective simple addition products **2–5**. The 1,3-dialkyl-1,3-dihalocyclobutanes **6** and **7**, which are thus easily



	a[1]	b[1]	c[1]	d[1]	e[2]	f[2]	g[3]	h[3]
R	H	CH_3	C_2H_5	C_3H_7	H	CH_3	C_2H_5	C_3H_7
X	Cl	Cl	Cl	Cl	Br	Br	Br	Br

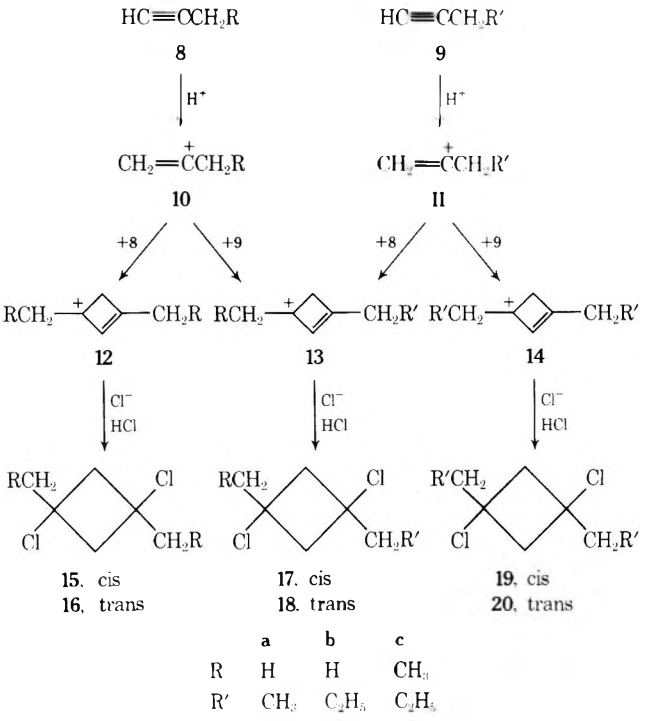
accessible in one-step reactions, are convenient starting materials for the short-path synthesis of other cyclobutane and cyclobutene compounds. Dehalogenation of **7e**[4,5] and of **7f**[3] produced the corresponding 1,3-dialkylbicyclo[1.1.0]butanes; reduction of **7e** yielded the stereoisomeric 1,3-dimethylcyclobutanes[6] and dehydrobromination of **7e** afforded 1,3-dimethylenecyclobutane and 1-methylene-3-methylcyclobutene.[7,8] The latter was used as a versatile starting material for the synthesis of a number of halogenated 1,3-dimethylcyclobutene and cyclobutane compounds.[8]

The scope of the synthetic utility of these 1,3-dialkyl-1,3-dihalocyclobutanes (**6, 7**) was thus far restricted, however, by the fact that cyclodimerizations of alkylacetylenes (**1**) can only afford cyclobutane derivatives which have two identical alkyl groups in 1,3 position. Since such cyclizations occur by cycloadditions of vinyl cations (e.g., **10** or **11**) to acetylenic substrates, it seemed possible that reactions of HCl with mixtures of two different acetylenes (**8** and **9**) could lead to cross-cyclizations by cycloaddition of the two vinyl cations **10** and **11** to the corresponding "foreign" acetylenes **9** and **8**, respectively. The products of such cross-cyclizations would be 1,3-dialkyl-1,3-dichlorocyclobutanes (**17** and **18**) bearing two different alkyl groups.

In the present paper we report about the reaction of anhydrous hydrogen chloride with mixtures of propyne and 1-butyne, of propyne and 1-pentyne, as well as of 1-butyne and 1-pentyne. The reactions were carried out in the liquid phase at ambient temperatures and afforded in each case liquid product mixtures. GLC analysis showed that these product mixtures contained the respective addition (**2–5**) and cyclodimerization products (**6, 7**) of the individual acetylenes **8** and **9**[9] as well as two additional components. The latter were in each case isolated as colorless liquids by preparative GLC and identified as the respective cross-cyclization products **17** and **18** on the basis of the following spectral data.

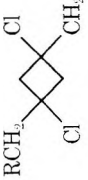
The mass spectra (Table I) exhibited the expected molecular ion triplets and a number of fragment ions which are typical for 1,3-dialkyl-1,3-dihalocyclobutanes.[1,10,11] These are the ions $(M - Cl)^+$, $(M - HCl)^+$, $(M - Cl_2)^+$, $(M - HCl_2)^+$ and the fragments $(C_3H_4ClR)^+$ and $(C_3H_4ClR')^+$ which result from bisection of the cyclobutane ring. The ^1H NMR spectra of the cis isomers **17** showed AA'BB' quartets for the signals of the methylene groups in the cyclobutane ring; the corresponding CH_2 groups in the trans isomers **18** appeared as singlet signals (Table II). This is in agreement with the ^1H NMR spectra of other stereoisomeric 1,3-dialkyl-1,3-dihalocyclobutanes.[1,10,11]

The quantitative results are summarized in Table III. The amounts of the total (i.e., homo- and cross-) cyclization products ranged from 9 to 35%. The highest selectivities of cyclization products (30 and 35%, respectively) were obtained from the reactions of equimolar mixtures of propyne–butyne and butyne–pentyne with equivalent amounts of hydrogen chloride. The use of excess hydrogen chloride led to a noticeable decrease of the cyclization reactions: reaction of HCl, butyne, and pentyne produced 35% of the combined 1,3-dialkyl-1,3-dichlorocyclobutanes when the reactants were applied in a molar ratio of 2:1:1, while a reactant ratio of 20:1:1 yielded only 10% of cyclic products.



	a	b	c
R	H	H	CH_3
R'	CH_3	C_2H_5	C_2H_5

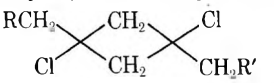
Table I. Mass Spectroscopic Data of *trans*-1,3-Dialkyl-1,3-dichlorocyclobutanes[a]



R	R′	Molecular ions	Rel abundances of corresponding ions[b]					
			M^+	$(M - Cl)^+$	$(M - HCl)^+$	$(M - CH_2Cl)^+$	$(M - Cl_2)^+$ $(M - HCl_2)^+$	$(C_3H_4ClR')^+$
H	CH_3	170, 168, 166	12, 65, 100	1037, 3289	2365, 6687	5665, 17 510	7013 9623	11 091, 29 870
H	C_2H_5	184, 182, 180	12, 67, 100	4168, 12 867	2136, 3148	11 444, 35 477	4666 30 328	90 367, 284 655
CH_3	C_2H_5	198, 196, 194	21, 63, 100	1012, 3284	886, 1771	5301, 16 718	1898 17 533	16 738, 46 350

[a] The mass spectra of the corresponding cis isomers showed the same ions, albeit with different intensities. [b] Based on the lowest molecular weight molecular ion as 100.

Table II. Parameters of ^1H NMR Spectra of 1,3-Dialkyl-1,3-dichlorocyclobutanes



R	R′	Isomer	Chemical shifts[a] of CH_2 groups in the ring, ppm
H	CH_3	Cis	2.95 (m)[b]
H	CH_3	Trans	2.87 (s)
H	C_2H_5	Cis	2.94 (m)[c]
H	C_2H_5	Trans	2.87 (s)
CH_3	C_2H_5	Cis	2.86 (m)[d]
CH_3	C_2H_5	Trans	2.82 (s)

[a] In CCl_4 as solvent, using Me_4Si as internal standard. [b] AA′BB′ spin system (J_{AB} = 15 Hz, δ_A 2.71, δ_B 3.18) which is further split due to diagonal spin coupling of ca. 2 Hz. [c] Same as *b* with J_{AB} = 15 Hz, δ_A 2.70, δ_B 3.18, and diagonal coupling ca. 2 Hz. [d] Same as *b* with J_{AB} = 15 Hz, δ_A 2.65, δ_B 3.07, and diagonal coupling ca. 2 Hz.

Of the possible stereoisomers, the *trans*-1,3-dialkyl-1,3-dichlorocyclobutanes were always formed predominantly with selectivities ranging between 79 and 88%. The amounts of the cross-cyclization products (**17, 18**) were always approximately equal to the sum of the homocyclization products (**15, 16, 19, 20**) of the individual alkylacetylenes.

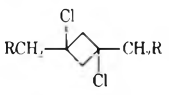
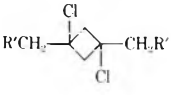
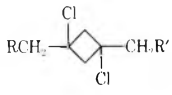
The quantitative results in Table III allow some conclusions concerning the relative reactivities of the alkylacetylenes applied: 1-butyne and 1-pentyne showed almost equal reactivities (column E, Table III), while propyne was considerably less reactive than either 1-butyne (column A, Table III) or 1-pentyne (column C, Table III) both in the HCl addition and in the cyclodimerization reactions. This is probably indicative of different rates of protonation of propyne on one hand and of butyne or of pentyne on the other hand. By contrast, it appears that in the cycloalkylation reactions, the vinyl cations which were formed in these experiments do not discriminate between the alkylacetylene from which they were derived and the corresponding "foreign" alkylacetylene, since, as mentioned above, the sum of homocyclization products was approximately equal to the sum of the cross-cyclization products, no matter whether pairs of substrates exhibiting similar or dissimilar reactivities were applied.

Experimental Section

Analytical Methods. The ^1H NMR spectra were recorded on a Varian-A-60, the ir spectra on a Beckman IR-8, and mass spectra on a Varian MAT CH-5 instrument. GLC analyses were carried out on a Varian Aerograph 1400-1 instrument, using the following conditions: column 5 m, 5 mm i.d., 5% nitrile silicone oil XE-60 on Chromosorb G; 24 ml N_2/min; 60–160 °C at 2 °C/min; injection port 180 °C. Preparative GLC was carried out on a Perkin-Elmer F-21, column 15 ft, 0.375 in. i.d., 5% Carbowax 20M on Chromosorb G. Conditions varied with the nature of the feed material.

General Procedure for the Reaction of Anhydrous Hydrogen Chloride with Alkylacetylenes. The reactions were carried out in thick-walled (3.5 mm) sealed glass tubes at ambient temperatures. Liquid reactants were directly introduced into the glass tube, while gaseous reactants, including anhydrous HCl, were condensed into the cooled (liquid air cooling) tube via a vacuum line system. The frozen reaction mixture was then evacuated, and the tube was sealed and transferred into a water bath which was kept at ambient temperatures. After the reaction was over, the tube was again cooled with liquid air and then opened. The unreacted gases were allowed to distill off via a drying tower while the tube was gradually warmed up from −70 to −10 °C in a cold bath. The crude reaction products were immediately analyzed by GLC and subsequently distilled in order to gain fractions in which the cross-cyclization products (**17, 18**) were enriched. These distillations

Table III. Typical Product Distributions from the Reactions xHCl + yHC≡C–CH_2R + zHC≡C–CH_2R′

Column		A	B	C	D	E	F
R; R′		H; CH_3	H; CH_3	H; C_2H_5	H; C_2H_5	CH_3; C_2H_5	CH_3; C_2H_5
x:y:z		2:1:1	4:3:1	2:1:1	4:3:1	2:1:1	20:1:1
Products, mol %[a]							
CH_2=C(Cl)CH_2R		11.2	17.3	7.6	17.2	7.8	
CH_3CCl=CHR						11.7	
$CH_3CCl_2CH_2$R		9.8	24.0	10.0	33.7	14.2	47.1
CH_2=C(Cl)CH_2R′		8.8	4.6	23.6	16.4	18.6	
CH_3CCl=CHR′		20.6	15.4				0.5
$CH_3CCl_2CH_2$R′		23.1	18.8	28.4	21.9	13.2	42.9
	cis	0.4	1.2	0.4	0.6	1.9	0.5
	trans	1.7	4.4	2.6	2.9	9.1	2.3
	cis	1.5	0.6	1.5	0.3	1.0	0.3
	trans	9.3	2.8	10.2	1.3	7.2	1.7
	cis	2.0	2.0	2.0	1.1	2.6	0.7
	trans	11.6	8.9	13.7	4.6	12.7	4.0
Molar ratios of							
R:R′ linear adducts		1:2.5	1:0.9	1:3.0	1:0.8	1:1.1	1:1.2
R:R′ cycloadducts		1:5.0	1:0.6	1:3.9	1:0.5	1:0.8	1:0.8
Homo-:cross-cyclizations		1:1.05	1:1.2	1:1.07	1:1.1	1:0.8	1:1

[a] Determined by GLC analysis, using the specific response factors of the individual compounds.

were carried out under mild conditions, i.e., low temperatures and reduced pressure. Partial fractionation was achieved by applying a series of receivers at different temperatures (0, −40, −78 °C).

Reaction of Anhydrous Hydrogen Chloride and an Equimolar Mixture of Propyne and 1-Butyne. A mixture of 12.8 g (0.35 mol) of hydrogen chloride, 7.1 g (0.18 mol) of propyne, and 9.5 g (0.18 mol) of 1-butyne was allowed to react at ambient temperatures for 20 days in a 350-ml glass tube. After removal of unreacted gases, 22.5 g of a reddish-brown, mobile liquid was obtained. The combined crude products (62.8 g) of three reactions were distilled and the fraction (15.1 g) obtained by distillation at ambient temperatures at 0.1 Torr in a receiver at −40 °C was submitted to preparative GLC (column temperature 90 °C, injection port 150 °C, 110 ml N_2/min).

***trans*-1,3-Dichloro-1-ethyl-3-methylcyclobutane (18a):** bp 164 °C; n^{20}D 1.4576; ^{1}H NMR (CCl_4, Me_4Si) 1.02 (t), 2.05 (q), J = 7 Hz, 1.91 (s), 2.87 ppm (s); ir (neat) 2970, 2940, 2880, 1460, 1420, 1380, 1290, 1270, 1165, 1120, 1090, 1020, 1000, 960, 930, 865, 800, 725 cm^{-1}.

Anal. Calcd for $C_7H_{12}Cl_2$: C, 50.32; H, 7.24; Cl, 42.44. Found C, 51.00; H, 7.38; Cl, 41.73.

***cis*-1,3-Dichloro-1-ethyl-3-methylcyclobutane (17a):**[12] ^{1}H NMR (CCl_4, Me_4Si) 1.01 (t), 1.85 (q), J = 7 Hz, 1.70 (s), 2.95 ppm (AA′BB′ system; see Table II).

Reaction of Anhydrous Hydrogen Chloride with an Equimolar Mixture of Propyne and 1-Pentyne. A mixture of 12.8 g (0.35 mol) of hydrogen chloride, 7.1 g (0.18 mol) of propyne, and 12.0 g (0.18 mol) of 1-pentyne was allowed to react for 23 days in a 350-ml glass tube. The crude product (24.7 g) was a reddish-brown, mobile liquid. The combined products (64 g) of three reactions were distilled and the fraction (10.3 g) boiling at 30–32 °C (0.07 Torr), collected at 0 °C, was submitted to preparative GLC (column temperature 100 °C, injection port 160 °C, 120 ml N_2/min).

***trans*-1,3-Dichloro-1-methyl-3-propylcyclobutane (18b):** bp 183 °C; n^{20}D 1.4579; ^{1}H NMR (CCl_4, Me_4Si) 0.97 (t, J = 6 Hz), 1.20–2.18 (m), 1.87 (s), 2.87 ppm (s); ir (neat) 2970, 2940, 2880, 2840, 1470, 1420, 1380, 1310, 1275, 1250, 1170, 1130, 1105, 1030, 950, 905, 810, 735 cm^{-1}.

Anal. Calcd for $C_8H_{14}Cl_2$: C, 53.06; H, 7.79; Cl, 39.15. Found: C, 53.75; H, 8.00; Cl, 38.46.

***cis*-1,3-Dichloro-1-methyl-3-propylcyclobutane (17b):**[12] ^{1}H NMR (CCl_4, Me_4Si) 0.95 (t, J = 6 Hz), 1.17–2.15 (m), 1.67 (s), 2.94 ppm (AA′BB′ system; see Table II).

Reaction of Anhydrous Hydrogen Chloride with an Equimolar Mixture of 1-Butyne and 1-Pentyne. A mixture of 18.2 g (0.5 mol) of hydrogen chloride, 13.5 g (0.25 mol) of 1-butyne, and 16.9 g (0.25 mol) of 1-pentyne was allowed to react for 26 days in a 350-ml glass tube to yield 46 g of a reddish-brown, mobile liquid. The combined products (82 g) of two reactions were distilled and the fraction (18.3 g) boiling at 34–37 °C (0.09 Torr), collected at 0 °C, was submitted to preparative GLC (column temperature 105 °C, injection port 160 °C, 140 ml N_2/min).

***trans*-1,3-Dichloro-1-ethyl-3-propylcyclobutane (18c):** bp 206–207 °C; n^{20}D 1.4584; ^{1}H NMR (CCl_4, Me_4Si) the signals of the ethyl and of the propyl group are mutually overlapped, the CH_2 group in the ring appears as singlet signal at 2.82 ppm; ir (neat) 2970, 2940, 2880, 1460, 1415, 1380, 1285, 1270, 1240, 1170, 1145, 1135, 1100, 990, 975, 945, 905, 860, 810, 730 cm^{-1}.

Anal. Calcd for $C_9H_{16}Cl_2$: C, 55.40; H, 8.27; Cl, 36.34. Found: C, 56.06; H, 8.32; Cl, 35.87.

***cis*-1,3-Dichloro-1-ethyl-3-propylcyclobutane (17c):**[12] ^{1}H NMR (CCl_4, Me_4Si) the signals of the ethyl and of the propyl group are mutually overlapped, the CH_2 group in the ring appears as a AA′BB′ quartet at 2.86 ppm (see Table II).

Acknowledgment. Support of this work by the Deutsche Forschungsgemeinschaft, by the Fonds der Chemischen Industrie, and by BASF-Aktiengesellschaft is gratefully acknowledged.

Registry No.—**17a,** 57637-65-7; **17b,** 57637-66-8; **17c,** 57637-67-9; **18a,** 57637-68-0; **18b,** 57637-69-1; **18c,** 57637-70-4; propyne, 74-99-7; 1-butyne, 107-00-6; 1-pentyne, 627-19-0.

References and Notes

(1) K. Griesbaum and M. El-Abed, *Chem. Ber.*, **106,** 2001 (1973).
(2) K. Griesbaum, *Angew. Chem.*, **76,** 782 (1964); *Angew. Chem., Int. Ed. Engl.*, **3,** 697 (1964).
(3) K. Griesbaum and W. Seiter, unpublished results.
(4) M. R. Rifi, *J. Am. Chem. Soc.*, **89,** 4442 (1967).
(5) K. Griesbaum and P. E. Butler, *Angew. Chem.*, **79,** 467 (1967); *Angew. Chem., Int. Ed. Engl.*, **6,** 444 (1967).
(6) K. Griesbaum, *J. Am. Chem. Soc.*, **86,** 2301 (1964).
(7) P. E. Butler and K. Griesbaum, *J. Org. Chem.*, **33,** 1956 (1968).
(8) K. Griesbaum and Y. Chu, *Chem. Ber.*, **107,** 838 (1974).
(9) They were identified by admixture of the corresponding authentic compounds to the crude product mixtures and by subsequent GLC analysis of the blends. The authentic compounds were available from previous work (see ref 1).
(10) K. Griesbaum, W. Naegele, and G. G. Wanless, *J. Am. Chem. Soc.*, **87,** 3151 (1965).
(11) K. Griesbaum, Z. Rehman, and Ul-J. Záhorszky, *Angew. Chem.*, **82,** 841 (1970); *Angew. Chem., Int. Ed. Engl.*, **9,** 812 (1970).
(12) This compound was isolated in amounts insufficient for elemental analysis.

Cyclopropanes. XXXVIII. Effect of 1-Substituents on the Stereochemical Stability of the Cyclopropyl Radical[1]

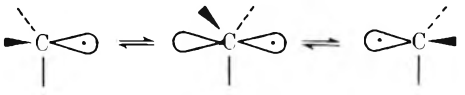
H. M. Walborsky* and P. C. Collins

Department of Chemistry, Florida State University, Tallahassee, Florida 32306

Received October 17, 1975

The *tert*-butyl peresters of chiral 1-X-2,2-diphenylcyclopropanecarboxylic acids (X = F, Cl, OCH_3) were prepared. The peresters were decomposed in tetrahydrofuran at 100 °C to yield, inter alia, 1-X-2,2-diphenylcyclopropane. The stereochemical results showed that the effect of the 1-substituent in stabilizing the σ radical was in the order of F > OCH_3 > Cl. This order follows what would be predicted by the Pauling–Walsh model based on the electronegativity of the substituent.

The stereochemistry of free radicals and the question of their geometry, whether they are planar or not, has been the subject of a number of reviews.[2] The consensus is that most acyclic hydrocarbon radicals (sp^3) are planar or π radicals. Cyclic hydrocarbons, if not strained, also fit into this category. The highly strained cyclopropyl ($sp^{2.3}$) radical and the vinyl (sp^2) radical are bent σ radicals.[3] Delocalizing substituents (π systems) attached to the radical site will convert the σ radical into a π radical. In contrast, electronegative substituents (O, F) attached to the radical site have a tendency to convert what would ordinarily be a π radical into a σ radical.[4]



σ π σ

Unless constrained, σ radicals such as cyclopropyl will invert configuration rapidly ($\sim 10^8$–10^{10} s^{-1}), with the inversion proceeding through a π-radical transition state or intermediate. In general, increasing the s character of the orbital containing the unpaired electron will result in stabilizing the σ radical.[4] Thus, both cyclopropyl and vinyl radicals are bent σ radicals and their inversion barriers are larger than those of their acyclic or saturated counterparts.[5]

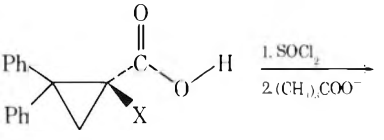
Two theories have been advanced to explain why electronegative substituents tend to cause the radical to be a σ radical. Pauling and Walsh[6] propose that the effect is due to a difference in electronegativity which would cause the orbital occupied by the odd electron to have a greater amount of s character and hence tend to be pyramidal. Any highly electronegative substituent attached to the free-radical center would therefore enhance the nonplanarity of the radical and the substituent effect would be F > OCH_3 > Cl. Dewar[7] argues that the electronegativity of the substituents is not the factor which accounts for the increased configurational stability of the free radicals and that the stabilization in, for example, the vinyl and cyclopropyl radicals is due to an antibonding interaction between the nonbonding electrons of the substituent and the MO's arising from interactions between the singly occupied carbon AO and the MO's of adjacent carbon bonds. Based on MINDO/3 calculations it was predicted that the barrier to inversion, caused by a substituent at the radical site, should increase in the order O < Cl < F. Clearly, the two theories are in conflict and it is the purpose of this paper to provide an experimental test of these two concepts.

Results and Discussion

Syntheses and Decomposition of *tert*-Butyl Peresters. The syntheses, resolution, and establishment of the absolute configurations of 1-X-2,2-diphenylcyclopropanecarboxylic acids **1** (X = F, **a**; Cl, **b**; Br, **c**; OCH_3, d) have previously been described.[8]

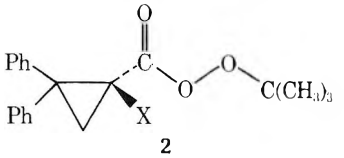
Table I. Percentage Yields of Decomposition Products

X	1	5	6	8	9	10
F	35.1	19.0		7.0		0.5
OCH_3	11.5	6.7	0.8			0.04
Cl	63.7	13.3				0.8
Br	56.3				1.3	1.2



1

X = F, **a**, (−)-(*S*)
X = Cl, **b**, (+)-(*S*)
X = Br, **c**, (+)-(*S*)
X = CH_3O, **d**, (−)-(*S*)



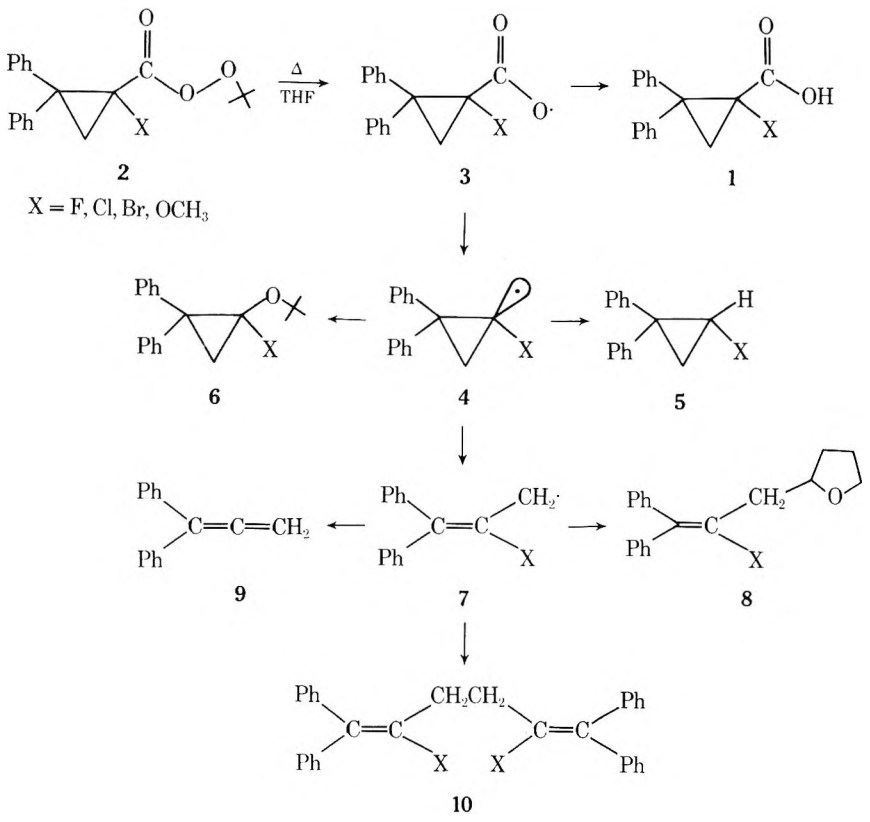
2

X = F, **a**, (−)-(*S*)
X = Cl, **b**, (+)-(*S*)
X = Br, **c**, (+)-(*S*)
X = CH_3O, **d**, (−)-(*S*)

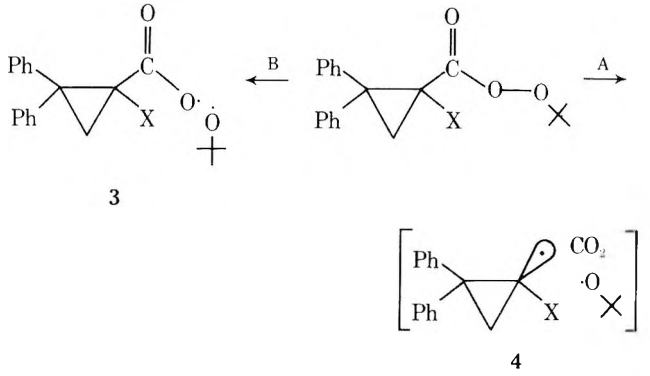
The *tert*-butyl peresters **2a–d** were prepared by converting the acids to their corresponding acid chlorides, using thionyl chloride, and adding them to a suspension of the sodium salt of *tert*-butyl hydroperoxide at −5 °C in diethyl ether.[9] The peresters are all quite stable and may be stored for prolonged periods at ambient temperature. Heating an approximately 0.05 M solution of the perester in tetrahydrofuran for 48–70 h at 100 °C caused complete decomposition to give a variety of products as shown in Scheme I. The percentage yields of the products are given in Table I. It may be assumed, based on the findings of DeTar and Weis,[10] that there is little induced decomposition taking place since the most concentrated solution of any perester was 0.07 M.

There are two possible mechanisms for the homolytic decomposition of the perester. One involves the concerted cleavage of the O–O bond along with the carboxy carbon–cyclopropyl ring bond to initially give the cyclopropyl radical **4**, a carbon dioxide molecule, and a *tert*-butoxy radical in the solvent cage (A). The other mechanism is a stepwise cleavage in which the O–O bond breaks first to give the cy-

Scheme I. Products from Perester Decomposition

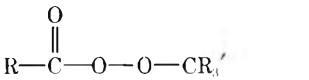


clopropylcarboxy radical 3 and a *tert*-butoxy radical (B). The cyclopropylcarboxy radical then loses carbon dioxide to give the cyclopropyl radical.



As has been shown,[11-13] the concerted cleavage mechanism would be expected to give very little, if any, of the acid 1. On the other hand, the stepwise decomposition mechanism would be expected to give a significant yield of acid 1 since the rate of cage breakdown would be at least as fast, if not faster, than decarboxylation. This would allow the abstraction of a hydrogen atom from the solvent by the acyloxy radical 3 to become competitive with decarboxylation to give the cyclopropyl radical 4.

In all the peresters studied there was a substantial yield of cyclopropylcarboxylic acid (1); thus the decomposition is probably proceeding by a stepwise mechanism. Using the arguments of Pryor[14] it is possible to understand why the cyclopropyl perester decomposes in a stepwise mechanism. Pryor pointed out that in peresters of the form



the less stable the R radical, the more stable the perester. This is because in the concerted mechanism some of the odd electron density is localized on the R group in the transition state. As the stability of R· increases, the probability of a rapid concerted scission of two bonds increases. However if R· is unstable then the perester is extremely stable and decomposes by a slow O–O bond scission in which none of the odd electron density is localized on the R group.

All the cyclopropyl peresters in this study are very stable, and since it is known that the cyclopropyl σ radical is the least stable of all the cycloalkyl radicals,[11] it is reasonable to suppose that the peresters decompose in a stepwise mechanism.

In Table I there appears to be an anomaly when X = OMe. Here the yield of recovered acid is substantially lower than in the other three cases. In addition, in only this case was the *tert*-butyl ketal 6 isolated. This ketal, resulting from the combination of a *tert*-butoxy radical with the cyclopropyl radical 4, could be formed in a number of ways.

The simplest mechanism would be a combination of the *tert*-butoxy radical and the cyclopropyl radical in the bulk solvent. However, it has been shown[2a,12] that a *tert*-butyl ether is often the result of an in-cage combination of the two radicals immediately after their formation. In most cases where the decomposition of a *tert*-butyl perester is used to generate the radical pair the decomposition proceeds by the concerted expulsion of carbon dioxide. The lower yield of acid and the presence of the ketal 6 may be an indication that when X = OMe the perester is decomposing by a concerted cleavage mechanism or a combination of concerted and stepwise mechanisms. On the other hand, there are a number of examples in which the decomposition proceeds by a purely stepwise mechanism and still gives cage coupling products. For example, acetyl peroxide[2a] decomposes to give a 3% yield of ethane, the product of an in-cage combination of two methyl radicals.

Table II. Optical Purity of Products Resulting from Hydrogen Atom Abstraction by the Various Cyclopropyl Radicals

X	% optical purity[a]	% retention of configuration[a]
F	46.8	73.5
OMe	8.4	54.2
Cl	0.0	50.0
Br		
CH_3[b]	0.0	50.0

[a] Average of at least three separate experiments. [b] Reference 12.

Koenig[15] has shown that the in-cage recombination product, 2-butyl *tert*-butyl ether, obtained from the thermolysis of (+)-(*S*)-*tert*-butylperoxy 2-methylbutyrate or from the thermolysis of (*S*)-*N*-nitroso-*N*-(α-methyl)butanoyl-*O*-*tert*-butylhydroxylamine showed from 1.8 to 2.4% retention of optical activity. In Koenig's system the intermediate radical is known to be a π radical so that the retention is the result of cage trapping. Thus the optical purity of the ketal **6** may be used as a test as to whether it is a cage or bulk combination product. If **6** results from combination in the bulk solvent then the optical purity would be expected to be approximately the same as that of the cyclopropyl ether **5**. If the ketal **6** results from an in-cage combination then the optical purity of **6** would be expected to be much higher than that of **5**. The ketal **6** isolated was found to be optically active, $[\alpha]_{Hg}^{24}$ −63° (*c* 0.34, $CHCl_3$). Although the optical purity of **6** has not been established[16] the high rotation observed indicates a substantial retention of optical activity and suggests that **6** probably results largely from a cage recombination reaction.

Aside from the cage recombination of the σ radical **4** with a *tert*-butoxy radical and the abstraction of a hydrogen atom from solvent, the radical may also ring open[11] to give the allyl π radical **7**. Since this radical is stabilized by delocalization it dimerizes to give **10**. As can be seen in Table I the yield of the dimer increases in the order F < Cl < Br. This is due to the ability of Cl, and especially Br, to stabilize the allyl radical. When X = Br the stabilization increases the propensity of **4** to ring open even before hydrogen atom abstraction, thus preventing the formation of hydrocarbon **5**. Moreover, when X = Br a product was isolated which gave an ir and NMR compatible with the structure 1,1-diphenylallene (**9**). This is a reasonable product considering the stability of the allyl radical **7** and the large size of bromine. These factors would combine to make the elimination of a bromine atom from **7** to give **9** very facile.[17] An alternative mechanism for the formation of **9** could be the elimination of a bromine atom from **7** to yield a 2,2-diphenylcyclopropyl carbene as an intermediate which then rearranges to allene **9** as previously demonstrated by Jones[18] in the decomposition of *N*-nitroso-*N*-(2,2-diphenylcyclopropyl)urea with base. At this time, no decision can be made between these alternatives. It is also noteworthy that only when X = F does radical **7** react with a tetrahydrofuranyl radical.

Effect of Substituent on the Stereochemistry of the Cyclopropyl σ Radical. The average optical purity and average percent retention of configuration of the substituted cyclopropyl hydrocarbons **5** are presented in Table II.

It can be seen that the optical purity decreases in the order F > OMe > Cl. Since this is the first study involving a single system where only the substituent is varied[19] and one which yields unambiguously free radicals, it is possible to make some comments as to whether the Walsh–Pauling[6] or the Dewar[7] theory on stereochemical stabilization of a free radical is the more viable.

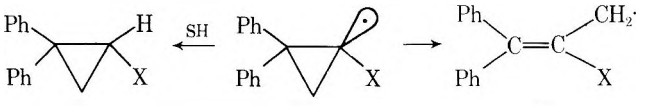
Table III. Mutually Consistent Group Electronegativities

Group	Empirical electronegativities	Group	Empirical electronegativities
F	3.95	OCH_3	3.70
Cl	3.03	CH_3	2.30
Br	2.80	H	2.28
I	2.47		

The Walsh–Pauling model is based on electronegativity; the more electronegative a substituent the more σ type is the radical to which the substituent is attached. Wells[20] has published a critical review on group electronegativities; a portion of his compilation of mutually consistent group electronegativities is presented in Table III. The electronegativity decreases in the order F > OMe > Cl, the same order as the decrease in the percent optical purity of the hydrocarbon **5**. This is also the same order that Kampmeier[21] observed for vinyl radicals. Kampmeier concluded, as do we, that this order can best be correlated with the electronegativity differences of the substituents. Clearly the order predicted by Dewar,[7] F > Cl > OCH_3, is not obtained.

Perhaps the electronegativity stabilizing argument is not the whole answer. It could be argued that the observed retention of configuration may be due to the increase in the rate of hydrogen abstraction from solvent by the radical (**4**). Should this be the case then, based on our observations, the radical reactivity order would be F > OCH_3 > Cl.

In an earlier study[11] we established the reactivity of **4** (X = CH_3) toward hydrogen atom donating solvents by determining the ratio of cyclopropyl hydrocarbon (**5**) to the sum of the products derived from **7** formed in the reaction. In



5 4 7

tetrahydrofuran the ratio of **4** (X = CH_3) was unity. As can be seen from Table I the ratios of **5** to the products derived from **7** for X = F, OCH_3, and Cl are 2.5, 188, and 17.[22] This would indicate that these radicals are reacting with solvent at a faster rate than when X = CH_3 and would establish the order of reactivity as CH_3O > Cl > F. On this basis one would conclude that this should also be the order of retention of configuration. This does not correlate with order observed and we conclude that the increase in the rate of hydrogen abstraction is not the determining factor for retention of configuration.

Experimental Section

Infrared spectra were obtained with a Perkin-Elmer Model 257 grating infrared spectrophotometer. Solution spectra were run on 3% solutions of either carbon tetrachloride or chloroform in a 0.5-mm sodium chloride cell. Ultraviolet spectra were run on a Perkin-Elmer Model 202 ultraviolet–visible spectrophotometer.

Rotations were measured at the 546.1-nm line of mercury on a Bendix-Ericson Model 987 ETL/NPC polarimeter. The estimated error limits of the rotations measured using the Bendix-Ericson polarimeter were calculated using the previously determined value of 0.002° for the standard deviation in recorded values of the rotation.

Nuclear magnetic resonance spectra were obtained on a Varian Associates A-60 or a Brucker 90-MHz spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained from an AEI Picker high-resolution mass spectrometer. Melting points were determined in capillary tubes using a Mel-Temp apparatus; the melting points are uncorrected. Vapor phase chromatography (VPC) was conducted on a Hewlett-Packard Model 5710A

programmed temperature gas chromatograph with a thermistor detector, using helium as a carrier gas. Silica gel $PF_{254+366}$ was used for preparative thin layer chromatography.

High-pressure liquid phase chromatography (HPLPC) was conducted on a Waters Model 6000 liquid chromatograph equipped with a differential uv detector. The column used was a 4 ft × 2 mm analytical column packed with Corasil 11. The solvent system was a 60:40 mixture of hexane–methylene chloride. The detector was calibrated by injection of known concentrations of previously identified compounds and, using the cut-and-weigh technique, relating the peak areas to the amount of sample injected. After calibration, the percentage yield was determined by injecting a weighed sampled of the neutral fraction of the decomposition products and relating the peak areas to those of the known concentrations.

Elemental analyses were run by J. Beller's Microanalytisches Laboratorium, Göttingen, Germany.

(±)-1-Methoxy-2,2-diphenylcyclopropanecarbonyl Chloride. A 2.68-g (0.094 mol) sample of the racemic acid[8] was dissolved in 1 ml of thionyl chloride and 2 drops of dimethylformamide were added. The reaction was stirred overnight after which the thionyl chloride was evaporated under vacuum and the residual oil recrystallized from high-boiling petroleum ether. Three recrystallizations gave 2.30 g (80%) of the acid chloride: mp 111–113 °C; ir ($CHCl_3$) 3005, 2930 (s, CH), 2830 (s, CH_3O), 1770 (s, C=O), 1600 (w, phenyl), 1500, 1450 cm^{-1} (s, phenyl); NMR (CCl_4) δ 7.5–7.0 (m, 10, phenyl), 3.25 (s, 3 H, CH_3O–), 2.45 (d, 1 H, cyclopropyl), 1.9 ppm (d, 1 H, cyclopropyl).

Anal. Calcd for $C_{17}H_{15}O_2Cl$: C, 71.20; H, 5.37. Found: C, 71.09; H, 5.51.

(−)-(*S*)-1-Methoxy-2,2-diphenylcyclopropanecarbonyl Chloride. In a similar manner to that used in the preparation of the racemic acid chloride 2.68 g (0.094 mol) of the optically active acid, $[\alpha]^{24}_{Hg}$ −75.9° (*c* 1.04, $CHCl_3$), was treated with thionyl chloride and dimethylformamide to give 2.75 g (97%) of acid chloride: mp 142–144 °C; $[\alpha]^{24}_{Hg}$ −120 ± 1.30° (c 0.380, $CHCl_3$); ir ($CHCl_3$) and NMR ($CDCl_3$) were identical with those of the racemic product.

Anal. Calcd for $C_{17}H_{15}O_2Cl$: C, 71.20; H, 5.37. Found: C, 71.28; H, 5.51.

***tert*-Butyl (±)-1-Methoxy-2,2-diphenylcyclopropanepercarboxylate.** *tert*-Butyl hydroperoxide was purified by twice extracting 5 g of the commercial product into 30 ml of cold 15% potassium hydroxide. The aqueous extract was saturated with ammonium chloride and the hydroperoxide separated as a clear, colorless liquid which was distilled under reduced pressure, bp 58 °C (20 mm).

To a suspension of 4.1 g of 52% sodium hydride oil dispersion (2.1 g pure, 0.09 mol) in 200 ml of anhydrous ether was added a solution of 9.0 g (0.01 mol) of purified *tert*-butyl hydroperoxide in 50 ml of anhydrous ether and the mixture stirred overnight. The white sodium salt of *tert*-butyl hydroperoxide was filtered off, washed three times with dry ether, and dried in a vacuum oven at 30 °C (5 mm) for 5 h.

A solution of 2.86 g (0.010 mol) of (±)-1-methoxy-2,2-diphenylcyclopropanecarbonyl chloride in 50 ml of anhydrous ether was added dropwise, over the course of 1 h, to a suspension of 2.24 g (0.020 mol) of the sodium salt to *tert*-butyl hydroperoxide in 200 ml of anhydrous ether at −5 °C. After hydrolyses with ice water, the ether layer was washed three times with saturated sodium chloride and dried over magnesium sulfate and the solvent removed under reduced pressure. The residue was recrystallized from a 3:1 pentane–ether solution at −30 °C as white needles: 1.73 g (51%); mp 101–103 °C (effervescence); ir (CCl_4) 3080–2940 (w, CH), 2840 (s, CH_3O–), 1772 (s, C=O), 1610, 1500, 1455 (phenyl), 1030 cm^{-1} (cyclopropyl); NMR ($CDCl_3$) δ 7.0–7.5 (m, 10 H, phenyl), 3.28 (s, 3 H, CH_3O–), 2.28 (d, 1 H, cyclopropyl), 1.80 (d, 1 H, cyclopropyl), 1.11 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.13; H, 7.03.

***tert*-Butyl (−)-(*S*)-1-Methoxy-2,2-diphenylcyclopropanepercarboxylate.** In a manner similar to that used for the preparation of the racemic perester 2.86 g (0.010 mol) of (−)-(*S*)-1-methoxy-2,2-diphenylcyclopropanecarbonyl chloride, $[\alpha]^{24}_{Hg}$ −120°, was allowed to react with the sodium salt of *tert*-butyl hydroperoxide to give 1.70 g (50%) of the perester: mp 115–116 °C (effervescence); $[\alpha]^{24}_{Hg}$ −110 ± 0.9° (c 0.540, $CHCl_3$); ir (CCl_4) and NMR (CCl_4) spectra were identical with those of the racemic perester.

Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.19; H, 7.01.

Procedure for the Thermal Decomposition of the Perester 2d. Run 1. A 0.534-g (1.6 mmol) sample of *tert*-butyl (−)-(*S*)-1-methoxy-2,2-diphenylcyclopropanepercarboxylate was dissolved in 100 ml of tetrahydrofuran that had been distilled under nitrogen from lithium aluminum hydride. A glass tube containing the solution was flushed with nitrogen for 10 min, sealed, and heated at 100 °C for 24 h. After the tube was cooled the solvent was removed under vacuum, and the residual oil dissolved in ether and washed three times with sodium bicarbonate. The aqueous extract was acidified to give recovered 1-methoxy-2,2-diphenylcyclopropanecarboxylic acid: 0.071 g (0.26 mmol, 16.8%), $[\alpha]^{24}_{Hg}$ −76.8 ± 0.49° (c 1.02, $CHCl_3$), complete retention of configuration.[8]

The neutral fraction was analyzed by preparative TLC using 50% methylene chloride–50% hexane. The fraction at R_f 0.50–0.56 was found to be 1-methoxy-2,2-diphenylcyclopropane by comparison of the ir and NMR spectra with those of an authentic sample: 0.21 g (0.092 mmol, 5.9%); $[\alpha]^{24}_{Hg}$ +4.58 ± 1.2° (c 0.414, $CHCl_3$); optical purity 6.17%; retention of configuration.[8]

Run 2. In a similar manner to that used in run 1, a 0.776-g (2.3 mmol) sample of the perester was decomposed. The recovered acid weighed 0.086 g (0.32 mmol, 13.9%), $[\alpha]^{24}_{Hg}$ −72.3 ± 0.46° (c 1.09, $CHCl_3$). The isolated 1-methoxy-2,2-diphenylcyclopropane weighed 0.056 g (0.25 mmol, 10%), $[\alpha]^{24}_{Hg}$ +8.27 ± 0.44° (*c* 1.12, $CHCl_3$), optical purity 11.2%, retention of configuration.[8]

Run 3. In a similar manner to that used in run 1, a 0.60-g (1.7 mmol) sample of the perester was decomposed. The recovered acid weighed 0.017 g (0.063 mmol, 3.7%), $[\alpha]^{24}_{Hg}$ −75.5 ± 0.88° (*c* 0.340, $CHCl_3$). The isolated 1-methoxy-2,2-diphenylcyclopropane weighed 0.018 g (0.071 mmol, 4.2%), $[\alpha]^{24}_{Hg}$ +5.94 ± 1.42° (*c* 0.352, $CHCl_3$), optical purity 7.95%, retention of configuration.[8]

Isolation of 1-Methoxy-1-*tert*-butoxy-2,2-diphenylcyclopropane. The band at R_f 0.58–0.61 of the preparative TLC was collected as a yellow oil: ir (CCl_4) 3180, 3160, 3020 (m, CH aromatic), 2980, 2930 (s, CH allyl), 3890 (m, CH_3O–), 1600, 1500, 1450 (m, C–C aromatic), 1390, 1370, 1260, 1215 (m, *tert*-butyl), 1150 cm^{-1} (s, C–O–C–O–C); NMR (CCl_4) δ 7.3–7.1 (m, 10 H, phenyl), 2.05 (s, 3 H, CH_3O–), 1.95 (d, 1 H, cyclopropyl), 1.85 (d, 1 H, cyclopropyl), 1.15 (s, 9 H, *tert*-butyl); mass spectra *m/e* (rel intensity) 296 (≪1) ($P\cdot^+$); 240 (16.1), 239 (27.8), 180 (100), 167 (71.0).

Anal. Calcd for $C_{20}H_{24}O_2$: *m/e* 296.1776. Found: *m/e* 296.1783 (deviation 0.7 mmu).

Unfortunately, there was insufficient material collected in the first three runs to give an accurate rotation on the polarimeter. In a fourth run, 2.51 g of the perester was dissolved in 180 ml of tetrahydrofuran and decomposed. After purification by TLC 0.017 g (0.058 mmol, 0.79%) of the ketal was collected, $[\alpha]^{24}_{Hg}$ −63.4 ± 1.45° (c 0.344, $CHCl_3$).

In an attempt to determine the optical purity of the recovered optically active ketal a sample of the racemic ketal was dissolved in carbon tetrachloride and placed in an NMR tube. The solution was deoxygenated by a freeze–pump–thaw cycle under a nitrogen atmosphere. In a glove bag, under a nitrogen atmosphere, tris[(3-heptafluoropropylhydroxymethylene)-*d*-camphorato]europium-(III) was added in 5-mg increments. After each addition the NMR of the solution was taken. The shift reagent was added beyond a 1:1 molar ratio up to the limit of line broadening without any significant shift being observed.

Isolation of 1,1,6,6-Tetraphenyl-2,5-dimethoxyl-1,5-hexadiene. The band at R_f 0.50–0.47 of the preparative TLC of the fourth run was collected as a yellow, amorphous solid: mp 135–137 °C; ir (CCl_4) 3070, 3030 (m, C–H aromatic), 2950, 2850 (w, C–H aliphatic), 1625 cm^{-1} (m, C=C stretch); NMR (CCl_4) δ 7.5–7.0 (m, 20, phenyl), 3.32 (s, 6, –OMe), 2.50 (s, 4, allylic); mass spectra *m/e* (rel intensity) 223 (100) (monomer), 208 (7.6) (monomer − CH_3), 191 (29.4) (monomer − HOMe).

Anal. Calcd for $C_{32}H_{30}O_2$: *m/e* 446.2246. Found: *m/e* 446.2247 (deviation 1.1 mmu).

The actual amount of the dimer was too small to accurately determine; this necessitated the use of an approximation method. By use of the HPLPC chromatograph the yields of **5**, **6**, and **10** were determined to be 47, 32, and 0.2% of that part of the neutral fraction that eluted off the column. On a relative basis the dimer yield would be 0.4% of the cyclopropyl hydrocarbon yield. Since the average percentage yield of **5** in the first two runs was 8%, the percentage yield of the dimer based on the starting perester was approximately 0.04%.

Other Possible Products. The total percentage yield of the four products **1**, **5**, **6**, and **10** was 24%. The rest was an intractable tar that gave a broad continuum of bands below R_f 0.5 on the preparative TLC and would not elute off the HPLPC column even after extensive flushing.

(±)-1-Chloro-2,2-diphenylcyclopropanecarbonyl Chloride. A 1.0-g (0.0037 mol) sample of the racemic acid[8] was dissolved in 2 ml of thionyl chloride and 2 drops of dimethylformamide were added. The reaction mixture was stirred for 4 h after which the thionyl chloride was evaporated under vacuum and the residual oil recrystallized from a 1:1 mixture of benzene–hexane. Three recrystallizations gave 1.0 g (95%) of the acid chloride: mp 83–89 °C; ir ($CHCl_3$) 3090, 3070, 3040 (m, C–H), 1778 (s, C=O), 1600, 1495, 1450 cm^{-1} (m, phenyl); NMR (CCl_4) δ 7.5–7.0 (m, 10, phenyl), 2.75 (d, 1, J = 6 Hz, ring H trans to C=O), 2.05 (d, 1, J = 6 Hz, ring H cis to C=O).

Anal. Calcd for $C_{16}H_{12}OCl_2$: m/e 290.0265. Found: m/e 290.0275 (deviation 1.0 mmu).

(+)-(*S*)-1-Chloro-2,2-diphenylcyclopropanecarbonyl Chloride. In a similar manner to that used in the preparation ofthe racemic acid chloride 9.0 g (0.033 mol) of the optically active acid was treated with thionyl chloride and dimethylformamide to give 9.5 g (99%) of acid chloride: mp 90–93 °C; $[\alpha]^{24}_{Hg}$ +51.0 ± 0.4° (c 1.262, $CHCl_3$); ir ($CHCl_3$) and NMR ($CDCl_3$) were identical with those of the racemic product.

Anal. Calcd for $C_{16}H_{12}OCl_2$: m/e 290.0265. Found: m/e 290.0257 (deviation 0.7 mmu).

***tert*-Butyl (±)-1-Chloro-2,2-diphenylcyclopropanepercarboxylate.** A solution of 1.0 g (3.4 mol) of (±)-1-chloro-2,2-diphenylcyclopropanecarbonyl chloride in 50 ml of anhydrous ether was added dropwise over the course of 1 h to a suspension of 0.78 g (7.0 mmol) of the sodium salt of *tert*-butyl hydroperoxide in 200 ml of anhydrous ether at −5°. After hydroxysis with ice water, the ether layer was washed three times with saturated sodium chloride and dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The residue was recrystallized from a 3:1 pentane–ether solution at −30 °C as white needles: 0.90 g (76%); mp 115–117 °C; ir (CCl_3) 3050, 3030, 2985, 2940, 2880 (m, C–H), 1775 (s, C=O), 1600, 1495, 1450 cm^{-1} (m, phenyl); NMR (CCl_4) δ 7.5–7.0 (m, 10 H, phenyl), 2.60 (d, J = 6 Hz, ring H trans to C=O), 1.90 (d, 10, J = 6 Hz, ring H cis to C=O), 1.20 (s, 9 H, *tert*-butyl).

Anal. Calcd for $C_{20}H_{21}O_3Cl$: C, 69.66; H, 6.14; Cl, 10.28. Found: C, 69.55; H, 6.18; Cl, 10.14.

***tert*-Butyl (+)-(*S*)-1-Chloro-2,2-diphenylcyclopropanepercarboxylate.** In a manner similar to that used in the preparation of the racemic perester 9.60 g (0.033 mol) of (−)-1-chloro-2,2-diphenylcyclopropanecarbonyl chloride was allowed to react with the sodium salt of *tert*-butyl hydroperoxide to give 8.90 g (79%) of the perester: mp 125–127 °C; $[\alpha]^{24}_{Hg}$ +2.15 ± 0.82° (c 0.612, $CHCl_3$); ir (CCl_4) and NMR (CCl_4) spectra were identical with those of the racemic perester.

Anal. Calcd for $C_{20}H_{21}O_3Cl$: C, 69.66; H, 6.14; Cl, 10.28. Found: C, 69.67; H, 6.19; Cl, 10.23.

Procedure for the Thermal Decomposition of the Perester 2b. Run 1. A 1.20-g (3.45 mmol) sample of *tert*-butyl (+)-(*S*)-1-chloro-2,2-diphenylcyclopropanepercarboxylate was dissolved in 100 ml of freshly distilled tetrahydrofuran, placed in a glass tube, flushed with nitrogen for 10 min, sealed, and heated at 100 °C for 24 h. After the tube was cooled the solvent was removed under vacuum, and the residual oil dissolved in ether and washed three times with sodium bicarbonate. The aqueous extract was acidified to give recovered 1-chloro-2,2-diphenylcyclopropanecarboxylic acid: 0.610 g (2.24 mmol, 65%); $[\alpha]^{24}_{Hg}$ +85.0 ± 0.4° (c 1.12, $CHCl_3$); complete retention of configuration.[8]

The neutral fraction was analyzed by preparative TLC using 50% methylene chloride–50% hexane. The fraction at R_f 0.90–0.85 was found to be 1-chloro-2,2-diphenylcyclopropane by comparison of the ir and NMR spectra with that of an authentic sample: 0.119 g (0.52 mmol, 15.1%); $[\alpha]^{24}_{Hg}$ +0.073 ± 0.209° (c 2.39, $CHCl_3$); racemic.

Run 2. In a similar manner to that used in run 1, a 1.25-g (3.62 mmol) sample of the perester was decomposed. The recovered acid weighed 0.563 g (2.07 mmol, 56.9%), $[\alpha]^{24}_{Hg}$ +85.9 ± 0.5° (c 1.066, $CHCl_3$). The isolated 1-chloro-2,2-diphenylcyclopropane weighed 0.090 g (0.39 mmol, 10.9%), $[\alpha]^{24}_{Hg}$ +0.070 ± 0.280° (c 1.79, $CHCl_3$), racemic.

Run 3. In a similar manner to that used in run 1, a 1.19-g (3.47 mmol) sample of the perester was decomposed. The recovered acid weighed 0.648 g (2.41 mmol, 69.4%), $[\alpha]^{24}_{Hg}$ +83.8 ± 0.4° (c 1.13, $CHCl_3$). The recovered hydrocarbon weighed 0.111 g (0.486 mmol, 14%), $[\alpha]^{24}_{Hg}$+0.079 ± 0.225° (c 2.22, $CHCl_3$), racemic.

Isolation of 1,1,6,6-Tetraphenyl-2,5-dichloro-1,5-hexadiene. In order to determine the other possible products a 2.03-g (5.87 mmol) sample of the racemic perester was decomposed for 50 h at 100 °C in tetrahydrofuran. The preparative TLC of the neutral fraction using 50% methylene chloride–50% hexane showed three bands with R_f 0.90–0.85, 0.84–0.79, and 0.53–0.37.

The band at R_f 0.84–0.79 was collected as colorless prisms: 0.020 g (0.75%); mp 94–96 °C; ir (CCl_4) 3070, 3040 (w, C–H aromatic), 2970, 2910 (s, C–H aliphatic), 1601 cm^{-1} (w, C=C stretch); NMR (CCl_4) δ 7.5–7.0 (m, 20, phenyl), 2.83 (s, 4, allylic); mass spectra m/e (rel intensity) 454 (8.3) (parent), 227 (100) (monomer), 191 (54.7) (monomer − HCl).

Anal. Calcd for $C_{30}H_{24}Cl_2$: m/e 454.1254. Found: m/e 454.1227 (deviation 2.7 mmu).

Other Possible Products. The band from the TLC with R_f 0.53–0.37 defied characterization. The NMR of the fraction showed numerous broad multiplets and when a sample was injected into the HPLPC it failed to elute. Further TLC did not isolate any distinguishable products.

(±)-1-Bromo-2,2-diphenylcyclopropanecarbonyl Chloride. A 1.0-g (3.2 mmol) sample of the racemic acid was dissolved in 1 ml of thionyl chloride and 2 drops of dimethylformamide were added. The reaction mixture was stirred overnight after which the thionyl chloride was evaporated under vacuum and the residual oil recrystallized from 1:1 benzene–hexane. Three recrystallizations gave 0.70 g (75%) of the acid chloride: mp 59–61 °C; ir ($CHCl_3$) 3090, 3060, 3030 (m, C–H), 1772 (s, C=O), 1600, 1580, 1475 cm^{-1} (m, phenyl); NMR (CCl_4) δ 7.5–7.0 (m, 10, phenyl), 2.85 (d, 1, J = 6 Hz, ring H trans to C=O), 2.18 (d, 1, J = 6 Hz, ring H cis to C=O).

Anal. Calcd for $C_{16}H_{12}OBrCl$: m/e 333.9761. Found: m/e 333.9776 (deviation 1.5 mmu).

***tert*-Butyl (±)-1-Bromo-2,2-diphenylcyclopropanepercarboxylate.** A solution of 1.0 g (3.0 mmol) of (±)-1-bromo-2,2-diphenylcyclopropanecarbonyl chloride in 50 ml of anhydrous ether was added dropwise over the course of 1 h to a suspension of 0.67 g (6.0 mmol) of the sodium salt to *tert*-butyl hydroperoxide in 200 ml of anhydrous ether at −5 °C. After hydrolysis with ice water, the ether layer was washed three times with saturated sodium chloride and dried over magnesium sulfate and the solvent removed under reduced pressure. The residue was recrystallized from a 3:1 pentane–ether solution at −30 °C as white needles: 0.90 g (77%); mp 132–134 °C; ir (CCl_3) 3090, 3060, 3030, 2990, 2940, 1772 (s, C=O), 1600, 1580, 1495, 1450 cm^{-1} (m, phenyl); NMR ($CDCl_3$) δ 7.0–7.5 (m, 10, phenyl), 2.68 (d, 1, J = 6 Hz, ring H trans to C=O), 1.93 (d, 1, J = 6 Hz, ring H cis to C=O), 1.20 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{20}H_{21}O_3Br$ (mol wt 389.29): C, 61.71; H, 5.44; Br, 20.52. Found: C, 61.61; H, 5.44; Br, 20.58.

***tert*-Butyl (−)-(*R*)-1-Bromo-2,2-diphenylcyclopropanepercarboxylate.** In a manner similar to that used in the preparation of the racemic perester (6.83 g (0.020 mol) of (−)-1-bromo-2,2-diphenylcyclopropanecarbonyl chloride was allowed to react with the sodium salt of *tert*-butyl hydroperoxide to give 6.29 g (79.4%) of the perester: mp 112–114 °C; $[\alpha]^{24}_{Hg}$ −36.9 ± 1.01° (c 0.494, $CHCl_3$); ir (CCl_4) and NMR (CCl_4) spectra were identical with those of the racemic perester.

Anal. Calcd for $C_{20}H_{21}O_3Br$ (mol wt 389.29): C, 61.71; H, 5.44; Br, 20.5. Found: C, 61.73; H, 5.41; Br, 20.55.

Procedure for the Thermal Decomposition of the Perester 2c. Run 1. A 2.789-g (7.17 mmol) sample of *tert*-butyl (±)-1-bromo-2,2-diphenylcyclopropanepercarboxylate was dissolved in 100 ml of freshly distilled tetrahydrofuran, placed in a glass tube, flushed with nitrogen for 10 min, sealed, and heated at 100 °C for 24 h. After the tube was cooled the solvent was removed under vacuum, and the residual oil dissolved in ether and washed three times with sodium bicarbonate. The aqueous extract was acidified to give recovered 1-bromo-2,2-diphenylcyclopropanecarboxylic acid: 1.281 g (4.04 mmol, 56.3%), $[\alpha]^{23}_{Hg}$ −132° (c 1.1, $CHCl_3$), complete retention of configuration.

The neutral fraction was analyzed by preparative TLC using 50% methylene chloride–50% hexane. Four bands were found: R_f 0.87–0.83, R_f 0.82–0.78, R_f 0.77–0.70, and a broad continuum from R_f 0.58 to the baseline.

Isolation of 1,1,6,6-Tetraphenyl-2,5-dibromo-1,5-hexadiene. The band from the TLC with R_f 0.77–0.70 was collected as a white, amorphous solid: 0.045 g (1.2%); mp 161–164 °C; ir ($CHCl_3$) 3080, 3020 (w, C–H aromatic), 2940, 2860 (w, C–H aliphatic), 1600 cm^{-1} (m, C=C stretch); NMR ($CHCl_3$) δ 7.3–6.9 (m, 20, phenyl), 2.83 (s, 4, allylic); mass spectra m/e (rel intensity) 542 (0.9) (parent), 273 and 271 (23.0) (monomer), 191 (54.1) (monomer − HBr).

Anal. Calcd for $C_{30}H_{24}Br_2$: m/e 544.0226. Found: m/e 544.0215 (deviation 1.1 mmu).

Isolation of 1,1-Diphenyl-1,2-propadiene. The band from the TLC with R_f 0.87–0.83 was collected as a yellow oil which weighed

0.0278 g. Analysis by LPC showed that the product was 56% pure, while analysis by VPC showed that the product was 73% pure although in neither case was it possible to calibrate the detector. A 1–2-mg portion was preparatively separated on the VPC using a 6 ft × 0.125 in. column packed with 5% W-98 silicone oil on 70–80 mesh Anakrom Q: ir (CCl_4) 3100, 3070, 3040 (w, C–H aromatic), 2970 (w, C–H vinylic), 1930 (m, C=C stretch, allene), 1600, 1500, 1460, 1450 cm^{-1} (m, C=C stretch phenyl); NMR (CCl_4) δ 7.4–7.2 (m, 10, phenyl), 5.2 (s, 1, vinyl).

Attempted Isolation of 1-Bromo-2,2-diphenylcyclopropane. No trace of the hydrocarbon **5** could be found in any of the TLC fractions of the decomposition products when the decomposition solvent was tetrahydrofuran. Changing the solvent to diethyl ether, chloroform, or thiophenol still did not produce any of the bromohydrocarbon.

Other Possible Products. The second band with R_f 0.77–0.70 showed a strong absorption in the NMR (CCl_4) from δ 7.3 to 7.0 but no other peaks. The ir (CCl_4) showed many phenyl absorption peaks but also a strong C–H vinylic absorption at 2970 and 2910 cm^{-1}. It is most likely that this fraction is a polymeric decomposition product of the allene.

(−)-(*S*)-1-Fluoro-2,2-diphenylcyclopropanecarbonyl Chloride. To a solution of 2.7 g (0.011 mol) of (−)-(*S*)-1-fluoro-2,2-diphenylcyclopropanecarboxylic acid,[8] $[\alpha]_{Hg}^{24}$ −147°, in 12 ml of thionyl chloride was added 0.5 ml of *N,N*-dimethylformamide and the reaction mixture stirred at ambient temperature for 4 h. The excess thionyl chloride was evaporated under reduced pressure and the residue dissolved in benzene. Recrystallization from benzene yielded 2.2 g (75%) of product: mp 100–104 °C; $[\alpha]_{Hg}^{24}$ −121.2° (c 0.52, acetone); ir (CCl_4) 3035, 3065, 3088 (m, C–H), 1793 (s, C=O), 1248 cm^{-1} (s, C–F); NMR ($CDCl_3$) δ 7.6–7.1 (m, 10, H), 2.2 (dd, 1, J_{FH} = 22.5, J_{H-H} = 6.0 Hz, cis ring H–F), 2.4 (dd, 1, J_{FH} = 15.0, J_{H-H} = 6.0 Hz, trans ring H–F).

Anal. Calcd for $C_{16}H_{12}OFCl$: *m/e* 274.0560. Found: *m/e* 274.0550 (deviation 1 mmu).

***tert*-Butyl (−)-(*S*)-1-Fluoro-2,2-diphenylcyclopropaneperoxycarboxylate (2a).** *tert*-Butyl hydroperoxide was purified by first extracting 5 g of the commercial hydroperoxide twice into 30 ml of cold 15% potassium hydroxide. The aqueous extract was saturated with ammonium chloride; the hydroperoxide separated as a clear, colorless liquid which was distilled under reduced pressure, bp 58 °C (20 mm).

To a suspension of 4.1 g of a 52% NaH oil dispersion (2.1 g pure, 0.09 mol) in 200 ml of anhydrous ether there was added a solution of 9.0 g (0.10 mol) of purified *tert*-butyl hydroperoxide in 50 ml of anhydrous ether and the mixture was stirred overnight. The white sodium salt of *tert*-butylhydroperoxide was filtered off, washed three times with dry ether, and dried in a vacuum oven at 30 °C (5 mm) for 5 h.

A solution of 3.62 g (0.013 mol) of (−)-1-fluoro-2,2-diphenylcyclopropanecarbonyl chloride in 50 ml of anhydrous ether was added dropwise over the course of 1 h to a suspension of 3.0 g (0.013 mol) of the purified sodium salt of *tert*-butyl hydroperoxide in 200 ml of anhydrous ether at −5 °C. After addition was complete the solution was stirred for an additional 1 h at −5 °C and then hydrolyzed with ice water. The ethereal layer was washed three times with saturated sodium chloride and dried over magnesium sulfate and the solvent removed under reduced pressure. The residue was recrystallized from ethyl ether at −30 °C as white needles: 0.814 g (19%); mp 105–106 °C; $[\alpha]_{Hg}^{24}$ −186° (*c* 0.58, $CHCl_3$); ir (CCl_4) 3080, 2870 (w, C–H), 1780 (s, C=O), 1605, 1490, 1450 (m, phenyl), 1248 cm^{-1} (s, C–F); NMR (CCl_4) δ 7.5–7.0 (m, 10, phenyl), 2.03 (dd, 1, J_{FH} = 36.5, J_{HH} = 7.0 Hz, trans ring H to F), 1.16 (s, 9, *tert*-butyl).

Anal. Calcd for $C_{20}H_{21}O_3F$: C, 73.14; H, 6.44; F, 5.78. Found: C, 73.04; H, 6.43; F, 5.7.

Thermal Decomposition of 2a. The perester was dissolved in 100 ml of anhydrous THF and placed in a thick-walled Pyrex decomposition tube. The sample was flushed with nitrogen for 10 min and then placed in an oven and heated at 100 °C for 44 h. After the tube was cooled the THF was removed under vacuum and the residual oil taken up in ether. The ether was washed three times with a 10% sodium bicarbonate solution and twice with a saturated sodium chloride solution and then dried over anhydrous sodium sulfate. The oily neutral residue remaining after the ether was removed under vacuum was initially purified by preparative TLC on silica gel using a 50% benzene–50% chloroform solution as the eluent. The developed TLC showed three bands: R_f 0.94–0.81, 0.76–0.69, 0.56–0.38. The recovered acid weighed 0.7821 g, 35.1%; $[\alpha]_{Hg}^{23}$ − 144° (c 1.1, acetone); complete retention of configuration.

In order to determine the identity and percentage composition of the reaction products, a 2.524-g (0.008 mol) sample of the racemic perester was decomposed. The total weight of the purified neutral fraction was 0.534 g. The isolation and identification of the reaction products are detailed below.

Isolation of 1-Fluoro-2,2-diphenylcyclopropane (5a). The uppermost band from the preparative TLC plate was extracted with chloroform and analyzed by VPC using an 8-ft column packed with 20% EGIP on 80/100 mesh Chromosorb P/AW at 200 °C. The 1-fluoro-2,2-diphenylcyclopropane was identified by comparison of the retention time with that of an authentic sample. A sample was collected and the ir was found to be identical with that of an authentic sample.[8] The average optical purity[8] (four runs), $[\alpha]_{Hg}^{24}$ −11.3, −8.10, −9.1, −12.7°, is 46.8%.

Isolation of 1,1-Diphenyl-2-fluoro-3-(2-tetrahydrofuranyl)-1-propene (8a). The second compund from the VPC analysis of the third band on the TLC plate was collected as a yellow oil: ir (CCl_4) 2980, 2770 (s, C–H THF), 1669 (s, tetrasubstituted C=C stretch), 1600, 1580, 1500, 1450 cm^{-1} (m, phenyl); NMR (CCl_4) δ 6.1–6.7 (m, 10, phenyl), 2.7–4.2 (m, 3, H on 2 and 5 positions of THF), 2.25–2.28 (m, 2, allyl), 1.7–2.2 (m, 4, H on 3 and 4 position of THF); uv (CH_3OH) λ_{max} 246 nm (ϵ 8970); mass spectra *m/e* (rel intensity) 282 (13.7) ($P^{\cdot+}$), 211 (5.1) ($P^{\cdot+}$ − THF), 191 (6.7) (211 − HF).

Anal. Calcd for $C_{19}H_{19}OF$: *m/e* 282.1419. Found: *m/e* 282.1419 (deviation 0.1 mmu).

Isolation of 1,1,6,6-Tetraphenyl-2,5-difluoro-1,5-hexadiene (10a). The uppermost band from the preparative TLC plate was extracted with chloroform and analyzed by VPC using an 8-ft column packed with 20% Apiezon L on Chromosorb P at 200 °C. The collected dimer was a yellow oil: ir (CCl_4) 3060, 3020 (w, C–H aromatic), 2920, 2860 (s, C–H aliphatic), 1669 cm^{-1} (m, aromatic C=C stretch); NMR (CCl_4) δ 7.5–7.0 (m, 20, phenyl), 2.2–2.0 (d, 4, allylic); uv (CH_3OH) λ_{max} 250 nm (ϵ 2820); mass spectra *m/e* (rel intensity) 422 (0.1) ($P^{\cdot+}$), 211 (45.8) (monomer), 191 (12.1) (monomer − HF).

Anal. Calcd for $C_{30}H_{24}F_2$: *m/e* 422.18604. Found: *m/e* 422.184965 (deviation 0.4 mmu).

Determination of Percentage Composition. The percentage composition of the neutral fraction was determined by taking a small sample of the unpurified neutral products, purifying it by preparative TLC, and extracting all but the baseline from the plate. A portion of this mixture was then analyzed on the VPC using the EGIP column. By a cut-and-weigh technique the relative areas of **5a**, **8a**, and **10** to each other were determined. The data are summarized in Table I.

Registry No.—(−)-(*S*)-**1a**, 30745-01-8; (±)-**1b**, 57719-61-6; (+)-(*S*)-**1b**, 57793-31-4; (±)-**1c**, 57719-62-7; (±)-**1d**, 30724-80-2; (−)-(*S*)-**1d**, 30745-02-9; (−)-(*S*)-**2a**, 57761-85-0; (±)-**2b**, 57719-63-8; (+)-(*S*)-**2b**, 57793-32-5; (±)-**2c**, 57719-64-9; (−)-(*R*)-**2c**, 57793-33-6; (±)-**2d**, 57719-65-0; (−)-(*S*)-**2d**, 57793-34-7; (−)-(*S*)-**5a**, 57719-66-1; (±)-**5b**, 57793-35-8; (*S*)-**5d**, 57793-36-9; **6d**, 57719-67-2; **8a**, 56701-23-6; **9**, 14251-57-1; **10a**, 57719-68-3; **10b**, 57719-69-4; **10c**, 57719-70-7; **10d**, 57719-71-8; (±)-1-methoxy-2,2-diphenylcyclopropanecarbonyl chloride, 57719-72-9; (−)-(*S*)-1-methoxy-2,2-diphenylcyclopropanecarbonyl chloride, 57793-37-0; *tert*-butyl hydroperoxide, 75-91-2; (±)-1-chloro-2,2-diphenylcyclopropanecarbonyl chloride, 57719-73-0; (+)-(*S*)-1-chloro-2,2-diphenylcyclopropanecarbonyl chloride, 57793-38-1; (±)-1-bromo-2,2-diphenylcyclopropanecarbonyl chloride, 57719-74-1; (−)-1-bromo-2,2-diphenylcyclopropanecarbonyl chloride, 57793-39-2; (−)-(*S*)-1-fluoro-2,2-diphenylcyclopropanecarbonyl chloride, 57719-75-2.

References and Notes

(1) The support of this work by Public Health Service Research Grant CA 04065, from the National Cancer Institute, is gratefully acknowledged.

(2) (a) J. K. Kochi, Ed., "Free Radicals", Vol. I and II, Wiley-Interscience, New York, N.Y., 1973; (b) J. W. Henderson, *Q. Rev. Chem. Soc.*, 397 (1973); (c) D. C. Nonhebel and J. C. Walton, "Free Radical Chemistry", Cambridge University Press, New York, N.Y., 1974.

(3) The term σ radical applied to those radicals in which the electron occupies an hybridized orbital and a π radical to those in which the electron is in a p orbital.

(4) R. W. Fessenden and R.H. Schuler, *J. Chem. Phys.*, **43**, 2704 (1965).

(5) M. J. S. Dewar and M. Shanshal, *J. Am. Chem. Soc.*, **91**, 3654 (1969).

(6) L. Pauling, *J. Chem. Phys.*, **51**, 2767 (1969); A. D. Walsh, *Discuss. Faraday Soc.*, **2**, 21 (1947).

(7) R. C. Bingham and M. J. S. Dewar, *J. Am. Chem. Soc.*, **95**, 7180, 1782 (1973).

(8) H. M. Walborsky, L. E. Allen, H.-J. Traenkner, and E. J. Power, *J. Org. Chem.*, **36**, 2937 (1971); H. M. Walborsky, L. Barash, A. E. Young, and F. J. Impastato, *J. Am. Chem. Soc.*, **83**, 2517 (1961).
(9) P. D. Bartlett and T. McBride, *J. Am. Chem. Soc.*, **87**, 1727 (1965).
(10) D. F. DeTar and C. Weis, *J. Am. Chem. Soc.*, **79**, 3045 (1957).
(11) H. M. Walborsky and J. C. Chen, *J. Am. Chem. Soc.*, **92**, 7573 (1970); **93**, 671 (1971).
(12) J. P. Lorand, *J. Am. Chem. Soc.*, **96**, 2867 (1974).
(13) J. P. Engstrom and F. D. Greene, *J. Org. Chem.*, **37**, 968 (1972).
(14) W. A. Pryor, "Free Radicals", McGraw-Hill, New York, N.Y., 1966, p 29.
(15) T. Koenig and J. M. Owens, *J. Am. Chem. Soc.*, **95**, 8484 (1973); **96**, 4052 (1974).
(16) The ketal **6** is difficult to synthesize optically pure. An attempt to use optically active shift reagents to determine optical purity was abortive. See M. D. McCreary, D. W. Lewis, D. L. Wernick, and G. M. Whitesides, *J. Am. Chem. Soc.*, **96**, 1078 (1974); H. L. Goering, J. N. Eikenberry, G. S. Koermer, and L. J. Lattimer, *ibid.*, **96**, 1493 (1974).
(17) D. J. Edge and J. K. Kochi, *J. Am. Chem. Soc.*, **94**, 6485 (1972).
(18) W. M. Jones, M. H. Grasely, and W. S. Brey, Jr., *J. Am. Chem. Soc.*, **85**, 2754 (1963).
(19) Other studies on the stereochemistry of 1-X-cyclopropyl radicals (means of generating radical) follow. X = F (R_3Sn–H), T. Ando et al., *J. Org. Chem.*, **35**, 33 (1970); T. Ando et al., *Bull. Chem. Soc. Jpn.*, **46**, 3513 (1973). X = F (Na–NH_3), M. Schlosser, G. Heinz, and C. V. Chan, *Chem. Ber.*, **104**, 1921 (1971). The results showed very high to complete retention of configuration. X = Cl (R_3SN–H), L. J. Altman and R. C. Baldwin, *Tetrahedron Lett.*, 2531 (1971); D. Seyferth, H. Yamazaki, and D. L. Alleston, *J. Org. Chem.*, **28**, 703 (1963); J. Hatem and B. Waegell, *Tetrahedron Lett.*, 2019 (1973). Results were inconclusive owing to steric factors. X = Cl (perester, *hν*), L. A. Singer and J. C. Chen, *Tetrahedron Lett.*, 939 (1971). Complete loss of configuration was shown. X = OCH_3 (Hunsdieker), T. Ando et al., *Chem. Lett.*, 1133 (1973). The results were inconclusive since only one geometric isomer was used. X = $COOCH_3$, CN (R_3Sn–H), T. Ando, K. Wakabayashi, H. Yamanaka, and W. Funasaka, *Bull. Chem. Soc. Jpn.*, **45**, 1576 (1972). Results showed complete loss of configuration.
(20) P. R. Wells, *Prog. Phys. Org. Chem.*, **6**, 111–145 (1968).
(21) M. S. Liu, S. Soloway, D. K. Wedegaertner, and J. A. Kampmeier, *J. Am. Chem. Soc.*, **93**, 3809 (1971).
(22) Based on the method of analysis these values can at best be viewed as qualitative.

Radical Chain Reactions of Halomethyldimethylsilanes

Il Nam Jung and William P. Weber*

Department of Chemistry, University of Southern California, Los Angeles, California 90007

Received October 3, 1975

Chloromethyldimethylsilyl or bromomethyldimethylsilyl radicals have been generated by photolysis of the corresponding silanes in the presence of mercury or thermolysis with di-*tert*-butyl peroxide. No products of coupling of the silyl radicals [XCH_2–$\dot{S}i(CH_3)_2$] were observed. The products of radical reactions of chloromethyldimethylsilane are time dependent. At short reaction time trimethylsilane and chloromethyldimethylchlorosilane are the major products, while the major product at long reaction time is trimethylchlorosilane. The radical reactions of bromomethyldimethylsilane are faster than those of chloromethyldimethylsilane. No time dependence of the products of radical reaction of bromomethyldimethylsilane was observed. Trimethylbromosilane was the major product of radical reaction of bromomethyldimethylsilane. These results can be explained by two consecutive radical chain processes rather than by a 1,2-halogen shift in the radical intermediates.

The hydrosilation reaction is perhaps the best studied example of a radical chain process involving silyl radicals as intermediates. Thus, the addition of trichlorosilane to 1-octene catalyzed by acetyl peroxide yields trichloro-*n*-octylsilane.[1] This reaction has been proposed to occur by the following mechanism.[1-4]

$$Cl_3Si\text{-}H + In\cdot \rightarrow Cl_3Si\cdot + In\text{-}H$$

$$Cl_3Si\cdot + R\text{-}CH{=}CH_2 \rightarrow Cl_3Si\text{-}CH_2\text{-}\dot{C}H\text{-}R$$

$$Cl_3Si\text{-}CH_2\text{-}\dot{C}H\text{-}R + Cl_3Si\text{-}H \rightarrow Cl_3Si\text{-}CH_2\text{-}CH_2\text{-}R + Cl_3Si\cdot$$

We should like to report a new radical chain process involving silyl radicals as intermediates. The reaction is the conversion of chloromethyldimethylsilane into trimethylchlorosilane under radical initiation. At first this reaction might appear to be a 1,2-radical rearrangement. Few examples of 1,2-radical rearrangements are known in organosilicon chemistry.[5-11] However, on examination this reaction appears to occur by two consecutive radical chain processes both of which involve silyl radical intermediates. The reaction was discovered quite by accident.

Photolysis of trimethylsilane in the vapor phase in the presence of mercury yields hexamethyldisilane and hydrogen.[12] The reaction is believed to involve silyl radicals formed by homolytic cleavage of the Si–H bond. Despite numerous possible complications, both the chemical and quantum yields for the reaction are high. In fact, the reaction has proved a valuable synthetic method to prepare disilanes.[13,14] However, if chloromethyldimethylsilane is photolyzed in the gas phase in the presence of mercury, the products are not the expected disilane, but rather trimethylchlorosilane, trimethylsilane, chloromethyldimethylchlorosilane, and small amounts of hexamethyldisiloxane and chloromethylpentamethyldisiloxane. A small amount of mercury is converted to mercuric chloride. The possibility that mercuric chloride, a weak Lewis acid, catalyzed these transformations was eliminated by control experiments. Thus, chloromethyldimethylsilane was recovered unchanged after refluxing with mercuric chloride. The alternative possibility that this reaction involved a free-radical process was supported by the following experiment. Heating chloromethyldimethylsilane at 136 °C in the presence of a catalytic amount of di-*tert*-butyl peroxide (2%) leads to a similar product mixture. Di-*tert*-butyl peroxide has been previously used to generate silyl radicals by hydrogen abstraction from silanes.[15-17]

The ratio of products is time dependent. (See Figure 1 and Table I). After 20 min at 136° the reaction of chloromethyldimethylsilane initiated by di-*tert*-butyl peroxide (2%) has already consumed almost 40% of the starting material. At this time, the major products were trimethylsilane (~20%) and chloromethyldimethylchlorosilane (~20%). Trimethylchlorosilane was present in small amount (1%). However, if the reaction mixture was heated for longer periods of time, the amounts of trimethylsilane and chloromethyldimethylchlorosilane decreased while the yield of trimethylchlorosilane increased. These results can be explained by a sequence of two radical chain reactions.

The reaction is initiated by abstraction of a hydrogen atom from the Si–H bond by a *tert*-butoxy radical to form the chloromethyldimethylsilyl radical. Abstraction of a chlorine atom from the starting material by this radical leads to chloromethyldimethylchlorosilane and the dimeth-

Table I. Time Dependence of Products from Chloromethyldimethylsilane + *t*-BuO·

Reaction time, min	$HSi(CH_3)_2CH_2Cl$, %	$(CH_3)_3SiH$, %	$ClSi(CH_3)_2CH_2Cl$, %	$(CH_3)_3SiCl$, %
10	91.2	4.4	3.5	0.9
20	60.3	20.9	15.6	1.2
40	41.0	23.9	24.0	10.3
80	28.5	28.8	25.2	17.3
160	23.9	27.6	28.4	20.1
400	8.5	22.6	22.6	46.3
900	0.0	4.1	4.3	91.0

ylsilylmethyl radical [$(CH_3)_2SiH–CH_2$·]. Silyl radicals are known to abstract halogen atoms from alkyl halides.[15,18–22] Abstraction of a hydrogen atom from the Si–H bond of the starting material by the dimethylsilylmethyl radical [$(CH_3)_2SiH–CH_2$·] leads to trimethylsilane and the chloromethyldimethylsilyl radical. This constitutes the initial radical chain reaction. It predicts that trimethylsilane and chloromethyldimethylchlorosilane will be produced in equal amounts as is observed. The second chain reaction sequence results from the buildup of trimethylsilane. Thus, the dimethylsilylmethyl radical [$(CH_3)_2SiH–CH_2$·] can abstract a hydrogen atom from either the starting material or from trimethylsilane. Abstraction of a hydrogen atom from trimethylsilane yields the trimethylsilyl radical and trimethylsilane. The trimethylsilyl radical will abstract a chlorine atom from the chloromethyldimethylchlorosilane to yield trimethylchlorosilane and the dimethylchlorosilylmethyl radical [$(CH_3)_2ClSi–CH_2$·]. The dimethylchlorosilylmethyl radical [$(CH_3)_2ClSi–CH_2$·] will abstract a hydrogen atom from trimethylsilane to yield trimethylchlorosilane and the trimethylsilyl radical. The trimethylsilyl radical may also abstract chlorine from chloromethyldimethylsilane. This sequence of reactions constitutes the second radical chain process. The second radical chain process depends on the concentration of trimethylsilane and chloromethyldimethylchlorosilane, which are the products of the first radical chain process. (See Figure 2.)

This second radical chain process was independently verified. Thus heating *n*-butyldimethylsilane and chloromethyldimethylchlorosilane together in the presence of a catalytic amount of di-*tert*-butyl peroxide leads to trimethylchlorosilane and *n*-butyldimethylchlorosilane in equal amounts (eq 1).

$$CH_3CH_2CH_2CH_2Si(CH_3)_2H + ClCH_2Si(CH_3)_2Cl \longrightarrow CH_3CH_2CH_2CH_2Si(CH_3)_2Cl + (CH_3)_3SiCl \quad (1)$$

Two other products formed, hexamethyldisiloxane and chloromethylpentamethyldisiloxane, can be minimized if care is taken to exclude moisture. Thus it is assumed that they are secondary products of hydrolysis of trimethylchlorosilane and chloromethyldimethylchlorosilane.

A similar radical reaction has been observed in the case of heating bromomethyldimethylsilane at 136° in the presence of a catalytic amount of di-*tert*-butyl peroxide. However, this reaction is faster than that of chloromethyldimethylsilane and so we were unable to observe a time dependence on the product ratios. At even 10 min the reaction was virtually complete. The following products were

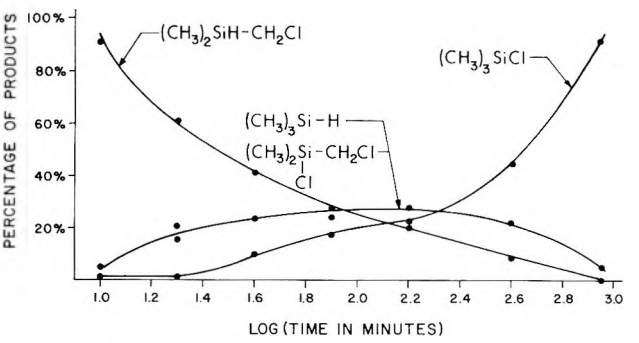


Figure 1. Time dependence of the product ratios in the radical chain reactions of chloromethyldimethylsilane initiated by di-*tert*-butyl peroxide.

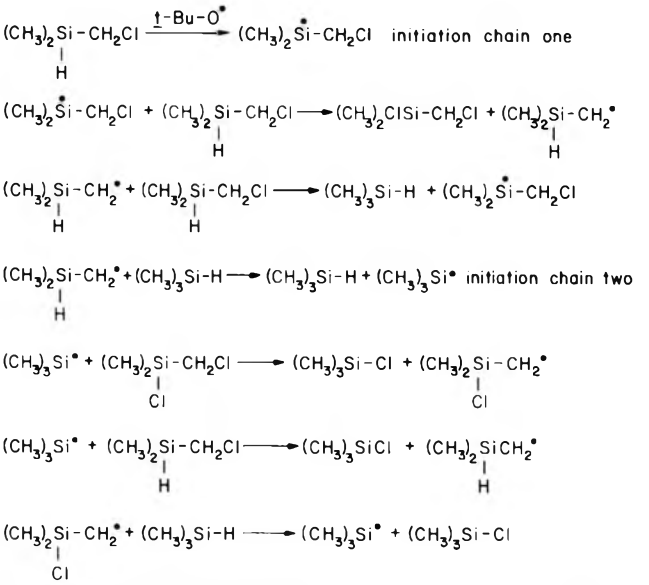


Figure 2. Radical chain reactions of chloromethyldimethylchlorosilane initated by di-*tert*-butyl peroxide.

obtained: trimethylbromosilane, bromomethyldimethylbromosilane, trimethylsilane, hexamethyldisiloxane, and bromomethylpentamethyldisiloxane.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer 337 spectrometer and were calibrated against known bands in a polystyrene film. NMR spectra were recorded on a Varian T-60 spectrometer. Ten percent solutions in carbon tetrachloride with methylene chloride as internal standard (δ 5.28) were used. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer at an ionizing voltage of 70 eV. Vapor phase chromatography was carried out on a Hewlett-Packard F & M 700 using a 20% polyphenyl ether on Chromosorb P 4 ft × 0.25 in. column. Microanalysis was performed by Elek Microanalytical Laboratories, Torrance, Calif. Boiling points were not corrected.

Bromination of Trimethylchlorosilane. Bromine (454 g, 2.8 mol) was slowly added to a solution of trimethylchlorosilane (1200 g, 11 mol) through which chlorine was being bubbled. The solution was illuminated with a 60-W incandescent lamp. This procedure involves in situ formation of bromine chloride.[23] The product was purified by distillation through a 20-cm Vigreux column. A fraction (510 g), bp 120–140 °C, was collected. In contrast to the literature report, this product was a 1:2 mixture of chloromethyldimethylchlorosilane[24] and bromomethyldimethylchlorosilane[23] as determined by NMR integration.

Preparation of Chloromethyldimethylsilane and Bromomethyldimethylsilane. This mixture (220 g) was reduced with lithium aluminum hydride (20.0 g, 1.2 equiv) in ether. Chloromethyldimethylsilane and bromomethyldimethylsilane were separated by fractional distillation through a vacuum jacketed 25-cm spiral wire column. Chloromethyldimethylsilane (38.2 g, 0.35 mol),

bp 80 °C (lit. bp 81.5 °C),[24] was obtained. Bromomethyldimethylsilane (78.5 g, 0.51 mol), bp 99 °C (lit. bp 99–101 °C), was obtained.

Photolysis of Chloromethyldimethylsilane. In a dry 500-ml cylindrical quartz flask connected to a reflux condenser were placed 12.0 g of chloromethyldimethylsilane, 2 drops of mercury, and a 0.5-in. Teflon-covered magnetic stirring bar. The flask was placed at the center of a circular array of 16 12-in. G.E. germicidal lamps (2537 Å). The bottom of the flask was heated using a heating mantle. The solution was stirred. The refluxing vapors were photolyzed for 12 h in an inert atmosphere of purified nitrogen. No mercury was left at the end of the reaction. However, some white solid later identified as mercuric chloride had been formed. The solution weighed 9.2 g. There had been a loss of 2.8 g. Yields reported reflect this loss. Since a water-cooled condenser had been used most of the trimethylsilane formed (lit. bp 6.7 °C)[26] would have been slowly lost. The loss of trimethylsilane will limit the second chain reaction. Thus the amount of chloromethyldimethylchlorosilane will be high. The products were analyzed by VPC: trimethylsilane (1.2%), trimethylchlorosilane (45.4%), chloromethyldimethylchlorosilane (23.2%), hexamethyldisiloxane (1.9%), and finally chloromethylpentamethyldisiloxane (3.2%).

Preparative Scale Thermolysis of Chloromethyldimethylsilane and Di-*tert*-butyl Peroxide. Freshly distilled chloromethyldimethylsilane (8.0 g, 0.074 mol) and 0.4 ml of di-*tert*-butyl peroxide were placed in an ampule (2 × 20 cm) which had been carefully dried. The solution in the ampule was degassed, the ampule sealed, and then heated at 136 °C for 15 h in a Haake R20 constant-temperature bath. At the end of this period, the solution was frozen and the ampule opened. The products were analyzed by VPC: trimethylsilane (3.1%), trimethylchlorosilane (84.8%), chloromethyldimethylchlorosilane (3.4%), hexamethyldisiloxane (3.2%), and chloromethylpentamethyldisiloxane (2.9%).

Preparative Scale Thermolysis of Bromomethyldimethylsilane and Di-*tert*-butyl Peroxide. The reaction of bromomethyldimethylsilane and di-*tert*-butyl peroxide was carried out in a similar fashion. The products were analyzed by VPC: trimethylsilane (3.6%), trimethylbromosilane (83.2%), bromomethyldimethylbromosilane (5.1%), hexamethyldisiloxane (4.4%), and bromomethylpentamethyldisiloxane (1.1%).

Time Dependence of the Product Ratios. Thermolysis of Chloromethyldimethylsilane with Di-*tert*-butyl Peroxide. In each of seven NMR tubes was placed 1 ml of chloromethyldimethylsilane and 10 μl of di-*tert*-butyl peroxide. The solution was degassed and the tubes were sealed. The tubes were heated at 136 °C in a constant-temperature bath. The tubes were withdrawn after various times. They were rapidly cooled to 0 °C and analyzed by NMR. See Table I for data.

***n*-Butyldimethylsilane.** In a 1-l. three-neck round-bottom flask equipped with a mechanical stirrer and a reflux condenser were placed 60.0 g (0.63 mol) of dimethylchlorosilane (Silar Laboratories, Inc.) and 180 ml of absolute diethyl ether. *n*-Butyllithium (2.1 M) in hexane (300 ml) was injected slowly into the solution with vigorous stirring under a dry nitrogen atmosphere. The solution was stirred overnight. The reaction mixture was poured into 300 g of ice. The organic layer was separated, dried over anhydrous magnesium sulfate, and filtered and the product separated by fractional distillation through a 30-cm vacuum-jacketed Vigreux column. A fraction, bp 99 °C (lit. bp 100.5–100.9 °C),[29] 48.2 g (0.4 mol), 63.5% yield, was obtained, ir Si–H 2095 cm^{-1}.

Cothermolysis of *n*-Butyldimethylsilane and Chloromethyldimethylchlorosilane. One milliliter of a 1:1 mixture (v/v) of *n*-butyldimethylsilane and chloromethyldimethylchlorosilane and 15 μl of di-*tert*-butyl peroxide was placed in an NMR tube. The solution was degassed and sealed. The tube was heated in a constant-temperature bath at 136 °C for 3 h. At the end of this time, the NMR spectrum showed no peak at δ 2.64 due to chloromethyldimethylchlorosilane. The products were analyzed by VPC. The following two compounds were separated by preparative VPC and identified by spectral methods: trimethylchlorosilane and *n*-butyldimethylchlorosilane, NMR s (6 H) δ 0.40, m (4 H) 0.91, m (5 H) 1.36, mass spectrum parent ion at *m/e* 150 and 152 with an intensity ratio 2:1.

Spectral Properties of Products. All of the products are known compounds. However, spectral data for these compounds is meager. For this reason we have chosen to report their NMR spectral data.

Chloromethyldimethylchlorosilane.[24] NMR s (6 H) δ 0.52, s (2 H) 2.64; mass spectra parent ion at *m/e* 142, 144, and 146 with intensity ratio of 9:6:1 indicating two chlorine atoms.

Bromomethyldimethylchlorosilane.[23] NMR s (6 H) δ 0.50, s (2 H) 2.35.

Trimethylsilane.[26] NMR d (9 H) δ 0.07, J = 4 Hz; m (1 H) 4.00, J = 4 Hz.

Chloromethyldimethylsilane.[24] NMR d (6 H) δ 0.22, J = 4 Hz; d (2 H) 2.82, J = 2 Hz; m (1 H) 4.13.

Bromomethyldimethylsilane.[25] NMR d (6 H) δ 0.22, J = 4 Hz; d (2 H) 2.48, J = 2 Hz; m (1 H) 4.09.

Chloromethylpentamethyldisiloxane.[27] NMR s (9 H) δ 0.07, s (6 H) 0.15, s (2 H) 2.62; ir 1055 cm^{-1} (Si–O–Si). Anal. Calcd for $C_6H_{17}ClOSi_2$: C, 36.61; H, 8.71. Found: C, 36.99; H, 8.43.

Bromomethyldimethylbromosilane.[28] NMR s (6 H) δ 0.73, s (2 H) 2.70; mass spectra parent ion at *m/e* 230, 232, and 234 with intensity ratio of 1:2:1 indicating two bromines.

Bromomethylpentamethyldisiloxane.[23] NMR s (9 H) δ 0.10, s (6 H) 0.21, s (2 H) 2.39, ir 1064 cm^{-1} (Si–O–Si). Anal. Calcd for $C_6H_{17}BrOSi_2$: C, 29.87; H, 7.10. Found: C, 29.85; H, 6.97.

Acknowledgment. This work was supported by the Air Force Office of Scientific Research, Grant 73-2424. We also thank Dr. T. C. Flood and Dr. H. Rosenberg for most stimulating discussions.

Registry No.—Trimethylchlorosilane, 75-77-4; bromine, 7726-95-6; di-*tert*-butyl peroxide, 110-05-4; *n*-butyldimethylsilane, 1001-52-1; *n*-butyldimethylchlorosilane, 1000-50-6; chloromethyldimethylchlorosilane, 1719-57-9; bromomethyldimethylchlorosilane, 16532-02-8; trimethylsilane, 993-07-7; chloromethyldimethylsilane, 3144-74-9; bromomethyldimethylsilane, 7393-54-6; chloromethylpentamethyldisiloxane, 17201-83-1; bromomethyldimethylbromosilane, 18191-42-9; bromomethylpentamethyldisiloxane, 18143-90-3.

References and Notes

(1) L. H. Sommer, E. W. Pietrusza, and F. C. Whitmore, *J. Am. Chem. Soc.*, **69**, 188 (1947).
(2) E. W. Pietrusza, L. H. Sommer, and F. C. Whitmore, *J. Am. Chem. Soc.*, **70**, 484 (1948).
(3) C. A. Burkhard and R. H. Krieble, *J. Am. Chem. Soc.*, **69**, 2687 (1947).
(4) For a review, see E. Ya. Lukevits and M. G. Voronkov, "Organic Insertion Reactions of Group IV ", Consultants Bureau, New York, N.Y., 1966.
(5) R. L. Dannley and G. Jalics, *J. Org. Chem.*, **30**, 3848 (1965).
(6) C. G. Pitt and M. S. Fowler, *J. Am. Chem. Soc.*, **90**, 1928 (1968).
(7) H. Sakurai, A. Hosomi, and M. Kumada, *Chem. Commun.*, 930 (1968).
(8) A. K. Shubber and R. L. Dannley, *J. Org. Chem.*, **36**, 3784 (1971).
(9) R. West and P. Boudjouk, *J. Am. Chem. Soc.*, **95**, 3983 (1973).
(10) J. W. Wilt, O. Kolewe, and J. F. Kraemer, *J. Am. Chem. Soc.*, **91**, 2624 (1969).
(11) J. W. Wilt and O. Kolewe, *J. Am. Chem. Soc.*, **87**, 2071 (1965).
(12) M. A. Nay, G. N. C. Woodall, O. P. Strausz, and H. E. Gunning, *J. Am. Chem. Soc.*, **87**, 179 (1965).
(13) D. Reedy and G. Urry, *Inorg. Chem.*, **11**, 2117 (1967).
(14) M. E. Childs and W. P. Weber, *J. Organomet. Chem.*, **86**, 169 (1975).
(15) J. Curtice, H. Gilman, and G. S. Hammond, *J. Am. Chem. Soc.*, **79**, 4754 (1957).
(16) P. J. Krusic and J. K. Kochi, *J. Am. Chem. Soc.*, **93**, 846 (1971).
(17) P. J. Krusic and J. K. Kochi, *J. Am. Chem. Soc.*, **91**, 3938 (1969).
(18) R. N. Hazeldine and J. C. Young, *J. Chem. Soc.*, 4503 (1960).
(19) Y. Nagai, K. Yamazaki, I. Shiojima, N. Kobori, and M. Hoyashi, *J. Organomet. Chem.*, **9**, P21 (1967).
(20) A. G. Brook and J. M. Duff, *J. Am. Chem. Soc.*, **91**, 2118 (1969).
(21) H. Sakurai and M. Murakami, *J. Am. Chem. Soc.*, **94**, 5080 (1972).
(22) H. Sakurai, M. Murakami, and M. Kumada, *J. Am. Chem. Soc.*, **91**, 519 (1969).
(23) J. L. Speier, *J. Am. Chem. Soc.*, **73**, 826 (1951).
(24) L. H. Sommer, W. P. Barie, Jr., and D. R. Weyenberg, *J. Am. Chem. Soc.*, **81**, 251 (1959).
(25) A. W. P. Jarvie and R. J. Rowley, *J. Organomet. Chem.*, **57**, 261 (1973).
(26) S. Tannenbaum, S. Kaye, and G. F. Lewenz, *J. Am. Chem. Soc.*, **75**, 3753 (1953).
(27) R. L. Krieble and J. R. Elliott, *J. Am. Chem. Soc.*, **67**, 1810 (1945).
(28) M. Kumada, J. I. Nakajima, M. Ishikawa, and Y. Yamamoto, *J. Org. Chem.*, **23**, 292 (1958).
(29) S. N. Borisov, N. P. Timofeevz, Y. A. Yuzhelevskii, E. G. Kagan and N. V. Kozlova, *J. Gen. Chem. USSR (Engl. Transl.)*, **42**, 374 (1972).

Radical Chlorination of Tetracyclo[3.3.0.0^{2,7}.0^{4,6}]octane and Tetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane with *tert*-Butyl Hypochlorite

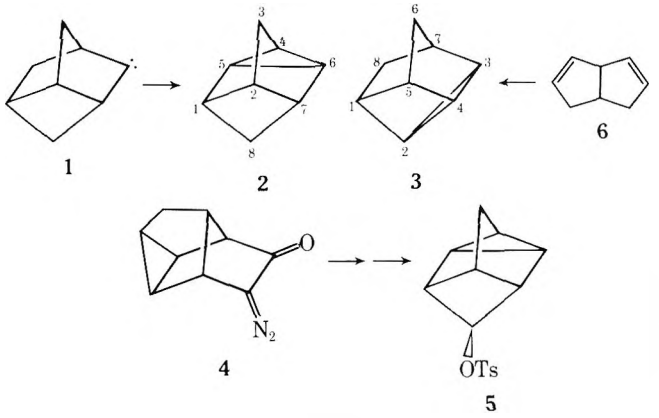
Peter K. Freeman* and Timothy D. Ziebarth

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331

Received September 11, 1975

Photochlorination of tetracyclo[3.3.0.0^{2,7}.0^{4,6}]octane (**2**) with *tert*-butyl hypochlorite in carbon tetrachloride results in C-3 methylene (58%) and C-1 bridgehead substitution (16%) leading to 3-chloro- and 1-chlorotetracyclo[3.3.0.0^{2,7}.0^{4,6}]octane, which are accompanied by three minor monochloride components. Radical chlorination of tetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane (**3**) with *tert*-butyl hypochlorite proceeds via C-1 and C-6 hydrogen abstraction generating a mixture of monochlorides consisting of 1-chlorotetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane (50%), *endo*-6-chlorotetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane (28%), and an equimolar mixture of *exo*-6-chlorotetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane and *exo*-8-chlorotetracyclo[3.3.0.0^{2,7}.0^{4,6}]octane (22%). The successful competition of bridgehead (in the [2.1.1] system) with cyclopropylcarbinyl abstraction in the case of tetracyclo[3.3.0.0^{2,7}.0^{4,6}]octane and bridgehead (in the [2.2.1] system) with trishomocyclopropenyl abstraction in the chlorination of tetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane appear to be dependent upon the antiperiplanarity of the bridgehead C–H bond and a transannular cyclopropane C–C bond.

Earlier studies in this laboratory characterized the interesting carbene insertion pathways of bivalent intermediate **1** that lead to the formation of tetracyclo[3.3.0.0^{2,7}.0^{4,6}]octane (**2**) and tetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane (**3**).[1] Subsequently, Coates and Yano[2] have synthesized the [3.3.0.0^{2,7}.0^{4,6}] system using a Wolff rearrangement of diazodeltacyclanone (**4**) and discovered that solvolysis of **5** in aqueous diglyme–$NaBH_4$ generates a mixture of the two tetracyclooctanes **2** and **3**. Recently, we have reported on an improved photochemical synthesis of tetracyclooctane **3**, which employs the [$_\pi 2_s$ + $_\pi 2_s$] intramolecular valence isomerization of diene **6**.[3]



With several routes to tetracyclooctanes **2** and **3** available, we initiated a study of radical substitution of these interesting substrates with the goals of providing a useful method of introducing a functional group and exploring the nature of hydrogen abstraction and radical rearrangement in the [3.3.0.0^{2,7}.0^{4,6}] (**2**) and [3.3.0.0^{2,4}.0^{3,7}] (**3**) ring systems. Initial experiments using chlorine as the chain transfer agent, however, failed to give monochlorides, since the rate for substitution was at least 100 times less than the rate for electrophilic addition to the cyclopropane moiety in either ring system. As a consequence, we turned to the chlorinating agent *tert*-butyl hypochlorite, which provides a radical substitution route described by the initiation and propagation steps of eq 1–3,[4] since it does not add to three-membered rings.[5]

$$t\text{-BuOCl} \xrightarrow{h\nu} t\text{-BuO}\cdot + \text{Cl}\cdot \quad (1)$$

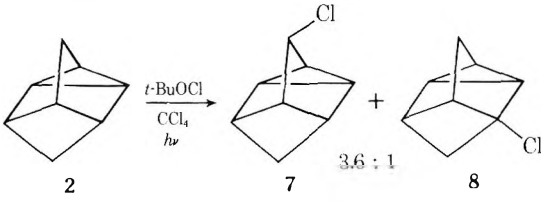
$$\text{RH} + t\text{-BuO}\cdot \rightarrow \text{R}\cdot + t\text{BuOH} \quad (2)$$

$$\text{R}\cdot + t\text{-BuOCl} \rightarrow \text{RCl} + t\text{-BuO}\cdot \quad (3)$$

Photochlorination of tetracyclo[3.3.0.0^{2,7}.0^{4,6}]octane (**2**) with *tert*-butyl hypochlorite in carbon tetrachloride yielded two major and three minor monochlorides in a ratio of 7:16:3:58:8, as determined by vapor phase chromatographic analysis. Mass spectral analysis revealed parent ion masses corresponding to a molecular formula of C_8H_9Cl for the major monochlorides, and lack of olefinic absorptions in ir and NMR spectra indicated that both isomers were tetracyclic.

The 16% component contained no protons α to chlorine in the NMR, establishing it as a bridgehead chloride. Substitution at C-2 and C-4 was ruled out because there are two distinct geminal couplings of 6 and 12 Hz in the NMR spectrum of this component. Of the two remaining bridgehead positions, C-5 was excluded since the endo C-8 proton (identifiable because of its distinct 6-Hz geminal coupling in both this monochloride and in parent hydrocarbon **2**) appears 70 Hz downfield from its chemical shift position in parent hydrocarbon **2**; thus it seems reasonable to assign the 1-chloro structure **8** to this component.[6]

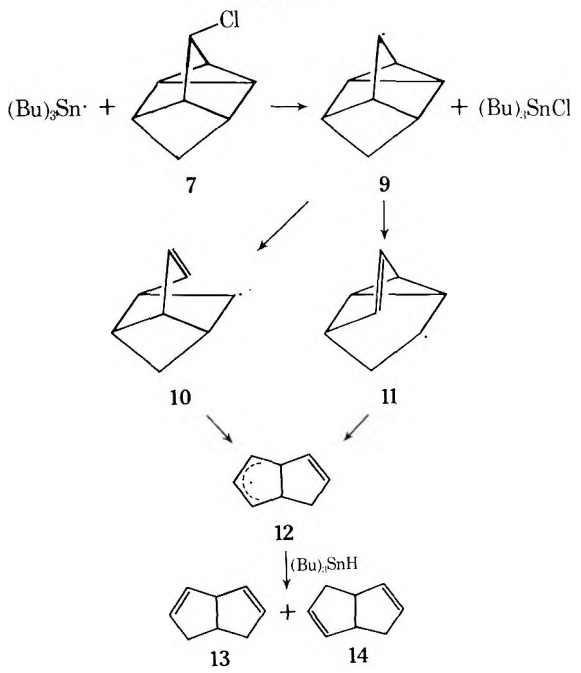
The most abundant product of the photochlorination of **2** was readily identified as 3-chlorotetracyclo[3.3.0.0^{2,7}.0^{4,6}]octane (**7**) by observation of a proton α to chlorine in the NMR spectrum of **7** at δ 4.05 in addition to at least three other unique protons. Substitution at C-8 would yield a structure containing only two unique protons other than the one α to chlorine.



Verification of these two product structures was attempted by subjecting them to free-radical reduction by treatment with tri-*n*-butyltin hydride using azobisisobutyronitrile (AIBN) initiation. Although **8** gave no reduction, the major chloride **7** gave 3% of parent hydrocarbon **2** and 97% of a mixture of bicyclo[3.3.0]octadienes **13** and **14**. The latter two products may arise by either of the fragmentation reactions outlined in Scheme I.

Photochlorination of tetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane (**3**) with *tert*-butyl hypochlorite in carbon tetrachloride yielded four monochlorides which appeared upon VPC analysis as three components in a ratio of 50:28:22. Ir and NMR spectral analyses in conjunction with mass spectral mea-

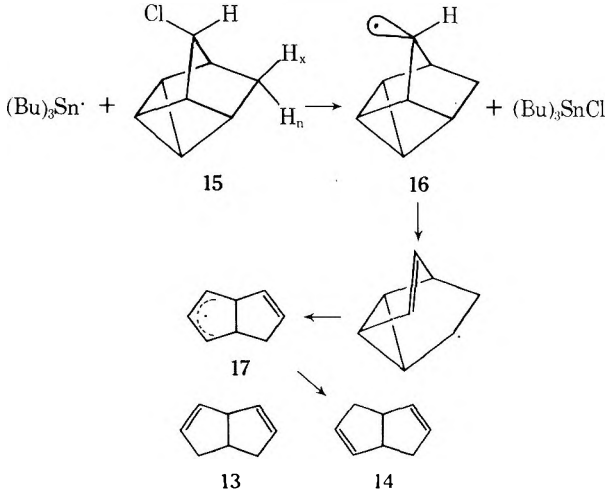
Scheme I



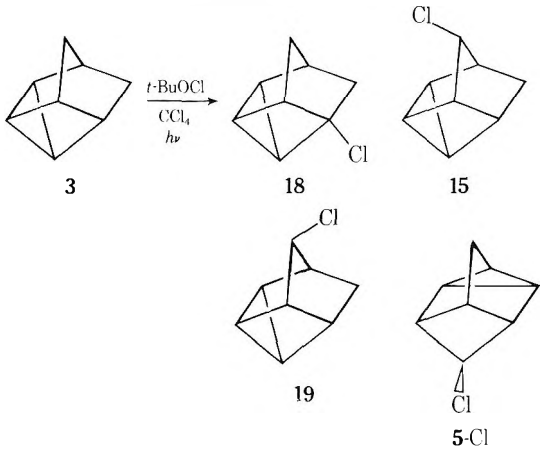
surements, which revealed parent ion masses of 140 and 142 (C_8H_9Cl), suggested that all components were tetracyclic.

Treatment of the 50% monochloride with tri-*n*-butyltin hydride (AIBN, 100°) yielded only parent hydrocarbon **3** in 10% yield. Lack of any protons α to chlorine and the presence of at least three magnetically nonequivalent protons in the NMR spectrum of this component identified it as a bridgehead chloride in the [3.3.0.$0^{2,4}$.$0^{3,7}$] system other than those derived by C-3 or C-7 substitution. Comparison of the NMR spectrum of this monochloride to that of parent hydrocarbon **3** reveals that the proton at C-3 is shifted downfield only 10 Hz in the chloride and has an unaltered splitting pattern, except for the loss of the C-1-H–C-3-H splitting of 0.9 Hz. These observations establish that the structure of this product is 1-chlorotetracyclo[3.3.0.$0^{2,4}$.-$0^{3,7}$]octane (**18**). The 28% product resulting from the photochlorination of **3** yielded parent hydrocarbon **3** (73%) and a mixture of bicyclooctadienes **13** and **14** (27%) upon reduction with tri-*n*-butyltin hydride (AIBN, 100°). Since the NMR spectrum of this chloride contains one proton α to chlorine (δ 3.47), the observed fragmentation must arise from radical **16** via a mechanism similar to that observed in the [3.3.0.$0^{2,7}$.$0^{4,6}$] ring system (Scheme II).

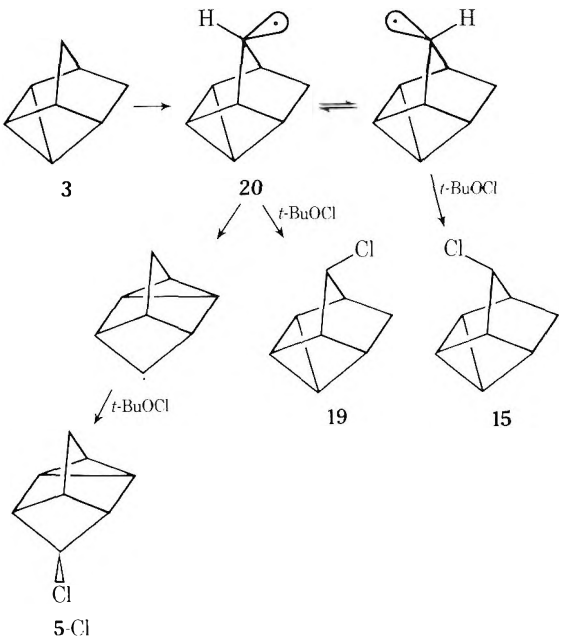
Scheme II



Elucidation of the stereochemistry of the chlorine atom in monochloride **15** was effected by observation of a 14 ± 4% nuclear Overhauser enhancement in the NMR signal of the exo C-8 proton (H_x) relative to the endo C-8 proton (H_n) as a result of irradiation of the proton α to chlorine.[8] Supporting this assignment is the observation of a singlet for the proton α to chlorine in the NMR spectrum of **15**. In the parent hydrocarbon, the exo C-6 and C-8 protons appear as singlets, whereas the endo C-6 and C-8 protons are coupled to the unique bridgehead proton by 2.3 Hz.[10]



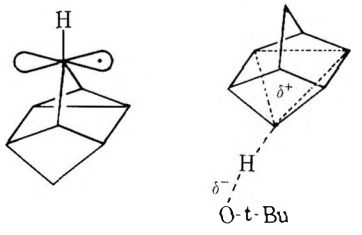
Vapor phase chromatographic and NMR analyses revealed that the 22% product from the photochlorination of **3** was actually a mixture of two isomers in approximately equal proportions. The presence of two protons α to chlorine (a singlet at δ 3.95 and a doublet with J = 2 Hz at δ 3.72) indicated that at least one of these isomers must be a rearrangement product, since in hydrocarbon **3** there are only two diastereotopic secondary positions and substitution at one of these led to chloride **15**. Reduction of the 22% chloride mixture with tri-*n*-butyltin hydride yielded hydrocarbon **2** (70%), hydrocarbon **3** (10%), and a mixture of dienes **13** and **14** (20%) when conducted at 60° with photoinitiation, whereas at 100° without irradiation, **3** was the major product (70%) with minor amounts of **2** (10%) and diene mixture **13** + **14** (20%) also observed. This interesting result suggests that both [3.3.0.$0^{2,7}$.$0^{4,6}$] and [3.3.0.$0^{2,4}$.$0^{3,7}$] ring systems are present in this mixture. Recalling the trishomocyclopropenyl relationship between hydrocarbons



2 and 3, a logical choice for the composition of this mixture would be *exo*-6-chlorotetracyclo[3.3.0.$0^{2,4}$.$0^{3,7}$]octane (**19**) and *exo*-8-chlorotetracyclo[3.3.0.$0^{2,7}$.$0^{4,6}$]octane (**5-Cl**), the latter having been formed by rearrangement of initially formed radical **20**, or by rearrangement after product formation, either in the reaction solution or during VPC collection. The tri-*n*-butyltin hydride reductions performed on the mixture of **19** and **5-Cl** suggest that indeed a radical–radical rearrangement is involved.

Discussion

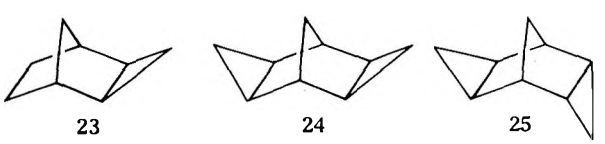
The predominant feature of interest that emerges from a consideration of the results of radical chlorination of tetracyclooctanes **2** and **3** is the important role played by abstraction of hydrogen from bridgehead positions. Abstraction of hydrogen from C-1 in **2** represents abstraction from the bridgehead position of bicyclo[2.1.1]hexane, a previously unprecedented radical reaction pathway.[11] This process takes place in competition with abstraction from C-3, a cyclopropylcarbinyl position in which the transition state may approach the idealized bisected geometry for a cyclopropylcarbinyl radical[12] (i.e., **21**) and from C-8 (maximum 7%), a trishomocyclopropenyl position similar to that of the C-8 position in *endo*-tricyclo[3.2.1.$0^{2,4}$]octane where anchimeric assistance to *tert*-butoxy radical abstraction ≥100 ± 18 (40°) is observed.[13] Thus in C-8 abstraction a transition state similar in nature to **22** might be anticipated.



21 22

The major monochloride in radical chlorination of tetracyclooctane **3** results from *tert*-butoxy hydrogen abstraction at C-1 (equivalent to C-5), which represents bridgehead abstraction in a bicyclo[2.2.1]heptane system.[14] This reaction pathway is followed in close competition with abstraction at C-6, a trishomocyclopropenyl position, again analogous to C-8 abstraction in the *endo*-tricyclo[3.2.1.$0^{2,4}$]octane ring system.

The bridgehead abstractions observed for radical chlorination of tetracyclic **2** and **3** are similar to those we have uncovered in *tert*-butyl hypochlorite chlorination of *exo*-tricyclooctane **23** and *exo,exo*- and *exo,endo*-tetracyclononanes (**24** and **25**)[13] and serve to emphasize the importance of the fused cyclopropane rings in tetracyclic **2** and **3**, even though a bisected cyclopropylcarbinyl radical conformation in the transition state is not possible. Antiperiplanarity of



23 24 25

the C-5–C-6 transannular bond with C-1-H(C-7-H) in **2** and C-2-C-3 with C-1-H (C-4–C-3 with C-5-H) in **3** appear to be the important features in rate enhancement at these bridgehead positions. In both cases a consideration of models reveals that the divergence from antiperiplanar alignment is approximately 8°, using a value of 8.5° for the angle that the maximum electron density of the C–C bond of cyclopropane makes with the internuclear direction.[15] Dependence on antiperiplanarity is emphasized by the total lack of bridgehead substitution at C-7 in tetracyclic **3**, in which case the C-7-H and transannular bond C-3–C-4 are much farther from antiperiplanar alignment (38°).

Experimental Section

All melting points were determined using a Büchi melting point apparatus. All melting points, boiling points, and reaction temperatures reported are uncorrected unless otherwise stated. Microanalyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, 5251 Elbach über Engelskirchen, West Germany, or Chemalytics, Inc., Tempe, Ariz. Infrared spectra were recorded on a Beckman Model IR-8 infrared spectrophotometer, unless stated otherwise. NMR spectra were recorded on a Varian Associates A-60 or HA-100 NMR spectrometer. Routine mass spectra were obtained using an Atlas CH7 mass spectrometer. High-resolution mass spectra were determined by the Department of Chemistry, University of Oregon, Eugene, Oreg., on a CEC 110B instrument. Vapor phase chromatographic analyses and collections were carried out using either an F and M Model 700 or an Aerograph Model A-90-P chromatograph equipped with thermal conductivity detectors. Injector and detector ports were generally operated at 200°, except when analyzing and collecting alkyl halides, when the temperature was reduced to 120° and the injector port lined with Pyrex glass tubing. Columns employed were made with aluminum tubing and contained the following: A, 17 ft × 0.25 in. 10% triscyanoethoxypropane (TCEP) on 70/80 Anakrom ABS; B, 20 ft × 0.125 in. 13% TCEP on 30/60 Chromosorb P (AW); C, 30 ft × 0.125 in. 5% TCEP on 70/80 Anakrom ABS; D, 8 ft × 0.25 in. 15% Carbowax 20M + 2% XF-1112 on 30/60 Chromosorb P (AW).

Product ratios and percentage yields calculated from chromatographic data are based on relative peak areas and were corrected, when necessary, for differences in molecular weight by the method of Eastman.[16] Peak areas were determined by electronic integration using a Hewlett-Packard Model 3373-B integrator unless stated otherwise.

Reduction of Chlorides with Tri-*n*-butyltin Hydride. Chloride reductions reported were conducted in two ways.

Method A. Thermal Initiation. A mixture of alkyl halide, ca. 1.5 equiv of tri-*n*-butyltin hydride, a catalytic amount of azobisisobutyronitrile (AIBN), and cyclohexane was sealed under N_2 in a Pyrex ampule and heated to 100° in an oil bath. The resulting solutions were invariably colorless.

Method B. Photoinitiation. A mixture of required reactants was prepared as in the thermal initiation procedure above, and heated to 60° in an oil bath with irradiation from a 275-W sunlamp at a distance of about 8 in. for 5 h. The resulting solutions were consistently yellow, and were analyzed as individually reported. *tert*-Butyl hypochlorite was prepared by a standard procedure,[17] distilled, and either used at once or stored in the dark at −20° in sealed, degassed ampules. Tri-*n*-butyltin hydride was prepared and distilled by the method of Kuivila[18] and stored at 5° in the dark.

Chlorination of Tetracyclo[3.3.0.$0^{2,7}$.$0^{4,6}$]octane (2) with *tert*-Butyl Hypochlorite. A 4-*m* solution of 75.0 mg (0.71 mmol) of **2** and 90 μl (1 equiv) of *t*-BuOCl in CCl_4 was irradiated in a sealed Pyrex tube at 39.85 ± 0.15° (standardized) with a 275-W sunlamp at a distance of 8 in. for 1 h. To the resulting solution was added 10.0 mg (0.084 mmol) of cyclohexyl chloride as an internal reference, and the mixture was analyzed by VPC on columns A, B, and C. No less than six components in addition to the cyclohexyl chloride and unreacted hydrocarbon were observed in the ratio of 7:16:3:58:8:8 in an overall yield of 34%. Components eluting after these peaks, although numerous, amounted to no more than 5% in yield. The first five components had parent *m/e* 140 and 142, corresponding to tetracyclic monochlorides. The last peak has *m/e* 174, 176, and 178 as well as ions at *m/e* 139 and 141, which corresponded to parent tetracyclic dichloride and P − Cl masses.

The 7% component, in addition to exhibiting *m/e* peaks corresponding to C_8H_9Cl, had ir absorptions at ν 3085, 3001, 2879, 1447, 1342, 1269, 1194, 1090, 1050, 1083, and 1021 cm^{-1}. The 3% component also had a molecular weight corresponding to a molecular formula of C_8H_9Cl and had ir absorptions at ν 3103, 2031, 2959, 2880, 1338, 1264, 966, 944, and 700 cm^{-1}. These two components were not identified further.

The 16% component was identified as 1-chlorotetracyclo[3.3.0.$0^{2,7}$.$0^{4,6}$]octane (**8**) by the spectral analysis summarized below and detailed in the discussion: ir (CCl_4) ν 3078, 3001, 2966, 2890, 2863, 1445, 1318, 1268, 1194, 1160, 1090, 1066, 990, 944, 918, and 874 cm^{-1}; NMR (100 MHz, CCl_4) δ 2.40 (d, *J* = 6 Hz, 1H, exo C-8), 2.35–2.15 (m, 3 H, C-2, C-7, and endo C-8), 1.95–1.65 (m, 4 H,

C-4, C-5, C-6, and syn C-3), 1.52 (d, J = 12 Hz, 1 H, syn C-3).

Anal. Calcd for C_8H_9Cl: m/e 140.039. Found: m/e 140.039.

The major product was identified as 3-chlorotetracyclo[3.3.0.0^{2,7}.0^{4,6}]octane (**7**) by a combination of spectral and chemical evidence outlined below, in the following experiment, and in the discussion: ir (CCl_4) ν 3085, 2994, 2891, 1339, 1318, 1276, 1249, 1229, 1205, 1147, 1047, 1037, 982, 961, 939, 847, and 650 cm^{-1}; NMR (100 MHz, CCl_4) δ 4.05 (t, J = 1.6 Hz, 1 H, C-3), 2.75 (m, 1 H, C-2), 2.45 (m, 1 H, C-4), 2.15 (m, 1 H, C-7, anti to chlorine), 2.00 (m, 2 H, C-1, syn to chlorine, and exo C-8), 1.80 (m with a protruding doublet with coupling of 7 Hz, 3 H, C-5, C-6, and endo C-8).

Anal. Calcd for C_8H_9Cl: C, 68.34; H, 6.45. Found: C, 68.22; H, 6.62.

The 8% monochloride, in addition to a mass corresponding to a molecular formula C_8H_9Cl, had the following ir absorptions: ν 3085, 2983, 2959, 2873, 1617, 1450. 1320, 1287, 1267, 1219, 1195, 1039, 948, 912, 854, 847, 828, 706, 681, and 654 cm^{-1}.

Reduction of 3-Chlorotetracyclo[3.3.0.0^{2,7}.0^{4,6}]octane (7) by Tri-*n*-butyltin Hydride. Chloride **7** (8 mg) was reduced by method A using a 24-h reaction time. Subsequent dilution of the product mixture with pentane and analysis by VPC on column D revealed two volatile peaks in the ratio of 3:97, and no chloride. The minor product had a VPC retention time equal to that of parent hydrocarbon **2**, but was not characterized further. The major product was identified as a 78:22 mixture of 2,7- and 2,6-*cis*-bicyclo[3.3.0]octadiene (**13** and **14**) by comparison of ir and NMR spectral data with those of authentic samples.[19]

Attempted Reduction of 1-Chlorotetracyclo[3.3.0.0^{2,7}.0^{4,6}]octane (8) by Tri-*n*-butyltin Hydride. Treatment of chloride **8** by method A for 5 days resulted in an essentially quantitative recovery of starting material and no hydrocarbon production as determined by VPC analysis.

Chlorination of Tetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane (3) with *tert*-butyl Hypochlorite. A 4-m solution of 0.141 g (1.33 mmol) of hydrocarbon **3** and 159 μl (ca. 1 equiv) of t-BuOCl in CCl_4 was irradiated in a sealed Pyrex ampule at 39.85 ± 0.15° (standardized) with a 275-W sunlamp at a distance of 8 in. for 1 h. To the resulting solution was added 10.5 mg of cyclohexyl chloride as an internal reference and the mixture was analyzed by VPC on columns A, B, and C. Three peaks, each with parent peaks at m/e 140 and 142 corresponding to monochlorides, were observed in the ratio of 50:22:28 in an overall yield of 28%. The 22% component had a peak shape indicating that it was a mixture of two components Dichlorides were not observed in greater than 10% overall yield.

The major component was identified as 1-chlorotetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane (**18**) by a combination of spectral and chemical analysis described below, in the discussion section, and in the following tri-*n*-butyltin hydride reduction: ir (CCl_4) ν 3104, 3020, 2982, 2891, 1439, 1343, 1248, 1250, 1220, 1058, 1020, and 682 cm^{-1}; NMR (100 MHz, CCl_4) δ 2.73–2.43 (m, 4 H, C-2, C-4, C-5, and C-7), 2.02–1.83 (m, 1 H, C-3), 1.69 (d, J = 10 Hz, 1 H, exo C-8), 1.23 (d, J = 10 Hz, 1 H, exo C-6), 0.92 (d, J = 10 Hz, 2 H, endo C-6 and C-8).

Anal. Calcd for C_8H_9Cl: m/e 140.039. Found: m/e 140.040.

The 22% component, although a mixture, was treated as a single component, since preparative VPC separation proved unsuccessful. This peak was assigned as a mixture of *endo*-6-chlorotetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane (**19**) (chloride B in the NMR assignments below) and *exo*-8-chlorotetracyclo[3.3.0.0^{2,7}.0^{4,6}]octane (**5-Cl**) (chloride A in the NMR assignments below) by a combination of spectral and chemical evidence outlined below, in the following reduction experiments, and in the discussion section: ir (CCl_4, collective) ν 3096, 3030, 2976, 2890, 1448, 1287, 1261, 973, 951, 911, 701, and 656 cm^{-1}; NMR (100 MHz, CCl_4) δ 3.95 (s, $W_{1/2}$ = 2 Hz, 1A H, endo C-8), 3.72 (d, J = 2 Hz, 1B H, exo C-6), 2.99 (broad m, $W_{1/2}$ = 8 Hz, 1B H, C-7), 2.58 (broad s, $W_{1/2}$ = 9 Hz, 2B H, C-1 and C-5), 2.53–2.38 (m, 2A H, C-1 and C-7, and 1B H, C-4), 2.20–2.05 (m, 1A H, C-2), 2.04–1.85 (m, protruding doublet, J = 9 Hz, 2B H, exo C-8 and C-2), 1.95–1.65 (m, 1A H, C-4, and 1B H, C-3), 1.52–1.40 (m, 4A H, C-3, C-5, and C-6), 1.37 (d, J = 9 Hz, 1B H, endo C-8).

Anal. Calcd for C_8H_9Cl: m/e 140.039. Found: m/e 140.036.

The 28% component was identified as *exo*-6-chlorotetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane (**15**) by spectral analysis, a nuclear Overhauser experiment, and tri-*n*-butyltin hydride reduction described below and in the discussion: ir (CCl_4) ν 3104, 3058, 3010, 2915, 1444, 1297, 1279, 954, 688, and 652 cm^{-1}; NMR (100 MHz, CCl_4) δ 3.47 (s, $W_{1/2}$ = 5 Hz, 1 H, C-6), 2.58–2.45 (m, 1 H, C-7), 2.43–2.08 (m, 4 H, C-1, C-2, C-4, and C-5), 2.00–1.76 (m, 1 H, C-3), 1.28 (doublet of doublets, J = 10, *ca.* 2 Hz, 1 H, exo C-8), 1.04 (d, J = 10 Hz, 1 H, endo C-8).

Anal. Calcd for C_8H_9Cl: m/e 140.039. Found: m/e 140.040.

Reduction of 1-Chlorotetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane (18) by Tri-*n*-butyltin Hydride. Using method A, 7.12 mg of chloride **18** was heated for 5 days. Dilution of the resulting solution with pentane followed by preparative VPC isolation, using column D, of the single volatile component, in addition to a large amount of unreacted chloride (estimated to be 90%), identified this product as parent hydrocarbon **3** by comparison of an ir spectrum and VPC retention time with those of an authentic sample.

Reduction of *exo*-6-Chlorotetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane (15) by Tri-*n*-butyltin Hydride. Application of method A for 24 h gave approximately 80% conversion of 7.0 mg of chloride **15** to two volatile components in the ratio of 100:37 which were isolated by preparative VPC using column D. The ir spectrum of the major product was identical with that of an authentic sample of hydrocarbon **3**. The minor product had an ir spectrum identical with that of 2,6-*cis*-bicyclo[3.3.0]octadiene (**14**). It was estimated that as much as 20% of the 2,7 isomer **13** could have been present.

Reduction of the Mixture of *endo*-6-Chlorotetracyclo[3.3.0.0^{2,4}.0^{3,7}]octane (19) and *exo*-8-Chlorotetracyclo[3.3.0.0^{2,7}.0^{4,6}]octane (5-Cl) by Tri-*n*-butyltin Hydride. Method A. Reduction of 6.0 mg of a mixture of chlorides **19** and **5-Cl** for 5 days, followed by VPC analysis using column D, revealed three volatile peaks in the ratio of 10:70:20, having retention times equal to **2**, **3**, and **13** and/or **14**, respectively. Preparative VPC followed by ir analysis confirmed the identity of the major product as hydrocarbon **3**.

Method B. Reduction of 7.0 mg of a mixture of chlorides **19** and **5-Cl**, followed by VPC analysis using column D, revealed three components in the ratio of 70:10:20 having retention times equal to **2**, **3**, and **13** and/or **14**, respectively. Preparative VPC followed by ir analysis identified the 70% component as hydrocarbon **2**, and the 20% component as 2,6-diene **14**, which could have contained up to 30% of the 2,7 isomer **13**.

Acknowledgments. The authors gratefully acknowledge the support of this work by the National Science Foundation and express their appreciation for an NSF Graduate Traineeship (T.D.Z.).

Registry No.—**2**, 5078-81-9; **3**, 4582-22-3; **5-Cl**, 57513-36-7; **7**, 57513-37-8; **8**, 57513-38-9; **15**, 57513-39-0; **18**, 57513-40-3; **19**, 57549-45-8; *tert*-butyl hypochlorite, 507-40-4; tributyltin hydride, 688-73-3.

References and Notes

(1) P. K. Freeman, T. D. Ziebarth, and V. N. M. Rao, *J. Org. Chem.*, **38**, 3823 (1973); P. K. Freeman, V. N. M. Rao, and G. E. Bigam, *Chem. Commun.*, 511 (1965).
(2) R. M. Coates and K. Yano, *Tetrahedron Lett.*, 2289 (1972).
(3) P. K. Freeman and T. D. Ziebarth, *J. Org. Chem.*, **38**, 3635 (1973).
(4) C. Walling and B. B. Jacknow, *J. Am. Chem. Soc.*, **82**, 6108 (1960).
(5) C. Walling and P. S. Fredericks, *J. Am. Chem. Soc.*, **84**, 3326 (1962).
(6) The magnetic anisotropy of the C(5)–Cl bond would not be expected to provide especially effective deshielding to reverse the normal order of chemical shifts of β C–H and γ C–H in chloroalkanes,[7a] since the angle subtended by C(5)–Cl–H (endo C-8) is 50°, approximating the angle (θ) of 54° 45′ required to reduce the term ($1 - 3\cos^2\theta$) and thus the contribution of magnetic anisotropy ($\sigma_{H,CCl}$) to zero.[7b]
(7) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy", Pergamon Press, Elmsford, N.Y.; (a) Vol. II, 1966, pp 670–676; (b) Vol. I, 1965, pp 130–140.
(8) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect; Chemical Applications", Academic Press, New York, N.Y., 1971, p 1. The magnitude of this nuclear Overhauser effect is less than the predicted enhancement based on an internuclear H–H distance of 2.20 Å (measured using a Dreiding model) and the work of Bell and Saunders;[9] however, the 14% signal enhancement was observed without rigorous degassing, as is necessary to obtain correlation with theory.
(9) R. A. Bell and J. K. Saunders, *Can. J. Chem.*, **48**, 1114 (1970).
(10) V. N. M. Rao, Ph.D. Dissertation, University of Idaho, 1965.
(11) R. Srinivasan and F. I. Sonntag, *J. Am. Chem. Soc.*, **89**, 407 (1967).
(12) J. K. Kochi, P. J. Krusic, and D. R. Eaton, *J. Am. Chem. Soc.*, **91**, 1877, 1879 (1969); G. A. Russell and H. Malkus, *ibid.*, **89**, 160 (1967); N. L. Bauld, R. Gordon, and J. Zoeller, Jr., *ibid.*, **89**, 3948 (1967).
(13) P. K. Freeman, T. D. Ziebarth, and R. S. Raghavan, *J. Am. Chem. Soc.*, **97**, 1875 (1975); P. K. Freeman, R. S. Raghavan, and G. L. Fenwick, *ibid.*, **94**, 5101 (1972).
(14) C. V. Smith and W. E. Billups, *J. Am. Chem. Soc.*, **96**, 4307 (1974).
(15) R. M. Stevens, E. Switkes, E. A. Laws, and W. N. Lipscomb, *J. Am. Chem. Soc.*, **93**, 2602 (1971); R. Hoffmann, *J. Chem. Phys.*, **40**, 2480 (1964).
(16) R. Eastman, *J. Am. Chem. Soc.*, **79**, 4243 (1957).
(17) H. M. Teeter and E. W. Bell, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 125.
(18) H. G. Kuivila and O. F. Beumel, Jr., *J. Am. Chem. Soc.*, **83**, 1246 (1961).
(19) W. von E. Doering and W. R. Roth, *Tetrahedron Lett.*, 715 (1963).

Regiospecific Baeyer–Villiger Oxidation of Polycyclic Ketones with Ceric Ion

Goverdhan Mehta* and Paras N. Pandey[1]

Department of Chemistry, Indian Institute of Technology, Kanpur-208016, U.P., India

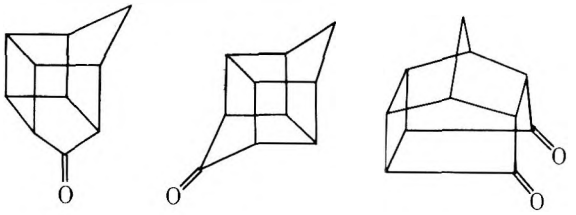
Tse-Lok Ho

Department of Chemistry, The University of Manitoba, Winnipeg, Canada

Received June 2, 1975

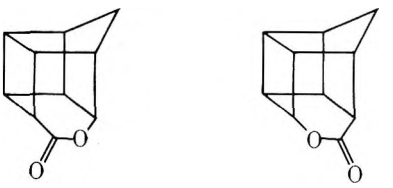
Efficient and preparatively useful Baeyer–Villiger (BV) oxidation of a few polycyclic ketones with ceric ion is reported. The BV oxidation of pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one (1,3-bishomocubanone, **1**) and pentacyclo[6.2.1.0^{2,7}.0^{4,10}.0^{5,9}]undecane-3,6-dione (**3**) with ceric ion proceeds regiospecifically and the results differ from those of conventional peracid oxidation. A plausible mechanism is advanced to explain the regiospecificity of ceric ion oxidations.

A variety of organic functional groups can be conveniently oxidized with ceric ion and many of these reactions find some useful synthetic applications.[2,3] It has been shown that alicyclic ketones are rapidly consumed by ceric ion to furnish ω-nitratocarboxylic acids as the main products via a pathway involving α-cleavage.[4] A sole exception[4] is the ceric ion oxidation of adamantanone, which furnishes the corresponding Baeyer–Villiger lactone in good yield. In pursuit of certain synthetic objectives, we have investigated the ceric ion oxidation of three pentacyclic ketones, pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one (1,3-bishomocubanone, **1**), pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decan-5-one (1,4-bishomocubanone, **2**), and pentacyclo[6.2.1.0^{2,7}.0^{4,10}.0^{5,9}]-undecan-3,6-dione (**3**), and find that these compounds undergo efficient Baeyer–Villiger (BV) type oxidation. Furthermore, the oxidation of unsymmetrical 1,3-bishomocubanone (**1**) and pentacyclic diketone **3** proceeds in a highly regiospecific manner to yield a lactone different from that obtained by the conventional peracid oxidation. We believe that this observation may be of general synthetic utility in carrying out regiospecific BV oxidations[5] of geometrically constrained polycyclic ketones with ceric ion.



1 **2** **3**

Reaction of 1,3-bishomocubanone (**1**) with a slurry of ceric ammonium sulfate (CAS) or ceric ammonium nitrate (CAN) in aqueous acetonitrile furnished a single product, mp 133–135 °C, in 78% yield. Mass spectral measurements (M$^+$ *m/e* 162) and strong infrared absorptions at 1760, 1180, and 1000 cm^{-1} suggested a δ-lactone (boat)[6] structure for the product. This contention was clearly supported by the ^{1}H NMR spectrum, which displayed a 1 H quartet at δ 5.05 (J_1 = 4 and J_2 = 3 Hz) due to the presence of a H–C–O–C=O type proton and mass spectral peaks at *m/e* 118 (M$^+$ − CO_2) and 117 (M$^+$ − CO_2H). These data are compatible with either structure **4** or **5** for the CAS oxidation product. At this stage, in order to confirm that the ceric ion oxidation product was indeed a BV product, peracid oxidation of **1** was investigated. When **1** was treated with *m*-chloroperbenzoic acid, a 5:1 mixture of two lactones was obtained. The major compound (M$^+$ *m/e* 162), mp 145–146 °C, showed typical δ-lactone (boat)[6] bands at 1755 and 1070 cm^{-1} and was distinctly different from the lactone obtained via CAS oxidation of **1**. Its ^{1}H NMR spectrum, as expected, showed a triplet at δ 4.71 (J = 6 Hz) due to a H–C–O–C=O type proton. This data was suggestive of either structure **4** or **5** for the lactone. The minor product from the peracid oxidation, however, proved to be identical with the lactone obtained from CAS oxidation. The ^{1}H NMR data for the two lactones, particularly the multiplicity of the low-field signal, was strongly indicative of their being positional isomers **4** and **5** but was of little diagnostic value in distinguishing them. The possibility of any skeletal rearrangement was ruled out on the basis of the mass spectral fragmentation, which showed strong peaks at *m/e* 66 ($C_5H_6^+$) diagnostic[7] of this system and resulting from the cleavage of the carbon skeleton in half. A strong peak at *m/e* 91 ($C_7H_7^+$) attributed[7] to tropylium ion was also observed in all of these compounds. A straightforward degradative scheme[8] was therefore designed and is summarized in Scheme I.

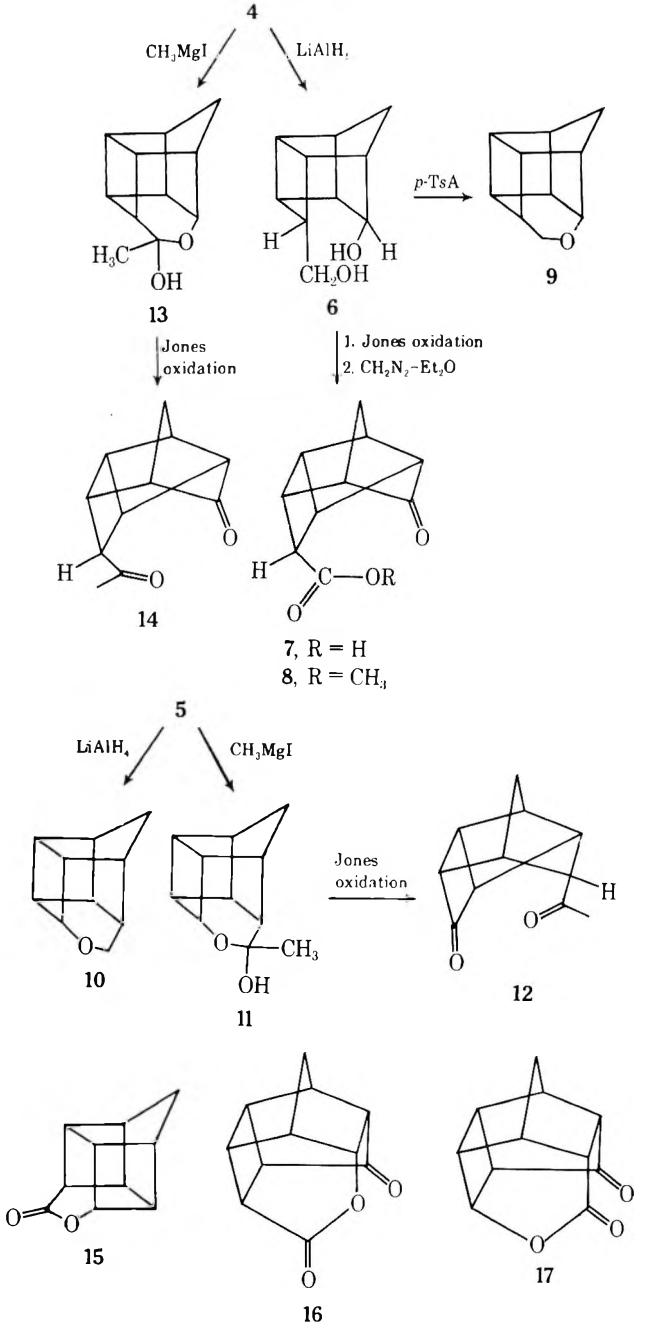


4 **5**

The CAS lactone was reduced by lithium aluminum hydride to the diol **6** and oxidized with Jones reagent to the keto acid **7**. Diazomethane esterification of **7** gave the keto ester **8**, which displayed ir absorptions at 1740 (cyclopentanone) and 1730 cm^{-1} (ester) along with expected ^{1}H NMR resonances and established the structure of this lactone as **4**. Lithium aluminum hydride reduction of the peracid lactone did not furnish any diol and only a pentacyclic ether **10** was formed.[9] An isomeric ether **9** was also prepared from the dehydration of diol **6** but again a distinction between **9** and **10** could not be made on spectral grounds. Addition of methylmagnesium iodide to the peracid lactone yielded the lactol **11** [ir 3550, 1050, 1055 cm^{-1}; ^{1}H NMR δ 1.38 (3 H, singlet)] which was oxidized with Jones reagent to the diketone **12** exhibiting cyclobutanone absorption (1775 cm^{-1}) in the ir spectrum. Analogous degradation of CAS lactone via the lactol **13** [ir 3500, 1010, 1050 cm^{-1}; ^{1}H NMR δ 1.6 (3 H, singlet)] yielded the isomeric dilactone **14** displaying a cyclopentanone absorption (1740 cm^{-1}). The structures of Ce^{4+} and peracid lactones were thus established as **4** and **5**, respectively.

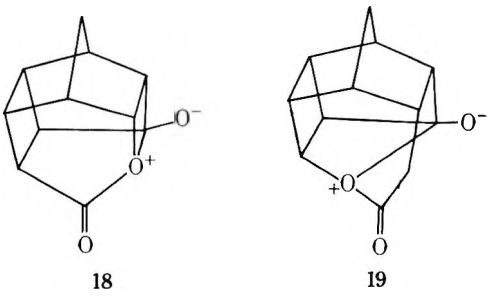
The symmetrical 1,4-bishomocubanone (**2**) on CAS oxidation furnished a crystalline lactone **15**, mp 130–132 °C, which showed ir bands at 1755 and 1260 cm^{-1} (δ-lactone)[6]

Scheme I



and a proton at δ 5.0 due to H–C–O–C=O type functionality. The same lactone was also obtained from the peracid oxidation of **2**.

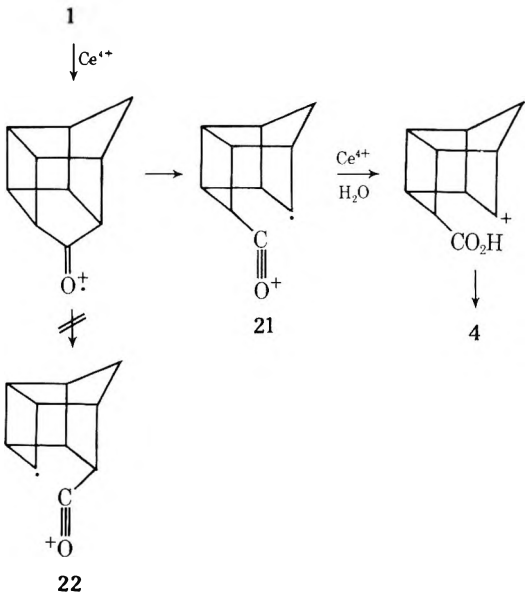
Oxidation of pentacyclic diketone **3** with CAN in aqueous acetonitrile yielded a single crystalline monolactone **16**, mp 280–282 °C, and its structure was derived from the following spectral characteristics. The δ-lactone **16** exhibited intense carbonyl bands at 1780 and 1725 cm^{-1} and displayed in its ^1H NMR spectrum a one-proton triplet at δ 5.17 (J = 7.5 Hz) due to H–C–O–C=O type grouping. The mass spectral (M^+ m/e 190) fragmentation with strong peaks at m/e 146 ($M^+ - CO_2$), 145 ($M^+ - CO_2H$), 118 ($M^+ - CO_2 - CO$), and 117 ($M^+ - CO_2 - CO - H$) was in complete harmony with a keto lactone structure. The hypsochromic shift of the δ-lactone carbonyl (1780 cm^{-1}) and the bathochromic shift of the cyclopentanone carbonyl (1725 cm^{-1}) in the ir spectrum of **16** can be attributed to the contribution of the form **18**. In the alternative structure **17** for this lactone such an spatial interaction **19** is precluded on account of unfavorable geometry. Reaction of **3** with *m*-



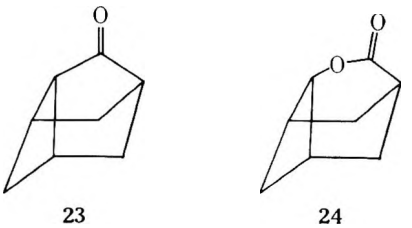
chloroperbenzoic acid under a variety of conditions led to the isolation of only a dilactone **20**, mp >300 °C, ir 1760 cm^{-1} (δ-lactone), MS M^+ m/e 207?, and no monolactonic product could be detected. The presence of a second carbonyl group in **3** complicates its peracid oxidation and in this case the preparative utility of ceric ion in effecting BV oxidation is clearly demonstrated.

A plausible mechanism for the formation of lactone **4** in the CAS oxidation of **1** is outlined in Scheme II and is in

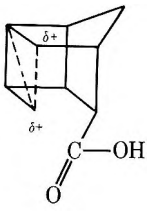
Scheme II



harmony with the currently accepted mechanism[3] of ceric ion oxidations.[11] The regiospecificity of this reaction can be attributed to the greater stability[12] of cyclopentyl radical intermediate **21** over the cyclobutyl radical intermediate **22**. This selective α-cleavage to furnish the more stable radical intermediate should be useful in the regiospecific BV oxidation of polycyclic ketones and the efficient **3** → **16** oxidation with ceric ion further strengthens this contention. On the other hand, regioselective formation of lactone **5** in the peracid oxidation of **1** clearly indicated preferential migration of cyclobutyl ring vs. the cyclopentyl ring. Recently, Monti and Ward[13] observed in the BV oxidation of tricyclo[3.2.1.$0^{3,6}$]octan-7-one (**23**) that the cyclobutyl migration was overwhelmingly favored and lactone **24** was exclusively formed. Such preferential migration of cyclobutyl



ring was not observed in simple model systems and therefore regiospecific formation of lactone **24** was attributed to the σ-assisted C–C bond cleavage and stabilization of the incipient positive charge through a cyclobutyl–cyclopropyl–carbinyl type resonance. The results obtained with **1** are likewise suggestive of σ participation by the strained C_3–C_4 cyclobutyl bond and stabilization of the developing positive charge via a cyclobutyl–cyclopropyl–carbinyl type resonance **25**. The rigid framework of **1** and the favorable geo-



25

metrical disposition of the C_3–C_4 bond make this participation possible and it is fully borne out by an examination of molecular models.

Experimental Section[14]

Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one (1,3-bishomocubanone, **1**),[15] pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decan-5-one (1,4-bishomocubanone, **2**),[16] and pentacyclo[6.2.1.0^{2,7}.0^{4,10}.0^{5,9}]undecane-3,6-dione (**3**)[17] were prepared according to the literature procedures.

Oxidation of Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one (1) with Ceric Ammonium Sulfate. To a magnetically stirred slurry of ceric ammonium sulfate (18 g, 28 mmol) in water (35 ml) in a 100-ml round-bottom flask, a solution of bishomocubanone **1** (1 g, 6.9 mmol) in acetonitrile (18 ml) was added. The reaction mixture was heated at 60 °C for 1 h and cooled to room temperature. Dilution with water, extraction with methylene chloride (2 × 25 ml), washing, drying, and evaporation of solvent gave 1.05 g of a waxy solid. Elution of this material from a silica gel (30 g) column with benzene yielded 0.86 g (78%) of pure lactone **4**, which on sublimation (80 °C at 1 mm) gave white, glistening solid: mp 133–135 °C; ir (KBr) 1760, 1180, 1000 cm^{-1} (lactone): ^{1}H NMR (CCl_4) δ 5.05 (H–C–O–C=O, 1 H, q, J_1 = 4, J_2 = 3 Hz), 1.25–3.2 (CH ring, 9 H, envelope); MS *m/e* 162 (M^+), 118 ($M^+ - CO_2$), 117 ($M^+ - CO_2H$), 105, 103, 91 ($C_7H_7^+$), 84, 79, 66 ($C_5H_6^+$). Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22. Found: C, 74.3; H, 6.00.

Oxidation of 1,3-Bishomocubanone (1) with *m*-Chloroperbenzoic Acid. To a solution of **1** (0.1 g, 0.7 mmol) in dry benzene (10 ml), *m*-chloroperbenzoic acid (0.15 g, 0.87 mmol, Aldrich) and a catalytic amount of *p*-toluenesulfonic acid (50 mg) were added with gentle swirling of the flask. Reaction was completed in 2 h (TLC) and the mixture was poured into water (10 ml), extracted with ether (2 × 20 ml), and washed with aqueous sodium bicarbonate (3 × 10 ml). Removal of solvent yielded a waxy solid, 0.10 g (90%), which was found to be a mixture of lactones **5** and **4** in a ratio of 5:1 (^{1}H NMR integration). Separation of the two lactones was achieved by preparative TLC on silica gel plates (20 × 20 cm) using benzene–ethyl acetate (4:1) as the solvent system. The fast moving minor component was identical with the lactone **4** formed in the CAS oxidation of **1**. The major component was sublimed (80 °C, 1 mm) to yield 0.05 g of white crystals: mp 145–146 °C; ir (KBr) 1755, 1365, 1070 cm^{-1} (lactone); ^{1}H NMR (CCl_4) δ 4.7 (H–C–O–C=O, 1 H, t, J = 6 Hz), 1.6–3.4 (CH ring, 9 H, envelope); MS *m/e* 162 (M^+), 118 ($M - CO_2$), 117 ($M^+ - CO_2 - H$), 91 ($C_7H_7^+$), 66 ($C_5H_6^+$). Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22. Found: C, 74.36; H, 6.3.

$LiAlH_4$ Reduction of Lactone 4. Lactone **4** (0.7 g, 4.3 mmol) in dry ether (25 ml) was added slowly to a slurry of lithium aluminum hydride (0.3 g, 7.9 mmol) in dry ether (15 ml). The reaction mixture was stirred for 12 h at room temperature and then quenched by adding slowly 3 ml of water and 1 ml of 15% potassium hydroxide. Extraction with methylene chloride (2 × 20 ml) yielded 0.6 g of crude diol. Crystallization from ether gave glistening white needles, 0.5 g (68.7%), of **6**: mp 125 °C; ir (KBr) 3450 (hydroxyl), 1000, 1075 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.5 (HCOH, 1 H, m), 4.03 (H_2COH, 2 H, m), 1.2–2.65 (CH ring and –OH, 11 H, envelope); MS *m/e* 148 ($M^+ - H_2O$), 117, 120 ($C_9H_{12}^+$), 91 ($C_7H_7^+$), 79 ($C_5H_3O^+$ or $C_6H_7^+$), 66 ($C_5H_6^+$). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.21; H, 8.35.

Acid-Catalyzed Cyclization of Diol 6 to Pentacyclic Ether 9. The above diol **6** (0.1 g, 0.6 mmol) in dry benzene (10 ml) containing *p*-toluenesulfonic acid (10 mg) was refluxed for 2 h. The reaction mixture was poured into sodium carbonate solution (10 ml, 5%) and extracted with ether (2 × 20 ml); washing, drying, and removal of solvent gave a waxy residue showing a single spot on TLC. Sublimation (60 °C, 1 mm) of this material yielded 0.08 g (89.7%) of **9** as a white, crystalline solid: mp 140 °C; ir (KBr) 1025 cm^{-1} (ether); ^{1}H NMR (CCl_4) δ 4.8 (HCO–, 1 H, m), 4.0 (–CH_2O–, 2 H, m), 1.2–2.75 (CH ring, 9 H, envelope); MS *m/e* 148 (M^+), 120 ($M^+ - CO$), 117, 91 ($C_7H_7^+$), 79 ($C_5H_3O^+$ or $C_6H_7^+$), 69 ($C_4H_5O^+$). Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: 80.89; H, 8.09.

Jones Oxidation of Diol 6. An ice-cooled, stirred solution of the diol **6** (0.2 g, 1.2 mmol) in 5 ml of acetone was treated dropwise with Jones reagent (2 ml) until the brown color persisted. The mixture was stirred for 4 h, diluted with water, and extracted with ether (2 × 25 ml). The organic layer was successively washed with sodium carbonate and brine and dried. Removal of solvent gave 0.04 g of product, which was identified as lactone **4**. The water layer was acidified with 15% HCl and extracted with methylene chloride (3 × 25 ml) to give 0.13 g of keto acid **7**: ir (KBr) 3375, 1740, 1725, 1245 cm^{-1}.

Keto Ester 8. To a solution of the above keto acid **7** (0.1 g) in dry ether, an ethereal solution of diazomethane was added until a permanent yellow color persisted. The reaction mixture was left aside for 1 h and excess of diazomethane was neutralized by careful addition of acetic acid. Removal of solvent and direct distillation gave keto ester **8** as a colorless liquid: bp 110–115 °C (bath, 1 mm); ir (neat) 1740, 1730, 1180 cm^{-1}; ^{1}H NMR (CCl_4) δ 3.67 (CH_3OC=O, 3 H, s), 1.5–3.1 (CH ring, 9 H, envelope); MS *m/e* 192 (M^+), 164 ($M^+ - CO$), 161 ($M^+ - OCH_3$), 131 ($M^+ - CO_2Me$), 114, 79 ($C_5H_3O^+$ or $C_6H_7^+$). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.53; H, 6.14.

$LiAlH_4$ Reduction of Lactone 5. Lactone **5** (0.7 g, 4.3 mmol) in dry ether (25 ml) was added slowly to a slurry of lithium aluminum hydride (0.3 g, 7.9 mmol) in dry ether (15 ml). The reaction mixture was stirred for 8 h at room temperature. Work-up as described earlier and extraction with methylene chloride (2 × 25 ml), drying, and removal of solvent gave 0.65 g of waxy product. Elution of this material from a silica gel column with benzene yielded 0.3 g (44.4%) of ether **10**. On sublimation (140 °C, at 1 mm) it gave a white, crystalline solid: mp 192 °C; ir (KBr) 1025, 995 cm^{-1}; ^{1}H NMR (CCl_4) δ 5.52 (HCO–, 1 H, m), 4.13 (H_2CO–, 2 H, t, J = 5 Hz), 1.3–3.3 (CH ring, 9 H, envelope); MS *m/e* 148 (M^+), 117, 91 ($C_7H_7^+$), 81 ($C_5H_5O^+$), 79 ($C_5H_3O^+$ or $C_6H_7^+$). Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.94; H, 7.95.

Addition of Methylmagnesium Iodide to Lactone 5. Methylmagnesium iodide [from 0.1 g of magnesium turnings and methyl iodide (0.6 g) in 25 ml of dry ether] was prepared according to usual procedure and lactone **5** (0.25 g, 1.5 mmol) in 5 ml of dry ether was added dropwise with continuous stirring. The reaction mixture was quenched after 3 h with 10% ammonium chloride (5 ml) and extracted with ether (2 × 25 ml); washing, drying, and evaporation of solvent yielded 0.3 g of crude lactol **11**, which was crystallized from benzene–petroleum ether (1:4) to furnish white, stout crystals: 0.2 g (72%); mp 114–115 °C; ir (KBr) 3550 (hydroxyl), 1055, 920 cm^{-1} (ether); ^{1}H NMR (CCl_4) δ 4.05 (–CHO–, 1 H, t, J = 5 Hz), 1.38 (H_3C–COH, 3 H, s), 1.8–3.2 (CH ring and OH, 10 H, envelope). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.39; H, 8.17.

Jones Oxidation of Lactol 11. To an ice-cold solution of lactol **11** (0.1 g, 0.56 mmol) in acetone (5 ml) was added Jones reagent (0.5 ml) dropwise until the yellow color persisted. The reaction mixture was stirred overnight at room temperature and then poured into water (10 ml). Extraction with ether (2 × 20 ml), washing with 10% sodium carbonate solution (2 × 10 ml) and brine, and removal of solvent gave diketone **12**, 0.075 g (76%), ir (neat) 1775 (cyclobutanone), 1720 cm^{-1}.

Addition of Methylmagnesium Iodide to Lactone 4. Methylmagnesium iodide [from 0.15 g of magnesium turnings and methyl iodide (0.9 g) in 25 ml of dry ether] was prepared according to the usual procedure and lactone **4** (0.4 g, 2.25 mmol) in 10 ml of dry ether was added dropwise with continuous stirring. The reaction mixture was quenched after 2 h with 10% ammonium chloride (10 ml) and extracted with ether (2 × 25 ml); washing, drying, and removal of solvent yielded 0.48 g of crude lactol **13**. Filtration from a silica gel column using 1:4 ethyl acetate–benzene as a solvent and crystallization from petroleum ether–benzene mixture furnished

white flakes: 0.31 g (70%); mp 89–90 °C; ir (KBr) 3500 (hydroxyl), 1010, 1050 cm^{-1} (ether); ^1H NMR (CCl_4) δ 4.8 (CHO–, 1 H, m), 1.6 (CH_3COH, 3 H, s), 1.3–3.95 (CH ring and OH, 10 H, envelope).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.41; H, 7.79.

Jones Oxidation of Lactol 13. To an ice-cold solution of lactol **13** (0.25 g, 1.4 mmol) in acetone (10 ml) was added Jones reagent (1 ml) dropwise until the yellow color persisted. The reaction mixture was stirred overnight at room temperature and then poured into water (15 ml). Extraction with ether (2 × 20 ml), washing with 10% sodium carbonate solution and brine, and removal of solvent yielded diketone **14**, 0.18 g (70%), ir (neat) 1740 (cyclopentanone), 1718 cm^{-1}.

Oxidation of Pentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decan-5-one (2) with Ceric Ammonium Sulfate. To a magnetically stirred slurry of ceric ammonium sulfate (3.5 g, 5.5 mmol) in water (7 ml) a solution of 1,4-bishomocubanone (0.2 g, 1.4 mmol) in acetonitrile (3.5 ml) was added. The reaction mixture was stirred at 60 °C for 3 h and worked up as described above to yield 0.2 g of a waxy solid. Direct sublimation (75 °C, 1 mm) gave 0.175 g (80%) of white crystals of **15**: mp 130–132 °C; ir (KBr) 1755, 1260, 1075 cm^{-1} (lactone); ^1H NMR (CCl_4) δ 5.0 (H–C–O–C=O, 1 H, m), 1.5–3.5 (CH ring, 10 H, envelope). Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.08; H, 6.17. Found: C, 74.13; H, 6.15.

Baeyer–Villiger Oxidation of 2 with *m*-Chloroperbenzoic Acid. To a solution of 1,4-bishomocubanone (**2**, 0.1 g, 0.7 mmol) in dry benzene (10 ml) was added *m*-chloroperbenzoic acid (0.15 g, 0.87 mmol, Aldrich) and a catalytic amount of *p*-toluenesulfonic acid with gentle swirling of the flask. Reaction was complete in 2 h (TLC) and usual work-up as described in the earlier case yielded 0.095 g (86%) of lactone **15** identical with the CAS oxidation product of **2**.

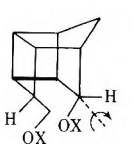
Oxidation of Pentacyclo[6.2.1.0^{2,7}.0^{4,10}.0^{5,9}]undecane-3,6-dione (3) with Ceric Ammonium Nitrate. To a magnetically stirred slurry of ceric ammonium nitrate (16 g, 30 mmol) in water (30 ml) a solution of diketone **3** (1 g, 5.7 mmol) in acetonitrile (20 ml) was added. The reaction mixture was stirred at 30 °C for 1 h and worked up as described above to yield 1.1 g of a solid residue. Direct recrystallization from methylene chloride–ether gave 0.9 g (82%) of colorless crystals of **16**: mp 280–282 °C; ir (CH_2Cl_2) 1780 (δ-lactone), 1725 cm^{-1} (cyclopentanone); ^1H NMR ($CDCl_3$) δ 5.17 (H–C–O–C=O, 1 H, t, J = 7.5 Hz), 2.45–3.4 (CH ring, 5 H, envelope), 1.7–2.3 (CH ring, 4 H, m); MS *m/e* 190 (M^+), 146 ($M^+ - CO_2$), 145 ($M^+ - CO_2H$), 118 ($M^+ - CO_2 - CO$), 117 ($M^+ - CO_2 - CO - H$), 91 ($C_7H_7^+$), 79 ($C_5H_3O^+$ or $C_6H_7^+$), 66 ($C_5H_6^+$). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.63; H, 5.19.

Beayer–Villiger Oxidation of 3 with *m*-Chloroperbenzoie Acid. To a solution of diketone **3** (0.25 g, 1.4 mmol) in dry benzene (15 ml) was added *m*-chloroperbenzoic acid (0.29 g, 1.4 mmol, Aldrich) and a catalytic amount of *p*-toluenesulfonic acid with gentle swirling of the flask. Reaction was complete in 2 h and usual work-up as described in the case of **1** yielded 0.28 g of dilactone **20**. Recrystallization from methylene chloride gave colorless microneedles (0.13 g, 43%): mp >300 °C; ir (CH_2Cl_2) 1760 cm^{-1} (δ-lactone); MS *m/e* 207? ($M^+ + 1$), 206 (M^+), 178 ($M^+ - CO$), 150 ($M^+ - 2CO$), 134 ($M^+ - CO_2 - CO$). The ^1H NMR spectrum of **20** could not be recorded owing to its insolubility in $CDCl_3$ and $(CD_3)_2C=O$. Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.86; H, 4.73. The mother liquor from the recrystallization of **20** showed the presence of unreacted starting material. When BV oxidation of diketone **3** (0.25 g, 1.4 mmol) was carried out with *m*-chloroperbenzoic acid (0.58 g, 2.8 mmol) as described above, dilactone **20** was obtained in 93% yield.

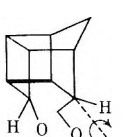
Registry No.—**1**, 15584-52-8; **2**, 15745-99-0; **3**, 2958-72-7; **4**, 57051-35-1; **5**, 57051-34-0; **6**, 57719-10-5; **7**, 57719-11-6; **8**, 57719-12-7; **9**, 57719-13-8; **10**, 57719-14-9; **11**, 57719-15-0; **12**, 57719-16-1; **13**, 57719-17-2; **14**, 57719-18-3; **15**, 57051-36-2; **16**, 57719-19-4; ceric ammonium sulfate, 7637-03-8; *m*-chloroperbenzoic acid, 937-14-4; lithium aluminum hydride, 16853-85-3; diazomethane, 334-88-3; methyl iodide, 74-88-4; ceric ammonium nitrate, 16774-21-3.

References and Notes

(1) Junior Research Fellow of CSIR (1973–present).
(2) W. H. Richardson in "Oxidation in Organic Chemistry", K. B. Wiberg, Ed., Part A, Academic Press, New York, N.Y., 1965, p 244.
(3) T. L. Ho, *Synthesis*, 347 (1973).
(4) P. Soucy, T. L. Ho, and P. Deslongchamps, *Can. J. Chem.*, **50**, 2047 (1972).
(5) C. H. Hassall, *Org. React.*, **9**, 73 (1957); P. A. S. Smith in "Molecular Rearrangements", Vol. 1, P. de Mayo, Ed., Wiley-Interscience, New York, N.Y., 1963, pp 568–591.
(6) N. B. Chapman, J. M. Key, and K. J. Toyne, *J. Org. Chem.*, **35**, 3860 (1970); S. A. Monti and S. S. Yuan, *ibid.*, **36**, 3350 (1971); R. R. Sauers and G. P. Ahern, *J. Am. Chem. Soc.*, **83**, 2789 (1961).
(7) W. L. Dilling and M. L. Dilling, *Tetrahedron*, **23**, 1225 (1967); W. L. Dilling, R. A. Plepys, and R. D. Kroening, *J. Am. Chem. Soc.*, **94**, 8133 (1972).
(8) Attempted base hydrolysis or methanolysis of **4** and **5** always lead to the quantitative recovery of the starting material and therefore a more circuitous degradative scheme was selected.
(9) To rationalize the different behavior of **4** and **5** toward lithium aluminum hydride, a tentative suggestion may be made. In the structures (**4a** and **5a**) of the reduction products before work-up, the substituents (H, OX in **4a** and H, CH_2OX in **5a**) would be displaced to a slight extent by twisting (cf. arrows) in order to minimize steric strain. This action as well as the tilting of the carbon atoms bearing these substituents upward are favored by the presence of the bond indicated in bold type. For ether formation from **4a**, the OX of the CH_2OX (X = H or Al) group must swing inward the molecular cavity in order to attain a good Sn2 transition state[10] and it is strongly opposed by steric interactions. On the other hand, the deformation of **5a** tends to align the attacking and the leaving groups in a better disposition.

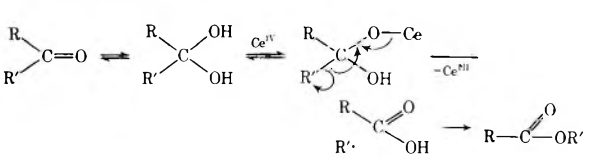


4a



5a

(10) L. Tenud, S. Farooq, J. Seible, and A. Eschenmoser, *Helv. Chim. Acta*, **53**, 2059 (1970).
(11) A referee has suggested that the ceric oxidation might preferably occur via the hydrates of the ketones as shown below:



However, we did not observe the deep red color of the solution upon mixing the oxidant with the substrates which is characteristic of ceric oxidation of alcohols.[3]
(12) We have not been able to locate experimental data in the literature to support this supposition but one can empirically analyze the situation as follows. The extracyclic bonds of cyclobutane have more s character than those of cyclopentane. Thus assuming that the free radicals have planar structures, they are more difficultly accommodated at a cyclobutane than a cyclopentane carbon.
(13) S. A. Monti and C. K. Ward, *Tetrahedron Lett.*, 697 (1971).
(14) Melting points and boiling points are uncorrected. Melting points were taken in capillaries on a Fisher-Johns melting point apparatus. Boiling points refer to bath temperature in those cases where short-path bulb-to-bulb distillations were carried out. The petroleum ether corresponds to fraction of bp 60–80 °C. All solvent extracts were dried over anhydrous sodium sulfate. Infrared spectra were recorded on a Perkin-Elmer Model 137B spectrophotometer as neat liquids or solids as KBr disks. ^1H NMR spectra were obtained on approximately 10–15% solutions in CCl_4 or $CDCl_3$ on a Varian A-60 spectrometer. The chemical shifts are reported in parts per million downfield from internal tetramethylsilane at 0.00 as internal standard. The abbreviations s, d, t, q refer to singlet, doublet, triplet, and quartet, respectively. Microanalyses were performed by Mr. A. H. Siddiqui in the microanalytical laboratory of our department.
(15) R. C. Cookson, J. Hudec, and R. O. Williams, *J. Chem. Soc. C*, 1382 (1967).
(16) W. L. Dilling, C. E. Reineke, and R. A. Plepys, *J. Org. Chem.*, **34**, 2605 (1969).
(17) R. C. Cookson, E. Crundwell, R. R. Hill, and J. Hudec, *J. Chem. Soc.*, 3062 (1964).

Dimethyl Sulfoxide–Trifluoroacetic Anhydride: a New Reagent for Oxidation of Alcohols to Carbonyls[1]

Kanji Omura, Ashok K. Sharma, and Daniel Swern*

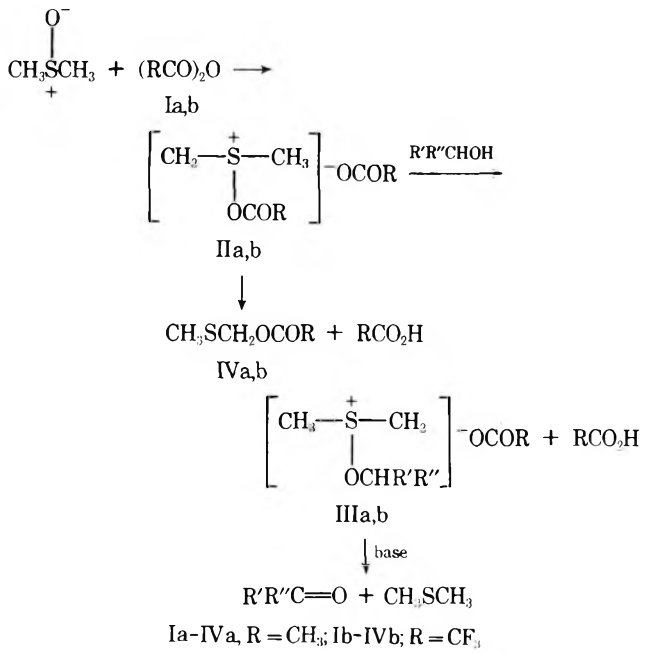
Fels Research Institute and Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122

Received November 21, 1975

Trifluoroacetoxydimethylsulfonium trifluoroacetate prepared in situ from dimethyl sulfoxide (Me_2SO) and trifluoroacetic anhydride (TFAA) below −50 °C in methylene chloride reacts rapidly with alcohols to give alkoxydimethylsulfonium trifluoroacetates and trifluoroacetic acid. Addition of triethylamine (TEA) to the alkoxysulfonium salts gives carbonyl compounds, alkyl trifluoroacetates, and alkyl methylthiomethyl ethers in varying and controllable amounts depending on the structure of the alcohols and reaction conditions. Yields of carbonyls increase in the order primary < secondary < allylic and benzylic alcohols. Yields of carbonyls from primary and secondary alcohols are highest when TEA is added to the alkoxysulfonium salts at room temperature rather than below −50 °C, or when larger amounts of solvent are employed. Under optimum conditions, yields of carbonyls are in the range of 60% from primary alcohols, 80–85% from secondary alcohols, and 80–100% from benzylic and certain allylic alcohols. Under appropriate conditions, selective oxidation of primary and secondary hydroxyl groups can be effected in the presence of allylic or benzylic hydroxyl groups. Reaction pathways to account for product distribution are proposed.

Acetic anhydride and certain other anhydrides in combination with dimethyl sulfoxide (Me_2SO) can oxidize alcohols to carbonyls under mild conditions.[2] The oxidation has been interpreted as follows (Scheme I). Acetic anhydride reacts slowly with Me_2SO at room temperature to give acetoxydimethylsulfonium acetate (IIa), which on reaction with alcohols is converted to alkoxydimethylsulfonium acetates (IIIa);[2] reaction of the alkoxysulfonium salts (IIIa) with base yields carbonyl compounds and dimethyl sulfide. The intermediate salts (IIa) undergo the Pummerer rearrangement to acetoxymethyl methyl sulfide (IVa) at room temperature.[3] Thus, oxidations conducted at or above room temperature can be inefficient; in addition, other side reactions can occur that lead to extensive formation of methylthiomethyl ethers (V) and esters (VIa,b).

Scheme I



$CH_3SCH_2OCHR'R''$ (V) $\qquad$ $R'R''CHOCOCR$ (VIa, R = CH_3; VIb, R = CF_3)

Although a Me_2SO–trifluoroacetic anhydride (TFAA) reagent should be similarly useful for alcohol oxidations, it has been reported to be ineffective because the presumed intermediate, trifluoroacetoxydimethylsulfonium trifluoroacetate (IIb), is unstable at room temperature and rearranges rapidly to trifluoroacetoxymethyl methyl sulfide (IVb), thereby precluding nucleophilic attack by alcohols to give the necessary alkoxydimethylsulfonium trifluoroacetates (IIIb).[4] (We have confirmed the formation of IVb by NMR.[5]) Furthermore, the reaction of Me_2SO with TFAA can be violent and explosive. Recently, however, we showed that reaction of Me_2SO with TFAA to form IIb can be easily controlled at low temperatures and the intermediate is stable at or below −30 °C.[5] A new method of synthesis of iminosulfuranes was achieved by allowing IIb to react with amines.[5] As an outgrowth of that study, we have investigated the reaction of Me_2SO–TFAA with alcohols, and this paper reports the results.

Results and Discussion

Procedure A. In a typical run, TFAA in methylene chloride is added dropwise with stirring to a cold (<−50 °C) solution of Me_2SO (excess) in dry CH_2Cl_2 over ca. 10 min. During the addition a white precipitate, presumed to be the salt IIb, forms. After 10 min, a solution of benzyl alcohol, for example, in CH_2Cl_2 is added dropwise to the mixture at that temperature over ca. 10 min. After the mixture is stirred for 30 min at or below −50 °C, triethylamine (TEA) is added dropwise below −50 °C. The mixture is then allowed to warm to room temperature and analyzed by gas chromatography. Benzaldehyde (84%) and benzyl trifluoroacetate (11%) are the sole products formed. The aldehyde can also be isolated as its 2,4-dinitrophenylhydrazone (80%).

The product distribution is not appreciably changed by (a) using nearly equimolar quantities of Me_2SO (12.1 mmol), TFAA (11.6 mmol), and benzyl alcohol (11.1 mol) (PhCHO, 81%; $PhCH_2OCOCF_3$, 11%); (b) blanketing the reaction with argon instead of dry air (86, 10%); (c) using toluene instead of CH_2Cl_2 (87, 8%); or (d) having a small amount of added trifluoroacetic acid (TFA, 3.0 mmol) present before adding the alcohol (85, 8%). Relatively large amounts of TFA in the system cause a decrease in yields of carbonyls; this effect was studied only with cyclohexanol and 2-octanol (Table I, runs 4 and 6). One equivalent of TFA, a reaction product, is not deleterious. If benzyl alcohol is added to Me_2SO before the TFAA, yields of aldehyde and ester are 78 and 20%, respectively. This indicates that, surprisingly, the reaction of TFAA with Me_2SO is faster than with the alcohol, a reaction that proceeds violently at

Table I. Procedure A:[a] Oxidation of Alcohols to Carbonyls with Me_2SO–TFAA at −50 °C

Run no.	Alcohols	Registry no.	Products, %[b] Carbonyls	Alkyl trifluoroacetates (VIb)	Methylthiomethyl ethers (V)
1	*n*-Decanol	112-30-1	37[c]	35	21
2	Phenethyl alcohol	60-12-8	32	34	≤9
3	Cyclohexanol	108-93-0	65[d]	22	12
4	Cyclohexanol[e]		47	39	13
5	2-Octanol	123-96-6	67	21	10
6	2-Octanol[f]		49	18	19
7	Cyclododecanol	1724-39-6	72[g]	15	N.E.[h]
8	Cyclododecanol[i]		79[j]	8	N.E.[h]
9	2-Cyclohexenol	822-67-3	82[k]	8	N.E.[h]
10	Cinnamyl alcohol	104-54-1	83[l]	14	N.E.[h]
11	Benzyl alcohol	100-51-6	84[m]	11	~0
12	*sec*-Phenethyl alcohol	98-85-1	97[n]	1	N.E.[h]
13	Benzhydrol	91-01-0	98+	0	N.E.[h]

[a] Alcohol (10 mmol), Me_2SO (20 mmol), TFAA (15 mmol), TEA (4 ml), and CH_2Cl_2 (20–25 ml); all steps at or below −50 °C (see Experimental Section). No detailed effort was made to optimize yields of carbonyls. [b] Yields estimated by GLC unless otherwise stated. The starting alcohols are entirely consumed or present in trace amounts after the reaction is complete. [c] As the 2,4-dinitrophenylhydrazone (2,4-D), mp 100–101 °C (lit.[7] mp 104 °C). [d] As the 2,4-D, mp 156–158 °C (lit.[8] mp 162 °C). [e] TFA (25 mmol) was added before TFAA. [f] TFA (27 mmol) was added before TFAA. [g] 71% as the 2,4-D, mp 147–149.5 °C (lit.[9] mp 152–153 °C). [h] Not examined. [i] A larger amount of CH_2Cl_2 (ca. 50 ml) was employed. [j] 79% as the 2,4-D, mp 147–149.5 °C. [k] 75% as the 2,4-D, mp 157–162 °C (lit.[10] mp 163 °C). [l] 81% as the 2,4-D, mp 245–250 °C (lit.[11] mp 248 °C). [m] 80% as the 2,4-D, mp 240–241 °C (lit.[12] mp 238–239 °C). [n] 94% as the 2,4-D, mp 245–247 °C (lit.[8] mp 249 °C).

Table II. Procedure B:[a] Oxidation of Alcohols to Carbonyls with Me_2SO–TFAA at Higher Temperatures

Run no.	Alcohols	Temp, °C	Products, %[b] Carbonyls	Alkyl trifluoroacetates (VIb)	Methylthiomethyl ethers (V)
14	*n*-Decanol	−20 to −26	28[c]	54	10
15	*n*-Decanol	5–10	0	98	N.E.[d]
16	Benzyl alcohol	−20 to −23	56	44	N.E.[d]
17	Benzyl alcohol	5–10	0	97	N.E.[d]
17a	*sec*-Phenethyl alcohol	5–10	0	>97	N.E.[d]

[a] Alcohol (10 mmol), Me_2SO (20 mmol), TFAA (15 mmol), TEA (4 ml), and CH_2Cl_2 (20–25 ml). Procedure A, Table I, except that reaction temperatures throughout are as listed until addition of TEA is complete. The mixtures were stirred for 10–15 min, instead of 30 min as in procedure A, after addition of the alcohols but before addition of TEA. [b] Yields estimated by GLC unless otherwise stated. [c] As the 2,4-D, mp 97–99.5 °C (lit.[7] mp 104 °C). [d] Not examined.

room temperature to form the ester.[6] Table I summarizes the results obtained with procedure A in the oxidation of benzyl and other alcohols to carbonyls.

Besides the anticipated carbonyls (32–98%) and trifluoroacetate esters (VIb, 0–35%), methylthiomethyl ethers (V, 0–21%) are obtained from primary and secondary alcohols.

In general, yields of carbonyls from alcohols increase in the order primary alcohols < secondary alcohols < allylic and benzylic alcohols while those of trifluoroacetates (VIb) and methylthiomethyl ethers (V) increase in the reverse order.

Procedure B. In procedure A, reaction temperatures are not permitted to exceed −50 °C until after addition of TEA. Procedure B explores the effect of higher reaction temperatures on products obtained.

As Table II shows, a considerable decrease in yields of *n*-decanal and benzaldehyde is observed when the reactions are carried out at −20 to −26 °C (compare run 14, Table II, with run 1, Table I, and run 16 with run 11); yields of trifluoroacetates are markedly increased. When the reactions are conducted at even higher temperatures (5–10 °C), no aldehydes are formed; trifluoroacetates are obtained quantitatively.

The alteration in products occurs because the required intermediate salts (IIb) undergo facile Pummerer rearrangement to IVb at the higher temperatures before conversion to alkoxysulfonium salts (IIIb), the necessary precursors to carbonyls. As we show below under procedure C, many of the salts (IIIb) are stable at the temperatures used here and if they had formed they would have been converted to carbonyls on reaction with TEA. The main source of trifluoroacetate esters is the TEA-assisted alcoholysis of IVb by the alcohols added after salts IIb have been converted to IVb by Pummerer rearrangement (see Experimental Section). Esters do not form in significant quantities at these higher reaction temperatures until TEA is added.

Procedure C. This procedure was studied to assess the thermal stability of alkoxysulfonium salts in the reaction system and to gain insight into the origin of the trifluoroacetates. Procedure C parallels procedure A exactly until addition of alcohol is complete (preparation of salts IIIb at low temperature). The mixture is then allowed to warm to room temperature (ca. 30–40 min) during which period it becomes homogeneous. After an additional 30 min at room temperature, TEA is added dropwise and the reaction mixture is analyzed by GLC. Results are summarized in Table III.

With typical primary and secondary alcohols (runs 18 and 19, Table III), yields of carbonyls increase significantly compared with those from procedure A (Table I). The increase in yield of carbonyls from primary alcohols is larger than that from secondary alcohols; currently we have no explanation for this. In sharp contrast, allylic and benzylic alcohols (except benzyl alcohol) (runs 23–27) yield no carbonyls and only trifluoroacetates in excellent yields (93–98%). The decrease in yield of benzaldehyde from 84% (run 11, Table I) to 40% (run 25, Table III), although substan-

Table III. Procedure C:[a] Oxidation of Alcohols to Carbonyls with Me_2SO–TFAA. Room Temperature Addition of TEA

Run no.	Alcohols	Products, %[b] Carbonyls	Alkyl trifluoroacetates (VIb)	Methylthiomethyl ethers (V)
18	1-Decanol	56[c]	24	8
19	Phenethyl alcohol	50[d]	27	≤11
20	Cyclohexanol	73[e]	17	5
21	2-Octanol	78	14	5
22	Cyclododecanol[f]	86[g]	8	N.E.[h]
23	2-Cyclohexenol	0	93	N.E.[h]
24	Cinnamyl alcohol	0	98	N.E.[h]
25	Benzyl alcohol	42	58	N.E.[h]
26	*sec*-Phenethyl alcohol	0	96	N.E.[h]
27	Benzhydrol	0	96	N.E.[h]

[a] Alcohol (10 mmol), Me_2SO (20 mmol), TFAA (15 mmol), and CH_2Cl_2 (20–25 ml) at −50 °C following procedure A, then addition of TEA (4 ml) after 30 min at room temperature. [b] Yields estimated by GLC unless otherwise stated. [c] As the 2,4-D, mp 100–102 °C (lit.[7] mp 104 °C). [d] Over 45% yield as the 2,4-D, mp 109–113 °C (lit.[11] mp 110 °C). [e] As the 2,4-D, mp 156–158 °C (lit.[8] mp 162 °C). [f] 50 ml of CH_2Cl_2 was used. [g] 85% as the 2,4-D, mp 146.5–149.5 °C (lit.[9] mp 152–153 °C). [h] Not examined.

tial, is not so drastic (run 25) and the yield of trifluoroacetate increases to almost 60% from 11%.

Solutions of alkoxysulfonium salts (IIIb) prepared from the Me_2SO–TFAA intermediate (IIb) and cyclohexanol or cyclododecanol are stable for at least 2 days at room temperature if moisture is excluded. Addition of TEA at that time yields cyclohexanone (73%) and cyclododecanone (86%), respectively, and the corresponding trifluoroacetates (17 and 8%) (see runs 20 and 22, Table III, for comparison). In contrast, the salt from benzyl alcohol and IIb gives considerably less benzaldehyde (42%) and considerably more trifluoroacetate (58%) even when TEA is added only 30 min after the reaction solution has been maintained at room temperature (run 25; compare with run 11, Table I). If 7 h is allowed to elapse at room temperature before TEA is added the yield of benzaldehyde drops to 5% and that of trifluoroacetate increases to 89%; after 14 h no aldehyde is obtained and the yield of ester is 99%.

Even more striking, *sec*-phenethyl alcohol (run 26) yields no ketone and exclusively trifluoroacetate if only 30 min elapses at room temperature before TEA is added to the salt IIIb (compare results with run 12, Table I, in which all steps are conducted at or below −50 °C). If TEA is added just as the solution of IIIb reaches room temperature the yield of ketone is 10% and that of ester 90%. In contrast, addition of TEA at 0–5 °C (about 20 min is required for the reaction to warm up from −50 to 5 °C) still provides a substantial yield of acetophenone (87% at 0–5 °C vs. 97% at −50 °C) and little *sec*-phenethyl trifluoroacetate (10%).

We conclude that (a) alkoxysulfonium salts (IIIb) from primary and secondary alcohols are relatively stable at room temperature in the reaction media with little decomposition or rearrangement for at least 2 days, (b) the corresponding salts from allylic and benzylic alcohols are considerably more reactive and, with the exception of IIIb from benzyl alcohol, are converted at room temperature exclusively to trifluoroacetates (benzyl alcohol is converted only partially to the ester under the conditions of Table III), and (c) IIIb from *sec*-phenethyl alcohol is converted to ester at a significant rate above 0 °C.

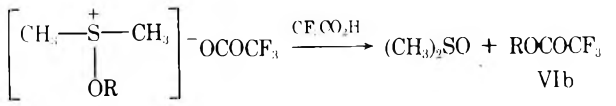
By-Product Formation. The formation of trifluoroacetates in virtually every run in yields as high as 98%, depending on the reaction conditions and the alcohol used, cannot be explained simply as the reaction between TFAA and alcohols. Even at −50 °C, TFAA reacts almost instantaneously and quantitatively with Me_2SO which is always present in some excess to yield a precipitate of IIb, thereby effectively eliminating the anhydride from the reaction medium *before* alcohols are added. Several other pathways may be invoked to account for ester formation; to obtain information bearing on that point we first ascertained whether esters are formed before or after the addition of TEA using selected model systems.

The cyclohexyloxydimethylsulfonium salt (IIIb) was prepared in solution from cyclohexanol (10 mmol) and IIb at −50 °C and the stirred mixture was allowed to warm to room temperature (procedure C, Table III). The homogeneous solution was divided into three parts. TEA was added to one part yielding cyclohexanone (72%), the trifluoroacetate (17%), and methylthiomethyl cyclohexyl ether (6%), results in excellent agreement with our earlier result (run 20). The second part was diluted with ether (to increase its volume and ease of handling) and the solution was shaken with excess aqueous sodium carbonate solution. The organic phase was analyzed by GLC: cyclohexanol (94%), methylthiomethyl cyclohexyl ether (V, 7%), cyclohexyl trifluoroacetate (VIb, 0%), cyclohexanone (0%). An authentic sample of the ester prepared from TFAA and cyclohexanol is stable to hydrolysis by aqueous sodium carbonate at room temperature; thus VIb cannot be the source of cyclohexanol. To the third part, authentic ester was added and the solution was treated with aqueous sodium carbonate as above. Analysis by GLC gave trifluoroacetate (100% recovery) as well as cyclohexanol (93%) and methylthiomethyl cyclohexyl ether. We conclude that cyclohexyl trifluoroacetate (as well as cyclohexanone) is formed only *after* TEA is added.

In contrast, *sec*-phenethyloxydimethylsulfonium salt (IIIb), worked up at room temperature in the same three-part manner as its cyclohexyloxy analogue, yielded *sec*-phenethyl trifluoroacetate (95–97%) exclusively on treatment with TEA or with aqueous sodium carbonate solution. No alcohol could be detected. The third part was evaporated to dryness under vacuum; the ir spectrum of the residue showed the presence of trifluoroacetate. We conclude that *sec*-phenethyl trifluoroacetate is completely formed at room temperature from IIIb *before* addition of TEA. The yield of ester can be held to less than 1%, however, by adding TEA at −50 °C (run 12, Table I).

Interestingly, when 1-decanol, benzyl alcohol, or *sec*-phenethyl alcohol is added to Me_2SO–TFAA that has been allowed to reach room temperature, and therefore contains no IIb but is a mixture of IVb and TFA, followed by TEA, an almost quantitative yield of trifluoroacetate esters is obtained (Table II). With 1-decanol or benzyl alcohol we did not ascertain whether the esters form before or after addition of TEA. With *sec*-phenethyl alcohol, however, the ester is formed only *after* addition of TEA (contrast with preceding paragraph). This was confirmed by working up a portion of the reaction mixture with aqueous sodium carbonate (no TEA used) and demonstrating that the organic components isolated consisted exclusively of ester (10%) and free alcohol (90%).

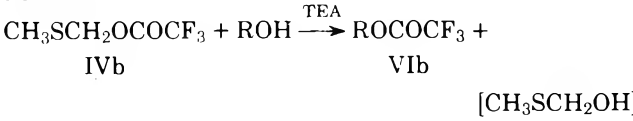
These apparently anomalous results are readily interpreted: when reaction temperatures are maintained at or below −50 °C up to the point where alcohol is to be added (procedures A and C) little or no Pummerer rearrangement to IVb has yet occurred and alkoxysulfonium salts (IIIb) form cleanly in all cases. The salts (IIIb) from benzylic and allylic alcohols, however, can more easily undergo solvolytic attack by trifluoroacetic acid (TFA) (1 mol of TFA is al-



IIIb, R = allylic or benzylic group

ways present per mole of salt) *at room temperature* than salts from primary and secondary alcohols, with displacement of Me_2SO. Thus even before TEA is added VIb form in excellent yields at the higher temperatures in the allylic and benzylic salt cases in which cations form more readily (by solvolysis).

In contrast, when reaction temperatures are at or above −30 °C and especially above 0 °C during the mixing of Me_2SO with TFAA (procedure B), the Pummerer rearrangement product (IVb) forms largely or exclusively.[5] Addition of an alcohol at that point cannot yield an alkoxysulfonium salt (IIIb) since intermediate IIb has been converted to IVb. The formation of esters VIb now occurs only *after* addition of TEA in a base-catalyzed alcoholysis reaction from IVb and alcohols, a process we have demonstrated experimentally with *sec*-phenethyl alcohol and 1-decanol and confirmed by model experiments with authentic IVb.

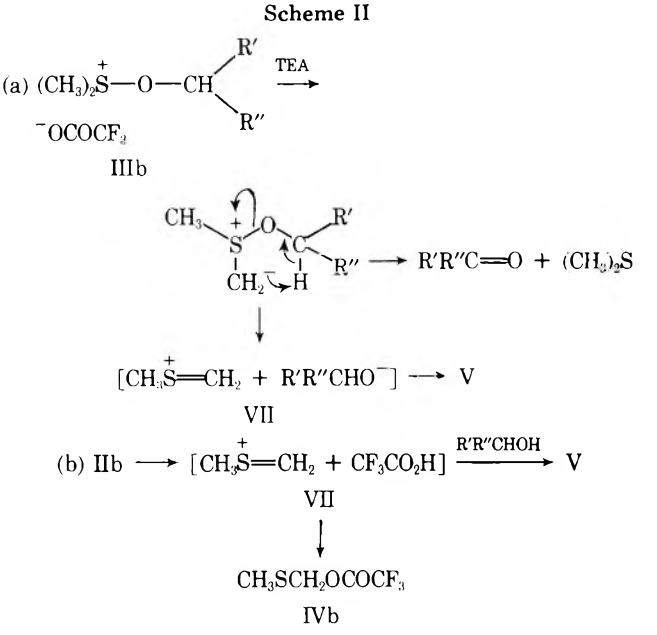


We have isolated IVb (65% yield) and have shown that it forms less than 1% of ester in methylene chloride solution on reaction with *sec*-phenethyl alcohol for 2 h at 5–10 °C with TEA *absent* (99% recovery of unreacted alcohol). In contrast, if TEA is *present* a 96% yield of ester is obtained within 10 min (4% recovery of unreacted alcohol). Similar results are obtained with 1-decanol; in the *absence* of TEA at least 96% of the alcohol remains unreacted whereas when TEA is *present* the alcohol is completely converted to the trifluoroacetate in less than 1 min.

Since TFA is also present in the reaction media before TEA is added, the possibility must be considered that VIb form, at least in part, by the direct esterification of alcohols in those cases where they are not able to be converted to alkoxysulfonium salts (IIIb) because the Pummerer rearrangement has already intervened (conditions of Table II) and has depleted the system of the required intermediate (IIb). Solutions of *sec*-phenethyl alcohol (10 mmol) and excess TFA (16 mmol) in methylene chloride at room temperature require 18 h to achieve 85% esterification, a reaction time far in excess of that employed in the oxidation reactions. If excess TEA is also present with TFA, direct esterification is completely inhibited. These results confirm that esterification observed in runs 14–17a, Table II, requires the presence of both IVb and TEA.

The formation of by-product methylthiomethyl ethers (V) from primary and secondary alcohols in Me_2SO–anhydride oxidation reactions of alcohols is well known.[2,4,13–15] We have shown that these by-products are present before or after addition of TEA to IIIb. Their formation can be readily explained (Scheme II): (a) treatment of alkoxydimethylsulfonium salts (IIIb) with TEA, the reaction leading to the desired carbonyls, can also yield V by a competitive Pummerer-type rearrangement and (b) the initial intermediate IIb before addition of TEA may also undergo a Pummerer rearrangement in which the reactive cationic intermediate, $CH_3S^+{=}CH_2$ (VII), is trapped partly by alcohol and partly by TFA thus explaining the formation of IVb along with V. Pathway b seems very unlikely as alcohol is rapidly converted to IIIb which does not reconvert to IIb and alcohol.

Scheme II



Solvent Effects. The use of larger volumes of solvent was investigated to try to eliminate or reduce the quantities of undesirable by-products and direct the reaction to carbonyl formation exclusively. Yields of cyclohexanone (83%), cyclododecanone (79%), and 1-decanal (63%) are usually significantly increased when a four- to fivefold increase in volume of methylene chloride is employed (procedures A and C). In contrast, yields of benzaldehyde (84%, procedure A, run 11) and 2-cyclohexenone (82%, procedure A, run 9) remain unchanged.

Also, yields of carbonyls are reported to increase at the expense of methylthiomethyl ethers as solvent polarity decreases.[15–17] We therefore prepared the *n*-decyloxydimethylsulfonium salt (IIIb) at low temperatures following procedure C (CH_2Cl_2, 20 ml). Addition of dry hexane (80 ml) followed by addition of TEA resulted in no change in yield of 1-decanal (64 vs. 63%) over that with a larger volume of neat methylene chloride but the yield in both cases was slightly higher than in more concentrated solutions (56%).

Primary and secondary alcohols are best converted to carbonyls (60–85%) with the Me_2SO–TFAA reagent by procedure C using larger quantities of solvent; allylic and benzylic alcohols are converted to carbonyls (80–100%) only by procedure A and the volume of solvent has no observable effect on yields.

Selective Oxidation. By procedure C primary and secondary alcohols can be oxidized to carbonyls in good yields but allylic and benzylic alcohols are converted to trifluoroacetates. It should, therefore, be possible to oxidize primary and/or secondary hydroxyl groups in molecules that also contain allylic or benzylic hydroxyl groups. These latter types are usually more easily oxidized by conventional methods. Furthermore, double bonds are inert toward the Me_2SO–TFAA reagent, a situation that does not prevail with conventional oxidants.

In preliminary studies, an equimolar mixture of cyclododecanol and *sec*-phenethyl alcohol was oxidized following procedure C. After addition of TEA, GLC analysis showed no acetophenone formation and exclusive conversion of the benzylic alcohol to its trifluoroacetate (97%). Addition of 2,4-dinitrophenylhydrazone reagent to the reaction mixture gave yellow crystals of the 2,4-dinitrophenylhydrazone of cyclododecanone (84%), mp 148–149.5 °C (lit.[9] 152–153 °C). A similar oxidation of an equimolar mixture of 1-decanol and 2-cyclohexenol yielded no cyclohexenone; only 2-

cyclohexenyl trifluoroacetate (97%) and 1-decanal (61%, as its 2,4-dinitrophenylhydrazone, mp 99–101 °C) were formed. The areas of selective oxidation and the oxidation of sterically hindered alcohols are being actively pursued.

Experimental Section[18,19]

General Procedures. Procedure A. Methylene chloride (10 ml) and Me_2SO (20 mmol) were placed in a 50-ml three-neck flask equipped with a magnetic stirrer, thermometer, addition funnel, and drying tube. The contents of the flask were cooled below −50 °C with a dry ice–acetone bath and TFAA (15 mmol) in CH_2Cl_2 (ca. 5 ml) was added dropwise to the stirred cold solution in ca. 10 min (exothermic). During the addition, a white precipitate of the salt IIb formed. After 10 min at −50 °C, a solution of an alcohol (10 mmol) in CH_2Cl_2 (5–10 ml) was added dropwise in ca. 10 min to the mixture maintained at −50 °C. The reaction of the alcohol with IIb was exothermic. The mixture was stirred at −50 °C for 30 min, followed by addition of TEA (4 ml) dropwise in ca. 10 min. The contents of the flask were maintained at or below −50 °C until addition of TEA was complete. The cooling bath was removed and the reaction mixture was allowed to warm up to room temperature (ca. 40 min) and then subjected to GLC analysis. When a larger quantity of CH_2Cl_2 was required to dissolve the alcohol (ca. 15 ml for benzhydrol and cyclododecanol), the total volume of CH_2Cl_2 was adjusted to ca. 25 ml by reducing the volume of CH_2Cl_2 used in the Me_2SO–TFAA reaction. Table I summarizes the results.

Procedure B. This procedure was identical with procedure A except that the temperature of the reaction mixture was kept at −20 to −26 °C (with a dry ice–acetone bath) or 5–10 °C (with an ice–water bath) until addition of TEA was complete. Also, TEA was added to the mixture after it was stirred for only 10–15 min, instead of 30 min as in procedure A after addition of the alcohol. Table II summarizes the results.

Procedure C. This procedure was identical with procedure A through the addition of alcohol. Stirring was continued for an additional 5 min at or below −50 °C, the dry ice–acetone bath was removed, and the stirred mixture was allowed to warm up to room temperature (ca. 40 min). The reaction mixture became homogeneous on warming. The solution was stirred for an additional 30 min at room temperature followed by dropwise addition of TEA (4 ml) in ca. 10 min at room temperature. Table III summarizes the results.

Product Separation, Identification, and Yields. Carbonyls. Carbonyls were quantitatively determined by GLC and/or isolation as their 2,4-dinitrophenylhydrazones. (Authentic carbonyls were used for standardizing GLC analysis.) A 2,4-dinitrophenylhydrazine (2,4-D) solution was prepared by dissolving 2,4-D (0.1 mol) in a mixture of sulfuric acid (100 ml) and water (150 ml) followed by dilution with ethanol (ca. 750 ml) to a total volume of 1 l. A 10–20% excess of the 2,4-D solution was added at room temperature to the reaction mixtures after TEA addition. When reactions were conducted with larger quantities of CH_2Cl_2 than 20–25 ml, the reaction mixtures were concentrated to ca. 30 ml before addition of the 2,4-D solution. Precipitation of the hydrazones was usually immediate but an additional 30 min was allowed to elapse before they were filtered. Yields of carbonyls by the hydrazone method agreed well with those obtained by GLC but were often a few percent lower.

Trifluoroacetates. Detection and determination of yields were done by GLC. Authentic esters were prepared simply by mixing the alcohols with a slight excess of TFAA in CH_2Cl_2 at room temperature. After the exothermic reaction ceased, the mixtures were left at room temperature until the alcohols were completely converted to esters. The solvent, excess TFAA, and TFA were evaporated under vacuum; the residues consisted of pure esters. The trifluoroacetates had typical carbonyl absorption bands around 1790 cm^{-1}. Carbonyls could be cleanly separated by GLC from the corresponding trifluoroacetates, with the exception of 2-octanone and 2-octyl trifluoroacetate, which had virtually the same retention times on both GLC columns used.[18]

Oxidation of 2-Octanol and Product Determination (Runs 5, 6, 21). Attempts to isolate 2-octanone as its 2,4-D were unsatisfactory. Since 2-octanone and 2-octyl trifluoroacetate could not be separated on the available GLC columns, determination of yields was accomplished by a combination of GLC and ir. An aliquot of the oxidation reaction mixture was dissolved in ether and the ether solution was washed successively with dilute sulfuric acid, aqueous potassium carbonate, and water and dried over anhydrous sodium sulfate. Solvent evaporation yielded a residue which was purified by preparative GLC (SE-30 column, 135 °C).[18] The ir spectrum of the fraction collected showed that it consisted only of ketone and trifluoroacetate; composition was estimated by comparing the absorbance at 1725 cm^{-1} (ketone) with that at 1789 cm^{-1} (trifluoroacetate), using authentic samples for reference. Total yield of ketone plus ester was obtained by GLC.

Methylthiomethyl Ethers. An aliquot of the reaction mixture was diluted with ether, washed successively with dilute sulfuric acid, aqueous sodium or potassium carbonates, and water, and dried over anhydrous sodium sulfate. The residue was chromatographed on a silica gel column. Elution with petroleum ether first yielded a mixture of carbonyl and trifluoroacetate. Further elution with the same solvent or with petroleum ether–benzene (9:1 v/v) yielded pure methylthiomethyl ethers as colorless liquids. Their purities were checked by GLC.

***n*-Decyl Methylthiomethyl Ether.** NMR δ 4.75 (s, 2 H), 3.63 (t, 2 H), 2.17 (s, 3 H), and 0.8–1.9 (m, 19 H); ir 675, 721, 1090 (s), 1195, 1257, 1298, 1373, 1435, 1466, 2845, and 2920 cm^{-1}.

Phenethyl Methylthiomethyl Ether. The ether separated by column chromatography was contaminated by a small quantity of unknown impurity.

NMR δ 7.0–7.4 (m), 4.49 (s), 3.68 (t), 2.82 (t), and 1.93 (s). (Integration is not shown because resonances of the impurity were superimposed on some of the resonances listed.) Ir 702, 1099 (s), 1152, 1209, 1390, 1443, 1461, 1504, 1554, 1611, 1697 (impurity), 2880, 2930, and 3040 cm^{-1}.

Cyclohexyl Methylthiomethyl Ether. NMR δ 4.53 (s, 2 H), 3.3–3.8 (m, 1 H), 2.07 (s, 3 H), and 1.0–2.0 (m, 10 H); ir 677, 727, 889, 935, 1072 (s), 1260, 1301, 1379, 1450, 2860, and 2940 cm^{-1}.

2-Octyl Methylthiomethyl Ether. NMR δ 4.53 (s, 2 H), 3.4–4.0 (m, 1 H), 2.17 (s, 3 H), 0.7–1.6 (m, 13 H), and 1.09 (d, 2 H); ir 684, 733, 1063 (s), 1126, 1306, 1384, 1474, 2870, and 2940 cm^{-1}. Yields of ethers were estimated by GLC using the isolated ethers as reference samples. Retention times of the ethers were much longer than those of the corresponding ketones or trifluoroacetates. No evidence could be obtained for the formation of benzyl methylthiomethyl ether (run 11); no GLC peaks were obtained other than those of benzaldehyde and benzyl trifluoroacetate.

Preparation of Pummerer Rearrangement Product (IVb). To a cooled, stirred solution (ca. −30 °C) of Me_2SO (4.0 ml, 56 mmol) in CH_2Cl_2 (10 ml), TFAA (7.3 ml, 51 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature at which point GLC analysis indicated that IVb was virtually the exclusive product. The reaction mixture was dissolved in *n*-pentane (100 ml) and washed with aqueous $NaHCO_3$ to remove TFA. The organic layer was separated, dried (Na_2SO_4), and fractionally distilled to yield IVb (5.8 g, 65%) as a colorless liquid: bp 59° (86 Torr); NMR δ 2.29 (s, 2 H), 5.37 (s, 3 H); ir 696, 725, 777, 896, 1142, 1180, 1230, 1305, 1375, 1435, 1790, and 2930–3000 cm^{-1}.

Reaction of Pummerer Rearrangement Product (IVb) with *sec*-Phenethyl Alcohol. A. TEA Absent. To a solution of IVb (1.3 g, 7.5 mmol) in CH_2Cl_2 (5 ml) a solution of *sec*-phenethyl alcohol (0.60 g, 4.9 mmol) in CH_2Cl_2 (5 ml) was added at 5–10 °C over 1 min. The mixture was maintained at 10 °C for 2 h with exclusion of moisture. Product analysis by GLC showed that the mixture consisted almost exclusively of unreacted alcohol (99%) contaminated with trifluoroacetate (ca. 1%).

B. TEA Present. This was conducted as in A but TEA (2.5 ml) was added to the mixture at 5–10 °C over 2 min. The reaction mixture was then stirred at 10 °C with periodic analysis by GLC. Within 10 min after addition of TEA, *sec*-phenethyl trifluoroacetate had formed in 96% yield. Some unreacted alcohol (4%) was still present in the reaction mixture even after 2 h.

Virtually identical results were obtained with 1-decanol. In the absence of TEA, the product ratio after 1 h was trifluoroacetate (4%) and unreacted alcohol (96%). In the presence of TEA, only trifluoroacetate was obtained after 1 min; the alcohol was completely consumed.

Reaction of *sec*-Phenethyl Alcohol with TFA. To a solution of the alcohol (10 mmol) in CH_2Cl_2 (25 ml), TFA (16 mmol) in CH_2Cl_2 (5 ml) was added in one portion at room temperature. The reaction solution was analyzed periodically by GLC. *sec*-Phenethyl trifluoroacetate was obtained in 12, 24, 39, 60, and 85% yield after 10, 30, 60, 150, and 1080 min, respectively. A duplicate of this reaction which also contained TEA (4 ml) showed only trace formation of ester; recovery of starting alcohol was almost quantitative.

Selective Oxidations. A. Equimolar Mixture of Cyclododecanol and *sec*-Phenethyl Alcohol (Procedure C). The reaction was carried out according to procedure C except that the following

quantities of solvent and reactants were used: cyclododecanol (10 mmol), *sec*-phenethyl alcohol (10 mmol), Me_2SO (24 mmol), TFAA (22 mmol), TEA (8 ml), and CH_2Cl_2 (ca. 100 ml). GLC of the reaction mixture showed that the products consisted of *sec*-phenethyl trifluoroacetate (97%), acetophenone (0%), cyclododecyl trifluoroacetate (5%), and cyclododecanone (84%). The reaction mixture was concentrated to ca. 40 ml under vacuum at room temperature, and excess 0.1 M 2,4-D-solution (120 ml) was added. A yellow precipitate of cyclododecanone 2,4-D, mp 148–149.5 °C (lit.[9] 152–153 °C), was obtained (85%).

B. Equimolar Mixture of 1-Decanol and 2-Cyclohexenol (Procedure C). The reaction was carried out according to procedure C as in A above except that the following quantities of solvent and reactants were used: 1-decanol (10 mmol), 2-cyclohexenol (10 mmol), Me_2SO (24 mmol), TFAA (21 mmol), TEA (8 ml), and CH_2Cl_2 (ca. 105 ml). GLC analysis of the reaction mixture showed that the products consisted of 2-cyclohexenyl trifluoroacetate (97%), 2-cyclohexenone (0%), *n*-decyl trifluoroacetate (26%), and 1-decanal (61%). The reaction mixture was concentrated to ca. 30 ml, and excess 0.1 M 2,4-D (120 ml) was added to the concentrate. Yellow crystals of 1-decanal 2,4-D, mp 99–101 °C (lit.[7] 104 °C), were obtained (61%).

Acknowledgment. We thank the National Cancer Institute of the U.S. Public Health Service (CA-07803 and 12227) and the Samuel S. Fels Fund for partial support of this research.

Registry No.—Ib, 407-25-0; IIb, 57738-66-6; IVb, 57738-67-7; V (R′ = H; R″ = C_9H_{19}), 57738-68-8; V (R′ = H; R″ = Ph-CH_2), 57738-69-9; V (R′, R″ = -$(CH_2)_5$-), 19182-88-8; V (R′ = CH_3; R″ = C_6H_{13}), 57738-70-2; Me_2SO, 67-68-5; TEA, 121-44-8.

References and Notes

(1) Presented in part before the Division of Organic Chemistry, 169th Meeting of the American Chemical Society, Philadelphia, Pa., April 1975.
(2) J. G. Moffatt in "Oxidation", Vol. 2, R. L. Augustine and D. J. Trecker, Ed., Marcel Dekker, New York, N.Y., 1971, pp 1–64; J. D. Albright, *J. Org. Chem.*, **39**, 1977 (1974).
(3) S. Oae, Y. Kitao, S. Kawamura, and Y. Kitaoka, *Tetrahedron*, **19**, 817 (1963).
(4) J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **89**, 2416 (1967).
(5) A. K. Sharma and D. Swern, *Tetrahedron Lett.*, 1503 (1974); A. K. Sharma, T. Ku, A. D. Dawson, and D. Swern, *J. Org. Chem.*, **40**, 2758 (1975).
(6) T. G. Bonner, P. M. McNamara, and B. Smethurst, *J. Chem. Soc. B*, 114 (1968).
(7) C. F. H. Allen, *J. Am. Chem. Soc.*, **52**, 2955 (1930).
(8) E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, 498 (1945).
(9) V. Prelog, L. Frenkiel, M. Kobelt, and P. Barman, *Helv. Chim. Acta*, **30**, 1741 (1947).
(10) P. D. Bartlett and G. F. Woods, *J. Am. Chem. Soc.*, **62**, 2933 (1940).
(11) O. L. Brady, *J. Chem. Soc.*, 756 (1931).
(12) J. D. Roberts and C. Green, *J. Am. Chem. Soc.*, **68**, 214 (1946).
(13) J. P. McCormick, *Tetrahedron Lett.*, 1701 (1974).
(14) C. R. Johnson and W. G. Phillips, *J. Org. Chem.*, **32**, 1926 (1967).
(15) C. R. Johnson and W. G. Phillips, *J. Am. Chem. Soc.*, **91**, 682 (1969).
(16) E. J. Corey and C. U. Kim, *J. Am. Chem. Soc.*, **94**, 7586 (1972).
(17) J. B. Hendrickson and S. M. Schwartzman, *Tetrahedron Lett.*, 273 (1975).
(18) Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were obtained as liquid films using a Pye Unicam SP 1000 infrared spectrophotometer. NMR spectra were obtained with a Varian A-60A spectrometer, using CCl_4 as solvent and Me_4Si as internal standard. Gas chromatographic analyses were performed on a Wilkens Aerograph Model A-700 using a 12 ft × 0.25 in. column packed with 20% dilauryl phthalate on Chromosorb P or a 10 ft × 0.25 in. column packed with 20% SE-30 on Chromosorb W with He as carrier gas. Me_2SO was distilled from calcium hydride under atmospheric pressure, and the heart cut was stored over Linde molecular sieve, Type 3A, in a brown bottle sealed with a serum cap. TFAA, containing ca. 0.1% of TFA as an impurity, was used as purchased. Triethylamine (TEA) was stored over NaOH pellets overnight, then distilled and stored over Linde molecular sieve, Type 3A, in a sealed bottle. Methylene chloride was distilled from phosphorus pentoxide and kept over Linde molecular sieve, Type 3A, in a sealed bottle. Cyclohexenol, 3-butyn-2-ol, and allyl alcohol were distilled under nitrogen before use. Other alcohols were used as received; their purity was >96%.
(19) **Note Added in Proof.** Benzoin yields benzil (88%, procedure A), ethyl lactate yields ethyl pyruvate (70%, A; 78%, C), and 2-chlorocyclohexane yields 2-chlorocyclohexanone (67%, A; 63%, C).

Friedel–Crafts Thioacylation with Ethoxycarbonyl Isothiocyanate. A One-Step Synthesis of Aromatic Thioamides

Eleftherios P. Papadopoulos

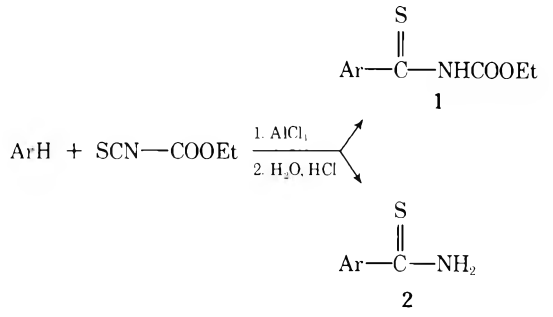
Department of Chemistry, University of New Mexico, Albuquerque, New Mexico 87131

Received October 29, 1975

The aluminum chloride catalyzed reaction of ethoxycarbonyl isothiocyanate with aromatic compounds yields *N*-ethoxycarbonylthioamides when equimolar amounts of the two reagents are allowed to react in dichloromethane at 0–3 °C. The same reaction, however, leads directly to the corresponding thioamides when run in an excess of the aromatic compound as solvent, at room or higher temperature.

In the course of an investigation of cyclization reactions of *N*-ethoxycarbonylthioamides, the need arose for a method of preparation of such derivatives of aromatic thioamides. A Friedel–Crafts thioacylation using ethoxycarbonyl isothiocyanate appeared to be the most straightforward approach to these compounds, in view of the known, aluminum chloride catalyzed reactions of isocyanates[1] and isothiocyanates[2] with aromatic compounds.

As anticipated, it has been found that ethoxycarbonyl isothiocyanate reacts readily with various aromatic compounds in the presence of anhydrous aluminum chloride. However, depending upon the conditions, the reaction yields either the expected *N*-ethoxycarbonylthioamide (**1**), or the thioamide itself (**2**). The latter result is closely analogous to the formation of benzamide when benzene reacts with chlorosulfonyl isocyanate in the presence of $AlCl_3$.[3] Typically, the reaction of equimolar quantities of reagents,



dissolved in CH_2Cl_2, run in the presence of 1.5 or 2.0 molar equiv of $AlCl_3$, at 0–3 °C, yields the original adduct **1**. On the other hand, when a large excess of the aromatic reagent is used as solvent and the reaction is run with 2.0 or more mol of $AlCl_3$ at ambient or higher temperature, addition of

Table I[a]

S
‖
Ar—C—NHCOOEt

					Ir, cm^{-1}		NMR, ppm			
1	Ar	Method	% yield[b]	Mp, °C	NH	CO	NH	Aromatic ring	R[c]	COOEt
a	C_6H_5	A	52	61–62.5[d]	3200	1760	12.0 (s, 1)	7.1–7.6 (m, 5)		4.1 (q, 2), 1.2 (t, 3)
b	4-MeC_6H_4	A	63	98–100	3200	1760	11.8 (s, 1)	7.4 (m, 2), 7.0 (m, 2)	2.3 (s, 3)	4.1 (q, 2), 1.2 (t, 3)
c	4-EtC_6H_4	A	67	60–62	3290, 3250	1740	11.8 (s, 1)	7.4 (m, 2), 7.0 (m, 2)	2.5 (q, 2), 1.1 (t, 3)	4.1 (q, 2), 1.2 (t, 3)
d	4-*i*-Pr-C_6H_4	A	60	70–72	3270	1740	11.9 (s, 1)	7.4 (m, 2), 7.1 (m, 2)	2.8 (m, 1), 1.2 (d, 6)	4.1 (q, 2), 1.2 (t, 3)
e	4-*t*-Bu-C_6H_4	A	41	111–113	3230	1740	11.8 (s, 1)	7.4 (m, 2), 7.1 (m, 2)	1.3 (s, 9)	4.0 (q, 2), 1.2 (t, 3)
f	2,5-DiMe-C_6H_3	B	84	66–68	3170	1770	12.2 (s, 1)	6.7 (m, 3)	2.2 (s, 3), 2.1 (s, 3)	4.1 (q, 2), 1.1 (t, 3)
g	2,4,6-Tri-MeC_6H_2	B	78	87–88	3250	1730	12.3 (s, 1)	6.6 (s, 2)	2.2 (s, 3), 2.1 (s, 6)	3.9 (q, 2), 1.1 (t, 3)
h	4-MeO-C_6H_4	C	90	88–90	3180	1750	11.7 (s, 1)	7.5 (m, 2), 6.7 (m, 2)	3.7 (s, 3)	4.1 (q, 2), 1.2 (t, 3)
i	4-EtO-C_6H_4	C	90	91–92.5	3190	1750	11.7 (s, 1)	7.6 (m, 2), 6.8 (m, 2)	4.0 (q, 2), 1.3 (t, 3)	4.2 (q, 2), 1.3 (t, 3)
j	4-ClC_6H_4	D	29	117–118	3180	1750	12.1 (s, 1)	7.5 (m, 2), 7.2 (m, 2)		4.1 (q, 2), 1.2 (t, 3)
k	4-BrC_6H_4	E	17	130–131.5	3180	1750	12.1 (s, 1)	7.4 (s, 4)		4.1 (q, 2), 1.2 (t, 3)

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified product with melting point lower than that of the analytical sample by 2–10 °C. [c] Alkyl or alkoxy substituent(s) attached to the aromatic ring. [d] Lit. mp 63 °C: J. Goerdeler and H. Schenk, *Chem. Ber.*, **44**, 782 (1966).

ice and hydrochloric acid at the end of the reaction period causes vigorous evolution of CO_2 and thioamide **2** is obtained as the product. In the case of anisole and phenetole, however, even the use of 4 mol of $AlCl_3$ or a reaction temperature of 100 °C fails to yield any of the thioamide. In general, a molar ratio of catalyst to isothiocyanate larger than 2:1 does not improve significantly the yield of either product. When monosubstituted benzenes are used as reagents, the major product arises from electrophilic attack at the para position relative to the original substituent, as has been observed in other similar reactions.[1,2] No attempt has been made in this study to identify or isolate any product corresponding to reaction at the ortho position of the aromatic ring.

Tables I and II display some physical and spectral constants of the compounds prepared, as well as the particular methods and yields of their preparation.

The nature of the product appears to be controlled mainly by two factors, the quantity of catalyst and the reaction temperature. For thioamide to be the major product, a molar ratio of $AlCl_3$ to isothiocyanate equal to at least 2:1 must be used. On the other hand, a low reaction temperature clearly favors the *N*-ethoxycarbonylthioamide. To a smaller extent, the outcome of the reaction also depends on its duration (a longer period of time favoring the thioamide) and the nature of the aromatic compound.

With regard to the formation of thioamide, it may be concluded that this results from further reaction of the originally formed *N*-ethoxycarbonyl derivative. This conclusion is supported by the formation of thiobenzamide as the only isolable product when the reaction of benzene is run under conditions which normally lead to compound **1a** (equimolar amounts of reagents, CH_2Cl_2 as solvent, 0–3 °C) but, before hydrolysis, a second equivalent of benzene is added and the reaction allowed to proceed at reflux.

The *N*-ethoxycarbonylthioamide formed in these reactions can be expected to be coordinated with $AlCl_3$ at the sulfur atom. In the presence of enough catalyst, further coordination at the carbonyl oxygen yields a strongly electrophilic ester group capable of reacting with the ring of the aromatic reagent in a Friedel–Crafts manner. Although such a reaction is also possible at the carbonyl carbon atom, it actually appears to occur at the α carbon of the ethyl group and to result in alkylation of the aromatic ring. The carbamate complex formed at the same time is later hydrolyzed to the corresponding carbamic acid which decarboxylates giving off CO_2.

The proposed interpretation of thioamide formation finds support in the known alkylation of aromatic compounds by treatment with esters and $AlCl_3$.[4,5] It is also consistent with the presence of ethylbenzene in the organic distillate obtained during isolation of the product, when benzene has reacted to form thiobenzamide. The fact that ethylbenzene is found by gas chromatography in about one-half of the theoretical amount may be attributed to its further alkylation, as well as reaction with the isothiocyanate. Indeed, the gas chromatogram of the organic distillate contains several minor peaks with retention times longer than that of ethylbenzene. Also, the NMR spectrum of crude thiobenzamide indicates the presence of a small quantity of *p*-ethylthiobenzamide. Significant reaction at the carbonyl carbon may be excluded, in view of the absence of a peak corresponding to ethyl benzoate from the above gas chromatogram. Furthermore, such a reaction would be inconsistent with formation of CO_2 during hydrolysis of the product. When chlorobenzene reacts to form 4-chlorothiobenzamide and the gases evolved upon hydrolysis are led through an aqueous $Ba(OH)_2$ solution, $BaCO_3$ is collected in about 90% of the theoretical amount. Finally, the observed diminishing tendency to yield the thioamide,

Table II[a]

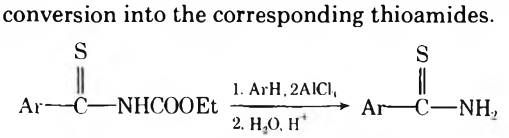
S
‖
Ar—C—NH_2

2	Ar	Method	% yield[b]	Mp, °C	Ir, cm^{-1} NH	Ir, cm^{-1} NH_2[c]	NMR, ppm NH_2	NMR, ppm Aromatic ring	NMR, ppm R[d]
a	C_6H_5	A, C, D	80–87	114–116[e]	3370, 3280, 3160	890	9.2 (s, 1), 9.6 (s, 1)	7.6–7.8 (m, 2), 7.1–7.3 (m, 3)	
b	4-MeC_6H_4	A, B	56–58	168–169[f]	3380, 3260, 3160	890	9.2 (s, 1), 9.5 (s, 1)	7.7 (m, 2), 7.0 (m, 2)	2.3 (s, 3)
c	4-EtC_6H_4	A	56	139–140	3360, 3270, 3150	890	9.2 (s, 1), 9.5 (s, 1)	7.7 (m, 2), 7.0 (m, 2)	2.6 (q, 2), 1.2 (t, 3)
d	4-*i*-PrC_6H_4[g]	A	62	147–148.5	3300–3140	900	9.2 (s, 1), 9.5 (s, 1)	7.7 (m, 2), 7.0 (m, 2)	2.8 (m, 1), 1.2 (d, 6)
e	4-*t*-BuC_6H_4	B	56	145.5–147.5	3380, 3270, 3130	900	9.2 (s, 1), 9.5 (s, 1)	7.7 (m, 2), 7.2 (m, 2)	1.3 (s, 9)
f	2,5-$DiMeC_6H_3$	A	86	94–96	3290, 3260	850	9.2 (s, 1), 9.7 (s, 1)	6.9 (s, 3)	2.2 (s, 6)
g	2,4,6-$TriMeC_6H_2$	A	91	208–210 dec	3370, 3250, 3120	890	9.2 (s, 1), 9.7 (s, 1)	6.7 (s, 2)	2.2 (s, 9)
h	4-$MeOC_6H_4$	F	79	148–149.5[h]	3360, 3280, 3160	890	9.1 (s, 1), 9.4 (s, 1)	7.8 (m, 2) 6.8 (m, 2)	3.8 (s, 3)
i	4-$EtOC_6H_4$	F	84	157.5–159[i]	3350, 3280	890	9.1 (s, 1), 9.4 (s, 1)	7.8 (m, 2) 6.8 (m, 2)	4.0 (q, 2), 1.3 (t, 3)
j	4-ClC_6H_4	B, C, D, E	61–64	127.5–129.5[j]	3250, 3130	890	9.5 (s, 2)	7.8 (m, 2), 7.3 (m, 2)	
k	4-BrC_6H_4	B, E	56–60	141.5–143[k]	3380, 3290, 3170	890	9.3 (s, 1), 9.4 (s, 1)	7.7 (m, 2), 7.4 (m, 2)	

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or partially purified product with melting point lower than that of the analytical sample by 2–10 °C. [c] NH_2 bending mode (wagging): K. A. Jensen and P. H. Nielsen, *Acta Chem. Scand.*, **20**, 597 (1966). This characteristic band of primary thioamides (absent from the spectra of the corresponding carboxamides) had earlier been attributed to C=S stretching: L. J. Bellamy and P. E. Rogasch, *J. Chem. Soc.*, 2218 (1960). [d] Alkyl or alkoxy substituent(s) attached to the aromatic ring. [e] Lit. mp 116–117°: M. M. Endicott, E. Wick, M. L. Mercury, and M. L. Sherril, *J. Am. Chem. Soc.*, 68, 1299 (1946). [f] Lit. mp 168°: Paterno and Spica, *Ber.*, 8, 441 (1875). [g] E. Czumpelik, *Ber.*, 2, 185 (1869). [h] Lit. mp 154°: S. Kakimoto, J. Seydel, and E. Wempe, *Arzneim.-Forsch.*, **12**, 127 (1962); *Chem. Abstr.*, **57**, 9812*i* (1952). [i] Lit. mp 162°: reference in *h*. [j] Lit. mp 124°: K. Kindler, *Justus Liebigs Ann. Chem.*, **450**, 1 (1926). [k] Lit. mp 141.5°: reference in *j*.

benzene, alkylbenzenes > halobenzenes ≫ alkoxybenzenes, parallels the increasing ability of the substituent of the aromatic reagent to coordinate with $AlCl_3$ and, therefore, the expected decreasing availability of $AlCl_3$ for coordination with the carbonyl oxygen.

Consistent with the previous arguments concerning the dealkylation and decarboxylation reactions is the following observation. If a solution of *N*-ethoxycarbonylthiobenzamide (**1a**) in benzene is mixed with 2 molar equiv of $AlCl_3$ and heated on a steam bath for 3–4 min, or let stand at room temperature for 4 h, hydrolysis of the mixture with ice and hydrochloric acid causes CO_2 evolution and precipitation of thiobenzamide. In both cases, the organic layer is found by gas chromatography to contain ethylbenzene. This seems to be a general reaction of *N*-ethoxycarbonylthioamides and provides a simple and efficient method for their conversion into the corresponding thioamides.



It is interesting to note that such dealkylation and decarboxylation of the anisole derivative **1h** proceed to a minor extent only upon brief heating with benzene and 2 mol of $AlCl_3$, but to completion when 3 mol of $AlCl_3$ are used. No reaction occurs when anisole is used instead of benzene. The results agree with the expected strong coordination of $AlCl_3$ with the methoxy group and are consistent with the earlier mentioned exclusive formation of the *N*-ethoxycarbonyl derivative **1h** or **1i** when anisole or phenetole react with EtOOC–NCS even under conditions which in all other cases lead to thioamides.

In conclusion, the reaction which has been described allows preparation of certain thioamides in one step from the corresponding aromatic compounds. It is subject to the usual limitations of the Friedel–Crafts reactions but, because of its simplicity and satisfactory yields, it compares favorably with other methods of preparation of thioamides[6–8] which are useful starting materials for the synthesis of various heterocyclic compounds.[6–8]

Under somewhat different conditions, the same reaction affords *N*-ethoxycarbonyl derivatives of aromatic thioamides in fair to good yields. When both types of compounds are present in the product, their separation from each other is easy, because thioamides are only sparingly soluble in dilute aqueous NaOH, whereas their *N*-ethoxycarbonyl derivatives dissolve easily in it and may subsequently be recovered by acidification of the alkaline solution. In addition to the earlier discussed dealkylation and decarboxylation by the action of $AlCl_3$ and an aromatic compound, *N*-ethoxycarbonylthioamides undergo as expected[9] the same overall reaction when treated with aqueous alkali. For a good yield of thioamide, however, this reaction must be run at room temperature over a relatively long period of time (48–72 h) because heating results in formation of the corresponding nitrile as by-product.

Experimental Section[10]

Preparation of *N*-Ethoxycarbonylthioamides (1). A. To a stirred cold (ice bath) solution of 0.050 mol of the aromatic compound and 6.5 g (0.050 mol) of ethoxycarbonyl isothiocyanate in 30 ml of CH_2Cl_2 was added 13.3 g (0.10 mol) of anhydrous $AlCl_3$, in small portions[11] (15–20 min) at 0–3°C. The reaction mixture was stirred at this temperature for 4 h and then it was hydrolyzed by careful addition of ice and dilute hydrochloric acid. Enough

CH_2Cl_2 was added to dissolve any solid organic material and the resulting solution was extracted with four 50-ml portions of 10% aqueous NaOH. This extract was washed with ethyl ether and acidified with concentrated hydrochloric acid (ice bath) to yield an oil which solidified upon cooling. The solid material was washed successively with dilute hydrochloric acid and water, dried, and washed again with petroleum ether (bp 30–60 °C), or cold ethyl ether, or cold aqueous ethanol. Purification of the crude product was accomplished by recrystallization from petroleum ether (bp 30–60 or 60–75 °C), benzene–petroleum ether (bp 60–75 °C), cyclohexane, or aqueous ethanol.

B. As in A, except that 10.0 g (0.075 mol) of $AlCl_3$ was used and the reaction mixture was stirred at 0–3 °C for 2 h after addition of the catalyst and before hydrolysis.

C. Anhydrous $AlCl_3$ (13.3 g, 0.10 mol) was added in one portion to 75 ml of the cold (ice bath) aromatic compound and a solution of 6.5 g (0.050 mol) of EtOOC–NCS in 25 ml of the aromatic compound was allowed to flow slowly (15–20 min) into the stirred slurry. The resulting mixture was stirred at 0–3 °C for 1 h, then the cooling bath was removed and stirring continued for a further 4 h. The subsequent treatment was as in A, except that ethyl ether was used to dissolve the organic materials following hydrolysis and prior to extraction with aqueous alkali.

D. As in C, except that the cooling bath was removed upon completion of addition of the isothiocyanate and the reaction mixture stirred for 6 h at room temperature.

E. As in C except that the reaction mixture was stirred at 0–3 °C for 6 h following addition of the isothiocyanate and prior to hydrolysis.

Preparation of Thioamides (2). A. Anhydrous $AlCl_3$ (13.3 g, 0.10 mol) was added in one portion to 75 ml of the cold (ice bath) aromatic compound and the resulting mixture was stirred for 1–2 min. The cooling bath was then removed and a solution of 6.5 g (0.050 mol) of ethoxycarbonyl isothiocyanate in 25 ml of the aromatic compound was allowed to flow slowly (15–20 min) into the stirred slurry. Following completion of this addition, the reaction mixture was stirred for 4 h and then it was cooled (ice bath) again and hydrolyzed by careful addition of a mixture of ice and dilute hydrochloric acid. Enough ethyl ether was added to dissolve any solid organic material and the resulting solution was washed successively with 10% aqueous NaOH and water. After it had been dried ($MgSO_4$), this solution was concentrated under reduced pressure and the precipitated solid was collected by filtration and washed with petroleum ether (bp 30–60 °C), or cold CCl_4, or cold aqueous ethanol. The crude product was then purified by recrystallization from EtOH–H_2O or benzene–petroleum ether (bp 60–75 °C).

B. As in A except that following addition of the isothiocyanate the reaction mixture was stirred at room temperature for 1 h and then on the steam bath for a further 2–3 h.

C. As in A except that $AlCl_3$ was added without cooling to a solution of 6.5 g of EtOOC–NCS in 100 ml of the aromatic compound and the reaction mixture was stirred first without external heating for 1 h and then on the steam bath for an additional 1 h.

D. As in C except that 20.0 g of $AlCl_3$ was used.

E. As in C except that the reaction mixture was stirred only at room temperature, for 24 h.

F. A solution of 1.0 g of *N*-ethoxycarbonylthioamide in 10 ml of 10% aqueous NaOH was let stand at room temperature for 48–72 h. The precipitated solid was collected, washed with water, mixed with dilute hydrochloric acid, collected again by filtration, and finally washed with water.

Dealkylation and Decarboxylation of *N*-Ethoxycarbonylthioamides. A mixture of 5 mmol of 1, 10 mmol of $AlCl_3$, and 5 ml of benzene was stirred on the steam bath for 3 min, then it was chilled and decomposed by addition of ice and dilute hydrochloric acid. The hydrolysis product was mixed with petroleum ether (bp 30–60 °C) and the precipitated 2 was collected by filtration and washed with water. Yields: **2a**, 75%; **2d**, 77%; **2h** (use of 15 mmol of $AlCl_3$), 71%; thiophene-2-thioamide (use of 15 mmol of $AlCl_3$), 89%.

Acknowledgments. Financial support from the Research Corporation, the Research Allocations Committee of the University of New Mexico, and the Department of Chemistry of the University of New Mexico is gratefully acknowledged.

Registry No.—**1a**, 5499-31-0; **1b**, 57774-66-0; **1c**, 57774-67-1; **1d**, 57774-68-2; **1e**, 57774-69-3; **1f**, 57774-70-6; **1g**, 57774-71-7; **1h**, 57774-72-8; **1i**, 57774-73-9; **1j**, 57774-74-0; **1k**, 57774-75-1; **2a**, 2227-79-4; **2b**, 2362-62-1; **2c**, 57774-76-2; **2d**, 53515-20-1; **2e**, 57774-77-3; **2f**, 57774-78-4; **2g**, 57182-71-5; **2h**, 2362-64-3; **2i**, 57774-79-5; **2j**, 2521-24-6; **2k**, 26197-93-3; ArH (Ar = C_6H_5), 71-43-2; ArH (Ar = 4-MeC_6H_4), 108-88-3; ArH (Ar = 4-EtC_6H_4), 100-41-4; ArH (Ar = 4-*i*-PrC_6H_4), 98-82-8; ArH (Ar = 4-*t*-BuC_6H_4), 98-06-6; ArH (Ar = 2,5-diMeC_6H_3), 106-42-3; ArH (Ar = 2,4,6-triMeC_6H_2) 108-67-8; ArH (Ar = 4-$MeOC_6H_4$), 100-66-3; ArH (Ar = 4-$EtOC_6H_4$), 103-73-1; ArH (Ar = 4-ClC_6H_4), 108-90-7; ArH (Ar = 4-BiC_6H_4), 108-86-1; ethoxycarbonyl isothiocyanate, 16182-04-0.

References and Notes

(1) F. Effenberger and R. Gleiter, *Chem. Ber.*, **97**, 472 (1964); J. W. McFarland and L. C. Yao, *J. Org. Chem.*, **35**, 123 (1970).
(2) K. K. Ginwala and J. P. Trivedi, *J. Indian Chem. Soc.*, **40**, 897 (1963); R. D. Desai, *ibid.*, **45**, 193 (1968); P. A. S. Smith and R. O. Kan, *J. Org. Chem.*, **29**, 2261 (1964).
(3) R. Graf, *Chem. Ber.*, **92**, 509 (1959).
(4) E. Bowden, *J. Am. Chem. Soc.*, **60**, 645 (1938).
(5) J. F. Norris and B. M. Sturgis, *J. Am. Chem. Soc.*, **61**, 1413 (1939).
(6) R. N. Hurd and G. DelaMater, *Chem. Rev.*, **61**, 45 (1961).
(7) W. Walter and J. Voss in "The Chemistry of Amides", J. Zabicky, Ed., Interscience, New York, N.Y., 1970, pp 415–432; N. Walter and K.-D. Bode, *Angew. Chem., Int. Ed. Engl.*, **5**, 447 (1966).
(8) F. Duus in "Organic Compounds of Sulfur, Selenium and Tellurium", Vol. 2, D. H. Reid, Ed., The Chemical Society, London, 1973, pp 228–233.
(9) E. P. Papadopoulos, *J. Org. Chem.*, **38**, 667 (1973).
(10) All reactions were run in a nitrogen atmosphere. Melting points were determined in a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer using mineral oil mulls. NMR spectra were obtained on a Varian EM360 spectrophotometer using solutions in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard.
(11) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. I, Wiley, New York, N.Y., 1967, p 24.

Halosulfonium Salts. IX. Halogen-Induced Ring Cleavages of 1,3-Oxathiolanes

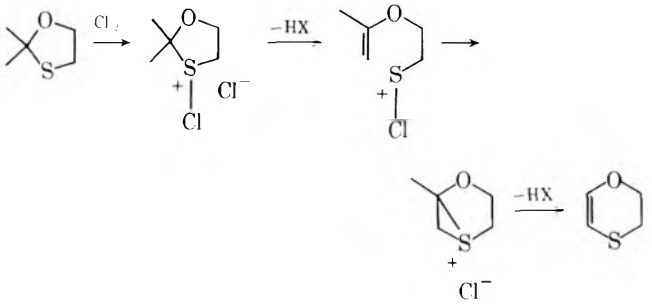
G. Edwin Wilson, Jr.,* and Muh-Guey Huang

Department of Chemistry, Polytechnic Institute of New York, Brooklyn, New York 11201

Received November 25, 1975

Halogenation of the 1,3-oxathiolanes derived from benzophenone, diisopropyl ketone, and cycloheptanone provides a route to regenerate the ketone in good yield. For diisopropyl ketone an additional product, α-(2-haloethylthiol)isopropyl isopropyl ketone, is obtained.

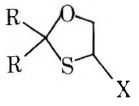
Chlorination of 1,3-oxathiolanes derived from ketones and aldehydes having an α-methylene provides 1,4-oxathienes as the primary product.[1] This reaction has been considered to proceed through the sequence of steps shown below for 2,2-dimethyl-1,3-oxathiolane. The work reported



here was undertaken to confirm this mechanism. The basic approach was to block the sequence at successive steps by use of appropriately substituted oxathiolanes.

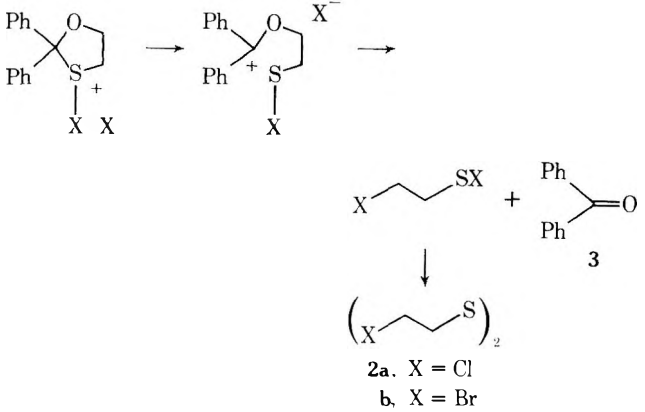
Results and Discussion

The absence of protons on the side chain β to the sulfur atom was expected to block the initial dehydrohalogenation and lead to α-halogenation[2] of the ring to form **1** in



1

analogy to the halogenation of tetrahydrothiophene;[3] however, an alternative route was followed. Thus, chlorination of 2,2-diphenyl-1,3-oxathiolane in carbon tetrachloride provided β-chloroethyl disulfide (**2a**), verified by spectral identity with authentic material,[4] and a quantitative yield of benzophenone (**3**).



2a, X = Cl
b, X = Br

The cleavage of halosulfonium salts to provide stabilized carbonium ions is well known.[5] The reaction described produced none of the expected hydrogen halide, and required only 0.5 equiv of chlorine. The reaction with bromine paralleled the chlorination and provided **2b** which was spectrally identical with authentic material.

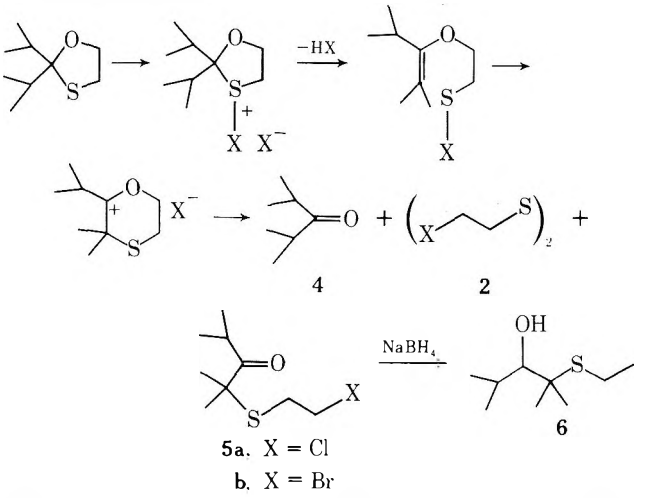
The origin of disulfide could involve either disproportionation of the sulfenyl halide to form the corresponding disulfide plus halogen or attack of the sulfenyl halide on the oxathiolane giving a thiosulfonium salt which would be subject to halide attack to afford the disulfide and benzophenone. The latter course was shown to be possible by a control experiment in which β-bromoethylsulfenyl bromide was generated in situ by the bromination of β-bromoethyl disulfide at low temperature, and allowed to react with oxathiolane. NMR analyses of the brominated solution of disulfide showed only one peak assignable to the accidentally degenerate methylene protons of the sulfenyl bromide. Upon addition of solid 2,2-diphenyl-1,3-oxathiolane, benzophenone and disulfide were formed as evidenced by NMR analysis of the final solution. This reaction is similar to that observed for the reaction of benzyl sulfenyl bromide with dibenzyl sulfide.[7]

Nucleophilic substitution by halide ion at C-4 leading to irreversible cleavage of the oxathiolane ring might be expected to give way to the formation of 2-halo- or 4-halo-1,3-oxathiolane by generating the halosulfonium salt at low temperature and thus preventing its decomposition. Addition of a base such as triethylamine to the halosulfonium salt at this temperature might then favor the Pummerer rearrangement leading to **1**. To test this possibility, a solution of triethylamine in carbon tetrachloride was introduced into a −70°C suspension of the halosulfonium salt. The products, after filtration of triethylammonium bromide (78% yield), contained 93% of benzophenone, 7% of disulfide, and 9% of the starting oxathiolane. Evidently, the acidity of the protons in the oxathiolane ring is so low that they play no role in the determination of the reaction products.

Blockage of the second dehydrohalogenation could be effected by employing an oxathiolane with no protons γ to the sulfur atom. Reaction of 2,2-diisopropyl-1,3-oxathiolane with bromine under the conditions used for the bromination of diphenyl oxathiolane gave, after isolation and characterization, diisopropyl ketone (**4**, 41%), the bis(2-bromoethyl) disulfide, and α-(2-bromoethylthio)isopropyl isopropyl ketone (**5b**, 40%). Structure **5b** was confirmed by spectral data and by reduction to **6**.

Chlorination of 2,2-diisopropyl-1,3-oxathiolane under similar conditions gave, in addition to diisopropyl ketone, four other products as shown by VPC analysis. A quantitative estimation and characterization of each individual peak was not possible since the peaks overlapped badly in the VPC. After repeated distillations and column chromatography the pure major product, α-(2-chloroethylthio)-isopropyl isopropyl ketone (**5a**), was obtained in 41% yield. The ir and NMR spectra of the **5a** also isolated are similar to those of **5b**. Sodium borohydride reduction gave the al-

cohol **6** identical in every respect with that obtained from the reduction of **5b**.



5a, X = Cl
b, X = Br

We have also observed predominant ketone formation upon bromination of the oxathiolane derived from cycloheptanone. In each case cycloheptanone was obtained in approximately 97% yield. This result probably arises because oxathiene formation is more difficult in this case owing to steric restraints on proton loss from the sulfocarbonium ion rather than because of lowered activation energy for ketone formation.

Experimental Section.

Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 521 spectrometer. NMR spectra were recorded with a Varian Associates Model A-60 spectrometer in carbon tetrachloride solution with Me_4Si as an internal standard at 0 ppm unless otherwise stated. VPC analyses were carried out on Aerograph Models 1520 and 220 vapor phase chromatographs employing helium as the carrier gas and columns of either XF1150 or DC11 or 60/80 mesh Chromosorb P. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Mass spectra were obtained on a Hitachi Model RMU-6E single-focusing mass spectrometer.

Reaction of 2,2-Diphenyl-1,3-oxathiolane with Chlorine. To a solution of 7.26 g (30 mmol) of 2,2-diphenyl-1,3-oxathiolane in 80 ml of methyl chloride, precooled at −78° with a dry ice–acetone bath, was added 0.8 ml (ca. 16 mmol) of chlorine over a 5-min period. The resulting yellow solution was retained at −78 °C for 5 h and at room temperature for 24 h. NMR analysis of this solution showed only signals corresponding to benzophenone and bis(2-chloroethyl) disulfide (**2a**). Identification of the NMR signals of **2a** was made by comparison of chemical shifts of the signals with those obtained from an authentic sample.[6] VPC analysis of the reaction mixture also confirmed the presence of benzophenone and **2a**. The residue remaining after evaporation of the solvent was placed on a column of 140 g of silica gel and eluted with a methylene–carbon tetrachloride (4:1) mixture. The progress of the elution was followed by NMR and VPC analyses. The early fractions containing 1.58 g (56%) of **2a** were combined. The isolated **2a** was identical in every respect with an authentic sample. The rest of the eluents were combined and evaporated to give 5.48 g (100%) of benzophenone. Compound **2a** gave ir absorptions at ν_{max} (neat) 2960, 1440, 1412, 1280, 1205, and 850 cm^{-1}, and NMR analysis showed two multiplets of an AA′BB′ pattern centered at 3.00 and 3.76 ppm (area ratio 1:1).

Reaction of 2,2-Diphenyl-1,3-oxathiolane with Bromine. To a solution of 3.63 g (15 mol) of 2,2-diphenyl-1,3-oxathiolane in carbon tetrachloride at 0 °C was added 2.56 g (15.5 mmol) of bromine in carbon tetrachloride. The mixture was allowed to warm to room temperature and then kept at 40–43 °C for an additional 18 h. NMR analyses of the cooled solution indicated the presence of benzophenone and bis(2-bromoethyl) disulfide (**2b**). The solvent was evaporated, and the residual material was put on a column of 50 g of silica gel and eluted with 2:1 chloroform–carbon tetrachloride. The first 150 ml of eluent was evaporated to yield 1.2 g (64%) of brown oil ($n^{26}D$ 1.6164, mp 25–26 °C) identified as **2b** by comparison of ir, NMR, and VPC spectra with those of an authentic sample. The final 325 ml of the eluent, after the discarding of 50 ml of an intermediate fraction, were concentrated to give 2.6 g (96%) of benzophenone. Compound **2b** gave ir absorption at ν_{max} (neat) 2960, 1432, 1250, 1185, 1095, and 615 cm^{-1}, and the NMR showed two multiplets centered at 3.16 and 3.50 ppm in a ratio of 1:1.

Bis(2-chloroethyl) Disulfide (2a). To 15.6 g (0.2 mol) of β-mercaptoethanol at room temperature was added 20 ml (ca. 0.175 mol) of 30% hydrogen peroxide dropwise with ice–water cooling. The resulting clear solution was maintained at 50–60 °C for 2 h and then 70 ml of concentrated hydrochloric acid was added at room temperature with constant stirring. The solution was then heated at 100 °C until two layers were observed. The organic layer was obtained by extracting twice with 100 ml of methylene chloride and dried. Vacuum distillation of the residue afforded 14.4 g (75.5%) of bis(2-chloroethyl) disulfide (**2a**), $n^{25}D$ 1.5641 (lit.[6] $n^{20}D$ 1.5656).

Bis(2-bromoethyl) Disulfide (2b). To a solution of 31.2 g (0.4 mol) of β-mercaptoethanol in 80 ml of chloroform was added 52.4 g (0.44 mol) of thionyl chloride in 30 ml of chloroform over a 1-h period. The clear solution was stirred at room temperature for 16 h, then solvent was removed in vacuo. Distillation gave 38.2 g (77%) of 1,2,3-oxadithiolane 2-oxide, bp 57–58 °C (0.5 mm), $n^{26}D$ 1.5757 (lit.[7] $n^{24}D$ 1.5782). A solution of 24.8 g (0.2 mol) of 1,2,3-oxadithiolane 2-oxide in 200 ml of carbon tetrachloride at 0 °C was brominated with 32 g (0.2 mol) of bromine. The final dark red solution was stirred at room temperature for 18 h, concentrated, and vacuum distilled to give 21.9 g (78%) of bis(2-bromoethyl) disulfide (**2b**), $n^{25}D$ 1.6203 (lit.[7] $n^{19}D$ 1.6190), bp 107–109 °C (0.5 mm).

Reaction of 2,2-Diphenyl-1,3-oxathiolane with Bromine in the Presence of Triethylamine. To a solution of 2.42 g (0.01 mol) of 2,2-diphenyl-1,3-oxathiolane in a mixture of 20 ml of methylene chloride and 30 ml of carbon tetrachloride maintained at −65 °C was added as quickly as possible 1.6 g (0.01 mol) of bromine in 10 ml of the solvent mixture. To the orange paste formed was then added 1.01 g (0.01 mol) of triethylamine rapidly at this temperature. The final yellow suspension was allowed to warm to room temperature. A solid material was removed by filtration, washed with cold carbon tetrachloride, and dried to give 1.34 g (78%) of triethylammonium bromide, mp 250–252 °C. The mother liquor was taken to dryness, giving a yellow oil. The oil was placed on 100 g of silica gel and eluted with carbon tetrachloride, the progress of elution being followed by NMR analysis. From the early fractions totaling 1 l. of eluent, 0.09 g (7%) of **2b** was obtained. The next fractions totaling 600 ml were combined and evaporated under vacuum, yielding 0.23 g (9%) of recovered starting material. The rest of the fractions were combined, and evaporation of the solvent left 1.54 g (93%) of benzophenone.

Reaction of 2,2-Diisopropyl-1,3-oxathiolane with Bromine. A solution of 34.9 g (0.2 mol) of 2,2-diisopropyl-1,3-oxathiolane in 200 ml of methylene chloride was brominated with 33.5 g (0.2 mol) of bromine in 100 ml of methylene chloride. After the reaction was complete and solvent removed in vacuo, the residual oil on VPC analysis showed two peaks corresponding to 41% of diisopropyl ketone and 59% of another product. Vacuum distillation of the residue gave in addition to low-boiling diisopropyl ketone, 20.1 g (40%) of α-(2-bromoethylthio)isopropyl isopropyl ketone (**5b**): bp 90–92 °C (0.3 mm); $n^{24}D$ 1.5004; ν_{max} (neat) 2970, 1690, 1378, 1361, 1029, 610 cm^{-1}; NMR (CCl_4) δ 1.08 (d, J = 6.6 Hz, 7 H), 1.45 (s, 6 H), 2.70 (m, 2 H), 3.33 ppm (m, 2 H).

Anal. Calcd for $C_9H_{17}OSBr$: C, 42.69; H, 6.77; S, 12.67; mol wt, 253. Found: C, 42.74; H, 6.82; S, 12.79; mol wt, 254 (mass spectrum, molecular ion), 252 (osmometric).

Reduction of α-(2-Bromoethylthio)isopropyl Isopropyl Ketone (5b). To a solution of 5 g (19.7 mmol) of the ketone **5b** in absolute ethanol was added 1.5 g (400 mmol) of sodium borohydride portionwise at 0 °C with constant stirring. After the addition was complete, the solution was stirred for an additional 30 min and then heated under reflux for 1 h. The resulting yellow suspension was cooled, the excess sodium borohydride was destroyed with 10% hydrochloric acid, the solution was made basic with 10% aqueous sodium carbonate, and finally the solid was removed by filtration. The organic layer was extracted twice with 80 ml of ethyl acetate, washed, and dried over anhydrous sodium sulfate, and the solvent was removed under vacuum. Distillation of the residue gave 1.90 g (55%) of α-ethylthioisopropyl isopropyl alcohol (**6**): bp 55–57 °C (0.4 mm); $n^{25}D$ 1.4761; ν_{max} (neat) 3350, 2960, 1460, 1380, 1360, and 1260 cm^{-1}; NMR (CCl_4) δ 3.15 (d, J = 3.0 Hz, 1 H), 248 (s, –OH), 2.50 (q, J = 15 Hz, 2 H), 2.0 (m, 1 H), 1.34 (s, 3 H), 1.17 (s, 3 H), 1.0 (m, 9 H).

Anal. Calcd for $C_9H_{20}OS$: C, 61.33; H, 11.44; S, 18.20; mol wt, 176. Found: C, 61.57; H, 11.60; S, 18.39; mol wt, 176 (mass spectrum, molecular ion).

Reaction of 2,2-Diisopropyl-1,3-oxathiolane with Chlorine. A solution of 17.4 g (0.1 mol) of 2,2-diisopropyl-1,3-oxathiolane in 150 ml of methylene chloride at −70 °C was chlorinated with 7.8 g (0.11 mol) of chlorine according to the procedure previously described. VPC analysis of the solution after the reaction was complete showed the presence of isopropyl ketone and five other products. Quantitative analysis of the product ratio was not possible owing to overlapping of the peaks on the VPC trace. The crude residue was fractionally distilled to give 8.6 g (41%) of major product, bp 85–90 °C (1.0 mm). Repeated distillation of the crude distillate did not remove the impurities. The analytical sample of this product was obtained by column chromatography on 100 g of silica gel using benzene–hexane (3:1) as eluent. The impurities were eluted in the early fractions. The later fractions were combined and concentrated to afford a pure liquid oil identified as α-(2-chloroethylthio)isopropyl isopropyl ketone (**5a**): $n^{25}D$ 1.4821; ν_{max} (neat) 2970, 2940, 2880, 1692, 1468, 1380, 1365, 1035 cm^{-1}; NMR (CCl_4) δ 1.07 (d, J = 7.0 Hz, 6 H), 1.40 (s, 6 H), 2.64 (m, 2 H), 3.42 (m, 2 H); mass spectrum m/e 208 (2.65), 139 (96.25), 137 (66.25), 63 (24.43), 59 (27.08), 43 (100), 41 (92.50), 39 (26.14), 27 (46.78).

Anal. Calcd for $C_9H_{17}OSCl$: C, 51.80; H, 8.21; S, 15.36; mol wt, 208.7. Found: C, 51.78; H, 8.07; S, 16.29; mol wt, 208 (mass spectrum, molecular ion).

Reduction of α-(β-Chloroethylthio)isopropyl Isopropyl Ketone (5a) with Sodium Borohydride. Six grams (28.8 mmol) of **5a** in 50 ml of absolute ethanol was reduced with 2.8 g (73 mmol) of sodium borohydride as previously described. The product, α-ethylthioisopropyl isopropyl alcohol (**6**), after work-up and distillation, was obtained in 77% yield.

Reaction of 1,4-Oxathiaspiro[4.6]undecane with Bromine. A solution of 34.4 g (0.2 mol) of 1,4-oxathiaspiro[4.6]undecane[8] and 33.6 g (0.21 mol) of bromine in 200 ml of carbon tetrachloride was allowed to react as above. After being refluxed for 24 h, the greenish solution was concentrated on the rotary evaporator and the residue was analyzed by VPC which showed mainly cycloheptanone and a small amount of high-boiling material. Distillation of the residue gave 20.7 g (93%) of cycloheptanone, identified by comparisons of the ir spectrum with that of commercial material, and 16.4 g of a gummy residue, apparently a polymeric material.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

Registry No.—**1** (R = Ph; X = H), 33735-40-9; **1** (R = *i*-Pr; X = H), 16047-99-7; **1** (R, R = $(CH_2)_6$; X = H), 184-31-6; **2a**, 1002-41-1; **2b**, 1002-40-0; **3**, 119-61-9; **4**, 565-80-0; **5a**, 57738-71-3; **5b**, 57738-72-4; **6**, 57738-73-5; chlorine, 7782-50-5; bromine, 7726-95-6; β-mercaptoethanol, 60-24-2; 1,2,3-oxadithiolane 2-oxide, 57738-74-6; triethylammonium bromide, 636-70-4; cycloheptanone, 502-42-1.

References and Notes

(1) G. E. Wilson, Jr., *J. Am. Chem. Soc.*, **87**, 3785 (1965).
(2) R. Pummerer, *Ber.*, **43**, 1410 (1910); W. E. Parham and M. D. Bhavsar, *J. Org. Chem.*, **28**, 2686 (1963); L. Horner and E. Jurgens, *Justus Liebigs Ann. Chem.*, **602**, 135 (1957); L. Horner and P. Kaiser, *ibid.*, **626**, 19 (1959).
(3) G. E. Wilson, Jr., and R. Albert, *Tetrahedron Lett.*, 6271 (1968); *J. Org. Chem.*, **38**, 2156, 2160 (1973).
(4) R. C. Fuson, C. C. Price, and D. M. Burnes, *J. Org. Chem.*, **11**, 475 (1946).
(5) K. C. Schreiber and V. P. Fernandez, *J. Org. Chem.*, **26**, 2478 (1961).
(6) K. C. Tsou, H. C. F. Su, and C. Segebarth, *J. Org. Chem.*, **26**, 4993 (1961).
(7) G. E. Wilson, Jr., and M. G. Huang, *J. Org. Chem.*, **35**, 3002 (1970).
(8) G. E. Wilson, Jr., M. G. Huang, and W. W. Schloman, Jr., *J. Org. Chem.*, **33**, 2133 (1968).

Kinetics of the Reactions of 2-Bromo-3,5-dinitrothiophene with Meta- and Para-Substituted Anilines in Methanol. The Application of Hammett and Ingold–Yukawa–Tsuno Equations[1a]

D. Spinelli,*[1b] G. Consiglio, R. Noto, and V. Frenna

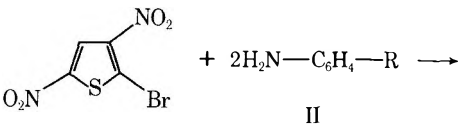
Institute of Organic Chemistry of the University, 90123 Palermo, Italy

Received October 7, 1975

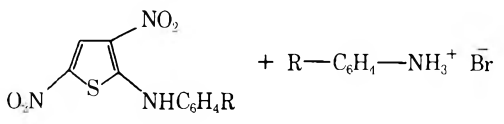
The rate constants of debromination of 2-bromo-3,5-dinitrothiophene by various meta- and para-substituted anilines have been measured in methanol at various temperatures and the Arrhenius parameters determined. The kinetic data have been analyzed, using the Ingold–Yukawa–Tsuno equation. The ρ (−3.00), r^- (0.99), and r^+ (0.38) values obtained are discussed.

The reactions of halogenonitroaromatic and heteroaromatic derivatives with substituted anilines have been studied by many research workers,[2] but no systematic quantitative studies, covering the whole range of substituent effects in the aniline moiety, have so far been carried out.

In the framework of our researches[3] on the applicability of linear free energy relationships to aromatic nucleophilic substitution reactions in the thiophene series, we now report kinetic data of the reaction of 2-bromo-3,5-dinitrothiophene (I) with various meta- and para-substituted anilines (II).



I II



III

Results

2-Bromo-3,5-dinitrothiophene (I) gave the expected anilino derivatives (III) on treatment with anilines (II) in almost quantitative yields as shown by TLC and uv–visible spectral analysis. The relevant physical and analytical data are shown in Table I.

Rate constants and activation parameters for the anilino debromination reactions of I are shown in Table II. All the reactions were first order both in I and II.[6] An increase of the rate of substitution was observed on introduction of electron-repelling substituents into the nucleophile. On the

Table I. Physical Data for Meta- and Para-Substituted *N*-(3,5-Dinitrothienyl)anilines (III)[a]

Substituent	Registry no.	Color	Crystn solvent	Mp, °C	λ_{max},[b] nm	Log ϵ[b]
p-OCH_3[c]	1033-84-7	Orange	Ethanol–dioxane	164[d]	406	4.20
p-CH_3[e]	21817-48-1	Orange	Ethanol	146–147	404	4.23
m-CH_3[c]	21817-49-2	Red	Ethanol–dioxane	150–151[f]	404	4.24
H[e]	959-38-6	Orange	Ethanol	162–163	402	4.24
p-Cl[c]	19320-18-4	Yellow	Ethanol–dioxane	184–185[g]	396	4.26
p-Br[c]	21817-46-9	Yellow	Ethanol–dioxane	173–174[h]	395	4.24
m-Cl[c]	21817-44-7	Yellow	Methanol–dioxane	193[i]	395	4.25
m-F	57738-59-7	Orange	Ethanol	123–125	396	4.25
m-Br	57738-60-0	Red	Methanol–dioxane	210–211	395	4.24
p-CO_2CH_3	57738-61-1	Yellow	Ethanol–dioxane	189–190	390	4.32
m-NO_2	57738-62-2	Red	Ethanol–dioxane	202	386	4.26
p-$COCH_3$	57738-63-3	Yellow	Ethanol–dioxane	196–197	394	4.35
p-CN	57738-64-4	Orange	Ethanol–dioxane	219–220	388	4.38
p-NO_2[e]	30514-82-0	Red	Ethanol–dioxane	210	396	4.45

[a] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds listed in the table. [b] In methanol. [c] See ref 4. [d] Lit. mp 158 °C. [e] See ref 5. [f] Lit. mp 148 °C. [g] Lit. mp 180 °C. [h] Lit. mp 172.5–173 °C. [i] Lit. mp 185–186 °C.

Table II. Rate Constants and Activation Parameters for the Reactions of 2-Bromo-3,5-dinitrothiophene (I) with Substituted Anilines (II) in Methanol

No.	Substituent	Registry no.	$10^3 k$, l. mol^{-1} s^{-1} (at various temperatures)[a]			$\Delta H^{\ddagger}$,[b] kcal mol^{-1}	$-\Delta S^{\ddagger}$,[c] cal mol^{-1} K^{-1}
1	*p*-OCH_3	104-94-9	304 (9.99)	521 (20.10)	796 (29.97)	7.6	33.7
2	*p*-CH_3	106-49-0	44.0 (0.05)	83.1 (10.08)	141 (20.05)	8.7	32.7
3	*m*-CH_3	108-44-1	64.6 (20.04)	107 (29.95)	178 (39.95)	8.7	34.3
4	H	62-53-3	12.2 (0.02)	23.0 (10.02)	41.9 (20.05)	9.2	33.4
5	*p*-Cl	106-47-8	9.40 (20.10)	16.5 (29.96)	27.3 (39.95)	9.2	36.3
6	*p*-Br	106-40-1	7.75 (19.76)	13.9 (30.02)	23.6 (40.05)	9.4	36.0
7	*m*-Cl	108-42-9	3.23 (19.95)	5.89 (30.00)	10.3 (40.02)	9.9	36.0
8	*m*-F	372-19-0	3.15 (20.10)	5.64 (29.98)	9.96 (40.01)	9.9	36.0
9	*m*-Br	591-19-5	3.08 (20.02)	5.72 (30.01)	10.1 (40.20)	10.1	35.4
10	*p*-CO_2CH_3	150-13-0	0.361 (20.03)	0.717 (30.00)	1.37 (40.08)	11.6	34.7
11	*m*-NO_2	99-09-2	0.278 (19.92)	0.524 (30.00)	0.951 (40.02)	10.6	38.7
12	*p*-$COCH_3$	98-86-2	0.215 (19.94)	0.429 (30.00)	0.88 (40.20)	12.1	33.9
13	*p*-CN	873-74-5	0.0627 (24.91)	0.126 (34.92)	0.254 (45.08)	13.1	35.9
14	*p*-NO_2	100-01-6	0.0114 (25.03)	0.0285 (34.93)	0.0716 (45.00)	17.3	25.0

[a] The rate constants are accurate to within ±3%. [b] At 20 °C, the maximum error is 0.5 kcal mol^{-1}. [c] At 20 °C.

other hand, the electron-attracting substituents markedly reduced the reaction rate with respect to hydrogen. The reactions studied were controlled by the enthalpy, and the nearly constant values of their activation entropy agree with the accepted mechanism[2b,7] (bimolecular, with large solvent participation in the transition state, and probable hydrogen bond formation).

Discussion

Hammett Relationship. The correlation of the reactivity data with Hammett substituent constants,[8] although giving, as expected, a negative ρ value, was not satisfactory (Table III). An examination of the Hammett plot (Figure 1) indicates that the para substituents notably deviate from the straight line for meta-substituted anilines ($\rho_{meta} = -3.03$).

Ingold–Yukawa–Tsuno (IYT) Relationship. It is generally recognized[9] that the Hammett relationship fails when a ±M substituent can interact with a reaction center ∓M in para position. In order to cover the deviations from the Hammett relationship observed for the para substituents, we have made use of the Ingold–Yukawa–Tsuno equation[10,9d]

$$\log k/k_H = \rho(\sigma^n + r^-\Delta\sigma_R^- + r^+\Delta\sigma_R^+)$$

Such a multiparameter treatment requires (a) a sufficient number (at least four) of *good* meta substituents and hydrogen, (b) a suitable number (at least four) of electron-withdrawing and/or -attracting substituents, and (c) a suitable number (at least four) of electron-donating and/or -repelling substituents.

The kinetic data at 20 °C related to meta-substituted anilines gives a good correlation (Table III) with σ^n values and the ρ value obtained can be utilized to calculate r^- and r^+ coefficients by means of the equations

$$\sigma - \sigma^n = r^{\pm}\Delta\sigma_R^{\pm}$$

where σ is the observed substituent parameter. The correlation of $\sigma - \sigma^n$ versus $\Delta\sigma_R^{\pm}$ gives, respectively, $r^- = 0.99 \pm 0.14$ ($R = 0.972$; $n = 5$) and $r^+ = 0.38 \pm 0.01$ ($R = 0.999$; $n = 5$). The least-squares line pertaining to the "*overall*" IYT equation ($\rho = -3.00$) is shown in Figure 2 and the relevant statistical data are reported in Table III.

The reasons of the deviations from a simple Hammett relationship for the anilines with electron-attracting para substituents and the consequent necessity of using an additive term, i.e., $r^-\Delta\sigma_R^-$, are evident on account of the definition of σ^- values by the anilinium cations dissociation reaction.[9d] Moreover, the necessity for using the term $r^+\Delta\sigma_R^+$ to cover the deviations due to the electron-repelling para substituents arises from the polarization of these substituents operated by the "ammonium" nitrogen in the rate-determining transition state.

Figures 1 and 2 show the considerable improvement in the linearity of the plot of log k against substituent parameter when the appropriate σ^+ and σ^- contributions are included. The value of the coefficient r^- points out that in the transition state the formation of the bond between

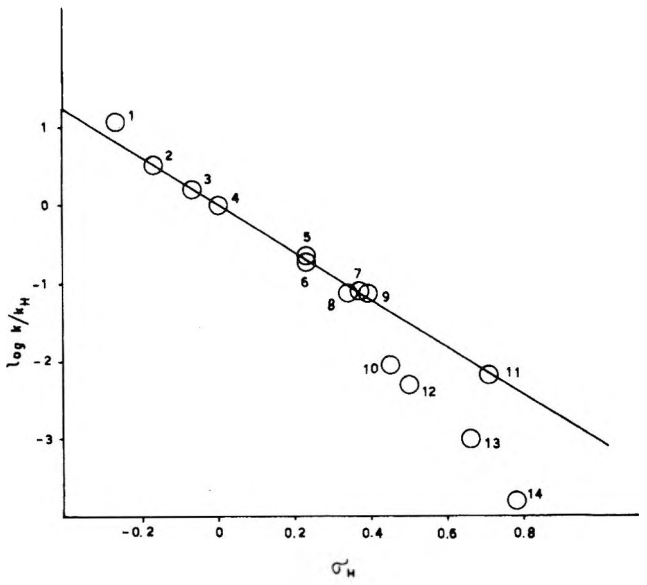


Figure 1. Hammett plot for anilino debromination reactions; the straight line refers to meta-substituted anilines ($\rho_{meta} = -3.03$).

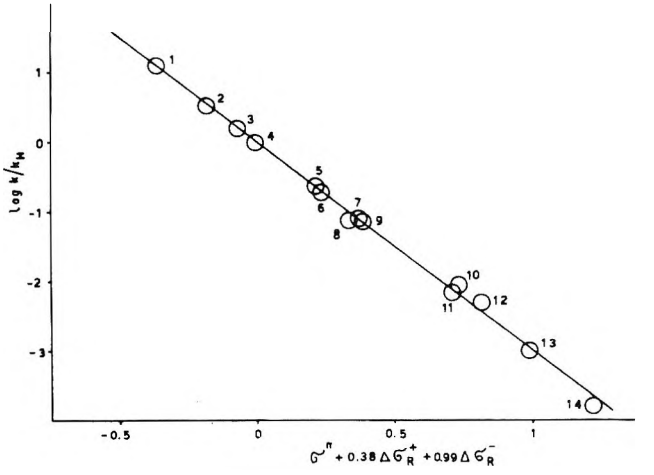


Figure 2. Least-squares line pertaining to the "overall" IYT equation ($\rho = -3.00$).

amino nitrogen and nuclear carbon of 2-bromo-3,5-dinitrothiophene has proceeded to a marked extent, i.e., the proclivity of the lone pair electrons on nitrogen to interact with the electron-attracting para substituents is significantly reduced in the transition state compared with that in the reactants.[14]

The observed necessity of using both r^+ and r^- contributions in the anilino debromination reaction induced us to apply the same treatment of data to the acid–base equilibrium of $ArNH_3^+$ in water, at 25 °C. The IYT analysis including only the substituents studied by us gives the values $\rho = -2.93 \pm 0.04$ ($R = 0.9991$; $n = 14$), $r^- = 1.00 \pm 0.04$ ($R = 0.9978$; $n = 5$; $i = 0.00 \pm 0.01$), and $r^+ = 0.23 \pm 0.04$ ($R = 0.9643$; $n = 5$; $i = -0.02 \pm 0.01$), closely resembling those observed by us for the anilino debromination reaction (see Table III). According to our interpretation of the ρ values,[3b] this means that the substituents present in aniline cause a similar variation of the position of the transition state in the reaction coordinates, with respect to X = H, for the reactions considered (see also below). On the other hand, the similar r^+ and r^- values obtained indicate a simi-

Table III. Linear Free Energy Relationships[a] for the Reaction of 2-Bromo-3,5-dinitrothiophene (I) with Meta- and Para-Substituted Anilines in Methanol at 20 °C and for the Dissociation of Anilinium Ions in Water at 25 °C

Relationships	$\rho \pm s_\rho$	s	R	i	Substituents
$\log k/k_H = \rho\sigma_H$	-4.10 ± 0.32	0.37	0.9660	0.06	1–14
$\log k/k_H = \rho\sigma^n$	-3.03 ± 0.09	0.06	0.9981	−0.01	3, 4, 7, 8, 9, 11
$\log k/k_H = \rho(\sigma^n + 0.38\Delta\sigma_R^+ + 0.99\Delta\sigma_R^-)$	-3.00 ± 0.05	0.08	0.9983	0.00	1–14
$\Delta pK_a = \rho\sigma^n$	-2.89 ± 0.10	0.06	0.9975	−0.02	3, 4, 7, 8, 9, 11
$\Delta pK_a = \rho(\sigma^n + 0.23\Delta\sigma_R^+ + 1.00\Delta\sigma_R^-)$	-2.93 ± 0.04	0.06	0.9991	0.02	1–14
	$\beta \pm s_\beta$				
$\log k/k_H = \beta\Delta pK_a$	1.05 ± 0.03	0.05	0.9986	0.01	3, 4, 7, 8, 9, 11
$\log k/k_H = \beta\Delta pK_a$	1.05 ± 0.02	0.11	0.9968	0.06	1–14

[a] ρ, reaction constant; β, Bronsted constant; s_ρ, standard deviation of ρ; s_β, standard deviation of β; s, standard error of estimate; R, correlation coefficient; i, intercept of the regression line with the ordinate [σ (or ΔpK_a) = 0]; substituents, actual substituents involved in the calculation of ρ and β, identified according to their number mentioned in Table II. The values of σ_H, σ^n, $\Delta\sigma_R^+$, $\Delta\sigma_R^-$, $\log k/k_H$, and pK_a used in correlations are shown in Table IV.

Table IV. Parameters Involved in the Calculation of ρ and β Values

Substituent	σ_H[a]	σ^n[b]	$\Delta\sigma_R^+(\Delta\sigma_R^-)$[b]	Log k/k_H[c]	σ[d]	pK_a[e]	σ[f]
1	−0.268	−0.09	−0.71	1.086	−0.36	5.36	−0.27
2	−0.170	−0.10	−0.22	0.534	−0.18	5.08	−0.18
3	−0.069	−0.069		0.188		4.71	
4	0.000	0.000		0.000		4.59	
5	0.227	0.29	−0.19	−0.647	0.21	3.98	0.20
6	0.232	0.30	−0.16	−0.724	0.23_5	3.89	0.23_5
7	0.373	0.373		−1.109		3.52	
8	0.337	0.337		−1.125		3.57	
9	0.391	0.391		−1.130		3.53	
10	0.45[g]	0.46	0.28	−2.063	0.68	2.38	0.76
11	0.710	0.710		−2.174		2.46	
12	0.502	0.502	0.32	−2.290	0.75	2.19	0.82
13	0.660	0.70	0.29	−2.986	0.98	1.74	0.98
14	0.778	0.778	0.45	−3.785	1.25	1.02	1.23

[a] σ values defined by L. P. Hammett,[8a] from ref 8b. [b] Values from ref 9d. [c] From k's calculated at 20 °C by the activation parameters. [d] Calculated for the anilino debromination reaction as in ref 9c. [e] Values from ref 11–13. [f] Calculated for the anilinium ions dissociation as in ref 9c. [g] Value for p-$CO_2C_2H_5$.

lar sensitivity of the two reactions to the changes in the nucleophilicity (polarizability) of the nitrogen atom as a function of the substituent present in the aniline moiety.

The log (k/k_H) for the anilino debromination reaction gives, for these reasons, a good correlation with ΔpK_a of $ArNH_3^+$ in water (see Tables III and IV). Even if the comparison between the two reactions is not completely homogeneous because of the difference in the solvent, the β value, near to unity, expresses the above-mentioned similarity of the two reactions; in consideration of other recent observations,[16] we do not think that it has any other physical meaning.

Experimental Section

Materials. 2-Bromo-3,5-dinitrothiophene was prepared and purified as previously reported.[17] Commercial samples of anilines were purified by crystallization or distillation under reduced pressure. The anilino derivatives were prepared and purified according to the general method reported in ref 5. The melting points, the crystallization solvents, and the analytical data are shown in Table I.

Kinetic Procedure. The kinetics were followed spectrophotometrically as previously described.[7b] The concentrations employed were 10^{-4}–10^{-3} M for 2-bromo-3,5-dinitrothiophene and 6×10^{-4} to 4×10^{-2} M for anilines as a function of their nucleophilicity. The rate constants for the *p*-nitroanilino debromination were determined by titration of the acid produced with 10^{-2} N sodium hydroxide, using a PHM 63 digital pH meter, *p*-nitroaniline at the wavelength of the maximum absorption of *p*-nitroanilino derivative having a high extinction coefficient.

The reaction of I with *p*-carbomethoxyaniline has been chosen to compare both kinetic procedures: the kinetic constants obtained by both methods are in excellent agreement.

Acknowledgments. The authors are grateful to the Consiglio Nazionale delle Ricerche for financial support.

Registry No.—I, 2160-38-5.

References and Notes

(1) (a) Presented to a meeting of the Società Chimica Italiana, Messina, 1974. (b) Cattedra di Chimica Organica of the University, Faculty of Pharmacy, 40100 Bologna, Italy.
(2) (a) H. J. Van Opstall, *Recl. Trav. Chim. Pays-Bas*, **52,** 901 (1933); A. Singh and D. H. Peacock, *J. Phys. Chem.*, **40,** 669 (1936); N. B. Chapman and R. E. Parker, *J. Chem. Soc.*, 3301 (1951); T. A. Emokpae, I. M. Dosunmu, and J. Hirst, *J. Chem. Soc., Perkin Trans. 2,* 1860 (1974), and references cited therein; N. B. Chapman, D. K. Chaudhury, and J. Shorter, *J. Chem. Soc.*, 1975 (1962), and references cited therein; J. Kavàlek, J. Haasovà, and V. Šterba, *Collect. Czech. Chem. Commun.*, **37,** 3333 (1972), and references cited therein; J. Kavalek, T. M. Chinh, V. Mikan, V. Sterba, and M. Vecera, *ibid.*, **38,** 1935 (1973), and references cited therein; (b) J. J. Ryan and A. A. Humffray, *J. Chem. Soc. B*, 1300 (1967), and references cited therein.
(3) (a) C. Dell'Erba and D. Spinelli, *Tetrahedron*, **21,** 1061 (1965); C. Dell'Erba, A. Guareschi, and D. Spinelli, *J. Heterocycl. Chem.*, **4,** 438 (1967); G. Guanti, C. Dell'Erba, and D. Spinelli, *ibid.*, **7,** 1333 (1970); D. Spinelli, G. Guanti, and C. Dell'Erba, *J. Chem. Soc., Perkin Trans. 2,* 441 (1972); D. Spinelli, G. Consiglio, and A. Corrao, *ibid.*, 1866 (1972); D. Spinelli, G. Consiglio, R. Noto, and A. Corrao, *ibid.*, 620 (1975); (b) D. Spinelli and G. Consiglio, *ibid.*, 989 (1975).
(4) R. D. Schuetz and C. O. Okafor, *Chim. Ther.*, **3,** 289 (1968); *Chem. Abstr.*, **70,** 57555j (1969).
(5) C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.*, **74,** 2965 (1952).
(6) S. D. Ross and I. Kuntz [*J. Am. Chem. Soc.*, **76,** 3000 (1954)] have shown the formation of a charge-transfer complex between aniline and 1-chloro-2,4-dinitrobenzene. The reaction of I with aniline was carried out at five different initial concentrations of aniline (range 0.005–0.1 M) but the rate coefficient was unaffected by the change in the aniline concentration. We believe that even if a charge-transfer complex was formed between I and anilines, in no case was the concentration of complex other than minute compared with the concentrations of reactants.
(7) (a) J. F. Bunnett, E. W. Garbisch, and K. M. Pruitt, *J. Am. Chem. Soc.*, **79,** 385 (1957); (b) D. Spinelli, C. Dell'Erba, and A. Salvemini, *Ann. Chim. (Rome)*, **52,** 1156 (1962).
(8) (a) L. P. Hammett, "Physical Organic Chemistry", 2nd ed, McGraw-Hill New York, N.Y., 1970; (b) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23,** 420 (1958).
(9) (a) H. Van Bekkum, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **78,** 815 (1959); (b) B. M. Wepster, *J. Am. Chem. Soc.*, **95,** 102 (1973); (c) A. J. Hoefnagel, J. C. Monshouwer, E. C. G. Snorn, and B. M. Wepster, *ibid.*, **95,** 5350 (1973); (d) A. J. Hoefnagel and B. M. Wepster, *ibid.*, **95,** 5357 (1973).
(10) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2nd ed, Cornell University Press, Ithaca, N.Y., 1969, p 1217; Y. Tsuno, T. Ibata, and Y. Yukawa, *Bull. Chem. Soc. Jpn.*, **32,** 960 (1959); Y. Yukawa and Y. Tsuno, *ibid.*, **32,** 965, 971 (1959); Y. Yukawa, Y. Tsuno, and M. Sawada, *ibid.*, **39,** 2274 (1966); **45,** 1198 (1972).
(11) P. D. Bolton and F. M. Hall, *J. Chem. Soc. B*, 259 (1969), and references cited therein.
(12) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases", Methuen, London, 1962.
(13) K. B. Whetsel, *Spectrochim. Acta*, **17,** 614 (1961).
(14) It seems likely that the degree of bond formation, as measured by r^-, is a function of the reactivity of the aromatic substrate. In fact the r^- value (0.68) for the reaction of picryl chloride with substituted anilines in 75% ethanol at 30 °C[2b] is lower than for the less reactive 2-bromo-3,5-dinitrothiophene. Taking into account that both reaction series are isoentropic and display much the same value of $\Delta S^{\ddagger}$, the trend of r^- values is in line with predictions from the Hammond postulate.[15]
(15) G. S. Hammond, *J. Am. Chem. Soc.*, **77,** 334 (1955).
(16) M. R. Crampton and M. J. Willison, *J. Chem. Soc., Perkin Trans. 2,* 238 (1974).
(17) R. Motoyama, K. Sato, and E. Imoto, *Nippon Kagaku Zhassi*, **82,** 1543 (1961).

Poly(tertiary phosphines and arsines). XIII. Some Neopentyl Poly(tertiary phosphines)[1,2]

R. Bruce King, John C. Cloyd, Jr.,[3] and Rolf H. Reimann[4]

Department of Chemistry, University of Georgia, Athens, Georgia 30602

Received July 15, 1975

Reaction of $(Me_3CCH_2)_2PH$ with $(Me_3CCH_2)_2PCH{=}CH_2$ in boiling toluene in the presence of potassium *tert*-butoxide gives the crystalline neopentyl di(tertiary phosphine) $(Me_3CCH_2)_2PCH_2CH_2P(CH_2CMe_3)_2$. A similar base-catalyzed reaction of $C_6H_5PH_2$ with $(Me_3CCH_2)_2PCH{=}CH_2$ in boiling tetrahydrofuran gives the liquid tertiary–secondary diphosphine $C_6H_5P(H)CH_2CH_2P(CH_2CMe_3)_2$. Base-catalyzed reaction of 2 equiv of $(Me_3CCH_2)_2PH$ with $Me_3CCH_2P(S)(CH{=}CH_2)_2$ in boiling tetrahydrofuran followed by desulfurization with sodium in boiling dioxane gives the viscous liquid neopentyl tri(tertiary phosphine) $Me_3CCH_2P[CH_2CH_2P(CH_2CMe_3)_2]_2$. Base-catalyzed reaction of phosphine with $(Me_3CCH_2)_2P(S)CH{=}CH_2$ gives the tetraphosphine trisulfide $P[CH_2CH_2P(S)(CH_2CMe_3)_2]_3$ which undergoes desulfurization with sodium metal in boiling dioxane to give the neopentyl tripod tetra(tertiary phosphine) $P[CH_2CH_2P(CH_2CMe_3)_2]_3$. The proton, phosphorus-31, and carbon-13 NMR spectra of these new neopentyl polyphosphines as well as the related neopentylphosphorus derivatives $(Me_3CCH_2)_3P$, $(Me_3CCH_2)_2P(O)H$, $(Me_3CCH_2)_nPX_{3-n}$ (n = 1 and 2; X = H, Cl, C_6H_5, and $CH{=}CH_2$), $(Me_3CCH_2)_3PS$, and $(Me_3CCH_2)_nP(S)R_{3-n}$ (n = 1 and 2; R = C_6H_5 and $CH{=}CH_2$) are described.

Previous papers of this series describe the preparation of poly(tertiary phosphines) in which the phosphorus atoms are linked by $-CH_2CH_2-$ bridges with the terminal positions on each phosphorus atom occupied by phenyl[5] and methyl[6] groups. Subsequent papers[1,7,8,9] describe extensive series of transition metal complexes formed by these phosphines.

In order to complement the donor properties of the methyl and phenyl poly(tertiary phosphines) toward transition metals, we were interested in obtaining analogous poly(tertiary phosphines) with terminal neopentyl groups. A neopentyl group [i.e., $(CH_3)_3CCH_2-$] provides a reasonable electronic approximation to a methyl group but is more sterically demanding than not only a methyl group but also even a phenyl group. For such reasons a comparison of the coordination chemistry of neopentyl poly(tertiary phosphines) with that of phenyl and methyl poly(tertiary phosphines) might provide a basis for differentiating between steric and electronic effects in this area of coordination chemistry. Furthermore, the neopentyl group, unlike the phenyl group but like the methyl group, has reasonably simple proton and carbon-13 NMR spectra thereby providing potentially useful probes for characterizing metal complexes.

Neopentylphosphorus chemistry relevant to the construction of poly(tertiary phosphines) with terminal neopentyl groups is rather obscure, although diphenylneopentylphosphine[10] has been described in the literature. For this reason, our synthetic objective of neopentyl poly(tertiary phosphines) first required the development of reliable and efficient procedures for preparing the necessary building blocks containing one phosphorus atom before methods of combining these building blocks to form the polyphosphines could be investigated. After obtaining the necessary neopentylphosphorus derivatives with only one phosphorus atom, exploration of various methods of combining such units led to the syntheses of the neopentyl di(tertiary phosphine) $(Me_3CCH_2)_2PCH_2CH_2P(CH_2CMe_3)_2$, the tri(tertiary phosphine) $Me_3CCH_2P[CH_2CH_2P(CH_2CMe_3)_2]_2$, and the tripod tetra(tertiary phosphine) $P[CH_2CH_2P(CH_2CCMe_3)_2]_3$. Since the synthetic methods employed in this work involve some problems not previously encountered in the earlier work with methyl[6] and phenyl[5] poly(tertiary phosphines), they are discussed in detail in this paper along with the NMR spectra of the new neopentylphosphorus derivatives.

Results and Discussion

A. Syntheses. In these syntheses of neopentyl poly(tertiary phosphines) the following features are of particular interest: (1) The lower reactivity of the neopentylphosphorus systems toward the base-catalyzed addition reactions. In some cases, conversion of a neopentylvinylphosphine into the corresponding sulfide is necessary in order to make the vinylphosphorus system acceptably reactive toward the phosphorus–hydrogen compound. The purpose of the sulfurization of neopentylvinylphosphines to increase their reactivity toward such addition reactions contrasts with the purpose of the previously used[6] sulfurization of methylvinylphosphines in order to make the methylphosphorus systems more readily prepared and handled. (2) Difficulties in desulfurizing some neopentylphosphine sulfides with $LiAlH_4$ making it necessary to use the more reactive sodium metal. Sodium metal is an unacceptable reagent for desulfurizing many organophosphorus sulfides, however, because of the possibility of unwanted carbon–phosphorus bond cleavage to give alkali metal phosphides,[11] particularly in the case of arylphosphorus derivatives. Neopentyl–phosphorus bonds as well as PCH_2CH_2P units in neopentylphosphorus derivatives seem to be reasonably resistant to cleavage with sodium metal in dioxane, although the reaction conditions (concentration, time, temperature, etc.) for the sodium metal desulfurizations described in this paper seem to be relatively critical possibly owing to detrimental carbon–phosphorus bond cleavage if the reaction conditions are too vigorous.

These special features of neopentylphosphorus chemistry probably arise from the steric bulk of the neopentyl group. This bulk of the neopentyl group may be responsible for other special properties of neopentylphosphines such as their lower sensitivity toward oxidation relative to other alkylphosphines [tris(neopentylphosphine) seems to be about as air stable as triphenylphosphine] and the unusual odors of many trivalent neopentylphosphorus compounds which are very different from the atrocious odors of most volatile trivalent phosphorus derivatives. Nevertheless, the neopentylphosphorus derivatives $Me_3CCH_2PCl_2$, $(Me_3CCH_2)_2PCl$, $Me_3CCH_2PH_2$, and $(Me_3CCH_2)_2PH$ were so sensitive to air oxidation and hydrolysis that their elemental analyses caused difficulties. However, the NMR spectra as well as the chemical reactions of these four compounds provided positive proof of their identities.

Table I. Neopentylphosphorus Derivatives Prepared in This Work

Registry no.	Compd[a]	Preparation[b]	Yield, %	Mp or bp (mm),[c] °C		Anal, % C	Anal, % H	Anal, % Other	^{31}P NMR[d] Found	^{31}P NMR[d] Calcd[e]
57620-64-1	Neo_3P	3NeoMgCl + PCl_3 in THF	27	57–59	Calcd	73.7	13.6	12.7 (P)	+57.5 s	+54
				75–80 (0.2)	Found	73.8	13.5	12.4 (P)		
57620-65-2	$Neo_2P(O)H$	Hydrolysis of 3NeoMgCl + PCl_3	23	69–71	Calcd	63.1	12.1		−21.5 (J_{PH} = 455 Hz)[i]	
					Found	63.1	12.2			
57620-66-3	Neo_2PCl	2NeoMgCl + PCl_3 in Et_2O	74	49–50 (0.4)	Calcd[f]	57.5	10.5	17.0 (Cl)	−102.3 s	
				110 (25)	Found[f]	55.4	10.3	16.3 (Cl)		
57620-67-4	$NeoPCl_2$	NeoMgCl + PCl_3 in Et_2O	67	57–65 (25)	Calcd[f]	34.7	6.4	41.0 (Cl)		
					Found[f]	36.3	6.5	37.1 (Cl)		
57620-68-5	Neo_2PPh	2NeoMgCl + $PhPCl_2$	64	93–95 (0.2)	Calcd	76.8	10.8	12.4 (P)	+42.2	+39
					Found	76.6	10.6	12.2 (P)		
7660-85-7	$NeoPPh_2$	NeoMgCl + Ph_2PCl in THF	68	125–130 (0.2) 116–122 (0.1)[h]		g			+23.6 s (+23.9)[h]	+24
57620-69-6	Neo_2PVi	ViMgBr + Neo_2PCl in THF	80	38 (0.3)	Calcd	72.0	12.5	15.5 (P)	+44.8 s	+42
				110 (32)	Found	72.2	12.7	15.6 (P)		
57620-70-9	$NeoPVi_2$	2ViMgBr + $NeoPCl_2$ in THF	55	72 (28)	Calcd	69.2	11.0	19.8 (P)	+31.9 s	+30
					Found	69.2	11.0	20.0 (P)		
57620-71-0	$Neo_3P(S)$	Neo_3P + S	91	169–171	Calcd	65.2	11.9	11.6 (S)	−36.9 s	
					Found	65.0	12.1	11.5 (S)		
57620-72-1	$Neo_2P(S)Ph$	Neo_2PPh + S	76	105–107	Calcd	68.0	9.6	11.3 (S)	−34.9 s	
					Found	67.8	9.6	11.4 (S)		
57620-73-2	$NeoP(S)Ph_2$	$NeoPPh_2$ + S	86	134–135	Calcd	70.9	7.3	11.1 (S)	−35.6 s	
					Found	70.7	7.4	10.9 (S)		
57620-74-3	$Neo_2P(S)Vi$	Neo_2PVi + S	98	89–90	Calcd	62.1	10.8	13.8 (S)	−33.1 s	
					Found	62.2	10.9	14.0 (S)		
57620-75-4	$NeoP(S)Vi_2$	$NeoPVi_2$ + S	95	19	Calcd	57.4	9.1	17.1 (S)	−30.9 s	
					Found	57.5	9.1	17.0 (S)		
57620-76-5	Neo_2PH	Neo_2PCl + $LiAlH_4$	64	57 (5)	Calcd	69.0	13.2	17.8 (P)	+98.1 (J_{PH} = 189 Hz)[i]	
					Found	69.1	13.5	17.4 (P)		
54772-70-2	$NeoPH_2$	$NeoPCl_2$ + $LiAlH_4$	52	98–100 (760)	Calcd[f]	57.5	12.5	29.8 (P)	+162.4	
					Found[f]	59.4	12.8	26.3 (P)		
57620-77-6	$Neo_2PCH_2CH_2PNeo_2$	Neo_2PH + Neo_2PVi	63	66–68	Calcd	70.6	12.8	16.6 (P)	+42.6 s	+43
					Found	70.7	13.1	16.4 (P)		
57620-78-7	$Neo_2PCH_2CH_2P(S)Me_2$	Neo_2PH + $Me_2P(S)Vi$	11	133–134	Calcd	57.1	11.0	10.9 (S)	+42.7 d (35)	+43
					Found	57.1	10.9	11.0 (S)	−38.1 d (35)	
57620-79-8	$PhP(H)CH_2CH_2PNeo_2$	$PhPH_2$ + Neo_2PVi	27	125–140 (0.2–0.8)	Calcd	69.7	10.3	20.0 (P)	+46.0 (J_{PH} = 192 Hz)[i]	+43
					Found	69.7	10.6	19.7 (P)	+43.7	
57620-80-1	$PhP[CH_2CH_2P(S)Neo_2]_2$	$PhPH_2$ + $2Neo_2P(S)Vi$	86	138	Calcd	62.8	10.0	11.1 (S)	+17.1 t (37)	+17
					Found	62.7	10.1	11.2 (S)	−42.7 d (37)	
57620-81-2	$NeoP[CH_2CH_2PNeo_2]_2$	See text	58	Liquid	Calcd	69.0	12.6	18.4 (P)	+43.0 d (20)	+43
					Found	67.7	12.3	17.7 (P)	+30.6 t (20)	+33
57620-82-3	$P[CH_2CH_2P(S)Neo_2]_3$	PH_3 + $3Neo_2P(S)Vi$	95	237	Calcd	59.1	10.7	13.2 (S)	+18.1 q (32)	+21
					Found	59.0	10.7	13.2 (S)	−43.6	
57620-83-4	$P(CH_2CH_2PNeo_2)_3$	$P[CH_2CH_2P(S)Neo_2]_3$ + Na in dioxane	65	77–81	Calcd	68.1	12.4	19.5 (P)	+42.8 d (20)	+43
					Found	68.0	12.4	19.7 (P)	+18.8 q (20)	+21

[a] Neo = neopentyl, Ph = phenyl, Vi = vinyl, Me = methyl. [b] For further details of these preparations see the Experimental Section. [c] The listed temperatures are boiling points if they are followed by a pressure in parentheses; otherwise they are melting points. [d] The multiplicities of the proton-decoupled phosphorus-31 resonances are indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet. Figures in parentheses are phosphorus–phosphorus coupling constants in hertz. [e] The additive alkyl group contributions of S. O. Grim, W. McFarlane, and E. F. Davidoff, *J. Org. Chem.*, 32, 781 (1967), with the additional values (see text) of 6 ppm for the vinyl group and 7 ppm for the PCH_2CH_2P unit were used for these calculations. [f] The sensitivity of these compounds to aerial oxidation and hydrolyses prevented reliable analytical data from being obtained. The proton, carbon-13, and phosphorus-31 NMR spectra as well as their mass spectra and chemical reactions unambiguously identify these compounds. [g] In view of the fact that neopentyldiphenylphosphine was already reported by S. O. Grim, W. McFarlane, and E. F. Davidoff, *J. Org. Chem.*, 32, 781 (1967), its analysis was omitted. [h] Literature values from Grim, McFarlane, and Davidoff. [i] These J(P–H) values were obtained from phosphorus-31 NMR spectra taken at 40.5 MHz on a Varian HA-100 spectrometer without proton decoupling.

B. NMR Spectra. The phosphorus-31, proton, and carbon-13 NMR spectra of all of the major new neopentylphosphorus derivatives were taken in order both to confirm their proposed formulas and structures and to establish the spectroscopic properties of neopentyl groups bonded to phosphorus atoms in different environments.

The phosphorus-31 NMR chemical shifts of all of the trivalent neopentylphosphorus derivatives in which the phosphorus atoms are bonded exclusively to carbon atoms can be related to the additive alkyl group contributions to phosphorus-31 NMR chemical shifts of Grim, McFarlane, and Davidoff.[10] In order to test these ideas fully, their values for the alkyl group contributions[12] were supplemented by the value of 6 ppm for the vinyl group contribution obtained by subtracting twice the phenyl group contribution of 3 ppm from the reported[10] phosphorus-31 chemical shift of 12 ppm for diphenylvinylphosphine and the value of 7 ppm for the contribution of a PCH_2CH_2P unit similarly derived from the reported[5] phosphorus-31 NMR chemical shifts of various phenyl poly(tertiary phosphines). In all cases the experimental phosphorus-31 NMR chemical shifts and those calculated from the additive group contributions (Table I) agree within 4 ppm; in most cases the agreement is much better.

The neopentyl methyl protons in all of the neopentylphosphorus derivatives exhibit a singlet around τ 9 in the proton NMR spectrum. The distance of four bonds between the neopentyl methyl protons and phosphorus atoms both makes $|^4J(P-H)|$ negligible and eliminates any significant effects on the chemical shifts of the neopentyl methyl protons arising from changes in the electronic and steric properties of the groups bonded to the phosphorus atom.

The "normal" proton NMR pattern for the neopentyl methylene protons was a doublet with $|^2J(PH)|$ around 4 Hz for trivalent neopentylphosphorus derivatives containing three phosphorus–carbon bonds and around 11 Hz for neopentylphosphine sulfides. This large change in the $|^2J(PH)|$ of the neopentyl methylene protons from neopentylphosphines to the corresponding neopentylphosphine sulfides resembles the similarly large change in the $|^2J(PH)|$ of the methylphosphorus protons from 2–3 Hz in methylphosphines to 12–13 Hz in the corresponding methylphosphine sulfides. In several trivalent neopentylphosphorus derivatives of the type $(Me_3CCH_2)_2PX$ (X = Cl, C_6H_5, and $CH{=}CH_2$) the neopentyl methylene protons exhibit a more complex pattern (Figure 1) which can be interpreted as an AB double doublet with J_{AB} = 14 Hz and with further but unequal couplings of the phosphorus atom to the A and B protons with one of these two $^2J(PH)$ couplings frequently being negligible. The two methylene protons in each of the equivalent neopentyl groups in these $(Me_3CCH_2)_2PX$ derivatives are thus diastereotopic apparently because from the viewpoint of a given neopentyl group the remaining three substituents on the phosphorus atom (a neopentyl group, a lone pair, and the X group) are so nonequivalent that the electron density pattern does not have an effective plane of symmetry bisecting the CH_2 unit of a neopentyl group.[13,14] A completely analogous effect has been previously observed[14] for the isopropyl methyl protons in $C_6H_5P[CH(CH_3)_2]_2$ where the two methyl groups are diastereotopic. A particularly unusual feature of the two diastereotopic methylene protons in a neopentyl group of a $(Me_3CCH_2)_2PX$ derivative is the large difference in the $|^2J(PH)|$ couplings from the phosphorus atom to these two protons.

The proton-decoupled carbon-13 NMR spectra of the neopentyl groups in the neopentylphosphorus derivatives exhibit the expected three doublets from the methylene,

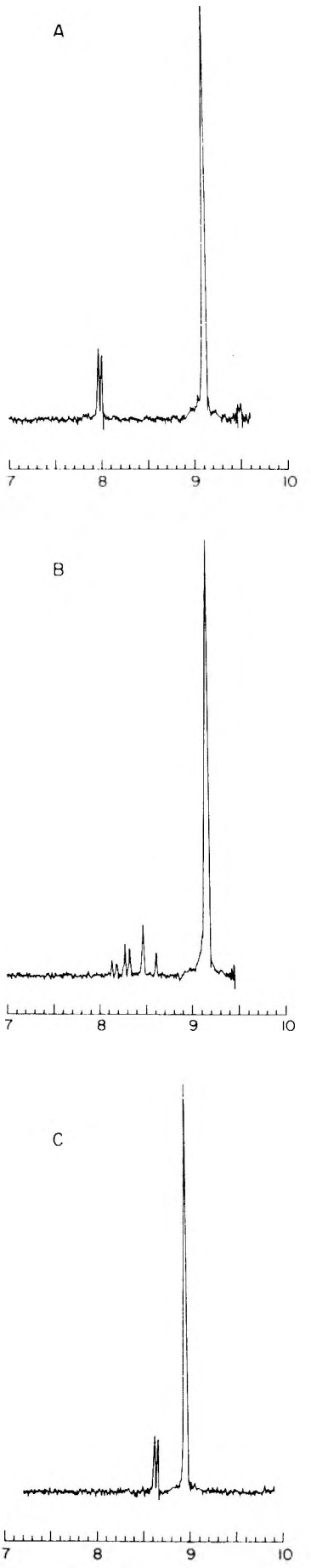


Figure 1. Proton NMR spectra of some neopentylphosphorus derivatives: A, $(Me_3CCH_2)_3P$; B, $(Me_3CCH_2)_2PC_6H_5$; C, $Me_3CCH_2P(C_6H_5)_2$.

quaternary, and methyl carbons each split by coupling with the phosphorus atom. The assignments of the neopentyl carbon resonances appeared obvious on the basis of their relative intensities but nevertheless were checked by off-resonance proton decoupling experiments on $(Me_3CCH_2)_2PH$. The resonances from the methyl and quaternary carbons overlap in the region around δ −31 so that both components of the quaternary carbon doublet could not be clearly separated in all cases. The neopentyl methylene carbon doublet appears in the range δ −37 to −60 and thus could be clearly identified in all compounds.

The carbon–phosphorus coupling constants as observed in the carbon-13 NMR spectrum undergo some interesting changes in going from neopentyl tertiary phosphines to the corresponding phosphine sulfides. The values of the carbon–phosphorus coupling constants in the trivalent neopentylphosphines are similar to the carbon–phosphorus coupling constants found by Mann[15] in the alkyl groups of other alkylphosphines. The $|^1J(CP)|$ from the methylene carbon to the phosphorus atom is 11–15 Hz in the neopentylphosphines but increases to 48–56 Hz in the corresponding neopentylphosphine sulfides. The $|^2J(CP)|$ from the quaternary carbon to the phosphorus atom occurs in a similar range to the $|^1J(CP)|$ (10–16 Hz) in the neopentyl phosphines but decreases to 4–5 Hz in the corresponding neopentylphosphine sulfides. The $|^3J(CP)|$ from the methyl carbons to the phosphorus atom is 9–10 Hz in the neopentylphosphines and decreases slightly to 6–7 Hz in the corresponding neopentylphosphine sulfides. Thus, the effect of sulfurization on the $J(CP)$ coupling constants involving the neopentyl groups in neopentyl phosphines decreases as the distances between the carbon atoms and the phosphorus atom increase although in the trivalent neopentylphosphines the three coupling constants $|^1J(CP)|$, $|^2J(CP)|$, and $|^3J(CP)|$ are rather similar (within a factor of 1.5) despite the different carbon–phosphorus distances.

The carbon-13 resonance from the two equivalent PCH_2CH_2P bridge carbons in the neopentyl di(tertiary phosphine) $(Me_3CCH_2)_2PCH_2CH_2P(CH_2CMe_3)_2$ is a singlet at δ −26.4 similar to the singlets at δ −28.0 and −25.4 reported[16,17] for the PCH_2CH_2P carbons in the related symmetrical di(tertiary phosphines) $R_2PCH_2CH_2PR_2$ (R = methyl and phenyl, respectively). These singlets for the PCH_2CH_2P carbon-13 resonances have been shown[16,17] to be consistent with equal magnitudes but opposite signs for the $^1J(CP)$ and $^2J(CP)$ coupling constants.

Experimental Section

Microanalyses were performed by Atlantic Microanalytical Laboratory, Atlanta, Ga., and Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Proton NMR spectra (Table II in the microfilm edition) were taken as pure liquids or in $CDCl_3$ solution and recorded at 100 MHz on a Varian HA-100 spectrometer. The phosphorus-31 (Table I) and carbon-13 (Table III in the microfilm edition) NMR spectra were taken using a Jeolco PFT-100 spectrometer operating at 40.3 and 25.03 MHz, respectively, in the Fourier transform mode with proton noise decoupling and a deuterium lock. The phosphorus-31 NMR spectra were taken on the pure liquids or in CH_2Cl_2 solution whereas the carbon-13 NMR spectra were taken in $CDCl_3$ solution unless otherwise indicated. Phosphorus-31 and carbon-13 chemical shifts are reported in parts per million relative to external 85% H_3PO_4 and internal tetramethylsilane, respectively, with positive values indicating upfield chemical shifts. Melting points (Table I) were taken in capillaries and are uncorrected.

Mass spectra of all of the new compounds listed in Table I except for the triphosphine disulfide, the tripod tetraphosphine trisulfide, and the tripod tetraphosphine were taken on the University of Georgia Perkin-Elmer Hitachi RMU-6 mass spectrometer. These mass spectra exhibited molecular ions with the correct *m/e* values as well as ions corresponding to losses of 15 and 56 mass units (CH_3 and C_4H_8, respectively) from the molecular ion. Full details of the fragmentation patterns and associated metastable ions in these 18 mass spectra will be reported elsewhere.

Tetrahydrofuran and dioxane were purified by distillation under nitrogen over sodium benzophenone ketyl immediately before use. Neopentyl chloride was purchased from Columbia Organic Chemicals, Columbia, S.C. Other commercially available starting materials were purchased from normal commercial sources as in previous related papers.[6]

A nitrogen atmosphere was routinely provided for the following three operations: (a) carrying out reactions, (b) handling air-sensitive organophosphorus compounds and the potassium *tert*-butoxide catalyst, and (c) filling evacuated vessels containing potentially air-sensitive materials. A three-necked flask with a fritted disk and stopcock at the bottom was used for filtration of air-sensitive organophosphorus solutions.[18]

Reactions of Neopentylmagnesium Chloride with Phosphorus Trichloride. A. To Give $(Me_3CCH_2)_3P$ and $(Me_3CCH_2)_2P(O)H$. A solution of neopentylmagnesium chloride was prepared from 16 g (0.67 g-atom) of magnesium turnings and 74 ml (64 g, 0.6 mol) of neopentyl chloride in 250 ml of tetrahydrofuran using a small amount of 1,2-dibromoethane to initiate the reaction. This neopentylmagnesium chloride solution was cooled to 0 °C and treated dropwise with 12.6 ml (19.8 g, 0.144 mol) of phosphorus trichloride. The reaction mixture was boiled under reflux for 4.5 h. After stirring overnight at room temperature, the tetrahydrofuran was removed at 25 °C (25 mm) and 200 ml of degassed diethyl ether added. The resulting slurry was cooled to 0 °C and then treated with 250 ml of saturated aqueous ammonium chloride. The ether layer was separated, the aqueous layer was washed three times with diethyl ether, and the combined diethyl ether solutions were dried over anhydrous sodium sulfate. After removal of the diethyl ether from the filtered solutions at 25 °C (25 mm), the liquid residue was distilled under vacuum. Sometimes a small forerun (~1 g) of $(Me_3CCH_2)_2PH$ was obtained; this was spontaneously inflammable in air when absorbed on tissue paper. The major fraction, bp 73–75 °C (0.3 mm), contained a mixture of $(Me_3CCH_2)_3P$ and $(Me_3CCH_2)_2P(O)H$ and solidified readily in the receiver. Fractional crystallization of this solid from ethanol gave $(Me_3CCH_2)_3P$ as the least soluble fraction; an analytical sample, mp 57–59 °C, could be obtained by a second crystallization from hot ethanol. Evaporation of the ethanol from the filtrate after isolating the $(Me_3CCH_2)_3P$ followed by a second vacuum distillation of the residue gave $(Me_3CCH_2)_2P(O)H$, mp 67–69 °C.

B. To Give $(Me_3CCH_2)_2PCl$. A solution of 0.4 mol of neopentylmagnesium chloride in 300 ml of diethyl ether was added dropwise over 2 h to a solution of 14 ml (22 g, 0.16 mol) of phosphorus trichloride in 300 ml of diethyl ether cooled in a 0 °C bath. After stirring overnight at room temperature, the ethereal solution was filtered under nitrogen from the precipitated magnesium salts. The diethyl ether was then removed at 25 °C (25 mm). Vacuum distillation of the residue gave 24.6 g (74% yield) of $(Me_3CCH_2)_2PCl$, bp 49–50 ° (0.4 mm), as the major fraction.

C. To Give $Me_3CCH_2PCl_2$. A solution of 0.3 mol of neopentylmagnesium chloride in 300 ml of diethyl ether was added dropwise over 3 h to a solution of 50 ml (78.5 g, 0.57 mol) of phosphorus trichloride in 500 ml of diethyl ether cooled in a −40 °C bath. After the addition was complete, the reaction mixture was allowed to warm slowly to room temperature. After stirring for 16 h at room temperature, the ethereal solution was filtered under nitrogen pressure. After removal of the diethyl ether at 25 °C (50 mm), vacuum distillation of the liquid residue gave 33–35 g (64–67% yield) of $Me_3CCH_2PCl_2$, bp 76–80 °C (48 mm), as the major fraction.

Preparations of Neopentylphenylphosphines. A tetrahydrofuran solution of neopentylmagnesium chloride was treated dropwise at 0 °C with a solution of the stoichiometric amount of the phenylphosphorus chloride [$C_6H_5PCl_2$ or $(C_6H_5)_2PCl$] in tetrahydrofuran. After warming to room temperature and boiling briefly under reflux, the tetrahydrofuran was removed at 40 °C (40 mm). Diethyl ether was added to the residue and the mixture hydrolyzed with saturated aqueous ammonium chloride. Distillation of the dried diethyl ether layer gave the neopentylphenyl phosphine as indicated in Table I.

Preparations of Neopentylvinylphosphines. A tetrahydrofuran solution of vinylmagnesium bromide was added dropwise to a solution of the stoichiometric amount of the neopentylphosphorus chloride [$Me_3CCH_2PCl_2$ or $(Me_3CCH_2)_2PCl$] in tetrahydrofuran at 0 °C. After warming to room temperature and boiling under reflux for 30 min to 2 h the neopentylvinylphosphine (Table I) was isolat-

ed by vacuum distillation after aqueous ammonium chloride hydrolysis similar to the isolation of the neopentylphenylphosphines outlined above.

Preparations of Neopentylphosphine Sulfides. Stoichiometric quantities of the tertiary neopentylphosphine and sulfur were boiled under reflux in benzene solution until all of the sulfur dissolved. Solvent was removed from the filtered benzene solution at 25 °C (25 mm). The phosphine sulfides $(Me_3CCH_2)_3PS$ and $(Me_3CCH_2)_2P(S)(C_6H_5)$ were recrystallized from mixtures of dichloromethane and ethanol. The phosphine sulfide $Me_3CCH_2P(S)(C_6H_5)_2$ was crystallized from hot pure ethanol. The phosphine sulfide $(Me_3CCH_2)_2P(S)CH{=}CH_2$ was purified by low-temperature crystallization from hexane. The phosphine sulfide $Me_3CCH_2P(S)(CH{=}CH_2)_2$ was too soluble and low melting to be purified effectively by recrystallization.

Preparation of $(Me_3CCH_2)_2PH$. A solution of 39.5 g (0.19 mol) of $(Me_3CCH_2)_2PCl$ in 100 ml of diethyl ether was added dropwise to 8.0 g (0.21 mol) of $LiAlH_4$ in 200 ml of diethyl ether at −10 °C. The reaction mixture was stirred at room temperature for 24 h and then hydrolyzed at 0 °C by the successive addition of 8 ml of water, 8 ml of 15% aqueous sodium hydroxide, and 24 ml of water. The ether solution was filtered under nitrogen from the precipitated aluminum salts and the diethyl ether removed at 30 °C (30 mm) after drying over anhydrous sodium sulfate. Vacuum distillation of the residue gave 20.9 g (64% yield) of $(Me_3CCH_2)_2PH$, bp 57 °C (5 mm).

Preparation of $Me_3CCH_2PH_2$. A solution of 43 g (0.25 mol) of $Me_3CCH_2PCl_2$ in 200 ml of diethyl ether was added dropwise over 2.5 h to a solution of 15 g (0.4 mol) of $LiAlH_4$ in 500 ml of diethyl ether at −78 °C. The resulting mixture was stirred overnight at room temperature and then hydrolyzed at 0 °C by the successive addition of 15 ml of water, 15 ml of 15% aqueous sodium hydroxide, and 45 ml of water. The diethyl ether solution was filtered under nitrogen from the precipitated solids. After removal of the diethyl ether and all materials boiling below 95 °C by distillation under nitrogen at atmospheric pressure, further atmospheric pressure distillation gave 13.8 g (53% yield) of $Me_3CCH_2PH_2$, bp 95–98 °C (760 mm).

Preparation of $(Me_3CCH_2)_2PCH_2CH_2P(CH_2CMe_3)_2$. A mixture of 8.19 g (0.047 mol) of $(Me_3CCH_2)_2PH$, 9.41 g (0.047 mol) of $(Me_3CCH_2)_2PCH{=}CH_2$, 0.5 g (0.0045 mol) of potassium *tert*-butoxide, and 150 ml of dry toluene was boiled strongly under reflux for at least 24 h. Toluene was then removed at 25 °C (1 mm). Recrystallization of the residue from warm ethanol followed by vacuum sublimation at 80–100 °C (0.1 mm) gave 11 g (63% yield) of $(Me_3CCH_2)_2PCH_2CH_2P(CH_2CMe_3)_2$, mp 66–68 °C.

Preparation of $C_6H_5P(H)CH_2CH_2P(CH_2CMe_3)_2$. A mixture of 4.5 g (0.04 mol) of phenylphosphine,[19] 16.2 g (0.08 mol) of $(Me_3CCH_2)_2PCH{=}CH_2$, sufficient potassium *tert*-butoxide to impart a yellow color (~0.5 g), and 200 ml of tetrahydrofuran was boiled under reflux for a total of 54 h with the addition of sufficient potassium *tert*-butoxide after 18 h to restore the yellow color. Tetrahydrofuran was then removed at 25 °C (25 mm) to leave a residue completely soluble in ethanol. Vacuum distillation of this residue resulted in the recovery of 8.9 g (55% recovery) of $(Me_3CCH_2)_2PCH{=}CH_2$, bp 45 °C (0.7 mm). The residue from this distillation was chromatographed on a degassed Florisil column in hexane solution. The column was eluted with dichloromethane. Testing the eluates with ethanolic nickel(II) chloride gave a red color when elution of the $C_6H_5P(H)CH_2CH_2P(CH_2CMe_3)_2$ began. The product was eluted with dichloromethane and solvent removed from the dichloromethane eluates at 25 °C (25 mm). Vacuum distillation of the resulting thick liquid gave 1.54 g (12.5% conversion, 27% yield) of colorless liquid $C_6H_5P(H)CH_2CH_2P(CH_2CMe_3)_2$, bp 125–140 °C (0.2–0.8 mm), infrared ν(PH) 2285 cm^{-1} (liquid film).

A similar procedure was used to prepare $(Me_3CCH_2)_2PCH_2CH_2P(S)Me_2$ from equimolar quantities of $(Me_3CCH_2)_2PH$ and $Me_2P(S)CH{=}CH_2$ except that the product was isolated by crystallization from a mixture of dichloromethane and hexane rather than by vacuum distillation.

Preparation of $Me_3CCH_2P[CH_2CH_2P(CH_2CMe_3)_2]_2$. A mixture of 20.0 g (0.115 mol) of $(Me_3CCH_2)_2PH$, 10.5 g (0.056 mol) of $Me_3CCH_2P(S)(CH{=}CH_2)_2$, ~1 g of potassium *tert*-butoxide, and 175 ml of tetrahydrofuran was boiled under reflux for 17 h. Solvent was removed at 40 °C (25 mm). The residue was crystallized from ethanol to give 21.2 g of white crystals, apparently impure $Me_3CCH_2P(S)[CH_2CH_2P(CH_2CMe_3)_2]_2$: mp 98–103 °C (unclear), proton-decoupled ^{31}P NMR spectrum δ −47.6 [triplet, J(PP) = 34 Hz] and +42.3 [doublet, J(PP) = 34 Hz]. Anal. Calcd for $C_{29}H_{63}P_3S$: C, 64.9; H, 11.8; S, 6.0. Found: C, 62.0; H, 11.2; S, 8.6. This material was used for the sodium reduction without attempts at further purification.

A mixture of 14.0 g (~0.26 mol) of the crude $Me_3CCH_2P(S)[CH_2CH_2P(CH_2CMe_3)_2]_2$, 2.0 g (0.087 g-atom) of sodium, and 130 ml of dioxane was heated under reflux for 3 h in a 130 °C oil bath. The resulting reaction mixture was filtered first through glass wool and finally through filter paper. Removal of solvent from the filtrate gave 10.9 g [~60% yield based on $Me_3CCH_2P(S)(CH{=}CH_2)_2$] of the tri(tertiary phosphine) $Me_3CCH_2P[CH_2CH_2P(CH_2CMe_3)_2]_2$ as a pale yellow, viscous liquid which could be evaporatively distilled at 170 °C (2 mm).

Attempts to obtain the pure crystalline tri(tertiary phosphine) were unsuccessful. White crystals separated from a methanol solution upon prolonged storage at −15 °C, but these melted upon filtration and warming. Reaction of this neopentyl tri(tertiary phosphine) with ethanolic nickel(II) chloride followed by addition of ethanolic ammonium hexafluorophosphate gave golden yellow needles of the nickel complex [(triphos)NiCl][PF_6]. Anal. Calcd for $C_{29}H_{63}ClF_6NiP_4$: C, 46.8; H, 8.5; Cl, 4.8. Found: C, 46.7; H, 8.6; Cl, 4.8. Degradation of this nickel complex with excess aqueous potassium cyanide followed by addition of dilute aqueous sodium hydroxide regenerated the free $Me_3CCH_2P[CH_2CH_2P(CH_2CMe_3)_2]_2$ as a yellow grease, which still could not be crystallized.

Preparation of $P[CH_2CH_2P(S)(CH_2CMe_3)_2]_3$. A boiling solution of 20.0 g (0.09 mol) of $(Me_3CCH_2)_2P(S)CH{=}CH_2$ in 200 ml of tetrahydrofuran containing 1.5 g (0.013 mol) of potassium *tert*-butoxide was treated with the phosphine gas generated by addition of a solution of 25 ml of water in 75 ml of dioxane to a slurry of 9.2 g (0.16 mol) of aluminum phosphide in 60 ml of dioxane. The gaseous phosphine was dried by passing through two −78 °C traps filled with glass beads before being bubbled below the level of the boiling tetrahydrofuran solution. After all of the phosphine had been added, the reaction mixture was boiled under reflux for an additional 3 h. The reaction mixture became gelatinous upon cooling. Removal of solvent at 30 °C (5 mm) gave 24.6 g (95% yield) of white $P[CH_2CH_2P(S)(CH_2CMe_3)_2]_3$. The analytical sample, mp 237 °C, was obtained by crystallization from a mixture of dichloromethane and hexane.

Preparation of $P[CH_2CH_2P(CH_2CMe_3)_2]_3$. A mixture of 3.0 g (0.0041 mol) of $P[CH_2CH_2P(S)(CH_2CMe_3)_2]_3$, 2.0 g (0.087 g-atom) of sodium metal, and 70 ml of dioxane was heated under reflux for 21 h by a 125 °C oil bath. The reaction mixture became blue after 30 min and milky at the end of the reaction period. The reaction mixture was filtered through glass wool and the dioxane then removed at 25 °C (1 mm). The residue was dissolved in a minimum of hot ethanol and the filtered ethanol solution cooled in a −10 °C freezer for 12 h to give 1.95 g (65% yield) of the crystalline tripod tetra(tertiary phosphine) $P[CH_2CH_2P(CH_2CMe_3)_2]_3$, mp 77–81 °C. This tripod tetra(tertiary phosphine) sublimes slowly at 210 °C (0.5 mm) but this is not recommended as a purification method because of significant decomposition.

Attempts to increase the scale of this reaction resulted in sharply reduced yields.

Acknowledgments. We are indebted to the Air Force Office of Scientific Research for partial support of this work under Grant AF-AFOSR-71-2000. We are also indebted to the National Science Foundation for a major equipment grant to the University of Georgia chemistry department toward the purchase of the Jeolco PFT-100 pulsed Fourier transform NMR spectrometer. We acknowledge the technical assistance of Mr. Courtney Pape in running the NMR spectra. Some of the initial studies on the reactions of neopentylmagnesium chloride with phosphorus trichloride were performed in spring 1973 by Mr. Michael Norins as part of an undergraduate research project. Mr. Michael Word assisted with the preparation of $(Me_3CCH_2)_2PCH_2CH_2P(S)Me_2$ as part of the University of Georgia 1974 Secondary Science Student training program supported by the National Science Foundation.

Registry No.—NeoCl, 753-89-9; PCl_3, 7719-12-2; $PhPCl_2$, 644-97-3; Ph_2PCl, 1079-66-9; ViBr, 75-01-4; S, 7704-34-9; $Me_2P(S)Vi$, 42495-78-3; $PhPH_2$, 638-21-1; PH_3, 7803-57-2.

Supplementary Material Available. Tables II and III (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) For part XII of this series see R. B. King and J. C. Cloyd, Jr., *Inorg. Chem.*, **14**, 1554 (1975).
(2) Portions of this work were presented at the 169th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1975, Abstract INOR-122.
(3) Postdoctoral research associate, 1971–1974.
(4) Postdoctoral research associate, 1974–1975, on leave from the National Chemical Research Laboratory, South African Council for Scientific and Industrial Research, Pretoria, South Africa.
(5) (a) R. B. King and P. N. Kapoor, *J. Am. Chem. Soc.*, **91**, 5191 (1969); (b) *ibid.*, **93**, 4158 (1971).
(6) (a) R. B. King, J. C. Cloyd, Jr., and P. K. Hendrick, *J. Am. Chem. Soc.*, **95**, 5083 (1973); (b) R. B. King and J. C. Cloyd, Jr., *ibid.*, **97**, 53 (1975).
(7) R. B. King, P. N. Kapoor, and R. N. Kapoor, *Inorg. Chem.*, **10**, 1841 (1971).
(8) R. B. King, R. N. Kapoor, M. S. Saran, and P. N. Kapoor, *Inorg. Chem.*, **10**, 1851 (1971).
(9) R. B. King and M. S. Saran, *Inorg. Chem.*, **10**, 1861 (1971).
(10) S. O. Grim, W. McFarlane, and E. F. Davidoff, *J. Org. Chem.*, **32**, 781 (1967).
(11) K. Issleib and H. Völker, *Chem. Ber.*, **94**, 392 (1961).
(12) Reference 10, Table II.
(13) J. W. Faller and A. S. Anderson, *J. Am. Chem. Soc.*, **91**, 1550 (1969).
(14) W. McFarlane, *Chem. Commun.*, 229 (1968).
(15) B. E. Mann, *J. Chem. Soc., Perkin Trans. 2*, 30 (1972).
(16) M. Akhtar, P. D. Ellis, A. G. MacDiarmid, and J. D. Odom, *Inorg. Chem.* **11**, 2917 (1972).
(17) R. B. King and J. C. Cloyd, Jr., *J. Chem. Soc., Perkin Trans. 2*, 938 (1975).
(18) R. B. King, J. C. Cloyd, Jr., and P. N. Kapoor, *J. Chem. Soc., Perkin Trans. 1*, 2226 (1973).
(19) W. Kuchen and H. Buchwald, *Chem. Ber.*, **91**, 2296 (1958); R. C. Taylor, R. Kolodny, and D. B. Walters, *Synth. Inorg. Met.-Org. Chem.*, **3**, 175 (1973).

Synthesis and Spectral Properties of the Isomeric Hydroxybenzo[*a*]pyrenes

H. Yagi, G. M. Holder,[1] P. M. Dansette,[2] O. Hernandez, H. J. C. Yeh, R. A. LeMahieu,[3] and D. M. Jerina*

National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland, 20014, and Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received July 22, 1975

Syntheses of the 12 isomeric hydroxybenzo[*a*]pyrenes are described. Previous syntheses of eight of these isomers have been repeated and improved upon. New syntheses of the 1-, 2-, 4-, 10-, and 12-hydroxybenzo[*a*]pyrenes are reported. Infrared, ultraviolet, fluorescence, and ^{1}H NMR spectra of the 12 phenols are provided to facilitate study of the metabolism of this important environmental carcinogen.

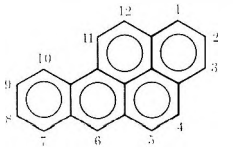
This laboratory has had a long-standing interest in the fundamental mechanisms and pathways through which aromatic compounds undergo oxidative metabolism within the cell.[4] Much of this interest was stimulated by our observation that aromatic ring substituents undergo intramolecular migration and retention (i.e., the NIH shift)[5] during the course of aromatic hydroxylation by monoxygenase enzymes.[6] Occurrence of the NIH shift suggested that aromatic hydroxylation was mediated by arene oxides and led ultimately to the identification of naphthalene 1,2-oxide as the obligatory intermediate in route to the several oxidative metabolites of naphthalene by mammals.[7] The past 5 years have seen a growing interest in the chemistry[8] and biochemistry[9] of arene oxides as this class of compounds has been shown to be potent frameshift mutagens in bacterial test systems, implicated in certain forms of metabolism induced cytotoxicity and necrosis, and shown to induce transformation of mammalian cells in culture (cf. ref 9). Although transformation of cells in culture cannot be directly equated with carcinogenesis in vivo, the possibility does exist that arene oxides are ultimate carcinogens[10] in mammals. For this reason, we have undertaken a comprehensive study of the carcinogen benzo[*a*]pyrene (BP).

Although BP must be classified as a relatively weak carcinogen[11] when compared to 3-methylcholanthrene or 7,12-dimethylbenzo[*a*]anthracene, BP is one of the most prevalent and ubiquitous environmental carcinogens to which man is exposed.[12] In addition, definitive studies of the metabolism of this hydrocarbon should be possible through the use of presently available techniques such as gas chromatography and high-pressure liquid chromatography. Interestingly, BP was the first chemical compound for which a causal relationship with cancer was established.[13]

An initial goal of this program has been the chemical synthesis of primary metabolites, arene oxides and phenols, of BP for use as reference standards in the study of the metabolism of BP. Despite the wide interest in the metabolism and carcinogenicity of this hydrocarbon, the synthesis of only eight of the 12 possible phenols had been described, and none of these were readily available for biological examination. The present study describes synthesis of the unknown phenols of BP and improvements on the prior synthetic procedures. Additionally, spectral and chemical properties of these isomers are reported.

Results and Discussion

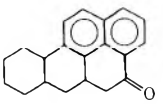
From a synthetic standpoint, the hydrocarbon BP can be considered to have four distinct regions into which the hydroxyl group must be introduced: the 1, 2, and 3 positions which are peculiar to pyrene residues in polycyclic aromatic hydrocarbons, the 4,5- and 11,12-K regions, the highly reactive 6 position which can be considered similar to 9,10 (meso) positions in anthracene, and the 7, 8, 9, and 10 positions in the benzo ring. Only two highly selective reactions



are known for the parent hydrocarbon, substitution at the 6 position and reaction of the 4,5-K region with osmium tetroxide to form the 4,5-dihydrodiol on hydrolysis of the osmate ester.[14] Thus, the only phenol which has been obtained by direct modification of the parent hydrocarbon is 6-hydroxy BP, which Fieser and Hershberg[15] obtained in good yield by acetoxylation of BP with lead tetracetate.

Synthesis of one of the two possible phenols at each of the K regions has been achieved via intramolecular cyclization of polycyclic hydrocarbon acetic acids in liquid HF to ketones which spontaneously isomerize to phenols. Thus, Fieser and Johnson[16] described the cyclization of 4-chrys-

Table I. Methods, Yields, and Melting Points of the Isomeric Phenols of BP Obtained from the Indicated Precursors[c]

Position of hydroxyl	Precursor	Method	Yield, % (mp,[a] °C)	Ref to prior synthesis
1	1e (Scheme I)	Pd, -3H_2 27 h	90[b] (dec)	20a, 21, 24
2	2e (Scheme III)	Pd, -3H_2 15 h	61 (227–228)	
3	3e (Scheme II)	Pd, 3H_2 7 h	95 (226–227)	20a
4		Pd, -4H_2 20 h	48 (220–222)	
5	4-Chryseneacetic acid (Scheme IV)	HF 0.5 h	43 (195–196)	16
6	6-Acetoxy BP	1. $Pb(OAc)_4$ 2. CH_3MgBr	62 (207–209)	15
7	7 (Scheme VI)	Pd, -H_2 4 h	62 (218–219)	18
8	8 (Scheme VI)	Pd, -H_2 10 h	67 (228)	19
9	9 (Scheme VI)	Pd, -H_2 10 h	80 (196)	19
10	10 (Scheme VI)	Pd, -H_2 10 h	70 (200–201)	
11	1-Benzo[*a*]anthraceneacetic acid	HF 1 h	71 (220)	17
12	12c diacetate (Scheme V)	1. DDQ, -HOAc, -H_2 2. hyd	66 (230–231)	

[a] For the most part, these numbers represent decomposition temperatures rather than true melting points. [b] Yield based on recovered ketone. See Experimental Section. [c] Previously undescribed phenols gave combustion analyses within ±0.3% calculated for $C_{20}H_{12}O$.

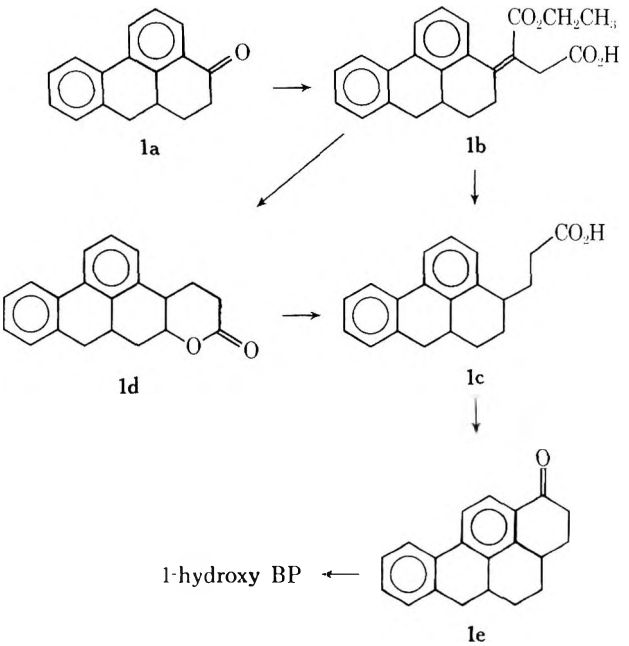
eneacetic acid to 5-hydroxy BP and Fieser and Heymann[17] the cyclization of 1-benzo[*a*]anthraceneacetic acid to 11-hydroxy BP. Prior to this study, syntheses of 4- and 12-hydroxy BP had not been described. For convenience, the immediate precursors to the hydroxy BP isomers are indicated in Table I.

For the 7, 8, and 9 positions on the benzo ring, the corresponding ketones of 7,8,9,10-tetrahydro BP have been dehydrogenated to the corresponding phenols.[18,19] 10-Hydroxy BP had not been previously reported.

Synthesis of the phenols at the 1, 2, and 3 positions have proved the most difficult. Cook et al.[20a] devised a multistep synthesis of a hexahydro BP ketone (Table I) which was then dehydrogenated to 3-hydroxy BP. Direct synthesis of 1-hydroxy BP[20a] was also described by acetoxylation of 6-chloro BP. The resulting 1-acetoxy-6-chloro BP was then converted to 1-methoxy BP in very low overall yield. Subsequently, we described a multistep synthesis of 1-hydroxy BP[21] which confirmed the structure of the material from the initial synthesis. 2-Hydroxy BP had not previously been reported.

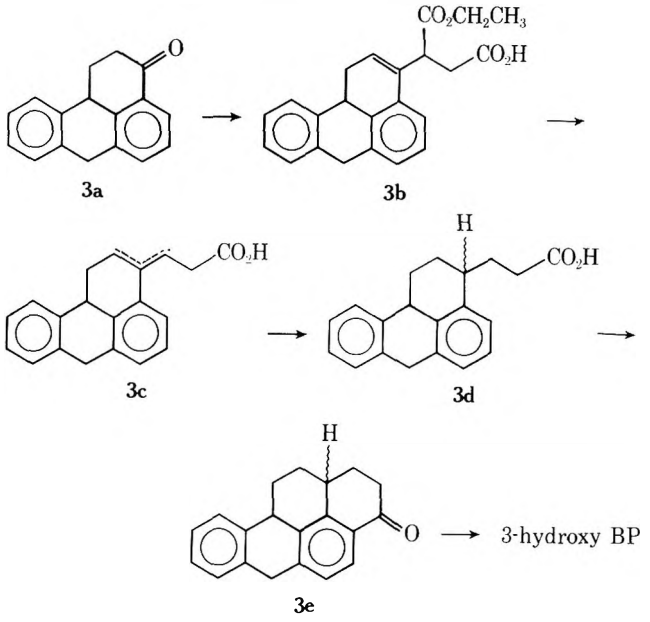
Synthesis. Since our initial report,[21] we have modified the synthetic route to 1-hydroxy BP such that the overall yield from 5,6,6a,7-tetrahydrobenz[*de*]anthracen-4-one (**1a**) was increased from 8% to 32%. Stobbe condensation of **1a** with diethyl succinate by the procedure of Daub and Johnson[22] afforded β-carbethoxy-β-(5,6,6a,7-tetrahydro-4*H*-benz[*de*]anthracen-4-ylidene)propionic acid (**1b**) in 85% yield. Previously, decarboxylation of **1b** was accompanied by disproportionation to **1c** (Scheme I) and β-(7*H*-benz[*de*]anthracen-4-yl)propionic acid (**7** in ref 21), which on cyclization with HF spontaneously dehydrogenated to 1-hydroxy BP.[21] Decarboxylation of the Stobbe product **1b** under reducing conditions provided the desired β-(5,6,6a,7-tetrahydro-4*H*-benz[*de*]anthracen-4-yl)propionic acid (**1c**) along with a small amount of lactone **1d** which was convertible to **1c**. Cyclization of **1c** to 3,3a,4,5,5a,6-hexahydrobenzo[*a*]pyren-1-(2*H*)-one (**1e**) proceeded as described.[21] The ketone **1e** was then dehydrogenated to 1-hydroxy BP. Our purpose in suppressing disproportionation during decarboxylation of **1b** and thereby improving the synthesis of **1e** resides in the possibility for conversion of **1e** into the presently unknown benzo[*a*]pyrene 1,2-oxide.[23] Once it had become clear through these synthetic studies[21] that the acetoxylation of 6-halo BP does indeed proceed at C-1 as described by Cook et al.,[20] Harvey and Cho[24] were able to improve greatly the original synthesis of 1-hydroxy BP through the use of modern techniques.

Scheme I



Both 2- and 3-hydroxy BP have been prepared by modification of the procedure which Cook et al.[20a] developed for the synthesis of 3-hydroxy BP. In this synthesis, 9-anthral-

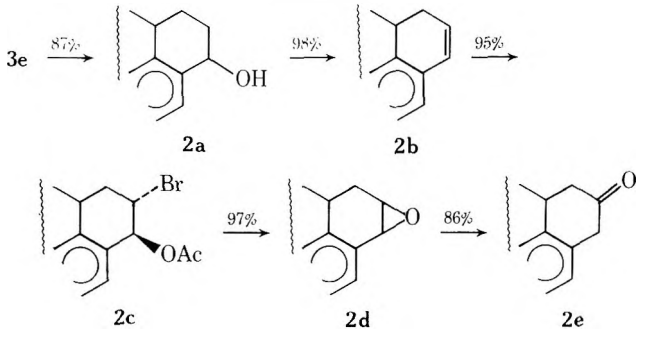
Scheme II



dehyde was converted through several steps to the ketone **3a** (Scheme II). Subsequently Daub and Doyle described an improved preparation of the precursors leading to **3a** via anthrone.[20b] Stobbe condensation of **3a** provided **3b** which appears to be mainly the isomer with the endocyclic double bond. Attempted decarboxylation of **3b** with hydrobromic acid resulted in disproportionation as well as decarboxylation in a fashion similar to that shown in Scheme I. This difficulty has been avoided by simply substituting hydrochloric acid for hydrobromic acid to obtain instead the acid **3c** which was reduced to a mixture of diastereomeric acids **3d** (XVA and XVB in ref 20) by sodium and amyl alcohol. The acids were cyclized to the diastereomeric ketones **3e,** both of which dehydrogenate smoothly to 3-hydroxy BP.

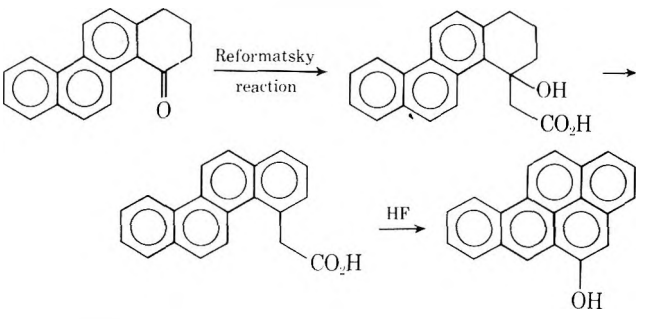
2-Hydroxy BP was synthesized by isomerization of 1,6,10b,11,12,12a-hexahydrobenzo[a]pyren-3-(2*H*)-one (**3e,** isomer XVIA in ref 20a) to the ketone at the 2 position (Scheme III, **2e**) and subsequent dehydrogenation (76% yield). Isomerization of the ketone **3e** was accomplished by (1) reduction to the alcohol **2a,** (2) dehydration to the hexahydro BP **2b,** (3) formation of the *trans*-bromohydrin acetate **2c,** (4) cyclization to epoxide **2d,** and (5) isomerization to the desired ketone **2e.** While the number of steps in this transformation is large, the method is highly practical in that the overall conversion was accomplished in nearly 70% yield.

Scheme III



Fieser's general approach to the synthesis of K-region phenols, particularly 5-hydoxy BP[16] and 11-hydroxy BP,[17] was found quite satisfactory. The general concept is typified by Scheme IV. We experienced little of the solubility

Scheme IV

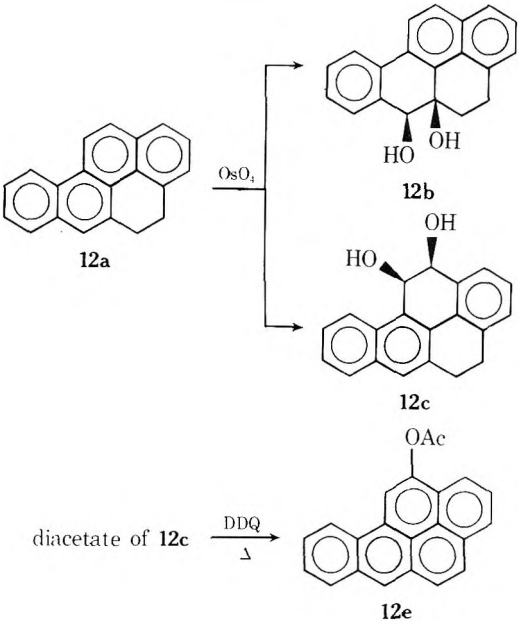


problem[16] which was observed in the Reformatsky reaction leading to 4-chryseneacetic acid, possibly because highly purified zinc was used. In addition, direct distillation of the crude Reformatsky products with sulfur, thus by-passing several intermediate steps, significantly improved the overall yield. Typical experiments en route to 11-hydroxy BP are described.

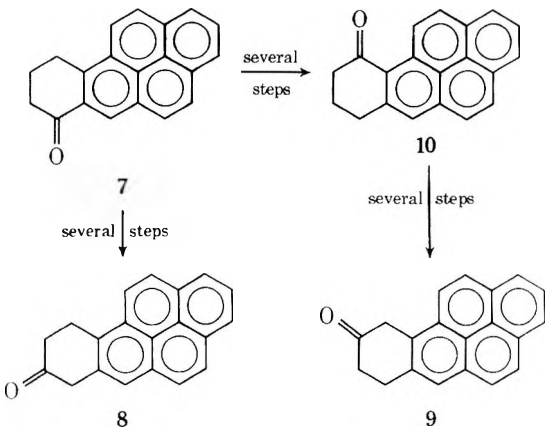
For synthesis of the unknown 4-hydroxy BP, dehydrogenation (Table I) of the known 5a,6,6a,7,8,9,10,10a-octahydrobenzo[a]pyren-4-(5*H*)-one[25] was found to proceed in 58% yield. In general, multiple dehydrogenations such as this proceed slower and in lower yield. Cyclization of 5-chryseneacetic acid, which could have been prepared en route to the above ketone, would probably represent a more convenient synthesis of 4-hydroxy BP.

The route employed for the synthesis of the remaining unknown K-region phenol, 12-hydroxy BP, was dictated by a desire to introduce functionality at the 11,12 position which would also be useful in the synthesis of the unknown BP 11,12-oxide.[23] In an attempt to direct the reaction of osmium tetroxide to the 11,12-K region, the more reactive 4,5-K region was first reduced to produce 4,5-dihydro BP (**12a,** Scheme V) and then the osmium tetroxide reaction was conducted. The two possible cis dihydro diols at the 5a,6- and 11,12-K regions (**12b**[26] and **12c**) were formed. Prior studies[27] on the dehydration of cis dihydro diols at the "bay region" of polycyclic hydrocarbons established that the hydroxyl group in the bay region occupies a highly axial environment and is thereby predisposed to elimination because of the trans-diaxial nature of such dehydrations. As expected, heating the diacetate of **12c** with DDQ

Scheme V



Scheme VI



in toluene cleanly produced 12-acetoxy BP which was readily hydrolyzed to the desired phenol. Less vigorous conditions for the oxidation allowed isolation of *cis*-11,12-diacetoxy-11,12-dihydro BP.[23]

The prior synthesis of 6-hydroxy BP was found to occur exactly as described.[15] This phenol was also obtained as a product from an attempted synthesis of BP 5a,6-oxide.[28]

The four isomeric phenols in the benzo ring of BP, including the unknown 10-hydroxy BP, were obtained by dehydrogenation (Table I) of the corresponding ketones of tetrahydro BP (**7–10**, Scheme VI). All of these ketones originate from 9,10-dihydrobenzo[*a*]pyren-7(8*H*)-one[18] (**7**). Conversion to 10-hydroxy-7,8,9,10-tetrahydro BP has been described.[29,30] Oxidation with chromium trioxide–pyridine provided ketone **10** (Scheme VI). Ketones **8** and **9** had ppreviously been obtained[19] by dehydration of tetrahydrodiols of BP at the 7,8 and 9,10 positions, respectively. Sequences analogous to that shown in Scheme III have proved far more satisfactory.

Spectral Properties. Complete infrared spectra of the phenols in KBr, ultraviolet and fluorescence spectra of the phenols and their corresponding phenolate anions, and 220-MHz ^{1}H NMR spectra of the phenols in tetrahydrofuran-d_8 are presented in the supplemental data provided with the microfilm version of this article. These spectra were determined on analytically pure samples of the 12 isomeric phenols and represent the first collection of data of this type for a carcinogenic polycyclic aromatic hydrocarbon. The absence of such tabulations has greatly hampered the study of the carcinogenicity and particularly the metabolism of aromatic carcinogens in the past.

Comparison of the infrared spectra for these phenols established that sufficient differences exist in fine structure to allow ready identification of individual isomers as well as identification and possible quantitation of complex mixtures. Fourier transform infrared coupled with gas or liquid chromatography could prove invaluable to quantitative metabolism studies. None of the phenols exhibited detectable amounts of keto tautomers in solid KBr.

Mass spectra of the hydroxy BP isomers (Table II) are characterized by intense molecular ions which, in most cases, show a fragment ion at M − 29 which is typical of phenols.[31] For the 2-, 3-, 5-, 9-, and 10-hydroxy BP isomers, the electron impact spectra show base peaks in the region of *m/e* 100, the intensities of which were variable among separate runs, possibly owing to variation in source pressure. The spectra, either by electron impact or chemical ionization with ammonia, do not appear to provide a suitable means of distinguishing among isomers. Mass spectrometry has been employed to confirm the molecular weight of phenols produced on metabolism of BP,[32] but should not be taken as evidence for the position of the hydroxyl group.

Table II. Electron Impact and Chemical Ionization Mass Spectra of the Isomeric Hydroxybenzo[*a*]pyrenes[a]

Position of hydroxyl	Electron impact (70 eV)		Chemical ionization (NH_3)	
	M^+ (268)	$M^+ - 29$	M^+ (269)	$M^+ - 29$
1	100	0	100	0
2	100	14	100	60
3	100	46	100	45
4	100	60	100	50
5	100	33	100	0
6	100	55	100	50
7	100	50	100	80
8	100	55	100	50
9	100	50	100	50
10	100	57	100	70
11	100	45	100	0
12	100	45	100	0

[a] Mass spectra were determined with a Finnigan Model 1015D gas chromatograph–mass spectrometer. Samples were introduced through the direct inlet port. Relative intensities are given for the molecular ion and the fragment after loss of 29, which are the only significant high mass signals.

^{1}H NMR spectra of the phenols were determined at 220 MHz in tetrahydrofuran-d_8. This solvent was selected because of the generally low solubility of the phenols in other solvents. 6-Hydroxy BP was studied as the acetate since the free phenol rapidly decomposed in tetrahydrofuran. A very broad envelope of absorption in the aromatic region suggested that radicals were present.

Chemical shifts (Table III) for the ring hydrogens in BP and the twelve phenols were assigned with the aid of double resonance and comparison with the spectra of related hydrocarbons.[33,34] Absolute assignment of H_1 vs. H_3 and H_4 vs. H_5 is particularly difficult because decoupling experiments do not allow distinction between these pairs. Hydrogens H_1 and H_3 are identical in the symmetric hydrocarbon pyrene. For BP, however, H_1 should be more deshielded relative to H_3 because of the ring current produced by asymmetric introduction of the additional ring.[34] A similar argument applies to H_4 and H_5. This principle was applied in making the assignments of Table III and may be subject to revision for the indicated pairs. The same assignment for BP has been made by Haight and Mallion[35] without justification for the relative assignment within these pairs. Cavalieri and Calvin[36] initially assigned H_1 and H_3 opposite to that in Table III but later revised[37] the assignment.[38]

In general, the H_{10} and H_{11} hydrogens of BP and the isomeric phenols appear at lowest field owing to van der Waals effects and edge deshielding by the aromatic ring in the bay position.[33,34] Introduction of the hydroxyl group into BP results in characteristic[34] upfield displacements in chemical shifts at positions equivalent to ortho, meta, and para hydrogens in the same ring by about 0.38–0.80, 0.13–0.21, and 0.48–0.47 ppm, respectively. Characteristic[34] downfield shifts of 0.33–0.45 ppm were observed for hydrogens at positions peri to a hydroxyl group. Similarily, pronounced downfield shifts of ~1.2 ppm were observed for the bay region hydrogen in 10- and 11-hydroxy BP. The above considerations adequately explain the chemical shifts presented in Table III.

BP represents a one-spin (H_6), a three-spin (H_1,H_2,H_3), a four-spin (H_7,H_8,H_9,H_{10}), and a pair of two-spin (H_4,H_5 and H_{11},H_12) systems. Magnitudes of the coupling constants are fairly characteristic[33,34] for polycyclic aromatic hydrocarbons in that J_{ortho} = 6.0–9.4, J_{meta} = 1.2–1.6, and

Table III. Chemical Shifts (ppm) Downfield from Internal Me_4Si for BP and the 12 Isomeric Phenols[a]

Registry no.	Compd	H_1	H_2	H_3	H_4	H_5	H_6	H_7	H_8	H_9	H_{10}	H_{11}	H_{12}
50-32-8	BP	8.23	7.95	8.08	7.92	8.00	8.54	8.28	7.73	7.80	9.11	9.12	8.33
13345-23-8	1-OH	(9.52)[b]	7.37	7.89	7.77[c]	7.77[c]	8.39	8.21	7.69	7.73	9.07	9.04	8.66
56892-30-9	2-OH	7.59	(8.93)	7.56	7.80	7.94	8.47	8.23	7.63	7.75	9.02	9.02	8.16
13345-21-6	3-OH	8.06	7.48	(9.34)	8.26	7.87	8.38	8.21	7.68	7.72	9.01	8.86	8.18
37574-48-4	4-OH	8.26	7.97	8.52	(9.37)	7.24	8.30	8.17	7.65	7.70	9.04	9.08	8.30
24027-84-7	5-OH	8.03	7.87	7.87	7.17	(9.39)	8.98	8.34	7.71[c]	7.82[c]	9.09	9.08	8.28
53555-67-2	6-OAc	8.23	7.94	8.08	7.95	8.02		8.31	7.79[c]	7.82[c]	9.14	9.10	8.29
37994-82-4	7-OH	8.18	7.91	8.04	7.87	8.03	8.99	(9.45)	7.07	7.59	8.54	9.03	8.26
13345-26-1	8-OH	8.18	7.88	8.04	7.86	7.93	8.34	7.51	(8.75)	7.38	8.95	9.00	8.26
17573-21-6	9-OH	8.15	7.89	8.01	7.81	7.94	8.44	8.15	7.35	(8.95)	8.31	8.91	8.24
56892-31-0	10-OH	8.20	7.91	8.03	7.89	7.96	8.48	7.80	7.53	7.16	(9.71)	10.32	8.25
56892-32-1	11-OH	8.00	7.85[c]	7.90[c]	7.82	7.96	8.55	8.25	7.71[c]	7.71[c]	10.27	(9.76)	7.63
56892-33-2	12-OH	8.61	7.92	8.09	7.84	7.96	8.33	8.22	7.67[c]	7.70[c]	8.87	8.33	(9.58)

[a] 6-Hydroxy BP was measured as the acetate owing to instability of the free phenol. Spectra were measured with a Varian 220-MHz spectrometer on degassed and sealed samples which contained 15 mg of each compound in 0.8 ml of tetrahydrofuran-d_8. Decoupling experiments with a Varian HA-100 spectrometer aided in the spectral assignments. [b] Numbers in parentheses indicate the chemical shift of the hydroxyl hydrogens. [c] In these pairs of signals, distinction between the two hydrogens was not possible.

Table IV. Ultraviolet Absorption Data for the Phenols (Methanol) and Phenolate Anions (0.1% NaOH in 90% Methanol)[c]

Position of hydroxyl	Phenols	Phenolate anions
1	257.5 266 (4.64) 298 398 276.5	261.5 (4.61) 310 424.5
2[a]	286.5 (4.67) 301[b] 382	264 (4.77) 302 387
3	258 (4.67) 307 380	237 (4.68) 314 394
4	267 (4.84) 299 375	271 (5.02) 311 390
5	262 (4.70) 302 381	257 (4.82) 317 405
6	256 302.5 (4.70) 391 379	251.5 (4.39) 312.5 433
7	268 303.5 (4.71) 399	251 (4.73) 318 438
8[a]	279 (4.75) 306[b] 383.5	264 296 (4.82) 386
9[a]	267 (4.75) 301.5 379 250	269 (4.75) 292 396
10	256 (4.57) 302 379	250.5 (4.61) 325 (4.61) 402
11	268 (4.80) 301 382	276 (4.80) 308[b] 395
12	255 295 (4.65) 380	260 (4.62) 308 418

[a] Unusual shifts in absorption were observed in alkali (see Discussion). [b] Not actual peaks but inflections or shoulders. [c] Logarithms of molar extinction coefficients for the most intense peak(s) are given. Samples were freshly prepared and read immediately for experiments in base.

$J_{para} < 1.0$ Hz. For BP, coupling constants of $J_{1,2} = 7.8$, $J_{1,3} = 1.0$, $J_{2,3} = 7.6$, $J_{4,5} = 9.1$, $J_{7,8} = 7.5$, $J_{7,9} = 1.5$, $J_{8,9} = 7.5$, $J_{8,10} = 1.8$, $J_{9,10} = 7.5$, and $J_{11,12} = 9.2$ Hz were observed. These values are nearly identical with the values of Haight and Mallion.[35] The corresponding values for the isomeric phenols were within ±0.2 Hz except when the presence of a hydroxyl group eliminated individual couplings.

Ultraviolet and fluorescence spectra of the phenols and their phenolate anions are tabulated in Tables IV and V. The ultraviolet spectra of the phenols are characterized by two broad absorption bands, the stronger in the 250–300-nm region and the weaker in the 360–400-nm region. The phenolate anions also show two broad absorption bands with a bathochromic shift relative to the phenol for both the long-wavelength band and the 300-nm component of the short-wavelength band with minor exceptions. Long-wavelength shifts of 10–15 nm from the ~300-nm region in the phenol appear as shoulders or inflections for the 2, 8, and 9 isomers. In addition, the 2 and 8 isomers show little shift for the long-wavelength band. Fluorescence of the phenols were relatively similar both in intensity and emission maxima with vibrational fine structure present in most instances. Greater variation in emission maxima and intensity were observed for the phenolate anions with the anions of the 5, 7, 8, and 10 isomers being only weakly or not fluorescent.

In general, the ultraviolet spectra of the phenols are sufficiently similar that distinction between single isomers and mixtures in which a single isomer substantially predominates is not possible. This has led some workers to the possibly erroneous conclusion that metabolism of BP produces only 3- and 9-hydroxy BP as phenolic metabolites.[39] Metabolism of BP is commonly monitored by the production of alkali extractable, fluorescent products and quantitated by comparison with the fluorescence observed from the phenolate anion of 3-hydroxy BP.[40] Since only the 3- and 9-hydroxy isomers are strongly fluorescent in alkali,[41] the assay selects for these products. When the assay was conducted by measuring the fluorescence of alkali extractable metabolites in acid where the fluorescence intensity of individual phenols are more comparable, increases in metabolism turnover numbers of up to 50% were found, suggesting that phenols were formed which were not fluorescent in alkali.[41]

Keto Tautomers. Recently Newman and Olson[42] reported the remarkably facile conversion of 5- and 6-acetoxy-7,12-dimethylbenzo[a]anthracene (K-region acetates) to the corresponding methyl ethers by simple treatment with methanolic HCl. Inspection of the ^1H NMR and infrared spectra of the corresponding phenols established that both exist largely as the keto tautomers, and thus formation of hemiketals followed by dehydration was suggested as the probable mechanism for the transformation.

Table V. Fluorescence Data[a] for the Phenols (Methanol) and Phenolate Anions (0.1% NaOH in 90% Methanol)[c]

Position of hydroxyl	Phenols		Phenolate anions, nm
	Maxima, nm	Intensity[b]	
1	427	350	520
2	417	198	508
3	434	1000	518
4	420	240	519
5	428	258	560
6	438	165	516
7	441	359	560
8	424	151	522
9	427	450	513
10	427	238	Nil
11	423	366	540
12	418	330	519

[a] Measured with a Perkin-Elmer Model MPF-3L fluorescence spectrophotometer in the direct mode with slit width settings of 2 nm for the excitation and emission monochromaters. [b] Relative fluorescence intensities of phenols measured with the above spectrofluorimeter settings at λ excitation 380 nm, and λ emission 434 nm. These are optimum for 3-hydroxy BP which has been arbitrarily set to 1000. The measurements were carried out on approximately 10^{-6} M solutions. [c] Samples were freshly prepared and read immediately for experiments in base.

Table VI. Methylation of Hydroxy BP Isomers with Methanol Saturated with Dry HCl[c]

Position of hydroxyl	Conditions		% conversion	
	Temp, °C	Time, h	Methyl ether	Chlorinated products
1	85	2	0	0
2	85	2	0	30[a]
3	85	2	0	0
4	5	48	100	
5	5	24	>95	Trace[a,b]
6	5	48	0	0
7	85	2	50	
8	85	2	50	
9	85	2	80	
10	85	2	50	
11	5	24	90	Trace[a]
12	5	24	50	Trace[a]

[a] The mass spectrum indicated that the product was a chlorinated phenol. [b] The mass spectrum indicated that the product was a methylated and chlorinated phenol. [c] Reactions were conducted in the dark under the indicated conditions. Products were isolated by TLC and conversions estimated by uv. Structures were confirmed by chemical ionization mass spectrometry with isobutane which showed losses of 15 mass units from the molecular ion characteristic of methyl ethers.

These authors proceeded to suggest that such a mechanism could account for the metabolism induced binding[10] of polycyclic hydrocarbons to biopolymers and thereby induce cancer. While there is no apparent correlation between carcinogenicity and the extent to which selected phenols exist as their keto tautomers,[43] this mechanism presently cannot be discounted as a potential pathway to explain some portion of the covalent binding of hydrocarbons to biopolymers in vivo, whether or not this mechanism of binding is associated with carcinogenesis. Dipple et al.[44] have studied the carcinogenicity of 5- and 6-hydroxy-7,12-dimethylbenzo[*a*]anthracene in mice and have found both phenols inactive in comparison to the parent hydrocarbon. However, comprehensive studies of all the possible phenols from any carcinogenic polycyclic hydrocarbon are presently unavailable.

The effect of methanolic HCl on the isomeric phenols of BP is shown in Table VI. Treatment for 24 h at 5 °C resulted in extensive O-methylation of all four K-region phenols. In addition, the four isomers in the benzo ring showed small amounts of reaction. When the reaction mixtures containing these phenols were heated at 85 °C for 2 h, extensive conversion was observed, whereas the 1-, 2-, 3-, and 6-hydroxy isomers were completely inactive under all conditions.

Neither infrared nor ^{1}H NMR gave indication that keto tautomers were present in dynamic equilibrium with the 12 phenols in this study. Results of the methylation studies indicate that tautomerism is quite facile for K-region phenols and does occur to a significant extent for the phenols in the benzo ring. Enhanced reactivity at the K region is anticipated on electronic grounds and parallels the observed[43] stability of the keto tautomers of 1-naphtol vs. 9-phenanthrol (K region). Methylation of the phenols in the benzo ring is understandable in light of the observation by Newman[45] that even 1- and 2-naphthol are converted to methyl ethers by methanolic HCl. The mechanism of these conversions has been confirmed by the observation that 9-phenanthrol is readily converted to the thio ether in thioethanol–HCl.

Biological Studies. Availability of all 12 of the isomeric phenols possible for BP has allowed a comprehensive approach to be taken in the study of the metabolism and carcinogenicity of the hydrocarbon. High-pressure liquid chromatography on Du Pont permaphase ODS columns with a water–methanol gradient has established that the phenols are eluted from the column in two unresolved peaks with the 2, 6, 8, and 9 isomers contained in the first peak.[46] A similar situation exists for the five phenanthrols where the 2 and 3 isomers elute first as a single peak.[27] In a study of the eight phenols for the two terminal rings of benzo[*a*]anthracene, the 2, 3, 9, and 10 isomers eluted first.[47] In almost all of these cases, the isomers which emerge from the column first correspond in position on the hydrocarbon to the 2 position on naphthalene. Metabolism of ^{14}C-BP[46] results in substantially higher production of phenols in the second peak, largely because unsymmetrical arene oxides tend to display highly directional opening[8,48] which favors the most stable carbonium ion intermediate. For the six metabolically probable arene oxides from BP,[23] only BP 9,10-oxide[46] should lead to substantial amounts of phenol in the first of the two groups of phenols emerging from the column. Interestingly, the only K-region arene oxide whose isomerization has been adequately studied[48] was found to produce the trans dihydrodiol exclusively on solvolysis at physiological pH.

We are presently examining the biological activity[49] of the 12 isomeric phenols of BP. Tests for mutagenicity toward histidine dependent *Salmonella typhimurium* and toward 8-azaguanine sensitive Chinese hamster V79 cells in culture have shown all 12 compounds to be relatively inactive[50] when compared to BP 4,5-oxide. The 1, 3, 6, 7, and 12 isomers are weakly mutagenic toward the bacterial strain TA 1538 while the 2, 3, 6, and 8 isomers show significant toxicity toward the mammalian cells. Mutagenicity of the 12 phenols after metabolic activation by hepatic microsomes, ability to transform mammalian cells in culture, and carcinogenicity on repeated application to the skin of mice are under study. The biological activity of the phenols will be compared to that of the corresponding arene oxides of BP of which the 4,5-, 7,8-, 9,10-, and 11,12-oxides[23,29] are presently available. The 7-, 9-, and 10-hydroxy BP isomers are relatively effective inhibitors of epoxide hydrase activity toward the 7,8- and 9,10-oxides, respectively, while the K-region phenols caused little inhibition of the hydration of the two K-region arene oxides. All 12 of the phenols gave

very low or negligible binding to polyguanylic acid when compared to 7,12-dimethylbenzo[a]anthracene 5,6-oxide.[51] BP 7,8-oxide is a potent carcinogen on mouse skin.[54]

Experimental Section

Routine ^{1}H NMR spectra were recorded with Varian A-60 and HA-100 instruments. High-resolution ^{1}H NMR spectra were recorded with a Varian HR-220 spectrometer. Tetrahydrofuran-d_8 was used as solvent for the phenols. Ultraviolet spectra were recorded with a Cary 15 recording spectrophotometer. Infrared spectra were determined in KBr disks with a Perkin-Elmer Model 421 grating infrared spectrophotometer. Fluorescence spectra of the phenols and the phenolate anions were determined with a Perkin-Elmer Model MPF-3L fluorescence spectrophotometer. Melting points were determined in open capillary tubes and are uncorrected. Microanalyses were performed by the Section on Analytical Services in this laboratory and were within ±0.3% for the indicated elements.

General Procedure for Dehydrogenation of Ketones to Phenols. Both sulfur and palladium black at high temperature have been employed in the final dehydrogenation step to convert ketones to phenols. Examination of both methods has shown palladium black to be generally superior. In a typical procedure, 2 mmol of ketone and 15 mmol of palladium black (Engelhard) were heated near reflux (>240 °C) for the indicated times (Table I) in 1-methylnaphthalene with a stream of argon gas passing through the solution. The use of high-quality 1-methylnaphthalene is essential. Commercial material was passed through a column of basic alumina (activity grade I) and eluted with petroleum ether. Prior to use, the material was distilled under vacuum. The crude reaction mixtures containing 1-, 2-, 3-, 4-, 7-, 8-, 9-, or 10-hydroxy BP were diluted with benzene and applied directly to a chromatographic column of 100 g of acidic alumina (activity grade I). Elution with benzene removes unreacted starting ketone, 1-methylnaphthalene, and nonpolar impurities. Further elution with acetone–benzene or acetone provided phenols of high purity. Final purification was by sublimation (190–210 °C, 0.03 mm) or recrystallization. Increase of the bath temperature above 210 °C usually results in faster decomposition than sublimation. All operations on the phenolic isomers were conducted in subdued light and samples were stored at −80 °C under argon gas.

1-Hydroxy BP.[21,24] A solution of 5,6,6a,7-tetrahydrobenz[*de*]anthracen-4-one (**1a**,[21] 1.0 g, 4.27 mmol) and diethyl succinate (2.23 g, 12.8 mmol) in dry Me_2SO[22] (10 ml) was added to a well-stirred suspension of NaH (8.6 mmol) in Me_2SO (3 ml) under argon. The dark mixture was stirred for 1.5 h at room temperature, cooled to 0 °C, quenched with acetic acid (5 ml), poured into water, and extracted into ether. Back extraction into 10% aqueous sodium carbonate, acidification of the aqueous phase, and extraction of the acid into ether provided 1.32 g (85%) of the Stobbe product **1b** on work-up: mp 189–191 °C dec from ethanol–water; mass spectrum *m/e* 362 (M^+). Anal. ($C_{23}H_{22}O_4$) C, H. ^{1}H NMR (100 MHz, $CDCl_3$) 3 H ester 1.05 (J = 7 Hz), H_{6a} 1.75, 2 H_5, 2 H_6, and 2 H_7, 2.2–3.1, 2 H allyl 3.59, 2 H ester 4.08 (J = 7 Hz), 5 aromatic protons 7.2–7.4, 2 aromatic protons 7.7–7.8 ppm.

A solution of crude **1b** (1.0 g, 2.8 mmol), acetic acid (21 ml), concentrated HCl (10.5 ml), water (15 ml), 2-propanol (10 ml), and triethylsilane (5 ml) was refluxed under argon for 16 h. Acetic acid (25 ml) and *p*-toluenesulfonic acid (100 mg) were added and reflux was continued for 5 h. The solution was poured into water and the products extracted into ether. Work-up as above provided a neutral fraction and an acidic fraction. Brief reduction of the latter with hydrogen in the presence of 5% palladium on carbon (50 mg) in THF to reduce a minor amount of olefinic material provided 0.62 g of acid **1c**, mass spectrum *m/e* 292 (M^+). The neutral fraction (**1d**) was refluxed for 16 h under nitrogen in a mixture of acetic acid (20 ml), concentrated HCl (3.5 ml), water (5 ml), and triethylsilane (2 ml). Work-up and reduction as above provided an additional 0.10 g of **1c**. Cyclization with liquid HF of the combined samples of acid **1c** as previously described[21] provided ketone **1e** in overall yield of 42% from the half-ester **1b**.

Conditions for dehydrogenation of **1e** to 1-hydroxy BP are given in Table I. The yield for this step was 90% after correction for recovered starting material (32% conversion). The phenol can be safely purified by column chromatography or vacuum sublimation (195 °C, 0.02 mm) but suffers extensive decomposition on attempted recrystallization.

3-Hydroxy BP. Cook et al.[20a] assigned the Stobbe condensation product from **3a** as the exocyclic isomer, β-(1,2,3,11b-tetrahydro-7*H*-benz[*de*]anthracen-3-yl)-β-ethoxycarbonylpropionic acid. However, the ^{1}H NMR spectrum (60 MHz, $CDCl_3$) of **3b** shows that it consists mainly of the isomer (mp 114–118 °C, lit.[20a] mp 115–116 °C) with the endocyclic double bond, β-(1,11b-dihydro-7*H*-benz[*de*]anthracen-3-yl)-β-ethoxycarbonylpropionic acid, based on a broad signal (~1 H) at δ 6.1. To 44 g of **3b**[20a] dissolved in 280 ml of acetic acid was added 140 ml of concentrated hydrochloric acid and 200 ml of water. The mixture was refluxed with stirring under argon gas for 8 h, cooled in ice, and 200 ml of water was added. The resultant solid was crystallized from ethyl acetate–cyclohexane to give 30.3 g (91.7%) of β-(7*H*-1,2-dihydrobenz[*de*]anthracen-3-yl)propionic acid (**3c**): mp 191–192.5 °C; mass spectrum *m/e* 290 (M^+); λ_{max} 218 nm (ε 21 500), 262 (ε 7500) in ethanol. Anal. ($C_{20}H_{18}O_2$) C, H.

To a refluxing solution of 30.0 g of **3c** in 2 l. of amyl alcohol under argon was added 67 g of sodium in pieces over 5 h. Reflux was continued for 30 h and the amyl alcohol was removed by steam distillation. Cooling and acidification gave a solid which on crystallization from ethanol–water gave 23.4 g (91.7%) of β-(1,2,3,11b-tetrahydrobenz[*de*]anthren-3-yl)propionic acid (**3d**) as a mixture of isomers: mp 149–152 °C; mass spectrum *m/e* 292 (M^+). Anal. ($C_{20}H_{20}O_2$) C, H.

To 300 ml of hydrogen fluoride cooled in ice and stirred was added 23.4 g of the isomeric mture **3d.** The resulting red solution was stirred at room temperature for 18 h before the hydrogen fluoride was removed in a stream of nitrogen. The residue was taken up in methylene chloride, washed with sodium bicarbonate solution, dried ($MgSO_4$), and concentrated in vacuo to an oil which slowly crystallized. Recrystallization from ethanol gave 12.0 g of 1,6,10b,11,12,12a-hexahydrobenzo[a]pyren-3(2*H*)-one (**3e**), isomer A: mp 183–184 °C (lit.[20] mp 185.5 °C); ^{1}H NMR (220 MHz, $CDCl_3$) 2 H_1, H_{10b}, 2 H_{11}, 2 H_{12}, and H_{12a}, 1.22–3.0, 2 H_6 3.64, 2 H_2 3.91 (J = 10 and 7 Hz), five aromatic protons 7.1–7.35, and H_4 7.80 ppm ($J_{4,5}$ = 10 Hz). Two recrystallizations of the solid obtained from ethanol filtrate gave 5.0 g of **3e,** isomer B: mp 147–153 °C (lit.[20] mp 156 °C); ^{1}H NMR (220 MHz, $CDCl_3$) 2 H_1, H_{10b}, 2 H_{11}, 2 H_{12} and H_{12a} 1.22–3.0, 2 H_6 3.64, 2 H_2 3.91 (J = 10 and 7 Hz), five aromatic protons 7.1–7.35, and H_4 7.83 ppm ($J_{4,5}$ = 10 Hz). Dehydrogenation of either isomer to 3-hydroxy BP and purification was as described.[20]

2-Hydroxy BP. To a suspension of 177 mg of the ketone **3e** (isomer A) in 40 ml of methanol was added 200 mg of sodium borohydride in portions with stirring. Stirring was continued for 1 h at room temperature, the bulk of solvent was evaporated, and the residue was treated with 50 ml each of water and chloroform. The chloroform extract was washed with water, dried (K_2CO_3), and evaporated to leave a solid which was recrystallized from chloroform–petroleum ether to give 156 mg (87%) of colorless needles of 1,2,3,6,10b,11,12,12a-octahydro-3-hydroxybenzo[a]pyrene (**2a**): mp 135–136 °C; ^{1}H NMR (60 MHz, $CDCl_3$) 2 H_6 3.92, H_3 4.74 and six aromatic protons 7.10–7.50 ppm. Anal. ($C_{20}H_{20}O$) C, H.

A mixture of 2.5 g of the alcohol **2a,** 120 ml of acetic acid, and 2 drops of concentrated hydrochloric acid was heated at 110 °C for 1.5 h with stirring. After cooling, the reaction mixture was poured into 200 ml of water and extracted with chloroform. The chloroform extract was washed with water, 10% ammonium hydroxide, and water and dried (K_2CO_3). Evaporation of the solvent gave an oil which was distilled (bp 225–230 °C, 0.1 mm) to give 2.28 g (98.5%) of colorless crystals which were recrystallized from methanol to give colorless prisms of 1,6,10b,11,12,12a-hexahydrobenzo[a]pyrene (**2b**): mp 87–88 °C; ^{1}H NMR (100 MHz, $CDCl_3$) three methylene protons and two methine protons 1.20–3.70, 2 H_6 3.79, H_2 5.90 ($^3J_{2,3}$ = 10, $^3J_{2,1}$ = 4, $^3J_{2,1}$ = 2 Hz), H_3 6.45 ($^3J_{3,2}$ = 10, $^3J_{3,1}$ = 1.5 Hz), and six aromatic protons 7.0–7.5 ppm. Anal. ($C_{20}H_{18}$) C, H.

A solution of 500 mg of the olefin **2b,** 268 mg of *N*-bromoacetamide, and 200 mg of lithium acetate in 100 ml of acetic acid was stirred at room temperature for 2.5 h. The reaction mixture was poured into 250 ml of water and the resulting crystals were collected by filtration. The crystals were dissolved in chloroform, washed with water, and dried (K_2CO_3). Evaporation of the solvent gave 700 mg (94.5%) of colorless crystals which were recrystallized from methanol to give colorless prisms of 3-acetoxy-2-bromo-1,2,3,6,10b,11,12,12a-octahydrobenzo[a]pyrene (**2c**): mp 120–122 °C; ^{1}H NMR (100 MHz, $CDCl_3$) $CH_3C{=}O$ 1.92, 2 H_6 3.91, H_2 4.48 ($^3J_{2,1}$ = 5, $^3J_{2,3}$ = 3 Hz), H_3 6.20 ($^3J_{3,2}$ = 3 Hz), and six aromatic protons 6.90–7.70 ppm. Anal. ($C_{22}H_{21}BrO_2$) C, H.

To a stirred suspension of 1.2 g of the bromohydrin acetate **2c** in 30 ml of dry tetrahydrofuran was added 1 g of dry sodium methoxide. Stirring was continued for 1.5 h at room temperature and the

reaction mixture was poured into 150 ml of water and extracted with chloroform (100 ml × 2). The chloroform extract was washed with water, dried (K_2CO_3), and evaporated to leave crystals which were recrystallized from ether to give 840 mg (97%) of colorless needles of 2,3-epoxy-1,2,3,6,10b,11,12,12a-octahydrobenzo[*a*]pyrene (**2d**): mp 145–147 °C; ^{1}H NMR (60 MHz, $CDCl_3$) H_2 3.60, H_3 3.78 ($^3J_{3,2}$ = 4 Hz), 2 H_6 3.88, and six aromatic protons 7.1–7.6 ppm; mass spectrum *m/e* 274 (M^+). Anal. ($C_{20}H_{18}O$) C, H.

To a stirred solution of 700 mg of the epoxide **2d** in 75 ml of benzene was added 0.1 ml of boron trifluoride etherate under cooling at 5 °C. Stirring was continued for 30 min and the reaction mixture was decomposed with 50 ml of water. The benzene extract was dried (K_2CO_3) and evaporated to leave slightly yellowish crystals which were recrystallized from ethanol to give 600 mg (86%) of colorless prisms of 1,6,10b,11,12,12a-hexahydrobenzo[*a*]pyren-2(3*H*)-one (**2e**): mp 155–156 °C; ^{1}H NMR (60 MHz, $CDCl_3$) 2 H_3 3.59, 2 H_6 3.90, and six aromatic protons 6.9–7.6 ppm; mass spectrum *m/e* 274 (M^+). Anal. ($C_{20}H_{18}O$) C, H.

Dehydrogenation (Table I) of **2e** provided 2-hydroxy BP, which was purified by chromatography and recrystallization from benzene in 61% yield. An additional 20% yield of partially dehydrogenated ketones of unknown structure was recovered. All of the starting **2e** was consumed.

4-Hydroxy BP. Dehydrogenation of 5a,6,6a,7,8,9,10,10a-octahydrobenzo[*a*]pyren-4(5*H*)-one[25] provided 4-hydroxy BP (Table I) in 48% yield after chromatography and sublimation. An additional 17% yield of partially dehydrogenated ketones free of starting material was also isolated. As was the case for the synthesis of 2-hydroxy BP, dehydrogenation was terminated once all the starting ketone had been consumed. Further dehydrogenation results in loss of the phenol and does not improve the yield.

5-Hydroxy BP. Cyclization (Table I) of 4-chryseneacetic acid[16] (Scheme IV) in HF followed by sublimation provided 5-hydroxy BP in 43% yield.

11-Hydroxy BP. A mixture of 1.7 g of 3,4-dihydrobenzo[*a*]anthracen-1(2*H*)-one (V in ref 17), 3.4 g of arsenic-free zinc (prewashed with hydrochloric acid, water, and acetone and dried at 100 °C), ethyl bromoacetate (1.5 ml), dry benzene (70 ml), and absolute ether (17 ml) was refluxed for 6 h after addition of one crystal of iodine. Ethanol (15 ml) and acetic acid (20 ml) were added to decompose the complex, and the organic layer was washed with dilute NH_4OH. Routine work-up provided 1.9 g of yellow prisms from ethanol, mp 114–115 °C. Anal. ($C_{22}H_{22}O_3$) C, H. The corresponding methyl ester of the Reformatsky alcohol (VI, ref 17) had mp 139–148 °C dec. An intimate mixture of the Reformatsky alcohol (1.4 g) and sulfur (190 mg) was heated at 210 °C for 2 h. The crude product was hydrolyzed with KOH (0.8 g) and ethanol (20 ml) at reflux for 1 h. The solution was diluted with water and washed with benzene to remove sulfur. Routine work-up provided 0.75 g of 1-benzo[*a*]anthraceneacetic acid (IX in ref 17) as colorless needles on crystallization from benzene–ligroin, mp 203–204 °C (lit.[17] 203.6–204.6 °C). The overall yield from V to IX (ref 17) of 52% compares well with the 22% previously reported. Cyclization was conducted as described to provide pure 11-hydroxy BP in 71% yield on recrystallization from benzene. Attempted sublimation of this material results in extensive decomposition.

12-Hydroxy BP. A solution of BP (9 g) in benzene (450 ml) was stirred with 3 g of 10% palladium on $SrCO_3$[52] and 4 atm hydrogen for 26 h. Gas chromatography (270 °C, 3% OV-17, 1.5 m, N_2 30 ml/min)–mass spectrometry established that the reaction mixture contained 5% BP and 3% perhydro BP along with the desired 4,5-dihydro BP (**12a**). Crystallization of the product from cyclohexane provided 7.0 g of [purity (GLC) ≥ 96%] colorless plates: mp 143–144 °C (lit.[52] mp 148.5–149 °C); ^{1}H NMR (100 MHz, CCl_4) 2 H_4 and 2 H_5 3.28, eight aromatic protons centered at 7.6 (multiplets), H_{11} 8.52 ($J_{11,12}$ = 9.2 Hz), and H_{10} 8.55 ppm (multiplets).

A mixture of 7 g of 4,5-dihydro BP (**12a**), 80 ml of pyridine, and 7 g of osmium tetroxide was stirred under argon gas for 7 days. Hydrolysis of the resulting osmate ester was carried out by stirring the reaction mixture under argon gas for 5 h after addition of 14 g of sodium bisulfite, 200 ml of water, and 160 ml of pyridine. The reaction mixture was diluted with 1.8 l. of water and the resulting yellowish solid recrystallized from carbon tetrachloride to afford 3.9 g of a mixture of the diols **12b** and **12c**. Pure 5a,6-dihydroxy-4,5,5a,6-tetrahydrobenzo[*a*]pyrene (1.2 g, 15%) was isolated by fractional recrystallization from THF as colorless needles, mp 205–208 °C dec. Anal. ($C_{20}H_{16}O_2$) C, H. Both mother liquors from the crystallization were combined and, after evaporation of solvents, were acetylated with 7 ml of acetic anhydride and 5 ml of pyridine for 36 h at 20 °C to provide 5.5 g of an oil which was separated by column chromatography (Merck 60 silica gel, petroleum ether–CH_2Cl_2–methanol, 50:10:0.2, followed by CH_2Cl_2–methanol, 100:2): 1.8 g (25%) of 4,5-dihydro BP, 2.9 g (28%) of 11,12-diacetoxy-4,5,11,12-tetrahydro BP [mp 155 °C from cyclohexane; ^{1}H NMR (60 MHz, $CDCl_3$) C_{11} and C_{12} $COCH_3$ 1.92 and 2.28, 2 H_4 and 2 H_5 3.04, H_{12} 6.35 and H_{11} 7.09 ppm ($J_{11,12}$ = 4.2 Hz). Anal. ($C_{24}H_{20}O_4$) C, H], 1.0 g (11%) of 6-acetoxy-5a-hydroxy-4,5,5a,6-tetrahydro BP, amorphous powder [^{1}H NMR (60 MHz, $CDCl_3$) C_6 $COCH_3$ 2.40, 2 H_4 3.2 (m) and 2 H_5 2.0 (m), H_6 6.21, seven aromatic protons centered at 7.35, and H_{10} and H_{11} 7.9 ppm], and 100 mg of 12-acetoxy-4,5-dihydro BP were obtained.

A mixture of the diacetate of **12c** (100 mg), DDQ (75 mg, Aldrich), and toluene (20 ml) was refluxed for 16 h. After filtration to remove hydroquinone the filtrate was washed with $Na_2S_2O_3$ solution, Na_2CO_3 solution, and water and dried ($MgSO_4$). Evaporation of the solvent gave 63 mg (76%) of yellow needles of 12-acetoxy BP (**12e**): mp 153–156 °C from CCl_4; ^{1}H NMR (60 MHz, $CDCl_3$) C_{12} $COCH_3$ 2.56, eight aromatic protons from 7.0–8.0, H_6 8.33, H_{10} 8.80 (m), and H_{11} 8.75 ppm. Anal. ($C_{22}H_{14}O_2$) C, H.

A mixture of **12e** (600 mg), THF (10 ml), methanol (10 ml), and ammonium hydroxide (5 ml) was stored at 20 °C for 48 h with stirring. The reaction mixture was evaporated to dryness and the solid was chromatographe on acidic alumina (100 g, benzene–20% acetone) to give 456 mg (87%) of yellow crystals of pure 12-hydroxy BP, mp 230–231 °C from benzene–petroleum ether.

7-Hydroxy BP. Dehydrogenation of 9,10-dihydrobenzo[*a*]pyren-7(8*H*)-one[29] (**7**) (Aldrich Chemical Co.) into 7-hydroxy BP (Table I) occurs in 62% yield after purification by chromatography and sublimation. The use of palladium black greatly improves the yield of this phenol.

8-Hydroxy BP. Conversion of 9,10-dihydrobenzo[*a*]pyren-7(8*H*)-one[29] (**7**) (Aldrich Chemical Co.) into 7,8,9,10-tetrahydrobenzo[*a*]pyrene 7,8-epoxide was essentially as described.[53] Isomerization of this compound to ketone **8** (Scheme VI) was as described for the conversion of **2d** into **2e**: 94% yield; yellowish plates, mp 174–176 °C (lit.[19] mp 174–176 °C); ^{1}H NMR (60 MHz, $CDCl_3$) 2 H_9 2.70 ($J_{9,10}$ = 7 Hz), 2 H_{10} 3.70, 2 H_7 3.60, and eight aromatic protons 7.80–8.30 ppm. Dehydrogenation (Table I) to the phenol proceeded in 67% yield after chromatography and sublimation.

9-Hydroxy BP. 10-Acetoxy-9-bromo-7,8,9,10-tetrahydrobenzo[*a*]pyrene[29] was converted to 7,8,9,10-tetrahydrobenzo[*a*]pyrene 9,10-epoxide in 95% yield as described for the conversion of **2c** into **2d**: colorless plates, mp 148–149° (lit.[53] mp 149°); ^{1}H NMR (100 MHz, $CDCl_3$) H_9 3.88, H_{10} 4.85 ($^3J_{9,10}$ = 4 Hz), seven aromatic protons 7.6–8.3, and H_{11} 7.45 ($J_{11,12}$ = 10 Hz). The oxide was isomerized to ketone **9** (Scheme VI) with BF_3 in 90% yield as described for the formation of **2e**: mp 178 °C (lit.[19] mp 178 °C); ^{1}H NMR (60 MHz, $CDCl_3$) 2 H_8 2.40, 2 H_7 2.92 ($J_{7,8}$ = 7 Hz), 2 H_{10} 3.67, and eight aromatic protons 7.30–8.20 ppm. Dehydrogenation (Table I) to the phenol proceeded in 80% yield after chromatography and sublimation.

10-Hydroxy BP. To a stirred mixture of chromium trioxide (1.11 g) and pyridine (10 ml) was added a solution of 10-hydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene[29,30] (1 g) in pyridine (7 ml) and stirring was continued at room temperature for 18 h. The mixture was decomposed with water (150 ml), and the product extracted into chloroform and filtered to remove insoluble material. The chloroform extract was washed with water, 10% hydrochloric acid, and water and dried (K_2CO_3). Evaporation of the solvent and sublimation of the resultant solid provided 760 mg (76%) of ketone **10** with mp 175–177 °C (lit.[30] mp 174–175 °C); ^{1}H NMR (100 MHz, $CDCl_3$) 2 H_8 2.25, 2 H_7 2.90 ($J_{7,8}$ = 7 Hz), 2 H_9 3.31 ($J_{9,8}$ = 7 Hz), seven aromatic protons 7.8–8.4, and H_{11} 8.6 ppm ($J_{11,12}$ = 10 Hz). Dehydrogenation (Table I) to the phenol proceeded in 70% yield after chromatography and sublimation.

Acknowledgment. The authors express their thanks to Dr. R. Kierstead of Hoffmann-La Roche for his support and interest in these studies and to Mr. N. Whittaker of the NIH for recording the infrared spectra.

Supplementary Material Available. Spectroscopic data (^{1}H NMR, uv, and ir) on the 12 hydroxy BP isomers (25 pages). Ordering information is given on any current masthead page.

Registry No.—**1a,** 54522-80-4; **1b,** 57652-51-4; **1c,** 54522-83-7; **1d,** 57652-52-5; **1e,** 54522-84-8; **2a,** 57652-53-6; **2b,** 57652-54-7; **2c,** 57652-55-8; **2d,** 57652-56-9; **2e,** 57652-57-0; **3a,** 57652-58-1; **3b,** 57652-59-2; **3c,** 57652-60-5; *cis*-**3d,** 57652-61-6; *trans*-**3d,** 57652-62-7; *cis*-**3e,** 57652-63-8; *trans*-**3e,** 57652-64-9; **7,** 3331-46-2; **8,**

17573-25-0; **9**, 17573-26-1; **10**, 57652-65-0; **12a**, 57652-66-1; **12b**, 57652-67-2; **12b** 6-acetate, 57652-68-3; **12c**, 57652-69-4; **12c** diacetate, 57652-70-7; **12e**, 57652-71-8; 5a,6,6a,7,8,9,10,10a-octahydrobenzo[a]pyren-4(5-*H*)-one, 57652-72-9; 4-chryseneacetic acid, 57652-73-0; 3,4-dihydrobenzo[a]anthracen-1(2*H*)-one, 57652-74-1; 1,2,3,4-tetrahydro-1-hydroxybenzo[a]anthracene-1-acetic acid ethyl ester, 57652-75-2; ethyl bromoacetate, 105-36-2; 1-benzo[a]anthraceneacetic acid, 57652-76-3; 10-acetoxy-9-bromo-7,8,9,10-tetrahydrobenzo[a]pyrene, 57652-77-4; 7,8,9,10-tetrahydrobenzo[a]pyren 9,10-epoxide, 36504-68-4; 10-hydroxy-7,8,9,10-tetrahydrobenzo[a]pyrene, 17573-24-9; 6-hydroxybenzo[a]pyrene, 33953-73-0.

References and Notes

(1) G. M. Holder is a Fogarty International Fellow on leave from the University of Sydney.
(2) P. M. Dansette is a guest worker at the NIH supported by the French CNRS.
(3) A portion of these studies was conducted by Dr. R. A. LeMahieu at Hoffmann-La Roche, Inc.
(4) Current efforts from this laboratory have attempted to establish the role of non-arene oxide pathways in the metabolism of aromatic hydrocarbons. See J. E. Tomaszewski, D. M. Jerina, and J. W. Daly, *Biochemistry*, **14**, 2024 (1975), and H. G. Selander, D. M. Jerina, and J. W. Daly, *Arch. Biochem. Biophys.*, **168**, 309 (1975).
(5) G. Guroff, J. W. Daly, D. M. Jerina, J. Renson, S. Udenfriend, and B. Witkop, *Science*, **157**, 1524 (1967).
(6) J. W. Daly, D. M. Jerina, and B. Witkop, *Experientia*, **28**, 1129 (1972).
(7) D. M. Jerina, J. W. Daly, B. Witkop, P. Zaltzman-Nirenberg, and S. Udenfriend, *J. Am. Chem. Soc.*, **90**, 6525 (1968); *Biochemistry*, **9**, 147 (1970).
(8) D. M. Jerina, H. Yagi, and J. W. Daly, *Heterocycles*, **1**, 267 (1973).
(9) For reviews see D. M. Jerina and J. W. Daly, *Science*, **185**, 573 (1974); P. Sims and P. L. Grover, *Adv. Cancer Res.*, **20**, 165 (1974).
(10) E. C. Miller and J. A. Miller in "Molecular Biology of Cancer", H. Bush, Ed., Academic Press, New York, N.Y., 1974, pp 377–402.
(11) J. Iball, *Am. J. Cancer*, **35**, 188 (1939); R. E. Kouri, R. A. Salerno, and C. E. Whitmire, *J. Natl. Cancer Inst.*, **50**, 363 (1973).
(12) Committee on the Biologic Effects of Atmospheric Pollutants, "Particulate Polycyclic Organic Matter", National Academy of Science, Washington, D.C., 1972.
(13) P. Pott, London, 1775; reprinted in *Natl. Cancer Inst., Monogr.*, **10**, 7 (1963).
(14) J. W. Cook and R. Schoental, *J. Chem. Soc.*, 170 (1948).
(15) L. F. Fieser and H. B. Hershberg, *J. Am. Chem. Soc.*, **61**, 1565 (1939).
(16) L. F. Fieser and W. S. Johnson, *J. Am. Chem. Soc.*, **62**, 575 (1940).
(17) L. F. Fieser and H. Heymann, *J. Am. Chem. Soc.*, **63**, 2333 (1941).
(18) L. F. Fieser, H. B. Hershberg, L. Long, and M. S. Newman, *J. Am. Chem. Soc.*, **59**, 475 (1937).
(19) P. Sims, *J. Chem. Soc. C*, 32 (1968).
(20) (a) J. W. Cook, R. S. Ludwiczak, and R. Schoental, *J. Chem. Soc.*, 1112 (1950); (b) G. H. Daub and W. C. Doyle, *J. Am. Chem. Soc.*, **74**, 4449 (1952).
(21) D. M. Jerina and J. R. L. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1702 (1974).
(22) G. H. Daub and W. S. Johnson, *J. Am. Chem. Soc.*, **72**, 501 (1950).
(23) To date, only the 4,5- (K region), 7,8-, 9,10-, and 11,12- (K region) arene oxides of BP have been synthesized. For pertinent synthetic procedures and references to other work see P. Dansette and D. M. Jerina, *J. Am. Chem. Soc.*, **96**, 1224 (1974); R. G. Harvey, S. H. Goh, and C. Cortez, *ibid.*, **97**, 3468 (1975), for the 4,5-oxide, ref 29 for the 7,8- and 9,10-oxides, and P. M. Dansette, O. Hernandez, D. M. Jerina, H. D. Mah, and H. Yagi, *J. Org. Chem.*, submitted for publication, for the 11,12-oxide as well as ref 8. Of the arene oxides at unsubstituted ring positions of BP, only the 1,2- and 2,3-oxides remain to be prepared.
(24) R. G. Harvey and H. Cho, *J. Chem. Soc., Chem. Commun.*, 373 (1975).
(25) D. D. Phillips and D. N. Chatterjee, *J. Am. Chem. Soc.*, **80**, 4360 (1958).
(26) Although O. Perin-Roussel, F. Perin, and P. Jacquignon, *Tetrahedron Lett.*, 1227 (1974), have suggested that the reaction of osmium tetroxide with a related hydrocarbon produces a trans dihydrodiol. Dr. J. Silverton at the NIH has established by x-ray crystallography that the structure of **12b** is indeed the expected cis isomer.
(27) D. M. Jerina, H. Selander, H. Yagi, M. C. Wells, J. F. Davey, V. Mahadevan, and D. T. Gibson, submitted.
(28) M. S. Newman and L. Lee, *J. Org. Chem.*, **39**, 1446 (1974).
(29) H. Yagi and D. M. Jerina, *J. Am. Chem. Soc.*, **97**, 3185 (1975).
(30) G. A. Kon and E. M. Roe, *J. Chem. Soc.*, 143 (1945).
(31) H. Budzikiewicz, C. Djerassi, and D. H. Williams in "Mass Spectrometry of Organic Compounds", Holden-Day, San Francisco, Calif., 1967, p 115.
(32) J. K. Selkirk, R. G. Croy, P. P. Roller, and H. V. Gelboin, *Cancer Res.*, **34**, 3474 (1974).
(33) K. D. Bartle and D. W. Jones, *Adv. Org. Chem.*, **8**, 317–423 (1972).
(34) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Elmsford, N.Y., 1969, pp 71–306.
(35) C. W. Haight and R. B. Mallion, *J. Mol. Spectrosc.*, **29**, 478 (1969).
(36) E. Cavalieri and M. Calvin, *Proc. Natl. Acad. Sci. U.S.A.*, **68**, 1251 (1971).
(37) E. Cavalieri and M. Calvin, *J. Chem. Soc., Perkin Trans. 1*, 1253 (1972).
(38) The studies on the exchange of BP in D_2SO_4 by Cavalieri and Calvin[36,37] suggest that the 3 position exchanges more rapidly than the 1 position. As these authors point out, this result is unexpected since calculations of reactivity and direct succinolyation favor C-1. Acetoxylation of 6-halo BP proceeds primarily at C-1.[20a,24] Chu in this laboratory prepared [$^2H_2$]-BP by bromination and reductive deuterolysis and found the product to be a mixture of [1,6-$^2H_2$]-BP and a minor amount (30%) of [3,6-$^2H_2$]-BP based on the ^1H NMR assignment in this study. Close proximity of signals prevents accurate integration of the spectrum. It is possible that exchange actually proceeds more rapidly at C-1 relative to C-3 and that the small differences in rate are not readily measured by ^1H NMR.
(39) Extensive chromatography on silica gel has led to the isolation of relatively pure 3-hydroxy BP as a metabolite of BP which was identified by untraviolet spectroscopy; see N. Kinoshita, B. Shears, and H. V. Gelboin, *Cancer Res.*, **33**, 1937 (1973), and references cited therein. While it is indeed clear that 3-hydroxy BP as well as 9-hydroxy BP must be major phenolic metabolites under selected incubation conditions, the nature and amounts of other phenols which were lost by decomposition and separation on chromatography is unknown. For further discussion see ref 41 and 46.
(40) D. W. Nebert and H. V. Gelboin, *J. Biol. Chem.*, **243**, 6242 (1968).
(41) G. Holder, H. Yagi, W. Levin, A. Y. H. Lu, and D. M. Jerina, *Biochem. Biophys. Res. Commun.*, **65**, 3163 (1975). Relative fluorescence data in this study differ from the data in Table V since fluorescence in the metabolism study was determined under conditions which are optimal for measurement of the metabolism of BP.[40]
(42) M. S. Newman and D. R. Olson, *J. Am. Chem. Soc.*, **96**, 6207 (1974).
(43) See D. M. Jerina, B. Witkop, C. L. McIntosh, and O. L. Chapman, *J. Am. Chem. Soc.*, **96**, 5578 (1974); R. H. Thomson, *Q. Rev., Chem. Soc.*, **10**, 27 (1956); as well as references cited therein.
(44) A. Dipple, L. S. Levy, and T. Iype, *Cancer Res.*, **35**, 6521 (1975).
(45) Personal communication from Professor M. S. Newman.
(46) G. Holder, H. Yagi, P. Dansette, D. M. Jerina, W. Levin, A. Y. H. Lu, and A. H. Conney, *Proc. Natl. Acad. Sci. U.S.A.*, **71**, 4356 (1974).
(47) Unpublished studies with Dr. D. T. Gibson at University of Texas. See D. T. Gibson, V. Mahadevan, D. M. Jerina, H. Yagi, and H. J. C. Yeh, *Science*, **189**, 295 (1975).
(48) P. Y. Bruice, T. C. Bruice, P. M. Dansette, H. G. Selander, H. Yagi, and D. M. Jerina, *J. Am. Chem. Soc.*, in press.
(49) These studies are being conducted in collaboration with the Department of Biochemistry and Drug Metabolism of Hoffman-La Roche, Inc., headed by Dr. A. H. Conney.
(50) A. W. Wood, R. L. Goode, R. L. Chang, W. Levin, A. H. Conney, H. Yagi, P. M. Dansette, and D. M. Jerina, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 3176 (1975).
(51) S. H. Blobstein, I. B. Weinstein, P. Dansette, H. Yagi, and D. M. Jerina, *Cancer Res.*, in press.
(52) W. Lijinsky and L. Zechmeister, *J. Am. Chem. Soc.*, **75**, 5495 (1953).
(53) J. F. Waterfall and P. Sims, *Biochem. J.*, **128**, 265 (1972).
(54) W. Levin, A. W. Wood, H. Yagi, P. M. Dansette, D. M. Jerina, and A. H. Conney, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 245 (1976).

The Ester Enolate Claisen Rearrangement. Construction of the Prostanoid Skeleton[1a]

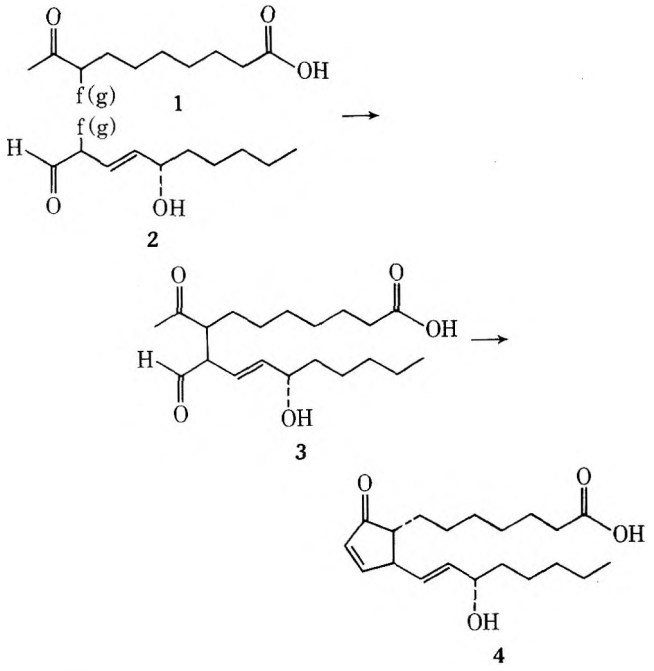
Robert E. Ireland,* Richard H. Mueller, and Alvin K. Willard[1b]

Gates and Crellin Laboratories, California Institute of Technology, Pasadena, California 91125

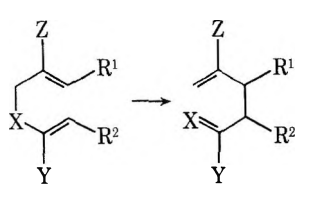
Received November 17, 1975

A convergent synthesis of the prostaglandin skeleton is described. The ester enolate modification of the aliphatic Claisen rearrangement is used to form the key C_8–C_{12} bond. Rearrangement of ester **18** provides the lactone **29** which is converted to the prostanoid **30**. Similarly, the lactone **52**, a potential intermediate in the synthesis of 12-methyl PGA_1, is obtained from ester **51**. Preparation of ester **51** features Claisen rearrangement of ester **38**, which leads to the dienoate **41** after desulfenylation. Model studies of reduction of γ,δ-epoxy-α,β-unsaturated esters to δ-hydroxy-β,γ-unsaturated esters are described. This reduction is accomplished with lithium in ammonia at −78 °C for conversion of epoxy ester **50** to ester **51**.

No family of molecules since the steroids has attracted the interest and effort of synthetic chemists as strongly as have the prostaglandins. Recent efforts have involved the search for flexible synthetic schemes which will allow preparation of a variety of analogues. We report here a synthetic approach which incorporates connection of a "top half" and a "bottom half" of the prostanoid skeleton in a key carbon–carbon bond forming reaction.

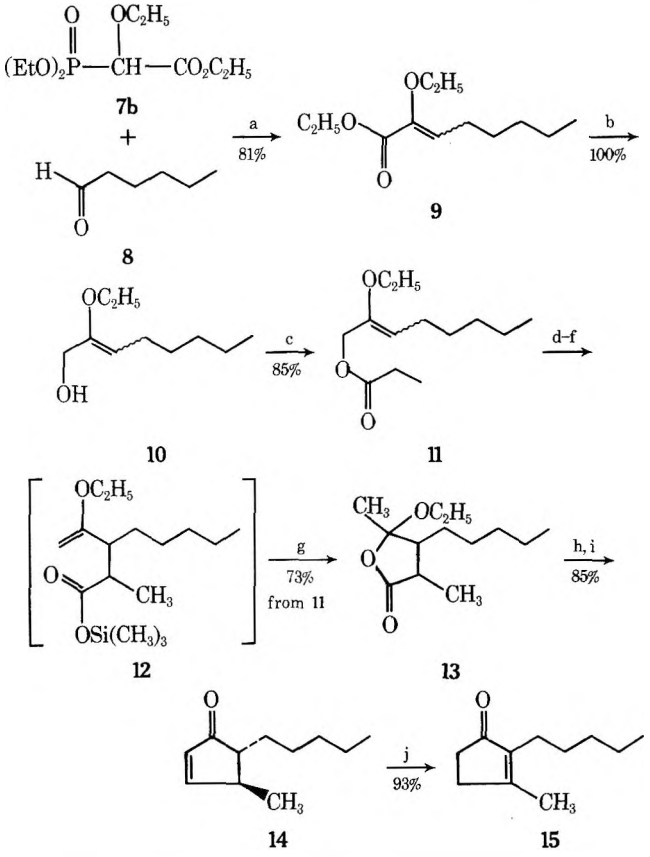


An intriguing possibility for this approach was formation of the carbon–carbon bond with an aliphatic Claisen rearrangement. This reaction (**5** → **6**) would not only provide an efficient means for formation of the desired bond but also would result in the proper number of suitably functionalized carbon atoms for subsequent formation of the cyclopentanone ring system.



The requirements that only one equivalent of each half of the molecule be employed in construction of the precursor **5** and that conditions of the reaction be compatible with a variety of functional groups prompted development of the ester enolate Claisen rearrangement.[2,3]

Scheme I. Synthesis of Dihydrojasmone (15)[a]



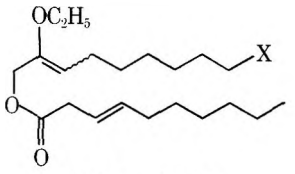
[a] a, NaH, THF; b, $LiAlH_4$, ether; c, propanoic anhydride, pyridine; d, LICA, THF, −78°C; e, TMSCl; f, 65°C, 7 h; g, CH_3SO_3H, EtOH; h, DIBAH, toluene, −78°C; i, NaOH, aqueous CH_3OH, 25°C; j, KOH, aqueous CH_3OH, reflux.

To demonstrate the viability of this approach, synthesis of dihydrojasmone (**15**), a virtual touchstone of cyclopentenone syntheses, was undertaken. The successful route is described in Scheme I.[2]

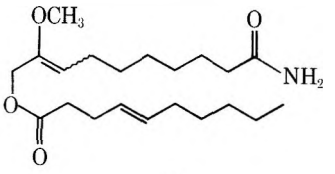
Phosphonates such as **7b**, introduced by Grell and Machleidt,[4] are a useful source of functionalized allylic alcohols such as **10**. When the ester **11** was subjected to enolization with lithium isopropylcyclohexylamide (LICA) and the enolate was trapped with trimethylchlorosilane (TMSCl), rearrangement[3] occurred without incident to give silyl ester **12**. The enol ether functionality not only serves as an ultimate source of a methyl ketone for aldol condensation but also is a convenient handle for reduction

of the silyl ester carbon to the aldehyde oxidation state. This reduction is accomplished by conversion of the silyl ester **12** to the lactone **13** with a trace of acid in ethanol followed by reaction with diisobutylaluminum hydride (DIBAH).[5] Finally, aldol condensation[6] and double bond migration[7] complete this synthesis of dihydrojasmone (**15**).[8]

This same approach was then used for the construction of the prostaglandin skeleton, with initial efforts focused on preparation and transformations of esters **16–18**.



16, X = C≡N
17, X = $CONH_2$



18

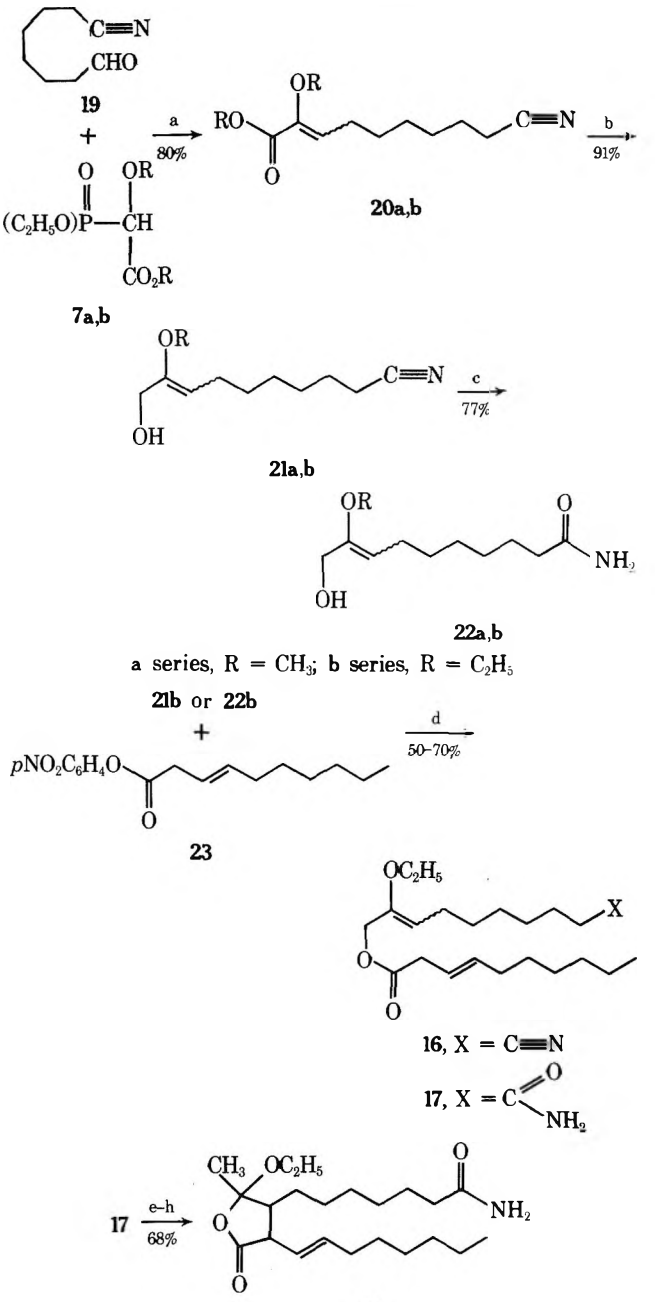
Use of readily available 7-cyanoheptanal (**19**)[9] as a substrate in the Wittig reaction produced equivalent amounts of the geometrical isomers of ester **20** (Scheme II). The methoxy series was adopted in later stages of these studies because it offered the advantage of simpler interpretation of NMR spectra of intermediates in the synthesis. Selective reduction of the cyano esters **20** with lithium borohydride[10] in tetrahydrofuran (THF) provided the desired alcohols **21**. An alternate masked carboxylic acid function, the primary amide **22**, was available by hydration of the nitrile in the presence of the enol ether with basic hydrogen peroxide. Reaction of the alcohol **21** or **22** with the *p*-nitrophenyl ester[11] of the acid in triethylamine was the most satisfactory procedure for preparation of esters fo these γ,δ-unsaturated acids.

With the esters **16** and **17** in hand, their further conversion to cyclopentenone derivatives was investigated. Enolization, silylation, and Claisen rearrangement of cyano ester **16** resulted in a mixture of products containing C-silylated nitrile. The silylation of aliphatic nitriles has now been studied and formation of C-silylated products, even with 1 equiv of base and trialkylchlorosilane, has been demonstrated.[12] Because of this problem, use of the nitrile as a masked carboxylic acid was abandoned in favor of the primary amide. Rearrangement of amide ester **17** proceeded in good yield to provide a intermediate silyl ester which was directly transformed to the lactone **24** with a trace of methanesulfonic acid in ethanol.

Attempted reduction of amide lactone **24** with 1 equiv of diisobutylaluminum hydride[5] resulted in complete recovery of the starting lactone; apparently the reagent is consumed by reaction with the acidic amide proton. The reduction was accomplished with 2 equiv of hydride reagent, but treatment of the reduction product with aqueous base to cause aldol condensation[6] produced neither cyclopentenone nor β-ketol. A possible reason for this is that the acidity of the β,γ-unsaturated aldehyde was resulting in extensive conjugation of the double bond.

If this were indeed the case, isolation of the double bond was a possible solution. This suggested preparation of ester **18** (Scheme III). Moving the double bond to a position where it would not interfere with the aldol condensation also simplified ester formation; now, the acid chloride **25** served well for preparation of the ester. Rearrangement of ester **18**, using lithium disopropylamide (LDA) and *tert*-butyldimethylchlorosilane (TBSCl),[3,13] led to the silyl ester **26** which, as above, could be converted with acid into the lactone **27**. Reduction with 2 equiv of DIBAH[5] and aldol condensation[6] with aqueous methanolic sodium hydroxide

Scheme II. Preparation and Transformations of Esters 16 and 17[a]



a series, R = CH_3; b series, R = C_2H_5

16, X = C≡N
17, X = $C(=O)NH_2$

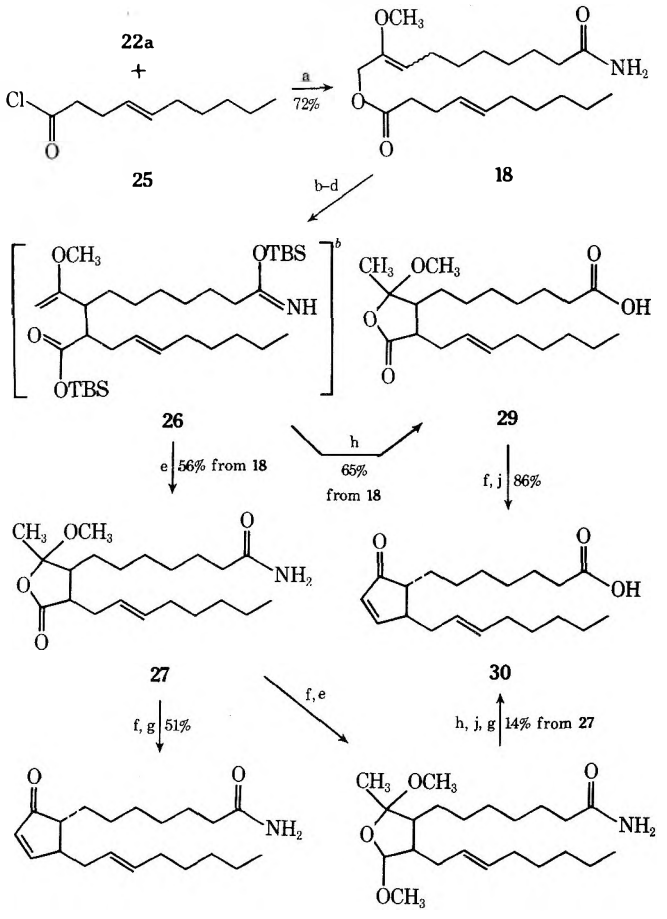
24

[a] a, NaH, THF; b, $LiBH_4$, THF; c, H_2O_2, NaOH, aqueous C_2H_5OH; d, Et_3N, 25°C; e, LICA, THF, −78°C; f, TMSCl; g, 67°C, 3.5 h; h, CH_3SO_3H, C_2H_5OH.

provided the cyclopentenone **28**. This verified that the trouble with these reactions on lactone **24** was the position of the double bond.

As the lactone **27** or the cyclopentenone **28**, the molecule could not be subjected to reaction conditions sufficiently vigorous to effect hydrolysis of the primary amide. This hydrolysis was attempted at the intermediate stage. Lactone **27** was reduced as before and the reduction product was protected as the acetal **31**. Saponification of the primary amide, acidic hydrolysis of the acetals, and finally aldol condensation in aqueous alcoholic base gave the cyclopentenone acid **30** in low yield. An alternate point in the synthetic scheme where saponification was possible was immediately after Claisen rearrangement. Basic hydrolysis of the silyl ester **26** followed by neutralization gave the lactone acid **29** in good yield. Reduction, again with 2 equiv of

Scheme III. Synthesis of Prostanoic Acid Derivatives 28 and 30[a]

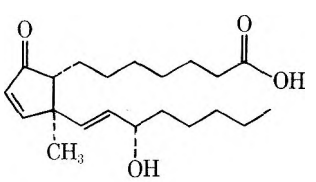


[a] a, Et_3N, CH_2Cl_2, 25°C; b, LDA, THF, −78°C; c, TBSCl; d, 67°C, 3 h; e, CH_3SO_3H, CH_3OH; f, DIBAH, Et_2O, −78°C; g, aqueous NaOH, CH_3OH, 25°C; h, aqueous NaOH, CH_3OH, reflux 16 h, then neutralize; i, HOAc, piperidine, C_6H_6; j, aqueous HCl. [b] TBS = *tert*-butyldimethylsilyl.

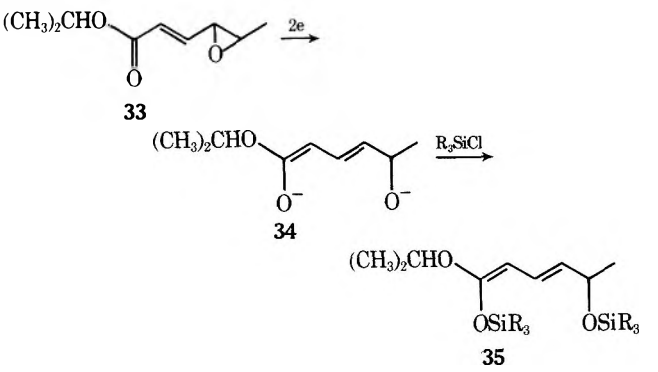
DIBAH,[6] and aldol condensation using piperidinium acetate[14] in refluxing benzene provided the cyclopentenone acid **30** in more satisfactory overall yield.

Having demonstrated that the prostaglandin skeleton could be constructed in this manner, we refocused attention on the problematic double bond in the lower side chain. An alternate solution would be to block apparent conjugation of theouble bond during the aldol condensation; a methyl group should serve this purpose well. The 12-methyl was also attractive because it should block in vivo deactivation of the PGA via migration of the enone double bond to produce the less active PGB structure.

Our synthetic approach to 12-methyl PGA_1 (**32**) would also give us the opportunity to investigate a sequence in which generation of the allylic alcohol functionality in the lower side chain is coupled to enolate formation necessary for the Claisen rearrangement. Two electron reduction of α,β-unsaturated γ,δ-epoxy esters such as **33** should give the enolate **34**. Silylation would provide the silyl ketene acetal **35**. If the alcohol portion of this molecule were an allylic alcohol, this process could be followed by Claisen rearrangement.



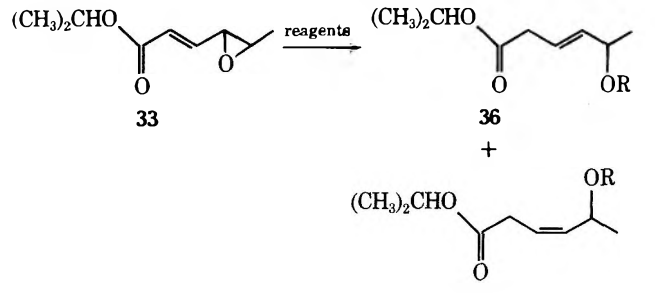
32



Epoxy esters such as **33** are readily available by peracid oxidation[15] of the corresponding dienoic esters. Several reduction methods were examined and are outlined in Table I.

Initial efforts were directed toward finding a system in which both reduction and silylation were possible in the same reaction mixture so that the reduction and Claisen rearrangement could be performed in a single step. A promising system for this transformation was sodium in THF–hexamethylphosphoramide (HMPA).[16,17] During initial attempts, reductions employing these conditions produced a myriad of products but little or none of the desired reduction product. Only under very specific conditions, 2–3 equiv of the Na–HMPA–THF solution added in one portion to a rapidly stirred solution of ester **33** in HMPA–THF at −78 °C followed by addition of TBSCl, could even low yields of the reduction products be obtained. The intermediate silyl ketene acetal **35**, which is formed under these conditions, it readily hydrolyzed to the siloxy esters **36b** and **37b** for analysis. Quenching the reaction mixture with solid ammonium chloride gave nearly identical yield of the alcohols **36a** and **37a** and demonstrated that the problems were arising during reduction, not silylation. A second distinct disadvantage of this method of reduction was that it produced the trans isomer **36b** and the cis isomer **37b** in nearly equal proportions (VPC analysis).

Table I. Reduction of Epoxy Ester 33



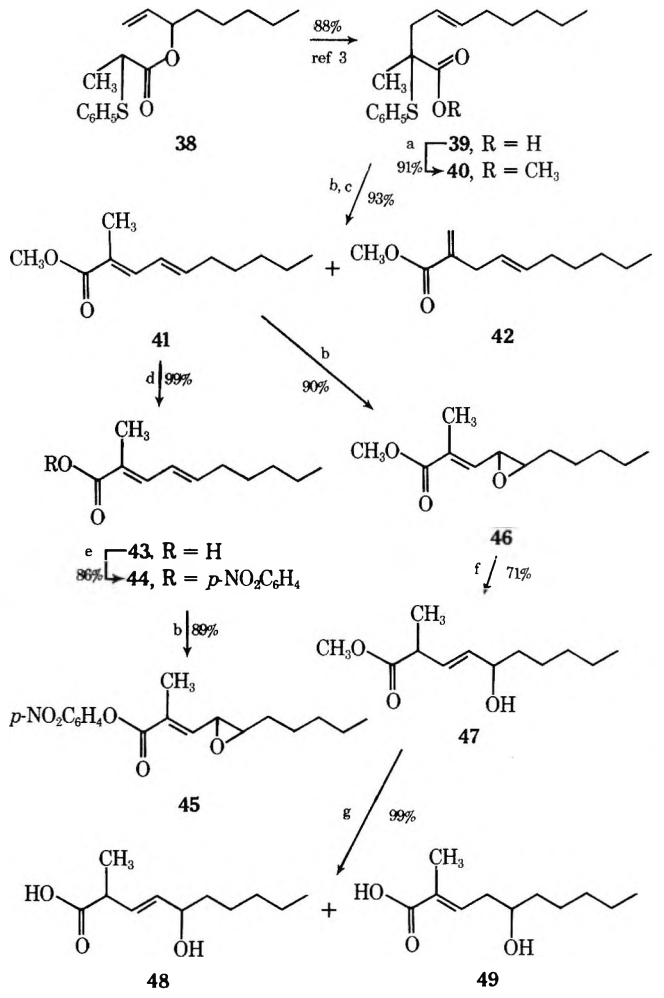
a series, R = H; b series, R = TBs

37

Entry	Reagents	R	Yield, %[a]	36/37[b]
1	1. 2 equiv Na, HMPA, THF, −78 °C 2. TBSCl 3. HOAc, H_2O	TBS	37	60/40
2	1. 3 equiv Na, HMPA, THF, −78 °C 2. NH_4Cl	H	42	
3	1. Zn, TBSCl, HMPA, THF, 67 °C		0	
4	1. 3 equiv Li, NH_3, THF, −78 °C 2. NH_4Cl	H	79	89/11

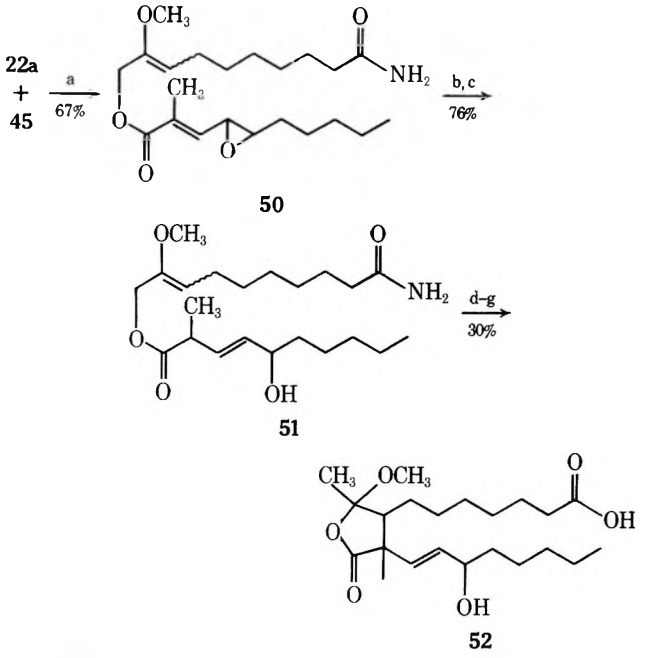
[a] After isolation and chromatography. [b] By VPC analysis.

Scheme IV. Preparation of the Acid Fragment for Ester 50[a]



[a] a, NaH, CH_3I, THF; b, MCPBA, $CHCl_3$; c, 60°C, 2 h; d, KOH, CH_3OH; e, *p*-nitrophenyl trifluoroacetate, Et_3N; f, 3 equiv Li, NH_3, THF, −78°C; g, LiOH, aqueous CH_3OH.

Scheme V. Preparation and Transformations of Ester 50[a]



[a] a, Et_3N, THF, 50°C, 57 h; b, 3 equiv Li, NH_3, THF, −78°C; c, NH_4Cl; d, LDA, THF, −78°C; e, TBSCl, HMPA; f, 67°C, 3 h; g, NaOH, aqueous CH_3OH, then neutralize.

Reduction with a mixture of zinc and TBSCl in HMPA–THF had proven useful in the preparation of silyl ketene acetals from α-bromo esters,[3] but this method failed to reduce the epoxy ester **33**. Finally a high yield of alcohols **36a** and **37a** was realized by reduction with lithium in ammonia–THF. The best results were obtained when the reduction was performed with 3 equiv of lithium at −78 °C for 1 min, and then the reaction mixture was quenched with solid ammonium chloride. In this case an 89:11 ratio of **36a** and **37a** was obtained (VPC analysis). These isomers were easily separated by silica gel chromatography after conversion[18] to the corresponding silyl ethers **36b** and **37b**.

The stereochemical assignment for these two isomers rests on infrared spectral data.[19] The major isomer exhibits a medium band at 970 cm^{-1}, indicative of a trans-disubstituted ethylene. No such band is present in the ir spectrum of the minor isomer.

Since the one-step process was effectively ruled out by the necessity of performing the reduction in ammonia, enolization of the reduction products had to be examined. Enolization of both the hydroxy esters **36a** and **37a** and the siloxy esters **36b** and **37b** with LDA followed by trapping with TBSCl gave the silyl ketene acetal **35**. Competing elimination was not a problem.

Efforts then turned to synthesis of the epoxy ester **50** or its reduced derivative **51**. The acid fragment for these esters was prepared as described in Scheme IV. The α-(phenylthio) ester **40** was readily available via Claisen rearrangement of allylic ester **38**[3] followed by esterification. Desulfenylation[20] by mild heating of the sulfoxides obtained by oxidation with MCPBA produced a mixture of unsaturated esters **41** and **42** in the ratio 78:22. The mixture of diastereomeric sulfoxides obtained in the oxidation was separated by silica gel chromatography, and the sulfoxides were independently pyrolyzed. The more mobile isomer gave the olefins in a 68:32 ratio (**41**:**42**) and the less mobile isomer in 90:10 ratio.

This synthesis of ester **41** also serves to demonstrate the possibility of employing the Claisen rearrangement for formation of a carbon–carbon double bond. The sulfur functionality serves to mask this double bond until a convenient stage is reached in the synthesis.

Oxidation of ester **41** with MCPBA[15] produced the epoxy ester **46** in high yield. The presence of only one geometrical isomer of this epoxy ester is clearly demonstrated by NMR analysis. This indicates that ester **41** is cleanly the *E,E* isomer. Attempts to saponify the epoxy ester **46** in order to obtain the corresponding acid were not encouraging. This sensitive epoxy acid was obtained in varying states of purity and attempted purification led to extensive decomposition.

The alternative approach of using the acid portion in already reduced form was also investigated. Epoxy ester **46** was reduced under the same conditions described above and gave a mixture of two separable components (93:7). The major component was assigned the trans stereochemistry **47** based on results obtained with ester **33**. The minor isomer was tentatively assigned cis stereochemistry. Saponification of ester **47** gave a mixture of acids containing 70% of the unsaturated acid **48** and 30% of the conjugated isomer **49**.

Since the difficulty in both of these approaches arose during attempted saponification of the methyl ester in order to prepare some activated ester derivative suitable for esterification, saponification of the ester at an earlier, less sensitive stage was desirable.

Hydrolysis of the dienoic ester **41** proceeded without difficulty. The *p*-nitrophenyl ester **44**[11] of the resulting acid

43 was sufficiently stable to permit partial purification by rapid chromatography on silica gel. This derivative was also readily oxidized with MCPBA[15] to provide the epoxy ester **45.** When stirred with the alcohol **22a** in THF–triethylamine, epoxy ester **45** was converted to the target ester **50** through ester exchange (Scheme V).

Reduction of ester **50** to hydroxy ester **51** proceeded normally. The minor isomer (cis?) found in the reduction of ester **46** was not detected but was probably present in the mixture.

Initial attempts to carry this ester on to 12-methyl PGA_1 (**32**) met with serious difficulties. Rearrangement and basic hydrolysis gave the lactone **52** in only 30% yield. The unsaturated acid **43** was a major side product. Reduction of lactone **52** with 3 equiv of DIBAH proceeded smoothly but attempted aldol condensation did not produce cyclopentenone under mild (piperidinium acetate[14]) or harsh (aqueous methanolic sodium hydroxide[6]) conditions. In view of these difficulties and in face of a report that 12-methyl PGA_2 was inactive,[21] the synthesis was not pursued further.

Although difficulties arose in late stages of some of the syntheses described here, the potential of the ester enolate Claisen rearrangement in convergent synthesis of complex organic molecules has been demonstrated. Particularly, the compatibility of this reaction with a wide variety of functionality should make it a useful addition to the synthetic chemist's armory of reactions.

Experimental Section[22]

Methyl Diethoxyphosphinylmethoxyacetate (7a). The procedure of Grell and Machleidt[4] was followed to prepare the phosphonate **7a** from methyl dimethoxyacetate: bp 110 °C (0.3 mm); NMR ($CDCl_3$) δ 1.33 (t, 6 H, J = 7 Hz, CH_3CH_2O–), 3.52 (s, 3 H, ether CH_3O–), 3.83 (s, 3 H, ester CH_3O–), 4.22 (m, 5 H, $CHCO_2$– and CH_3CH_2O); ir (neat) 1750 (C=O), 1260, 1120, 1015, 970 cm^{-1}.

Anal. Calcd for $C_8H_{17}O_6P$: C, 40.00; H, 7.13. Found: C, 40.12; H, 7.08.

Ethyl 2-Ethoxy-2-octenoate (9). A stirred suspension of 2.78 g (0.116 mol) of sodium hydride (mineral oil free) in dry THF was treated during 30 min with the dropwise addition of 30.0 g (0.112 mol) of phosphonate **7b.** Following the addition, the reaction mixture was stirred for an additional 30 min and then cooled to 0 °C. Hexanal (11.2 g, 0.112 mol) was added dropwise to this solution over a 30-min period. Near the end of the addition, a gummy precipitate formed. The reaction mixture was stirred for an additional 30 min at 25 °C and then treated with 50 ml of water. Benzene extraction,[23] including an aqueous ammonium chloride wash, followed by distillation of the residue afforded 19.5 g (81%) of a mixture (1:3) of unsaturated esters **9:** bp 60–63 °C (0.08 mm); NMR ($CDCl_3$) δ 0.87 (br t, 3 H, $-CH_2CH_2CH_3$), 1.33 (t, 6 H, J = 7 Hz, $-OCH_2CH_3$), 3.73 (br t, 2 H, J = 7 Hz, $=COCH_2CH_3$), 4.24 and 4.21 (q's, 2 H, J = 7 Hz, $CO_2CH_2CH_3$), 6.24 and 5.26 (t's 1 H, ratio 1:3, J = 7 and 7.5 Hz, vinylic H's); ir ($CHCl_3$) 1725 (C=O), 1640 (C=C), 1380, 1160, 1040 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.34; H, 10.38.

2-Ethoxy-2-octenyl Propanoate (11). To a suspension of 2.0 g (53 mmol) of lithium aluminum hydride in 120 ml of dry ether was added 10.0 g (47 mmol) of the esters **9** over a 30-min period. Following the addition, the reaction mixture was stirred for an additional 15 min before excess hydride was destroyed by addition of ethyl acetate. Work-up according to the procedure of Fieser[24] afforded 7.75 g of crude alcohols **10** which were used without further purification. This material was treated with 15 g of propanoic anhydride in 20 ml of dry pyridine at 25 °C for 20 h. Distillation of the reaction mixture gave 8.9 g (85%) of the ester **11:** bp 72–85 °C (0.1 mm); NMR ($CDCl_3$) δ 2.33 (q, 2 H, J = 7 Hz, $CH_3CH_2CO_2$–), 3.65 (q, 2 H, J = 7 Hz, CH_3CH_2O–), 4.57 and 4.62 (s's, 2 H, $-OCH_2C$=C), 4.64 and 4.86 (t's, 1 H, J = 7 Hz, vinylic H's); ir (neat) 1725 (C=O), 1640 cm^{-1} (C=C).

Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.58; H, 10.50.

5-Ethoxy-3,5-dimethyl-4-pentyloxacyclopentan-2-one (13). A solution of 7.1 mmol of LICA in 20 ml of dry THF was cooled to −78 °C. To this rapidly stirred solution was added 1.50 g (6.6 mmol) of ester **11** over 3 min. Following the addition, 0.850 ml (6.7 mmol) of TMSCl was added in one portion and the reaction mixture was stirred at −78 °C for an additional 3 min. The cooling bath was removed and the reaction mixture was allowed to warm to 25 °C. The mixture was then stirred at reflux for 7 h to effect rearrangement. After cooling to 25 °C the reaction mixture was treated with 2 ml of ethanol and sufficient methanesulfonic acid to obtain pH 1–2. Extraction[23] with petroleum ether afforded 1.6 g of a yellow oil which was evaporatively distilled at 80 °C (0.2 mm) to give 1.1 g (73%) of the lactone **13.** A portion of this material (400 mg) was purified further by medium-pressure chromatography[22] on 2.5 × 50 cm of silica gel with 50% dichloromethane–benzene. Elution with 550 ml of this solvent system gave the analytical sample: NMR ($CDCl_3$) δ 1.10 (t, 3 H, J = 7 Hz, CH_3), 1.40 (d, 3 H, J = 8 Hz, CH_3CH–), 3.63 (q, 2 H, J = 7 Hz, $-CH_2O$–); ir (neat) 1792 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.46; H, 10.49.

4-Methyl-5-pentyl-2-cyclopentenone (14). A solution of 450 mg (2.0 mmol) of lactone **13** in 10 ml of dry toluene was cooled to −78 °C. To this stirred solution was added 2.4 ml (2.3 mmol) of DIBAH in benzene over 5 min. The reaction mixture was stirred for 30 min at −78 °C and then treated with 0.5 ml of methanol and allowed to warm to 25 °C. Benzene extraction[23] gave 440 mg of a colorless oil which was dissolved in 10 ml of methanol and treated with 10 ml of 5% aqueous sodium hydroxide solution. This mixture was stirred at 25 °C for 20 min after which benzene extraction[23] and evaporative distillation of the residue at 80 °C (1 mm) gave 280 mg (85%) of colorless cyclopentenone **14:** NMR ($CDCl_3$) δ 0.90 (br t, 3 H, J = 7 Hz, CH_3CH_2–), 1.22 (d, 3 H, J = 7 Hz, CH_3CH–), 6.14 (dd, 1 H, J = 6 and 2 Hz, =CHC=O), 7.55 (dd, 1 H, J = 6 and 2.5 Hz, CH=C–C=C); ir (neat) 1710 (C=O), 1580 cm^{-1} (C=C).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.49; H, 10.90.

3-Methyl-2-pentyl-2-cyclopenten-1-one (15). A mixture of 118 mg (0.711 mmol) of cyclopentenone **14** and 200 mg of potassium hydroxide in 10 ml of water and 5 ml of methanol was stirred at reflux for 40 min. Extraction[23] with dichloromethane and evaporative distillation of the residue at 80 °C (1 mmol) gave 110 mg (93%) of colorless dihydrojasmone (**15**): NMR δ 0.88 (br t, 3 H, J = 7 Hz, CH_3), 1.2 (m, 6 H), 2.05 (s, 3 H, $C=CCH_3$); ir (neat) 1700 (C=O), 1650 cm^{-1} (C=C).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.55; H, 10.95.

Methyl 9-Cyano-2-methoxynon-2-enoate (20a). To a mechanically stirred suspension of 2.64 g (0.11 mol) of sodium hydride (mineral oil free) in 150 ml of dry THF was added 24.0 g (0.10 mol) of phosphonate **7a** over 40 min. The mixture was stirred for an additional 1 h and then cooled to 0 °C. During 30 min, the reaction mixture was treated with 13.9 g (0.1 mol) of 7-cyanoheptanal (**19**) while vigorous stirring was maintained. Toward the end of the addition a gummy precipitate formed. The reaction mixture was allowed to warm gradually to 25 °C over 1 h. After cautious addition of 80 ml of water, ether extraction[23] gave a slightly orange liquid which was subjected to short path distillation to give 17.9 g (80%) of the cyano esters **20a,** bp 120–128 °C (0.015 mm). NMR analysis indicated that this was approximately an equal mixture of double bond isomers. A portion of this material (378 mg) was purified further by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with 30% ether–petroleum ether at a flow rate of 1 ml/min. Elution with 150 ml gave 174 mg of the Z isomer. An analytical sample was prepared by evaporative distillation at 110 °C (0.001 mm); NMR ($CDCl_3$) δ 3.67 (s, 3 H, ether CH_3O–), 3.78 (s, 3 H, ester CH_3O–), 6.23 (t, 1 H, J = 7 Hz, vinylic H); ir ($CHCl_3$) 2250 (C≡N), 1720 (C=O), 1651 (C=C), 1270, 1120, 990 cm^{-1}.

Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.09; H, 8.43; N, 6.26.

Further elution with 10 ml of the same solvent system gave 68 mg of a mixture of the E and Z isomers. Continued elution with 80 ml of this solvent system gave 123 mg of the E isomer. An analytical sample was prepared by evaporative distillation at 110 °C (0.001 mm): NMR ($CDCl_3$) δ 3.58 (s, 3 H, ether CH_3O–), 3.78 (s, 3 H, ester CH_3O–), 5,20 (t, 1 H, J = 7 Hz, vinylic H); ir ($CHCl_3$) 2250 (C≡N), 1725 (C=O), 1640 (C=C), 1376, 1170, 1130 cm^{-1}.

Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.00; H, 8.48; N, 6.19.

10-Hydroxy-9-methoxydec-8-enenitrile (21a). To a vigorously stirred suspension of 685 mg (18 mmol) of sodium borohydride and 1.56 g (18 mmol) of anhydrous lithium bromide[10] in 20 ml of

dry THF was added 2.0 g (8.89 mmol) of the cyano ester **20a.** This mixture was stirred at 25 °C for 52 h. At the end of this period, 20 ml of water was added and the reaction mixture was stirred for 40 min. After addition of another 20-ml portion of water, ether extraction[23] gave 2.1 g of a colorless oil which still contained some ester (ir analysis). This material was subjected again to the same treatment and gave 1.59 g (91%) of the crude cyano alcohol **21a** as a colorless liquid. A portion of this material was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with 80% ether–petroleum ether at a flow rate of 1 ml/min followed by evaporative distillation at 100 °C (0.001 mm) and gave the analytical sample: NMR ($CDCl_3$) δ 3.54 and 3.65 (s, 3 H total, CH_3O), 4.13 (br s, 2 H, $-CH_2O-$), 4.6 (m, 1 H, vinylic H's); ir ($CHCl_3$) 3600 and 3470 (OH), 2250 (C≡N) 1670 (C=C), 1465, 1140, 1110, 1055, 1015 cm^{-1}.

Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; h, 9.71; N, 7.10. Found: C, 66.87; H, 9.59; N, 7.01.

10-Hydroxy-9-methoxydec-8-enamide (22a). A solution of 1.97 g (10.0 mmol) of the crude cyano alcohol **21a** in 50 ml of ethanol was added in one portion to an ice-cooled, stirred mixture of 90 ml of 10% aqueous hydrogen peroxide and 3 ml of 40% aqueous sodium hydroxide solution. After 10 min the ice bath was removed and the reaction mixture was stirred at room temperature for 2 h. Dichloromethane extraction[23] gave 1.65 g (77%) of a white solid. A portion of this material (130 mg) was purified further by medium-pressure chromatography[22] on a 1.25 × 50 cm of silica gel with 50% acetone–ether at a flow rate of 1 ml/min. Elution with 265 ml of this solvent system gave 101 mg of a white solid. One recrystallization from ehter containing a small amount of dichloromethane gave the analytical sample as a mixture of double bond isomers: mp 51–58 °C; NMR ($CDCl_3$) δ 3.53 and 3.65 (s, 3 H total, CH_3O-), 4.09 (m, 2 H, CH_2O-), 4.8 (m, 1 H, vinylic H), 6.0 (br s, 2 H, NH_2); ir ($CHCl_3$) 3700–3100 (several bands, OH, NH_2), 1675 (C=O), 1590, 1465, 1390, 1010 cm^{-1}.

Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.41; H, 9.88; N, 6.46.

Ethyl 9-Cyano-2-ethoxynon-2-enoate (20b). In a manner similar to that described for the methyl derivative **20a,** phosphonate **7b** and cyano aldehyde **19** were converted into a mixture of esters **20b** (84%): bp 120–136 °C (0.1 mm); NMR ($CHCl_3$) δ 2.33 (m, 4 H, $=CCH_2-$ and $-CH_2C\equiv N$), 4.25, 4.21, and 3.75 (q's, 4 H total, J = 7 Hz, CH_3CH_2O-), 6.21 and 5.22 t's, 1 H total, J = 7 Hz, vinylic H); ir (neat) 2250 (C≡N), 1725 (C=O), 1640 cm^{-1} (C=C).

Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.39; H, 9.13; N, 5.57.

9-Ethoxy-10-hydroxydec-8-enenitrile (21b). In a manner similar to that described for cyano alcohol **21a,** the mixture of esters **20b** was reduced with lithium borohydride[10] to give the cyano alcohol **21b** (100%): NMR ($CDCl_3$) δ 3.66 (q, 2 H, J = 7 Hz, CH_3CH_2O-), 4.12 (br s, 2 H, $=CCH_2O-$), 4.4 (m, 1 H, vinylic H); ir ($CHCl_3$) 3600 and 3470 (OH), 2240 (C≡N), 1665 (C=C), 1385, 1105, 1050, 1010 cm^{-1}.

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.2;; H 10.09; N, 6.60.

9-Ethoxy-10-hydroxydec-8-enamide (22b). In a manner similar to that described for hydroxy amide **22a,** the cyano alcohol **21b** was converted into the hydroxy amide **22b** (72%): NMR ($CDCl_3$) δ 3.15 (br s, 1 H, OH), 3.68 (q, 2 H, J = 7 Hz, CH_3CH_2O-), 4.13 and 4.10 (s, 2 H total, $-CH_2OH$), 4.47 and 4.76 (t, 1 H total, J = 7.5 and 8 Hz, vinylic H), 6.2 (br s, 2 H, NH_2); ir ($CHCl_3$), 3700–3150 (several bands, OH, NH_2), 1675 (C=O, C=C), 1590 cm^{-1}.

Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.79; H, 10.17; N, 6.14.

9-Cyano-2-ethoxy-2-nonenyl (*E*)-3-Decenoate (16). To a solution of 1.40 g (6.0 mmol) of *p*-nitrophenyl trifluoroacetate[11] in 3 ml of dry pyridine was added 1.0 g of (*E*)-3-decenoic acid.[25] This mixture was stirred for 2 h at 25 °C. Pentane extraction,[23] including an acid wash and a base wash, gave 1.37 g (80%) of *p*-nitrophenyl (*E*)-3-decenoate (**23**) which was not purified further: NMR ($CDCl_3$) δ 2.07 (m, 2 H, $=CCH_2$), 3.30 (d, 2 H, J = 5 Hz, $=CCH_2CO_2-$), 5.65 (m, 2 H, CH=CH), 7.25 (d, 2 H, J = 8 Hz, aromatic H's), 8.25 (d, 2 H, J = 8 Hz, aromatic H's); ir (neat) 1765 (C=O), 1620, 1595, 1530, 1495, 1350, 1115 cm^{-1}.

This crude *p*-nitrophenyl ester **23** was dissolved in 3 ml of dry triethylamine and was treated with 1.3 g (6.1 mmol) of the cyano alcohol **21b.** This mixture was stirred at 25 °C for 16 h. Pentane extraction,[23] including a base wash, gave 1.6 g of an oil which was filtered through 7 g of silica gel with benzene to give 1.14 g (50%) of cyano ester **16** as a colorless oil: NMR ($CDCl_3$) δ 2.96 (br d, 2 H, J = 4 Hz, $-CH_2CO_2-$), 3.63 (q, 2 H, J = 7 Hz, CH_3CH_2O-), 4.48 (s, and t, 3 H, J = 7 Hz, $-OCH_2C=CH-$), 5.50 (m, 2 H, CH=CH); ir (neat) 2250 (C≡N), 1737 (C=O), 1668 cm^{-1} (C=C).

Anal. Calcd for $C_{22}H_{37}NO_3$: C, 72.69; H, 10.26; N, 3.85. Found: C, 72.69; H, 10.27; N, 3.78.

9-Carbamoyl-2-ethoxy-2-nonenyl (*E*)-3-decenoate (17). The *p*-nitrophenyl ester **23** (4.8 mmol) was added to 1.0 g (4.4 mmol) of the hydroxy amide **22b** in 2 ml of dry triethylamine. This mixture was stirred for 36 h at 25 °C. Ether extraction,[23] including a base wash, gave a yellow oil which was purified by chromatography of 10 g of silica gel with 300 ml of ether. The ether fraction contained 1.4 g (83%) of a slightly yellow oil which solidified upon standing. A portion of this material was recyrstallized from petroleum ether to afford the analytical sample: mp 53–54 °C; NMR ($CDCl_3$) δ 3.03 (d, 2 H, J = 5 Hz, CH_2CO_2-), 3.68 (q, 2 H, J = 7 Hz, CH_3CH_2O-), 4.60 (s and t, 3 H, J = 7 Hz, $CH_2C=CH-$), 5.53 (m, 2 H, CH=CH), 5.8 (br, 2 H, NH] $_2$); ir ($CHCl_3$) 1725 (ester C=O), 1675 (amide C=O), 1590, 1115, 1060, 965, 910 cm^{-1}.

Anal. Calcd for $C_{22}H_{39}NO_4$: C, 69.25; H, 10.30; N, 3.67. Found: C, 69.34; H, 10.27; N, 3.64.

4-(6-Carbamoylhexyl)-5-ethoxy-5-methyl-3-(1-octenyl)oxacyclopentan-2-one (24). A solution of 1.64 mmol of LICA in 3 ml of dry THF was cooled to −78 °C. To this rapidly stirred mixture was added a solution of 206 mg (0.54 mmol) of ester **17** in 1 ml of dry THF over 35 s. After an additional 2 min at −78 °C, 0.250 ml (1.95 mmol) of TMSCl was added in one portion. The reaction mixture was stirred for an additional 3 min at −78 °C and then allowed to warm to 25 °C. The mixture was then stirred at reflux for 3.5 h to effect rearrangement. After cooling to 25 °C, the mixture was treated with 0.1 ml of ethanol and sufficient methanesulfonic acid to give pH 1–2. Immediate dichloromethane extraction[23] afforded 227 mg of a yellow oil. This material was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with 20% acetone–benzene. Elution with 300 ml of this solvent mixture afforded 141 mg (68%) of the lactone amide **24** as a colorless oil: NMR ($CDCl_3$) δ 1.60 [s, 3 H, $CH_3C(O)_2-$], 3.66 (q, 2 H, J = 7 Hz, CH_3CH_2O-), 5.5–6.3 (br m, 4 H, CH=CH and NH_2); ir ($CHCl_3$) 3700–3150 (several bands, NH_2), 1765 (lactone C=O), 1675 (amide C=O), 1590 cm^{-1}.

Anal. Calcd for $C_{22}H_{39}NO_4$: C, 69.25; H, 10.30; N, 3.67. Found: C, 69.10; H, 10.30; N, 3.71.

(*E*)-4-Decenoyl Chloride (25). A solution of 1.37 g (8.05 mmol) of (*E*)-4-decenoic acid[3] in 15 ml of dry benzene was treated with 1.4 ml (1.90 g, 16 mmol) of thionyl chloride. This mixture was stirred at reflux for 1 h. After the reaction mixture had cooled to 25 °C, the benzene and excess thionyl chloride were removed by rotary evaporation at reduced pressure followed by addition and similar removal of a second 15-ml portion of benzene. The residue was evaporatively distilled at 50–55 °C (0.05 mm) and 1.41 g (93%) of the acid chloride as a colorless liquid: NMR ($CDCl_3$) δ 2.95 (m, 2 H, C-2 H's), 5.45 (m, 2 H, CH=CH); ir ($CHCl_3$) 1800 (C=O), 1405, 970, 915, 730, 685 cm^{-1}.

9-Carbamoyl-2-methoxy-2-nonenyl (*E*)-4-Decenoate (18). A solution of 1.37 g (6.37 mmol) of the hydroxy amide **22a** and 3.53 ml (2. 55 g, 25 mmol) of dry triethylamine in 25 ml of dry dichloromethane was cooled to 0 °C. To this stirred solution was added 1.20 g (6.37 mmol) of the acid chloride **25** in 10 ml of dichloromethane. The reaction mixture was allowed to warm to 25 °C over 1 h and then was stirred for 11 h. Extraction[23] with 10% dichloromethane–ether, including a base wash, gave 2.02 g of a yellow oil which crystallized upon standing. This material was purified by medium-pressure chromatography[22] on 2.5 × 50 cm of silica gel with 40% acetone–ether at a flow rate of 2 ml/min. After elution with 210 ml of this solvent system, the next 160 ml afforded 1.60 g (72%) of the ester **18** as a white, waxy solid containing two isomers. A portion of this material was recrystallized from hexane and gave white platelets: mp 52.5–60 °C; NMR ($CDCl_3$) δ 3.47 and 3.55 (s, 3 H total, CH_3O), 4.57 (m, 2 H, $-CH_2O-$), 4.8 (m, 1 H, enol ether vinylic H), 5.42 (m, 2 H, CH=CH), 5.7 (br, 2 H, NH_2); ir ($CHCl_3$) 3540, 3500, and 3420 (NH_2), 1730 (ester C=O), 1675 (amide C=O), 1590, 1160, 1120, 1070, 970 cm^{-1}.

Anal. Calcd for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81. Found: C, 68.64; H, 10.13; N, 3.84.

4-(6-Carbamoylhexyl)-5-methoxy-5-methyl-3-(2-octenyl)oxacyclopentan-2-one (27). A solution of 1.5 mmol of LDA in 3.0 ml of dry THF was cooled to −78 °C. To this rapidly stirred solution was added 184 mg (0.5 mmol) of the ester **18** in 1 ml of THF over 1 min. After an additional 2 min at −78 °C, 1.0 ml (1.52 mmol) of TBSCl in HMPA was added in one portion. This mixture was stirred at −78 °C for an additional 2 min after which the cooling bath was removed and the reaction mixture was allowed to

warm to 25 °C over 20 min. The reaction mixture was then stirred at reflux for 3.5 h. Extraction[23] with 75% ether–petroleum ether afforded 369 mg of a nearly colorless oil. This oil was dissolved in 3 ml of THF and 1 ml of methanol; one drop of methanesulfonic acid was added and the mixture was stirred for 35 min at 25 °C. Extraction[23] with 75% ether–petroleum ether, including a base wash, gave 198 mg of a colorless oil. This material was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with 25% acetone–ether at a flow rate of 1 ml/min. After elution with 110 ml of this solvent system, the next 10 ml gave 45 mg of a mixture of compounds which by NMR analysis appeared to contain 50% of the desired lactone. Continued elution with 65 ml of the same solvent system gave 102 mg (56%) of a mixture of diasteriomers of the lactone **27** as a colorless oil: NMR ($CDCl_3$) δ 1.35 (br s, methylenes), 1.43 and 1.53 [s, 3 H total, $CH_3C(O)_2$–], 3.33 (br s, 3 H, CH_3O–), 5.5 (br m, 4 H, CH=CH and NH_2); ir ($CHCl_3$) 1765 (lactone C=O), 1680 (amide C=O), 1590, 1385, 975, 910 cm^{-1}.

Anal. Calcd for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81. Found: C, 68.72; H, 9.99; N, 3.62.

5-(6-Carbamoylhexyl)-4-(2-octenyl)-2-cyclopentenone (28). A. Reduction with DIBAH. A solution of 102 mg (0.278 mmol) of lactone **27** in 4 ml of dry ether was cooled to −78 °C. To this stirred solution was added 0.885 ml (0.612 mmol) of a solution of DIBAH in benzene over a period of 3 min. The reaction mixture was stirred at −78 °C for an additional 30 min, then 0.15 ml of methanol was added to the mixture and the cold bath was removed. After the reaction mixture had warmed to 25 °C, 0.15 ml of water and 0.2 g of Celite were added. The reaction mixture was stirred vigorously for 15 min. Anhydrous sodium sulfate (0.2 g) was again subjected to vigorous stirring for 15 min. The reaction mixture was then filtered with the aid of 75 ml of ether. The filtrate was evaporated at reduced pressure and gave 95 mg (92%) of a crude lactol which was not purified further.

B. Aldol Condensation. A solution of 69 mg of (0.187 mmol) of the crude lactol in 5 ml of ethanol and 5 ml of 5% aqueous sodium hydroxide solution was stirred for 20 min at 25 °C. Ether extraction[23] gave 53 mg of a colorless oil. This material was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with 30% acetone–ether at a flow rate of 1 ml/min. After elution with 120 ml of this solvent system, continued elution with 35 ml afforded 33 mg (51%) of the cyclopentenone **28** as a colorless oil: NMR ($CDCl_3$) δ 2.05 (t, 2 H, J = 7 Hz, CH_2C=O), 5.42 (m, 2 H, CH=CH), 5.73 (m, 2 H, NH_2), 6.10 (dd, 1 H, J = 6 and 1 Hz, =CHC=O), 7.56 (dd, 1 H, J = 6 and 2 Hz, CH=C–C=O); ir ($CHCl_3$) 3550–3100 (several bands, NH_2), 1685 (enone and amide C=O), 1590, 970 cm^{-1}; uv (EtOH) λ_{max} 219 nm (ε 10 000).

Anal. Calcd for $C_{20}H_{33}NO_2$: C, 75.19; H, 10.41; N, 4.38. Found: C, 75.05; H, 10.47; N, 4.41.

4-(6-Carboxyhexyl)-5-methoxy-5-methyl-3-(2-octenyl)oxacyclopentan-2-one (29). A solution of 2.04 mmol of LDA in 7 ml of dry THF was cooled to −78 °C. To this stirred solution was added 1.8 ml of dry HMPA followed by 250 mg (0.679 mmol) of the ester **18** in 2 ml of THF over 4 min. The reaction mixture was stirred for an additional 2 min and then 0.59 ml (2.04 mmol) of TBSCl in hexane was added. After an additional 2 min at −78 °C, the cold bath was removed and the reaction mixture was allowed to warm to 25 °C. The mixture was then stirred at reflux for 3 h. Extraction[23] with 75% ether–petroleum ether gave a nonmobile oil. This material was stirred at reflux in a solution of 1.2 g of sodium hydroxide, 6 ml of water, and 15 ml of methanol for 16 h. The cooled reaction mixture was poured into 30 ml of water and extracted with three 25-ml portions of ether (extracts discarded). The basic solution was cooled to 0 °C and acidified by addition of 90 ml of 0.4 N H_2SO_4 with stirring. Dichloromethane extraction[23] gave 220 mg of an oil. This material was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with petroleum ether–dichloromethane–THF–acetic acid (50:10:3:2) at a flow rate of 1 ml/min. After elution with 60 ml of this solvent system, continued elution with 50 ml gave 162 mg (65%) of a mixture of diastereomers of the lactone acid **29** as a colorless oil: NMR ($CDCl_3$) δ 1.43 and 1.53 [s, 3 H total, $CH_3C(O)_2$–], 3.36 (s, 3 H, CH_3O–), 5.65 (m, 2 H, CH=CH); ir ($CHCl_3$) 1765 (lactone C=O), 1710 (acid C=O), 1380, 975 910 cm^{-1}.

Anal. Calcd for $C_{21}H_{36}O_5$: C, 68.45; H, 9.85. Found: C, 68.42; H, 9.72.

5-(6-Carboxyhexyl)-4-(2-octenyl)-2-cyclopentenone (30). A. Reduction with DIBAH. A solution of 168 mg (0.450 mmol) of the lactone acid **29** in 15 ml of dry ether was cooled to −78 °C. To this stirred solution was added 1.17 ml (1.01 mmol) of DIBAH in benzene over a 4-min period. The reaction mixture was then stirred at −78 °C for an additional 30 min. The mixture was then treated with 0.6 ml of methanol to quench excess hydride and was stirred for an additional 5 min at −78 °C. The reaction mixture was then rinsed into a mixture of 5 ml of acetic acid and 10 g of ice with 25 ml of ether. This mixture was stirred for 5 min, after which ether extraction[23] afforded 166 mg (quantitative crude yield) of a keto aldehyde: NMR ($CDCl_3$) δ 1.33 (m, $-CH_2-$), 2.16 and 2.23 (s, 3 H total, CH_3C=O), 5.38 (m, 2 H, CH=CH), 9.41 (br s, 1 H, CO_2H), 9.69 (m, 1 H, CHO).

B. Aldol Condensation. This keto aldehyde was dissolved in 15 ml of dry benzene and was treated with 5.7 μl of acetic acid and 9.9 μl of piperidine. This mixture was stirred at reflux with continuous removal of water by means of a Dean-Stark apparatus charged with 4A molecular sieves. After 4.75 h, TLC analysis indicated that some starting keto aldehyde remained. The reaction mixture was again treated with 5.7 μl of acetic acid and 9.9 μl of piperidine and reflux was continued for 2 h. Ether extraction,[23] including a wash with 20% aqueous sodium dihydrogen phosphate solution, gave 197 mg of a slightly yellow oil. Purification by preparative TLC[22,26] on 13 × 20 × 0.2 cm of silica gel with hexane–dichloromethane–THF–acetic acid (30:10:5:3) afforded 126 mg (86% from lactone **29**, R_f 0.23–0.38) of cyclopentenone **30** as a colorless oil: NMR ($CDCl_3$) δ 5.44 (m, 2 H, CH=CH), 6.15 (dd, 1 H, J = 6 and 1 Hz, =CHC=O), 7.60 (dd, 1 H, J = 6 and 2 Hz, CH=CC=O), 10.07 (br s, 1 H, CO_2H); ir ($CHCl_3$) 3400–2600 (CO_2H), 1705 (enone and acid C=O), 1590, 950 cm^{-1}; uv (EtOH) λ_{max} 219 (ε 9400).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.90; H, 9.90.

3-(6-Carbamoylhexyl)-2,5-dimethoxy-2-methyl-4-(2-octenyl)oxacyclopentane (31). A solution of 133 mg (0.361 mmol) of the crude lactol, which resulted from reduction of lactone **27** (vide supra), in 7 ml of methanol was cooled to 0 °C. To this solution was added one drop of methanesulfonic acid and the reduction mixture was stirred at 0 °C for 3 h. Ether extraction,[23] including a base wash, gave 128 mg (93%) of a slightly brown oil. A portion of this material (75 mg) was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with 30% acetone–ether at a flow rate of 1 ml/min. After elution with 135 ml of this solvent, continued elution with 125 ml afforded 53 mg of a mixture of several diastereomers of the bis acetal **31** as a colorless oil: NMR ($CDCl_3$) δ 3.27, 3.32, 3.37, and 3.40 (s, CH_3O), 4.65 (m, 1 H, –OCHO–), 5.43 (m, 2 H, CH=CH), 5.68 (m, 2 H, NH_2); ir ($CHCl_3$) 1675 (amide C=O), 1590, 1380, 1100, 975 cm^{-1}.

Anal. Calcd for $C_{22}H_{41}NO_4$: C, 68.89; H, 10.77; N, 3.65. Found: C, 68.91; H, 10.76; N, 3.66.

Preparation of Cyclopentenone 30 from Bis Acetal 31. A solution of 128 mg (0.334 mmol) of the crude bis acetal **31** in 25 ml of methanol and 8 ml of 20% aqueous sodium hydroxide solution was stirred at reflux for 8 h. The reaction mixture was poured into 150 ml of pH 7 buffer (Beckman) containing a small amount of bromothymol blue. The blue solution was neutralized by dropwise addition of concentrated hydrochloric acid at 0 °C until a light green color was obtained. Dichloromethane extraction[23] gave 95 mg of a brown oil. This material was partially purified by filtration through 15 g of silica gel. Elution with 40 ml of ether gave 48 mg of an oil. This material was dissolved in 7.5 ml of THF and 3 ml of water. To this solution was added 0.3 ml of concentrated hydrochloric acid and the mixture was stirred at 25 °C for 1.5 h. At the end of this period, 0.75 ml of 40% aqueous sodium hydroxide solution and 3 ml of methanol were added. The reaction mixture was stirred at 25 °C for 25 min. The reaction mixture was then poured into 20 ml of 5% hydrochloric acid. Ether extraction[23] gave 44 mg of an orange oil. Chromatography of this material on 15 g of silica gel with 30 ml of 75% ether–petroleum ether, 30 ml of 90% ether–petroleum ether, and finally 60 ml of ether gave 15 mg (14% from lactone **27**) of the cyclopentenone acid **30**.

Isopropyl 4,5-Epoxy-2-hexenoate (33). A solution of 5.8 g (37.7 mmol) of isopropyl sorbate in 100 ml of dichloromethane was cooled to 0 °C. To this solution was added 11.5 g (56.5 mmol) of 85% *m*-chloroperbenzoic acid during a 10-min period. Following this addition, the reaction mixture was stirred at 0 °C for 30 min and at 25 °C for 4 h. Excess peracid was then destroyed by dropwise addition of 10% aqueous sodium bisulfite solution and the product was isolated by ether extraction,[23] including a base wash. The residual liquid was purified by chromatography on 200 g of silica gel. After elution with 500 ml of 10% ether–petroleum ether and then 250 ml of 20% ether–petroleum ether, continued elution with the latter solvent system gave 4.9 g (76%) of the epoxy ester **33**. An analytical sample was obtained by preparative VPC[22] (200 °C, 8 ft × 0.25 in. 10% Carbowax 20M, 60 ml/min, thermocouple)

followed by evaporative distillation at 40 °C (0.08 mm): NMR ($CDCl_3$) δ 1.25 [d, 6 H, J = 6 Hz, $(CH_3)_2C$], 1.35 (d, 3 H, J = 6 Hz, C-6 H), 2.95 (q of d, 1 H, J = 5 and 2 Hz, C-5 H), 3.13 (dd, 1 H, J = 6 and 2 Hz, C-4 H), 5.07 [septet, 1 H, J = 6 Hz, $(CH_3)_2CHO$–], 6.07 (d, 1 H, J = 15 Hz, C-2 H), 6.67 (dd, 1 H J = 15 and 6 Hz, C-3 H); ir ($CHCl_3$) 1710 (C=O), 1660 (C=C), 1110, 975, 940, 830 cm^{-1}.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.52; H, 8.36.

Reduction of Ester 33. A. With Lithium in Ammonia. A mixture of 24 ml of dry THF and 96 ml of dry ammonia was cooled to −78 °C. To this stirred solution was added 63 mg (9 mmol) of lithium wire in six freshly cut pieces. After 10 min at −78 °C, a solution of 510 mg (3 mmol) of the ester **33** in 2 ml of dry THF was added to the rapidly stirred reaction mixture as fast as possible. After 40 s, the blue color faded and 9 g of solid ammonium chloride was added. Stirring was continued at −78 °C for 2 min, after which the cooling bath was removed and ammonia allowed to evaporate over 4 h. Dichloromethane extraction[23] gave 480 mg of a colorless oil which was purified further by chromatography on 15 g of silica gel with 50% ether–petroleum ether. After elution with 40 ml of this solvent mixture, continued elution with 80 ml gave 410 mg (79%) of a mixture of alcohols **36a** and **37a**. Analysis by VPC[22] (160 °C, 8 ft × 0.25 in. 10% Carbowax 20M 60 ml/min, thermocouple) indicated that the mixture contained an 89:11 ratio of isomers: NMR ($CDCl_3$) δ 1.22 [d, 6 H, J = 6 Hz, $(CH_3)_2C$], 1.25 (d, 3 H, J = 6 Hz, C-6 H's), 2.3 (br, 1 H, OH), 3.00 (m, 2 H, C-2 H's), 4.27 (m, 1 H, C-5 H), 5.00 [septet, 1 H, J = 6 Hz, $(CH_3)_2CH$–], 5.67 (m, 2 H, C-3 H and C-4 H); ir ($CHCl_3$) 3600 and 3400 (OH), 1720 (C=O), 1375, 1110, 1060, 970 cm^{-1}.

Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.70; H, 9.44.

Isopropyl (*E*)-5-(*tert*-Butyldimethylsilyloxy)-3-hexenoate (36b) and Isopropyl (*Z*)-5-(*tert*-Butyldimethylsilyloxy)-3-hexenoate (37b). Following the procedure of Corey,[18] a mixture of 462 mg (2.69 mmol) of the alcohols **36a** and **37a** from the lithium in ammonia reduction above, 483 mg (3.22 mmol) of TBSCl, and 457 mg (6.73 mmol) of imidazole in 5 ml of dry DMF was stirred at 25 °C for 17 h. Pentane extraction[23] gave 731 mg of a slightly yellow oil which was filtered through 15 g of silica gel with 80 ml of 5% ether–petroleum ether. This afforded 526 mg (68%) of a colorless oil. Analysis by VPC[22] (160 °C, 8 ft × 0.25 in. 10% Carbowax 20M, 60 ml/min, thermocouple) indicated that this consisted of two isomeric components. The minor isomer (10%) had a retention time of 11.5 min; the major isomer (90%) had a retention time of 13.0 min. These isomers were separated by medium-pressure chromatography[22] on 0.9 × 60 cm of silica gel with 5% ether–petroleum ether at a flow rate of 0.5 ml/min. The more mobile component was the minor isomer which was assigned the Z stereochemistry **37b**. An analytical sample was prepared by evaporative distillation at 50 °C (0.05 mm): NMR ($CDCl_3$) δ 0.03 [s, 6 H, $(CH_3)_2Si$], 0.87 [s, 9 H, $(CH_3)_3CSi$], 1.18 (d, 3 H, J = 6 Hz, C-6 H's), 1.22 [d, 6 H, J = 6 Hz, $(CH_3)_2C$], 1.37 (d, 2 H, J = 5 Hz, C-2 H's), 4.5 (m, 1 H, C-5 H), 5.00 [septet, 1 H, J = 6 Hz, $(CH_3)_2CH$–], 5.55 (m, 2 H, C-3 H and C-4 H); ir ($CHCl_3$) 1725 (C=O), 1260, 1110, 915, 875, 835 cm^{-1}, no band at 970 cm^{-1}.

Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 62.94; H, 10.58.

The less mobile component was the major isomer and was assigned the E stereochemistry **36b**. An analytical sample was prepared by evaporative distillation at 50 °C (0.05 mm): NMR ($CDCl_3$) δ 0.05 [s, 6 H, $(CH_3)_2Si$], 0.90 [s, 9 H, $(CH_3)_3CSi$], 1.20 (d, 3 H, J = 6 Hz, C-6 H's), 1.22 [d, 6 H, J = 6 Hz, $(CH_3)_2C$], 2.98 (d, 2 H, J = 5 Hz, C-2 H's), 4.27 (m, 1 H, C-5 H), 5.02 [septet, 1 H, J = 6 Hz, $(CH_3)_2CHO$–], 5.5 (m, 2 H, C-3 H and C-4 H); ir ($CHCl_3$) 1720 (C=O), 1260, 1110, 970, 910, 835 cm^{-1}.

Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 63.00; H, 10.58.

Reduction of Ester 33. B. With Sodium in HMPA–THF, Followed by Silylation with TBSCl. A solution of sodium in HMPA–THF was prepared according to the procedure of House.[17] Titration of an aliquot of this solution with sec-butyl alcohol in xylene indicated that it was 0.35 M in sodium. Addition of a second aliquot to water followed by titration with standard HCl to a phenolphthalein endpoint indicated that the solution was 0.32 M in total base.

A solution of 170 mg (1 mmol) of ester **33** in 13.7 ml of THF was cooled to −78 °C. To this rapidly stirred solution was added 5.88 ml (2.0 mmol) of the Na–HMPA–THF solution in one portion. Decolorization occurred after 70 s. After an additional 2 min at −78 °C the yellow solution was treated with 0.65 ml (2.2 mmol) of TBSCl in hexane and was stirred at −78 °C for an additional 2 min. The cooling bath was then removed and the reaction mixture was stirred at 25 °C for 20 min. Pentane extraction[23] gave a yellow oil which was dissolved in 5 ml of THF and treated with 1 ml of 70% aqueous acetic acid solution. This solution was stirred at 25 °C for 1 h to effect hydrolysis of the silyl ketene acetal. Pentane extraction,[23] including a base wash, gave a nearly colorless oil which was purified by chromatography on 10 g of silica gel with 10% ether–petroleum ether. Elution with 35 ml of this solvent mixture gave 113 mg (39%) of a mixture of silyl ethers **36b** and **37b**. Analysis by VPC[22] (160 °C 8 ft × 0.25 in. 10% Carbowax 20M, 60 ml/min, thermocouple) indicated that this material consisted of a mixture of Z silyl ether **37b** (40%) and E silyl ether **36b** (60%).

C. With Sodium in HMPA–THF Followed by Protonation. A solution of sodium in HMPA–THF[17] was prepared as in B above. Titration of total base with standard HCl indicated that the solution was 0.256 M in sodium. A solution of 170 mg (1.0 mmol) of ester **33** in 43 ml of dry THF and 4 ml of dry HMPA was cooled to −78 °C. To this rapidly stirred solution was added 11.7 ml (3.0 mmol) of the Na–HMPA–THF solution in one portion. The blue color persisted and was discharged after 1 min by addition of 9 g of sodium ammonium chloride. After an additional 2 min at −78 °C, the reaction mixture was allowed to warm to 25 °C over 30 min. Pentane extraction gave 127 mg of a yellow oil which was purified by chromatography on 15 g of silica gel with 50% ether–petroleum ether. After elution with 54 ml of this solvent mixture, continued elution with 40 ml gave 73 mg (42%) of a mixture of alcohols **36a** and **37a**.

D. With Zinc in HMPA–THF.[3] A mixture of 340 mg (2.0 mmol) of epoxy ester **33**, 600 mg (4 mmol) of TBSCl, and 0.5 g of zinc dust in 10 ml of dry THF and 2.5 ml of dry HMPA was stirred at reflux for 16 h. Pentane extraction[23] gave a colorless oil. NMR analysis indicated that this material consisted of only the starting ester **33**.

Enolization of Hydroxy Esters 36a and 37a. A solution of 2.2 mmol of LDA in 20 ml of dry THF was cooled to −78 °C. To this solution was added 4.0 ml of dry HMPA. This rapidly stirred solution was treated with the dropwise addition of 172 mg (1.0 mmol) of a mixture of the hydroxy ester **36a** (90%) and **37a** (10%) in 2 ml of dry THF over 4 min. Following the addition, the reaction mixture was stirred at −78 °C for an additional 2 min and then 0.65 ml (2.2 mmol) of TBSCl in hexane was added in one portion. After an additional 2 min, the reaction mixture was allowed to warm to 25 °C and was stirred for 30 min. Pentane extraction[23] gave a slightly yellow oil which contained none of the starting esters and was identified as the ketene acetal **35** (NMR analysis). This material was dissolved in 5 ml of THF and was treated with 1 ml of 70% aqueous acetic acid. After 1.5 h, VPC[22] analysis (160 °C, 6 ft × 0.125 in., 4% SE-30, 60 ml/min, flame ionization) employing hexadecane as an internal standard (corrected for sensitivities) indicated that the siloxy esters **36b** and **37b** were present in 56% yield. VPC[22] analysis (160 °C, 8 ft × 0.25 in., 10% Carbowax 20M, 60 ml/min, thermocouple) demonstrated that the mixture consisted of 90% of the E ester **36b** and 10% of the Z ester **37b**.

Enolization of the Siloxy Esters 36b and 37b. A solution of 0.6 mmol of LDA in 5 ml of dry THF was cooled to −78 °C and 1.0 ml of dry HMPA was added. To this rapidly stirred mixture was added a solution of 143 mg (0.5 mmol) of a mixture of the silyl ethers **36b** (90%) and **37b** (10%) and 90 mg (0.6 mmol) of TBSCl in 0.5 ml of dry THF over 4 min. After an additional 2 min at −78 °C, the reaction mixture was allowed to warm to 25 °C and was stirred for 30 min. Pentane extraction[23] gave a slightly yellow oil which contained none of the starting esters **36b** or **37b** (NMR analysis). The ketene acetal was hydrolyzed and the reaction mixture analyzed as described above. The siloxy esters were present in 64% yield. This consisted of ester **36b** (90%) and ester **37b** (10%).

Methyl (*E*)-2-Methyl-2-(phenylthio)-4-decenoate (40). A solution of 3.37 g (11.53 mmol) of (*E*)-2-methyl-2-(phenylthio)-4-decenoic acid[3] in 40 ml of dry HMPA was treated with 353 mg of sodium hydride (minrral oil free) in small portions over a 10-min period. Following the addition, the reaction mixture was stirred at 25 °C for 1.25 h and then treated with 2.49 ml (5.68 g, 40 mmol) of iodomethane in one portion. This mixture was stirred at 25 °C for 3 h and then diluted with 100 ml of 5% hydrochloric acid solution. Ether extraction,[23] including a wash with 10% aqueous sodium thiosulfate solution, gave 3.40 g of a slightly yellow oil. This material was purified by chromatography on 170 g of silica gel with 5% ether–petroleum ether. After elution with 540 ml of this solvent system, continued elution with 360 ml gave 3.21 g (91%) of the methyl ester **40**. An analytical sample was prepared by evaporative distillation at 120° (0.05 mm): NMR ($CDCl_3$) δ 1.38 (s, 3 H, CH_3),

2.00 (m, 2 H), 1.8–2.9 (4 H), 5.43 (m, 2 H, CH=CH), 7.4 (m, 5 H, C_6H_5); ir ($CHCl_3$) 1725 (C=O), 1435, 1375, 1025, 970 cm^{-1}.

Anal. Calcd for $C_{18}H_{26}O_2S$: C, 70.56; H, 8.55; S, 10.46. Found: C, 70.62; H, 8.62; S, 10.49.

Methyl (*E,E*)-2-Methyl-2,4-decadienoate (41) and Methyl (*E*)-2-Methylene-4-decenoate (42). A solution of 3.0 g (9.80 mmol) of the α-(phenylthio) ester **40** in 125 ml of dichloromethane was cooled to 0 °C. To this stirred solution was added a solution of 1.99 g (9.80 mmol) of 85% *m*-chloroperbenzoic acid in 25 ml of dichloromethane over a period of 1 h. Following the addition, the reaction mixture was stirred at 0° for an additional 1 h. Ether extraction,[23] including a base wash, gave a mixture of sulfoxides. This material was dissolved in 65 ml of carbon tetrachloride and was stirred at 60 °C for 2 h. The reaction mixture was cooled to 25 °C and the solvent was removed at reduced pressure. The residue was partially purified by passage through 100 g of silica gel with 200 ml of 30% ether–petroleum ether and afforded 2.0 g of a colorless oil. VPC[22] analysis (200 °C, 8 ft × 0.25 in. 10% Carbowax 20M, 60 ml/min, thermocouple) indicated that this material consisted of only two volatile components. The minor component (retention time 3.5 min) accounted for 22% of the mixture and the major component (retention time 7.5 min), 78%. These isomers could be separated by medium-pressure chromatography[22] on 2.5 × 50 cm of silica gel with 2% ether–petroleum ether at a flow rate of 2 ml/min. After elution with 380 ml of this solvent system, continued elution with 300 ml gave 387 mg (20%) of the minor component which was identified as the α-methylene ester **42**. An analytical sample was prepared by evaporative distillation at 60° (0.1 mm): NMR ($CDCl_3$) δ 0.5–1.5 (9 H), 2.0 (m, 2 H, C-6 H's), 3.0 (m, 2 H, C-3 H's), 3.77 (s, 3 H, CH_3O), 5.50 (m, 3 H, vinylic H's). 6.15 (br s, 1 H, vinylic H syn to ester); ir ($CHCl_3$) 1715 (C=O), 1630 (C=C), 1435, 1140, 975, 950 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.38; H, 10.18.

After elution with an additional 20 ml of the same solvent system, continued elution with 430 ml gave 1.411 g (73%) of the major isomer which was identified as the fully conjugated isomer **41**. An analytical sample was prepared by evaporative distillation at 60°C (0.05 mm): NMR ($CDCl_3$) δ 0.7–1.6 (9 H), 1.90 (br s, 3 H, vinylic CH_3), 2.2 (m, 2 H, C-6 H's), 3.71 (s, 3 H, CH_3O–), 6.23 (m, 2 H, C-4 H and C-5 H), 7.13 (br d, 1 H, J = 8 Hz, C-3 H); ir ($CHCl_3$) 1700 (C=O), 1640 and 1610 (C=C), 1435, 1110, 970 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.42; H, 10.16.

In a separate experiment it was possible to separate and independently pyrolyze the two diastereomeric sulfoxides. The mixture of sulfoxides from oxidation of 2.0 g (6.54 mmol) of the ester **40** was subjected to chromatography on 200 g of silica gel. After elution with 400 ml of 30% and 300 ml of 40% ether–petroleum ether, continued elution with 225 ml of 50% ether–petroleum ether gave 712 mg of the more mobile sulfoxide contaminated with decomposition products. Further elution with 150 ml of the same solvent mixture gave 346 mg of the less mobile sulfoxide, also contaminated with decomposition products. Rapid rechromatography on 50 g of silica gel with 60% ether–petroleum ether afforde pure samples of each of the sulfoxides.

The more mobile isomer (isomer A, R_f[22] 0.21, 30% ether–petroleum ether, 523 mg) was characterized by the following spectral data: NMR ($CDCl_3$) δ 1.17 (s, 3 H, CH_3), 1.9 (m, 2 H, $=CCH_2$–), 2.60 (d, 1 H, J = 7 Hz, C-3 H), 2.88 (d, 1 H, J = 6 Hz, C-3 H), 3.60 (s, 3 H, CH_3O), 5.43 (m, 2 H, CH=CH). 7.48 (s, 5 H, C_6H_5); ir ($CDCl_3$) 1720 (C=O), 1370, 1080, 1035, 970 cm^{-1}.

The less mobile isomer (isomer B, R_f[22] 0.12 30% ether–petroleum ether, 144 mg) was characterized by the following spectral data: NMR ($CDCl_3$) δ 1.38 (s, 3 H, CH_3), 1.9 (m, 2 H, $=CCH_2$–), 2.37 (d, 1 H, J = 7 Hz, C-3 H), 2.60 (d, 1 H, J = 6 Hz, C-3 H), 3.63 (s, 5 H, C_6H_5); ir ($CHCl_3$) 1725 (C=O), 1375, 1085, 1045, 975, 910 cm^{-1}.

Each sulfoxide was heated in carbon tetrachloride at 60 °C for 2 h. The products were isolated as described above and analyzed by VPC[22] (200 °C, 8 ft × 0.25 in. 10% Carbowax 20M, 60 ml/min, thermocouple). The following results were obtained.

Sulfoxide	41/42	Yield of olefins
Isomer A (high R_f)	68/32	99% from sulfoxide
Isomer B (low R_f)	90/10	97% from sulfoxide
Original mixture	78/22	93% from ester **40**

Methyl 4,5-Epoxy-2-methyl-2-decenoate (46). The unsaturated ester **41** (3.1 g, 15.8 mmol) was dissolved in 100 ml of chloroform and 40 mg of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide,[27] a free-radical inhibitor, was added. To this solution was added 4.02 g (19.8 mmol) of 85% *m*-chloroperbenzoic acid and the resulting solution was stirred at 25 °C for 6 h. Ether extraction,[23] including a base wash and a 10% aqueous sodium bisulfite wash, gave the crude epoxy ester **46** which was purified by medium-pressure chromatography[22] on 2.5 × 50 cm silica gel with 10% ether–petroleum ether at a flow rate of 2.7 ml/min. After elution with 560 ml of this solvent mixture, continued elution with 300 ml afforded 3.0 g (90%) of the epoxy ester **46** as a colorless oil. An analytical sample was prepared by evaporative distillation at 70 °C (0.1 mm): NMR ($CDCl_3$) δ 0.5–1.7 (11 H), 1.98 (d, 3 H, J = 1.5 Hz, C-2 CH_3), 2.88 (m, 1 H, C-5 H), 3.33 (dd, 1 H, J = 2 and 8 Hz, C-4 H), 3.75 (s, 3 H, CH_3O–), 6.30 (br d, 1 H, J = 8 Hz, C-3 H); ir ($CHCl_3$) 1715 (C=O), 1655 (C=C), 1435, 1315, 1260, 1160, 1105, 915, 870 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.84; H, 9.42.

Methyl (*E*)-5-Hydroxy-2-methyl-3-decenoate (47). A mixture of 24 ml of dry THF and 96 ml of dry ammonia was cooled to −78 °C. To this stirred solution was added 63 mg (9 mmol) of lithium wire in six pieces. This solution was stirred for 10 min at −78 °C and then 636 mg (3.0 mmol) of epoxy ester **46** in 2 ml of THF was added in one portion. The blue color persisted for 1 min at which time it was discharged by addition of 9 g of solid ammonium chloride. After an additional 2 min at −78 °C, the cooling bath was removed, 75 ml of hexane was cautiously added to the reaction mixture, and the ammonia was allowed to evaporate over 4 h. Ether extraction[23] gave 595 mg of colorless oil which was purified by chromatography on 50 g of silica gel with 40% ether–petroleum ether. After elution with 80 ml of this solvent system, contined elution with 20 ml gave 26 mg (4%) of a minor isomer which was tentatively assigned *Z* stereochemistry of ester **47**. An analytical sample was prepared by evaporative distillation at 90 °C (0.05 mm): NMR ($CDCl_3$) δ 0.9–1.5 (12 H), 1.97 (m, 2 H, C-6 H's), 2.5 (m, 2 H, C-2 H and OH), 3.68 (s, 3 H, CH_3O–), 4.28 (m, 1 H, C-5 H), 5.57 (m, 2 H, C-3 H and C-4 H); ir ($CHCl_3$) 3600–3400 (OH), 1725 (C=O), 1455, 1005, 970 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.36; H, 10.32.

After elution with an additional 10 ml of the same solvent system, continued elution with 85 ml gave 440 mg (69%) of the major *E* isomer **47**. An analytical sample was prepared by evaporative distillation at 90 °C (0.05 mm): NMR ($CDCl_3$) δ 0.5–1.9 (15 H), 3.13 (m, 1 H, C-2 H), 3.68 (s, 3 H, CH_3O–), 4.07 (m, 1 H, C-5 H), 5.67 (m, 2 H, C-3 H and C-4 H); ir ($CHCl_3$) 3600 and 3550–3400 (OH), 1725 (C=O), 1455, 1045, 970 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.22; H, 10.30.

Attempted Hydrolysis of Hydroxy Ester 47. A solution of 140 mg (0.654 mmol) of epoxy ester **46** and 157 mg (6.54 mmol) of lithium hydroxide[28] in 4.7 ml of methanol and 1.6 ml of water was stirred at 25 °C for 2.5 h. After dilution with water and acidification with concentrated hydrochloric acid, ether extraction[23] gave 129 mg (99%) of a nearly colorless oil. TLC[22] analysis (ether) indicated that this consisted of two acid components, the more mobile of which quenched fluorescence. An ether solution of 32 mg of this material was treated with excess diazomethane[29] for 20 min at 0 °C. The excess diazomethane was destroyed by dropwise addition of acetic acid after which ether extraction[23] gave 33 mg of a colorless oil. This material showed only one spot by TLC analysis (50% ether–petroleum ether). Purification was accomplished by medium-pressure chromatography[22] on 0.9 × 60 cm silica gel with ether at a flow rate of 0.5 ml/min. After elution with 26 ml of this solvent, continued elution with an additional 14 ml afforded 31 mg (91%) of a colorless oil. NMR analysis indicated that this consisted of 70% of ester **47** [δ 3.68 (s, CH_3O)] and 30% of another methyl ester [δ 3.73 (s, CH_3O) and 6.90 (br t, J = 7 Hz, vinylic H)] which was tentatively assigned the structure of the methyl ester arising from conjugated acid **49**. Similar results were obtained when the saponification was attempted with potassium hydroxide in methanol.

(*E,E*)-2-Methyl-2,4-decadienoic Acid (43). A mixture of 3.0 g (15.3 mmol) of the methyl ester **41** and 1.5 g of potassium hddroxide in 10 ml of methanol was stirred at reflux for 1.5 h. The reaction mixture was then diluted with 100 ml of water and extracted with two 50-ml portions of ether (extracts discarded). After acidification of the basic solution with concentrated hydrochloric acid, ether extraction[23] gave 2.76 g (99%) of the acid **43** as white crystals,

mp 53–56 °C. The analytical sample was prepared by two recrystallizations of this material from petroleum ether at −20 °C: NMR ($CDCl_3$) δ 0.6–1.8 (9 H], 1.93 (br s, 3 H, C-2 CH_3), 2.2 (m, 2 H, C_6H_5), 6.2 (m, 2 H, C-4 H and C-5 H), 7.3 (d, 1 H, J = 10 Hz, C-3 H), 11.0 (br s, 1 H, CO_2H); ir ($CHCl_3$) 3500–2500 (CO_2H), 1680 (C=O), 1250, 1035, 970 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.34; H, 9.75.

9-Carbamoyl-2-methoxy-2-nonenyl (*E*)-4,5-Epoxy-2-methyl-3-decenoate (50). A. *p*-Nitrophenyl 2-Methyl-2,4-decadienoate (44). A solution of 2.65 g (14.56 mmol) of unsaturated acid **43** in 20 ml of dry triethylamine was cooled to 0 °C. To this solution was added 3.42 g (14.56 mmol) of *p*-nitrophenyl trifluoroacetate[11] in one portion. This homogeneous solution was stirred at 0 °C for 30 min, during which an orange lower layer separated. Stirring was then continued for 3 h at room temperature. Ether extraction,[23] including a base wash and a 20% aqueous monosodium phosphate wash, gave an orange oil which was passed through 50 g of silica gel with 300 ml of dichloromethane. This afforded 3.8 g (86%) of the *p*-nitrophenyl ester **44** as a slightly yellow oil: NMR ($CDCl_3$) δ 0.6–1.6 (9 H), 2.07 (br s, 3 H, C-2 CH_3), 2.2 (m, 2 H, C-6 H's), 6.3 (m, 2 H, C-4 and C-5 H), 7.32 (d, 2 H, J = 9 Hz, aromatic), 8.28 (d, 2 H, J = 9 Hz, aromatic).

B. *p*-Nitrophenyl 4,5-Epoxy-2-methyl-2-decenoate (45). The *p*-nitrophenyl ester **44** (3.8 g, 12.54 mmol) was dissolved in 100 ml of chloroform. To this solution was added 3.19 g (15.68 mmol) of 85% *m*-chloroperbenzoic acid and 40 mg of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide.[27] This mixture was stirred for 2 h at 25 °C and for 2 h at reflux. Ether extraction,[23] including a 10% aqueous sodium bisulfite wash and a base wash, followed by passage of the residue through 40 g of silica gel with 240 ml of dichloromethane, gave 3.55 g (89%) of the epoxy ester **45** as a slightly yellow oil: NMR ($CDCl_3$) δ 0.5–1.9 (11 H), 2.13 (d, 3 H, J = 1.5 Hz, C-2 CH_3), 3.0 (m, 1 H, C-5 H), 3.45 (dd, 1 H, J = 2 and 8 Hz, C-4 H), 6.60 (br d, 1 H, J = 9 Hz, C-3 H), 7.30 (d, 2 H, J = 9 Hz, aromatic), 8.30 (d, 2 H, J = 9 Hz, aromatic).

C. Preparation of Ester 50. A solution of 1.76 g (8.2 mmol) of the hydroxy amide **22a** and 2.62 g (8.2 mmol) of the *p*-nitrophenyl ester **45** in 5 ml of dry THF and 5 ml of dry triethylamine was stirred at 50 °C for 57 h. Extraction[23] with 30% dichloromethane–ether, including a base wash, gave 3.2 g of an orange semisolid. This material was purified by medium-pressure chromatography[22] on 2.5 × 50 cm of silica gel with 30% acetone–ether at a flow rate of 2 ml/min. After elution with 300 ml of this solvent system, continued elution with 240 ml gave 2.17 g (67%) of the epoxy ester **50** as a nearly colorless oil which solidified upon standing. A portion of this waxy solid was dried at reduced pressure to provide the analytical sample: NMR ($CDCl)_3$ δ 0.5–1.9 (19 H), 2.02 (s, 3 H, vinylic CH), 2.10 (m, 4 H, $=CCH_2C-$ and CH_2CONH_2), 2.8 (m, 1 H, C-5 H, epoxide), 3.33 (dd, 1 H, J = 2 and 8 Hz, C-4 H, epoxide), 3.50 and 3.60 (s, 3 H total, CH_3O-), 4.62 and 4.65 (s, 2 H total, $=CCH_2O-$), 5.5 (br, 2 H, NH_2), 6.30 (br d, 1 H, J = 8 Hz, CH=C–CO_2-); ir ($CHCl_3$) 3530, 3490 and 3400 (NH_2), 1710, (C=O, ester), 1675 (C=O, amide), 1590, 1310, 1155, 870 cm^{-1}.

Anal. Calcd for $C_{22}H_{37}NO_5$: C, 66.81; H, 9.43; N, 3.54. Found: C, 66.90; H, 9.48; N, 3.49.

9-Carbamoyl-2-methoxy-2-nonenyl 5-Hydroxy-2-methyl-3-decenoate (51). A mixture of 24 ml of dry THF and 96 ml of dry ammonia was cooled to −78 °C. To this stirred solution was added 21 mg (3 mmol) of lithium wire in three pieces. This solution was stirred for 10 min at −78 °C, after which 395 mg (1 mmol) of the epoxy ester **50** in 2 ml of dry THF was added in one portion. The blue color persisted for 1 min after which it was discharged by addition of 9 g of solid ammonium chloride. After an additional 2 min at −78 °C, the cooling bath was removed and the ammonia was allowed to evaporate over 4.5 h. Dichloromethane extraction[23] gave 345 mg of a yellow oil which was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with 30% acetone–ether. After elution with 110 ml of this solvent system, continued elution with 75 ml afforded 290 mg (73%) of the hydroxy ester **51**. A portion of this material was dried at reduced pressure to provide the analytical sample: NMR ($CDCl_3$) δ 0.5–1.9 (22 H), 2.08 (m, 4 H, $=CCH_2C-$ and CH_2CONH_2), 3.1 (m, 1 H, $-CHCO_2-$), 3.50 and 3.57 (s, 3 total, CH_3O-), 4.05 (m, 1 H, –CHOH), 4.53 and 4.60 (s, 2 H total, $=CCH_2O-$), 5.63 (m, 4 H, CH=CH and NH_2); ir ($CHCl_3$) 3600–3250 (OH and NH_2), 1725 (C=O, ester), 1675 (C=O, amide), 1590, 1460, 970, 915 cm^{-1}.

Anal. Calcd for $C_{22}H_{39}NO_5$: C, 66.47; H, 9.89; N, 3.52. Found: C, 66.44; H, 9.76; N, 3.45.

4-(6-Carboxyhexyl)-3-(3-hydroxyoctenyl)-5-methoxy-3,5-dimethyloxacyclopentan-2-one (52). A solution of 2.78 mmol of LDA in 10 ml of dry THF was cooled to −78 °C. Following addition of 2.4 ml of dry HMPA, 285 mg (0.718 mmol) of the ester **51** in 2 ml of THF was added dropwise over 4 min to the rapidly stirred solution. After an additional 2 min at −78 °C, 0.840 ml (2.87 mmol) of TBSCl in hexane was added in one portion and stirring was continued for 2 min at −78 °C. The cooling bath was removed and the reaction mixture was allowed to warm to 25 °C, after which the mixture was stirred at reflux for 3 h. Extraction[23] with 75% ether–petroleum ether gave 508 mg of a yellow oil. This material was stirred at reflux with 1.2 g of sodium hydroxide in 6 ml of water and 15 ml of methanol for 16 h. After dilution with water, the reaction mixture was extracted into two 50-ml portions of ether (extracts discarded) and then acidified by addition of 80 ml of 0.4 N sulfuric acid to the ice-cooled, stirred solution. Dichloromethane extraction[23] gave 237 mg of a brown semisolid. This was purified by medium-pressure chromatography[22] on 1.25 × 50 cm of silica gel with petroleum ether–dichloromethane–THF–acetic acid (50:10:3:2). Following elution with 40 ml of this solvent system, continued elution with 10 ml gave 40 mg of the unsaturated acid **41**. Continued elution with 40 ml gave 44 mg of material which was tentatively identified as the *tert*-butyl dimethylsilyl ether of the desired lactone **52**: NMR ($CDCl_3$) δ 0.07 [s, 6 H, $(CH_3)_2Si$], 0.92 [s, 9 H, $(CH_3)_3CSi$], 2.13 (m, 2 H, $-CH_2CO_2-$), 3.37 (s, 3 H, CH_3O-), 4.07 (m, 1 H, CHOSi), 5.63 (m, 2 H, CH=CH).

After elution with an additional 295 ml of the same solvent system, continued elution with 200 ml gave 65 mg (30%) of the desired lactone acid **52** as a colorless oil. A portion of this material was dried at reduced pressure and provided the analytical sample: NMR ($CDCl_3$) δ 0.6–2.0 (28 H), 2.3 (m, 2 H, CH_2CO_2-), 3.36 (s, 3 H, CH_3O), 4.12 (m, 1 H, –CHOH), 5.7 (m, 2 H, CH=CH), 6.2 (br, 2 H, OH and CO_2H); ir ($CHCl_3$) 3600–3400 (OH), 3200–2600 (CO_2H), 1760 (C=O, lactone), 1710 (C=O, acid), 1380, 1030, 970, 910 cm^{-1}.

Anal. Calcd for $C_{22}H_{38}O_6$: C, 66.30; H, 9.61. Found: C, 66.52; H, 9.67.

Registry No.—**7a,** 16141-79-0; **7b,** 57679-65-9; **8,** 66-25-1; (*E*)-**9,** 57679-66-0; (*Z*)-**9,** 57679-67-1; (*E*)-**10,** 57679-68-2; (*Z*)-**10,** 57679-69-3; **11,** 38134-43-9; **13,** 38134-44-0; **14,** 57679-70-6; **15,** 1128-08-1; **16,** 57679-71-7; **17,** 57679-72-8; (*EE*)-**18,** 57679-73-9; (*EZ*)-**18,** 57679-74-0; **19,** 13050-09-4; (*E*)-**20a,** 57679-75-1; (*Z*)-**20a,** 57679-76-2; (*E*)-**20b,** 57679-77-3; (*Z*)-**20b,** 57679-78-4; **21a,** 57679-79-5; **21b,** 57679-80-8; (*E*)-**22a,** 57679-81-9; (*Z*)-**22a,** 57679-82-0; **22b,** 57679-83-1; **23,** 57679-84-2; **24,** 57679-85-3; **25,** 57679-86-4; **27,** 57679-87-5; **28,** 57679-88-6; **29,** 57679-89-7; **30,** 57679-90-0; **31,** 57679-91-1; **33,** 27981-16-4; **36a,** 57679-92-2; **36b,** 57679-93-3; **37a,** 57679-94-4; **37b,** 57679-95-5; **40,** 57679-96-6; **40** sulfoxide isomer 1, 57679-97-7; **40** sulfoxide isomer 2, 57679-98-8; **41,** 57679-99-9; **42,** 57680-00-9; **43,** 57680-01-0; **44,** 57680-02-1; **45,** 57680-03-2; **46,** 57680-04-3; **47,** 57680-05-4; **50,** 57680-06-5; **51,** 57680-07-6; **52,** 57680-08-7; **52** TBS ether, 57680-09-8; *p*-nitrophenyl trifluoroacetate, 658-78-6; (*E*)-3-decenoic acid, 53678-20-9; (*E*)-4-decenoic acid, 57602-94-5; isopropyl sorbate, 55584-26-4.

References and Notes

(1) (a) Grateful acknowledgment is made for support for this work by the National Science Foundation and the National Institutes of Health. (b) National Science Foundation Predoctoral Fellow, 1972–1975.
(2) R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, **94,** 5897 (1972).
(3) R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, in press.
(4) W. Grell and H. Machleidt, *Justus Liebigs Ann. Chem.*, **699,** 53 (1966).
(5) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91,** 5675 (1969); J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **46,** 2799 (1963); G. Saucy and R. Borer, *ibid.*, **54,** 2121 (1972).
(6) D. P. Strike and H. Smith, *Tetrahedron Lett.*, 4393 (1970).
(7) G. Stork, G. L. Nelson, F. Rouessac, and O. Gringore, *J. Am. Chem. Soc.*, **93,** 3091 (1971).
(8) R. A. Ellison, *Synthesis*, 397 (1973).
(9) M. Ohno, N Naruse, and I. Terasawa, "Organic Syntheses", Collect Vol. V, Wiley, New York, N.Y., 1973, p 266.
(10) H. C. Brown, "Hydroboration", W. A. Benjamin, New York, N.Y., 1962, p 245.
(11) S. Sakakibara and N. Inukai, *Bull. Chem. Soc. Jpn.*, **37,** 1231 (1964).
(12) D. S. Watt, *Synth. Commun.*, **4,** 127 (1974).
(13) M. W. Rathke and D. F. Sullivan, *Synth. Commun.*, **3,** 67 (1973).
(14) P. M. McCurry, Jr., and K. Abe, *Tetrahedron Lett.*, 1387 (1974).
(15) P. L. Stotter and J. B. Eppner, *Tetrahedron Lett.*, 2417 (1973); G. A. Koppel, *ibid.*, 1507 (1972).
(16) H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6,** 1046 (1967); *Bull. Soc. Chim. Fr.*, 791 (1968).
(17) K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger, and D. K. Roe, *J. Am. Chem. Soc.*, **92,** 2783 (1970); H.

O. House, R. W. Giese, K. Kronberger, J. P. Kaplan, and J. F. Simeone, *ibid.*, **92**, 2800 (1970).
(18) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
(19) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules", Wiley, New York, N.Y., 1956, pp 40–42.
(20) B. M. Trost and T. N. Salzmann, *J. am. Chem. Soc.*, **95**, 6840 (1973).
(21) E. J. Corey, C. S. Shiner, R. P. Volante, and C. R. Cyr, *Tetrahedron Lett.*, 1161 (1975).
(22) Boiling points are uncorrected. Infrared (ir) spectra were determined on a Perkin-Elmer 237B grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded using a Varian T-60 spectrometer. Chemical shifts are reported as δ values in parts per million relative to Me_4Si (δ Me_4Si 0.0 ppm) as an internal standard. Deuteriochloroform for NMR and chloroform for ir spectra were filtered through neutral alumina before use.

Vapor phase chromatographic (VPC) analyses were determined on either a Hewlett-Packard 5750 equipped with a flame ionization detector or a Varian 920 equipped wihh a thermal conductivity detector using helium as the carrier gas under the indicated conditions. The indicated liquid phase was absorbed on 60–80 mesh Chromosorb W AW DMCS.

Silica gel columns used the 0.05–0.2-mm silica gel manufactured by E. Merck & Co. Darmstadt, Germany. Acidic silica gel refers to Silicar CC-4 special "for column chromatography", sold by Mallinckrodt Chemical Works, St. Louis, Mo. Preparative medium-pressure chromatography was performed using glass columns of the indicated length and diameter with fittings supplied by Laboratory Data Control, Riviera Beach, Fla., and an instrument minipump supplied by Milton Roy Co., St. Petersburg, Fla. (instrumentation designed by R. H. Mueller, these laboratories, and copies are available on request). The columns were packed with silica gel H "for TLC acc. to Stahl" (10–40 μ) manufactured by E. Merck & Co., Darmstadt, Germany. Solvents were degassed under water aspirator vacuum prior to use.

Analytical thin layer chromatography was conducted on 2.5 × 10 cm precoated TLC plates, silica gel 60 F-254, layer thickness 0.25 mm, manufactured by E. Merck & Co., Darmstadt, Germany.

"Dry" solvents were dried immediately prior to use. Ether and tetrahydrofuran (THF) were distilled from lithium aluminum hydride; pyridine, triethylamine, diisopropylamine, *N*-isopropylcyclohexylamine, trimethylchlorosilane (TMSCl), hexamethylphosphoramide (HMPA), benzene, and toluene were distilled from calcium hydride; dimethylformamide (DMF) was dried over 4A molecular sieves and fractionally distilled at reduced pressure; methanol was dried over 3A molecular sieves; ammonia was distilled from a blue solution of sodium directly into the reaction flask; dichloromethane, methyl iodide, and hexane was distilled from phosphorus pentoxide. Petroleum ether refers to the Analyzed Reagent grade hydrocarbon fraction, bp 30–60 °C, which is supplied by J. T. Baker Co., Phillipsburg, N.J., and was not further purified.

Diisobutylaluminum hydride (DIBAH) was used as a standard solution in benzene (ca. 1.0 M). Lithium isopropylcyclohexylamide (LICA) and lithium diisopropylamide (LDA) were prepared as described previously.[3] Standard solutions of *tert*-butyldimethylchlorosilane (TBSCl) in hexane (ca. 3.3 M) or HMPA (ca. 1.5 M) were employed.

Reactions were run under an argon atmosphere arranged with a mercury bubbler so that the system could be alternately evacuated and filled with argon and left under a positive pressure.

Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.
(23) In cases where the products were isolated "by solvent extraction", the procedure generally followed was to dilute the reaction mixture with the indicated solvent or to extract the aqueous solution with several portions of the indicated solvent; then the combined organic layers were washed with several portions of water followed by saturated brine. The organic layer was dried over anhydrous sodium or magnesium sulfate, then filtered, and the solvent was evaporated from the filtrate under reduced pressure (water aspirator) using a rotary evaporator. The use of the terms "base wash" or "acid wash" indicate washing the organic solution with saturated aqueous sodium bicarbonate solution or with dilute aqueous hydrochloric acid, espectively, prior to the aforementioned wash with water.
(24) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 584.
(25) M. Gouge, *Ann. Chim. (Paris)*, **6**, 648 (1951).
(26) N. H. Anderson, *J. Lipid Res.*, **10**, 316 (1969).
(27) Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, H. Kakoi, *J. Chem. Soc., Chem. Commun.*, **64**, (1972).
(28) E. Andre and J. Henry, *C. R. Acad. Sci.*, **263**, 1084 (1966).
(29) H. M. Fales, T. M. Jaouni, and J. F. Babashak, *Anal. Chem.*, **45**, 2302 (1973).

Carbon-13 Nuclear Magnetic Resonance Spectra of Morphine Alkaloids[1]

Frank I. Carroll,*[2a] Charles G. Moreland,[2b] George A. Brine,[2a] and John A. Kepler[2a]

Chemistry and Life Sciences Division, Research Triangle Institute, Research Triangle Park, North Carolina 27709, and Department of Chemistry, North Carolina State University at Raleigh, Raleigh, North Carolina 27607

Received September 22, 1975

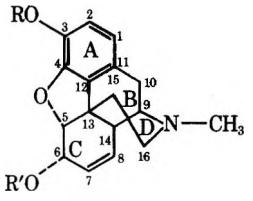
Carbon-13 chemical shifts were measured for 25 morphine, 14-hydroxymorphine, and 6,14-*endo*-etheno- and 6,14-*endo*-ethanotetrahydrothebaine compounds. The signal due to each carbon was assigned. The ^{13}C assignments of the protonated carbons were aided by single frequency off-resonance decoupling experiments and were confirmed in questionable cases by deuterium labeling experiments. Substituent effects were used to assign chemical shifts to nonprotonated as well as protonated carbons. Comparison of the chemical shifts of the morphine and 14-hydroxymorphine systems to those of the 6,14-*endo*-etheno- and 6,14-*endo*-ethanotetrahydrothebaine systems showed that the spatial configuration of rings A, B, and D of the two systems was similar. The ^1H and ^{13}C NMR data for the various compounds were compared.

It has been demonstrated that natural abundance carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy is an extremely useful physical method for the structure elucidation of alkaloids. Although several papers have presented correlations of structure with ^{13}C NMR spectra for many classes of alkaloids,[3] only limited studies have been reported for the physiologically and sociologically important morphine series of alkaloids.[4,5]

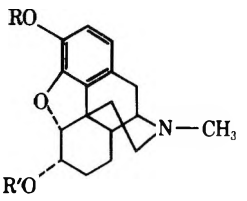
As a result of the continuing interest in the chemistry and pharmacology of the morphine class of alkaloids, we have synthesized many of the more active morphine type narcotics and narcotic antagonists as well as several of their biotransformation products. In this paper we present a study of the ^{13}C NMR spectra of the morphine alkaloids **1–11** shown in Chart I. The structures shown in Chart I are planar representations of the various morphine systems and illustrate the numbering used throughout this paper.

X-ray analysis of morphine (1a) hydriodide has shown that ring B is rigidly held in a distorted half-chair form and that rings C and D possess a boat and a chair form, respectively, with the 6α substituent in a bowsprit orientation.[6] ^1H NMR studies have shown that morphine as well as other Δ^7-morphine type alkaloids including 14-hydroxy analogues possess a similar conformation.[7] In contrast the ^1H NMR data[7] and chemical behavior[8] show that ring C of the C-7, C-8 saturated compounds such as **2a, 2b, 7a,** and **7b** exists in a chair conformation in which the 6α substituent is axial. The absolute stereochemistry of 19-propylthevinol (**9c**) hydrobromide has been established by an x-ray crystallographic study and shown to be as represented in struc-

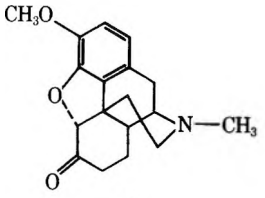
Chart I



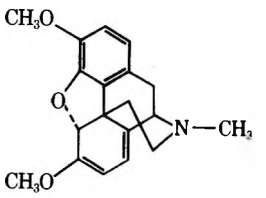
1a, R = R′ = H
b, R = CH$_3$; R′ = H
c, R = R′ = CH$_3$CO
d, R = H; R′ = CH$_3$CO



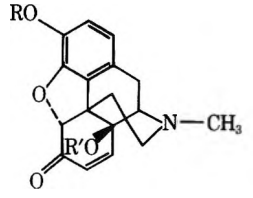
2a, R = R′ = H
b, R = CH$_3$; R′ = H



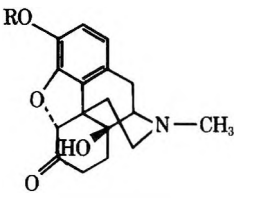
3



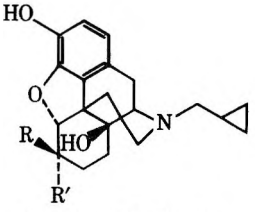
4



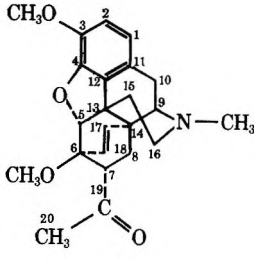
5a, R = R′ = H
b, R = CH$_3$; R′ = H
c, R = R′ = CH$_3$CO
d, R = CH$_3$; R′ = CH$_3$CO



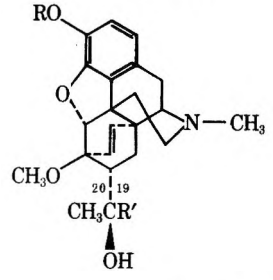
6a, R = H; R′ = CH$_2$CH=CH$_2$
b, R = H; R′ = CH$_2$-c-C$_3$H$_5$
c, R = CH$_3$; R′ = H



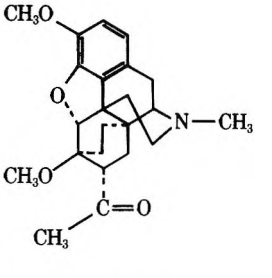
7a, R′ = OH; R = H
b, R = OH; R′ = H



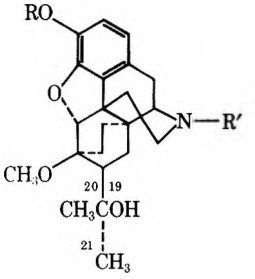
8



9a, R = H; R′ = CH$_2$CH$_2$CH$_3$
b, R = R′ = CH$_3$
c, R = CH$_3$; R′ = CH$_2$CH$_2$CH$_3$



10



11a, R = H; R′ = CH$_2$-c-C$_3$H$_5$
b, R = R′ = CH$_3$
c, R = CH$_3$; R′ = CN

ture **9c**.[9] The stereochemistry of **9c** as well as several other 6,14-*endo*-etheno- and 6,14-*endo*-ethanotetrahydrothebaine derivatives such as **10** and **11** has been confirmed by ^{1}H NMR studies.[10]

Results and Discussion

The structural and stereochemical information available from the x-ray and ^{1}H NMR studies described above was considered along with the application of ^{13}C NMR chemical shift theory,[3b,11] single frequency off-resonance decoupling (sford) experiments, deuterium labeling experiments, and comparisons to structurally related compounds[4,12,13] to arrive at the complete ^{13}C NMR chemical shift assignments of compounds 1–11 listed in Tables I–III.

Morphine Systems (Table I).[14] The two aromatic protonated carbons, C-1 (d)[15] and C-2 (d), of morphine (**1a**) and codeine (**1b**)[16] were easily differentiated from the olefinic carbons C-7 (d) and C-8 (d) by the upfield shift of the latter resonances on reduction of the double bond. Carbon 1 and C-2 were distinguished by the larger ortho effect from the C-3 hydroxyl substituent compared to the para effect from the C-4 *O*-alkyl moiety. Likewise, the even larger ortho effect of the C-3 methoxyl substituent caused the C-2 resonance in **1b** (and **2b**) to appear upfield relative to that in **1a** (and **2a**). Carbon 7 and C-8 of **1a** (and **1b**) were differentiated by the upfield shift of the C-7 resonance on going from **1a** to either 3,6-diacetylmorphine (**1c**) or 6-acetylmorphine (**1d**). The upfield shift was due to the γ effect of the C-6 acetoxyl group.[17]

The assignment of the C-3 (s) and C-4 (s) resonances was accomplished by comparing the compounds possessing a C-3 hydroxyl group to those containing a C-3 methoxyl group. On changing the hydroxyl group to the methoxyl group, substituent constants for methine carbons in substituted benzenes predict that the C-3 resonance should be shifted downfield by ca. 3–4 ppm while the C-4 resonance should go upfield by ca. 2 ppm owing to the larger ortho effect of the C-3 methoxyl substituent.[18] This was observed not only in going from **1a** to **1b** but also in going from **1a** and **2a** (C-3 hydroxyl) to dihydrocodeinone (**3**) and thebaine (**4**) (C-3 methoxyl). In addition, the C-3 resonance in heroin (**1c**) was upfield relative to **1a** and **1b** owing to the expected smaller α effect of the C-3 acetoxyl group.[18] In all the compounds the C-5 (d) signal appeared as a downfield resonance due to oxygen substitution. The C-6 signals of **1** and **2** appeared in the sford spectra as doublets in the 66–68-ppm range (due to hydroxyl substitution) that were replaced by a downfield singlet in the spectrum of **3** (C-6 carbonyl).

In compounds **1–4** the C-9 (d) and C-16 (t) resonances were downfield due to nitrogen substitution and easily distinguished from the carbons not attached to a heteroatom. In going from compounds **1–4** to the 14-hydroxy series (see Table II), the C-9 resonances were shifted downfield 2–4 ppm due to the additional β effect. Carbon 16 was distinguished by its consistency throughout the series. Carbon 10 (t) and C-15 (t), the two remaining methylenes, were distinguished by the fact that C-15 possessed more α and β substituents and fewer γ substituents than C-10 and thus appeared at lower field. (These assignments were also supported by the deuterium labeling experiments described below.) The C-10 methylene is at unusually high field in all the compounds except **4**. This is due to the combined γ effects from C-8, C-16, and the NCH$_3$. In the case of **4**, the skew relationship between C-8 and C-10 is prevented by the C-ring diene system.[19] Carbon 11, C-12, and C-13 all gave singlets in the sford spectra. The C-13 singlet was distinguished from the C-11 and C-12 signals by its high field position. Differentiation of the C-11 and C-12 singlets was

Table I. Carbon-13 NMR Chemical Shifts of Morphine Systems[a,b]

Identification of carbon[c]	1a[d]	1b[e]	1c[e]	1d[e]	2a[d]	2b[e]	3[e]	4[e]
1	118.60	119.39	119.10	119.34	118.08	118.75	119.73	118.85
2	116.36	112.81	121.63	117.20	116.77	112.90	114.63	112.26
3	138.45	142.12	132.02	138.41	138.03	141.18	142.82	142.45
4	146.30	146.17	149.14	145.53	146.08	145.97	144.75	144.40
5	91.49	91.15	88.47	87.88	90.04	90.22	90.95	88.81
6	66.38	66.18	67.89	68.27	66.19	66.86	207.26	152.15
7	133.43	133.39	129.24	129.78	25.71	26.72	39.21	95.59
8	128.50	127.83	128.21	128.02	19.61[f]	19.70[b]	25.21	111.19
9	58.09	58.76	58.67	58.62	59.02	59.40	59.40	60.47
10	20.20	20.38	20.43[f]	20.33	19.61[f]	18.92[b]	19.70	29.17
11	125.53	126.71	131.48	125.09	125.30	126.70	125.02	127.33
12	131.04	131.10	131.24	129.29	130.13	130.02	126.12	131.96
13	42.97	42.90	42.57	42.62	42.10	41.88	45.60	45.70[f]
14	40.63	40.33	40.38	39.94	38.24	40.08	40.33	132.94
15	35.56	35.40	34.92	34.71	37.27	37.06	34.61	36.73
16	46.05	46.28	46.28	46.33	46.10	46.48	46.83	45.70[f]
NCH_3	42.83	42.76	42.77	42.38	42.83	42.66	42.30	42.09
3 OCH_3		56.18				56.08	56.58	56.09
6 OCH_3								54.58
3 CH_3CO			20.43					
3 CH_3CO			168.16					
6 CH_3CO			20.43[f]	20.67				
6 CH_3CO			170.20	170.36				

[a] Chemical shifts are in parts per million relative to tetramethylsilane. [b] Signals in any one column may be reversed. [c] Numbering of carbons is shown in Chart I. [d] In dimethyl sulfoxide-d_6 solution. [e] In chloroform-d solution. [f] These resonances were twice as intense as those of other similar carbons.

Table II. Carbon-13 NMR Chemical Shifts of 14-Hydroxymorphine Systems[a,b]

Identification of carbon[c]	5a[d]	5b[e]	5c[e]	5d[e]	6a[e]	6b[e]	6c[e]	7a[e]	7b[e]
1	119.54	119.33	119.50	119.38	119.65	119.70	119.21	118.94	118.89
2	117.45	114.80	122.97	114.86	117.89[f]	117.92	114.63	117.63	117.53
3	139.15	142.47	132.13	144.23	138.81	138.77	142.65	137.37	139.81
4	142.91	144.06	147.35	146.41	143.45	143.41	144.65	145.57	142.30
5	86.57	86.89	87.66	87.01	90.21	90.36[g]	90.13	90.51[h]	95.78[i]
6	194.80	194.00	192.29	193.05	209.67	209.86	208.21	66.77	72.62
7	132.81	134.37	134.07	133.84	35.97	36.02[g]	35.90	22.97[b,h]	26.00[i]
8	150.61	147.29	145.94	145.94	31.04	31.20	31.20[b]	28.64	30.53
9	62.92	63.93	58.05	57.93	62.00	61.87	64.34	61.94	62.14
10	22.05	22.22	22.74	22.28	22.57	22.51	21.69	22.69[b]	22.63
11	124.08	124.79	130.48	125.61	123.76	123.85	124.67	125.23	123.72
12	130.86	130.25	131.07	129.90	128.82	128.84	129.14	130.84	131.38
13	46.38	46.42	46.77	46.65	50.78	50.88	49.94	47.26	47.26
14	67.70	67.57	76.56	76.73	70.53	70.27	70.10	69.89	70.38
15	28.92	29.74	28.73	28.86	30.27	30.44[j]	30.26[b]	33.22	29.56
16	45.12	44.95	45.13	45.24	43.20	43.48[j]	45.01	43.07	43.90
NCH_3	42.33	42.37	42.54	42.54			42.48		
OCH_3		56.64		56.58			56.58		
14 CH_3CO			169.91	169.79					
14 CH_3CO			21.50[b]	21.45					
3 CH_3CO			168.03						
3 CH_3CO			20.56[b]						
NCH_2					57.48	59.05		59.40	59.06
$CH_2{=}CH$					117.89[f]				
CH_2CH					134.98				
						9.23		9.18	9.23
						3.88 3.65		3.82 3.62	3.91[f]

[a-f] See footnotes to Table I. [g] The ^{13}C NMR spectrum of a sample of naltrexone which was partially deuterated in the 5 and 7 positions showed reduced intensities for the 90.36 and 36.02 ppm resonances. [h] The ^{13}C NMR spectrum of a sample of 6α-naltrexol which was partially deuterated in the 5 and 7 positions showed reduced intensities for the 90.51 and 22.97 ppm resonances. [i] The ^{13}C NMR spectrum of a sample of 6β-naltrexol which was partially deuterated in the 5 and 7 positions showed reduced intensities for the 95.78 and 26.00 ppm resonances. [j] The ^{13}C NMR spectrum of a sample of naltrexone which was partially deuterated in the 15,16 position showed reduced intensities for the 30.44 and 43.88 ppm resonance.

accomplished by comparing **1a** to **1c**. As shown in Chart I, C-11 is para to C-3 while C-12 is meta to C-3. Consequently, on changing the C-3 substituent from hydroxyl to acetoxyl, the C-11 resonance should be shifted downfield by ca. 5–6 ppm while that of C-12 should remain unchanged.[18] This type of shift was noted in going from **1a** to **1c** as well as from **5a** to **5c** (Table II). In addition, C-12 is bonded to C-13, a tertiary carbon, while C-11 is bonded to C-10, a primary carbon. Consequently, the C-11 singlet was broader than that of C-12 owing to long-range coupling to the

Table III. Carbon-13 NMR Chemical Shifts of 6,14-*endo*-Etheno- and 6,14-*endo*-Ethanotetrahydrothebaine System[a,b]

Identification of carbon[c]	8[e]	9a[e]	9b[e]	9c[e]	10[e]	11a[e]	11b[e]	11c[e]
1	119.15	119.44	119.05	119.00	119.05	119.34	118.95	119.59
2	113.39	116.27	113.69	113.63	113.83	116.66	114.03	114.76
3	141.59	137.58	141.58	141.53	141.63	137.58	141.49	142.22
4	147.76	146.60	147.92	147.87	146.60	145.60	146.80	147.05
5	95.00	98.81	98.61	98.61	94.47	97.05	96.76	96.22
6	81.02	83.98	83.98	83.93	77.40	80.42	80.18	79.64
7	50.47	46.43	48.48	46.52	49.40	47.69	47.65	47.45
8	29.74	30.42	30.86	30.43	30.23	32.14	32.23	31.45[b]
9	59.76	59.83	59.83	59.79	61.21	58.33	61.16	59.40
10	22.21	22.13	22.09	22.04	21.84	22.77	21.75	28.87
11	127.96	127.19	128.22	128.22	128.56	127.54	128.61	125.73
12	133.78	133.73	134.12	134.12	132.31	132.17	132.32	130.22
13	47.24	47.20	47.01	46.94	45.60	47.06	46.04	45.60
14	43.01	42.67[b]	42.71	42.62	35.41	35.94	35.89	35.30
15	33.26	33.31[g]	33.40	33.40	35.02	35.35	35.36[h]	33.30
16	45.24	45.40[g]	45.35	45.30	45.06	43.70	45.01[h]	41.35
17	125.73	124.60	124.71	125.00	17.36	17.50	17.41	17.02
18	135.66	135.14	135.05	134.99	28.46	29.55[b]	29.75	31.55[b]
19	208.68	75.25	73.25	74.67	210.54	74.57	74.18	73.89
20	30.23	23.89	25.16[b]	23.89	33.60	24.77[b]	24.72[b]	24.72[b]
21		42.87[b]	28.57[b]	43.06		29.79[b]	29.75[b]	29.55[b]
22		15.65		15.70				
23		14.53		14.58				
3 OCH_3	56.46		56.72	56.62	56.62		56.77	56.67
6 OCH_3	53.24	55.06	55.06	54.92	52.09	52.52	52.57	52.67
NCH_3	43.31	43.35	43.40	43.35	43.36		43.35	
NCH_2						59.79		
>CH						9.11		
CH_2 (cyclopropyl)						3.99 3.31		
N—CN								117.88

[a-f] See footnotes to Table I. [g] The ^{13}C NMR spectrum of etorphine which was partially deuterated in the 15,16 positions showed reduced intensities for the 33.31 and 45.40 ppm resonances. [h] The ^{13}C NMR spectrum of a sample of diprenorphine which was partially deuterated in the 15,16 positions showed reduced intensities for the 35.36 and 45.01 ppm resonances.

methylene protons of C-10. In the case of codeine Wehrli has shown that C-11 had a smaller T_1 value than C-12.[20] The C-14 resonance was a doublet in the sford spectrum which shifted downfield in the 14-hydroxy derivatives (Table II). The *N*-methyl and *O*-methyl resonances appeared in the expected regions as quartets in the sford spectra.

Dihydromorphine (**2a**) and dihydrocodeine (**2b**) differ from **1a** and **1b** only in having the C-7, C-8 double bond reduced. The resulting methylenes were differentiated by comparing the spectra to the data obtained on alkylcyclohexanes.[21] The rather large shift difference between the C-7 (t) and C-8 (t) signals was due to the γ effect of the axial C-6 α-hydroxyl substituent as well as C-10 methylene on C-8. Dihydrocodeinone (**3**) possesses a C-6 carbonyl function in addition to the C-7 and C-8 methylenes. The C-6 singlet was easily identified as the lowest field resonance in the spectrum. The C-7 (t) and C-8 (t) of **3** were now differentiated by comparison to alkylcyclohexanones.[22] In this case, the C-8 and C-12 signals were further upfield than expected. This is probably due to conformational changes in ring C of **3**. Except for C-6, C-7, C-8, C-10 (see comments above), and C-14, the chemical shifts for thebaine (**4**) were essentially identical with those of **2**. In the sford spectrum C-6 and C-14 appeared as singlets in the expected low-field region. Carbon 7 and C-8 gave doublets in the olefinic region. The C-7 doublet was upfield from the C-8 doublet owing to the γ effect of the C-6 methoxyl substituent and the electron-donating effect of the oxygen at C-6.

14-Hydroxymorphine Systems (Table II). All of the compounds in Table II were characterized by possessing a C-14 singlet at 67–77 ppm due to the C-14 hydroxyl or acetoxyl substituent. These substituents also caused a downfield shift (β effect) of the C-8, C-13, and C-9 resonances and an upfield shift (γ effect) of C-7 and C-15 resonances relative to similar compounds in Table I that do not contain a C-14 substituent. The aromatic carbons followed a pattern similar to the compounds in Table I. The larger downfield shift for C-2, C-4, and C-11 in the case of **5c** was due to the larger ortho and para effects of the C-3 acetoxyl function compared to the hydroxyl or methoxyl groups.[18] The C-3 resonance of 3,14-diacetoxymorphinone (**5c**) was again upfield relative to the other compounds owing to the expected smaller α effect of the C-3 acetoxyl group.[18] As before, C-5 (d) appeared at low field owing to oxygen substitution. Surprisingly, there is only a small γ interaction between C-5 and the C-14 hydroxyl substituent. In the case of naltrexone (**6b**), the fact that the 90.36-ppm resonance was reduced in intensity in the spectrum of a naltrexone-5,7,7-d_3 confirms this assignment for C-5.

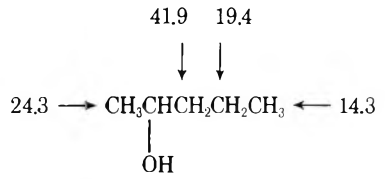
The carbonyl carbon (C-6) of **5a–d** and **6a–c** was easily identified as the lowest field resonance in the spectra. The C-6 singlet of **5a–d** appeared at higher field relative to **6a–c** owing to the conjugation of C-6 with the C-7, C-8 double bond of **5a–d.** This downfield singlet (sford) was replaced by a doublet in the 66–73-ppm region in the case of 6α-naltrexol (**7a**) and 6β-naltrexol (**7b**). The C-6 doublet of **7a,** in which the hydroxyl group is axial, appeared at a higher field than that of **7b,** which possesses an equatorial hydroxyl group. The C-8 (d) resonance of **5a–d** was at considerably lower field than the C-7 (d) resonance owing to conjugation with the C-6 carbonyl group.[23]

In 6α-naltrexol (**7a**) and 6β-naltrexol (**7b**) the assignment of the C-7 and C-8 resonances was confirmed by examining the spectra of samples containing deuterium on

C-5 and C-7. In these compounds, the C-7 signal now appeared upfield from the C-8 signal, in contrast to their relative positions in dihydromorphine (**2a**) and dihydrocodeine (**2b**). This shift is due to the effect of the axial C-14 hydroxyl substituent. In addition, the C-8 signal of **7a** appeared at higher field relative to **7b.** This was attributed to the larger γ effect on C-8 from the axial C-6 hydroxyl group of **7a.**

Compounds **5a–d** and **6c,** all of which possess NCH_3 groups, showed similar resonances for C-16 (t). Naloxone (**6a**), naltrexone (**6b**), and the naltrexols (**7a** and **7b**), all of which contain a larger *N*-alkyl substituent, showed resonances at slightly higher field for C-16 owing to the additional γ effects. The *N*-methyl, *O*-methyl, and acetyl methyl groups appeared as quartets (sford) in the expected region. The chemical shifts of the methylene carbon (t) and the two olefinic carbons (d) of the *N*-allyl group of naloxone (**6a**) were assigned by comparison to other allyl compounds.[24] The chemical shifts for the cyclopropyl groups in **6b, 7a,** and **7b** appeared at very high field. The cyclopropyl methine (d) came at ca. 9 ppm and the cyclopropyl methylene (t) appeared at ca. 3–4 ppm.

6,14-*endo*-Etheno- and 6,14-*endo*-Ethanotetrahydrothebaine Systems (Table III). The assignments for C-1–C-5, C-9–C-13, C-15, C-16, and the *N*-methyl, *N*-cyclopropylmethyl, and *O*-methyl followed the same reasoning presented for the compounds listed in Tables I and II. In the case of etorphine (**9a**) and diprenorphine (**11a**) the correctness of the C-15 and C-16 assignments was verified by demonstrating that **9a** and **11a** which were partially deuterated in the 15,16 position showed reduced intensities for these resonances. These results combined with the constancy of the C-15, C-16 resonances in all the compounds listed in Tables I–III support the C-15 and C-16 assignments in these cases as well. Carbon 6 and C-14 appeared as singlets (sford) which were shifted upfield on reduction of the C-17, C-18 double bond. Carbon 7 gave a new downfield doublet in the sford spectrum not present in the first two classes of compounds. The C-8 signal was the only remaining triplet in the case of thevinone (**8**), 19-methylthevinol (**9b**), and dihydrothevinone (**10**). It was also noted that the chemical shift of C-8 was affected by changing the substituent on the nitrogen which is γ to C-8 (compare **11b** to **11c**). Carbon 17 (d) and C-18 (d) were easily recognized by their low-field positions in the case of **8** and **9.** These doublets (sford) were replaced by two new triplets in the case of **10** and **11,** in which the C-17, C-18 double bond had been reduced. The C-17 and C-18 atoms are comparable to the C-8 and C-7 atoms, respectively, in the morphine systems. Thus, C-17 in compounds **8–11** was shifted upfield by a large γ interaction with C-10 similar to C-8 in the case of the morphine compounds listed in Tables I and II. Reduction of the C-17, C-18 double bond also resulted in a large downfield shift of C-14 and a smaller downfield shift of C-9 and C-8. Fulmor and co-workers[10] have noted that the C-9 and C-8 protons are also affected by reduction of the C-17, C-18 double bond. Carbon 19 was a singlet in all the compounds. In the case of **8** and **10** this resonance appeared at very low field owing to the oxo group, and in the case of the other compounds it was observed as a new peak in the C–O region. In compounds **8** and **10,** C-20 gave a quartet which appeared in the region expected for a methyl next to a carbonyl group. In the case of **9b** and **11a–c,** C-20 and C-21 were nonequivalent methyl groups that were easily distinguished by their multiplicities. The C-20, C-21, C-22, and C-23 carbons of **9a** and **9c** could be assigned by comparison to the assignments of 2-pentanol.[25] The C-21 and C-22 resonances were at slightly lower and higher field, respectively, in our compounds owing to the additional β and γ effects in these compounds.



The x-ray crystallographic studies[1] of van den Hende and Nelson[9] on the 6,14-*endo*-etheno analogue **9c** indicated that the spatial configuration of rings A, B, and D of this compound resembled that of codeine and morphine. Owing to the added C-7, C-8 bridge, ring C had a different conformation. The close similarities of the chemical shifts of C-10, C-16, and the aromatic carbons of **8–11** to comparable compounds listed in Tables I and II showed that the conformations of rings A, B, and D of the 6,14-*endo*-etheno- and 6,14-*endo*-ethanotetrahydrothebaine systems were similar to the simple morphine systems in $CDCl_3$.

The chemical shift of C-5 in **8** and **10,** which possess a C-19 keto group, was upfield ca. 3 ppm relative to **9** and/or **11** derivatives which contain a C-19 hydroxyl substituent. Apparently the conformation of the methyl of the C-6 methoxy group, which is γ to C-5, was different in the two cases. This arises from the fact that the C-19 hydroxyl proton of **9** and/or **11** can form an intramolecular hydrogen bond to the oxygen of the C-6 methoxyl group.[9]

Experimental Section

Morphine (**1a**), dihydrocodeine (**2b**), thebaine (**4**), and **6c** were obtained from S. P. Penick and Co., Lyndhurst, N.J. Codeine (**1b**) was purchased from Merck Chemical Co., Rahway, N.J. Naloxone (**6a**) and naltrexone (**6b**) were supplied by Endo Laboratories, Inc., Garden City, N.J.

3,6-Diacetylmorphine (**1c**) was prepared from **1a** by acetylation with acetic anhydride.[26] 6-Monoacetylmorphine (**1d**) was synthesized in three steps from **1a** using procedures described for the corresponding *N*-nor compound.[27] Catalytic hydrogenation of **1a** afforded dihydromorphine (**2a**). Dihydrocodeinone (**3**) was obtained in two steps from **4** by literature procedures.[28,29]

Treatment of **4** with *m*-chloroperbenzoic acid in acidic media afforded 14-hydroxycodeinone (**5b**),[30] which was acetylated to get 14-acetoxycodeinone (**5d**).[31] O-Demethylation of **5b** by the method of Weiss[32] gave 14-hydroxymorphinone (**5a**), which was subsequently acetylated to get 3,6-diacetoxymorphinone (**5c**).[33] 6α-Naltrexol (**7a**) was obtained by reducing **6b** with either $NaBH_4$ in THF or L-Selectride.[34] The 6β-alcohol **7b** was prepared by the formidinesulfinic acid reduction of **6b.**[35]

The Diels–Alder reaction of thebaine (**4**) with methyl vinyl ketone afforded 7α-acetyl-6,14-*endo*-ethenotetrahydrothebaine (thevinone, **8**).[36] Treatment of **8** with the appropriate Grignard reagent afforded 19-methylthevinol (**9b**) and 19-propylthevinol (**9c**), while catalytic hydrogenation of **8** gave dihydrothevinone (**10**).[37] Addition of MeMgI to **10** provided dihydro-19-methylthevinol (**11b**).[37] 3-O-Demethylation of **9c** with KOH at 210 °C yielded 7α-(1-hydroxy-1-methylbutyl)-6,14-*endo*-ethenotetrahydrooripavine (etorphine, **9a**).[38] N-Demethylation of **11b** with CNBr gave *N*-cyano-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethanotetrahydronorthebaine (**11c**).[38] Subsequent treatment of **11c** with KOH at 225–230 °C removed the *N*-cyano group and effected 3-O-demethylation. The resultant *N*-nor compound was N-alkylated in DMF with cyclopropylmethyl bromide in the presence of excess $NaHCO_3$ to get *N*-cyclopropylmethyl-7α-(1-hydroxy-1-methylethyl)-6,14-*endo*-ethanotetrahydronororipavine (diprenorphine, **11a**).

Naltrexone-5,7,7-d_3 was prepared by heating **6b** at 80 °C in a sealed tube with potassium *tert*-butoxide and D_2O–DMF.[39] Reduction of naltrexone-5,7,7-d_3 provided samples of 6α-naltrexol-5,7,7-d_3 and 6β-naltrexol-5,7,7-d_3. Naltrexone-15,16-d_2, etorphine-15,16-d_2, and diprenorphine-15,16-d_2 were obtained by reducing the corresponding 15,16-didehydro compounds with deuterium gas over a 10% Pd/C catalyst. The 15,16-didehydro compounds were prepared by oxidation of the respective bases with $Hg(OAc)_2$ in HOAc.[40,41]

The ^{13}C NMR spectra were determined at 25.03 MHz on a modified JEOL JNM-PS-100 FT NMR interfaced with a Nicolet 1085 Fourier-transform computer system. The samples were spun in 10 mm o.d. tubes. The spectra were recorded at ambient temperature by using the deuterium resonance of the solvent as the internal lock signal. Chloroform-*d* or dimethyl sulfoxide-d_6 were used as the solvent and all δ values reported in the tables were in parts per million downfield from Me_4Si: $\delta^{Me_4Si} = \delta^{CDCl_3} + 76.91 = \delta^{Me_2SO\text{-}d_6} + 39.56$. All proton lines were decoupled by a broad band (~2500 Hz) irradiation from an incoherent 99.538-MHz source. Interferograms were stored in 8K of computer memory (4K output data points in the transformed phase corrected real spectrum), and chemical shifts were measured on 5000 Hz sweep width spectra. Typical pulse widths were 12.5 μs (45° flip angle), and the delay time between pulses was fixed at 1.0 s. Normally 1012 (twice as many for single frequence off-resonance experiments) data accumulations were obtained on a 100 mg/2 ml of solvent sample. The precision of the chemical shifts is ±0.05 ppm.

Acknowledgment. We thank Dr. M. E. Wall of this laboratory for his kind encouragement and support of this work and Dr. S. G. Levine, North Carolina State University at Raleigh, for helpful discussions involving this work. We also thank Dr. F. M. Hauser, Dr. T. Chen, Dr. D. Prakash, A. Philip, D. Kohl, D. Kotchmar, and R. Austin for their invaluable assistance on the syntheses, and R. Mazzeo for his assistance in obtaining the spectral data.

Registry No.—**1a,** 57-27-2; **1b,** 76-57-3; **1c,** 561-27-3; **1d,** 2784-73-8; **2a,** 509-60-4; **2b,** 125-28-0; **3,** 125-29-1; **4,** 115-37-7; **5a,** 41135-98-2; **5b,** 508-54-3; **5c,** 50798-31-7; **5d,** 978-76-7; **6a,** 465-65-6; **6b,** 16590-41-3; **6c,** 57664-96-7; **7a,** 20410-98-4; **7b,** 49625-89-0; **8,** 15358-22-2; **9a,** 14521-96-1; **9b,** 16180-23-7; **9c,** 16180-26-0; **10,** 16196-82-0; **11a,** 14357-78-0; **11b,** 16196-64-8; **11c,** 16671-47-9.

References and Notes

(1) This work was supported under Contract HSM-42-73-228 with the National Institute on Drug Abuse, Division of Research, Biomedical Research Branch.
(2) (a) Research Triangle Institute; (b) North Carolina State University.
(3) (a) E. Wenkert, J. S. Bindra, C. J. Chang, D. W. Cochran, and F. M. Schell, *Acc. Chem. Res.*, **7,** 46 (1974); (b) C. G. Moreland, A. Philip, and F. I. Carroll, *J. Org. Chem.*, **39,** 2413 (1974), and references cited therein.
(4) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley-Interscience, New York, N.Y., 1972.
(5) Y. Terui, K. Tori, S. Maeda, and Y. K. Sawa, *Tetrahedron Lett.*, 2853 (1975).
(6) M. Mackay and D. C. Hodgkin, *J. Chem. Soc.*, 3261 (1955).
(7) S. Okuda, S. Yamaguchi, Y. Kawazoe, and K. Tsuda, *Chem. Pharm. Bull.*, **12,** 104 (1964).
(8) H. L. Holmes and G. Stork in "The Alkaloids", Vol. II, Part II, R. H. Manske, Ed., Academic Press, New York, N.Y., 1952, Chapter 8.
(9) J. H. van den Hende and N. R. Nelson, *J. Am. Chem. Soc.*, **89,** 2901 (1967).
(10) W. Fulmor, J. E. Lancaster, G. O. Morton, J. J. Brown, C. F. Howell, C. T. Nora, and R. A. Hardy, Jr., *J. Am. Chem. Soc.*, **89,** 3322 (1967).
(11) G. E. Maciel in "Topics in Carbon-13 NMR Spectroscopy", Vol. 1, G. C. Levy, Ed., Wiley, New York, N.Y., 1974, Chapter 2.
(12) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, and references cited therein.
(13) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, and references cited therein.
(14) Terui and co-workers[5] have reported ^{13}C NMR spectral data for some of the compounds listed in Tables I and II. Their assignments are in agreement with ours; however, their method of establishing the assignments as well as the interpretation of unusual chemical shifts differ from ours.
(15) The letter in parenthesis refers to the signal multiplicity obtained from single frequency off-resonance experiments; s = singlet, d = doublet, t = triplet, and q = quartet.
(16) Johnson and Jankowski have reported the ^{13}C NMR spectrum of codeine phosphate (Spectra 479 in ref 4). However, they were able to make assignments to only 8 of the 18 carbons. Taking into account that their spectrum was of the salt in D_2O, our assignments are in agreement with theirs.
(17) See E. Wenkert, M. J. Gasić, E. W. Hagaman, and L. D. Kwart, *Org. Magn. Reson.*, **7,** 51 (1975), and references cited therein, for effect of ^{13}C NMR chemical shifts on acylation of allyl alcohols.
(18) Reference 13, p 196.
(19) The γ effect of the NCH_3 group on C-10 is exemplified by the downfield shift of C-10 on going from **11b** (NCH_3) to **11c** (NCN) (see Table III). In the case of the model compounds 3-methoxymorphinone (NH) and 3-methoxy-*N*-methylmorphinone (NCH_3) Terui and co-workers[5] noted that the C-10 resonance was at higher field in the latter compound.
(20) F. W. Wehrli, *J. Chem. Soc., Chem. Commun.*, 379 (1973).
(21) Reference 13, p 163.
(22) Reference 13, p 173.
(23) Reference 12, p 67.
(24) Reference 13, p 188.
(25) Reference 13, p 141.
(26) C. R. Wright, *J. Chem. Soc.*, **27,** 1031 (1874).
(27) K. C. Rice and A. E. Jacobson, *J. Med. Chem.*, **18,** 1033 (1975).
(28) L. Small, H. M. Fitch, and W. E. Smith, *J. Am. Chem. Soc.*, **58,** 1457 (1936).
(29) M. Freund and E. Speyer, *Ber.*, **53,** 2250 (1920).
(30) F. M. Hauser, T. Chen, and F. I. Carroll, *J. Med. Chem.*, **17,** 1117 (1974).
(31) R. E. Lutz and L. Small, *J. Org. Chem.*, **4,** 220 (1939).
(32) U. Weiss, *J. Org. Chem.*, **22,** 1505 (1957).
(33) J. Fishman, M. L. Cotter, and B. I. Norton, *J. Med. Chem.*, **16,** 556 (1973).
(34) Aldrich Chemical Co. We are grateful to Dr. R. Reuning for calling this reagent to our attention.
(35) N. Chatterjie, C. E. Inturrisi, H. B. Dayton, and H. Blumberg, *J. Med. Chem.*, **18,** 490 (1975).
(36) K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, **89,** 3267 (1967).
(37) K. W. Bentley, D. G. Hardy, and B. Meek, *J. Am. Chem. Soc.*, **89,** 3273 (1967).
(38) K. W. Bentley and D. G. Hardy, *J. Am. Chem. Soc.*, **89,** 3281 (1967).
(39) (a) D. H. R. Barton, A. J. Kirby, and G. W. Kirby, *J. Chem. Soc. C,* 929 (1968); (b) D. H. R. Barton, R. James, G. W. Kirby, D. W. Turner, and D. A. Widdowson, *J. Chem. Soc. C,* 1529 (1968).
(40) J. W. Lewis, M. J. Rance, and G. R. Young, *J. Med. Chem.*, **17,** 465 (1975).
(41) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77,** 439 (1955).

Alkaloids of *Vinca rosea* L. (*Catharanthus roseus* G. Don). XXXVII. Structure of Vincathicine[1]

S. S. Tafur, J. L. Occolowitz, T. K. Elzey, Jonathan W. Paschal, and Douglas E. Dorman*

Lilly Research Laboratories, Indianapolis, Indiana 46206

Received September 22, 1975

The structure of the dimeric alkaloid vincathicine is deduced from physical and chemical methods. The conversion of leurosine to vincathicine under acidic conditions is described.

Vincathicine (1), a dimeric indole alkaloid showing moderate oncolytic activity in experimental animals, was first isolated by Svoboda and Barnes.[2] On the basis of ultraviolet, infrared, and ^1H nuclear magnetic resonance (NMR) spectroscopies, these authors suggested that vincathicine included an oxindole moiety. Since this initial report, no further work on the structure of vincathicine has been published. The more recent discovery that vincathicine is chemically related to leurosine[3] has rekindled interest in this alkaloid.

Table I. ^{1}H NMR Data for Vinblastine and Vincathicine

	Proton	VLB[a]	Vincathicine[a]
Vindoline portion	2	3.70	3.67
	9	6.63	6.45
	11-OCH_3	3.77	3.76
	12	6.10	6.08
	14	5.27	5.23
	15	5.82	5.79
	16-OH	9.5	9.5
	17	5.46	5.40
	18-CH_3	0.80	0.57[b]
	21	2.64	2.58
	$COOCH_3$	3.77	3.77
	NCH_3	2.70	2.69
	$OCOCH_3$	2.09	2.05
"Indole" portion	9′	~7.1	7.60[c]
	10′		7.33[d]
	11′		7.57[d]
	12′	~7.5	7.66[c]
	18′-CH_3	0.87	0.53[b]
	NH	8.03	
	$COOCH_3$	3.59	3.65

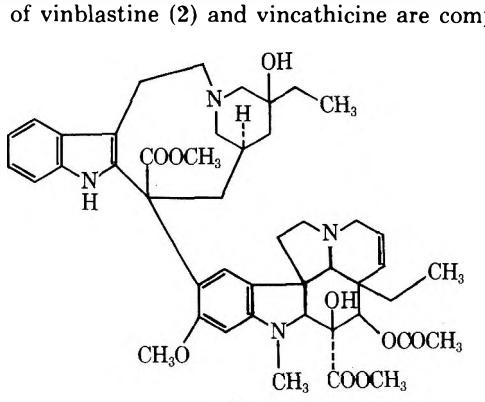
[a] Spectra taken in deuteriochloroform. Chemical shifts are measured in parts per million from internal Me_4Si. [b-d] Resonances so designated cannot be differentiated in assignment.

Vincathicine is isomeric with leurosine (MS: found, 808.4038; calcd for $C_{46}H_{56}N_4O_9$, 808.4047). Peaks which can be attributed to fragmentation of the vindoline moiety of dimeric alkaloids[4] were present in the mass spectrum of vincathicine. These included *m/e* 649 (M − $C_6H_7O_5$), 469 ($C_{26}H_{33}N_2O_6$), 282 ($C_{14}H_{20}NO_5$), and 135 and 122. A peak at *m/e* 353 ($C_{21}H_{25}N_2O_3$) corresponds to the molecular ion less the vindoline radical.

Vincathicine proved to be particularly prone to intermolecular transmethylation in the mass spectrometer. By determining the spectrum from a film at the lowest possible temperature, the transmethylation peak at *m/e* 822 and peaks at *m/e* 765 and 750, nominally M − C_2H_3O and M − $C_2H_2O_2$, respectively, were eliminated.

A relatively intense peak at *m/e* 366 ($C_{22}H_{26}N_2O_3$), which is unshifted in the spectra of 16-acetylvincathicine and 17-deacetylvincathicine and occurs at *m/e* 368 in the spectrum of dihydrovincathicine, must arise from the modified velbanamine moiety plus CH. It is difficult to account for this peak, as the additional carbon atom would have to arise by the unlikely fission of the aromatic ring of the vindoline moiety. We believe that this peak arises from a hitherto unobserved intramolecular transmethylation. In support of this contention is a peak at *m/e* 661 (M − $C_5H_7O_5$), corresponding to loss of the oxygenated ethylene bridge of the vindoline moiety less CH, indicating that the itinerant carbon is transferred from the oxygenated ethylene bridge of vindoline to the modified velbanamine moiety.

In Table I, the chemical shifts of the identifiable ^{1}H resonances of vinblastine (**2**) and vincathicine are compared.



2

It will be noted that the two spectra correspond well in the vindoline halves of the molecules except for protons at positions 9 and 18. In our experience,[5] chemical shift changes of this sort are frequently attributable to significant changes in the structure and/or conformation of the other half of the molecule. In support of this, the ^{1}H NMR spectra of the modified velbanamine portions of vinblastine and vincathicine are quite different. It is particularly significant that the N proton which usually occurs in the spectra of these alkaloids is missing. This fact argues against the possibility of an oxindole structure.[2]

^{13}C NMR spectra of vincathicine are shown in Figure 1. The lower spectrum was measured under normal conditions and with full proton decoupling. The middle spectrum of Figure 1 was measured using an inversion-recovery pulse sequence designed to identify methyl and nonprotonated carbon resonances. The upper spectrum, measured using the same pulse sequence in conjunction with off-resonance decoupling, distinguishes the resonances of methylene and methine carbons. This procedure[6] allows clear distinction of the resonances of methyl, methylene, methine, and nonprotonated carbons (see Table II).

The ^{13}C spectrum of vincathicine shows 25 resonances whose chemical shifts and multiplicities are consistent with the spectrum of the dihydroindole (10-vindolinyl) portion of vinblastine.[6,7a] This supports the conclusion, drawn from mass spectral and NMR evidence (vide supra), that vincathicine contains a 10-vindolinyl moiety, and "subtraction"[1] of these resonances from the full ^{13}C NMR spectrum of vincathicine should yield the spectrum of the other half of the molecule. Of these 21 resonances, the two due to the carbomethoxyl group are easily assigned. This leaves seven resonances due to sp^2-hybridized carbons, rather than the eight typical of an indole system. Furthermore, one of these resonances occurs in the "carbonyl" region of the spectrum. The chemical shift (187.0 ppm) of this resonance is different than observed for the carbonyl resonance of oxindoles,[7b] thereby supporting the above conclusion that vincathicine does not include an oxindole moiety. The chemical shifts of these seven resonances are, in fact, in good agreement with those of a 3*H*-indolenine system.[8] Also in support of the indolenine structure was the fact that vincathicine was reduced by borohydrides under mild conditions[9] to yield a dihydro derivative containing a new exchangeable proton.

In the remainder of the ^{13}C NMR spectrum of this unknown half of vincathicine, there are 12 resonances, i.e., one more than in the other dimeric alkaloids.[5,6,7a] The spectra of Figure 1 clearly demonstrate three of these resonances to represent nonprotonated carbons (75.8, 63.1, and 57.1 ppm), while one is due to a methyl (7.0 ppm). The chemical shift of this methyl is very similar to those of a series of alkaloids containing an ethyl group attached to a nonprotonated carbon bearing an oxygen atom.[5,6,7a,10] Because the carbomethoxyl chemical shifts appear similar to those of other examples, one may suppose that this group is attached to a quaternary carbon 16′ as usual. The remaining singlet resonance can be attributed to the quaternary carbon of an indolenine system. Of the remaining eight resonances, two were shown to be due to methines and the remainder to methylenes.

The key to the structure of vincathicine is derived from chemical evidence. During their early work with leurosine, Neuss and his co-workers discovered that under a variety of acidic conditions, this alkaloid was converted to two major products, one of which was vincathicine.[2] On the basis of this evidence and the recent proposal[7a,11] of **3** as the structure of leurosine, we may therefore propose that vincathicine has either structure **1** or **4** (Figure 2). Either

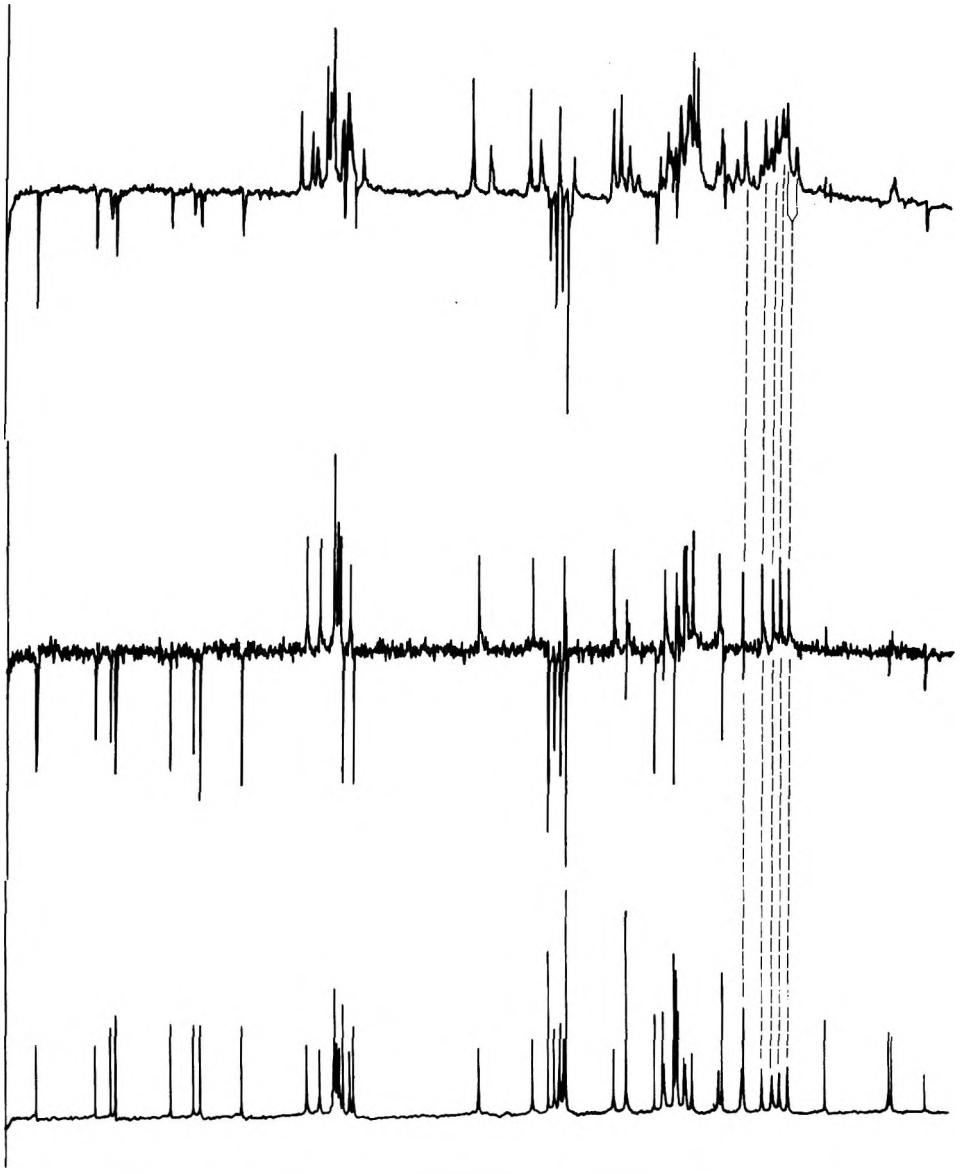


Figure 1. ^{13}C NMR spectra of vincathicine. Lower: spectrum measured using $(-\pi/2-T-\pi/2-)$ pulse sequence with T = 3 s. Middle: spectrum measured using $(-\pi-\tau-\pi/2-T-)$ pulse sequence with τ = 0.35 s and T = 5 s. Upper: spectrum measured as in middle, but with specific decoupling at about δ 7.

structure fits the constraints imposed by the multiplicities of the carbon resonances, and both include the 3*H*-indolenine system. Carbon chemical shifts, however, strongly favor structure **1**. From structure **4**, for example, one would expect that one of the methine resonances would occur in the region of chemical shifts typical of carbinyl carbons (C-15′).[12] A model for this resonance might be the chemical shift of the similarly substituted carbon 15′ vincadioline (75.2 ppm).[6] In fact, the two doublet resonances occur at substantially higher field (28.9 and 49.2 ppm). In contrast, one of the singlet resonances of vincathicine (75.8 ppm) is at lower field than would be expected from structure **4**. From these and other arguments, we therefore favor structure **1** for vincathicine. Also consistent with the tertiary alcohol structure **1** is the fact that acetylation has no effect on the indolenine half of the molecule.

In fact, the assumption of **1** as the correct structure leads to a reasonable, if tentative, assignment of all the carbon resonances of vincathicine (cf. Table II). Thus, the C-15′ resonance of vincathicine is nearly 8 ppm lower field than its position in vinblastine,[6,7a] consistent with its more highly branched character.[13] Carbons 6′ and 20′ are also deshielded relative to vinblastine, a result expected by virtue of the fact that each of these carbons has one more β-carbon[13] in vincathicine. It is surprising that C-14′ is slightly more shielded in vincathicine, since this carbon also is subject to an additional β effect. A study of molecular models suggests that in structure **1**, this carbon is subject to severe steric interactions.[14]

Studies of molecular models also show that in both **1** and **4**, the 18′-methyl protons would be expected to be shielded by the diamagnetic anisotropy of the 3*H*-indolenine system, as, in fact, is observed (Table I). In the case of **1**, however, the models also suggest that one of the 19′-methylene protons would be spatially proximal to H-9′. Such a situation should give rise to a nuclear Overhauser effect (NOE)[15] between these protons. Irradiation of the overlapping methyl triplets near δ 0.5 led to no observable changes in the aromatic region, indicating that the rotameric states available to the ethyl group do not bring the 18′-methyl protons close to H-9′, a conclusion supported by the models. Irradiation at approximately δ 1.8, however, leads both to changes in the appearance of the overlapping methyl triplets and to a small (5%) but reproducible increase in the

Table II. ^{13}C NMR Spectrum of Vincathicine

Dihydroindole portion				"Indole" portion			
Carbon	δ[a]	"T_1"[b]	Ord[c]	Carbon	δ[a]	"T_1"[b]	Ord[c]
2	83.0	d/t	d	2′	187.0	s	
3	50.6[d]	d/t	t	3′	52.6[d]	d/t	t
5	50.9[d]	d/t	t	5′	55.0[d]	d/t	t
6	43.6	d/t	t	6′	32.2[e]	d/t	t
7	53.0	s		7′	57.1[f]	s	
8	122.8	s		8′	144.2	s	
9	123.6	d/t	d	9′	124.6[g]	d/t	d
10	120.6	s		10′	127.7[g]	d/t	d
11	159.1	s		11′	124.1[g]	d/t	d
12	94.3	d/t	d	12′	121.3[g]	d/t	d
13	152.8	s		13′	154.0	s	
14	124.6	d/t	d	14′	28.9	d/t	d
15	130.5	d/t	d	15′	49.2	d/t	d
16	79.6	s		16′	63.1[f]	s	
17	76.3	d	d	17′	38.7[e]	d/t	t
18	7.6	CH_3		18′	7.0	CH_3	
19	30.6	d/t	t	19′	34.4[e]	d/t	t
20	42.8	s		20′	75.8	s	
21	65.7	d/t	d	21′	63.1[d]	d/t	t
*$COOCH_3$	170.7	s		*$COOCH_3$	174.8	s	
$COO*CH_3$	52.2	CH_3		$COO*CH_3$	52.6	CH_3	
$N*CH_3$	38.4	CH_3					
CH_3*COO	171.7	s					
$*CH_3COO$	21.1	CH_3					
$AR\text{-}O*CH_3$	55.4	CH_3					

[a] Chemical shifts in parts per million from internal Me_4Si. [b] Subdivision of carbon types by inversion-recovery pulse sequence (see text): "s" represents singlet (nonprotonated carbon), "CH_3" signifies a methyl resonance, and "d/t" means doublet or triplet (i.e., methines or methylenes, respectively). [c] Subdivision of resonances on the basis of off-resonance decoupling (ord): "d" indicates doublet and "t" indicates triplet. [d-g] Resonances so designated cannot be distinguished in assignment.

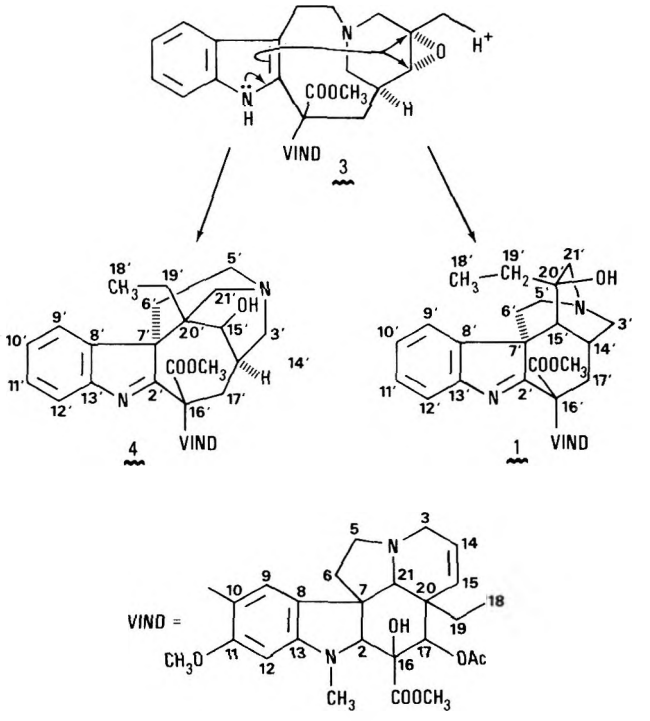


Figure 2. Acid-catalyzed conversion of leurosine (3) to vincathicine (1).

integral of the overlapping H-9′ and H-12′ resonances. These results therefore support the proposal of 1 as the structure of vincathicine.

Experimental Section

Vincathicine was isolated by the method of Svoboda and Barnes.[2] Proton NMR spectra were measured on a Varian HA-100 spectrometer, while ^{13}C NMR spectra were measured on a JEOL PFT-100 spectrometer equipped with a JEOL EC-100 data system. All spectra were measured at ambient temperature (ca. 30 °C) in chloroform solution; concentrations ranged from 0.05 to 0.1 M. The conditions of data accumulation and transformation should lead to line broadening of less than 0.7 Hz. Chemical shifts are considered accurate to ±0.1 ppm. Mass spectra were measured on a Varian MAT Model 731 mass spectrometer using direct introduction of sample.

16-Acetylvincathicine. An excess of acetic anhydride was added to a solution of 35 mg of vincathicine in dry pyridine and was stirred at room temperature overnight. After evaporating to dryness in vacuo, the reaction mixture was shown by TLC on silica gel in ethyl acetate–95% ethanol (3:1) to contain a small amount of unreacted vincathicine and one reaction product. Preparative TLC separation afforded 17.4 mg of a monoacetate of vincathicine (M^+ 850). The ^1H NMR data were consistent with placement of the acetyl at C-16.[5]

Dihydrovincathicine. To a solution of 2 ml of HCl in 48 ml of methanol, 700 mg of sodium cyanoborohydride was added. Two hundred milligrams of vincathicine was added with stirring and refluxed for 60 min. Fifty milliliters of water was added to the reaction solution, and the methanol was removed in vacuo. The solution was made alkaline with ammonium hydroxide and extracted with chloroform. The chloroform extract was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness in vacuo. TLC on silica gel in ethyl acetate–methanol (1:1) indicated unreacted vincathicine and one reduction product. Preparative TLC yielded 40 mg of dihydrovincathicine (M^+ 810).

In alkaline solution, the C-17 acetyl is readily hydrolyzed. Consequently, attempts to reduce vincathicine with sodium borohydride in alkaline or neutral solution yielded only 17-deacetylvincathicine (M^+ 766).

Registry No.—1, 57665-10-8; 2, 865-21-4.

References and Notes

(1) Previous paper: S. Tafur, W. E. Jones, D. E. Dorman, E. E. Logsdon, and G. H. Svoboda, *J. Pharm. Sci.*, **64**, 1953 (1975).
(2) G. H. Svoboda and A. J. Barnes, Jr., *J. Pharm. Sci.*, **53**, 1227 (1964).
(3) N. Neuss and S. Tafur, patent applied for.
(4) N. Neuss et al., *J. Am. Chem. Soc.*, **86**, 1440 (1964); D. J. Abraham and N. R. Farnsworth, *J. Pharm. Sci.*, **58**, 694 (1969).
(5) D. E. Dorman, J. W. Paschal, and T. K. Elzey, unpublished results.
(6) D. E. Dorman and J. W. Paschal, submitted for publication.
(7) (a) E. Wenkert et al., *Helv. Chim. Acta*, **58**, 1560 (1975); (b) E. Wenkert et al., *Chem. Commun.*, 961 (1970).

(8) E. Kleinpeter and R. Borsdorf, *J. Prakt. Chem.*, **315**, 765 (1973).
(9) W. A. Remers in "Chemistry of the Heterocyclic Compounds: Indoles Part One", W. J. Houlihan, Ed., Wiley-Interscience, New York, N.Y., 1972, p 169.
(10) E. Wenkert et al., *Acc. Chem. Res.*, **7**, 46 (1974).
(11) E. Wenkert et al., *J. Am. Chem. Soc.*, **95**, 4990 (1973).
(12) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Am. Chem. Soc.*, **92**, 1338 (1970).
(13) D. M. Grant and E. G. Paul, *J. Am. Chem. Soc.*, **86**, 2984 (1964).
(14) D. M. Grant and B. V. Cheney, *J. Am. Chem. Soc.*, **89**, 5315 (1967).
(15) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect", Academic Press, New York, N.Y., 1971.

Diterpenoid Total Synthesis, an A → B → C Approach. VIII. Introduction of Oxygen at Carbon-11. Total Synthesis of (±)-Carnosic Acid Dimethyl Ether and (±)-Carnosol Dimethyl Ether[1]

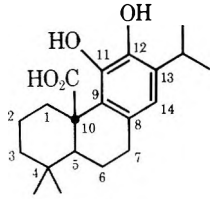
Walter L. Meyer,* Richard A. Manning, Erich Schindler, Robert S. Schroeder,[1d] and D. Craig Shew

Department of Chemistry, University of Arkansas, Fayetteville, Arkansas 72701, and Department of Chemistry, Indiana University, Bloomington, Indiana*

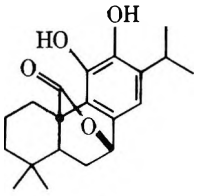
Received July 22, 1975

Total syntheses of the title compounds are described. Condensation of 10-carbethoxy-4,4-dimethyl-*trans*-7-decalone (**4**)[2] with ethyl formate followed by DDQ dehydrogenation produces the 8-formyl-Δ^8-7-octalone **6**, which is the key intermediate. Michael addition of *tert*-butyl acetoacetate or *tert*-butyl isovalerylacetate to **6** followed by acid-catalyzed *tert*-butyl ester cleavage, decarboxylation, and cyclodehydration of the resulting adducts affords trans-syn-cis tricyclic enediones **8a** and **8b**, which are dehydrogenated to 7-keto-12-phenols **9a** and **9b**, respectively. Hydrogenolysis of **9b** leads to 12-phenol **10a**, into which an 11-methoxy substituent was introduced by coupling with *p*-nitrobenzenediazonium chloride, O-methylation, sodium dithionite reduction, diazotization, and methanolysis to produce **14**. Ester cleavage (*t*-BuOK–Me_2SO) affords (±)-carnosic acid dimethyl ether. Alternatively, Michael addition of 1-methylsulfinyl-4-methyl-2-pentanone to **6** produces an adduct **22** which was subjected to Pummerer rearrangement, enol etherification, base-catalyzed cyclization, and O-methylation to afford **25b**. Hydrogenolysis gives **14**, while treatment with sodium borohydride followed by sodium hydride gives (±)-carnosol dimethyl ether. On exposure to hydrochloric acid in dimethyl sulfoxide, adduct **22** cyclizes with sulfoxide elimination, giving **9b**. Preparation of **4** by hydrogenation of the corresponding octalone is discussed, and the by-products sometimes encountered are identified as **28**, **29**, **30**, **31**, **33**, and **34**. Lactone **32** is described in connection with structure determination of **30**.

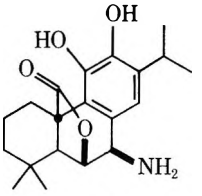
One of the advantages of the general A → B → C approach to diterpenoid synthesis which we have described[1a,3] is its potential for direct adaptability to construction of terpenoids containing a functional group rather than methyl at the angular position. Such a system is exemplified by carnosic acid (**1**)[4,5] and its derivatives carnosol (**2**)[6–10] (picrosalvin[7]) and rosmaricine (**3**).[5,11] Although the



1



2



3

latter two of these substances now appear to be artifacts from isolation rather than natural products,[5] the unusual state of oxidation at the angular position in carnosic acid and the interesting niche which has been proposed for it or analogous angular acids in diterpenoid biosynthesis[8] led us to investigate the total synthesis of such substances.

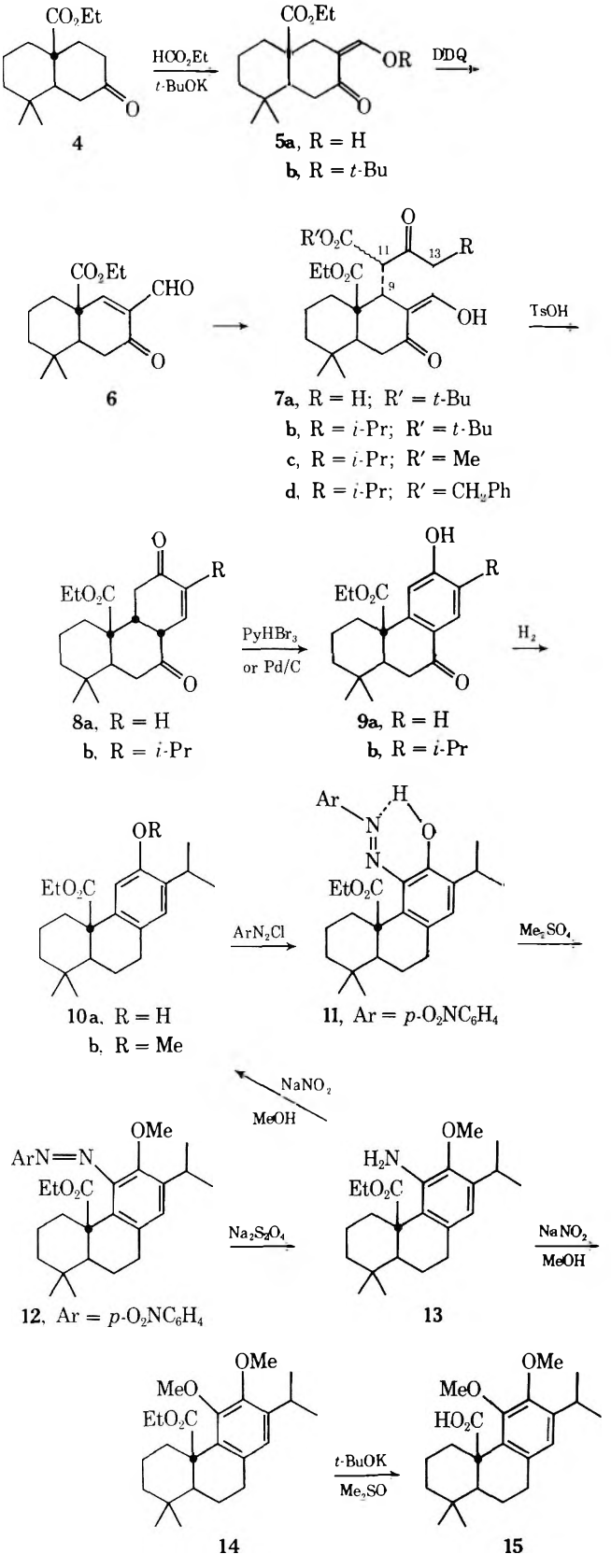
The A/B Ring System. The ideal bicyclic starting point for extension of this general synthetic plan[3] to the carnosic acid system is 10-carbethoxy-4,4-dimethyl-*trans*-7-decalone (**4**),[2] which contains both the appropriate oxidation level at the angular carbon and the necessary configuration of the A/B ring fusion. Preparation of this keto ester by an efficient and stereoselective route has already been reported.[12] Several improvements in the reactions leading to its synthetic progenitor, the corresponding Δ^5-7-octalone,[12] have subsequently been discovered and are recorded in the Experimental Section; they have raised the overall yield of the octalone to 87% from 6-carbethoxy-2,2-dimethylcyclohexanone. Some difficulties were encountered in reproducing the hydrogenation of this octalone to decalone **4**, but, as will be described later in this paper, these problems are largely circumvented by adjusting the solvent for the reduction.

Conversion of decalone **4** to the corresponding 8-formyl-Δ^8-7-octalone (**6**), the principal intermediate for attachment of ring C, followed the usual path[1a,3] (Scheme I). As anticipated,[1a] condensation of the decalone with ethyl formate affords its 8-hydroxymethylene derivative **5a**[13] to the exclusion of the 6-hydroxymethylene isomer. Dehydrogenation of enol **5a** by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[1a,14] was found to be considerably improved by acetic acid catalysis, and under carefully controlled conditions this reaction leads to formyl enone **6** in 92% yield.

With the angular carboxyl in place and the skeletal configuration under control at this early stage of the synthesis, the major structural feature requiring attention in extension of the general synthetic scheme[3] to carnosic acid and its derivatives is the 11-hydroxyl group which is present in those natural products. Two fundamental approaches have been examined for obtaining such 11,12-dioxygenated systems rather than the 12-hydroxy compounds which were the objectives of initial work.[1a,3,15] In the first, an 11 oxygen is introduced into an 11-unsubstituted intermediate after ring C has been constructed. In the second, the C-ring elaboration scheme is varied so as to obtain an 11 functional group as an integral part of the ring extension sequence.

Carnosic Acid through 11-Unsubstituted Intermediates. As a model for the initial C-ring construction sequence, aldehyde **6** was treated with the sodium enolate of *tert*-butyl acetoacetate in benzene[3] or dimethyl sulfoxide

Scheme I



(Scheme I). ^{1}H NMR spectra of the crude adducts, which are formed rapidly and in high yield in either solvent, show two acetyl resonances, two *tert*-butyl resonances, and resonances from two different 9,11-proton systems, but otherwise are in accord with expectation for structure **7a**, as are their ir spectra. Thus two diastereomers of the adduct are produced, in relative amounts which depend on reaction conditions, as has subsequently been found common for such reactions. Evidence that these products differ in configuration at C-11 but that both correspond to a β configuration of the 9 hydrogen will be presented and discussed in a subsequent paper.[16] Reaction of the crude adduct mixture with *p*-toluenesulfonic acid in acetic acid[1a,3] affords a product with the correct ir and ^{1}H NMR spectroscopic properties[16] for enedione **8a**, and this is converted in 35% yield to phenolic ketone **9a** by dehydrogenation over 30% palladium on carbon with maleic acid as a hydrogen acceptor.[1a,17]

Analogous Michael addition of the sodium enolate of *tert*-butyl isovalerylacetate[1a] to aldehyde **6** affords adduct **7b**, again as a mixture of C-11[16] diastereomers. While one of these adducts could be obtained in pure form by fractional crystallization, for synthetic purposes the mixture was not separated, but was directly exposed to *p*-toluenesulfonic acid in glacial acetic acid to induce *tert*-butyl ester cleavage, decarboxylation, and cyclodehydration, with formation of the trans-syn-cis[16] tricyclic enedione **8b** in 80% yield from aldehyde **6**. By this time use of pyridinium bromide perbromide in acetic acid as a superior technique for C-ring aromatization had been discovered,[1a] and treatment of enedione **8b** with this reagent affords keto phenol **9b** in 90% yield. Hydrogenolysis over palladium on carbon leads to the phenolic ester **10a**. As a measure of the efficiency of this C-ring elaboration sequence, the overall yield from decalone **4** to phenol **10a** is 64%.

Introduction of the C-11 oxygen function followed the sequence utilized by Brieskorn et al.[8] for conversion of ferruginol to 11-hydroxyferruginol (Scheme I). Use of methanol rather than ethanol as solvent for coupling *p*-nitrobenzenediazonium chloride with phenol **10a** is highly advantageous, for the latter solvent is a much more effective reductant in this system than is the former,[18] and converts much of the diazonium salt to nitrobenzene before it can attack the phenol. Consequently yields of azo phenol **11** are 89% in methanol vs. 50% in ethanol. Like the corresponding ferruginol derivative,[8] this phenol is hydrogen bonded to the azo group as indicated by the absence of characteristic OH ir absorption; the same interaction is also probably responsible for its abnormally intense long wavelength uv absorption (480 nm, ϵ 8200, for phenol **11**, compared with 485 nm, ϵ 1000, for the corresponding ether **12**).[19]

Reaction of the azo phenol with dimethyl sulfate affords its methyl ether as a 4:1 mixture of chromatographically separable products. The major component, a red, crystalline solid, was completely characterized to conform to the assigned structure **12**. The minor substance, a purple oil, was not obtained in pure form, but its ir spectrum shows functional group absorptions identical with those of the major product, and sodium dithionite reduction of the 4:1 mixture produces amino ether **13** quantitatively. Thus we believe that both methylation products correspond to the azo ether constitution and represent stereoisomers about the N=N bond. It is, of course, not surprising that azo phenol **11** is not an analogous isomer mixture, for in that case only the anti isomer can be stabilized by intramolecular hydrogen bonding; such association is not possible for either of the ethers, and the syn ether becomes more competitive with the anti ether in stability.

Diazotization and methanolysis converts amino ether **13** into three compounds. The predominant product is the desired ethyl (±)-carnosate dimethyl ether (**14**), with ir and ^{1}H NMR spectra superimposable on those of a sample of the (+) enantiomer prepared by diethyl sulfate esterification of (+)-carnosic acid dimethyl ether.[20] Accompanying it are significant amounts of the 12-monomethoxy derivative

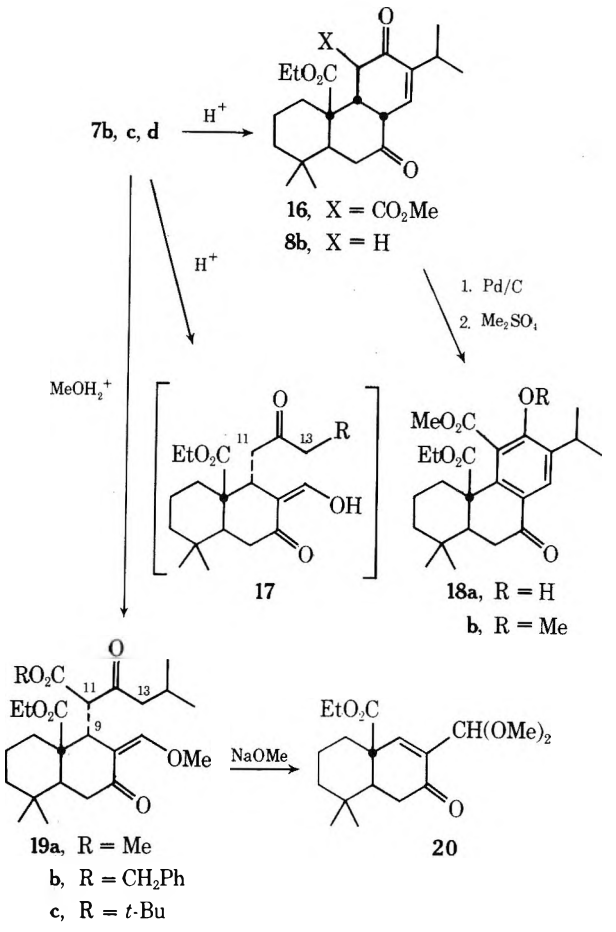
10b and 12-monophenol **10a** in a 3:2 ratio. The latter was identified by comparison with the sample obtained earlier in this synthesis, and the former was independently prepared by methylation of that phenol. These substances obviously result from reductions of the diazonium group which are competitive with its methanolysis,[18] with methanol serving as the reductant in production of at least **10b** and perhaps both compounds; whether the unusual formation of the phenol precedes, follows, or accompanies the reduction process (for example, with the o-methoxy group serving as an intramolecular reductant) was not established.

Inasmuch as extreme steric hindrance would be expected to render saponification of the angular ester very slow,[12] cleavage to acid **15** was carried out by potassium *tert*-butoxide in dimethyl sulfoxide,[21] conditions which could in the case of ethyl esters involve an elimination to form ethylene by way of attack at β carbon of the ethyl group, a much more exposed site than the carbonyl carbon. Whether such a mechanism is involved was not examined, but synthetically the reaction follows the desired course, smoothly producing (±)-carnosic acid dimethyl ether (**15**) in 80% yield. Like the synthetic ester this substance has ir and ^{1}H NMR properties indistinguishable from those of the naturally derived sample,[20] the structure of which is thus confirmed by total synthesis as well as by degradative work. Inasmuch as the dextrorotatory dimethyl ether has been demethylated by boron tribromide,[5] the present research lacks only resolution of the racemic dimethoxy acid to constitute a formal total synthesis of carnosic acid itself.

Carnosol and Carnosic Acid through 11-Substituted Intermediates. Although the foregoing synthesis attained the desired goal, preparation of the 11,12-dioxygenated diterpenoid system, the general C-ring elaboration sequence seemed susceptible to major strategic improvement. At the stage of Michael adducts **7** a functional substituent already exists at the 11 position, and the synthesis involved its removal followed by several steps to reintroduce a function at the same point. Much more efficient, obviously, would be either a pathway in which the 11 substituent of an adduct such as **7** is retained during cyclization so it can be subsequently converted to the required hydroxyl, or a sequence in which the 11 substituent is replaced by the necessary oxygen prior to cyclization. Several routes designed to incorporate these features have been examined, and although only one has thus far been carried to fruition, certain results from others have provided important information regarding properties of adducts like **7** and their derivatives.

The first alternative involves use of adducts similar to **7b** in which the potential 11 substituent will be stable during cyclization and can later be selectively manipulated even in the presence of the angular carbethoxy group. The corresponding methyl and benzyl ester adducts **7c** and **7d** were potential candidates to satisfy these criteria, and each is produced as a mixture of two 11 diastereomers[16] by addition of the appropriate β-keto ester to aldehyde **6**. However, their acid-catalyzed cyclization to 11-substituted enediones such as **16** (Scheme II) is not readily accomplished. Standard conditions for conversion of *tert*-butyl ester **7b** to enedione **8b** leave methyl ester **7c** largely unaltered, and with benzyl ester **7d** produce a substantial quantity of the decarbobenzoxylated enedione **8b.** Thus, although they are often less acid sensitive than their *tert*-butyl counterparts, for this purpose benzyl esters are still too reactive to survive any of the acidic conditions which we have found to induce cyclization. These results strongly suggest that ester cleavage and decarboxylation of the *tert*-butyl esters precede cyclization, which occurs with intermediacy of the unisolated ketones **17.** Cyclization prior to decarboxylation is undoubtedly inhibited because formation of the requisite 12,13-enol competes poorly with formation of a conjugated 11,12-enol.

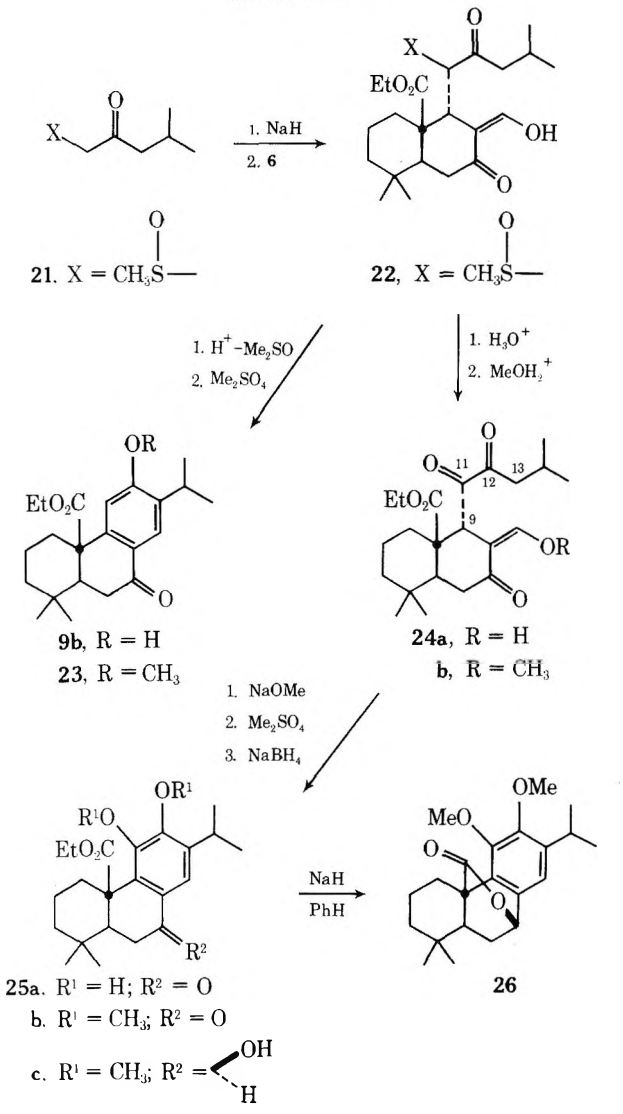
Scheme II



Longer exposure of methyl ester **7c** to acid also leads to formation of enedione **8b,** but in this instance it is not clear whether loss of the carbomethoxy group occurs before or after cyclization, for use of a short reaction time but a much greater acid concentration produces a complex mixture which spectroscopically appears to contain several isomers of the 11-carbomethoxy enedione **16.** A keto phenol with ir, uv, and ^{1}H NMR absorption appropriate for structure **18a** (including only one ArH and one OCH_3) can be isolated after dehydrogenation of such mixtures over palladium on carbon, and subsequent reaction with dimethyl sulfate produces a substance with *two* methoxyls and *one* ethoxyl (^{1}H NMR), as expected for ether diester **18b.** Thus this process apparently *can* allow retention of the 11-carbomethoxy substituent. Inasmuch as yields in the aromatization are undoubtedly capable of improvement (these investigations predated recognition of pyridinium bromide perbromide as the preferred reagent for such transformations[1a]), the sequence holds considerable potential for use under appropriate circumstances. However, it was not pursued in the present system after preliminary experiments indicated that a C-11 methyl ester would be difficult to distinguish chemically from the angular ethyl ester in spite of the steric hindrance of the latter. The 11-ester is also very hindered, and a variety of attempts to chemically differentiate the two functions were unsuccessful.

Base- rather than acid-catalyzed cyclodehydration of an adduct such as **7** does not occur under conditions which would permit retention of an 11-ester function, of course,

Scheme III



because both the hydroxymethylene proton and the C-11 proton are much more acidic than the C-13 proton which requires abstraction to initiate the appropriate aldol reaction. Furthermore, removal of the hydroxymethylene proton can lead to reversal of the Michael addition by which the adduct is produced, and in fact this is the primary result from protracted exposure of adduct **7c** to several basic reagents.

This particular retro-Michael process should be blocked in the corresponding hydroxymethylene enol ethers **19.** In spite of the fact that deprotonation at C-11 would still be seriously competitive with that at C-13 in such derivatives, the possibility of bringing about the necessary intramolecular Michael addition–elimination sequence was examined in order to learn if an unfavorable equilibrium for C-13 deprotonation of the enol ether could be offset by a favorable equilibrium for C-8 deprotonation of the vinylogous β-diketone system in the potential cyclization product **16.** Acid-catalyzed enol etherification of the adducts occurs rapidly and efficiently, even without loss of the acid-sensitive *tert*-butyl group in the case of **7b,** with the methyl enol ethers **19a–c** usually being produced as mixtures of two C-11 diastereomers.[16] However, these derivatives do not cyclize in base. Treatment of ether **19a** with sodium methoxide in either methanol or dioxane leads primarily to loss of the side chain and formation of acetal **20,** identified through its alternate preparation by reaction of aldehyde **6** with methanolic acid. Apparently the nucleophilic methoxide ion attacks enol ether **19a** at the methoxymethylene carbon, and the less basic β-keto ester enolate departs in a process resembling the SN2′ mechanism. This undesirable reaction is avoided by using a bulkier and thus less nucleophilic base such as potassium *tert*-butoxide in benzene, but that reagent still does not engender cyclization; it simply leaves enol ether **19a** unchanged after 62 h at room temperature. Other basic systems we examined also failed to induce the transformation of interest.

The key to the second major strategic alternative for completion of the 11,12-dihydroxy diterpenoid system lies in selecting a C-ring synthon of general structure **21** such that the group X can first serve to activate its α carbon for enolate formation and then, in the adduct **22,** is subject to simple transformation into an oxygen substituent (Scheme III). Ideally this new substituent would be a keto group, so that in compounds like **24** enolization of the 12-ketone would of necessity be toward C-13, and aldol cyclodehydration would lead directly to the dihydroxy aromatic system. Furthermore, the presence of an 11-ketone should allow epimerization of the C-9 side chain to the thermodynamically preferred β (equatorial) configuration in future extensions of the synthetic pathway to C-hydroaromatic substances.

The sulfoxide grouping appeared to neatly satisfy these requirements, and thus we examined Michael addition of the sodium enolate of 1-methylsulfinyl-4-methyl-2-pentanone (**21**) to keto aldehyde **6.** Within 25 min at room temperature in dimethyl sulfoxide this reaction forms adduct **22** in quantitative yield as a mixture of two separable crystalline diastereomers. These adducts are believed to differ in configuration only at C-11 or at sulfur, because both diastereomers lead to the same α-diketone **24a** when asymmetry at C-11 is destroyed under conditions where the C-9 configuration is not altered (see below). They are assigned the 9β-H configuration in analogy to the keto ester adducts.[16]

Pummerer rearrangement[22] of either adduct or their mixture quantitatively produces α-diketone **24a.** When this reaction was carried out in a fully deuterated solvent system (D_2O–acetic acid-d_1), the C-9 H singlet at τ 5.42 in the ^1H NMR spectrum of the α-diketone was not appreciably diminished in relative intensity, indicating that little or no deuterium is incorporated at that point and that thus little or no enolization of the product toward C-9 occurs under these conditions. Accordingly this α-diketone has the same 9 configuration as does its precursor **22.**

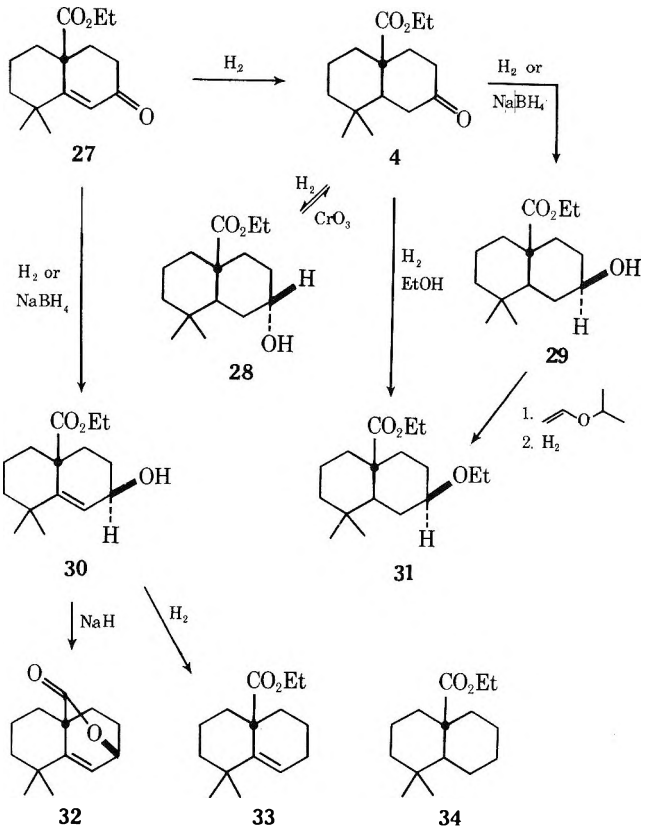
For reasons that are not clear, exposure of the α-diketone to *p*-toluenesulfonic acid in acetic acid does not bring about cyclization under conditions which presumably convert the related 12-monoketone **17** to enedione **8b.** However, unlike the enol ethers of β-keto ester adducts (**19**), in this system the corresponding hydroxymethylene enol ether **24b** is devoid of protons substantially more acidic than that at C-13, and the side chain at C-9 is now in a functional state which is incapable of anionic departure in an SN2′ reaction. Thus the reactions which interfere with base-catalyzed ring closure of the former systems have been blocked, and ether **24b,** which is formed in methanolic *p*-toluenesulfonic acid without enol etherification at the α-diketo function, readily undergoes the expected Michael cyclization, elimination, and aromatization in methanolic sodium methoxide, producing keto catechol **25a** in 73% yield. Methylation followed by hydrogenolysis affords ethyl (±)-carnosate dimethyl ether identical with the sample prepared by the earlier sequence. As a comparison of the two routes, we would note that from the bicyclic aldehyde **6** to this dimethoxy ester the first pathway proceeds in 28% yield over eight steps whereas the latter involves six steps with an overall yield of 53%.

A further advantage of the β-keto sulfoxide sequence is that the 7-keto group need not be removed until after the C-ring functionality is intact, and consequently that carbonyl is available for manipulation should 7-functional substances like carnosol or rosmaricine be synthetic targets. For example, sodium borohydride reduction of dimethoxy ketone **25b** stereoselectively affords the 7β-hydroxy derivative **25c,** which upon exposure to potassium *tert*-butoxide in benzene[4] is converted to (±)-carnosol dimethyl ether (**26**). The racemic lactone has identical ir and ^{1}H NMR spectroscopic properties with those of a naturally derived sample,[23] confirming the assigned structural relationships.

Finally, the β-keto sulfoxide adducts prove to be promising not only for synthesis of the 11,12-dioxygenated systems which were the main goal of this research, but also for substances such as the ferruginol types, etc., where only 12 hydroxylation is required.[1a] Exposure of adduct **22** to concentrated hydrochloric acid in dimethyl sulfoxide brings about not the Pummerer rearrangement but an acid-catalyzed cyclization with elimination of the methylsulfinyl group, to directly produce the 7-keto 12-phenol **9b** in 97% yield. This product was identified by comparison of its methyl ether with that of the keto phenol prepared earlier from adduct **7b** by the two-step sequence cyclization–aromatization. Study of the sequence of events in this conversion, most notably whether elimination precedes or follows cyclization, is presently incomplete. Nonetheless, its potential synthetic utility is obvious.

Hydrogenation of 10-Carbethoxy-4,4-dimethyl-Δ^5-7-octalone (27). Early in this paper we mentioned that difficulties were encountered in attempts to reproducibly prepare decalone **4** by hydrogenation of octalone **27** in ethanol over palladium on carbon catalysts. This reaction has been unusually erratic. In some instances the decalone is produced in high yield with only traces of by-products, as described earlier.[12] On numerous occasions, however, with no intentional differences in conditions but with different commerical samples of catalyst, the rate of hydrogen uptake has not changed radically after absorption of 1 equiv and ketone **4** has been accompanied by substantial quantities of other reduction products (Scheme IV). These substances, which vary considerably in relative amounts from run to run, have been identified as ethyl ether **31** (often the predominant by-product and sometimes the major component of the reduction mixture),[24] 7α- and 7β-*trans*-decalols **28** and **29** (the former never in more than trace amounts), and 7β-octalol **30,** as well as the previously described octalin **33**[12,25] and decalin **34**.[12] The constitution and configuration of ether **31,** which is also produced nearly quantitatively by hydrogenation of either octalone **27** or decalone **4** in the presence of acid, are verified by its alternate synthesis (Scheme IV) from hydroxy ester **29,** the structure of which was substantiated earlier.[26] Jones oxidation[27] of hydroxy ester **28** affords *trans*-decalone **4,** which confirms the α orientation of its 5 hydrogen and thereby demonstrates that it differs from the 7β-hydroxy isomer **29** only in configuration at C-7. Although octalol **30** has not been isolated from the abnormal hydrogenation products, ^{1}H NMR spectra of these mixtures often contain all of the resonances characteristic of the octalol formed by sodium borohydride reduction of enone **27.** Treatment of this octalol with sodium hydride produces a lactone (**32**), and inasmuch as this reaction must involve intramolecular attack of a 7β-alkoxide on the 10-ethoxycarbonyl group[12,26] it confirms assignment of the 7β-hydroxy configuration to the octalol;[28] this assignment is also in accord with the existence of a 2.5-Hz spin coupling, and thus a ca. 90° dihedral angle,[29] between the 6 and 7 protons in the octalol and several derivatives.

Scheme IV



Apparently at least two competitive pathways are involved in the early stages of hydrogenation of octalone **27,** one leading to decalone **4** which becomes the probable source of ether **31**[30] and decalols **28** and **29,**[31] and the other producing octalol **30** and thence the octalin and decalin.[12,32] The relative rates of all these processes are obviously critically dependent on undefined properties of the catalyst which vary among samples, rendering the reaction of capricious synthetic utility. It is nonetheless significant that none of the products corresponds to a cis ring fusion, and but for the very small amount of 7α-decalol **28,** hydrogen attachment at C-7 is also α; thus the various reduction reactions all involve selective approach of catalyst from the less hindered α face of the ring system.[34] Efforts to characterize the precise nature and sequence of the various reduction steps and the properties of the catalyst which so dramatically control their relative rates, or to perfect the reduction in ethanol, were not pursued, however, after it was found that in ethyl acetate the octalone is usually hydrogenated almost exclusively (ca. 95%) to the decalone.

Experimental Section

General procedures and techniques were the same as described earlier.[1a] Unless otherwise specified, HCl, NaOH, KOH, $NaHCO_3$, K_2CO_3, and Na_2CO_3 solutions were aqueous. Brine refers to saturated aqueous NaCl. General procedures for isolation of reaction products are abbreviated as follows: (A) the specified organic solution was washed with the indicated sequence of aqueous solutions followed by water or brine and dried ($MgSO_4$ unless otherwise specified), and solvent was removed either in vacuo or by evaporation on the steam bath under a stream of dry N_2; (B) the indicated aqueous mixture was thoroughly extracted with the specified organic solvent followed by the steps in procedure A; (C) the reaction mixture was added to water followed sequentially by the steps in procedures B and A.

10-Carbethoxy-4,4-dimethyl-Δ^5-octalone-7 (27) was prepared as described earlier.[12] The yield of distilled 2-carbethoxy-2-(3′-ketobutyl)-6,6-dimethylcyclohexanone was 93% when methyl vinyl ketone was distilled as well as dried just before use, and the yield in its cyclodehydration to octalone **27** was 93% when the pyr-

rolidine:diketone molar ratio was increased to 3.3, the aqueous extract was acidified with three times the prescribed amount[12] of concentrated HCl, and base treatment of the aqueous extract[1a] was included in the isolation procedure.

10-Carbethoxy-4,4-dimethyl-5α-decalone-7 (4). Hydrogenation of 6.25 g (0.025 mol) of **27**, mp 69.5–70.5 °C, over 267 mg of 30% Pd/C in 130 ml of EtOAc at 1 atm required 1.25 h, after which H_2 absorption ceased. Isolation as described[12] afforded 5.98 g (95%) of recrystallized **4**, mp 45–46 °C (lit.[12] mp 45–46.5 °C).

10-Carbethoxy-4,4-dimethyl-8-hydroxymethylene-5α-decalone-7 (5a). To a stirred solution of 5.7 g (0.15 *g*-atom) of K in 120 ml of dry *t*-BuOH was added 5.7 g (22.6 mmol) of **4**, mp 45–46 °C; 10 min later 10 ml (0.12 mol) of ethyl formate (dried over K_2CO_3 and distilled from P_2O_5, bp 50–52 °C) in 10 ml of *t*-BuOH was added dropwise during 25 min. After 4.5 h the solution had become very viscous and 14 ml of glacial HOAc was quickly added. Isolation C (ether and $CHCl_3$; water and $NaHCO_3$ wash) afforded 6.25 g (100%) of **5a** as a pale yellow viscous oil, the ^1H NMR spectrum of which showed no resonances attributable to major contamination: uv max (95% EtOH) 272 nm (ε 1640); (base) 312 nm (ε 4400);[35] ir ($CHCl_3$) 1710, 1665, 1640, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) τ −4.28 (s, broad, 1 H), 1.90 (s, 1 H), ca. 5.90 and 6.00 (m,[36] 2 H), 8.82 (t, J = 7 Hz, 3 H), 9.08 (s, 3 H), 9.22 (s, 3 H). Attempted purification by crystallization, sublimation, or chromatography led to decomposition, so the crude material was used in further work.

When concentrated HCl was used to acidify the reaction mixture, **5a** was accompanied by 5–20% (^1H NMR integration of the *tert*-butyl resonance) of the **8-*tert*-butoxymethylene derivative 5b.** This substance was isolated from a Florisil chromatogram of the mother liquors from the subsequent oxidation. Recrystallization from petroleum ether–$CHCl_3$ afforded **5b** as long, white needles: mp 108–109 °C; uv max (95% EtOH or base) 277 nm (ε 15 500); (acid) 273 nm (ε 10 100); (base, after acid) 312 nm (ε 11 300); ir ($CHCl_3$) 1715, 1670, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.40 (m, 1 H), ca. 5.90 and 5.94 (m,[36] 2 H), 8.68 (s, 9 H), 8.82 (t, J = 7 Hz, 3 H), 9.12 (s, 3 H), 9.23 (s, 3 H).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.64; H, 9.30.

10-Carbethoxy-4,4-dimethyl-8-formyl-5α-Δ⁸-oetalone-7 (6). To a solution of 6.35 g (22.6 mmol) of crude **5a** (no contamination detectable by ^1H NMR) and 51 drops (ca. 18 mmol) of glacial HOAc in 55 ml of dioxane was quickly added 5.05 g (22.3 mmol) of DDQ (mp 213–215 °C dec), and the mixture was stirred for 5.5 min. Solvent was rapidly removed in vacuo at ca. 23° and the residual gum was thoroughly extracted with seven 30-ml portions of petroleum ether–$CHCl_3$ (6:1) which were combined with 50 ml of ether, washed with $NaHCO_3$ until the washings were colorless, dried, and evaporated in vacuo to produce 6.41 g (102%) of yellow semisolid which was washed with cold ether to give 5.80 g (92%) of **6**, mp 93–94 °C. Recrystallization from $CHCl_3$–petroleum ether (bp 30–60 °C) afforded yellowish crystals: mp 92–93.5 °C; uv max (95% EtOH) 245 nm (ε 5100); (base) 302 nm (ε 20 500); ir ($CHCl_3$) 1720, 1700, 1680, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) τ 0.00 (s, 1 H), 2.78 (s, 1 H), 5.87 (q, J = 7 Hz, 2 H), 8.77 (t, J = 7 Hz, 3 H), 9.07 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.11; H, 8.00.

10-Carbethoxy-4,4-dimethyl-8-hydroxymethylene-9α-(1′-carbo-*tert*-butoxy-2′-oxopropyl)-5α-decalone-7 (7a). Sodium hydride (9.3 mg, 0.39 mmol, as 16 mg of a 58% mineral oil dispersion) was added to a solution of 70 mg (0.44 mmol) of *tert*-butyl acetoacetate[37] in 8 ml of C_6H_6 in a N_2 atmosphere; after gas evolution ceased (ca 20 min) 100 mg (0.36 mmol) of **6** was added. After 10 min 3 drops of glacial HOAc were added and isolation C ($CHCl_3$) afforded 146 mg (92%) of two isomers of **7a** as a pale yellow, viscous oil: ir ($CHCl_3$) 1738 (sh), 1718, 1642, 1587 cm^{-1}; ^1H NMR ($CDCl_3$) τ −4.58 (s, broad, 1 H), 1.90 (s, 1 H), ca. 5.90 and 6.00 (m,[36] 2 H), 6.32 and 6.50 (AB, J = 7.5 Hz, isomer A) and 6.33 (s, isomer B) (total 2 H), 7.77 (s, isomer B) and 7.95 (s, isomer A) (total 3 H), 8.53 (s, isomer A) and 8.63 (s, isomer B) (total 9 H), 8.83 (t, J = 7 Hz, 3 H), 9.03 (s, 3 H), 9.17 (s, 3 H); relative intensities of the resolved signals from isomers A and B were in the approximate ratio of 3:1.

Alternatively, NaH (8.0 mg of a 58% dispersion in mineral oil, 0.19 mmol) was added to a solution of 57 mg (0.36 mmol) of *tert*-butyl acetoacetate in 4 ml of Me_2SO and after 15 min 50 mg (0.18 mmol, mp 90–92 °C) of **6** was added. After 5 min 3 drops of glacial HOAc were added and the mixture was processed as above to afford 79 mg (100%) of **7a** as pale yellow crystals (by ^1H NMR a 3:1 mixture of C-11 isomers, B preponderant). Recrystallization from pentane afforded 35 mg of pure isomer B as matted white crystals, mp 110–111 °C.

Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31. Found: C, 65.89; H, 8.24.

10-Carbethoxy-17-nor-5α,8β,9β-podocarp-13-ene-7,12-dione (8a). A 162-mg (0.37 mmol) sample of crude **7a** was treated with 30 mg of TsOH in 4 ml of glacial HOAc for 1 h at 110 °C. The mixture was cooled, diluted with ether and water, and neutralized with solid Na_2CO_3. Isolation B (ether) afforded 99 mg (78%) of mostly crystalline **8a**, further purification of which was not attempted: ir ($CHCl_3$) 1712, 1685, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.95 (dd, J = 10 and 6 Hz, 1 H), 3.85 (d, J = 10 Hz, 1 H), ca. 5.70 and 5.80 (m,[36] 2 H), 6.22 (t, J = 5 Hz, 1 H), 6.55 (t, J = 14 Hz, 1 H), 8.68 (t, J = 7 Hz, 3 H), 9.08 (s, 3 H), 9.17 (s, 3 H).

10-Carbethoxy-12-hydroxy-17-norpodcarpa-8,11,13-trien-7-one (9a). A solution of 99 mg (0.31 mmol) of crude **8a** and 38 mg (0.21 mmol) of maleic acid in 5 ml of 80% EtOH containing 80 mg of 30% Pd/C was refluxed for 13 h under N_2, cooled, filtered, diluted with ether, and washed with 5% $NaHCO_3$. The phenol was extracted into 1% NaOH. Acidification followed by isolation B (ether) left 37 mg (37%) of residue which was sublimed, affording **9a** as a colorless glass which did not crystallize and was thus characterized only spectrally: ir ($CHCl_3$) 3610, 3300, 1720, 1670, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) τ 5.98 (q, J = 7 Hz, 2 H), 8.90 (t, J = 7 Hz, 3 H), 9.07 (s, 3 H), 9.15 (s, 3 H).

10-Carbethoxy-4,4-dimethyl-8-hydroxymethylene-9-(1′-carbo-*tert*-butoxy-2′-oxo-4′-methylpentyl)-5α-decalone-7 (7b). This adduct was prepared as described for **7a**, using 113 mg of a 58% NaH dispersion in mineral oil (2.7 mmol), 540 mg (2.70 mmol) of *tert*-butyl isovalerylacetate, bp 94–99 °C (0.7–0.9 mm),[1a] and 500 mg (1.80 mmol) of **6**, mp 93–94 °C, in 40 ml of C_6H_6. Reaction was quenched with 1 ml of glacial HOAc after 20 min, and 1.13 g of crude **7b** was isolated as described for **7a** with the addition of a $NaHCO_3$ wash of the $CHCl_3$ solution. This product was contaminated with *tert*-butyl isovalerylacetate but not by **6** (^1H NMR assay). A sample was washed with and recrystallized from pentane to afford an analytical sample of a 2:1 mixture of C-11 isomers[16] of **7b** (integration of the *tert*-butyl resonance) as white needles: mp 105–127 °C; uv max (95% EtOH) 288 nm (ε 7600); (base) 306 nm (ε 16 000); ir ($CHCl_3$) 1735 (sh), 1715, 1635, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) τ −4.65 (s, broad, 1 H), 1.87 (s, 1 H), ca. 5.90 and 6.00 (m,[36] 2 H), 6.33 (s, 2 H), 8.55 (s, isomer A) and 8.65 (s, isomer B) (total 9 H), 8.83 (t, J = 7 Hz, 3 H), 9.02–9.17 (12 H).

Anal. Calcd for $C_{27}H_{42}O_7$: C, 67.76; H, 8.85. Found: C, 67.74; H, 8.83.

Recrystallization from $CHCl_3$–petroleum ether (bp 30–60 °C) afforded colorless prisms, mp 121–123 °C, which appeared (^1H NMR) to be mainly the preponderant isomer (B): uv max (95% EtOH) 285 nm (ε 7000); ir ($CHCl_3$) 1735 (sh), 1715, 1640, 1590 cm^{-1}.

Anal. Calcd for $C_{27}H_{42}O_7$: C, 67.76; H, 8.85. Found: C, 67.57; H, 8.87.

10-Carbethoxy-17-nor-5α,8β,9β-abiet-13-ene-7,12-dione (8b). Crude **7b** (5.20 g, contaminated with *tert*-butyl isovalerylacetate, ca. 4.3 g, 9.0 mmol of available adduct assuming quantitative addition to 9.0 mmol of **6**) and 67 mg of TsOH in 70 ml of glacial HOAc was heated under reflux for 3 h and cooled, 200 mg of NaOAc was added, and solvent was distilled in vacuo to provide a yellow gum which was partitioned between $CHCl_3$ and water. Isolation B ($CHCl_3$, $NaHCO_3$ wash) provided a residue which was washed thoroughly with cold pentane to afford 2.52 g (78% based on **6**) of **8b** as white needles, mp 134–135.5 °C. Recrystallization from EtOAc provided the analytical sample: mp 135–135.5 °C; uv max (95% EtOH) 232 nm (ε 9000); (base) 255 nm (ε 7600), 440 (20 000); ir ($CHCl_3$) 1710, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) τ 3.28 (dd, J = 6 and 1 Hz, 1 H), ca. 5.73 and 5.83 (m,[36] 2 H), 6.27 (t, J = 5 Hz, 1 H), 8.70 (t, J = 7 Hz, 3 H), 8.97 (d, J = 7 Hz, 3 H), 9.02 (d, J = 7 Hz, 3 H), 9.10 (s, 3 H), 9.17 (s, 3 H).

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.52; H, 8.94.

10-Carbethoxy-12-hydroxy-17-norabieta-8,11,13-trien-7-one (9b). Aromatization was conducted as described for (±)-sugiol,[1a] using 2.00 g (5.55 mmol) of **8b**, mp 134.5–135.5 °C, and 1.79 g (5.75 mmol) of pyridinium bromide perbromide, mp 132 °C dec, in 120 ml of glacial HOAc. After 30 min isolation C ($CHCl_3$, $NaHCO_3$ wash) provided 2.19 g of white, amorphous solid which was washed with cold pentane to afford 1.79 g (90%) of **9b**, mp 176–180 °C. Recrystallization from EtOAc gave **9b** as a white powder: mp 184–185 °C; uv max (95% EtOH) 238 nm (ε 20 000), 290 (13 900); (base) 257 nm (ε 13 100), 349 (30 000); ir ($CHCl_3$) 3590, 3350 (br), 1715, 1665,

1600, 1575, 1500, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) τ 1.85 (s, 1 H), 2.07 (s, 1 H), 3.08 (s, 1 H), ca. 5.96 and 6.00 (m,[36] 2 H), 8.77 (d, J = 7 Hz, 6 H), 8.88 (t, J = 7 Hz, 3 H), 9.05 (s, 3 H), 9.13 (s, 3 H).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.70; H, 8.43. Found: C, 73.57; H, 8.33.

10-Carbethoxy-12-hydroxy-17-norabieta-8,11,13-triene (10a). A mixture of 598 mg (1.67 mmol) of **9b,** mp 176–180 °C, 105 mg of 30% Pd/C, and 1 drop of concentrated H_2SO_4 in 40 ml of EtOAc was hydrogenated at 1 atm for 2 h and filtered, 100 mg of catalyst and 1 drop of H_2SO_4 were added, and hydrogenation was repeated for 2 h.[38] Filtration and isolation A afforded 576 mg (99%) of **10a** as a fine white powder, mp 129–132 °C, which was recrystallized from pentane–EtOAc to afford white prisms: mp 134–135 °C; uv max (95% EtOH) 286 nm (ϵ 3500); (base) 305 nm (ϵ 4600); ir ($CHCl_3$) 3585, 3410 (br), 1710 cm^{-1}; ^1H NMR ($CDCl_3$) τ 3.15 (s, 1 H), 3.25 (s, 1 H), 3.58 (s, 1 H), 6.00 (q, J = 7 Hz, 2 H), 8.82 (d, J = 7 Hz, 6 H), 8.90 (t, J = 7 Hz, 3 H), 9.03 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.37. Found: C, 76.89; H, 9.26.

10-Carbethoxy-11-*p*-nitrophenylazo-12-hydroxy-17-norabieta-8,11,13-triene (11). The procedure follows one of Brieskorn et al.[8] A solution of 400 mg (2.90 mmol) of *p*-nitroaniline, mp 147–148 °C, in 3.0 ml of concentrated HCl was diluted with 1.5 ml of water and cooled to 0 °C, and an ice-cold solution of 200 mg (2.90 mmol) of $NaNO_2$ in 1.0 ml of water was slowly added with vigorous stirring. After 15 min at 0 °C this solution was added over 5 min to a solution of 1.0 g (0.43 g-atom) of Na in 75 ml of MeOH containing 385 mg (1.12 mmol) of **10a,** mp 130–133 °C, to afford a deep blue solution which was stirred for 45 min at 0 °C, diluted with 150 ml of water, and acidified with glacial HOAc. Isolation B ($CHCl_3$, $NaHCO_3$ wash) afforded 910 mg of red oil which was filtered through 20 g of Al_2O_3 with pentane and 10% ether–pentane to produce 510 mg (92%) of red oil. Rechromatography afforded 18 mg of $PhNO_2$ followed by 490 mg (89%) of **11** as a deep red glass which crystallized from pentane as red needles: mp 154–155 °C; uv max (95% EtOH) 380 nm (ϵ 19 700), 480 (8200); (base) 380 nm (ϵ 16 000), 515 (8300); ir ($CHCl_3$) 1710, 1525, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) τ ca. 1.67 and 2.05 (m, A_2B_2, J_{ortho} = 9 Hz, 4 H), 2.97 (s, 1 H), 5.95 (q, J = 7 Hz, 2 H), 8.77 (d, J = 7 Hz, 6 H), 8.88 (t, J = 7 Hz, 3 H), 9.00 (s, 3 H), 9.13 (s, 3 H).

Anal. Calcd for $C_{28}H_{35}N_3O_5$: C, 68.13; H, 7.15; N, 8.51. Found: C, 68.57; H, 7.40; N, 8.80.

10-Carbethoxy-11-*p*-nitrophenylazo-12-methoxy-17-norabieta-8,11,13-triene (12). According to the Brieskorn et al. procedure[8] a solution of 600 mg (1.22 mmol) of amorphous **11** (no impurities detectable by ^1H NMR) and 1.2 ml (12.4 mmol) of Me_2SO_4 in 120 ml of dry acetone was refluxed for 16 h over 25 g of anhydrous K_2CO_3. Filtration and distillation of solvent in vacuo left a deep purple oil which was chromatographed on 20 g of Al_2O_3 to give a first fraction (pentane and 10% C_6H_6–pentane) of 407 mg of red glass which appeared (^1H NMR) to be pure **12** and a second fraction (25% ether–pentane) of 83 mg (79% total) of deep purple glass which had ir ($CHCl_3$) 1705, 1590, 1525, 1335 cm^{-1}. The red isomer was rechromatographed and crystallized from pentane to afford an analytical sample of **12** as light red needles, mp 121–122 °C. Recrystallization from 95% EtOH afforded dark red prisms: mp 137–137.5 °C; uv max (95% EtOH) 279 nm (ϵ 14 500), 347 (11 200), 485 (1000); ir ($CHCl_3$) 1710, 1605, 1590, 1530, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) τ ca. 1.68 and 1.97 (m, A_2B_2, J_{ortho} = 9 Hz, 4 H), 2.97 (s, 1 H), 6.03 (q, J = 7 Hz, 2 H), 6.47 (s, 3 H), 8.77 (d, J = 7 Hz, 6 H), 8.97 (t, J = 7 Hz, 3 H), 9.02 (s, 3 H), 9.20 (s, 3 H).

Anal. Calcd for $C_{29}H_{37}N_3O_5$: C, 68.61; H, 7.35; N, 8.28. Found: C, 68.86; H, 7.28; N, 8.46.

10-Carbethoxy-11-amino-12-methoxy-17-norabieta-8,11,13-triene (13). According to the general Brieskorn et al. procedure[8] a mixture of 590 mg (1.16 mmol) of amorphous **12** (chromatographed isomer mixture, no impurities detectable by ^1H NMR) and 9.5 g (54.6 mmol) of $Na_2S_2O_4$ in 140 ml of 95% EtOH was brought to reflux and enough water (ca. 70 ml) was added to form a homogeneous solution which was refluxed for 3 h. Isolation C ($CHCl_3$) afforded 558 mg of brown gum. Filtration through 10 g of Al_2O_3 with 1:1 hexane–C_6H_6 gave 436 mg (100%) of white solid, recrystallization of which from cyclohexane afforded 409 mg (94%) of pure **13** as white plates, mp 143–144 °C. The analytical sample had mp 143.5–144 °C; uv max (95% EtOH) 297 nm (ϵ 2900); (acid) 282 nm (ϵ 2300), 295 (ϵ 2300); ir ($CHCl_3$) 3455, 3370, 1690, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) τ 3.65 (s, 1 H), 5.70 (s, broad, 2 H), 5.93 (q, J = 7 Hz, 2 H), 6.35 (s, 3 H), 8.80 (d, J = 7 Hz, 3 H), 8.82 (d, J = 7 Hz, 3 H), 8.83 (t, J = 7 Hz, 3 H), 9.02 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.44; N, 3.75. Found: C, 73.93; H, 9.14; N, 4.03.

Ethyl (±)-Carnosate Dimethyl Ether (14). The procedure follows one of Brieskorn et al.[8] A solution of 100 mg (0.268 mmol) of **13,** mp 143–144 °C, in 22 ml of absolute MeOH was acidified with 17 drops of concentrated H_2SO_4, cooled to 5 °C, and mixed with a solution of 25 mg (0.36 mmol) of $NaNO_2$ in 3 ml of MeOH. The mixture was kept at 5 °C for 15 min, allowed to warm to ca. 23 °C, refluxed for 30 min, cooled, and neutralized with $NaHCO_3$. Isolation B ($CHCl_3$) afforded 120 mg of crude product.

The crude products from several experiments (880 mg), all of which had similar ^1H NMR spectra, were chromatographed on 15 g of Al_2O_3 and eluted with cyclohexane, cyclohexane–C_6H_6 (9:1, 3:1, 1:1, and 1:3), and C_6H_6. The first two fractions (210 mg) consisted of 40% **10b** and 60% **14** (GLC, 250°). Fractions 3–7 (370 mg) were 97% **14** and 3% **10b.** Fractions 8–10 contained 120 mg of **10b** and **14** and 30 mg of **10a.**

Pure **10b** (15% total yield estimated from GLC) was identical (ir) with the authentic sample described below.

Phenol **10a** (10% total yield estimated from GLC) was purified by crystallization and recrystallization from pentane–EtOAc, mp 133–135 °C, ir identical with that of the sample described above.

Fractions 3–7 slowly crystallized at room temperature. Two recrystallizations from MeOH afforded **14** (60% total yield estimated from GLC) as white needles: mp 89.5–90°; spectral properties (ir, ^1H NMR) indistinguishable from those of a sample prepared from (+)-**15;** uv max (95% EtOH) 276 nm (ϵ 610); ir ($CHCl_3$) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) τ 3.35 (s, 1 H), ca. 5.85 and 5.95 (m,[36] 2 H), 6.28 (s, 3 H), 6.33 (s, 3 H), 8.78 (t, J = 7 Hz, 3 H), 8.80 (d, J = 7 Hz, 6 H), 9.03 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.49; H, 9.42.

Ethyl (+)-Carnosate Dimethyl Ether (14). A 100-mg (0.27 mmol) sample of (+)-carnosic acid dimethyl ether[20] was refluxed for 12 h with 50 mg (9.3 mmol) of Et_2SO_4 and 2 g of anhydrous K_2CO_3 in 10 ml of dry acetone, filtered, evaporated, taken up in ether, washed with dilute NH_4OH, dried, and concentrated. Filtration through acidic Al_2O_3 with C_6H_6 and a few drops of ether afforded (+)-**14** as a colorless oil; GLC (250 °C) showed a single peak; ir and ^1H NMR identical with those of the synthetic racemate.

10-Carbethoxy-12-methoxy-17-norabieta-8,11,13-triene (10b). Phenol **10a** (205 mg, 0.596 mmol, mp 128–133 °C) was methylated as described for **11,** using 8 g of anhydrous K_2CO_3 and 0.5 ml of Me_2SO_4 in 40 ml of dry acetone. The crude product from removal of acetone was taken up in $CHCl_3$–ether. Isolation A (dilute NH_4OH wash) gave 210 mg of pale yellow solid which was recrystallized from 95% EtOH to afford 198 mg (93%) of **10b** as colorless plates, mp 65–66 °C. The analytical sample had mp 66–66.5 °C; uv max (95% EtOH) 240 nm (ϵ 7100), 281 (ϵ 3800), 288 (ϵ 3700); ir ($CHCl_3$) 1705 cm^{-1}; ^1H NMR ($CDCl_3$) τ 3.13 (s, 1 H), 3.25 (s, 1 H), 6.00 (q, J = 7 Hz, 2 H), 6.30 (s, 3 H), 8.83 (d, J = 7 Hz, 6 H), 8.90 (t, J = 7 Hz, 3 H), 9.03 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.65. Found: C, 77.42; H, 9.64.

(±)-Carnosic Acid Dimethyl Ether (15). A solution of 105 mg (0.270 mmol) of (±)-**14** (98% pure by GLC) and 0.50 g of freshly prepared *t*-BuOK in 5 ml of Me_2SO was heated for 2 h at ca. 95 °C, poured onto ice, acidified with 1.5 ml of concentrated HCl, and extracted with $CHCl_3$–ether which was extracted with 1% NaOH. The basic extract was acidified with concentrated HCl, and isolation B ($CHCl_3$) provided 90 mg (92%) of pale yellow solid. Recrystallization from 95% EtOH afforded 80 mg (82%) of (±)-**15** as white prisms, mp 226–228 °C. The analytical sample had mp 230.5–231.5 °C; ir and ^1H NMR identical with those of (+)-**15**;[20] uv max (95% EtOH) 276 nm (ϵ 700); ir ($CHCl_3$) 3000 (br), 1690 cm^{-1}; ^1H NMR ($CDCl_3$) τ 3.35 (s, 1 H), 6.28 (s, 3 H), 6.37 (s, 3 H), 8.82 (d, J = 7 Hz, 6 H), 9.05 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.46; H, 8.96.

Methyl Isovalerylacetate. Methyl α-isovalerylacetoacetate was prepared by the procedure described for the analogous *tert*-butyl ester.[1a] The diketo ester was obtained from methyl acetoacetate, bp 170 °C, in 63% yield as a colorless oil: bp 110–111 °C (0.7 mm); ir (film) 1710 cm^{-1}; ^1H NMR (CCl_4) τ 6.27 (s, 3 H), 7.72 (s, 3 H), 9.07 (d, J = 7 Hz, 6 H). A MeOH solution of this diketo ester was treated with a catalytic amount of base for 12 h as described for preparation of the corresponding *tert*-butyl ester[1a] to provide 63% of methyl isovalerylacetate as a colorless liquid: bp 85–87 °C (1.25 mm); ir (film) 1745, 1705 cm^{-1}; ^1H NMR (CCl_4) τ 5.07 (s, 1

H, enol), 6.33 (s, 3 H, enol), 6.37 (s, 3 H, keto), 6.63 (s, 2 H, keto), 9.08 (d, J = 7 Hz, 6 H).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.73; H, 8.92. Found: C, 60.94; H, 9.09.

10-Carbethoxy-4,4-dimethyl-8-hydroxymethylene-9-(1'-carbomethoxy-2'-oxo-4'-methylpentyl)-5α-decalone-7 (7c). An 850-mg (5.40 mmol) sample of methyl isovalerylacetate, bp 85–87 °C (1.25 mm), in 50 ml of Me_2SO was treated with 226 mg of a 58% NaH dispersion in mineral oil (5.40 mmol) for 30 min, 1.00 g (3.60 mmol) of **6**, mp 93–94 °C, was quickly added, and stirring was continued for 30 min. The yellow solution was acidified with 1 ml of glacial HOAc, diluted with 150 ml of water, and extracted with ether which was washed with 20% K_2CO_3. The potassium salt which formed at the interface was separated, dissolved in 50 ml of water, and acidified with concentrated HCl. Isolation B (ether; water and $NaHCO_3$ wash) afforded 750 mg (48%) of **7c** as a light yellow oil. A mixture of aldehyde **6**,[39] starting β-keto ester, and mineral oil was recovered from the initial ether extracts. Crude **7c** crystallized from cold petroleum ether (bp 30–60 °C), and three washings with the same solvent provided an analytical sample of a ca. 1:1 mixture of isomers (^{1}H NMR integration of the OCH_3 resonance) as a white powder: mp 75–95 °C; uv max (95% EtOH) 285 nm (ε 6900); (base) 285 nm (ε 18 000), 304 (18 000); ir ($CHCl_3$) 1740 (sh), 1720, 1645, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) τ 1.88 (s, broad, 1 H), 5.92 and 5.95 (q's each J = 7 Hz, total 2 H), 6.27 and 6.43 (s's, total 3 H), 8.83 (t, J = 7 Hz, 2 H), 9.02 (s, 3 H), 9.07 (d, J = 7 Hz, 6 H), 9.17 (s, 3 H).

Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31. Found: C, 66.22; H, 8.05.

Benzyl Isovalerylacetate. Benzyl acetoacetate, bp 156–158 °C (10 mm), was acylated with isovaleryl chloride, bp 116–116.5 °C, as described for the corresponding *tert*-butyl ester.[1a] Attempted distillation resulted in decomposition, so the crude product (90% yield; ^{1}H NMR showed no resonance from major impurities) was used directly: ^{1}H NMR (CCl_4) τ 2.73 (s, 5 H), 4.87 (s, 2 H), 7.82 (s, 3 H), 9.18 (d, J = 7 Hz, 6 H). Base cleavage was conducted as described for preparation of methyl isovalerylacetate. The benzyl β-keto ester was obtained in 69% yield as a colorless liquid: bp 160–161 °C (1.0 mm); ir (film) 1740, 1710 cm^{-1}; ^{1}H NMR (CCl_4) τ 2.78 (s, 5 H), 4.97 (s, 2 H), 6.72 (s, 2 H), 9.17 (d, J = 7 Hz, 6 H).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.57; H, 7.92.

10-Carbethoxy-4,4-dimethyl-8-hydroxymethylene-9-(1'-carbobenzoxy-2'-oxo-4'-methylpentyl)-5α-decalone-7 (7d). This adduct was prepared as described for **7c** using 22 mg of a 58% NaH dispersion in mineral oil (0.54 mmol), 122 mg (0.540 mmol) of benzyl isovalerylacetate, bp 160–161 °C (1.0 mm), and 100 mg (0.360 mmol) of **6**, mp 93–94 °C, in 8 ml of Me_2SO. Preliminary isolation involved addition of 5 drops of glacial HOAc and 10 ml of water, extraction with ether, washing with water, extraction into 1% NaOH, and acidification with 5% HCl. Final isolation (method B, ether, water and $NaHCO_3$ wash) provided 141 mg (76%) of light yellow oil which contained ca. 75% **7d** and 25% **6** (^{1}H NMR assay).[39] This adduct was used without further purification: ^{1}H NMR ($CDCl_3$) τ 1.90 (s, broad, 1 H), 2.72 (s, 5 H), 4.85 (s, 2 H), 5.05 (s, 2 H), 5.97 (m, 2 H).

10-Carbethoxy-11-carbomethoxy-5α,8β,9β-17-norabiet-13-ene-7,12-dione (16). A solution of 333 mg (0.76 mmol) of crude **7c** and 150 mg of TsOH in 4 ml of glacial HOAc was heated for 2 h at 100 °C and processed as in the preparation of **8a** to yield 284 mg (85%) of a mixture of products as an oil with ir ($CHCl_3$) 1720, 1670, 1600 cm^{-1}. The ^{1}H NMR spectrum contained several absorptions in the OCH_3, OCH_2, CCH_3, and vinyl regions, suggesting the presence of several isomers of **16**. This material was used directly in the next reaction.

10-Carbethoxy-11-carbomethoxy-12-hydroxy-17-norabieta-8,11,13-trien-7-one (18a). A mixture of 323 mg (0.77 mmol) of crude **16** (oil), 100 mg (0.87 mmol) of maleic acid, and 150 mg of 30% Pd/C in 15 ml of 80% ethanol was heated to reflux under N_2, solvent was slowly removed in vacuo during ca. 1 h, and the residue was heated at 100 °C for 1 h, suspended in ether, filtered, and washed with 5% $NaHCO_3$. The phenol was extracted into 1% NaOH and isolated as described for **9a**. The semisolid residue, 115 mg (35%), was sublimed to afford **18a** as a colorless glass. Crystallization could not be effected, so **18a** was characterized spectrally only: uv max (95% EtOH) 239, 282 nm; ir ($CHCl_3$) 1730, 1670, 1600, and 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$) τ 1.92 (s, 1 H), ca. 5.80 and 5.93 (m,[36] 2 H), 6.15 (s, 3 H), 8.74 (d, J = 7 Hz, 3 H), 8.77 (d, J = 7 Hz, 3 H), 8.80 (t, J = 7 Hz, 3 H), 9.07 (s, 3 H), 9.10 (s, 3 H).

10-Carbethoxy-11-carbomethoxy-12-methoxy-17-norabieta-8,11,13-trien-7-one (18b). A mixture of 104 mg (0.29 mmol) of crude **18a**, 3.5 g of anhydrous K_2CO_3, and 10 drops of Me_2SO_4 in 15 ml of dry acetone was refluxed for 12 h, cooled, filtered, and concentrated. The residue was chromatographed with C_6H_6 on silica gel to afford 98 mg (92%) of ether **18b** as a slightly yellow oil which could not be induced to crystallize and was therefore characterized only spectrally: ir ($CHCl_3$) 1725, 1672, 1585 cm^{-1}; ^{1}H NMR ($CDCl_3$) τ 1.87 (s, 1 H), 5.90 (q, J = 7 Hz, 2 H), 6.12 (s, 3 H), 6.22 (s, 3 H), 8.75 (d, J = 7 Hz, 3 H), 8.77 (d, J = 7 Hz, 3 H), 8.83 (t, J = 7 Hz, 2 H), 9.05 (s, 3 H), 9.15 (s, 3 H). TLC (1:1 C_6H_6–$CHCl_3$) showed only one spot.

10-Carbethoxy-4,4-dimethyl-8-methoxymethylene-9-(1'-carbomethoxy-2'-oxo-4'-methylpentyl)-5α-decalone-7 (19a). A solution of 308 mg (0.707 mmol) of **7c**, mp 75–95 °C, and 51 mg of TsOH in 25 ml of absolute MeOH was refluxed for 20 min, cooled, treated with 200 mg of NaOAc, and concentrated in vacuo. The residual gum was distributed between water and ether, and isolation B (ether, 1% NaOH wash) afforded 321 mg (100%) of **19a** as a colorless oil, a 3:1 mixture of C-11 epimers (^{1}H NMR integration of the vinyl resonance). Crystallization from and washing with petroleum ether and recrystallization from petroleum ether–EtOAc provided a sample of the minor isomer as white needles: mp 116–117 °C; uv max (95% EtOH) 269 nm (ε 11 000); ir ($CHCl_3$) 1750, 1715, 1675, 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$) τ 2.92 (s, 1 H), 5.92 (q, J = 7 Hz, 2 H), 6.00 (d, J = 8 Hz, 1 H), 6.25 (s, 3 H), 6.27 (s, 3 H), 8.80 (t, J = 7 Hz, 3 H), 9.08 (s, 3 H), 9.12 (d, J = 7 Hz, 6 H), 9.20 (s, 3 H).

The combined mother liquors from the above crystallization were left at ca. 23 °C for 24 h and the crystalline product was washed with cold petroleum ether and recrystallized from petroleum ether–EtOAc to give a pure sample of the major isomer as white prisms: mp 105–106 °C; uv max (95% EtOH) 269 nm (ε 13 000); ir ($CHCl_3$) 1740 (sh), 1720, 1675, 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$) τ 2.85 (s, 1 H), 5.90 (q, J = 7 Hz, 2 H), 5.95 (d, J = 5 Hz, 1 H), 6.22 (d, J = 4 Hz, 1 H), 6.28 (s, 3 H), 6.43 (s, 3 H), 8.80 (t, J = 7 Hz, 3 H), 9.02 (s, 3 H), 9.12 (s, 3 H), 9.15 (d, J = 7 Hz, 6 H).

10-Carbethoxy-4,4-dimethyl-8-methoxymethylene-9-(1'-carbobenzoxy-2'-oxo-4'-methylpentyl)-5α-decalone-7 (19b). Crude **7d** (141 mg, contaminated with ca. 25% of **6**) was converted to its methyl enol ether as described for **7c**, using 10 mg of TsOH in 10 ml of dry MeOH. The crude product (135 mg, ca. 93% based on available **7d**) consisted of a 3:2 mixture of isomers of **19b** (^{1}H NMR integration of the OCH_3 resonances) containing ca. 25% of **20** (identified by comparison of the extraneous ^{1}H NMR peaks with the spectrum of an authentic sample) from the aldehyde contaminant: ^{1}H NMR ($CDCl_3$) τ 2.70 (s, 5 H), 2.92 (s, isomer A) and 2.98 (s, isomer B) (total 1 H), 4.83 (s, isomer B) and 4.90 and 5.17 (AB, J = 12 Hz, isomer A) (total 2 H), 5.95 (q, J = 7 Hz, 2 H), 6.30 (s, isomer B) and 6.42 (s, isomer A) (total 3 H), 8.83 (t, J = 7 Hz, 3 H), 9.13 (m, 12 H), and resonance from **20**.

10-Carbethoxy-4,4-dimethyl-8-methoxymethylene-9-(1'-carbo-*tert*-butoxy-2'-oxo-4'-methylpentyl)-5α-decalone-7 (19c). Adduct **7b** (1.421 g, 3.03 mmol, mp 110–125 °C) was converted to its methyl enol ether as described for **7c**, using 32 mg of TsOH in 25 ml of dry MeOH for 10 min to afford 1.345 g (90%) of a crude 5:1 mixture of isomers of **19c** (^{1}H NMR integration of the =CH and OCH_3 resonances). Washing with cold petroleum ether and recrystallization from petroleum ether–EtOAc afforded the major isomer as white prisms: mp 125–126 °C; ir ($CHCl_3$) 1740 (sh), 1715, 1670, 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) τ 2.85 (d, J = 0.6 Hz, 1 H), 5.93 (q, J = 7 Hz, 2 H), 5.98 (d, J = 5 Hz, 1 H), 6.28 (s, 3 H), 6.38 (d, J = 5 Hz, 1 H), 8.62 (s, 9 H), 8.82 (t, J = 7 Hz, 3 H), 9.05 (d, J = 7 Hz, 6 H), 9.10 (s, 3 H), 9.22 (s, 3 H).

Anal. Calcd for $C_{28}H_{44}O_7$: C, 68.26; H, 9.01. Found: C, 68.33; H, 8.97.

10-Carbethoxy-4,4-dimethyl-8-dimethoxymethyl-Δ^8-5α-oetalone-7 (20). Formyl enone **6** (110 mg, 0.360 mmol) was treated with 8 mg of TsOH in 10 ml of dry MeOH as described for enol etherification of **7c** to give 111 mg (95%) of pure (^{1}H NMR assay) **20** as a yellow oil: ir (film) 1725, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) τ 3.32 (d, J = 1 Hz, 1 H), 4.77 (d, J = 1 Hz, 1 H), 5.88 (q, J = 7 Hz, 2 H), 6.68 (s, 3 H), 6.75 (s, 3 H), 8.78 (t, J = 7 Hz, 3 H), 9.10 (s, 3 H), 9.20 (s, 3 H).

1-Methylsulfinyl-4-methylpentan-2-one (21). The procedure follows one by Moore.[40] A mixture of 8.3 g of a 58% NaH dispersion in mineral oil (0.20 mol of NaH) and 280 ml of Me_2SO was heated for 2 h at 66° under N_2, cooled to 20 °C, and 13.02 g (0.10 mol) of ethyl isovalerate, bp 134 °C,[41] was added over 15 min. The

solution was stirred for 30 min, poured into 300 g of ice water containing 52.5 g of NH_4Cl, and extracted with $CHCl_3$ which was concentrated in vacuo. The residual oil in 30 ml of ether was extracted with six 15-ml portions of water which were saturated with NaCl, extracted with six 15-ml portions of $CHCl_3$, dried, and evaporated in vacuo to produce 10.4 g of yellow oil. Distillation through a short-pass distillation head packed with glass wool afforded a forerun (0.75 g) of Me_2SO, followed by 8.35 g (52%) of **21**: bp 103–108 °C (0.3 mm); ir (film) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) τ 6.15 and 6.23 (AB, J = 14 Hz, 2 H), 7.35 (s, 3 H), 9.07 (d, J = 7 Hz, 6 H).[41]

10-Carbethoxy-4,4-dimethyl-8-hydroxymethylene-9-(1′-methylsulfinyl-2′-oxo-4′-methylpentyl)-5α-decalone-7 (22). This adduct was prepared as described for **7c**, using 226 mg of a 58% dispersion of NaH in mineral oil (5.40 mmol), 880 mg (5.40 mmol) of **21**, bp 103–108 °C (0.3 mm), and 1.00 g (3.60 mmol) of **6** in 50 ml of dry Me_2SO. Formation of the homogeneous enolate solution required 30 min and a 25-min reaction time was allowed before acidification with 1.5 ml of HOAc. Isolation as described for adduct **7b** provided 1.71 g (100%) of white semisolid. This was taken up in $CHCl_3$, extracted with 1% NaOH to remove the adduct from mineral oil, and acidified with 5% HCl to afford 1.581 g (99%) of a 1:1 mixture of stereoisomers (^1H NMR assay) of **22**, free of **6** or **21** (^1H NMR). A sample was washed thoroughly with cold ether and recrystallized from $CHCl_3$ to afford one isomer as a white powder: mp 167–168 °C; uv max (95% EtOH) 277 nm (ε 8500); (base) 310 nm (ε 15 500); ir ($CHCl_3$) 1710, 1635, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) τ 1.87 (s, 1 H), 5.88 (d, J = 4 Hz, 1 H), ca. 5.88 and 5.98 (m,[36] 2 H), 6.75 (d, J = 4 Hz, 1 H), 7.60 (s, 3 H), 8.85 (t, J = 7 Hz, 3 H), 9.02 (d, J = 7 Hz, 6 H), 9.02 (s, 3 H), 9.15 (s, 3 H).

Anal. Calcd for $C_{23}H_{36}O_6S$: C, 62.70; H, 8.24. Found: C, 62.80; H, 8.17.

The mother liquors from the above purification were taken up in ether and cooled to −20 °C, and the precipitate was recrystallized from $CHCl_3$–ether to provide a sample of a second isomer as a white powder: mp 137–140 °C (comparison of the SCH_3 resonances indicated contamination with 5% of the first isomer); uv max (95% EtOH) 280 nm (ε 7200); (base) 309 nm (ε 15 000); ir ($CHCl_3$) 1710, 1640, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) τ 1.48 (s, 1 H), ca. 5.86 and 5.96 (m,[36] 2 H), 6.37 and 6.58 (AB, J = 9 Hz, 2 H), 7.48 (s, 3 H), 8.83 (t, J = 7 Hz, 3 H), 8.97 (d, J = 7 Hz, 6 H), 9.05 (s, 3 H), 9.10 (s, 3 H).

10-Carbethoxy-4,4-dimethyl-8-hydroxymethylene-9-(1′,2′-dioxo-4′-methylpentyl)-5α-decalone-7 (24a). A solution of 430 mg (0.979 mmol) of an isomeric mixture of adducts **22**, mp 130–142 °C, in 12 ml of 50% aqueous HOAc was refluxed for 4 h[22] and diluted with 10 ml of brine. Isolation B ($CHCl_3$, water and $NaHCO_3$ wash) afforded 385 mg (100%) of **24a** as a bright yellow oil devoid of significant impurities (^1H NMR): ir ($CHCl_3$) 1705, 1635, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) τ 1.93 (s, 1 H), 5.42 (s, 1 H), ca. 5.82 and 5.95 (m,[36] 2 H), 8.80 (t, J = 7 Hz, 3 H), 9.05 (d, J = 7 Hz, 6 H), 9.07 (s, 3 H), 9.22 (s, 3 H). The relative intensity of the C-9 H singlet at τ 5.42 was not significantly diminished in spectra of the product from conducting this reaction in 50% D_2O–DOAc.

10-Carbethoxy-4,4-dimethyl-8-methoxymethylene-9-(1′,2′-dioxo-4′-methylpentyl)-5α-decalone-7 (24b). A 245-mg (0.625 mmol) sample of crude **24a** was O-methylated as described for **7c** using 17 mg of TsOH in 15 ml of dry MeOH for 15 min to provide 231 mg (91%) of crude yellow solid. Recrystallization from petroleum ether gave 209 mg (82%) of **24b**, mp 84–86 °C. Further recrystallization provided an analytical sample as yellow plates: mp 87.5–88 °C; ir ($CHCl_3$) 1710, 1670, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.78 (d, J = 1.5 Hz, 1 H), 5.22 (d, J = 1.5 Hz, 1 H), ca. 5.85 and 5.89 (m,[36] 2 H), 6.27 (s, 3 H), 8.77 (t, J = 7 Hz, 3 H), 9.05 (d, J = 7 Hz, 6 H), 9.12 (s, 3 H), 9.25 (s, 3 H).

Anal. Calcd for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43; mol wt, 406. Found: C, 68.05; H, 8.37; mol wt, 406 (mass spectrum).

10-Carbethoxy-11,12-dihydroxy-17-norabieta-8,11,13-trien-7-one (25a). A solution of 490 mg (1.21 mmol) of **24b**, mp 84–86 °C, and 138 mg (2.54 mmol) of NaOMe in 20 ml of dry MeOH was refluxed for 6 h, acidified with glacial HOAc, and taken to dryness to afford a yellow gum which was taken up in 10 ml of ether. Isolation A (water and $NaHCO_3$ wash) left 440 mg (95%) of crude oil which was crystallized from cold petroleum ether to afford 225 mg of amorphous solid. Concentration of the mother liquors gave an additional 103 mg (73% total) of **25a**, mp 110–118 °C. Recrystallization from EtOAc provided pure **25a** as a white powder: mp 123–124 °C; uv max (95% EtOH) 237 nm (ε 17 500), 290 (11 300); (base) 262 nm (ε 10 700), 366 (24 700); ir ($CHCl_3$) 3505, 3310, 1710 (sh), 1675, 1615, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.27 (s, 1 H), 2.45 (s, 1 H), 3.38 (s, 1 H), ca. 5.78 and 5.82 (m,[36] 2 H), 8.75 (d, J = 7 Hz, 3 H), 8.78 (d, J = 7 Hz, 3 H), 8.78 (t, J = 7 Hz, 3 H), 9.00 (s, 3 H), 9.08 (s, 3 H).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07. Found: C, 70.69; H, 8.08.

10-Carbethoxy-11,12-dimethoxy-17-norabieta-8,11,13-trien-7-one (25b). Diphenol **25a** (100 mg, 0.268 mmol, mp 110–118 °C) was methylated as described for **10a** using 0.25 ml of Me_2SO_4 and 2.0 g of K_2CO_3 in 5 ml of acetone for 7 h. Isolation as described for **10b** afforded 105 mg (98%) of **25b** as a pale yellow oil which crystallized from MeOH as white prisms (96 mg, 90%), mp 90–92 °C. Recrystallization from MeOH provided colorless prisms: mp 91–92 °C; uv max (95% EtOH) 224 nm (ε 25 400), 273 (13 400); ir ($CHCl_3$) 1720, 1680, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.20 (s, 1 H), ca. 5.84 and 5.94 (m,[36] 2 H), 6.17 (s, 3 H), 6.33 (s, 3 H), 8.75 (d, J = 7 Hz, 3 H), 8.80 (d, J = 7 Hz, 3 H), 8.80 (t, J = 7 Hz, 3 H), 9.03 (s, 3 H), 9.13 (s, 3 H).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.80; H, 8.61.

Ethyl (±)-Carnosate Dimethyl Ether (14). Hydrogenolysis of 80 mg (0.20 mmol) of **25b**, mp 90–92 °C, in 8 ml of EtOAc containing one drop of concentrated H_2SO_4 and 10 mg of 30% Pd/C required 45 min at 1 atm. Filtration (Celite) and isolation A ($NaHCO_3$ wash) afforded 75 mg (98%) of **14** as an oil which slowly crystallized. Recrystallization from MeOH provided pure **14**, mp 89–90 °C, identical (melting point, ir, ^1H NMR) with the sample described above.

Ethyl (±)-7β-Hydroxycarnosate Dimethyl Ether (25c). The procedure follows one of McChesney.[23] A mixture of 244 mg (0.608 mmol) of **25b**, mp 90–92 °C, and 360 mg (0.980 mmol) of $NaBH_4$ in 15 ml of 95% EtOH was stirred for 4 h and diluted with 15 ml of water and 25 ml of brine. Isolation B (ether) gave 240 mg (97%) of white solid, mp 110–114 °C. Recrystallization from petroleum ether–EtOAc afforded 261 mg (88%) of **25c** as white prisms, mp 115–116 °C. Pure **25c** had mp 116–117 °C; uv max (95% EtOH) 274 nm (ε 680); ir ($CHCl_3$) 3580, 3465 (br), 1720 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.75 (s, 1 H), 5.30 (broad t, J = 9 Hz, 1 H), ca. 5.81 and 5.93 (m,[36] 2 H), 6.27 (s, 3 H), 6.35 (s, 3 H), 8.75 (t, J = 7 Hz, 3 H), 8.78 (d, J = 7 Hz, 3 H), 8.80 (d, J = 7 Hz, 3 H), 9.03 (s, 3 H), 9.18 (s, 3 H).

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 71.32; H, 8.99.

(±)-Carnosol Dimethyl Ether (26). The procedure follows one of Linde.[4] A solution of 74 mg (0.18 mmol) of **25c**, mp 115–116 °C, and 41 mg (0.37 mmol) of freshly prepared t-BuOK in 5 ml of dry C_6H_6 was stirred for 8 h, acidified with 3 drops of glacial HOAc, and diluted with brine. Isolation B (ether, $NaHCO_3$ wash) left 69 mg of white glass which was filtered through 5 g of Al_2O_3 with 1:1 petroleum ether–$CHCl_3$ to provide 53 mg (82%) of **26**, mp 150–154 °C. Recrystallization from dry MeOH afforded pure **26** as white prisms: mp 155–156 °C [lit.[4] mp for (+)-**26**, 155–156 °C]; uv max (95% EtOH) 272 nm (ε 930); ir ($CHCl_3$) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) τ 3.17 (s, 1 H), 4.62 (dd, J = 2 and 4 Hz, 1 H), 6.22 (s, 3 H), 6.23 (s, 3 H), 8.80 (d, J = 7 Hz, 3 H), 8.82 (d, J = 7 Hz, 3 H), 9.08 (s, 3 H), 9.15 (s, 3 H); ir and ^1H NMR identical with those of (+)-**26**.[23]

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.70; H, 8.44. Found: C, 73.83; H, 8.36.

10-Carbethoxy-12-methoxy-17-norabieta-8,11,13-trien-7-one (23). A solution of 150 mg (0.341 mmol) of an isomeric mixture of adducts **22**, mp 130–142 °C, and 0.25 ml of concentrated HCl in 4 ml of Me_2SO was stirred for 14 h and diluted with 20 ml of 50% brine. Isolation B (4:1 ether–$CHCl_3$, $NaHCO_3$ wash) provided 119 mg (97%) of crude **9b**. This was refluxed for 12 h in 15 ml of dry acetone with 2.0 g of K_2CO_3 and 0.3 ml of Me_2SO_4. The neutral product was isolated as described for **10b** as 120 mg of yellow oil which was filtered through 10 g of Al_2O_3 with 1:1 petroleum ether–$CHCl_3$ to afford 81 mg (64%) of colorless oil which crystallized from petroleum ether. Recrystallization from MeOH provided **23** as colorless needles: mp 112.5–113 °C; uv max (95% EtOH) 281 nm (ε 16 800), 236 (ε 25 600); ir ($CHCl_3$) 1710, 1660, 1595, 1560, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) τ 2.07 (s, 1 H), 3.17 (s, 1 H), ca. 5.94 and 6.01 (m,[36] 2 H), 6.13 (s, 3 H), 8.78 (d, J = 7 Hz, 3 H), 8.80 (d, J = 7 Hz, 3 H), 8.87 (t, J = 7 Hz, 3 H), 9.03 (s, 3 H), 9.12 (s, 3 H).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; 8.66. Found: C, 74.07; H, 8.53.

10-Carbethoxy-12-methoxy-17-norabieta-8,11,13-triene (10b). Keto ester **23** (45 mg, 0.12 mmol, mp 112–113 °C) was hydrogenated for 45 min at 1 atm over 14 mg of 30% Pd/C in 10 ml of EtOAc containing 1 drop of concentrated H_2SO_4. Filtration and

isolation A ($NaHCO_3$ wash) gave 43 mg (100%) of white solid which was recrystallized from MeOH to afford pure **10b** as colorless plates, mp 64.5–65.5°, melting point, ir, ^1H NMR identical with those of the specimen described above.

By-Products from "Abnormal" Hydrogenation of Enone 27 in Ethanol. Hydrogenation of 24 g of **27**, mp 68–70 °C, at 1 atm over 300 mg of 30% Pd/C in 125 ml of 95% EtOH was intentionally allowed to proceed until H_2 uptake appeared to have stopped completely (ca. 1.5 molar equiv absorbed), in order to maximize the amounts of by-products sometimes detected by GLC and ^1H NMR in products from hydrogenation as described earlier.[12] Initial rapid absorption of approximately the theoretical amount of H_2 was followed by a period of slower but easily observable consumption, which was then followed by a long period of extremely slow absorption. The usual isolation[12] afforded an oil which was held at 80 °C and 0.025 mm for several hours (to remove EtOH erroneously believed to be present because ^1H NMR showed an "extra" OEt resonance) and chromatographed over 2 lb of Merck neutral Al_2O_3 (90 × 4 cm), with pentane, ether, $CHCl_3$, C_6H_6, MeOH, and mixtures thereof as eluents.

(1) Fractions 22–42 (5–10% ether–pentane) consisted of 9.3 g of **31** as a colorless, mobile oil, 99+% pure by GLC: ir (film) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) τ 5.92 (q, J = 7 Hz, 2 H), 6.53 (q, J = 7 Hz, 2 H), ca. 6.78 (m, broad, 1 H), 8.77 (t, J = 7 Hz, 3 H), 8.87 (t, J = 7 Hz, 3 H), 9.10 (s, 3 H), 9.22 (s, 3 H).

Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.68. Found: C, 72.27; H, 10.52.

(2) Fractions 56–59 (ether) comprised 3.6 g of **4**, mp 44.2–45.8 °C.

(3) Fractions 69–75 (20% $CHCl_3$–ether and 10% C_6H_6–ether) comprised 140 mg of **28** as a yellowish oil which slowly solidified. Fractional vacuum sublimation in a horizontal tube afforded pure **28** as white microcrystals: mp 51–53 °C; ir ($CHCl_3$) 3615, 3450 (broad), 1710 cm^{-1}; ^1H NMR ($CDCl_3$) τ 5.80 (m, $W_{1/2} \simeq 7$ Hz, 1 H), 5.90 (q, J = 7 Hz, 2 H), 8.75 (t, J = 7 Hz, 3 H), 9.13 (s, 3 H), 9.27 (s, 3 H).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.82; H, 10.30. Found: C, 70.55; H, 9.93.

(4) Fractions 80–81 (MeOH) comprised 4.0 g of **29** as a yellowish oil. Molecular distillation in a micro-Hickman flask (120 °C, 0.05 mm) afforded pure **29** as a colorless oil: ir (film) 3375 (broad), 1725 cm^{-1}; ^1H NMR ($CDCl_3$) τ ca. 5.86 and 5.90 (m,[36] 2 H), ca. 6.43 (m, broad, 1 H), 7.08 (s, 1 H), 8.73 (t, J = 7 Hz, 3 H), 9.10 (s, 3 H), 9.23 (s, 3 H). Ir, ^1H NMR, and GLC are identical with those of a sample from $NaBH_4$ reduction of **4**.[26]

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.82; H, 10.30. Found: C, 70.72, H, 10.11.

10-Carbethoxy-4,4-dimethyl-7β-ethoxy-5α-decalin (31). The procedure follows one of Ireland et al.[42] A solution of 100 mg of $Hg(OAc)_2$ and 255 mg (1.00 mmol) of redistilled **29** in 10 ml of freshly distilled isopropyl vinyl ether, bp 51 °C, was gently refluxed for 6 h, K_2CO_3 (1.0 g) was added to inactivate the catalyst, and after 10 min at reflux the solution was decanted and evaporated under N_2 on the steam bath to afford an oil which was chromatographed over Al_2O_3 (Merck, 32 × 1 cm) in petroleum ether. The vinyl ether was eluted with 50 ml of 15% ether in pentane as 204 mg (73%) of a cloudy, mobile oil: ^1H NMR ($CDCl_3$) τ 3.67 (dd, J = 6.5 and 14 Hz, 1 H), 5.75 (dd, J = 1 and 14 Hz, 1 H), ca. 5.86 and 5.90 (m,[36] 2 H), 6.05 (dd, J = 1 and 6.5 Hz, 1 H), ca. 6.27 (m, broad, 1 H), 8.73 (t, J = 7 Hz, 3 H), 9.10 (s, 3 H), 9.23 (s, 3 H). The crude vinyl ether (204 mg, 0.728 mmol) was hydrogenated at 1 atm in 20 ml of 95% EtOH over 35 mg of 5% Rh/Al_2O_3. Theoretical H_2 uptake was very rapid. Filtration and evaporation afforded 100% of **31** (99+% pure by GLC) which was identical (ir, ^1H NMR, GLC) with the sample described above.

10-Carbethoxy-4,4-dimethyl-5α-decalone-7 (4). The procedure follows one of Djerassi et al.[43] Under N_2 0.12 ml of Jones reagent[27] (2.675 g of CrO_3 in 2.30 ml of concentrated H_2SO_4 diluted to 10.0 ml with water) was added rapidly with stirring to a cold solution (10–15 °C) of **28** (110 mg, 0.321 mmol) in 20 ml of acetone (redistilled from $KMnO_4$). After 5 min, isolation C (ether and $CHCl_3$, 5% $NaHCO_3$ wash) provided 100 mg (91%) of a yellow oil which solidified. Recrystallization afforded white crystals, mp 45–46 °C, identical (^1H NMR, mixture melting point) with authentic **4**.

10-Carbethoxy-4,4-dimethyl-Δ⁵-7β-octalol (30). A solution of 1.02 g (4.1 mmol) of **27**, mp 70–71 °C, and 1.51 g (40 mmol) of $NaBH_4$ in 150 ml of 95% EtOH was stirred for 2 h. Isolation C ($CHCl_3$, Na_2SO_4 drying) afforded 1.11 g (100%) of **30** as a brown oil which could not be crystallized or distilled without decomposition: ir (film) 3420, 1725, 1645 cm^{-1} (w); ^1H NMR ($CDCl_3$) τ 4.28 (d, J = 2.2 Hz, 1 H), ca. 5.80 and 5.92 (m,[36] 2 H), ca. 5.78 (m, broad, 1 H), 6.63 (s, 1 H), 8.73 (t, J = 7 Hz, 3 H), 8.90 (s, 3 H), 9.08 (s, 3 H). TLC, GLC, and ^1H NMR all indicated the absence of a second isomer or major amounts of contaminants.

10-Carboxy-4,4-dimethyl-Δ⁵-7β-octalol Lactone (32).[44] A mixture of 490 mg (1.94 mmol) of crude **30** and 53 mg of a 53% NaH–mineral oil dispersion (1.2 mmol of NaH) in 25 ml of C_6H_6 was stirred for 5 h in an N_2 atmosphere. Isolation C ($CHCl_3$, Na_2SO_4 drying) left 396 mg (93%, assuming presence of 25 mg of mineral oil) of **32** as a colorless oil. Evaporative distillation afforded an analytical sample: bp 119–122 °C (bath, 0.3 mm); ir (film) 1740, 1655 (w), 1620 cm^{-1} (w); ^1H NMR ($CDCl_3$) τ 3.88 (d, J = 5.5 Hz, 1 H), 4.95 (m, 1 H), 8.71 (s, 3 H), 8.73 (s, 3 H).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found:[44] C, 75.68; H, 9.18.

Registry No.—**4**, 57593-80-3; **5a** 57593-81-4; **5b**, 57593-82-5; **6**, 57593-83-6; **7a** 11α-H epimer, 57593-84-7; **7a** 11β-H epimer, 57593-85-8; **7b** 11α-H epimer, 57593-86-9; **7b** 11β-H epimer, 57593-87-0; **7c** 11α-H epimer, 57593-88-1; **7c** 11β-H epimer, 57593-89-2; **7d** 11α-H epimer, 57607-04-2; **7d** 11β-H epimer, 57593-90-5; **8a**, 57593-91-6; **8b**, 57636-84-7; **9a**, 57593-92-7; **9b**, 57636-85-8; **10a**, 57636-86-9; **10b**, 57593-93-8; **11**, 57593-94-9; **12** syn isomer, 57593-95-0; **12** anti isomer, 57593-96-1; **13**, 57593-97-2; (+)-**14**, 57636-87-0; (±)-**14**, 10438-43-4; (+)-**15**, 20337-29-5; (±)-**15**, 20483-07-2; **16**, 57593-98-3; **18a**, 57593-99-4; **18b**, 57594-00-0; **19a** 11α-H epimer, 57594-01-1; **19a** 11β-H epimer, 57594-02-2; **19b** 11α-H epimer, 57594-03-3; **19b** 11β-H epimer, 57594-04-4; **19c** 11α-H epimer, 57594-05-5; **19c** 11β-H epimer, 57594-06-6; **20**, 57594-07-7; **21**, 16697-72-6; **22**, 20483-08-3; **23**, 57594-08-8; **24a**, 57594-09-9; **24b**, 57607-05-3; **25a**, 20483-10-7; **25b**, 20482-69-3; **25c**, 20482-68-2; **26**, 20483-06-1; **27**, 57594-10-2; **28**, 57594-11-3; **29**, 57594-12-4; **30**, 57594-13-5; **31**, 57594-14-6; **32**, 57594-15-7; *tert*-butyl acetoacetate, 1694-31-1; *tert*-butyl isovalerylacetate, 39140-54-0; methyl isovalerylacetate, 30414-55-2; methyl α-isovalerylacetoacetate, 57594-16-8; methyl acetoacetate, 105-45-3; benzyl isovalerylacetate, 57594-17-9; benzyl acetoacetate, 5396-89-4; isovaleryl chloride, 108-12-3; benzyl α-isovalerylacetoacetate, 57594-18-0.

References and Notes

(1) (a) Part VII: W. L. Meyer, G. B. Clemans, and R. A. Manning, *J. Org. Chem.*, **40**, 3686 (1975). (b) Abstracted in part from Ph.D. Dissertations of R.A.M. and D.C.S., University of Arkansas, 1971 and 1969, respectively, and R.S.S., Indiana University, 1970. (c) Supported by Grants AM-4215 and AM-10123 from the National Institute of Arthritis and Metabolic Diseases, and the University of Arkansas Research Reserve Fund. (d) National Aeronautics and Space Administration Trainee, 1965–1967, and National Institutes of Health Predoctoral Fellow, 1967–1968. (e) Preliminary communications: W. L. Meyer and E. Schindler, *Tetrahedron Lett.*, 4261 (1966); D. C. Shew and W. L. Meyer, *ibid.*, 2963 (1968).

(2) Throughout this discussion the numbering system shown in structure **1** will be used for tricyclic intermediates, and the corresponding A/B numbering system will be used for bicyclic compounds, with the *gem*-dimethylated ring taken as ring A. The stereochemical notations α and β indicate a trans or cis relationship to the C-10 angular group, respectively. All synthetic compounds have been examined only in racemic form, although the prefix (±) is omitted and only one enantiomer is depicted in structural formulas.

(3) W. L. Meyer, R. W. Huffman, and P. G. Schroeder, *Tetrahedron*, **24**, 5959 (1968).

(4) H. Linde, *Helv. Chim. Acta*, **47**, 1234 (1964).

(5) E. Wenkert, A. Fuchs, and J. D. McChesney, *J. Org. Chem.*, **30**, 2931 (1965).

(6) A. I. White and G. L. Jenkins, *J. Am. Pharm. Assoc., Sci. Ed.*, **31**, 33, 37 (1942).

(7) C. H. Brieskorn and A. Fuchs, *Chem. Ber.*, **95**, 3034 (1962).

(8) C. H. Brieskorn, A. Fuchs, J. B. Bredenberg, J. D. McChesney, and E. Wenkert, *J. Org. Chem.*, **29**, 2293 (1964).

(9) C. R. Narayanan and N. K. Venkatasubramanian, *Tetrahedron Lett.*, 3639 (1965).

(10) C. R. Narayanan and H. Linde, *Tetrahedron Lett.*, 3647 (1965).

(11) L. D. Yakhontova and M. I. Anisimova, *Zh. Obshch. Khim.*, **32**, 1337 (1962); L. D. Yakhontova and A. D. Kuzokow, *ibid.*, **33**, 308 (1963).

(12) W. L. Meyer and A. S. Levinson, *J. Org. Chem.*, **28**, 2184 (1963).

(13) This enol was accompanied by 5–25% of *tert*-butyl enol ether **5b** when isolation from the *t*-BuOK–*t*-BuOH medium was initiated by acidification with concentrated HCl; see Experimental Section for data substantiating the structure assignment. This mild, rapid, and under other circumstances potentially useful acid-catalyzed enol etherification was avoided by acidification with acetic acid.

(14) J. A. Edwards, M. C. Calzada, L. C. Ibanez, M. E. Cabezas Rivera, R. Urguiza, L. Cardona, J. C. Orr, and A. Bowers, *J. Org. Chem.*, **29**, 3481 (1964).

(15) W. L. Meyer, G. B. Clemans, and R. W. Huffman, *Tetrahedron Lett.*, 4255 (1966).

(16) Detailed consideration of data from several series of compounds which relates to the 9 configuration in adducts like **7** and their derivatives and to the double bond location and 8,9 configuration in enediones like **8**

will be included in the next paper of this series; cf. D. C. Shew and R. A. Manning, Ph.D. Dissertations, University of Arkansas, 1969 and 1971, respectively.
(17) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **80**, 1613 (1958), and references cited therein.
(18) N. Kornblum in "Organic Reactions", Vol. 2, R. Adams, Ed., Wiley, New York, N.Y., 1944, Chapter 7.
(19) W. R. Brode, L. Seldin, P. E. Spoerri, and G. M. Wyman, *J. Am. Chem. Soc.*, **77**, 2762 (1955).
(20) We are grateful to Professor E. Wenkert for samples of (+)-carnosic acid dimethyl ether and (+)-carnosol dimethyl ether.
(21) F. C. Chang and N. F. Wood, *Tetrahedron Lett.*, 2969 (1964).
(22) G. A. Russell and G. J. Mikol, *J. Am. Chem. Soc.*, **88**, 5498 (1966).
(23) J. D. McChesney, Ph.D. Dissertation, Indiana University, 1965.
(24) The hydrogenation by-product mentioned in footnote 21 of ref 12 is also **31** and not the still unknown *cis*-decalone.
(25) W. L. Meyer, D. L. Davis, L. Foster, A. S. Levinson, V. L. Sawin, D. C. Shew, and R. F. Weddleton, *J. Am. Chem. Soc.*, **87**, 1573 (1965).
(26) W. L. Meyer, D. L. Davis, A. W. McCollum, J. W. Morgan, N. S. Starr, and D. A. Templer, *J. Am. Chem. Soc.*, **94**, 466 (1972).
(27) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(28) Saponification of **30** and acid-catalyzed lactonization of the resulting hydroxy acid also affords **32**, but this result is less useful as evidence for the configuration of **30** in view of the possible intervention of an allylic 7-carbonium ion during lactonization (R. W. Huffman and W. L. Meyer, unpublished results).
(29) E. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **86**, 5561 (1964).
(30) M. Verzele, M. Acke, and M. Anteunis, *J. Chem. Soc.*, 5598 (1963); S. Nishimura, T. Itaya, and M. Shiota, *Chem. Commun.*, 422 (1967).
(31) The alternative possibility that some or all of **28–31** are formed through intermediacy of a Δ^6 enol which results from initial 1,4 reduction of the enone should not be discounted, however; cf. R. L. Augustine, D. C. Migliorini, R. E. Foscante, C. S. Sodano, and M. J. Sisbarro, *J. Org. Chem.*, **34**, 1075 (1969), and references cited therein.
(32) The observation that **33** was reduced only very slowly, if at all, at 1 atm over the limited number of Pd/C samples which were examined suggests that hydrogenolysis of **30** may proceed through a π-allyl adsorbed intermediate[33] to form a mixture of **33** and its unisolated Δ^6 isomer, with the latter rather than **33** being the precursor of decalin **34**.
(33) Cf. W. R. Moore, *J. Org. Chem.*, **84**, 3788 (1962); J. J. Rooney, F. G. Gault, and C. Kemball, *J. Catal.*, **1**, 255 (1962).
(34) Hydrogenation of 10-carbethoxy-4,4-dimethyl-Δ^5-octalin derivatives to afford mixtures of trans- and cis-fused products has been observed, however, with systems other than the 7-ketone, including **33** itself; cf. R. F. C. Brown, *Aust. J. Chem.*, **17**, 47 (1964); R. S. Schroeder, Ph.D. Dissertation, Indiana University, 1970.
(35) The low extinction coefficients indicate that the sample used for these uv determinations had undergone partial decomposition.
(36) This ethoxyl resonance shows distinct ABC_3 character with $J_{AB} = J_{AC} = 7$ Hz, but was not precisely analyzed; these chemical shifts are only estimated visually, ±0.02 ppm; cf. ref 25.
(37) We are grateful to the Eastman Chemical Co. for a generous gift of this material.
(38) We were unable to find conditions which would bring about this hydrogenolysis without sequential exposure to two fresh batches of catalyst.
(39) It is possible that the recovered **6** is formed by retro-Michael reaction during the alkaline extraction process, and it is therefore in general desirable to avoid this step in the isolation sequence.
(40) T. L. Moore, *J. Org. Chem.*, **32**, 2786 (1967).
(41) The ethyl isovalerate was prepared from isovaleryl chloride obtained from K and K Laboratories, Inc., Plainview, N.Y. Although the ester distills sharply at 134 °C it contains ca. 10% of an impurity (τ 8.85, d, J = 7 Hz) which originated in the acid chloride and could not be removed by careful distillation of either the acid chloride or the ester.[1a] A related impurity (τ 8.88) is present in the distilled β-keto sulfoxide.
(42) R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, **27**, 1620 (1962); R. F. Church and R. E. Ireland, *ibid.*, **28**, 17 (1963).
(43) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).
(44) This experiment was conducted by Mr. B. H. Fahoum; microanalysis by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Sesquiterpene Lactones of *Eupatorium hyssopifolium*. A Germacranolide with an Unusual Lipid Ester Side Chain[1]

Werner Herz* and Ram P. Sharma

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306

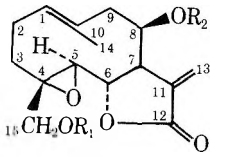
Received October 6, 1975

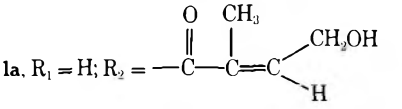
The isolation and structure determination of three new closely related germacranolides, eupassopin, eupassopilin, and eupassofilin, from *Eupatorium hyssopifolium* L. are reported. Eupassofilin is highly unusual in being the first ester of D(−)-3-hydroxyoctadecanoic acid isolated from a higher plant. Generalizations for the ease of hydrolysis of five-carbon unsaturated ester side chains in germacranolides are presented.

Chemical examination of several *Eupatorium* species *sensu stricto*[2] has produced a number of cytotoxic and antitumor germacranolides and guaianolides.[3–7] In the present communication, we report the isolation and structure determination from *Eupatorium hyssopifolium* L. of three new noncrystalline germacranolides, eupassopin, eupassopilin, and eupassofilin, the last of which is linked in an unprecedented way to a D(−)-β-hydroxystearoyl ester side chain.[8]

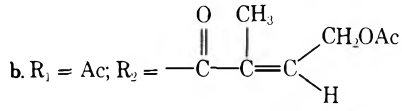
For the sake of convenience we discuss first the structure of eupassopin (**1a**), $C_{20}H_{26}O_7$ (high-resolution mass spectrum), $[\alpha]D$ −137.5°, which was a conjugated γ-lactone of the type partially shown in A (ir bands at 1760 and 1650 cm^{-1}), as evidenced by the usual criteria of narrowly split doublets at 6.25 and 5.67 ppm (H_a and H_b) in the ^1H NMR spectrum (Table I) and the appropriate signals in the ^{13}C NMR spectrum, particularly the triplet at 122.8 ppm (Table II). D_2O exchange sharpened a two-proton AB system at 3.89 d and 3.75 d (J = 12 Hz) and a two-proton broad doublet at 4.24 ppm (J = 6 Hz); hence eupassopin appeared to contain two primary hydroxyl groups.

Acetylation of eupassopin indeed furnished a diacetate **1b** (two new acetate signals at 2.14 and 2.08 ppm), but while the two-proton broad doublet had moved downfield from 4.24 to 4.80 ppm as expected (see Table I), only one of

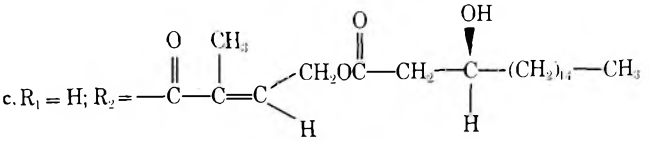




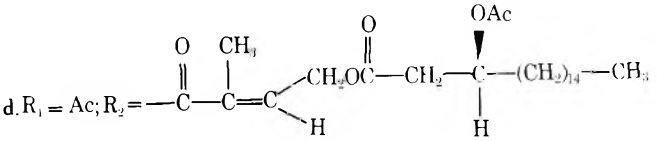
1a, $R_1 = H$; $R_2 =$



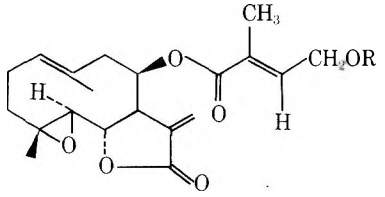
b. $R_1 = Ac$; $R_2 =$



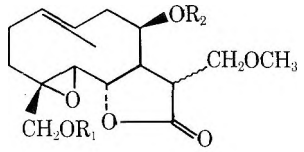
c. $R_1 = H$; $R_2 =$



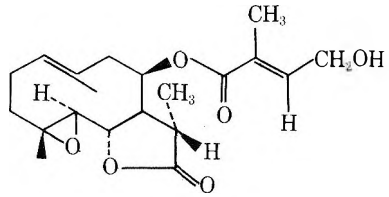
d. $R_1 = Ac$; $R_2 =$



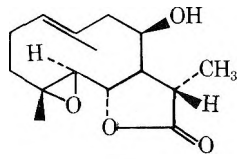
2a, R = H
b, R = Ac



3a, R_1, R_2 = H
b, R_1, R_2 = Ac



5

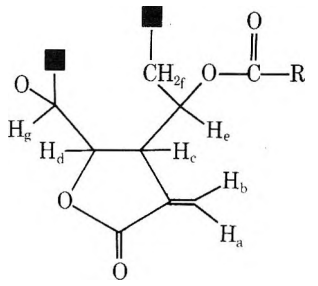


6

Table I. ^{1}H NMR Spectra of *E. Hyssopifolium* Constituents and Derivatives[a]

Compd	H-1	H-5	H-6	H-7	H-8	H-9	H-13	H-14[b]	H-15	H-3′	H-4′[c]	H-5′[b]	Misc
1a	5.29 dd br (11, 2)	2.97 d (9)	4.77 dd (9, 9)	3.12 m	5.67 d br (5, <1, <1)	2.70 dd (15, 5) 2.33 d br (15, <1)	6.25 d (3.5) 5.67 d (3.2)	1.65 br	3.89 d (12) 3.75 d (12)	6.71 m	4.24 d br (6)	1.72 br	
1b	5.39 dd br (11, 2)	3.02 d (9)	4.5 dd (9, 9)	3.3 m	5.76 d br (5, <1, <1)	2.80 dd (15, 5) 2.46 d br (15, <1)	6.37 d (3.5) 5.76 d (3.2)	1.74 br	4.80 d (12) 3.80 d (12)	6.70 m	4.80 d br (6)	1.88 br	2.08 (Ac) 2.14 (Ac)
1c	5.33 dd br (11, 2)	2.98 d (9)	4.88 dd (9, 9)	3.11 m	5.74 d br (5, <1, <1)	2.77 dd (15, 5) *d*	6.36 d (3.5) 5.74 d (3.2)	1.70 br	3.89 d (12) 3.79 d (12)	6.69 m	4.77 d br (6)	1.84 br	4.03 m (OH) 1.24 (~24 H) 0.86 t (7)[b]
1d	5.36 dd br (11, 2)	2.97 d (9)	4.46 dd (9, 9)	3.17 m	5.74 d br (5, <1, <1)	2.80 dd (15, 5) 2.44 d br (15, <1)	6.36 d (3.5) 5.74 d (3.2)	1.73 br	4.73 d (12) 3.79 d (12)	6.70 m	4.75 d br (6)	1.86 br	2.01, 2.12 (Ac) 5.21 q (6.5) 1.24 (~24 H) 0.87 t (7)[b]
2a	5.28 dd br (11, 2)	2.82 d (9)	4.41 dd (9, 9)	3.17 m	5.70 d br (5, <1, <1)	2.73 dd (15, 5) 2.35 d br (15)	6.31 d (3.5) 5.70 d (3.2)	1.67 br	1.33[b]	6.88 m	4.30 d br (6)	1.75 br	
2b	5.33 dd br (11, 2)	2.85 d (9)	4.41 dd (9, 9)	3.21 m	5.77 d br (5, <1, <1)	2.85 dd (15, 5) 2.40 d br (15)	6.36 d (3.5) 5.73 d (3.2)	1.70 br	1.35[b]	6.66 m	4.71 d br (6)	1.84 br	2.07 (Ac)
3a	5.25 dd br (11, 2)	2.92 d (9)	4.71 dd (9, 9)	*d*	4.33 d br (5, <1, <1)	*d*	3.70 dd (10.5, 3.5) 3.60 dd (10.5, 3.5)	1.83 br	3.90 d (12) 3.71 d (12)				3.35 (OMe)
3b	5.37 dd br (11, 2)	2.87 d (9)	4.20 dd (9, 9)	*d*	5.37 d br (5, <1, <1)	*d*	3,6 m[c]	1.71 br	4.64 d (12) 3.74 d (12)				3.34 (OMe) 2.09, 2.11 (Ac)
5	5.27 dd br (11, 2)	2.76 d (9)	4.33 dd (9, 9)	*d*	5.40 d br (5, <1, <1)	*d*	1.26 d[b] (6.8)	1.68 br	1.35[b]	6.83 m	4.35 d br (6)	1.82	
6[e]	5.26 dd br (11, 2)	2.95 d (9)	4.79 dd (9, 9)	*d*	4.43 t br[f] (5)	*d*	1.29 d[b] (6.8)	2.01 br	1.39[b]				

[a] Run in $CDCl_3$ at 270 MHz on a Bruker HX-270 instrument with Me_4Si as internal standard, unless otherwise specified. Values are in parts per million: d, doublet; t, triplet; q, quintet; br, broadened singlet. Unmarked signals are singlets. Values in parentheses are coupling constants in hertz. [b] Intensity three protons. [c] Intensity two protons. [d] Signal obscured. [e] Run in pyridine d_5. [f] Changes to broad doublet on D_2O exchange.

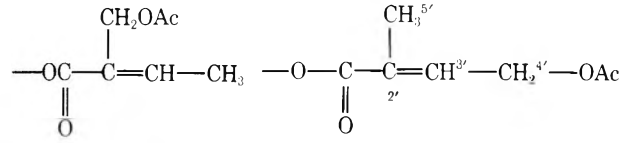


A

the protons in the AB system originally near 3.8 ppm had experienced the expected paramagnetic shift, the other signal remaining at 3.80 ppm. Consequently, it appeared initially that eupassopin contained one primary and one secondary hydroxyl group. However, the ^{13}C NMR spectrum (Table II) displayed two low-field triplets at 59.6 and 60.8 ppm which could only be assigned to two primary carbon atoms carrying hydroxyl groups. Decoupling experiments on **1b** which confirmed this assignment are described below. A possible explanation for the unusual behavior on acetylation of the AB system representing $-CH_2OH$ will be presented later.

Spin-decoupling experiments on **1b** involving H_a and H_b established the location of the H_c multiplet at 3.30 ppm. Irradiation at the frequency of H_c collapsed H_c and H_b into singlets, converted a doublet of doublets at 4.50 ppm (J_1 = J_2 = 9 Hz) into a doublet, and affected a broadened doublet at 5.76 ppm (partially obscured by H_b). Thus H_d and H_e were at 4.50 and 5.76 ppm, respectively, or the reverse. The chemical shift of the lower field proton suggested that it was under an ester rather than under a lactone oxygen, especially since the ir spectrum indicated the presence of an additional carbonyl function usually associated with a conjugated ester (at 1710 cm^{-1} in **1a**, 1715 cm^{-1} in **1b**). Hence the signal at 4.50 ppm was provisionally assigned to H_d and the signal at 5.76 ppm to H_e.

On the basis of the molecular formula, the unsaturated ester function had to consist of five carbon atoms. Since the low-resolution mass spectrum of **1a** exhibited prominent peaks at *m/e* 262 ($M^+ - C_5H_8O_3$) and 99 ($C_5H_7O_2$, base peak), it was concluded that an ester side chain of type B or C was present in **1b**; a clear decision in favor of C was possible on inspection of the NMR spectrum, which revealed the presence of a vinyl multiplet at 6.70 ppm (H-3′) coupled to a two-proton doublet at 4.80 ppm (H-4′) and the broad vinyl methyl of H-5′ at 1.88 ppm.



B C

Irradiation at 5.76 ppm (H_b and H_e) affected the H_c multiplet, collapsed a doublet of doublets at 2.80 ppm (J_1 = 5, J_2 = 15 Hz) to a doublet (J = 15 Hz), and sharpened a broadened doublet (J = 15 Hz) at 2.46 ppm. Irradiation at 2.80 ppm converted the broadened doublet of H_e to a broadened singlet and the broadened doublet at 2.46 ppm to a broad singlet. Analogously, irradiation at the frequency corresponding to 2.46 ppm converted the signal at 2.80 ppm to a doublet (J = 5 Hz) and affected the signal at 5.76 ppm. Consequently, H_e was adjacent to a methylene group (H_f of A) which was in turn adjacent to a quaternary center.

Irradiation at the frequency of H_d collapsed a sharp doublet at 3.02 ppm (J = 9 Hz) to a singlet. The proton responsible for this signal (H_g) was undoubtedly epoxidic because of its chemical shift, the empirical formula of eupassopin, which required one extra oxygen, and because the signal did not undergo a paramagnetic shift on acetylation of **1a** to **1b**. This assignment was also in agreement with the presence in the ^{13}C NMR spectrum of three doublets in the range 66–75 ppm, the doublets of C_d and C_e appearing at 75.0 and 74.0 ppm, respectively, and that of the carbon carrying H_g at 66.8 ppm (single frequency off-resonance decoupling). The other terminus of the epoxide ring was represented by a carbon singlet at 64.5 ppm.

Table II. ^{13}C NMR Spectra of Constituents of *E. Hyssopifolium*[a]

Carbon atom[b]	1a	1c	2a
1	128.8 d	128.8 d	128.5 d
2	31.8 t	32.0 t	35.6 t
3	23.9 t	23.9 t	23.9 t
4	64.5	64.4	61.8
5	66.8 d	67.0 d	66.2 d
6	75.0 d	74.8 d	75.6 d
7	49.8 d	49.8 d	49.1 d
8	74.0 d	74.2 d	74.0 d
9	44.0 t	44.1 t	43.5 t
10	132.2	132.1	131.2
11	127.0	129.3	126.7
12	169.0	168.5	168.5
13	122.8 t	122.7 t	122.3 t
14	12.8 q	12.9 q	12.4 q
15	60.8 t	60.8 t	16.9 q
1′	166.2	165.7	165.9
2′	136.4	136.3	136.0
3′	142.9 d	137.3 d	142.6 d
4′	59.6 t	61.2 t	59.1 t
5′	19.6 q	19.6 q	19.4 q
1″		172.5	
2″		41.6 t	
3″		60.2 d	
4″		37.0 t	
5″–16″		32.1 t 32.0 t 29.8 t (8 by difference) 29.4 t 25.6 t	
17′		22.8	
18′		14.2 q	

[a] Run in $CDCl_3$ on a Bruker HX-270 instrument. Unmarked signals are singlets. [b] Assignments based on predicted shifts, comparisons with data in our files and in the literature, and by single frequency off-resonance decoupling.

To complete the empirical formula, the following additional facts had to be accommodated. (1) The presence of a second primary hydroxyl group whose protons were mutually coupled but not coupled to any of the remaining eight protons indicated by the ^1H NMR spectrum and by molecular spectrometry. (2) The presence of the function $-CH{=}C{-}CH_3$ revealed by a slightly broadened three-proton resonance at 1.74 ppm and a broad doublet at 5.39 ppm in the ^1H NMR spectrum of **1b** and confirmed by a singlet at 132.2 ppm, a doublet at 128.8 ppm, and a quartet at 12.8 ppm in the ^{13}C NMR spectrum of **1a**.

Irradiation at the frequency of the vinyl proton not only sharpened the vinyl methyl signal, but caused some changes in the methylene region. Conversely, irradiation at 1.74 ppm converted the vinyl proton resonance to a doublet of doublets which required that the vinyl proton be next to a methylene group. The remaining two protons of the empirical formula must also be part of a methylene group since the ^{13}C NMR spectrum exhibited three methylene triplets at 44.0 (C-9), 31.8 (C-2), and 23.9 ppm (C-3). Consequently, the gross formula of eupassopin must be represented by **1a**.

Before taking up the stereochemistry of eupassopin, we would like to discuss the structure of eupassofilin (**1c**), whose NMR spectrum was very similar to that of **1a**. In addition to the signals present in **1a**, eupassofilin had an additional one-proton multiplet at 4.03 ppm, a triplet at 0.86 ppm, and a very strong broad peak centered at 1.24 ppm integrating for more than 24 protons, as well as some more protons in the methylene region between 2 and 2.5 ppm. The two-proton H-4′ signal of **1a** was shifted downfield to 4.77 ppm, thus suggesting that the primary hydroxyl group of the five-carbon side chain was now esterified. This conclusion was reinforced by the observation that the ir spectrum of eupassofilin displayed a double-strength peak at 1715 cm^{-1}. Extended purification did not alter the spectral characteristics of **1c**; hence it was suspected that the five-carbon side chain of **1a** might be esterified in eupassofilin by a lipid moiety. Unfortunately, conventional electron impact mass spectrometry on **1c** resulted in loss of the entire side chain and did not permit determination of the nature of the lipid fragment. On the other hand, chemical ionization mass spectrometry yielded a significant peak at *m/e* 300 which, it was believed, could correspond to a fragment of formula $C_{18}H_{36}O_3$.

Acetylation of **1c** afforded a diacetate **1d**, partially as the result of acetylation of the primary hydroxyl group present at C-15 of **1a** and **1c** (NMR spectrum). Simultaneously, however, the multiplet of **1c** at 4.03 ppm had moved downfield to 5.21 ppm and now appeared as a quintet (J = 6.5 Hz), an observation which suggested that the newly formed acetoxyl was adjacent to two methylene groups.

The ^{13}C NMR spectrum of eupassofilin (Table II) exhibited all the frequencies of **1a** as well as a carbonyl carbon frequency at 172.5 ppm due to the additional ester function, a doublet at 68.2 ppm undoubtedly associated with the secondary hydroxyl group, a quartet at 14.2 ppm, presumably the terminal methyl of the lipid side chain and associated with the protonic methyl triplet at 0.86 ppm, a very strong triplet at 29.8 ppm due to at least six methylene groups, and seven well-separated triplets at 22.8, 25.6, 29.4, 32.0, 32.1, 37.0, and 41.6 ppm. Analysis of these chemical shifts[9] suggested that the hydroxyl group might possibly be located at C-3 of the lipid side chain, i.e., that eupassofilin might be the 3-hydroxystearoyl ester **1c** of eupassopin, if the chemical ionization results could be given credence.

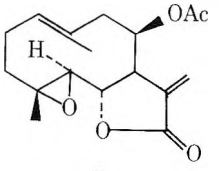
This conclusion was placed on a secure footing by hydrolysis of eupassofilin with methanolic sodium methoxide, a procedure which permitted isolation of the lipid fragment as the methyl ester. Two products were obtained and isolated by preparative TLC. The more polar material was identified as **3a**, also obtained by hydrolysis of **1a** with potassium carbonate in aqueous methanol (vide infra). The less polar substance was methyl D(−)-3-hydroxyoctadecanoate (**4**): mp 55 °C; $[\alpha]_D$ −12.5° (lit. mp 55.5–56.5 °C, $[\alpha]_D$ −15°);[10] molecular formula $C_{19}H_{38}O_3$ (high-resolution mass spectrum); low-resolution mass spectrum identical with that reported for methyl (±)-3-hydroxyoctadecanoate[11] and highly characteristic of a β-hydroxy fatty acid ester (see Experimental Section); ^1H NMR spectrum fully consonant with the proposed formula (see Experimental Section).

The isolation of D(−)-3-hydroxystearic acid as an ester component of a secondary metabolite produced by a higher plant is very unusual. The substance has been isolated previously[9] from species of the red yeast *Rhodotorula* which produce extracellular glycolipids consisting of a mixture of mannitol and pentitol esters of D(−)-3-hydroxypalmitic and D(−)-3-hydroxystearic acids, one molecule of the long-chain acid being attached to each polyol molecule and most of the remaining hydroxyl groups, including the one in the fatty acid moiety, being acetylated. The only higher plant source reported so far as we know is *Cistus ladaniferus* L.,[10] the gum resin of which contains a mixture of D(−)-β-hydroxy acids in the range C_{18}–C_{30}.

The molecular formula of eupassopilin, the third constituent of *E. hyssopifolium*, contained one oxygen less than that of **1a**. In the NMR spectrum, the two-proton AB system at C-15 was absent and replaced by a methyl singlet at 1.33 ppm. The remaining signals were essentially identical with those of **1a** (Table I); hence formula **2a** could be written for eupassopilin. This was also in full agreement with the ^{13}C NMR spectrum (Table II).

We now turn to the stereochemistry of the three new germacranolides. If it be assumed that H-7 is α as in all compounds whose absolute stereochemistry has been established by x-ray analysis or chemical correlations, the large value of $J_{6,7}$ (9 Hz) and $J_{5,6}$ (9 Hz) requires that the H-6 be β and H-5 be α. That the lactone ring is trans fused is also supported by the magnitude of $J_{7,13a}$ and $J_{7,13b}$ (>3 Hz).[12] Furthermore, in going from **1a** to **1b**, or from **1c** to **1d**, H-6 moves upfield which means that it comes into the shielding cone of the acetate carbonyl at C-15. Molecular models show that this is possible only if H-6 and the C-4, C-15 bond point in the same direction, i.e., the C-4, C-15 bond must be β as well. The models further suggest that this is possible only if the epoxide is derived from a C-4, C-5 trans double bond. Lastly, the very small value of $J_{7,8}$ (<1 Hz) requires that the ester side chain be β oriented; the absence of an NOE between H-1 and the C-10 methyl group suggests that the 1,10 double bond is trans.

Unequivocal proof for the proposed stereochemistry was obtained in the following manner. Since eupassopilin (**2a**) was available in relatively large quantity, it was hydrolyzed with K_2CO_3 in aqueous methanol to **3a** and the crystalline product acetylated to **3b**. The chemical shifts of C-1, C-5, C-6, C-7, and C-8 and the coupling constants $J_{5,6}$, $J_{6,7}$, and $J_{7,8}$ were very similar to those of lipiferolide (**7**), a substance of established stereochemistry which was reported[14] at the time when our work was in progress. In order to establish a direct correlation with lipiferolide, eupassopilin (**2a**) was reduced with sodium borohydride and the product **5** hydrolyzed with potassium carbonate in aqueous methanol to **6**. The melting point, rotation, and spectroscopic properties of this material were identical in all respects with those of 11,13-dihydrodeacetyllipiferolide.[14,15]

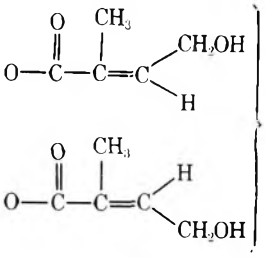
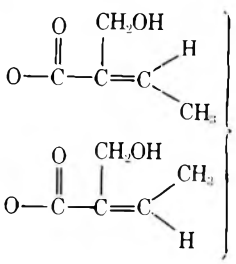
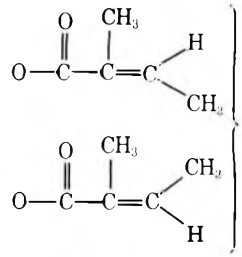
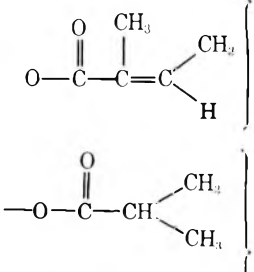
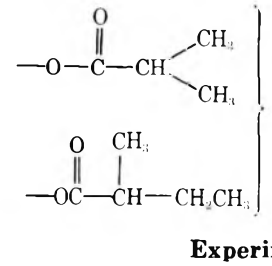
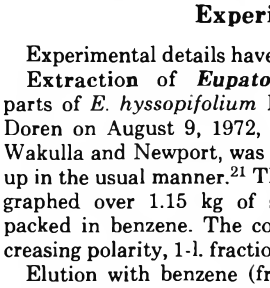


7

With the stereochemistry of the new substances established, a comment on the CD curves is in order. Eupassopilin and eupassofilin exhibit a negative Cotton effect in the 250-nm region, whereas eupassopin displays a positive Cotton effect. Thus it appears that the side chain attached to C-8 has some effect on the CD curve, a possibility to which we have referred earlier[16] and which obviously interferes with application of the Stöcklin–Waddell–Geissman rule.[17]

It has been mentioned earlier that on acetylation of **1a** (and of **1c**) only one of the protons on C-14 exhibits the expected downfield shift. The most probable explanation, derived from inspection of molecular models, is that restricted rotation around the C-4, C-15 bond results in a fixed conformation which places one of the protons in the shielding cone of the carbonyl attached to C-8 (or possibly the epoxide function[18]).

Our experience with the compounds from *E. hyssopifolium* and a large number of other sesquiterpene lactones[19] containing five-carbon unsaturated ester side chains most of which are gummy leads us to make some concluding remarks about the ease with which such side chains can be removed. These procedures, which generally lead to crystalline substances, may be useful to other workers and are listed below.

	Hydrolyzed by
	K_2CO_3—MeOH—H_2O for 20—30 min at room temperature
	
	K_2CO_3—MeOH—H_2O extremely slow at room temperature $NaOCH_3$—MeOH for 2–4 h at room temperature
	K_2CO_3—MeOH—H_2O no reaction at room temperature $NaOCH_3$—MeOH for 6—12 h at room temperature
	
	K_2CO_3—MeOH—H_2O no reaction at room temperature $NaOCH_3$—MeOH no reaction at room temperature
	

Experimental Section

Experimental details have been specified previously.[20]

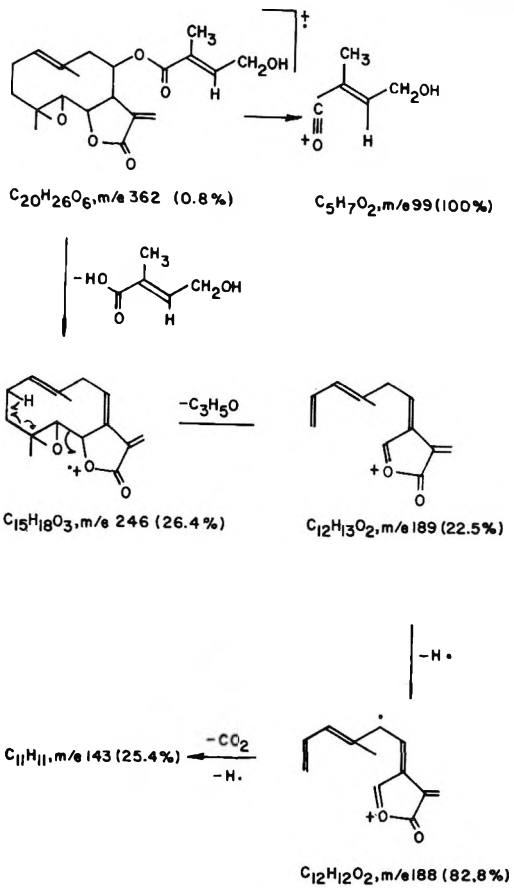
Extraction of *Eupatorium hyssopifolium*. Above-ground parts of *E. hyssopifolium* L., wt 11.5 kg, collected by Mr. R. F. Doren on August 9, 1972, in Wakulla County, Florida, between Wakulla and Newport, was extracted with chloroform and worked up in the usual manner.[21] The crude gum, wt 80.5 g, was chromatographed over 1.15 kg of silicic acid (Mallinckrodt 100 mesh) packed in benzene. The column was eluted with solvents of increasing polarity, 1-l. fractions being collected.

Elution with benzene (fractions 1–10) gave an oil (wt 10.2 g) which appeared to be a complex mixture of several compounds. Elution with benzene–$CHCl_3$ (10:1, fractions 11–20) gave a pale yellow gum (1.5 g) which on further purification over silica gel (Merck $PF_{254-356}$, solvent benzene–ethyl acetate, 6:1) gave 1.1 g of eupassofilin (**1c**) which could not be induced to crystallize: $[\alpha]^{22}D$ −143° (*c* 0.14, MeOH); CD curve $[\theta]_{275}$ 0, $[\theta]_{250}$ +954 (max); uv end absorption; ir bands (film) at 3450 (–OH), 1765 (lactone), 1715 (double intensity, esters), 1650 (exocyclic double bond), 1250, 1140, and 1080 cm^{-1}.

Anal. Calcd for $C_{38}H_{60}O_9$: C, 69.06; H, 9.15; O, 21.79. Found: C, 68.51; H, 9.15; O, 22.55.

The low-resolution mass spectrum failed to give the molecular ion; the first major peak appeared at *m/e* 262 which corresponds to loss of the entire side chain of 23 carbon atoms. Other significant peaks appeared at *m/e* 244 (M^+ − side chain − H_2O), 232 (M^+ − side chain − CH_3OH), and 99 (base peak). The chemical ionization spectrum gave a significant peak at *m/e* 300 which could correspond to $C_{18}H_{36}O_3$.

Scheme I. Mass Spectral Fragmentation of Eupassopilin



Acetylation of 0.11 g of **1c** with 1 ml of acetic anhydride in 0.5 ml of pyridine at room temperature overnight gave after the usual work-up 0.10 g of the diacetate **1d** as a gum: ir bands at 1770, 1715, 1650, 1730, 1140, and 1040 cm^{-1}.

Anal. Calcd for $C_{42}H_{64}O_{11}$: C, 67.60, H; 8.60; O, 23.65. Found: C, 66.94; H, 8.70; O, 23.91.

Further elution of the column with benzene–$CHCl_3$ (10:1, fractions 21–30) gave 3.5 g of gum which showed a major spot on TLC. Purification by preparative TLC (silica gel PF 254–356, solvent benzene–ethyl acetate, 5:1) yielded eupassopilin (**2a**) as a noncrystallizable gum: $[\alpha]^{22}D$ −161° (*C* 0.31, MeOH); CD curve $[\theta]_{290}$ 0, $[\theta]_{235}$ −7590 (minimun); ir bands (film) at 3450 (OH), 1765 and 1650 (conjugated lactone), 1710 (ester), 1250, 1140, 1030, 740 cm^{-1}; high-resolution mass spectrum *m/e* (composition, %) 362 (M^+, $C_{20}H_{26}O_6$, 0.8), 263 ($M^+ - C_5H_7O_2$, $C_{15}H_{19}O_4$, 8.1), 262 ($M^+ - C_5H_8O_2$, $C_{15}H_{18}O_4$, 2.7), 247 ($M^+ - C_5H_7O_3$, $C_{15}H_{19}O_3$, 4.6), 246 ($M^+ - C_5H_8O_3$, $C_{15}H_{18}O_3$, 26.4), 245 ($M^+ - C_5H_9O_3$, $C_{15}H_{17}O_3$, 17.9), 228 ($C_{15}H_{16}O_2$, 15.1), 189 ($C_{12}H_{13}O_2$, 22.5), 188 ($C_{12}H_{12}O_2$, 81.8), 143 ($C_{11}H_{11}$, 25.4), 142 ($C_{11}H_{10}$, 11.9), 99 ($C_5H_7O_2$, 100). Scheme I is a rationalization of the major peaks.

Anal. Calcd for $C_{20}H_{26}O_6$: mol wt, 362.1728. Found: mol wt, 362.1744 (MS).

Acetylation of 0.1 g of **2a** at room temperature overnight gave, after the usual work-up, the monoacetate **2b** as a gum: yield 0.094 g; ir bands ($CHCl_3$) at 1770 and 1650 (conjugated lactone), 1735 (acetate), 1720 (esters), 1230, 1140, and 900 cm^{-1}. The low-resolution mass spectrum gave M^+ at *m/e* 404 ($C_{22}H_{28}O_7$); other major peaks were at *m/e* 362 ($M^+ - C_2H_2O$), 345 ($M^+ - C_2H_3O_2$), 263 ($M^+ - C_7H_9O_3$), 246 ($M^+ - C_7H_{10}O_4$), 188 ($C_{12}H_{12}O_2$), and 99 (base peak).

Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98; O, 27.69. Found: C, 64.58; H, 6.79; O, 27.99.

Elution of the column with benzene–$CHCl_3$ (1:1, fractions 31–40) gave the major component (15.1 g). Purification by preparative TLC over silica gel (solvent benzene–ethyl acetate, 1:1) gave eupassopin (**1a**) as a gum: $[\alpha]^{22}D$ −137.5° (*c* 0.4, MeOH); CD curve $[\theta]_{290}$ 0, $[\theta]_{235}$ −6038 (minimum); ir bands (film) at 3400 (OH), 1760 and 1650 (conjugated lactone), 1710 (ester), 1250, 1140, and

1030 cm^{-1}. The low-resolution mass spectrum gave the molecular ion at *m/e* 378 ($C_{20}H_{26}O_7$); other major peaks were at *m/e* 346 ($M^+ - CH_3OH$), 262 ($M^+ - C_5H_8O_3$), 244 ($M^+ - C_5H_8O_3 - H_2O$), 231 ($M^+ - C_5H_8O_3 - CH_3OH$), and 99 ($C_5H_7O_2$, base peak).

Anal. Calcd for $C_{20}H_{26}O_7$: mol wt, 378.1678. Found: mol wt, 378.1680 (MS).

Acetylation of 0.15 g of **1a** with 1 ml of acetic anhydride in 0.5 ml of pyridine at room temperature overnight gave the noncrystalline diacetate **1b**, ir bands (film) at 1770 and 1655 (lactone), 1740, 1735 (two acetates), 1710 (ester), 1250, 1140, 1040, and 740 cm^{-1}. The low-resolution mass spectrum gave the molecular ion at *m/e* 462 ($C_{24}H_{30}O_9$); other major peaks were at *m/e* 470 ($M^+ - C_2H_2O$), 402 ($M^+ - CH_3CO_2H$), 360 ($M^+ - C_2H_2O - CH_3CO_2H$), 342 ($M^+ - 2CH_3CO_2H$), 304 ($M^+ - C_7H_{10}O_4$), 267 ($M^+ - C_2H_2O - C_7H_{10}O_4$), 244 ($M^+ - CH_3CO_2 - C_7H_{10}O_4$), 188, and 99 (base peak).

Anal. Calcd for $C_{24}H_{30}O_9$: C, 62.33; H, 6.54; O, 31.13. Found: C, 62.08; H, 6.24; O, 30.59.

Preparation of 3a and 3b. A solution of 0.15 g of **1a** in 15 ml of MeOH, 2 ml of water, and 0.5 g of K_2CO_3 was stirred in a nitrogen atmosphere for 25 min when TLC indicated that all of **1a** had reacted. The mixture was diluted with water and extracted with $CHCl_3$. The washed and dried extract was evaporated; the solid residue was purified by preparative TLC on silica gel (solvent benzene–ethyl acetate, 1:1) to give 0.05 g of **3a**: mp 145°; ir bands at 3440, 3400, 1750, 1050, and 980 cm^{-1}; low-resolution mass spectrum peaks at *m/e* 312 (M^+), 281 ($M^+ - CH_3O$), 249 ($M^+ - CH_3O - CH_3OH$), 231 ($M^+ - OCH_3 - CH_3OH - H_2O$).

Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74; O, 30.73. Found: C, 61.67; H, 7.68; O, 31.06.

Acetylation of 0.062 g of **3a** at room temperature for 24 h gave a solid which was recrystallized from ethyl acetate and methanol to yield **3b**: wt 0.06 g; mp 180 °C; ir bands (Nujol) at 1790, 1725, 1250, 1270, 1170, 1050, and 990 cm^{-1}; low-resolution mass spectrum peaks at *m/e* 396 (M^+), 354 ($M^+ - C_2H_2O$), 336 ($M^+ - CH_3CO_2H$), 294 ($M^+ - C_2H_2O - CH_3CO_2H$), 276 ($M^+ - 2CH_3CO_2H$).

Anal. Calcd for $C_{20}H_{28}O_8$: C, 60.59; H, 7.12; O, 32.29. Found: C, 61.29; H, 7.07; O, 32.07.

Methanolysis of Eupassofilin. A solution of 0.2 g of **1c** in 10 ml of MeOH and 0.1 g of sodium methoxide was stirred in a nitrogen atmosphere for 30 min (TLC control). The mixture was worked up as described in the previous section. The crude product was separated by preparative TLC (silica gel, solvent benzene–ethyl acetate, 2:1) into two major bands. The less polar material (R_f 0.8) was recrystallized from ethyl acetate and characterized as the methyl ester of D(−)-3-hydroxyoctadecanoic acid (**4**): yield 0.020 g; mp 55 °C; $[\alpha]_D$ −12.5° (*c* 1.0, $CHCl_3$); ir bands at 3500, 1725, 1250, 1180, and 1000 cm^{-1}. The low-resolution mass spectrum gave the molecular ion peak at *m/e* 314 ($C_{19}H_{38}O_3$); other major peaks were at *m/e* 296 ($M^+ - H_2O$), 283 ($M^+ - CH_3O$), 264 ($M^+ - CH_3OH-2H_2O$), 222, 103 ($C_4H_7O_3$, base peak), and 74. The ^1H NMR spectrum exhibited a one-proton multiplet at 4.00 ppm, a methoxyl singlet at 3.72 ppm, a methyl triplet (J = 7 Hz) at 0.88 ppm, and a large peak centered at 1.24 ppm integrating for more than 24 protons. In addition there was a doublet of doublets at 2.52 ppm (J = 16, 4 Hz) and at 2.41 ppm (J = 16, 8.5 Hz) in the form of an AB system, characteristic of two nonequivalent protons adjacent to a carbonyl group. Irradiation at 4.00 ppm collapsed each doublet of doublets to a doublet (J = 16 Hz).

Anal. Calcd for $C_{19}H_{38}O_3$: mol wt, 314.2821. Found: mol wt, 314.2823 (MS).

The more polar band (R_f 0.35) was identical with **3a**.

Correlation of Eupassopilin with Lipiferolide. A. A solution of 0.2 g of **2** in 10 ml of MeOH was cooled to 0°C and stirred with 0.1 g of $NaBH_4$ in 10 ml of MeOH until TLC indicated consumption of starting material (4 h). The mixture was diluted with water, acidified with acetic acid, and extracted with $CHCl_3$. The washed and dried extracts were evaporated and the residue purified by preparative TLC (solvent benzene–ethyl acetate, 6:1). The major band was eluted with $CHCl_3$; evaporation of the solvent furnished **5** as a gum, wt 0.15 g, ir bands (film) at 3450, 1770, 1710, 1650, 1250, 1130, and 740 cm^{-1}. The high-resolution mass spectrum gave the molecular ion (0.4%); other major peaks were at *m/e* (composition, %) 346 ($M^+ - H_2O$, $C_{20}H_{26}O_5$, 4), 265 ($M^+ - C_5H_7O_2$, $C_{15}H_{21}O_4$, $C_{15}H_{20}O_3$, 20.1), 190 ($M^+ - C_5H_8O_3 - C_3H_6O$, $C_{12}H_{14}O_2$, 14), 175 ($C_{12}H_{15}O$, 13.9), 145 ($C_{11}H_{13}$, 17.7), and 99 ($C_5H_7O_2$, 100).

Anal. Calcd for $C_{20}H_{28}O_6$: mol wt, 364.1884. Found: mol wt, 364.1902 (MS).

B. A solution of 0.15 g of **5** in 12 ml of MeOH containing 0.25 g of K_2CO_3 in 1.5 ml of water was stirred at room temperature in a nitrogen atmosphere, the reaction being followed by TLC. The reaction was complete after 30 min. The product was worked up as usual, purified by preparative TLC (solvent benzene–ethyl acetate, 4:1), and recrystallized from ethyl acetate: yield 0.06 g; mp 166–167 °C (lit. mp 166–167 °C);[14] $[\alpha]_D$ −109° (c 0.24, MeOH); ir bands (KBr) at 3500, 1735, 1190, 1070, 990, and 875 cm^{-1}. The ir and NMR traces were identical with similar traces of 11,13-dihydrodeacetylipiferolide (α-oriented C-13 methyl group)[14] supplied by Professor Doskotch. The high-resolution mass spectrum gave the molecular ion (9%); other major peaks were at *m/e* (composition, %) 248 ($M^+ - H_2O$, $C_{15}H_{20}O_3$, 62.9), 230 ($M^+ - 2H_2O$, $C_{15}H_{18}O_2$, 23.2), 208 ($M^+ - C_3H_6O$, $C_{12}H_{16}O_3$, 44.1), 190 ($M^+ - H_2O - C_3H_6O$, $C_{12}H_{14}O_2$, 81.4), and 175 ($C_{12}H_{15}O$, 100).

Anal. Calcd for $C_{15}H_{22}O_4$: mol wt, 266.1517. Found: mol wt, 266.1510 (MS).

Registry No.—**1a**, 57718-77-1; **1b**, 57718-78-2; **1c**, 57718-79-3; **1d**, 57718-80-6; **2a**, 57718-81-7; **2b**, 57718-82-8; **3a**, 57718-83-9; **3b**, 57718-84-0; **4**, 57793-27-8; **5**, 57718-85-1; **6**, 56064-69-8.

References and Notes

(1) Work supported in part by U.S. Public Health Service Grant CA-13121 through the National Cancer Institute.
(2) For a recent redefinition of the genus *Eupatorium*, see R. M. King and H. Robinson, *Taxon*, **19**, 769 (1970).
(3) *E. cannabinum* L.: F. Gyzicki, *Pharmazie*, **6**, 686 (1950); L. Dolejs and V. Herout, *Collect. Czech. Chem. Commun.*, **27**, 2654 (1962); R. W. Doskotch and F. S. El Feraly, *J. Org. Chem.*, **35**, 1928 (1970); B. Drozdz, H. Graborzyk, Z. Samek, M. Holub, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **37**, 1546 (1972); W. Herz and I. Wahlberg, *J. Org. Chem.*, **38**, 2485 (1973).
(4) *E. cuneifollum* Willd.: S. M. Kupchan, M. Maruyama, R. J. Hemingway, J. C. Hemingway, S. Shibuya, T. Fujita, P. D. Cradwick, A. D. V. Hardy, and G. A. Sim, *J. Am. Chem. Soc.*, **93**, 4914 (1971); S. M. Kupchan, T. Fujita, M. Maruyama, and R. W. Britton, *J. Org. Chem.*, **38**, 1260 (1973); S. M. Kupchan, M. Maruyama, R. J. Hemingway, S. Shibuya, and T. Fujita, *ibid.*, **38**, 2189 (1973).
(5) *E. formosanum* Hoyata: K. H. Lee, H. C. Huang, E. S. Huang, and H. Furukawa, *J. Pharm. Sci.*, **61**, 629 (1972); A. T. McPhail, K. D. Onan, K. H. Lee, T. Ibuka, and H. C. Huang, *Tetrahedron Lett.*, 3203 (1974).
(6) *E. rotundifolium* L.: S. M. Kupchan, J. C. Hemingway, J. M. Cassidy, J. R. Knox, A. T. McPhail, and G. A. Sim, *J. Am. Chem. Soc.*, **89**, 465 (1967); S. M. Kupchan, J. E. Kelsey, M. Maruyama, and J. M. Cassidy, *Tetrahedron Lett.* 3517 (1968); S. M. Kupchan, J. E. Kelsey, M. Maruyama, J. M. Cassidy, J. C. Hemingway, and J. R. Knox, *J. Org. Chem.*, **34**, 3876 (1969).
(7) *E. semiserratum* DC.: S. M. Kupchan, T. Fujita, M. Maruyama, and R. W. Britton, *J. Org. Chem.*, **38**, 1260 (1973).
(8) Flavonoid constituents of this and other *Eupatorium* species have been reported previously: H. Wagner, M. A. Iyengar, L. Hörhammer, and W. Herz, *Phytochemistry*, **11**, 1504 (1972); H. Wagner, M. A. Iyengar, P. Dull, and W. Herz, *ibid.*, **11**, 1506 (1972); H. Wagner, M. A. Iyengar, O. Seligmann, L. Hörhammer, and W. Herz, *ibid.*, **11**, 2630 (1972); W. Herz, S. Gibaja, S. V. Bhat, and A. Srinivasan, *ibid.*, **11**, 2859 (1972); S. M. Kupchan, W. Sigel, J. R. Knox, and M. S. Udayamurthy, *J. Org. Chem.*, **34**, 1460 (1969); S. K. Talapatra, D. S. Bhar, and B. Talapatra, *Aust. J. Chem.*, **27**, 1137 (1974).
(9) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N.Y., 1972.
(10) A. P. Tulloch and J. F. T. Spencer, *Can. J. Chem.*, **42**, 830 (1964).
(11) G. Eglinton, D. H. Hunneman, and A. McCormick, *Org. Mass Spectrom.*, **1**, 593 (1968).
(12) J. de Pascual Teresa and B. Bermejo Jimenez, *An. Fis. Quim.*, **B62**, 569 (1966).
(13) Z. Samek, *Tetrahedron Lett.*, 671 (1970).
(14) R. W. Doskotch, S. L. Keely, C. D. Hufford, and F. S. El-Feraly, *Phytochemistry*, **14**, 769 (1975).
(15) We wish to express our thanks to Professor R. W. Doskotch for copies of the NMR and ir spectra of this substance.
(16) P. J. Cox, G. A. Sim, and W. Herz, *J. Chem. Soc., Perkin Trans. 2*, 459 (1975).
(17) W. Stöcklin, T. G. Waddell, and T. G. Geissman, *Tetrahedron*, **26**, 2397 (1970).
(18) W. Herz and A. L. Hall, *J. Org. Chem.*, **39**, 11 (1974).
(19) E.g., W. Herz, S. V. Bhat, and A. Srinivasan, *J. Org. Chem.*, **37**, 2532 (1972); W. Herz, and I. Wahlberg, *Phytochemistry*, **12**, 1421 (1973); *J. Org. Chem.*, **38**, 2485 (1973); W. Herz, J. Poplawski, and R. P. Sharma, *ibid.*, **40**, 199 (1975); W. Herz and R. P. Sharma, *ibid.*, **40**, 392 (1975); B. Karlsson, A.-M. Pilotti, A.-C. Wiehager, I. Wahlberg, and W. Herz, *Tetrahedron Lett.*, 2245 (1975); W. Herz and R. P. Sharma, *Phytochemistry*, **14**, 1561 (1975); W. Herz, I. Wahlberg, C. S. Stevens, and P. S. Kalyanaraman, *Phytochemistry*, **14**, 1803 (1975); W. Herz and R. P. Sharma, *J. Org. Chem.*, **40**, 3118 (1975); W. Herz and P. S. Kalyanaraman, *J. Org. Chem.*, **40**, 3486 (1975).
(20) W. Herz, A. Srinivasan, and P. S. Kalyanaraman, *Phytochemistry*, **14**,
(21) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).

New Hydroxylated *ent*-Kauranoic Acids From *Eupatorium album*[1]

Werner Herz* and Ram P. Sharma

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306

Received October 6, 1975

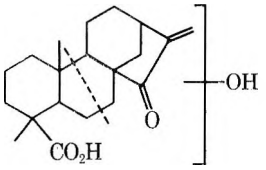
Eupatorium album L. gave four new hydroxylated *ent*-kauran-19-oic acids as well as a small amount of a sesquiterpene lactone mixture. Identification of the new substances as *ent*-11α,15α-dihydroxykaur-16-en-19-oic acid (**1a**), (16*R*)-*ent*-11α-hydroxy-15-oxokauran-19-oic acid (**2a**), *ent*-11α-hydroxy-15-oxokaur-16-en-19-oic acid (**3a**), and *ent*-11α,12α,15α-trihydroxykaur-16-en-19-oic acid (**4a**) by means of chemical correlations, ^{1}H NMR, and ^{13}C NMR spectrometry is described.

A number of sesquiterpene lactones with cytotoxic and antitumor activity has been isolated from *Eupatorium* species *sensu stricto*.[2] In the present paper we describe isolation and structure determination from *Eupatorium album* L. of four new 11-hydroxylated *ent*-kaurane derivatives **1a, 2a, 3a,** and **4a.** Proof of structure was achieved by extensive use of ^{1}H and ^{13}C NMR spectrometry and conversion of **3a** to the known (16*R*)-*ent*-15-oxokauran-19-oic acid (**5**).[3] The sesquiterpene lactone fraction of *E. album* was small and could not be resolved into its constituents.[4]

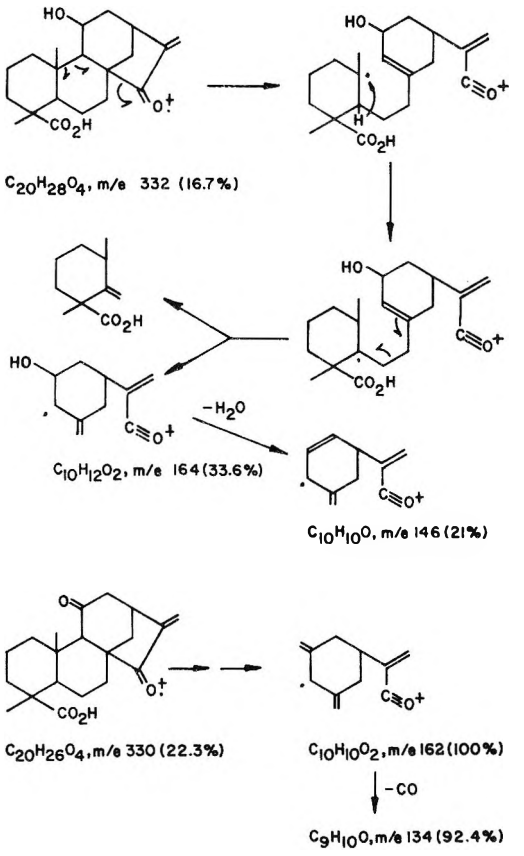
We commence with **3a,** $C_{20}H_{28}O_4$ (elemental analysis and high-resolution mass spectrum), which was an α,β-unsaturated ketone (λ_{max} 237 nm, ϵ_{max} 8000) involving an exocyclic methylene group (NMR singlets at 5.85 and 5.26 ppm) attached to a cyclopentanone (ir band at 1715 cm^{-1}). The presence of a carboxyl group suggested by the ir spectrum (broad absorption in the 2500–3400-cm^{-1} region) was confirmed by treatment with diazomethane; however, instead of the expected methyl ester **3c,** there was obtained the methyl ester pyrazoline **6** whose formation also served to confirm the functionalization of the five-membered ring.

The remaining oxygen atom of the empirical formula was a secondary hydroxyl group revealed by an NMR doublet at 4.05 ppm (sharpened on D_2O exchange) which moved downfield to 5.11 ppm (J = 3 Hz) on acetylation of **3a** to **3b.** Since the NMR spectrum also exhibited two methyl singlets at 1.26 and 0.92 ppm, the new substance was a tetracyclic diterpene which belonged to the kaurene or the phyllocladene series.

The problem of locating the hydroxyl group on the carbon skeleton presented considerable difficulties. The appearance of –CHOR as a doublet appeared to limit the attachment of the hydroxyl group to C-14; however, irradiation at the frequency of H-13 (3.05 ppm)[5] effected no change in the signal at 4.05 ppm. On the assumption that at least one, if not two, coupling constants had to be close to zero, C-1, C-3, C-6, C-7, C-11, and C-12 appeared possible loci for the hydroxyl group. C-12 was eliminated because equatorial orientation of the hydroxyl group on C-12 (to explain absence of coupling between H-12 and H-13) required coupling between H-11α, H-11β, and H-12 and therefore a doublet of doublets or a triplet. C-1, C-3, and C-6 were eliminated on the basis of the mass spectra of **3a** and its oxidation product **7** which exhibited a very strong peak at *m/e* 164 ($C_{10}H_{12}O_2$) and the base peak at *m/e* 162 ($C_{10}H_{10}O_2$), respectively. This corresponds to the fragment on the right resulting from the scission depicted below as the result of the preferred cleavage of the C-9, C-10 bond

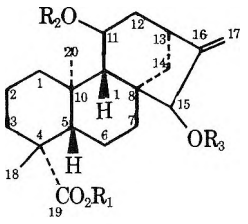


Scheme I. Mass Spectral Fragmentation of 3a and 7

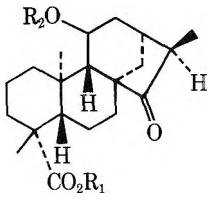


and places the hydroxyl group on C-11 because of the restrictions imposed earlier. A rationalization of some of the significant peaks in the high-resolution mass spectra of **3a** and **7** is presented in Scheme I.

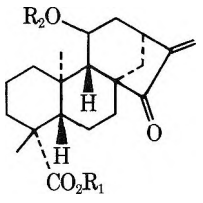
That the hydroxyl group was at C-11 was also indicated by analysis of the ^{13}C NMR spectra (Table I). In kaurene, the triplets of C-2, C-6, and C-11 are found near 20 ppm, the triplets of C-1, C-3, C-5, C-7, and C-12 appearing at much lower field.[7] As the ^{13}C NMR spectrum of **3a** exhibited only two triplets near 20 ppm, it was clear that C-11 was oxygenated, C-2 and C-6 having been eliminated earlier. Moreover, comparison with the ^{13}C NMR spectrum of **3b** showed that the C-9 doublet and the C-12 triplet had undergone diamagnetic shifts of 4.2 and 2.6 ppm, respectively, thus clearly pointing to C-11 as the locus of the hydroxyl group. This was further corroborated by the spectroscopic properties of **7**; in the ^{1}H NMR spectrum the C-20 methyl resonance exhibited the expected paramagnetic shift of about 1 ppm, while in the ^{13}C NMR spectrum the signals of C-9 and C-11 had undergone the expected downfield shifts. The small downfield shift of C-8 may be due to removal of a 1,3 interaction or to deshielding by the



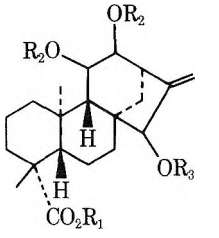
1a, R_1, R_2, R_3 = H
b, R_1 = Me; R_2, R_3 = H



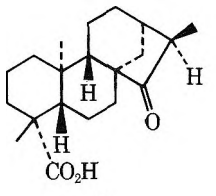
2a, R_1, R_2 = H
b, R_1 = Me; R_2 = H
c, R_1 = Me; R_2 = Ac



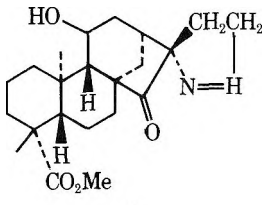
3a, R_1, R_2 = H
b, R_1 = H; R_2 = Ac
c, R_1 = Me; R_2 = H
d, R_1 = H; R_2 = Ms



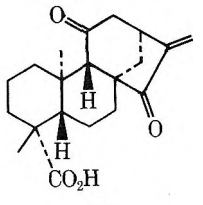
4a, R_1, R_2, R_3 = H
b, R_1 = Me; R_2, R_3 = H
c, R_1 = Me; R_2, R_3 = Ac



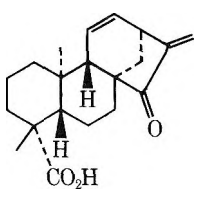
5



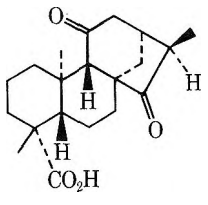
6



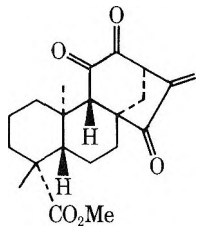
7



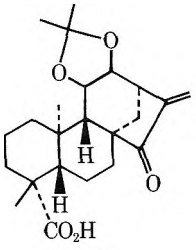
8



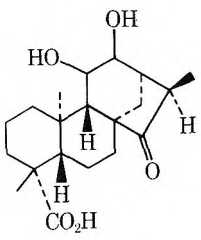
9



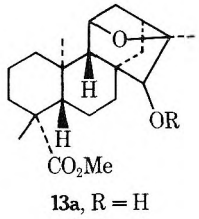
10



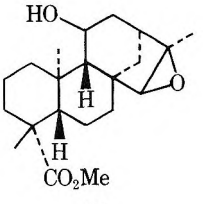
11



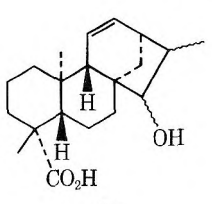
12



13a, R = H
b, R = Ac



14



15

newly formed carbonyl group;[8] the much larger downfield shift of C-10 may be the result of a combination of such effects.[9] The lack of a significant change in the C-12 signal is not explained readily.

Conclusive proof for the attachment of the hydroxyl group to C-11 was provided in the following manner. $POCl_3$–pyridine dehydration of **3a** provided **8**, whose new double bond was located unequivocally between C-11 and C-12. The ^1H NMR spectrum exhibited a new AB system of two vinyl protons ($J_{A,B}$ = 10 Hz) at 5.51 (H-11) and 6.09 (H-12) ppm. Irradiation at the frequency of H-13 (dd br at 3.24 ppm) converted the signal at 6.09 ppm to a broadened doublet ($J_{12,13}$ = 7 Hz) and caused some changes in the methylene region. Irradiation at the frequency of H-12 collapsed the signal of H-11 to a doublet ($J_{9,11}$ = 3 Hz) as well as converting the H-13 resonance to a broadened doublet ($J_{12,14a}$ = 3 Hz).

Before considering the stereochemistry of **3a**, we would like to discuss two other substances, **1a** and **2a**, that were also isolated from *E. album* and could be correlated with **3a**. The empirical formula of **1a**, $C_{20}H_{30}O_4$, combined with the absence of ultraviolet absorption and the ir band at 1715 cm^{-1}, the upfield shift of the exocyclic methylene resonances to 5.11 and 5.03 ppm (broad singlet and doublet), and the additional presence of a proton under hydroxyl (broadened triplet at 3.77 ppm), indicated that it differed from **3a** only by reduction of the ketone to a hydroxyl group. This was confirmed by double resonance experiments, since irradiation at the frequencies of both H-17 protons simultaneously affected H-15, but residual coupling indicated that H-15 was long range coupled to other protons as well. Finally $NaBH_4$ reduction of **3a** (−20 °C) gave **1a** in 80% yield; the latter was converted to a methyl ester which was identical with authentic methyl ester **1b** in every respect.

The third compound **2a**, $C_{20}H_{30}O_4$, was an isomer of **1a**. In the NMR spectrum the two signals of the exocyclic methylene protons were replaced by a methyl doublet at 1.22 ppm (J = 7 Hz); the absence of the multiplet at 3.77 ppm, the absence of conjugation evidenced by the uv spectrum, and the presence of an ir band at 1725 cm^{-1} suggested that **2a** was a dihydro derivative of **3a**. This was confirmed by catalytic hydrogenation of **3a** and subsequent methylation of the product to **2b**. Incidentally, in **1a**, **1b**, **2a**, and **2b**, the signal of H-11 was a broadened doublet or a doublet of doublets, instead of a sharp doublet as in **3a–c**.

As regards the stereochemistry of the three substances **1a**, **2a**, and **3a** the magnitude of the coupling constants involving H-11 in these substances and their derivatives ($J_{9\beta,11} = J_{11,12\beta} \simeq$ 0–2, $J_{9a,11}$ = 3–4.5 Hz) made it obvious that the hydroxyl group was axial. The chemical shift of the C-10 methyl group in all compounds was indicative of the fact that the C-10 methyl and the C-4 carboxyl are cis to each other and therefore both axial. The ORD spectrum of **2a** exhibited a strong negative Cotton effect,[11] hence ring D is β oriented and **1a**, **2a**, and **3** belong to either the phyllocladene or the *ent*-kaurene series. Catalytic hydrogenation of **7** afforded **9** which exhibited a strong positive Cotton effect, thus suggesting that rings B and C are cis fused and that the new substances belong to the *ent*-kaurane series.[11] Finally, hydrogenation of **8** gave a quantitative yield of a substance whose physical properties corresponded in all respects to those reported for 15-oxo(16*R*)-*ent*-kauran-19-oic acid (**5**).[3,12]

Since $NaBH_4$ reduction of **3a** at low temperature resulted in a good yield of **1a** and since the reagent is known to attack from the least hindered side, the C-15 hydroxyl group of **1a** is assigned the β configuration.

The stereochemistry of the C-16 methyl group of **2a** was

Table I. ^{13}C NMR Spectra of *ent*-Kauranoic Acid Derivatives[a]

Carbon no.	1a	2c	3a	3b	4a	4c	7	10[b]
1	40.5 t	39.6 t	39.8 t	40.1 t	40.5 t	40.6 t	40.1 t	39.7 t
2	19.4 t	18.8 t	19.0 t	18.9 t	19.4 t	19.2 t	18.9 t	18.5 t
3	38.2 t	37.9 t	37.9 t	38.0 t	38.2 t	38.2 t	38.0 t	37.7 t
4	45.0	43.9	43.8	44.1	45.1	44.9	44.1	44.2
5	56.5 d	55.9 d	56.7 d	56.1 d	56.4 d	56.3 d	55.7 d	55.6 d
6	21.6 t	20.1 t	20.1 t	20.1 t	21.5 t	21.3 t	20.1 t	19.9 t
7	39.3 t	34.4 t	34.0 t	33.9	38.4 t	38.2 t	32.3 t	31.6 t
8	42.5	51.1	50.8	50.8	43.9	44.1	52.8	52.5
9	54.4 d	58.1 d	63.1 d	58.9 d	54.5 d	54.2 d	67.3 d	65.9 d
10	38.2	38.7	39.1	39.3	37.9	37.9	51.5	41.7
11	66.5 d	67.5 d	66.1 d	68.6 d	68.3 d	67.2 d	206.7	?
12	39.4 t	31.5 t	41.0 t	38.4 t	72.4 d	73.3 d	40.4 t	?
13	39.3 d	34.5 d	37.2 d	36.9 d	46.1 d	43.4 d	36.6 d	53.7 d
14	36.1 t	37.1 t	36.8 t	36.5 t	36.1 t	36.4 t	35.9 t	36.2 t
15	82.5 d	221.6	210.8	209.3	82.2 d	81.5 d	209.5	?
16	158.1	49.1 d	150.5	150.1	153.2	147.4	147.6	?
17	106.2 t	10.8 q	112.8 t	113.2 t	108.5 t	109.2 t	107.4 t	?
18	29.1 q	28.7 q	29.0 q	29.3 q	29.1 q	28.8 q	29.2 q	28.9 q
19	180.4	177.6	181.4	183.1	180.6	177.5	182.4	?
20	15.7 q	15.5 q	15.7 q	16.0 q	16.4 q	16.2 q	17.2 q	16.5 q

[a] Run in $CDCl_3$ on a Bruker HX-270 instrument. Unmarked signals are singlets. Assignments are based on predicted shifts, comparisons with data in the literature [see, for example, ref 7 and I. Yamaguchi, N. Takahashi, and K. Fujiha, *J. Chem. Soc., Perkin Trans. 1*, 992 (1975)] and selective single frequency off-resonance decoupling. [b] Insufficient sample available to permit clear visualization of signals marked ?. No off-resonance spectrum was recorded.

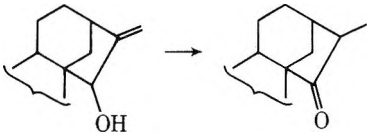
established by double irradiation experiments involving H-16 and H-17 of **2c** which led to the determination of $J_{13,16}$ as 7 Hz. This required that the methyl group be β oriented (expected dihedral angle between H-13 and H-16 $\simeq$ 10°) rather than α (dihedral angle $\simeq$ 90°). The appearance of the H-11 proton as a triplet (J = 3.5 Hz) instead of a doublet of doublets as in **2a** and **2b** indicated a change in conformation of ring C on acetylation. This is attributed to an increase in the strong interaction between the β-oriented hydroxyl group at C-11 and the β-oriented methyl group on C-16 which results in flattening of ring C.[13]

There remains the fourth, most polar compound, **4a**, whose empirical formula $C_{20}H_{30}O_5$, polarity, and NMR spectrum, which exhibited three signals in the regions appropriate for protons under hydroxyl at 3.80, 3.65, and 3.77 ppm, suggested the presence of three secondary hydroxyl groups. This was confirmed by conversion of the methyl ester **4b** to a triacetate **4c**.

Comparison of the ^1H NMR and ^{13}C NMR spectra of **1a** and **4a** made it obvious that the only difference between the two compounds was attachment of the additional hydroxyl group of **4a** to C-12. Aside from the replacement of a triplet at 39.4 ppm by a new doublet at 72.4 ppm, the only significant differences in the ^{13}C NMR spectrum of **4a** were downfield shifts of C-13 (39.3 → 46.1) and C-11 (66.5 → 68.3). This conclusion was fully corroborated by decoupling experiments on **4a**. Irradiation at the frequencies of H-17 (5.08 br and 5.04 d, J = 2.5 Hz) affected the broad triplet (J = 2.5 Hz) of H-15 at 3.77 ppm and vice versa. Irradiation at the frequency of H-13 (2.47 ppm) converted a doublet of doublets at 3.65 ppm (H-12) to a doublet (J = 3.5 Hz), while irradiation at the frequency of H-12 not only affected the resonance of H-13 by collapsing it to a doublet (J = 4.5 Hz), but also collapsed the doublet of H-11 at 3.80 ppm (partially obscured by the H-15 resonance) to a singlet. Irradiation at the frequency of H-11 and H-15 sharpened the signal of H-17 and collapsed the signal of H-12 to a doublet (J = 4.5 Hz).

Oxidation of **4b** furnished the triketone **10** whose properties were in complete agreement with the postulated structure. Successful conversion of **4a** to an acetonide **11** indicated that the two hydroxyl groups were cis. The values of $J_{9,11}$ ($\simeq$ 0), $J_{11,12}$ (3.5 Hz), and $J_{12,13}$ (4.5 Hz) require that the C-11 hydroxyl be axial and the C-12 hydroxyl equatorial.[14] As in the case of **1a**, **2a**, and **3a**, the chemical shift of the C-10 methyl group showed that the C-10 methyl and C-4 carboxyl were both axial and the negative Cotton effect of a substance **12** obtained by isomerization of **4a** with 5% Pd–C–H_2[15] indicated that **4a** belonged to the phyllocladene or the *ent*-kaurane series. Thus, although owing to lack of material, correlation of **4a** with an *ent*-kaurane has not yet been achieved, the similarity of chemical shifts exhibited by **1a** and **4a** leaves little doubt that the fourth diterpene isolated from *E. album* is also an *ent*-kaurane and is correctly represented by formula **4a**.

We conclude by recording the behavior of **1b** on treatment with acid, a reaction which normally results in the hydride shift A → B if the 15-hydroxyl group is β oriented,[17]



A B

and confirmed the structure assigned to the substances described in this report. After an NMR tube containing a sample of **1b**, prepared by $NaBH_4$ reduction of **3a** and subsequent methylation, had been allowed to stand at room temperature for 1 month, during which period the $CDCl_3$ solvent had evaporated, fortuitous redetermination of the NMR spectrum revealed that **1b** had undergone conversion to a new compound and that this substance was different from **2b**. Work-up of the material from the sample tube resulted in isolation of an 80% yield of the ether **13a** (vide infra) and a 10% yield of **2b**. During the same period a sample of **1b** prepared directly from **1a** stored in $CDCl_3$ at 0 °C had not undergone any change, but on adding a drop of HCl and shaking the spectrum immediately changed to that of **13a**. Exposure of **1b** to methanolic HCl for 24 h at room temperature[18] again resulted in at least 90% isomerization to **13a**.

The structure **13a** assigned to the new ether was based on the following facts. The two signals of the exocyclic methylene group had been replaced by a methyl singlet at 1.30 ppm. The H-15 signal, formerly a narrowly split

broadened triplet at 3.77 ppm, had changed to a slightly broadened singlet at 2.77 ppm which again moved downfield to 4.40 ppm on acetylation to **13b**. The H-11 signal had experienced a slight downfield shift to 4.27 ppm ($J_{9\beta,11} = J_{11,12\alpha} = 3$; $J_{11,12\beta} = 0$ Hz) and was unaffected by acetylation. These changes, as well as the observation that **13a** was unaffected by further treatment with dilute sulfuric acid, eliminated **14** as an alternative structure. The facile formation of **13a** is obviously due to the proximity of the axial 11-hydroxyl group to C-15 as required by the models which also suggest that the somewhat abnormal upfield shift of H-15 in **13a** is due to shielding by the ether oxygen.

Several 11β-hydroxylated[19] *ent*-kauranes analogous to **1a**, **2a**, and **3a** have been isolated recently from a liverwort.[20] The NMR spectral data given by Connolly and Thornton[20] seem to indicate that two of the three vicinal couplings involving H-11 of these substances were also small or zero, although the authors did not comment on this. The unusual non-acid-catalyzed A → B rearrangement under catalytic hydrogenation conditions was also observed and may be characteristic of kauranes carrying an axial hydroxyl in the 11 position.

Experimental Section

Experimental details have been specified previously.[21] All NMR spectra were run on a Bruker HX-270 NMR spectrometer in $CDCl_3$ solution.

Extraction of *Eupatorium album*. Above-ground parts of *E. album* L., wt 1.33 kg, collected by R. K. Godfrey on Nov 5, 1961, in a clearing 16 miles west of Tallahassee (Godfrey no. 61639), was extracted with $CHCl_3$ and worked up in the usual fashion.[22] The crude gum, wt 20 g, was chromatographed on a column of 500 g of silicic acid (Mallinckrodt 100 mesh) packed in benzene, 200-ml fractions of increasing polarity being collected. Elution with benzene–$CHCl_3$ (1:1) did not furnish any material. Elution with benzene–$CHCl_3$ (1:10, fractions 11–16) gave a gummy sesquiterpene lactone mixture (0.2 g) which could not be separated successfully.

Elution with benzene–$CHCl_3$ (1:10, fractions 17–24) gave a semisolid which on fractional crystallization from ethyl acetate gave first 80 mg of **1a** as needles: mp 155–157 °C; $[\alpha]^{22}D$ −85° (*c* 0.185, MeOH); ir bands (Nujol) at 3400 (OH), 1690 (CO_2H), 1600 (double bond), 1250, 1060, and 970 cm^{-1}; NMR signals ($CDCl_3$ and a drop of pyridine-d_5) at 5.11 br and 5.03 d (2.5, H-17), 4.00 d br (4.5, H-11), 3.77 t br (2.5, H-15), 2.60 m ($W_{1/2}$ = 12 Hz, H-13), 1.24 (H-18 methyl), and 0.90 ppm (H-20). The high-resolution mass spectrum displayed the molecular ion peak (4.9%), other major peaks were at *m/e* (composition, %) 319 ($C_{19}H_{27}O_4$, 5.5), 288 ($C_{19}H_{28}O_2$, 7.1), 273 ($C_{18}H_{25}O_2$, 6.3), 260 ($C_{17}H_{24}O_2$), 255 ($C_{18}H_{23}O$, 7.8), 245 ($C_{16}H_{21}O_2$, 8.5).

Anal. Calcd for $C_{20}H_{30}O_4$: mol wt, 334.2143. Found: mol wt, 334.2131 (MS).

Methylation of 20 mg of **1a** with diazomethane and recrystallization of the product from methanol afforded **1b** as prisms: mp 125–127 °C; $[\alpha]^{22}D$ −90° (*c* 0.70, MeOH); ir bands ($CHCl_3$) at 3400, 1715 (methyl ester), 1600, 1275, 1150, 1100, 1040, 980, and 900 cm^{-1}; NMR signals at 5.11 br and 5.03 d (2.5, H-17), 4.00 d br (4.5, H-11), 3.77 t br (2.5, H-15), 3.65 (methoxyl), 1.18 (H-18), and 0.90 ppm (H-20). The low-resolution mass spectrum afforded the molecular ion peak at *m/e* 348; other major peaks were at *m/e* 330 ($M^+ - H_2O$), 315 ($M^+ - H_2O - CH_3$), 312 ($M^+ - 2H_2O$), 289 ($M^+ - CO_2CH_3$), 288, 287, 271, and 253.

Anal. Calcd for $C_{21}H_{32}O_4$: mol wt, 348.2300. Found: mol wt, 348.2299 (MS).

The second crop from the fractional crystallization of **1a** consisted mainly of **2a**. Repeated recrystallization from ethyl acetate furnished pure 2a as needles: wt 35 mg; mp 215–217 °C; $[\alpha]^{22}D$ −210° (*c* 0.10, MeOH); ORD curve (MeOH) $[\alpha]_{450}$ −290, $[\alpha]_{320}$ −450 (min), $[\alpha]_{300}$ −225 (max), $[\alpha]_{260}$ −450 (sh), $[\alpha]_{230}$ −750 (last reading); CD (MeOH) $[\theta]_{297}$ −623 (min); ir bands ($CHCl_3$) at 2500–3300 (–OH), 1725 (cyclopentanone), 1690 (CO_2H), 1200, 1015, and 960 cm^{-1}; NMR signals at 3.92 dd (4.5, 2, H-11), 1.23 (H-18), 1.22 d (7, H-17), and 0.90 ppm (H-20). The low-resolution mass spectrum gave the molecular ion peak at *m/e* 334.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04, O, 191.13. Found: 71.43; H, 9.36; O, 20.42.

It was subsequently discovered that the mixture of **1a** and **2a** could be separated by repeated TLC on silica gel (Merck $PF_{254-356}$, solvent benzene–ethyl acetate, 6:1) by developing the plate several times, although **1a** and **2a** exhibit the same R_f if the plate is developed only once.

Methylation of 20 mg of **2a** with diazomethane and recrystallization from ethyl acetate gave **2b**: mp 195–197 °C; $[\alpha]^{22}D$ −205° (*c* 0.70, MeOH); ir bands ($CHCl_3$) at 3450, 1720 (combination of cyclopentanone and methyl ester), 1200, 1150, 1090, and 980 cm^{-1}; NMR signals at 3.90 dd (4.5, 2, H-11), 3.62 (methoxyl), 1.24 d (7, H-17), 1.18 (H-18), and 0.80 ppm (H-20). The low-resolution mass spectrum exhibited the molecular ion peak at *m/e* 345; other significant peaks were at *m/e* 330 ($M^+ - H_2O$), 289 ($M^+ - CO_2Me$), 288, 287, 271.

Anal. Calcd for $C_{21}H_{32}O_4$: mol wt, 348.2300. Found: mol wt, 348.2299 (MS).

Acetylation of 20 mg at **2b** with 1 ml of acetic anhydride and 0.5 ml of pyridine for 24 h at room temperature followed by the usual work-up and recrystallization from ethyl acetate furnished 18 mg of **2c**: mp 175–177 °C; $[\alpha]^{22}D$ −125° (*c* 0.046, MeOH); ir bands ($CHCl_3$) at 1720 (very strong, combination of cyclopentanone and esters), 1235, 1170, 1020, and 960 cm^{-1}; NMR signals at 5.05 t (3.5, H-11), 3.63 (methoxyl), 1.92 (Ac), 1.16 (H-18), 1.14 d (7, H-17), and 0.83 ppm (H-20). The high-resolution mass spectrum exhibited the molecular ion (2.3%); other major peaks were at 348 ($C_{21}H_{32}O_4$, 2.7), 330 ($C_{21}H_{30}O_3$, 49.8), 315 ($C_{20}H_{27}O_3$, 11.5), 302 ($C_{20}H_{30}O_2$, 9.6), 298 ($C_{20}H_{26}O_2$, 10.8), 287 ($C_{19}H_{27}O_2$, 7.3), 271 ($C_{19}H_{27}O$, 95.4), 270 ($C_{19}H_{16}O$, 32.0), 255 ($C_{18}H_{23}O$, 30.2), 234 ($C_{15}H_{22}O_2$, 38.4), 197 ($C_{15}H_{17}$, 16.8), 150 ($C_{10}H_{14}O$, 27.3), 121 (C_9H_{13}, 100), and 91 (C_7H_7, 78.6).

Anal. Calcd for $C_{23}H_{34}O_5$: mol wt, 390.2405. Found: mol wt, 390.2394 (MS).

Further elution of the column with $CHCl_3$ (fractions 25–30) gave solid **3a**, which was recrystallized from methanol: yield 260 mg; mp 268–270 °C; $[\alpha]^{22}D$ −150° (*c* 0.0225, MeOH); ir bands ($CHCl_3$) at 2500–3300 (–OH), 1715 (cyclopentanone), 1690 (carboxyl), 1640 (conjugated double bond), 1240, 1170, 1050, and 940 cm^{-1}; uv spectrum λ_{max} 237 nm (ϵ_{max} 8000); NMR signals at 5.85 and 5.26 (H-17), 4.05 d (3.5, H-11), 3.05 m ($W_{1/2}$ = 12 Hz, H-13), 1.26 (H-18), and 0.92 ppm (H-20). The high-resolution mass spectrum exhibited the molecular ion peak (16.7%); other major peaks were at *m/e* 288 ($M^+ - CO_2$, $C_{19}H_{28}O_2$, 3.9), 287 ($M - CO_2H$, $C_{19}H_{27}O_2$, 5.4), 286 ($M^+ - CO_2H - H$, $C_{19}H_{26}O_2$, 25.1), 83 (C_5H_7, 100), or are detailed in Scheme I.

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49; O, 19.25; mol wt, 332.1986. Found: C, 72.32; H, 8.33; O, 19.70; mol wt, 332.1988 (MS).

Methylation of 10 mg of **3a** with excess diazomethane in the usual fashion and crystallization of the residue from ethyl acetate afforded 11 mg of **6**: mp 143–145 °C; ir bands ($CHCl_3$) at 3500 (OH), 1770 (cyclopentanone), 1715 (ester), 1235, 1150, 1100, 1040, and 1090 cm^{-1}; NMR signals at 4.05 d (3.5, H-11), 3.67 (OMe), 1.24 (H-18), and 0.92 ppm (H-20).

Anal. Calcd for $C_{22}H_{32}O_4N_2$: mol wt, 388.2361. Found: mol wt, 388.2383 (MS).

Acetylation of 60 mg of **3a** in 1 ml of pyridine with 1.5 ml of acetic anhydride at room temperature for 48 h, at which time TLC analysis indicated that 90% of starting material had reacted, work-up of the mixture in the usual fashion, and purification of the crude product by preparative TLC (silica gel, solvent benzene–ethyl acetate, 3:1) yielded 50 mg of **3b**: mp 253–255 °C; $[\alpha]^{22}D$ −175° (*c* 0.20, MeOH); ir bands ($CHCl_3$) at 3200–2500 (carboxyl –OH), 1730 (cyclopentenone and acetate), 1690 (CO_2H), 1640 (conjugated double bond) 1235, 1035, 1030, and 940 cm^{-1}; NMR signals at 5.88 and 5.23 (H-17), 5.11 d (3, H-11), 3.06 m ($W_{1/2}$ = 12 Hz, H-13), 1.83 (Ac), 1.22 (H-18), and 0.95 ppm (H-20). The low-resolution mass spectrum exhibited peaks at *m/e* 374 (M^+) 332 ($M^+ - C_2H_2O$), 314 ($M^+ - CH_3CO_2H$), 316, 298, 295, 268, 253, 219, 218, 173 (base peak), 148, 147, 146, 121, and 119.

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07; O, 21.36. Found: C, 70.73; H, 8.13, O, 21.44.

Elution of the column with $CHCl_3$–MeOH (49:1, fractions 31–35) gave semisolid material. Repeated recrystallization from methanol and ethyl acetate gave 210 mg of **4a**: mp 215–217 °C; $[\alpha]^{22}D$ −81° (*c* 0.342, MeOH); ir bands ($CHCl_3$) at 3400–2500 (–OH), 1690 (carboxyl), 1200, 1100, and 1030 cm^{-1}; NMR signals ($CDCl_3$ and 2 drops of pyridine-d_5) at 5.08 br and 5.04 d (2.5, H-17), 3.80 d (3.5, H-11), 3.77 t br (2.5, H-15), 3.65 dd (4.5, 3.5, H-12), 2.47 t br (4.5, H-13), 1.15 (H-18), and 0.85 ppm (H-20). The NMR spectrum of the analytical sample indicated the presence of ethyl acetate, also revealed by the elemental analysis. The low-resolution mass spec-

trum exhibited peaks at *m/e* 350 (M^+), 332 ($M^+ - H_2O$), 314 ($M^+ - 2H_2O$), 271, 243, 229, and 213.

Anal. Calcd for $C_{22}H_{30}O_5 \cdot \frac{1}{2}EtOAc$: C, 66.98; H, 8.69; O, 24.33. Found: C, 67.35; H, 8.62; O, 24.01. High-resolution mass spectrum: Calcd for $C_{20}H_{30}O_5$: 350.2093. Found: 350.2110.

Methylation of 20 mg of **4a** and recrystallization of the crude product from ethyl acetate provided **4b:** mp 169–170 °C; $[\alpha]^{22}D$ −105° (c 0.188, MeOH); ir bands ($CDCl_3$) at 3400, 1715, 1220, 1150, 1100, 1060, 1030, and 900 cm^{-1}. The high-resolution mass spectrum gave the molecular ion peak (10.8%); other major peaks were at *m/e* (composition, %) 346 ($C_{21}H_{30}O_4$, 1.2), 287 ($C_{19}H_{27}O_2$, 12.3) 285 ($C_{19}H_{25}O_2$, 4.3), 147 ($C_{10}H_{11}O$, 16.5), 123 (C_9H_{15}, 34.8), and 119 (C_9H_{11}, 95.7).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95; mol wt, 364.2249. Found: C, 69.67; H, 8.80; O, 21.86; mol wt, 364.2244 (MS).

Acetylation of 80 mg of **4b** for 48 h at room temperature followed by the usual work-up and recrystallization of the crude product from ethyl acetate–MeOH yielded 75 mg of **4c:** mp 165–167 °C; ir bands ($CHCl_3$) at 1730 (very strong), 1600, 1235, 1150, 1100, 1080, 1030, and 915 cm^{-1}; NMR signals at 5 c (H-17, H-15, H-11), 2.67 br ($W_{1/2}$ = 12 Hz, H-13), 2.16, 1.98, 1.92 (Ac), 1.17 (H-18), and 0.86 ppm (H-20). The low-resolution mass spectrum had peaks at *m/e* 490 (M^+), 448 ($M - C_2H_2O$), 430 ($M^+ - CH_3CO_2H$), 388 ($M - C_2H_2O - CH_3CO_2H$), 370 ($M - 2CH_3CO_2H$), 328 ($M - 2CH_3CO_2H - C_2H_2O$), 310 ($M^+ - 3CH_3CO_2H$), 268, 251, and 234.

Anal. Calcd for $C_{27}H_{38}O_8$: mol wt, 490.2566. Found: mol wt, 490.2572 (MS).

Further elution of the column with $CHCl_3$–MeOH (49:1, fractions 36–38) gave 0.3 g of a gummy mixture of sesquiterpene lactones.

Conversion of to 3a 1b. A solution of 15 mg of **3a** in 5 ml of MeOH was stirred with 20 mg of $NaBH_4$ at −20 °C. After 5 h 80% of starting material had been consumed (TLC control). The mixture was diluted with water, acidified with dilute acetic acid, and extracted with chloroform. The washed and dried extract was evaporated and the residue esterified with diazomethane. Preparative TLC (solvent benzene–ethyl acetate, 2:1) and elution of the major product gave **1b** (80%), identical in every respect with material prepared from **1a.**

Hydrogenation of 3a. A solution of 10 mg of **3a** in 15 ml of ethanol was hydrogenated with 50 mg of 5% Pd/C for 1 h. Filtration and evaporation gave **2a** which, for ease of comparison, was esterified to **2b** (yield quantitative), identical with **2b** prepared from **2a** in every respect.

Catalytic Isomerization of 1b. Attempted reduction of **1b** with 5% Pd/C in a hydrogen atmosphere as described above followed by the usual work-up gave **2b** in quantitative yield.

Preparation of 7. A solution of 50 mg of **3a** in 25 ml of AR acetone was oxidized with 0.2 ml of Jones reagent by stirring at room temperature. After 15 min excess reagent was destroyed by addition of 2-propanol. The mixture was diluted with water and extracted with $CHCl_3$. The washed and dried extract was evaporated; the residue was purified by preparative TLC (silica gel, solvent benzene–ethyl acetate, 3:1), and recrystallized from ethyl acetate: yield 20 mg; mp 295 °C dec; ir bands ($CHCl_3$) at 2600–3400 (OH), 1715 (cyclopentenone and cyclohexanone), 1690 (carboxyl), 1640 (conjugated double bond), 1200, 1135, and 1050 cm^{-1}; NMR signals at 6.01 and 5.40 (H-17), 3.26 m (H-13), 1.28 (H-18), and 1.02 ppm (H-20); uv spectrum λ_{max} 230 nm (ϵ_{max} 10 000). The high-resolution mass spectrum exhibited the molecular ion peak (22.3%); other major peaks were at *m/e* (composition, %) 312 ($M^+ - H_2O$, $C_{20}H_{24}O_3$, 9.6), 284 ($M^+ - CO_2H - H$, $C_{19}H_{24}O_2$, 33), 269 ($M^+ - CO_2H - H - CH_3$, $C_{18}H_{21}O_2$, 33), 256 ($C_{18}H_{24}O$, 8.2), 215 ($C_{14}H_{15}O_2$, 13.1), 149 ($C_{10}H_{13}O$, 41.2), 148 ($C_{10}H_{12}O$, 26), 91 (C_7H_7, 53.6), and the peaks shown in Scheme I.

Anal. Calcd for $C_{20}H_{26}O_4$: mol wt, 330.1830. Found: mol wt, 330.1827 (MS).

Hydrogenation of 7. A solution of 5 mg of **5** in 10 ml of ethanol was hydrogenated over 50 mg of 5% Pd/C at atmospheric pressure for 2 h and filtered. The filtrate and washings were evaporated. The residue **9** was recrystallized from MeOH: mp 185–187 °C dec; ir bands ($CHCl_3$) at 1720 (cyclopentanone), 1705 (cyclohexanone and carboxyl), 1200, 1110, and 980 cm^{-1}; ORD curve (MeOH) $[\alpha]_{450}$ −72, $[\alpha]_{340}$ +455 (max), $[\alpha]_{315}$ 0, $[\alpha]_{300}$ −650 (last reading); CD (MeOH) $[\theta]_{300}$ +3980.

The high-resolution mass spectrum exhibited the molecular ion peak (4%); other major peaks were at *m/e* (composition, %) 304 ($M^+ - CO$, $C_{19}H_{28}O_3$, 19.7), 286 ($M^+ - CO_2H - H$, $C_{19}H_{26}O_2$, 19.1), 258 ($M^+ - CO_2H - H - CO$, $C_{18}H_{26}O$, 12.3), 203 ($C_{14}H_9O$, 19.8), 175 ($C_{13}H_{19}$, 17.8), 151 ($C_{10}H_{15}O$, 43.5), 149 ($C_8H_5O_3$, 65.4), 138 ($C_9H_{14}O$, 100), 123 ($C_8H_{11}O$, 33.4), 121 (C_8H_9O, 15.7).

Anal. Calcd for $C_{20}H_{28}O_4$: mol wt, 332.1986. Found: mol wt, 332.1992 (MS).

Conversion of 3a to 8. A. An ice-cold mixture of 11 mg of **3a,** 0.5 ml of dry pyridine, and 0.1 ml of $POCl_3$ was stirred at 0 °C for 15 min and then at room temperature for 0.5 h. The mixture was poured on ice–water and extracted with water. The washed and dried extract was evaporated and the residue purified by preparative TLC (silica gel, solvent benzene–ethyl acetate, 6:1). Recrystallization from ethyl acetate afforded 6 mg of **8:** mp 165–167 °C; ir bands ($CHCl_3$) at 2600–3400, 1720 (cyclopentenone), 1690 (carboxyl), 1640 (double bond), 1250, and 1170 cm^{-1}; NMR signals at 6.09 dd br (10, 7, H-12), 5.58 (H-17a), 5.51 dd (10, 3, H-11), 5.01 (H-17b), 3.24 dd br (7, 3, H-13), 1.26 (H-18), and 0.87 ppm (H-20). The low-resolution mass spectrum exhibited the molecular ion peak at *m/e* 314; other major peaks were at *m/e* 268 and 158.

Anal. Calcd for $C_{20}H_{26}O_3$: mol wt, 314.18818. Found: mol wt, 314.18809 (MS).

B. Hydrogenation of 4 mg of **8** in 10 ml of ethanol with 50 mg of 5% Pd/C at atmospheric pressure for 2 h and recrystallization from MeOH afforded 4 mg of **5:** mp 225–227 °C; $[\alpha]^{22}D$ −105° (c 0.09, $CHCl_3$) [reported[3] mp 226–228 °C, $[\alpha]D$ −99° (c 0.192, $CHCl_3$)]; ir bands ($CHCl_3$) at 2600–3400, 1725 (cyclopentanone), 1690 (carboxyl), 1260, and 1180 cm^{-1} [reported ir bands (CS_2) 1723, 1692 cm^{-1}]; NMR signals at 1.23 (H-18), 1.09 d (7, H-17), and 1.00 ppm (H-20). The low-resolution mass spectrum exhibited the molecular ion peak at *m/e* 318; other major peaks were at *m/e* 303 ($M^+ - CH_3$), 274 ($M^+ - CO_2$), 259 ($M^+ - CO_2 - CH_3$), and 244 ($M^+ - CO_2 - 2CH_3$).

Anal. Calcd for $C_{20}H_{30}O_3$: mol wt, 318.2194. Found: mol wt, 318.2193 (MS).

Reaction of 17 mg of **3a** in 0.35 ml of pyridine and 0.1 ml of methanesulfonyl chloride overnight at room temperature followed by the usual work-up gave 18 mg of **3d** which was purified by preparative TLC (silica gel, solvent benzene–ethyl acetate, 4:1) and was characterized by its NMR spectrum only, signals at 5.90 and 5.30 (H-17), 5.15 d br (3.5, H-11), 2.83 (methanesulfonate), 1.22 (H-18), and 0.98 ppm (H-20). The product, wt 15 mg, was dissolved in 10 ml of Me_2SO and heated with 50 mg of $NaBH_4$ at 100 °C for 12 h. The cooled reaction mixture was diluted with water and extracted with $CHCl_3$. The washed and dried extracts were evaporated and the residue was purified by preparative TLC and identified as **15** by its NMR spectrum, signals at 5.85 dd (10, 9, H-12) and 5.58 dd (10, 3, H-11), 3.51 d br (10.5, H-15), 1.21 (H-18), 0.88 d (7, H-17), and 0.84 ppm (H-20). The low-resolution mass spectrum gave a very weak molecular ion peak at *m/e* 318 (M^+); other peaks were at *m/e* 300 ($M^+ - H_2O$), 285 ($M^+ - H_2O - CH_3$), 270 ($M^+ - H_2O - 2CH_3$), and 255 ($M^+ - H_2 - CO_2H$).

Anal. Calcd for $C_{20}H_{30}O_3$: mol wt, 318.2194. Found: mol wt, 318.2199 (MS).

Because of the very poor yield of **15,** this route was abandoned.

Reactions of 4a and 4b. A. Oxidation of 80 mg of **4b** in 50 ml of AR acetone with 0.2 ml of Jones reagent in the manner described for **3a** and preparative TLC of the crude product over silica gel (solvent benzene–ethyl acetate, 4:1) furnished 22 mg of **10** as a gum: ir bands at 1720 (very broad), 1650, 1150, 1100, and 970 cm^{-1}; uv spectrum λ_{max} 232 nm (ϵ_{max} 6000); NMR signals at 6.30 br, 5.66 br (H-17), 3.95 d br (4, H-13), 3.64 (methoxyl), 1.26 (H-18), and 0.86 ppm (H-20). The high-resolution mass spectrum gave the molecular ion (37.2%); other major peaks were at *m/e* (composition, %) 330 ($C_{20}H_{26}O_4$, 8.8), 302 ($C_{19}H_{26}O_3$, 31.5), 283 ($C_{18}H_{19}O_3$, 25.3), 270 ($C_{18}H_{22}O_2$, 7.9), 242 (34.3), and 227 ($C_{16}H_{19}O$, 13.2).

Anal. Calcd for $C_{21}H_{26}O_5$: mol wt, 358. 1779. Found: mol wt, 358.1776 (MS).

B. A solution of 9 mg of **4a** in 1 ml of acetone containing a crystal of *p*-toluenesulfonic acid was allowed to stand overnight at room temperature, placed on a column of silica gel (1 g), and eluted with an additional 20 ml of acetone. Evaporation of the eluate and crystallization of the residue gave 8 mg of the acetonide **11:** mp 255–257 °C; ir bands (Nujol) at 3400, 1690, 1260, and 1170 cm^{-1}; NMR signals at 5.27 br and 5.13 d (1.8, H-17), 4.12 m (H-11 and H-12), 3.75 t br (1.8, H-15), 2.55 t br (4.5, H-13), 1.45 and 1.30 (acetonide methyls), 1.24 (H-18), and 0.88 ppm (H-20). The low-resolution mass spectrum exhibited the molecular ion at *m/e* 390; other major peaks were at *m/e* 375 ($M^+ - CH_3$), 332 ($M^+ - C_3H_6O$), 314 ($M^+ - C_3H_6O - CH_3$), 299 ($M^+ - C_3H_6O - CH_3 - H_2O$), 287, and 268.

Anal. Calcd for $C_{23}H_{32}O_5$: mol wt, 390.2406. Found: mol wt, 390.2410 (MS).

C. Catalytic isomerization of 7 mg of **4a** to **12** with 5% Pd/C in a hydrogen atmosphere was carried out in the same manner as previously described for **1a**. The product **12**, wt 7 mg, was recrystallized from methanol: mp 225–227 °C; ir bands (Nujol) at 3400, 1720, 1690, 1260, 1170, and 1060 cm^{-1}; NMR signals ($CDCl_3$ plus 2 drops of pyridine-d_5) at 3.95 m (H-11 and H-12), 2.61 br ($W_{1/2}$ = 12 Hz, H-13), 13.7 d (7, H-17), 1.23 (H-18), and 0.93 ppm (H-20); ORD curve (MeOH) $[\alpha]_{150}$ −60, $[\alpha]_{400}$ −60, $[\alpha]_{317}$ −240 (min), $[\alpha]_{300}$ −60 (max), $[\alpha]_{275}$ −125, $[\alpha]$ −250 (sh), $[\alpha]_{235}$ −360 (last reading). The low-resolution mass spectrum gave the molecular ion peak at *m/e* 350; other peaks were at *m/e* 332 ($M^+ - H_2O$), 314 ($M^+ - 2H_2O$), 304 ($M^+ - CO_2H - H$), 287 ($M^+ - CO_2H - H_2O - H$), 271, 259, and 213.

Anal. Calcd for $C_{20}H_{30}O_5$: mol wt, 350.2093. Found: mol wt, 350.2110 (MS).

Isomerization of 1b to 13a. A. A sample of **1b** prepared by $NaBH_4$ reduction of **3a**, subsequent methylation, and preparative TLC (vide supra) was used almost entirely for determination of the NMR spectrum. After 1 month at room temperature, during which time the solvent had evaporated, the NMR spectrum was redetermined and exhibited the significant differences mentioned in the Discussion. TLC indicated the presence of two constituents (approximately 9:1). Preparative TLC on silica gel resulted in isolation of the less polar product **13a**, crude wt ~15 mg. After recrystallization from ethyl acetate, it melted at 95–97 °C: ir bands ($CHCl_3$) at 3500 (OH), 1715 (ester), 1225, 1160, 1090, 1070, 980, and 830 cm^{-1}; NMR signals at 4.27 t (J = 3 Hz, H-11), 3.63 (methoxyl), 2.88 (slightly broadened, H-15), 1.30 (H-17), 1.17 (H-18), and 0.87 ppm (H-20). The low-resolution mass spectrum gave the molecular ion peak at *m/e* 348; other major peaks were at *m/e* 333 ($M^+ - CH_3$), 330 ($M^+ - H_2O$), 289 ($M^+ - CO_2Me$), 288, 287, and 274.

Anal. Calcd for $C_{21}H_{32}O_4$: mol wt, 348.2300. Found: mol wt, 348.2303 (MS).

Acetylation of **13a** in the usual fashion gave, after recrystallization from ethyl acetate, **13b**: mp 118–120 °C; ir bands at 1720, 1235, 1070, and 970 cm^{-1}; low-resolution mass spectral peaks at *m/e* 390 (M^+), 348 ($M^+ - C_2H_2O$), 330 ($M^+ - CH_3CO_2H$), 315 ($M^+ - CH_3CO_2H - CH_3$), 306, 287, and 271.

Anal. Calcd for $C_{23}H_{34}O_5$: mol wt, 390.2406. Found: mol wt, 390.2410 (MS).

The minor material, crude wt ~3 mg, was originally thought to be starting material since **1b** and **2b** have the same R_f. Recrystallization from ethyl acetate and determination of the melting point and the NMR spectrum identified it as **2b**.

B. A solution of 5 mg in **1b** in 1 ml of methanol and 5 drops of 10% aqueous HCl was allowed to stand at room temperature. The solvent was evaporated, first under the water pump and then in vacuo. The NMR spectrum of the residue was that of **13a**, indicating that the proportion of **2b** was 10% or less.

C. A 10-mg sample of pure **13a** was refluxed with 0.5 ml of sulfuric acid and 0.5 ml of water in 10 ml of ethanol for 24 h. After the usual work-up of the reaction mixture, TLC analysis of the crude product indicated absence of **2b** and recovery of **13a** which was subsequently isolated in nearly quantitative yield.

Registry No.—**1a**, 57719-76-3; **1b**, 57719-77-4; **2a**, 57719-78-5; **2b**, 57719-79-6; **2c**, 57719-80-9; **3a**, 57719-81-0; **3b**, 57719-82-1; **3d**, 57719-83-2; **4a**, 57719-84-3; **4b**, 57719-85-4; **4c**, 57719-86-5; **5**, 57793-40-5; **6**, 57719-87-6; **7**, 57719-88-7; **8**, 57719-89-8; **9**, 57719-90-1; **10**, 57738-57-5; **11**, 57719-91-2; **12**, 57719-92-3; **13a**, 57719-93-4; **13b**, 57719-94-5; **15**, 57719-95-6.

References and Notes

(1) This work was supported in part by Grant CA-13121 from the U.S. Public Health Service through the National Cancer Institute. We are greatly indebted to Mr. John Shedd for carrying out the chromatographic separation of the crude extract.

(2) For references to earlier work and to a redefinition of the genus *Eupatorium*, see our previous paper on constituents of *E. hyssopifolium* L.: W. Herz and R. P. Sharma, *J. Org. Chem.*, preceding paper in this issue.
(3) D. E. U. Ekong and A. U. Ogan, *J. Chem. Soc.*, 311 (1968).
(4) The flavonoid constituents of the polar extract of *E. album* have been described earlier: H. Wagner, M. A. Iyengar, L. Hörhammer, and W. Herz, *Phytochemistry*, **11**, 1504 (1972).
(5) For a recent reference to the chemical shift of H-13 in 15-oxo-16-kaurenes, see I. Kubo, T. Kamikawa, T. Isabe, and T. Kubota, *Bull. Chem. Soc. Jpn.*, **47**, 1277 (1974).
(6) Analogous with the primary process in the mass spectra of 11-keto steroids; see H. Budzikiewicz in "Biochemical Applications of Mass Spectrometry", G. R. Waller, Ed., Wiley-Interscience, New York, N.Y., 1972, p 251.
(7) We are indebted to Dr. J. R. Hanson, University of Sussex, for this information. Valuable data on ^{13}C NMR spectra of kaurenolides appear in an article by J. R. Hanson, G. Savona, and M. Siverns, *J. Chem. Soc., Perkin Trans. 1*, 2001 (1974).
(8) For an analogy, see the comparison between 11α-hydroxyandrostane[9] and 11-ketoandrostane.[10]
(9) H. Eggert, C. L. VanAntwerp, N. S. Bhacca, and C. Djerassi, *J. Org. Chem.*, **41**, 71 (1976).
(10) H. Eggert and C. Djerassi, *J. Org. Chem.*, **38**, 3788 (1973).
(11) L. H. Briggs, R. C. Cambie, and P. S. Rutledge, *J. Chem. Soc.*, 5374 (1963).
(12) An unsuccessful attempt to relate **3a** to a known compound via the mesylate **3d** is described in the Experimental Section.
(13) A. J. McAlees and R. McCrindle, *J. Chem. Soc., Perkin Trans. 1*, 861 (1975).
(14) In the ^{13}C NMR spectrum of the triacetate **4c**, only C-12 experienced the expected downfield shift (72.4 → 73.3), whereas the signals of C-11 and C-15 were shifted upfield (68.3 → 67.3, 82.2 → 81.5). Similarly only C-13 and C-16 exhibited a β shift (46.0 → 43.4, 153.2 → 146.4) whereas C-8 and C-9 remained essentially unchanged. Somewhat similar seemingly anomalous results have been observed in the acylation of 1,3-diols of the olean-12-enes: K. Tori, S. Seo, A. Shimaoka, and Y. Tomita, *Tetrahedron Lett.*, 4227 (1974).
(15) Rearrangement under these conditions normally occurs on acid catalysis and is limited to substances containing a β-oriented C-15 hydroxyl group.[16,17] In a similar way, treatment of **1a** with 5% Pd/C–H_2 caused isomerization to **2a**. For an account of the behavior of **1b** on treatment with acid, see below.
(16) J. R. Cannon, P. W. Chow, P. R. Jefferies, and G. V. Meehan, *Aust. J. Chem.*, **19**, 861 (1966).
(17) M. F. Barnes and J. MacMillan, *J. Chem. Soc.*, 361 (1967).
(18) These are the conditions ordinarily employed for the A → B isomerization.
(19) The rules used for nomenclature of diterpenoids are clear but frequently lead to confusion. The prefix ent indicates that the substance in question belongs to the enantiomeric series. Since in a systematic name the prefix precedes the number specifying the location of the substituent, an 11β-hydroxylated *ent*-kaurane becomes an *ent*-11α-hydroxykaurane.
(20) J. D. Connolly and I. M. S. Thornton, *J. Chem. Soc., Perkin Trans. 1*, 737 (1973).
(21) W. Herz, A. Srinivasan, and P. S. Kalyanaraman, *Phytochemistry*, **14**, 233 (1975).
(22) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).

Solid Phase Peptide Synthesis. A Study on the Effect of Trifluoroacetic Acid Concentration on the Removal of the *tert*-Butyloxycarbonyl Protecting Group[1]

Ronald Eric Reid

Institut für Genetik der Universität Köln, 5 Köln-Lindenthal, Weyertal 121, Federal Republic of Germany

Received July 21, 1975

An acid concentration of 20% (v/v) TFA in CH_2Cl_2 was used to remove the α-amino protecting group during the solid phase synthesis of the tri- and tetrapeptides corresponding to the carboxy terminus of bovine pancreatic RNase A. Thin layer chromatography of the cleaved and desalted tripeptide showed significant amounts of the deletion peptides alanylvaline and serylvaline in addition to the expected alanylserylvaline. Similar analysis of the tetrapeptide showed five major ninhydrin positive by-products. Inadequate removal of the α-amino protecting group was determined to be the chief cause of these impurities. A study on the synthesis of the tri- and tetrapeptides using a variety of acid concentrations between 20 and 50% (v/v) TFA in CH_2Cl_2 indicated that 40–45% TFA was the weakest possible acid concentration that could be employed to remove the α-amino protecting group quantitatively and produce a reasonably pure tri- and tetrapeptide on the solid support used.

One of the main advantages of the solid phase synthesis of peptides[2] is the potential for automation. The ideal automated procedure would require a set of tactics which could be repeated for a large number of amino acids in a variety of sequences.[3]

The Boc[4] group has found wide acceptance as the α-amino protecting group in solid phase synthesis.[5] Removal of the Boc group from the α-amino function has been accomplished by 4 N HCl–dioxane,[6] 1 N HCl–glacial acetic acid,[7] TFA,[8–12] 50% (v/v) TFA–CH_2Cl_2,[13] 20% (v/v) TFA–CH_2Cl_2,[14,15] and a variety of TFA concentrations in CH_2Cl_2 between 20 and 50%.

In spite of the desire to have one concentration of acid which can be used to remove the Boc group throughout the entire synthesis of a peptide, there have been instances[16] where quantitative removal of the Boc group has required a variety of acid concentrations throughout the synthesis.

The ease of preparation of various concentrations of anhydrous TFA as opposed to the preparation of various anhydrous HCl concentrations has given this acid widespread use for the removal of the Boc group. A 50% concentration of TFA in CH_2Cl_2, the most widely used concentration of TFA for Boc group removal, has been shown to cause branching at lysine residues where the side chain has been protected by the benzyloxycarbonyl group.[17] It is also known that a 50% TFA solution results in a small amount of cleavage of the ester bond linking the peptide to the resin with a concomitant loss of the growing peptide chain.[13]

Despite the availability of a more stable protecting group for the side chain of lysine[17] as well as the observation that the reduction of the concentration of TFA from 50 to a 20% (v/v) solution in CH_2Cl_2 had only a minor effect on the stability of the ester bond linking the peptide to the resin,[15] the tendency has been to use lower acid concentrations for the removal of the Boc group.

In order to study the effectiveness of various concentrations of TFA in CH_2Cl_2 on the removal of the Boc group, the tripeptide and tetrapeptide from the carboxy terminus of RNase A were chosen as the model peptides. The reasons for selecting these peptides were twofold. Firstly, several studies have been carried out on the use of synthetic analogues of the carboxy terminus of RNase A to regenerate activity from pepsin and carboxypeptidase inactivated RNase A.[18–22] If the solid phase synthesis of a model peptide corresponding to the carboxy terminus of RNase A could be studied step by step to determine the ideal conditions for coupling each individual amino acid, then a series of analogues could be prepared in a reasonably pure state without the necessity of analyzing every step for complete Boc group removal and coupling. Secondly, it is possible that the difficulty in removing the Boc groups or achieving complete coupling of the amino acids may be caused in part by steric hindrance from the bulky protected side chains of the amino acid derivatives. Since the carboxy terminal tripeptide contains the bulky valine and benzyl protected serine as well as one alanine which has relatively little hindrance and the tetrapeptide contains, in addition, the bulky aspartic acid β-benzyl ester, a study of these peptides may give some indication as to whether large and/or protected side chains have a major effect on the deprotection of the α-amino group and subsequent coupling reaction during solid phase peptide synthesis.

The tripeptide was synthesized by coupling Boc-alanine and Boc-*O*-benzylserine to Boc-valine resin using DCC after removing the Boc group with 20% TFA in CH_2Cl_2. After cleavage of the peptide from the resin using HBr in TFA[23] and desalting on Sephadex G-10, the product obtained showed one neutral spot by electrophoresis on cellulose thin layer plates using 0.1 M pyridine acetate at pH 6.0. However, thin layer chromatography on silica gel in the solvent system 1-butanol–glacial acetic acid–water (4:1:1) resulted in three major ninhydrin positive spots at R_f 0.38, 0.31, and 0.27 and four weak ninhydrin positive spots at R_f 0.53, 0.44, 0.21, and 0.15.

Preparative TLC of the impure product resulted in seven samples (Table I) which, after desalting, produced partial purification of the three major spots as shown by rechromatographing the samples.

Rechromatography of sample 3 (Table I) showed one major spot at the expected R_f value and a very weak spot at R_f 0.31. Amino acid analysis following acid hydrolysis showed nearly equimolar quantities of valine and alanine with a trace amount of serine.

Rechromatography of sample 4 (Table I) showed that the major component of this sample had an R_f of 0.38 with a minor component at R_f 0.31 and a very weak spot at R_f 0.27. Comparison of the amino acid analyses of samples 3 and 4 showed that the latter had considerably more serine and less alanine than the former.

Sample 5 (Table I) showed a major spot at R_f 0.31 with a spot of minor intensity at R_f 0.27 when examined by TLC. A second preparative TLC of sample 5 resulted in a product which gave a single spot of R_f 0.31 on TLC and amino acid analysis showed a trace of alanine and near equal quantities of serine and valine.

Table I. Preparative TLC of Ala-Ser-Val Synthesized Using 20% (v/v) TFA–CH_2Cl_2

Sample no.	R_f value in original chromatogram	R_f values of ninhydrin positive spots in TLC of sample after preparative TLC			Amino acid content of sample (nM of amino acid)		
		Major	Minor	Weak[a]	Ala[b]	Ser[b,c]	Val
1[d,e]	0.53		0.53 and 0.44		4.0 (0.82)	7.6 (1.56)	4.9 (1)
2[d,e]	0.44		0.53 and 0.44		6.5 (1.07)	8.6 (1.42)	6.1 (1)
3	0.38	0.38		0.31	81.3 (0.98)	3.1 (0.04)	83.1 (1)
4	0.31	0.38	0.31	0.27	54.4 (0.68)	21.2 (0.27)	79.6 (1)
5	0.27	0.31	0.27		84.6 (0.72)	98.0 (0.83)	118.4 (1)
	[f]	0.31			Trace	68.4 (0.92)	74.6 (1)
6	0.21	0.27			133.0 (0.90)	119.0 (0.80)	148.4 (1)
7[d]	0.15		0.21 and 0.15		12.6 (1)	6.7 (0.53)[g]	

[a] An estimation of the relative intensity of the spots. [b] The values in parentheses are relative to valine. [c] Uncorrected for serine destruction during acid hydrolysis. [d] Not separated by preparative TLC. [e] Difficult to detect by ninhydrin as the spots faded rapidly. [f] Sample no. 5 was again subjected to preparative TLC and material with R_f 0.31 was isolated. [g] This value in parentheses is relative to alanine.

Rechromatography of sample 6 (Table I) resulted in a single spot of R_f 0.27 and amino acid analysis showed equal quantities of alanine, serine, and valine.

Preparative TLC could therefore show that the ninhydrin positive spot at R_f 0.27 was the required alanylserylvaline tripeptide while the spot of R_f 0.31 was the serylvaline dipeptide. The spot of R_f 0.38, although very slightly impure after preparative TLC, was concluded to be the alanylvaline dipeptide.

The two spots of highest R_f values (0.53 and 0.44) faded rapidly after spraying with ninhydrin and were not completely separated by preparative TLC. Amino acid analysis (Table I) of the two samples from preparative TLC showed that some separation may have taken place since sample 1 had a lower alanine content than sample 2. Both samples contained both spots as shown by TLC; however, the relative intensities could not be determined. When a sample was taken from the synthesis vessel at the serylvaline resin stage, the spot of R_f 0.53 was found, whereas the spot of R_f 0.44 did not occur until after alanine had been coupled. Therefore it was concluded that the material with R_f 0.53 was probably an impurity of the serylvaline dipeptide, while the spot of R_f 0.44 was perhaps due to an impurity of the alanylserylvaline peptide. However, a definite identification of these impurities had not been made.

The spots of R_f 0.21 and 0.15 were not separated by preparative TLC, but the amino acid analysis of sample 7 containing both spots (Table I) showed the presence of serine and alanine. Again, a sample of the peptide resin taken at the serylvaline resin stage showed only the spot of R_f 0.15 while that with R_f 0.21 appeared after coupling alanine. When these impurities were compared on TLC with a sample of free serine and free alanine, the alanine was shown to have an R_f value of 0.21 and serine an R_f value of 0.15. Therefore, these two impurities were concluded to be alanine and serine, respectively. Although the presence of serine in the alanylserylvaline samples suggested inefficient washing, other experiments which involved three 20-min acid treatments for deprotection also resulted in the presence of detectable amounts of serine in the product. Since the serine could not be removed after three acid treatments, inefficient washing would not explain its presence in the product. Free valine had an R_f of 0.37 and could not be separated from the alanylvaline dipeptide if it was present at all.

The impurities in the tripeptide product could have resulted from either incomplete removal of the α-amino protecting groups or incomplete coupling of the amino acid derivatives. If incomplete coupling was responsible, then a change in the acid concentration for α-amino deprotection would not be expected to alter the number and amount of impurities to any extent. However, if incomplete Boc group removal was responsible then alteration of the acid concentration used for α-amino group deprotection should result in a change in impurities.

Table II. A Study of the Ala/Val Ratios after Coupling Boc-Ala to Boc-*O*-benzylserylvaline Resin[a] Deprotected with 20 and 50% TFA[b]

Acid concn,[b] %	Sample no.[c]	Ala/Val ratio[d]
20	1	0.92
	2	0.87
	3	0.90
50	1	1.09
	2	0.99
	3	1.08

[a] Synthesized by deprotecting Boc-valine resin with 50% (v/v) TFA in CH_2Cl_2 prior to coupling Boc-*O*-benzylserine. [b] By volume in CH_2Cl_2. [c] Three couplings performed, taking a sample after each coupling. [d] From amino acid analysis after HBr–TFA cleavage from resin, desalting, and acid hydrolysis.

To discover which of the above possibilities was responsible for the impurities found in the product, Boc-valine resin was deprotected with 20% TFA in CH_2Cl_2 and Boc-*O*-benzylserine was coupled. The Boc-*O*-benzylserylvaline resin was then divided into two fractions. One fraction was deprotected with 20% TFA in CH_2Cl_2 and coupled with Boc-alanine three times taking a small sample of the resin peptide after each coupling. The second fraction was deprotected using 50% TFA in CH_2Cl_2 and coupled with Boc-alanine three times taking samples after each coupling. The alanine/valine ratios from amino acid analysis of the samples after cleavage from the resin, desalting, and acid hydrolysis are shown in Table II. There was no major difference in the alanine/valine ratios within the group of three samples from each of the experiments; however, the alanine/valine ratios of the three samples from the experiment using 50% TFA were approximately 17% higher than those of the three samples from the experiment using 20% TFA, indicating a better incorporation of alanine after deprotection of the Boc-*O*-benzylserylvaline resin by 50% TFA. The TLC of the six samples showed no major difference in the spot intensities within each group; however, the 50% samples showed a great decrease in the intensity of the spot attributed to the serylvaline dipeptide as well as an increase in the intensity of the spot attributed to the alanylvaline dipeptide when compared with the 20% samples. These results indicated that the majority of the impurities was due to incomplete removal of the α-amino protecting group during the acid treatment. However, it cannot be ruled out

that a small amount of the impurities, a change in which cannot be detected by TLC, was due to incomplete coupling.

The tripeptide was synthesized seven times by the solid phase method using acid concentrations from 20 to 50% TFA in CH_2Cl_2 at 5% intervals in order to obtain an acid concentration which gave a maximum of product with a minimum of impurities. The TLC of the products obtained are shown in Figure 1. There was an indication of a decrease in the impurities proceeding from 20 to 25% TFA and a slight further decrease from 25 to 30%; however, there was no further visible decrease in impurities between 30 and 50% TFA. The amino acid analyses of these products (Table III) showed only a slightly low alanine content of the product prepared using 20% TFA.

In order to quantitate the impurities and have a closer look at the effect of acid concentrations on impurities between 30 and 50% TFA, the peptide was synthesized using different acid concentrations and employing the Dorman titration[24] to examine Boc removal and amino acid coupling. Table IV shows the results obtained.

Examination of the effect of different acid concentrations on deprotection of the Boc-valine resin indicated that an acid concentration of 45% gives maximum removal of the Boc group. Boc removal from the Boc-*O*-benzylserylvaline resin showed an increase (18%) on proceeding from 20 to 25% TFA reaching a maximum at 40%. It was also observed that, in general, deprotection of the Boc-valine resin was better than deprotection of the Boc-*O*-benzylserylvaline resin, although not to any significant extent except in the peptide prepared with 20% TFA. The erratic behavior of the Boc-alanyl-*O*-benzylserylvaline resin during titration after the deprotection step cannot be explained at the present time.

Table III. Amino Acid Composition of Tripeptides Prepared Using Different Acid Concentrations for Boc Group Removal

Acid concn[a]	Amino acid ratio of cleaved and desalted peptide[b]		
	Ala	Ser[c]	Val
20	0.90	0.89	1
25	0.99	0.91	1
30	0.97	0.91	1
35	1.01	0.95	1
40	0.96	0.86	1
45	1.02	0.98	1
50	1.12	1.01	1

[a] Percent by volume TFA in CH_2Cl_2. [b] Values relative to valine. [c] No correction for serine destruction during acid hydrolysis.

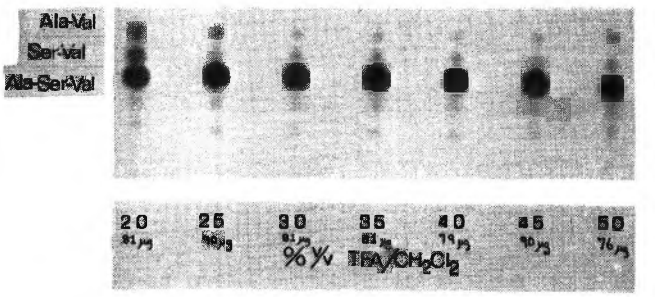


Figure 1. Thin layer chromatogram of crude tripeptide products synthesized using different TFA concentrations to remove the Boc group. The amount of sample applied to the plate is listed under the acid concentration.

In order to calculate the percentage of impurities in each of the samples (Table V), coupling was assumed to be 100% and the calculations were made from the percent deprotection in Table IV. Using the 20% TFA in CH_2Cl_2 experiment as an example, the calculations were performed as follows: Boc-valine resin was 87% deprotected (Table IV) thus leaving 13% as Boc-valine resin. A 100% coupling of Boc-*O*-benzylserine would result in a product consisting of 87% Boc-*O*-benzylserylvaline resin and 13% Boc-valine resin. Deprotection of this mixture of products was 73% complete (Table IV), assuming that the deprotection is equally distributed between the Boc-*O*-benzylserylvaline resin and Boc-valine resin; after 100% coupling of Boc-alanine, the mixture would consist of 73% of 87% or 63.5% Boc-alanine-*O*-benzylserylvaline resin, 27% of 87% or 23.5% Boc-*O*-benzylserylvaline resin, 73% of 13% or 9.5% Boc-alanylvaline resin, and 27% of 13% or 3.5% Boc-valine resin.

These calculations showed that the valine and alanylvaline impurities, which were due to incomplete deprotection of Boc-valine resin, reached a minimum at 45% TFA, while the serylvaline impurity due to incomplete deprotection of the Boc-*O*-benzylserylvaline resin reached a minimum at 40% TFA. The maximum yield of the alanylserylvaline tripeptide occurred at about 45% TFA. Figure 2 was a graph of these results.

Both Figure 1 and Table V indicated an unusually high content of alanylvaline and serylvaline in the tripeptide product obtained from the synthesis using 50% TFA in CH_2Cl_2. This was a surprising result and since it was expected that 50% TFA would be as efficient as, or better than, 40 or 45% TFA in removing the Boc group, the impurities probably resulted from incomplete coupling of Boc-*O*-benzylserine and Boc-alanine.

It was important to remember that the values of the free amino groups (Table I) and hence the percentage impurities (Table V) were relative values only since the highest

Table IV. Preparation of Ala-Ser-Val Using Different Concentrations of Acid and Monitoring the Synthesis by the Dorman Procedure[a,b]

Acid concn[c]	Boc-Val resin deprotection, μequiv Cl^-/g[d]	Boc-Ser(Bzl) coupling, μequiv Cl^-/g	Boc-Ser(Bzl)-Val resin deprotection, μequiv Cl^-/g	Boc-Ala coupling, μequiv Cl^-/g	Boc-Ala-Ser(Bzl)-Val resin deprotection, μequiv Cl^-/g
20	157 (87)[e]	6 (3)	132 (73)	5 (3)	168 (93)
25	164 (91)	5 (3)	164 (91)	7 (4)	179 (99)
30	170 (94)	6 (3)	166 (92)	8 (4)	163 (91)
35	173 (96)	8 (4)	170 (94)	7 (4)	170 (94)
40	172 (96)	8 (4)	173 (96)	7 (4)	180 (100)
45	176 (98)	7 (4)	172 (96)	7 (4)	167 (93)
50	170 (94)	5 (3)	169 (94)	10 (6)	172 (96)

[a] Amino acid analysis of Boc-Val resin indicated 163 μM Val/g Boc-Val resin. [b] The accuracy and precision of the Dorman monitoring of total amino groups after deprotection were determined by six chloride determinations on a 500-mg sample of 40% TFA deprotected Boc-Val resin and found to be ±6 and ±1.6%, respectively. [c] Percent by volume of TFA in CH_2Cl_2. [d] μequiv Cl^- is assumed to be equivalent to μM free amino groups. [e] Numbers in parentheses indicate the percent free amino groups relative to the 40% TFA–CH_2Cl_2 deprotection of Boc-Ala-Ser(Bzl)-Val resin.

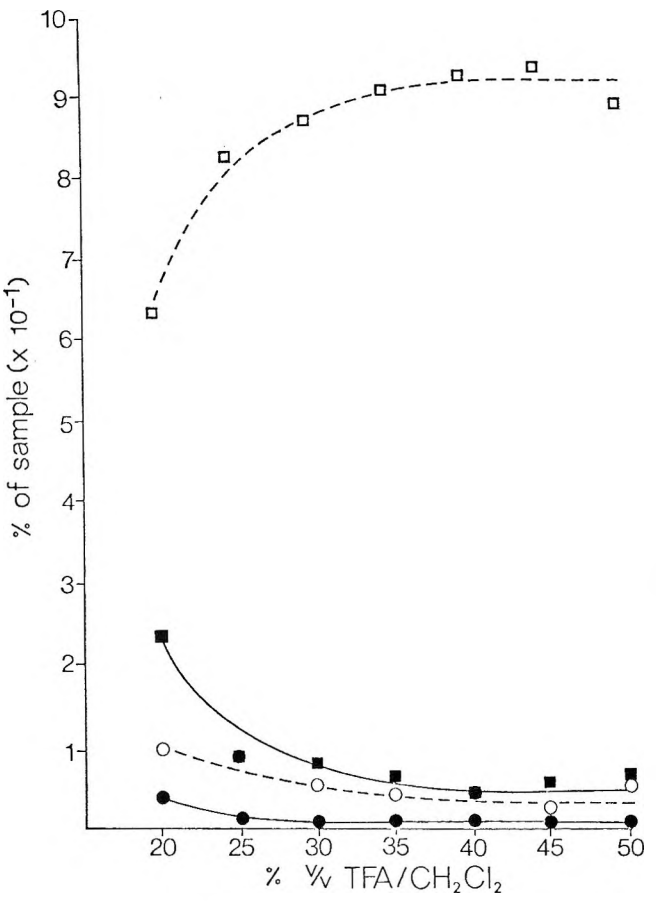


Figure 2. Comparison of decreasing formation of impurities (●—●, valine; ■—■, serylvaline; O- - -O, alanylvaline) and increasing yield of product (□- - -□, alanylserylvaline) with increasing TFA concentrations during synthesis of the alanylserylvaline tripeptide.

Table V. Percentage of Impurities in Tripeptides Prepared Using Various Acid Concentrations[a,b]

Acid concn[c]	% Val	% Ala-Val	% Ser-Val	% Ala-Ser-Val[d]
20	3.5	9.5	23.5	63.5
25	0.8	8.2	8.2	82.8
30	0.5	5.5	7.5	86.5
35	0.2	3.8	5.8	90.2
40	0.2	3.8	3.8	92.2
45	0.1	1.9	3.9	94.1
50	0.4	5.6	5.6	88.4

[a] Assuming 100% coupling. [b] Calculated from percent deprotection in Table IV (see text). [c] Percent by volume TFA in CH_2Cl_2. [d] This column shows the increasing yield of tripeptide product with increasing acid concentration.

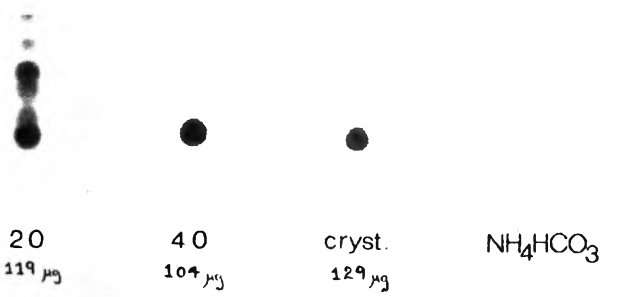


Figure 3. Comparison of the crude tetrapeptide synthesized with 20% (v/v) TFA in CH_2Cl_2 (20) with the crude tetrapeptide synthesized with 40% (v/v) TFA in CH_2Cl_2 (40) and the crystallized tetrapeptide (cryst). Residual NH_4HCO_3 in the samples after desalting and lyophilization migrates to the same position as the alanlyserylvaline tripeptide thus making the estimation of purity of the tetrapeptide difficult. The amount of the sample applied to the plate is listed under the appropriate label.

value for the chloride determination was arbitrarily taken as 100% removal of the Boc group.

The tripeptide resin prepared using 20% TFA to remove the α-amino protecting group was further deprotected with 20% TFA and Boc-aspartic acid β-benzyl ester was coupled to form the tetrapeptide resin. After HBr–TFA cleavage from the resin and desalting on Sephadex G-10, electrophoresis on cellulose thin layer plates in 0.1 M pyridine acetate at pH 6 and 600 V showed one neutral ninhydrin positive spot and one large, diffuse spot of net negative charge. Thin layer chromatography of this peptide resulted in six ninhydrin positive spots of major intensity at R_f values of 0.38, 0.31, 0.27, 0.25, 0.20, and 0.15. The first three spots of R_f 0.38, 0.31, and 0.27 could be identified (by analogy to the tripeptide studies) as alanylvaline, serylvaline, and alanylserylvaline, respectively. The other three spots were the result of coupling aspartic acid and therefore were likely to be aspartylalanylvaline, aspartylserylvaline, and aspartylalanylserylvaline.

Since the TLC and Dorman titration studies on the tripeptide indicated that 40% TFA was the weakest acid concentration that could be used to remove the Boc group, the tetrapeptide was resynthesized using 40% TFA to deprotect the α-amino function.

The cleaved, desalted peptide was run on TLC and compared to the tetrapeptide synthesized using 20% TFA (Figure 3). A small amount of the serylvaline dipeptide and the alanylserylvaline tripeptide was still present in this crude tetrapeptide; however, when compared with the tetrapeptide synthesized using 20% TFA the purity was considerably improved.

The tetrapeptide synthesized using the 40% TFA could be further purified by ion exchange chromatography on DEAE cellulose using an ionic gradient. After ion exchange chromatography, desalting, and treatment of the lyophilized product with aqueous HCl to form the hydrochloride salt, the tetrapeptide could be crystallized from an aqueous methanol solution by addition of dry ether. The hydrochloride salt of the tetrapeptide synthesized using 20% TFA and purified in the same manner could not be crystallized.

In conclusion, these studies indicated that a minimum of 40% TFA in CH_2Cl_2 should be employed to remove the Boc group during the solid phase synthesis of the tetrapeptide corresponding to the carboxy terminus of RNase A using the solid support described in the Experimental Section.

No convincing evidence could be found to show that steric hindrance by the amino acid side chains contributed significantly to the formation of impurities in the tripeptide or tetrapeptide by hindering α-amino group deprotection or the subsequent coupling reaction.

The mechanical properties of different supports may differ considerably[3] and therefore certain supports may require higher acid concentrations for Boc removal, while others may give the same result at lower acid concentrations; hence the need for careful study of the mechanical properties of the solid support before commencing a synthesis.

Experimental Section

Boc-alanine, Boc-valine, Boc-*O*-benzylserine, and Boc-aspartic acid β-benzyl ester were purchased from Fluke AG, Buchs, Switzerland, and Serva Feinbiochemica, Heidelberg, Germany. Melting

points and R_f values on precoated silica gel thin layer plates were determined for all derivatives. Chloromethylated copolystyrene–1% divinylbenzene resin (Bio-Beads SX-1, 200–400 mesh, 1.25 meq uiv of chlorine per gram, control no. 10948) was obtained from Bio Rad. All solvents and reagents were of analytical grade except for *N,N*-dimethylformamide, which was spectroscopic grade.

Thin layer chromatography was carried out on precoated silica gel plates purchased from Merck in the solvent system 1-butanol–glacial acetic acid–water (4:1:1). Electrophoresis was carried out on precoated cellulose plates purchased from Merck and samples were run in 0.1 M pyridine acetate at pH 6.0 for 40 min at 600 V (~4 mA) in a Camag electrophoresis unit. After thin layer chromatography or electrophoresis, ninhydrin positive material was detected by thoroughly drying the plates and spraying with a 5–10% solution of ninhydrin in a buffer consisting of glacial acetic acid–pyridine–acetone (2:1:64).

Peptide resins and free peptides were prepared for amino acid analysis as described elsewhere[13] and analyzed on a Beckmann Unichrome Amino Acid Analyzer.

Solid Phase Synthetic Procedure. The synthetic procedure was initially carried out in a mechanical shaker of the type described in ref 5. The synthesis of peptides incorporating the Dorman titration procedure was carried out using the Peptider purchased from Penninsula Laboratories, San Carlos, Calif. The amount of valine esterified to the resin varied between 0.139 and 0.269 mM/g Boc-valine resin. α-Amino group deprotection was carried out with redistilled TFA in CH_2Cl_2, and neutralization was performed using a 10% solution of triethylamine in CH_2Cl_2. Couplings were performed using *N,N'*-dicyclohexylcarbodiimide in CH_2Cl_2 (250 mg/ml). Initially, two 1-h couplings were performed but this was later reduced to one 1-h coupling step when the Dorman titration was employed because TLC studies indicated that there was no visible change in impurities after the first coupling. A threefold excess of Boc-amino acid and DCC was used for each coupling.

One cycle of the synthesis including the Dorman titration was performed on 500 mg of amino acid resin as follows: 1, 2 × 3 min, CH_2Cl_2, 10 ml/wash; 2, 1 × 3 min, TFA–CH_2Cl_2, 10 ml; 3, 2 × 10 min, TFA–CH_2Cl_2, 10 ml; 4, 6 × 3 min, CH_2Cl_2, 10 ml/wash; 5, 1 × 1 min, 10% $(CH_3CH_2)_3N$–CH_2Cl_2, 10 ml; 6, 1 × 6 min, 10% $(CH_3CH_2)_3N$–CH_2Cl_2, 10 ml; 7, 6 × 3 min, CH_2Cl_2, 10 ml/wash; 8, 1 × 3 min, 0.3 M pyridine hydrochloride–CH_2Cl_2, 10 ml; 9, 1 × 10 min, 0.3 M pyridine hydrochloride–CH_2Cl_2, 10 ml; 10, 4 × 3 min, CH_2Cl_2, 20 ml/wash; 11, 3 × 3 min, dimethylformamide, 20 ml/wash; 12, 1 × 1 min, 10% $(CH_3CH_2)_3N$–dimethylformamide, 10 ml; 13, 1 × 6 min, 10% $(CH_3CH_2)_3N$–dimethylformamide, 10 ml; 14, 4 × 3 min, dimethylformamide, 10 ml/wash; 15, 6 × 3 min, CH_2Cl_2, 10 ml/wash; 16, 1 × 10 min, Boc-amino acid–CH_2Cl_2, 10 ml; 17, 1 × 60 min, DCC; 18, 3 × 3 min, CH_2Cl_2, 10 ml/wash; 19, 3 × 3 min, CH_3CH_2OH (absolute), 10 ml/wash; 20, 3 × 3 min, CH_2Cl_2, 10 ml/wash. The washings in steps 12–14 were collected for chloride determination.

The peptide samples were cleaved from the resin by bubbling HBr through a suspension of the resin in 50% TFA–CH_2Cl_2 for 80 min. The suspension was filtered and the resin washed with concentrated TFA (2 × 5 ml) and then the combined filtrate and washings were evaporated to dryness. The residue was dissolved in 0.05 M NH_4HCO_3, adjusted to pH 8.2 with 1 N NaOH, and stirred for 1 h at room temperature to reverse any N to O acyl shift which may have occurred during the HBr cleavage. After lyophilization, the sample was dissolved in 0.05 M NH_4HCO_3 and desalted by application to Sephadex G-10 and elution with the bicarbonate buffer. The peptide was detected in the eluate by reading the fractions at 230 nm.

Estimation of Free Amino Groups on the Resin. Free amino groups were determined according to the method described by Dorman.[24] Washes 12–14 above were collected, acidified with 20 ml of 1 N HNO_3, and titrated with 0.1 N silver nitrate. Titrations were performed automatically using the Autoburette ABU 12, Titragraph SBR 2c, and Titrator TTT 1c purchased from Radiometer Copenhagen.

Preparative Thin Layer Chromatography. Approximately 20 mg of crude peptide was dissolved in 2 ml of deionized water and 0.2 ml of this solution was applied to each of ten precoated silica gel plates (20 × 20 cm, 0.25 mm in thickness). The plates were developed to a height of approximately 13 cm (4–5 h) in 1-butanol–glacial acetic acid–water (4:1:1). Then they were thoroughly dried and the center covered with tinfoil leaving 2 cm exposed on both sides. The exposed sides were sprayed with ninhydrin and the corresponding spots on both sides were joined by drawing straight lines across the plates above and below the spots. The centers of the plates were thus divided into seven sections which were separately scraped from the plates. The corresponding sections of the plates were combined and extracted three times with 30% (v/v) glacial acetic acid–water. Centrifugation for 15 min at 3000 rpm in a Heraeus Christ centrifuge was required to remove completely silica gel from the samples which were then lyophilized and desalted on Sephadex G-10 using 0.05 M NH_4HCO_3 as eluent. The samples so isolated were then rechromatographed to determine purity.

Ion Exchange Chromatography and Crystallization of the Tetrapeptide. After the tetrapeptide prepared using 40% TFA was cleaved from the resin, desalted, and lyophilized, it was dissolved (30 mg) in 2 ml of 0.05 M pyridine acetate at pH 6.0 and applied to a DEAE cellulose column (2.5 × 11.5 cm). After 50 ml of 0.05 M pyridine acetate buffer had passed through the column a linear ionic gradient was started at 0.05 M pyridine acetate, pH 6.0 (100 ml), to 0.5 M pyridine acetate, pH 6.0 (100 ml). The eluted peptide was detected by alkaline hydrolysis and the ninhydrin reaction on 0.1-ml aliquots of the fractions. The tubes containing the major fraction eluting at 160 ml were combined and lyophilized. The lyophilized product was desalted on Sephadex G-10 using the bicarbonate buffer mentioned above.

A sample of the tetrapeptide (13 mg) was dissolved in 0.2 ml of aqueous HCl, pH 1.7, and centrifuged to remove suspended particles. Approximately 1 ml of methanol was added to the solution followed by ether until the solution became cloudy. The cloudy solution was then refrigerated for 3 weeks. This resulted in the recovery of 7.25 mg of crystalline tetrapeptide.

Acknowledgments. I would like to thank Dr. B. Gutte for his many suggestions and continued interest in this work. I am indebted to Mrs. M. Hoffman for her excellent technical assistance and Mr. K. Bärwald and Mr. W. Kullmann for many helpful discussions. I would also like to thank Mr. G. Leipertz for his excellent photographic work.

Registry No.—Boc-alanine, 15761-38-3; Boc-valine, 13734-41-3; Boc-*O*-benzylserine, 23680-31-1; Boc-aspartic acid β-benzyl ester, 7536-58-5; aspartylalanylserylvaline, 57739-05-6; alanylserylvaline, 57694-90-3; TFA, 76-05-1.

References and Notes

(1) This work was supported by the Deutsche Forschungsgeminschaft through SFB 74.
(2) R. B. Merrifield, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **21**, 412 (1962).
(3) G. R. Marshall and R. B. Merrifield, "Biochemical Aspects of Reactions on Solid Supports", G. R. Stark, Ed., Academic Press, New York, N.Y., 1971, Chapter 3.
(4) The nomenclature and symbols follow the Tentative Rules of the IUPAC–IUB Commission on Biochemical Nomenclature, *J. Biol. Chem.*, **241**, 2491 (1966); **242**, 555 (1967); **247**, 977 (1972).
(5) J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis", W. H. Freeman, San Francisco, Calif., 1969, p 13.
(6) J. M. Stewart and D. W. Wooley, "Hypotensive Peptides", E. G. Ereos, N. Back, and F. Sicuteri, Ed., Springer-Verlag, West Berlin, 1966, p 23.
(7) R. B. Merrifield, *J. Am. Chem. Soc.*, **86**, 304 (1964).
(8) P. Kusch, *Kolloid-Z. Z. Polym.*, **208**, 138 (1966).
(9) C. B. Anfinsen, D. Ontjes, M. Ohno, L. Corley, and A. Eastlake, *Proc. Natl. Acad. Sci. U.S.A.*, **58**, 1806 (1967).
(10) M. Manning, *J. Am. Chem. Soc.*, **90**, 1348 (1968).
(11) H. Takashima, V. DuVigneaud, and R. B. Merrifield, *J. Am. Chem. Soc.*, **90**, 1323 (1968).
(12) Abbreviations used are: TFA, trifluoroacetic acid; DCC, dicyclohexylcarbodiimide; TLC, thin layer chromatography.
(13) B. Gutte and R. B. Merrifield, *J. Biol. Chem.*, **246**, 1922 (1971).
(14) C. L. Krumdieck and C. M. Baugh, *Biochemistry*, **8**, 1568 (1969).
(15) B. Gutte, *J. Biol. Chem.*, **250**, 889 (1975).
(16) F. C-H. Chou, R. K. Chawla, R. F. Kibler, and R. Shapira, *J. Am. Chem. Soc.*, **93**, 267 (1971).
(17) B. W. Erickson and R. B. Merrifield, *J. Am. Chem. Soc.*, **95**, 3757 (1973).
(18) M. C. Lin, B. Gutte, S. Moore, and R. B. Merrifield, *J. Biol. Chem.*, **245**, 5169 (1970).
(19) B. Gutte, M. C. Lin, D. G. Caldi, and R. B. Merrifield, *J. Biol. Chem.*, **247**, 4763 (1972).
(20) M. C. Lin, B. Gutte, D. G. Caldi, S. Moore, and R. B. Merrifield, *J. Biol. Chem.*, **247**, 4768 (1972).
(21) R. S. Hodges and R. B. Merrifield, *Int. J. Pept. Protein Res.*, **6**, 397 (1974).
(22) R. S. Hodges and R. B. Merrifield, *J. Biol. Chem.*, **250**, 1231 (1975).
(23) See ref 5, p 40.
(24) L. C. Dorman, *Tetrahedron Lett.*, 2319 (1968).

The β-Phenacyl Ester as a Temporary Protecting Group to Minimize Cyclic Imide Formation during Subsequent Treatment of Aspartyl Peptides with HF[1,2]

C. C. Yang and R. B. Merrifield*

The Rockefeller University, New York, New York 10021

Received August 6, 1975

The rearrangement of a series of aspartic acid containing peptides to the corresponding cyclic aspartoyl imides by HF was studied. Boc-Glu(OBzl)-Asp(OBzl)-Gly-Thr(Bzl)-Resin (I) produced 99% of the aspartoyl tetrapeptide after 1 h at 0 °C in HF–10% anisole, while Boc-Glu(OBzl)-Asp(OBzl)-Ser(Bzl)-Leu-Resin and Boc-Glu(OBzl)-Asp(OBzl)-Ala-Leu-Resin each gave 25%. Since it was known that aspartyl peptides containing a free β-carboxyl group do not readily undergo the rearrangement, a synthesis was designed in which a temporary β-protecting group was selectively removed after the synthesis of the peptide chain but before the HF cleavage. For that purpose β-phenacyl N^{α}-*tert*-butyloxycarbonyl-L-aspartate was synthesized and used for the solid-phase synthesis of the tetrapeptides. Treatment of the protected peptide resins with 1 N sodium thiophenoxide in DMF for 8 h at 25 °C quantitatively removed the phenacyl ester. Subsequent cleavage of the peptide resins in HF–anisole and analysis of the resulting peptides by ion-exchange chromatography showed that the level of cyclic imide by-products was reduced as much as 40-fold. Thus, even in the extreme case, the phenacyl ester derivative of I gave only 2.4% of the by-product. The aspartoyl derivatives of the tetrapeptides were isolated and characterized by ir spectroscopy, amino acid analysis, and electrophoretic mobility. The mixtures resulting from mild alkaline hydrolysis of the cyclic imides were separated by ion-exchange chromatography into the α- and β-aspartyl tetrapeptides, which were identified by comparison with synthetic standards of the two isomers.

In the course of a solid-phase synthesis[3] of an active bovine growth hormone (125–133) fragment, a side reaction associated with the -Asp-Gly- sequence was encountered. This reaction was shown to be the formation of a cyclic aspartoyl imide derivative during the HF cleavage step. The sensitivity of aspartic acid amides and esters to imide formation under basic or acidic conditions or at elevated temperature is well known,[4–16] and the rearrangement has even been observed during recrystallization[14] and catalytic hydrogenolysis[17] of peptides containing aspartyl residues. The imide is subject to nucleophilic attack at either carbonyl, with ready formation of a mixture of α- and β-aspartyl peptides. The phenomenon has been observed in classical solution syntheses and in solid-phase syntheses but it has been of particular concern in the latter case because of the marked susceptibility to this rearrangement of -Asp(OBzl)-Ser(Bzl)-[13] and -Asp(OBzl)-Gly-[14] sequences and to a lesser extent of other β-benzyl-aspartyl sequences[15,16] when subjected to HBr–TFA or HF. It was known,[13,14] however, that -Asp-Ser(Bzl)- or -Asp-Gly- sequences containing a free β-carboxylic acid showed little tendency to undergo cyclization under these conditions. Consequently, synthetic strategies to circumvent this rearrangement during solid-phase synthesis were designed in which the protecting group on the β-carboxyl of aspartic acid was removed prior to the exposure to strong anhydrous acid.

Our first application of this principle involved the use of a *tert*-butyl ester for the β-carboxyl protection in combination with the Bpoc group for N^{α} protection and a relatively acid-labile *p*-alkoxybenzyl ester anchoring bond to the solid support.[3] An alternative form of this strategy for the solid-phase synthesis of aspartic acid containing peptides has now been developed in which the aspartyl residue is incorporated into the peptide chain as its β-phenacyl ester and is deprotected by sodium thiophenoxide before cleavage from the resin support by HF (Figure 1).

Phenacyl esters have been used for many years as derivatives of carboxylic acids for identification purposes and more recently as temporary protecting groups for organic synthesis.[18] They were introduced into peptide synthesis by the Zervas laboratory[19,20] and by Ledger and Stewart[21] as potentially useful derivatives for both α-carboxyl and side-chain carboxyl protection. A phenacyl ester linkage has also been adapted to solid-phase synthesis for anchoring the peptide chain to the resin support.[22–24]

Results

The Rearrangement to Cyclic Aspartoyl Peptides and Its Dependence on Sequence. The nonapeptide, H-Arg-Glu-Leu-Glu-Asp-Gly-Thr-Pro-Arg-OH, corresponding to residues 125–133 of bovine pituitary growth hormone, was synthesized as described previously[3] by a standard solid-phase method[25–27] in which aspartic acid was protected as a β-benzyl ester. The peptide was cleaved from the resin with anhydrous HF in the presence of 10% anisole at 0 °C for 1 h. Paper electrophoresis at pH 6.5 (pyridine–0.1 M acetic acid) showed one major neutral component plus two minor components, one negatively and one positively charged. From the structure of the peptide a net negative charge was expected at this pH. When the peptide was treated with mild aqueous base it showed the expected mobility (R_{Asp} 0.27). This agreed with the mobility of the natural peptide and correlated well with empirical charge–mobility relationship suggested by Offord.[28] Amino acid analyses of an acid hydrolysate gave correct ratios, but an enzymatic hydrolysate by leucine aminopeptidase was low in Asp, Thr, Gly, Pro, and Arg. It was concluded that the cleavage reaction in HF had given rise to the cyclic aspartoyl peptide which then opened in base to give a mixture of the α- and β-aspartyl nonapeptides.

In order to identify the residues responsible for the observed loss of negative charge in the nonapeptide it was resynthesized and small portions were removed after each coupling. The peptides were cleaved in HF and the net charge at pH 6.5 of the major component was determined by paper electrophoresis. The data in Table I indicate that the expected net charge was found for all peptides in the series until the first glutamic acid residue was added. This hexapeptide, and all subsequent peptides, contained one negative charge less than expected, suggesting a direct role for glutamic acid. Several synthetic model peptides (Table II) showed that neither H-Glu(OBzl)-Asp(OBzl)-R nor H-Glu(OBzl)-Asp(OBzl)-Gly-R produced appreciable amounts of the rearranged product, but that H-Glu(OBzl)-Asp(OBzl)-Gly-Thr(Bzl)-R did give rise to a major product

Table I. Observed and Expected Net Electrostatic Charge of Peptides at pH 6.5[a]

Peptide-resin precursor[b]	Net electrostatic charge[c] Observed	Expected
H-Pro-Arg(Tos)-R	+1	+1
H-Thr(Bzl)-Pro-Arg(Tos)-R	+1	+1
H-Gly-Thr(Bzl)-Pro-Arg(Tos)-R	+1	+1
H-Asp(OBzl)-Gly-Thr(Bzl)-Pro-Arg(Tos)-R	0	0
H-Glu(OBzl)—Asp(OBzl)-Gly-Thr(Bzl)-Pro-Arg(Tos)-R	0	−1
H-Leu-Glu(OBzl)—Asp(OBzl)-Gly-Thr(Bzl)-Pro-Arg(Tos)-R	0	−1
H-Glu(OBzl)-Leu-Glu(OBzl)—Asp(OBzl)-Gly-Thr(Bzl)-Pro-Arg(Tos)-R	−1	−2
H-Arg(Tos)-Glu(OBzl)-Leu-Glu(OBzl)—Asp(OBzl)-Gly-Thr(Bzl)-Pro-Arg(Tos)-R	0	−1

[a] Paper electrophoresis in pyridine–0.1 M acetic acid buffer, pH 6.5, 1500 V, 1 h. [b] All peptide resins had good amino acid analyses. The peptide resins were in the form of TFA salts. They were cleaved and deprotected in HF–10% anisole, 1 hr, 0 °C, before electrophoresis. The same results were obtained when the peptide resins were protected with N^{α}-Boc. [c] The net electrostatic charge E of the major ninhydrin-positive spot was determined from the observed mobility, m, the molecular weight M of the free peptide, and the charge–mobility relationship of Offord.[28]

Table II. Observed and Expected Net Electrostatic Charge of Peptides at pH 6.5[a]

Peptide-resin precursor	Net electrostatic charge Observed	Expected
H-Glu(OBzl)—Asp(OBzl)-R	−2	−2
H-Glu(OBzl)—Asp(OBzl)-Gly-R	−2	−2
H-Glu(OBzl)—Asp(OBzl)-Gly-Thr(Bzl)-R	−1	−2

[a] See Table I.

Table III. Observed and Expected Net Electrostatic Charge of Peptides at pH 6.5[a]

Peptide-resin precursor	Net electrostatic charge Observed	Expected
H-Gln-Asp(OBzl)-Gly-Thr(Bzl)-R	0	−1
H-Ala-Asp(OBzl)-Gly-Thr(Bzl)-R	0	−1
H-Ala-Asp(OBzl)-Gly-Ala-R	0	−1
H-Asp(OBzl)-Gly-R	−1	−1
H-Asp(OBzl)-Gly-Thr(Bzl)-R	−1	−1

[a] See Table I.

lacking one negative charge, suggesting that a lactone may have formed between the γ-carboxyl of glutamic acid and the hydroxyl of threonine during the HF treatment. However, there was no evidence of lactone formation by infrared spectroscopy or by chemical methods.[11] In addition, paper electrophoresis did not reveal detectable amounts of an N → O shift product. Further model peptides (Table III) then showed that neither the glutamyl nor threonyl residue was essential for the loss of negative charge, since the rearrangement still occurred when both residues were replaced by alanine as in H-Ala-Asp(OBzl)-Gly-Ala-R.

The data from the model peptides all supported the original expectation that the rearrangement involved imide formation at the Asp-Gly bond, with the restriction that both the amino and carboxyl termini of the dipeptide sequence must be in amide linkage for appreciable reaction to occur.

All of the model di- and tripeptides examined after HF cleavage and deprotection actually showed, in addition to the major component, small amounts of ninhydrin-positive material with the electrophoretic mobility expected for the

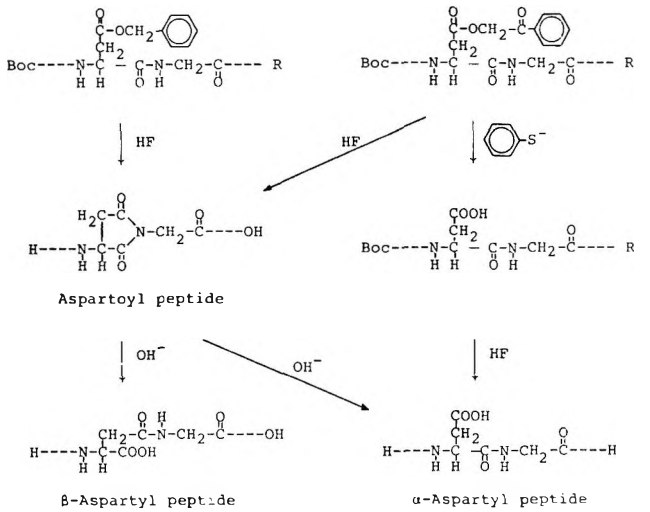


Figure 1. A strategy to minimize imide formation during solid-phase synthesis of aspartic acid containing peptides.

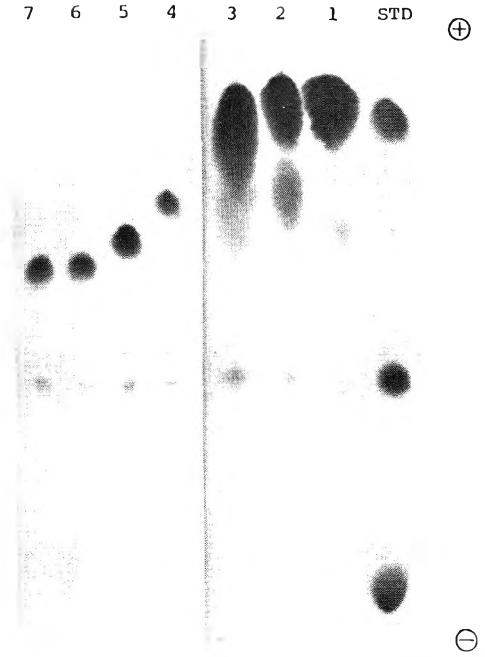


Figure 2. Preparative paper electrophoresis of peptides derived from HF treatment of protected peptide resins. Whatman 3MM paper, 1500 V, 90 min, in pyridine–0.2 M acetic acid, pH 6.5. Sample 1, H-Glu(OBzl)-Asp(OBzl-Gly-R; 2, H-Glu(OBzl)-Asp(OBzl)-Ser(Bzl)-R; 3, H-Glu(OBzl)-Asp(OBzl)-Ala-R; 4, H-Asp(OBzl)-Gly-R; 5, H-Asp(OBzl)-Gly-Thr(Bzl)-R; 6, H-Asp(OBzl)-la-Leu-R; 7, H-Asp(OBzl)-Ser(Bzl)-Leu-R; standard, Asp, Ala, Arg.

cyclic aspartoyl derivative (Figure 2). Preparative electrophoresis was used to quantitate the proportions of product. The peptides were eluted, hydrolyzed, and analyzed for amino acid content. The data of Table IV show again that the bulk of the product migrated in the position expected for the peptide containing a free aspartic acid carboxyl group (either α or β) but, depending on the size and composition of the peptide, 1–12% of a component was found in each sample that migrated in the position of the corresponding peptide with one less negative charge. Analysis showed the presence of each of the amino acids of the parent peptide. This is consistent with a cyclic aspartoyl derivative, but the quantitative number is a maximum value for imide since products derived from other side reactions or incomplete deprotection would not have been distinguished by this simple technique.

Evidence for the Cyclic Imide Structure. When the peptide resin H-Glu(OBzl)-Asp(OBzl)-Gly-Thr(Bzl)-R was cleaved in HF (0 °C, 1 h), the crude peptide showed the loss of one net negative charge (see Table II). The peptide was divided into two equal parts, one of which was treated for 24 h with 1% triethylamine in water and then lyophilized. KBr pellets were prepared and an infrared difference spectrum was measured, using the base-treated peptide as the reference and the untreated peptide as the sample (Figure 3). The sample showed absorption maxima at 1780 and 1710 cm^{-1} which are characteristic of succinimide derivatives.[14,29,30] The infrared spectrum of base-treated, open-chain peptide did not have peaks in this region; instead it absorbed at 1650 cm^{-1}. Both solutions of the peptide were put on an Aminex 50W-X4 cation exchange column and eluted with pyridine acetate buffer (0.1 M, pH 3.20). The base-treated peptide showed two peaks whereas the untreated peptide had only one major peak, which eluted much later from the cation exchange column. The three components were isolated and hydrolyzed and each was shown to contain equimolar amounts of all four amino acids. The above experiments support the conclusion that the side reaction of H-Glu(OBzl)-Asp(OBzl)-Gly-Thr(Bzl)-R in HF was the nucleophilic displacement of the β-benzyl ester of the aspartyl residue by the amide nitrogen of the Asp-Gly peptide bond to form an aspartimide ring. When the cyclized peptide was treated with aqueous base the imide ring was broken, the result being a mixture of α-aspartyl and β-aspartyl tetrapeptides, which could be resolved on the cation exchange column. The peptide that was not treated with base was still in the cyclic imide form and had one less negative charge and was eluted later. Two other tetrapeptides, Glu-Asp-Ala-Leu and Glu-Asp-Ser-Leu, behaved in a similar way.

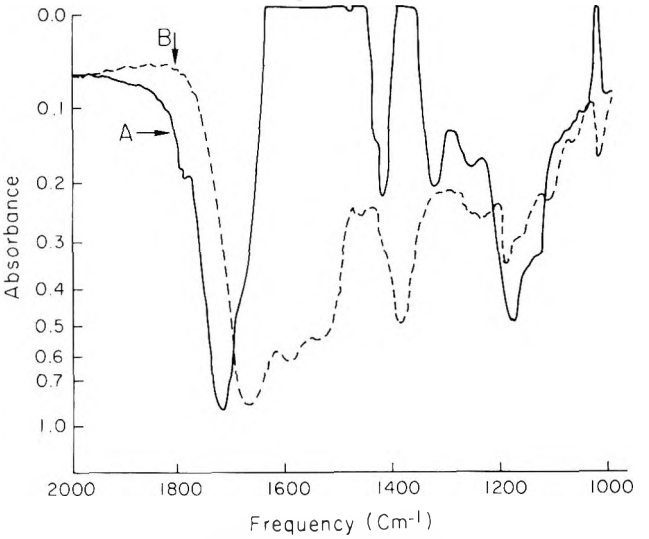


Figure 3. Infrared spectra of aspartyl and aspartoyl tetrapeptides. Curve A (solid line): the difference spectrum with the aspartoyl derivative, H-Glu-Asp-Gly-Thr-OH, in the sample cell and a mixture of α- and β-aspartyl peptides, H-Glu-Asp-Gly-Thr-OH, in the reference cell. Curve B (dashed line): the spectrum of a mixture of α- and β-aspartyl peptides, H-Glu-Asp-Gly-Thr-OH.

The identification of the α-aspartyl and β-aspartyl tetrapeptides was accomplished by enzyme digestion and by comparison with the synthetic α- and β-peptides. Since the β-peptide bond is known to resist leucine aminopeptidase and aminopeptidase M digestions[31,11] any residue C-terminal to the β-peptide bond should be released in much lower yield. The α-aspartyl peptide should be hydrolyzed by both enzymes without difficulty. The results presented in Table V indicate that, for each tetrapeptide, the second peak to be eluted from the ion exchange column by pH 3.20 pyri-

Table IV. Relative Amounts of Aspartyl and Aspartoyl Peptides Following Treatment of Peptide Resins with HF[a]

Peptide resin	Aspartyl peptide, %	Aspartoyl peptide, %
OBzl H-Asp—Gly-R	98.6	1.4
OBzl OBzl H-Glu—Asp—Gly-R	96.6	3.4
OBzl Bzl H-Asp—Gly—Thr-R	98.4	1.6
OBzl OBzl H-Glu—Asp—Ala-R	92.2	7.8
OBzl OBzl Bzl H-Glu—Asp—Ser-R	88.1	11.9
OBzl H-Asp—Ala—Leu-R	95.9	4.1
OBzl Bzl H-Asp—Ser—Leu-R	96.7	3.3

[a] Estimated by amino acid analysis of peptides separated by paper electrophoresis. See Experimental Section.

A standard tetrapeptide, containing only an α-aspartyl bond, was obtained by carrying out the reactions described in Figure 4. The corresponding standard tetrapeptide con-

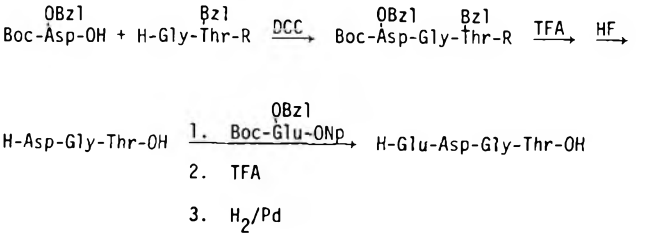


Figure 4. Synthesis of standard H-Glu-Asp-Gly-Thr-OH.

taining only a β-aspartyl bond was prepared from Boc-Asp-OBzl in exactly the same way. Only trace amounts of aspartyl peptide formation (see Table IV) were observed in the synthesis of the tripeptide intermediates. They were removed by preparative paper electrophoresis at pH 6.5. Finally, the glutamyl residue was coupled to the two tripeptides by active ester reaction[32] and the protecting groups were removed with trifluoroacetic acid and catalytic hydrogenolysis.

The two tetrapeptides isolated from the alkaline treatment of the cyclic, aspartoyl tetrapeptide were then identified by comparing their elution times on the long column of the amino acid analyzer (Table VI) with those of the standard α- and β-peptides. This identification agreed with that from the enzymatic digestions.

Table V. Amino Acid Analyses of Enzymatic Hydrolysates of Chromatographically Separated α- and β-Aspartyl Tetrapeptides

	Asp link[a]	H-Glu-Asp-Gly-Thr-OH				H-Glu-Asp-Ala-Leu-OH				H-Glu-Asp-Ser-Leu-OH			
Leucine-aminopeptidase[b]	α	1.0	0.84	0.88	0.97	1.0	1.10	0.95	1.04	1.0	1.06	0.87	1.06
	β	1.0	0.30	0.30	0.31	1.0	0.33	0.36	0.46	1.0	0.35	0.31	0.39
Aminopeptidase M[b]	α	1.0	0.95	1.04	0.90	1.0	0.96	0.99	1.07	1.0	0.89	0.76	1.01
	β	1.0	0.13	0.10	0.22	1.0	0.20	0.14	0.36	1.0	0.19	0.15	0.32

[a] The carboxyl group of aspartic acid that was in peptide linkage was determined by comparing the elution time from the chromatographic column with that of standard tetrapeptides of known structure. [b] The conditions are given in the Experimental Section. These amino acid analyses are for the 24-h digestion time.

dine acetate was completely digested in 24 h to essentially equimolar amounts of each amino acid, whereas the first peak was only 10–30% digested at the aspartyl–X bond. It was concluded that the first peak contained the β-aspartyl peptide. For this analysis 24-h digestion was near optimal, since after 12-h digestion the α-aspartyl peptides were incompletely hydrolyzed, while at 36 h the β-aspartyl bonds were extensively hydrolyzed.

The ion exchange column of the amino acid analyzer using sodium citrate buffers gave a sharp separation of the α, β, and imide forms of these tetrapeptides (Table VI) and allowed an accurate, quantitative determination of the distribution of peptides resulting from the HF cleavage reaction on the three model tetrapeptides (Table VII). Boc-Glu(OBzl)-Asp(OBzl)-Gly-Thr(Bzl)-Resin produced 99% of the aspartoyl tetrapeptide (imide) after 1 h at 0 °C in HF–10% anisole, while Boc-Glu(OBzl)-Asp(OBzl)-Ser-(Bzl)-Leu-Resin and Boc-Glu(OBzl)-Asp(OBzl)-Ala-Leu-Resin each gave 25% imide. The remainder was the α-aspartyl peptide, and no β-aspartyl peptide was detectable. The proportions of the isomers produced by opening the ring of the aspartoyl tetrapeptides at alkaline pH (aqueous triethylamine) was also quantitated (Table VII). Under these conditions, the β-aspartyl isomer predominated and ranged from 71% to 80% of the total.

Table VI. Chromatographic Separation of the Model Tetrapeptides

Peptide	Elution time, min[a]		
	β-Peptide	α-Peptide	Imide
Glu-Asp-Gly-Thr	54	70	116
Glu-Asp-Ala-Leu	102	130	139
Glu-Asp-Ser-Leu	97	131	157

[a] Separations were made on a Beckman Automatic Amino Acid Analyzer (Model 121, long column, 55 cm). Starting buffer was Durrum Pico A for 100 min (pH 3.25, 0.2 N Na^+) followed by Beckman buffer (pH 4.25, 0.2 N sodium citrate). Flow rate for both buffers was 66 ml/h. Column was maintained at 55 °C.

The Use of β-Phenacyl Aspartate to Avoid the Rearrangement. In order to test the proposal that temporary protection of the aspartyl residue by a β-phenacyl ester, followed by deprotection with sodium thiophenoxide before cleavage with HF, would avoid the formation of cyclic imide by-products, it was necessary to synthesize β-phenacyl N^{α}-*tert*-butyloxycarbonyl-L-aspartate, Boc-Asp(OPac)-OH. The compound was first prepared by a multistep series of reactions starting with the well-characterized β-ben-

Table VII. Distribution of Tetrapeptides[a]

Peptide	Peptides after HF cleavage, %						Peptides in Et_3N hydrolysate of imide, %		
	β-Benzyl-Asp peptide			β-Phenacyl-Asp peptide[b]					
	α	β	Imide	α	β	Imide	α	β	Imide
Glu-Asp-Gly-Thr	1	0	99	97.6	0	2.4	29	71	0
Glu-Asp-Ala-Leu	75	0	25	95.8	0	4.2	26	74	0
Glu-Asp-Ser-Leu	75	0	25	90.5	0	9.5	20	80	0

[a] Using the ion exchange column described in Table VI. [b] The phenacyl ester group was removed in sodium thiophenoxide prior to HF cleavage.

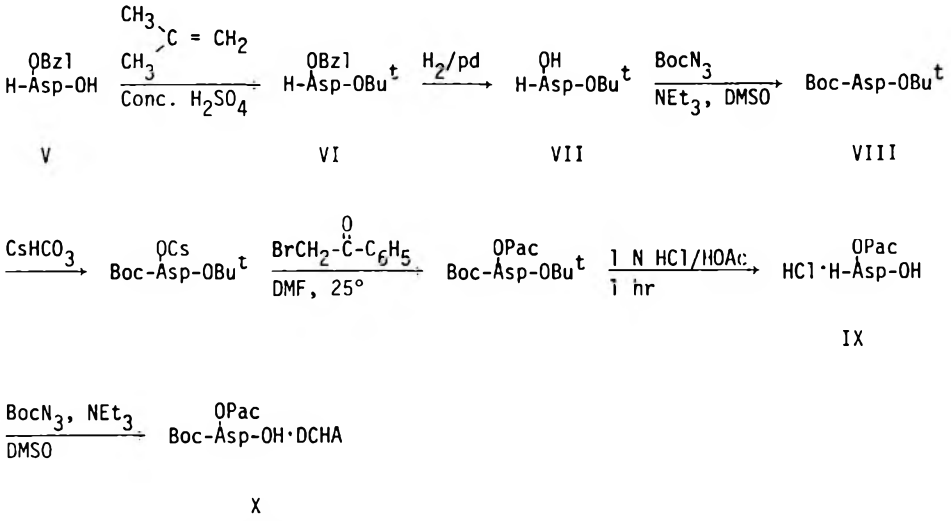


Figure 5. Synthesis of β-phenacyl N^{α}-*tert*-butyloxycarbonyl-L-aspartate.

zyl L-aspartate[33,34] as shown in Figure 5. The Boc-Asp(OPac)-OH intermediate could also be prepared by a shorter route via lithium copper L-aspartate using the general method of Ledger and Stewart.[21] The phenacyl group was stable to 50% trifluoroacetic acid in methylene chloride and to HF (0 °C, 1 h), but was readily cleaved by nucleophiles such as 1 M sodium thiophenoxide in DMF, with virtually complete retention of the optical purity of the aspartic acid. The rate of removal of the phenacyl ester from Boc-Asp(OPac)-OH by 30 equiv of 1 M sodium thiophenoxide in DMF at 25 °C was followed by withdrawing aliquots at various times, removing the Boc group with TFA, and measuring quantitatively on the amino acid analyzer both the aspartic acid formed and the Asp(OPac) remaining. The latter appeared as a somewhat broadened peak at 259 min in a standard analytical run in which the leucine peak was at 202 min. The operational color factor was 0.35 relative to aspartic acid. The first-order rate constant was found to be 1.0×10^{-3} s^{-1}, corresponding to a half-time of approximately 11 min (Figure 6).

The tetrapeptide resin, H-Glu(OBzl)-Asp(OPac)-Gly-Thr(Bzl)-R, was synthesized by standard solid-phase methods as before, but with the use of the new β-phenacyl N^{α}-*tert*-butyloxycarbonyl-L-aspartate. The phenacyl group was removed with sodium thiophenoxide (1 M in DMF, 25 °C, 8 h) and the resulting peptide resin, containing a free β-carboxyl group, was then cleaved and fully deprotected by treatment with HF–10% anisole (0 °C, 0.5 h). The crude tetrapeptide prepared in this way contained only 2.4% of the cyclized peptide, no β-peptide, and 97.6% of the α-peptide (Table VII). This result confirmed the validity of this experimental strategy and showed that the phenacyl ester is a suitable temporary protecting group for the β-carboxyl of aspartic acid to minimize the undesired cyclic imide formation.

This procedure also reduced the acid-catalyzed formation of imide in tetrapeptides containing -Asp-Ser- and -Asp-Ala- sequences, but the side reaction was not suppressed to the same extent as in the -Asp-Gly- peptide (Table VII). A more detailed study of the reaction conditions will be necessary before the limits of imide formation can be defined.

Discussion

The results of this study support and extend the information on the now well-established acid-catalyzed side reaction of peptides containing aspartic acid esters that leads to cyclic imides. The rate of the reaction depends on several factors. It proceeds rapidly in the cold in strong anhydrous acids such as HBr in trifluoroacetic acid[13,14] or HF[10] but slowly in trifluoroacetic acid or acetic acid. However, at elevated temperatures it has been observed in acetic acid and even in ethanol[14] or water.[8,9] Under the usual solid-phase synthetic conditions imide formation is a major side reaction only when the β-carboxyl of the aspartyl residue is present as an ester; the free carboxylic acid is much less reactive.[13,14,35] Even when the β-carboxyl is esterified the cyclization to imide does not always occur.

There is clearly a dependence of aspartimide formation on sequence, although this factor has not been extensively examined in any single study. There are certain generalities for which there is agreement, but there are specific examples in which differing conclusions have been drawn by various laboratories. The differences probably can be attributed to variations in time, temperature, reagents, methods of detection, and particularly in the structure surrounding the -Asp-X- sequence. The first study on the possibility of imide formation during solid-phase synthesis[11] showed that Boc-Leu-Asp(OBzl)-Ala-Val-Resin did not lead to detectable levels of imide and that none was produced from

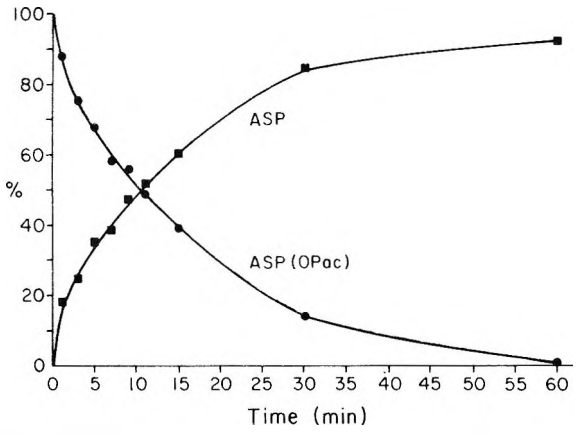


Figure 6. The rate of removal of the β-phenacyl ester from Boc-Asp(OPac)-OH by 1 M sodium thiophenoxide. Sodium thiophenoxide (264 mg, 2.00 mmol) was dissolved in 1.50 ml of dry DMF, added to 21.7 mg (0.062 mmol) of Boc-Asp(OPac)-OH in 0.50 ml of DMF, and stirred at 25 °C. At intervals, 50-μl aliquots were mixed with 150 μl of TFA and after 30 min were diluted with 1.50 ml of pH 2.2 citrate buffer. The concentrations of Asp and Asp(OPac) were determined quantitatively on the amino acid analyzer.

H-Asp(OBzl)-Arg(NO_2)-Val-Tyr(Bzl)-Val-His(Bzl)-Pro-Phe-Resin during the synthesis of angiotensin II. It was concluded from these two examples that this did not appear to be a major side reaction in solid-phase synthesis. However, other peptides were soon found in which the reaction did occur. The -Asp-Ser- sequence of Boc-Gly-Asp(OBzl)-Ser(Bzl)-Gly-Resin was found to be partially cyclized in 1 h at 25 °C by HBr-TFA.[13] The resulting aspartoyl peptide was then converted by alkali to a mixture of the α- and β-aspartyl tetrapeptides. The Ser(Bzl)-containing tetrapeptide, H-Glu(OBzl)-Asp(OBzl)-Ser(Bzl)-Leu-Resin, studied here was found to give 25% of imide after 1 h at 0 °C in HF and Baba et al.[16] obtained a similar result with Z-Asp(OBzl)-Ser(Bzl)-OCH_3 in HF, but in other peptides the -Asp(OBzl)-Ser(Bzl)- sequence was reported to be stable to cyclization.[14] The -Asp-Gly- sequence in Boc-His(Bzl)-Ser(Bzl)-Asp(OBzl)-Gly-Thr(Bzl)-Phe-Resin was very susceptible to aspartimide formation during treatment with HBr–TFA,[14] and in the present work 99% of the product isolated after HF treatment of H-Glu(OBzl)Asp(OBzl)-Gly-Thr(Bzl)-Resin was the imide. Z-Asp(OBzl)-Gly-OBzl also cyclized in HF,[16] but Kenner showed that Asp(OBu^t)-Gly did not cyclize in TFA.[36]

In general, the resistance to cyclization is correlated with the size of the residue following aspartic acid. Whereas glycine peptides were sensitive, alanine peptides were resistant in HBr[11] but cyclized in HF,[16,37,38] while valine peptides were quite stable in HF.[39] Histidine represents one notable exception. Z-Asp(OBzl)-His-OCH_3[16] was extensively cyclized during HF treatment even at −25 °C in spite of its bulky side chain, suggesting that electronic effects also play a role in this rearrangement.

The present work has brought to light another parameter which had not been recognized before. For an appreciable aspartimide formation to occur both the amino group and the terminal carboxyl group of the -Asp-X-sequence must be blocked. Thus, none of the following peptides were significantly cyclized in 1 h at 0 °C by HF: Glu-Asp, Glu-Asp-Gly, Asp-Gly, Asp-Gly-Thr, Asp-Gly-Thr-Pro-Arg, Asp-Ala-Leu, Asp-Ser-Leu. However, the addition of a single residue at each exposed end of the -Asp-X- sequence led to a susceptible peptide, as in Glu-Asp-Gly-Thr, Ala-Asp-Gly-Thr, Ala-Asp-Gly-Ala, Glu-Asp-Ala-Leu, or Glu-Asp-Ser-Leu. The previously observed[11] stability of Asp-Ala-Val and angiotensin II may, therefore, have been a consequence of the N-terminal position of the Asp(OBzl) residue rather than of a general resistance of the -Asp(OBzl)-Ala- or -Asp(OBzl)-Arg(NO_2)- sequences. The data of Baba et al.[16] are interesting in this regard because they show rearrangement in the series of dipeptides: Z-Asp(OBzl)-Gly-OBzl, Z-Asp(OBzl)-Ser(Bzl)-OCH_3, Z-Asp(OBzl)-His-OCH_3, and Z-Asp(OBzl)-Ala-OBzl. These results and ours are compatible if we make two reasonable assumptions: first, that the intramolecular imide formation was rapid compared with acidolytic cleavage of the benzyloxycarbonyl group, in which case their Z group would have prevented protonation of the α-amino group and could have performed the same function as our Glu or Ala residues; and second, that their methyl and benzyl esters were more stable to HF than our oxymethylpolystyrene esters and the rate of imide formation falls between the rate of acidolysis of unsubstituted and substituted benzyl esters. Since the resin ester is an alkyl-substituted benzyl ester it is expected to be more labile to acid. If the resulting C-terminal carboxyl becomes protonated, the nitrogen of the aspartyl peptide bond would become less nucleophilic, and the rate of imide formation would be diminished. The values recorded in Table IV for the extent of imide formation in the di- and tripeptides must be considered as upper limits because in this simple electrophoresis experiment the structures of the products were not actually determined. Other factors could have caused loss of a negative charge or generation of an additional positive charge (e.g., incomplete deprotection or N → O shifts) and have led to an overestimation of imide. In contrast, the quantitative measure of the aspartoyl tetrapeptides by column chromatography is quite reliable.

The reaction mechanism of cyclic imide formation suggested by Ondetti et al.[14] is probably the correct one. It involves protonation of the β-carbonyl oxygen and elimination of $^-$OR or $^-$OH by nucleophilic attack of the aspartyl amide nitrogen. The overall rate will depend on both steric and electronic effects which in turn depend on the nature of the side chain of the adjacent residue and on the presence or absence of charges at either end of the -Asp-X- sequence. Acylation of anisole via the acylium ion, which had been observed for glutamyl peptides,[38] was not observed for aspartyl peptides in either the previous or present study.

The new approach which we have taken to avoid aspartimide formation depends on the observation[13,14,35] that the acid-catalyzed cyclization reaction was greatly retarded when the β-carboxyl group of the aspartyl residue was free. The incorporation of this idea into a suitable synthetic scheme requires the use of a temporary protecting group for aspartic acid that can be removed selectively before exposure to strong acid. The β-phenacyl ester is suitable for that purpose. It can be used in combination with N^{α}-Boc protection and is quite stable to the conditions of the synthesis. Since phenacyl esters are labile to strong nucleophiles[18] it might be expected that aminolysis by the amino group of a nearby peptide chain could occur at the neutralization step of the synthesis. If this intrachain aminolysis were to occur with alkyl oxygen cleavage, as it does with the strongly nucleophilic sodium thiophenoxide, the products would be the free β-carboxylate and the phenacyl amine; if acyl oxygen cleavage were to occur a crosslinked β-amide would be formed. In either case the reaction would result in a chain termination. The relatively limited number of experiments which have been examined have shown no indication that either of these cleavages has occurred. Stalakatos et al.[19] showed phenacyl esters to be stable to 3.5 N HBr in HOAc and to refluxing TFA, and we also find that β-phenacyl L-aspartate is stable to cleavage by TFA or HF

(0 °C, at least 1 h). However, β-phenacyl aspartyl peptides are readily cyclized to aspartimides in strong anhydrous acids and the phenacyl group must be removed before the HF cleavage step. The deprotection of the phenacyl ester at the end of the synthesis proceeded smoothly and quantitatively ($T_{1/2}$ = 11 min) under the conditions described by Sheehan and Daves.[18] Stalakatos et al.[19] obtained an 80% yield of Z-Gly from Z-Gly-OPac in 30 min at 25°. Thiophenoxide is a strong nucleophile although it is only a weak base, and in these very mild conditions both the benzyl ester and β-lactam of benzyl benzylpencillinate were essentially stable at 5 °C for 18 h.[18] Only 5.6% of the peptide was removed from Boc-Glu(OBzl)-Asp(OPac)-Ser(Bzl)-Val-resin in 24 h at 25 °C by 1 M sodium thiophenoxide in DMF. Shigezane and Mizoguchi[24] synthesized Boc-Leu-Leu-Val-Tyr(Bzl)-resin on an oxyacetyl-resin and cleaved the anchoring phenacyl ester bond with 1 M sodium thiophenoxide in DMF for 24 h at room temperature without noticeable side reaction; the Leu-Leu-Val-Tyr-OEt·HCl which was derived from the product was shown to have the same specific rotation and other properties as a sample synthesized by conventional methods. Nevertheless, it was important to consider the possibility that small amounts of racemization might occur under these conditions. Boc-L-Asp(OPac)-OH was, therefore, deprotected first with TFA and then with 1 M sodium thiophenoxide and the optical purity of the resulting aspartic acid was estimated by the Manning–Moore method.[40] The Leu-Asp diastereomers were present in a ratio of 0.994 LL and 0.006 LD, indicating virtually complete retention of optical purity throughout the eight steps of synthesis and two steps of deprotection.

The usefulness of the β-phenacyl ester method to minimize aspartimide formation was tested by the synthesis of three tetrapeptides. In the case of Boc-Glu(OBzl)-Asp(OPac)-Gly-Thr(Bzl)-Resin the tetrapeptide recovered after deprotection of the phenacyl ester by thiophenoxide and cleavage with HF–10% anisole contained 97.6% of the α-aspartyl peptide, no β-aspartyl peptide, and only 2.4% of the cyclic aspartoyl peptide. This represented a 40-fold decrease in the by-product compared with that obtained when the aspartyl residue was protected with a β-benzyl ester and cleaved directly with HF–anisole. Although the side reaction was not reduced to zero, we consider this to be a very useful result. With the corresponding tetrapeptides containing Ala and Ser(Bzl) in place of Gly, 4.2 and 9.5%, respectively, of aspartoyl peptides were found. It is possible that some imide formation had already occurred before the HF reaction and that these values did not arise from treatment of the peptide containing a free β-carboxyl, although we assume that they did because the isolated H-Glu-Asp-Ala-Leu-OH tetrapeptide (containing a free β-carboxyl and no imide) also yielded 4% of the aspartoyl peptide upon treatment with HF–anisole. In view of the results of Baba et al.[16] it seems probable that a more detailed study of the HF reaction conditions, especially the temperature, may lead to a further reduction of this side reaction. Based on the results reported here we have adopted this phenacyl ester approach for the solid-phase synthesis of peptides that are susceptible to aspartimide formation.

Experimental Section

Sodium thiophenoxide was prepared according to Sheehan and Daves[18] and was recrystallized from DMF by the addition of ether. Methylene chloride was distilled over sodium carbonate; pyridine and triethylamine were distilled over ninhydrin. All other reagents were obtained commercially and used without further purification. Leucine aminopeptidase was purchased from Worthington Biochemical Corp., Freehold, N.J., α-*p*-nitrophenyl γ-benzyl N^{α}-*tert*-butyloxycarbonyl-L-glutamate from Cyclo Chemical Corp., and α-benzyl L-aspartate from Fox Chemical Co., Los Angeles, Calif. All melting points are uncorrected. Amino acid analyses[41] were performed on the Beckman Automatic Amino Acid Analyzer, Model 121. Resin hydrolyzates were carried out in evacuated sealed tubes on 10–20-mg samples of peptide resins with concentrated HCl, glacial acetic acid, and phenol (88%) (2:1:1) at 110 °C for 22–24 h. Peptide hydrolyzates were in 6 N HCl containing a few drops of phenol under similar conditions. Thin layer chromatography was carried out on silica gel G with the solvent system I (CMA), chloroform–methanol–acetic acid (85:10:5), and solvent system II (BAW), 1-butanol–acetic acid–water (4:1:1). Electrophoretic mobilities are expressed as fractions, R_{Asp} or R_{Arg}, of the distances traveled by aspartic acid or arginine in the same electropherograms, with the center of a neutral amino acid spot taken as the point of zero mobility.

Preparative Paper Electrophoresis. Electrophoresis was carried out in a cold room on Whatman 3MM chromatography paper in pyridine acetate buffer, pH 6.5 (0.1 M in acetic acid), at 1500 V for 90 min. Peptides (1–5 mg) were applied on a line at the center of paper. Following electrophoretic separation, these peptides were located by cutting small strips from both edges of the paper and developed with ninhydrin spray. Corresponding portions of the moist undeveloped paper were cut and eluted with 50 ml of the same buffer. The eluates were lyophilized and the residues were carefully extracted three times (1 ml each) with 6 N HCl containing one drop of phenol. The extracts were hydrolyzed and analyzed for amino acid content.

Synthesis of Model Peptides. Boc-Glu(OBzl)-Asp(OBzl)-Gly-Thr(Bzl)-Resin (I). All of the model peptides were synthesized by a standard solid-phase procedure similar to those described earlier.[11,25-27] N^{α}-*tert*-Butyloxycarbonyl-*O*-benzyl-L-threonine-copoly(styrene–1%-divinylbenzene)resin (0.20 mmol Thr/g) was deprotected with 20% TFA in CH_2Cl_2 for 20 min at 25 °C. The resin was filtered, washed four times with CH_2Cl_2, neutralized with 10% Et_3N in CH_2Cl_2 for 10 min, and washed four times with CH_2Cl_2. A threefold excess of Boc-Gly in CH_2Cl_2 was added, followed by a threefold excess of DCC in just enough CH_2Cl_2 to cover the resin. The reaction vessel was shaken for 90 min. The resin was filtered and washed three times each with CH_2Cl_2, DMF, and CH_2Cl_2, once with 10% Et_3N, and three times with CH_2Cl_2. A second coupling with 1 equiv of Boc-Gly and DCC was carried out as before. β-Benzyl N^{α}-Boc-L-aspartate and γ-benzyl N^{α}-Boc-L-glutamate were added by repetitions of the deprotection, neutralization, and double coupling cycle.

Isolation of L-Glutamyl-L-aspartoylglycyl-L-threonine (II). Boc-Glu(OBzl)-Asp(OBzl)-Gly-Thr(Bzl)-Resin (200 mg) was stirred for 1 hr at 0 °C in 10 ml of HF containing 1 ml of anisole. The HF and most of the anisole were removed by vacuum and the residual anisole and derivatives were extracted with ether. The peptide was extracted with 10% aqueous acetic acid and lyophilized. The amino acid analysis of a hydrolysate of the crude peptide gave the following molar ratios: Asp (1.00), Thr (1.05), Glu (1.01), Gly (1.06). Paper electrophoresis at pH 6.5 (pyridine–0.1 M acetic acid) showed a major spot at R_{Asp} 0.49. The crude peptide (10 mg) was put on a preparative cation exchange column (Aminex 50W-X4, 40 × 2.5 cm), and was eluted at 60 ml/h with pyridine acetate buffer (pH 3.20, 0.1 M in acetic acid). The column was maintained at 40 °C by water jacket. The eluate from the column was divided into two streams, with a ratio of 90:10%. The 90% stream was directed to a fraction collector (3 min per fraction) and the other stream went into the coil of the amino acid analyzer to react with ninhydrin. Ninhydrin-positive tubes 114–125 were pooled, concentrated in vacuo, and lyophilized to give 7.5 mg of the aspartoyl derivative of the tetrapeptide, H-Glu-Asp-Gly-Thr-OH. The amino acid analysis of an acid hydrolysate of this cyclized peptide gave the following molar ratios: Asp (1.00), Thr (0.95), Glu (1.02), Gly (1.04).

Alkaline Hydrolysis of the Imide-Containing Tetrapeptide II and Isolation of H-Glu-α-Asp-Gly-Thr-OH (III) and H-Glu-β-Asp-Gly-Thr-OH (IV). Peptide II (4 mg) was dissolved in water (1 ml), and the solution was made alkaline (pH 8–9) by dropwise addition of triethylamine and stirred at room temperature overnight. Water (3 ml) was added to the reaction mixture and the soluon was frozen and lyophilized. The resulting material was put on a preparative cation exchange column to separate the α- and β-peptides. The experimental conditions used in α- and β-peptide separations were essentially the same as those used for the isolation of the aspartoyl derivative (II), as described in the previous paragraph. There were two well-separated ninhydrin-positive peaks which appeared on the recorder at 138 and 198 min. The test

tubes in the fraction collector corresponding to these two peaks were lyophilized. The first peak eluted was shown to be H-Glu-β-Asp-Gly-Thr-OH (IV) and the second was shown to be H-Glu-α-Asp-Gly-Thr-OH (III). The quantities of the β- and α-peptides were 2.8 (71%) and 1.2 mg (29%), respectively, as determined both by integration of the peaks and by the amino acid analyses of the lyophilized peptides. Both peptides III and IV gave essentially identical amino acid analyses and moved together (R_{Asp} 0.19) on paper electrophoresis at pH 6.5 (pyridine–0.1 M acetic acid), but on the long column of amino acid analyzer they were separated into two peaks 16 min apart (see Table VI).

Enzymatic Digestions. The leucine aminopeptidase digestion was carried out as described by Hofmann et al.[42] with small modifications. The peptide (1 mg) was dissolved in 0.025 M, pH 8.5 Tris buffer (0.5 ml), 0.005 M with respect to magnesium chloride, and the pH was readjusted to 8.5 with solid Tris. Leucine aminopeptidase (0.1 mg) in 0.5 ml of 0.1 M Tris buffer, pH 8.5, 0.005 M with respect to magnesium chloride, was preincubated for 3 h at 40 °C, then added to the peptide and the digest was incubated at 40 °C. Aliquots of the digest were withdrawn after 6, 12, 24, and 36 h; digestion was stopped by dilution with 1 N acetic acid (3 ml) and then the samples were lyophilized and analyzed for amino acids. Aminopeptidase M digestion was performed by mixing 0.1 ml of enzyme solution (4 mg in 1 ml of 0.5% NH_4HCO_3) and 0.1 ml of peptide solution (1 mg in 1 ml of 0.5% NH_4HCO_3) and incubating the mixture at 37 °C. Aliquots were withdrawn after 6, 12, 24, and 36 h, lyophilized, and analyzed for the amino acids. Some of the data are given in Table V.

Synthesis of Standard Tetrapeptides. H-Glu-β-Asp-Gly-Thr-OH (IV). The synthesis of the peptide was accomplished by the combination of solid-phase and solution reactions shown in Figure 4. The tripeptide resin, H-β-Asp-Gly-Thr-R (100 mg, 0.25 mmol peptide/g resin) was synthesized by the same procedure as for peptide I but with the use of α-benzyl N^{α}-Boc-L-aspartate for the aspartyl residue. The peptide resin was treated with HF (2 ml) at 0 °C for 1 h with anisole (0.2 ml) as scavenger. After the HF and anisole were removed, the resulting tripeptide was put on paper electrophoresis at pH 6.5 (pyridine–0.1 M acetic acid). The electropherogram showed a major spot with R_{Asp} 0.6 and a neutral spot. The crude peptide (7 mg) was purified by preparative electrophoreses at pH 6.5 using pyridine–0.1 *M* acetic acid as buffer (see preparative electrophoresis in this section). The purified tripeptide was isolated (5 mg). This peptide gave a good amino acid analysis, and was homogeneous on paper electrophoresis at pH 6.5 (R_{Asp} 0.61). This mobility value agreed with the prediction for the tripeptide carrying a negative charge. The crude tripeptide (4 mg, 13 μmol) was dissolved in DMF (4 ml) mixed with α-*p*-nitrophenyl γ-benzyl N^{α}-*tert*-butyloxycarbonyl-L-glutamate (23.9 mg, 52 μmol) and triethylamine (13 μmol in 1 ml of DMF). The ensuing yellowish solution was left at room temperature for 24 h. The solvent was removed under high vacuum and the resulting oily material was treated with TFA (3 ml) for 30 min. The TFA was removed by a water aspirator. The residue was then dissolved in 2 ml of a mixed solvent (water–methanol–acetic acid, 4:2:1) and 5 mg of 5% palladium on barium sulfate was added. The mixture was shaken under hydrogen (40 psi) for 12 h. After hydrogenolysis was completed and the catalyst was filtered off, the solution was diluted with water and was lyophilized. The product was purified on the preparative cation exchange column as described in the isolation of the aspartoyl derivative, II. The desired β-aspartyl tetrapeptide IV (3.3 mg, 58%) eluted at 139 min. An acid hydrolyzate gave good amino acid ratios.

The corresponding α-aspartyl standard, H-Glu-α-Asp-Gly-Thr-OH (III), was synthesized in the same way except that the aspartic acid residue was introduced as β-benzyl N^{α}-Boc-L-aspartate. This tetrapeptide eluted at 197 min on the ion exchange column. The other two pairs of standards, H-Glu-β-Asp-Ala-Leu-OH, H-Glu-α-Asp-Ala-Leu-OH, H-Glu-β-Asp-Ser-Leu-OH, and H-Glu-α-Asp-Ser-Leu-OH, were prepared by these same general procedures. Their elution times are shown in Table VI.

β-Benzyl L-Aspartate (V). The synthesis of compound V was carried out as described by Benoiton:[33] yield 22 g (51%); mp 218–220 °C; $[\alpha]^{25}D$ +28.4° (c 1, 1 N HCl) [lit.[33] mp 218–220 °C; $[\alpha]^{20}D$ +28.1° (c 1, 1 N HCl); lit.[34] mp 212 °C; $[\alpha]^{20}D$ +28.6° (c 1, 1 N HCl)]. The product showed a single spot on TLC in solvent mixture I (CMA), R_f 0.12; on paper electrophoresis at pH 2.3 (1 N acetic acid, 75 min, 1000 V) it had the same mobility, R_{Arg} 0.30, as the authentic β-benzyl L-aspartate (obtained from Fox Chemical Co.).

Anal. Calcd for $C_{11}H_{13}O_4N$: C, 59.18; H, 5.58; N, 6.28. Found: C, 59.44; H, 5.88; N. 6.28.

α-*tert*-Butyl-β-benzyl L-Aspartate Hydrochloride (VI). Isobutene (110 ml) was added to a solution of 12 g (0.052 mol of β-benzyl L-aspartate V in a mixture of 100 ml of dioxane and 10 ml of concentrated sulfuric acid in a 500-ml pressure bottle. The mixture was mechanically shaken at room temperature for 4 h. The solution was poured immediately into a cold mixture of 400 ml of 1 N sodium hydroxide, and the aqueous phase was extracted three times with ether. The combined organic phase was dried over sodium sulfate and evaporated under vacuum to about 5 ml. After the addition of 50 ml of ether, dry hydrogen chloride was bubbled through the solution and crystalline compound VI started to precipitate. Recrystallization from ethyl alcohol gave 11 g (67%): mp 115–117 °C (lit.[43] 115–117 °C); $[\alpha]^{25}D$ +23.1° (c 1, EtOH). The product was homogeneous on TLC in solvent mixture I (CMA) (R_f 0.6).

Anal. Calcd for $C_{15}H_{22}NO_4Cl$: C, 57.05; H, 7.02; N, 4.44; Cl, 11.23. Found: C, 57.09; H, 6.88; N, 4.34; Cl, 11.02.

α-*tert*-Butyl L-Aspartate VII. A suspension of α-*tert*-butyl-β-benzyl L-aspartate hydrochloride (VI, 10 g) in 200 ml of ether was treated with 40 ml of 25% potassium carbonate solution, the liberated ester was immediately extracted into ether, and the aqueous solution was washed again with 50 ml of ether. The ether was dried over sodium sulfate and evaporated in vacuo. The oily residue was dissolved in 95% ethanol (125 ml), 1 g of 5% palladium on barium sulfate was added, and the bottle was shaken under hydrogen (50 psi) overnight. After hydrogenolysis was completed, the catalyst was filtered off and the solution was concentrated to 50 ml. When 400 ml of acetone was added, a gel formed which changed to a crystalline precipitate on stirring. The yield was 4.5 g (75%); mp 178–179 °C dec; $[\alpha]^{25}D$ +24.9° (c 1, CH_3COOH).

Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.43, H, 7.81; N, 7.33.

α-*tert*-Butyl N^{α}-*tert*-Butyloxycarbonyl-L-aspartate (VIII). α-*tert*-Butyl L-aspartate (VII, 4.5 g) was dissolved in 30 ml of dimethyl sulfoxide (redistilled over NaOH pellets), followed by *tert*-butyl azidoformate (4 ml) and triethylamine (6.5 ml). The mixture was stirred for 20 h at room temperature. The solution was diluted with three volumes of water and extracted three times with ether to remove any unreacted *tert*-butyl azidoformate. The aqueous phase was chilled in an ice bath, acidified with citric acid to pH 3.5, and extracted three times with ethyl acetate. The ethyl acetate was extracted three times with small portions of a saturated sodium chloride solution, dried over magnesium sulfate, and evaporated under reduced pressure. The residual oily material was recrystallized from ethyl acetate–hexane: yield 6.5 g (94%); mp 97–98 °C; $[\alpha]^{25}D$ −14° (c 1, C_2H_5OH). The resulting material was homogeneous on TLC in solvent system I (CMA), R_f 0.83, and system II (BAW), R_f 0.78.

Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.96; H, 8.01; N, 4.84. Found: C, 53.69; H, 8.02; N, 4.74.

β-Phenacyl L-Aspartate Hydrochloride (IX). A. Compound VIII (6.4 g, 22.1 mmol) was stirred at 25 °C with α-bromoacetophenone (6.4 g, 32 mmol) in DMF (60 ml), followed by triethylamine (2.9 ml).[18] The solution was kept at room temperature for 2 h and at 55 °C for 6 h. The reaction was monitored by TLC. Slow decomposition of the *tert*-butyl ester bond was detected during the heating period. When the reaction was completed DMF and triethylamine were removed under high vacuum at 35–40°. The residual oily material was treated with anhydrous 1 N HCl in glacial acetic acid for 1 h. The ensuing solution was then concentrated in vacuo, redissolved in 50 ml of ice water, and extracted three times with ether and once with benzene to remove the unreacted α-bromoacetophenone. The aqueous phase was concentrated to about 15 ml and acetone was added to cause the precipitation of β-phenacyl L-aspartate HCl salt (IX): yield 4 g (61%); mp 144–145 °C; $[\alpha]^{25}D$ +15.6° (c 1, 1 N HCl); TLC in solvent system I (CMA), R_f 0.05, system II (BAW) R_f 0.39.

Anal. Calcd for $C_{12}H_{14}NO_5Cl$: C, 50.09; H, 4.91; N, 4.87; Cl, 12.32. Found: C, 50.13; H, 4.05; N, 4.90; Cl, 11.96.

B. A second esterification procedure, with much milder reaction conditions, was also used to prepare compound IX. Compound VIII (4.6 g, 15.9 mmol) was dissolved in 95% ethanol (50 ml) and the solution was adjusted to neutrality by slow addition of cesium bicarbonate[44] as measured with a pH meter. During the neutralization some precipitate formed, which was redissolved by addition of 20 ml of water. The final pH of the solution was about 7. The resulting clear solution was then flash evaporated, and after repeated evaporation to dryness with benzene, the cesium salt of compound VIII was obtained as a white solid. This was then dried over P_2O_5 in vacuo overnight. The resulting cesium salt was dissolved in

DMF (50 ml) at 25° and α-bromoacetophenone (3.6 g, 18 mmol) was added. A white precipitate formed within a few minutes and the suspension was stirred overnight at room temperature. The reaction mixture was filtered and the filtrate was concentrated to an oil which was dissolved in 10 ml of ethanol. This crude sample was placed on a Dowex 1 × 2 column (2.7 × 15 cm), OH^- form, which had been equilibrated with ethanol and then was eluted with ethanol. Fractions containing α-*tert*-butyl β-phenacyl N^{α}-*tert*-butyloxycarbonyl-L-aspartate were located by TLC and evaporated to dryness. The resulting material was treated with anhydrous 1 N HCl in acetic acid at 25 °C for 1 h. Acetic acid was evaporated off to yield a solid material, which was then suspended in 50 ml of H_2O and extracted three times with ether and once with benzene. The aqueous phase was concentrated to a volume of 10–15 ml and acetone was added to cause precipitation of β-phenacyl L-aspartate hydrochloride (IX): yield 3.7 g (80%); mp 144–145 °C; mobilities on TLC were identical with those of the previous synthesis.

C. β-Phenacyl L-aspartate was conveniently prepared as the zwitterion[45] via the lithium–copper salt by the general method A of Ledger and Stewart.[21] The yield after recrystallization from water was 15%. The elemental analysis was correct; the mobilities on TLC and corrected specific rotation were identical with those of preparations A and B; mp 177–179 °C.

β-Phenacyl N^{α}-Boc-L-aspartate DCHA Salt (X). Compound IX (1 g, 5.3 mmol) was dissolved in dimethyl sulfoxide (10 ml) followed by the addition of *tert*-butyl azidoformate (1.5 ml) and triethylamine (1.5 ml). Within a few minutes, a white precipitate formed, which was filtered off. To the remaining filtrate was added 100 mg of anhydrous $MgSO_4$. The filtrate was stirred for 10–12 h (TLC indicated that the reaction was near completion). The reaction mixture was poured into chilled (0 °C) citric acid solution and adjusted to pH 3 with citric acid. The solution was extracted three times with ethyl acetate, and the combined organic phases were washed three times with small portions of a saturated NaCl solution, dried over $MgSO_4$, and evaporated. The resulting oil was dissolved in 5 ml of ethyl acetate and cooled in a dry ice bath. Dicyclohexylamine was added dropwise until the solution became slightly basic to litmus paper. A precipitate formed which was triturated with cold (0 °C) ether and collected by filtration: yield 1.4 g (75%); mp 139–140°; $[\alpha]^{25}D$ +8.0° (c 1, ethanol); TLC (CMA), R_f 0.67, (BAW) R_f 0.9.

Anal. Calcd for $C_{29}H_{44}N_2O_7$: C, 65.39; H, 8.33; N, 5.26. Found: C, 65.37; H, 8.08; N, 5.51.

The Boc group was cleaved from X by TFA and the phenacyl group was removed by sodium thiophenoxide treatment (1 M in DMF, 25 °C, 8 h). The resulting aspartic acid was treated with L-leucine *N*-carboxyanhydride and the dipeptide diastereomers were separated chromatographically by the method of Manning and Moore.[40] The mixture contained 99.4% L-Leu-L-Asp and only 0.6% L-Leu-D-Asp.

β-Phenacyl N^{α}-*tert*-butyloxycarbonyl-L-aspartate (50 mg, obtained from compound X by removing DCHA with citric acid) was treated with HF–10% anisole for 1 h at 0 °C. Following removal of HF and anisole, the residue was dissolved in acetic acid (2 ml) and spotted on a TLC plate with β-phenacyl L-aspartate HCl salt (IX) and L-aspartic acid as standards. TLC showed that HF treatment of β-phenacyl N^{α}-*tert*-butyloxycarbonyl-L-aspartate gave a spot identical in R_f value with the β-phenacyl L-aspartate HCl salt. No detectable amount of aspartic acid was observed.

Synthesis of Tetrapeptides via the β-Phenacyl Aspartic Acid Ester. H-Glu-α-Asp-Gly-Thr-OH (II). The same solid-phase synthesis procedure described for peptide I was used for the synthesis of peptide II except that β-phenacyl Boc-aspartate DCHA (X) was used instead of β-benzyl Boc-L-aspartate. The phenacyl group was removed from 50 mg of the fully protected peptide resin by stirring at 25 °C for 8 h with 1 M sodium thiophenoxide (132 mg in 1 ml of DMF). The partially protected peptide resin was filtered, washed well with DMF and CH_2Cl_2, and dried. The peptide was then cleaved and deprotected with HF–10% anisole at 0 °C for 0.5 h. The crude product was separated and quantitated on the amino acid analyzer as described in Table VI. A large peak (97.6% of total) of H-Glu-α-Asp-Gly-Thr-OH eluted at 70 min. This was identical with the standard α-aspartyl peptide that had been prepared for reference. A small peak (2.4%) of cyclized H-Glu-Asp-Gly-Thr-OH eluted at 116 min.

Acknowledgments. The authors wish to express their gratitude to Dr. R. Hodges for his valuable suggestions and to Mrs. Bonnie Guernsey and Miss Anita Bach for their expert assistance.

Registry No.—II, 57718-76-0; III, 57680-10-1; IV, 57680-11-2; V, 2177-63-1; VI, 52615-97-1; VII, 57680-12-3; VIII, 34582-32-6; IX, 57680-13-4; X, 57680-15-6; H-Pro-Arg(Tos)-OH, 57680-16-7; H-Thr(Bzl)-Pro-Arg(Tos)-OH, 57680-17-8; H-Gly-Thr(Bzl)-Pro-Arg(Tos)-OH, 57680-18-9; H-Asp(OBzl)-Gly-Thr(Bzl)-Pro-Arg(Tos)-OH, 57680-19-0; H-Glu(OBzl)-Asp(OBzl)-Gly-Thr(Bzl)-Pro-Arg(Tos)-OH, 57680-20-3; H-Leu-Glu(OBzl)-Asp(OBzl)-Gly-Thr(Bzl)-Pro-Arg(Tos)-OH, 57680-21-4; H-Glu(OBzl)-Leu-Glu(OBzl)-Asp(OBzl)-Gly-Thr(Bzl)-Pro-Arg(Tos)-OH, 57680-22-5; H-Arg(Tos)-Glu(OBzl)-Leu-Glu(OBzl)-Asp(OBzl)-Gly-Thr(Bzl)-Pro-Arg(Tos)-OH, 57680-23-6; H-Glu(OBzl)-Asp(OBzl)-OH, 57680-27-4; H-Glu(OBzl)-Asp(OBzl)-Gly-OH, 57680-25-8; H-Glu(OBzl)-Asp(OBzl)-Gly-Thr(Bzl)-OH, 57680-26-9; H-Gln-Asp(OBzl)-Gly-Thr(Bzl)-OH, 57680-27-0; H-Ala-Asp(OBzl)-Gly-Thr(Bzl)-OH, 57680-28-1; H-Ala-Asp(OBzl)-Gly-Ala-OH 57680-29-2; H-Asp(OBzl)-Gly-OH, 47094-17-7; H-Asp(OBzl)-Gly-Thr(Bzl)-OH, 57680-30-5; H-Glu(OBzl)-Asp(OBzl)-Ala-OH, 57680-31-6; H-Glu(OBzl)-Asp(OBzl)-Ser(Bzl)-OH, 57680-32-7; H-Asp(OBzl)-Ala-Leu-OH, 57694-98-1; H-Asp(OBzl)-Ser(Bzl)-Leu-OH, 57680-33-8; Boc-Glu(OBzl)-Asp(OBzl)-Gly-Thr(Bzl)-OH, 57680-34-9; HF, 7664-39-3; isobutene, 115-11-7; *tert*-butyl azidoformate, 1070-19-5; α-bromoacetophenone, 70-11-1; dicyclohexylamine, 101-83-7.

References and Notes

(1) This work was supported in part by a Reproductive Biology grant from the Rockefeller Foundation, by Grant AM 01260 from the U.S. Public Health Service, and by a grant from the Hoffmann-La Roche Foundation.
(2) Abbreviations used: Boc, *tert*-butyloxycarbonyl; Bpoc, 2-(4-biphenylyl)-2-propyloxycarbonyl; Bzl, benzyl; Bu^t, *tert*-butyl; DCC, dicyclohexylcarbodiimide; DCHA, dicyclohexylamine; DMF, *N,N*-dimethylformamide; Et_3N, triethylamine; Pac, phenacyl; R, resin; TFA, trifluoroacetic acid; Tos, *p*-toluenesulfonyl; Z, benzyloxycarbonyl. Aspartoyl indicates the bivalent amino acid radical derived from aspartic acid, Organic Nomenclature, IUPAC rule 58.3, "Handbook for Chemical Society Authors", *Chem. Soc., Spec. Publ.*, **No. 14** (1961). Aspartoylglycine is the cyclic imide formed by diacylation of the amino group of glycine by the two carboxyl groups of aspartic acid. Other nomenclature and symbols follow the Tentative Rules of the IUPAC-IUB Commission on Biochemical Nomenclature, *J. Biol. Chem.*, **241**, 2491 (1966); **242**, 555 (1967); **247**, 977 (1972).
(3) S. S. Wang, C. C. Yang, I. D. Kulesha, M. Sonenberg, and R. B. Merrifield, *Int. J. Pept. Protein Res.*, **6**, 103 (1973).
(4) E. Sondheimer and R. W. Holley, *J. Am. Chem. Soc.*, **76**, 2467 (1954).
(5) A. Battersby and J. C. Robinson, *J. Chem. Soc.*, 259 (1955).
(6) B. Iselin and R. Schwyzer, *Helv. Chim. Acta*, **45**, 1499 (1962).
(7) S. A. Bernhard, A. Berger, H. H. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *J. Am. Chem. Soc.*, **84**, 2421 (1962).
(8) B. Riniker and R. Schwyzer, *Helv. Chim. Acta*, **47**, 2357 (1964).
(9) I. H. Page, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, 23, 693 (1964).
(10) R. W. Hanson and H. N. Rydon, *J. Chem. Soc.*, 836 (1964).
(11) G. R. Marshall and R. B. Merrifield, *Biochemistry*, **4**, 2394 (1965).
(12) G. Fölsch, *Acta Chem. Scand.*, **20**, 459 (1966).
(13) R. B. Merrifield, *Recent Prog. Horm. Res.*, **23**, 451–482 (1967).
(14) M. A. Ondetti, A. Deer, J. T. Sheehan, J. Pluscec, and O. Kocy, *Biochemistry*, **7**, 4069 (1968).
(15) D. E. Nitecki, G. Senyk, E. B. Williams, and J. W. Goodman, *Intra-Sci. Chem. Rep.*, **5**, 295 (1971).
(16) T. Baba, H. Sugiyama, and S. Seto, *Chem. Pharm. Bull.*, **21**, 207 (1973).
(17) When Z-Arg(NO_2)-Glu(OBzl)-Leu-Glu(OBzl)-Asp-Gly-Thr(Bzl)-Pro-Arg(NO_2)-OH was hydrogenolyzed at 50 psi over Pd–$BaSO_4$ in methanol–acetic acid–water (10:1:1) for 24 h the product contained an appreciable amount of the aspartimide derivative.
(18) J. C. Sheehan and G. D. Daves, Jr., *J. Org. Chem.*, **29**, 2006 (1964).
(19) G. C. Stalakatos, A. Paganou, and L. Zervas, *J. Chem. Soc.* 1191 (1966).
(20) J. Taylor-Papadimitriou, C. Yovanidis, A. Paganou, and L. Zervas, *J. Chem. Soc.*, 1830 (1967).
(21) R. Ledger and F. H. C. Stewart, *Aust. J. Chem.*, **18**, 1477 (1965).
(22) F. Weygand in "Peptides 1968", E. Bricas, Ed., North-Holland Publishing Co., Amsterdam, 1968, pp 183–184.
(23) T. Mizoguchi, K. Shigezane, and N. Takamura, *Chem. Pharm. Bull.*, **17**, 411 (1969).
(24) K. Shigezane and T. Mizoguchi, *Chem. Pharm. Bull.*, **21**, 972 (1972).
(25) R. B. Merrifield, *J. Am. Chem. Soc.*, **86**, 304 (1964).
(26) R. B. Merrifield, *Adv. Enzymol.*, **32**, 221 (1969).
(27) B. Gutte and R. B. Merrifield, *J. Biol. Chem.*, **246**, 1922 (1971).
(28) R. E. Offord, *Nature (London)*, **211**, 591 (1966).
(29) N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy", Academic Press, New York, N.Y., 1964, p 385.
(30) C. J. Pouchert, "The Aldrich Library of Infrared Spectra", Aldrich Chemical Co., Milwaukee, Wis., 1973, p 352.
(31) D. V. Khairallah, F. M. Bumpus, I. H. Page, and R. R. Smeby, *Science*, **140**, 672 (1963).
(32) M. Bodanszky and N. J. Williams, *J. Am. Chem. Soc.*, **89**, 685 (1967).
(33) L. Benoiton, *Can. J. Chem.*, **40**, 570 (1962).

(34) L. Zervas and C. Hamalidis, *J. Am. Chem. Soc.*, **87**, 699 (1965).
(35) E. E. Haley, B. J. Corcorn, F. E. Dorer, and D. J. Buchanan, *Biochemistry*, **5**, 3229 (1966).
(36) G. W. Kenner and J. H. Seely, *J. Am. Chem. Soc.*, **94**, 3259 (1972).
(37) R. S. Hodges and R. B. Merrifield, *Int. J. Pept. Protein Res.*, **6**, 397 (1974).
(38) R. Feinberg and R. B. Merrifield, *J. Am. Chem. Soc.*, **97**, 3485 (1975).
(39) S. S. Wang, personal communication.
(40) J. M. Manning and S. Moore, *J. Biol. Chem.*, **243**, 5591 (1968).
(41) D. H. Spackman, W. H. Stein, and S. Moore, *Anal. Chem.*, **30**, 1190 (1958).
(42) K. Hofmann, H. Yajima, T. Lin, H. Yanaihara, C. Yanaihara, and J. Humes, *J. Am. Chem. Soc.*, **84**, 4481 (1962).
(43) R. W. Roeske, *J. Org. Chem.*, **28**, 1251 (1963).
(44) B. F. Gisin, *Helv. Chim. Acta*, **56**, 1476 (1973).
(45) Unpublished work of Mr. Wesley Cosand.

Ring Contractions of 5-Diazouracils. I. Conversions of 5-Diazouracils into 1,2,3-Triazoles by Hydrolysis and Methanolysis

T. Craig Thurber and Leroy B. Townsend*

Department of Chemistry and Department of Biopharmaceutical Sciences, University of Utah, Salt Lake City, Utah 84112

Received June 3, 1975

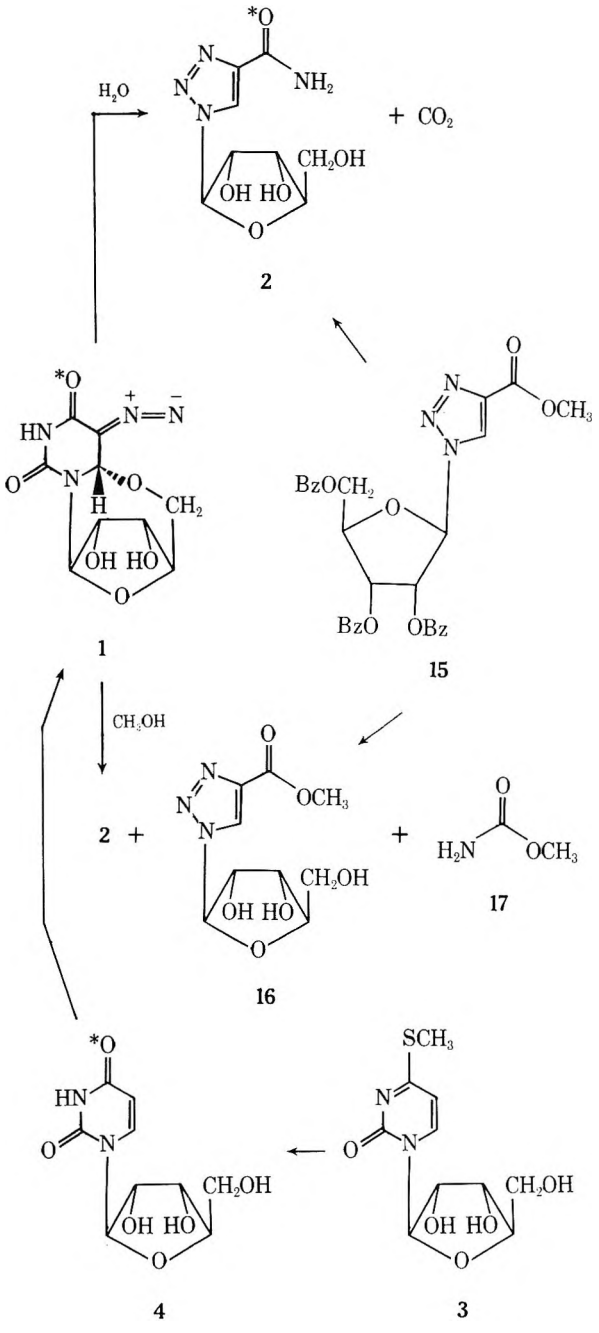
The hydrolysis of $O^{5'}$-6(*S*)-cyclo-5-diazouridine (**1**) to 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (**2**) and carbon dioxide was shown to proceed via initial attack at C-2 by using oxygen-18 label in the C-4 position. Similar reactions of $O^{5'}$-6(*S*)-cyclo-5-diazo-2′-deoxyuridine (**5**), 5-diazouracil-6-methanolate (**7**), and 5-diazo-1-methyluracil-6-methanolate (**11**) gave the expected triazole derivatives. The unsuccessful hydrolysis of $O^{5'}$-6(*S*)-cyclo-5-diazo-3-methyluridine (**13**) was shown to be due to the absence of an initial attack by water. Methanolysis of **1** gave **2**, methyl 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxylate (**16**), and methyl carbamate (**17**). Methanolysis of **11** gave 1-methyl-1,2,3-triazole-4-carboxamide (**12**), **17**, and methyl 1-methyl-1,2,3-triazole-4-carboxylate (**18**). Methanolysis of **7** gave methyl *N*-(1,2,3-triazol-4-ylcarbonyl)carbamate (**20**) which established that these ring contractions proceeded via a N-1–C-2 bond cleavage. Diazotization of O^{2}-2′-cyclo-5-amino-5′-deoxyuridine (**28**) gave a product which suggested that these ring contractions require the formation of a tautomeric carbinolamidine prior to nucleophilic attack. Methanolysis of 5-(3,3-dimethyl-1-triazeno)uridine (**36**) gave **2** and **16**. This reaction was probably the result of direct nucleophilic attack on **36** rather than a prior decomposition of the triazeno group to a diazo group since 5-(3,3-dimethyl-1-triazeno)-1,3-dimethyluracil (**38**) was recovered quantitatively under similar reaction conditions. A partial hydrolysis of **11** labeled with oxygen-18 at C-2 showed a retention of isotopic label and suggested that the transition state for ring opening involved a partial C–N bond cleavage rather than the formation of a tetrahedral intermediate. The results are discussed in terms of a mechanism in which a proton at N-3 of the uracil ring must tautomerize to the O-2 position and the diazo ether derivative of this tautomer must be formed prior to ring opening.

Our initial interest in this area involved a structural reinvestigation[1] of 5-diazouracils and their possible synthetic utility for the preparation of 5-substituted uracil derivatives. This had been suggested[2] in the literature and a few reports of nucleophilic displacement reactions had been published.[3–5] Our preliminary studies, to determine the susceptibility of the diazo group of $O^{5'}$-6(*S*)-cyclo-5-diazouridine[1] (**1**) toward nucleophilic displacement, revealed that displacement reactions did not occur at low temperatures. In an effort to find a suitable solvent for conducting displacement reactions at elevated temperatures, we investigated the stability of **1** in acetonitrile at 100°. We observed a ring contraction of **1** to afford 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide[6] (**2**). We could find no precedent for this unusual reaction in the literature, which prompted us to initiate a study on the scope and mechanism of this reaction.

Results and Discussion

A solution of **1** in acetonitrile was heated in a stainless steel reaction vessel at 100° and the solution was then allowed to stand at ambient temperature to afford a white solid (**2**). Initial data indicated that **1** had been converted to uridine via a simple nitrogen elimination, since there was observed an absence of absorption bands in the 4.65-μ region of the ir spectrum and specific peaks [B + H (112), B + 2H (113), S (133), M − 30 (214)] in the low-resolution mass spectrum were essentially identical with those reported for uridine.[7] However, the uv spectrum of **2** revealed the absence of any absorption maximum in the 230–346-nm region. Elemental analyses (C, H, N) for **2** were found to be consistent with the empirical formula $C_8H_{12}N_4O_5$ and established that a ring carbonyl group had been lost instead of diatomic nitrogen. The structure of **2** was established on the basis of the following data.

The ^{1}H NMR spectrum (Figure 1) of **2** revealed a pattern of peaks in the δ 3.5–6.5 region which were indicative[8] of a ribofuranosyl moiety. The presence of D-ribose was confirmed by the treatment of **2** with dilute acid, followed by a direct paper chromatographic comparison of the hydrolysate with similarly treated samples of D-ribose, D-arabinose, and D-xylose (Table I). The facile hydrolysis of **2** suggested a *N*-glycosyl bond. The ^{1}H NMR spectrum (Figure 1) of **2** revealed the presence of two broad singlets (δ 7.75 and 7.50) which were exchanged on the addition of deuterium oxide to the ^{1}H NMR sample. This was suggestive of a carboxamide group and additional evidence for the presence of an amide group was obtained by a positive hydroxylamine–ferric chloride test.[9] Only one unassigned absorption peak remained in the ^{1}H NMR spectrum and it was assumed to be an aromatic proton on the basis of its chemical shift (δ 8.80). These data were all consistent with a disubstituted, five-membered heterocycle with three ring nitrogens (triazole). The formation of a triazole could occur by loss of the carbonyl group in the C-2 position of **1** followed by annulation between N-1 and the diazo group. If ring opening and rearrangement had occurred in the proposed manner, then the structure must be 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide[10–12] (**2**). A rigorous comparison of this nucleoside with an authentic sample prepared



by one of the reported[10] procedures established that these compounds were identical in every respect (Table II).

A quantitative yield of starting material (1) was recovered when this reaction was repeated using anhydrous acetonitrile, which suggested that water was required for the ring opening and ring contraction. A quantitative yield of 2 was obtained when water (5%) was included in the reaction, which established that water was indeed an essential reactant. Therefore, ring opening was the result of hydrolysis, with two possible positions (C-2 and C-4) at which nucleophilic attack by water followed by ring opening could occur. Either route would lead to a carbamic acid derivative which should decarboxylate[13] under the reaction conditions and evolve carbon dioxide. This prompted us to collect gases from the reaction mixture by attaching an evacuated glass bulb to the bleed valve of the reaction vessel, which allowed the gases to escape into the bulb. A mass spectrum, of the contents of the bulb, revealed that carbon dioxide had in fact been evolved as evidenced by a molecular ion at *m/e* 44.

The nucleoside (1) labeled with oxygen-18 at the C-4 position was required to establish which carbonyl group of 1 had been eliminated. Acid-catalyzed hydrolysis of 1-(β-D-ribofuranosyl)-4-methylthio-2-pyrimidone[14] (3) in oxygen-18 enriched (10%) water furnished the uridine (*4) required for the preparation of *1. Compound *4 was converted to *1 by bromination, amination, and subsequent diazotization[1] without a loss of isotopic label (Table III). Reaction of *1 gave *2 under the above conditions and a mass spectrum of *2 (Table III) demonstrated a complete retention of label. The isotopic content of *2 was determined by calculating the relative percentage of the second isotope peak of the ion fragment at *m/e* 214 (M − 30). The isotopic content of *2, by an analysis of the B + 2H ion fragment, was precluded since an additional small ion fragment occurs at the same mass in the spectrum of 2. However, it was possible to assign the isotope of *2 to the carboxamide group since there was very little possibility of oxygen migration from the C-4 position of 1 to the ribofuranose moiety of 2. Further studies demonstrated no involvement of the carbohy-

Table I
Chromatographic Comparison of the Hydrolysate[a] of 2 with Authentic Pentoses

Compd	R_f A[b]	R_f B[b]
Hydrolysate of 2	0.303	0.206
D-Ribose	0.305	0.209
D-Arabinose	0.250	0.138
D-Xylose	0.244	0.244

[a] 10-mg samples in 1 *N* hydrochloric acid (2 ml) were heated on a steam bath for 30 min and then neutralized by the addition of 0.8 *N* sodium hydroxide. Samples were then applied to Whatman No. 1 chromatography paper and developed (descending) a distance of 18 in. Components were detected as dark spots by spraying with an aniline–phthalic acid mixture[c] followed by heating for 10 min at 120°. [b] Solvent systems: A, 1-butanol–acetic acid–water (3:1:4 v:v:v, organic phase); B, 1-butanol–acetic acid–water (3:1:1 v:v:v). [c] S. M. Partridge, *Nature (London)*, 164, 443 (1949).

Table II
Comparison of
1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxamide (2)

	From 1	From 15
Mp, °C	202–204	202–204
Uv, λ_{max} (water)	210 nm (ε 12212)	210 nm (ε 12444)
Ir, μ	2.96 (NH_2) 5.97 (C=O)	2.96 (NH_2) 5.97 (C=O)
^{1}H NMR (Figure 1), δ	8.8 (s, 1 H5)	8.8 (s, 1 H5)
$[\alpha]^{26}$D (c 1, H_2O)	−61.0°	−61.6°
TLC,[a] R_f A	0.45	0.45
B	0.39	0.39
C	0.66	0.66
EI MS[b] M	244/0	244/0
M − CH_2O	214/1.8	214/2.0
B + C_2H_4	155/3.7	155/3.8
B + CH_2O	141/3.0	141/3.3
B + 2H	113/21.5	113/21.6
B + H	112/100.0	112/100.0
CI MS (CH_4)		
M + C_3H_5	285/7	285/7
M + C_2H_5	273/30	273/4
MH	245/38	245/24
BH_2	113/100	113/100

[a] Thin layer chromatography was performed on 5 × 20 cm glass plates coated to a thickness of 0.25 mm with Mallinckrodt SilicAR 7GF. Solvent systems: A, chloroform–methanol (3:1 v:v); B, ethyl acetate–ethanol (9:1 v:v); C, ethyl acetate–1-propanol–water (4:1:2 v:v:v, organic phase). [b] M = molecular ion; B = base moiety. Reported as *m/e*/rel intensity.

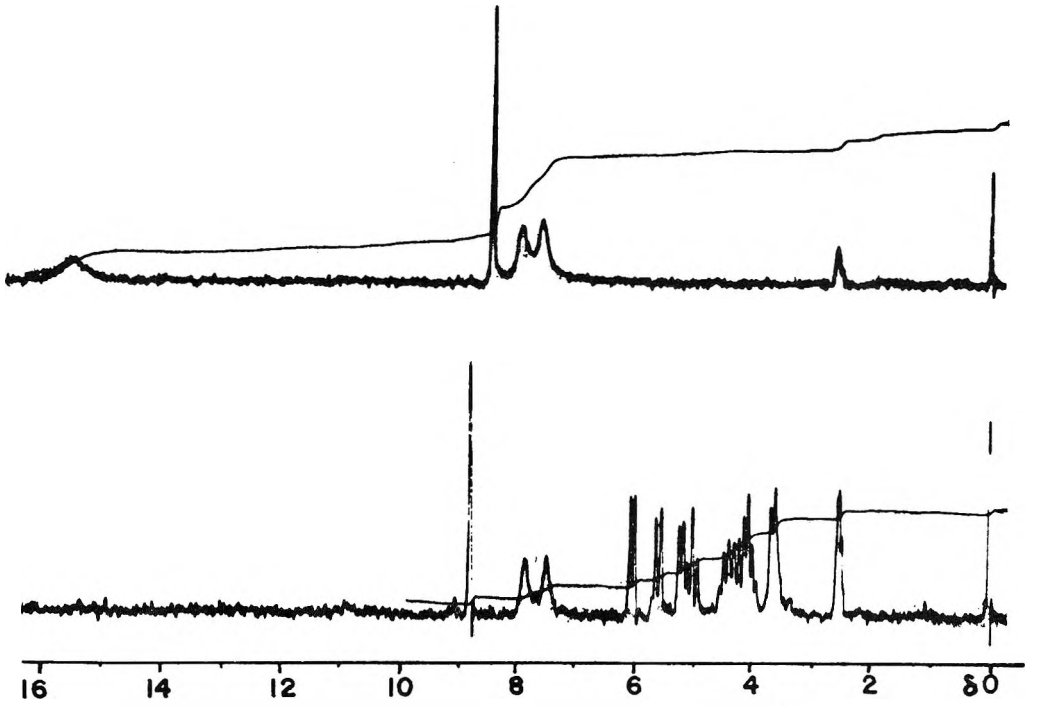


Figure 1. ^{1}H NMR spectra (Me_2SO-d_6) of 1,2,3-triazole-4-carboxamide (**8**) (top) and 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (**2**) (bottom).

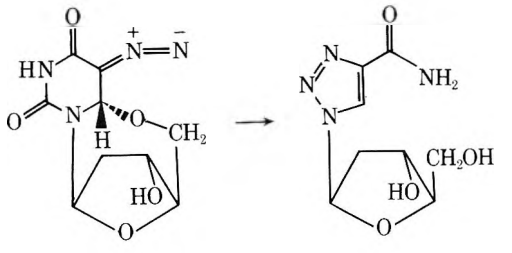
Table III
Oxygen-18 Enrichments[a]

Compd	Ion measured, *m/e*	% oxygen-18
*3	226 (M − H_2O)	9.75
*1	139 (BH)	8.70
*2	214 (M − 30)	8.70
*40	126 (M)	5.65
*11	153 (M − CH_3O)	5.39
*11 + *41[b]	153 (M − CH_3O or M − OH)	4.91

[a] Corrected for the natural abundance of oxygen-18. [b] Mixture obtained from partial reaction of 11* with water (see text).

drate moiety in the reaction and with the isotope being assigned to the carboxamide group, several conclusions were drawn from the observed retention of label. This indicated that the carboxamide group of **2** originated from the N-3 and C-4 positions of **1**, that the carbonyl group in the C-2 position of **1** was eliminated during the reaction, and also that the C-4 oxygen atom of **1** was not exchanged by solvent (water) under the reaction conditions.

A solution of $O^{5'}$-6(*S*)-cyclo-5-diazo-2′-deoxyuridine[1] (**5**) in 5% aqueous acetonitrile was heated at 100° for 18 hr to afford a compound which was assigned the structure 1-(2-deoxy-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (**6**)

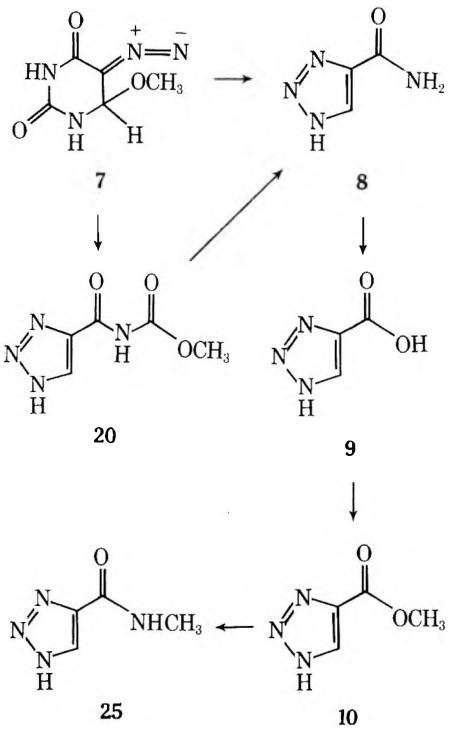


5 **6**

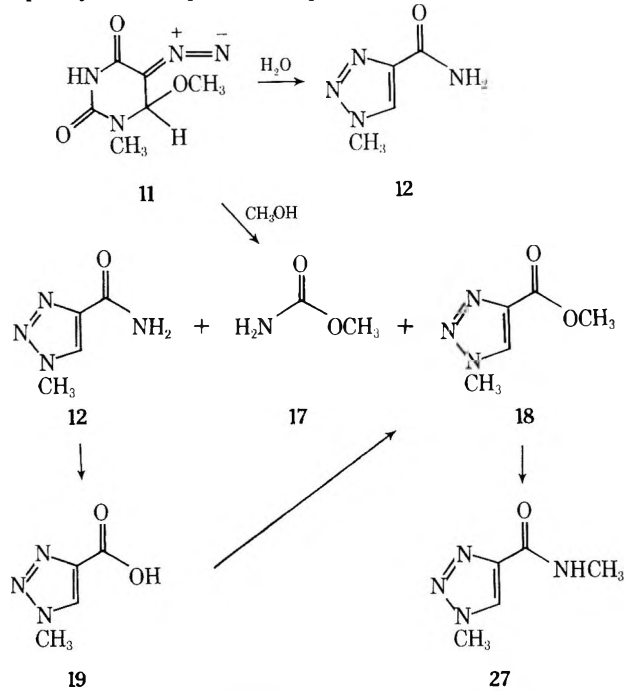
by a comparison of its spectral data with the spectral data of **2**. The anomeric proton of **6** appeared as a pseudotriplet ($J_{1'2'}$ = 6 Hz) having a peak width of 12 Hz and allowed assignment[15] of the β configuration to **6**. This demonstrated that the 2′-hydroxyl group was not involved in the reaction and that compounds such as deoxynucleosides (which are particularly sensitive to hydrolysis,[22,23] glycosyl bond cleavage) can be converted to 1,2,3-triazoles by this method. This was of considerable interest since the syntheses of 1-glycosyl-1,2,3-triazoles have been previously accomplished by cycloaddition of various glycosyl azides with substituted acetylenes[10,16-20] and by the acid-catalyzed fusion[11] of 4-substituted 1,2,3-triazoles with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose. It is of interest that **2** is a structural isomer of the broad spectrum antiviral nucleoside 1-(β-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide.[21] The synthesis of **6** by the reported methods (vide supra) would have furnished complex isomeric mixtures. It would appear that the preferred synthesis of 1-glycosyl-1,2,3-triazoles would be by ring contraction of 5-diazouracils.

5-Diazouracil-6-methanolate[1] (**7**) was heated at 100° for 18 hr in 5% aqueous acetonitrile to give a solid which had a melting point similar to that reported[24] for 1,2,3-triazole-4-carboxamide (**8**). A ^{1}H NMR spectrum (Figure 1) revealed two broad exchangeable singlets (δ 7.93 and 7.63), an aromatic proton (δ 8.48), and a broad, exchangeable peak (δ 15.6) which was assigned to a tautomeric ring proton. Elemental analyses (C, H, N) correlated with the empirical formula $C_3H_4N_4O$ and the ir and uv spectra of **8** were consistent with the assigned structure. Compound **8** was also converted to 1,2,3-triazole-4-carboxylic acid (**9**) by treatment with sodium hydroxide and into methyl 1,2,3-triazole-4-carboxylate (**10**) by esterification of **9**. The physical properties of these two compounds were in good agreement with the values reported[25-27] in the literature. This also established that an alkyl group at N-1 was not necessary for the ring contraction to occur.

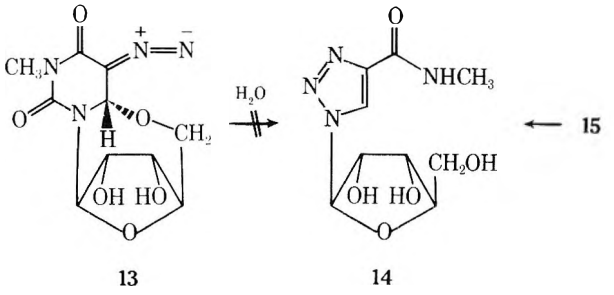
Reaction of 5-diazo-1-methyluracil-6-methanolate[28] (**11**) under similar conditions gave a compound which we assumed was 1-methyl-1,2,3-triazole-4-carboxamide (**12**). However, the structure assignment for **12** was complicated by a discrepancy between our observed physicochemical



properties and those reported[29] for 12 in the literature. This required us to unequivocally establish the structure of our product. A preliminary communication[30] from our laboratory has established the structure of our product as 12. The difference in physicochemical properties between 12 obtained by the ring contraction of 11 and 12 as reported[29] in the literature may be due to the presence of an isomeric impurity in the reported compound.



There was no detectable reaction when $O^{5'}$-6(*S*)-cyclo-5-diazo-3-methyluridine[31] (13) was heated at 100° in 5% aqueous acetonitrile. Although a disappearance of starting material did occur when the temperature was increased to 150°, the major product was a tar, with two minor components being detected by thin layer chromatography. These minor components had the same mobility, in three solvent systems, as 3-methyluracil and 3-methyluridine. If 13 had undergone a ring contraction similar to those described above, the product would have been 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-*N*-methylcarboxamide (14). Treatment of methyl 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxylate[10] (15) with methylamine furnished 14.



A chromatographic comparison of 14 with the above mixture showed no detectable amount of 14. This was of considerable interest since the only difference between 1 and 13 was the presence of a methyl group at N-3. An experiment in which 13 was heated at 100° for 18 hr in 5% aqueous acetonitrile with water enriched (10%) in oxygen-18 furnished only unreacted 13 which was analyzed by mass spectroscopy for oxygen-18 content. The mass spectrum failed to show any ion fragments with a second isotope larger than that due to the natural abundance of oxygen-18 and established that water had not attacked C-2. The failure of 5-diazouracils, with a methyl group at N-3, to undergo ring contraction was investigated further (vide infra).

The above studies suggested that hydrolysis by water should furnish carbamic acid intermediates upon ring opening. It appeared that we could isolate the carbamic acid intermediates as their methyl esters, if the nucleophile responsible for hydrolysis was changed from water to methanol. This would establish the presence of carbamates and identify the initial bond broken in the ring-opening process.

A solution of 1 in anhydrous methanol was heated at 100° for 18 hr and cooled to room temperature, and a thin layer chromatogram of the solution revealed the presence of two nucleoside products. The minor component had the same chromatographic mobility as 2. The major component was not visible under ultraviolet light (254 nm) but could be detected by charring with 10% sulfuric acid. These two components were separated by dry pack column chromatography and the minor component was found to be identical in all respects with 2. Elemental analyses for the major component were consistent with the empirical formula $C_9H_{13}N_3O_6$, which did not support an esterified carbamic acid intermediate. A ^1H NMR spectrum of the major component revealed a pattern of peaks in the δ 3.5–3.6 region which were indicative[8] of a ribofuranosyl moiety and an aromatic proton at δ 8.83. However, the two broad exchangeable singlets for the amide group of 2 were replaced by a methyl group absorption at δ 3.82, which suggested that the compound was methyl 1-(β-D-ribofuranosyl)-1,2,3-triazole-4-carboxylate (16). An independent synthesis of 16 was accomplished by treatment of 15 with sodium methoxide in methanol and the two samples were found to be identical in every respect.

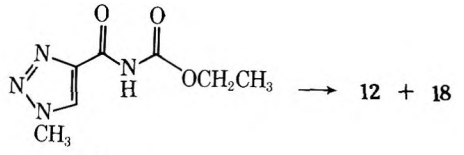
The formation of 16 by this reaction was of considerable interest, since the study of 1 labeled with oxygen-18 at C-4 had established that C-4 was not attacked by water. It would appear that the carbamate ester (if formed) had been hydrolyzed under the reaction conditions to give a mixture (2 and 16), and that methyl carbamate (17) must also be present in the reaction mixture. The reaction was repeated and the crude reaction mixture was examined for the presence of a third component by ^1H NMR spectroscopy, which revealed the presence of 2 and 16 in the ratio 5:1.

Two additional peaks were observed [δ 3.54 (s, 3) and 6.38 (bs, 2)], with the integrated intensities of the methyl group of **16** being equal to the integrated intensity of the absorption at δ 3.54. These data were consistent with the formation of methyl carbamate (**17**) in an equimolar ratio with **16**. Methyl carbamate (**17**) was subsequently isolated from the reaction mixture by sublimation and found to be identical with a commercial sample.[32]

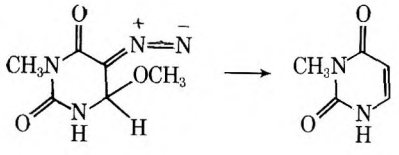
The methanolysis of **11** gave a mixture of **12** (major product), **17**, and methyl 1-methyl-1,2,3-triazole-4-carboxylate (**18**), although a higher temperature (135°) was required for completion in 18 hr. A conversion of **12** to 1-methyl-1,2,3-triazole-4-carboxylic acid (**19**) was accomplished by treatment with sodium hydroxide and esterification of **19** by treatment with methanol in the presence of dry hydrogen chloride gave **18**. Identification of **18** from the mixture was made by a comparison of **18** prepared by this independent synthesis from **12** (vide supra).

5-Diazouracil-6-methanolate (**7**) was heated at 132° in 5% methanolic acetonitrile[33] to give a product which was characterized as methyl *N*-(1,2,3-triazol-4-ylcarbonyl)-carbamate (**20**) on the basis of the following data. Elemental analyses and a molecular ion at *m/e* 170 in the mass spectrum were consistent with the empirical formula $C_5H_6N_4O_3$. The ^{1}H NMR spectrum revealed the presence of a methyl group (δ 3.77), an aromatic proton (δ 8.74), and a very broad exchangeable absorption centered at approximately δ 10.6 which was consistent with the presence of at least one NH proton. The empirical formula and downfield chemical shift of the aromatic proton from the peak for the aromatic proton of **8** ($\Delta\delta$ 0.29) suggested that the major difference between **20** and **8** was the group at the C-4 position which was deshielding the C-5 proton of **20**. The structure for **20** was consistent with these data and additional confirmation was obtained by hydrolysis of **20** with sodium hydroxide to give **8**.

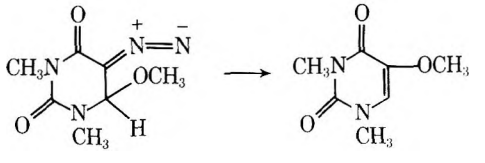
The isolation and characterization of **20** from this reaction established that initial ring opening had occurred between N-1 and C-2. Although we assumed that the ring contractions of other 5-diazouracils had occurred by ring opening in the same position, we elected to show that the *N*-formyl methylcarbamate functional group could be hydrolyzed in methanol to afford a mixture of methyl ester and amide. This was accomplished by heating a solution of ethyl *N*-(1-methyl-1,2,3-triazol-4-ylcarbonyl)carbamate[34] (**21**) in methanol at 135° to give a mixture of **12** and **18**.



21



22 **24**



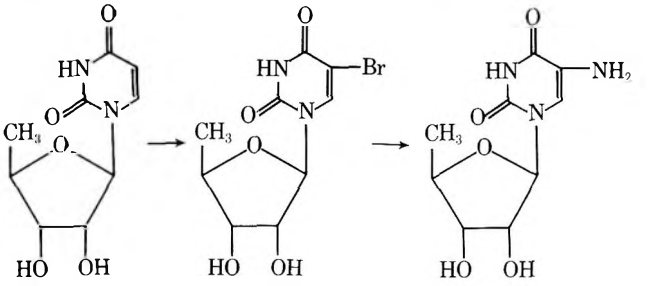
23 **26**

Similar reactions of 5-diazo-3-methyluracil-6-methanolate[28] (**22**) and 5-diazo-1,3-dimethyluracil-6-methanolate[28] (**23**) with methanol did not afford the expected triazole derivatives. When **22** was heated at 100° with 5% methanolic acetonitrile, the only product which could be isolated was 3-methyluracil[35] (**24**). The expected products, **10** and 1,2,3-triazole-4-*N*-methylcarboxamide (**25**) (prepared by treatment of **10** with methylamine), were used for a direct comparison (TLC, ^{1}H NMR) with the reaction mixture obtained from **22** and established that neither of these triazoles were present in detectable amounts.

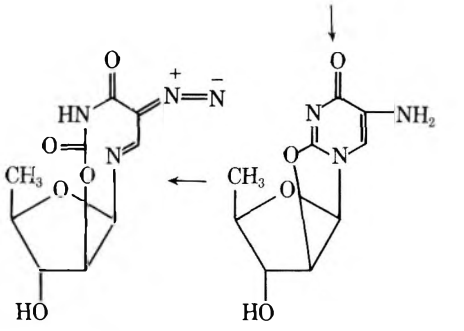
A similar reaction of **23** gave only 5-methoxy-1,3-dimethyluracil[36] (**26**). The expected products, **18** and 1-methyl-1,2,3-triazole-4-*N*-methylcarboxamide (**27**) (prepared by treatment of **18** with methylamine), were used for a direct comparison (^{1}H NMR) with the reaction mixture obtained from **23** and established that neither of these triazoles were present in detectable amounts.

The difference between **13, 22,** and **23** (which do not give triazoles) and **1, 5, 7,** and **11** (which do give triazoles) is replacement of the N-3 proton by a methyl group. The unsuccessful conversion of 5-diazouracils having a methyl group at N-3 (**13, 22** and **23**) to triazoles was attributed to the absence of nucleophilic attack at C-2 in the case of **13**. However, failure of the N-3 alkylated compounds to form triazoles cannot be accounted for on the basis of inductive effects alone, since it was shown that the presence of methyl, hydrogen, ribose, and 2-deoxyribose at N-1 did not significantly alter the formation of triazoles. The difference between these two series of compounds can be rationalized if it is assumed that a proton at N-3 must first tautomerize to the C-2 oxygen atom to form a carbinolamidine, which then undergoes attack by water. Unfortunately, there are no reports in the literature which can be cited in favor of this proposal, but data which supported this proposal were obtained by a study of the diazotization of O^2-2′-cyclo-5-amino-5′-deoxyuridine (**28**).

5′-Deoxyuridine[37] (**29**) was treated with bromine in the presence of acetic anhydride and acetic acid to furnish a syrup which gave 5-bromo-5′-deoxyuridine (**30**) after treatment with methanolic ammonia. Treatment of **30** with liquid ammonia furnished 5-amino-5′-deoxyuridine (**31**), which on treatment with diphenyl carbonate and sodium



29 **30** **31**



32 **28**

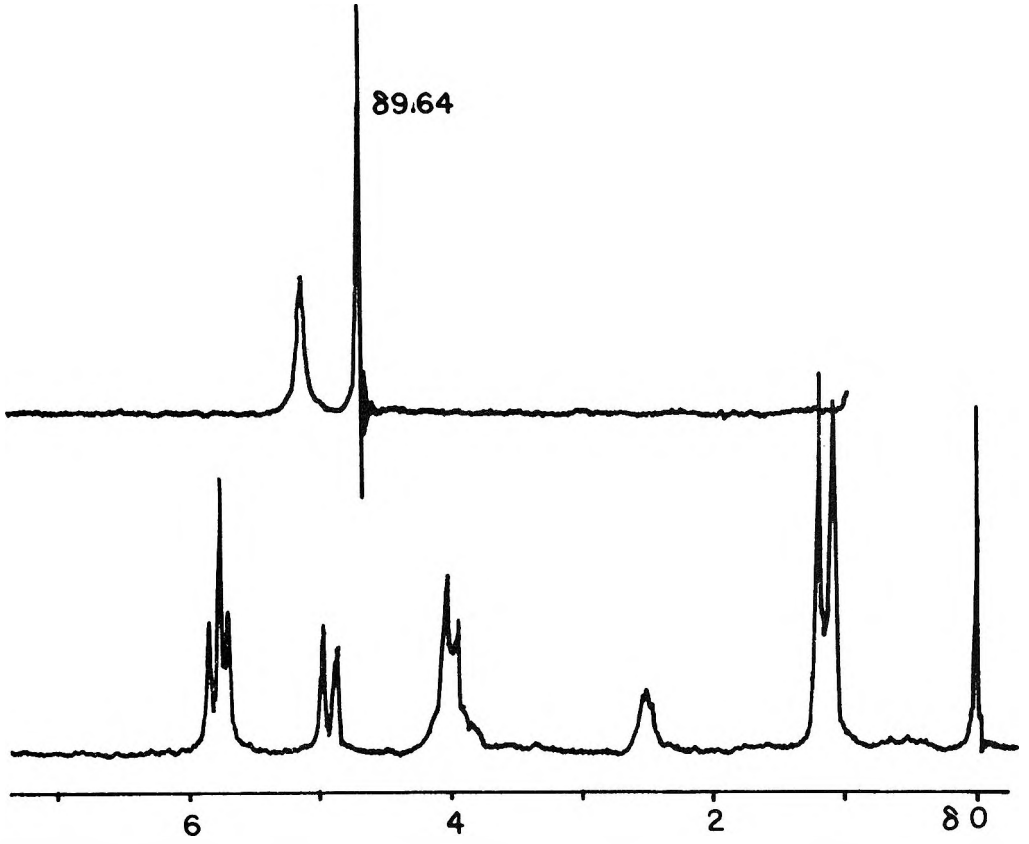


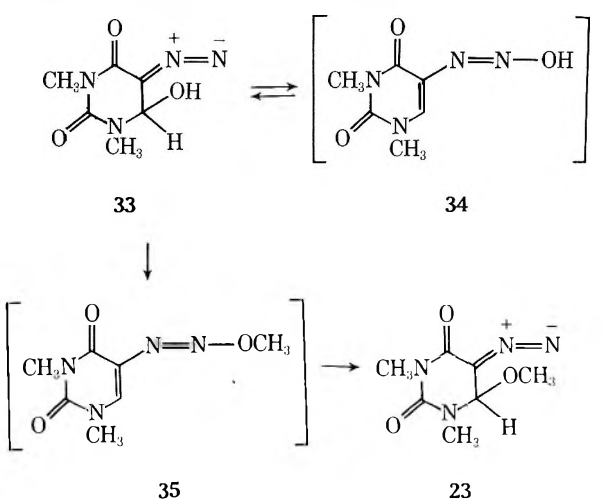
Figure 2. ^{1}H NMR spectrum (Me_2SO-d_6) of diazo compound **32**. The top spectrum is a continuation of the bottom spectrum with an upfield offset of 300 Hz.

bicarbonate in *N,N*-dimethylacetamide gave **28**. The structural characterizations of **30** and **31** were accomplished by comparisons of their physicochemical properties with those of the corresponding uridine derivatives. The structural assignment for **28** was facilitated by the appearance of two absorption maxima (289 and 258 nm) in the ultraviolet absorption spectrum. Treatment of **28** with nitrous acid gave a compound which was characterized as 5-diazo-10-hydroxy-9-methyl(7a*S*,9*S*,10*S*,10a*R*)tetrahydrofurano[2,3-*h*]-1,3,7-perhydro-3*H*-oxadiazonin-6-ene-2,4-dione (**32**) on the basis of the following data. Elemental analyses gave the empirical formula $C_9H_{10}N_4O_5$. The molecular ion was observed at *m/e* 255 (MH^+) in the chemical ionization mass spectrum (CH_4 reagent gas). A strong absorption at 4.65 μ in the ir spectrum which was characteristic[1] of similar structures and a loss of diatomic nitrogen (*m/e* 227, MH − N_2) in the CI mass spectrum supported the presence of a diazo group. The CI mass spectrum also revealed the presence of a large ion fragment (*m/e* 211) which corresponded to a loss of carbon dioxide and suggested the presence of an acyclic carbamate structure as a portion of the molecule. The ultraviolet absorption maximum of **32** occurred at higher energy (248 nm) with a larger extinction coefficient (ϵ 36200) than those observed for 5-diazouracils[1] and suggested that the 5-diazouracil chromophore had been drastically altered. The ^{1}H NMR spectrum (Figure 2) of **32** confirmed the structural assignment by revealing the presence of an NH proton (δ 10.1), a single hydroxyl group proton (δ 5.77) and a strong vicinal coupling (J = 6.0 Hz) for the carbohydrate 1 and 2 protons. The N=CH proton of **32** was also found downfield from the C-6 proton of anhydro-5-diazouracil[1] (δ 9.64, $\Delta\delta$ 0.51) and established that diazotization of **28** had not resulted in glycosidic bond cleavage. Therefore, the structure **32** was consistent with the data and established that diazotization of **28** had occurred with hydrolytic ring opening between N-1 and C-2.

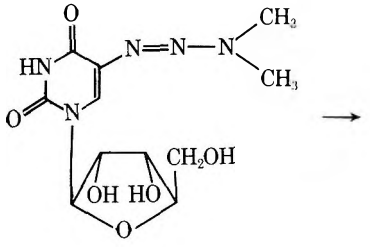
An examination of structure **28** reveals the similarity between this structure and the tautomer which could be formed by migration of an N-3 proton of 5-diazouracils to the O-2 position. The observed hydrolytic ring opening of **28** by diazotization would appear to lend credence to the above argument that the carbinolamidine tautomer of 5-diazouracils is the actual specie which undergoes ring opening during hydrolysis and methanolysis.

The unsuccessful conversion of **22** to triazoles on methanolysis is not necessarily due to a lack of ring opening of an N-1/O-2 carbinolamidine tautomer. Our data have only established that the methanolysis of **22** gives the product of nitrogen elimination and, therefore, that an alternate reaction occurs at a rate faster than the reaction which would lead to triazoles.

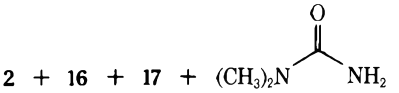
We have previously[28] presented evidence for an equilibrium in water between 5-diazo-1,3-dimethyluracil-6-hydrate (**33**) and the isomeric diazotic acid (**34**). We also pro-



posed[28] that diazo ether derivatives (e.g., **35**) were intermediates in the conversions of 5-diazouracil-6-hydrates to the 6-methanolate derivatives (e.g., **23**). The question of whether the diazotic acids or diazo ethers with structures similar to **34** and **35** were the actual species which underwent hydrolysis and methanolysis during the ring contractions prompted us to study the reaction of 5-(3,3-dimethyl-1-triazeno)uridine[1] (**36**) with methanol. Compound **36** may be viewed structurally as being very similar to **34** and **35** with the major difference being that the diazotic acid or ester has been isolated as its *N,N*-dimethyltriazeno derivative. A solution of **36** in dry methanol was heated in an oil bath at 90° and TLC of the reaction mixture revealed the presence of two nucleoside components (same chromatographic mobilities as **2** and **16**), which were separated and identified as **2** (3%) and **16** (74%) by comparisons with authentic samples. Small amounts of methyl carbamate (**17**) and 1,1-dimethylurea (**37**) were also isolated from the reaction mixture. The formation of **37** would appear to be the result of an elimination of dimethylamine from **36** followed by a reaction of dimethylamine with methyl carbamate (**17**).

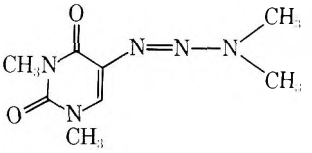


36



37

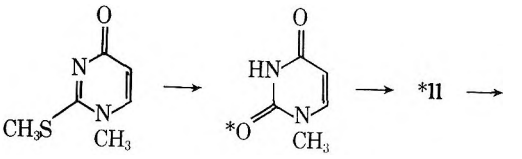
A similar experiment in which 5-(3,3-dimethyl-1-triazeno)-1,3-dimethyluracil[28] (**38**) was heated at 85° in dry



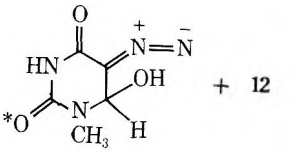
38

methanol resulted in the recovery of unchanged **38**. This would suggest that the reaction of **36** to give **2** and **16** was most likely the result of direct methanolysis of **36** rather than an initial decomposition of the 5-(3,3-dimethyl-1-triazeno) group to the corresponding 5-diazouracil.

We decided to study the nature of the structural requirements for attack by water. The most feasible approach, without doing a kinetic study, was to study an incomplete reaction of **11** with water, in which the C-2 position of **11** had been labeled with oxygen-18. Acid-catalyzed hydrolysis of 1-methyl-2-methylthio-4-pyrimidone[35] (**39**) in oxygen-18 enriched (10%) water furnished [2-^{18}O]-1-methyluracil (***40**), which then was converted to ***11** by the previously reported procedures[28,35] without loss of oxygen-18 isotope (Table III). The reaction of ***11** with 5% aqueous acetonitrile gave a mixture which was characterized by its ^{1}H NMR spectrum and revealed the presence of starting material (**11**), the product of C-6 exchange with water[28] (**41**), and **12** in the ratio 1:1:3. Therefore, the reaction had progressed to more than half completion and a mass spectrum of this mixture was examined for isotopic content. It could

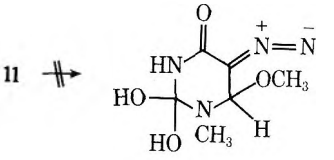


39 **40**



41

not be determined whether the specie observed in the mass spectrum was ***11**, ***41**, or a mixture of the two, since the spectra of both compounds gave the ion fragment *m/e* 153 (M − OCH_3 or M − OH) as the highest mass peak. The important feature was the presence of isotopic label in an abundance similar to the isotopic label originally present in ***11**. This established that an exchange of the C-2 oxygen atom had not occurred under the reaction conditions and suggested that the transition state may involve a predominance of carbon–nitrogen bond cleavage for ring opening rather than the formation of a tetrahedral intermediate with two hydroxyl groups (e.g., **42**) attached to C-2 (in equilibrium) prior to the transition state.[38] The presence of **41** in the reaction mixture also established that an exchange of the C-6 substituent (methoxyl in the case of **11**) can occur prior to ring opening.



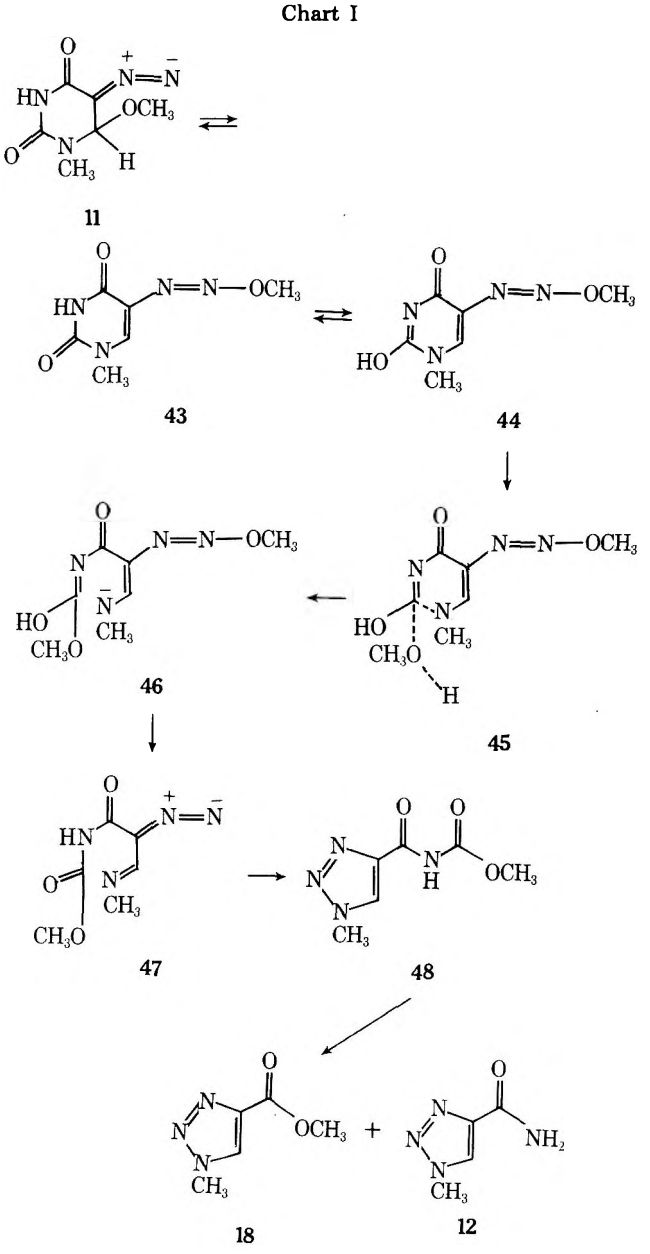
42

The results described above are consistent with the outline of Chart I, which illustrates the reaction of **11** with methanol. In this chart, **11** is in mobile equilibrium with its isomeric diazo ether (**43**). The diazo ether **43** is in tautomeric equilibrium with **44** which undergoes the rate-determining attack by methanol at C-2 to give the anion **46** with the transition state (**45**) involving partial N-1–C-2 bond cleavage. Tautomerism of **46** and elimination of methoxide ion by an electron shift gives **47**, which then rotates about the 5-6 bond and annulates between N-1 and the diazo group to give methyl *N*-(1-methyl-1,2,3-triazol-4-ylcarbonyl)carbamate (**48**). Compound **48** is assumed to be unstable under the reaction conditions and is converted into **18** and **12**.

The outline illustrated in Chart I provides a rational account of the experimental observations. It accounts for the exchange of the C-6 methoxyl group of **11** for a hydroxyl group during the partial hydrolysis of ***11**, the failure of the N-3 methylated compounds to be converted to triazoles, and for the observed conversion of the triazeno derivative **36** into triazoles on heating in methanol. Isotopic retention during the partial hydrolysis of ***11** is also accounted for by the transition state **45**. Annulation of **47** has ample precedence in the literature.[39-41] The intermediacy of **48** in the reaction of **11** with methanol is consistent with the isolation of **20** and with the competitive formation of esters and amides during methanolysis of N-1 alkylated 5-diazouracils.

By evoking the intermediacy of **46**–**48** the chart also accounts for the lack of 1,2,3-triazole-4-carboxylic acids dur-

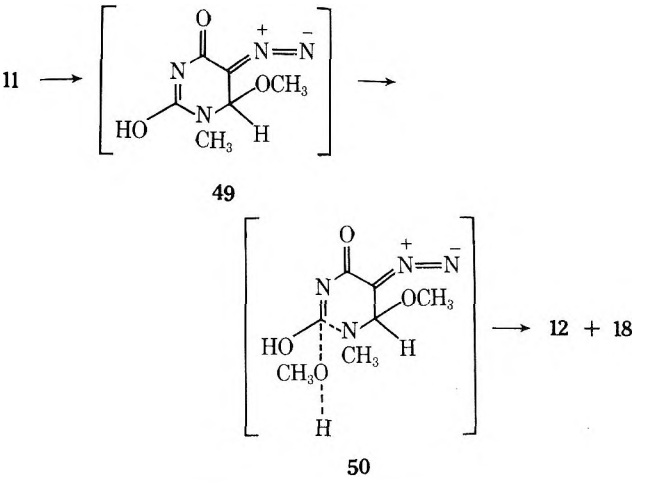
Chart I



ing the hydrolysis of 5-diazouracils, since the similar carbamic acid intermediates may decarboxylate[13] at a rate faster than the rate of hydrolysis to the acids. In contrast to decarboxylation, these intermediates may undergo competitive ester exchange and methanolysis to give both **12** and **18**.

We caution that this agreement of experiment with the model does not prove that the model is absolutely correct. However, we feel that it justifies using the model as a basis for interpretation at this time.

If the model is correct in its broader aspects, it may yet be faulty in detail. To be specific, our experiments do not require **44** to be the only intermediate which ring opens after attack by methanol. We cannot exclude the possibility that **11** first tautomerizes to afford **49**, which then undergoes a rate-limiting attack by methanol as illustrated by the transition state **50**. We find this transition state (**50**) attractive on the grounds that the driving force for ring opening between N-1 and C-2 would be the extended conjugation resulting after ring opening and expulsion of the C-6 methoxyl group. However, this transition state (**50**) is unattractive on the grounds of the stability of the *N,N*-dimethyltriazeno group (which is not hydrolyzed under the



reaction conditions), the facile conversion of **36** into triazoles, and also by the detectable[28] equilibrium between **33** and the isomeric diazotic acid (**34**) in aqueous solution.

Experimental Section

Ultraviolet spectra were recorded on a Beckman DK-2 or Beckman Acta CIII recording spectrophotometer. Infrared spectra were determined on a Beckman IR8 spectrophotometer in compressed potassium bromide disks and ^1H NMR spectra (Me_2SO-d_6 and Me_2SO-d_6–deuterium oxide) on a Varian A56/60 instrument using 2,2-dimethylsilapentane-5-sulfonate (DSS) as internal standard and chemical shifts are expressed as parts per million (δ) from DSS. Electron impact mass spectra were recorded on a Hewlett-Packard 5930A Dodecopole instrument, ion source and direct inlet temperatures of 190°, ionizing energy 70 eV. Chemical ionization mass spectra were recorded on a Varian CH 7 instrument, modified for high-pressure operation,[42] using methane reagent gas, ion source and direct inlet temperatures of 190°, reagent gas pressure in the ion source 0.5 Torr. All samples for mass spectra were introduced by direct probe. Specific rotations were determined on a Perkin-Elmer 141 digital readout polarimeter. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Anhydrous methanol was obtained by distillation from calcium hydride and anhydrous acetonitrile was obtained by distillation from phosphorus pentoxide. These solvents were stored over activated Linde type 3A 4–8 mesh molecular sieves. Concentrations in vacuo were performed at or below 40°. Thin layer chromatography was performed on 5 × 20 cm glass plates coated to a thickness of 0.25 mm with Mallinckrodt SilicAR 7GF. Samples for elemental analyses were dried at 0.5 Torr in an Abderhalden apparatus using phosphorus pentoxide as the desiccant and the solvent as indicated.

Hydrolysis of $O^{5'}$-6(*S*)-Cyclo-5-diazouridine (1) to Afford 1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxamide (2). $O^{5'}$-6(*S*)-Cyclo-5-diazouridine[1] (**1**, 100 mg) was finely powdered in a mortar and added to 5% (v/v) aqueous acetonitrile (10 ml). The mixture was sealed in a stainless steel reaction vessel, heated for 18 hr in an oil bath which was maintained at 100°, and then allowed to cool to room temperature. The bleed outlet of the reaction vessel was connected to a 100-ml gas collection bulb which had been flushed with nitrogen and evacuated to 0.2 Torr. The bleed valve of the reaction vessel was opened and carbon dioxide was allowed to collect in the bulb. The reaction mixture was evaporated to dryness in vacuo to give **2** (89.4 mg, quantitative), mp 198–201°. A small sample was recrystallized for analysis from hot methanol and dried for 18 hr at the reflux temperature of toluene (Table II).

Anal. Calcd for $C_8H_{12}N_4O_5$: C, 39.35; H, 4.95; N, 22.94. Found: C, 39.42; H, 5.24; N, 22.60.

[4-^{18}O]Uridine (*3). 4-Thiouridine[43] (2.18 g) was methylated by the literature[14] procedure to give 4-methylthiouridine (**4**, 3.42 g) as a hard foam which may have contained some sodium iodide. This foam was used for the preparation of *3 without further purification. The foam was dissolved in a mixture of oxygen-18 enriched (10%) water (2 ml) and ethanol (25 ml) and concentrated hydrochloric acid (4 drops) was then added to the solution. The mixture was heated to reflux temperature, reflux temperature was maintained for 2 hr, and the solution then evaporated in vacuo to afford a hard foam. The foam was coevaporated with ethanol (25 ml), then dissolved in hot ethanol (3 ml) and the solution was ap-

plied to the top of a column (2 × 43 cm) of silica gel which had been packed in chloroform. The column was eluted with a chloroform–methanol mixture (3:1 v/v), with 100-ml fractions being collected. Fractions 7–12 contained uridine as determined by TLC in the same solvent system. These fractions were combined and concentrated in vacuo to afford a hard foam. This foam was dissolved in ethanol (8 ml) and then allowed to stand at 5° for 48 hr to give 38 (1.10 g, 55%), mp 167–169° (lit.[44] mp 164–165°) (see Table III).

Hydrolysis of $O^{5'}$-6(*S*)-Cyclo-5-diazo-2'-deoxyuridine (5) to Afford 1-(2-Deoxy-β-D-ribofuranosyl)-1,2,3-triazole-4-carboxamide (6). 5-Diazo-2'-deoxyuridine[1] (**5**, 275 mg) was added to 5% (v/v) aqueous acetonitrile (15 ml) and the solution sealed in a stainless steel reaction vessel. The reaction vessel was heated for 18 hr in an oil bath maintained at 100° and then allowed to stand at room temperature for 18 hr. The colorless crystals which had separated from solution were collected by filtration and dried for 2 hr at the reflux temperature of methanol to give **6** (219 mg, 90%): mp 151–152°; uv λ_{max} (methanol) 210 nm (ε 11900); ^{1}H NMR δ 8.77 (s, 1, H5), 7.85 (bs, 1, NH), 7.53 (bs, 1, NH), 6.59 (t, 1, W = 12, 1'H); ir 2.96 (NH_2), 5.97 μ (C=O); MS *m/e* 198/2.9 (M − 30), 139/15 (B + 29), 117/49 (S), 113/13 (B + 2H), 112/23 (B + H).

Anal. Calcd for $C_8H_{12}N_4O_4$: C, 42.11; H, 5.30; N, 24.55. Found: C, 42.00; H, 5.01; N, 24.25.

Hydrolysis of 5-Diazouracil-6-methanolate (7) to Afford 1,2,3-Triazole-4-carboxamide (8). 5-Diazouracil-6-methanolate[2] (**7**, 1 g) was dissolved in a mixture of acetonitrile (250 ml) and water (10 ml) by heating slightly on a steam bath. The solution was sealed in a stainless steel reaction vessel, heated for 18 hr at 100° (internal temperature), and allowed to cool to room temperature and the mixture was evaporated to dryness in vacuo. The solid was recrystallized from glacial acetic acid (20 ml) to give **8** (638 mg, 98%), mp 261–263° (lit.[24] mp 253–254°), uv λ_{max} (water) 197 nm (ε 9400).

Anal. Calcd for $C_3H_4N_4O$: C, 32.15; H, 3.60; N, 49.98. Found: C, 32.39; H, 3.83; N, 49.95.

1,2,3-Triazole-4-carboxylic Acid (9). 1,2,3-Triazole-4-carboxamide (**8**, 2.82 g) was dissolved in 0.99 *N* sodium hydroxide (56.2 ml) and the solution was heated for 7 days on a steam bath. An additional quantity of 0.99 *N* sodium hydroxide (25.5 ml) was then added to the solution and heating was continued for another 24 hr. The solution was allowed to cool to room temperature and then acidified by the addition of 0.96 *N* hydrochloric acid (84.2 ml). Colorless crystals separated from the solution after standing for 18 hr at 5° and were collected by filtration to give **9** (1.64 g, 58%), mp 230–233° (lit.[25,26] mp 222–224° and 214–215°), uv λ_{max} (water) 211 nm (ε 6800).

Methyl 1,2,3-Triazole-4-carboxylate (10). Compound **9** (1.24 g) was added to a solution of dry hydrogen chloride (2 g) in methanol (100 ml). The mixture was heated at reflux temperature for 3.5 hr and then evaporated to dryness in vacuo. The residue was coevaporated with methanol (2 × 20 ml) and then crystallized by trituration with chloroform (20 ml at −30°) for 30 min. The insoluble white solid was collected by filtration and recrystallized from hot methanol (10 ml) to give **10** (1.05 g, 76%): mp 144–145° (lit.[27] mp 145°); uv λ_{max} (water) 219 nm (ε 8100); ir 3.17 (NH), 5.8 μ (C=O) [lit.[27] 3.2 (NH) and 5.8 μ (C=O)].

Hydrolysis of 5-Diazo-1-methyluracil-6-methanolate (11) to Afford 1-Methyl-1,2,3-triazole-4-carboxamide[30] (12). 5-Diazo-1-methyluracil-6-methanolate[30] (**11**, 500 mg) was dissolved in 5% (v/v) aqueous acetonitrile (15 ml) and the solution was placed in a stainless steel reaction vessel. The sealed reaction vessel was heated for 3.5 hr in an oil bath maintained at 100° and then allowed to stand at ambient temperature for 18 hr. The white solid which had separated from solution was collected by filtration and washed with methanol (5 ml) to give **12** (266 mg, 78%), mp 261–263°. A small sample was recrystallized from methanol for analysis and dried for 18 hr at the reflux temperature of toluene, melting point unchanged, uv λ_{max} (water) 210 nm (ε 11800).

Anal. Calcd for $C_4H_6N_4O$: C, 38.09; H, 4.80; N, 4.42. Found: C, 38.19; H, 4.56; N, 44.45.

Methanolysis of $O^{5'}$-6(*S*)-Cyclo-5-diazouridine (1) to Afford Methyl Carbamate (17), Methyl 1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxylate (16), and 1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxamide (2). $O^{5'}$-6(*S*)-Cyclo-5-diazouridine[1] (**1**, 300 mg) was dissolved in anhydrous methanol (20 ml) and the solution sealed in a stainless steel reaction vessel. The reaction vessel was heated for 18 hr in an oil bath maintained at 100° and then allowed to cool to room temperature. SilicAR CC7 (2.5 g) was added to the solution and the resulting mixture was evaporated to dryness in vacuo and the residue applied to the top of a vacuum packed dry column (1 × 18 cm) of SilicAR CC7. The column was eluted with a chloroform–methanol mixture (5:1 v/v), with 5-ml fractions being collected. Fraction 3 was evaporated to dryness in vacuo and the residue was allowed to sublime at ambient temperature and pressure to give methyl carbamate (**17**): mp 54–55°; ir 2.88 (NH_2) and 5.90 μ (C=O); MS *m/e* 75/41 (M), 59/3 (M − NH_2), 44/100 (M − CH_3O); ^{1}H NMR δ 3.54 (s, 3, CH_3) and 6.47 (bs, 2, NH_2). A commercial sample of **17** had identical properties. The yield of **17** was determined from the ^{1}H NMR spectrum of the crude reaction mixture obtained from another run (see text). Fractions 5–7 contained **16** as determined by TLC in the same solvent system and were combined, evaporated to dryness in vacuo, and recrystallized from methanol (3 ml) to give **16** (208 mg, 75%): mp 150–153°; uv λ_{max} (methanol) 214 nm (ε 11000); $[\alpha]^{26}$D −55.0° (*c*, 1, water).

Anal. Calcd for $C_9H_{13}N_3O_6$: C, 41.70; H, 5.06; N, 16.21. Found: C, 41.61; H, 5.07; N, 16.22.

Fractions 11–13 contained **2** and were evaporated to dryness in vacuo and the residue recrystallized from methanol (3 ml) to give **2** (20.2 mg, 8%) as determined by TLC in the same solvent system, mp 198–200°, uv λ_{max} (water) 210 nm (ε 11400).

1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxamide (2). Compound **16** (14.8 mg, obtained by methanolysis of **1**) was added to methanol which had been previously saturated at 0° with ammonia (10 ml). The reaction vessel was tightly stoppered, and the mixture was allowed to stand at room temperature for 18 hr and then evaporated in vacuo to dryness to give pure **2** (quantitative), mp 202–204°, TLC and ir spectrum identical with those of a sample of **2** obtained from the reaction of **15** with methanolic ammonia.

Methyl 1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxylate (16). Compound **15** (495 mg) was dissolved in methanol (25 ml) and sodium methoxide (5 mg) was then added. The solution was stirred at room temperature for 3.5 hr and then neutralized by the addition of an excess of dry ice. The solution was evaporated in vacuo to afford a syrup which crystallized on trituration with diethyl ether (20 ml) for 1 hr. The white solid was collected by filtration, recrystallized from methanol (4 ml), and dried for 4 hr at the reflux temperature of toluene to give **16** (139 mg, 62%): mp 151–153°; uv λ_{max} (water) 214 nm (ε 10700); $[\alpha]^{26}$D −55.9° (c 1, water).

Anal. Calcd for $C_9H_{13}N_3O_6$: C, 41.70; H, 5.06; N, 16.21. Found: C, 41.75; H, 5.08; N, 16.05.

Methanolysis of 5-Diazo-1-methyluracil-6-methanolate (11) to Afford 1-Methyl-1,2,3-triazole-4-carboxamide[30] (12), Methyl 1-Methyl-1,2,3-triazole-4-carboxylate (18), and Methyl Carbamate (17). 5-Diazo-1-methyluracil-6-methanolate[28] (**11**, 2.58 g) was dissolved in dry methanol (20 ml). The solution was sealed in a stainless steel reaction vessel, heated for 18 hr in an oil bath maintained at 135°, and then allowed to cool to room temperature. The white solid which had separated from solution was collected by filtration and washed with methanol (5 ml) to give **12** (1.12 g, 63%), mp 261–263°, uv λ_{max} (water) 210 nm (ε 11000). The filtrate was concentrated to 10 ml in vacuo and allowed to stand at room temperature for 2 hr to give **18** (292 mg, 15%), mp 158–161°. A small sample of **18** was recrystallized from methanol for analysis and dried for 3.5 hr at the reflux temperature of toluene, melting point unchanged, uv λ_{max} (water) 215 nm (ε 10200).

Anal. Calcd for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.79; H, 5.22; N, 30.04.

The filtrate was evaporated to dryness in vacuo and the residue was extracted with chloroform (15 ml). The chloroform extract was evaporated to dryness in vacuo and the residue was sublimed at 70° (16 Torr) to give **17** (53 mg, 6%), mp 52–53°, ir and ^{1}H NMR spectra identical with those of a commercial[32] sample.

1-Methyl-1,2,3-triazole-4-carboxamide (12). Compound **18** (75 mg, from the methanolysis of **11**) was added to a solution of methanol which had been previously saturated at −5° with ammonia (5 ml). The reaction vessel was tightly stoppered and the mixture was allowed to stand at room temperature for 18 hr. The solution was then evaporated to dryness in vacuo, the residue was triturated with methanol (1.5 ml) for 30 min, and the insoluble material was collected by filtration to give **12** (64.4 mg, 96%), mp 260–262°, uv λ_{max} (water) 210 nm (ε 11300).

Methyl-1,2,3-triazole-4-carboxylic Acid (19). Compound **12** (900 mg) was added to 0.99 *N* sodium hydroxide (8.30 ml). The solution was heated for 24 hr at reflux temperature, cooled to room temperature, and then acidified by the addition of 0.96 *N* hydrochloric acid (8.60 ml). The solution was allowed to stand at 5° for 18 hr and the white solid which had separated from solution was collected by filtration to give **19** (796 mg, 88%), mp 240–242°. An

additional quantity of **19** (82 mg, 97%), mp 240–242°, was obtained by concentrating the filtrate to 5 ml at reflux temperature and then allowing the solution to stand at 5° for 18 hr. A small sample was recrystallized from water for analysis and dried for 5 hr at the reflux temperature of toluene, melting point unchanged, uv λ_{max} (water) 211 nm (ϵ 8600).

Anal. Calcd for $C_4H_5N_3O_2$: C, 37.80; H, 3.97; N, 33.06. Found: C, 37.71; H, 4.18; N, 33.18.

Methyl 1-Methyl-1,2,3-triazole-4-carboxylate (18). 1-Methyl-1,2,3-triazole-4-carboxylic acid (**19**, 853 mg) was added to a mixture of dry hydrogen chloride (0.5 g) and methanol (25 ml). The mixture was heated for 18 hr at reflux temperature and the solution was then evaporated to dryness in vacuo. The residue was coevaporated with methanol (2 × 25 ml), dissolved in hot methanol (20 ml), and then allowed to stand at 5° for 18 hr to give **18** (793 mg, 84%), mp 159–161°. A small sample was recrystallized for analysis from methanol and dried for 3 hr at the reflux temperature of benzene, melting point unchanged, uv λ_{max} (water) 215 nm (ϵ 10200).

Anal. Calcd for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.48; H, 5.16; N, 29.56

Methanolysis of 5-Diazouracil-6-methanolate (7) to Afford Methyl *N*-(1,2,3-Triazol-4-ylcarbonyl)carbamate (20). 5-Diazouracil-6-methanolate[1] (**7**, 500 mg) was dissolved in a mixture of methanol (1 ml) and acetonitrile (19 ml). The solution was sealed in a stainless steel reaction vessel, heated for 18 hr in an oil bath maintained at 132°, and then allowed to cool to room temperature. The solution was evaporated to dryness in vacuo to give **20** (500 mg, quantitative), mp 194–196°. A small sample was recrystallized from methanol for analysis and dried for 2.5 hr at the reflux temperature of toluene, mp 202–204°, uv λ_{max} (water) 228 nm (ϵ 10600).

Anal. Calcd for $C_5H_6N_4O_3$: C, 35.30; H, 3.55; N, 32.93. Found: C, 35.39; H, 3.63; N, 33.09.

Hydrolysis of Methyl *N*-(1,2,3-Triazol-4-ylcarbonyl)carbamate (20) to Afford 1,2,3-Triazole-4-carboxamide (8). Methyl *N*-(1,2,3-triazol-4-ylcarbonyl)carbamate (**20**, 146 mg) was added to 1.73 of 0.99 *N* sodium hydroxide. The solution was heated on a steam bath for 24 hr and then allowed to cool to room temperature. The solution was acidified by the addition of 1.02 *N* hydrochloric acid (1.69 ml) at which time a gas was evolved. The solution was evaporated to dryness in vacuo and the white solid which remained was then triturated with water (1 ml). The insoluble material was collected by filtration and dried for 1.5 hr at the reflux temperature of toluene to give 8 (47.7 mg, 50%), mp 256–259°, uv λ_{max} (water) 197 nm (ϵ 9300).

1,2,3-Triazole-4-*N*-methylcarboxamide (25). Compound **10** (500 mg) was dissolved in a solution of methanol which had been previously saturated at 30° with methylamine (15 ml). The solution was sealed in a stainless steel reaction vessel, heated for 18 hr in an oil bath maintained at 80°, and allowed to cool to room temperature. The solution was evaporated to dryness in vacuo, and the residue was coevaporated with methanol (2 × 10 ml) and then allowed to stand at 5° for 18 hr to give colorless crystals which were collected by filtration. The crystals were recrystallized from hot ethanol (20 ml) and dried at the reflux temperature of toluene for 18 hr to give **26** (375 mg, 83%), mp 258–261°, uv λ_{max} (water) 211 nm (ϵ 9900).

Anal. Calcd for $C_4H_6N_4O$: C, 38.09; H, 4.80; N, 44.42. Found: C, 38.11; H, 4.74; N, 44.62.

1-Methyl-1,2,3-triazole-4-*N*-methylcarboxamide (27). Compound 18 (342 mg) was added to a solution of methanol which had been previously saturated at 30° with methylamine (20 ml). The solution was sealed in a stainless steel reaction vessel, heated for 18 hr in an oil bath maintained at 80°, and then allowed to cool to room temperature. The solution was evaporated to dryness in vacuo and the residue coevaporated with methanol (10 ml). The solid was recrystallized from methanol (15 ml) to give **27** (297 mg, 87%), mp 215–216°. A small sample was recrystallized from methanol for analysis and dried for 3 hr at the reflux temperature of toluene, melting point unchanged, uv λ_{max} (water) 214 nm (ϵ 11700).

Anal. Calcd for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.99; H, 5.79; N, 39.84.

Methanolysis of 5-(3,3-Dimethyl-1-triazeno)uridine (36) to Afford Methyl Carbamate (17), *N,N*-Dimethylurea (37), Methyl 1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxylate (16), and 1-(β-D-Ribofuranosyl)-1,2,3-triazole-4-carboxamide (2). 5-(3,3-Dimethyl-1-triazeno)uridine[1] (**36**, 590 mg) was dissolved in dry methanol (25 ml). The solution was sealed in a stainless steel reaction vessel, heated for 18 hr in an oil bath maintained at 90°, and then allowed to cool to room temperature. The solution was examined by TLC (chloroform–methanol, 5:1 v/v) and appeared to contain two nucleoside components: a major component with a R_f of 0.8 (ester **18**) and a minor component with R_f 0.2 (amide **2**). SilicAR CC7 (3 g) was added to this solution. The mixture was evaporated to dryness in vacuo and the residue was applied to the top of a vacuum packed dry column (2 × 20 cm) of SilicAR CC7 (50 g). The column was eluted with the same solvent and 1-ml fractions were collected. Fractions 1–6 contained a brown oil which was sublimed at ambient temperature and 16 Torr to give **17** (2 mg, 1.4%), mp 51–53°. The sublimation apparatus was then immersed in an oil bath at 120° and evacuated to 16 Torr. Compound **37** (36 mg, 17%) condensed on the cold finger: mp 165–169° (lit.[44] mp 182°); ir 3.05 and 3.15 (NH_2), 6.25 μ (C=O); ^{1}H NMR δ 2.70 (s, 6, 2-CH_3) and 5.60 (bs, 2, NH_2); MS *m/e* 88/57 (M), 72/9 (M − NH_2), 44/100 [$N(CH_3)_2$ and M − $N(CH_3)_2$]. Fractions 7–13 contained the faster moving nucleoside component (**16**, 334 mg, 69% after recrystallization from methanol): mp 153–155°; uv λ_{max} (water) 214 nm (ϵ 10600); $[\alpha]^{26}D$ −57.0° (c 1, water). Fractions 18–24 contained a mixture of three components (as determined by TLC in the same solvent system). An additional quantity of **16** (22.4 mg, 76%, mp 151–153°) was obtained from these fractions by crystallization from methanol (2 ml). Fractions 25–44 contained only one compound and were evaporated to dryness in vacuo to give **2** (13.4 mg, 3%), mp 202–204°, uv λ_{max} (water) 210 nm (ϵ 12000).

[2-^{18}O]-1-Methyluracil (*40). 1-Methyl-2-methylthio-4-pyrimidone[35] (**39**, 4.68 g) was added to a solution of oxygen-18 enriched (10%) water (1.55 ml) and ethanol (20 ml) and concentrated hydrochloric acid (0.04 ml) was then added. The mixture was heated at reflux for 18 hr, an additional quantity (0.5 ml) of concentrated hydrochloric acid was then added, and heating at reflux temperature was continued for an additional 2 days. The mixture was allowed to cool to room temperature, and the white solid which had separated from solution was collected by filtration, washed with ethanol (3 ml), and recrystallized from water (35 ml) to give ***40** (3.21 g, 85%), mp 231–233. The filtrate was evaporated to dryness in vacuo, the residue was dissolved in water (4 ml), and the pH of the solution was adjusted to 7 with 1 *N* sodium hydroxide. The solution was then evaporated to dryness in vacuo and the residue recrystallized from water (1 ml) to give an additional quantity of ***40** (313 mg, 94%), mp 231–233°. The literature[35] reports mp 232–233° for 1-methyluracil.

5-Bromo-5′-deoxyuridine (30). 5′-Deoxyuridine[37] (**29**, 500 mg) was added to acetic anhydride (3 ml) and the mixture was cooled to 10°. A solution of bromine (380 mg) in acetic acid (0.3 ml) was added to the mixture and the solution was allowed to stand at 5° for 20 hr. Additional bromine (1 drop) was then added, the solution was evaporated to a syrup in vacuo, and the syrup was stored in vacuo (16 Torr) for 48 hr using potassium hydroxide pellets as the desiccant. A solution (25 ml) of methanol, which had been previously saturated at −5° with ammonia, was added to the syrup. The vessel was tightly stoppered and the mixture was allowed to stand at room temperature for 20 hr. The solution was evaporated to a syrup in vacuo, and the syrup was dissolved in ethanol (5 ml) and allowed to stand at room temperature for 18 hr to give **30** (518 mg, 77%), mp 181–183°. A small sample was recrystallized from ethanol for analysis and dried at the reflux temperature of toluene for 5 hr, mp 184–185°, uv λ_{max} (methanol) 279 nm (ϵ 9900).

Anal. Calcd for $C_9H_{11}N_2O_5Br$: C, 35.07; H, 3.60; N, 9.09. Found: C, 34.80; H, 3.41; N, 9.21.

5-Amino-5′-deoxyuridine (31). 5-Bromo-5′-deoxyuridine (**30**, 1.16 g) and anhydrous liquid ammonia (15 ml) were heated at 50° in a stainless steel reaction vessel for 24 hr and the ammonia was then removed in vacuo to give a hard foam. This foam was dissolved in 1 *N* hydrochloric acid (12 ml), the solution was passed through a column (1.5 × 17 cm) of Dowex 50W-X2 (H^+) ion exchange resin, and the column was washed with water (75 ml). The column was then eluted with 1 *N* hydrochloric acid and 10-ml fractions were collected. Fractions 4–11 were combined and evaporated to a thick suspension in vacuo. This suspension was coevaporated with ethanol (2 × 100 ml). The solid was recrystallized from ethanol (50 ml) with sufficient water (approximately 5 ml) being added to effect solution at reflux temperature which furnished the hydrochloride salt of **31** (744 mg, 71%): mp 225° dec; uv λ_{max} (water) 294 nm (ϵ 7700), (pH 1) 264 nm (ϵ 11000).

Anal. Calcd for $C_9H_{13}N_3O_5 \cdot HCl \cdot 0.5H_2O$: C, 37.44; H, 5.24; N, 14.56. Found: C, 37.62; H, 5.24; N, 14.51.

The hydrochloride salt of **31** (710 mg) was dissolved in water (25 ml) and the pH of the solution adjusted to 7 by the addition of

Dowex 1X2 (OH^-) ion exchange resin. The resin was removed by filtration and washed with water (10 ml) and the filtrate evaporated to dryness in vacuo. The solid was recrystallized from water (5 ml) and dried for 6 hr at the reflux temperature of toluene to give **31** (565 mg, 92%), mp 226–228°, uv λ_{max} (water) 293 nm (ϵ 8000), (pH 1) 265 nm (ϵ 10000).

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.45; H, 5.39; H, 17.28. Found: C, 44.55; H, 5.20; N, 17.26.

O^2-2′-Cyclo-5-amino-5′-deoxyuridine (28). 5-Amino-5′-deoxyuridine (**31**, 2.44 g), diphenyl carbonate (3.89 g), and sodium bicarbonate (163 mg) were combined and *N,N*-dimethylacetamide (10 ml) added to the mixture. The mixture was heated for 25 min in an oil bath maintained at 170° and then added dropwise with good stirring to diethyl ether (200 ml). The solid was collected by filtration, washed with diethyl ether (160 ml), recrystallized from methanol (125 ml), and dried for 12 hr at the reflux temperature of toluene to give **28** (1.92 g, 85%), mp 262–263°, uv λ_{max} (methanol) 289 nm (ϵ 7200) and 258 (6300).

Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 48.03; H, 4.94; N, 18.66.

Diazotization of O^2-2′-Cyclo-5-amino-5′-deoxyuridine (28) to Give Diazo Compound 32. Compound **28** (806 mg) was added to 1.02 *N* hydrochloric acid (5.27 ml) at 0° and 0.95 *M* aqueous sodium nitrite solution (4.15 ml) was added dropwise to the mixture over a period of 8 min while maintaining the temperature at 0–2°. After the addition was complete, the mixture was stirred in the cold for 30 min and then added to 35 ml of a chloroform–acetonitrile (3:2 v/v) mixture. The resulting mixture was stirred at room temperature for 10 min, the organic layer was decanted, and the aqueous layer was again stirred for 10 min with 35 ml of the chloroform–acetonitrile mixture. The organic layer was decanted, and the aqueous layer was concentrated to 6 ml in vacuo and then extracted with 3 × 15 ml of the chloroform–acetonitrile mixture. The organic solutions were then combined, dried ($MgSO_4$) at 5° for 18 hr, and then concentrated to a syrup in vacuo. The syrup was dissolved in hot 1-propanol (6 ml) and the solution allowed to stand at 5° for 18 hr to give light yellow crystals which were collected by filtration and dried for 3 hr at the reflux temperature of methanol to give **32** (542 mg, 60%): mp 148–149°; uv λ_{max} (methanol) 249 nm (ϵ 30,000); ir 2150 cm^{-1} (diazo).

Anal. Calcd for $C_9H_{10}N_4O_5$: C, 42.53; H, 3.97; N, 22.04. Found: C, 42.59; H, 4.23; N, 21.89.

1-(β-D-Ribofuranosyl)-$O^{5'}$-6(*S*)-Cyclo-5-diazo-1,6-dihydro-3-methylpyrimidine-2,4(6*H*)-dione [$O^{5'}$-6(*S*)-Cyclo-5-diazo-3-methyluridine, 13]. 5-Amino-3-methyluridine[45] (1.0 g) was dissolved in 50% (v) aqueous acetic acid (8.90 ml) and the solution was cooled to 0° in an ice–salt bath. A 6.9% aqueous solution of sodium nitrite (3.70 ml) was added dropwise to the solution over a peroid of 12 min while maintaining the temperature at 0–2°. After the addition was complete, the solution was stirred in the cold for 10 min and then concentrated to a syrup in vacuo. The syrup was coevaporated first with toluene (2 × 20 ml), then ethanol (2 × 20 ml), the residue was dissolved in hot ethanol (20 ml), and the solution was allowed to stand at 5° for 18 hr to give **13** (790 mg, 76%), mp 192–193°. A small sample was recrystallized from ethanol for analysis and dried for 18 hr at the reflux temperature of toluene: melting point unchanged; uv λ_{max} (methanol) 265 nm (ϵ 17000); ir 4.73 μ (diazo).

Anal. Calcd for $C_{10}H_{12}N_4O_6$: C, 42.29; H, 4.24; N, 19.73. Found: c, 42.24; H, 4.24; N, 19.73.

Acknowledgments. The authors wish to thank Mr. L. H. Wojcik and Dr. J. A. McCloskey for the determination of mass spectra. This work was supported by Public Health Service Research Grant CA 11147 from the National Cancer Institute.

Registry No.—**1**, 38099-07-9; **2**, 31843-67-1; **5**, 38099-08-0; **6**, 57362-79-5; **7**, 35124-90-4; **8**, 53897-99-7; **9**, 16681-70-2; **10**, 21977-71-9; **11**, 53897-98-6; **12**, 39039-49-1; **13**, 57362-80-8; **15**, 31843-61-5; **16**, 57362-81-9; **17**, 598-55-0; **18**, 57362-82-0; **19**, 16681-71-3; **20**, 57362-83-1; **25**, 57362-84-2; **27**, 57362-85-3; **28**, 57362-86-4; **30**, 19556-65-1; **31**, 57362-87-5; **31** HCl, 57362-88-6; **32**, 57362-89-7; **36**, 38099-11-5; **37**, 598-94-7; **39**, 6330-98-9; **40**, 57362-90-0; 4-thiouridine, 13957-31-8; 5′-deoxyuridine, 15958-99-3; bromine, 7726-95-6; 5-amino-3-methyluridine, 57362-91-1.

References and Notes

(1) T. C. Thurber and L. B. Townsend, *J. Heterocycl. Chem.*, **9**, 629 (1972).
(2) J. P. Paolini, R. K. Robins, and C. C. Cheng, *Biochim. Biophys. Acta*, **72**, 114 (1963).
(3) J. Gut, J. Moranek, C. Parkanji, M. Prystas, J. Skoda, and F. Sorm, *Collect. Czech. Chem. Commun.*, **24**, 3154 (1959).
(4) T. J. Bardos, R. R. Herr, and T. Enkoji, *J. Am. Chem. Soc.*, **77**, 960 (1955).
(5) S. H. Chang, I. K. Kim, D. S. Park, and B-S. Hahn, *Daehan Hwahak Hwoejee*, **9**, 29 (1965).
(6) Preliminary communication: T. C. Thurber and L. B. Townsend, *J. Am. Chem. Soc.*, **95**, 3081 (1973).
(7) K. Biemann and J. A. McCloskey, *J. Am. Chem. Soc.*, **84**, 2005 (1962).
(8) L. B. Townsend in "Synthetic Procedures in Nucleic Acid Chemistry", Vol. II, W. W. Zorbach and R. S. Tipson, Ed., Wiley, New York, N.Y., 1973, p 287.
(9) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", Wiley, New York, N.Y., 1964, p 137.
(10) G. Alonso, M. T. Garcia-Lopez, G. Garcia-Munoz, R. Madronero, and M. Rico, *J. Heterocycl. Chem.*, **7**, 1269 (1970).
(11) F. A. Lehmkuhl, J. T. Witkowski, and R. K. Robins, *J. Heterocycl. Chem.*, **9**, 1195 (1972).
(12) O. Makabe, S. Fukatsu, and S. Umezawa, *Bull. Chem. Soc. Jpn.*, **45**, 2577 (1972).
(13) A. F. Hegarty and L. N. Frost, *J. Chem. Soc., Perkin Trans. 2*, 1719 (1973).
(14) T. Ueda and J. J. Fox, *J. Med. Chem.*, **6**, 697 (1963).
(15) M. J. Robins and R. K. Robins, *J. Am. Chem. Soc.*, **84**, 4464 (1962).
(16) F. Michael and G. Baum, *Chem. Ber.*, **90**, 1595 (1957).
(17) J. Baddiley, J. G. Buchanan, and G. Osborne, *J. Chem. Soc.*, 1651 (1958); 3603 (1958).
(18) G. Garcia-Munoz, J. Iglesias, M. Lora-Tamazo, and R. Madronero, *J. Heterocycl. Chem.*, **5**, 699 (1968).
(19) H. El Khadem, D. Horton, and M. H. Mershreki, *Carbohydr. Res.*, **16**, 409 (1971).
(20) R. E. Harmon, R. A. Earl, and S. K. Gupta, *Chem. Commun.*, 296 (1971).
(21) R. W. Sidwell, J. H. Huffman, G. P. Khare, L. B. Allen, J. T. Witkowski, and R. K. Robins, *Science*, **177**, 705 (1972).
(22) J. Cadet and R. Teoule, *J. Am. Chem. Soc.*, **96**, 6517 (1974).
(23) R. Shapiro and M. Danzig, *Biochim. Biophys. Acta*, **5**, 319 (1973).
(24) S. Yamada, T. Mizoguchi, and A. Ayata, *Yakugaku Zasshi*, **77**, 452 (1957).
(25) C. Pedersen, *Acta Chem. Scand.*, **13**, 888 (1959).
(26) R. Huttel and G. Wenzel, *Justus Liebigs Ann. Chem.*, **593**, 207 (1955).
(27) R. P. Woerner and H. Reimlinger, *Chem. Ber.*, **103**, 1908 (1970).
(28) T. C. Thurber and L. B. Townsend, *J. Heterocycl. Chem.*, **12**, 711 (1975).
(29) O. Makabe, S. Fukatsu, and S. Umezawa, *Bull. Chem. Soc. Jpn.*, **45**, 2577 (1972).
(30) T. C. Thurber, R. J. Pugmire, and L. B. Townsend, *J. Heterocycl. Chem.*, **11**, 645 (1974).
(31) The synthesis of **13** is described in the Experimental Section of this paper. The structural assignment for **13** was accomplished by a method similar[1] to that used for the structural assignment for **1**.
(32) A commercial sample of **17** was purchased from J. T. Baker Co., Plainsville, N.J.
(33) Reaction of **7** in refluxing methanol with the inclusion of triethylamine (10 mol %) gave a product which had the same chromatographic mobility as uracil. A chromatographic comparison of the reaction mixture with **20** revealed that **20** was not formed in a detectable amount. This precluded a kinetic study of possible base catalysis and suggested that ring opening does not proceed by an ElcB mechanism.
(34) T. C. Thurber and L. B. Townsend, manuscript in preparation.
(35) D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 217 (1955).
(36) H. Blitz and H. Paetzold, *Justus Liebigs Ann. Chem.*, **433**, 64 (1923).
(37) I. Wempen, I. L. Doerr, L. Kaplan, and J. J. Fox, *J. Am. Chem. Soc.*, **82**, 1624 (1960).
(38) An alternate explanation for the isotopic retention is that if **42** is formed prior to the transition state, the rate of ring opening is much greater than the rate of dehydration.
(39) M. E. Hermes and F. D. Marsh, *J. Am. Chem. Soc.*, **89**, 4760 (1967).
(40) R. Huisgen, K. V. Fraunberg, and J. J. Strum, *Tetrahedron Lett.*, 2589 (1969).
(41) R. E. Harmon, F. Stanley, S. K. Gupta, and J. Johnson, *J. Org. Chem.*, **35**, 3444 (1970).
(42) M. L. Vestal, T. A. Elwood, L. H. Wojcik, and J. H. Futrell, presented at the Twentieth Annual Conference on Mass Spectrometry and Allied Topics, Dallas, Texas, June 4–9, 1972.
(43) P. E. Garrett in "Synthetic Procedures in Nucleic Acid Chemistry", Vol. II, W. W. Zorbach and R. S. Tipson, Ed., Interscience, New York, N.Y., 1972, p 439.
(44) "Handbook of Chemistry and Physics", 47th ed, R. C. Weast, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1966.
(45) D. W. Visser, G. Barron, and R. Beltz, *J. Am. Chem. Soc.*, **75**, 2017 (1953).

Endocyclic vs. Exocyclic Attack in Nucleophilic Displacement Reactions on Five- and Six-Membered Cyclic Onium Salts

Ernest L. Eliel,* Robert O. Hutchins, Robert Mebane, and Rodney L. Willer

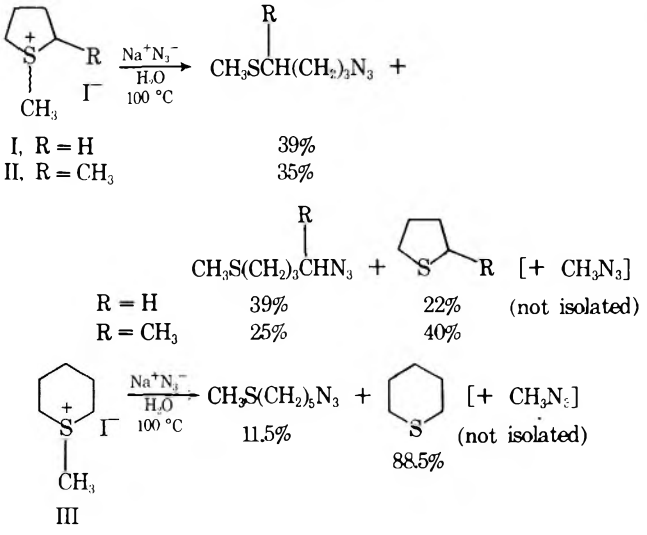
W. R. Kenan, Jr., Laboratories, University of North Carolina, Chapel Hill, North Carolina 27514

Received September 2, 1975

Nucleophilic attack of azide or methanethiolate on *S*-methylthiolanium iodide (five-membered ring) leads mainly to ring opening and to a lesser extent to displacement on methyl. In contrast, the analogous reactions with *S*-methylthianium iodide (six-membered ring) lead largely to displacement of methyl. Similarly, reaction of thiophenolate with *N,N*-dimethylpyrrolidinium tosylate leads largely to ring opening whereas the analogous reaction with *N,N*-dimethylpiperidinium tosylate gives rise only to thioanisole (product of methyl attack). Ring opening of *S*,2-dimethylthiolanium iodide with azide occurs predominantly at the primary (in preference to the secondary) ring carbon and when both α carbons in the ring are secondary, as in the reaction of *S*,2,6-trimethylthiolanium iodides with methanethiolate, displacement occurs nearly entirely at the exocyclic methyl.

In connection with another problem, we had occasion to study the reaction of *S*-methylthiolanium iodide (I) and *S*,2-dimethylthiolanium iodide (II) with sodium azide. We found that the major products in both reactions were those of ring opening, as shown in Scheme I, top. The thiolanes resulting from methyl attack were formed in minor amount. In contrast, the reaction of *S*-methylthianium iodide (III) with azide gave largely methyl azide and thiane, the products of methyl attack, and only a small amount of ring-opened product (Scheme I, bottom).

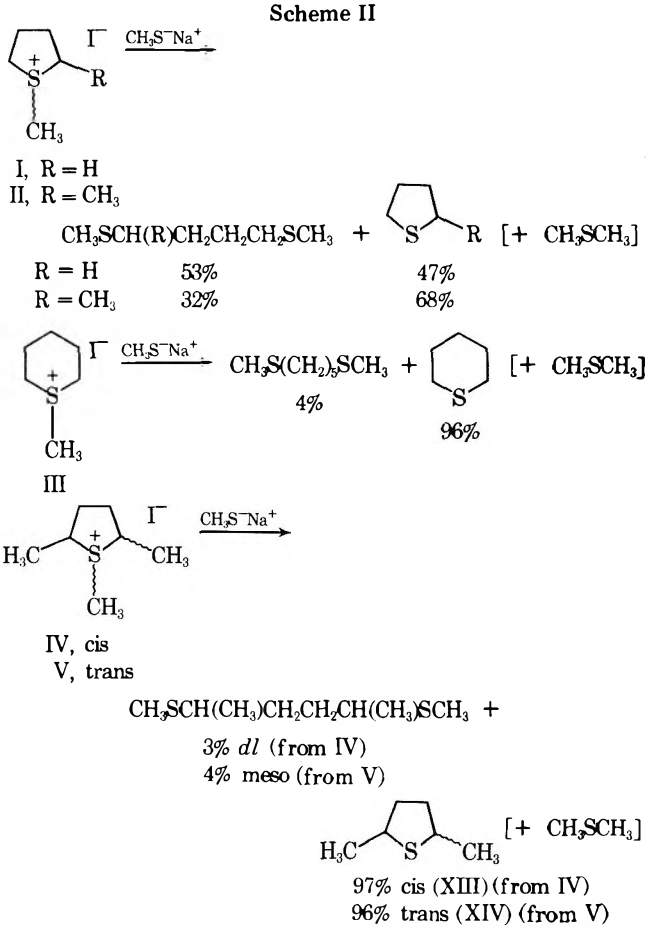
Scheme I



Predominant attack of the nucleophile on the ring in preference to the exocyclic methyl group in compounds I and II is a cause for surprise. The reaction of a good nucleophile such as azide on a thiolanium salt is most probably of the SN2 type[1] and therefore should follow the usual preference[2] $CH_3 > CH_2 > CH$. Indeed, for the specific case of displacement of hydroxide on acyclic sulfonium salts $RSMe_2^+$ or R_2SMe^+ it was found[3] many years ago that methyl is displaced faster than ethyl (with isopropyl the reaction changes over to SN1). In the present work it was shown that reaction of $(CH_3CH_2CH_2)_2SCH_3^+$ with CH_3S^- gives 18 times as much $(CH_3CH_2CH_2)_2S$ (and CH_3SCH_3), after correction for statistical factors, as $CH_3SCH_2CH_2CH_3$.

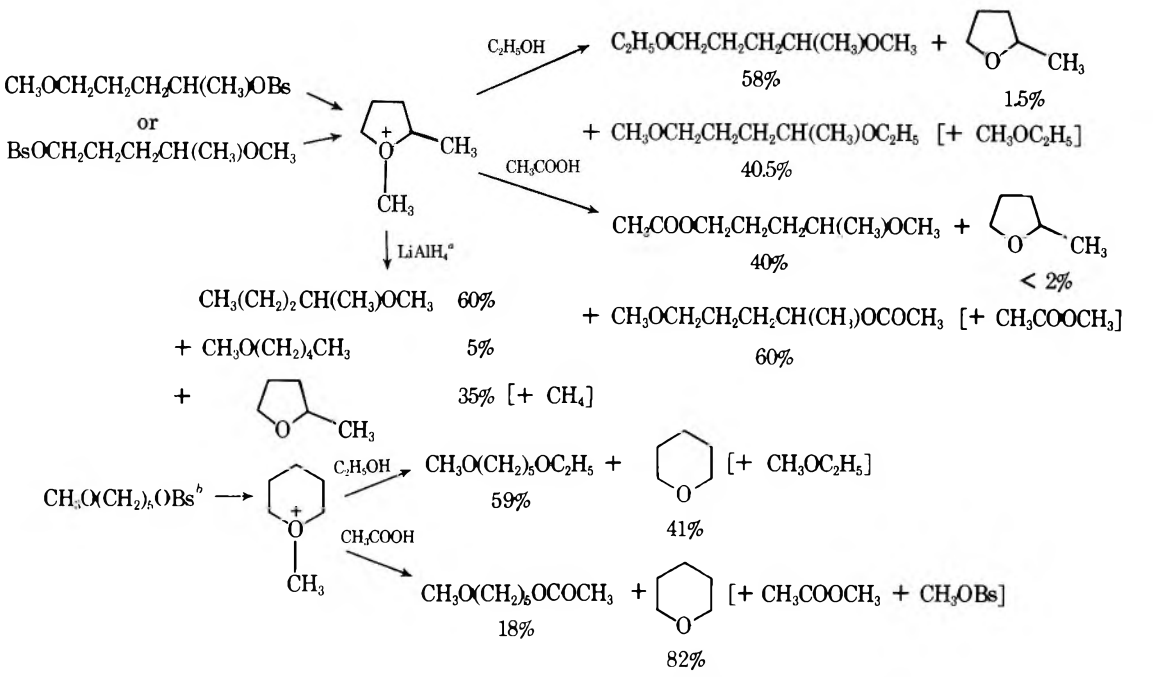
To check whether there was anything unusual about azide displacement, we repeated the reaction with methyl thiolate, including in the series also the *cis*- and *trans*-2,6-dimethylthiolane derivatives IV and V. The results are shown in Scheme II. (Attack at the CH_2 and CHR position in II cannot be distinguished in this case.) Although the exact proportions of ring opening and methyl attack are somewhat different for methyl thiolate and azide displacement, the overall picture is the same: in the five-membered ring, ring opening at a CH_2 position (but not at a CHMe position) is preferred to methyl displacement whereas in the six-membered ring methyl displacement is by far the preferred mode of nucleophilic attack.

Scheme II



At this juncture, three hypotheses suggested themselves. One, based on analogy with other reactions of sulfonium salts,[4] was that a tetracovalent sulfurane intermediate might be involved and that, for geometrical reasons,[5] such a sulfurane might preferentially undergo ring opening when the ring is five membered but methyl loss when the ring is six membered. A second possibility was that the reactions had some SN1 character in the five-membered ring and that therefore methylene attack should predominate over methyl attack. This hypothesis could essentially be

Scheme III



[a] 10% neighboring group participation from 4-methoxy-1-pentyl brosylate, 30% from 5-methoxy-2-pentyl brosylate. [b] 59% participation in ethanolysis, 98% in acetolysis. The 5-methoxypentyl ethyl ether yield in the ethanolysis includes material which has not passed through the cyclic ion.

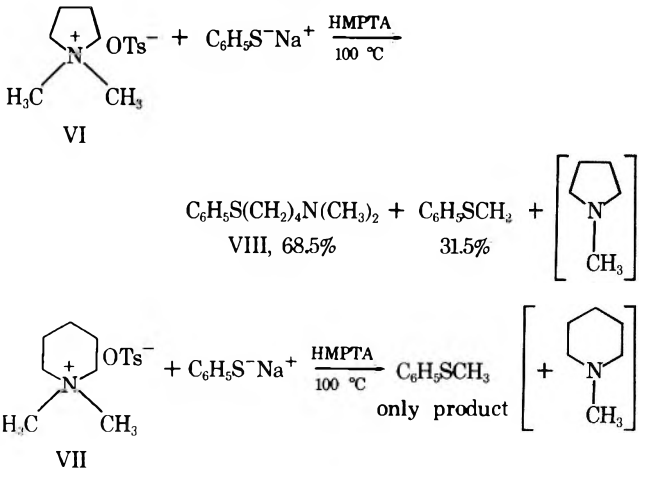
ruled out, at least for the CH_3S^- nucleophile, since it was found that attack at a secondary center (as in II, IV, and V) was not favorable. (Additional counterarguments are discussed below.) The third hypothesis is that the strain of the five-membered ring, reinforced by the absence of eclipsing in nucleophilic attack on that ring, should promote ring opening; in contrast, the lack of strain in the six-membered ring, combined with the likelihood of eclipsing of the nucleophile with ring hydrogens occurring in the transition state to ring opening, would lead to a preference for exocyclic attack.

To distinguish between the first and third hypotheses, it became important to decide whether there is anything unusual about sulfur as the leaving group. It turns out that experiments to this end are already available: Winstein and Allred[6] have studied the behavior of five- and six-membered cyclic methyl oxonium ions, formed through neighboring group participation processes, in ethanolysis, acetolysis and (in the case of the five-membered compound) lithium aluminum hydride reduction. The published results are summarized in Scheme III.

In the five-membered ring, acetolysis and ethanolysis give rise almost exclusively to ring opening. However, attack at the methylene and methine side of the ring occurs to nearly the same extent, suggesting that the reaction is SN1 like. Indeed, the intervention of open carbonium ions in a similar case (but involving a double bond in the ring) has been demonstrated.[7] Hydride reduction does not suffer from this drawback but only 10–30% of the reaction proceeds by neighboring group participation, i.e., via the cyclic oxonium salt. In the six-membered ring, both ethanolysis and acetolysis led to appreciable methyl attack; the quantitative interpretation of these results for our purposes is, however, complicated by incomplete participation in the ethanolysis and internal return in the acetolysis.

While the work of Winstein and Allred makes it very unlikely that the results we observed have anything to do with the presence of sulfur, we felt that it would be worthwhile to study a reaction which was clearly SN2 and involved a first-row element in the leaving group. Since nucleophilic displacements on preformed oxonium salts would involve considerable experimental difficulties, we opted instead to look at the cyclic ammonium salts *N,N*-dimethylpyrrolidinium tosylate (VI) and *N,N*-dimethylpiperidinium tosylate (VII). The results of nucleophilic displacement reactions of VI and VII with sodium thiophenolate in hexamethylphosphoric triamide[8] at 100 °C (the reaction did not proceed at an appreciable rate in boiling water) are shown in Scheme IV. Once again, reaction with the five-membered ring involves predominantly (68.5%) ring opening whereas the six-membered ring led exclusively to attack on methyl and formation of thioanisole. (The expected product of ring opening was produced by an independent synthesis and was shown, by gas chromatography, to be totally absent from the reaction products.)

Scheme IV



A summary of ring vs. methyl attack in various five- and six-membered methyl onium salts with various nucleophiles is given in Table I. The results are corrected for statistical factors where pertinent. It is clear that in all cases studied, ring opening occurs to a substantial extent in the

Scheme V

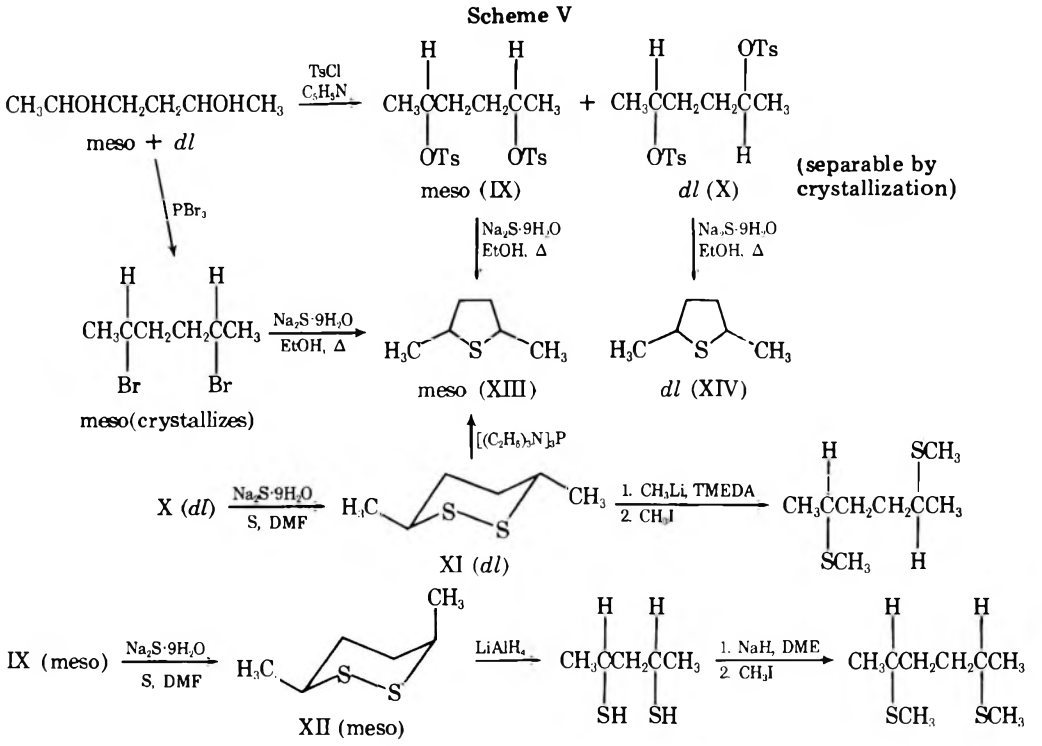
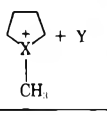
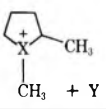
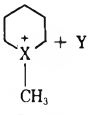


Table I. Ratio of Methylene to Methyl Displacement in Cyclic Onium Salts[a]

X	Y			
S	N_3^-	1.77	0.88[b]	0.065
S	CH_3S^-	0.56	0.47	0.02
O	C_2H_5OH	n.a.[c]	38.7[d]	Small[e]
O	CH_3COOH	n.a.	>20.0[f]	0.11
O	$LiAlH_4$	n.a.	1.71[g]	n.a.
NCH_3	$C_6H_5S^-$	2.17	n.a.	0

[a] Corrected by statistical factor of 2 for compounds having one XCH_3 and two ring methylene positions. The results for X = O are from ref 8, the others from the present study. [b] Ratio of methylene to methine attack ca. 1.4. [c] Not available. [d] Ratio of methylene to methine attack 1.43. [e] This ratio is less than 0.70—probably considerably less since most of the product of apparent ring opening is in fact formed by direct nucleophilic displacement on the precursor of the cyclic onium salt without participation of the methoxy group. [f] Ratio of methylene to methine attack 0.67. [g] Ratio of methylene to methine attack 12.

five-membered rings, so much so that the reaction may be of preparative usefulness. In contrast, very predominant or exclusive attack on exocyclic methyl occurs in the six-membered ring. The transition state in an SN2 reaction presumably involves substantial progress along the reaction coordinate and the concomitant bond breaking of the endocyclic bond in the five-membered ring entails substantial relief of strain whereas no such relief occurs in the nearly strainless six-membered ring. In addition, inspection of models indicates that attack of a nucleophile from the rear of the ring X–C bond in a five-membered ring places the nucleophile in the favored staggered position with respect to the hydrogens of the adjacent CH_2 group. In contrast, such attack in the six-membered ring would lead to eclipsing of the nucleophile with one of the adjacent C–H bonds. Both factors may contribute to the observed preference for ring cleavage in the five- as contrasted to the six-membered ring.

The syntheses of the methyl ethers of *meso*- and *dl*-2,5-hexanedithiol, the free meso dithiol, *trans*- and *cis*-3,6-dimethyl-1,2-dithiane (XI, XII), and *cis*- and *trans*-2,5-dimethylthiolane (XIII, XIV) are summarized in Scheme V and are described in the Experimental Section. It is of interest that *cis*-2,5-dimethylthiolane (XIII) can be prepared either from *meso*-2,5-hexanediol ditosylate (IX) by a reaction (with sodium sulfide) involving two inversions or from the *dl*-ditosylate X by reactions involving three inversions in all (cyclic disulfide formation by Na_2S_2 followed by internal nucleophilic displacement triggered by hexaethylphosphorous triamide).[9]

Experimental Section

***meso*- and *dl*-2,5-Hexanediol Di-*p*-toluenesulfonates (IX, X).** Solutions of 88.7 g (0.75 mol) of 2,5-hexanediol (Aldrich) in 150 ml of pyridine and 310 g (1.63 mol) of *p*-toluenesulfonyl chloride in 450 ml of dry pyridine were cooled to 0 °C and then slowly mixed with cooling in an ice bath. After 3 days at 0 °C the solution was poured, with rapid stirring, onto a mixture of 700 g of ice, 400 ml of water, and 50 ml of concentrated hydrochloric acid. The precipitated solid was collected and washed thoroughly with water. Drying in a vacuum desiccator gave 239 g of off-white crystals. Four recrystallizations from methanol yielded 30 g of *meso*-2,5-hexanediol ditosylate (IX), mp 115.5–117 °C (lit.[10] 112–115 °C). One further recrystallization raised the melting point to 116–117 °C. The filtrates upon concentration yielded an additional 1.8 g. Further crystallization of the concentrated mother liquors followed by repeated recrystallization yielded 34.3 g of *dl*-2,5-hexanediol ditosylate (X), mp 80–83 °C (lit.[10] 81–91 °C, but for the optically active material).

***meso*-2,5-Dibromohexane** was prepared as described in the literature,[11] yield 40.8%, mp 39–40 °C (lit.[11] 39 °C).

***cis*-2,5-Dimethylthiolane (XIII).** A solution of 36.6 g (0.1 mol) of sodium sulfide nonahydrate in 500 ml of 95% ethanol was prepared and half of it placed in a 3-l. three-necked flask equipped with two dropping funnels and a condenser. The solution was heated to reflux and the remaining half of the solution and a solution of 42.7 g (0.1 mol) of *meso*-2,5-hexanediol ditosylate (IX) in 100 ml of dry dimethylformamide (DMF) were simultaneously added from the two addition funnels over a period of 1.5 h. The mixture was refluxed for 40 h and then steam distilled. The distillate was diluted with water and extracted with four portions of methylene chloride which were combined, cleared with water (three times), dried over $MgSO_4$, and concentrated on a rotary evaporator. Distillation of the residue yielded 8.2 g (70%) of *cis*-2,5-dimethylthiolane (XIII), bp 62–63 °C (45 Torr) [lit.[12] 60 °C (45 Torr)].

In a second preparation, the yield was 76%. The same material could be prepared in the same way in 74% yield starting with *meso*-2,5-dibromohexane. The product was further purified by distillation at reduced pressure from sodium metal.

NMR δ_{Me_4Si} ($CDCl_3$) 1.20–2.60 (m, 4 H, CH_2CH_2), 1.40 (d, 6 H, J = 7 Hz, CH_3), 3.80 ppm (m, 2 H, CHS).

***trans*-2,5-Dimethylthiolane (XIV).** This material was prepared similarly as the cis isomer but starting with the *dl*-ditosylate X, yield 63%, bp 78–82 °C (90 Torr) [lit.[12] 58 °C (44 Torr)].

NMR δ_{Me_4Si} ($CDCl_3$) 1.20–2.60 (m, 4 H, CH_2CH_2), 1.35 (d, 6 H, J = 7 Hz, CH_3), 3.78 ppm (m, 2 H, CHS).

***trans*-3,6-Dimethyl-1,2-dithiacyclohexane (XI).** The procedure was adapted from that of Dodson and Nelson.[10] To a solution of 12.0 g (0.05 mol) of sodium sulfide nonahydrate and 1.61 g (0.05 g-atom) of sulfur in 200 ml of DMF was added 22.3 g (0.05 mol) of *dl*-2,5-hexanediol ditosylate (X). The dark solution was heated with stirring at 80 °C for 21.5 h and was then poured with stirring onto 100 g of ice and 400 ml of water. The organic material was extracted with four portions of methylene chloride which were combined, cleared with three portions of water, dried over $MgSO_4$, and concentrated. Distillation of the residue afforded 4.13 g (56%) of pale yellow product, bp 36–40 °C (0.75 Torr). Redistillation gave 3.97 g of colorless liquid which was analyzed by GLC (10-ft 20% Carbowax 20M, temperature 122–160 °C, 15 °C/min rise) and shown to contain the trans (XI) and cis (XII) isomers in a 93:7 ratio. The material was purified to 99% purity by low-temperature recrystallization from petroleum ether (bp 30–60 °C) at −20°. The NMR spectrum agreed with that reported.[13]

***cis*-3,6-Dimethyl-1,2-dithiacyclohexane (XII)** was prepared similarly from 11.15 g (0.025 mol) of the meso ditosylate IX and was obtained in 61% yield, bp 78–80 °C (5 Torr). The crude product, analyzed as indicated above, indicated a cis/trans ratio of 96:4 plus two contaminants of lower retention time, one of which appeared to be XIII or XIV. The NMR spectrum of the material agreed with that reported.[13]

Reaction of *trans*-3,6-Dimethyl-1,2-dithiacyclohexane (XI) with Hexaethylphosphorous Triamide. The general procedure of Harpp et al.[9] was employed. A solution of 1.483 g (10 mmol) of XI and 2.73 g (11 mmol) of the triamide[14] $[(C_2H_5)_2N]_3P$ in 10 ml of dry benzene was stirred at room temperature for 12 h. Since no reaction appeared to have occurred (GLC analysis), the solution was boiled at reflux for 18.5 h. Still only 10% reaction had occurred. The benzene was removed and the residue heated at 150 °C. Even after 35 h reaction was not complete, so 10 additional drops of $(Et_3N)_3P$ were added and heating continued for 11.5 h. At this point GLC showed absence of starting material. The reaction mixture was diluted with water and extracted four times with petroleum ether (bp 30–60 °). The combined organic layers were cleared with water, dried ($MgSO_4$), and concentrated and the residue distilled to give 0.53 g (45.7%) of *cis*-2,5-dimethylthiolane (XIII), identical in NMR spectrum with the material described earlier.

***meso*-2,5-Hexanedithiol.** A solution of 4.44 g (30 mmol) of XII in 10 ml of anhydrous ether was added dropwise to a stirred slurry of 0.864 g (22.8 mmol) of lithium aluminum hydride in 20 ml of anhydrous ether over a 15-min period. The mixture was refluxed for 1.0 h, cooled, cautiously hydrolyzed with water, and treated with 10% sulfuric acid until clear. The layers were separated and the aqueous phase extracted with two portions of ether. The combined ether layers were cleared with water, dried ($MgSO_4$), and concentrated. Distillation of the residue afforded 4.08 g (91%) of a colorless product, bp 76–78 °C (5 Torr) [lit.[15] 87–88 °C (12 Torr) for a mixture of diastereomers]. GLC analysis similar to that described earlier indicated two close peaks (presumably meso and *dl* isomers) in a 97.9:2.1 ratio.

***meso*-2,5-Bismethylthiohexane.** To a solution of *meso*-2,5-hexanedithiol (3.00 g, 20 mmol) in 50 ml of dimethoxyethane, cooled in an ice bath, sodium hydride (1.854 g of 57% dispersion in oil, 1.056 g, 44 mmol) was added in portions. After stirring for 15 min, 6.38 g (45 mmol) of methyl iodide was added portionwise over 30 min and the mixture was stirred for an additional 2 h in the ice bath followed by warming to room temperature (3 h). The mixture was poured into 500 ml of water and extracted four times with ether. The combined ether layers were cleared three times with water, dried over $MgSO_4$, and concentrated. Distillation of the residue afforded, after a forerun, 1.85 g (52%) of product, bp 68–70 °C (0.7 Torr). Analysis by GLC essentially as described above indicated a purity of only 79%. The material was purified (GLC criterion) by redistillation, at reduced pressure, from a mixture of sodium and sodium hydroxide.

NMR δ_{Me_4Si} (C_6H_6) 1.13 (d, J = 7 Hz, 6 H, CCH_3), 1.56 (skew t, 4 H, CH_2), 1.80 (s, 6 H, SCH_3), ca. 2.4 ppm (flat, broad, ca. 2 H, CHS).

Anal. Calcd for $C_8H_{18}S_2$: C, 53.87; H, 10.17. Found: C, 53.78; H, 10.30.

***dl*-2,5-Bismethylthiohexane.** To ca. 1.6 g (10 mmol) of tetramethylethylenediamine cooled to 10 °C in a flask equipped with magnetic stirrer was added 4.4 ml of 2.3 M methyllithium in ether by means of a syringe through a septum; a white precipitate formed. Then 1.48 g (10 mmol) of XI (95% pure) was added through a syringe and the syringe was rinsed with 2 ml of anhydrous ether which was also added to the flask. Stirring was continued at 10–15 °C for 2 h, after which time methyl iodide (1.7 g, 12 mmol) in 10 ml of anhydrous ether was added gradually from a syringe over a 20-min period. Stirring was continued at 10–15° for 1 h and then at room temperature for 2 h. The mixture was then poured into 50 ml of water and extracted three times with ether. The combined ether layers were twice cleared with water, dried over $MgSO_4$, and concentrated. Distillation of the residue from sodium afforded 1.04 g (60%) of product, bp 78–80 °C (1 Torr).

NMR δ_{Me_4Si} (C_6H_6) 1.13 (d, J = 7 Hz, 6 H, CCH_3), 1.57 (broad t, 4 H, CH_2), 1.80 (s, 6 H, SCH_3), 2.3–2.6 ppm (broad, ca. 2 H, CHS).

Anal. Calcd for $C_8H_{18}S_2$: C, 53.87; H, 10.17. Found: C, 53.98; H, 10.40.

Preparation of Thiolanium and Thianium Methiodides. The preparation of thiolanium, 2-methylthiolanium, and thianium methiodides (I, II, III) has been described previously.[2,16] The methiodides of XIII and XIV were prepared analogously in refluxing ether, 2-day reaction time, IV, 54% yield (presumably the anti isomer), mp 190–192 °C dec; V, 51% yield, mp 186–189 °C dec (lit.[12] reports vaporization at 140–142 and 141–143 °C, respectively).

***N,N*-Dimethylpyrrolidinium *p*-Toluenesulfonate.** To a solution of 6.3 g (0.074 mol) of *N*-methylpyrrolidine in 80 ml of sodium-dried benzene was added 16 g (0.086 mol) of methyl *p*-toluenesulfonate. An additional 200 ml of benzene was added and the solution heated to incipient boiling for 10 min. After cooling the crude product was collected, washed with several portions of benzene, and dried, yield 17.66 g of yellow crystals. Recrystallization from ethanol–ethyl acetate yielded 14.34 g (71.5%) of product as white crystals, mp 163 °C.

***N,N*-Dimethylpiperidinium *p*-Toluenesulfonate.** A solution of 6.93 g (0.07 mol) of *N*-methylpiperidine and 13.1 g (0.07 mol) of methyl *p*-toluenesulfonate in 50 ml of absolute methanol was heated, with stirring, to incipient boiling for 10 min. After cooling the crystalline product was collected, washed with several portions of cold ethanol, and dried to give 18.34 g of crystalline product. Recrystallization from ethanol–ethyl acetate afforded 14.34 g (71.9% yield) of white crystals, mp 160 °C.

Reaction of Sulfonium Salts with Sodium Methylmercaptide. A solution of sodium hydroxide (15 mmol, 600 mg) in 25 ml of water was placed in a thick-walled tubular vessel containing a small stirring bar. A solution of 5 mmol of the sulfonium iodide in 25 ml of water was added, nitrogen was bubbled through the solution for several minutes, and the solution was then frozen, connected to a vacuum line, and degassed by at least three freeze–thaw cycles at 1 mm or less. To the frozen solution 3.0 ml of methanethiol (cooled by dry ice) was added, nitrogen flow was resumed, and the mixture was allowed to melt and mix with stirring; then 1.5 ml of additional methanethiol was added. Sitrring was continued at room temperature under nitrogen for several hours to allow evaporation of excess methanethiol. (The solution is 0.1 M in sulfonium salt and 0.3 M in CH_3SNa.) The solution was then again degassed and the vessel sealed off under vacuum. It was placed in an oil bath for periods of time ranging from 48 to 66.5 h, cooled to room temperature, frozen, and opened, and 10–15 ml of *n*-hexane containing exactly 5 mmol of diphenylmethane or decane as internal standard was added. After thorough shaking the hexane layer was subjected to gas chromatography. Each analysis was carried out at least five times; analysis on 10 ft × 0.125 in. 20% Carbowax 10% KOH on Chromosorb W column; columns were programmed for a temperature rise, over 60 min, from 80–110 °C lower limit to 200 °C upper limit.

The analytical results (response factors in parentheses) were as follows: I, thiane (1.689) 42%, thioether (1.060) 48%; II, thiane (1.601) 68–70%, thioether (1.002) 32–30%; III, thiane (1.688) 96%, thioether (0.981) 4%; IV, thiane XIII (1.422) 90%, thioether (0.948) 3.3%; V, thiane XIV (1.359) 91%, thioether (0.935) 3–9%; $(CH_3CH_2CH_2)_2SCH_3^+I^-$, $(CH_3CH_2CH_2)_2S$ (1.346) 82%, $CH_3SCH_2CH_2CH_3$ (2.069) 18%.

Reaction of Cyclic Ammonium Salts with Sodium Thiophe-

nolate. The dry *N,N*-dimethylpyrrolidinium or *N,N*-dimethylpiperidinium salt (0.1 mol) and 1.2 g (0.03 mol) of NaOH were dissolved in 50 ml of hexamethylphosphoramide (HMPA) in a 100-ml tubular thick-walled vessel containing a small stirring bar. Nitrogen was passed through the solution for 1 h after which 3.30 g (0.03 mol) of previously distilled thiophenol was added. The mixture was thus 0.2 M in the ammonium salt and 0.6 M in thiophenolate. Nitrogen flow was continued for 15 min and the mixture was then degassed by at least three freeze–dry cycles at 2 mm. The vessel was sealed under vacuum and placed in an oil bath at 100 °C for 48 h. The tubes were then removed, cooled, frozen, and opened. The contents were diluted with 180 ml of distilled water and extracted continuously with 150 ml of pentane for 24 h. To the extract was added exactly 0.01 mol of dodecane as internal standard and analysis was carried out by GLC using a 10% UCW-98 column programmed between 150 and 200 °C. A second extraction of the HMPA solution with pentane led to extraction of no additional product, as shown by GLC. Salt VI gave thioanisole (response factor relative to internal standard 1.63), 32% and amino thioether VIII (response factor 0.93), 68% in a total yield of 86%; salt VIII gave only thioanisole in 93% analytical yield.

1-Phenyl-6-methyl-6-aza-1-thiaheptane. A mixture of 27.1 g (0.1 mol) of *N,N*-dimethylpyrrolidinium tosylate, 12 g (0.3 mol) of NaOH, and 100 ml of HMPA was placed in a three-necked flask fitted with a reflux condenser and stirred for 1 h while nitrogen gas was passed through. Previously distilled thiophenol (32.5 g, 0.295 mol) was added and the solution heated to 100 °C for 24 h. The solution was then cooled, diluted with 300 ml of water, and extracted continuously with 250 ml of petroleum ether (bp 30–60 °C) for 48 h. The petroleum ether layer was cleared several times with water and several times with 10% aqueous hydrochloric acid, dried over $MgSO_4$, and concentrated. Distillation gave 1.3 g (13.7%) of thioanisole. The acidic water layer was made basic with 10% aqueous sodium hydroxide and extracted several times with portions of diethyl ether. The ether layer was dried and concentrated. Distillation of the residue afforded 8.81 g (42%) of product, bp ca. 160 °C (25 Torr), about 95% pure by GLC analysis. The material was purified by preparative gas chromatography for elemental analysis and response factor determination.

Anal. Calcd for $C_{12}H_{19}NS$: C, 68.90; H, 9.09. Found: C, 68.96; H, 9.21.

^1H NMR 1.6 (CH_2CH_2, m, 4 H), 2.1 (NMe_2 and CH_2S, m, 8 H), 2.85 (CH_2NMe_2, t, 2 H), 7.2 ppm (aromatic, m, 5 H).

Reaction of *meso*-*S*,2,5-Trimethylthiolanium Iodide with Sodium Mercaptide. A boiling solution of 25.2 g (0.63 mol) of sodium hydroxide in 500 ml of water was purged by bubbling through nitrogen for 2 h. After an additional 3 h at room temperature with N_2 purging, the solution was frozen, 40 ml of CH_3SH (cooled) was added, and the flask was allowed to warm to room temperature under nitrogen. An additional 10 ml of CH_3SH was added, followed by 54.4 g (0.21 mol) of the sulfonium salt IV. With continuing nitrogen blanketing the solution was boiled for 59 h, cooled, and extracted three times with methylene chloride. The combined methylene chloride layers were washed with water, dried over $MgSO_4$, and concentrated. Distillation of the residue afforded 16.8 g (69%) of *cis*-2,5-dimethylthiolane (XIII), bp 93–95 °C (160 Torr), spectrally identical with an authentic sample. GLC analysis (10-ft Carbowax 20M column) showed only traces of 2,5-bismethylthiohexane. Distillation of the pot residue afforded 0.86 g (2.3%) of 2,5-bismethylthiohexane, bp 68–71 °C (1 Torr), containing only traces of 2,5-dimethylthiolane, as indicated by GLC. Analysis by NMR (XL-100) using mixtures of authentic *dl*- and *meso*-2,5-bismethylthiohexane isomers for comparison demonstrated the product to be very largely the *dl* isomer (ca. 90–95%) with but a small amount (ca. 5–10%) of the meso isomer present.

7-Methyl-1-phenyl-7-aza-1-thiaoctane. 2-Phenylthiotetrahydropyran. A solution of 44.0 g (0.40 mol) of thiophenol in 65.6 g (0.80 mol) of dihydropyran containing a few crystals of *p*-toluenesulfonic acid was boiled at reflux for 2 h in a 250-ml flask. The mixture was cooled and neutralized with anhydrous potassium carbonate and the excess dihydropyran was removed by distillation at reduced pressure. The product was collected at 89–90 °C (0.5 Torr), yield 68.2 g (87%).

5-Phenylthio-1-pentanol.[17] Following an earlier-described procedure,[18] 133.5 g (1.0 mol) of aluminum chloride was dissolved, by slow addition with stirring, in 500 ml of dry ether cooled to 0 °C (ice–salt bath) in a 1-l. three-necked flask equipped with a reflux condenser, mechanical stirrer, and addition flask (later replaced by an addition funnel). After 30 min of stirring, 9.5 g (0.25 mol) of lithium aluminum hydride was added and the solution stirred for an additional 30 min. A solution of 68 g (0.35 mol) of 2-thiophenyltetrahydropyran in 200 ml of dry ether was then added over a 1-h period with stirring. The solution was boiled for 3 h and cooled, and 50% aqueous sodium hydroxide added dropwise with vigorous stirring until a fine white precipitate had formed. The mixture was filtered and the residue extracted for 3 h with ether in a Soxhlet extractor. The combined ether solution was dried over sodium sulfate, filtered, and concentrated and the residue distilled, bp 150–151 °C (0.5 Torr), yield 51 g (70%).

5-Phenylthio-1-bromopentane. To a solution of 51 g (0.26 mol) of the above alcohol in 50 ml of dry CCl_4 cooled to −5 °C in a 250-ml round-bottomed flask was added, dropwise, 70.2 g (0.26 mol) of PBr_3 over a period of 1 h. The flask was equipped with a reflux condenser with drying tube and the solution was allowed to warm to room temperature overnight. It was then heated on a steam bath for 1 h, cooled, and poured onto ice. After stirring for 1 h, the oily bottom layer was separated, washed with two 50-ml portions of 5% aqueous sodium carbonate followed by two 50-ml portions of water, and dried over Na_2SO_4. The drying agent was filtered and the product distilled, bp 145–146 °C (0.5 Torr), yield 85%.

7-Methyl-1-phenyl-7-aza-1-thiaoctane. A solution of 7.13 g (0.0275 mol) of the above bromide in 50 ml of ethanol was placed in a flask fitted with an ice–methanol condenser. The flask was cooled to 0 °C and 12.5 g (0.275 mol) of chilled anhydrous dimethylamine was added. After 4 h at 0 °C the solution was allowed to come slowly to room temperature. After standing for 48 h the reaction mixture was diluted with 200 ml of water, made basic with 10% aqueous sodium hydroxide, and extracted several times with ether. The combined ether extracts were dried over K_2CO_3 and concentrated and the residue distilled in a Kugelrohr apparatus. GLC of the product (10% UCW98) showed three components. The material was dissolved in 100 ml of 10% hydrochloric acid and the aqueous layer extracted with ether and then made basic with 10% aqueous NaOH. The ether layer was dried (K_2CO_3) and concentrated and the residue distilled in a Kugelrohr apparatus, yield 2.85 g (46.5%), bp ca. 250 °C (25 Torr).

Anal. Calcd for $C_{13}H_{21}NS$: C, 69.95; H, 9.41. Found: C, 69.74; H, 9.50.

NMR δ 1.5 ($CH_2CH_2CH_2$, m, 6 H), 2.2 (NMe_2 and CH_2S, m, 8 H), 2.8 (CH_2NMe_2, t, 2 H), and 7.1 ppm (aromatic, m, 5 H).

Reaction of 1-Methylthiolanium Iodide (I) and 1-Methylthianium Iodide (III) with Sodium Azide in Water. Water solutions, 0.1 M in sulfonium iodide and 0.3 M in sodium azide or 1.0 M in sulfonium iodide and 2.0 M in azide, were used for the analytical and preparative runs, respectively. The solutions were placed in 100-ml, thick-walled tubes and degassed by three freeze–evacuate–thaw cycles and the tubes sealed and placed in an oil bath at 100 °C for 48 h, then removed from the bath, cooled, and opened. In the analytical runs, 20–30 ml of diethyl ether was added, the water layers extracted by shaking, and the ether layer separated, dried, and analyzed by GLC on a 6 ft × 0.125 in. 10% UC-W-98 on Chromosorb W (80–100 mesh) column at 110 (I) or 125 °C (III), flow rate 120 ml/min He. Product compositions are summarized in Table II. In the preparative runs, the contents of the tubes were transferred to a small separatory funnel with the aid of some ether and extracted with ether. The ether layer was separated, dried over sodium sulfate, filtered, and concentrated and the residue distilled through a short Vigreux column. Yields and properties of products are included in Table II.

Reaction of *S*,2-Dimethylthiolanium Iodide (II) with Sodium Azide. The reaction was carried out on both analytical and preparative scales, as described for I above. The analytical run showed a ratio of azides to 2-methylthiolane of 1.52:1 corresponding to 60% azide(s) and 40% thiolane. (This value is approximate since it is based on the response ratio of 1.391 of the products of azide displacement on III. The corresponding ratio for I is 1.376.) The preparative experiment produced, upon distillation of the product, a forerun of 2-methylthiolane, identified by infrared spectrum, and a fraction of bp 95–105 °C (18 Torr) which displayed a broad band at 5.2 μm in the ir (azide). The NMR spectrum suggested the presence of two components (two methyl doublets at 1.30 and 1.32 ppm, $CHCH_3$, J = 6.5 Hz, two methyl singlets at 2.08 and 2.10 ppm, SCH_3). All attempts to separate the two components by GLC failed. Reduction of 6 g of the apparent azide mixture with a fourfold excess of ethereal $LiAlH_4$ yielded ca. 4 g of a mixture of two amines which could be analyzed on a 12 ft × 0.125 in. Theed (5% on Chromosorb W) column, ratio ca. 40:60. The amines were separated on a 12 ft × 0.375 in. preparative Theed (5% on Chromosorb A) column and identified as the reduction

Table II

Salt	Products	Yield, % Analytical	Yield, % Preparative	Bp, °C (Torr)
I	$(CH_2)_4S$	22	15	118–122[a]
	$CH_3S(CH_2)_4N_3$	78	68	86–87 (15)[b,c]
III	$(CH_2)_5S$	88.5	75	140–145[d]
	$CH_3S(CH_2)_5N_3$	11.5	~6	98–100 (15)[e,f]

[a] Lit. 119–120°C (760 Torr). [b] Calcd for $C_5H_{11}N_3S$: C, 41.35; H, 7.64. Found: C, 41.16; H, 7.53. [c] NMR $\delta^{(CDCl_3)}_{Me_4Si}$ 1.67 (4 H, m, CCH_2CH_2C), 2.08 (s, 3 H, SCH_3), 2.50 (distorted t, SCH_2), 3.28 ppm (distorted t, CH_2N_3). [d] Lit. 140–142°C (760 Torr). [e] Identical with authentic sample; see below. [f] NMR $\delta^{(CDCl_3)}_{Me_4Si}$ 1.6 [6 H, broad m, $C(CH_2)_3C$], 2.02 (s, 3 H, SCH_3), 2.45 (distorted t, 2 H, SCH_2), 3.23 ppm (distorted t, 2 H, CH_2N_3).

products of the expected two azides by their NMR spectra (10% $CDCl_3$ solution).

2-Amino-6-thiaheptane, $CH_3SCH_2CH_2CH_2CH(CH_3)NH_2$: δ 1.06 (d, 3 H, J = 6.5 Hz, $CHCH_3$), 1.56 (broad s, 2 H, exchanges with D_2O, NH_2), 1.39–1.78 (m, 4 H, $CH_2CH_2CHMeNH_2$), 2.07 (s, 3 H, CH_3S), 2.48 (distorted t, 2 H, $J \approx 7$ Hz, CH_3SCH_2), 2.87 ppm (approximate sextet, $J \approx 6.2$ Hz, $CH_2CHMeNH_2$).

1-Amino-4-methyl-5-thiahexane, $CH_3SCH(CH_3)CH_2CH_2CH_2NH_2$: δ 1.25 (d, 3 H, $CHCH_3$, J = 6.5 Hz), 1.54 (m, 4 H, CH_2CH_2CHMe), 1.67 (broad s, 2 H, exchanges with D_2O, NH_2), 2.03 (s, 3 H, CH_3S), 2.67 (m, 3 H, CH_2NH_2 and $CH_2CHMeSCH_3$).

1-Azido-6-thiaheptane. 6-Thiaheptan-1-ol.[18] To 500 ml of ether contained in a 1-l. three-necked round-bottom flask equipped with a mechanical stirrer, dropping funnel, and reflux condenser, cooled to 0 °C, was slowly added 133.5 g (1.0 mol) of aluminum chloride with continued cooling. After stirring for 2 h, 9.5 g (0.25 mol) of $LiAlH_4$ was added in small portions over 15 min. After stirring for an additional 2 h, 20 g (0.15 mol) of 2-methylthiotetrahydropyran,[18] bp 60–61 °C (15 Torr) [lit.[19] 47–48 °C (5 Torr)], dissolved in 25 ml of dry ether was added dropwise over 1 h. The solution was heated to reflux for 3 h and cooled and 50% aqueous NaOH was added slowly until a fine white precipitate had formed. The precipitate was filtered and extracted in a Soxhlet extractor with ether for 12 h. The extract was combined with the remaining ether layer, dried over sodium sulfate, and concentrated and the residue distilled, bp 67–69 °C (0.5 Torr) [lit.[20] 121 °C (16 Torr)], yield 16 g (79%).

1-Azido-6-thiaheptane. To 10.0 g (0.075 mol) of the above alcohol in 200 ml of dry pyridine cooled to 0 °C (ice–salt bath) was added 29.0 g (0.15 mol) of *p*-toluenesulfonyl chloride. After standing for 12 h in the refrigerator the solution was poured onto 500 g of ice and stirred for 1 h. The oily tosylate was extracted with three 100-ml portions of ether and the combined ether extracts washed with two 50-ml portions of water, dried over sodium sulfate, and concentrated at reduced pressure. The residue weighed ca. 20 g. It was dissolved in 100 ml of DMF, 16.25 g (0.25 mol) of sodium azide was added, and the mixture was boiled at reflux with magnetic stirring for 24 h. The solution was poured into 500 ml of ice water and the oil which separated taken up in 50 ml of ether. The water layer was extracted two times and taken up in 50-ml portions of ether. The ether extracts were combined, dried over sodium sulfate, and concentrated. The residual yellow liquid was distilled through a short Vigreux column to yield 9.2 g (77%) of product, bp 97–99 °C (15 Torr).

Anal. Calcd for $C_6H_{13}N_3S$: C, 45.25; H, 8.23. Found: C, 44.98; H, 8.17.

Acknowledgment. This work was supported by NSF Grant GP-35669 and by the University of North Carolina (Science Development Grant). R.M. was a summer research participant supported by the W. R. Kenan, Jr., Chemistry Department Endowment.

Registry No.—I, 28608-92-6; II, 57774-87-5; III, 38131-89-4; IV, 57774-88-6; V, 57774-89-7; VI, 57774-90-0; VII, 42883-76-1; VIII, 57774-91-1; IX, 53585-64-1; X, 57819-13-3; XI, 57819-14-4; XII, 2506-33-4; XIII, 5161-13-7; XIV, 57774-92-2; 2,5-hexanediol, 2935-44-6; *p*-toluenesulfonyl chloride, 98-59-9; *meso*-2,5-dibromohexane, 54462-67-8; hexaethylphosphorous triamide, 2283-11-6; *meso*-2,5-hexanedithiol, 53585-65-2; *dl*-2,5-hexanedithiol, 53585-66-3; *meso*-2,5-bismethylthiohexane, 57774-93-3; *dl*-2,5-bismethylthiohexane, 57774-94-4; *N*-methylpyrrolidine, 120-94-5; methyl *p*-toluenesulfonate, 80-48-8; *N*-methylpiperidine, 626-67-5; sodium methylmercaptide, 5188-07-8; sodium thiophenolate, 930-69-8; thiophenol, 108-98-5; 2-phenylthiotetrahydropyran, 20965-36-0; dihydropyran, 25512-65-6; 5-phenylthio-1-pentanol, 57774-95-5; 5-phenylthio-1-bromopentane, 21782-59-2; 7-methyl-1-phenyl-7-aza-1-thiaoctane, 57774-96-6; sodium azide, 26628-22-8; 1-amino-4-methyl-5-thiohexane, 57774-97-7; 2-amino-6-thiaheptane, 57774-98-8; 6-thiaheptanol, 57774-99-9; 1-azido-6-thiaheptane, 57775-00-5; 2-methylthiotetrahydropyran, 31053-11-9; 1-azido-5-thiahexane, 57775-01-6.

References and Notes

(1) Y. Pocker and A. J. Parker, *J. Org. Chem.*, **31**, 1526 (1966).
(2) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2d ed, G. Bell and Sons, London, 1969, Chapter VII.
(3) J. L. Gleave, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 236 (1935).
(4) E.g., J. C. Martin, J. A. Franz, and R. J. Arhart, *J. Am. Chem. Soc.*, **96**, 4604 (1974).
(5) Cf. F. H. Westheimer, *Acc. Chem. Res.*, **1**, 70 (1968).
(6) E. L. Allred and S. Winstein, *J. Am. Chem. Soc.*, **89**, 3991, 4008, 4012 (1967). See also E. R. Novak and D. S. Tarbell, *ibid.*, **89**, 73 (1967).
(7) J. R. Hazen and D. S. Tarbell, *Tetrahedron Lett.*, 5927 (1968).
(8) R. O. Hutchins and F. J. Dux, *J. Org. Chem.*, **38**, 1961 (1973).
(9) D. N. Harpp, J. G. Gleason, and J. P. Snyder, *J. Am. Chem. Soc.*, **90**, 4181 (1968); D. N. Harpp and J. G. Gleason, *ibid.*, **93**, 2437 (1971).
(10) R. M. Dodson and V. C. Nelson, *J. Org. Chem.*, **33**, 3966 (1968).
(11) N. Kornblum and J. H. Eicher, *J. Am. Chem. Soc.*, **71**, 2259 (1949).
(12) E. V. Whitehead, R. A. Dean, and F. A. Fidler, *J. Am. Chem. Soc.*, **73**, 3632 (1951).
(13) N. Isenberg and H. F. Herbrandson, *Tetrahedron*, **21**, 1067 (1965).
(14) Preparation: L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, pp 425, 431.
(15) C. G. Overberger, J. J. Ferraro, and F. W. Orttung, *J. Org. Chem.*, **26**, 3458 (1961).
(16) O. Hofer and E. L. Eliel, *J. Am. Chem. Soc.*, **95**, 8045 (1973).
(17) T. Nambara and N. Matsuhisa, *Yakugaku Zasshi*, **83**, 642 (1963); *Chem. Abstr.*, **59**, 7411*g* (1963).
(18) E. L. Eliel, B. E. Nowak, and R. A. Daignault, *J. Org. Chem.*, **30**, 2448 (1965).
(19) F. Kipnis and J. Ornfelt, *J. Am. Chem. Soc.*, **73**, 822 (1951).
(20) G. M. Bennett and F. Heathcoat, *J. Chem. Soc.*, 268 (1929).

Chemistry of *o*-Amino Aldehydes. Reaction of 4-Aminopyrimidine-5-carboxaldehyde and 1,3-Cyclohexanedione

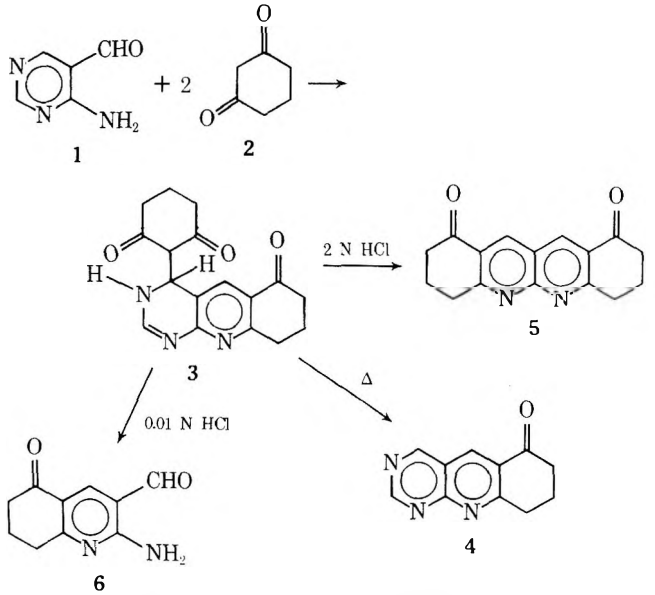
Thomas G. Majewicz and Paul Caluwe*

Department of Chemistry, State University of New York, College of Environmental Science and Forestry, Syracuse, New York 13210

Received August 29, 1975

4-Aminopyrimidine-5-carboxaldehyde and 1,3-cyclohexanedione react in a 1:2 molar ratio with formation of an addition product in quantitative yield. Spectroscopic data and chemical evidence are in agreement with a 1,3-cyclohexanedione-substituted dihydropyrimidine structure (**3**). Its transformation in 2 N HCl results in a very efficient annelation sequence leading to four linearly fused rings (**5**) from monocyclic starting materials in high yield. Reactions in 0.01 N HCl, on the other hand, give 2-amino-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxaldehyde (**6**). The accumulation of functional groups in this simple molecular framework is noteworthy. Pyrolysis of **3** results in the elimination of the 1,3-cyclohexanedione moiety with formation of 6-oxo-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinoline (**4**). The mechanism of the formation of **3** and its transformation into products is discussed.

The versatility of 4-aminopyrimidine-5-carboxaldehyde (**1**) in the synthesis of substituted 2-aminonicotinaldehydes and of polycondensed 1,8-naphthyridines was explored previously in this laboratory.[1,2] Friedländer condensations of this *o*-amino aldehyde and aromatic ketones led to the formation of the pyrido[2,3-*d*]pyrimidine system, which upon hydrolysis generated a new *o*-amino aldehyde functional group. This sequence, however, was not successful for aliphatic ketones such as acetone and cyclohexanone. In related investigations leading to 1,8-naphthyridines it was demonstrated that 2-aminonicotinaldehyde and cyclohexanediones condensed readily with formation of mono or bis condensation products depending on the molar ratio of the reagents.[3] It was hoped that a similar sequence with **1** would result in the formation of polycyclic systems containing the pyrido[2,3-*d*]pyrimidine moiety. Hydrolysis of this heterocyclic unit would then yield o-amino aldehydes for further elaboration of N-heterocyclic compounds. This paper deals with the reaction of 4-aminopyrimidine-5-carboxaldehyde (**1**) and 1,3-cyclohexanedione (**2**).



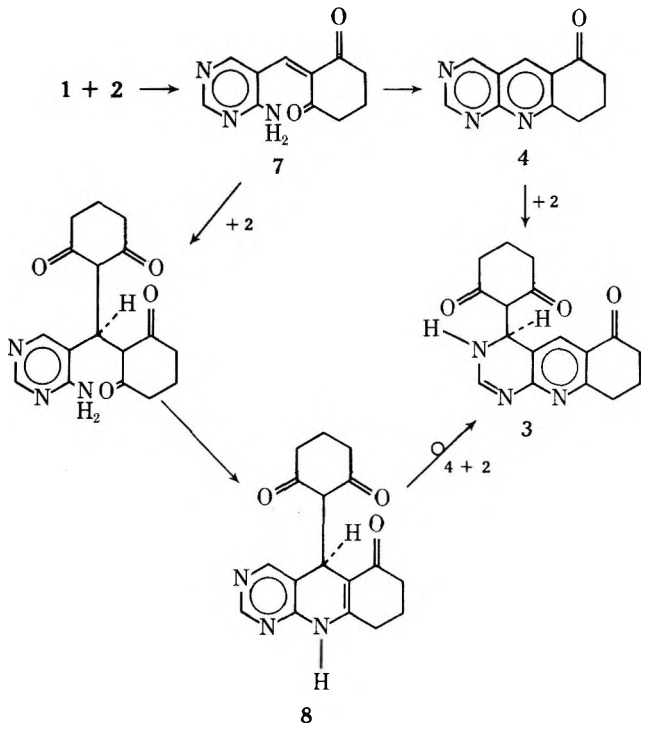
An ethanolic solution of 4-aminopyrimidine-5-carboxaldehyde and 1,3-cyclohexanedione in a 1:2 molar ratio formed a white, thick precipitate in quantitative yield after a few hours at 75 °C. Isolation proved it to be a 1:2 addition product of the amino aldehyde and the 1,3-dione, with loss of two molecules of water. Such addition products are typically formed in the reaction of aldehydes and **2** or dimedone. In the present case the second molecule of water would be lost by intramolecular Schiff base formation. A product of the same molar composition was formed in the reaction of **2** and 2-aminonicotinaldehyde.[3] Strong absorptions in the infrared spectrum for the NH and C=O functional groups are observed at 3200–3100, 1680, 1640, and 1555 cm−1.

Two structures, **3** and **8**, can be envisioned for the addition product. NMR data are consistent with structure **3**. A singlet at δ 6.37 is assigned to the methine proton in the dihydropyrimidine ring. In structure **8** the corresponding proton would be incorporated in a dihydropyridine system and would absorb at higher field, as observed previously in the addition product of **2** and 2-aminonicotinaldehyde.[3] A singlet at δ 8.41 is assigned to the proton on the pyridine ring in **3**, whereas the absorption at δ 7.89 agrees well for the amidine type proton.[4] As expected, both the NH and the enolic OH are exchanged in deuterated acetic acid. Chemical transformations of the 1:2 addition product are in agreement with its formulation as a dihydropyrimidine derivative (see below).

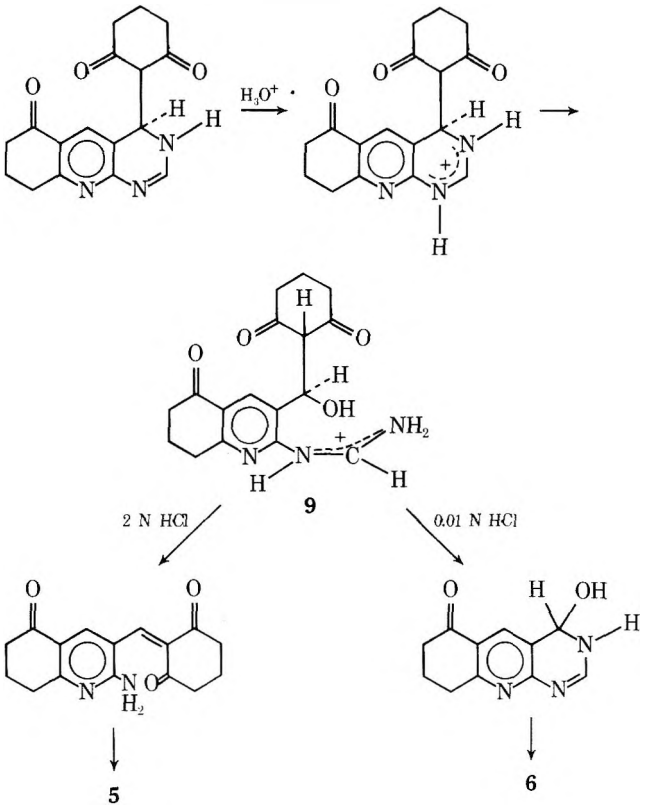
The formation of **3** results from intramolecular Schiff base formation on the α,β-unsaturated carbonyl system (**7**), followed by Michael addition of 1,3-cyclohexanedione on the electron-deficient pyrimidine ring of **4** (Scheme I). An alternative pathway, based on the known tendency of 1,3-cyclohexanediones to form 2:1 addition products with aldehydes, cannot be excluded. Michael addition of **2** on **7** followed by ring closure would lead to **8**, which would then rearrange to its thermodynamically more stable isomer **3**. All attempts to isolate **8** from the reaction mixture were unsuccessful.[5] The second mole of 1,3-cyclohexanedione required in both reaction sequences is readily supplied by retroaldol condensation.

The thermal decomposition of **3** was of interest in order to evaluate the mechanism proposed in Scheme I. Pyrolysis of **3**, carried out in a sublimation apparatus at 170 °C and 1 mmHg, resulted in a mixture of 6-oxo-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinoline (**4**) and 1,3-cyclohexanedione (**2**), identified by their ir, NMR, and mass spectrum. This dissociation can be observed directly by introducing **3** in the direct inlet of a mass spectrometer. The molecular ions and typical fragmentation patterns of **2** and **4** were observed, whereas no peak at *m/e* 311, corresponding to **3**, was found. Dissolving the sublimate in ethanol resulted in rapid formation of a precipitate (**3**), identical in all respects with the product obtained from **1** and **2**. Fractional sublimation, followed by benzene extraction of the sublimate, gave pure **4** in 20% yield.[6] Addition of 1,3-cyclohexanedione to an ethanolic solution of this material resulted equally in the fast formation of **3** in quantitative yield. Nucleophilic additions

Scheme I



Scheme II



of dimedone on similar fused pyrimidines, such as pteridine[7] and quinazoline,[8] have been reported.

The tedious pyrolysis of **3**, the low yield, and the difficulties encountered in the purification of **4**, prompted us to investigate alternative pathways for the utilization of the pyrimidine moiety in **3**. Refluxing a solution of **3** in 2 N HCl for a brief period of time gave 1,10-dioxo-1,2,3,4,7,8,9,10-octahydrodibenzo[*b*,*g*]-1,8-naphthyridine (**5**) in 90% yield. Analytical and spectroscopic data are in full agreement with the proposed structure. This facile transformation results in an efficient annelation reaction wherein four linearly fused rings are formed from readily available monocyclic reagents in a two-step synthesis in excellent yield. Refluxing a solution of **3** in 0.01 N HCl, on the other hand, gave a different product identified as 2-amino-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxaldehyde (**6**), in 70% yield. The accumulation of functional groups in a simple structural framework and the mild reaction conditions used for their introduction is noteworthy.

Apparently the 1,3-cyclohexanedione moiety in **3** is retained under the reaction conditions leading to **5**, while it is lost during the synthesis of **6**. The high-yield synthesis of **5** further substantiates the structural assignment of the 1:2 addition product **3**. Indeed, an adduct of the alternative structure **8** would have to dissociate in order to form the diketone **5**. However, the instability of 1,3-cyclohexanedione[9] in boiling strong acid would prevent its complete readdition to **4**. Furthermore, formation of **4** under these reaction conditions would result in its rapid hydrolysis to **6**. This was established by the quantitative hydrolysis of **4**, obtained from **3** by pyrolysis, in boiling 2 N HCl. However, this o-amino aldehyde (**6**) was not formed under the reaction conditions employed for the synthesis of **5**. Furthermore, experiments directed toward displacement of the 1,3-cyclohexanedione moiety in **3** by the analogous dimedone, carried out by adding an excess of dimedone to the reaction mixture, did not result in the incorporation of the latter in the final product (**5**), as evidenced by the absence of methyl absorptions in the NMR spectrum of the diketone. The transformations of **3** in acid medium further support the structural assignment made earlier for the 1:2 addition product of 4-aminopyrimidine-5-carboxaldehyde and 1,3-cyclohexanedione.

The products obtained from **3** at different pH are clearly determined by the acidity of the reaction medium. It is noteworthy that increasing acidity of the reaction mixture (from 0.01 to 2 N HCl) resulted in a gradual increase in the formation of **5** and a corresponding decreasing yield of **6**. The concentration of **3** itself did not affect the type of product formed; in fact **5** and **6** can by synthesized at identical concentration of **3**, as described in the Experimental Section. The key element in the mechanism of the facile transformations of **3** is the loss of the 1,3-dione moiety at intermediate pH and its incorporation into the final product at low pH. Protonation of **3** and subsequent hydrolytic cleavage of the pyrimidine moiety results in the formation of a resonance stabilized N-substituted formamidinium ion (**9**) (Scheme II). At low pH dehydration of the β-hydroxy ketone moiety leads to the formation of an α,β-unsaturated ketone. This sequence of reaction steps irreversibly retains the 1,3-cyclohexanedione moiety, since protonation of the basic formamidine system prevents the backward reaction (via Michael addition of the terminal amine on the α,β-unsaturated ketone). Hydrolysis of the formamidine moiety followed by ring closure results in the diketone **5**. At pH ≃3, however, a free terminal amine in the amidine moiety of **9** is available for nucleophilic displacement to regenerate a pyrimidine system, with loss of the 1,3-dione moiety. The instability of 1,3-cyclohexanedione[9] in hot mineral acid makes this step essentially irreversible. Further hydrolysis of the newly formed pyrimidine nucleus results in the formation of **6** along well-established pathways.[10] The proposed mechanism leading to **6** implies that the product derived from the protonated formamidine should also be observed at intermediate pH. Indeed **5** was isolated in 20% yield from the reaction conducted in 0.01 N HCl. An alternative formulation for the sequence leading to **6** or its im-

mediate precursor would be retro-aldol condensation of the intermediate β-hydroxy ketone, followed by hydrolysis of the formamidine moiety.

Finally, it should be noted that the base-catalyzed reaction of **3** modeled after the transformations of Michael adducts with similar fused pyrimidines,[11] resulted in the formation of **5** in poor yield, while **6** was not obtained under these reaction conditions.

Experimental Section

General. NMR spectra were recorded with a Varian A-60 and/or Varian XL-100 with FT spectrometer using Me_4Si as an internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU6E instrument; infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. All melting points are uncorrected. Microanalyses were done by Instranal Laboratory Inc., Rensselaer, N.Y.

4-(2',6'-Dioxocyclohexyl)-6-oxo-3,4,6,7,8,9-hexahydropyrimido[4,5-*b*]quinoline (3). A solution of 5.0 g (40 mmol] of 4-aminopyrimidine-5-carboxaldehyde (**1**) and 9.2 g (82 mmol) of 1,3-cyclohexanedione in 125 ml of absolute ethanol was heated for 6 h at 75 °C and then refluxed for 15 min. The white, voluminous precipitate was collected and washed extensively with ethanol to yield 12.75 g (100%) of analytically pure **3**: mp 255 °C dec; ir (Nujol) 3200–3100, 1680, 1640, 1555 (broad), 1420, 1345, 1310, 1290, 1260, 1225, 1150, 1070, 1000, 900, 850–800 (broad), 770, 735 cm^{-1}; NMR δ (CD_3COOD) 8.41 (s, 1) 7.89 (s, 1), 6.37 (s, 1) 3.00 (unresolved m, 2) 2.65–1.90 (unresolved m, 10).

Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.49; H, 5.47; N, 13.62.

6-Oxo-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinoline (4). Thermal decomposition of **3** was conducted in an efficient sublimation apparatus at 170 °C and 1 mmHg. The sublimate was removed frequently. The combined fractions were extracted with benzene and the benzene evaporated to dryness. The residue was recrystallized from cyclohexane to yield **4** in 20% yield (decomposes without melting). An analytical sample was prepared by sublimation at 150 °C and 1 mmHg: ir (Nujol) 1680, 1590, 1535, 1430, 1250, 1225, 1195, 1175, 1125, 1075, 1000, 985, 935, 910, 885, 820, 805, 740 cm^{-1}; NMR δ ($CDCl_3$) 9.68 (s, 2, H2–H4) 9.1 (s, 1, H5) 3.48 (t, 2, H9, J_{H8-H9} = 6 Hz), 2.88 (t, 2, H7, J_{H7-H8} = 6 Hz), 2.38 (m, 2, H8); mass spectrum M^+ at *m/e* 199.

Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.25; H, 4.61; N, 21.03

1,10-Dioxo-1,2,3,4,7,8,9,10-octahydrodibenzo[*b,g*]-1,8-naphthyridine (5). A solution of 5.0 g of **3** in 4 l. of 2 N HCl was refluxed for 45 min. The solution was cooled rapidly, neutralized (Na_2CO_3), and extracted thoroughly with ethyl acetate. The solvent was evaporated and the residue recrystallized from ethanol to yield 3.75 g (88%) of **5**, mp 245 °C dec. An analytical sample was prepared by sublimation at 120 °C and 1 mmHg: ir (Nujol) 1685, 1600, 1530, 1460, 1415, 1405, 1355, 1310, 1250, 1230, 1200, 1165, 1120, 1010, 1000, 970, 900, 810 cm^{-1}; NMR δ ($CDCl_3$) 8.86 (s, 2, H11, H12) 3.42 (t, 4, H4, H7, J_{H3-H4} = 6 Hz), 2.86 (t, 4, H2, H9, J_{H2-H3} = 6 Hz), 2.36 (m, 4, H3, H8); mass spectrum M^+ at *m/e* 266 (60%), 238 (100%).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.19; H, 5.32; N, 10.57

2-Amino-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxaldehyde (6). A solution of 5.0 g of **3** in 4 l. of 0.01 N HCl was refluxed for 45 min. The solution was cooled rapidly, neutralized, and extracted continuously with ether. The ether was evaporated and the residue washed with 25 ml of methanol (to remove diketone **5**) to yield 2.1 g (70%) of **6**, recrystallized from ethanol, mp 236–237 °C. An analytical sample was prepared by sublimation at 90 °C and 1 mmHg: ir (Nujol) 3360, 3260, 3100, 2720, 1655, 1620, 1585, 1535, 1400, 1350, 1265, 1195, 1160, 1120, 1000, 950, 900, 795, 770, 745, 720 cm^{-1}; NMR δ ($CDCl_3$) 9.88 (s, 1, HCO) 8.50 (s, 1, H4) 2.95 (t, 2, H8, J_{H7-H8} = 6 Hz), 2.65 (t, 2, H6, J_{H6-H7} = 6 Hz), 2.18 (m, 2, H7); mass spectrum M^+ at *m/e* 190 (80%), 162 (100%).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.31; H, 5.27; N, 14.77.

Acknowledgment. This research was sponsored by the U.S. Army Research Office, Durham, N.C. We wish to express appreciation to Professor M. Szwarc, without whose help this investigation would not have been possible.

Registry No.—**1**, 16357-83-8; **2**, 504-02-9; **3**, 57694-94-7; **4**, 57694-95-8; **5**, 57694-96-9; **6**, 57694-97-0.

References and Notes

(1) G. Evens and P. Caluwe, *J. Org. Chem.*, **40**, 1438 (1975).
(2) P. Caluwe and T. G. Majewicz, *J. Org. Chem.*, **40**, 2566 (1975).
(3) T. G. Majewicz and P. Caluwe, *J. Org. Chem.*, **40**, 3407 (1975).
(4) A. Albert and H. Mizuno, *J. Chem. Soc. B*, 2423 (1971).
(5) Even when excess **1** is used, **4** could not be isolated from the reaction medium; the only product observed was **3**. 1,3-Cyclohexanedione became the limiting reagent under these reaction conditions.
(6) It proved difficult to remove 1,3-cyclohexanedione from the sublimate, even by resublimation. Any remaining **2** reacted rapidly with **4** in organic solvents with re-formation of **3**. This is responsible for the low yield.
(7) A. Albert and H. Mizuno, *J. Chem. Soc., Perkin Trans. 1*, 1615 (1973).
(8) A. Albert and J. J. McCormack, *J. Chem. Soc. C*, 1117 (1966); 63 (1968).
(9) H. Stetter, "Newer Methods of Preparative Organic Chemistry", Vol. II, W. Foerst, Ed., Academic Press, New York, N.Y., 1963, p 51, and references cited therein.
(10) See ref 1 and references cited therein.
(11) A. Albert and W. Pendergast, *J. Chem. Soc., Perkin Trans. 1*, 1794 (1973).

Carbon-13 Nuclear Magnetic Resonance Spectral Properties of Alkenylidenecyclopropanes

Daniel J. Pasto* and John K. Borchardt

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

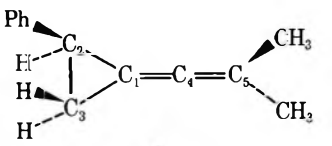
Received August 1, 1975

The ^{13}C chemical shifts in a series of alkenylidenecyclopropanes have been measured and have been assigned to specific carbon atoms and substituent shift effects have been analyzed. A comparison of the ^{13}C chemical shifts in the alkenylidenecyclopropanes with those in allenes and methylenecyclopropanes reveals considerable differences in the chemical shifts of the ring and allene carbon atoms. The internal carbons (C_1 and C_4) of alkenylidenecyclopropanes are strongly shielded relative to the corresponding carbon atoms in allenes and methylenecyclopropanes, while the terminal allene and ring carbons are deshielded. These effects are postulated to arise from a strong conjugative interaction between the in-plane (relative to the three-membered ring) C_4–C_5 π bond with the Walsh-type orbitals of the three-membered ring.

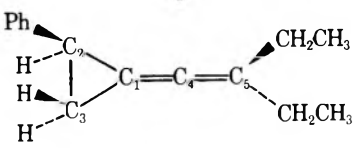
Recent chemical studies with alkenylidenecyclopropanes,[2,3,4] methylenecyclopropanes,[4,5] and vinylcyclopropanes[6] have revealed substantial differences in reactivity and mode of reaction with the cycloaddition reagents 4-phenyl-1,2,4-triazoline-3,5-dione[2,4,6] (PTAD) and chlorosulfonyl isocyanate.[3,5] The reactivity and mode of reaction of the alkenylidenecyclopropanes have been interpreted in terms of an interaction between the Walsh-type orbitals[7] of the three-membered ring and the C_4–C_5 π bond which is not present in the methylene- or vinylcyclopropanes, a rationale which has been supported by preliminary theoretical calculations.[2] In a continuing study of the chemical and physical properties of such systems we have completed a study of the ^{13}C NMR spectral properties of alkenylidenecyclopropanes for comparison with allenes and methylenecyclopropanes. Articles describing the results of studies on the bonding in alkenylidenecyclopropanes using photoelectron spectroscopic and theoretical techniques,[8] and a kinetic study of the cycloaddition reaction with PTAD[9] have already appeared.

Results and Discussion

Assignment of Chemical Shifts.[10] Assignment of the resonances to specific carbons in the alkenylidenecyclopropanes has been accomplished on the basis of multiplicities in nondecoupled spectra, the magnitudes of the coupling constants, the absolute values of the chemical shifts, and substituent shift effects. Initial chemical shift assignments were based on the complete analysis of the nondecoupled spectra of 1 and 2. The methyl groups attached to C_5 in 1



1

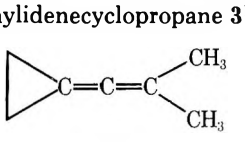


2

appear as quartets at δ 22.3 and 22.8 with J values of 126 Hz typical for methyl groups. The higher field resonance has been tentatively assigned to the methyl cis to the phenyl on the basis of the observed shielding of the α-carbon atoms in cis alkenes relative to trans alkenes ($\Delta\delta$ ~6 ppm) which has been attributed to steric polarization.[11,12] The methyl resonances of the other isobutenylidenecyclopropanes reported in this article consistently fall in the range δ 21.3–22.8. The resonance of C_2 appears as a doublet (δ 26.9, J = 171 Hz), while that for C_3 appears as a triplet (δ 18.4, J = 168 Hz). The larger values for these coupling constants are typical of those observed in cyclopropane derivatives.[13a] The aromatic ^{13}C resonances were assigned on the basis of their multiplicities, the ipso carbon appearing as a lower field singlet, the ortho carbons as a double doublet, and the meta and para carbons as double triplets (see Table I for specific values of the coupling constants).

The assignment of the resonances of C_1, C_4, and C_5 were made by comparison of the shifts of these carbons in 1 and 2. The substitution of methyl by ethyl results in a deshielding of C_5 (δ 102.3 to 113.8; i.e., a β substituent effect),[14] a shielding of C_4 (δ 189.8 to 186.9; a γ substituent effect),[14] and a deshielding of C_1 (δ 83.5 to 87.0; a δ substituent effect).[14] The much lower field resonance of C_4 is consistent with those observed for the central carbons of allenes.[15] The resonances in the spectra of the other alkenylidenecyclopropanes were assigned by comparison with those in 1 and applying known trends in substituent shifts.[13b]

Analysis of Substituent Effects in Alkenylidenecyclopropanes. In order to estimate the ^{13}C chemical shifts in the parent alkenylidenecyclopropane 3[16] for comparison



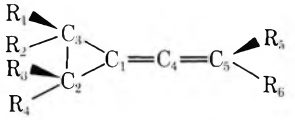
3

with the ^{13}C chemical shifts in allenes and methylenecyclopropanes it is necessary to carry out a detailed analysis of the substituent shift effects in the alkenylidenecyclopropanes. The introduction of a methyl group in 1 at C_3 trans to the phenyl (i.e., 5) produces a β-alkyl shift at C_2 of +4.5 ppm whereas in the cis compound 6 the shift is +1.8 ppm indicating a steric shift of −2.7 ppm. In the polymethyl series 7–11 the β-alkyl shift is +4.6 to +5.3 ppm with a much smaller apparent steric shift of ~−0.6 ppm. Similar, but larger, α and β steric shifts are observed at C_2 (or C_3) (see Table II).

Substantial steric shifts of the resonances of the methyl carbons are observed in the *cis*- and *trans*-methylphenyl ($\Delta\delta$ 6.0 ppm between 5 and 6) and dimethyl compounds ($\Delta\delta$ 5.3 ppm between 7 and 8), values of $\Delta\delta$ which compare very closely with those observed between the α carbons of cis and trans alkenes ($\Delta\delta$ ~6 ppm).[11]

Comparison and Analysis of the ^{13}C Chemical Shifts in Alkenylidenecyclopropanes, Tetramethylallene, Methylenecyclopropane, and 2-Methylpropene. In order to adequately compare the ^{13}C chemical shifts of alk-

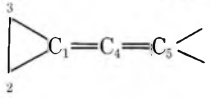
Table I. ^{13}C Chemical Shifts in



Compd	R_1	R_2	R_3	R_4	δ^a C_1	C_2	C_3	C_4	C_5	R_1	R_2	R_3	R_4	R_5[h]	R_6[h]
1	C_6H_5	H	H	H	83.5	18.4 (168)	26.9 (171)	189.8	102.3	b				22.3 (126)	22.8 (126)
2	C_6H_5	H	H	H	87.0	19.1 (165)	25.6 (170)	186.9	113.8	c				CH_2: 28.3 (128) CH_3: 14.8 (125)	28.4 (128) 14.8 (125)
4[d]	C_6H_5	H	H	H	85.9 86.3	22.2	26.2	189.0 189.3	108.3 108.4	d				19.4 19.7	CH_2: 30.3, 30.3 CH_3: 14.9, 14.8
5[e]	C_6H_5	H	H	CH_3	88.0	26.0	32.1	187.1	99.2	e			18.2	21.4	21.5
6	C_6H_5	H	CH_3	H	85.3	21.8	28.3	188.3	99.1	f		12.26 (128)		21.2 (127)	21.4 (127)
7[g]	CH_3	H	H	CH_3	88.6	22.5	22.5	186.3	97.7	18.0			18.0	21.7	21.7
8[g]	CH_3	H	CH_3	H	88.0	18.1	18.1	186.2	97.9	12.7		12.7		21.4	21.9
9	CH_3	CH_3	H	H	87.8	20.8 (165)	24.6	185.7	98.0	24.6 (125)	24.6 (125)			21.5 (127)	21.5 (127)
10	CH_3	CH_3	CH_3	H	92.7	24.2 (162)	26.6	184.7	97.1	26.4 (122)	26.6 (122)	19.0 (129)		21.7 (127)	22.0 (127)
11	CH_3	CH_3	CH_3	CH_3	98.0	28.4	28.4	184.5	97.4	22.8 (129)	22.8 (129)	22.8 (129)	22.8 (129)	22.6 (125)	22.6 (125)

[a] Values in parentheses under the δ's are J's in hertz when determined. [b] Aromatic peaks at δ 128.7 (dt, J = 157, 7.3 Hz), 129.1 (dt, J = 162, 7.3 Hz), 131.9 (dd, J = 162, 7.3 Hz), 144.3 (s). [c] Aromatic peaks at δ 127.3 (dt, J = 159, 7 Hz), 127.7 (dt, J = 159, 7 Hz), 129.6 (dd, J = 158, 7 Hz), 142.9 (s). [d] Coupling constants were not determined. See ref 12. Aromatic peaks at δ 128.7, 129.1, 131.9, 144.3. [e] Coupling constants were not determined. Aromatic resonances at δ 126.1, 126.8, 128.1, and 141.9. [f] Aromatic peaks at δ 126.5 (dt, J = 158, 6 Hz), 128.2 (dt, J = 157, 6 Hz), 129.6 (dd, J = 152, 6 Hz), 137.7. [g] Coupling constants were not determined. [h] CH_3 except in compound 4.

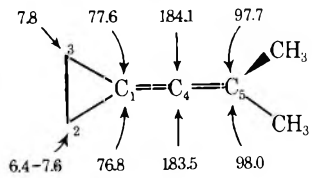
Table II. Substituent and Steric Shifts (ppm) in



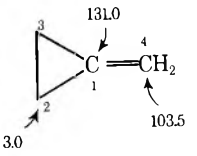
Carbon atom (compds)	α effect	α steric effect	β effect	β steric effect	γ effect	δ effect
C_1 (4–6)			+4.5	−2.7		(+0.9 to +2.6)[a]
(7–11)			+4.6 to +5.3	−0.6		
C_2 (or C_3) (4–6)	+7.6	−4.2	+4.2	−2.8		
(7–11)	+8.5	−4.4	+6.1 to +6.4	−4.0 to −4.4		
C_4 (4–6)					−2.7[b] (+1.2)[c]	
(7–11)					−1.0 to −1.6[d]	
C_5 (4–6)			+5.7 to +6.0		e	

[a] Parenthesized shifts arising from substituent changes at the allene terminus. + shifts indicate shifts to lower field, − shifts to higher field. [b] Apparent steric shift of +1.2 ppm. [c] Apparent steric shift of −0.7 to −2.2 ppm. [d] Apparent steric shift is less than the limits of experimental uncertainty. [e] Substituent shift is less than the limits of experimental uncertainty.

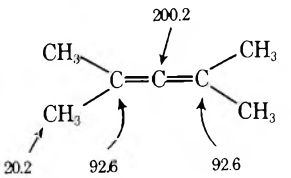
enylidenecyclopropanes with those in allenes and methylenecyclopropanes one must derive chemical shifts for compounds of comparable substitution.[16] Starting with **7** and **9**, neither of which are complicated by cis steric effects, and using the substituent shifts given in Table II the ^{13}C chemical shifts of **3** are estimated to be those shown below (the δ's above the structure are derived by extrapolation from **7**, those below from **9**).



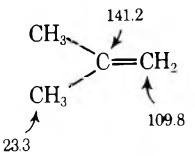
3



12



14



13

The effect of the three-membered ring on the ^{13}C chemical shifts in **3** can be estimated by comparing the chemical shifts of 2-methylpropene (**13**) and methylenecyclopropane[17] (**12**). Formation of the three-membered ring results in a shielding of the saturated carbon atoms (20.3 ppm) and a deshielding of the vinyl carbons (10.2 ppm on going from C_2 of **13** to C_1 of **12**, and 6.3 ppm on going from C_1 of **13** to C_4 of **12**). Should similar changes in chemical shifts occur in the transformation of tetramethylallene (**14**) to **3**, one would expect the values of the chemical shifts to be $\delta_{C_2(C_3)}$ −0.1, δ_{C_1} 82.4, and δ_{C_4} 193.9. Comparison of these values with those observed in **3**, along with a comparison of the chemical shift of a terminal allene carbon of **14** with that of C_5 in **3**, reveals that C_1 and C_4 experience additional shielding of 4.8–5.6 ppm at C_1 and 9.8–10.4 ppm at C_4 in **3**, while $C_2(C_3)$ and C_5 experience additional deshielding of 6.5–7.9 ppm at $C_2(C_3)$ and 5.1–5.4 ppm at C_5.

An analysis of the bonding in **3** provides a possible explanation for the observed shielding of C_1 and C_4 in the alkenylidenecyclopropanes. A reasonably strong interaction exists between the in-plane C_4–C_5 π bond and the Walsh-type orbitals of the three-membered ring[2,8] (estimated to be approximately 80% that in 1,3-butadiene[8]) which results in considerable triple bond character in the C_1–C_4 bond with concomitant weakening of the C_4–C_5 π and C_1–C_2 (C_1–C_3) σ bonds. CNDO calculations indicate bond orders of 0.9291 for the C_4–C_5 π bond, 0.3504 for the C_1–C_4 in-plane "π bond" interaction, 0.9192 for the exocyclic double bond, and 0.9043 for the C_1–C_2 (C_1–C_3) σ bond. This added electron density, or "triple bond" character of the C_1–C_4 bond apparently results in shielding of C_1 and C_4 comparable to that observed in alkynes which appear at 40–60 ppm higher field than the sp^2-hybridized carbons of alkenes.[18] The deshielding of C_2 (C_3) and C_5 appears to be the result of lowered electron density at these carbon atoms. Studies are currently under way on the synthesis and physical properties of alkenylidenecyclobutanes, -cyclopentanes, and -cyclohexanes for comparison with the alkenylidenecyclopropanes.

Registry No.—**1**, 4544-23-4; **5**, 33530-27-7; **6**, 33530-26-6; **7**, 37817-46-2; **8**, 37817-36-0; **9**, 28438-32-6; **10**, 14803-30-6; **11**, 13303-30-5.

References and Notes

(1) Supported in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society.
(2) D. J. Pasto and J. K. Borchardt, *J. Am. Chem. Soc.*, **96**, 6944 (1974); D. J. Pasto, A. F.-T. Chen, and G. Binsch, *ibid.*, **95**, 1553 (1973); D. J. Pasto and A. F.-T. Chen, *ibid.*, **93**, 2562 (1971).
(3) D. J. Pasto, A. F.-T. Chen, G. Ciurdaru, and L. A. Paquette, *J. Org. Chem.*, **38**, 1015 (1973); D. J. Pasto and J. K. Borchardt, *J. Am. Chem. Soc.*, **96**, 6937 (1974).
(4) D. J. Pasto and A. F.-T. Chen, *Tetrahedron Lett.*, 2995 (1972).
(5) D. J. Pasto, A. F.-T. Chen, L. A. Paquette, and G. Ciurdaru, *Am. Chem. Soc., Div. Pet. Chem., Prepr.*, **18**, 131 (1973).
(6) D. J. Pasto and A. F.-T. Chen, *Tetrahedron Lett.*, 713 (1973).
(7) A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949); *Nature (London)*, **159**, 167, 712 (1947).
(8) D. J. Pasto, T. P. Fehlner, M. E. Schwartz, and H. F. Baney, *J. Am. Chem. Soc.*, **98**, 530 (1976).
(9) D. J. Pasto, J. K. Borchardt, T. P. Fehlner, H. F. Baney, and M. E. Schwartz, *J. Am. Chem. Soc.*, **98**, 526 (1976).
(10) The NMR spectra were recorded on 20–30% solutions in deuteriochloroform containing ~5% tetramethylsilane (Me_4Si) at 40 °C on a Varian Associates XL-100 spectrometer equipped with a Transform Technology TT100 Fourier system. Chemical shifts (δ) are given relative to internal Me_4Si.
(11) D. M. Grant and B. V. Cheney, *J. Am. Chem. Soc.*, **89**, 5315 (1967).
(12) It is interesting to point out that in the preparation of alkenylidenecyclopropanes unsymmetrically substituted at the allene end an equimolar mixture of diastereoisomers are formed. The ^{13}C NMR spectra of such mixtures show distinct resonances for C_1, C_4, C_5, and the groups attached to the end of the allene (see data for **4** in Table I).
(13) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972: (a) p 333; (b) p 55.
(14) For a discussion of substituent effects see pp 55–60 of ref 13 and references cited therein.
(15) J. K. Crandall and S. A. Sojka, *J. Am. Chem. Soc.*, **94**, 5084 (1972); R. Steur, J. van Dongen, M. DeBie, and W. Drenth, *Tetrahedron Lett.*, 3307 (1971).
(16) Attempts to prepare **3**, or the monomethyl derivative, have been futile, ethylene and propylene being too unreactive to condense with dimethylallenecarbene.
(17) H. Gunther and W. Herrig, *Chem. Ber.*, **106**, 3938 (1973).
(18) D. E. Dorman, M. Jautelat, and J. D. Roberts, *J. Org. Chem.*, **38**, 1026 (1973).

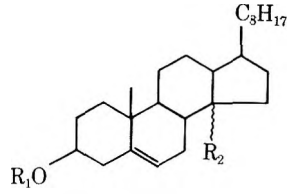
Synthesis of 14β-Cholest-5-en-3β-ol

Mario Anastasia,* Antonio Scala, and Giovanni Galli

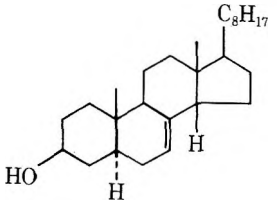
Institute of Chemistry, School of Medicine, University of Milan, I-20133 Milano, Italy, and Institute of Pharmacology and Pharmacognosy, Laboratory of Applied Biochemistry, School of Pharmacy, University of Milan, I-20129 Milano, Italy

Received July 25, 1975

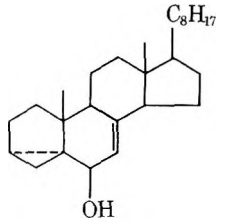
A previous work from this laboratory on the intermediary role of some sterols in the biosynthesis of cholesterol (**1a**) indicates that a cis B/C ring junction, opposite to the trans ring junction of natural compounds, does not prevent the conversion of a sterol molecule to **1a** by liver enzymes.[1] On the basis of this observation it could be postulated that also sterols with a cis C/D ring junction might be enzymatically transformed. In addition, sterols with a modified stereochemistry with respect to that of the natural compounds could exhibit an inhibitory effect on the biosynthesis of **1a** as it has been shown for the triterpenoid euphol, which differs from lanosterol only in stereochemistry.[2] The synthesis of 5α,14β-cholest-7-en-3β-ol (**2**), a sterol suitable to check the influence of a cis fusion of C/D rings on sterol



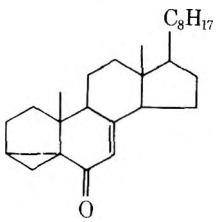
1a, R_1 = H; R_2 = α-H
b, R_1 = H; R_2 = β-H
c, R_1 = C_2H_5CO; R_2 = α-H
d, R_1 = C_2H_5CO; R_2 = β-H
e, R_1 = CH_3CO; R_2 = α-H
f, R_1 = CH_3CO; R_2 = β-H
g, R_1 = 3,5-$(NO_2)_2C_6H_3CO$; R_2 = α-H
h, R_1 = 3,5-$(NO_2)_2C_6H_3CO$; R_2 = β-H



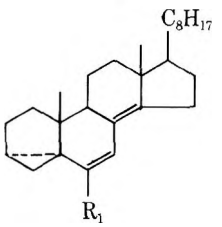
2



3



4



5a, R_1 = H
b, R_1 = *O*-alkyl
c, R_1 = *O*-acyl
d, R_1 = $OSi(CH_3)_3$

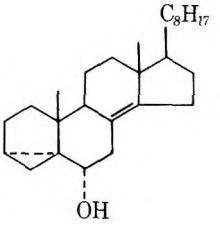
biosynthesis, has been described elsewhere.[3] A simple synthesis of 14β-cholest-5-en-3β-ol (**1b**) from 3α,5α-cyclocholest-7-en-6β-ol (**3**) is now described, since **1b** may be a metabolite in the enzymatic transformation of **2**. The oxidation of **3** to the corresponding ketone **4** either with manganese dioxide in chloroform[4] or with chromium trioxide in pyridine[5] gave unsatisfactory results in our hands; the compound was recovered unchanged after treatment with manganese dioxide at temperatures below 40 °C, whereas dehydration took place with the formation of consistent amounts of the diene **5a** both by oxidation with manganese dioxide at temperatures above 40 °C or by oxidation with chromium trioxide in pyridine. Approximately 80% yield of pure 3α,5α-cyclocholest-7-en-6-one (**4**) was obtained, with a solution of chromium trioxide in pyridine–dichloromethane (1:3.6).

A simple method to obtain 14β-steroids was proposed recently by Mincione et al., consisting in hydroboration of 8(14)-ene steroids at controlled temperature.[6] In our case it was necessary to isomerize the Δ^7 double bond of the unsaturated ketone **4** to the 8(14) position. Treatment of **4** with various bases results in an equilibrium mixture of 7- and 8(14)-double bond isomers. Unfortunately, the 8(14)-double bond isomer is unstable and reverts to the original during work-up.[4b] On the other hand, a heteroannular 6,8(14) diene structure **5b** or **5c** can be anticipated for dienol derivatives of ketone **4**, the 6,8(9) homoannular isomer being less stable as shown by uv absorption of simple unsubstituted dienes.[7] Reduction of the dienol derivative would give a homoallylic alcohol **6** suitable for the following hydroboration reaction. Dienol ethers **5b** and their thio analogues were not considered as suitable derivatives of **4** because of their stability under basic conditions, which precludes generation of the $\Delta^{8(14)}$-6-one system under the usual reducing conditions (i.e., $NaBH_4$). Dienol esters **5c** were also excluded since the acidic conditions required for their preparation[8] cleave the cyclopropane ring.[4b,9]

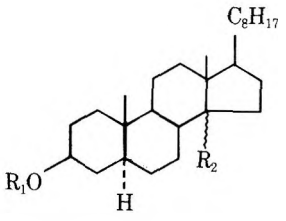
Trimethylsilyl enol ethers can be obtained by addition of trimethylsilyl chloride to sodium enolates generated by heating a solution of the ketone in glyme with sodium hydride.[10] Under these conditions the cyclopropane ring is unaffected.[5a] Application of this procedure with minor modifications to the unsaturated ketone **4** resulted in the formation of 6-trimethylsilyloxy-3α,5α-cyclocholesta-6,8(14)-diene (**5d**) in nearly quantitative yield. This compound was crystallized from 2-propanol. Its spectral properties were in agreement with the proposed structure; the uv absorption spectrum (λ_{max} 263 nm, ε 24 200) was consistent with a 6,8(14) heteroannular diene;[7] double bond stretching frequencies were at 1620 and 1650 cm^{-1}.[11] The ^1H NMR spectrum showed the 10β- and 13β-methyl signals at δ 0.79 and 0.88, respectively, in accordance with the signals at δ 0.76 and 0.89 of the corresponding methyl groups of diene **5a**;[12] the vinylic proton at position 7 gave a sharp singlet and multiplet at very high fields confirming the presence of the cyclopropane ring. The mass spectrum of the compound showed the molecular ion at the expected value. No ion corresponding to the formal loss of trimethylsilanol was present. This behavior under the electron impact which has been already observed for 3-trimethylsilyloxycholesta-3,5-diene[13] confirmed the presence of a trimethylsilyl dienol ether system in the molecule. No hydrolysis of the trimethylsilyloxy group was observed during the

isolation and the purification both by chromatographic methods and by crystallization.

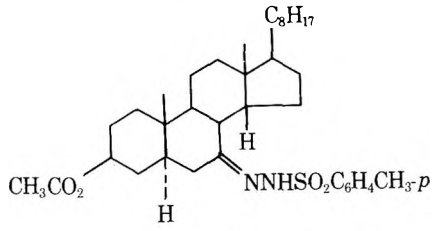
The trimethylsilyl derivative **5d** was reduced with sodium borohydride in 2-propanol to 3α,5α-cyclocholest-8(14)-en-6α-ol (**6**). The structure was assigned on the basis of ^{1}H NMR information. A downfield shift of the 13β-methyl signal with respect to the 13β-methyl signal of 3α,5α-cyclocholestan-6α-ol[14] was observed which was attributable to the presence of the 8(14) double bond.[15a] As expected, cyclopropane protons were present at very high fields. A quadruplet centered at δ 2.73 ($J_{6\beta,7\beta}$ = 5, $J_{7\alpha,7\beta}$ = −13 Hz) was assigned to the equatorial 7β proton whereas absorption of axial 7α proton was included in the methylene envelope. The axial (i.e., β) configuration in a chair conformation was attributed to the 6 hydrogen since this proton signal was present in the ^{1}H NMR spectrum as the X part of an AMX system;[15b] the quadruplet centered at δ 3.83 ($J_{6\beta,7\alpha}$ = 11.5, $J_{6\beta,7\beta}$ = 5 Hz) collapsed to a doublet ($J_{6\beta,7\alpha}$ = 11.5 Hz) by irradiation at δ 2.73. The mass spectrum of **6** was almost identical with that of diene **5a** owing



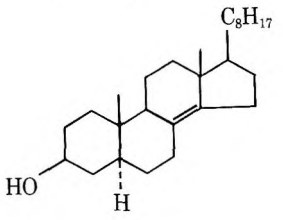
6



7a, R_1 = H; R_2 = β-H
b, R_1 = CH_3CO; R_2 = β-H
c, R_1 = CH_3CO; R_2 = α-H
d, R_1 = 3,5-$(NO_2)_2C_6H_3CO$; R_2 = β-H
e, R_1 = C_2H_5CO; R_2 = α-H
f, R_1 = C_2H_5CO; R_2 = β-H



8



9

to the thermal or electronic loss of water; a prominent ion at *m/e* 199 attributable to the presence of the 3α,5α-cyclo-6,8(14)-diene system was present in the spectrum.[16]

It is known that hydroboration of 8(14)-ene steroids occurs with the addition of boron predominantly at the 15 position[6] whereas the cyclopropane ring is opened only at elevated temperature.[17] Therefore the alcohol **6** was hydroborated at 50–60 °C in diglyme and protonolysis of boron was obtained by refluxing in diglyme–propionic acid for 48 h.[18] Under these conditions the 3β-propionyloxy-5-ene system was generated from the 3α,5α-cyclo-6α-hydroxy system in agreement with the results obtained by other authors by treatment of a 3α,5α-cyclo-6β-methoxy steroid with acetic acid.[19] A 1:1.5 mixture of propionates **1c** and **1d** was obtained from the reaction.

It has been reported that addition of boron occurs to the carbon atom β to the enol ether substituent.[20] This fact prompted us to check the hydroboration reaction of the trimethylsilyloxy derivative **5d.** Treatment of the compound with diborane under a variety of conditions, followed by protonolysis, resulted in a mixture of compounds containing only traces of the two isomers **1c** and **1d.**

Separation of pure 14β diastereoisomer **1d** from **1c** was obtained by one crystallization of the mixture of the two isomers from methanol; **1c** crystallized whereas **1d** was recovered 95–99% pure by evaporation of the mother liquors. Attempts to crystallize **1d** and **1f** from a number of solvents were unsuccessful: crystallization of the free alcohol **1b** was achieved by keeping a solution of the compound in methanol for 1 month at −20 °C. An easily crystallizable derivative was found to be the 3,5-dinitrobenzoate **1h.** Considering solubilities in common organic solvents and GLC retention time values it can be deduced that 14β isomers are more soluble and less retained than the corresponding 14α isomers.

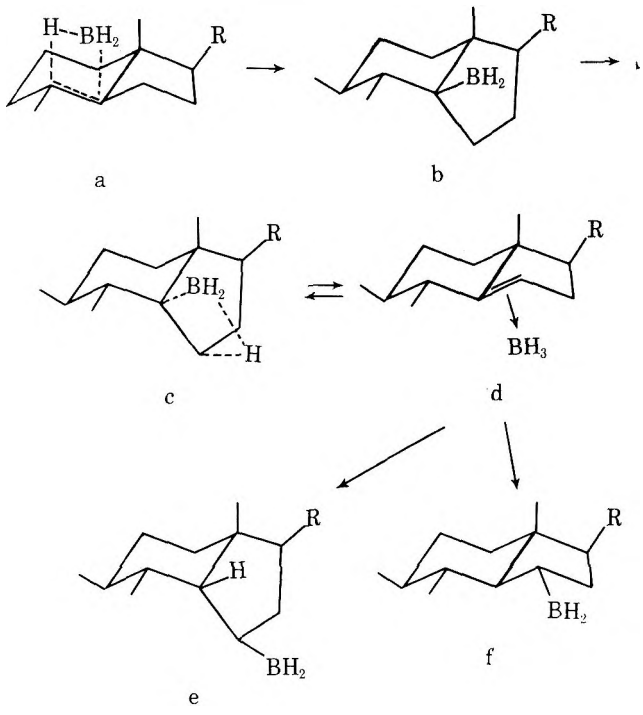
The structure of **1f** was assigned on the basis of its spectroscopic properties; the δ values of signals of 10β- and 13β-methyl groups in the ^{1}H NMR spectrum were in agreement (±0.04 ppm) with those calculated on the basis of Zürcher's rule;[15c,d] 3α- and 6-proton signals in the ^{1}H NMR spectra of both **1g** and **1h** were observed at the same fields and showed identical half-band widths. The mass spectra of **1e**[21] and **1f** showed similar fragmentation patterns differing only for the relative intensities of peaks at *m/e* 120, 213, 247, 255, and 260. Moreover, the evaporation temperature of **1f** was about 40 °C lower with respect to that of **1e** when analyzed by direct introduction in the ion source.

The structure of **1f** was confirmed by hydrogenation and transformation to crystalline **7d,** which was also obtained either by sodium borohydride reduction of 5α,14β-cholestan-3β-ol-7-one acetate tosylhydrazone (**8**)[3] and subsequent saponification and esterification or by hydroboration of 5α-cholest-8(14)-en-3β-ol (**9**) followed by protonolysis, fractional crystallization, saponification, and esterification. The ^{1}H NMR information for **7b** was consistent with the assigned structure; 10β- and 13β-methyl signals were at the calculated values (±0.04 pm);[15a,d] the 3α proton absorbed at the same field and with identical half-band width as the 3α proton of **7c.** The acetates **7b** and **7c**[22] showed mass spectra differing only for the relative intensities of a number of peaks. The diagnostic value for the 14β isomer can be attributed to triplets centered at *m/e* 216 and 276, respectively.

Hydroboration of 8(14)-ene sterols yields 15-boron compounds as the end products.[6] The excess diborane produced at the hydroboration stage may catalyze the low-temperature isomerization.[23] However, a reaction mechanism can be postulated implying relatively nonpolar transition states, by which the influence of steric factors on the direction of the addition might be explained.[24] According to this mechanism, diborane adds first to the β side of the molecule since addition to the α side would give rise to an highly unstable B/C ring junction. On the basis of model examination, the conformation of ring C in transition state a should revert to chair in compound b. Compounds e and f with a boron at 15β and 15α position, respectively, would be formed from compound b through transition state c and π complex d (Scheme I).

It has been reported that protonolysis of 15α-boron compounds requires 8 h.[25] However, the above reported 1.5:1 ratio of 14β to 14α isomers was obtained after only 47 h; on the other hand only the 14α isomer was detectable after 8 h. The different rate is attributable to the lower rate of formation of the cyclic transition state owing to hindrance of

Scheme I



the boron atom in the 15β configuration.[26] The observed 1.5:1 ratio between 14β and 14α isomers significantly differs from the reported 5:1 ratio.[6] This discrepancy might be caused by the more drastic reaction conditions utilized by us (time and temperature) which favor side reactions as demonstrated by the decreased yields of **1c** and **1d** after 72 reaction h.

The availability of **1b** opens the way to various biological investigations. The inhibition of **1a** biosynthesis is a first possibility. The transformation of **1b** in tissues should also be examined with special regard to the possible role of the compound in modulating the synthesis of steroid hormones.

Experimental Section

All melting points are uncorrected. Infrared spectra were taken as Nujol mulls and absorptions are reported as reciprocal centimeters, NMR spectra were taken on a Perkin-Elmer R-24 as chloroform-d_1 solutions and are reported as δ units relative to Me_4Si, and optical rotations were taken as chloroform solutions. Gas–liquid chromatography (GLC) was done on a 3% SE-30 column (2 m × 2.5 mm). The mass spectra were determined on an LKB 9000 spectrometer either by GLC (on 3% SE-30 column, 2 m × 2.5 mm) or by direct inlet (d.i.).

3α,5α-Cyclocholest-7-en-6-one (4). Finely ground crude 7-dehydrocholesteryl tosylate[27] (12g) (contaminated with cyclohydrocarbon **5a**, 3% as determined by uv and TLC) was added to a solution of potassium hydrogen carbonate (6 g), water (0.5 l.), and acetone (2 l.) at 56 ± 0.5 °C. After 5 min the solution was concentrated to 800 ml under vacuum at 30 ± 0.5 °C. The resulting mixture was cooled to −15 °C. The obtained cyclopropyl alcohol **3** (9.5 g), mp 96 °C,[4a] containing 3% of hydrocarbon **5a** (TLC), was dissolved in pyridine (10 ml) and added to a solution of chromium trioxide (9.5 g) in pyridine (90 ml) and methylene chloride (360 ml). The mixture was stirred for 1.5 h at room temperature under nitrogen. The reaction mixture was poured into ice-cold water and extracted with methylene chloride. Evaporation of the solvent yielded crude ketone **4** which was crystallized from diisopropyl ether (7.8 g): mp 131 ° C (lit.[4a] mp 129–130 °C); $[\alpha]^{21}D$ + 87°; uv λ_{max} (EtOH) 249 nm (ϵ 12 400); ir 1650 cm^{-1}; NMR δ 5.82 (m, C-7 H), 1.08 (s, C-10 Me), 0.66 (s, C-13 Me); mass spectrum (d.i.) *m/e* 382 (M^+), 380, 367, 365, 269, 267, 243, 229.

Anal. Calcd for $C_{27}H_{42}O$: C, 84.75; H, 11.07. Found: C, 84.90; H, 11.33.

6-Trimethylsilyloxy-3α,5α-cyclocholesta-6,8(14)-diene (5d). To a 80% dispersion (395 mg) of sodium hydride in mineral oil previously washed with anhydrous hexane and dried under nitrogen, 980 mg of ketone **4** in 15 ml of diglyme was added and the mixture was heated to 80 °C under nitrogen. After 2 hr the evolution of hydrogen ceased and the solution was cooled to room temperature. Triethylamine (10 ml) and trimethylsilyl chloride (6.5 ml) were added, and after the mixture was stirred at 25 °C for 1 h it was diluted with hexane and filtered through a pad of Celite. The filtrate was washed with a saturated NaCl solution, dried on Na_2SO_4, filtered, and evaporated in vacuo to give 950 mg of dienol silyl ether **5d.** Crystallization from 2-propanol gave pure **5d** (796 mg): mp 82 °C; $[\alpha]^{21}D$ +112°; uv λ_{max} (isooctane) 263 nm (ϵ 24 200); ir 1650, 1620 cm^{-1}; NMR δ 5.5 (s, C-7 H), 0.88 (s, C-13 Me), 0.79 (s, C-10 Me), 0.3–0.6 (m, cyclopropyl H); mass spectrum (GLC) *m/e* 454 (M^+), 439, 341, 336, 314, 299.

Anal. Calcd for $C_{30}H_{50}OSi$: C, 79.22; H, 11.18. Found: C, 79.23; H, 11.21.

3α,5α-Cyclocholest-8(14)-en-6α-ol (6). Trimethylsilyl dienol ether **5d** (650 mg) and $NaBH_4$ (70 mg) were dissolved in 2-propanol (60 ml). The mixture was stirred at 60 °C for 2 h. The solvent was removed under reduced pressure, ice-cold water was added, and the mixture was extracted with ether. The organic layer was washed with water and saturated NaCl solution. After drying (Na_2SO_4), the solvent was evaporated and alcohol **6** was crystallized (450 mg) from acetone: mp 107 °C; $[\alpha]^{21}D$ +72°; ir 3400, 1620 cm^{-1}; NMR δ 3.83 (q, C-6β H), 2.73 (q, C-7β H), 0.92 (s, C-10 Me), 0.86 (s, C-13 Me), 0.3–0.6 (m, cyclopropyl H); mass spectrum (d.i.) *m/e* 366 ($M^+ - H_2O$), 351, 253, 199.

Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.01; H, 11.28.

3β-Propionyloxy-14β-cholest-5-ene (1d). Diborane generated by addition of $NaBH_4$ (7 g) in diglyme (50 ml) to a stirred solution of boron trifluoride etherate (50 g, freshly distilled) in dry diglyme (50 ml) was bubbled under a hydrogen flow over a period of 2 h into a stirred solution of alcohol **6** (2 g) in dry diglyme (50 ml) previously heated at 55 °C. After completion of $NaBH_4$ addition, the flask containing the diborane generating mixture was heated for 1 h at 70–80 °C, the hydrogen flow being maintained to ensure the complete transfer of diborane to the hydroboration flask. The solution was then cooled to −80 °C (dry ice–acetone), propionic acid (5 ml, freshly distilled) was added carefully, and the solution was stirred for 1 h. Upon return to room temperature, more propionic acid (45 ml) was added and the solution was heated at 140 °C for 48 h at which time it was evaporated in vacuo at 70 °C. The residue was treated with $NaHCO_3$ saturated solution and extracted with petroleum ether (bp 30–50 °C); the organic layer was washed with a saturated NaCl solution, dried (Na_2SO_4), and evaporated in vacuo to give a pale yellow oil (2.58 g) which was chromatographed on silica gel G–Celite (50:50 v/v) (50 g).

Fractions eluted with hexane–benzene (90:10 v/v) (996 mg) contained a mixture of propionates **1c** and **1d** (GLC and mass spectrometry). Keeping a methanolic solution of the two isomers at −15 °C for 12 h, crystalline **1c** (410 mg) was obtained containing 3% **1d** (GLC). Recrystallization from the same solvent gave pure **1c**, mp 123–124 °C,[28] whose physical constants (GLC, ir, and mass spectrum) was identical with those of an authentic specimen.

Solvent removal from first mother liquors gave propionate **1d** (580 mg), which was purified from trace impurities by column chromatography on silica gel G–Celite (50:50 v/v). The residue from evaporation of hexane–benzene (90:10 v/v) fractions was pure **1d**, a colorless oil. The presence of **1c** was excluded by GLC (240 °C), since a single peak was present in the gas chromatogram with relative retention time (rrt) 0.86 (**1c**: rrt 1): ir 1730 cm^{-1}; NMR δ 5.62 (m, C-6 H), 4.8 (m, C-3α H), 1.0 (s, C-10 Me), 0.98 (s, C-13 Me); mass spectrum (GLC) *m/e* 368 ($M^+ - C_3H_6O_2$), 353, 260, 255, 213.

Anal. Calcd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.07. Found: C, 81.62; H, 10.98.

14β-Cholest-5-en-3β-ol (1b). The ester **1d** (290 mg) was saponified in methanolic KOH and worked up as usual. The oily residue was crystallized from methanol at −20 °C. After 1 month the crystalline **1b** (240 mg) was filtered: mp 38 °C; $[\alpha]^{21}D$ +29°; ir 3310 cm^{-1}; mass spectrum *m/e* 386 (M^+), 371, 368, 301, 273, 255; GLC (240 °C) rrt 0.87 (rrt of **1a**, 1).

The acetate **1f** was a colorless, viscous oil: ir 1730 cm^{-1}; NMR δ 5.62 (m, C-6 H), 4.79 (m, C-3α H), 2.01 (s, CH_3CO), 1.02 (s, C-10 Me), 0.97 (s, C-13 Me) (calcd,[15a,d] 1.000 and 0.984, respectively); GLC (24 °C) rrt 0.86 (rrt of **1e**, 1).

The crystalline 3,5-dinitrobenzoate **1h** had mp 157 °C from acetone; $[\alpha]^{21}D$ +32°; ir 3095, 1740 cm^{-1}; NMR δ 9.13 (m, aromatic

H), 5.44 (m, C-6 H), 4.93 (m, C-3α H), 1.08 (s, C-10 Me), 1.02 (s, C-13 Me) (calcd,[15a,29] 1.086 and 1.010, respectively).

Anal. Calcd for $C_{34}H_{48}N_2O_6$: C, 70.31; H, 8.33; N, 4.82. Found: C, 70.63; H, 8.16; N, 4.77.

5α,14β-Cholestan-3β-ol (7a). A. The acetate **1f** (180 mg) was dissolved in acetic acid (20 ml) and hydrogenated over PtO_2 (20 mg) at room temperature and atmospheric pressure. After the stoichiometric hydrogen was taken up, the catalyst was removed by filtration and the filtrate was concentrated to dryness. The solution of the residue in ether was washed acid free with 5% $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel G–Celite (50:50 v/v). The hexane–benzene eluates (95:5 v/v) were concentrated to dryness to yield acetate **7b:** oil; ir 1730 cm^{-1}; NMR δ 4.9 (m, C-3α H), 2.03 (s, CH_3CO), 0.95 (s, C-13 Me), 0.84 (s, C-10 Me) (calcd,[15a,d] 0.950 and 0.800, respectively); GLC (240 °C) rrt 0.87 (rrt of **7c**, 1).

After saponification of **7b** with methanolic KOH, the oily alcohol **7a** was obtained, mass spectrum (GLC) *m/e* 388 (M^+).

Anal. Calcd for $C_{27}H_{48}O$: C, 83.43; H, 12.45. Found: C, 83.32; H, 12.30.

The alcohol **7a** was transformed as usual into 3,5-dinitrobenzoate **7d:** mp 155–156 °C from acetone; $[\alpha]^{21}D$ +38°; ir 3120, 1740 cm^{-1}.

Anal. Calcd for $C_{34}H_{50}N_2O_6$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.10; H, 8.79; N, 4.51.

B. Compound **8**[3] (300 mg) and $NaBH_4$ (600 mg) were dissolved in methanol (20 ml) and refluxed for 4 h. The solution was worked up as usual to yield oily **7a**, which after esterification was transformed into 3,5-dinitrobenzoate **7d** (260 mg), mp 155–156 °C.

C. The alcohol **9** (950 mg) in dyglime (50 ml) was hydroborated under the same conditions described for the preparation of propionate **1d.** After addition of propionic acid the mixture was heated at 140 °C for 48 h, at which time the solution was worked up as above. The residue was chromatographed on silica gel G–Celite (50:50 v/v).

Fractions eluted with hexane–benzene (95:5 v/v) (420 mg) contained a mixture of propionates **7e** and **7f** (GLC and GLC–mass spectrometry). Upon standing of their solution at −15 °C for 12 h and filtration of crystalline material the mother liquor was evaporated to yield propionate **7f** (250 mg) as an oil: ir 1730 cm^{-1}; mass spectrum (GLC) *m/e* 444 (M^+), 370, 355, 290, 257, 230, 217, 216, 215.

Compound **7f** was saponified to alcohol **7a**, which was transformed into 3,5-dinitrobenzoate **7d**, mp 155–156 °C.

Acknowledgments. This research was supported by the Italian Research Council. We thank Professor A. Fiecchi for helpful discussions.

Registry No.—**1b**, 57759-45-2; **1c**, 633-31-8; **1d**, 57759-46-3; **1f**, 57759-47-4; **1h**, 57759-48-5; **3**, 57679-64-8; **4**, 57674-64-3; **5d**, 57674-65-4; **6**, 57674-66-5; **7a**, 57759-49-6; **7b**, 57759-50-9; **7d**, 57759-51-0; **7e**, 57674-67-6; **7f**, 57759-52-1; **8**, 57674-68-7; **9** 566-99-4; 7-dehydrocholesteryl tosylate, 57674-69-8; trimethylsilyl chloride, 75-77-4.

References and Notes

(1) A. Fiecchi, M. Galli Kienle, A. Scala, G. Galli, R. Paoletti, and E. Grossi Paoletti, *J. Biol. Chem.*, **247**, 5898 (1972).
(2) D. J. Baisted, S. R. Klemp, and M. L. Smith, *Biochem. Biophys. Res. Commun.*, **29**, 258 (1967).
(3) M. Anastasia, A. Fiecchi, and A. Scala, *J. Chem. Soc., Perkin Trans. 1*, submitted for publication.
(4) (a) W. E. Harvey and K. Bloch, *Chem. Ind. (London)*, 595 (1961); (b) D. H. R. Barton, P. G. Feakins, J. P. Poyser, and P. G. Sammes, *J. Chem. Soc. C*, 1584 (1970).
(5) (a) G. H. R. Summers, *J. Chem. Soc.* 4489 (1958); (b) M. J. Thompson, C. F. Cohen, and S. M. Lancaster, *Steroids*, **5**, 745 (1965).
(6) E. Mincione and F. Feliziani, *J. Chem. Soc., Chem. Commun.*, 942 (1973).
(7) L. Dorfman, *Chem. Rev.*, **52**, 53 (1953).
(8) H. J. E. Lowenthal, "Protective Groups in Organic Chemistry", J. F. W. McOmie, Ed., *Plenum Press, New York, N.Y.*, 1973, p. 337.
(9) J. Hora, L. Labler, A. Kasal, V. Cerny, F. Sorm, and K. Slama, *Steroids*, **8**, 887 (1966).
(10) G. Stork and P. F. Huldrick, *J. Am. Chem. Soc.*, **90**, 4462 (1968).
(11) H. O. House, L. J. Czuba, M. Gall, and H. O. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
(12) I. F. Eckhard, H. Heaney, and B. A. Marples, *J. Chem. Soc. C*, 2098 (1969).
(13) H. Hoellinger, N.-H. Nam, and L. Pichat, *C. R. Acad. Sci., Ser. C*, **276**, 715 (1973).
(14) V. Cerny, A. Kasal, and F. Sorm, *Collect. Czech. Chem. Commun.*, **34**, 1235 (1970).
(15) (a) N. S. Baccha and D. M. Williams, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1966, p 13; (b) *ibid., pp 47 and 70;* (c) *H. Mory, K. Shibata, K. Tsuneda, and M. Saway, Chem. Pharm. Bull.*, **16**, 1593 (1968); (d) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).
(16) D. H. R. Barton, J. P. Poser, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 53 (1972).
(17) B. Rickborn and S. E. Wood, *Chim. Ind. (Milan)*, 162 (1966).
(18) H. C. Brown and K. Murray, *J. Am. Chem. Soc.*, **81**, 4108 (1959).
(19) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 3374 (1952).
(20) (a) H. C. Brown and R. L. Sharp, *J. Am. Chem. Soc.*, **90**, 2915 (1968); (b) D. J. Pasto and C. C. Cumbo, *ibid.*, **86**, 4343 (1964).
(21) G. Galli and S. Maroni, *Steroids*, **10**, 189 (1967).
(22) H. Budzikiewicz and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 1430 (1962).
(23) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **88**, 1433 (1966); **89**, 561 (1967).
(24) (a) A. Stretwieser, Jr., L. Verbit, and R. Bittman, *J. Org. Chem.*, **32**, 1530 (1967); (b) J. Klein, E. Dunkelblum, and M. A. Wolff, *J. Organomet. Chem.*, **7**, 377 (1967).
(25) G. Jones and C. Djerassi, *Steroids*, **10**, 653 (1967).
(26) L. H. Toporcer, R. E. Dessy, and S. I. E. Green, *J. Am. Chem. Soc.*, **87**, 1236 (1965).
(27) P. Karrer and H. Asmis, *Helv. Chim. Acta*, **35**, 1926 (1952).
(28) A. Windaus and C. Ulbrig, *Ber. Dtsch. Chem. Ges.*, **47**, 2384 (1914).
(29) W. Arnold, W. Meister, and G. Englert, *Helv. Chim. Acta*, **57**, 1561 (1974).

Synthesis of 3-*epi*-Cholecalciferol and 5,6-*trans*-3-*epi*-Cholecalciferol

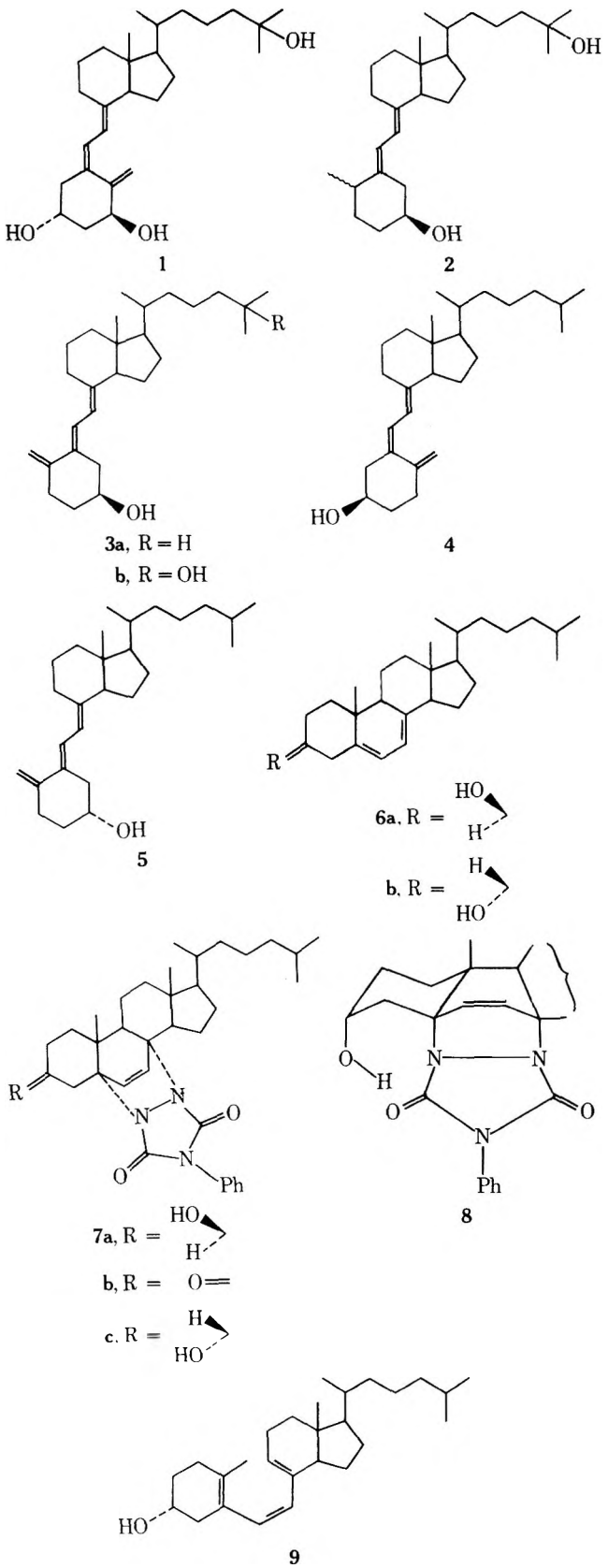
D. John Aberhart,* John Yeou-Ruoh Chu, and Adam Chi-Tung Hsu

Department of Chemistry, The Catholic University of America, Washington, D.C. 20064

Received August 27, 1975

It is now known that vitamin D_3 undergoes a two-stage metabolic process involving hydroxylation, first at C-25 (occurring in liver), then at the C-1α position (in kidney) to produce what is apparently the final biologically active form, 1α,25-dihydroxycholecalciferol (I).[1] Recent studies on synthetic ring A analogs of vitamin D_3 and its hydroxylated metabolites have provided considerable information on structure–activity relationships in such compounds. In particular, the continued presence of intestinal calcium transport ability, even in nephrectomized rats, of 25-hydroxydihydrotachysterol (**2**), 5,6-*trans*-cholecalciferol (**3a**), and 5,6-*trans*-25-hydroxycholecalciferol (**3b**), suggests that the principal requirement for such activity may be the presence of a hydroxyl group in ring A having approximately the same position, relative to the transoid diene system, as that of the 1α-hydroxyl in the normal metabolite, **1**.[1b] Further, such results suggest that the 3β-hydroxyl of **1** may be of little importance in determining the biological activity of vitamin D_3 derivatives. This is supported by the recent finding that 3-deoxy-1α-hydroxycholecalciferol exhibits high biological activity and produced a greater maximum in intestinal calcium transport than did the natural metabolite.[2a] Furthermore, 3-methoxy-1α-hydroxycholecalciferol has pronounced intestinal calcium transport activity in vitamin D deficient rats.[1b]

In order to provide further information on the relationships between structure and biological function in ring A analogues of cholecalciferol, we undertook syntheses of the analogues in which the configuration of the 3-hydroxyl group is inverted, namely 3-*epi*-cholecalciferol (**4**) and 5,6-*trans*-3-*epi*-cholecalciferol (**5**). The latter is of particular interest because it possesses a hydroxyl in the same relative position as the 1β-hydroxyl of the (as yet) unknown 3-deoxy-1β-hydroxycholecalciferol. The hydroxyl will also be similar in location to that of the biologically active 3-



deoxy-1α-hydroxycholecalciferol. The hydroxyls may be expected to be primarily equatorial (although some axial alcohol will be present),[2b,c] and thus nearly identically located with respect to the transoid diene system.

The desired compounds **4** and **5** were previously synthesized by Inhoffen[3] and co-workers, but were apparently not tested for biological activity. In the present work, **4** and **5** were prepared by a considerably easier route, from a readily available precursor.

7-Dehydrocholesterol (**6a**) was treated with 4-phenyl-1,2,4-triazoline-3,5-dione to yield, essentially quantitatively, adduct **7a**,[4] which upon treatment with Jones reagent gave the ketone in good yield. Part of our motivation for pursuing this route was the supposition that **7b** could be dehydrogenated to the Δ^1 analogue, which might serve as a suitable precursor of 1α-hydroxy-7-dehydrocholesterol. However, we have not as yet been able to carry out this desired transformation. On treatment with sodium borohydride, ketone **7b** gave the 3α-alcohol, **7c**, as the main product, the bulky triazolinedione moiety providing steric interference with the usual α-attack by this reductant. Although a small amount of the 3β-alcohol **7a** was formed, the separation of 3β and 3α isomers in this case was remarkably easy, the 3α isomer being considerably less polar on silica gel than the 3β isomer. This fact is readily rationalized when it is considered that the 3α-hydroxyl is capable of forming a strong intramolecular hydrogen bond with the 5α-nitrogen, as in **8**. This has the effect of lessening the interaction of the hydroxyl with the absorbent material. In the ir spectrum (CCl_4) of **7c**, a broad absorption band for a bonded hydroxyl, ν_{max} 3450 cm^{-1}, persists practically unchanged over the concentration range of 0.2–0.004 M. In contrast, in the ir of the 3β-alcohol **7a**, the hydroxyl absorption changes over this concentration range from primarily bonded (ν_{max} 3460 cm^{-1}, broad) to nonbonded (ν_{max} 3695, 3640, sharp) with only weak hydrogen-bonded hydroxyl absorption remaining.

Upon treatment of the 3α-hydroxyl adduct **7c** with lithium aluminum hydride, cholesta-5,7-dien-3α-ol[5] (**6b**) was formed as expected,[6] although the yield was not high. Photolysis[7] of **6b** gave a mixture from which the main product, 3-*epi*-precholecalciferol (**9**), was isolated by preparative TLC. This was then thermally isomerized to 3-*epi*-cholecalciferol (**4**). A portion of **4** was further isomerized with iodine in petrol[8] to 5,6-*trans*-3-*epi*-cholecalciferol (**5**). The uv and NMR spectra (see Experimental Section) of compounds **6b**, **9**, **4**, and **5** supported the structures shown, and were closely analogous to the spectra of the corresponding 3β-hydroxy compounds.[9]

Compounds **4** and **5** are currently being examined for biological activity and the results will be published elsewhere.

Experimental Section

Melting points were taken on a hot stage apparatus and are uncorrected. Ir spectra were taken on a Perkin-Elmer Model 337 spectrometer. Uv spectra were taken on a Beckman DB-G spectrometer. NMR spectra were obtained using a Varian A-60 instrument. Camag Kieselgel DF-O was used for thin layer chromatography (TLC). Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

7-Dehydrocholesterol–4-Phenyl-1,2,4-triazoline-3,5-dione Adduct (7a). This was prepared by addition of 4-phenyl-1,2,4-triazoline-3,5-dione (1.79 g, 10 mmol) in ethyl acetate (20 ml) to 7-dehydrocholesterol (3.84 g, 10 mmol) in ethyl acetate (20 ml) in an ice bath. The solution was evaporated and the product crystallized from MeOH as needles: mp 155 °C (lit.[3] 155 °C); $[\alpha]^{25}D$ −91° (*c* 1.4, $CHCl_3$); ν_{max} (CCl_4) (0.2 M) 3450 (br), 1755, 1698, 1400, 1291, 1155, 1078, 1043, 1018, 690 cm^{-1}; NMR ($CDCl_3$) δ 0.77 (3 H, s), 0.79 (3 H, s), 0.8–3.5 (35 H, m), 4.35 (1 H, broad m), 6.10 and 6.34 (2 H, AB, J_{AB} = 8 Hz), 7.34 (5 H, br s).

Cholesta-5,7-dien-3-one–4-Phenyl-1,2,4-triazoline-3,5-dione Adduct (7b). 7-Dehydrocholesterol adduct **7a** (3.2 g, 5.7 mmol) in acetone (320 ml) at room temperature was treated with Jones reagent (8 M, 3 ml, 24 mmol) added with stirring over 15 min. Water (200 ml) was added followed by 5% $NaHSO_3$ (30 ml), and the mixture was extracted with ether. The extract was washed with 5% $NaHSO_3$ and saturated NaCl, dried (Na_2SO_4), and evaporated to yield the crude product, **7b**, crystallized from MeOH as prisms: mp 141–144 °C; $[\alpha]^{28}D$ −77° (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 1750, 1725 (sh), 1690, 1600, 1400 cm^{-1}; NMR ($CDCl_3$) δ 0.70 (3 H,

s), 0.8–2.8 (35 H, m), 2.76 (4α H) and 3.65 (4β H) (2 H, AB, J_{AB} = 19 Hz), 6.25 and 6.62 (2 H, AB, J_{AB} = 8 Hz), 7.54 (5 H, br s).

Anal. Calcd for $C_{35}H_{47}N_3O_3$: C, 75.37; H, 8.49. Found: C, 75.60; H, 8.64.

Cholesta-5,7-dien-3α-ol-4-Phenyl-1,2,4-triazoline-3,5-dione Adduct (7c). Ketone **7b** (3.0 g, 5.4 mmol) in MeOH (85 ml) and $CHCl_3$ (20 ml) was treated at room temperature with sodium borohydride (3 g, 0.12 mol) added over 40 min. After stirring for 2 h at room temperature, ether (400 ml) was added. The solution was washed with dilute HCl and saturated NaCl, dried (Na_2SO_4), and evaporated to a gum. The product was isolated by preparative TLC (EtOAc–hexane, 1:2) giving **7c**, 1.1 g, crystallized from MeOH as needles: mp 186–188 °C; $[\alpha]^{28}D$ −94° (c 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3430 (br), 1750, 1690, 1420, 1395, 1167, 1152, 1085, 690 cm^{-1}; NMR ($CDCl_3$) δ 0.79 (3 H, s), 0.85–3.0 (37 H, m), 4.25 (1 H, m), 5.27 (1 H, br s, D_2O exchangeable), 6.23 and 6.49 (2 H, AB, J_{AB} = 8 Hz), 7.42 (5 H, br s).

Anal. Calcd for $C_{35}H_{49}N_3O_3$: C, 74.82; H, 8.83. Found: C, 75.10; H, 8.82.

Cholesta-5,7-dien-3α-ol (6b). 3-Epi adduct **7c** (553 mg, 1.02 mmol) in anhydrous THF (50 ml) was refluxed with $LiAlH_4$ (500 mg, 13.2 mmol) under N_2 in the dark for 11 h. After standing for 8 h at room temperature, the mixture was cooled in ice, and ethyl acetate (5 ml) was added dropwise followed by H_2O (1 ml) and ether (100 ml). The mixture was dried (Na_2SO_4), filtered, and evaporated to a semicrystalline residue. The major product was isolated by preparative TLC (ethyl acetate–hexane, 1:4, R_f 0.6) giving **6b**, 191 mg, as needles from MeOH: mp 128–130 °C; $[\alpha]^{30}D$ −51° (c 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3620, 3450 (br), 1480, 1400, 1005 cm^{-1}; λ_{max} (EtOH) 252 nm (infl, ε 4260), 262 (infl, 7180), 269 (9550), 280 (10 500), 291 (6150); NMR ($CDCl_3$) δ 0.62 (3 H, s), 0.81 (3 H, s), 0.9–2.5 (35 H, m), 4.10 (1 H, dd, $J_1 = J_2$ = 3 Hz), 5.40 and 5.66 (2 H, AB, J_{AB} = 6 Hz, further coupled with J = 2 Hz).

Anal. Calcd for $C_{27}H_{44}O$: C, 84.56; H, 11.49. Found: C, 84.31; H, 11.53.

3-*epi*-Precholecalciferol (9). 3-*epi*-7-Dehydrocholesterol (**6b**, 191 mg) in ether (400 ml), in a quartz reaction vessel equipped with an inlet for rapid flushing with N_2, was irradiated for 30 min in a Rayonet RPR-100 reactor equipped with RPR-3000 Å lamps. The solution was then evaporated in vacuo at room temperature to an oil. The major product was isolated by preparative TLC (ethyl acetate–hexane, 1:9, R_f 0.5) giving 3-*epi*-precholecalciferol (**9**): 95 mg (glass); $[\alpha]^{28}D$ +34° (c 1.9, $CHCl_3$); ν_{max} ($CHCl_3$) 3620, 3450 (br), 1450, 1380, 1218, 1035 cm^{-1}; λ_{max} (EtOH) 260 nm (8200); NMR ($CDCl_3$) δ 0.71 (3 H, s), 0.84 (3 H, d, J = 6 Hz), 0.7–2.8 (34 H, m), 3.91 (1 H, m), 5.56 (1 H, br s), 5.71 and 6.03 (2 H, AB, J_{AB} = 12 Hz).

3-*epi*-Cholecalciferol (4). The 3-*epi*-precholecalciferol (93 mg) was refluxed for 3 h in benzene (20 ml) and MeOH (2 ml) under N_2 in the dark. The solution was evaporated in vacuo to a glass which was separated by preparative TLC (EtOAc–hexane, 1:9, R_f 0.4) giving **4**; 65 mg; $[\alpha]^{26}D$ −5.4° (c 2, $CHCl_3$); ν_{max} ($CHCl_3$) 3630, 3450 (br), 1480, 1450, 1395, 1050, 910 cm^{-1}; λ_{max} (EtOH) 264 nm (ε 17 000); NMR ($CDCl_3$) δ 0.55 (3 H, s), 0.87 (3 H, d, J = 6 Hz), 1.0–3.0 (33 H, m), 3.94 (1 H, m), 4.90 (1 H, d, J = 3 Hz), 5.12 (1 H, br s, $W_{1/2}$ = 5 Hz), 6.09 and 6.34 (2 H, AB, J_{AB} = 12 Hz).

5,6-*trans*-3-*epi*-Cholecalciferol (5). 3-*epi*-Cholecalciferol (**4**, 30 mg) in petroleum ether (bp 35–60 °C, 40 ml) was treated with a solution of iodine (1 mg) in petroleum ether (10 ml) for 2 h in "diffuse daylight"[7] (the flask was placed near a window on a bright, hazy day at noon). After evaporation of the solvent in vacuo, the product was separated by preparative TLC (ethyl acetate–hexane, 1:9) giving recovered **4** (15 mg) and the faster running **5** (10 mg), as a noncrystalline glass: $[\alpha]^{26}D$ +34° (c 1, $CHCl_3$); λ_{max} (EtOH) 272 nm (ε 22 000); NMR ($CDCl_3$) δ 0.54 (3 H, s), 0.8–3.3 (36 H, complex multiplet), 3.9 (1 H, broad m), 4.71 (1 H, br s), 5.00 (1 H, br s), 5.88 and 6.62 (2 H, AB, J_{AB} = 12 Hz).

Acknowledgment. This work was supported by Grant AM 17057 from the National Institute of Arthritis, Metabolism, and Digestive Diseases.

Registry No.—**4**, 57651-82-8; **5**, 57651-83-9; **6a**, 434-16-2; **6b**, 57651-84-0; **7a**, 57637-86-2; **7b**, 57637-87-3; **7c**, 57651-85-1; **9**, 57651-22-6; 4-phenyl-1,2,4-triazoline-3,5-dione, 15988-11-1.

References and Notes

(1) (a) J. L. Ohmdahl and H. F. DeLuca, *Physiol. Rev.*, **53**, 327 (1973); (b) H. K. Schnoes and H. F. DeLuca, *Vitam. Horm. (N.Y.)*, **32**, 385 (1974).
(2) (a) A. W. Norman, M. N. Mitra, W. H. Okamura, and R. M. Wing, *Science*, **188**, 1013 (1975); (b) R. M. Wing, W. H. Okamura, M. R. Pirio, S. M. Sine, and A. W. Norman, *ibid.*, **185**, 939 (1974); G. N. LaMar and D. L. Budd, *J. Am. Chem. Soc.*, **96**, 7317 (1974).
(3) H. H. Inhoffen, K. Irmscher, H. Hirschfeld, U. Stache, and A. Kreutzer, *J. Chem. Soc.*, 385 (1959).
(4) C. Kaneko, A. Sugimoto, Y. Eguchi, S. Yamada, M. Ishikawa, S. Sasaki, and T. Suda, *Tetrahedron*, **30**, 2701 (1974).
(5) 3-*epi*-7-Dehydrocholesterol was previously synthesized by a longer route: A. Windaus and J. Naggatz, *Justus Liebigs Ann. Chem.*, **542**, 204 (1939); 3-*epi*-vitamin D_3 was not obtained in pure form, although a crude irradiation product exhibited low biological activity.
(6) D. H. R. Barton, T. Shioiri, and D. A. Widdowson, *Chem. Commun.* 937 (1970); *J. Chem. Soc. C*, 1968 (1971).
(7) (a) D. E. M. Lawson, B. Pelc, P. A. Bell, P. W. Wilson, and E. Kodicek, *Biochem. J.*, **121**, 673 (1971); (b) B. Pelc and E. Kodicek, *J. Chem. Soc. C*, 3415 (1971); (c) D. R. Crump, D. H. Williams, and B. Pelc, *J. Chem. Soc., Perkin Trans. 1*, 2731 (1973); (d) E. Abillon and R. Mermet-Bouvier, *J Pharm. Sci.*, **62**, 1688 (1973); (e) T. Kobayashi and M. Yasumura, *J. Nutr. Sci. Vitaminol.*, **19**, 123 (1973).
(8) (a) A. Verloop, A. L. Koevoet, and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **74**, 1125 (1955); (b) D. E. M. Lawson and P. A. Bell, *Biochem. J.*, **142**, 37 (1974).
(9) Compounds **3** and **4** have not been directly compared with the compounds prepared by Inhoffen. However, the physical constants are in reasonable agreement (except for the noncrystallinity of our 5,6-trans, **4**; the quantity obtained was too small for crystallization).

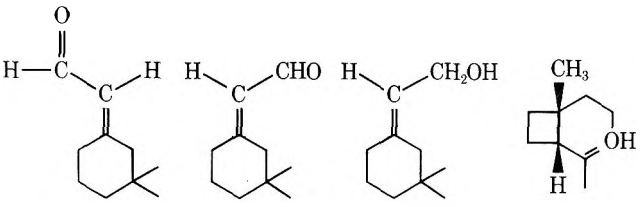
A Facile Synthesis of the Cyclohexyl Constituents of the Boll Weevil Sex Pheromone

S. William Pelletier* and Naresh V. Mody

Natural Products Laboratory, Department of Chemistry, University of Georgia, Athens, Georgia 30602

Received September 18, 1975

The four monoterpene compounds [(*E*)-3,3-dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde (**1**), (*Z*)-3,3-dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde (**2**), (*Z*)-3,3-dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanol (**3**), and (+)-*cis*-2-isopropenyl-1-methylcyclobutaneethanol (**4**)] that comprise the pheromone of

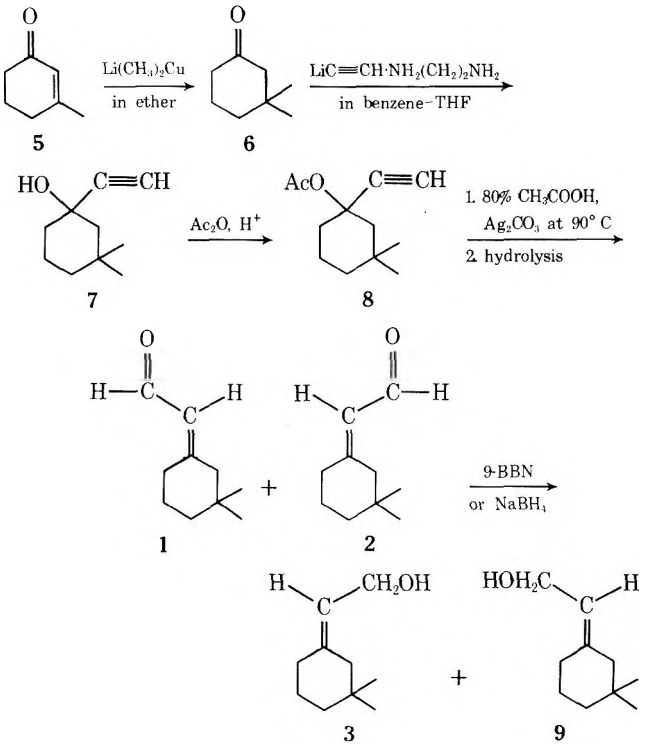


1 2 3 4

male boll weevil *Anthonomus grandis* Boheman were identified and first synthesized by Tumlinson et al.[1] These sex attractants are currently of considerable interest since they may provide a generally nontoxic method of surveying and controlling boll weevil population.[1] The growing concern over the environmental pollution and ecological imbalance caused by insecticides has further stimulated interest in this area. The commercial importance of these sex attractants prompted us to develop an efficient, high-yield synthesis of these compounds.[2,3] This paper describes a facile route from commercially available 3-methyl-2-cyclohexenone to the *E* and *Z* aldehyde components (**1** and **2**) in 80% overall yield. Separation of the aldehyde mixture,[4] followed by reduction of aldehyde **2** with $NaBH_4$ or 9-BBN, affords a route to the component Z alcohol (**3**) in an essentially quantitative yield. Scheme I outlines the synthesis of sex pheromone components **1**, **2**, and **3**.

The known 3,3-dimethylcyclohexanone (**6**), the same intermediate utilized in the previous syntheses,[1,2] was prepared from commercially available 3-methyl-2-cyclohexenone (**5**) by conjugate addition of lithium dimethylcopper in 98% yield.[5] Addition of lithium acetylide–ethylenedi-

Scheme I



amine complex[6] in benzene and THF to **6** afforded, in a yield of 96%, 1-ethynyl-3,3-dimethylcyclohexanol (**7**). A study was subsequently undertaken to determine the stereoselectively of a Meyer–Schuster type rearrangement of compound **7**. The latter was converted into the corresponding acetate **8** by treating with acetic anhydride in the presence of catalytic amounts of phosphoric acid for 12–15 h at room temperature or refluxing with acetic anhydride and pyridine under a nitrogen atmosphere for 2.5 h in 85–90% yield. Compound **8** was refluxed at 90°C with 80% acetic acid, sodium carbonate, and catalytic amounts of silver carbonate[7,8] under an argon atmosphere for 1.5 h. The resulting mixture was hydrolyzed to give the desired aldehydes **1** and **2** in a 47:53 mixture[9] in 88–90% yield. Compound **8** showed very little stereoselectivity in a Meyer–Schuster type rearrangement. Aldehydes **1** and **2** can also be synthesized directly from compound **7** in a yield of 85% without isolating the intermediate compound **8**. This route provided aldehydes **1** and **2** in an overall yield[10] of 82% from 3,3-dimethylcyclohexanone (**6**). A mixture of aldehydes **1** and **2** was reduced with $NaBH_4$ *or* 9-BBN[11] to give the corresponding mixture of *Z* alcohol (**3**) and its *E* isomer (**9**) in quantitative yield.

Experimental Section

Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. Infrared (ir) spectra were determined as film with a Perkin-Elmer Model 257 G spectrometer. Mass spectra were taken with a Hewlett-Packard 5930 quadrupole mass spectrometer operating with an ionization energy of 70 eV. NMR spectra were taken in deuteriochloroform with a Varian T-60 spectrometer. Tetramethylsilane was used as an internal standard. Bulb-to-bulb evaporative distillation was carried out using Buchi Kugelrohrofen.

3,3-Dimethylcyclohexanone (6). To a cold (0°C) solution of lithium dimethylcuprate, prepared from 9.0 g (47 mmol) of copper(I) iodide and 111 mmol of methyllithium in 145 ml of ether, was added dropwise with stirring over a 20-min period a solution of 5.00 g (45.5 mmol) of redistilled 3-methyl-2-cyclohexenone (**5**), bp 84–85°C (13 mm). During the addition some methylcopper separated from the reaction mixture as a yellow precipitate. The resulting mixture was stirred at room temperature for 20 min and then poured into an aqueous solution (pH ~8) of ammonium chloride and ammonia. The combined ether phase and extracts were washed with brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo to give 5.55 g (98%) of 3,3-dimethylcyclohexanone (**6**): bp 58–60°C (15 mm); ν_{max} (film) 1725 cm^{-1}; NMR δ 0.95 (s, 6 H, geminal CH_3) and 2.06 [s, 2 H, $-COCH_2C(CH_3)_2$].

1-Ethynyl-3,3-dimethylcyclohexanol (7). Lithium acetylide–ethylenediamine (1.1 g, 11 mmol) was placed in the nitrogen-flushed reactor, followed by 10 ml of dry benzene and tetrahydrofuran (50:50 mixture). Stirring was started, the mixture was warmed to 35°C, and 1.26 g (10 mmol) of ketone (**6**) was added dropwise over a period of 5 min, while maintaining temperature at 35°C by cooling. This mixture was stirred for 2 h at room temperature. Water (10 ml) was added slowly to hydrolyze the mixture after which it was brought to gentle reflux and held for 15 min. The organic layer was separated, dried with anhydrous $MgSO_4$, and concentrated in vacuo to give 1.46 g (96%) of 1-ethynyl-3,3-dimethylcyclohexanol (**7**): ν_{max} (film) 3415, 3310 and 2350 cm^{-1} ($-C\equiv CH$, very weak); NMR[12] ($CDCl_3$) δ 0.98 and 1.00 (two singlets for geminal methyl group), 1.70 [s, 2 H, $RR'C-CH_2C(CH_3)_2$], 2.30 (s, 1 H, –OH), and 2.48 (s, 1 H, $-C\equiv CH$).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.60. Found: C, 79.08; H, 10.57.

Acetylation of 1-Ethynyl-3,3-dimethylcyclohexanol (7). To a solution of 1-ethynyl-3,3-dimethylcyclohexanol (**7**, 500 mg) in 3 ml of acetic anhydride, a few drops of phosphoric acid (catalytic amount) were added. After a few minutes the solution became warm and turned light pink in color. The resulting mixture was allowed to stand for 12–15 h at room temperature, and then extracted with petroleum ether. The extract was washed with water and dried over $MgSO_4$. On removal of the solvent, an oily acetate (**8**) was obtained in 90% yield: ν_{max} 3280, 2100 (very weak), 1750 cm^{-1}; NMR ($CDCl_3$) δ 0.98 and 1.00 (two singlets for geminal methyl group), 2.04 (s, 3 H, $-OCOCH_3$), 2.60 (s, 1 H, $-C\equiv CH$).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.18; H, 9.34. Found: C, 73.98; H, 9.26.

Aldehydes 1 and 2. To acetate **8** (970 mg) dissolved in 3 ml of 80% acetic acid were added 50 mg of sodium carbonate and 20 mg of silver carbonate. The reaction mixture was refluxed at 90°C under an argon atmosphere for 1.5 h. After cooling the resulting mixture was poured into ice water (10 ml), and the mixture was extracted with methylene chloride. The combined extracts were washed with water, 5% aqueous $NaHCO_3$, and water, dried ($MgSO_4$), and evaporated to give 669 mg (88%) of a mixture of aldehydes **1** and **2**, showing properties consistent with those reported by Tumlinson:[1] ν_{max} (film) 1680 and 1640 cm^{-1}; NMR ($CDCl_3$) peaks at δ 0.90 (s, 6 H, geminal CH_3), 2.00 (s, 2 H, CH_2 trans to aldehyde group), 5.74 (d, 1 H, $-C=CH-$), 10.02 (d, 1 H, –CHO) were assigned to **1**, while those at δ 0.95 (s, 6 H, geminal CH_3), 2.40 (s, 2 H, CH_2 cis to aldehyde group), 5.88 (d, 1 H, $-C=CH-$), and 9.98 (d, 1 H, –CHO) were assigned to **2**. Aldehydes **1** and **2** were identical with authentic samples.[10]

Alcohols 3 and 9. To a solution of 100 mg of the mixture of aldehydes **1** and **2** in absolute ethanol (6 ml), 50 mg of $NaBH_4$ was added. The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was hydrolyzed with water and extracted three times with methylene chloride. The combined extracts were washed with water, dried over anhydrous $MgSO_4$, and evaporated in vacuo to give alcohols **3** and **9** in a quantitative yield. The spectral properties of **3** and **9** were consistent with those reported by Tumlinson and co-workers.[1]

Registry No.—**1**, 26532-25-2; **2**, 26532-24-1; **3**, 26532-23-0; **5**, 1193-18-6; **6**, 2979-19-3; **7**, 57559-98-5; **8**, 57559-99-6; **9**, 30346-27-1.

References and Notes

(1) (a) J. H. Tumlinson, D. D. Hardee, R. C. Gueldner, A. C. Thompson, P. A. Hedin, and J. P. Minyard, *Science*, **166**, 1010 (1969); (b) J. H. Tumlinson, R. C. Gueldner, D. D. Hardee, A. C. Thompson, P. A. Hedin, and J. P. Minyard, *J. Org. Chem.*, **36**, 2616 (1971).
(2) J. H. Babler and T. R. Mortell, *Tetrahedron Lett.*, 669 (1972).
(3) R. H. Bedoukian and J. Wolinsky, *J. Org. Chem.*, **40**, 2154 (1975).
(4) For a description of the procedure to separate aldehydes **1** and **2** refer to J. H. Tumlinson, R. C. Gueldner, D. D. Hardee, A. C. Thompson, P. A. Hedin, and J. P. Minyard in "Chemicals Controlling Insect Behavior," M. Beroza, Ed., Academic Press, New York, N.Y., 1970, p 50.
(5) H. O. House and W. F. Fischer, Jr., *J. Org. Chem.*, **33**, 949 (1968).
(6) O. F. Beumel, Jr., and R. F. Harris, *J. Org. Chem.*, **29**, 1872 (1964).
(7) G. Saucy, R. Marbet, H. Lindlar, and O. Isla, *Helv. Chim. Acta.*, **42**, 1945 (1959).
(8) W. R. Benn, *J. Org. Chem.*, **33**, 3113 (1968).
(9) The ratio of 47:53 was determined via integration of vinyl hydrogen NMR absorption band for each isomer as well as by GLC. For separation of these aldehydes see ref 4.

(10) We wish to thank Dr. R. C. Gueldner of the Boll Weevil Research Laboratory, USDA, Mississippi State, Miss. 39762, for comparing our samples with authentic samples.
(11) S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **40**, 1864 (1975).
(12) NMR assignment of compound **7** was based on deuterium exchange study.

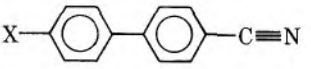
Synthesis of 4-Cyano-4′-halobiphenyls

J. M. McNamara† and W. B. Gleason*

Department of Chemistry, Carleton College, Northfield, Minnesota 55057

Received October 28, 1975

As part of a study of intermolecular halogen–cyanide interactions in the solid state it was desired to prepare very pure samples of the 4-cyano-4′-halobiphenyls. Pummerer and Seligsberger[1] have previously reported the synthesis of Ia and Niwa[2] has reported the synthesis of Ib and Ic. We



Ia, X = I
b, X = Br
c, X = Cl

wish to report the synthesis of these compounds by a different and very simple route involving the displacement of halogen with CuCN in refluxing dimethylformamide[3] (for the iodide and bromide) and *N*-methylpyrrolidone[4] (for the chloride).

For the synthesis of Ia and Ib the reaction was run with 1 equiv of CuCN per mole of the dihalogenated biphenyl. The reaction mixture was very conveniently separated by preparative thin layer chromatography. In a few runs the main components of the reaction mixture were isolated and were approximately those expected for a statistical reaction. An attempt was made to run the displacement reaction on 4,4′-dichlorobiphenyl in refluxing dimethylformamide but even at long reaction times no product could be detected. Use of the higher boiling solvent *N*-methylpyrrolidone, an excess of CuCN, and long reflux times were necessary for a successful synthesis of Ic.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Laser Raman spectra were obtained with a Jeol Model JRS-S1 spectrometer equipped with an argon ion laser. Preparative thin layer chromatography was done on silica gel G PF-254 (E. Merck) using benzene as developer. Compounds were detected using an ultraviolet lamp and products extracted with methanol–chloroform (1:19). Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

4-Cyano-4′-iodobiphenyl (Ia). 4,4′-Diiodobiphenyl (0.50 g, 1.2 mmol), cuprous cyanide (0.11 g, 1.2 mmol), and 15 ml of dimethylformamide were placed in a 50-ml round-bottomed flask and refluxed for 2.5 hr. After cooling, 35 ml of ferric chloride solution (200 g of hydrated $FeCl_3$ and 50 ml of concentrated HCl in 300 ml of water) was added to the reaction vessel. The resulting mixture was heated at 60–70 °C for 20 min. The dimethylformamide–ferric chloride mixture was extracted three times with approximately 20 ml of toluene. The reddish toluene layer was then extracted with 50 ml of 10% HCl, 20 ml of water, and 50 ml of 5% NaOH. The toluene layer was dried over $MgSO_4$ and filtered. The toluene was evaporated at reduced pressure and the residue fractionated by preparative thin layer chromatography. The desired product has R_f 0.51 in benzene. The crude product was sublimed at 135 °C (1 mm), affording 4-cyano-4′-iodobiphenyl (160 mg, 42%). An analytical sample recrystallized from absolute ethanol melted at 179.5–181.5 °C (lit.[1] 166 °C), laser Raman (crystal) 2225 cm^{-1} (–C≡N).

Anal. Calcd for $C_{13}H_8NI$: C, 51.17; H, 2.64; N, 4.59; I, 41.59. Found: C, 51.05; H, 2.59; N, 4.58; I, 41.65.

4-Bromo-4′-cyanobiphenyl (Ib). The procedure was identical with one used for the iodo compound, except that 4,4′-dibromobiphenyl (0.50 g, 1.6 mmol) and cuprous cyanide (0.14 g, 1.6 mmol) were refluxed in dimethylformamide for 4.0 h. The R_f of 4-bromo-4′-cyanobiphenyl is 0.50 in benzene. The crude product was sublimed at approximately 120 °C (1 mm), producing 4-bromo-4′-cyanobiphenyl (210 mg, 50%). A sample recrystallized from absolute ethanol had mp 153.5–155 °C (lit.[2] 144 °C), laser Raman (crystal) 2225 cm^{-1} (–C≡N). An analysis of this compound was not performed. Its identity has been confirmed unambiguously by a complete x-ray analysis.[5]

4-Chloro-4′-cyanobiphenyl (Ic). The procedure used was similar to the one used for the iodo compound, except that 4,4′-dichlorobiphenyl (0.50 g, 2.2 mmol) and cuprous cyanide (0.40 g, 4.46 mmol) were refluxed for 93.0 h in *N*-methylpyrrolidone. The R_f of the product is 0.48 in benzene. The crude product was sublimed at about 105 °C (1 mm), affording 4-chloro-4′-cyanobiphenyl (110 mg, 23%). An analytical sample recrystallized from absolute ethanol melted at 133–133.5 °C (lit.[2] 129–130°C), laser Raman (crystal) 2225 cm^{-1} (–C≡N).

Anal. Calcd for $C_{13}H_8NCl$: C, 73.07; H, 3.77; N, 6.56; Cl, 16.60. Found: C, 73.24; H, 3.78; N, 6.45; Cl, 16.40.

Acknowledgment. We thank Professor Stuart Fenton for the laser Raman spectra and Professor Doyle Britton for his continued interest in this work.

Registory No.—Ia, 57774-34-2; Ib, 57774-35-3; Ic, 57774-36-4; cuprous cyanide, 544-92-3; 4,4′-diiodobiphenyl, 3001-15-8; ; 4,4′-dibromobiphenyl, 92-86-4; 4,4′-dichlorobiphenyl, 2050-68-2.

References and Notes

(1) R. Pummerer and L. Seligsberger, *Chem. Ber.*, **64**, 2477 (1931).
(2) H. Niwa, *Chem. Abstr.*, **52**, 7233 (1958).
(3) L. Friedman and H. Shechter, *J. Org. Chem.*, **26**, 2522 (1961).
(4) M. S. Newman and H. Boden, *J. Org. Chem.*, **26**, 2525 (1961).
(5) P. Kronebusch, W. B. Gleason, and D. Britton, *Cryst. Struct. Commun.*, accepted for publication.

† NSF Undergraduate Research Participant, summer 1975.

A Convenient Synthesis of Labile Optically Active Secondary Alkyl Bromides from Chiral Alcohols

Robert O. Hutchins,* Divakar Masilamani, and Cynthia A. Maryanoff

Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

Received September 25, 1975

Recent interest and reports[1–3] concerning the synthesis of optically active secondary alkyl halides prompts this disclosure of our experience in the area and of a convenient preparative procedure for active bromides, including those which are prone toward racemization.

Conceivably, one of the simplest approaches to the preparation of active halides involves treatment of the corresponding chiral alcohol with a phosphorus trihalide as in eq 1–4. Unfortunately, in practice this method has met with considerable difficulty primarily because the reactions represented by eq 3 and 4 are slow and have afforded halides of much lower optical purity.[1,4–6] To alleviate this problem, HX is commonly swept out (CO_2 or N_2) which essentially eliminates the last two steps (eq 3 and 4).

This produces product of high optical purity but the resulting low yields (i.e., 23% 2-bromooctane from 2-octanol)[1,7] severely limit the usefulness of the procedure, espe-

Table I. Preparation of Secondary Bromo Compounds from Chiral Alcohols with Phosphorus Tribromide

Alcohol	α^{25}D obsd, deg (optical purity, %)	Unreacted phosphite esters	Treatment with HBr	Product	Yield, %	α^{25}D obsd, deg (optical purity, %)[a]
1-Phenylethanol	−44.2 (100)[12]	Absent		α-Phenylethyl bromide	70–75	+160.8 (94)[12]
	+44.2 (100)[12]	Present	No	α-Phenylethyl bromide	35.1	−85.7 (49)[12]
	+42 (95)[12]	Present	Yes	α-Phenylethyl bromide	71	−143 (88%)[12]
2-Octanol	−7.39 (90.7)[2]	Absent		2-Octyl bromide	67	+39.3 (97)[1]
	−7.39 (90.7)[2]	Present	Yes	2-Octyl bromide	62	+37.8 (94)[1]
2-Pentanol	+9.97 (88.5)[15]	Absent		2-Pentyl bromide	~60	−42.7 (89)[1]
	+9.97 (88.5)[15]	Present	Yes	2-Pentyl bromide	62	−40.5 (84)[1]

[a] The values are corrected for the optical purity of the starting material and are for neat liquids.

$$\begin{array}{l} \mathrm{ROH} + \mathrm{PX_3} \longrightarrow \mathrm{ROPX_2} + \mathrm{HX} \\ \qquad\qquad\qquad\qquad \downarrow \mathrm{ROH} \qquad (1) \\ \mathrm{HX} + (\mathrm{RO})_3\mathrm{P} \xleftarrow{\mathrm{ROH}} (\mathrm{RO})_2\mathrm{PX} + \mathrm{HX} \end{array}$$

$$(\mathrm{RO})_3\mathrm{P} + \mathrm{HX} \xrightarrow{\text{fast}} (\mathrm{RO})_2\mathrm{PHO} + \mathrm{RX} \qquad (2)$$

$$(\mathrm{RO})_2\mathrm{PHO} + \mathrm{HX} \xrightarrow{\text{slow}} \mathrm{ROPH(OH)O} + \mathrm{RX} \qquad (3)$$

$$\mathrm{ROPH(OH)O} + \mathrm{HX} \xrightarrow{\text{slow}} \mathrm{H_3PO_3} + \mathrm{RX} \qquad (4)$$

cially for bromides. Our studies suggest that this loss of optical activity is due primarily to racemization of the product and not to inherent racemization in steps 3 and 4. Thus, if care is taken to maintain the reaction and isolation temperatures relatively mild (5 °C to room temperature or below), good yields of bromides of high optical purity are obtained. The general procedure involves treatment of a solution of the chiral alcohol and twofold molar excess of pyridine[8] in ether at −25 °C with phosphorus tribromide over a 1-h period followed by stirring for 1–2 days at 4 °C to complete cleavage of the intermediate phosphite ester.[9] This latter step is crucial since we observed that attempts to distill the product bromoalkanes in the presence of partially converted phosphite esters results in poor yields and a considerable loss in optical purity, presumably because the higher temperatures required to distill the halide leads to extensive racemization. For example, 1-phenylethyl bromide distills smoothly at room temperature at 0.01–0.02 mm in the absence of phosphite esters to give 70–75% yields and an optical purity of 94% (from 100% optically pure 1-phenylethanol). However, in the presence of phosphite esters, the distillation bath temperature (>70 °C) required to obtain product is detrimental to both yield (35%) and optical purity (49%).[10] However, treatment of the phosphite-containing mixture with HBr prior to work-up improves the yield to 71% and the optical purity to 84%. These observations along with results for other chiral alcohols are summarized in Table I. Thus, as long as reaction and isolation temperatures are kept low and complete conversion of intermediate phosphite esters is accomplished, the reaction of chiral alcohols with PBr_3 to afford the corresponding bromides appears to offer an efficient synthetic method for these useful intermediates.[11]

Experimental Section

Materials. The (+) and (−) isomers of 1-phenylethanol were resolved by the method of Kenyon.[14] Optically active 2-octanol and 2-pentanol were obtained from Norse Chemical Co. A 0.06 M solution of sodium methylsulfide in HMPT was prepared by passing methanethiol (Matheson) through a suspension of an appropriate amount of sodium hydride in 100 ml of dry HMPT at 0 °C until the solution became clear, followed by warming to room temperature to evaporate excess methanethiol.

General Procedure for Making Chiral Secondary Bromo Compounds. The following representative procedure for 1-phenylethyl bromide is presented. Optically pure 1-phenylethanol (9.5 g, 0.078 mol, α^{25}D −44.2°) and dry pyridine (14 g, 0.177 mol) were dissolved in 50 ml of anhydrous ether contained in a 300-ml flask fitted with a mechanical stirrer, pressure-equalizing funnel, and alcohol thermometer. The solution was cooled to −25 to −15 °C using a dry ice–acetone bath. A solution of PBr_3 (24 g, 0.088 mol) in 75 ml of dry ether was added over a period of 1 h, during which time the temperature was kept between −15 and −25 °C. The reaction mixture was then stirred at −10 °C for another 1 h and finally at 5° for 1–2 days in a cold room. The excess PBr_3 was destroyed with ice–water, and the ether layer was separated, washed successively with equal volumes of ice–water, 85% orthophosphoric acid, and cold saturated $NaHCO_3$ solution and twice with ice–water, and dried ($MgSO_4$). A 5-ml portion of the ether solution was withdrawn and evaporated. The infrared spectrum of the residue was examined for peaks at 1250, 950–1000, and 2400 cm^{-1} characteristic of partially converted phosphite esters. If the above peaks were present, the ether solution of the reaction mixture was stirred magnetically in a three-neck 300-ml flask protected by a drying tube. Dry HBr gas was bubbled through the ether solution at a slow rate for about 15 min. The temperature was maintained at ca. 25 °C. When monitoring by ir demonstrated the complete conversion of the phosphite ester, the ether solution was carefully washed with ice–water, saturated $NaHCO_3$ solution, and ice–water and dried ($MgSO_4$). Concentration on a rotary evaporator at room temperature followed by distillation at 0.01–0.02 mm pressure at room temperature gave 10.5 g (73%) of 1-phenylethyl bromide. The observed specific rotation (α^{25}D +160.8°) corresponds to 94% optical purity.[1]

(+)-(*R*)-Methyl 1-Methylbenzyl Sulfide. (−)-(*S*)-1-Phenylethyl bromide (0.5 g, 2.7 mmol, α^{25}D −85.71°) was weighed in a 50-ml flask provided with a nitrogen seal and a magnetic stirrer. A 0.6 M solution of $NaSCH_3$ in HMPT (10 ml) was transferred into the flask with a syringe through a rubber septum. The mixture was stirred for 10 min, poured into a solution of NaCl in water, and acidified with 1 M HCl until the solution was acidic to methyl orange. The mixture was extracted twice with pentane, and the pentane extract was washed with saturated $NaHCO_3$ and water and dried ($MgSO_4$). Concentration and distillation afforded 0.315 g of (+)-(*R*)-methyl 1-methylbenzyl sulfide, bp 58–60 °C (1 mm), n^{25}D 1.5450 [lit.[12] bp 58–59 °C (1 mm), n^{25}D 1.5491]. The observed specific rotation (α^{25}D +95.71°) corresponds to 48.8% optical purity (based on the value of 196° maximum).[12]

Registry No.—(−)-1-Phenylethanol, 1445-91-6; (+)-1-phenylethanol, 1517-69-7; (−)-2-octanol, 6169-06-8; (+)-2-pentanol, 31087-44-2; (+)-α-phenylethyl bromide, 1459-14-9; (−)-α-phenylethyl bromide, 3756-40-9; (+)-2-octyl bromide, 1191-24-8; (−)-2-pentyl bromide, 29117-44-0; (+)-*R*-methyl 1-methylbenzyl sulfide, 57793-28-9; phosphorus tribromide, 7789-61-9.

References and Notes

(1) For a review of procedures see H. R. Hudson, *Synthesis*, **1**, 112 (1969).
(2) J. San Filippo, Jr., and L. J. Romano, *J. Org. Chem.*, **40**, 1514 (1975).
(3) D. Landini, S. Quici, and F. Rolla, *Synthesis*, **7**, 430 (1975).
(4) D. G. Goodwin and H. R. Hudson, *J. Chem. Soc.*, **13**, 1333 (1968).
(5) T. M. Cook, E. J. Coulson, W. Gerrard, and H. R. Hudson, *Chem Ind. (London)*, 1506 (1962).
(6) E. J. Coulson, W. Gerrard, and H. R. Hudson, *J. Chem. Soc.*, 2364 (1965).
(7) W. Gerrard and H. R. Hudson, *J. Chem. Soc.*, 2310 (1964).
(8) The pyridine is utilized to trap the liberated HBr to ensure its presence for the slow cleavage reactions represented by eq 3 and 4.
(9) The conversion of the phosphite ester to bromide may not be complete even after 2 days. This can be readily checked in the crude product by infrared spectroscopy. Incomplete conversion of the ester will result in

strong bands at 1250, 950–1000, and 2400 cm^{-1}, characteristic of P–O, P–O–C, and P–H absorptions, respectively. In the event that cleavage is incomplete, the ether solution is treated with dry HBr at room temperature until the monitored bands above disappear (usually 15 min). The loss of optical purity in this operation is ca. 5% (Table I).
(10) As noted by others,[12] 1-phenylethyl bromide is readily prone toward racemization. For instance, at 27 °C in a 1:1 mixture of HMPT and pentane the optical half-life is only ca. 8 h. When pure, the neat bromide has an optical half-life of about 125 days but racemization seems to be catalyzed by impurities.
(11) In the event that the chiral bromo derivative is part of the synthetic sequence, it is often profitable to use it without purification in order to minimize racemization. If necessary, the optical purity of the produced bromo compound may be obtained by conversion to the corresponding methylsulfide (with inversion) via treatment with sodium methylsulfide–HMPT (see Experimental Section). The methylsulfide derivatives are formed in nearly quantitative yields and can be purified by distillation without fear of racemization. The maximum rotations for a number of such methylsulfides are available[1,12,13a] for evaluation of the optical purities of the bromides.
(12) H. M. R. Hoffman and E. D. Hughes, *J. Chem. Soc.*, 1244 (1964).
(13) H. M. R. Hoffman, *J. Chem. Soc.*, 1249 (1964).
(14) E. Downer and J. Kenyon, *J. Chem. Soc.*, 1156 (1939); A. Houssa and J. Kenyon, *ibid.*, 2260 (1930).
(15) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

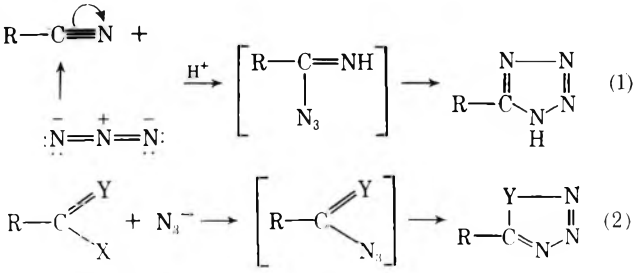
Role of Protic and Dipolar Aprotic Solvents in Cycloaddition Reactions Involving Anionic 1,3-Dipoles. Action of Inorganic Azides on Imidoyl Chlorides[1]

Pankaja K. Kadaba

Division of Medicinal Chemistry, College of Pharmacy, University of Kentucky, Lexington, Kentucky 40506.

Received September 3, 1975

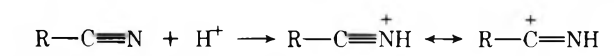
While conventional 1,3-cycloaddition reactions involve the participation of 1,3 dipoles that are polar molecules, cycloadditions of anionic dipoles constitute reactions of an anionic 1,3-dipolar system, such as an azide ion, with a multiple bond.[2] The anionic dipole can undergo either a "direct" or "indirect" cycloaddition. The reaction of the azide ion with nitriles[3] provides an example of "direct" addition (eq 1). The action of inorganic azides on imidoyl chlorides and related compounds[3] may be considered to be an example of "indirect" addition (eq 2).



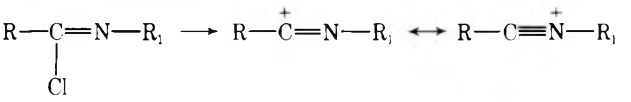
X = halogen, alkoxyl, or other displaceable group and Y = a C unit or a substituted or unsubstituted heteroatom which may or may not, together with R, be part of a cyclic system. Imidoyl chlorides, X = Cl and Y = N–R′

Although reactions of the azide ion with multiple bonds are very useful in heterocyclic synthesis,[3-5] no kinetic or other mechanistic studies exist on many of these reactions. Azide addition may be conceived to occur in a single step following a 1,3-cycloaddition pathway or in a two-step reaction via an azido intermediate. In the reaction of hydrazoic acid with alkynes leading to triazoles, a synchronous 1,3-cycloaddition mechanism is considered more probable.[6] Kinetic data for the addition of azide ion to aromatic diazonium chlorides indicate that the reaction follows a concerted course.[7] Few anionic 1,3 cycloadditions have been proven to proceed in a stepwise manner;[8] in fact, the addition of 2-(*N*,*N*-diisopropylcarbamoyl)allyllithium to the –N=N– bond appears to be the first instance where experimental evidence exists for an anionic 1,3 cycloaddition occurring in a nonconcerted manner.[8]

No kinetic studies are available for the reaction of the azide ion with nitriles (eq 1) or with imidoyl chlorides (eq 2). In the azide–nitrile reaction, an azocarbonium ion appears to be formed first, followed by azide addition.[9] The

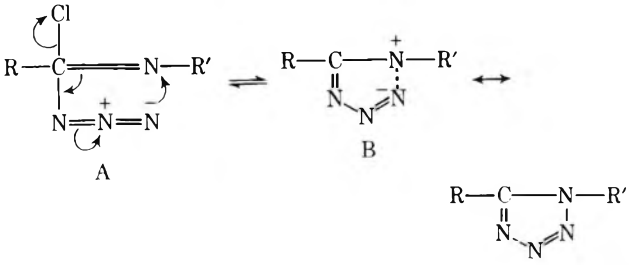


facts, that the reaction is subject to general acid catalysis and that electronegative substituents on the nitrile facilitate addition, are in support of this mechanism.[9]



A very similar mechanism could be conceived for the azide–imidoyl chloride reactions as well. Very recent studies on the rates of solvolysis of substituted imidoyl chlorides indicate that a unimolecular mechanism involving the formation of an azocarbonium ion intermediate is in operation.[10] However, the possibility of an addition–elimination mechanism for chloride displacement should not be ignored. Such a mechanism is known to be involved in the reaction of azide ion with a number of alkyl- and aryl-substituted β-chlorovinyl ketones[11] [eq 2, X = Cl and Y = C–C(=O)–R_1]. Also, there is evidence that anionic nucleophiles, such as the azide ion, react with acyl halides (eq 2, X = Cl and Y = O) via an addition–elimination reaction.[12] Kinetic studies on chloride substitution with amines in diarylimidoyl chlorides have indicated that an addition–elimination mechanism, where bond forming is important, predominates when $\sigma_{N\text{-}Ph\text{-}substituent} > 0.3$, while an azocarbonium ion mechanism, where bond breaking is important, prevails when $\sigma_{N\text{-}Ph\text{-}substituent} < 0.3$.[13]

Azide addition to the imidoyl chloride (in the addition–elimination mechanism), may be conceived to proceed in a two-step reaction via an azidoazomethine (imidoyl azide) intermediate, or in a single step concerted cycloaddition.[14] The linear azido group must adopt a "bent" configuration[15,16] for cyclization, and as it bends, the resonance form B becomes increasingly important, until cyclization occurs, when the terminal azide nitrogen comes within bonding distance of the azomethine nitrogen.[17] A concerted 1,3-anionic addition is quite likely when a bent transition state similar to B becomes energetically favorable.



In view of the important role of solvents in determining chemical reactivity,[18] recently a program was initiated in our laboratories to understand the true role of protic and dipolar aprotic solvents in 1,3-cycloaddition reactions and how it could be utilized to advantage in heterocyclic synthesis.[19] In the normal 1,3 cycloadditions where no discrete ions are involved, solvent effects, although definite, have been found to be of a small order and to arise mainly from

solvation of the partially charged transition state.[19] In the anionic cycloadditions, on the other hand, solvent effects of a much higher order may be expected, and solvation of the anionic dipole would be contributing largely toward these effects.

Small anions are known to be much less solvated in dipolar aprotic than in protic solvents;[18] hence, anionic cycloadditions will be greatly retarded and will occur with difficulty in protic solvents. Indeed, the poor results recorded in the great majority of reactions where inorganic azides are involved[3-5] appear to be a direct outcome of the solvation effects in the solvent media used. In these reactions, it has been customary to use as the source of the anionic dipole solutions of hydrazoic acid in hydrocarbon solvents such as benzene, toluene, or xylene or to use sodium azide, either alone or mixed with acetic acid, in protic solvents such as ethanol–water mixture, 2-propanol, or butanol. These reactions usually require the use of high pressures and temperatures and extended reaction periods; often, in addition to the main products, other undesirable side products are also formed.[3-5]

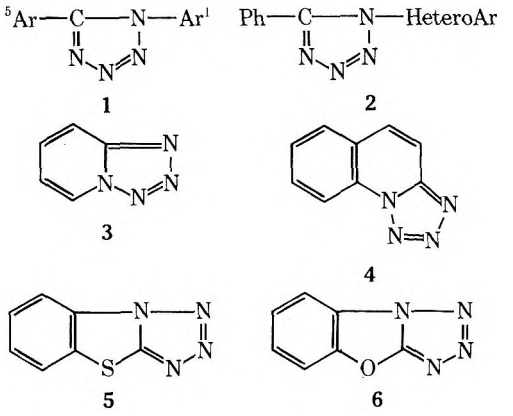
In dipolar aprotic solvents, on the other hand, the greater reactivity of the anion, poorly solvated relative to the transition state, will greatly facilitate the reaction. Also, dipolar aprotic solvents solvate cations strongly and since they have high dielectric constants, electrolytes are strong in these solvents; the anions are thus free to actively participate in the reaction without the stabilizing influence of ion-pair formation.[18] It should thus be possible to perform 1,3-cycloaddition reactions involving the azide anion much more advantageously in dipolar aprotic than in protic or hydrocarbon solvents. Indeed, this has been found to be the case, as reported here.

Although DMF and Me_2SO have been found to facilitate the addition of inorganic azides to nitriles (eq 1) in one isolated study,[9] as the mechanism of action of these solvents was not known at that time, it prevented further studies in this direction. Thus the scope and utility of solvation effects in anionic 1,3 cycloadditions have not been explored to any extent. This paper reports studies on the action of inorganic azides on imidoyl chlorides.

This reaction constitutes a general method for the synthesis of 1-mono- and 1,5-disubstituted tetrazoles. However, the nonaqueous medium in which it is normally carried out, using hydrazoic acid, requires high temperatures and pressures, and the tetrazoles formed are often accompanied by products derived from carbodiimides such as ureas, not to mention the disadvantages involved in handling anhydrous hydrazoic acid.[20] The use of buffered aqueous sodium azide solutions makes it convenient to handle the azide and eliminates rearrangement products. However, nucleophilic displacement of chloride by both azide and water occurs, producing, in addition to the tetrazoles, large amounts of the starting amides;[21] this entails tedious fractionations and an appreciable loss in yield.

By carrying out the reaction in a dipolar aprotic solvent such as DMF, it is possible to use solid sodium azide and achieve anhydrous reaction conditions as well as convenience in handling the azide. The action of DMF as a solvent is twofold; while it provides for greater reactivity of the azide anion, which is poorly solvated, it ensures greater stability of the large polarizable transition state (having properties similar to B), well solvated in this solvent. Thus DMF helps to attain mild reaction conditions and very short reaction periods. It is also possible that DMF might contribute significantly toward shifting the azidoazomethine–tetrazole equilibrium in the direction of the latter.[22] Reactions using DMF proceed smoothly and exclusively to give tetrazoles in high yield and purity; there is no formation of any undesirable side products. Both open and cyclic imidoyl chlorides react in this manner; the latter, however, are less reactive and require the use of ammonium azide. The best sources of anions for reactions in dipolar aprotic solvents are lithium or ammonium salts, since these are very soluble.[18] The reaction works equally well for aromatic as well as heterocyclic substituted imidoyl chlorides.

The superior versatility of this reaction procedure becomes well apparent when compared with results obtained in conventional solvents. While phenyl-4-nitrobenzimidoyl chloride reacts with sodium azide in DMF to give 90% pure tetrazole **1** in 1 h, in acetone–water mixture,[21] after an extended reaction period followed by numerous fractionations for product purification, the yield of tetrazole drops down to 62%. 2-Bromopyridine reacts with ammonium azide in DMF to give 75% tetrazole in 21 h, but in ethanol–water mixture, only 20% product is obtained.[23] 2-Chloropyridine is less reactive in DMF as expected.[18] 2-Chlorobenzo-1,3-thiazole yields 91% pure tetrazole **5** in 30 min by reaction with ammonium azide in DMF; in ethanol–water mixture, the yield is reduced to a mere 3%, and if ammonium azide is replaced by sodium azide, there is no reaction whatsoever in the protic solvent.[23]



Experimental Section[25]

Synthesis of 1,5-Substituted Tetrazoles in DMF. The open-chain imidoyl chlorides required for the preparation of **1** and **2** were obtained by heating a mixture of the appropriate amide (0.04 mol) and PCl_5 (0.04 mol) in a round-bottom flask connected to a water aspirator through a drying tube, so that the HCl and $POCl_3$ formed during the reaction were removed continuously from the system as they originated. The entire operation took less than 20 min. The imidoyl chloride residues were then dissolved in DMF with minimum exposure to air and used immediately in tetrazole synthesis.

In a typical reaction, a mixture of commercial NaN_3 (0.075 mol) and DMF (25–50 ml) (Eastman White Label) was placed in a two-necked flask attached with drying tube and adding funnel, and immersed in a water bath maintained at 20–25 °C throughout the reaction. The solution of the imidoyl chloride (0.04 mol) in DMF (50–75 ml) (the amount of DMF varied according to the solubility of the imidoyl chloride, but the total volume in the overall reaction mixture always remained at 100 ml) was then added dropwise with stirring (a magnetic stirrer was found most convenient for this purpose) to the suspension of NaN_3 in DMF over a period of 45 min. After the addition was completed, the stirring was continued for an additional 15–30 min. The reaction mixture was treated with water, just enough to produce a cloudiness, and then cooled, when the 1,5-substituted tetrazoles (**1** and **2**) separated out as shining, crystalline compounds. Often, a similar treatment of the filtrate yielded an additional amount of tetrazole.

The products were filtered, washed with a few milliliters of EtOH–H_2O mixture, and pressed dry. The crystalline material was then washed well with water to remove inorganic matter such as NaCl and unreacted NaN_3. The tetrazoles thus obtained were pure and had the same melting points and NMR spectra before and after crystallization from appropriate solvents.

The aryl-substituted tetrazoles (**1**) prepared in this manner,

along with yield, melting point, and NMR in $CDCl_3$ with Me_4Si as internal standard, included 1,5-diphenyl-, 84, 145–146 °C, δ 7.49 (m, 10, ArH); 1-phenyl-5-*p*-nitrophenyl-, 90, 182–183 °C, δ 8.32 (d, 2, ArH), 7.80 (d, 2, ArH), 7.58 (m, 5, ArH); 1-phenyl-5-*o*-nitrophenyl-, 70, 179–181 °C, δ 8.28–8.05 (m, 1, ArH), 7.88–7.42 (m, 3, ArH), 7.35 (m, 5, ArH); 1-phenyl-5-*p*-anisyl-, 70, 114–116 °C, δ 7.18–7.78 (m, 7, ArH), 6.88 (d, 2, ArH), 3.77 (s, 3, OCH_3); 1-*p*-nitrophenyl-5-phenyl-, 72, 155–157 °C, δ 8.45 (d, 2, ArH), 7.70 (d, 2, ArH), 7.57 (s, 5, ArH); 1-*p*-chlorophenyl-5-phenyl-, 87, 113–114 °C, δ 7.52 (m, 9, ArH); 1-*p*-tolyl-5-phenyl-, 70, 130–132 °C, δ 7.51 (m, 5, ArH), 7.31 (s, 4, ArH), 2.37 (s, 3, CH_3); 1-*p*-anisyl-5-phenyl-, 84, 130–132 °C, δ 7.55 (m, 5, ArH), 7.36 (d, 2, ArH), 7.04 (d, 2, ArH), 3.83 (s, 3, OCH_3); 1-α-naphthyl-5-phenyl-, 70, 129–131 °C, δ 8.07 (m, 3, ArH), 7.80–7.10 (m, 9, ArH); 1-*o*-nitrophenyl-5-phenyl-, 94, 166–168 °C, δ 8.40–8.02 (m, 1, ArH), 7.93–7.50 (m, 3, ArH), 7.45 (m, 5, ArH); 1-(2-methyl-4-nitrophenyl)-5-phenyl-, 93, 153–154 °C, δ 8.40–8.07 (m, 2, ArH), 7.60 (s, 1, ArH), 7.48 (m, 5, ArH), 2.20 (s, 3, CH_3).

The heteroaryl substituted tetrazoles (**2**) included 1-4-pyridyl-5-phenyl-, 75, 167–168 °C, δ ($CDCl_3$) 8.85 (d, 2, PyH), 7.57 (s, 5, ArH), 7.42 (d, 2, PyH); 1-(4,6-dimethyl-2-pyridyl)-5-phenyl-, 70, 94–96 °C.

Anal. Calcd for $C_{12}H_9N_5$: C, 64.57; H, 4.04; N, 31.39. Found: C, 64.44; H, 4.03; N, 31.40. Calcd for $C_{14}H_{13}N_5$: C, 66.93; H, 5.18; N, 27.89. Found: C, 66.88; H, 5.10; N, 27.78.

The cyclic imidoyl chlorides were obtained commercially. The tetrazoles **4–6** were prepared by heating on a steam bath a mixture of the imidoyl chloride (0.02 mol) and NH_4N_3 (0.03 mol, generated in situ from equivalent amounts of NaN_3 and NH_4Cl) in DMF (20 ml). While **4** required 2 h of heating, 30 min was sufficient for **5** and **6**. The reaction mixture, when diluted with water and cooled, yielded the tetrazoles as a clean, crystalline mass: **4**, 94%, mp 155–156 °C, δ ($CDCl_3$) 8.62 (dd, 1, H), 8.15–7.55 (m, 5, H); **5**, 91%, mp 108–109 °C, δ (Me_2SO-d_6) 8.23 (m, 2, H), 7.65 (m, 2, H); **6**, 85%, mp 69–71 °C.

Replacement of NH_4N_3 by NaN_3 caused the yield of **4** to drop to 14%, mp 148–152 °C.

When the reaction was performed in EtOH–H_2O mixture (14 ml of EtOH + 6 ml of H_2O) using NH_4N_3, **5** was obtained in 2.9% yield, mp 108–109.5 °C. In EtOH–H_2O, when NaN_3 was used, no reaction occurred, and the imidoyl chloride was recovered unchanged. The reactions were repeated, heating for a period of 2 h. NH_4N_3 in EtOH–H_2O gave 29% **5**, while NaN_3 in the same solvent yielded 2.1% **5**, mp 100–104 °C.

The mixture of 2-chloropyridine (0.02 mol) and NH_4N_3 (0.03 mol) in DMF (20 ml) was heated in an oil bath at 115–118° for 30 h. The reaction mixture was then made basic with NaOH (10% solution), evaporated to dryness under reduced pressure, and extracted with $CHCl_3$. Evaporation of the solvent yielded tetrazole **3**: yield 80%; mp 158–159 °C, δ ($CDCl_3$) 8.86 (deg. ddd, 1, H_5), 7.98 (deg. ddd, 1, H_8), 7.74 (deg. ddd, 1, H_7), 7.29 (deg. ddd, 1, H_6).

2-Bromopyridine under identical reaction conditions gave a 75% yield of **3** in 21 h. In refluxing EtOH–H_2O (14 ml of EtOH + 6 ml of H_2O), the yield of **3** was reduced to 20%. When the heating period was reduced to 7 h, in DMF using NH_4N_3, the tetrazole was obtained in 45 and 53% yields from the 2-chloro- and 2-bromopyridines, respectively.

Acknowledgment. The author thanks Miss Lini S. Kadaba for technical assistance.

Registry No.—**1** (Ar^1 = Ar^5 = Ph), 7477-73-8; **1** (Ar^1 = Ph; Ar^5 = *p*-NO_2Ph), 14213-27-5; **1** (Ar^1 = Ph; Ar^5 = o-NO_2Ph), 57761-69-0; **1** (Ar^1 = Ph; Ar^5 = *p*-anisyl), 57761-70-3; **1** (Ar^1 = *p*-NO_2Ph; Ar^5 = Ph), 57761-71-4; **1** (Ar^1 = *p*-ClPh; Ar^5 = Ph), 57761-72-5; **1** (Ar^1 = *p*-tolyl; Ar^5 = Ph), 52411-70-8; **1** (Ar^1 = *p*-anisyl; Ar^5 = Ph), 57761-73-6; **1** (Ar^1 = α-naphthyl; Ar^5 = Ph), 57761-74-7; **1** (Ar^1 = o-NO_2Ph; Ar^5 = Ph), 57761-75-8; **1** (Ar^1 = 2-Me-4-NO_2Ph; Ar^5 = Ph), 57761-76-9; **2** (Ar = 4-pyridyl), 57761-77-0; **2** (Ar = 4,6-dimethyl-2-pyridyl), 57761-78-1; **3**, 274-87-3; **4**, 235-25-6; **5**, 248-02-2; **6**, 57761-79-2; NaN_3, 26628-22-8; *N*-phenylbenzimidoyl chloride, 4903-36-0; *N*-phenyl-*p*-nitrobenzimidoyl chloride, 5466-94-4; *N*-phenyl-*o*-nitrobenzimidoyl chloride, 57761-80-5; *N*-phenyl-*p*-methoxybenzimidoyl chloride, 38968-72-8; *N*-*p*-nitrophenylbenzimidoyl chloride, 34918-79-1; *N*-*p*-chlorophenylbenzimidoyl chloride, 34918-76-8; *N*-*p*-tolylbenzimidoyl chloride, 15999-95-8; *N*-*p*-anisylbenzimidoyl chloride, 34918-74-6; *N*-α-naphthylbenzimidoyl chloride, 57353-87-4; *N*-*o*-nitrophenylbenzimidoyl chloride, 3493-72-9; *N*-(2-methyl-4-nitrophenyl)benzimidoyl chloride, 57761-81-6; *N*-4-pyridylbenzimidoyl chloride, 57761-82-7; 2-chloroquinoline, 614-62-4; 2-chlorobenzothiazole, 615-20-3; 2-chlorobenzoxazole, 615-18-9; NH_4N_3, 12164-94-2; 2-chloropyridine, 109-09-1; 2-bromopyridine, 109-04-6; *N*-(4,6-dimethyl-2-pyridyl)benzimidoyl chloride, 57761-83-8.

References and Notes

(1) This is part 9 in "Heterocyclic Synthesis via 1,3-cycloaddition Reactions". For part 8, see P. K. Kadaba, *J. Heterocycl. Chem.*, **12**, 143 (1975).
(2) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 2, 565, 633 (1963).
(3) F. R. Benson in "Heterocyclic Compounds", Vol. 8, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1967, p 1.
(4) T. L. Gilchrist and G. E. Gymer, *Adv. Heterocycl. Chem.*, **16**, 33 (1974).
(5) K. A. Jensen and C. Pedersen, *Adv. Heterocycl. Chem.*, **3**, 263 (1964); J. H. Boyer in "Heterocyclic Compounds", Vol. 7, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1961, p 384.
(6) M. E. C. Biffin, J. Miller, and D. B. Paul in "The Chemistry of the Azido Group", S. Patai, Ed., Wiley-Interscience, New York, N.Y., 1971, p 127.
(7) R. Huisgen and I. Ugi, *Chem. Ber.*, **90**, 2914 (1957); I. Ugi and R. Huisgen, *ibid.*, **91**, 531 (1958).
(8) W. Bannwarth, R. Eidenschink, and T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, **13**, 468 (1974).
(9) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958).
(10) A. F. Hegarty, J. D. Cronin, and F. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, 429 (1975).
(11) A. N. Nesmeyanov and M. I. Rybinskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 816 (1962); English translation, 761 (1962); S. Maiorana, *Ann. Chim. (Rome)*, **56**, 1531 (1966).
(12) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).
(13) Z. Rappoport and R. Ta-Shma, *Tetrahedron Lett.*, 3813 (1971).
(14) P. A. S. Smith in "Molecular Rearrangements", P. de Mayo, Ed., Wiley-Interscience, New York, N.Y., 1963, p 457.
(15) E. Lieber, J. S. Curtice, and C. N. R. Rao, *Chem. Ind. (London)*, 586 (1966).
(16) J. D. Roberts, *Chem. Ber.*, **94**, 273 (1961).
(17) G. A. Reynolds, J. A. Van Allan, and J. F. Tinker, *J. Org. Chem.*, **24**, 1205 (1959).
(18) A. J. Parker, *Adv. Phys. Org. Chem.*, **5**, 173 (1967); *Adv. Org. Chem.*, **5**, 1 (1965); *Chem. Rev.*, **69**, 1 (1969).
(19) P. K. Kadaba, *Tetrahedron*, **25**, 3053 (1969); **22**, 2453 (1966); *Synthesis*, 71 (1973).
(20) P. A. S. Smith and E. Leon, *J. Am. Chem. Soc.*, **80**, 4647 (1958).
(21) J. Vaughan and P. A. S. Smith, *J. Org. Chem.*, **23**, 1909 (1958).
(22) C. Temple and J. A. Montgomery, *J. Am. Chem. Soc.*, **86**, 2946 (1964).
(23) In view of the fact that data reported in the literature do not seem convincing, we chose to perform the experiments under identical conditions in protic and dipolar aprotic solvents, so that the advantages of using the latter as the solvent medium can be brought out clearly and candidly. For example, it is reported[24] that 2-chlorobenzo-1,3-thiazole yields 74% of the tetrazole derivative when refluxed for 8 h with sodium azide in ethanol–water mixture. Repeating the reaction in a like manner, we found it is impossible to obtain the tetrazole in an yield greater than 3%.
(24) J. A. Van Allen and C. A. Maggiulli, French Patent 1 392 310 (1965), Kodak-Pathe; *Chem. Abstr.*, **63**, 7017 (1965).
(25) Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were not corrected for thermometer stem exposure. The NMR sectra were determined using a Varian EM-360 60-MHz NMR spectrometer. Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo.

Preparation and Reactions of Highly Active Cadmium and Zinc Slurries by Metal Atom–Solvent Cocondensations

Summary: Active cadmium and zinc slurries were prepared by the cocondensation of the metal vapor with excess solvent at 77 K, followed by warming to room temperature, and then allowed to react with alkyl bromides and iodides in several solvents, polar and nonpolar.

Sir: There are a few limited reports in the literature dealing with the direct reaction of cadmium metal with alkyl halides. Only alkyl iodides and unsaturated bromides were found to react in the highly polar solvating media hexamethylphosphoric triamide (HMPT), DMSO, and DMF.[1] As would be expected, the RCdX and R_2Cd were formed as solvent adducts, e.g., RCdI·HMPA. Similarly, there are reports of zinc dust reactions with alkyl iodides and bromides in solvents such as dimethoxyethane, diglyme, DMSO, and DMF with formation of solvated RZnI and RZnBr.[2] High temperature and/or zinc–copper couples have been employed for zinc activation for direct RX reactions.[3] In addition, Rieke and co-workers[4] have reported that the reduction of $ZnBr_2$ with potassium in diglyme or dimethoxyethane also yields a very active form of zinc.

We report here a procedure for production of very active slurries of cadmium and zinc in pure, clean, finely divided forms that are reactive with alkyl halides in all types of solvents, polar and nonpolar.

Cadmium slurries in diglyme, dioxane, THF, hexane, and toluene were produced by condensing ~9 g of Cd with ~60 ml of solvent at 77 K. Colored matrices were formed that turned black on melt down (cf. Table I for exact amounts of reagents). Alkyl iodides were added usually before melt down, followed by warming and then reflux. For example

$$\text{Cd vapor} + \text{hexane} \xrightarrow{77\ \text{K warm}} \longrightarrow$$

$$\text{Cd*–hexane slurry} \xrightarrow[\text{reflux}]{\text{RI}} R_2Cd + CdI_2$$

The amount of RCd species present was determined by hydrolysis with 10% HCl, followed by quantitative determination of RH formed by vacuum line manipulations, pressure–volume measurements, and GLC techniques. The highest yields of RCd compounds were obtained in diglyme and dioxane solvents although in hexane, toluene, and THF the yields were still acceptable (cf. Table I). We have not yet carried out a detailed investigation concerning whether RCdI or R_2Cd are produced in different solvents or as solvent adducts. Only a small amount of Et_2Cd was isolable by vacuum pumpoff from a Cd–toluene slurry–EtI reaction (1% Et_2Cd by hydrolysis).

Dialkylzinc compounds were isolable from Zn*RX reactions by vacuum pumpoff. Usually, however, the yields of RZn species were simply determined by hydrolysis of the reaction mixture. In diglyme quantitative yields of R_2Zn (presumably) were obtained. Lower yields were observed in hexane and toluene. The Zn slurries retained their activity if manipulated under an atmosphere of dry nitrogen.

Table I. Zn and Cd Reactions with Alkyl Halides

Mol of Zn	RX	Mol of RX	Reflux time, h[a]	% yield of R_2M[b]	Solvent
0.127	EtBr	0.04	18	100.0	Diglyme
0.107	*n*-PrBr	0.04	23	100.0	Diglyme
0.077	*n*-BuBr	0.04	17	100.0	Diglyme
0.149	*n*-PrBr	0.04	23	93.5	Dioxane
0.357	*n*-PrBr	0.04	22	89.0	THF
0.203	*n*-PrBr	0.04	17	57.7	Hexane
0.126	*n*-PrBr	0.04	16	28.5	Toluene
Mol of Cd	**RX**	**Mol of RX**	**Reflux time, h**	**% yield**	**Solvent**
0.083	EtI	0.04	19.5	82.7	Diglyme
0.026	EtI	0.04	12.5	74.0	Dioxane
0.088	EtI	0.04	20.5	61.8	Hexane
0.069	EtI	0.04	17.5	61.7	THF
0.115	EtI	0.04	18.0	54.5	Toluene

[a] At reflux temperature of solvent–substrate mixture at reduced pressure. [b] Yield based on RX as limiting reagent.

These slurries were produced by the codeposition of metal vapors (atoms) and excess solvent on the walls of a metal atom reactor[5] at 77 K, followed by warming. The method is quite versatile since many metals and a wide range of solvents can be employed. In some cases the slurries are so fine that they can be handled by syringe, similar to Mg–THF slurries which we reported earlier.[6] There is need for a great deal of research in this area since different clustered forms with different properties are produced when different solvents are employed (with the same metal).[7]

$$\text{Zn*–solvent} + RX \rightarrow R_2Zn + ZnX_2$$

$$X = Br, I$$

Acknowledgment. Generous support of the National Science Foundation (GP-42376) is acknowledged with gratitude.

References and Notes

(1) J. Chenault and F. Tatitouet, *C. R. Hebd. Seances Acad. Sci., Ser. C.*, 264 (2), 213 (1967); also 266, 499 (1966) [*Chem. Abstr.*, **67**, 32758c (1967); **64**, 17632c (1966)].
(2) L. I. Zakharkin and O. Yu Okhlobystin, *Izv. Akad. Nauk. SSR, Otd. Khim. Nauk.*, 193 (1963); [*Chem. Abstr.*, **58**, 12589b (1963)].
(3) E. Frankland, *Justus Liebigs Ann. Chem.*, **85**, 329 (1853); A. Job and R. Reich, *Bull. Soc. Chim. Fr.*, **33**, 1414 (1923); N. K. Hota and C. J. Willis, *J. Organomet. Chem.*, **9**, 169 (1967); J. Nasek, *Collect. Czech. Chem. Commun.*, **29**, 597 (1964) [*Chem. Abstr.*, **60**, 8053g (1964)]; R. C. Kurg and R. J. C. Tank, *J. Am. Chem. Soc.*, **76**, 2262 (1954); E. LeGoff, *J. Org. Chem.*, **24**, 2048 (1964); C. R. Noller, *Org. Synth.*, **12**, 86 (1932).
(4) R. D. Rieke, S. J. Uhm, and P. M. Hudnall, *J. Chem. Soc., Chem. Commun.*, **8**, 269 (1973).
(5) Metal atom reactors, sometimes called vapor synthesis reactors, are now commercially available from Kontes Glass Co., Vineland, N. J. For a review of metal vapor chemistry, cf. K. J. Klabunde, *Acc. Chem. Res.*, **8**, 393 (1975).
(6) K. J. Klabunde, H. F. Efner, L. Satek, and W. Donley, *J. Organomet. Chem.*, **71**, 309 (1974).
(7) K. J. Klabunde, H. F. Efner, T. O. Murdock, and R. Ropple, *J. Am. Chem. Soc.*, **98**, 1021 (1976).

Thomas O. Murdock, Kenneth J. Klabunde*

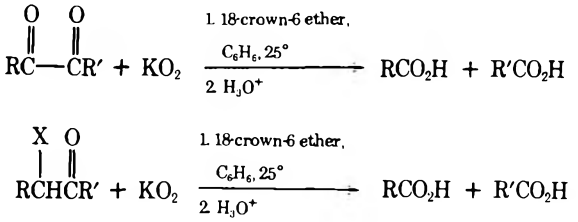
Department of Chemistry, University of North Dakota
Grand Forks, North Dakota 58202

Received October 17, 1975

Oxidative Cleavage of α-Keto, α-Hydroxy, and α-Halo Ketones, Esters, and Carboxylic Acids by Superoxide[1]

Summary: The reaction of α-keto, α-hydroxy, and α-halo ketones, esters, and carboxylic acids with potassium superoxide in benzene in the presence of 18-crown-6 ether results in the oxidative cleavage of these compounds to carboxylic acids in a reaction which, in several respects, is reminiscent of the behavior of certain dioxygenases.

Sir: In previous reports we have demonstrated that superoxide is a potent and synthetically useful oxygen nucleophile.[2,3] This communication describes the results of our continuing investigation of the reactivity of this reagent and in particular its reactions with α-keto, α-hydroxy, and α-halo ketones, esters, and carboxylic acids. These studies reveal that such substrates undergo facile oxidative cleavage to produce the respective carboxylic acids in fair to excellent yields. A summary of the results obtained on treatment of various representative substrates is given in Table I.



R′ = OH, OR, alkyl, aryl; X = OH, Cl, Br

The following description is typical of the experimental procedures employed in the reaction of potassium superoxide[4] with α-keto, α-hydroxy, and α-halo ketones, esters, and carboxylic acids. *dl*-Camphoroquinone (0.831 g, 5.00 mmol) was added to a mixture of 18-crown-6 ether[5] (0.528 g, 2.00 mmol) and powdered potassium superoxide (1.42 g, 20.0 mmol) in dry benzene.[6] The resulting mixture was vigorously stirred for 12 h, then cautiously poured into 20 ml of water. The aqueous layer was separated and acidified with 3 M HCl and subsequently extracted with three 40-ml portions of ethyl ether. The combined ether extracts were dried ($MgSO_4$) and concentrated to dryness under reduced pressure. The residual white solid was recrystallized from aqueous ethanol to give 0.87 g (87%) of *dl*-camphoric acid, mp 205–206° (lit.[7] mp 208°).

Certain aspects of this reaction deserve brief comment. First, the results shown in Table I indicate that the oxidative cleavage of α-substituted ketones, esters, and carboxyl-

Table I. Reactions of Potassium Superoxide with Various α-Keto, α-Hydroxy, and α-Halo Ketones, Esters, and Carboxylic Acids

Substrate	mM of KO_2/mM of substrate[a]	Product[b]	Yield,[c] %
Benzil	3/1	Benzoic acid	87
Camphoroquinone	4/1	Camphoric acid	87
1,2-Cyclohexadione	4/1	Adipic acid	53
2-Ketoglutaric acid	4/1	Succinic acid	42[d]
2-Ketophenylacetic acid	4/1	Benzoic acid	93
Ethyl 2-ketophenylacetate[e]	4/1	Benzoic acid	93
Benzoin	3/1	Benzoic acid	98
2-Hydroxycyclohexanone	4/1	Adipic acid	69
Mandelic acid	4/1	Benzoic acid	94 (81)[f]
2-Hydroxystearic acid	12/1	Heptadecanoic acid	77
1-Hydroxycycloheptanecarboxylic acid	4/1	1-Hydroxycycloheptanecarboxylic acid	*g*
1-Cyclohexylmandelic acid	4/1	1-Cyclohexylmandelic acid	*g*
Ethyl Mandelate	4/1	Benzoic acid	93
2-Chlorocyclohexanone	4/1	Adipic acid	60
2-Chlorocyclooctanone	4/1	Octanedioic acid	62
3-Bromocamphor	4/1	Camphoric acid	54
Phenacyl chloride	4/1	Benzoic acid	72
2-Bromo-2-phenyl-acetic acid	4/1	Benzoic acid	90
2-Bromooctanoic acid	4/1	Heptanoic acid	58[h]
Methyl 2-bromo-2-cyclohexane acetate	4/1	Cyclohexanecarboxylic acid	54[h]

[a] Unless otherwise indicated, all reactions were carried out for 24 h using a 1:10 ratio of 18-crown-6 to KO_2. Understandably, reaction times were noticeably shorter at higher ratios. [b] Products were characterized by comparison of spectral data. Solids were further characterized by their melting points and liquids by their GLC retention times. [c] Unless otherwise indicated, reported values refer to isolated, recrystallized product yields, based on substrate. [d] Because of its solubility characteristics, considerable difficulty was experienced in isolating this material from the crude reaction mixture. Control experiments suggest that the values given represent minimal isolated yields. Conversion yields generally ranged from 20 to 30% higher. [e] For a discussion of the cleavage of esters by superoxide, see ref 2b. [f] Carried out in dry DMSO. [g] A nearly quantitative recovery of starting material was obtained in this instance. [h] Determined by GLC analysis.

ic acids by superoxide seems applicable to a spectrum of substrates, including not only α-keto and α-hydroxy carbonyl compounds but α-halo ketones, esters, and acids as well. This latter reaction, in particular, provides a convenient and unique procedure for the degradative cleavage of α-halo carbonyl compounds. Second, the fact that both 1-hydroxycloheptanecarboxylic acid and α-cyclohexylmandelic acid can be quantitatively recovered after treatment with potassium superoxide suggests that the successful oxidative cleavage of α-hydroxy carbonyl compounds requires the presence of an α hydrogen on the hydroxy-bearing carbon. Third, the reaction of superoxide with α-keto and α-hydroxy carbonyl compounds resembles, in several respects, the behavior of certain dioxygenases. Specifically, the oxidative cleavage of α-keto carboxylic acids is reminiscent of the reaction of those enzymes which use α-ketoglutarate as a cosubstrate.[8] This oxygenase catalyzes the overall reaction

$$S + O_2 + HO_2CCH_2CH_2C(O)CO_2H \xrightarrow{\text{enzyme}} SO + HO_2CCH_2CH_2CO_2H + CO_2$$

where one atom of oxygen is introduced into the substrate (S) and another into the resulting succinic acid. Typical substrates oxidized by such enzymes are alkane derivatives such as proline peptides, betaines, and the methyl group of thiamine. Hamilton[9] has proposed that these reactions proceed through the intermediacy of persuccinic acid formed by the oxidative decarboxylation of α-ketoglutaric acid. The attractiveness of this proposal is enhanced by the fact that peracids are putative intermediates resulting from the demonstrated reaction of superoxide with carboxylic esters.[2b] What relevancy, if any, these observations have to the mechanism of dioxygenase action in these instances remain uncorroborated and is currently under further investigation. However, the possibility that superoxide, either free or coordinated, is involved in these processes is made more reasonable by the fact that these oxygenases are Fe(II)-containing enzymes whose reaction with molecular oxygen provides a plausible means for the biosynthesis of the requisite superoxide.

Aside from their synthetic utility[10] and their possible relevancy to the mechanisms of oxidation by certain dioxygenase enzymes, the results reported here may offer some insight into the role of superoxide in biological disorders. Further observations related to the scope and mechanism(s) of these reactions will be presented in future papers.

References and Notes

(1) Supported by the Research Corporation, Rutgers Research Council, Charles and Johanna Busch Memorial Fund, and Biomedical Sciences Support Grant.

(2) (a) J. San Filippo, Jr., C.-I. Chern, and J. S. Valentine, *J. Org. Chem.*, **40**, 1678 (1975); (b) J. San Filippo, Jr., L. J. Romano, C.-I. Chern, and J. S. Valentine, *ibid.*, **41**, 586 (1976); (c) see also R. A. Johnson and E. G. Nidy, *ibid.*, **40**, 1680 (1975).

(3) These results have recently been applied to the synthesis of a naturally occurring prostaglandin; see E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Lett.*, 3183 (1975).

(4) Working in a glovebag, lumps of potassium superoxide, purchased from K and K Chemicals, were ground to a fine consistency in a mortar and pestle.

(5) G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, *J. Org. Chem.*, **39**, 2445 (1974).

(6) Similar, although generally more rapid, reactions are observed using DMSO solvent. However, product isolation is made significantly easier by the use of benzene as the reaction solvent.

(7) M. Janczewski and T. Bartnik, *Roczniki Chem.*, **36**, 1243 (1962); *Chem. Abstr.*, **59**, 5050*h* (1962).

(8) M. T. Abbott and S. Udenfriend in "Molecular Mechanisms of Oxygen Activation", O. Hayaishi, Ed., Academic Press, New York, N.Y., 1974, Chapter 5; G. A. Hamilton, Chapter 10.

(9) G. A. Hamilton in "Progress in Bioorganic Chemistry", Vol. 1, E. T. Kaiser and F. J. Kezdy, Ed., Wiley, New York, N.Y., 1971, p 83.

(10) The principal reagents used for the selective cleavage of α-keto and α-hydroxy carbonyl compounds are periodic acid and lead tetraacetate. Unlike lead tetraacetate, periodic acid requires an aqueous solvent media; however, lead tetraacetate has the disadvantage that the side reactions which frequently accompany the use of this reagent can sometimes become the dominant reaction pathway. The oxidative cleavage of α-halo carbonyl compounds has not been reported for either of these reagents. For a discussion and comparison of the relative merits of both periodic acid and lead tetraacetate in oxidative cleavage reactions, see H. O. House in "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1971, Chapter 7.

Joseph San Filippo, Jr.,* Chuen-Ing Chern

School of Chemistry, Rutgers University
New Brunswick, New Jersey 08903

Joan S. Valentine

Department of Chemistry, Douglass College
Rutgers University, New Brunswick, New Jersey 08903

Received December 5, 1975

Synthesis of Unsymmetrical Conjugated Diynes via the Reaction of Lithium Dialkynyldialkylborates with Iodine

Summary: Unsymmetrical conjugated diynes may be prepared in satisfactory yield by the reaction of iodine in tetrahydrofuran with lithium dialkynyldisiamylborates, $Li^+[Sia_2BC{\equiv}CR(C{\equiv}CR')]$; a convenient, essentially one-pot procedure for the preparation of unsymmetrical conjugated diynes from commercially available borane–methyl sulfide and acetylenes is presented.

Sir: Treatment of lithium 1-alkynyltrialkylborates and lithium ethynyltrialkylborates with iodine under very mild conditions produces the corresponding acetylenes in essentially quantitative yields (eq 1).[1,2] More recently, it has

$$Li^+[R_3BC{\equiv}CR']^- \xrightarrow[\text{THF, } -78°]{I_2} RC{\equiv}CR' \quad (1)$$

been reported that symmetrical diynes and enynes may be prepared in excellent yield from lithium dialkynyldialkylborates (eq 2)[3] or lithium alkynylalkenyldialkylborates (eq 3),[4] respectively.

$$Li^+[R_2B(C{\equiv}CR')_2]^- \xrightarrow[\text{THF, } -78°]{I_2} R'C{\equiv}CC{\equiv}CR' \quad (2)$$

$$Li^+[R_2B(C{\equiv}CR')(CH{=}CHR'')]^- \xrightarrow[\text{THF, } -78°]{I_2} R'C{\equiv}CCH{=}CHR'' \quad (3)$$

Investigations in our laboratory into the synthesis and reactions of alkynyldialkylboranes have led to the development of a convenient, general, and quantitative method for the synthesis of base-free alkynyldialkylboranes from methyl dialkylborinates. Treatment of the 1-alkynyldisiamylboranes with lithium alkynes produces cleanly the corresponding lithium dialkynyldisiamylborates. This procedure, in contrast to the earlier one,[3] makes possible the synthesis of lithium dialkynyldisiamylborates containing two different alkynyl groups. Treatment of this "ate" complex with iodine gives the corresponding diyne, symmetrical or unsymmetrical as desired, in excellent yield (eq 4).

$$Sia_2BC{\equiv}CR + LiC{\equiv}CR' \xrightarrow[-78°]{\text{THF}} Li^+[Sia_2B(C{\equiv}CR)(C{\equiv}CR')]^-$$

$$Li^+[Sia_2B(C{\equiv}CR)(C{\equiv}CR')]^- \xrightarrow[THF,\ -78°]{I_2} RC{\equiv}CC{\equiv}CR' \quad (4)$$

It proved possible to carry through the synthesis without the isolation of the intermediate 1-alkynyldisiamylborane. Consequently, the synthesis of the symmetrical or unsymmetrical conjugated diynes may be carried out in an essentially one-pot process, as outlined in reactions 5.

$$BH_3{\cdot}S(CH_3)_2 + 2(CH_3)_2C{=}CHCH_3 \xrightarrow[0°\text{ to }25°]{THF} Sia_2BH + S(CH_3)_2$$

$$Sia_2BH + MeOH \xrightarrow[25°]{THF} Sia_2BOMe + H_2$$

$$Sia_2BOMe + LiC{\equiv}CR \xrightarrow[-78°]{THF} Li^+[Sia_2BC{\equiv}CR(OMe)]^-$$

$$3Li^+[Sia_2BC{\equiv}CR(OMe)]^- + 4BF_3{\cdot}OEt_2 \xrightarrow[-78°\text{ to }25°]{THF} 3Sia_2BC{\equiv}CR + (MeO)_3B + 3LiBF_4$$

$$Sia_2BC{\equiv}CR + LiC{\equiv}CR' \xrightarrow[-78°]{THF} Li^+[Sia_2BC{\equiv}CR(C{\equiv}CR')]^-$$

$$Li^+[Sia_2BC{\equiv}CR(C{\equiv}CR')]^- \xrightarrow[THF,\ -78°]{I_2} RC{\equiv}CC{\equiv}CR' \quad (5)$$

The results are summarized in Table I.

Table I. Preparation of Unsymmetrical Conjugated Diynes, RC≡CC≡CR', via Iodination of Lithium Disiamyldialkynylborates, $Li^+[Sia_2BC{\equiv}CR(C{\equiv}CR')]^-$

		Yield, %[a]	
R	R'	Procedure A[b]	Procedure B[c]
n-Hexyl	Ethyl	95	61
n-Hexyl	Cyclohexyl	80	73
n-Hexyl	*tert*-Butyl	79	60
n-Hexyl	Phenyl	79	61
Cyclohexyl	*tert*-Butyl		70

[a] By GLC on a 10% Dow 710 or 10% SE-30 column. [b] From isolated $Sia_2BC{\equiv}CR$. $Sia_2BC{\equiv}C$-*n*-Hex isolated quantitatively from Sia_2BOMe. [c] "One-pot" procedure not involving isolation of any intermediate.

The procedure for the preparation of 1-cyclohexyl-1,3-decadiyne is representative. In a dry, nitrogen-flushed, 500-ml flask, fitted with a gas inlet tube with stopcock, septum inlet, and magnetic stirring bar, are placed 50 ml of tetrahydrofuran and 100 mmol (10.2 ml of 9.8 M) borane–methyl sulfide.[5] The stopcock in the gas inlet tube is closed and the flask immersed in an ice–salt bath. 2-Methyl-2-butene (14.7 g, 210 mmol) is added via syringe and the reaction mixture stirred at room temperature for 2 h. Methanol (3.2 g, 100 mmol) is added dropwise, the hydrogen evolved is safely vented, and the solution is stirred for an additional hour.

Meanwhile, in a separate 250-ml flask, fitted as before, is generated lithium 1-octyne (100 mmol) by the dropwise addition of *n*-butyllithium (40 ml of a 2.5 M solution) to a dry ice–acetone cooled solution of 1-octyne (11 g, 100 mmol) in 75 ml of tetrahydrofuran.

The 500-ml flask containing the freshly prepared methyl disiamylborinate is cooled to −78 °C and the lithium 1-octyne solution added via double-ended needle.[5] The 250-ml flask is rinsed with 5 ml of tetrahydrofuran to ensure complete transfer, and the solution stirred 30 min at −78°. Boron trifluoride etherate (18.8 g, 133 mmol) is added to the reaction via syringe and the mixture stirred for 15 min at −78°, warmed to room temperature, and recooled to −78°. To this mixture is added a solution of 100 mmol of lithium cyclohexylethyne in tetrahydrofuran prepared as was the lithium 1-octyne above.

The reaction mixture is stirred at −78° for 30 min. Iodine (25.7 g, 100 mmol), dissolved in 50 ml of tetrahydrofuran, is added dropwise to the cold reaction mixture. The resulting solution with an orange suspension is stirred for 1 h at −78° and then warmed to room temperature. The reaction mixture is washed twice with 25 ml of 3 M sodium hydroxide. Oxidation to remove residual organoborane is accomplished by the addition of 35 ml of 3 M sodium hydroxide and the addition of 35 ml of 30% hydrogen peroxide at such a rate so as to maintain the temperature under 50°. The aqueous layer is then saturated with potassium carbonate and the organic layer separated. The aqueous layer is extracted once with ether and the combined organic layers dried over anhydrous potassium carbonate. The volatiles are evaporated. Distillation under reduced pressure gave 1-cyclohexyl-1,3-decadiyne (12.1 g, 56% from borane–methyl sulfide): bp 129–131 °C (0.5 mm); $n^{20}D$ 1.5102. Mass spectroscopic examination showed a parent ion of 216.816 (calcd for $C_{16}H_{24}$: 216.817).

The reaction of iodine with lithium disiamyldialkynylborates represents a new method for the preparation of both symmetrical and unsymmetrical conjugated diynes. The procedure presented here provides a direct route to unsymmetrical conjugated diynes, circumventing the more limited scope of the previous procedure[6] as well as the need to isolate either a 1-bromoalkyne[6] or a borane intermediate.[3]

References and Notes

(1) A. Suzuki, N. Miyaura, S. Abiko, M. Itoh, H. C. Brown, J. A. Sinclair, and M. M. Midland, *J. Am. Chem. Soc.*, **95**, 3080 (1973).
(2) M. M. Midland, J. A. Sinclair, and H. C. Brown, *J. Org. Chem.*, **39**, 731 (1974).
(3) A. Pelter, K. Smith, and M. Tabata, *J. Chem. Soc., Chem. Commun.*, 857 (1975).
(4) E. Negishi, G. Lew, and T. Yoshida, *J. Chem. Soc., Chem. Commun.*, 874 (1973).
(5) For a book-length treatment of the principles and techniques of organoboron chemistry, see H. C. Brown, G. W. Kramer, A. B. Levy, and M. M. Midland, "Organic Syntheses *via* Boranes", Wiley-Interscience, New York, N.Y., 1975.
(6) W. Chodkiewicz, *Justus Liebigs Ann. Chem.*, **2**, 819 (1957); J. Rauss, P. Cadiot, and A. Willemart, *C. R. Hebd. Seances Acad. Sci.*, **250**, 558 (1960).

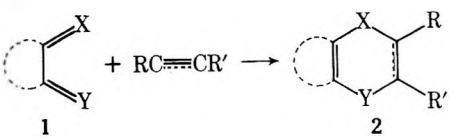
(7) Graduate research assistant on Grant MPS-05136 A01 supported by the National Science Foundation.

James A. Sinclair,[7] Herbert C. Brown*
Richard B. Wetherill Laboratory
Purdue University, West Lafayette, Indiana 47907
Received December 16, 1976

Metal Complexes in Organic Synthesis. I. Cycloaddition of Dimethyl Acetylenedicarboxylate with the Bis Copper(II) Complexes Formed from o-Nitrosophenols. Synthesis of 2,3-Dicarbomethoxy-4-hydroxy-1,4-benzoxazines

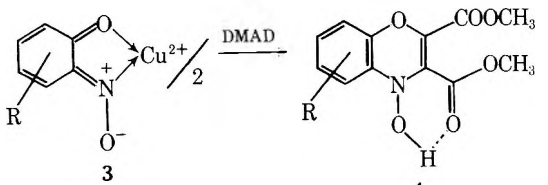
Summary: The heterodiene system in the bis copper(II) complexes formed from *o*-nitrosophenols undergoes smooth [4 + 2] cycloaddition with dimethyl acetylenedicarboxylate to give 1,4-benzoxazines in excellent yield.

Sir: Cycloadditions of diheterodienes with olefins and acetylenes constitute simple procedures for the preparation of a wide range of 1,2-, 1,3- and 1,4-heterocyclic systems.[1,2] The least investigated of these three processes is that involving 1,4-diheterodienes **1** (X, Y = O, S, N), and, as far as we are aware, no successful cycloaddition of a diheterodiene of the type **1** (X = O; Y = NR) with an olefin or acetylene has yet been described (i.e., **1** → **2**).



1 **2**

We now report that the bis copper(II) complexes **3** derived from *o*-nitrosophenols[3] react smoothly with dimethyl acetylenedicarboxylate (DMAD) in hot aqueous 1,2-dimethoxyethane (1:8)[4] to give high yields of the expected products of formal [4 + 2] cycloaddition across the diheterodiene system, namely the 1,4-benzoxazines **4**. The following

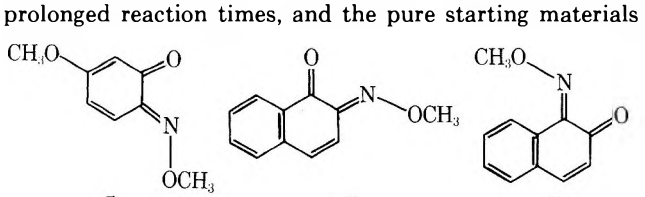


3 **4**

4	R	Yield, %	Mp, °C
a	6-CH_3	98	186–187
b	6-Cl	93	186–188
c	6-Br	92	196–197
d	7-CH_3O	96	181–183
e	7-$(CH_3)_2N$	61	170–172
f	5,6-(CH=CHCH=CH)	91	159–160
g	7,8-(CH=CHCH=CH)	72	163–164
h	5,6- and 7,8-(CH=CHCH=CH)	80	175–176

general procedure was used for all condensations. A solution of 0.02 mol of DMAD in 10 ml of 1,2-dimethoxyethane was added to a stirred suspension of 0.005 mol of the copper complex in 150 ml of 1,2-dimethoxyethane and 20 ml of water, and the mixture was heated under reflux for 3 h. The yellow-brown reaction mixture was then allowed to cool to room temperature; insoluble copper residues were removed by filtration and the crude product, contaminated with the excess DMAD, was obtained by evaporation of the filtrate under reduced pressure. This material was dissolved in hot 1,2-dimethoxyethane, the solution was treated with charcoal and filtered, and the solvent was removed by distillation under reduced pressure. The crystalline solid thus obtained was washed with cold ether (4 × 5 ml) to remove DMAD and recrystallized from ethyl acetate–hexane.[5]

It is well known that *o*-nitrosophenols can exist partially or completely in the *o*-benzoquinone monoxime form; standard control experiments, however, readily established that the latter form is unreactive to DMAD. Thus, treatment of 5-methoxy-2-nitrosophenol, 1-nitroso-2-naphthol, and 2-nitroso-1-naphthol with DMAD did not yield any detectable amount of the benzoxazines **4d, 4f,** and **4g;** pure nitrosophenols were recovered in 75–80% yield. The remainder of the product was a red, polymeric tar. Similarly, the methyl ethers **5–7** failed to react with DMAD, even after prolonged reaction times, and the pure starting materials



5 **6** **7**

were recovered in 80–90% yield. These results are not entirely unexpected, as the Diels–Alder reactivity of heterodienes, especially those which contain nitrogen, is known to differ substantially from that of homodienes, although no definitive explanation for this behavior has yet been advanced.[6]

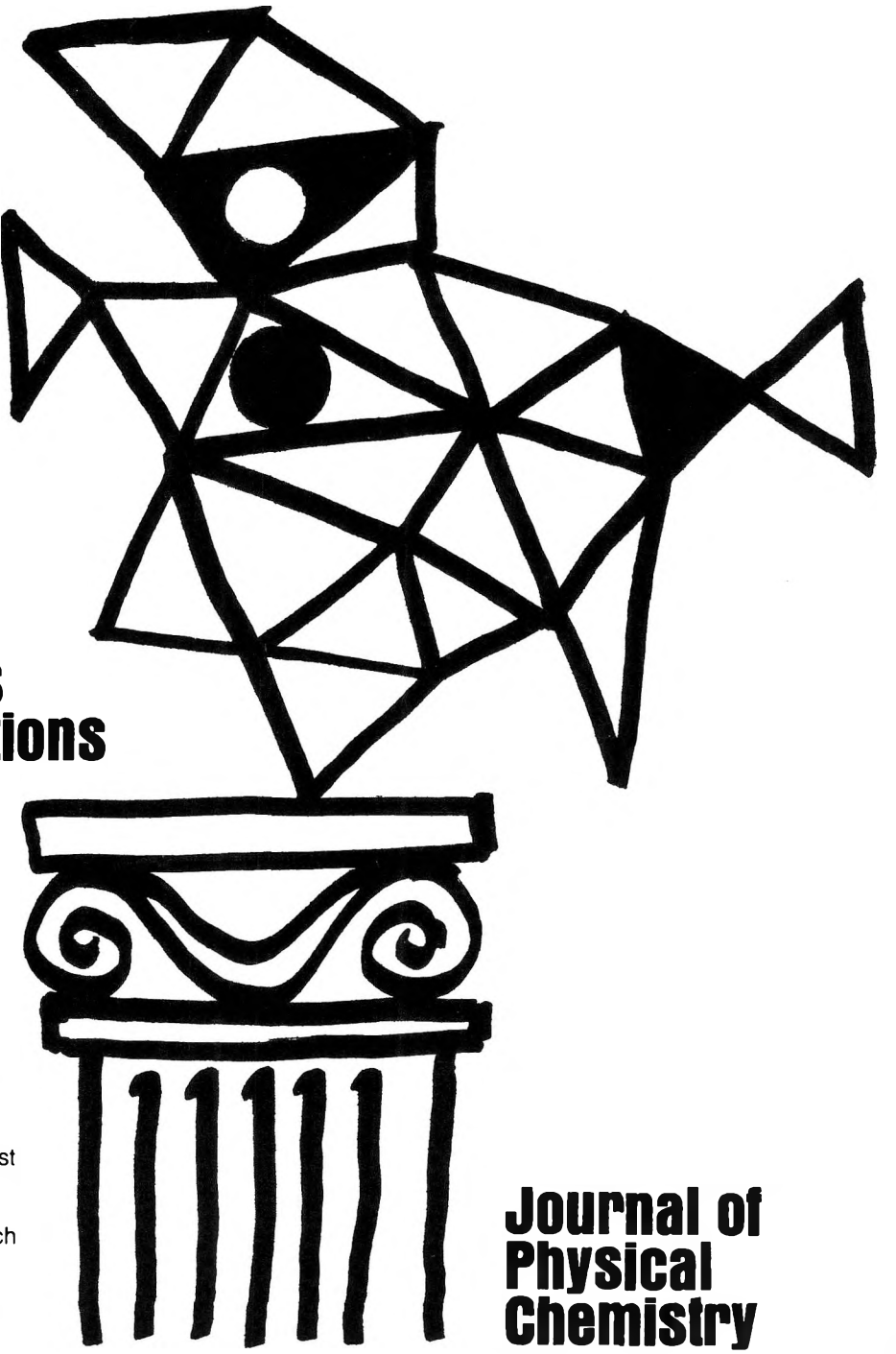
Analysis of the ESR spectra of a variety of the complexes **3,** on the other hand, and careful measurement of the solution magnetic susceptibilities of representative complexes clearly indicated that in these compounds the total electron distribution in the ligand groups is not uniform; there is, rather, an effective electron transfer from the ligands to the copper.[7] That is the formal oxidation state of the copper ion in the chelate is perturbed toward copper(I), and hence weak π-bonding between the copper ion and the triple bond of the acetylene might be anticipated.[8] Moreover, the complexes **3** have a square pyramidal structure with water of hydration at the apex;[9] hence suitable alignment of the dienophile for cycloaddition is possible. The role of the copper ion in these condensations could, therefore, be twofold, namely (i) to polarize electron density toward the termini of the diheterodiene system and (ii) to create a "coordinative template" for reaction. Consequently, it is not surprising that DMAD fails to react with the cobalt(III) complexes derived from o-nitrosophenols which, though structurally analagous to **3,** are coordinatively saturated.

References and Notes

(1) "1,4-Cycloaddition Reactions. The Diels–Alder Reaction in Heterocyclic Synthesis", J. Hamer, Ed., Academic Press, New York, N.Y., 1967.
(2) G. Desimoni and G. Tacconi, *Chem. Rev.*, **75,** 651 (1975).
(3) The complexes **3** can be easily obtained in excellent yield either by room temperature nitrosation of the appropriate phenol in the presence of copper(II) sulfate in a buffered medium [G. Cronheim, *J. Org. Chem.*, **12,** 1 (1947)] or by the direct reaction of a preformed *o*-nitrosophenol with copper(II) acetate in aqueous acetic acid [J. Charalambous, M. J. Frazer, and F. B. Taylor, *J. Chem. Soc. A*, 2787 (1969)].
(4) The presence of water in the reaction medium is essential. The role of the water is not known for certain, but is probably associated with hydration of the copper ion which is released after cycloaddition has taken place.
(5) Yields quoted in the text refer to pure, recrystallized products. Analytical and spectroscopic data for the benzoxazines **4a–h** are fully consistent with the assigned structures.
(6) Ref 1, p 180.
(7) T. S. B. Sayer, Ph.D. Thesis, University of East Anglia, 1975. For example, for the bis copper(II) complex derived from 4-methyl-2-nitrosophenol in mobile toluene solution, g_{iso} = 2.120, A_{iso}(Cu) = 81 G, and $A_{iso}(^{14}N)$ = 12.5 G; for frozen toluene solution samples, $g_{\|}$ = 2.160, $g_{\perp}$ = 2.040, $A_{\|}$ = 200 G, and $A_{\perp}$ = 21.5 G; for solid samples, $g_{\|}$ = 2.206 and $g_{\perp}$ = 2.049 at 298 K and $g_{\|}$ = 2.211 and $g_{\perp}$ = 2.047 at 77 K. Solution susceptibility values were obtained by a modification of the Evans method [D. F. Evans, *J. Chem. Soc.*, 2003 (1959)] in which ^{13}C rather than ^{1}H shifts were used; for the above complex μ_{eff} was 1.505 ($\chi_g \times 10^{-6}$ = 2.582) in DMF and 1.550 ($\chi_g \times 10^{-6}$ = 2.759) in DMSO. These values should be compared with that of 1.76 obtained by Gouy balance measurements (Charalambous et al.; see ref 3).
(8) π bonding of acetylenes with cooper(I) is a well-established phenomenon; see, e.g., F. F. Mango, *Coord. Chem. Rev.*, **15,** 109 (1975).
(9) All of the complexes are monohydrates.

Alexander McKillop,* Trevor S. B. Sayer
School of Chemical Sciences
University of East Anglia
Norwich NR4 7TJ, England

Received November 7, 1975



New concepts new techniques new interpretations

. . . together with valuable reports on classical areas

They are all waiting for you between the covers of our well-balanced JOURNAL OF PHYSICAL CHEMISTRY. Whatever your particular interest in physical chemistry, you'll find the JOURNAL's broad range of experimental and theoretical research reports are relevant and beneficial to your work. Each biweekly issue brings you an average of 30 authoritative, comprehensive reports on fundamental aspects of atomic and molecular phenomena, as well as timely notes, communications and reports plus the proceedings of selected symposia.

Join your fellow physical chemists who rely on JPC as an excellent biweekly source of data in both new and classical areas. Just complete and return the form to start your own subscription.

. . . *another ACS service*

Journal of Physical Chemistry

The Journal of Physical Chemistry
American Chemical Society **1976**
1155 Sixteenth Street, N.W.
Washington, D.C. 20036

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

	U.S.	*Canada***	*Latin America***	*Other Nations***
ACS Member One-Year Rate*	☐ $24.00	☐ $30.25	☐ $29.75	☐ $30.25
Nonmember	☐ $96.00	☐ $102.25	☐ $101.75	☐ $102.25

Bill me ☐ Bill company ☐ Payment enclosed ☐

Air freight rates available on request.

Name _____

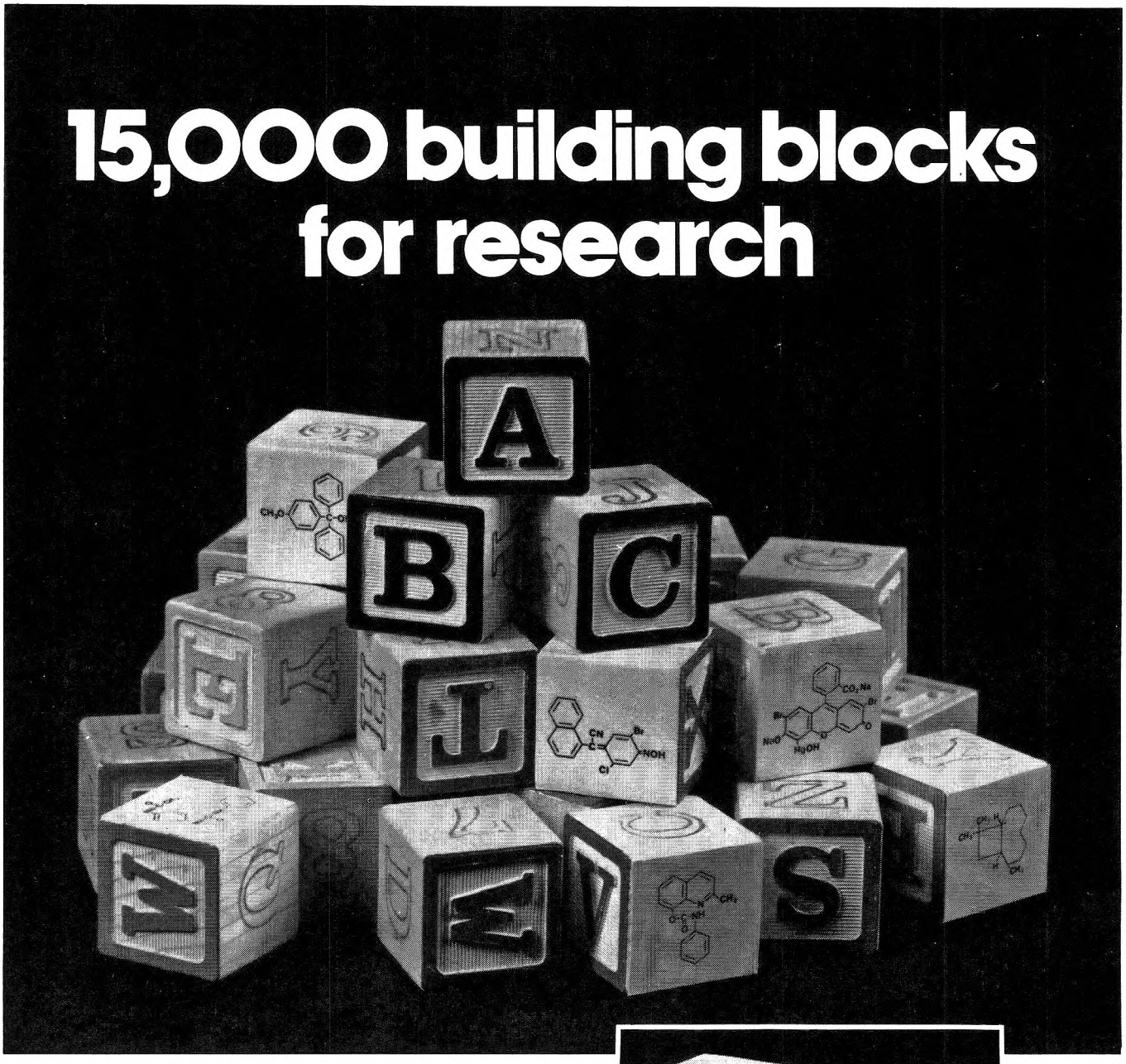
Street _____ Home ☐ Business ☐

City _____ State _____ Zip _____

Journal subscriptions start January '76

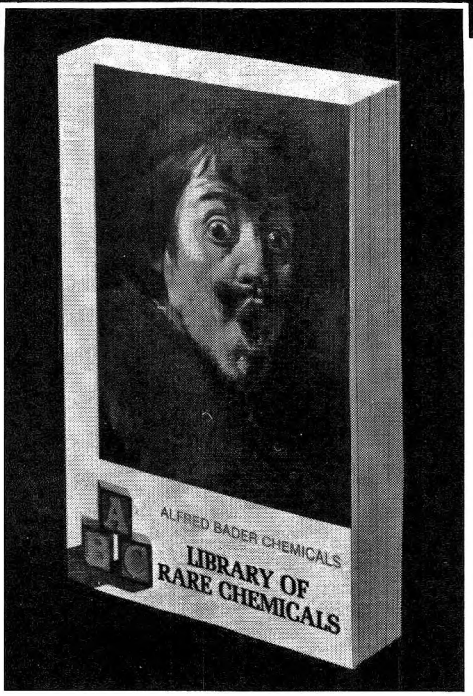
*NOTE: Subscriptions at ACS member rates are for personal use only. **Payment must be made in U.S. currency, by international money order, UNESCO coupons, U.S. bank draft, or order through your book dealer.

15,000 building blocks for research



Announcing: The Alfred Bader Library of Rare Chemicals

This is the Third Edition, the largest collection of computer-coded rare chemicals we've ever published. Use them to find new structure-activity relationships in your screening program, for testing a new reaction, or for comparison with unknown chemicals. All compounds are listed by name, structure, and molecular formula, with a special section describing our free Computer Search service. For your free copy, send your name, the name of your school or firm, address, and zip code to ABC in care of



Aldrich Chemical Company, Inc.

940 WEST SAINT PAUL AVENUE, MILWAUKEE, WI 53233

ALDRICH®