VOLUME 40 MAY 30, 1975 NUMBER 11 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

References especially selected for their usefulness to Journal of Organic Chemistry readers

Here are 13 standard works of the profession filled with just the findings and techniques you may spend valuable job-time hunting down.

Discover how much easier these references make locating the valuable information you need—each FREE for 10 days when you complete and mail the attached coupon.

1. CATIONIC POLYMERIZATION OF OLEFINS: A Critical Inventory, by Joseph P. Kennedy

Gives you a comprehensive inventory of most all cationically polymerizable or oligomerizable olefins described in the scientific literature up to 1973. Includes a system of cationically polymerizable olefins and discussion of their polymerization behavior, a phenomenology of cationic monomers, and a critical evaluation of prior work in the field. 1975, $22.50

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS SERIES, VOL. 14 PYRIDINE AND ITS DERIVATIVES, SUPPLEMENTS, edited by R. A. Abramovitch

2. PART 4. A new volume bringing you up-to-date on pyridine alcohols, aldehydes and ketones, sulfur and selenium compounds of pyridine, and pyridines and reduced pyridines of pharmacological interest. Reference tables tell you at a glance whether a reaction has been carried out, or if a compound has been prepared and by what method. 1975, $65.00

3. PART 2. "...written by experts...reactions...summarized in well set out tables. Numerous and clear diagrams illustrating reaction schemes enable the busy heterocyclic chemist to spot areas of interest and thereby derive inspiration by simply browsing through the book." Chemistry and Industry. Covers pyridine-1-oxides, alkylpyridines and arylpyridines, halopyridines, and organometallic compounds of pyridine. 1973, $60.50

4. PART 3. Supplies you with detailed data on nitropyridines and reduction products (except amines), aminopyridines, pyridinecarboxylic acids, pyridine side-chain carboxylic acids, and pyridinols, and pyridones. 1974, $82.50

5. HETEROCYCLES IN ORGANIC SYNTHESIS, by A. I. Meyers

How functionalized organic compounds and structures of diverse architecture can be prepared by using heterocycles as precursers, reagents, or as vehicles for formation. 1974, $21.50

6. PROGRESS IN PHYSICAL ORGANIC CHEMISTRY, Vol. 11,
edited by Andrew Streitwieser, Jr. and Robert W. Taft

Helps you keep abreast of recent progress through authoritative reviews and critical essays. This volume reports on solvent effects on transition states and reaction rates, thermo dynamics of ionization and solution of aliphatic, and more. 1974, $27.50

7. TOPICS IN STEREOCHEMISTRY, Vol. 8,
edited by Ernest L. Eliel and Norman L. Allinger

Simplifies keeping up with this fast-paced field. All references are **less** than a year old at time of appearance. Vol. 8 covers non-chair conformations of six-membered rings, torsion angle concept in conformational analysis, stereochemical aspects of ^{13}C NMR spectroscopy, more. 1974, $27.00

8. REAGENTS FOR ORGANIC SYNTHESIS, Vol. 4,
by Mary Fieser and Louis F. Fieser

A new, fast reference to reagent literature published in 1970-1972, with some references to literature published in 1973. Here are references to 297 reagents reviewed by the Fiesers for the first time, as well as new references to 380 reagents previously published. 1974, $24.95

ORGANIC REACTIONS SERIES
edited by William G. Dauben

9. VOL. 20. Presents current techniques for obtaining cyclopropanes from unsaturated compounds, methylene, iodide, and zinc-copper couple. Reference data on sensitized photo-oxygenation of olefins, and more, contained in this volume, too. 1973, $24.75

10. VOL. 21. Contains modern methods—in tabular form—for preparing monofluoroaliphatic compounds, as well as techniques for fluorination by sulfur tetrafluoride. 1974, $22.50

11. ORGANIC SYNTHESES, Vol. 53, edited by Arnold Brossi

A manual of techniques for preparing 3-acetyl-2, 4-dimethylfuran, adamantanone, 1-phenyl-4-phosphorinanone, 3, 5-dinitrobenzaldehyde, and dozens of others. Procedures checked by independent laboratory under the direction of Organic Syntheses, Inc. 1973, $10.50

12. ORGANIC SYNTHESES: Collective Vol. 5,
edited by Henry E. Baumgarten

A convenient reference updating the procedures presented in Vols. 40-49 of the Organic Syntheses Series. Contains much user-feedback on techniques concerning safety, corrections, more. 1973, $33.00

13. HOMOGENEOUS HYDROGENATION,
by Brian R. James

An exhaustive, comprehensive reference to the entire field of homogeneous hydrogenation. Complete critical coverage of literature from mid-30's through 1970. Treats hydrogenation of unsaturated fats, Ziegler-type catalysts, summarizes various catalytic cycles, much more. "There is no doubt practioners will want it on their shelves." **Journal of Organometallic Chemistry.** 1973, $30.25

WILEY-INTERSCIENCE
a division of JOHN WILEY & SONS, Inc.
605 Third Avenue
New York, N.Y. 10016
In Canada
John Wiley & Sons, Canada, Ltd.
22 Worcester Road, Rexdale, Ontario

FREE 10-DAY TRIAL
Clip and mail today to:
WILEY-INTERSCIENCE, Dept. 790,
P. O. Box 4569,
Grand Central Station, N.Y., N.Y. 10017

Please rush me the book(s) I've checked below to read and use FREE for 10 days (restricted to continental U.S. and Canada). At the end of that time, if I am satisfied with my order, I will send you the amount indicated for each book received, plus postage and handling. Otherwise, I will return the book(s) and owe nothing.

☐ SAVE MONEY: If you include payment (plus sales tax where applicable), we pay postage and handling charges. Same return privilege, full refund guaranteed. (We normally ship within 10 days. If payment accompanies order and shipment cannot be made within 90 days, payment will be refunded.)

☐ Please bill me (restricted to continental U.S. and Canada).

☐ 1. Polymerization, 0-471-46909-2, $22.50
Heterocyclic Compounds, Vol. 14
☐ 2. Part 4, 0-471-37916-6, $65.00
☐ 3. Part 2, 0-471-37914-X, $60.50
☐ 4. Part 3, 0-471-37915-8, $82.50
☐ 5. Heterocycles, 0-471-60065-2, $21.50
☐ 6. Chemistry, Vol. 11, 0-471-83357-6, $27.50
☐ 7. Stereochemistry, Vol. 8, 0-471-23755-8, $27.00
☐ 8. Reagents, Vol. 4, 0-471-25881-4, $24.95
☐ 9. Reactions, Vol. 20, 0-471-19621-5, $24.75
☐ 10. Reactions, Vol. 21, 0-471-19622-3, $22.50
☐ 11. Organic Syntheses, Vol. 53, 0-471-10615-1, $10.50
☐ 12. Collective Vol. 5, 0-471-05707-X, $33.00
☐ 13. Hydogenation, 0-471-43915-0, $30.25
☐ Please send me a list of local bookstores carrying your titles.

Name _____
Address _____
City/State/Zip _____
Prices subject to change without notice.

MAIL TODAY 092-A5122-WI

THE JOURNAL OF Organic Chemistry

Published by the
AMERICAN CHEMICAL SOCIETY
1155 16th Street, N.W.
Washington, D.C. 20036

BOOKS AND JOURNALS DIVISION

John K Crum *Director*

Virginia E. Stewart
Assistant to the Director

Charles R. Bertsch *Head, Editorial Processing Department*

D. H. Michael Bowen *Head, Journals Department*

Bacil Guiley *Head, Graphics and Production Department*

Seldon W. Terrant *Head, Research and Development Department*

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 Processing Department, American Chemical Society, 20th and Northampton Sts., Easton, Pa. 18042: Department Head, Charles R. Bertsch; Associate Department Head, Marianne C. Brogan; Production Editor, Eileen B. Segal; Assistant Editor, Fern S. Jackson; Editorial Assistant, Andrew J. D'Amelio; Production Assistant, Jane U. Lutick.

Advertising Office: Centcom, Ltd., 50 W. State St., Westport, Conn. 06880.

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

Business and Subscription Information

Send all new and renewal subscriptions *with payment* to Office of the Controller, 1155 16th Street, N.W., Washington, D.C. 20036. Subscriptions should be renewed promptly to avoid a break in your series. All correspondence and telephone calls regarding changes of address, claims for missing issues, subscription service, the status of records, and accounts should be directed to Manager, Membership and Subscription Services, American Chemical Society, P.O. Box 3337, Columbus, Ohio 43210. Telephone (614) 421-7230. For microfiche service, contact ACS Journals Department, 1155 16th Street, N.W., Washington, D.C. 20036. Telephone (202) 872-4444.

On changes of address, include both old and new addresses with ZIP code numbers, accompanied by mailing label from a recent issue. Allow four weeks for change to become effective.

Claims for missing numbers will not be allowed (1) if loss was due to failure of notice of change in address to be received before the date specified, (2) if received more than sixty days from date of issue plus time normally required for postal delivery of journal and claim, or (3) if the reason for the claim is "issue missing from files."

Subscription rates (hard copy or microfiche) in 1975: $20.00 to ACS members, $80.00 to nonmembers. Extra postage $6.00 in Canada and PUAS, $6.50 other foreign. Supplementary material (on microfiche only) available on subscription basis, 1975 rates: $15.00 in U.S., $19.00 in Canada and PUAS, $20.00 elsewhere. All microfiche airmailed to non-U.S. addresses; air freight rates for hard-copy subscriptions available on request.

Single copies for current year: $4.00. Rates for back issues from Volume 20 to date are available from the Special Issues Sales Department, 1155 16th St., N.W., Washington, D.C. 20036.

Subscriptions to this and the other ACS periodical publications are available on microfilm. For information on microfilm, write Special Issues Sales Department at the address above.

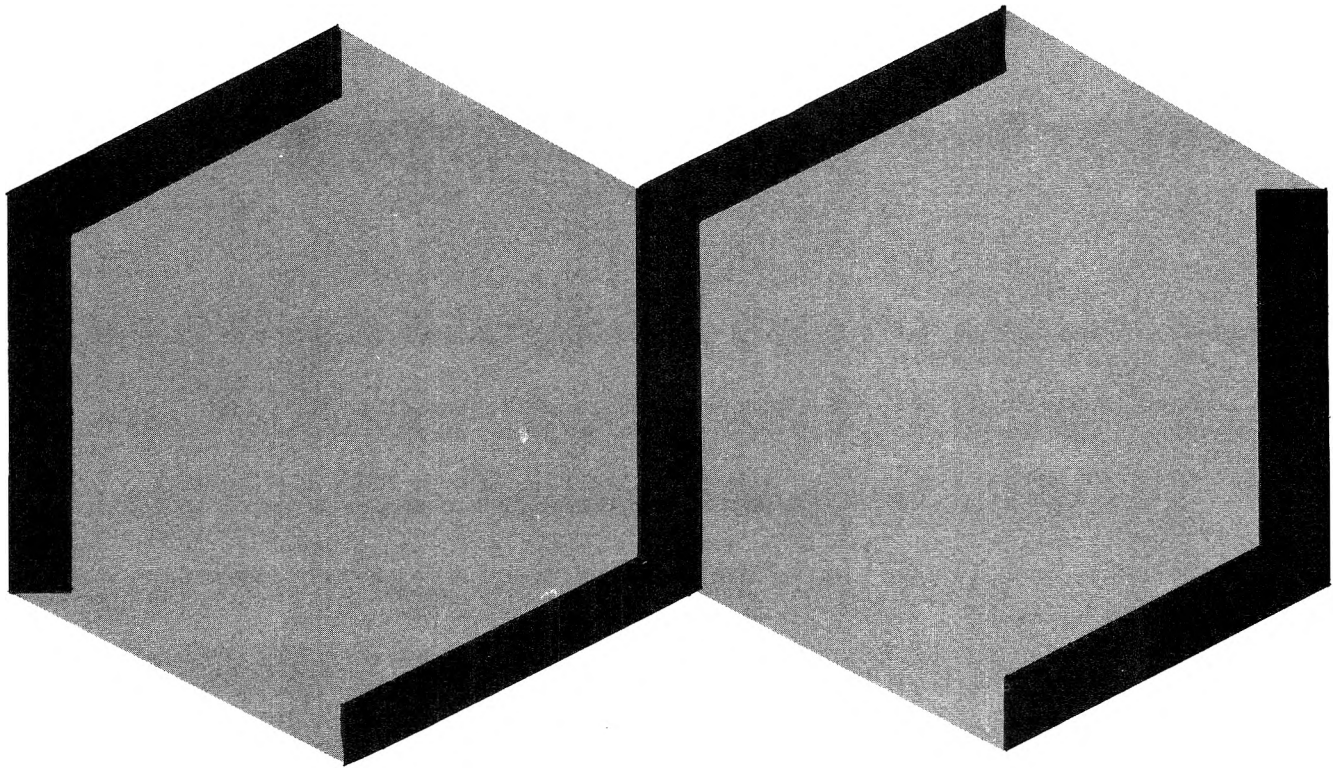
Notice to Authors last printed in the issue of January 10, 1975

JOCEAH 40 (11) 1529–1682 (19' 5)
ISSN 0011-3263

THE JOURNAL OF Organic Chemistry®

VOLUME 40, NUMBER 11 MAY 30, 1975

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
1155 Sixteenth Street, N.W.
Washington, D.C. 20036

1975

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*	☐ $20.00	☐ $26.00	☐ $26.00	☐ $26.50
Nonmember	☐ $80.00	☐ $86.00	☐ $86.00	☐ $86.50

Bill me ☐ Bill company ☐ Payment enclosed ☐

Air freight rates available on request.

Name _____

Street _____ Home ☐ Business ☐

City _____ State _____ Zip _____

Journal subscriptions start on January '75

*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.

■ Supplementary material for this paper is available separately, in photocopy or microfiche form. Ordering information is given in the paper.

* 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 JOURNAL OF Organic Chemistry®

VOLUME 40, NUMBER 11

MAY 30, 1975

Stereoselectivity in the Addition of Dihalocarbenes to 4-*tert*-Butylmethylenecyclohexane and 4-*tert*-Butyl(dichloromethylene)cyclohexane[1]

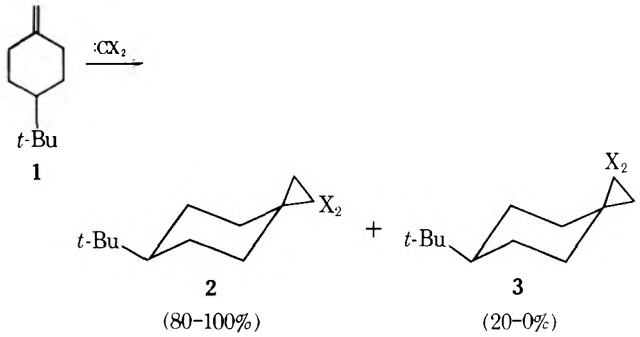
Ellis V. Couch, John A. Landgrebe,* and Edwin T. Castaneda

Department of Chemistry, University of Kansas, Lawrence, Kansas 66045

Received October 30, 1974

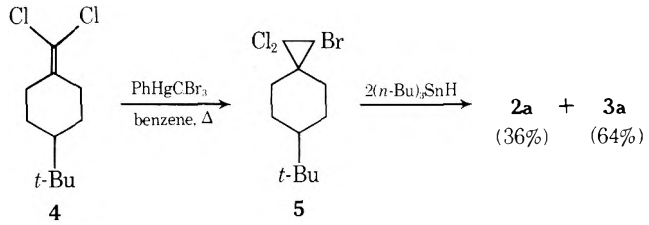
The attack of dichlorocarbene or dibromocarbene on 4-*tert*-butylmethylenecyclohexane (1) produced 80–100% of *E* adduct **2a** resulting from exclusive or predominant equatorial attack. However, the addition of dibromocarbene to 4-*tert*-butyl(dichloromethylene)cyclohexane (4) followed by reduction of the bromine atoms produced a mixture of 36% *E* adduct **2a** and 64% *Z* adduct **3a**, indicating that the equatorial to axial preference for attack by $:CBr_2$ on deactivated olefin **4** is substantially less than for attack by $:CCl_2$ on olefin **1**. The relative rate of addition of $:CCl_2$ to methylenecyclohexane vs. olefin **1** was found to be 1.06 ± 0.02 at 25° in pentane.

The recent proposal that electronic factors may be important in determining the relative amount of axial vs. equatorial attack on double bonds exocyclic to a six-membered ring[2] suggested to us that a study of the stereoselectivity of addition of dihalocarbenes to methylenecyclohexanes containing double bonds of very different nucleophilicities would be of interest.[3]



a, X = Cl
b, X = Br

When allowed to react with dichlorocarbene generated by the treatment of ethyl trichloroacetate with sodium methoxide,[4] by the thermal decomposition of sodium trichloroacetate in 1,2-dimethoxyethane,[5] or by the thermal decomposition of phenyl(bromodichloromethyl)mercury in benzene,[6] olefin **1** produced a single, sharp-melting, crystalline product, which exhibits a singlet at τ 8.85 for the cyclopropyl protons in the NMR spectrum. Combustion analysis and spectral data readily confirmed the expected, 1,1-dichloro-6-*tert*-butylspiro[2.5]octane structure. The *E* stereochemistry of spirooctane **2a** was assigned on the basis of a comparison of the NMR spectrum of the compound with that for the corresponding *Z* isomer synthesized by an alternate route (vide infra).



The treatment of dichloro olefin **4** with phenyl(tribromomethyl)mercury followed by reduction of both bromine atoms with tri-*n*-butyltin hydride resulted in a mixture of **2a** and **3a**, crystalline material with a broad melting range. The mixture exhibits two singlets for cyclopropyl protons in the NMR spectrum at τ 8.81 and 8.85, respectively (relative peak areas ca. 1.8:1). It has often been noted that axial methyl and methylene protons on cyclohexane rings absorb at higher field in the NMR spectrum than those which are equatorial.[7-9] For example, the oxymethylene group of oxyspiran **6** absorbs at 0.075 ppm higher field than that of oxyspiran **7**.[8] Therefore the spirooctane with the cyclopropyl methylene absorption at τ 8.85 was assigned structure **2a** while that with the methylene absorption at τ 8.81 was assigned structure **3a**.

As a confirmation of these assignments, the tetradeuterated isomer **8** was prepared from the corresponding α-deu-

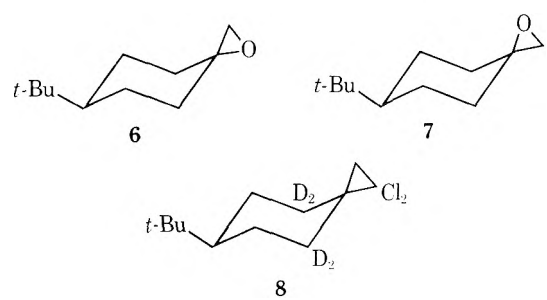


Table I
Summary of Stereoselectivity Results for Addition of Dihalocarbenes to Olefins 1 and 4

Olefin	Carbene	% of attack	
		Axial	Equatorial
1	$:CCl_2$	0–20	100–80
1	$:CBr_2$	0–20	100–80
4	$:CBr_2$	36	64

terated ketone by the same synthetic route used to prepare the pure sample of **2a**. A comparison of $W_{1/2}$, the difference in the width at half-height of the cyclopropyl methylene NMR signal and the internal tetramethylsilane signal, between compounds **2a** and **8** showed a 44% decrease for the 90% tetradeuterated isomer **8**. Such a decrease is indicative of the removal of long-range coupling between the axial cyclopropyl protons and the axial cyclohexane protons adjacent to the spiro carbon atom. This phenomenon has been successfully applied to determining the stereochemistry of oxyspiro systems such as **6**.[8]

Because the attack of $:CCl_2$ on olefin **1** and of $:CBr_2$ on deactivated olefin **4** both involve dominant approach from the equatorial direction, we can be confident in assigning the *E* stereochemistry to the single crystalline product isolated from the treatment of olefin **1** with phenyl(tribromomethyl)mercury.

Of special interest is the observed change in the relative amount of axial and equatorial attack as outlined in Table I. That the 4-*tert*-butyl group is not influencing the observed results relative to what might be anticipated for methylenecyclohexane and (dichloromethylene)cyclohexane is suggested by the fact that the relative rate of addition of $:CCl_2$ to methylenecyclohexane vs. olefin **1** was found to be only 1.06 ± 0.02 at 25° in pentane.

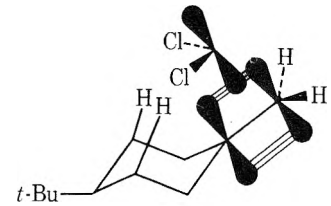
Differences in the stereochemistry of addition of reagents to cyclohexanones were first attributed to the dominance of either "steric approach control" or "product development control".[10] Later workers developed arguments in terms of the relative steric effects of α-axial and β-axial hydrogens toward a group approaching the exocyclic double bond,[11] or in terms of steric vs. torsional factors in the transition state for attack.[12] More recently Klein[2] and Anh[13] have proposed an electronic effect based on the relative size of the π-orbital lobes of the appropriate frontier orbital attacked by a nucleophilic or electrophilic reagent. Their results predict preferential attack by nucleophiles from the axial direction and by electrophiles from the equatorial direction (in the absence of other steric or polar interactions).

Early studies established the electrophilic behavior of $:CCl_2$[14] and $:CBr_2$[15] in additions to olefins. Furthermore, although $:CBr_2$ is recognized to be slightly more reactive (less discriminating) than $:CCl_2$,[14–17] it also exhibits greater steric effects.[14,18,19] The data of Table I show that in spite of the greater steric bulk of $:CBr_2$ relative to $:CCl_2$, reaction of the former intermediate with deactivated olefin **4** resulted in substantially more axial attack than was observed for the reaction of $:CCl_2$ with **1**.

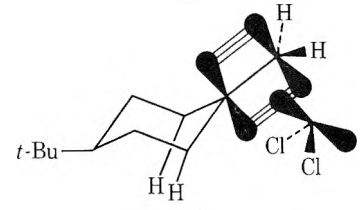
Consider the arguments of Marshall[11a] (and/or Richer[11b]), who suggested that very short distance of the attacking reagent from the exocyclic double bond of a methylenecyclohexane (in the transition state) can be accommodated more readily from the axial than from the equatorial direction, while for long distances the opposite is true. One would indeed expect the transition state for $:CBr_2$ attack on deactivated olefin **4** to be more advanced (shorter divalent carbon to olefin distance) than that for $:CCl_2$ attack on **1**.[17] However, the distance of approach of a reagent to the double bond suggested by the model of Marshall[11a] in order to make axial attack important is less than 2 Å and would represent a product-like transition state,[20] which seems unlikely for the exothermic addition of $:CBr_2$ to **4**.

On the other hand, if we recognize that the electrophilicity of the carbene relative to the nucleophilicity of the olefin is less for the attack of $:CBr_2$ on **4** than for the attack of $:CCl_2$ on **1**, less distinction between axial and equatorial attack preference might be expected for the former reaction based on the electronic arguments outlined by Klein.[2,21]

However, an alternate explanation is possible. Theoretical analysis of the addition of singlet $:CF_2$ to isobutylene[25] indicates a preferred π approach represented by transition states **9** (axial attack) or **10** (equatorial attack) for the addition of $:CCl_2$ to olefin **1**. In each case the p orbital of the divalent carbon is in the same plane occupied by the π-bond of the methylenecyclohexane. (The filled sp^2 orbitals of the carbenes are not shown.) Steric interactions between the chlorines and the β-axial hydrogens in **9** suggest a preference for transition state **10**.

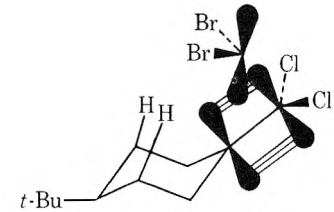


9

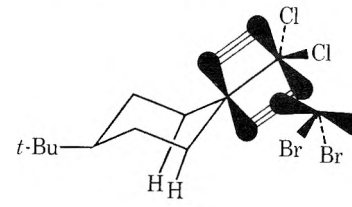


10

In the reaction of $:CBr_2$ with the deactivated olefin **4** the transition state should be somewhat more advanced than for the addition of $:CCl_2$ to **1**, and the BrCBr plane should be more tilted (as shown in **11** and **12**) toward the orientation it will assume in the product than is the ClCCl plane shown in structures **9** and **10**. If the amount of tilt in the BrCBr plane in **11** relative to that of the ClCCl plane of **9** increases the distance between the halogen and the β-axial hydrogens by more than 0.3 Å, the difference in the sum of the covalent and van der Waals radii for bromine vs. chlorine, the steric interaction in **11** should be less than that in



11



12

9. Because of the large distance between the halogen and the α-axial hydrogens in transition states **10** and **12**, the energy difference should not be very sensitive to changes in the angle of tilt of the XCX plane. Therefore a decrease in the activation energy difference for axial vs. equatorial approach would be expected for attack of $:CBr_2$ on **4** relative to attack of $:CCl_2$ on **1**. Further experimentation to test these concepts is in progress.

Experimental Section

Melting points and boiling points (capillary) are uncorrected. Elemental analyses were performed by the Department of Medicinal Chemistry at the University of Kansas, by Galbraith Laboratories, Inc., Knoxville, Tenn., or by Chemalytics Laboratories, Tempe, Ariz. Ir spectra were obtained from a Beckman IR-8 with a 1604-cm^{-1} (polyester vs. air) reference peak. NMR spectra were obtained on a Varian A-60 or A-60A spectrometer. Mass spectra were obtained on a Varian MAT CH-5 spectrometer.

Phenyl(bromodichloromethyl)mercury, mp 108–110° dec (lit.[26] mp 110–111° dec), was prepared in 73–77% yield by the method of Seyferth and Lambert.[27]

Phenyl(tribromomethyl)mercury, mp 117–119° dec (lit.[27] mp 119–120° dec), was prepared in 60% yield by the above procedure.

4-*tert*-Butylmethylenecyclohexane (1). Sodium hydride (5.04 g, 0.21 mol) was added to dimethyl sulfoxide (140 ml, distilled from CaH_2) and this mixture was stirred at 60° for 6 hr (N_2 blanket) until visible evolution of hydrogen had ceased. Methyltriphenylphosphonium bromide (75 g, 0.21 mol) was added to the cooled mixture (yellow color). After a few mintues 4-*tert*-butylcyclohexanone (38.1 g, 0.25 mol, recrystallized from 95% ethanol, Dow) dissolved in warm dimethyl sulfoxide (40 ml) was added and the mixture was stirred at 60° for several hours. At no time during the reaction was the temperature permitted to go over 75°. The solution was cooled to 25°, water (100 ml) was added, and the product was isolated by extraction with pentane and chromatography of the residue on Florisil (60–100 mesh, 20 g/g of crude product) with petroleum ether (bp 60–110°) as eluent. The first four fractions (100 ml total) were evaporated and the liquid residue was distilled (50-cm wire spiral column) to give **1** (21.5 g, 0.14 mol, 67.3%), bp 70° (10 mm) [lit.[28] bp 185–187° (760 mm)]. Ir and NMR spectra were consistent with those reported.[28]

***(E)*-1,1-Dichloro-6-*tert*-butylspiro[2.5]octane (2a). Parham Method.**[4] Ethyl trichloroacetate (9.57 g, 0.05 mol) was added dropwise (30 min) to a mixture of 4-*tert*-butylmethylenecyclohexane (8.7 g, 0.057 mol), sodium methoxide (3.78 g, 0.07 mol), and pentane (50 ml) cooled in an ice bath, and stirred magnetically for several hours. The reaction mixture was filtered, the filtrate was washed and dried, and the solvent was removed. Olefin, methyl ethyl carbonate, and any remaining ethyl trichloroacetate were removed by fractional vacuum distillation (Nester-Faust autoannular still). Residual yellow solid was recrystallized from absolute ethanol to give white, solid **2a** (3 g, 0.0128 mol, 25.6%): mp 97–97.5°; ir (CS_2) 2900 (s), 2870 (sh), 1430, 1395 (w), 1364, 1272, 1240, 1169 (w), 1138, 1050 (sh), 1040 (cyclopropyl), 1020 (sh), 961, 880, 820 (w), 752 (CCl_2), and 663 cm^{-1}; NMR ($CDCl_3$) broad absorption τ 7.8–8.7 (7 H) and a singlet 8.86 (cyclopropyl CH_2) superimposed on a broad absorption 8.70–9.05 (total 4 H), singlet 9.15 (9 H, *t*-Bu).

Anal. Calcd for $C_{12}H_{20}Cl_2$: C, 61.28; H, 8.57. Found: C, 61.49; H, 8.70.

(An NMR spectrum of the crude product did not reveal the presence of **3a**, although ≤20% could have gone undetected.)

Seyferth Method.[6] Phenyl(bromodichloromethyl)mercury (13.2 g, 0.03 mol), olefin **1** (13.6 g, 0.09 mol), and benzene (35 ml, distilled from CaH_2) were stirred and maintained at reflux for 2 hr. Phenylmercuric bromide (9.8 g, 0.027 mol) was filtered, benzene and excess olefin were evaporated, and the solid residue was recrystallized from ethanol–water to yield **2a** (4 g, 0.017 mol, 56.7%): mp 97–97.5°; ir and NMR spectra were identical with those from product produced by Parham or Wagner methods.

Anal. Calcd for $C_{12}H_{20}Cl_2$: C, 61.28; H, 8.57. Found: C, 61.17; H, 8.40.

Wagner Method.[5] Sodium trichloroacetate (16.69 g, 0.09 mol) was added to a solution of **1** (14.52 g, 0.096 mol) and 1,2-dimethoxyethane (50 ml, freshly distilled from CaH_2), stirred, and kept at reflux overnight. The mixture was filtered, pentane (50 ml) was added to the filtrate, and the resulting solution was washed (saturated NaCl), dried ($MgSO_4$), and evaporated. Distillation of excess olefin (10 mm) from the residue gave **2a** (8.2 g, 0.035 mol, 39%), which was recrystallized from petroleum ether: mp 97–97.5°; ir and NMR spectra were identical with those of the compound produced by the Parham and Seyferth methods. Binary mixtures of this product with that from each of the other generation methods melted sharply at 97–97.5°, as did a ternary mixture. Samples gave a single peak by VPC on 10% OV-210 on 80–100 mesh Gas-Chrom Q (6 ft × 0.125 in. glass).

***(E)*-1,1-Dibromo-6-*tert*-butylspiro[2.5]octane (2b).** Potassium *tert*-butoxide (5.7 g, 0.05 mol), olefin **1** (6.5 g, 0.043 mol), and pentane (50 mol. olefin-free, dry) were combined. Bromoform (10.11 g, 0.04 mol, freshly distilled from CaH_2 and passed through a column of alumina) was added dropwise (30 min) while the mixture was stirred and cooled (ice bath) over a period of 2 hr. The mixture was washed, dried ($MgSO_4$), and evaporated to give a solid which was recrystallized from ethanol–water (4.6 g, 0.142 mol, 35.5%): mp 112–113°; ir (CS_2) 2965 (s), 2870 (sh), 1395 (w), 1365, 1270, 1244 (w), 1167 (w), 1140 (w), 1039, 1019 (sh), 960 (w), 819 (w), 730 (w), and 690 cm^{-1} (s); NMR (CCl_4) broad absorption τ 7.9–9.7 (ca. 7 H), singlet 8.66 (cyclopropyl CH_2) superimposed on a broad absorption 8.7–9.1 (ca. 4 H), singlet 9.13 (9 H, *t*-Bu).

Anal. Calcd for $C_{12}H_{20}Br_2$: C, 44.47; H, 6.22; Br, 49.31. Found: C, 44.60; H, 6.39; Br, 49.19.

1-*tert*-Butyl-4-(dichloromethylene)cyclohexane (4). Dichloromethylenetriphenylphosphorane was prepared by the method of Speziale, Ratts, and Bissing[29] with commercial potassium *tert*-butoxide (11.2 g, 0.1 mol) suspended in a mixture of *tert*-butyl alcohol (7.4 g, 0.1 mol, distilled from CaH_2 and stored over 5-Å molecular sieves) and heptane (300 ml, distilled from CaH_2 and stored over 5-Å molecular sieves). Addition of triphenylphosphine (26.2 g, 0.1 mol) to the cold (0°), stirred slurry (N_2 blanket) followed by dropwise addition (1 hr) of chloroform (11.9 g, 0.1 mol, passed through neutral alumina prior to use) in dry heptane (100 ml) produced the bright yellow Wittig reagent.

After concentration of the solution under vacuum to ca. two-thirds of the original volume, 4-*tert*-butylcyclohexanone (24.0 g, 0.156 mol) was added in 4-g portions (30 min) with the temperature maintained below 10° by an ice bath. Stirring was continued for 2 hr with the ice bath and 5 hr at room temperature. After 48 hr, the reaction mixture was filtered and the filtrate was concentrated on a rotary evaporator with a water bath at 45–50°.

The residue was chromatographed twice on neutral alumina with Skelly B and mixtures of Skelly B with benzene to give crude olefin **4**, which was then recrystallized from petroleum ether to give a small yield of crystalline product (ca. 3 g, 0.014 mol, 9%): mp 53–54.5°; ir (CCl_4) 2970 (s), 2880, 2860, 1618, 1480, 1470, 1440, 1390, 1368, and 1305 cm^{-1} (w) as well as other peaks below 1300 cm^{-1}; NMR ($CDCl_3$) broad doublet τ 6.74 (2 H, J = 13 Hz, 2- and 6-equatorial hydrogens), broad absorptions 7.4–8.23 and 8.23–8.70 (total 7 H), singlet 8.84 (9 H, *t*-Bu); parent ion cluster in mass spectrum (21°, 70 eV) *m/e* (rel intensity) 220 (100), 221 (11.7), 222 (63), 223 (7.5), 224 (10), 225 (1.5); theoretical intensities for $C_{11}H_{18}Cl_2^+$ are 100:12.1:64.8:7.8:10.5:1.3.

Anal. Calcd for $C_{11}H_{18}Cl_2$: C, 59.74; H, 8.20. Found: C, 59.85; H, 8.25.

1,1-Dibromo-2,2-dichloro-6-*tert*-butylspiro[2.5]octane (5). Phenyl(tribromomethyl)mercury (3.05 g, 5.75 mmol) was added to dry benzene (75 ml) followed by olefin **4** (1.11 g, 5 mmol) dissolved in dry benzene (35 ml). The solution was stirred and maintained at reflux (N_2 blanket) for 3 hr and filtered to give phenylmercuric bromide corresponding to >90% decomposition of the starting mercurial. The filtrate was evaporated with the bath temperature at 22° and the solid residue was chromatographed on 25 g of neutral alumina with carbon tetrachloride as eluent. Recrystallization of the crude product from carbon tetrachloride produced colorless crystals (ca. 1.0 g, 2.5 mmol, 50%): mp 138–140°; ir (CCl_4) 2970 (s), 2880, 1470, 1460, 1445, 1390 (w), 1365 cm^{-1} as well as other peaks below 1300 cm^{-1}; NMR ($CDCl_3$) complex multiplet τ 7.95–9.00 (9 H), singlet 9.12 (9 H, *t*-Bu); mass spectrum (54°, 70 eV) parent ion cluster beginning at *m/e* 390 too weak for accurate rel intensity comparison, *m/e* (rel intensity) for $M^+ - CH_3$ are 375 (43), 376 (5.4), 377 (100), 378 (16), 379 (89), 380 (11), 381 (29), 382 (5.4), 383 (5.4); theoretical intensities for $C_{11}H_{15}Cl_2Br_2^+$ are 38.4:4.6:100:12.1:89.5:10.8:31.7:3.8:3.9.

Anal. Calcd for $C_{12}H_{18}Cl_2Br_2$: C, 36.67; H, 4.63. Found: C, 36.85; H, 4.62.

Reduction of 1,1-Dibromo-2,2-dichloro-6-*tert*-butylspiro[2.5]octane. Tri-*n*-butyltin hydride (0.538 g, 1.85 mmol) was added to halospirooctane **5** (0.33 g, 0.84 mmol) and the stoppered reaction vessel was shaken and cooled during the exothermic reac-

tion so as to maintain ca. 25°. After 72 hr at 25°, the reaction mixture was chromatographed on neutral alumina (30 g) with carbon tetrachloride as the eluent. Crude product from the chromatography was recrystallized from absolute ethanol and sublimed to give white, crystalline material (ca. 200 mg, 0.90 mmol, 49%), mp 58–62°, which proved to be a 1.8:1 mixture of *Z* isomer **3**, and *E* isomer **2**: NMR ($CDCl_3$) complex absorption τ 7.95–8.65 (7 H), singlets at 8.81 and 8.85 (cyclopropyl CH_2) superimposed on a broad absorption at 8.65–9.05 (total 4 H, height ratio of downfield to upfield singlet ca. 1.8:1), singlet 9.12 (9 H, *t*-Bu); parent ion cluster in mass spectrum (51°, 70 eV) *m/e* (rel intensity) 234 (100), 235 (14), 236 (65), 237 (9), 238 (12), 239 (2); theoretical intensities for $C_{12}H_{20}Cl_2^+$ are 100:13.2:64.8:8.6:10.5:1.4.

Anal. Calcd for $C_{12}H_{20}Cl_2$: C, 61.27; H, 8.59. Found: C, 61.50; H, 8.43.

2,2,6,6-Tetradeuterio-4-*tert*-butylcyclohexanone. 4-*tert*-Butylcyclohexanone (12.2 g, 0.079 mol), sodium carbonate (0.2 g, 2 mmol), and deuterium oxide (20 ml, 1.0 mol, 99.89% D) were heated and stirred overnight in a tightly stoppered flask at 70° (oil bath). The reaction mixture was extracted with ether, the resulting solution was dried ($CaSO_4$), and the ether was evaporated to give partially deuterated ketone (11.4 g). After three additional exchanges 7 g of deuterated ketone was produced which analyzed for 20.1 atom % excess deuterium,[30] which corresponds to 90.5% deuterium substitution.

2,2,6,6-Tetradeuterio-4-*tert*-butylmethylenecyclohexane. Dimethyl sulfoxide (40 ml) was added to sodium hydride (1.44 g, 60 mmol, obtained from a dispersion in mineral oil, Ventron) followed by the addition (4 min) of methyltriphenylphosphonium bromide (17.8 g, 50 mmol) in warm DMSO (20 ml). Deuterated ketone (7.0 g, 44 mmol) was added rapidly and the reaction mixture was worked up as described for olefin **1** to give tetradeuterated olefin **1** (2.65 g, 15 mmol, 34%), bp 65° (10 mm), slightly contaminated with ketone: ir (CCl_4) 3070 (w), 2950 (s), 2860 (sh), 1650, 1480, 1395 (w), 1365, 1240 (w), 1060 (w), 1010 (w), 916 (w), 885 (s), 730 cm^{-1} (w); NMR (CCl_4) singlet τ 5.49 (2 H, vinyl), broad absorption 7.6–9.0 (5 H), singlet 9.15 (9 H, *t*-Bu).

***(E)*-1,1-Dichloro-4,4,8,8-tetradeuterio-6-*tert*-butylspiro[2.5]octane (8).** Deuterated olefin (1.59 g, 10 mmol) was combined with phenyl(bromodichloromethyl)mercury (4.61 g, 10.5 mmol) in benzene (20 ml) and the reaction and work-up were conducted as previously described for the Seyferth method. Phenylmercuric bromide (3.6 g, 10.1 mmol, 96.2%) was isolated. Product **8**, was recrystallized from ethanol (1.20 g, 5 mmol, 50%): ir (CS_2) virtually identical with that of protiated compound **2a**; NMR (CCl_4) showed expected diminution of cyclohexane signal. The product analyzed for 16.6 atom % excess deuterium,[30] which corresponds to 83% deuterium substitution.

Measurement of NMR Half Band Widths. Compounds **2a** (0.0719 g) and **8** (0.0903 g) were dissolved separately in sufficient carbon tetrachloride containing Me_4Si (2.5% by volume) that the cyclopropyl peak and the Me_4Si peak were approximately equal in height. A few drops of benzene (spectral grade) were added to each sample to provide a lock for the 100-MHz spectrometer. Spectra were obtained twice from both a Varian HA-100 and a Varian A-60A spectrometer each time. In each case a 50-cycle sweep width, a sweep time of 0.5 Hz, a filter band width of 4, and a radiofrequency field setting of 0.1 were employed.

The cyclopropyl proton peak was swept repeatedly, the width at half-height was measured to the nearest 0.01 Hz for each sweep, and these sweep widths were averaged for the peak. The sweep offset was adjusted to bring the Me_4Si peak on scale and a similar series of sweeps were made, half-height widths measured, and an average obtained for the Me_4Si proton peak in the same sample. The difference between sample and Me_4Si peak widths, rather than an absolute measurement of the sample peak width, was employed to minimize random variations in spectrometer sensitivity between spectra.[8]

The average value for $\Delta W_{1/2}$ for the cyclopropyl CH_2 of spiran **2a** was 0.70 ± 0.13 Hz, while that for tetradeuterated spiran **8** was 0.39 ± 0.05 Hz.

Competitive Addition of Dichlorocarbene to Methylenecyclohexane and Olefin 1. Methylenecyclohexane (2.40 g, 25 mmol) and olefin **1** (3.80 g, 25 mmol) were dissolved in 5 ml of olefin-free pentane (stored over Na wire). This solution was added to a suspension of sodium methoxide (0.81 g, 15 mmol) in pentane (5 ml). Ethyl trichloroacetate (0.952 g, 5 mmol) was added dropwise and the mixture was stirred at 25° for 1.5 hr after all the ester had been added. The reaction mixture was filtered and the residue was rinsed with pentane. Combined pentane solutions were dried ($CaSO_4$) and evaporated for 10 min under aspirator vacuum with no external heatirg.

Aliquots were analyzed on 10% OV-210 (80–100 mesh Gas-Chrom Q, 6 ft × 0.125 in. glass column). The average value (several injections) for the ratio k(methylenecyclohexane)/k(4-*tert*-butylmethylenecyclohexane) corrected by a detector sensitivity factor was 1.06 ± 0.02.

Acknowledgments. Partial support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the General Research Fund of the University of Kansas is hereby acknowledged. One of the authors (J.A.L.) expresses gratitude to the Department of Chemistry of the University of California, Berkeley, Calif., for providing facilities and secretarial support during the preparation of the manuscript and for helpful discussions with Professor F. R. Jensen.

Registry No.—**1**, 13294-73-0; **1**-*2,2,6,6-d*$_4$, 54789-06-9; **2a**, 54789-07-0; **2b**, 54789-08-1; **3a**, 54831-18-4; **4**, 54789-09-2; **5**, 54789-10-5; **8**, 54831-19-5; dichlorocarbene, 1605-72-7; dibromocarbene, 4371-77-1; 4-*tert*-butylcyclohexanone, 98-53-3; ethyl trichloroacetate, 515-84-4; phenyl(bromodichloromethyl)mercury, 3294-58-4; sodium trichloroacetate, 650-51-1; dichloromethylenetriphenylphosphorane, 6779-08-4; phenyl(tribromomethyl)mercury, 3294-60-8.

References and Notes

(1) Taken in part from the Ph.D. Dissertation of E. V. Couch.
(2) J. Klein, *Tetrahedron*, **30**, 3349 (1974).
(3) For information on relative reactivities in the addition of dichlorocarbene to various methylenecycloalkanes see E. V. Couch and J. A. Landgrebe, *J. Org. Chem.*, in press.
(4) W. E. Parham and E. E. Schweizer, *J. Org. Chem.*, **24**, 1733 (1959).
(5) W. M. Wagner, *Proc. Chem. Soc.*, 229 (1959).
(6) D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y.-P. Mui, H. D. Simmons, Jr., A. J. H. Treiber, and S. R. Dowd, *J. Am. Chem. Soc.*, **87**, 4259 (1965).
(7) C. W. Shoppee, F. P. Johnson, R. E. Lack, J. S. Shannon, and S. Sternhell, *Tetrahedron, Suppl.*, **No. 8**, Part II, 421 (1966).
(8) R. G. Carlson and N. S. Behn, *J. Org. Chem.*, **32**, 1363 (1967).
(9) Although exceptions to this generalization have been noted,[7] structural conditions for these exceptions do not exist in our compounds.
(10) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).
(11) (a) J. A. Marshall and R. D. Carroll, *J. Org. Chem.*, **30**, 2748 (1965); (b) J. C. Richer, *ibid.*, **30**, 324 (1965).
(12) M. Cherest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968).
(13) N. T. Anh, O. Eisenstein, J.-M. Lefour, and M.-E. T. H. Dau, *J. Am. Chem. Soc.*, 95, 6146 (1973).
(14) W. von E. Doering and W. A. Henderson, Jr., *J. Am. Chem. Soc.*, **80**, 5274 (1958).
(15) P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 5430 (1956).
(16) R. A. Moss, "Carbenes", Vol. I, M. Jones, Jr., and R. A. Moss, Ed., Wiley-Interscience, New York, N.Y., 1973, Chapter 2.
(17) P. S. Skell and M. S. Cholod, *J. Am. Chem. Soc.*, **91**, 7131 (1969).
(18) R. A. Moss, "Selective Organic Transformations", Vol. I, B. S. Thyagara, Ed., Wiley-Interscience, New York, N.Y., 1970, p 35 ff.
(19) O. M. Nefedov and R. M. Shafran, *Zh. Obshch. Khim.*, **37**, 1561 (1967).
(20) The perpendicular distance from the dibromo carbon to the opposite cyclopropane carbon–carbon bond in the product **5** is ca. 1.3 Å.
(21) Results published on the epoxidation of methylenecyclohexanes[8] as well as on the attack by HCl,[22] *N*-bromosuccinimide,[23] and dimethyloxosulfonium methylide[24] on olefin **1** appear to contradict the electronic model of Klein.
(22) S. D. Elakovich and J. D. Traynham, *Tetrahedron Lett.*, 1435 (1971).
(23) R. G. Carlson and R. Ardon, *J. Org. Chem.*, **36**, 216 (1971).
(24) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
(25) (a) R. Hoffmann, D. M. Hayes, and P. S. Skell, *J. Phys. Chem.*, **76**, 664 (1972); (b) R. Hoffmann, *J. Am. Chem. Soc.*, **90**, 1475 (1968).
(26) D. Seyferth and J. M. Burlitch, *J. Organomet. Chem.*, **4**, 127 (1965).
(27) D. Seyferth and R. L. Lambert, Jr., *J. Organomet. Chem.*, **16**, 21 (1969).
(28) S. Siegel and B. Dumchovsky, *J. Am. Chem. Soc.*, **84**, 3132 (1962).
(29) A. J. Speziale, K. W. Ratts, and D. E. Bissing, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 361.
(30) Analyses for deuterium were performed by Dr. J. Nemeth, Department of Chemistry, University of Illinois, Urbana, Ill. (falling drop method).

Preparation and Determination of Absolute Rotations and Configurations of 6,7-Dimethoxy-1,2-dimethyl-*exo*-2-benzonorbornenyl Derivatives[1]

Harlan L. Goering,* Andrew C. Backus, Chiu-Shan Chang, and Divakar Masilamani

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

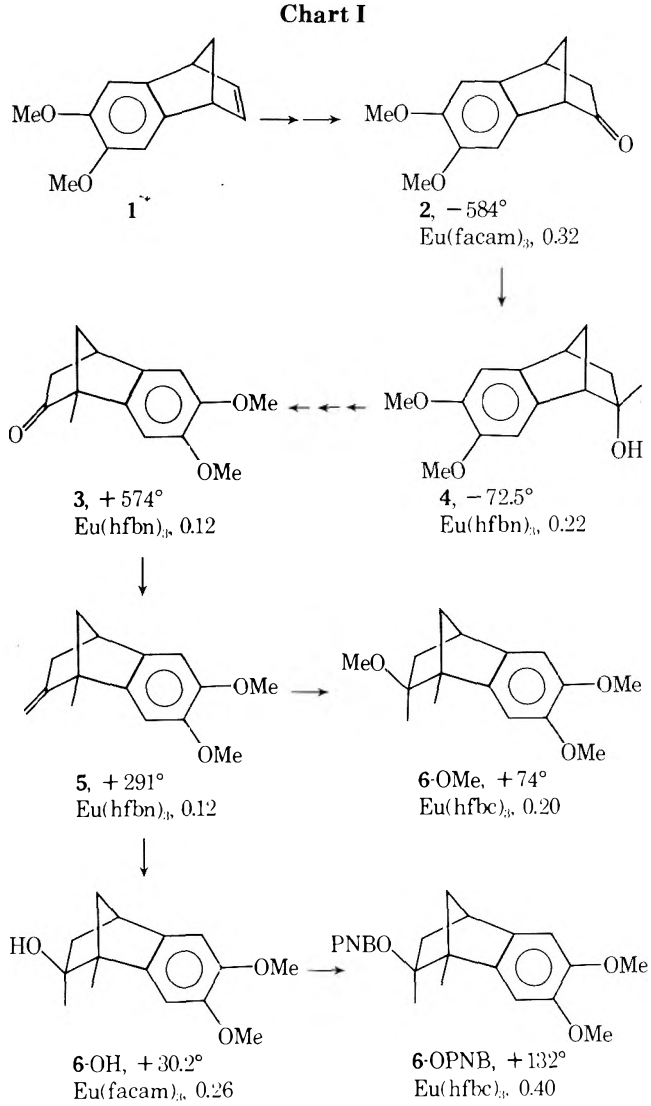
Received November 26, 1974

6,7-Dimethoxybenzonorbornadiene (**1**) has been prepared and converted to racemic and optically active 6,7-dimethoxy-2-benzonorbornenone (**2**). The latter was converted to 6,7-dimethoxy-1-methyl-2-methylenebenzonorbornene (**5**) in five steps, which in turn was converted to various racemic or optically active 6,7-dimethoxy-1,2-dimethyl-*exo*-2-benzonorbornenyl derivatives (**6**-OMe, **6**-OH, and **6**-OPNB). The absolute configuration of **2**, and thus of all subsequent compounds in the series, can be deduced from the asymmetric hydroboration involved in the preparation of **2**. Enantiomeric compositions of all active compounds were determined with optically active NMR lanthanide shift reagents.

We have recently investigated the symmetry properties of ionic intermediates in the 6,7-dimethoxy-1,2-dimethyl-*exo*-2-benzonorbornenyl system.[2] This paper reports the synthesis of the necessary compounds and the correlation of optical configurations and rotations required for that investigation.

6,7-Dimethoxybenzonorbornadiene (**1**) was prepared from 4,5-dimethoxyanthranilic acid[3] and cyclopentadiene and converted to racemic and optically active 6,7-dimethoxy-1,2-dimethyl-*exo*-2-benzonorbornenyl derivatives (**6**) as outlined in Chart I.

Chart I



The key intermediate in this synthesis is 6,7-dimethoxy-1-methyl-2-methylenebenzonorbornene (**5**), which was obtained from 6,7-dimethoxy-1-methyl-2-benzonorbornenone (**3**) by the Wittig reaction. The latter was prepared by the series of reactions used earlier to convert norcamphor to 1-methyl-2-norbornanone[4,5] and 2-benzonorbornenone to 1-methyl-2-benzonorbornenone.[6] This sequence involves conversion of **1** to 6,7-dimethoxy-2-benzonorbornenone (**2**) in two steps, hydroboration followed by oxidation of the resulting 6,7-dimethoxy-*exo*-2-benzonorbornenol. Asymmetric hydroboration with tetraisopinocamphenyldiborane[7] led to optically active **2**, which was the precursor for all of the active compounds. The most active samples were about 60% optically pure.

Conversion of **2** to 6,7-dimethoxy-2-methyl-*endo*-2-benzonorbornenol (**4**) with methylmagnesium bromide followed by acid-catalyzed rearrangement of **4** in acetic acid gave 6,7-dimethoxy-1-methyl-*exo*-2-benzonorbornenyl acetate. This step results in the configurational change shown in Chart I. Reductive cleavage of the acetate with lithium aluminum hydride followed by Oppenauer oxidation gave **3**.

Absolute configurations and rotations are shown in Chart I. The configurational assignments are based on the assumption that asymmetric hydroboration of **1** and benzonorbornadiene[6,8] give similar enantiomeric compositions. In each case hydroboration with tetraisopinocamphenyldiborane derived from (−)-α-pinene leads to the (−) ketone and magnitudes of induced asymmetry are similar for the two systems. It has been shown[8] that the absolute configuration of (−)-2-benzonorbornadiene corresponds to the structure for (−)-**2** in Chart I.

The absolute rotations were determined from rotations and enantiomeric compositions of homogeneous optically active samples. Enantiomeric compositions were determined directly with optically active NMR lanthanide shift reagents.[9,10] From induced shifts of the various signals it is apparent that the binding constant for the ortho methoxyl groups is larger than for the keto (**2** and **3**), hydroxyl (**4** and **6**), or ester (**6**-OPNB) groups.[11] Several optically active shift reagents were investigated, including tris(3-trifluoroacetyl-*d*-camphorato)europium(III) [Eu(facam)$_3$],[10] tris(3-heptafluorobutyryl-*d*-camphorato)europium(III) [Eu(hfbc)$_3$],[10] tris(3-pentafluorobenzoyl-*d*-camphorato)europium(III) [Eu(fbc)$_3$], and tris(3-heptafluorobutyryl-*d*-nopinato)europium(III) [Eu(hfbn)$_3$]. The shift reagent giving the maximum nonequivalence of one set of enantiotopic methoxyl signals, and the magnitudes of the nonequivalences ($\Delta\Delta\delta$ in parts per million) are included in Chart I.

Optically active **5** was converted to 6,7-dimethoxy-1,2-dimethyl-*exo*-2-benzonorbornenol (**6**-OH) by oxymercura-

tion–demercuration.[12] The enantiomeric composition of the product was the same as that of the reactant. Similarly, 6,7-dimethoxy-1,2-dimethyl-*exo*-2-benzonorbornenyl methyl ether (**6**-OMe) was prepared from **5** without change in optical purity by methoxymercuration–demercuration.[6,13] 6,7-Dimethoxy-1,2-dimethyl-*exo*-2-benzonorbornenyl *p*-nitrobenzoate (**6**-OPNB) was prepared from **6**-OH and purified by recrystallization, which increases the optical purity. The most active samples were about 70% optically pure.

6,7-Dimethoxy-2-benzonorbornenone (**2**) was also converted to 6,7-dimethoxy-2-methylenebenzonorbornene (Wittig reaction), which in turn was converted to 6,7-dimethoxy-2-methyl-*exo*-2-benzonorbornenol (the exo isomer of **4**) by oxymercuration–demercuration.

Experimental Section

6,7-Dimethoxybenzonorbornadiene (1). This compound was prepared by the Diels–Alder addition of 4,5-dimethoxybenzyne to cyclopentadiene. The benzyne was derived from 4,5-dimethoxyanthranilic acid, mp 185° (lit. mp 186°),[3] which was prepared by catalytic hydrogenation (45 psi, PtO_2,30 min) of 6-nitroveratric acid, mp 189° (lit. mp 189–190°).[3] The latter was obtained by oxidation (basic permanganate) of 6-nitroveratraldehyde.[14]

4,5-Dimethoxyanthranilic acid was converted to **2-carboxy-4,5-dimethoxybenzenediazonium chloride** as follows. In a typical preparation[15,16] a solution of 80 g (0.41 mol) of 4,5-dimethoxyanthranilic acid in 600 ml of absolute ethanol was cooled to 10° and 40 ml of concentrated hydrochloric acid was added with vigorous stirring. To the resulting pasty mixture was added 59 ml of isoamyl nitrite, after which stirring was continued and 600 ml of anhydrous ether was added. The diazonium chloride was filtered, washed with anhydrous ether, dried briefly under reduced pressure, and stored in a refrigerator until used. The yield of crude diazonium chloride was 102 g (0.42 mol). The diazonium chloride was prepared shortly (<24 hr) before use.

The Diels–Alder addition of 4,5-dimethoxybenzyne to cyclopentadiene was carried out as follows. To a stirred suspension of 25 g of the above diazonium chloride in 160 ml of 1,2-dichloroethane at 85° was added 9 ml of freshly distilled cyclopentadiene followed by 13.6 ml of propylene oxide. The refluxing mixture was stirred until gas evolution ceased (ca. 2.5 hr). Then the reaction mixture was neutralized with aqueous sodium hydroxide and steam distilled. After removal of most of the solvent the temperature rose to 98° and the subsequent fraction contained essentially pure **1**, which separates as a solid. Extraction with ether followed by drying and removal of the ether gave 7 g (35%) of residual **1**, which after purification by recrystallization from an ether–pentane mixture followed by sublimation had mp 82–83°; NMR ($CDCl_3$) δ 2.23 (m, 2 H), 3.81 (s, 8-H), 6.78 (m, 2 H), 6.92 (s, 2 H).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.23; H, 6.93. Found: C, 77.33; H, 7.09.

6,7-Dimethoxy-2-benzonorbornenone (2). Racemic and optically active **2** were prepared from **1** in about 80% yield by procedures described earlier[8] for conversion of benzonorbornadiene to racemic and optically active 2-benzonorbornenone. This method involves hydroboration with diborane in tetrahydrofuran for racemic products or with tetraisopinocamphenyldiborane in diglyme for active products, followed by oxidation of the resulting dimethoxy-*exo*-2-benzonorbornenol. The product (**2**), mp 106–107°, was purified by recrystallization from ether–pentane mixtures followed by sublimation. The NMR spectrum ($CDCl_3$) had overlapping methoxyl singlets at δ 3.80 and an aromatic singlet (2 H) at δ 6.87.

Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.56; H, 6.42. Found: C, 71.40; H, 6.47.

Asymmetric hydroboration of **1** with tetraisopinocamphenyldiborane, derived from (+)-α-pinene, $[\alpha]^{25}D$ 40.2° (neat) (~78% optically pure), led to (+)-**2**, $[\alpha]^{25}D$ 351° (*c* 2.9, $CHCl_3$) (60% optically pure).[17] Similar results were obtained in several other preparations. These results are similar to those reported earlier[6,8] for the parent benzonorbornadiene system with regard to signs of rotations and magnitudes of the induced asymmetry.

6,7-Dimethoxy-2-methyl-*endo*-2-benzonorbornenol (4). A solution of 13 g (0.06 mol) of 6,7-dimethoxy-2-benzonorbornenone (**2**) in 60 ml of dry tetrahydrofuran was added at room temperature to 60 ml (0.18 mol) of 0.3 *M* methylmagnesium bromide in ether. The mixture (under dry nitrogen) was stirred during the addition and stirring was continued for an additional 30 min, after which the reaction mixture was refluxed for 2 hr. The excess methylmagnesium bromide was decomposed by careful addition of a saturated aqueous solution of ammonium chloride, after which 10% hydrochloric acid was added to dissolve the precipitate. The resulting solution was extracted with three 200-ml portions of ether and the ether extract was dried and concentrated to 13 g (93%) of a brown residual syrup which consisted of 93% **4** contaminated with 7% of the endo isomer. Recrystallization from ether followed by vacuum distillation gave **4**: mp 60–61°; NMR (CCl_4) δ 1–2 (m, 5 H), 1.45 (s, 3 H), 2.88 (s, 1 H), 3.12 (s, 1 H), 3.74 (s, 6 H), 6.75 (2 s, 2 H).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.79; H, 7.69. Found: C, 71.60; H, 7.53.

By the above procedure, except that the reflux period was increased to 5 hr, 20 g of homogeneous (+)-**2**,[17] $[\alpha]^{25}D$ 351° (*c* 2.9, $CHCl_3$), was converted to 19.3 g (90%) of (+)-**4**. A homogeneous sample of (+)-**4**,[17] $[\alpha]^{25}D$ 44.8° (*c* 1.0, $CHCl_3$), was obtained by preparative GC (10% FAPP on 45/60 Chromosorb W). The NMR spectrum in the presence of Eu(hfbn)$_3$ indicated that this sample was 62% optically pure.

6,7-Dimethoxy-1-methyl-2-benzonorbornenone (3). Crude **4** was converted to **3** in 56% overall yield by the three-step process described earlier for the parent benzonorbornenyl system[6] (the two intermediates were not purified). The product (**3**) was purified by recrystallization (and decolorizing with Norite) from ether at −78° followed by sublimation and had mp 102–103°; NMR (CCl_4) δ 1.38 (s, 3 H), 1.7–2.4 (m, 4 H), 3.41 (s, 1 H), 3.78 (s, 6 H), 6.72 (2 s, 2 H).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.41; H, 6.90. Found: C, 72.61; H, 6.80.

In the same manner 17.6 g of the (+)-**4** described above was converted to 15.7 g (90%) of crude (−)-**3**. A homogeneous sample of (−)-**3**,[17] $[\alpha]^{25}D$ −342° (*c* 0.98, $CHCl_3$), was obtained by preparative GC (10% FAPP on 45/60 Chromosorb W). The NMR spectrum in the presence of Eu(hfbn)$_3$ indicated the sample to be 60% optically pure.

6,7-Dimethoxy-1-methyl-2-methylenenorbornene (5). This compound was prepared from the above ketone (**3**) by the Wittig reaction using the procedure described earlier for similar transformations in the 1-methylnorbornyl[5] and 1-methylbenzonorbornenyl[6] systems. The yield of **5**, after purification by recrystallization from ether, was 75%: mp 39–41°; NMR (CCl_4) δ 1.52 (s, 3 H), 1.6–2.5 (m, 4 H), 3.2 (s, 1 H), 3.72 (s, 6 H), 4.5–4.8 (2 t, 2 H), 6.55 (2 s, 2 H).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.26; H, 7.83. Found: C, 78.47; H, 7.86.

By the same procedure 6.0 g of the above crude (−)-**3** was converted to 6.0 g (100%) of crude (+)-**5** (a residual brown oil). A homogeneous sample of (+)-**5**,[17] $[\alpha]^{25}D$ −176° (*c* 1.32, $CHCl_3$), was obtained by preparative GC (column described above). The NMR spectrum in the presence of Eu(hfbn)$_3$ indicated the sample to be 60% optically pure.

6,7-Dimethoxy-1,2-dimethyl-2-*exo*-benzonorbornenol (6-OH). Oxymercuration–demercuration of **5** according to a previously described procedure[12] gave **6**-OH in 93% yield. The crude product (white precipitate) was purified by sublimation (80°, 1 mm) followed by recrystallization from ether: mp 75–76°; NMR (CCl_4) δ 0.8 (s, 3 H), 1.34 (s, 3 H), 1.2–2.2 (m, 5 H), 3.06 (s, 1 H), 3.74 (s, 6 H), 6.62 (s, 2 H).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.58; H, 8.06. Found: C, 72.33; H, 8.00.

The same procedure was used to convert 6 g of the above crude (−)-(**5**) to 5.5 g (85%) of crude (−)-**6**-OH. A homogeneous sample of (−)-**6**-OH),[17] $[\alpha]^{25}D$ −17.6° (*c* 1.5, $CHCl_3$), was obtained by preparative GC (10% FAPP on 45/60 Chromosorb W at 170°). Under these conditions the tertiary alcohol is stable.

6,7-Dimethoxy-2-methylenebenzonorbornene. This compound was prepared from **2** by the Wittig reaction using the procedure reported earlier for similar systems.[5,6] The yield of crude product was 85%. The product was purified by two recrystallizations from ether–pentane mixtures followed by sublimation (65°, 1 mm): mp 49–50°; NMR ($CDCl_3$) δ 3.80 (s, 6 H), 4.66 and 5.05 (2 s, 2 H), 6.80 (s, 2 H).

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.78; H, 7.41. Found: C, 77.60; H, 7.62.

6,7-Dimethoxy-2-methyl-*exo*-2-benzonorbornenol. This tertiary alcohol (exo isomer of **4**) was of interest for developing procedures for preparing tertiary benzonorbornenyl *p*-nitrobenzoates.

Oxymercuration–demercuration of the above dimethoxy-2-methylenebenzonorbornene by the procedure used to convert **5** to **6-OH** gave a product which after recrystallization from ether and sublimation (90°, 1 mm) had mp 83–84°; NMR ($CDCl_3$) δ 0.96 (s, 3 H), 3.81 (s, 6 H), 6.81 (d, 2 H).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.79; H, 7.69. Found: C, 71.60; H, 7.53.

6,7-Dimethoxy-2-methyl-*exo*-2-benzonorbornenyl *p*-Nitrobenzoate. Of several procedures[6] attempted the following gave the highest yields. To a solution of 0.56 g (2.26 mmol) of the above tertiary alcohol in 4 ml of completely dry pyridine was added 0.97 g (5.25 mmol) of freshly recrystallized (CCl_4) *p*-nitrobenzoyl chloride. The acid chloride was added in small amounts and after each addition the reaction flask was shaken well at room temperature. The clear orange solution solidified in about 5 min. After 15 min, water was added dropwise with shaking after each addition. After addition of 5 ml of water the reaction mixture was extracted several times with ether and the ether extract was washed with water, aqueous sodium bicarbonate, and again with water. The solvent was removed under reduced pressure and the residual product was placed under high vacuum to remove the pyridine. The yield of crude product was 0.82 g (89%). After recrystallization twice from ether, 0.52 g (57%) of pure tertiary *p*-nitrobenzoate was obtained: mp 146–147°; NMR ($CDCl_3$) δ 1.35 (s, 3 H), 3.91 (s, 6 H), 8.25 (s, 4 H).

Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.80; H, 5.48; N, 3.66. Found: C, 65.65; H, 5.57; N, 3.61.

6,7-Dimethoxy-1,2-dimethyl-*exo*-2-benzonorbornenyl *p*-Nitrobenzoate (6-OPNB). This ester was prepared by the above procedure except that the reaction temperature was 55° instead of room temperature and the reaction mixture was stirred instead of shaken. Also, the reaction time at 55° was increased to 27 hr and the product was extracted with benzene.[18] The tertiary ester, **6-OPNB**, was obtained in 65% yield. A small amount of unreacted **6-OH** was separated and recovered by sublimation (100°, 1 mm). The product was purified by column chromatography (Al_2O_3 with benzene as eluent) followed by recrystallization from ether–pentane mixtures. The purified nearly colorless **6-OPNB** had mp 165–166°; NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.7 (s, 3 H), 1.6–2.8 (m, 4 H), 3.2 (s, 1 H), 3.93 (s, 6 H), 6.86 (s, 2 H), 8.3 (s, 4 H).

Anal. Calcd for $C_{22}H_{23}NO_6$: C, 66.50; H, 5.79; N, 3.53. Found: C, 66.33; H, 5.76; N, 3.56.

By this procedure 5.3 g of the above crude (−)-**6-OH** was converted to (−)-**6-OPNB** which, after purification, had mp 168–169°; $[\alpha]^{25}D$ −85.7° (c 1.1, $CHCl_3$). The NMR spectrum in the presence of Eu(hfbc)$_3$ indicated that this material was 65% optically pure.

(−)-6,7-Dimethoxy-1,2-dimethyl-*exo*-2-benzonorbornenyl Methyl Ether [(−)-6-OMe]. A sample of (−)-**5**, $[\alpha]^{25}D$ −143° (c 1.5, $CHCl_3$), was converted to (−)-**6-OMe**, which after purification by preparative GC had mp 64–66°;[17] $[\alpha]^{25}D$ −36.3° (c 0.3, $CHCl_3$); NMR ($CDCl_3$) δ 0.72 (s, 3 H), 1.3–1.7 (m, 2 H), 1.32 (s, 3 H), 2.04–2.3 (m, 2 H), 3.08 (s, 1 H), 3.20 (s, 3 H), 3.74 (d, 6 H), 6.6 (s, 2 H). The NMR spectrum in the presence of Eu(hfbc)$_3$ indicated that this sample was 49% optically pure.

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.00; H, 8.60.

3-Heptafluorobutyryl-*d*-nopinone (H-hfbn). *d*-Nopinone, bp 86° (9.5 mm), $[\alpha]^{25}D$ 26.7° (*c* 2.1 $CHCl_3$), was prepared[19] from (−)-β-pinene, $[\alpha]^{25}D$ −20.4° (neat), in 79% yield. A mixture of 4.6 g (0.118 mol) of sodium amide and 15.56 g (0.110 mol) of *d*-nopinone in 150 ml of dimethoxyethane was refluxed under nitrogen for about 2 hr, after which the reaction mixture was cooled to 0° and 9.1 g (0.039 mol) of heptafluorobutyryl chloride (Pierce Chemical Co.) in 25 ml of dimethoxyethane was added over a 30-min period. The reaction mixture was stirred at 0–5° for an additional 20 min and diluted with 400 ml of ice water. The mixture was acidified with concentrated hydrochloric acid and extracted several times with pentane. The pentane extract was washed with aqueous sodium bicarbonate and water. After drying, the extract was concentrated to 24.3 g of red liquid. Copper chelate purification[9] of the crude β-diketone followed by distillation gave 10.5 g (78%) of 3-heptafluorobutyryl-*d*-nopinone: bp 84–86° (4 mm); $[\alpha]^{25}D$ 14.7° (*c* 1.1, $CHCl_3$); NMR (CCl_4) δ 0.93 and 1.36 (2 s, 6 H, CH_3), 1.2–1.6 (m, 1 H), 2.2–2.4 (m, 1 H), 2.44–2.84 (m, 4 H), 14.9 (s, 1 H, enol H); ir (CCl_4) 1670 (C=O), 1630 cm^{-1} (C=C).

Tris(3-heptafluorobutyryl-*d*-nopinato)europium(III) [Eu(hfbn)$_3$]. This chelate was prepared from the above diketone and europium(III) chloride hexahydrate (99.99%) by the general method reported earlier.[10] As in the cases of Eu(facam)$_3$ and Eu(hfbc)$_3$,[10] Eu(hfbn)$_3$ was obtained as a bright yellow, glassy powder which was dried at 70° under high vacuum for several hours. This product had $[\alpha]^{25}D$ 25.6° (c 1.9, CCl_4); NMR (CCl_4) δ 1.0–2.0, 3.4 (all resonances broad); ir ($CHCl_3$) 1620 (C=O), 1480 cm^{-1} (C=C).

Anal. Calcd for $C_{39}H_{36}F_{21}O_6Eu$: C, 40.43; H, 3.12. Found: C, 40.67; H, 3.15.

Determination of Enantiomeric Compositons. Enantiomeric compositions were determined with a 100-MHz instrument as outlined previously.[10] Pertinent data are summarized in Table I,

Table I
Determination of Enantiomeric Compositions of 6,7-Dimethoxybenzonorbornenyl Derivatives[a]

Compd	Reagent	R/S[b]	$\Delta\Delta\delta$, ppm[c]
2	Eu(facam)$_3$	1.07	0.32[e]
4	Eu(hfbn)$_3$	1.04	0.22[e]
3	Eu(hfbn)$_3$	1.17	0.12[e]
5	Eu(hfbn)$_3$	1.31	0.12[d]
6-OH	Eu(facam)$_3$	1.07	0.26[e]
6-OPNB	Eu(hfbc)$_3$	1.09	0.45[d]
6-OMe	Eu(hfbc)$_3$	1.00	0.20[e]

[a] The solvent was carbon tetrachloride for all determinations. [b] Shift reagent/substrate molar ratio; shift reagent concentration ~0.2 *M*. [c] Separation of low-field methoxyl signal. [d] Separation of high-field methoxyl signal.

which shows the optically active shift reagent which gave the largest nonequivalence for each compound, the shift reagent/substrate molar ratio (S/R), and the set of enantiotopic signals used for the determinations.

Registry No.—**1**, 54576-19-1; (±)-**2**, 54576-22-6; (+)-**2**, 54630-83-0; (±)-**3**, 54576-23-7; (−)-**3**, 54712-33-3; (±)-**4**, 54630-84-1; (+)-**4**, 54630-85-2; (±)-**4** exo isomer, 54630-86-3; (±)-**4** exo isomer *p*-nitrobenzoate, 54576-24-8; (±)-**5**, 54576-25-9; (+)-**5**, 54617-82-2; (−)-**5**, 54630-87-4; (±)-**6-OH**, 54576-26-0; (−)-**6-OH**, 54630-88-5; (±)-**6-OPNB**, 54576-27-1; (−)-**6-OPNB**, 54656-19-8; (−)-**6-OME**, 54576-28-2; 4,5-dimethoxybenzyne, 54632-05-2; cyclopentadiene, 542-92-7; 6,7-dimethoxy-2-methylenebenzonorbornene, 54576-29-3; *p*-nitrobenzoyl chloride, 122-04-3; H-hfbn, 54576-30-6; *d*-nopinone, 24903-95-5; heptafluorobutyryl chloride, 375-16-6; tris(3-heptafluorobutyryl-*d*-nopinato)europium(III), 54576-31-7; europium(III) chloride hexahydrate, 13759-92-7.

References and Notes

(1) This work was supported by the National Science Foundation (GP-6555X) and the Air Force Office of Scientific Research (AFOSR-71-1974).
(2) H. L. Goering, C.-S. Chang, and D. Masilamani, unpublished work.
(3) C. A. Fetscher and M. T. Bogert, *J. Org. Chem.*, **4**, 71 (1939).
(4) J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *J. Am. Chem. Soc.*, **83**, 3986 (1961).
(5) H. L. Goering, C. Brown, S. Chang, J. V. Clevenger, and K. Humski, *J. Org. Chem.*, **34**, 624 (1969).
(6) H. L. Goering, J. V. Clevenger, and K. Humski, *J. Org. Chem.*, **37**, 3019 (1972).
(7) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Am. Chem. Soc.*, **86**, 397 (1964).
(8) D. J. Sandman, K. Mislow, W. P. Giddings, J. Dirlam, and G. C. Hanson, *J. Am. Chem. Soc.*, **90**, 4877 (1968).
(9) M. D. McCreary, D. W. Lewis, D. L. Wernick, and G. M. Whitesides, *J. Am. Chem. Soc.*, **96**, 1038 (1974).
(10) H. L. Goering, J. N. Eikenberry, G. S. Koermer, and Charles J. Lattimer, *J. Am. Chem. Soc.*, **96**, 1493 (1974).
(11) A similar observation has been reported by G. E. Wright and T. Y.-T. Wei, *Tetrahedron*, **29**, 3775 (1973).
(12) H. C. Brown, J. H. Kawakami, and S. Ikegami, *J. Am. Chem. Soc.*, **89**, 1525 (1967).
(13) H. C. Brown and M.-H. Rei, *J. Am. Chem. Soc.*, **91**, 5646 (1969).
(14) C. A. Fetscher, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 735.
(15) M. Stiles, R. G. Miller, and U. Burkhardt, *J. Am. Chem. Soc.*, **85**, 1792 (1963); R. G. Miller and M. Stiles, *ibid.*, **85**, 1798 (1963).
(16) We are indebted to L. F. Friedman for experimental details on which this procedure is based.
(17) Except for NMR spectra in the presence of optically active shift reagents, optically active samples had the same spectral properties (ir and NMR) as racemic samples.
(18) The 1,2-dimethyl tertiary alcohol, **6-OH**, reacts much slower than the endo (**4**) or exo 2-methyl tertiary alcohols with *p*-nitrobenzoyl chloride.
(19) J. Meinwald and P. G. Gassman, *J. Am. Chem. Soc.*, **82**, 5445 (1960).

Unusual Reactivity in a Highly Substituted Olefin. The 2,2,8,8,10-Pentamethyl-1(9)-octalin System

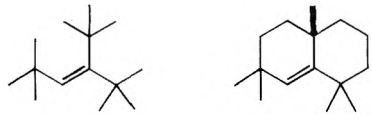
Alan R. Hochstetler

Givaudan Corporation, Clifton, New Jersey 07014

Received November 22, 1974

Epoxidation of the highly hindered octalin **2** afforded the corresponding epoxide mixture **3** and **4** in a 70:30 ratio. Attempted oxidation of the double bond with sodium dichromate or potassium permanganate gave only the cis epoxide **4**, as did ozonolysis. Hydroboration afforded the crystalline dialkyldiborane **11**, which failed to undergo normal oxidation with basic hydrogen peroxide. Borane **11** reacted smoothly in solution with molecular oxygen, affording directly the trans fused decalone **12**. High-temperature hydroboration of **2** proceeded normally to afford an 88:12 mixture of diols **9** and **10**. These experimental results are largely explicable in terms of severe steric hindrance of the double bond in **2**, and a direct comparison with the reactivity of the closely related acyclic olefin **1** is made.

Steric effects on the properties and reactivities of appropriately substituted olefins have been the subject of a number of recent investigations.[1] Syntheses of sterically hindered olefins are generally difficult to achieve, and it is only recently that a synthesis of the highly hindered olefin tri-*tert*-butylethylene (**1**) has been effected by Abruscato and Tidwell.[2] These authors have also reported on the effect of such steric hindrance on the Raman,[2] ultraviolet,[3] and ^{13}C NMR spectra,[4] and on the chemical reactivity of the double bond in **1**.[5]



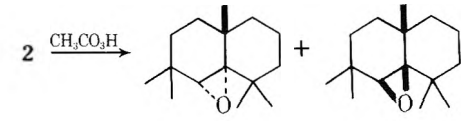
1 **2**

The influence of steric effects on the reactivity of the double bond in **1** stems both from hindrance to attack by the *tert*-butyl groups and from torsional strain at the double bond induced by relief of steric compression.[6] Separation of these two effects is not possible in such acyclic systems such as **1** but they can be largely separated if the double bond is incorporated into an appropriately substituted ring system.

During the course of a systematic investigation of the chemistry of the sesquiterpene hydrocarbon (−)-thujopsene we had previously reported the conversion of (−)-thujopsene to the optically active olefin **2**.[8] Olefin **2** possesses the same substitution pattern as **1** but differs from **1** in several important ways. The torsional angle of **1** has been calculated[7] to be 16°, which is considerably larger than the 0.5–5° reported[6a] for a number of cyclohexene skeletons. The torsional angle should be considerably less in **2**, since the nonbonded interactions giving rise to torsional strain in **1** have now become bonded interactions by incorporation into the octalin skeleton; consequently the effect on reactivity of the double bond in **2** should be principally steric hindrance alone. The octalin system also is considerably more rigid with no free rotation of the σ bonds directly attached to the double bond. Finally, the octalin system affords an analysis of the stereochemistry of the attack on the double bond since the two sides are now nonequivalent.

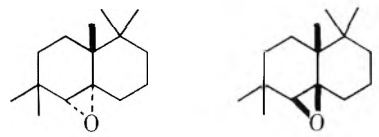
Hydrogenation of 2. Treatment of **2** with 55 psi of hydrogen over PtO_2 at 75° afforded no uptake of hydrogen and the starting material was recovered unchanged, whereas less stringent conditions were shown to effect the reduction of **1**.[5]

Epoxidation. Treatment of **2** with buffered peracetic acid proceeded normally and at a reasonable rate to afford epoxide mixture **3** (70%) and **4** (30%) in high yield. These



3 **4**

two isomers were not separable by GLC and the isomer ratio was determined by the integration of the respective epoxide proton singlets occurring at δ 2.68 for the major trans epoxide **3** and at δ 2.78 for the minor cis epoxide **4**. These stereochemical assignments can be unequivocally made from this chemical shift difference. Earlier studies have shown that in steroidal systems not containing any unsaturated functionality in proximity to the epoxide, the α-epoxide proton in 5β,6β-epoxy steroids always occurs at lower field than the β-epoxide proton in the corresponding 5α,6α-epoxy steroids.[9,10] The same chemical shift order has also been shown[8] to occur in the closely related epoxides **5** and **6**, where the trans epoxide **5** showed a one-proton singlet at δ 2.31 and the cis epoxide **6** the corresponding singlet at δ 2.60.



5 **6**

Oxidation. Attempts at oxidation of the double bond employing refluxing basic aqueous potassium permanganate[11] gave only recovered starting material. Assuming that lack of mutual solubility precluded reaction, the oxidation was then carried out with potassium permanganate in acetic acid at 25°.[12] Under these conditions no olefin **2** was recovered and a 67% yield of cis epoxide **4** was obtained. Similar results (79% yield) were also obtained when sodium dichromate in acetic acid–acetic anhydride was employed as the oxidizing agent. Within the limits of the NMR analytical method (2%) no trans epoxide **3** could be detected employing either oxidizing agent. No evidence was obtained for any rearranged products under either of the above conditions.

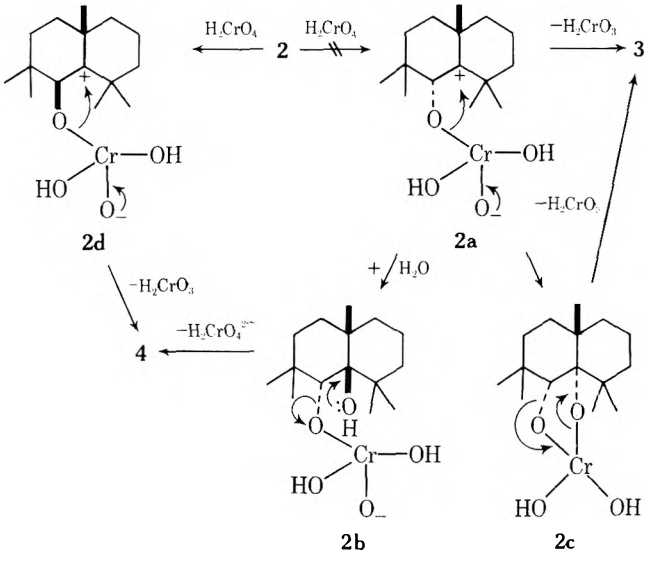
Epoxide formation under such conditions is not new. The tetraarylethylenes have been shown to form good yields of the corresponding epoxide with either reagent,[12,13] with stereoisomeric epoxides formed from unsymmetrically substituted tetraarylethylenes.[13] In the present case only one stereoisomer is found with either reagent.

Irrespective of the exact mechanistic nature of peracid epoxidations, whether via a concerted mechanism[14] or via a

1,3-dipolar addition reaction,[15] in molecules containing no other functionality peracids preferentially attack olefinic double bonds from the least hindered side. In the case of olefin **2** this least hindered side must be the α face, since the major epoxide **3** possesses the trans ring fusion.

Little is known concerning the detailed mechanism of the oxidation of alkenes.[13] Allylic oxidation[16] cannot occur on olefin **2**, since no allylic hydrogens are available for abstraction. Direct attack of the chromium(VI) species from the apparently least hindered α face of olefin **2** would lead to an intermediate species such as structure **2a** in Scheme I. Although β-face addition of water to give **2b** followed by

Scheme I



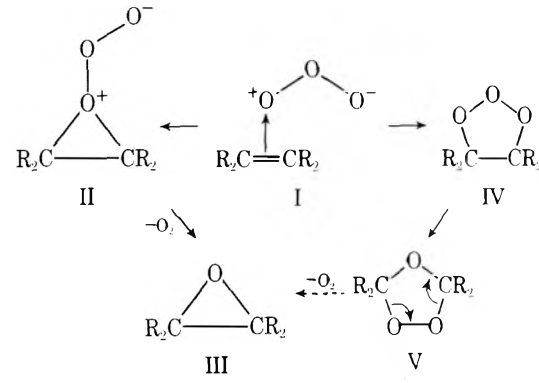
internal nucleophilic displacement[13] of the chromium(IV) species would afford the observed cis epoxide **4**, this mechanism cannot be operative here, since similar results were obtained with anhydrous sodium chromate and with potassium permanganate in an anhydrous reaction mixture. Alternate decomposition of intermediate **2a** directly or via cyclic intermediate **2c** would lead to the trans epoxide **3**, which is not observed, as the product. Consequently, the preferred attack of the oxidizing agent must be from the apparently more hindered β face via the intermediate **2d** (or its cyclic five-membered ring counterpart) with the oxidizing agent cis to the angular methyl group. Decomposition of this intermediate then leads to the observed cis epoxide **4**.

A similar mechanism can also be advanced to explain the identical stereochemical outcome when potassium permanganate in acetic acid is employed.

The nature of the transition state for epoxide formation under these conditions is unknown. Clearly this transition state does not resemble the reactant-like transition state of the peracid epoxidation or a predominance of the trans epoxide **3** would have been found.

Ozonolysis. Ozonolysis of **2** at 0° in ethylene dichloride afforded the cis epoxide **4** in 70% isolated yield. Detailed analysis of the NMR spectrum showed that only 3% of the trans epoxide **3** was present.

Numerous examples are found in the literature of the formation of epoxides during the ozonolysis of olefins.[17] These epoxides, termed partial cleavage products,[18] generally are found when there is considerable steric hindrance to the double bond. Recent work has indicated that in the ozonolysis reaction an initial π complex I is formed.[19] As the bulk of the R groups increases, 1,3-dipolar cycloaddition to give the normal initial ozonide (1,2,3-trioxalane IV) becomes unfavorable and collapse to the σ complex II occurs instead.[18,20] Loss of molecular oxygen from II then affords the partial cleavage product, epoxide III.



The above mechanism, although accounting for epoxide formation from hindered olefins, is difficult to reconcile with the observed cis ring fusion of the major epoxide **4** obtained by ozonolysis of **2** unless the attack of ozone is exclusively from the apparent more hindered β face of olefin **2**. Decomposition of σ complex II would not be expected to alter the stereochemistry of initial attack on the double bond.

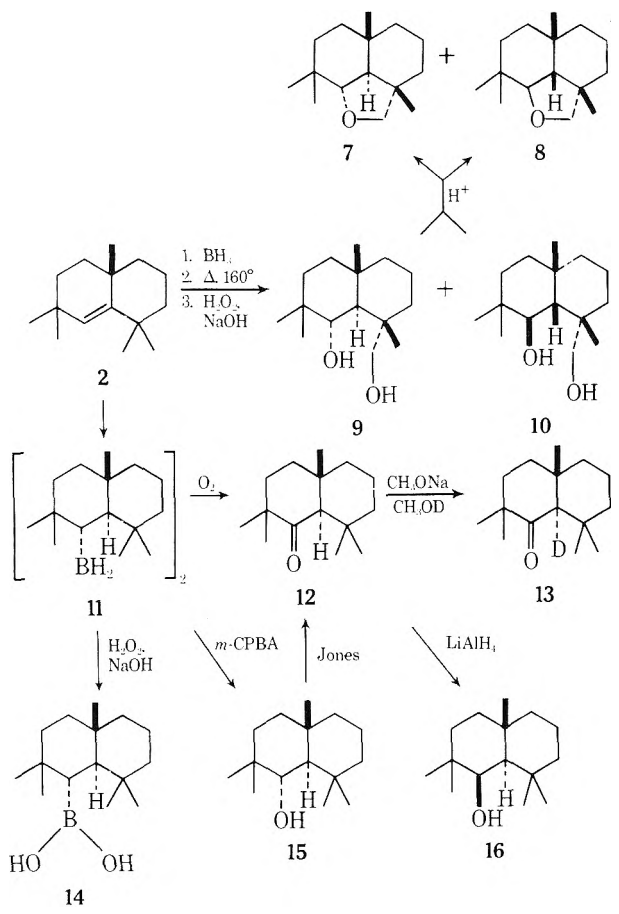
An alternate explanation would involve formation of the 1,2,4-trioxalane V from the initial ozonide IV, with the single oxygen on the more hindered face cis to the angular methyl group of **4** and the peroxy bridge on the less hindered trans face. Loss of oxygen from the peroxy bridge would then afford the observed cis stereochemistry of **4**. This explanation is unlikely for two reasons. First, steric considerations argue against the initial formation of the ozonide IV from either face. Second, no loss of oxygen to give epoxides has ever been observed from ozonide structures such as V.[18]

Epoxide **4** cannot be produced in the course of the ozonolysis reaction by some peroxidic ozonolysis product. This peroxidic product presumably would afford the same stereochemical outcome as the peracetic acid epoxidation which affords principally the trans epoxide **3**.

No information is available on the nature of the transition state which leads to epoxides upon ozonolysis of hindered olefins. If this transition state appears reactant-like the product distribution should reflect that found in the peracetic acid epoxidation. If the transition state appears product-like then no particular distribution can be predicted, since the relative stabilities of epoxides **3** and **4** are not known. On the basis of present evidence we cannot assign a mechanistic rationale completely consonant with these ozonolysis results.

Our results differ significantly from those reported for the ozonolysis products of tri-*tert*-butylethylene (**1**), where normal cleavage products were obtained and no epoxide formation was noted.[5] Analysis of our crude ozonolysis mixture by VPC showed only traces of three minor components at the retention time expected for the keto aldehyde normal ozonolysis product.

Hydroboration. In contrast to the relative ease of epoxidation of **2**, hydroboration proceeded quite slowly so that extended reaction times were necessary to avoid recovery of sizable amounts of starting material. Reactions run at room temperature for 20 hr generally afforded 85–90% reaction. In all cases a white precipitate was found in the reaction mixture and in one case was carefully filtered under nitrogen from the tetrahydrofuran solvent. Spectral data clearly showed a simple B–H stretching frequency at 2495 cm^{-1} and a strong band at 1570 cm^{-1} for the diborane



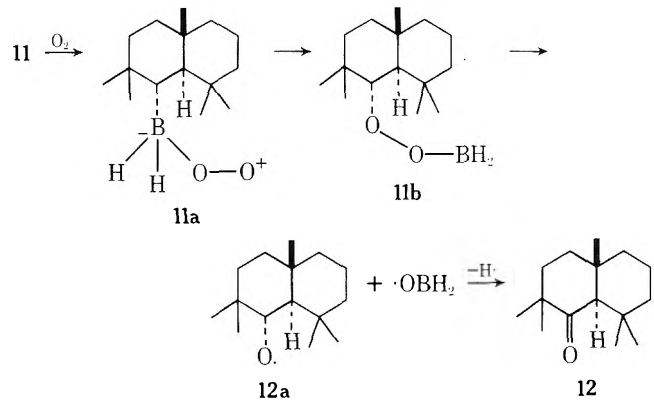
hydrogen bridge.[21] These data indicate that the precipitate is the *sym*-dialkyldiborane **11**. We will discuss later the trans ring fusion stereochemistry assigned to the dimer **11**.

Normal alkaline hydrogen peroxide oxidation[22] of the hydroboration mixture containing **11** afforded no expected secondary alcohol **15** but rather the alkyl boronic acid **14**, the simple hydrolysis product of dialkyldiborane **11**. To our knowledge this is the first report of an alkylborane obtained in a hydroboration reaction which fails to oxidize under the above conditions. The failure must be due to excessive steric hindrance to attack of the hydroperoxide anion on the boron atom to afford the necessary tetrahedral boron intermediate. Attempts at direct oxidation of **11** to ketone **12** with aqueous chromic acid[23] also failed; the sole product obtained was again the boronic acid **14**.

Oxidation to the desired alcohol **15** was finally achieved by the use of the more effective oxidizing agent *m*-chloroperbenzoic acid.[24] The trans ring fusion was assigned from the NMR spectrum, which showed a coupling constant of 11 Hz for the α hydrogen, as expected for the trans diaxial coupling of decalol **15**. Jones oxidation of decalol **15** afforded the corresponding trans ketone **12**.

Ketone **12** was also formed directly from borane **11** by direct oxidation with molecular oxygen; no evidence was obtained for the formation of decalol **15** or of the corresponding hydroperoxide.[25] The mechanism of formation of ketone **12** is not entirely clear. We have already noted that borane **11** does not undergo the normal rearrangement reactions with alkaline hydrogen peroxide, thus rendering tenable the proposal[26] that, in systems where ionic attack may not be favored, radical reactions become more important. Although we fail to observe any ketone **12** or decalol **15** under the alkaline hydrogen peroxide oxidation conditions, radical reactions may indeed be the mode of formation of **12** in the reaction with molecular oxygen. In the present case this reaction may proceed by coordination of the oxygen molecule to the boron atom of the highly hindered borane **11**, followed by a migration of the alkyl group from boron to oxygen[27] as outlined in Scheme II. Radical

Scheme II



decomposition of the intermediate peroxide **11b** would generate radical **12a**, which by loss of a hydrogen radical would afford the observed ketone **12**.[28] Borane **11** must be the precursor of the intermediate peroxide **11b**; subjection of pure boronic acid **14** under the reaction conditions afforded no ketone **12** and **14** was recovered unchanged.

The trans ring fusion stereochemistry of optically active decalone **12** was unambiguously determined by analysis of the ORD curve, which showed a strong negative Cotton effect. The absolute sterochemistry at the chiral angular methyl center in octalin **2** is known[8] to be as shown and none of the reactions leading to decalone **12** have involved that center. Application of the octant rule[29] in the present case clearly predicts a negative Cotton effect for the trans-fused decalone **12**, whereas a positive Cotton effect would be predicted for the corresponding cis-fused isomer, whether in the steroid or the nonsteroid conformation.

Additional confirmation for the trans ring fusion of **12** was provided by equilibration experiments. Ketone **12** was recovered unchanged upon basic treatment. The possibility that no enolization had occurred was disproved by the incorporation of one deuterium atom upon equilibration in basic CH_3OD solution, and the loss of the one-proton singlet at δ 2.33 in the NMR spectrum of the deuterated ketone **13**.

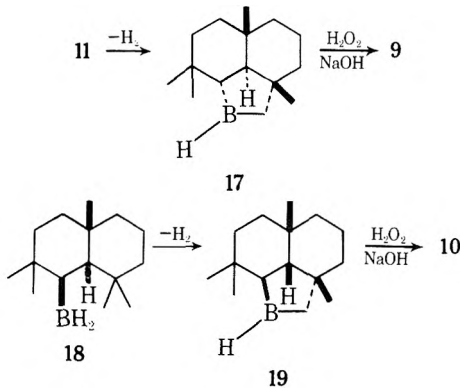
Lithium aluminum hydride reduction of **12** afforded a secondary alcohol **16** different from the hydroboration–oxidation alcohol **15**, as expected from reduction of the least hindered α face of the carbonyl group. The NMR spectrum showed a doublet for the α proton with a coupling constant of 4 Hz, as expected for the axial–equatorial relationship of the C-1 and C-9 protons in **16**.

No evidence had been obtained thus far on the presence of any products obtainable from initial hydroboration of **2** from the β face leading to the cis ring fusion. Inspection of molecular models revealed a close proximity of the boron atom in **11** to the α-methyl group at C-8, and the same proximity in the steroid conformation of the corresponding alkylborane derived from β-face attack. Heating of the hydroboration mixture to 160° in diglyme, followed by normal alkaline hydrogen peroxide treatment, afforded in good yield the crystalline diol **9** as the major product. All attempts at isolation and purification of the minor diol **10** failed.

Evidence for the presence of diol **10** was obtained by acid-catalyzed cyclization of the crude diol mixture above to an 88:12 mixture of isomeric ethers. These were separated by column chromatography and afforded spectral

data consistent with the assigned structures of 7 for the major ether and 8 for the minor ether.

Diol 9 thus arises from oxidation of internal dialkylborane 17, in turn formed by loss of the elements of hydrogen from 11. Similarly, diol 10 is formed by oxidation of 19[31]



derived from 18. Such cyclizations of alkylboranes have been well documented[5,30] in other systems where a δ hydrogen is appropriately oriented with respect to the boron atom.

It is interesting to note that no difficulty was encountered in the alkaline hydrogen peroxide oxidation of the dialkylborane mixture 17 and 19 to the respective diols 9 and 10, whereas alkylborane 11 fails to oxidize under these conditions. This result is reasonably explained by the reduced steric interactions to attack at the boron atom in 17 and 19, since the former nonbonded interaction from the α-methyl group at C-8 in 11 now has been minimized by bond formation to the boron atom.

In the case of olefin 2 we have already shown that epoxidation occurs principally (70%) from the less hindered α face. The hydroboration results also indicate that the α face is preferred (88%) in that reaction to an even greater extent. These observations are in general agreement with earlier studies showing only slight differences in the stereochemical outcome of epoxidation as compared to hydroboration on the same molecule.[32]

Finally, our results differ from the reported[5] hydroboration–oxidation of tri-*tert*-butylethylene (1). For olefin 1 no crystalline alkylborane could be isolated, and normal alkaline hydrogen peroxide treatment of the alkylborane gave a mixture of the corresponding secondary alcohol, the ketone derived from this alcohol, and the corresponding tetrahydrofuran ether. The ether may arise from cyclization of the diol derived from the internal dialkylborane, which in the case of 1 is formed at 25°. For olefin 2, however, this low temperature is not sufficient to form intermediates 17 and 19, which are only obtained by refluxing in diglyme (160°). In the case of olefin 2 diol 9 could readily be isolated, whereas no diol could be isolated from olefin 1 owing to facile cyclization to the tetrahydrofuran ether.

Experimental Section[33]

(*S*)-2,2,8,8,10-Pentamethyl-1(9)-octalin (2). This octalin was prepared as previously described from (−)-thujopsene.[8]

Epoxidation of 2. To a mixture of octalin 2 (15.0 g, 73 mmol), ethylene dichloride (30 ml), and sodium carbonate (7 g) was added 40% peracetic acid (25 g, 131 mmol) at 30° over 10 min. After an additional 3 hr at 40°, water (60 ml) was added and the layers were separated. The organic phase was washed once with sodium carbonate solution and the solvent was removed under reduced pressure. Distillation afforded 14.2 g (88%) of a colorless oil: bp 74–76° (0.5 mm); n^{20}D 1.4784; $[\alpha]^{25}$D +37.5° (neat); ir (liquid film) 1028, 1020, 960, 31, 919, 830 cm^{-1}; NMR ($CDCl_3$) δ 0.73, 1.01, 1.04, 1.11, 1.18, (s, 3 each), 2.68 (s, 1, from major isomer 3), 2.78 (s, 1, from minor isomer 4); mass spectrum *m/e* (rel intensity) 222 (M^+, 14), 207 (13), 140 (52), 123 (53), 95 (41), 81 (73), 69 (66), 55 (55), 43 (63), 41 (100). No separation could be achieved by gas chromatography. Integration of the proton singlets at δ 2.78 and 2.68 showed a mixture of 30% epoxide 4 and 70% of *trans*-1(*R*),9(*S*)-epoxy-2,2,8,8,10(*S*)-pentamethyldecalin (3).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.10; H, 11.84.

Oxidation of 2. A. Aqueous Potassium Permanganate. A mixture of olefin 2 (10.3 g, 50 mmol), water (200 ml), potassium hydroxide (1 g), and potassium permanganate (37 g) was heated at reflux for 6 hr.[11] The mixture was cooled, filtered, and extracted with hexane. The solvent was removed under reduced pressure, affording 10.0 of material with an ir spectrum identical with that of starting olefin 2.

B. Potassium Permanganate–Acetic Acid. A mixture of olefin 2 (10.3 g, 50 mmol), acetic acid (250 ml), and potassium permanganate (27 g) was stirred at 25° with slight cooling for 4 hr.[12] The mixture was then filtered and water (750 ml) was added. The mixture was extracted with hexane and the solvent was removed under reduced pressure. Distillation afforded 7.4 g (67%) of *cis*-1(*S*),9(*R*)-epoxy-2,2,8,8,10(*S*)-pentamethyldecalin (4); bp 71–72° (0.5 mm); n^{20}D 1.4785; $[\alpha]^{25}$D +25° (neat); ir (liquid film) 1018, 958, 930, 918, 852, 649 cm^{-1}; NMR ($CDCl_3$) δ 0.80, 1.10 (s, 3 each), 1.00 (s, 9), 2.78 (s, 1); mass spectrum *m/e* (rel intensity) 222 (M^+, 8), 140 (28), 125 (31), 123 (45), 95 (33), 81 (57), 69 (57), 67 (26), 55 (49), 43 (64), 43 (64), 41 (100). No absorption at δ 2.68 in the NMR spectrum for the one-proton singlet of epoxide 3 was detectable.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.11; H, 11.70.

C. Sodium Dichromate. To a solution of olefin 2 (9.0 g, 43.7 mmol), acetic acid (20 ml), and acetic anhydride (60 ml) was added sodium dichromate dihydrate (26 g) portionwise at 30° over 0.5 hr. After stirring at 40° for 3 hr, the solution was poured into water (150 ml) and extracted with benzene. The combined organic extracts were washed with sodium carbonate solution and the solvent was removed under reduced pressure. Distillation afforded 7.6 g (79%) of epoxide 4 which exhibited spectral data identical with those of the epoxide obtained in part B above.

Similar results, although at a slower rate, were obtained when anhydrous sodium chromate was employed.

Ozonolysis of 2. A solution of olefin 2 (10.3 g, 50 mmol) in ethylene dichloride (100 ml) was ozonized at 0° for 4 hr. The ozonolysis mixture was then added to a suspension of zinc dust (10 g) in 10% aqueous acetic acid (100 ml) and heated to 75° for 1 hr. The mixture was cooled and extracted with ethylene dichloride. After removal of the solvent under reduced pressure, the residue was analyzed by VPC and found to contain no olefin 2, epoxide 4 (92%), and three minor components (total of 8%) at much longer retention times. Distillation of this residue afforded 7.8 g (71%) of epoxide 4 which exhibited spectral characteristics identical with those of the epoxide 4 obtained from the oxidation above. Detailed analysis of the NMR spectrum showed the presence of 3% of the isomeric epoxide 3.

Hydroboration of 2. A. Dialkyldiborane 11. A solution of olefin 2 (5.1 g, 25 mmol) and 25 ml (25 mmol) of 1 *M* diborane in tetrahydrofuran solution was allowed to stir under nitrogen at 25° for 20 hr. The resultant precipitate was carefully filtered under nitrogen, affording 1.6 g (34%) of dialkyldiborane 11 which exhibited the following properties: mp 120–122° dec; ir (KBr) 2495 (B–H), 1570 (BH_2B bridge), 1186, 1074, 777 cm^{-1}; NMR ($CDCl_3$) δ 0.80, 0.85 (s, 3 each), 0.96 (s, 9); mass spectrum *m/e* (rel intensity) 221 (1), 206 (7), 191 (32), 121 (18), 95 (37), 69 (19), 58 (27), 43 (100), 41 (29).

Anal. Calcd for $C_{30}H_{58}B_2$: C, 81.79; H, 13.30; B, 4.91. Found: C, 79.66; H, 13.16; B, 5.02.

A satisfactory carbon analysis could not be obtained. These crystals proved to be stable in air, but reacted rapidly with molecular oxygen in solution (see part D below).

B. Alkylboronic Acid 14. A solution of olefin 2 (10.3 g, 50 mmol) and 50 ml (50 mmol) of 1 *M* diborane in tetrahydrofuran solution was stirred under nitrogen at 25° for 20 hr. The mixture was cooled and carefully treated with water (5 ml), followed by 10% aqueous sodium hydroxide (30 ml) and 35% hydrogen peroxide (25 ml). The mixture was allowed to stir at 40° for 4 hr and then was thoroughly extracted with hexane. The solvent was removed under reduced pressure, affording 12 g of crude solid, mp 126–130°. This solid was recrystallized from hexane, affording 9.1 g (72%) of boronic acid 14: mp 145–146°; $[\alpha]^{25}$D +18° (c 0.05, $CHCl_3$); ir (KBr) 3300 (OH), 1315, 1020, 765 cm^{-1}; NMR ($CDCl_3$) δ 0.88, 0.92, 1.08 (s, 3 each), 0.96 (s, 6), 4.52 (s, 2); mass spectrum

m/e (rel intensity) 252 (M^+, 31), 237 (62), 153 (44), 123 (29), 109 (30), 95 (68), 81 (54), 69 (93), 55 (80), 43 (43), 41 (100).

Anal. Calcd for $C_{15}H_{29}BO_2$: C, 71.44; H, 11.59; B, 4.29. Found: C, 71.16; H, 11.60; B, 4.53.

An attempt to oxidize the crude hydroboration mixture with an acid solution of sodium dichromate[22] again afforded only the boronic acid **14**.

These crystals of boronic acid **14** were stable to oxygen in ether solvents.

C. 2,2,8,8,10(*S*)-Pentamethyl-*trans*-decal-*trans*-1(*S*)-ol (15). A solution of olefin **2** (10.3 g, 50 mmol) and 50 ml (50 mmol) of 1 *M* diborane in tetrahydrofuran solution was stirred under nitrogen at 25° for 22 hr. To this mixture was added a solution of 85% *m*-chloroperbenzoic acid (31 g, 150 mmol) in chloroform (175 ml) at 35° over 0.5 hr. After an additional 1 hr at 35° the mixture was cooled and treated with 30% aqueous sodium hydroxide (50 ml). The organic phase was washed neutral with water and the solvent was removed under reduced pressure. Distillation afforded 6.8 g (61%) of an 11:89 mixture of two peaks by vpc. The minor peak was identical with a 70:30 mixture of epoxides **3** and **4** (by epoxidation of unreacted **2**). A sample of the major isomer (**15**) was purified by preparative gas chromatography and exhibited the following characteristics: mp 42–44°; $[\alpha]^{25}D$ +2.5° (c 20%, $CHCl_3$); ir (liquid film) 3570 (OH), 1075, 1020, 977 cm^{-1}; NMR ($CDCl_3$) δ 0.91, 0.96, 1.13 (s, 3 each), 1.02 (s, 6), 3.61 (d, J = 11 Hz, 1).

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 79.94; H, 12.59.

D. (*S*)-2,2,8,8,10-Pentamethyl-*trans*-1-decalone (12). A solution of olefin **2** (15.3 g, 75 mmol) and 75 ml (75 mmol) of 1 *M* diborane in tetrahydrofuran solution was stirred under nitrogen at 25° for 17 hr. The nitrogen purge line was removed and connected to an oxygen tank and a slow stream of oxygen was passed into the solution. The temperature rose to 45° in 0.5 hr, at which point the precipitate (alkylborane **11**) initially present had all dissolved. After an additional 1.5 hr the temperature began to drop and the solution cooled to room temperature. Oxygen feed was continued for an additional 1.0 hr. Water (80 ml) was then added and the mixture was extracted with hexane. The solvent was removed under reduced pressure and afforded 16 g of residue. The ir spectrum showed a sizable carbonyl absorption. This residue was chromatographed on 200 g of silica. Elution with hexane afforded 3.4 g of recovered unreacted olefin **2**. Continued elution with 0.5% ether in hexane gave 5.1 g (40%) of decalone **12** which exhibited the following characteristics: bp 72–74° (0.5 mm); mp 29–30°; $n^{20}D$ 1.4840; $[\alpha]^{25}D$ −63° (neat); ir (liquid film) 1703 (C=O), 1081, 970, 951, 843 cm^{-1}; NMR ($CDCl_3$) δ 0.87, 0.92, 1.01, 1.17, 1.21 (s, 3 each), 2.33 (s, 1); NMR (C_6H_6) δ 0.68, 1.00, 1.02, 1.05, 1.32 (s, 3 each), 2.20 (s, 1); mass spectrum *m/e* (rel intensity) 222 (M^+, 3), 207 (11), 151 (100), 123 (18), 82 (15), 69 (15), 67 (15), 55 (14), 43 (14), 41 (27); CD (*c* 0.0140, dioxane) θ_{337} 0, θ_{310} −10,690, θ_{306} −10,120, θ_{301} −10,477, θ_{235} 0; ORD ϕ_{326} −6557°, ϕ_{319} −4561°, ϕ_{315} −4707°, ϕ_{305} 0°, ϕ_{280} +6058°.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.24; H, 11.79.

Elution with 10% ether in hexane afforded 3.9 g (27%) of alkylbornic acid **14** which was identical with the same material isolated in part B above.

Oxidation of 2,2,8,8,10(*S*)-Pentamethyl-*trans*-decal-*trans*-1(*S*)-ol (15). The standard Jones oxidation procedure[34] was employed on 2.8 g (12.5 mmol) of decalol **15**. Short-path distillation afforded 2.4 g (86%) of decalone **12** which was identical with the same material isolated in part D above.

9-Deuterio-2,2,8,8,10(*S*)-Pentamethyl-*trans*-1-decalone (13). A solution of ketone **12** (120 mg, 5.4 mmol) and 5 ml (5 mmol) of 1 *M* sodium methoxide in methanol-*O*-*d* was allowed to reflux under nitrogen for 18 hr. The solution was cooled and hexane (15 ml) was added. The organic layer was separated and washed neutral with water. The solvent was removed under reduced pressure and the residue was distilled, affording 110 mg (92%) of decalone **13**: bp 70–75° (0.5 mm); ir (liquid film) 2120 (C–D), 1703 (C=O), 1290, 1178, 1110, 1025, 993, 958, 912, 830 cm^{-1}; NMR ($CDCl_3$) δ 0.87, 0.91, 1.00, 1.16, 1.20 (s, 3 each; mass spectrum *m/e* (rel intensity) 223 (M^+, 8), 208 (5), 151 (100), 123 (18), 69 (17), 55 (11), 41 (19).

Identical treatment of ketone **12** with sodium methoxide in methanol gave only recovered starting material.

2,2,8,8,10(*S*)-Pentamethyl-*trans*-decal-*cis*-1(*R*)-ol (16). Under a nitrogen atmosphere was charged lithium aluminum hydride (200 mg, 5 mmol) and anhydrous ether (20 ml). Ketone **12** (1.1 g, 5 mmol) dissolved in ether (5 ml) was then added over 5 min and the mixture was allowed to reflux for 0.5 hr. The mixture was cooled and water (0.4 ml) was carefully added, followed by 10% aqueous sodium hydroxide (0.4 ml). After an additional 2 hr the mixture was filtered and the solvent was removed under reduced pressure. The residue was distilled, affording 1.05 g (94%) of decalol **16** contaminated (by VPC) with 5% of the isomeric decalol **15**: bp 80–85° (0.5 mm); $n^{20}D$ 1.4919; $[\alpha]^{25}D$ +19° (neat); ir (liquid film) 3730 (nonbonded OH), 3570 (bonded OH), 1085, 1032, 1020, 985, 968, cm^{-1}; NMR ($CDCl_3$) δ 0.92 (s, 3), 0.95, 1.23 (s, 6 each), 3.66 (d, J = 4 Hz, 1).

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.29; H, 12.55.

8(*S*)-Hydroxymethyl-2,2,8,10(*S*)-tetramethyl-*trans*-decal-*trans*-1(*S*)-ol (9). A solution of olefin **2** (15.3 g, 75 mmol) and 75 ml (75 mmol) of a 1 *M* solution of diborane in tetrahydrofuran was stirred under nitrogen at 25° for 18 hr. Anhydrous diglyme (75 ml) was then added and the tetrahydrofuran was removed by distillation. The solution was then heated at 160° for 3 hr. The solution was cooled, and water (5 ml) was carefully added, followed by 10% aqueous sodium hydroxide (35 ml) and 35% hydrogen peroxide (35 ml). After stirring for 2 hr at 30° the mixture was filtered. Water (250 ml) was added and the mixture was well extracted with hexane. The hexane extracts were washed with water and the solvent was removed under reduced pressure. Crystallization of the residue from hexane afforded 10.6 g (59%) of diol **9**: mp 148–150°; $[\alpha]^{25}D$ +7° (c 0.1, $CHCl_3$); ir (KBr) 3230 (OH), 1060, 1030, 1008 cm^{-1}; ir (KBr) 3230 (OH), 1060, 1030, 1008 cm^{-1}; NMR ($CDCl_3$) δ 0.91, 1.01, 1.14, 1.26 (s, 3 each), 3.45 (d, J = 10.5 Hz, 1), 2.94, 3.73 (AB, J = 11.5 Hz, 2), 3.85 (s, 1, OH); mass spectrum *m/e* (rel intensity) 222 (M − 18, 1), 109 (35), 95 (26), 81 (38), 67 (35), 55 (60), 43 (66), 41 (100).

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.08; H, 11.99.

Chromatography of the crystallization residue on silica did not separate the minor diol **10** from the remaining major diol **9**.

2aβ,5aβ,8,8-Tetramethyl-8aβH,8bαH-decahydronaphtho[1,8-*bc*]furan (7). A sample of diol **9** (5.0 g, 20.8 mmol), *p*-toluenesulfonic acid (0.8 g), and benzene (100 ml) was allowed to reflux with a water separator for 2.5 hr. The cooled solution was washed once with sodium bicarbonate solution and the solvent was removed under reduced pressure. Distillation of the residue afforded 4.2 g (91%) of ether **7**: by 70–72° (0.3 mm); $n^{20}D$ 1.4872; $[\alpha]^{25}D$ +27° (neat); ir (liquid film) 1070, 1049, 1039, 971 cm^{-1}; NMR ($CDCl_3$) δ 0.87, 1.01, 1.07, 1.14 (s, 3 each), 3.67 (d, J = 11.5 Hz, 1), 3.47, 3.53 (AB, J = 8 Hz, 2); mass spectrum *m/e* (rel intensity) 222 (M^+, 22), 208 (15), 151 (100), 123 (39), 109 (68), 95 (68), 81 (58), 67 (40), 55 (54), 43 (50), 41 (77).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.94; H, 12.05.

2aβ,5aβ,8,8,-Tetramethyl-8aαH,8bβH-decahydronaphtho-[1,8-*bc*]furan (8). A sample (4.5 g) of the mother liquors from crystallization of diol **9** was treated as above with *p*-toluenesulfonic acid (0.7 g) in benzene (90 ml). The isolated crude mixture (4 g) was chromatographed on 60 g of silica. Early fractions eluted with 5% ether in hexane afforded a pure sample of the ether **7** described above. Continued elution with 5% ether in hexane afforded a pure sample of ether **8**. After recrystallization from hexane at 0°, ether **8** exhibited the following properties: mp 84–86°; $[\alpha]^{25}D$ +2.5° (c 0.1, $CHCl_3$); ir (KBr) 1030, 995, 933, 923, 852, 800 cm^{-1}; NMR ($CDCl_3$) δ 0.89, 0.92 (s, 3), 1.05 (s, 6), 3.28, 3.48 (AB, J = 7.5 Hz, 2), 3.61 (d, J = 9 Hz, 1); mass spectrum *m/e* (rel intensity) 222 (M^+, 10), 207 (12), 177 (29), 151 (100), 109 (22), 95 (33), 81 (23), 55 (26), 41 (36).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.98; H, 12.01.

Determination of the Ratio of Ethers 7 and 8 from the High-Temperature Hydroboration of 2. The hydroboration procedure outlined above for the isolation of diol **9** was run on one-tenth the scale. The crude product was then treated with *p*-toluenesulfonic acid (0.1 g) in benzene (25 ml) at reflux with a water separator for 3.0 hr. The cooled solution was washed with sodium bicarbonate solution and the solvent was removed under reduced pressure. Distillation of the residue afforded 1.40 g of mobile oil, bp 70–75° (0.3 mm). Analysis by VPC showed two components, identified as ether **7** (88%) and ether **8** (12%). The hydroboration reaction thus occurs principally from the α face of olefin **2**.

Reduction of 2. A sample of olefin **2** (20.6 g, 0.1 mol), acetic acid (90 g), and platinum oxide (200 mg) was charged into a Parr shaker and heated at 75° under 55 lb of hydrogen pressure for 3 hr. No hydrogen uptake was observed during this time. The mixture was cooled and filtered, then added to water (200 ml) and well extract-

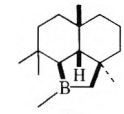
ed with hexane. The organic extracts were washed with sodium bicarbonate solution and the solvent was removed under reduced pressure, affording 20.5 g of recovered olefin **2**.

Acknowledgment. The author wishes to thank Mr. C. Dmochowski and Mrs. A. Cerasia for their able technical assistance during the course of the above investigation.

Registry No.—**2**, 32540-36-6; **3**, 54689-00-8; **4**, 54713-02-9; **7**, 54689-01-9; **8**, 54713-03-0; **9**, 54689-02-0; **11**, 54724-65-1; **12**, 54689-03-1; **13**, 54713-04-1; **14**, 54689-04-2; **15**, 54689-05-3; **16**, 54689-06-4; peracetic acid, 79-21-0; potassium permanganate, 7722-64-7; sodium dichromate, 10588-01-9; diborane, 19287-45-7; *m*-chloroperbenzoic acid, 937-14-4.

References and Notes

(1) C. L. Dean, D. G. Garratt, T. T. Tidwell, and G. H. Schmid, *J. Am. Chem. Soc.*, **96**, 4958 (1974), and references cited therein.
(2) G. J. Abruscato and T. T. Tidwell, *J. Am. Chem. Soc.*, **92**, 4125 (1970).
(3) G. J. Abruscato, R. G. Binder, and T. T. Tidwell, *J. Org. Chem.*, **37**, 1787 (1972).
(4) G. J. Abruscato, P. D. Ellis, and T. T. Tidwell, *J. Chem. Soc., Chem. Commun.*, 988 (1972).
(5) G. J. Abruscato and T. T. Tidwell, *J. Org. Chem.*, **37**, 4151 (1972).
(6) (a) W. L. Mock, *Tetrahedron Lett.* 475 (1972), and references cited therein; (b) O. Ermer and S. Lifson, *J. Am. Chem. Soc.*, **95**, 4121 (1973).
(7) O. Ermer and S. Lifson, *Tetrahedron*, **30**, 2425 (1974).
(8) A. R. Hochstetler, *J. Org. Chem.*, **39**, 1400 (1974).
(9) A. D. Cross, *J. Am. Chem. Soc.*, **84**, 3206 (1962).
(10) K. Janowski and J. Y. Daigle, *Synthesis*, 32 (1971).
(11) P. D. Bartlett, G. L. Fraser, and R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 495 (1941).
(12) J. G. Keppler, *Recl. Trav. Chim. Pays-Bas*, **76**, 49 (1957).
(13) K. B. Wiberg in "Oxidation in Organic Chemistry", Part A, K. B. Wiberg, Ed., Academic Press, New York, N.Y., 1965.
(14) (a) P. D. Bartlett, *Rec. Chem. Prog.*, **11**, 51 (1950); (b) K. D. Bingham, G. D. Meakins, and G. H. Whitham, *Chem. Commun.*, 445 (1966).
(15) H. Kwart and D. M. Hoffmann, *J. Org. Chem.*, **31**, 419 (1966).
(16) K. B. Wiberg and S. D. Nelson, *J. Org. Chem.*, **29**, 3353 (1964).
(17) P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).
(18) P. S. Bailey and A. G. Lane, *J. Am. Chem. Soc.*, **89**, 4473 (1967).
(19) P. S. Bailey, J. W. Ward, and R. E. Hornish, *J. Am. Chem. Soc.*, **93**, 3552 (1971).
(20) P. R. Story, R. W. Murray, and R. D. Youssefyeh, *J. Am. Chem. Soc.*, **88**, 3144 (1966).
(21) H. C. Brown in "Hydroboration", W. A. Benjamin, New York, N.Y., 1962, pp 178–190.
(22) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **81**, 6423 (1959).
(23) H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2951 (1961).
(24) J. R. Johnson and M. G. Van Campen, Jr., *J. Am. Chem. Soc.*, **60**, 121 (1938).
(25) H. C. Brown and M. M. Midland, *J. Am. Chem. Soc.*, **93**, 4078 (1971).
(26) D. J. Pasto, S. K. Arora, and J. Chow, *Tetrahedron*, **25**, 1571 (1969).
(27) A. G. Davies and R. B. Moodie, *Chem. Ind. (London)*, 1622 (1957).
(28) S. B. Mirviss, *J. Am. Chem. Soc.*, **83**, 3051 (1961).
(29) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).
(30) (a) H. C. Brown, K. J. Murray, H. Müller, and G. Zweifel, *J. Am. Chem. Soc.*, **88**, 1443 (1966); (b) T. J. Logan and T. J. Flautt, *ibid.*, **82**, 3446 (1960); (c) A. R. Hochstetler, *J. Org. Chem.*, **37**, 1883 (1972).
(31) An alternate structure i for internal dialkylborane **19** is highly unlikely, since both rings must adopt a boat conformation for i to form.



i

(32) D. J. Pasto and F. M. Klein, *J. Org. Chem.*, **33**, 1468 (1968).
(33) Melting points were determined on a Hoover capillary melting point apparatus and are uncorrected. Spectra were recorded on a Perkin-Elmer 457 grating ir spectrophotometer, a Varian A-60A NMR spectrometer, and a Perkin-Elmer 270 double-focusing mass spectrometer at 70 eV. ORD and CD measurements were performed using a Jasco ORD/UV-5 spectropolarimeter with CD attachment for optical rotation measurements. Gas chromatography was carried out on an F & M 720 instrument equipped with a 2 m × 0.25 in. copper column packed with 15% Carbowax 20M on Chromosorb P with helium as the carrier gas. Combustion analyses were determined by Instranal Laboratory Inc., Rensselaer, N.Y.
(34) K. Bowden, I. M. Heilbron, E. H. R. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

Addition of Aryl Nitrenes to Olefins[1]

Rudolph A. Abramovitch,* Stanley R. Challand, and Yorinobu Yamada

Department of Chemistry, University of Alabama, University, Alabama 35486

Received January 16, 1975

Pentafluoronitrosobenzene undergoes an "ene"-type reaction with a variety of olefins. When triethyl phosphite is added to the olefin *before* the addition of the nitroso compound (inverse addition), pentafluorophenylnitrene is formed which adds stereospecifically to a number of olefins to give the corresponding aziridines. The possibility of a 1,3-dipolar addition of the nitrene precursor followed by elimination of triethyl phosphate has been discounted. Pentafluorophenylnitrene, generated photochemically from the azide, behaves analogously, but thermal decomposition of the azide in the presence of olefins gives products arising from an initial 1,3-dipolar adduct. 4-Azidotetrachloropyridine behaves similarly but the derived nitrene is less electrophilic.

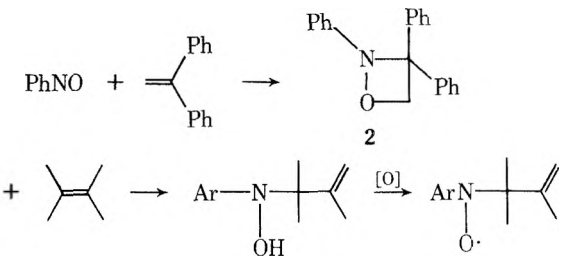
Authenticated examples of the addition of thermally generated discrete nitrenes to olefinic bonds to give aziridines have appeared infrequently in the literature, since azides, the usual nitrene precursors, themselves react with aliphatic multiple bonds at temperatures generally lower than those required to generate the corresponding free nitrene.[2] The issue is further complicated by the fact that the 1,2,3-triazolines thus produced may subsequently lose nitrogen to give the same aziridines as would be expected from nitrene addition.[3]

The addition of ethoxycarbonylnitrene, generated by photolysis of ethyl azidoformate at ambient temperature, to olefins to give *N*-carbethoxyaziridines has been studied extensively.[4] It was shown that both singlet and triplet nitrene added to the olefin but that only the singlet species added stereospecifically.[5] Addition of triplet nitrene occurred via a 1,3-diradical intermediate which resulted in stereochemical scrambling. Addition to conjugated dienes is usually in the 1,2 manner,[5] rather than 1,4 manner,[6] except in certain cases such as the additions to pyrroles or to thiophenes, e.g., the additions of *N*-carbethoxynitrene to pyrroles or to thiophenes,[7a] or those which proceed via a triplet diradical, e.g., the addition of cyanonitrene to cyclooctatetraene.[7b]

Evidence for the direct addition of aryl nitrenes to olefins is scanty, there being only one clear-cut example, that of aziridine formation during the photolysis of ferrocenyl azide in cyclohexene.[8] Formation of 1,2,3-triazolines in the thermal reaction of aryl azides with olefins or acetylenes is well known,[3,9] as is the reaction with certain other unsaturated species, such as enol ethers[10] and enamines.[11] With highly polarized double bonds such as these, the addition is usually regiospecific.

We have previously shown that pentafluorophenylni-

trene, generated by triethyl phosphite deoxygenation of pentafluoronitrosobenzene (**1**, Ar = C_6F_5), undergoes addition to aromatic bonds under conditions under which other less electrophilic aryl nitrenes do not.[12] Furthermore, since the procedure does not use an azide as the starting material, it offered promise as a means of investigating the behavior of an aryl nitrene toward olefins. A number of reports have, however, appeared in the literature exemplifying the reactivity of aryl nitroso compounds toward olefins. Varying types of reactivity are found. For instance, nitrosobenzene adds to 1,1-diphenylethylene in a [2 + 2] manner to give oxazetidine (**2**),[13] whereas with styrene a mixture of nitrones is obtained.[14] When the olefin possesses allylic hydrogens an "ene"-type reaction is favored; for example, tetramethylethylene gives the hydroxylamine **3**, which undergoes rapid aerial oxidation to the nitroxide **5**[15] (which

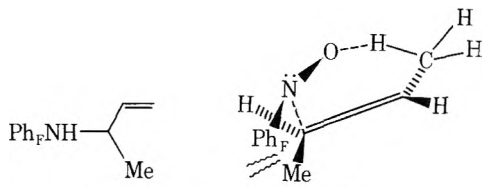


2

3, Ar = Ph
4a, Ar = Ph_F
4b, Ar = p-$CF_3C_6H_4$

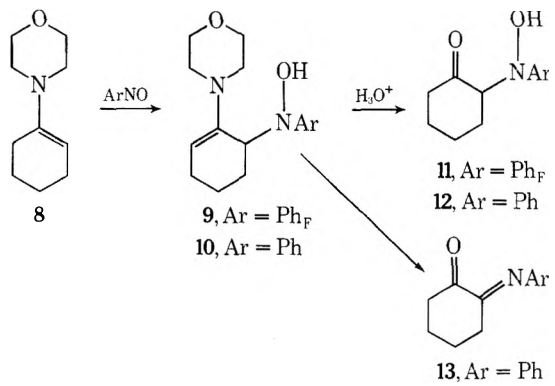
5, Ar = Ph

we had independently confirmed). In view of these facts, the reactivity of **1** toward our projected olefinic substrates was investigated. An immediate reaction with tetramethylethylene took place, giving hydroxylamine **4a** in quantitative yield. p-Nitrosobenzotrifluoride behaved similarly. Unlike **3**, **4a** showed no tendency toward aerial oxidation. A similar reaction was observed between **1** and *cis*-2-butene, but with *trans*-2-butene under similar conditions a complex mixture of products was obtained in which amine **6** was apparent. This difference in behavior suggests that steric effects might be important in the highly ordered transition state in keeping with a concerted "ene"-type mechanism, **7**. Styrene, cyclohexene, 1-methylcyclohexene, and



6 **7**

1,2-dimethylcyclohexene also gave complex mixtures in which the amines analogous to **6** were detected (cf. ref 15c), but the enamine **8** gave a hydroxylamine (**9**) analogous to **3**



8

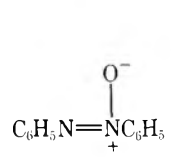
9, Ar = Ph_F
10, Ar = Ph

11, Ar = Ph_F
12, Ar = Ph

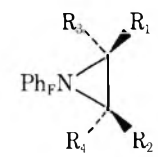
13, Ar = Ph

and **4**. A similar reaction with nitrosobenzene has been reported[16] to give **10** which could be hydrolyzed to **12** by brief treatment with dilute aqueous acid, and to **13** by longer treatment (15 hr). Only hydroxylamine **11** was obtained from **9**, however, even after prolonged acid treatment. No appreciable reaction took place between **1** and stilbenes, or *n*-butyl vinyl ether.

For the projected nitrene additions, the problem of reaction of the precursor with substrate was overcome by employing inverse addition. Thus, when **1** was added to a solution of triethyl phosphite in excess tetramethylethylene, decafluoroazoxybenzene (**14**), hydroxylamine **4**, and the expected aziridine, **15**, were formed in 14, 5.5, and



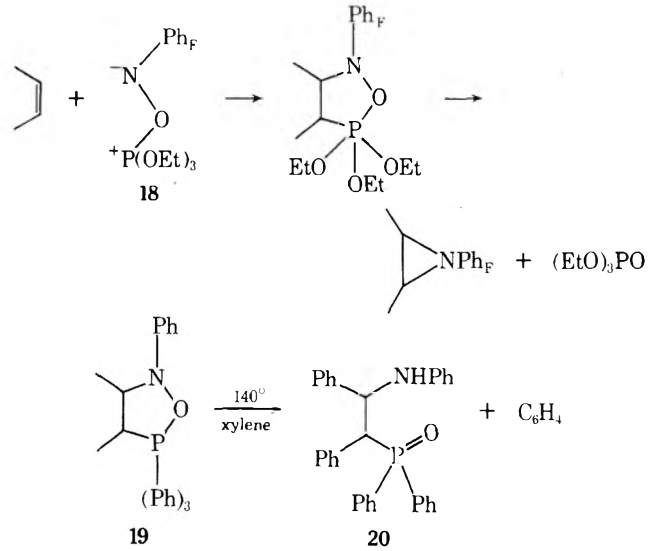
14



15, $R_1 = R_2 = R_3 = R_4 = Me$
16, $R_1 = R_2 = Me$; $R_3 = R_4 = H$
17, $R_1 = R_4 = Me$; $R_2 = R_3 = H$

30.5% yields, respectively. The ^1H NMR spectrum of **15** showed only one signal, a narrow triplet (J = 1.7 Hz) at δ 1.30. The coupling is probably due to through-space interaction with the ortho fluorine substituents of the aromatic ring, since an authentic sample of *N-tert*-butylpentafluoroaniline, prepared from hexafluorobenzene and *tert*-butylamine, exhibited a similar splitting of the signal due to the methyl groups. Models of both these compounds confirmed that the methyl protons and ortho fluorines come into very close proximity to one another when the bonds are suitably rotated. The possibility that **15** might be formed from hydroxylamine **4** was eliminated by showing that **4** was stable to triethyl phosphite under the reaction conditions.

Reaction with *cis*- and *trans*-2-butene in a similar manner gave, along with **14**, the respective aziridines **16** and **17**. The reaction proceeded stereospecifically. In the NMR spectrum, the three-membered ring protons of **16** gave rise to a multiplet at δ 2.33 while those of **17** gave a signal at δ 2.28. That the trans aziridine (**17**) should give rise to a signal for the ring protons at *higher* field is in good agreement with the published data for *N*-acyl-2,3-dialkylaziridines.[17] The complete stereospecificity of the reaction thus demonstrated tends to rule out any stepwise diradical process, such as might be expected if a triplet nitrene were involved,[5] but does not exclude the possibility of dipolar addition of the nitrenoid **18** followed by extrusion of triethyl



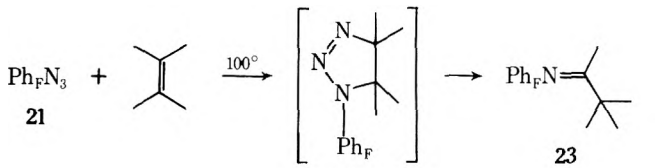
18

19 **20**

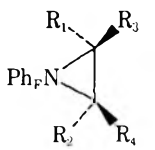
phosphate, in a manner analogous to the thermal extrusion of nitrogen from triazolines. This possibility was closely scrutinized.

Huisgen has reported the isolation of a closely related species, **19**, and shown it to be stable at room temperature,[18] whereas our reaction proceeds spontaneously, even at −78°. In addition, **19** undergoes thermal decomposition in boiling xylene to give **20**, no aziridine being formed. Furthermore, if the reactive intermediate in the deoxygenation were indeed a dipolar species, then it would be expected to be more reactive toward good dipolarophiles, such as methyl acrylate, than toward nonpolar olefins such as the butenes. In fact, when **1** was deoxygenated in the presence of excess methyl acrylate or dimethyl maleate, no adduct could be detected, the only isolable product being **14**. This behavior should be contrasted with the reaction between phenyl azide and methyl acrylate, a known 1,3-dipolar cycloaddition, which takes place under mild conditions to give a 1,2,3-triazoline in high yield.[19a] Deoxygenation of *p*-trifluoromethylnitrosobenzene with $(EtO)_3P$ in the presence of tetramethylethylene did not yield in aziridine. A low yield of 4,4′-di(trifluoromethyl)azoxybenzene was isolated.[19b]

When pentafluorophenyl azide (**21**) was heated at 100° in tetramethylethylene, the expected[20] triazoline **22** was not obtained. Instead, extrusion of nitrogen was accompanied by rearrangement, resulting in the imine **23**. Oehlschlager and Zalkow have reported similar rearrangements in related systems.[21] **23** gave pentafluoroaniline and *tert*-butyl methyl ketone on acid hydrolysis. On the other hand, photolysis of **21** in tetramethylethylene (below the temperature at which 1,1-dipolar addition occurs) gave **15** in 60% yield, and in *cis*- and *trans*-2-butene gave **16** and **17**, respectively, and stereospecifically, each in 18% yield.



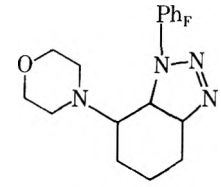
These observations strongly suggest the participation of a common intermediate in the deoxygenation and azide photolysis reactions but not in the azide thermolysis, and this is most likely the corresponding singlet nitrene. Other comparison between the nitroso compound deoxygenations and azide photolyses provided further evidence. Thus, cyclohexene gave the expected aziridine, **24**, in 35 and 39% yields, respectively. Likewise, stereospecific aziridine formation occurred when **21** was photolyzed in *cis*- and *trans*-1,2-dichloroethylene, a substrate with which no thermal reaction occurred, even at 100°. An aziridine was also obtained with 4-methyl-2-pentene but no reaction occurred with the highly deactivated trichloroethylene.



24, $R_1 = R_2 = H$; $R_3R_4 = -(CH_2)_4-$
25, $R_1 = R_2 = H$; $R_3 = R_4 = Cl$
26, $R_1 = R_4 = H$; $R_2 = R_3 = Cl$
27, $R_1 = R_2 = H$; $R_3 = R_4 = Ph$
28, $R_1 = R_4 = H$; $R_2 = R_3 = Ph$

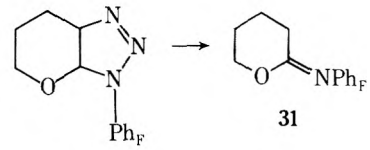
Reactions with aryl-substituted ethylenes showed more variations. Deoxygenation of **1** in the presence of *trans*-stilbene gave the expected single aziridine **28** in 32% yield, but with *cis*-stilbene only 0.6% of the geometrically isomeric aziridine **27** was isolated. Photolysis of **21** in the presence of stilbenes gave no adducts at all; this might be due to absorption of the radiation by the olefinic substrate which was present in high relative concentration in these experiments.

Reaction of the enamine **8** with **1** proved to be more rapid than the deoxygenation of **1** by triethyl phosphite inasmuch as, even at low temperature, only **9** was isolated. Reaction of **8** with **21** also occurred rapidly at room temperature to give triazoline **29** with the expected orientation.[22]



29

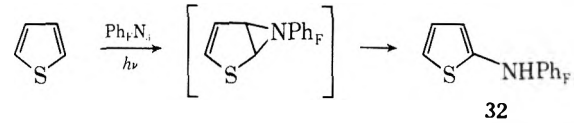
Vinyl ethers are known to display similar activity toward aryl azides.[23] The primary adducts formed in such reactions usually eliminate a molecule of nitrogen to give an aziridine, but when the nitrogen atom bears a strongly electronegative substituent, an imine results from loss of nitrogen.[24] The latter was observed when **21** was added to dihydropyran, **31** being the product isolated, presumably via **30**.



30 **31**

These observations precluded an investigation of the behavior of enamines and vinyl ethers toward aryl nitrenes generated under the conditions used in this paper.

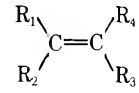
Irradiation of ethyl azidoformate in the presence of certain five-membered aromatic heterocycles has been reported to give both 1,2 and 1,4 adducts via a nitrene intermediate.[7a,25] Irradiation of **21** in pyrrole gave only tars, but in thiophene the apparent substitution product **32** was obtained, probably formed via the initial addition of C_6F_5N as in the case of benzene derivatives.[12]



32

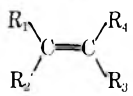
In an extension of the studies with pentafluorophenylnitrene the properties of 2- and 4-azidotetrachloropyridine were investigated briefly. After this work was completed, a report appeared[26] on the chemistry of 4-azidotetrafluoropyridine, whose derived nitrene is also highly electrophilic in character. 4-Azidotetrachloropyridine, synthesized from pentachloropyridine and sodium azide, readily underwent thermal cycloaddition to tetramethylethylene to give eventually the imine **33** (cf. formation of **23**) in 79% yield. The reaction was slow at room temperature, however, and photolysis under these conditions resulted in formation of the aziridine **34** in 14% yield, along with a small amount of the hydrogen abstraction product **35**. The latter could arise from the triplet nitrene. Photolysis of 4-azidotetrachloropyridine in cyclohexene gave only amine **35**, no adduct being formed, suggesting that the derived nitrene is much less electrophilic than the corresponding fluorinated species, as expected. 2-Azidotetrachloropyridine gave only

Table I
Deoxygenation of Pentafluoronitrosobenzene with Triethyl Phosphite in



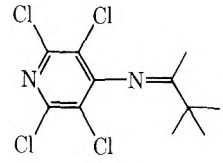
Registry no.	R_1	R_2	R_3	R_4	Temp, °C	Aziridine, %	14, %
563-79-1	Me	Me	Me	Me	−10	30	14
590-18-1	H	Me	Me	H	−20	17	27
624-64-6	Me	H	Me	H	−20	18	35
110-83-8	H	$-(CH_2)_4-$		H	0	35	13
103-30-0	Ph	H	Ph	H	−20	26	
645-49-8	H	Ph	Ph	H	−45	1	
624-48-6	H	CO_2Me	CO_2Me	H	−40		48
96-33-3	CO_2Me	H	H	H	−45		53

Table II
Photolysis of PhF_5N_3 at 300 nm in

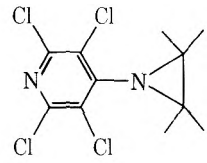


Registry no.	R_1	R_2	R_3	R_4	Time, hr	Aziridine, %
	Me	Me	Me	Me	48	60
	H	Me	Me	H	48	18
	Me	H	Me	H	85	18
156-59-2	H	Cl	Cl	H	6 days	21
156-60-5	Cl	H	Cl	H	168	27
	H	$-(CH_2)_4-$		H	12	39
1674-10-8	Me	$-(CH_2)_4-$		Me	70	11
691-38-3	Me	H	*i*-Pr	H	88	20
	Ph	H	Ph	H		
	H	Ph	Ph	H		

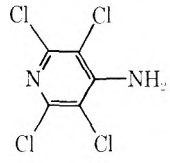
tars when heated in tetramethylethylene, but did yield a triazole (**36**) (82%) with dimethyl acetylenedicarboxylate.



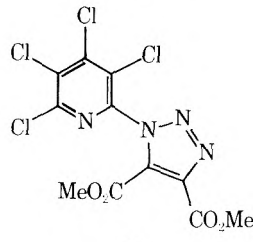
33



34



35



36

The addition of pentafluorophenylnitrene to olefins is summarized in Tables I and II.

Experimental Section

General. Melting points are uncorrected and were taken on an Electrothermal apparatus; infrared spectra were determined on a Perkin-Elmer 257, NMR spectra on a Varian HA-100 or Hitachi R-20B, and mass spectra on a CEC-104 instrument. Silica gel for column chromatography was Baker 60–200 mesh. Silica gel for TLC was Merck PF_{254}. Light petroleum refers to the fraction of bp 30–60°. Drying of solutions was invariably with anhydrous sodium sulfate.

Pentafluoronitrosobenzene was prepared by performic acid oxidation of pentafluoroaniline and purified by distillation according to the method of Tatlow.[27] Pentafluorophenyl azide was prepared by diazotization of pentafluorophenyl hydrazine,[28] or by reaction of hexafluorobenzene with sodium azide in dimethyl sulfoxide.[29] Photolyses were carried out in a Rayonet photochemical reactor.

Reaction of Pentafluoronitrosobenzene and Other Nitrosobenzenes with Tetramethylethylene. Pentafluoronitrosobenzene (140 mg) was added to excess tetramethylethylene and shaken until dissolved. Evaporation of the excess olefin gave colorless crystals of ***N*-(1,1,2-trimethyl)-2-propenylpentafluorophenylhydroxylamine** (191 mg, 96%): mp 78–79° (light petroleum); ir (KBr) 3310 (br), 1636, 1490, 1372, 1362, 1150, 1140, 990, 962, 900 cm^{-1}; NMR (CCl_4) δ 5.40 (s, 1, exchanged with D_2O), 5.00 (m, 2), 1.93 (s, 3), 1.27 (t, J = 1.7 Hz, 6); MS *m/e* (rel abundance) 281 (1), 280 (1), 265 (2), 263 (3), 250 (2), 224 (8), 208 (9), 197 (3), 183 (9), 167 (3), 117 (10), 83 (100).

Anal. Calcd for $C_{12}H_{12}F_5NO$: C, 51.21; H, 4.27. Found: C, 51.19; H, 4.36.

Catalytic reduction over 10% Pd/C in ether at 25° (1 atm) gave the saturated side-chain molecule as an oil, bp 120–122° (1 mm), MS *m/e* 240 ($M^{\cdot+}$ − F), 85 (100).

Anal. Calcd for $C_{12}H_{14}F_5NO$: C, 50.88; H, 4.95. Found: C, 51.16; H, 5.11.

A similar reaction using nitrosobenzene gave analytically pure **3** in 77% yield after one recrystallization, mp 59–60° (light petroleum) (lit.[15b] mp 58°).

Addition of *p*-nitrosobenzotrifluoride to tetramethylethylene gave ***N*-(1,1,2-trimethyl-2-propenyl)-4-trifluoromethylphenylhydroxylamine** (85%), mp 76–77° (light petroleum).

Anal. Calcd for $C_{13}H_{16}F_3NO$: C, 60.22; H, 6.18. Found: C, 60.12; H, 6.28.

Reaction of Pentafluoronitrosobenzene with 2-Butenes. Pentafluoronitrosobenzene (141 mg) and *cis*-2-butene (3 ml) in methylene chloride (3 ml) was allowed to stand at −20° for 2 hr, after which the solvents were evaporated and the residue was recrystallized from light petroleum to give ***N*-(1-methyl)-2-propenylpentafluorophenylhydroxylamine** (109 mg, 60%): mp 72–73°; ir (NaCl) 3295, 1643, 1500, 1370, 1328, 1070, 990, 946, 830 cm^{-1}; NMR (CCl_4) δ 6.39 (s, 1, exchanged with D_2O), 5.54–6.13 (q, 1), 5.20 (dd, J = 4 Hz, 1), 3.75–4.22 (q, 1), 1.28 (d, J = 7 Hz, 3); MS *m/e* (rel abundance) 253 ($M^{\cdot+}$, 0.3), 252 (1), 220 (2), 208 (2), 197 (6), 194 (10), 182 (2), 167 (5), 117 (8), 93 (4), 55 (100).

Anal. Calcd for $C_{10}H_8F_5NO$: C, 47.44; H, 3.16. Found: C, 47.90; H, 3.33.

TLC of the mother liquors gave **36** (8 mg) as an oil.

Reaction under the same conditions with *trans*-2-butene gave an oily residue which was subjected to preparative TLC and elution with $CHCl_3$–light petroleum (1:9 v/v) to give *N*-(1-methyl)-2-propenylpentafluoroaniline (44 mg, 8.5%) (**6**): ir (film) 3375, 3078, 1650, 1513, 1372, 1351, 1260, 1020, 989, 926 cm^{-1}; NMR (CCl_4) δ 5.52–6.08 (septet, 1), 5.22 (dd, J = 8 and 2 Hz, 1), 5.00 (d, J = 4 Hz, 1), 4.23 (m, 1), 3.40 br (s, 1, exchanged with D_2O), 1.36 (d, J = 7 Hz, 3); MS *m/e* (rel abundance) 237 ($M^{\cdot+}$, 6), 222 (6), 195 (30), 183 (22), 181 (98), 167 (100), 155 (26), 131 (76), 117 (92), 93 (49), 69 (35).

Reaction of 1 with 1-(*N*-Morpholino)-1-cyclohexene. Pentafluoronitrosobenzene (890 mg) in methylene chloride was added to 1-(*N*-morpholino)-1-cyclohexene (734 mg) in methylene chloride (10 ml) and stirred for 1 hr at 25°. Removal of the solvent gave a residue of **1-(*N*-morpholino)-6-(*N*-pentafluorophenylhydroxylamino)-1-cyclohexene (9**, 601 mg, 40%): mp 95–96° (light

petroleum); ir (KBr) 3290, 1640, 1500, 990 cm^{-1}; MS *m/e* (rel abundance) 364 ($M\cdot^+$, 2), 167 (100), 166 (98), 86 (17), 80 (12).

Anal. Calcd for $C_{16}H_{17}F_5N_2O_2$: C, 52.76; H, 4.68. Found: C, 52.59; H, 4.81.

Similar results were obtained when the reaction was carried out in the presence of triethyl phosphite (see general conditions below) at −40° (yield of hydroxylamine 34%). No aziridine was observed under these conditions.

Hydrolysis of 9. A mixture of **9** (0.24 g) in methylene chloride (5 ml) and 10% HCl (7 ml) was stirred at room temperature for 72 hr. Extraction with CH_2Cl_2, washing with water, drying (Na_2SO_4), and evaporation gave **2-*N*-pentafluorophenylhydroxylaminocyclohexanone** (11, 0.13 g, 70%), mp 117–118° (ether): ir (KBr) 3480, 1710, 1495, and 990 cm^{-1}; MS *m/e* (rel abundance) 294 ($M\cdot^+$, 11), 167 (22), 127 (55), 97 (100).

Anal. Calcd for $C_{12}H_{10}F_5NO_2$: C, 49.00; H, 3.10. Found: C, 48.99; H, 3.21.

Reaction of 1 with Cyclohexene. Pentafluoronitrosobenzene (255 mg) in CH_2Cl_2 (2 ml) was added over 0.5 hr to a stirred solution of cyclohexene (2 ml) in CH_2Cl_2 (3 ml) at 30° under N_2. After stirring for a further 0.5 hr the solvents were evaporated and the residue was subjected to preparative TLC. Elution with benzene–light petroleum (1:3 v/v) gave ***N*-(3-cyclohexenyl)pentafluoroaniline** (39 mg, 11.4%): bp 70–75° (0.1 mm); ir (film) 3390 cm^{-1}; NMR (CCl_4) δ 5.82 (m, 2), 4.14 (s, 1, exchanged with D_2O), 3.43 (m, 1), 2.03 (m, 2), 1.76 (m, 4); MS *m/e* (rel abundance) 263 ($M\cdot^+$, 9), 81 (100).

Anal. Calcd for $C_{12}H_{10}F_5N$: C, 54.80; H, 3.80. Found: C, 55.01; H, 3.64.

Further elution gave an unidentified yellow oil (10 mg) [ir (film) 1723, 1674, 1642, and 1324 cm^{-1}] and intractable oils and gums.

Deoxygenation of Pentafluoronitrosobenzene in Tetramethylethylene. Pentafluoronitrosobenzene (575 mg) in chlorobenzene (2 ml) was added dropwise to a stirred solution of triethyl phosphite (485 mg) in tetramethylethylene (3 g) at −10°. The resulting brown solution was evaporated down to a small volume and the residue was chromatographed on silica gel (5 × 20 cm). Elution with light petroleum gave chlorobenzene. Elution with light petroleum–benzene (4:1 v/v) gave an oil which crystallized on standing to **2,2,3,3-tetramethyl-1-pentafluorophenylaziridine** (235 mg, 30.5%): mp 70–72° (light petroleum); ir (KBr) 1498, 1440, 1377, 1201, 1172, 1035, 986, 790 cm^{-1}; NMR (CCl_4) δ 1.30 (t, J = 1.7 Hz); MS *m/e* (rel abundance) 265 ($M\cdot^+$, 7), 250 (9), 223 (7), 208 (48), 196 (6), 183 (100), 167 (7), 155 (21), 136 (26), 117 (21), 83 (24), 82 (26), 67 (40), 41 (22).

Anal. Calcd for $C_{12}H_{12}F_5N$: 54.38; H, 4.53. Found: C, 54.43; H, 4.60.

Further elution with light petroleum–benzene (1:4 v/v) gave decafluoroazoxybenzene (77 mg, 14.0%), mp 52–54°, identical with an authentic sample.[11] Elution with benzene–light petroleum (1:1 v/v) gave **4** (45 mg, 5.5%), mp 77–79°.

Similarly prepared were the following.

***trans*-2,3-Dimethyl-1-pentafluorophenylaziridine** (18.0%): bp 70–75° (1.5 mm); ir (film) 2990, 1500, 1450, 1380, 1170, 1104, 1038, 987 cm^{-1}; NMR (CCl_4) δ 2.28 (br q, J = 5 Hz, 2), 1.30 (d, J = 5 Hz, 6); MS *m/e* (rel abundance) 237 ($M\cdot^+$, 34), 222 (22), 208 (25), 195 (100), 194 (90), 181 (27), 167 (60), 117 (59).

Anal. Calcd for $C_{10}H_8F_5N$: C, 50.63; H, 3.38. Found: C, 50.68; H, 3.47.

***cis*-2,3-Dimethyl-1-pentafluorophenylaziridine** (17.3%): mp 68–70° (sublimed in vacuo); ir (NaCl) 2990, 1503, 1460, 1307, 1172, 1078, 1026, 988 cm^{-1}; NMR (CCl_4) δ 2.33 (m, 2), 1.34 (d, J = 5 Hz, 6); MS *m/e* (rel abundance) 237 ($M\cdot^+$, 34), 222 (27), 208 (30), 195 (100), 194 (92), 167 (49), 117 (52).

Anal. Calcd for $C_{10}H_8F_5N$: C, 50.63; H, 3.38. Found: C, 50.57; H, 3.45.

7-Pentafluorophenyl-7-azabicyclo[4.1.0]heptane (35.0%): bp 55–60° (0.5 mm); ir (film) 1500, 1191, 1032, 1008, 978, 941, 814 cm^{-1}; NMR (CCl_4) δ 2.96 (m, 2), 2.50 (br d, 4), 1.9–2.1 (m, 4); MS *m/e* (rel abundance) 263 ($M\cdot^+$, 16), 181 (64), 167 (70), 131 (62), 117 (69), 81 (100).

Anal. Calcd for $C_{12}H_{10}F_5N$: C, 54.76; H, 3.80. Found: C, 54.77; H, 3.80.

***trans*-2,3-Diphenyl-1-pentafluorophenylaziridine** (26.0%): mp 88–89° (light petroleum); ir (KBr) 1600, 1510, 1450, 1187, 1068, 1000, 812, 750, 697 cm^{-1}; NMR (CCl_4) δ 7.30 (s, 10), 3.85 (t, J = 1.7 Hz, 2); MS *m/e* (rel abundance) 361 ($M\cdot^+$, 72), 360 (54), 270 (28), 257 (28), 194 (42), 178 (46), 167 (100), 152 (28), 117 (29), 77 (95).

Anal. Calcd for $C_{20}H_{12}F_5N$: C, 66.50; H, 3.33. Found: C, 66.57; H, 3.40.

Deoxygenation of Pentafluoronitrosobenzene in *cis*-Stilbene. Pentafluoronitrosobenzene (723 mg) in methylene chloride (10 ml) was added dropwise to a stirred solution of *cis*-stilbene (1.62 g) and triethyl phosphite (604 mg) in methylene chloride (40 ml) at −45°. After a further 5 min, the solvent was evaporated and the residue was chromatographed on silica gel (5 × 20 cm). Elution with light petroleum–benzene (9:1 v/v) gave recovered *cis*-stilbene and a fraction showing additional infrared absorptions to those of *cis*-stilbene. On prolonged standing, this fraction deposited crystals of ***cis*-2,3-diphenyl-1-pentafluorophenylaziridine** (6 mg, 0.6%): mp 113–115° (light petroleum); ir (KBr) 3020, 1490, 1450, 1390, 1045, 1000, 975, 760, 745, 690 cm^{-1}; NMR (CCl_4) δ 7.07 (s, 10), 3.65 (br s, 2) ; MS *m/e* (rel abundance) 361 ($M\cdot^+$, 5), 360 (5), 194 (13), 181 (39), 180 (100), 179 (92), 167 (63), 89 (37), 77 (34).

Anal. Calcd for $C_{20}H_{12}NF_5$: mol wt, 361.0887. Found: mol wt, 361.0905.

Deoxygenation of Pentafluoronitrosobenzene in Dimethyl Maleate. A solution of pentafluoronitrosobenzene (0.99 g) in methylene chloride (10 ml) was added quickly at −40° to a solution of dimethyl maleate (1.75 g) and triethyl phosphite (0.83 g) in methylene chloride (20 ml). A brown solution resulted. After 5 min the solvent was evaporated and the residual oil was chromatographed on a column of silica gel (100 g) to give decafluoroazoxybenzene (0.46 g, 48%), mp 53–54°, undepressed on admixture with an authentic sample.

A similar result was obtained when methyl acrylate and *n*-butyl vinyl ether were used as the substrates. The yields of azoxy compound were 53.0 and 10.4%, respectively.

Deoxygenation of *p*-Trifluoromethylnitrosobenzene in Tetramethylethylene. To a cold solution (0°) of tetramethylethylene (6 ml) and triethyl phosphite (0.86 g) was rapidly added a solution of *p*-trifluoronitrosobenzene (0.92 g) in methylene chloride (3 ml). After 30 min the solution was worked up and the product was chromatographed on a column of silica gel (30 g) to give 4,4′-trifluoromethylazoxybenzene (0.11 g, 12%), mp 103–105°, identical with an authentic sample.

When the reaction was carried out at −50° the yield of azoxy compound was 23.1%.

Decomposition of Pentafluorophenyl Azide in Tetramethylethylene and other Olefins. A. Thermolysis. Pentafluorophenyl azide (424 mg) in tetramethylethylene (10 ml) was degassed and then heated in a sealed tube at 100° for 48 hr. Excess olefin was evaporated from the cooled mixture and the residue was distilled to give **2,2-dimethyl-3-pentafluorophenyliminobutane** (**23**, 496 mg, 97%): bp 65° (0.5 mm); ir (film) 2960, 1650, 1505, 1370, 1150, 1145, 1000, 950, 840 cm^{-1}; NMR (CCl_4) δ 1.84 (s, 3), 1.27 (s, 9); MS *m/e* (rel abundance) 265 ($M\cdot^+$, 12), 250 (9), 209 (14), 208 (100), 183 (11), 167 (14), 117 (12), 57 (21).

Anal. Calcd for $C_{12}H_{12}F_5N$: C, 54.43; H, 4.51. Found: C, 54.40, H, 4.55.

A solution of **23** (353 mg), methanol (1 ml), and 25% sulfuric acid (5 ml) was stirred at 25° for 72 hr, after which the mixture was extracted with methylene chloride and the extracts were washed with water and dried. Evaporation of the solvent gave a residue shown to contain pinacolone and pentafluoroaniline by GLC analysis and comparison with authentic samples.

B. Photolysis. Pentafluorophenyl azide (436 mg) in tetramethylethylene (10 ml) was degassed and then photolysed in a sealed Pyrex tube with 300-nm radiation at 25° for 48 hr. The solvent was then evaporated and the crystalline residue, after preparative TLC and elution with benzene–light petroleum (1:4 v/v), gave 2,2,3,3-tetramethyl-1-pentafluorophenylaziridine (336 mg, 60%), mp 70–72° (light petroleum), identical with the previously prepared sample.

Similarly prepared were the following.

cis- and *trans*-2,3-dimethyl-1-pentafluorophenylaziridine (18.0 and 18.0%) (from *cis*- and *trans*-2,3-dimethyl-2-butene, respectively), and 7-pentafluorophenyl-7-azabicyclo[4.1.0]heptane (38.6%) (from cyclohexene), all identical with previously prepared compounds.

***cis*-2,3-Dichloro-1-pentafluorophenylaziridine** (27.0%): mp 124–125° (light petroleum) (from *cis*-dichloroethylene); ir (KBr) 1520, 1350, 1090, 1005, 870, 855, 710 cm^{-1}; NMR (CCl_4) δ 4.54 (dd, J = 0.75 Hz); MS *m/e* (rel abundance) 281 ($M\cdot^+$, $^{37}Cl_2$, 1.5), 279 ($^{37}Cl^{35}Cl$, 9), 277 ($M\cdot^+$, $^{35}Cl_2$, 14), 244 (12), 242 (30), 217 (6), 207 (15), 194 (100), 174 (15), 167 (33), 117 (42), 93 (70).

Anal. Calcd for $C_8H_2Cl_2F_5N$: C, 34.53; H, 0.72. Found: C, 34.57; H, 0.80.

***trans*-2,3-Dichloro-1-pentafluorophenylaziridine** (21.0%): mp 54–56° (light petroleum) (from *trans*-dichloroethylene); ir

(NaCl) 1500, 1320, 1260, 1250, 1093, 1050, 890, 840, 810, 775 cm^{-1}; NMR (CCl_4) δ 4.70 (m); MS *m/e* (rel abundance) 281 ($M\cdot^+$, $^{37}Cl_2$, 1), 279 ($^{37}Cl^{35}Cl$, 6), 277 ($M\cdot^+$, $^{35}Cl_2$, 10), 244 (16), 207 (8), 194 (50), 181 (8), 167 (33), 117 (33), 109 (100), 83 (33).

Anal. Calcd for $C_8H_2Cl_2F_5N$: C, 34.53; H, 0.72. Found: C, 34.47; H, 0.78.

1,6-Dimethyl-7-pentafluorophenyl-7-azabicyclo[4.1.0]heptane (11.3%): mp 42–43° (light petroleum) (from 1,2-dimethylcyclohexene); ir (KBr) 2940 1510, 1450, 1395, 1205, 1150, 1060, 1000, 800 cm^{-1}; NMR (CCl_4) δ 1.32–2.2 (br d, 8), 1.19 (t, J = 3 Hz, 6); MS *m/e* (rel abundance) 291 ($M\cdot^+$, 12), 276 (12), 209 (100), 167 (50), 117 (52).

Anal. Calcd for $C_{14}H_{14}F_5N$: mol wt, 291.1047. Found: mol wt, 291.1042.

***trans*-2-Methyl-3-isopropyl-1-pentafluorophenylaziridine** (19.7%): bp 90–100° (0.5 mm) (from 2-methyl-3-pentene); ir (film) 2970, 1500, 1170, 1040, 990 cm^{-1}; NMR (CCl_4) δ 2.50 (br d, 1), 1.95 (m, 11), 1.60 (m, 1), 1.19 (d, J = 4.5 Hz, 6), 1.08 (s, 3), 0.96 (s, 2); MS *m/e* (rel abundance) 265 ($M\cdot^+$, 11), 250 (26), 211 (22), 196 (100), 167 (22), 117 (22), 84 (16).

Anal. Calcd for $C_{12}H_{12}F_5N$: C, 54.34; H, 4.53. Found: C, 54.50; H, 4.58.

Thermolysis of Pentafluorophenyl Azide in Dihydropyran. Pentafluorophenyl azide (326 mg) and dihydropyran (2.5 g) were sealed in a Pyrex tube and heated at 120° for 24 hr. Excess dihydropyran was removed from the cooled mixture, leaving an oil which crystallized to give **δ-valerolactone pentafluoroanil** (208 mg, 70%): mp 57–59° (light petroleum); ir (KBr) 2960, 1650, 1500, 1400, 1340, 1280, 1255, 1080, 1000 cm^{-1}; NMR (CCl_4) δ 4.20 (t, J = 5 Hz, 2), 2.70 (t, J = 5 Hz, 2), 1.95 (m, 4); MS *m/e* (rel abundance) 265 ($M\cdot^+$, 10), 181 (100), 153 (11), 135 (20), 116 (20).

Anal. Calcd for $C_{11}H_8F_5NO$: C, 49.80; H, 3.02. Found: C, 49.83; H, 3.07.

The same product was also obtained (90%) when the reaction was conducted at 25° for 12 days.

Photolysis of Pentafluorophenyl Azide in Thiophene. Pentafluorophenyl azide (326 mg) in thiophene (10 ml) was sealed in a Pyrex tube and irradiated at 300 nm at 25° for 64 hr. The excess thiophene was then evaporated and the residue was subjected to preparative TLC. Elution with light petroleum gave **2-pentafluoroanilinothiophene** (48 mg, 11.5%): mp 55–60° (light petroleum); ir (KBr) 3400, 1525, 1090, 1020, 820, 790 cm^{-1}; NMR (CCl_4) δ 7.17 (dd, J = 4 and 3 Hz, 1), 6.79 (d, J = 4 Hz, 1); MS *m/e* (rel abundance) 265 ($M\cdot^+$, 100), 246 (58), 245 (38), 220 (35), 201 (18), 174 (14), 168 (9), 167 (4), 117 (56), 99 (50), 71 (88).

Anal. Calcd for $C_{10}H_4F_5NS$: C, 46.00; H, 1.51. Found: C, 46.01; H, 1.58.

4-Azidotetrachloropyridine. Pentachloropyridine (2.5 g) and sodium azide (1.0 g) were heated in boiling acetonitrile (50 ml) for 10 hr. The mixture was poured into water and extracted with chloroform. Drying and evaporation of the chloroform extracts gave a yellow oil, which was subjected to preparative TLC. Elution with light petroleum gave starting material (1.7 g) and **4-azidotetrachloropyridine** (0.80 g, 22.1%): mp 47–48° (light petroleum); ir (KBr) 2150, 1525, 1400, 1355, 1330, 1185, 1110, 920, 900, 765 cm^{-1}.

Anal. Calcd for $C_5Cl_4N_4$: C, 23.25; H, 0.0. Found: C, 23.43; H, 0.0.

Decomposition of 4-Azidotetrachloropyridine in Tetramethylethylene. A. Thermolysis. 4-Azidotetrachloropyridine (463 mg) in tetramethylethylene (5 ml) was heated at 120° in a sealed tube for 24 hr. Excess olefin was evaporated and the residue was subjected to preparative TLC. Elution with light petroleum gave **2,2-dimethyl-3-(4-tetrachloropyridyl)iminobutane** (454 mg, 79.5%): mp 100–101° (light petroleum); ir (KBr) 2990, 1670, 1530, 1375, 1350, 1320, 1250, 1155, 1000, 940, 850, 785, 735 cm^{-1}; NMR ($CDCl_3$) δ 1.80 (s, 3), 1.28 (s, 9); MS *m/e* (rel abundance) 320 ($M\cdot^+$, $^{37}Cl_4$, 0.1), 318 ($^{37}Cl_3{}^{35}Cl$, 0.7), 316 ($^{37}Cl_2{}^{35}Cl_2$), 314 ($^{37}Cl^{35}Cl_3$, 7), 312 ($M\cdot^+$, $^{35}Cl_4$, 5), 273 (9), 271 (14), 258 (42), 256 (100), 254 (72), 214 (14), 117 (14).

Anal. Calcd for $C_{11}H_{12}Cl_4N_2$: C, 42.04; H, 3.82. Found: C, 42.20; H, 3.88.

B. Photolysis. 4-Azidotetrachloropyridine (487 mg) in tetramethylethylene (5 ml) was irradiated at 300 nm in a sealed tube for 6.5 days at 25°. Excess olefin was evaporated and the residue was subjected to preparative TLC. Elution with light petroleum gave **2,2,3,3-tetramethyl-1-(4-tetrachloropyridyl)aziridine** (85 mg, 14.3%): mp 151–152° (light petroleum); ir (KBr) 2940, 1525, 1510, 1430, 1340, 1245, 1205, 1120, 1050, 990, 800, 750 cm^{-1}; NMR (CCl_4) δ 1.40 (s); MS *m/e* (rel abundance) 320 ($M\cdot^+$, $^{37}Cl_4$, 0.2) 318 ($^{37}Cl_3{}^{35}Cl$, 2), 316 ($^{37}Cl_2{}^{35}Cl_2$, 11), 314 ($^{37}Cl^{35}Cl_3$, 22), 312 ($M\cdot^+$, $^{35}Cl_4$, 17), 280 (61), 278 (56), 268 (44), 266 (100), 264 (78), 247 (22), 245 (22), 216 (28), 214 (17), 181 (11), 154 (22), 153 (28), 144 (17), 118 (17).

Anal. Calcd for $C_{11}H_{12}Cl_4N_2$: C, 42.04; H, 3.82. Found: C, 41.98; H, 3.83.

Also eluted was 4-aminotetrachloropyridine (6.1 mg, 1.4%), mp 215–216° (lit.[30] mp 212–215°).

When the photolysis was carried out in cyclohexene the only isolable product was the primary amine (12.1%), mp 212–214°.

Thermolysis of 2-Azidotetrachloropyridine in Dimethyl Acetylenedicarboxylate. 2-Azidotetrachloropyridine[30] (627 mg) and dimethyl acetylenedicarboxylate (503 mg) were heated in boiling chloroform for 43 hr. Evaporation of the solvent gave a residue which was subjected to preparative TLC. Elution with light petroleum gave **4,5-dimethoxycarbonyl-1-(2-tetrachloropyridyl)-1,2,3-triazole** (814 mg, 85.2%): mp 125–126° [chloroform–light petroleum (1:1 v/v)]; ir (KBr) 2960, 1750, 1725, 1590, 1530, 1450, 1330, 1300, 1260, 1230, 1140, 110, 970, 840, 810, 770 cm^{-1}; NMR ($CDCl_3$) δ 4.00 (s, 3), 3.90 (s, 3); MS *m/e* (rel abundance) 378 ($M\cdot^+$, $^{37}Cl_4$, 0.2), 376 ($^{37}Cl_3{}^{35}Cl$, 1.5), 374 ($^{37}Cl_2{}^{35}Cl_2$, 6), 372 ($^{37}Cl^{35}Cl_3$, 6), 370 ($M\cdot^+$, $^{35}Cl_4$, 9), 340 (12), 285 (50), 272 (18), 257 (18), 255 (31), 253 (25), 219 (50), 216 (100), 214 (75), 181 (37), 179 (43), 155 (25), 153 (25), 144 (19), 109 (25).

Anal. Calcd for $C_{11}H_6Cl_4N_4O_4$: C, 33.00; H, 1.50. Found: C, 33.10; H, 1.61.

***N-tert*-Butylpentafluoroaniline.** Hexafluorobenzene (5 g), *tert*-butylamine (3.7 g), and sodium carbonate (2.5 g) were heated in a sealed tube at 100° for 14 hr. The cooled, filtered mixture was evaporated to give ***N-tert*-butylpentafluoroaniline** (0.7 g, 11%): bp 130–135° (20 mm); ir (film) 3400, 3340, 1470, 1367 cm^{-1}; NMR (CCl_4) δ 2.95 (br s, 1, exchanged with D_2O), 1.28 (t, J = 1.7 Hz, 9).

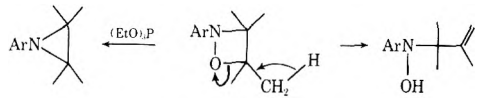
Anal. Calcd for $C_{10}H_{10}F_5N$: C, 50.18; H, 4.19. Found: C, 50.19; H, 4.33.

Registry No.—**1**, 1423-13-8; **3**, 28943-93-3; **4a**, 30287-20-8; **4b**, 54698-78-1; **6**, 54698-79-2; **8**, 670-80-4; **9**, 54698-80-5; **11**, 54698-81-6; **15**, 39904-17-1; **16**, 39830-50-7; **17**, 39830-49-4; **21**, 1423-15-0; **23**, 54698-82-7; **25**, 54698-94-1; **26**, 54698-95-2; **27**, 54698-96-3; **28**, 39830-51-8; **32**, 54698-83-8; **33**, 54698-84-9; **34**, 54698-85-0; **36**, 54698-86-1; *N*-(1,1,2-trimethyl)propylpentafluorophenylhydroxylamine, 54698-87-2; *N*-(1-methyl)-2-propenylpentafluorophenylhydroxylamine, 54698-88-3; *N*-(3-cyclohexenyl)pentafluoroanilene, 54698-89-4; 7-pentafluorophenyl-7-azabicyclo[4.1.0]heptane, 54698-90-7; *p*-trifluoromethylnitrosobenzene, 34913-26-3; 1,6-dimethyl-7-pentafluorophenyl-7-azabicyclo[4.1.0]heptane, 54698-91-8; *trans*-2-methyl-3-isopropyl-1-pentafluorophenylaziridine, 54698-97-4; dihydropyran, 110-87-2; δ-valerolactone pentafluoroanil, 54698-92-9; thiophene, 110-02-1; pentachloropyridine, 2176-62-7; 4-azidotetrachloropyridine, 51379-64-7; 2-azidotetrachloropyridine, 54698-93-0; dimethyl acetylenedicarboxylate, 762-42-5; *N-tert*-butylpentafluoroaniline, 13471-90-4; hexafluorobenzene, 392-56-3; *tert*-butylamine, 75-64-9; nitrosobenzene, 586-96-9.

References and Notes

(1) For preliminary communication, see R. A. Abramovitch and S. R. Challand, *J. Chem. Soc., Chem. Commun.*, 1160 (1972).
(2) R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes", S. Patai, Ed., Interscience, New York, N.Y., 1963, p 835.
(3) P. A. S. Smith in "Nitrenes", W. Lwowski, Ed., Interscience, New York, N.Y., 1970, p 111.
(4) W. Lwowski in "Nitrenes", W. Lwowski, Ed., Interscience, New York, N.Y., 1970, p 191.
(5) W. Lwowski and J. S. McConaghy, *J. Am. Chem. Soc.*, **89**, 2357, 4450 (1967).
(6) A. Mishra, S. N. Rice, and W. Lwowski, *J. Org. Chem.*, **33**, 481 (1968); M. P. Sammes and A. Rahman, *J. Chem. Soc., Perkin Trans. 1*, 344 (1972).
(7) (a) K. Hafner and W. Kaiser, *Tetrahedron Lett.*, 2185 (1964); (b) A. G. Anastassiou, *J. Am. Chem. Soc.*, **90**, 1475 (1968).
(8) R. A. Abramovitch, C. I. Azogu, and R. G. Sutherland, *Chem. Commun.*, 134 (1971).
(9) R. A. Abramovitch and E. P. Kyba in "Chemistry of the Azido Group", S. Patai, Ed., Interscience, New York, N.Y., 1971, p 260.
(10) R. Huisgen, L. Möbius, and G. Szeimies, *Chem. Ber.*, **98**, 1138 (1965).
(11) R. Fusco, S. Rossi, and G. Bianchetti, *Gazz. Chim. Ital.*, **91**, 849 (1961).
(12) R. A. Abramovitch, S. R. Challand, and E. F. V. Scriven, *J. Am. Chem. Soc.*, **95**, 1374 (1972); R. A. Abramovitch, S. R. Challand, and E. F. V. Scriven, *J. Org. Chem.*, **37**, 2705 (1972); R. A. Abramovitch and S. R. Challand, *J. Heterocycl. Chem.*, **10**, 683 (1973).
(13) J. Hamer and A. Macaluso, *Tetrahedron Lett.*, 381 (1963).
(14) N. F. Hepfinger, C. E. Griffin, and B. L. Shapiro, *Tetrahedron Lett.*, 1365 (1963).
(15) (a) A. B. Sullivan, *J. Org. Chem.*, **31**, 2811 (1966); (b) G. T. Knight, *Chem. Commun.*, 1016 (1970); (c) G. T. Knight and B. Pepper, *ibid.*, 1507 (1971).

(16) J. W. Lewis, P. L. Myers, and J. A. Ormerod, *J. Chem. Soc., Perkin Trans. 1*, 2521 (1972).
(17) T. A. Foglia, L. M. Gregory, and G. Meerken, *J. Org. Chem.*, **35**, 3779 (1970).
(18) J. W. Wulff and R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **6**, 457 (1967).
(19) (a) R. Huisgen, G. Szeimies, and L. Möbius, *Chem. Ber.*, **99**, 475 (1966). (b) The possibility was considered that an oxazetidine was formed by addition of nitrosoarene to the butene which could either ring open to the hydroxylamine or be deoxygenated by triethyl phosphite to the aziridine. This was rendered much less likely by the observation that though



both *p*-trifluoromethylnitrosobenzene and PhNO give "ene"-type products with 2,3-dimethyl-2-butene they do not give any aziridine in the inverse addition in the presence of $(EtO)_3P$. That aziridines are also formed from $C_6F_5N_3$ by photolysis also supports the electrophilic nitrene hypothesis for the addition to olefinic double bonds.
(20) R. E. Banks and A. Prakash, *J. Chem. Soc., Perkin Trans. 1*, 1365 (1974).
(21) A. C. Oehlschlager and L. H. Zalkow, *J. Org. Chem.*, **28**, 3303 (1963).
(22) R. Huisgen and G. Szeimies, *Chem. Ber.*, **98**, 1153 (1965).
(23) P. Scheiner, *J. Org. Chem.*, **32**, 2022 (1967).
(24) G. L'Abbé, *Chem. Rev.*, **68**, 345 (1968).
(25) Reference 3, p 211.
(26) R. E. Banks and G. R. Sparkes, *J. Chem. Soc., Perkin Trans. 1*, 2964 (1972).
(27) G. M. Brooke, J. C. Burdon, and J. C. Tatlow, *Chem. Ind. (London)*, 832 (1961).
(28) J. M. Birchall, R. N. Haszeldine, and A. R. Parkinson, *J. Chem. Soc*, 4966 (1962).
(29) Pentafluorophenyl azide was also obtained in 26% yield by heating sodium azide with hexafluorobenzene. In view of the explosive nature of the possible by-products of this reaction (see footnote 11, ref 20) this procedure is not generally recommended.
(30) Prepared by heating 2-fluorotetrachloropyridine with sodium azide; cf. Y. N. Ivashchenko, S. D. Moshchitzki, L. S. Sologul, and G. A. Zalesskii, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **6**, 895 (1973).

Purine *N*-Oxides. LXI. 3-Hydroxy-2,3-dihydro-2-oxopurine[1]

Tzoong-Chyh Lee, Fuk Luen Lam, and George Bosworth Brown*

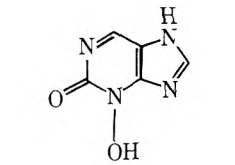
Memorial Sloan-Kettering Cancer Center, New York, New York 10021

Received December 24, 1974

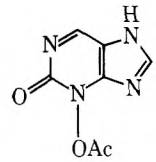
The synthesis and reactivity of 3-hydroxy-2,3-dihydro-2-oxopurine (1) is described. The acetyl and tosyl esters of 1 react with water to give some 2,8-dihydroxypurine and hydrolysis products, while the acetyl ester of 1 prepared in situ reacts with methionine at room temperature to give almost quantitative yield of 2-hydroxy-8-methylmercaptopurine. The xanthine oxidase oxidation of 1 gave good yield of 3,8-dihydroxy-2,3-dihydro-2-oxopurine. The photoirradiation of 1 at pH 3.0 produces 2-hydroxypurine (21%) and a small amount of 2,8-dihydroxypurine (1%), while at pH 9.0 it gives mostly a ring-opened imidazole derivative, a small amount of 2-hydroxypurine, and a trace of 2,8-dihydroxypurine.

It has been reported from this laboratory that esters of 3-hydroxyxanthine[2-6] and some of its methylated derivatives undergo an elimination–substitution reaction to yield 8-substituted xanthines, even at room temperature and in nearly neutral solution. The subsequent studies of some analogs[7-9] of 3-hydroxyxanthines have shown that some π-excessive ring systems can undergo an elimination–substitution reaction similar to that of the esters of 3-hydroxyxanthine.

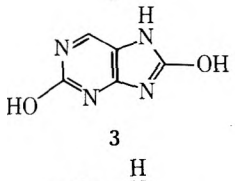
This paper describes the reactions of 3-hydroxy-2,3-dihydro-2-oxopurine (1). This was prepared by condensation



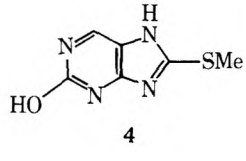
1



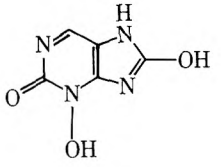
2



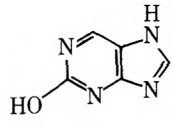
3



4



5



6

of 5-aminocytosine 1-oxide[7] with triethyl orthoformate in boiling ethanol. Although the reaction was carried out heterogenously, the overall yield of 1 was found to be quite satisfactory. The identity of the compound was confimed by NMR, uv spectra, elemental analysis, and mass spectrum. The uv spectrum of 1 in both acid and neutral media resembles those of 2-hydroxypurine[10] (2,3-dihydro-2-oxopurine).[11,12] The uv of the neutral species of 1 shows a bathochromic shift of 5 nm in long-wavelength major band with respect to that of its parent purine, as do the uv spectra of 3-hydroxyxanthine and its analogs,[7-9] thus confirming that the neutral species of 1 does exist in the *N*-hydroxy form as shown. The basic pK_a (1.79) of 1 was found to be similar to that of 2-hydroxypurine (1.69), which indicates that the addition of the 3-hydroxy function to 2-hydroxypurine has little effect on the protonation. The 3-hydroxy-2,3-dihydro-2-oxopurine is very insoluble in water and purification was achieved only by reprecipitation. Unlike 2-hydroxypurine,[13] which ring opens to 4,5-diaminopurine even in pH 5 solution, 1 undergoes ring opening slowly only in strong acid solution at room temperature (in 3 *N* HCl $t_{1/2}$ = 4 days). Like 3-hydroxyxanthine, 1 reacted with acetic anhydride to form the acetyl ester of 1 but the isolation of ester in pure form was not successful owing to its ready hydrolysis. When the freshly prepared acetyl ester was boiled with ethanol, it did not give any 8-ethoxy-2-hydroxypurine; instead a small amount of 2,8-dihydroxypurine[10] (2,3,7,8-tetrahydro-2,8-dioxopurine, 3) and unreacted 1 were obtained. Similar treatment of the acetoxypurine with pH 7.00 buffer also gave a small amount of 3. Reaction of 1 with tosyl chloride in pyridine at room temperature for a prolonged period of time gave some 3, but upon refluxing in pyridine most of the 1 decomposed to non-uv absorbing material and no 3 was detectable. The acetyl ester of 1 prepared in situ by the addition of acetic anhydride to an aqueous solution of 1 with methionine present gave almost a quantitative amount of 2-hydroxy-

8-methylmercaptopurine (**4**),[10,14] which was identified by comparison of the uv and chromatographic data with those of an authentic sample. In the absence of methionine, the acetyl ester prepared in situ did not react with water at room temperature to give **3**, but upon prolonged stirring in water the ester hydrolyzed to give **1**. The high yield of **4** was clearly due to the stronger nucleophile, methionine, and constant regeneration of the ester by acetic anhydride. The elimination–substitution reactions of the ester of **1** may proceed via an AE mechanism, that is, the addition of the nucleophile to C-8 followed by elimination and aromatization to the final product.

Xanthine oxidase[15] was found to oxidize the position 8 preferentially, to give mainly 3,8-dihydroxy-2,3-dihydro-2-oxopurine (**5**)[16] with only a small amount of 3-hydroxyxanthine. Since **5** is isomeric to 3-hydroxyxanthine, the identity was readily established by comparison of the uv spectrum of **5** to that of 3-hydroxyxanthine, and by elemental analysis.

Similarities in the reactivities of **1** and 3-hydroxyxanthine suggest that **1** is a potential oncogen, and have led us to compare its photochemical reactions with other purine *N*-oxides.[17] The irradiation of the neutral molecule (at pH 3.0) with 3000-Å light resulted in photoreduction to **6** (21%) and a minor 8-substitution product, identified as 2,8-dihydroxypurine (1%). In contrast, no 8-substitution products were observed from the irradiation of 1- and 3-hydroxyxanthines under similar conditions. Irradiation of the anion (at pH 9.0) also gave 7% of **6**, a trace of **3**, and a major product for which a positive Pauly test suggests an imidazole derivative.

The results of this work show that the acetyl ester of **1** has nearly the same reactivity as that of the corresponding ester of 3-hydroxyxanthine, notably the reaction to give an excellent yield of **4**. Should an ester of **1** be formed in vivo it is likely to react with various sulfur-containing amino acids and other nucleophiles. In collaboration with Dr. M. N. Teller a comparison of the oncogenicity of **1** with that of 3-hydroxyxanthine in rats is planned.[18,19]

Experimental Section

The uv spectra were determined with a Cary 15 spectrophotometer. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. NMR spectra were determined with a Varian A-60 spectrometer, in Me_2SO-d_6 with tetramethylsilane as an internal reference. The melting points are uncorrected. Paper chromatography, ascending, on Whatman No. 1 paper was used to check the purity of each of the compounds prepared. For Dowex-50 chromatography BioRad AG-50, ×8, 200–400 mesh (H^+) resin was used. Photolyses were carried out with a Rayonet photochemical reactor equipped with a 300-nm lamp and a Merry-Go-Round apparatus. All solutions were flushed with a stream of N_2 at least for 30 min prior to irradiation.

3-Hydroxy-2,3-dihydro-2-oxopurine (1). 5-Aminocytosine 1-oxide hydrochloride[7] (4,5-diamino-2-hydroxypyrimidine 3-*N*-oxide, 1.0 g) was added to a solution of triethyl orthoformate (5 ml) in ethanol (99%, 25 ml). The reaction was carried out heterogeneously, with the solid heated in suspension under reflux for 5 hr. The mixed precipitate (780 mg) was collected by filtration. The precipitate was suspended in water (5 ml) and the acidity was adjusted to pH 6 with 1 *N* NaOH, from which the free base of **1** (670 mg, 79%) was isolated directly. An analytical sample was prepared by reprecipitation from dilute alkali by acid: mp 204° dec; NMR (TFA) δ 9.00, 9.23; uv (pH −0.2), 325 nm ($\epsilon \times 10^{-3}$ 5.99), 262 (6.88); (pH 3.6) 355 (2.67), 318 (5.24), 283 (3.08), 274 (3.12), 213 (14.1); (pH 7.3) 334 (5.56), 277 (4.64), 271 (4.54); (pH 11) 325 (5.99), 283 (6.86); pK_a's 1.78 ± 0.11, 5.38 ± 0.05, 9.28 ± 0.03; chemical ionization mass spectrum *m/e* 153 (M + 1), 151 (M − 1), 137 (M + 1 − 16), 136 (M + 1 − 17), 110 (M + 1 − 44).

Anal. Calcd for $C_5H_4N_4O_2$: C, 39.48; H, 2.65; N, 36.83. Found: C, 39.35; H, 2.70; N, 36.90.

Reaction of 3-Hydroxy-2,3-dihydro-2-oxopurine with Tosyl Chloride. Tosyl chloride (380 mg) was added to a solution of **1** (152 mg) in pyridine (5 ml), and the mixture was stirred at room temperature for 1 week. The dark brown solid (89 mg) was precipitated by the addition of ether. The NMR spectrum of the product showed multiplet signals for pyridine protons (10.0–5.8 ppm). The solid was dissolved in a small amount of 1 *N* NaOH, and the solution was absorbed in a Dowex-50 (H^+) column. Elution with 1 *N* HCl gave 2,8-dihydroxypurine[12] (11 mg), and with 2 *N* HCl gave 5-aminocytosine 1-oxide[7] (18.1 mg) and 5-aminocytosine (29 mg).

3-Acetoxy-2,3-dihydro-2-oxopurine (2). Acetic anhydride (1 ml) was added to a solution of **1** (132 mg) in acetic acid (2 ml) and stirred at room temperature for 2 weeks. Ether (50 ml) was added to the reaction mixture, and the precipitate formed was collected and dried in vacuo. NMR in TFA showed the signals at 2.30 (CH_3CO–), 8.98, and 9.22 ppm (6- and 8-H). The compound was too unstable to permit purification, and it was used without further purification.

3,8-Dihydroxy-2,3-dihydro-2-oxopurine. A. Freshly prepared **2** (118 mg, 0.608 mmol) was boiled with methanol (25 ml) for 4 hr. The solution was evaporated to dryness in vacuo. Chromatography of the residue over a Dowex-50 (H^+) column with 0.1–2 *N* HCl gave 2,8-dihydroxypurine[13] (5.97×10^{-2} mmol, 10%), **1** (2.38×10^{-1} mmol, 39%), and 4,5-diaminopyrimidine (1.22×10^{-1} mmol, 20%).

B. Freshly prepared **2** (150 mg, 0.72 mmol) in pH 7.0 phosphoric acid buffer (0.05 M, 45 ml) was stirred at room temperature for 24 hr. The mixture was absorbed on a Dowex-50 (H^+) column. Eluting with 1 *N* HCl gave a small amount of 3,8-dihydroxy-2,3-dihydro-2-oxopurine (<1%).

C. Heating **2** in Ac_2O–HOAc for 2 hr yielded 2,8-dihydroxypurine (13%).

2-Hydroxy-8-methylmercaptopurine (4). Acetic anhydride (100 μl) was added to a mixture of **1** (80.9 mg, 0.54 mmol) and *dl*-methionine (164 mg, 1.1 mmol) in water (20 ml) at room temperature. After 24 hr of stirring at room temperature, the insoluble, unchanged starting material (39 mg, 49%) was separated by filtration, and the filtrate was adsorbed in Dowex-50 (H^+) column. Elution of the column with 1 *N* HCl gave the 2-hydroxy-8-mercaptopurine[14] (1.32 mmol, 25%) followed by 8-methionium-2-hydroxypurine (2.23×10^{-2} mmol, 4.2%). The latter was converted to **4** by heating with 0.01 *N* NaOH on a steam bath for 2 hr. The filtered, unchanged starting material (39 mg) was treated the same way as above in water (25 ml) and gave a quantitative yield of **4**.

3,8-Dihydroxy-2,3-dihydro-2-oxopurine (5). Xanthine oxidase (0.4 ml, with activity to oxidize xanthine to uric acid at 45 μmol min^{-1} ml^{-1}) was added to 3-hydroxy-2,3-dihydro-2-oxopurine (100 mg, 2000 ml of water) solution and stirred at room temperature for 7 days. The solution was concentrated to a small volume (10 ml) and the insoluble starting material (46 mg, 46%) was collected. Chromatography of the filtrate over a Dowex-50 (H^+) column with 0.5 *N* HCl gave a trace of 3-hydroxyxanthine (0.32 mg, 0.3%, followed by a small amount of unknown material, and 3,8-dihydroxy-2,3-dihydro-2-oxopurine (40.2 mg, 36%), $FeCl_3$ blue color: uv (pH 0) 272 nm (ϵ 8.25×10^3); mp 270° dec.

Anal. Calcd for $C_5H_4N_4O_3$: C, 35.72; H, 2.40; N, 33.33. Found: C, 35.52; H, 2.62; N, 33.15.

Registry No.—**1**, 54643-52-6; **2**, 54643-53-7; **4**, 10179-94-9; **5**, 54643-54-8; 5-aminocytosine 1-oxide hydrochloride, 54643-55-9.

References and Notes

(1) This investigation was supported in part by NCI Grants CA 08748 and CA 15274 and by AEC Contract No. AT(11-1)-3521.
(2) U. Wölcke, N. J. M. Birdsall, and G. B. Brown, *Tetrahedron Lett.*, 785 (1969).
(3) N. J. M. Birdsall, T.-C. Lee, and U. Wölcke, *Tetrahedron*, **27**, 5961 (1971).
(4) N. J. M. Birdsall, U. Wolcke, T.-C. Lee, and G. B. Brown, *Tetrahedron*, **27**, 5969 (1971).
(5) N. J. M. Birdsall, J. C. Parham, U. Wölcke, and G. B. Brown, *Tetrahedron*, **28**, 3 (1973).
(6) D. R. Sutherland and G. B. Brown, *J. Org. Chem.*, **38**, 1291 (1973).
(7) T.-C. Lee, *J. Org. Chem.*, **38**, 703 (1973).
(8) T.-C. Lee, G. Salemnick, and G. B. Brown, *J. Org. Chem.*, **38**, 3102 (1973).
(9) T.-C. Lee, G. Salemnick, and G. B. Brown, *J. Org. Chem.*, **39**, 2963 (1974).
(10) The keto–enol tautomerism of hydroxypurine is well known. For brevity the name does not necessarily refer to its predominant tautomer.
(11) S. F. Mason, *J. Chem. Soc.*, 2071 (1954).
(12) D. J. Brown and S. F. Mason, *J. Chem. Soc.*, 682 (1957).
(13) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).

(14) A. Albert, J. Chem. Soc. B, 438 (1966).
(15) We appreciate the advice of Dr. G. Stohrer on the use of xanthine oxidase.
(16) Alternatively: 3-hydroxy-2,8-dioxo-2,3,7,8-tetrahydropurine, in analogy to the 8-oxo form for most such purine derivatives.
(17) F. L. Lam, J. C. Parham, and G. B. Brown, J. Org. Chem., 39, 1391 (1974), and references cited therein.
(18) G. B. Brown, M. N. Teller, I. Smullyan, N. J. M. Birdsall, T.-C. Lee, J. C. Parham, and G. Stohrer, Cancer Res., 33, 1113 (1973).
(19) M. N. Teller, G. Stohr, and H. Dienst, Cancer Res., 30, 179 (1970).

Reactions of α-Azidovinyl Ketones with β-Keto Esters

Gerrit L'abbé,* Georges Mathys, and Suzanne Toppet

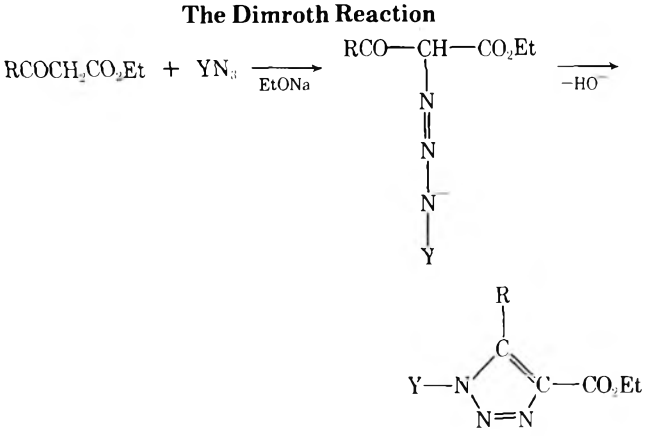
Department of Chemistry, University of Leuven, Celestijnenlaan 200F, B-3030 Heverlee, Belgium

Received December 3, 1974

The base-catalyzed reactions of ethyl acetoacetate with α-azidochalcone, α-azido-(*m*-nitrobenzylidene)acetophenone, and α-azidobenzylideneacetone, as well as the reaction of ethyl benzoylacetate with α-azidobenzylideneacetone, were found to give substituted triazolycyclohexanones (**5a,b** and **8a,b**). Ethyl benzoylacetate also reacted with α-azidochalcone or its nitro-substituted derivative, but yielded the N-1-substituted triazoles **10a,b**. Structure assignment of all the products was essentially based upon ^1H and ^{13}C NMR analysis and further confirmed by analytical and other spectral data.

The reaction of aryl azides and alkyl azides with active methylene compounds under basic conditions to give *v*-triazoles (Scheme I) is called the Dimroth reaction after its discoverer.[1] The mechanism of this synthetically important reaction has been shown to involve a two-step cycloaddition process via a triazene intermediate.[2]

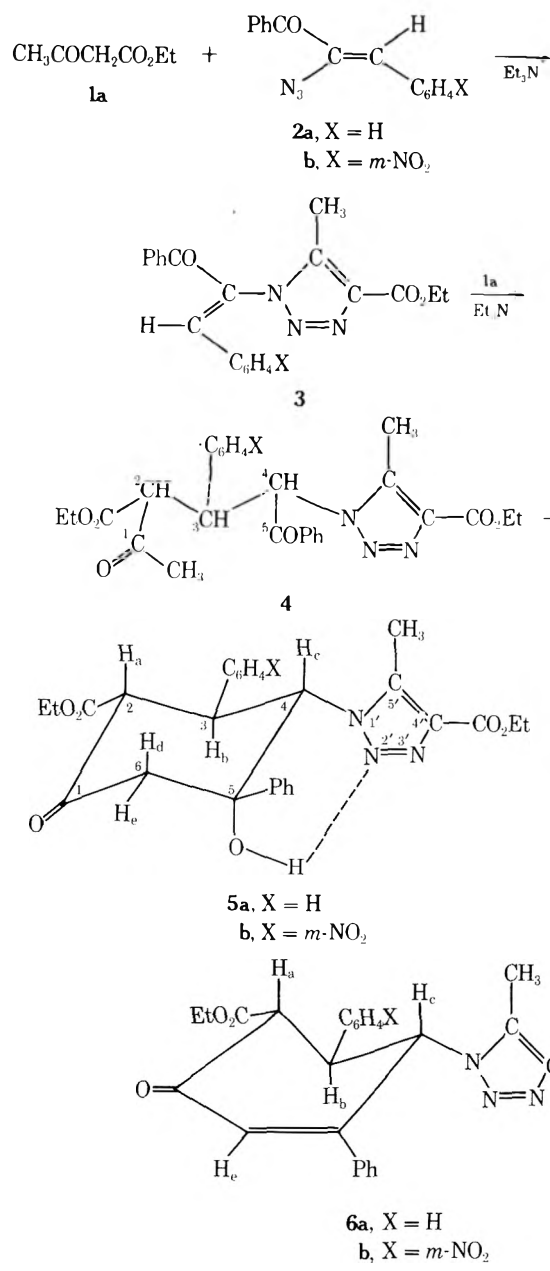
Scheme I
The Dimroth Reaction



Recently, the Dimroth reaction has been extended to simple vinyl azides[3] and β-azidovinyl ketones.[4] In both cases vinyl-substituted *v*-triazoles were obtained. In this paper, we describe our results of the reactions of α-azidovinyl ketones with β-keto esters where the initially formed vinyltriazoles underwent further reaction with the active methylene compounds.

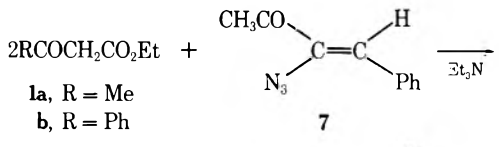
Chemical Results. Treatment of ethyl acetoacetate (**1a**) with α-azidochalcone (**2a**) or its nitrosubstituted derivative **2b** in the presence of triethylamine furnished white, crystalline products to which structures **5a** and **5b** are assigned on the basis of analytical and spectral properties (see discussion NMR). From Scheme II it is apparent that the initially formed Dimroth product **3** has undergone a Michael-type addition with the active methylene compound **1a** in the presence of triethylamine to give **4**. This reaction is expected to occur readily, since the electron density of the olefinic double bond is decreased by the presence of two strong electron-withdrawing substituents. Under the basic reaction conditions, **4** then underwent an intramolecular aldolization, resulting in the formation of **5a,b**. Under acid-

Scheme II



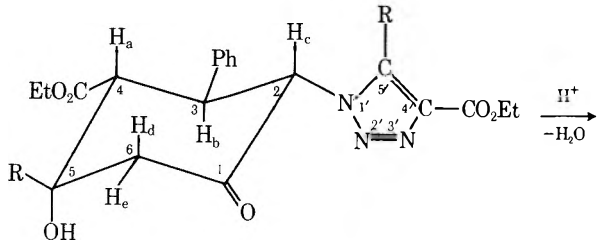
ic conditions, dehydration of **5a,b** occurred to give **6a,b** in high yields.

Ring closure of the Michael adduct **4** in Scheme II thus occurred between the methyl group attached to C_1 and the carbonyl in position 5. If the phenyl group in position 5 is replaced by a methyl group, cyclization proceeded in the other direction as found for the reactions of ethyl acetoacetate (**1a**) and ethyl benzoylacetate (**1b**) with α-azidobenzylideneacetone (**7**). Compounds **8a,b** then were obtained as the only reaction products. Acid-catalyzed dehydration of **8a,b** furnished **9a,b** in high yields.

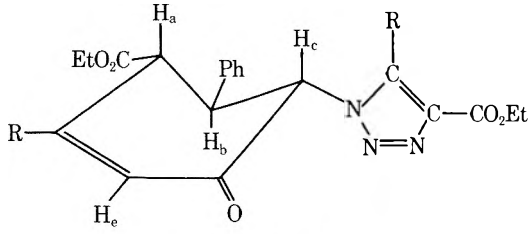


1a, R = Me
b, R = Ph

7

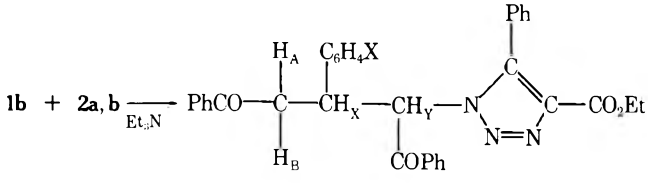


8a, R = CH_3
b, R = Ph



9a, R = CH_3
b, R = Ph

Cyclization to a cyclohexanone cannot occur when the methyl group attached to C_1 in **4** is replaced by a phenyl or substituted phenyl group. Thus, when ethyl benzoylacetate (**1b**) was treated with **2a** or **2b** in the presence of triethylamine, products **10a** and **10b** were obtained which resulted from base-induced decarbethoxylation of the Michael adducts.

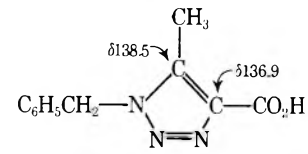


10a, X = H
b, X = *m*-NO_2

Discussion of the ^{1}H and ^{13}C NMR Spectra. The NMR data (Tables I and II) which have led to structure elucidation of the triazole derivatives will now be discussed briefly.

The ^{1}H NMR spectra of compounds **5a** and **5b** showed the presence of only one type of methyl group for both CH_3CH_2 functions. The protons H_a, H_b, and H_c occupy axial positions as evidenced by the large coupling constants J_{ab} and J_{bc} (ca. 12 Hz). Furthermore, the hydroxyl proton of **5a** in $CDCl_3$ was found as a doublet, coupled to the axial proton H_d which resonated as a doublet of doublets. The magnitude of this long-range coupling (J = 2.5 Hz) is indicative of a W arrangement and, hence, points to an axial position for the hydroxyl function.[5] We further suggest that the favorable W arrangement is aided by hydrogen bonding of the hydroxyl proton with the N-2′ atom of the neighboring triazole ring. Addition of D_2O in $CDCl_3$ caused a fast disappearance of the hydroxyl absorption, while at the same time the H_a proton (but not H_c) exchanged slowly for deuterium. In DMSO-d_6 solution at 90°, the H_d absorption (but not H_e) also disappeared completely.[6] All the evidences presented above thus indicate that the large substituents occupy the preferred equatorial positions in the cyclohexanone ring. For the sake of completeness, we also mention here that the ketones **5a** and **5b** equilibrate with their respective enols upon standing in DMSO-d_6 at room temperature. This was seen in the NMR spectrum by the presence of a second ethyl absorption and a low-lying OH singlet at δ 12 (hydrogen bonding with the ester group in position 2). The keto–enol equilibrium compositions are as follows: 90.5:9.5 for **5a** and 85.5:14.5 for **5b.**

Compound **5a** was also subjected to ^{13}C NMR analysis (see Table II). Assignment of the carbon atom absorptions of the triazole moiety was based on comparison with model compound **11**, prepared from benzyl azide and ethyl acetoacetate by the method of Dimroth.[1] Noteworthy from Table II is the higher field absorption of the ketone carbon atom (δ 202.6) compared with the value found for cyclohexanone (δ 208.8).[7] The difference in chemical shift (6 ppm) is the same as that found for the C=O carbon absorptions of acetone (δ 206.0) and ethyl acetoacetate (δ 200.5)[8] and, hence, is due to the presence of an ester function in β position to the ketone group.



11

Compounds **6a** and **6b,** obtained by acid dehydration of **5a** and **5b,** were also fully characterized by their NMR spectra (see Tables I and II). The observed coupling constants in the ^{1}HNMR spectra are consistent with literature data.[9] A comparison of the ^{13}C NMR data of compounds **5a** and **6a** in Table II shows the expected upfield shift of the C_1 atom absorption by introduction of a double bond in conjugation with the ketone function.[7] In DMSO-d_6 solution, **6a** and **6b** were converted completely into their respective enols upon standing at room temperature. The isomerization process was slow for **6a** (within 1 month) but fast for **6b** (within a few minutes). The ^{1}H NMR data given in Table I for **6b** are those of the enol form.

As mentioned in the previous section, **1a** reacted with **7** to give **8a** and not the analog of **4a** (with Me instead of Ph in position 5). This was apparent from the ^{1}H NMR spectra, where H_c and H_d (in addition to OH) exchanged for deuterium upon addition of D_2O in DMSO solution. Proton H_a in **8a** is no longer flanked by two electron-withdrawing groups and did not exchange.

The ^{1}H NMR spectra of **8a** in several solvents (see Table I) pointed to an equilibrium between two forms. Indeed, the absorption lines for H_a, H_b, H_c, and the triazole methyl groups were broadened (in $CDCl_3$ and acetone-d_6) or dedoubled (in DMSO-d_6). When a DMSO-d_6 solution was heated to ca. 100°, the dedoubling disappeared and only one form was seen, having coupling constants J_{ab} and J_{bc} of 12 Hz. On the contrary, when an acetone-d_6 solution of **8a** was cooled to −20°, the H_c and triazole CH_3 signals were dedoubled and the two forms were clearly distinguished. Both forms showed large values for J_{ab} and J_{bc} (12 Hz), consistent with axial positions for the H_a, H_b, and H_c

Table I
100-MHz ^{1}H NMR Data

Compd	Solvent	Chemical shifts, ppm						Coupling constants, Hz			
		H_a	H_b	H_c	H_d and H_e	OH	CH_3 in $C_{5'}$	J_{ab}	J_{bc}	J_{de}	Other J values
5a	$CDCl_3$	4.39 (d)	4.70 (dd)	5.24 (d)	3.49 (dd) and 2.98 (d)	5.50 (d)	1.78 (s)	12	11	14	$J_{d,OH} = 2.5$
	DMSO-d_6	4.42 (d)	4.68 (dd)	5.64 (d)	4.08 (d) and 2.70 (d)	5.95 (s)	1.61 (s)	12	11	14	
5b	DMSO-d_6	4.51 (d)	4.94 (dd)	5.85 (d)	3.99 (d) and 2.77 (d)	6.17 (s)	1.62 (s)	12	11	14	
6a	$CDCl_3$	4.28 (d)	4.46 (dd)	5.96 (br, d)	6.54 (d)		2.03 (s)	13	9.5		$J_{ce} \simeq 2.2$
	DMSO-d_6	4.64 (d)	4.10 (br, m)	6.75 (br, d)	6.56 (d)		2.00 (br, s)	13	10		$J_{ce} \simeq 2$
6b (enol)	$CDCl_3$		4.33 (d)	5.70 (d)	6.96 (s)	12.2	2.63 (s)		1.2		
						CH_3 in C_5					
8a	$CDCl_3$	3.40 (d)	4.40 (br)	5.64 (br)	2.84 (s)	1.44 (s)	2.40 (br)	12			
	Acetone-d_6	3.74 (d)	4.60 (br)	5.90 (br)	3.20 (d) and 2.72 (d)	1.46 (s)	2.34 (br)	12		14	
	DMSO-d_6	3.62 (br, d)	4.59 (br, dd)	5.85 and 6.30 (br)	3.24 (d) and 2.62 (d)	1.40 (s)	2.15 and 2.56 (br)			14	
8b	DMSO-d_6	4.08 (d)	4.75 (dd)	5.42 (d)	3.72 (d) and 2.56 (d)			12	12	14	
9a	$CDCl_3$	4.09 (m)	4.57 (dd)	5.30 (d)	6.19 (m)	2.07 (d)	2.22 (s)	11	13		$J_{a,e} = 2$; $J_{CH_3,H_e} = 0.5$
	DMSO-d_6	4.28 (m)	4.28 (m)	6.18 (m)	6.35 (s)	2.05 (s)	2.30 (s)				
9b	DMSO-d_6	4.92 (dd)	4.39 (dd)	5.72 (d)	6.50 (d)			11	13		$J_{ae} = 2.0$

Table II
^{13}C NMR Chemical Shifts[a] with Respect to Me_4Si (DMSO-d_6 as Solvent)

Compd	C_1	C_2	C_3	C_4	C_5	C_6	$C_{4'}$ and/or $C_{5'}$[b]	CH_3 in $C_{5'}$	Other absorptions
5a	202.6	61.9	46.25	65.8	77.35	52.3	138.3 and 139.7	7.7	CO_2Et in positions C_2 and $C_{4'}$, respectively, at 167.8 and 161.05
6a	192.4	57.95	51.3	60.6	158.3	126.4	136.7 and 140	8.05	CO_2Et in positions C_2 and $C_{4'}$, respectively, at 167.9 and 161.0
11							136.9 and 138.5	8.7	CO_2H at 162.9; CH_2 at 50.8
8a	200.65	67.85	46.1	56.9	72.5	53.7	139.9 and 138.7	7.9	CH_3 in position C_5 at 28; CO_2Et in positions C_4 and $C_{4'}$, respectively, at 170.3 and 161.4
9a	190.3	64.6	48.8	54.6	159.6	126.5	140.4 and 137	8.3	CH_3 in position C_5 at 21.3; CO_2Et in positions C_4 and $C_{4'}$, respectively, at 170.2 and 161.2

[a] In parts per million. [b] The signal attributions for the C_4 and C_5 carbon atoms are only tentative, since the absorptions of the phenyl carbon atoms attached to the cyclohexanone of compounds 5a, 6a, 8a, and 9a are situated in the same region.

atoms. This means that the equilibrium phenomenon cannot be explained by a conformational change of the cyclohexanone ring. A reasonable explanation is hindered rotation of the triazole ring resulting in a slow equilibrium between two forms. This is in line with the fact that dedoubling was most pronounced for the H_c and triazole methyl protons.

Noteworthy from the tabulated ^{13}C NMR data of **8a** is the upfield shift of the C_1 absorption (δ 200.65) compared with that in cyclohexanone (δ 208.8). This is attributed to the presence of a triazole ring in the α position to the ketone function. Indeed, this effect was also observed for compound **10a** (CH_YCOPh carbon absorption at δ 193.5 compared with the CH_2COPh carbon absorption at δ 198.1).

In contrast to the ^{1}H NMR spectrum of **8a**, that of **8b** did not clearly show the presence of conformational isomers, although the H_a, H_b, and H_c absorptions were broadened. Again, the hydroxyl proton at δ 5.64 exchanged for deuterium upon addition of D_2O. The acidic protons H_c and H_d exchanged at 90°, but H_a remained unaffected.

The ^{1}H NMR spectrum of **10a** (see Experimental Section) exhibited an ABX pattern with additional coupling between H_X and H_Y. For **10b**, the H_A and H_B protons happened to be magnetically equivalent in DMSO-d_6 solution, resulting in a simplification of the NMR pattern. During

the formation of **10a,b**, an ester group has been eliminated (decarbethoxylation under basic conditions). That this is not the triazole ester group is apparent from the ^{13}C NMR spectrum of **10a**, which showed a characteristic CO_2Et carbon absorption at δ 161.2 (compare this value with those reported in Table II).

Experimental Section

All melting points were obtained on a Leitz apparatus and are uncorrected. The ^1H NMR spectra were recorded with a Varian XL-100 spectrometer using Me_4Si as an internal reference. For ^{13}C NMR spectra, the XL-100 apparatus was equipped with a device for pulsed Fourier transform operation. Peak assignments were made by using the off-resonance spin-decoupling technique and by effecting selective proton decoupling experiments. Furthermore, the replacement of H for D in the deuteration experiments facilitated the interpretation of the ^{13}C NMR spectra.

The α-azidovinyl ketones used in this work were prepared as reported[10] by the reaction of α,β-dibromo ketones with 2 equiv of sodium azide in DMF at room temperature.

Reaction of Ethyl Acetoacetate (1a) with α-Azidochalcone (2a). Compound **1a** (0.02 mol) was allowed to react with **2a** (0.01 mol) in the presence of triethylamine (0.02 mol) with (2 ml) or without DMF as solvent. After 2 months the reaction was finished as observed by the disappearance of the azide band in the ir spectrum at ca. 2130 cm^{-1}. The precipitate (70%) was filtered and crystallized from ethanol (350 ml) to give white needles of **5a** (68%): mp 206–208°; ir (KBr) 3440 (br, OH), 1750, and 1720 with shoulder at 1700 cm^{-1}.

Anal. Calcd for $C_{27}H_{29}N_3O_6$ (491): C, 65.93; H, 5.90; N, 8.55. Found: C, 65.75; H, 5.90; N, 8.70.

Reaction of Ethyl Acetoacetate (1a) with α-Azido(*m*-nitrobenzylidene)acetophenone (2b). Compound **1a** (0.02 mol) was allowed to react with **2b** (0.01 mol) in the presence of triethylamine (0.02 mol) and DMF (2 ml) as solvent. The reaction, followed spectroscopically, was finished after 4 days. The precipitate was collected by filtration and washed with ethanol to give **5b** in 74% yield: mp 213–215° (EtOH); ir (KBr) 3460 (br, OH), 1740, 1720, 1700, 1530, and 1355 cm^{-1}.

Anal. Calcd for $C_{27}H_{28}N_4O_8$ (536): C, 60.45; H, 5.22; N, 10.45. Found: C, 60.55; H, 5.25; N, 10.40.

Reaction of Ethyl Acetoacetate (1a) with α-Azidobenzylideneacetone (7). When **1a** (0.02 mol) was allowed to react with **7** (0.01 mol) in the presence of triethylamine (0.02 mol) at room temperature, the reaction stopped after ca. 1 month, although the ir spectrum still showed the presence of 70% unreacted azide. The precipitate (26%) was collected, washed with ether, and crystallized from ethanol (150 ml) to give white needles of **8a** (23%) which decomposed at 178°, ir (KBr) 3500 (br, OH), 1730–1700 cm^{-1}.

Anal. Calcd for $C_{22}H_{27}N_3O_6$ (429): C, 61.55; H, 6.30; N, 9.80. Found: C, 61.50; H, 6.35; N, 9.85.

Reaction of Ethyl Benzoylacetate (1b) with α-Azidobenzylideneacetone (7). The reaction of **1b** (0.02 mol) with **7** (0.01 mol) in triethylamine (0.02 mol) at room temperature stopped after 6 days, leaving 60% of **7** unreacted. The precipitate was removed, dried, and crystallized from ethanol (40 ml) to give white needles of **8b** in 13% yield: mp 241–243°; ir (KBr) 3480 (br, OH) and 1705 cm^{-1}.

Anal. Calcd for $M^{\cdot+}$ (determined by high-resolution exact-mass measurements): 553.2212. Found: 553.2207.

From the mother liquor 1.12 g of unreacted azide was recovered.

Reaction of Ethyl Benzoylacetate (1b) with α-Azidochalcone (2a). Compound **1b** (0.02 mol) reacted with **2a** (0.01 mol) in the presence of triethylamine (0.02 mol) with evolution of gas. After completion of the reaction (14 days), the mixture was treated with ether (25 ml) to give **10a** in 60% yield. Crystallization from ethanol furnished white needles: mp 168–170°; ir (KBr) 1715 and 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, 3 H, J = 7 Hz), 3.6 (dd, H_A, J_{AB} = 17, J_{AX} = 4 Hz), 4.03 (dd, H_B, J_{AB} = 17, J_{BX} = 9 Hz), 4.24 (q, 2 H, J = 7 Hz), 4.72 (m, H_X), 6.17 (d, H_Y, J_{XY} = 6 Hz), 6.72–6.84 (m, 2 H), 7.10 (s, 5 H), 7.24–7.58 (m, 11 H), and 7.84–7.98 (m, 2 H).

Anal. Calcd for $C_{34}H_{29}N_3O_4$ (543): C, 75.13; H, 5.34; N, 7.73. Found: C, 75.10; H, 5.35; N, 7.75.

Reaction of Ethyl Benzoylacetate (1b) with α-Azido(*m*-nitrobenzylidene)acetophenone (2b). A DMF solution (2 ml) of **1b** (0.002 mol), **2b** (0.01 mol), and triethylamine (0.02 mol) was allowed to react at room temperature. After complete reaction (31 hr), the resulting oil was poured into water and this mixture was extracted three times with chloroform (50 ml). The combined chloroform extracts were washed with water and dried over $MgSO_4$. Removal of the solvent yielded a brown oil which was treated with ether (30 ml) to give **10b** in 50% yield: mp 198–201° (EtOH); ir (KBr) 1720, 1685, 1530, and 1350 cm^{-1}; NMR ($CDCl_3$) δ 1.13 (t, 3 H, J = 7 Hz), 3.64 (d, 2 H, J_{AX} = 7 Hz), 4.16 (q, 2 H, J = 7 Hz), 4.88 (m, H_X), 6.42 (d, H_Y, J_{XY} = 8.5 Hz), 6.90–7.05 (m, 2 H), 7.3–7.9 (m, 15 H), 7.9–8.1 (m, 2 H).

Anal. Calcd for $C_{34}H_{28}N_4O_6$ (588): C, 69.38; H, 4.76; N, 9.52. Found: C, 69.50; H, 4.70; N, 9.55.

Dehydration of Compounds 5a, 5b, 8a, and 8b. A solution of **5a,b** or **8a,b** (1 g) in ethanol (40 ml) containing 3 ml of sulfuric acid was refluxed for 3 hr. The solution was then cooled to room temperature and poured into water (100 ml). The white precipitate was filtered, washed several times with water until neutral reaction, dried in vacuo over P_2O_5 at 50°, and crystallized from ethanol.

Compound **6a** was obtained in 72% yield after crystallization: mp 181–184°; ir (KBr) 1740, 1720, 1680, and 1615 cm^{-1}; mass spectrum $M^{\cdot+}$ (6%) *m/e* 473.

Anal. Calcd for $C_{27}H_{27}N_3O_5$ (473): C, 68.49; H, 5.71; N, 8.88. Found: C, 68.25; H, 5.75; N, 8.90.

Compound **6b** was obtained in 88% yield after crystallization: mp 165–167.5°; ir (KBr) 1715, 1655, 1630, 1530, and 1350 cm^{-1}; mass spectrum $M^{\cdot+}$ (59%) *m/e* 518.

Anal. Calcd for $C_{27}H_{26}N_4O_7$ (518): C, 62.54; H, 5.02; N, 10.81. Found: 62.55; H, 5.05; N, 10.80.

Compound **9a** was obtained in 82% yield after crystallization: mp 176–178°; ir (KBr) 1725, 1680, and 1630 cm^{-1}.

Anal. Calcd for $M^{\cdot+}$ (determined by high-resolution exact-mass measurements): 411.179408. Found: 411.17998.

Compound **9b** was obtained as white needles in 86% yield after crystallization from ethanol (25 ml): mp 184–186°; ir (KBr) 1715, 1680, and 1610 cm^{-1}.

Anal. Calcd for $M^{\cdot+}$ (determined by high-resolution exact-mass measurements): 535.21070. Found: 535.21169.

Acknowledgment. The authors are indebted to the IWONL (Belgium) for a fellowship to one of them (G.M.).

Registry No.—**1a**, 141-97-9; **1b**, 94-02-0; **2a**, 26309-08-0; **2b**, 51002-98-3; **5a**, 54698-61-2; **5b**, 54698-62-3; **6a**, 54698-63-4; **6b**, 54698-64-5; **7**, 26309-09-1; **8a**, 54698-65-6; **8b**, 54698-66-7; **9a**, 54698-67-8; **9b**, 54698-68-9; **10a**, 54698-58-7; **10b**, 54698-59-8; **11**, 54698-60-1.

References and Notes

(1) O. Dimroth, *Ber.*, **35**, 1029, 4041 (1902).
(2) C. E. Olsen and C. Pedersen, *Tetrahedron Lett.*, 3805 (1968); R. L. Tolman, C. W. Smith, and R. K. Robins, *J. Am. Chem. Soc.*, **94**, 2530 (1972); G. L'abbé, *Ind. Chim. Belge*, **36**, 3 (1971).
(3) G. L'abbé and A. Hassner, *J. Heterocycl. Chem.*, **7**, 361 (1970).
(4) S. Maiorana, *Ann. Chim. (Rome)*, **56**, 1531 (1966).
(5) C. A. Kingsbury, R. S. Egan, and T. J. Perun, *J. Org. Chem.*, **35**, 2913 (1970).
(6) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, pp 241–242.
(7) J. B. Stothers, "Carbon-13 NMR Spectroscopy", A. T. Blomquist and H. Wasserman, Ed., Academic Press, New York, N.Y., 1972, p 279.
(8) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra. A Collection of Assigned, Coded and Indexed Spectra", Wiley-Interscience, New York, N.Y., 1972, Spectra No. 28 and 181.
(9) J. J. Barieux, J. Gore, and J. C. Richer, *Bull. Soc. Chim. Fr.*, 1020 (1974).
(10) A. Hassner, G. L'abbé, and M. J. Miller, *J. Am. Chem. Soc.*, **93**, 981 (1971); P. Ykman, G. Mathys, G. L'abbé, and G. Smets, *J. Org. Chem.*, **37**, 3213 (1972).

A Practical Route to Bisbenzylisoquinolines by an Improved Ullmann Diphenyl Ether Synthesis

Michael P. Cava* and Ali Afzali

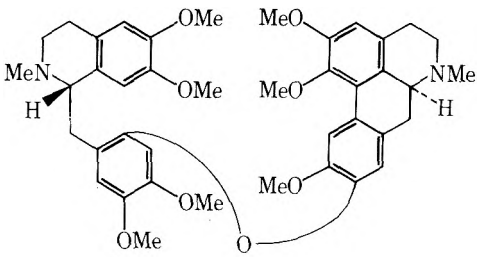
Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19174

Received January 14, 1975

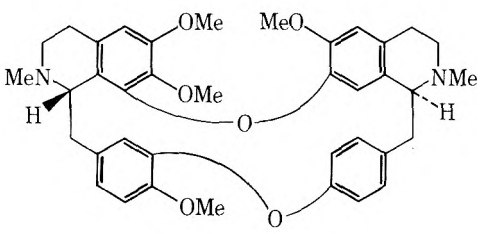
An improved Ullmann diphenyl ether synthesis is reported. In this procedure, the aromatic halide and phenol components are heated with pentafluorophenylcopper (**16**) in dry pyridine. Thus, 6′-bromolaudanosine (**4**) was condensed with phenol to give 6′-phenoxylaudanosine (**7**). Condensation of individual enantiomers of bromide **4** with the phenolic alkaloids (*S*)-armepavine (**15**), (*R*)-nuciferoline (**11**), cassythicine (**9**), and *N*-methylcassyfiline (**10**) gave the bisbenzylisoquinolines **17**, **18**, **19**, **20**, and **21**; all yields were in the 42–54% range, based upon bromide **4**.

The significant tumor-inhibitory activity of thalicarpine (**1**) and tetrandrine (**2**) has stimulated interest in practical synthetic approaches to these compounds, and to other potentially biologically active bisbenzylisoquinolines.[1]

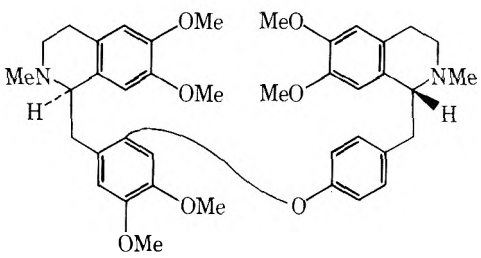
The classical Ullmann-type synthesis of a bisbenzylisoquinoline involves the direct coupling of a phenolic benzylisoquinoline with a halogenated benzylisoquinoline in the presence of copper or one of its salts or oxides. This approach has the great advantage that the two halves of the molecule may be prepared separately as pure enantiomers before the final coupling step. This advantage is usually outweighed, however, by a low yield in the final Ullmann reaction. For example, the crystalline *R,R* enantiomer (**3**) of *O*-tetramethylmagnolamine (**17**) was obtained in only 2% yield by the Ullmann coupling of (*R*)-6′-bromolaudanosine (**5**) with (*R*)-armepavine (**14**).[2] Similarly, thalicarpine (**1**) has been synthesized by the Ullmann coupling of (*S*)-6′-bromolaudanosine (**6**) with (*S*)-*N*-methyllaurotetanine (**8**);[3] the unsatisfactory nature of this reaction, however,



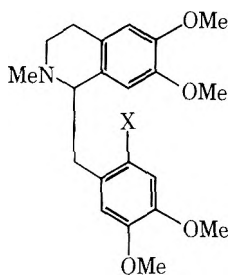
1



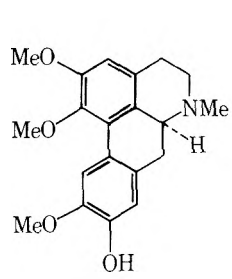
2



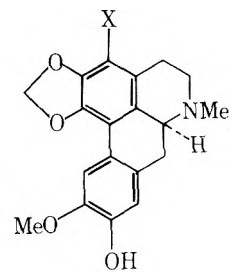
3 (*R, R*)



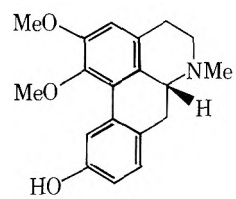
4, X = Br (*dl*)
5, X = Br (*R*)
6, X = Br (*S*)
7, X = OPh (*dl*)



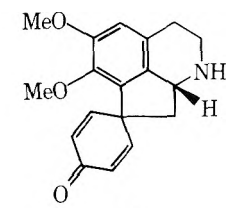
8



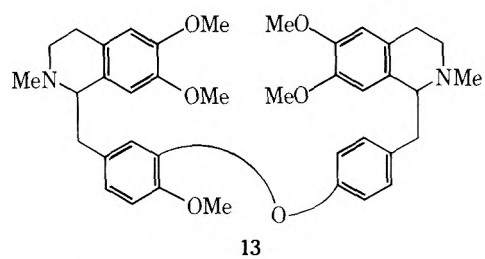
9, X = H
10, X = OMe



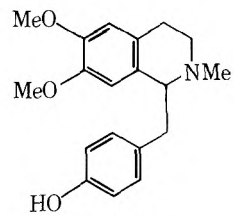
11



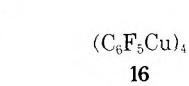
12



13



14 (*R*)
15 (*S*)



16

prompted an extensive study of an alternate and more practical thalicarpine synthesis in which the diphenyl ether linkage was formed at a very early stage of the synthesis.[4] The avoidance of an ultimate Ullmann step also was the key point of strategy in a recent synthesis of *dl*-*O*-methyldauricine (**13**, *R,R, S,S*).[1]

A 1964 kinetic study of the condensation of phenol with bromobenzene led to the proposal that cuprous phenoxide was formed as an intermediate, regardless of the oxidation state of the copper catalyst used.[5] A more recent study has given direct support to this hypothesis. In this work,[6] the reaction of phenol with phenylcopper in ether at −10° gave cuprous phenoxide as a violet precipitate which was very sensitive to both oxygen and moisture; reaction of cuprous phenoxide with bromobenzene in diglyme at 125° for 17 hr gave diphenyl ether in 38% yield, the yield being increased to 46% in the presence of pyridine. These results prompted us to investigate the utility of the relatively stable, soluble, and commercially available[7] pentafluorophenylcopper (**16**, PFPC)[8] as a condensing agent in the synthesis of bisbenzylisoquinoline-type structures.

The reaction of *dl*-6′-bromolaudanosine (**4**) with phenol was chosen as a model for our study. The best empirically determined Ullmann procedure in the benzylisoquinoline series involves the use of potassium carbonate and cupric oxide in hot pyridine for long reaction periods.[3,9] Under these conditions, crystalline 6′-phenoxylaudanosine (**7**) was obtained from phenol and bromide **4** in a maximum yield of 13%; TLC indicated that considerable debromination of **4** to laudanosine had occurred as a side reaction.

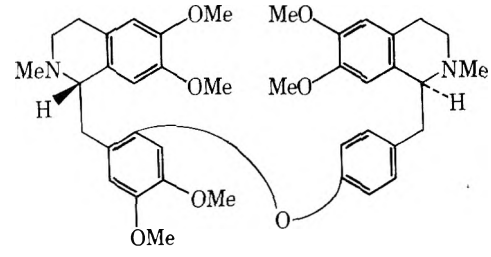
When equimolar amounts of bromide **4**, phenol, and PFPC were heated in acetonitrile, a red-brown precipitate, *presumably cuprous phenoxide, soon separated*. After 24 hr of refluxing, however, the precipitate had not dissolved and starting bromide was recovered in 95% yield. The desired reaction took place, however, when diglyme containing a small amount of pyridine was used as the solvent, the ether **7** being isolated in 31% yield. The yield of **7** was increased to 52% when pyridine alone was used as the solvent.

The synthesis of the natural (*S,S*) enantiomer (**17**) of *O*-tetramethylmagnolamine was next studied in order to test our procedure in the synthesis of a true bisbenzylisoquinoline. This was also a significant test case, since the classical Ullmann method is stated to give the corresponding *R,R* enantiomer **3** in only 2% yield.[2] Indeed, condensation of equimolar amounts of (*S*)-6′-bromolaudanosine (**6**), (*S*)-armepavine (**15**), and PFPC in diglyme–pyridine gave the crystalline bisbenzylisoquinoline **17** in 32% yield; the yield rose to 42% when pyridine alone was used as the solvent. When the pyridine reaction was repeated using a ratio of 1 equiv of bromide **6** to 2 equiv each of PFPC and phenol **15**, ether **17** was isolated in 53% yield, 85% of the excess (*S*)-armepavine being recovered.

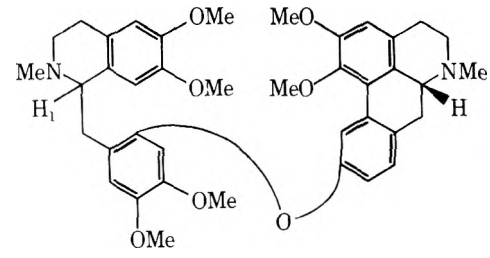
In view of the antitumor activity of thalicarpine (**1**), we chose to apply our procedure to the synthesis of some closely related unnatural benzylisoquinoline–aporphine structures, namely **18**–**21**.

(*R*)-Nuciferoline (**11**)[10] was prepared readily from natural stepharine (**12**)[11] by N-methylation, followed by a dienone–phenol rearrangement. Reaction of (*R*)-6′-bromolaudanosine (**5**) with an excess of **11** and PFPC gave the crystalline base **18** in 47% yield. Use of the enantiomeric *S* bromide **6** in this reaction gave the corresponding amorphous diastereomeric product **19** in comparable yield.

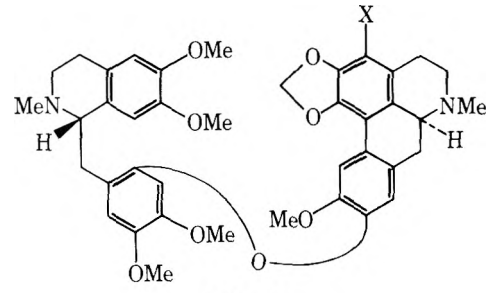
Cassythicine (**9**)[12] and *N*-methylcassyfiline (**10**)[13] were prepared from the phenolic base fraction of *Cassytha filiformis* by N-methylation, followed by countercurrent separation. Reaction of (*S*)-6′-bromolaudanosine (**6**) and PFPC with the above phenolic bases gave the crystalline thalicarpine analogs **20** and **21** in yields of 51 and 42%, respectively, based upon bromide **6**. Dimers **20** and **21**, which have the same stereochemistry as thalicarpine, are biogenetically reasonable structures which will probably be isolated eventually from natural sources.



17



18, H_1 ···(*R*)
19, H_1 ▬ (*S*)



20, X = H
21, X = OMe

Antitumor testing of the bisbenzylisoquinolines prepared in this work is in progress, as well as the extension of our Ullmann procedure to the synthesis of other natural and unnatural bisbenzylisoquinolines.

Experimental Section

Melting points are uncorrected. NMR spectra were determined with Varian A-60A and Varian A-100 spectrometers in $CDCl_3$ using tetramethylsilane as internal standard. Infrared spectra (KBr), ultraviolet spectra (EtOH), and mass spectra were determined using Perkin-Elmer Models 137, 202, and 270B spectrometers, respectively. Preparative TLC separations were carried out using KSGF silica plates; grade II basic alumina was used for column chromatography. The usual work-up for nonphenolic bases consisted in extraction of the total bases into 5% H_2SO_4, basification to pH 9 with ammonia, extraction into the organic solvent indicated, extraction of phenolic bases (if present) into 5% NaOH, washing the solvent (H_2O), drying ($MgSO_4$), and evaporation; recovery of any phenolic bases from the 5% NaOH wash was achieved by addition of excess NH_4Cl, followed by solvent extraction. Pentafluorophenylcopper is abbreviated as PFPC. New procedures for the resolution of laudanosine and armepavine are included, since the literature methods were, in our hands, unsatisfactory. Diglyme was distilled from $LiAlH_4$. Pyridine was dried by passing it through a 5A molecular sieve column, and stored (nitrogen) over molecular sieve. All Ullmann reactions were carried out under nitrogen in carefully dried equipment. Molecular weights of all new compounds were confirmed by mass spectrometry.

***dl*-Laudanosine and Its Resolution.** Sodium borohydride (5.0 g) was added in portions with stirring to a solution of 3,4-dihydropapaverine hydrochloride[14] (50 g) in methanol (250 ml). The solution was stirred (room temperature) for 1 hr, formalin (37%, 20 ml) was then added, and stirring was continued for an additional 1 hr.

Excess $NaBH_4$ was added, and after a further 1 hr, water (1000 ml) was added. The precipitate was filtered, dried, and crystallized from hexane to give white needles of *dl*-laudanosine (36 g, 70%), mp 114–115° (lit.[2] mp 114–115°).

A solution of *dl*-laudanosine (2.0 g) and (−)-mandelic acid (880 mg) in MeOH (20 ml) was diluted with ether (200 ml). On standing at room temperature, the salt of the *S* base (1.43 g) separated as white needles, mp 132–134°, $[\alpha]D$ +42°. Treatment of the latter with ammonia liberated (*S*)-laudanosine, which crystallized (hexane) as prisms, mp 87–88°, $[\alpha]D$ +98°.

The mother liquor from the above salt was evaporated and treated with ammonia, and the basic material was worked up as usual ($CHCl_3$). A solution of the resulting base and (+)-mandelic acid (340 mg) in MeOH (15 ml) was diluted with ether (150 ml) to give white needles of the salt, mp 133–134°, $[\alpha]D$ −42°. Ammonia treatment of the latter gave (*R*)-laudanosine, which crystallized from hexane as prisms, mp 86–87°, $[\alpha]D$ −97° (lit.[2] mp 89°, $[\alpha]D$ −97.48°).

***dl*-6′-Bromolaudanosine (4) and Its Enantiomers 5 and 6.** A solution of bromine (2.4 g) in acetic acid (30 ml) was added dropwise with stirring to an ice-cooled solution of *dl*-laudanosine (4.3 g) and sodium acetate (1.43 g) in 10% aqueous acetic acid (190 ml). The mixture was stirred for an additional 2 hr, during which time the initial yellow precipitate dissolved. After basification (KOH), the precipitate was extracted into ether. The usual work-up, followed by crystallization from $CHCl_3$–ether, gave **4** as needles (3.8 g, 76%), mp 124–125° (lit.[15] mp 128°).

Bromination of (*S*)-laudanosine and (*R*)-laudanosine was carried out in the same way, to give (*S*)-6′-bromolaudanosine (**5**) and the enantiomer **6**, both having mp 145–146° (lit.[2,3] mp 140–141°).

Resolution of *dl*-Armepavine. A mixture of *dl*-armepavine (3.43 g) and (−)-mandelic acid (1.675 g) was dissolved in hot absolute EtOH (110 ml). After cooling to room temperature and standing for a further 1 hr, the crystals which separated were filtered, washed with ether, and recrystallized from EtOH. The resulting colorless needles (1.7 g, mp 125–126°) were basified with ammonia and worked up as usual for basic material. Crystallization from acetone–ether gave (*S*)-armepavine (1.15 g), mp 136–137°, $[\alpha]D$ +108.5° (*c* 1.0, MeOH).

The mother liquor from the (−)-mandelate was evaporated, and the remaining base (2.35 g) was recovered by ammonia treatment and CH_2Cl_2 extraction. A solution of this base and (+)-mandelic acid (1.10 g) in hot EtOH (70 ml) afforded, after cooling, filtration of the solid, and recrystallization from acetone–ether, crystals (1.80 g), mp 126–127°. Regeneration of the base from this salt, followed by acetone–ether crystallization, gave (*R*)-armepavine (0.90 g), mp 136–137°, $[\alpha]D$ −107° (*c* 0.9, MeOH) (lit.[11] mp 138–139°).

(*R*)-Nuciferoline (11). A solution of stepharine[11] (5.0 g) in a mixture of 37% formalin (12 ml) and formic acid (12 ml) was heated (steam bath) for 5 hr. Ammonia basification followed by the usual work-up (CH_2Cl_2) gave alkaloidal material which was dissolved in 20% hydrochloric acid (100 ml) and heated (steam bath) for 3 hr. Ammonia basification, followed by the usual work-up (CH_2Cl_2), afforded, after crystallization from acetone, microcrystals of **11** (3.5 g, 68%), mp 229–231°, $[\alpha]D$ −140° (*c* 0.35, $CHCl_3$) (lit.[10] mp 227–229°, $[\alpha]D$ −157° (*c* 0.18, EtOH)).

Ullmann Condensation of *dl*-6′-Bromolaudanosine (4) with Phenol. A. Using Cupric Oxide. A mixture of cupric oxide (0.080 g), powdered potassium carbonate (0.150 g), bromide **4** (0.450 g), phenol (0.150 g), and pyridine (5 ml) was refluxed for 18 hr, additional cupric oxide (0.050 g) being added after the first 8 hr. Solvent evaporation, followed by the usual work-up for basic material, gave an oil which was chromatographed on alumina. Benzene elution, followed by crystallization (hexane–ether), gave white plates of *dl*-6′-phenoxylaudanosine (**7**, 0.06 g, 13%): mp 102–103°; NMR δ 2.39, 3.56, 3.80 (s, 3 H each), 3.73 (s, 6 H), 6.18, 6.65 (s, 1 H each), 6.55 (s, 2 H), and 6.9–7.15 (m, 5 H).

Anal. Calcd for $C_{27}H_{31}NO_5$: C, 72.15; H, 6.90; N, 3.11. Found: C, 72.21; H, 7.02; N, 2.85.

B. Using Pentafluorophenylcopper (PFPC) in Diglyme. A solution of phenol (0.100 g) and PFPC (0.250 g) in diglyme (4 ml) was heated at 100° for 30 min. Pyridine (2 ml) was added, followed by a solution of bromide **4** (0.435 g) in diglyme (4 ml). After heating for a further 18 hr, the mixture was poured into water (250 ml) and the product was isolated as in section A to give pure **7** (0.154 g, 34%), mp 102–103°.

C. Using PFPC in Pyridine. A solution of bromide **4** (0.440 g), phenol (0.135 g), and PFPC (0.250 g) in pyridine (10 ml) was heated at 110–115° for 6 hr. Additional PFPC (0.10 g) in pyridine (1 ml) was added and heating was continued for a further 5 hr. Work-up as in section A afforded crystalline ether **7** (0.235 g, 52%), mp 102–103°.

(*S,S*)-*O*-Tetramethylmagnolamine (17). A solution of (*S*)-6′-bromolaudanosine (**6**, 0.435 g), (*S*)-armepavine (0.650 g), and PFPC (0.500 g) in pyridine (10 ml) was heated at 115–120° for 7 hr. The mixture was poured into water (200 ml) and extracted with benzene. Work-up of the benzene phase for nonphenolic bases was followed by alumina (6 g) chromatography (1:1 chloroform–benzene elution), preparation TLC purification (7% methanol in chloroform, R_f 0.22), and hexane–ether crystallization to give white needles to ether **17** (0.351 g, 53%): mp 148–149.5°; $[\alpha]D$ +89° (*c* 0.5, MeOH) (lit.[16] mp 148–149°, $[\alpha]D$ +86.22°); NMR δ 2.42, 2.50, 3.58, and 3.60 (s, 3 H each), 3.74 (s, 6 H), 3.80 (s, 6 H), 6.12 (s, 2 H), 6.48 (s, 1 H), 6.51 (s, 2 H), 6.57 (s, 1 H), 6.73 (1 H, d, J = 8 Hz), and 6.98 (1 H, d, J = 8 Hz).

Anal. Calcd for $C_{40}H_{48}N_2O_7$: C, 71.85; H, 7.18; N, 4.19. Found: C, 71.30; H, 6.82; N, 3.97.

Unreacted excess (*S*)-armepavine (85%) was isolated from the phenolic base fraction of the original reaction mixture.

Aporphine–Benzylisoquinoline Dimer 18. A solution of (*R*)-nuciferoline (0.630 g) and PFPC (0.450 g) in pyridine (7 ml) was heated gradually to 120°. (*R*)-6′-Bromolaudanosine (**5**, 0.435 g) in pyridine (5 ml) was added and heating was continued for 5 hr. Solvent evaporation, followed by the usual nonphenolic base work-up, gave an oil which was chromatographed on alumina, the column being eluted successively with benzene and chloroform. The material eluted by chloroform was further purified by preparative TLC (10% MeOH in $CHCl_3$, R_f 0.3–0.4), followed by crystallization from hexane to give **18** as white microcrystals (0.280 g, 47%): mp 146–148°; $[\alpha]D$ −109° (*c* 0.37, MeOH); λ_{max} 208 nm (log ε 4.62), 230 sh (4.28), 270 (4.27), 305 (3.76); mass spectrum *m/e* (rel intensity) 668 (4), 462 (7), 437 (6), 206 (100); NMR δ 2.42, 2.50 (s, 3 H each), 3.50, 3.71, 3.76 (s, 6 H each), 6.15, 6.48, 6.53 (s, 1 H each), 6.55 (2 H, s), 6.75 (1 H, d, J = 6 Hz), 7.13 (1 H, d, J = 6 Hz), and 7.87 (1 H, s).

Anal. Calcd for $C_{40}H_{46}N_2O_7$: C, 72.07; H, 6.90; N, 4.20. Found: C, 71.86; H, 6.89; N, 4.21.

Aporphine–Benzylisoquinoline Dimer 20. A mixture of (*S*)-6′-bromolaudanosine (**6**, 0.430 g), cassythicine[12] (**9**, 0.580 g), PFPC (0.510 g), and pyridine (10 ml) was refluxed for 5 hr. The mixture was poured into water (100 ml) and the product was extracted into benzene. The usual work-up for nonphenolic bases gave an oil which was first chromatographed on a short silica column (5% MeOH in chloroform eluent), then purified further by preparative TLC (2:2:1 $CHCl_3$–EtOAc–MeOH, R_f 2.6–3.1). Crystallization from methanol gave **20** as white needles (0.340 g, 51%): mp 177–178°; $[\alpha]D$ +41° (*c* 0.2, $CHCl_3$); λ_{max} 283 nm (log ε 4.20), 303 (4.01); mass spectrum *m/e* (rel intensity) 680 (<2); NMR δ 2.41, 2.47, 3.77 (s, 3 H each), 3.87 (s, 6 H), 3.90 (s, 3 H), 3.98 (s, 3 H), 5.94 (s, 1 H), 5.99 and 6.17 (2 H, close doublets, $-OCH_2O-$), 6.50 (s, 3 H), 6.57 (s, 1 H), 6.62 (s, 1 H), and 7.75 (s, 1 H).

Anal. Calcd for $C_{40}H_{44}N_2O_8$: C, 67.29; H, 6.47; N, 4.11. Found: C, 66.81; H, 6.50; N, 3.78.

Aporphine–Benzylisoquinoline Dimer 21. A mixture of bromide **6** (0.500 g), *N*-methylcassyfiline[13] (**10**, 0.680 g), PFPC (0.500 g), and pyridine (10 ml) was heated at 115–120° for 5 hr. The reaction mixture was worked up as for the synthesis of base **20** (see above). Crystallization from methanol gave white needles of **21** (0.343 g, 42%): mp 197–199°; $[\alpha]D$ +28° (*c* 0.2, $CHCl_3$); λ_{max} 285 nm (log ε 4.47), 301 (3.95), 310 (4.14); mass spectrum *m/e* 710 (rel intensity) (1); NMR δ 2.44, 2.48, 3.58 (s, 3 H each), 3.77 (s, 6 H), 3.82, 3.94, 4.01 (s, 3 H each), 5.94 (s, 1 H), 6.00 and 6.18 (2 H, close doublets, $-OCH_2O-$), 6.54 (s, 2 H), 6.58 (s, 1 H), 6.64 (s, 1 H), and 7.70 (s, 1 H).

Anal. Calcd for $C_{41}H_{46}N_2O_9$: C, 66.35; H, 6.47; N, 3.94. Found: C, 65.92; H, 6.56; N, 3.57.

Acknowledgment. We are grateful to the National Institutes of Health for a grant (CA-11445) in support of this work. We also thank Dr. M. J. Mitchell for the *Cassytha* alkaloids used in this study, Dr. W. A. Sheppard (E. I. du Pont de Nemours and Co.) for valuable discussions of organocopper chemistry, and Dr. I. Noguchi and Mr. J. Skiles for the improved resolution of laudanosine.

Registry No.—**4**, 54712-52-6; **5**, 4829-34-9; **7**, 54677-43-9; **9**, 5890-28-8; **10**, 3984-08-5; **11**, 1862-49-3; **12**, 2810-21-1; **17**, 7283-30-9; **18**, 54677-44-0; **20**, 54677-45-1; **21**, 54677-46-2; *dl*-laudanosine, 1699-51-0; (−)-mandelic acid, 611-71-2; (*S*)-laudanosine (−)-mandelate, 54677-47-3; (*S*)-laudanosine, 2688-77-9; (+)-mandelic acid,

17199-29-0; (*R*)-laudanosine (+)-mandelate, 54677-48-4; (*R*)-laudanosine, 85-63-2; *dl*-armepavine, 5884-67-3; (*S*)-armepavine (−)-mandelate, 54677-49-5; (*S*)-armepavine, 14400-96-5; (*R*)-armepavine (+)-mandelate, 54677-50-8; (*R*)-armepavine, 524-20-9; phenol, 108-95-2; cupric oxide, 1317-38-0; pentafluorophenylcopper, 18206-43-4.

References and Notes

(1) S. M. Kupchan and H. W. Altland, *J. Med. Chem.*, **16**, 913 (1973), and references cited therein.
(2) M. Tomita and B. Ito, *Yakugaku Zasshi*, **78**, 103 (1958).
(3) M. Tomita, H. Furukawa, S. T. Lu, and S. M. Kupchan, *Chem. Pharm. Bull.*, **15**, 959 (1967).
(4) S. M. Kupchan, A. J. Liepa, V. Kameswaran, and K. Sempuka, *J. Am. Chem. Soc.*, **95**, 2995 (1973).
(5) H. Weingarten, *J. Org. Chem.*, **29**, 3624 (1964).
(6) T. Kawaki and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, **45**, 1499 (1972).
(7) Peninsular Chemical Co., Gainesville, Fla.
(8) A Cairncross and W. A. Sheppard, *J. Am. Chem. Soc.*, **90**, 2186 (1968).
(9) For the study with model compounds see M. Tomita, K. Fumitani and Y. Aoyagi, *Chem. Pharm. Bull.*, **13**, 1341 (1965).
(10) K. Bernauer, *Helv. Chim. Acta*, **47**, 2122 (1964).
(11) M. P. Cava, K. Nomura, S. K. Talapatra, M. J. Mitchell, R. H. Schlessinger, K. T. Buck, J. L. Beal, B. Douglas, R. F. Raffauf, and J. A. Weisbach, *J. Org. Chem.*, **33**, 2785 (1968).
(12) M. P. Cava, K. V. Rao, B. Douglas, and J. A. Weisbach, *J. Org. Chem.*, **33**, 2443 (1968).
(13) S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Aust. J. Chem.*, **19**, 297 (1966).
(14) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 100 (1951).
(15) C. Schoepf and K. Thierfelder, *Justus Liebigs Ann. Chem.*, **537**, 143 (1939).
(16) K. Ito and T. Aoki, *Yakugaku Zasshi*, **79**, 325 (1959).

Synthesis of the Potentially Cytotoxic Compound 5-[Bis(2-chloroethyl)amino]-1,3-phenylene Biscarbamate

Mark A. Thorn,* George H. Denny, and Robert D. Babson

Merck Sharp and Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey 07090

Received February 6, 1975

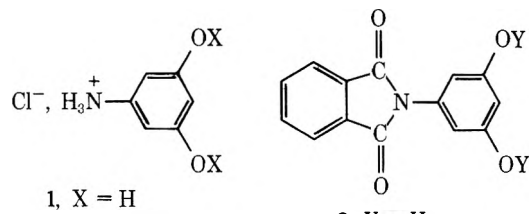
5-Aminoresorcinol hydrochloride (1) reacted with ethylene oxide to give **2**, which could not be converted to its bis(2-chloroethyl)amino derivative in the presence of standard reagents. Compound **1** was therefore converted to **3** by treatment with phthalic anhydride and thence to **4** by reaction with benzyl bromide under alkaline conditions. Removal of the phthalimido group with hydrazine, followed by treatment with hydrochloric acid, gave the hydrochloride **5**, which reacted with ethylene oxide to produce **6**. Bistosylation to **7**, followed by treatment with lithium chloride in acetone, afforded the mustard **8** in high yield. Removal of the blocking groups to give **9** was accomplished with refluxing trifluoroacetic acid in the presence of anisole as a benzyl cation scavenger, the product being isolated and characterized as its trifluoroacetic acid solvate. Treatment of **9** with cyanogen bromide gave the dicyanate **10** as a crude powder which underwent addition of water to give the dicarbamate **11** upon treatment with hydrochloric acid. Compounds **8**–**11** are potentially cytotoxic nitrogen mustards.

The presence of the *O*-carbamate group as a structural feature of a number of antitumor compounds[1] suggests that this group might be incorporated in concert with other structural moieties of known antitumor propensities. The synthetic objective undertaken in the present work was to incorporate two *O*-carbamate functions into the structure of an aromatic nitrogen mustard, the latter being a structural class having established antitumor activity.[2] Furthermore, it has been demonstrated in certain instances that more favorable antitumor activity was obtained with meta-substituted aromatic nitrogen mustards than with the corresponding ortho or para derivatives.[3]

Phenolic derivatives of aniline mustard have been prepared by Artico and Ross[4] and more recently by Edwards et al.[5] In addition, two nitrogen mustards of the pyrocatechol series have been described by Vasil'eva and Berlin.[6]

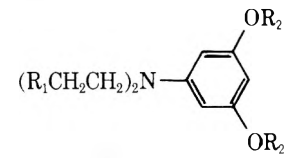
Synthetic strategy directed toward the synthesis of **11** was focused at first on schemes originating with demethylation of the known compound 1-[bis(2-chloroethyl)amino]-3,5-dimethoxybenzene.[7] Conventional reagents and conditions for demethylation of phenolic ethers, such as hot hydrochloric acid, gave consistently unsatisfactory results. Attention was next given to the synthesis of **2** as a possible substrate for mustard synthesis. The diol **2** was prepared by treating 5-aminoresorcinol hydrochloride (**1**)[8] with ethylene oxide. It was found, however, that **2** underwent extensive decomposition when attempts were made to replace the aliphatic hydroxyl groups by chloro groups using a variety of methods.

Protection of the aromatic hydroxyl groups was therefore a necessity before attempting further structural modification of **1**. This required that the amino function itself be protected at the outset. This was accomplished by phthalimidation according to a modification of the general method of Wanag,[9] using phthalic anhydride in acetic acid to provide **3**. Subsequent formation of the bisbenzyl ether **4** was undertaken with the expectation that eventual removal



1, X = H
5, X = CH_2Ph

3, Y = H
4, Y = CH_2Ph



2, R_1 = OH; R_2 = H
6, R_1 = OH; R_2 = CH_2Ph
7, R_1 = OTs; R_2 = CH_2Ph
8, R_1 = Cl; R_2 = CH_2Ph
9, R_1 = Cl; R_2 = H; CF_3COOH solvate
10, R_1 = Cl; R_2 = CN
11, R_1 = Cl; R_2 = $CONH_2$

Ph = phenyl
Ts = *p*-toluenesulfonyl

could be accomplished without difficulty,[5] a prediction which fortunately proved to be correct. Synthesis of **4** proceeded in a satisfactory manner by treatment of **3** with benzyl bromide in dimethylformamide in the presence of sodium methoxide as a proton acceptor. The phthalimido group was next removed with hydrazine in aqueous ethanol and the product was isolated as the hydrochloride **5**. Conventional treatment of **5** with ethylene oxide in aqueous acetic acid gave the diol **6**, now ready for the crucial and sensitive construction of the bis(2-chloroethyl)amino moiety. Among the possible conditions explored were tosyl chloride–pyridine,[10] phosphorus oxychloride–chloroform (or benzene),[4,11] and thionyl chloride–pyridine.[12] Each of these attempts at direct conversion gave intractable gums or oils whose NMR spectra suggested the presence of degraded starting material. Mesyl chloride–pyridine[13] resulted in the formation of crude bis(methanesulfonate). Use of the system triphenylphosphine–carbon tetrachloride[14] provided some encouragement as the NMR spectrum of the reaction product showed the presence of the desired mustard. However, a number of attempts to separate the desired compound from the by-products and unchanged starting material were not successful.

Synthesis of the protected mustard **8** was performed in two steps via displacement of the bistosylate **7** according to a modification of the method of Werner,[15] in which the system lithium chloride–acetone[16] was used. Consistently high (>90%) yields were realized in the displacement step. Conditions used for debenzylation of **8** to **9** were generally those described by Marsh and Goodman,[17] with the inclusion of anisole as a benzyl cation scavenger as described by Sakakibara et al.[18] Use of the reagent trifluoroacetic acid proved to be a fortunate choice here, in view of the fact that purification proceeded in a facile manner to provide the stabilized trifluoroacetic acid solvate of the product. Subsequent experiments showed that when the trifluoroacetic acid was removed [Amberlite IR-45 (OH^-); methanol solution] the resultant desolvated **9** was obtained as an unstable oil.[19] Conversion of **9** to **11** proceeded in two stages via the dicyanate **10** using the cyanogen halide method, developed by Grigat and Pütter.[20] Preliminary experiments in which the model compound resorcinol was converted to its dicarbamate showed commercial cyanogen bromide to be an effective reagent.[21] Furthermore, it was established with the model system that prior neutralization of the trifluoroacetic acid of solvation with triethylamine permits the reaction with cyanogen bromide to proceed without difficulty. Application of this method to the conversion of **9** to **11** was seen to proceed in a facile manner. The dicyanate **10** was isolated during a probe preparation as a reasonably pure solid having a correct infrared spectrum. A satisfactory purification method was not found for **10**, and it was usually not isolated during the preparation of **11**.

It is planned to have the new compounds described herein screened for antitumor activity by the Drug Research and Development Branch, National Institutes of Health.

Experimental Section

Melting points were obtained on a Thomas-Hoover Unimelt using open capillary tubes and are uncorrected. An atmosphere of nitrogen was maintained above each of the reaction mixtures. Evaporations were performed at diminished pressure on a rotary evaporator. Petroleum ether refers to that fraction boiling at 30–60°. Analyses indicated in the table only by the symbols of the elements were within ±0.3% of the theoretical values. The ir spectra were obtained on a Perkin-Elmer Model 137 recording spectrophotometer and the uv spectra by G. B. Smith and staff using a Cary Model 118 spectrophotometer. Varian Associates A-60A and JEOL C-60HL instruments were used by A. W. Douglas and staff for recording NMR spectra. In each case where the preparation of a new compound is described it was found to have ir (Nujol), NMR (DMSO-d_6), and uv spectra which were in accord with expectation. The authors are grateful to R. N. Boos (and J. L. Gilbert) and associates for microanalyses. Assistance in the preparation of intermediates was provided by J. J. Seman and M. A. Ryder.

5-Aminoresorcinol Hydrochloride (1). Concentrated ammonium hydroxide (3 l.) was added over a 3-min period to 500 g (3.1 mol) of solid phloroglucinol dihydrate, while stirring and cooling. Upon completion of the addition a stream of ammonia was bubbled through the reaction mixture for 30 min. The cooling bath was removed and stirring was continued at room temperature for 46 hr. Vacuum concentration (bath, 50°) of the clear brown solution gave a solid, to which was added 1 l. of 5 *N* HCl, and the mixture was concentrated under vacuum (nitrogen was no longer required) to a yellow solid. Crystallization from 1.5 l. of warm acetone (Darco G-60) gave 419 g (84%) of **1**. A sample of the product decomposed without melting when heated to 260°, consistent with melting point behavior described in the literature.[8] A high level of purity was substantiated by examination of spectra (ir and NMR) and elemental determinations.

5-Phthalimidoresorcinol (3). A mixture was prepared from 200 g (1.24 mol) of **1**, 276 g (1.87 mol) of phthalic anhydride, and 2.6 l. of glacial acetic acid. This was stirred and to it was added all at once 112 g (1.36 mol) of anhydrous sodium acetate. The mixture was heated under reflux for 75 min, then poured, with stirring, into 6 l. of hot water. This was boiled for 5 min, and the solid was collected by filtration and washed with 700 ml of hot water. The light tan product amounted to 268 g (85%) of pure **3**; when heated the compound decomposed above 300° without prior melting.

5-Phthalimidoresorcinol Dibenzyl Ether (4). A clear solution was prepared by dissolving 616 g (2.42 mol) of **3** in 3.45 l. of DMF. This was cooled in an ice bath and to it was added 279 g (5.16 mol) of sodium methoxide at a rate such that the temperature did not exceed 25°. A suspension was obtained to which was added cautiously 616 ml (887 g, 5.2 mol) of benzyl bromide, again keeping the temperature close to 25°. Stirring was continued for 24 hr, whereupon the turbid mixture was poured into 10.3 l. of vigorously agitated water. A gum was obtained which was separated and vacuum dried at room temperature. Trituration of this with 6 l. of hot ethanol caused solidification. The mixture was cooled, and the solid was collected and washed with 1 l. of ethanol, then dried to give 854 g (81%) of nearly pure product. A sample prepared in a separate run using the same procedure was crystallized from acetone to give white crystals of **4**, mp 137–139°.

5-Aminoresorcinol Dibenzyl Ether Hydrochloride (5). To a stirred suspension of 28 g (0.064 mol) of **4** in 179 ml of ethanol was added 9.3 g (0.16 mol of $N_2H_4 \cdot H_2O$) of an 85% aqueous solution of hydrazine hydrate. The reaction mixture was heated under reflux for 2 hr (thickening of the reaction mixture required the addition of 100 ml of ethanol during this period). Concentration under vacuum (room temperature) gave a white paste which was slurried with 156 ml of ether and the mixture was combined with 156 ml of 40% aqueous KOH. The layers were separated, the aqueous layer was extracted with four 150-ml portions of ether, and the combined ether solutions were dried (K_2CO_3), decolorized (Norit A), and filtered through a pad of Celite 545. The filtrate was reduced in volume to 175 ml, cooled, and treated with a stream of gaseous HCl (30 min). The precipitated solid was washed with ether and dried to give a first crop of 12.8 g, mp 188–189°. Concentration of the ethereal mother liquors to a volume of 75 ml gave an additional 4.4 g (same melting point), bringing the total crude yield to 17.2 g (79%).[22] These crops were combined and crystallized twice from ethanol (Darco G-60) to give 10.7 g (49%) of pure **5**, mp 191–193°.

5-[Bis(2-hydroxyethyl)amino]resorcinol Dibenzyl Ether (6). In a flask protected from moisture and equipped with a cold-finger condenser containing a Dry Ice–acetone mixture were placed 250 g (0.73 mol) of **5** and 1.61 l. of 50% aqueous acetic acid. The mixture was stirred and cooled to 0°, then to it was added all at once 242 ml (4.86 mol) of ethylene oxide. Stirring was continued for 19 hr while the flask and its surrounding bath came to room temperature. Residual ethylene oxide was removed with a stream of nitrogen (1.5 hr) causing a solid to separate. This was collected by filtration, washed with water, and dried to yield 231 g (80%) of **6**, mp 94–95°. A sample for analyses was recrystallized from ethanol, mp 93–96°.

5-[Bis(2-tosyloxyethyl)amino]resorcinol Dibenzyl Ether (7). A solution was prepared from 5.0 g (0.013 mol) of **6** and 21 ml of pyridine (dried over KOH). This was cooled to −5° and to it was added in one portion 5.3 g (0.028 mol) of *p*-toluenesulfonyl chlo-

ride. Following 30 min of stirring at 0 to −5° the reaction mixture was kept overnight in the refrigerator. It was next cooled to 0° and 62 ml of water was added in small portions while keeping the temperature below 5°. An orange oil separated. To the mixture was added 50 ml of $CHCl_3$, and after being stirred for 30 min the layers were separated and the aqueous layer was back-extracted with two 50-ml portions of $CHCl_3$. The combined $CHCl_3$ layers were dried (Na_2SO_4), treated with Darco G-60, and concentrated to dryness (bath, 50°). The resultant oil was evaporated successively with two 50-ml portions each of ethanol, acetone, and petroleum ether. It was next covered with 50 ml of ethanol and warmed to 50°, with stirring, for 30 min. Light orange crystals were obtained which were washed successively with cold 10-ml portions of ethanol, petroleum ether, and ether. When dried the product amounted to 6.7 g (75%) of pure **7**, mp 86–89°.

5-[Bis(2-chloroethyl)amino]resorcinol Dibenzyl Ether (8). A glass-lined reaction vessel was charged with 60.0 g (0.085 mol) of **7**, 14.5 g (0.34 mol) of dry lithium chloride, and 600 ml of dry acetone. The vessel was sealed and heated at 80° for 8 hr with agitation. Upon cooling a solid was seen to have separated. This was removed by filtration and washed with acetone, the combined filtrate and wash liquors then being concentrated to dryness. This solid residue was stirred thoroughly with 250 ml of $CHCl_3$, leaving behind a granular solid (mp >275°) which was separated by filtration. The filtrate was next washed with 250 ml of water and the aqueous layer was back-extracted with 250 ml of $CHCl_3$. The combined $CHCl_3$ layers were dried ($MgSO_4$), filtered, and concentrated to dryness.

A total of 178 g (0.254 mol) of **7** was processed in this manner in three separate runs. The combined crude solids were crystallized from hot ethanol (600 ml) and the crystalline product was washed successively with 100-ml portions of cold ethanol and petroleum ether to yield 104 g (95%) of **8**, mp 88–89°.

5-[Bis(2-chloroethyl)amino]resorcinol Solvate with Trifluoroacetic Acid (9). A solution was prepared from 98.7 g (0.23 mol) of **8**, 987 ml of trifluoroacetic acid, and 31.6 ml (31.5 g, 0.29 mol) of anisole. The reaction mixture was stirred and heated under reflux for 5 hr, then cooled and concentrated to an oil (bath 50°). This was evaporated with three 1-l. portions of C_6H_6 and triturated with 1 l. of $CHCl_3$. Overnight storage under $CHCl_3$ in the refrigerator gave a crystalline solid which was washed with cold $CHCl_3$ and vacuum dried at room temperature to provide 70.2 g (84%) of **9**, mp 138–143°. Differential thermal analysis (20 deg/min) showed a melting point endotherm at 144° followed immediately by a decomposition exotherm.

The description of compound **9** as a solvate (rather than a salt) is based on the following experimental observations. Firstly, potentiometric titration ($HClO_4$–HOAc solvent) showed equiv wt 371 (calcd for $C_{10}H_{13}Cl_2NO_2 \cdot C_2HF_3O_2$, equiv wt 364), without first generating the free amine as is necessary with amine hydrochlorides [using excess $Hg(OAc)_2$]. This substantiated the availability of the electron pair on nitrogen under these conditions. Furthermore, the NMR spectra of the solvate **9** and the desolvated compound showed identical methylene proton signals. The only difference was in the position and integration of the active envelope, an expected result of the difference in acidity. This indicated an absence of protonation on nitrogen by trifluoroacetic acid, which would be expected to produce a chemical shift difference and splitting of the absorption. Also, the infrared spectrum of **9** showed a distinct carbonyl band at 5.7 μ, characteristic of molecular trifluoroacetic acid, in contrast to the known shift of this absorption to longer wavelengths which accompanies salt formation. Finally, thermogravimetric analysis showed a weight loss of 21% at 100° (browning), which is well below the observed melting point, indicating the release of solvent as opposed to the dissociation of a salt.

5-[Bis(2-chloroethyl)amino]-1,3-phenylene Biscarbamate (11). To a stirred solution (at 3°) of **9** (10 g, 28 mmol) in acetone (100 ml) containing 4.0 ml (28 mmol) of triethylamine was added in one portion a solution of cyanogen bromide (10 g, 97 mmol) in 100 ml of acetone, causing a temperature increase to 8°. The temperature was lowered to −5° and 8.0 ml (56 mmol) of additional triethylamine was added over a 6-min period (temperature about 0°). The reaction mixture was stirred at 0° for 0.5 hr and then poured with stirring into 750 ml of cold water, giving a solid which was collected and washed with water. In a separate preparation this solid was washed with ether to give the crude dicyanate **10**, mp 73–75°, ir ν_{CN} 4.4 μ. The combined filtrate and wash liquors were extracted with an equal volume of $CHCl_3$, which on concentration gave a brown oil. This was combined with the solid dicyanate from above, dissolved in 75 ml of acetone, cooled to 0°, and treated with 28 ml of 20% HCl at such a rate that the temperature did not rise above 5°. The temperature was maintained at 0° for 15 min, then allowed to come to room temperature (30 min), and the solution was finally concentrated to dryness (bath, 50°) giving a brown glass. This became crystalline when triturated with 50 ml of ethanol and left at room temperature for 64 hr. The product was washed lightly with ethanol and then with ether, giving 5.7 g (61%) of white crystalline **11**, mp 187–188° dec. If necessary, it could be recrystallized from acetone.

5-[Bis(2-hydroxyethyl)amino]resorcinol (2). A solution of **1** (10 g, 0.062 mol) in ethanol (100 ml) containing 230 mg of *p*-toluenesulfonic acid monohydrate was treated with ethylene oxide (61.6 ml, 1.24 mol) in the usual way (see preparation of **6**). Concentration (bath, 50°) gave a syrup which solidified when triturated with 15 ml of acetone to give 4.8 g (36%) of yellow crystals, mp 157–159° dec. A sample for analysis was obtained by crystallization from ethanol, mp 161–162° dec.

Acknowledgment. This investigation was supported by Contract NIH-72-2002 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

Registry No.—**1**, 6318-56-5; **2**, 54845-06-6; **3**, 54845-07-7; **4**, 54845-08-8; **5**, 54845-09-9; **6**, 54845-10-2; **7**, 54845-11-3; **8**, 54845-12-4; **9**, 54845-13-5; **10**, 54845-14-6; **11**, 54845-15-7; ammonium hydroxide, 1336-21-6; phloroglucinol, 108-73-6; phthalic anhydride, 85-44-9; ethylene oxide, 75-21-8; *p*-toluenesulfonyl chloride, 98-59-9; cyanogen bromide, 506-68-3.

Supplementary Material Available. Spectral and analytical data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-1556.

References and Notes

(1) See W. C. Fleming, W. W. Lee, and D. W. Henry, *J. Med. Chem.*, **16**, 570 (1973), for pertinent references.
(2) Examples of clinically useful aromatic nitrogen mustards are L-3-[*p*-[bis(2-chloroethyl)amino]phenyl]alanine (melphalan) and 4-[*p*-[bis(2-chloroethyl)amino]phenyl]butyric acid (chlorambucil).
(3) I. Niculescu-Duvăz, V. Feyns, V. Savaniu, M. Ionescu, A. Şerban, and A. Cambanis, *Rev. Roum. Chim.*, **14**, 535 (1969).
(4) M. Artico and W. C. J. Ross, *Biochem. Pharmacol.*, **17**, 893 (1968).
(5) P. D. Edwards, D. L/ D. Foster, L. N. Owen, and M. J. Pringle, *J. Chem. Soc.*, 2397 (1973).
(6) M. N. Vasil'eva and A. Ya. Berlin, *Zh. Obshch. Khim.*, **32**, 3088 (1962).
(7) A. H. Sommers, U. Biermacher, S. B. Brehm, and J. H. Short, *J. Med. Chem.*, **13**, 581 (1970).
(8) (a) J. Pollak, *Monatsh. Chem.*, **14**, 401 (1893); (b) U.S. Patent 2,572,284 (1951).
(9) G. Wanag, *Chem. Zentralbl.*, **II**, 3815 (1939).
(10) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).
(11) A. Cohen and R. S. Tipson, *J. Med. Chem.*, **6**, 822 (1963).
(12) L. A. Brooks and H. R. Snyder, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 698.
(13) L. Goodman, R. Spencer, G. Casini, O. Crews, and E. Reist, *J. Med. Chem.*, **8**, 251 (1965).
(14) (a) J. B. Lee and T. J. Nolan, *Can. J. Chem.*, **44**, 1331 (1966); (b) J. B. Lee and I. M. Downie, *Tetrahedron*, **23**, 359 (1967).
(15) W. Werner, *J. Prakt. Chem.*, **314**, 577 (1972).
(16) (a) P. L. Julian and A. Magnani, *J. Am. Chem. Soc.*, **71**, 3207 (1949); (b) G. Eglinton and M. C. Whiting, *J. Am. Chem. Soc.*, 3650 (1950); (c) G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Lett.*, 1393 (1969).
(17) J. P. Marsh, Jr., and L. Goodman, *J. Org. Chem.*, **30**, 2491 (1965).
(18) S. Sakakibara, Y. Nobuhara, Y. Shimonishi, and K. Kiyoi, *Bull. Chem. Soc. Jpn.*, **38**, 120 (1965).
(19) Alternate means of debenzylation (H_2–5% Pd/C, concentrated HCl, HCl–HOAC, $BF_3 \cdot Et_2O$, liquid HF–anisole, CF_3CO_2H at room temperature) were unsuccessful, resulting in large amounts of degraded material and/or starting material.
(20) E. Grigat and R. Putter, *Chem. Ber.*, **97**, 3012, 3018 (1964).
(21) Preparation of resorcinol dicarbamate using carbamyl chloride (H_2NCOCl) was also successful. However, it failed with **9**, apparently because the tertiary nitrogen atom was sufficiently basic to catalyze decomposition of the H_2NCOCl.
(22) In a repeat preparation using this procedure a crude yield of 97% was realized.

Synthesis of Fluorescent Labeled Derivatives of Aminopropylpyrimidines

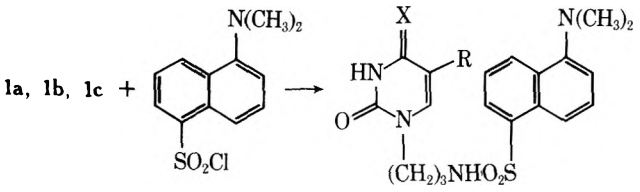
W. A. Summers, J. Y. Lee, and J. G. Burr*

Department of Chemistry, University of Oklahoma, Norman, Oklahoma 73069

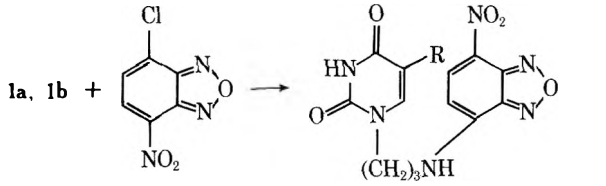
Received September 16, 1974

The preparation of some 1-(3-aminopropyl)pyrimidines (1) is discussed and their conversion to fluorescent compounds (2 and 3) with *N,N*-dimethylaminonaphthalenesulfonyl chloride and 7-chloro-4-nitrobenzo-2-oxa-1,3-diazole, respectively, is elaborated.

In order to explore the energy donor capabilities of the excited states of the pyrimidines, uracil, thymine, and cytosine, we have prepared a series of compounds in which the pyrimidine is bound via a trimethyleneamino chain to an appropriate fluor. The fluors chosen for the work reported here were 5-dimethylaminonaphthalenesulfonyl[1] and 7-nitrobenzo-2-oxa-1,3-diazole.[2] The compounds thus prepared are shown as **2a–c** and **3a,b**. Energy transfer in



2a, X = O; R = CH_3
b, X = O; R = H
c, X = NH; R = H



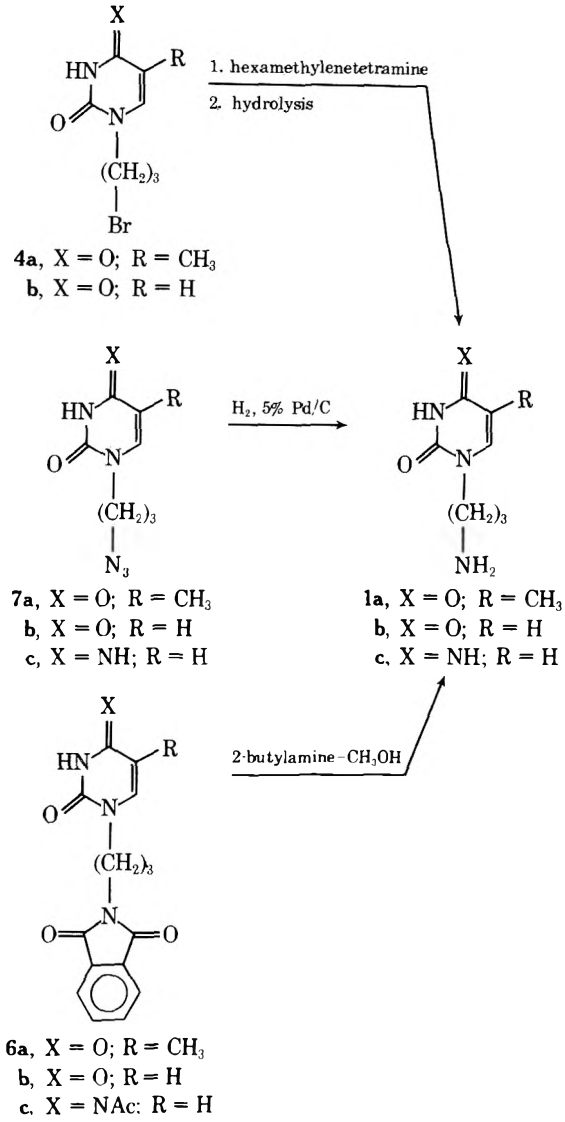
3a, R = CH_3
b, R = H

these compounds and their photochemistry are reported elsewhere.[3] The pertinence of this work to the photochemistry and photobiology of these pyrimidine bases has been established by other work, from this laboratory[4-7] and in the laboratories of others.[8,9]

Recently,[10] Brown, Eisinger, and Leonard reported the preparation of 1,3-(bispyrimidinyl)propanes and 1-pyrimidinyl-3-purinylpropanes from 1-(3-aminopropyl)pyrimidines. Our synthetic scheme is based on their procedures, but we report several alternate procedures for preparing the amines.

We chose two readily available fluorogenic reagents, 5-dimethylaminonaphthalenesulfonyl chloride (dansyl chloride, DNS Cl) and 4-chloro-7-nitrobenzo-2-oxa-1,3-diazole (NBD Cl), and converted 3-aminopropylthymine, -uracil, and -cytosine into their corresponding fluorescent derivatives. Attempts to prepare a third type of compound, 1-[3-(α-naphthylamino)propyl]thymine, though successful synthetically, afforded a product which underwent rapid discoloration on standing. This instability, it was felt, would preclude later spectroscopic studies and thus further elaboration of the series was suspended.

In the course of our experimental work three routes were investigated for the preparation of the aminopropylpyrimidines: (1) Delepin (Sommelet) reaction,[11] (2) aminolysis of phthalimidopropylpyrimidines, and (3) catalytic reduction of azidopropylpyrimidines.[12] All afforded good yields of amine with the exceptions that preparation of the uracil



4a, X = O; R = CH_3
b, X = O; R = H

7a, X = O; R = CH_3
b, X = O; R = H
c, X = NH; R = H

1a, X = O; R = CH_3
b, X = O; R = H
c, X = NH; R = H

6a, X = O; R = CH_3
b, X = O; R = H
c, X = NAc; R = H

derivative by method 1 produced only minor quantities of desired amine, and aminolysis of the phthalimidopropyl derivatives was successful only with refluxing 2-butylamine–methanol.

Catalytic reduction of the appropriate azide also afforded the amine and, in our hands, was a simpler reaction to run than that previously described using Raney nickel.[10] Reduction in alcoholic or aqueous alcoholic solutions over 5% Pd on carbon proceeded rapidly with a minimum of work-up necessary.

The insensitivity of dansyl chloride toward hydrolysis in aqueous solutions[6] permitted the use of aqueous systems for the preparation of the fluorescent derivatives. Dimethylformamide, dimethyl sulfoxide, and pyridine were found to be unsatisfactory solvents, since the percent conversion of amine to fluorescent derivative was low. When

Table I
Absorption and Emission Properties of the Fluorescent Derivatives of Aminopropylpyrimidines

Compd	Absorption maxima, nm (ε)[a]	Emission maximum,[b] nm
2a	258.5 (18,300)	517
	335 (4800)	
2b	258 (20,000)	517
	334 (4960)	
2c	286 (19,100)	517
	320 (1800)	
N-Propyl-5-dimethylamino-naphthalene-1-sulfonamide	251 (12,600)	517
	334 (4800)	
3a	270 (9400)	523
	340 (7100)	
	475 (23,000)	
3b	261 (10,100)	523
	340 (7000)	
	476 (22,900)	
4-Propylamino-7-nitro-benzo-1,3-diazole	342 (7140)	523
	478 (21,400)	

[a] l. M^{-1} cm^{-1} in alcohol or 50% aqueous alcohol. [b] Data obtained on a Perkin-Elmer Model MPF-3L in 30% aqueous ethanol.

aqueous acetonitrile (pH 8) was used, the yields of fluorescent derivative became quantitative and the work-up simpler. All the dansyl derivatives crystallized from the reaction mixture and were readily purified by silica chromatography. The compounds are soluble in most organic solvents and slightly soluble in water. Use of preparative TLC is not recommended for purification of these materials, since we observed some decomposition on the plate during and after development. Some decomposition was also noted after prolonged periods in water.

NBD chloride is more susceptible to hydrolysis in aqueous systems and initial studies indicated that hydrolysis may be competitive with the amination, particularly at high pH. The preparation of the NBD derivatives could be accomplished in refluxing ethanol with anhydrous potassium carbonate as a base. The NBD derivatives were crystalline solids with low solubility in most solvents.

The ultraviolet spectra of all the derivatives exhibit maxima characteristic of both chromophores with about 2.4% hypochromism at the pyrimidine absorption maximum for **3a** and no new absorption bands. Table I lists the absorption and emission data for the fluorescent derivatives prepared.

Experimental Section

1-(3-Aminopropylthymine) hydrochloride (**1a** HCl), 1-(3-bromopropyl)uracil (**4b**), and (3-bromopropyl)-N^4-acetylcytosine were prepared by previously reported procedures.[10] Dansyl chloride, NBD chloride (Pierce Chemical Co.), and *N*-(3-bromopropyl)phthalimide (Aldrich Chemical Co.) were used without further purification. Infrared spectra were recorded on a Beckman IR 18A, ultraviolet spectra on an Hitachi Perkin-Elmer 124, NMR spectra on a Varian T-60, and mass spectra on a Hitachi Perkin-Elmer REM-5E. Melting points were observed on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz., and all samples were dried at 92° (3 Torr) over P_2O_5 prior to analysis.

1-[*N*-(3-Phthalimidopropyl)]thymine (6a). Thymine (5.0 g, 39.0 mmol) was dissolved in DMSO (100 ml) and then treated with potassium carbonate (5.5 g, 40 mmol) and *N*-(3-bromopropyl)phthalimide (5.35 g, 20.0 mmol) for 11 hr at room temperature. After the precipitate was filtered, the filtrate was vacuum concentrated to a viscous, yellowish liquid. This liquid was diluted with water (1:1) and the suspension was extracted with chloroform (5 × 100 ml). The chloroform fractions were combined and concentrated at reduced pressure. The resulting oil was dissolved in a small volume of ethyl acetate and induced to crystallize with ether. A total of 3.89 g was isolated (66% based on alkylating agent): mp 197–198°; ir 3.17, 3.3, 3.52, 5.62, 5.82, 5.90, 7.20, 9.4, 11.2, 13.7 μ; uv max (MeOH) 267 nm (ε 19,100); NMR ($CDCl_3$) δ 1.88 (d, 3 H, 5-CH_3), 2.1 (m, 4 H), 3.7 (m, broad, 2 H), 7.1 (d, 1 H, thymine 6-H), 7.5 (m, 4 H). Anal. Calcd for $C_{16}H_{15}N_3O_4$: C, 61.33; H, 4.83; N, 13.41. Found: C, 61.29; H, 4.83; N, 13.29.

1-[*N*-(3-Phthalimidopropyl)]uracil (6b). Uracil (5.0 g, 45 mmol) was alkylated in a manner similar to thymine with *N*-(3-bromopropyl)phthalimide (5.35 g, 19 mmol). A total of 2.99 g was isolated representing 53% yield, mp 188–189°. The NMR and ir spectra were characteristic, uv max (MeOH) 264 nm (ε 20,100). Anal. Calcd for $C_{15}H_{13}N_3O_4$: C, 60.12; H, 4.39; N, 14.04. Found: C, 59.98; H, 4.78; N, 13.94.

1-[*N*-(3-Phthalimidopropyl)]-N^4-acetylcytosine (6c). N^4-Acetylcytosine (5.0 g, 38.2 mmol) was alkylated in a similar fashion with *N*-(3-bromopropyl)phthalimide (11.0 g, 38.1 mmol). A total of 9.82 g of a white, crystalline (EtOAc) solid was isolated (75%): mp 208–210°; ir 3.12, 5.65, 5.9, 6.0, 6.65, 7.2, 7.6, 9.5, 11.3, 13.7 μ; uv max (MeOH) 272 (ε 16,400), 250 nm (s); NMR ($CDCl_3$) δ 2.28 (s, 3 H, acetyl CH_3), 3.5 (m, 2 H), 3.8 (m, 2 H), 3.97 (m, 2 H), 7.5 (d, 1 H), 7.8 (d, 2 H), 7.87 (d, 2 H), 7.95 (d, 1 H). Anal. Calcd for $C_{17}H_{16}N_4O_4$: C, 59.99; H, 4.74; N, 16.46. Found: C, 60.01; H, 5.01; N, 16.28.

1-(3-Azidopropyl)thymine (7a). 1-(3-Bromopropyl)thymine (**4a**, 614 mg, 2.5 mmol) and sodium azide (195 mg, 3.00 mmol) were refluxed in acetonitrile for 18 hr. Afterward the solid was filtered and the solution was concentrated to a gum, which slowly crystallized. The material was recrystallized from water and afforded 399.1 mg (76%): mp 98–100°; ir 4.89 μ; uv max (MeOH) 271 nm (ε 9200); NMR ($CDCl_3$) δ 1.93 (s, 3 H), 2.26 (m, 2 H), 3.42 (m, 2 H), 3.88 (m, 2 H), and 7.1 (s, 1 H). Anal. Calcd for $C_8H_{11}N_5O_2$: C, 45.91; H, 5.30; N, 33.49. Found: C, 45.45; H, 5.01; N, 33.45.

1-(3-Azidopropyl)uracil (7b). 1-(3-Bromopropyl)uracil (**4b**, 1.167 g, 5.0 mmol) and sodium azide (330 mg, 5.0 mmol) were used to prepare 642 mg (55%) of azido derivative, in the manner described above: mp 74.5–76°; ir 4.75 μ; uv max (MeOH) 266 nm (ε 10,400); NMR ($CDCl_3$) δ 2.14 (m, 2 H), 3.44 (t, 2 H), 3.90 (m, 2 H), 5.24 (d, 1 H, J = 4 Hz), and 7.23 (m, 1 H). Anal. Calcd for $C_7H_9N_5O_2 \cdot 2H_2O$: C, 40.75; H, 4.89; N, 33.97. Found: C, 40.29; H, 4.47; N, 33.77.

Aminopropylthymine (1a) from the Amine Hydrochloride.

A. 1-(3-Aminopropyl)thymine hydrochloride[10] was dissolved in a minimum volume of water and then made basic with aqueous ammonia or saturated potassium carbonate. This aqueous solution was then continuously extracted with chloroform. In a typical case 11.5 g of the amine hydrochloride afforded after extraction 4.3 g of free amine: mp 119–120°; ir 2.95 (broad), 5.58, 5.98, 7.4, 8.5, and 12.65 μ; uv max (EtOH–H_2O) 270 nm (ε 9400). Anal. Calcd for $C_8H_{11}N_3O_2$: C, 52.45; H, 7.10; N, 22.95. Found: C, 52.19; H, 6.89; N, 22.74.

B. The alternative approach was to reflux the amine salt in absolute ethanol in the presence of anhydrous potassium carbonate for 18 hr. The insoluble salt was filtered and the filtrate was concentrated and chilled to induce crystallization. A typical experiment converted 1.4 g of salt (in ethanol with 1.5 g of potassium carbonate) to 900 mg of free amine, mp 120–121°. This sample was identical with the analyzed sample and homogeneous in four TLC systems.

1-(3-Aminopropyl)uracil (1b). 1-[*N*-(3-Phthalimidopropyl)]-uracil (**6b**, 2.0 g, 6.5 mmol) was treated with a solution of 2-butylamine–methanol (1:4 v/v) at reflux for 2 days. The reaction mixture was concentrated to dryness and then partitioned between ethyl acetate and water. The aqueous phase was neutralized with ammonium bicarbonate and then applied in large volume to a C-244 column in NH_4^+ form and eluted with a linear concentration gradient of ammonium bicarbonate (1 l. of 1 M NH_4HCO_3 to 1 l. of water). A total of 140 fractions were collected and the product was distributed from fractions 87 to 110. These were pooled and freeze-dried, and the resulting white powder was dried at 3 Torr over P_2O_5 for 24 hr at 92°, affording 485 mg of an off-white powder. The product was very hygroscopic and tended to gum on exposure to air. It was homogeneous in four TLC systems and electrophoresis: NMR (TFA/TMS) δ 2.42 (t, 2 H), 3.53 (m, 2 H), 4.18 (t, 2 H), 6.15 (d, 1 H, J = 7.8 Hz), 7.07 (s, 2 H), 7.75 (d, 1 H, J = 7.8 Hz); uv max (a bicarbonate salt, H_2O) 261 nm (ε 10,400).

1-(3-Aminopropyl)cytosine (1c). 1-(3-Bromopropyl)-N^4-acetylcytosine (**4c**, 1.506 g, 5.5 mmol) was refluxed for 24 hr in 100 ml of acetonitrile with sodium azide (379 mg, 5.75 mmol). After the solid was filtered, the filtrate was concentrated and applied to a silica gel column in chloroform. Elution with chloroform and then

chloroform–methanol (195:5) afforded 888 mg of a white, crystalline solid (mp 110–112°, remelt, 136–137°). This material was treated with a solution of aqueous ammonia (27%) and pyridine (3:1) for 72 hr. After the solvents were removed a white, crystalline solid was obtained (435 mg, mp 193.5–196°). This material, 1-(3-azidopropyl)cytosine, (400 mg), was dissolved in ethanol–water (1:1) and submitted to catalytic reduction with 5% Pd on carbon at 1 atm. After 10 hr no azide remained. The catalyst was filtered and the reaction mixture was concentrated to a gum. The gum was carefully dissolved in 95% ethanol (small volume). Dilution with 1:1 isopropyl alcohol–ethyl acetate rendered the solution cloudy, and on standing crystallization occurred, affording, after filtering and drying, 314 mg of a white solid, mp 159–162°. Anal. Calcd for $C_7H_{12}N_4O$: C, 49.99; H, 7.19. Found: C, 49.93; H, 7.00. The material was homogeneous in four TLC systems and electrophoresis.

The preparation of aminopropylthymine (**1a**) and aminopropyluracil (**1b**) from the corresponding azides followed the same procedure as above.

***N*-Propyl-5-dimethylaminonaphthalene-1-sulfonamide.** DNS Cl (270 mg, 1 mmol) was dissolved in 25 ml of acetonitrile and the dark yellow solution was treated with propylamine (1 ml). After 30 min no dansyl chloride remained by TLC. The solution was concentrated and partitioned between chloroform and water. The organic phase was filtered over 10 g of silica gel. The filtrate was concentrated to a gum, which was dissolved in 5–10 ml of 95% ethanol. The solution was then rapidly diluted with 10 ml of water and immediately chilled. The cloudy solution afforded, after 18 hr, 280 mg of a white, crystalline solid, representing 96% yield: mp 86–88°; ir 3.02, 7.55, 8.57, 8.70, 8.75, and 12.7 μ; uv max (MeOH) 251 nm (ϵ 12,600), 334 (4800); NMR (pyridine-d_5) δ 0.75 (t, 3 H), 2.74 (s, 6 H), 3.02 (q, 2 H), 4.8 (broad s, 1 H), 7.0 (m, 4 H), and 7.65 (m, 2 H); MS (70 eV) *m/e* (rel intensity) 292 (100, M^+), 171 (130, $M^+ - C_3H_8NSO_2$), 154 (20). Anal. Calcd for $C_{15}H_{20}N_2O_2S$: C, 61.60; H, 6.89; N, 9.58; S, 10.97. Found: C, 61.85; H, 6.93; N, 9.29; S, 10.85.

***N*-3-[1-(5-Methyl-2,4-dihydroxypyrimidinyl)]propyl-5-dimethylaminonaphthalene-1-sulfonamide (2a).** 1-(3-aminopropyl)thymine (**1a**, 230 mg, 1.25 mmol) was dissolved in 25 ml of acetonitrile, 5 ml of water, and 5 ml of saturated aqueous sodium bicarbonate. To this mixture was added dansyl chloride (340 mg, 1.26 mmol). The reaction mixture was stirred for 60 min, at which time TLC revealed that no free amine nor amine salt were present. The reaction mixture was concentrated to small volume and recrystallization began. The slurry was chilled at 0° for 12 hr and filtered. After drying in air, 421.4 mg was recovered. The white solid was homogeneous in five TLC systems: mp 194–195°; ir 5.9 (broad), 7.56, 8.05, 8.2, 8.62, 8.75, and 13.9 μ; uv max (MeOH) 258.5 nm (ϵ 18,300), 335 (4800); NMR (pyridine-d_5) δ 1.88 (s, 3 H), 2.78 (s, 6 H), 3.14 (d, 2 H, J = 7 Hz), 3.75 (m, 2 H), 4.84 (s, 1 H, broad), 7.0 (d, 2 H), 7.2 (s, 1 H), 7.26 (m, 2 H), and 7.55 (m, 2 H); MS (70 eV) *m/e* (rel intensity) 416 (100, M^+), 235 (10, M^+ – PrTh), 171 (75, M^+ – APT-SO_2). Anal. Calcd for $C_{20}H_{24}N_4O_4S$: C, 57.67; H, 5.81; N, 13.45; S, 7.69. Found: C, 58.05; H, 5.97; N, 13.31; S, 7.49.

***N*-3-[1-(2,4-Dihyroxypyrimidinyl)]propyl-5-methylaminonaphthalene-1-sulfonamide (2b).** 1-(3-Aminopropyl)uracil (**1b**, 330 mg, 1.95 mmol) was converted in the manner described above into the fluorescent dansyl derivative. The crude product was chromatographed on silica gel with $CHCl_3$ and afforded 423.2 mg (55%) of crystalline solid from $CHCl_3$–CCl_4 (2:1): mp 142–143°; ir 5.9 (broad), 7.56, 8.06, 8.2, 8.62, 8.75, and 13.9 μ; uv max (MeOH) 334 nm (ϵ 4960), 258 (20,000); NMR (pyridine-d_5) δ 1.8 (m, 2 H), 2.8 (s, 6 H), 3.4 (m, 2 H), 3.7 (m, 2 H), 5.50 (d, 1 H, J = 7.0 Hz), 6.95 (d, 1 H, J = 7.0 Hz), 7.0 (d, 2 H), 7.26 (m, 2 H), and 7.55 (m, 2 H). Anal. Calcd for $C_{19}H_{22}N_4O_4S$: C, 56.70; H, 5.51; N, 13.92; S, 7.97. Found: C, 56.68; H, 5.43; N, 13.70; S, 7.68.

***N*-3-[1-(2-Hydroxy-4-aminopyrimidinyl)]propyl-5-dimethylaminonaphthalene-1-sulfonamide (2c).** 1-(3-Aminopropyl)cytosine (**1c**, 168 mg, 1 mmol) was converted by the above-described procedure to the fluorescent dansyl derivative. The crude product was purified by column chromatography on silica gel. The product was eluted with $CHCl_3$–MeOH (19:1). After fractions were pooled and concentrated to a greenish oil, the product was obtained crystalline by diluting a hot EtOH solution with ten volumes of cold water. The greenish, translucent solution was then concentrated on a rotary evaporator at reduced pressure. A greenish-yellow solid crystallized from the solution: 183.3 mg (46%); mg 133–136°; ir 2.82, 2.9, 5.9 (s), 6.65, 7.65, 8.8, and 12.7 μ; uv max (MeOH) 320 nm (ϵ 1800), 286 (19,000); NMR (pyridine-d_5) δ 1.93 (m, 2 H), 2.7 (s, 6 H), 3.12 (m, 2 H), 3.83 (m, 2 H), 5.75 (d, H, J = 7.0 Hz), 7.15 (d, 1 H, J = 7.0 Hz). Anal. Calcd for $C_{19}H_{23}N_5O_3S$: C, 56.84; H, 5.77; N, 17.44; S, 7.99. Found: C, 56.86; H, 6.26; N, 16.62; S, 8.34.

4-Propylamino-7-nitrobenzo-2-oxa-1,3-diazole. To a solution of propylamine (200 mg, 3.4 mmol) in ethyl acetate was added NBD chloride (190 mg, 0.9 mmol). The solution was maintained at 60° under reflux for 2 hr. After evaporation of the solvent, the residue was triturated with chloroform and then water. The brown solid remaining was chromatographed on silica gel in ethyl acetate. The material isolated from the column was crystallized in carbon tetrachloride–chloroform (2:1), affording 120 mg of red-brown crystals (55%): mp 110–112°; ir 3.02, 3.25, 6.16, 6.45, 6.64, 8.35, 10.8, 11.7 μ; uv max (50% MeOH–H_2O) 342 nm (ϵ 7140), 478 (21,400); NMR (TFA) δ 1.1 (t, 3 H), 1.8 (m, 2 H), 3.62 (t, 2 H), 6.5 (d, 1 H, J = 10 Hz), and 8.7 (d, 1 H, J = 10 Hz); MS (70 eV) *m/e* (rel intensity) 222 (95, M^+), 193 (100), 117 (85), 103 (23). Anal. Calcd for $C_9H_{10}N_4O_3$: C, 48.65; H, 4.51; N, 25.23. Found: C, 48.56; H, 4.63; N, 24.95.

4-[3-[1-(5-methyl-2,4-dihydroxypyrimidinyl)]propylamino]-7-nitrobenzo-2-oxa-1,3-diazole (3a). 1-(3-Aminopropyl)thymine (**1a**, 280 mg, 1.5 mmol) was dissolved in 8 ml of absolute ethanol and then added to the amine solution. This mixture was refluxed for 3.5 hr. Afterward the ethanol was evaporated to dryness at reduced pressure. The resulting brown slurry was triturated first with chloroform and then with water. A brown solid (250 mg, 76%) was obtained by filtration. This material was crystallized from 1:1 ethanol–dimethylformamide to afford a red-brown solid: 205 mg (62%); mp 246–250°; ir 3.08, 3.13, 6.04, 6.38, 7.8, 8.0, 12.7, and 12.9 μ; uv max (50% EtOH–H_2O) 270 nm (ϵ 9300), 340 (7100), and 475 (23,000); NMR (TFA) δ 2.0 (s, 3 H), 2.4 (m, 2 H), 3.8 (t, 2 H, J = 5 Hz), 4.2 (t, 2 H, J = 5 Hz), 6.5 (d, 1 H, J = 10 Hz), 7.57 (s, 1 H), 8.7 (d, 1 H, J = 10 Hz); MS (70 eV) *m/e* (rel intensity) 346 (5, M^+), 310 (10), 204 (40), 180 (100). Anal. Calcd for $C_{14}H_{14}N_6O_5$: C, 48.56; H, 4.05; N, 24.28. Found: C, 48.56; H, 4.27; N, 24.12.

4-[3-[1-(2,4-Dihydroxypyrimidinyl)]propylamino]-7-nitrobenzo-2-oxa-1,3-diazole (3b). 1-(3-Aminopropyl)uracil (**1b**) bicarbonate salt (217 mg, 1 mmol) and NBD Cl (220 mg, 1.1 mmol) were combined by the procedure described above to afford 230 mg of a black-brown solid, which was then repeatedly extracted with 2-propanol (5 × 50 ml). All the alcohol extracts were pooled and concentrated to small volume and then chilled. The solid was filtered and air dried: 158 mg; mp 297–301°; ir similar to that of **3a**; uv max (50% EtOH–H_2O) 261 nm (ϵ 10,000), 340 (7000), 476 (22,900); NMR (pyridine-d_5) δ 2.3 (t, 2 H), 3.8 (m, 2 H), 4.21 (t, 2 H), 6.15 (d, 1 H, J = 7.8 Hz), 6.45 (d, 1 H, J = 10 Hz), 7.75 (d, 1 H, J = 7.8 Hz), and 8.65 (d, 1 H, J = 10 Hz). An analytical sample was recrystallized from hot 2-propanol (mp 298–301°). Anal. Calcd for $C_{13}H_{12}N_6O_5$: C, 46.97; H, 3.64; N, 25.30. Found: C, 47.04; H, 3.54; N, 24.15.

Acknowledgment. This work was supported by Grant GM 19362 from the Department of Health, Education and Welfare.

Registry No.—**1a**, 46187-50-2; **1a** HCl, 54517-89-4; **1b**, 54494-30-3; **1c**, 22919-47-7; **2a**, 54494-27-8; **2b**, 54517-90-7; **2c**, 54517-91-8; **3a**, 54494-28-9; **3b**, 54494-29-0; **4a**, 22919-50-2; **4b**, 22917-77-7; **4c**, 22917-95-9; **6a**, 54517-92-9; **6b**, 54517-93-0; **6c**, 38718-31-9; **7a**, 54517-94-1; **7b**, 54517-95-2; **7c**, 54517-96-3; thymine, 65-71-4; uracil, 66-22-8; N^4-acetylcytosine, 14631-20-0; *N*-(3-bromopropyl)-phthalimide, 5460-29-7; *N*-propyl-5-dimethylaminonaphthalene-1-sulfonamide, 54517-97-4; dansyl chloride, 605-65-2; 4-propylamino-7-nitrobenzo-2-oxa-1,3-diazole, 54517-98-5; propylamine, 107-10-8; 4-chloro-7-nitrobenzo-2-oxa-1,3-diazole, 10199-89-0.

References and Notes

(1) G. Weber, *Biochem. J.*, **145**, 51 (1952).
(2) P. B. Ghosh and M. W. Whitehouse, *Biochem. J.*, **108**, 155 (1968).
(3) J. G. Burr, W. A. Summers, and Y. J. Lee, *J. Am. Chem. Soc.*, **97**, 245 (1975).
(4) W. A. Summers, Jr., and J. G. Burr, *J. Phys. Chem.*, **76**, 3137 (1972).
(5) W. A. Summers, C. Enwall, J. G. Burr, and R. L. Letsinger, *Photochem. Photobiol.*, **17**, 295 (1973).
(6) J. G. Burr, E. H. Park, and A. Chan, J. Am. Chem. Soc., **94**, 5866 (1972).
(7) J. G. Burr, *Adv. Photochem.*, **6**, 193 (1968).
(8) S. Y. Wang, Ed., "Photochemistry of Nucleic Acids", Academic Press, New York, N.Y., in press.
(9) M. Daniels and W. Hauswirth, *Science*, **171**, 675 (1971).
(10) D. Brown, J. Eisinger, and N. J. Leonard, *J. Am. Chem. Sci.*, **90**, 7302. (1968).
(11) A. Galat and G. Elion, *J. Am. Chem. Soc.*, **61**, 3585 (1939); J. Angyal, *Org. React.*, **8**, 197 (1974).
(12) J. G. Moffatt, D. Wagner, and P. H. Verheyden, *J. Org. Chen.*, **36**, 250 (1971).

Optically Active Amines. XIX.[1] Circular Dichroism of Ortho-, Meta-, and Para-Substituted β-Phenylalkylamine Hydrochlorides. Further Applications of the Salicylidenimino Chirality Rule[2]

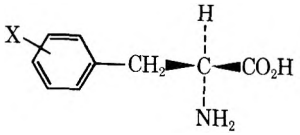
Howard E. Smith,*[3a] Elizabeth P. Burrows,[3a] and Fu-Ming Chen[3b]

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235, Tennessee Neuropsychiatric Institute, Nashville, Tennessee, and Department of Chemistry, Tennessee State University, Nashville, Tennessee 37203

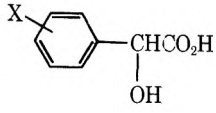
Received October 29, 1974

o- and *m*-chloroamphetamine have been resolved and the absolute configurations of the respective enantiomers determined by catalytic hydrogenolysis to amphetamine. The established absolute configurations of (*R*)-(−)-*o*-, (*S*)-(+)-*m*-, and (*S*)-(+)-*p*-chloroamphetamine are compared with predictions based on Snatzke's sector rule for the correlation of absolute configuration with the sign of the ^1L_b Cotton effect and with predictions based on the salicylidenimino chirality rule for the correlation of absolute configuration with the sign of the Cotton effects near 255 and 315 (325) nm in the CD spectrum of the *N*-salicylidene (*N*-5-bromosalicylidene) derivative. Snatzke's rule does not correctly predict the sign of the ^1L_b Cotton effect for the meta isomer. The salicylidenimino chirality rule, however, correctly predicts the sign of the Cotton effects near 255 and 325 nm observed for the *N*-5-bromosalicylidene derivatives, the *S* configuration in each case producing strong positive Cotton effects. These results confirm the configurational assignments for the nonstimulant anorectic agent (+)-fenfluramine and for the enantiomers of the psychotomimetic amine 1-(2,5-dimethoxy-4-methylbenzyl)ethylamine, made on the basis of the CD spectra of the respective *N*-salicylidene derivatives.

Few systematic studies have been made concerning the effect of ring substitution on the Cotton effects of chiral benzenoid compounds. The quadrant sector rules[4-6] for correlation of the sign of the ^1L_b Cotton effect with the absolute configuration of chiral 1-substituted indans[4] and α- and β-phenylalkylamines and their hydrochlorides[6] cannot be applied to ortho- and meta-substituted phenylalkyl compounds, since the symmetry of the chromophore is altered. Snatzke,[7] however, has proposed another sector rule based on the nodal planes of the benzene ring and Platt's spectroscopic moments[8,9] by which the direction of the overall spectroscopic moment vector is used to predict the sign of the ^1L_b Cotton effects of chiral ortho-, meta-, and para-disubstituted benzenes. If the spectroscopic moments of the two substituents are of the same sign and approximately the same magnitude, this rule predicts a ^1L_b Cotton effect for the ortho and meta compounds of opposite sign to that observed for the para compound. Experimental verification was found in the case of the substituted phenylalanines. Both L-phenylalanine (**1a**) and L-tyrosine (**1b**) show positive circular dichroism (CD) bands at about 260 nm[10-12] while the corresponding bands for L-*o*- and L-*m*-hydroxyphenylalanine (**1c** and **1d**) are negative.[12] Snatzke



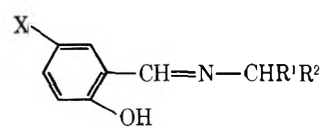
1a, X = H
b, X = *p*-OH
c, X = *o*-OH
d, X = *m*-OH



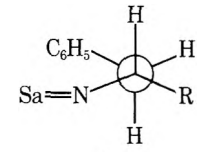
2, X = Br, Cl, F, or OCH_3

noted, however, that earlier data[13] for ring-substituted mandelic acids (**2**) did not agree with prediction. He attributed this failure to the presence of the chiral center adjacent to the benzene ring and a consequent change in the relative population of conformers resulting from rotation of the chiral center about its attachment bond on introduction of a substituent. The implication was strong that compounds having the chiral center separated from the ring by a methylene group should not be thus affected and should conform to the rule.

For the establishment of the absolute configurations of chiral α- and β-arylalkylamines, we have devised an alternate CD method, formulated as the salicylidenimino chirality rule.[14] This rule correlates the sign of the Cotton effects near 255 and 315 (325) nm in the CD spectra of *N*-salicylidene (**3a**) [*N*-5-bromosalicylidene (**3b**)] derivatives of the



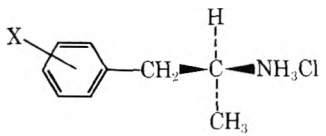
3a, X = H
b, X = Br



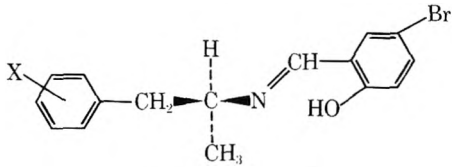
4

amines with their absolute configurations. For β-phenylalkylamine derivatives the sign of these Cotton effects is positive for a right-handed screw pattern as shown in **4**, the screw sense depending on both the absolute configuration and preferred conformation of the derivative. The Cotton effects arise by the coupled oscillator mechanism[15] and are the result of interaction of the electric dipole transition moments of the salicylidenimino chromophore, oriented approximately parallel to the attachment bond, with the ^1L_a and $^1B_{a,b}$ benzenoid transitions of the phenyl chromophore. The effective transition moment directions of the latter are along the phenyl group attachment bond. The transverse components of these moments are assumed to be cancelled by rotation of the phenyl group about its attachment bond. Substitution at various positions of the benzene ring of a particular chiral β-phenylalkylamine should have little effect on the Cotton effects near 255 and 315 (325) nm, except for possible minor variations in intensity reflecting changes in the magnitude of the effective transition moments along the phenyl group attachment bond due to the substituent.

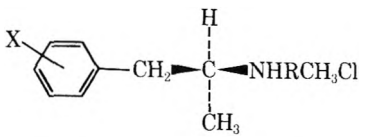
Our continuing interest in the determination of the absolute configuration of chiral amines by CD methods[14] and in the pharmacological effects of stereoisomeric chlorinated amphetamines[16] has prompted us to prepare enantiomers of *o*- and *m*-chloroamphetamine hydrochloride (**5a** and **6a**) and to use them to assess the validity of both Snatzke's sector rule and the salicylidenimino chirality rule. To this end we compare the CD spectra of (*R*)-**5a** and (*S*)-**6a** and the corresponding free bases (*R*)-**5b** and (*S*)-**6b** with those of (*S*)-(+)-*p*-chloroamphetamine hydrochloride[16,17] [(*S*)-**7a**]



(*S*)-**5a**, X = *o*-Cl
(*S*)-**6a**, X = *m*-Cl
(*S*)-**7a**, X = *p*-Cl
(*S*)-**8a**, X = H



(*S*)-**5c**, X = *o*-Cl
(*S*)-**6c**, X = *m*-Cl
(*S*)-**7c**, X = *p*-Cl
(*S*)-**8c**, X = H



(*S*)-**6d**, X = *m*-Cl; R = H
(*S*)-**6e**, X = *m*-Cl; R = CH_3
(*S*)-**7d**, X = *p*-Cl; R = H
(*S*)-**7e**, X = *p*-Cl; R = CH_3

Table I
Spectral Data for Amphetamine Hydrochlorides and Their *N*-Methyl Derivatives in Methanol[a]

		Wavelength, nm (ϵ^b or $[\theta]^c$)										
		^1L_b							^1L_a			
Compd	Max											
(*R*)-5a	EA	273 (160)		265 (200)	262 (190)[d,e]	258 (170)[d]	252 (120)[d]					212 (9200)
	CD	274 (+110)		267 (+100)						220 (+4100)		
(*S*)-6a	EA	274 (220)		267 (260)		260 (200)	253 (130)[d]	247 (80)[d]				213 (9200)
	CD	275 (+310)		268 (+350)		261 (+280)				222 (+8400)		
(*S*)-6d	EA	274 (220)		267 (270)		260 (200)	254 (140)[d]	247 (90)[d]				213 (9100)
	CD	275 (+240)		268 (+280)		261 (+180)				222 (+2300)		
(*S*)-6e	EA	274 (250)		267 (290)		260 (230)	254 (160)[d]	248 (120)[d]				213 (10,000)
	CD	275 (+270)		267 (+270)		261 (+180)				222 (+3200)		
(*S*)-7a	EA	276 (240)		268 (280)		261 (220)	255 (160)[d]	248 (110)[d]		224 (9500)[d]		220 (11,000)
	CD	277 (+160)		268 (+170)		262 (+140)			227 (+13,000)	223 (+9000)		
(*S*)-7d	EA	276 (230)		268 (280)		261 (220)	255 (160)[d]	249 (110)[d]		224 (9500)[d]		220 (11,000)
	CD	277 (+150)		268 (+180)		261 (+120)			227 (+8800)	222 (+4100)		
(*S*)-7e	EA	276 (230)		268 (280)		261 (220)	255 (160)[d]	248 (110)[d]		224 (9700)[d]		220 (11,000)
	CD	277 (+120)		268 (+180)		261 (+160)			227 (+10,000)	223 (+8200)		
(*S*)-8a	EA	267 (80)	264 (120)[e]	261 (120)[d]	258 (170)[e]		248 (100)	243 (60)[d]	237 (30)[d]			207 (7800)
	CD	268 (+210)		261 (+230)		254 (+160)	248 (+120)	243 (+110)	237 (+70)	215 (+8800)		

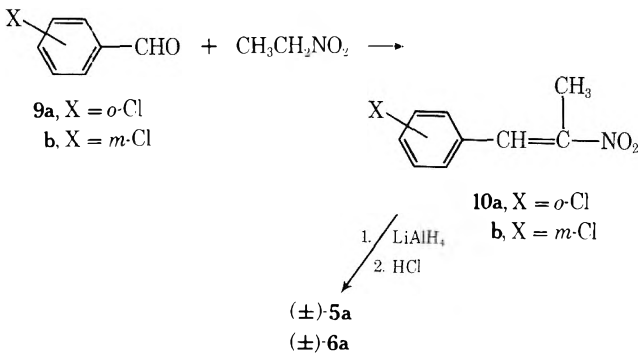
[a] c 1.38×10^{-3} to 8.29×10^{-2} g/100 ml; length 1 cm; temperature 25°. [b] Molar absorptivity. [c] Molecular ellipticity. [d] Shoulder. [e] Transition to a non-totally symmetric vibrational mode.

and (*S*)-(+)-amphetamine hydrochloride [(*S*)-**8a**] and their free bases. The structural features of these amines are well suited for this purpose in that the chiral center is separated from the benzene ring by a methylene group, and the spectroscopic moments of a chlorine and a methyl substituent are nearly identical in sign and magnitude.[8,9] We also examine the effect of *N*-methyl substituents on the CD spectra of meta- and para-substituted β-phenylalkylamine hydrochlorides (**6d, 6e, 7d,** and **7e**). Finally, in extension of the salicylidenimino chirality rule to ortho- and meta-substituted β-phenylalkylamines, we compare the CD spectra of *N*-5-bromosalicylidene derivatives **5c–8c.**

Results and Discussion

Synthesis and Proof of Configuration. The most efficient synthesis of the racemic amines involved condensation of the requisite aldehyde (**9**) with nitroethane[19] followed by lithium aluminum hydride ($LiAlH_4$) reduction of the resulting chlorophenylnitropropene (**10**) (Scheme I).

Scheme I



An earlier paper[20] described the resolution of (±)-**5b** using (+)-tartaric acid, but we have found that the amine so obtained was 65% racemic (cf. Experimental Section). L-*N*-Acetylleucine had proven to be the acid of choice for the resolution of (±)-**7b**[16] and was equally successful with (±)-**5b.**

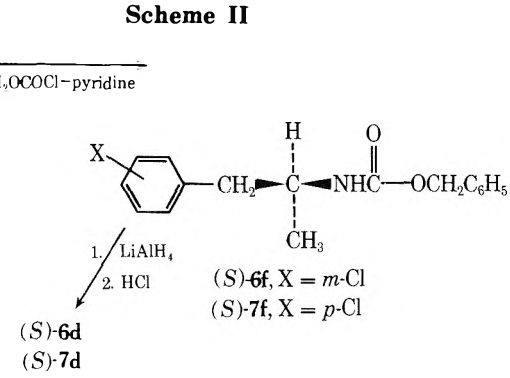
A recent patent[21] described a resolution of (±)-**6b** using (−)-dibenzoyltartaric acid to give a free base which we have found to be no more than 76% resolved. In our hands, this same resolving agent gave partially racemic (*R*)-**6a.** Optically pure (*S*)-**6a** was obtained, however, using (+)-dibenzoyltartaric acid and the partially resolved amine from the original resolution mother liquors.

The configurations of (*S*)-**7a** and (*S*)-**8a** are well known,[16] and the configurations of (*R*)-**5a** and (*R*)-**6a** were established by conversion of each to (*R*)-**8a** by catalytic hydrogenolysis. The samples of (*R*)-**8a** in each case were shown by gas–liquid chromatography (GLC) of the free base to be at least 99% pure. The enantiomers of **8a** are known to racemize on heating with Raney nickel,[22] and some racemization took place during hydrogenolysis of (*R*)-**6a** in hydrochloric acid. Hydrogenolysis of the free base (*R*)-**5b** over palladium on carbon in ethanolic acetic acid was not accompanied by racemization.

The *N*-methyl derivatives of **6a** and **7a** were prepared by $LiAlH_4$ reduction of the corresponding *N*-carbobenzoxy derivatives **6f** and **7f** (Scheme II). Thus (*S*)-**6d** and (±)-, (*S*)-, and (*R*)-**7d** were prepared from the respective amines. The *N,N*-dimethyl derivatives [(*S*)-**6e** and (±)-, (*S*)-, and (*R*)-**7e**] were prepared by reductive (Eschweiler–Clarke) methylation of **6b** and **7b** of the respective configurations with formaldehyde in aqueous formic acid.

Circular Dichroism of Amine Hydrochlorides and Amines. The electronic (isotropic) absorption (EA) and

Scheme II



CD data of the optically active amine hydrochlorides are summarized in Table I. The fine structure pattern in the ^1L_b band (ca. 235–275 nm) and the ^1L_a band (ca. 210–225 nm) in the CD spectra of **5a–8a** can be understood in terms of progressions dominated by the totally symmetric vibrational modes of 1050 cm^{-1} in o-chlorotoluene, 1000 cm^{-1} in *m*-chlorotoluene, 797 and 1092 cm^{-1} in *p*-chlorotoluene, and 1000 cm^{-1} in toluene.[23] The data in Table I also show that *N*-methyl substitution has little effect except to reduce the intensity of the ^1L_a Cotton effects shown by the methylated derivatives relative to the respective parent compounds.

As predicted by Snatzke's rule,[7] the ortho-substituted hydrochloride [(*R*)-**5a**] shows a ^1L_b Cotton effect of the same sign as those of the unsubstituted [(*S*)-**8a**] and the para-substituted hydrochlorides [(*S*)-**7a,** (*S*)-**7d,** and (*S*)-**7e**] of the opposite configuration. Contrary to prediction, however, those of the meta-substituted hydrochlorides [(*S*)-**6a,** (*S*)-**6d,** and (*S*)-**6e**] have the same sign as those of the unsubstituted and para-substituted hydrochlorides of the same configuration. The CD data for the amines (Table II), obtained by measurement with solutions prepared from the respective hydrochlorides in 0.1 *N* methanolic potassium hydroxide, show that the ^1L_b Cotton effect for an amine is not significantly different from that of its hydrochloride. It appears then that, aside from possible sign inversion due to transitions to non-totally symmetric vibrational modes,[11,24] caution should be exercised in correlation of the ^1L_b Cotton effect of an arylalkylamine with its absolute configuration, especially when the ring is polysubstituted.

It is noteworthy that, while hydrochlorides (*S*)-**6a,** (*S*)-**7a,** and (*S*)-**8a** all show optical rotations in water at the D

Table II
Circular Dichroism Data for Amphetamines in 0.1 *N* Methanolic Potassium Hydroxide[a]

Compd	λ, nm ($[\theta]^b$) Max	Cutoff
(*R*)-5b	275 (+66)	
	267 (+74)	230 (−)
(*S*)-6b	276 (+170)	
	268 (+190)	
	261 (+130)	235 (+)
(*S*)-7b	277 (+260)	
	270 (+300)	
	263 (+190)	225 (+)
(*S*)-8b	269 (+140)	
	262 (+150)	
	255 (+110)	225 (+)

[a] Weighed amounts of hydrochlorides, *c* 8.01 × 10^{-2} to 8.62 × 10^{-2} g/100 ml; length 1 cm; temperature 25°. [b] Molecular ellipticity.

Table III
Spectral Data for *N*-5-Bromosalicylidene Derivatives in Absolute Ethanol[a]

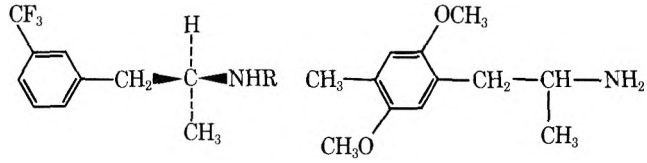
Compd	EA max, λ, nm (ε[c])	CD: Longest and shortest λ, nm ([θ][b])	CD: Max, λ, nm ([θ][b])	CD: Min, λ, nm ([θ][b])	CD: [θ][b] = ±0 λ, nm[d]
(*R*)-**5c**		500 (±0)			470
	416 (520)		416 (−1200)	376 (−800)	
	327 (3800)		327 (−12,000)	282 (−1500)	
	274 (1600)[e]				
	254 (10,000)		256 (−38,000)		232
		232 (±0)			
	219 (35,000)				
(*S*)-**6c**		500 (±0)			465
	417 (600)		417 (+1700)	380 (+1000)	
	328 (3900)		328 (+13,000)	285 (+1600)	
	275 (1800)[e]				
	254 (11,000)		255 (+38,000)		237
		233 (−5900)			
	220 (37,000)				
(*R*)-**7c**[f]		500 (±0)			455
	415 (600)		415 (−1500)	380 (−900)	
	328 (3700)		326 (−14,000)	280 (−900)	
	276 (1700)[e]				
	254 (10,000)[e,g]		255 (−43,000)		237
		233 (+2200)			
(*S*)-**8c**[f]		500 (±0)			470
	415 (740)		411 (+2200)	370 (+1100)	
	327 (3600)		327 (+12,000)	277 (+1000)	
	276 (1600)[e]				
	254 (10,000)[e]		254 (+35,000)		237
		233 (−8200)			
	220 (31,000)				

[a] *c* 2.65 × 10^{-3} to 6.78 × 10^{-2} g/100 ml; length 1 cm; temperature 25°. [b] Molecular ellipticity. [c] Molar absorptivity. [d] Each first entry at a longer wavelength than a maximum indicates the interval from the longest wavelength examined for which [θ] ≈ ±0. [e] Shoulder. [f] Data from ref 16. [g] Spectrum below 225 nm not determined.

line of the same sign as their ^1L_b and ^1L_a Cotton effects in methanol (positive), (*R*)-**5a** has a negative rotation at the D line and positive ^1L_b and ^1L_a Cotton effects. Thus it appears that the inaccessible (below 210 nm) $^1B_{a,b}$ Cotton effect for (*R*)-**5a** must be very strongly negative. In comparing CD spectra of the free bases (Table II), it is possibly significant that at cutoff (225–235 nm) (*R*)-**5b** is negative and the others positive.

Circular Dichroism of *N*-5-Salicylidene Derivatives. The EA and CD data for the *N*-5-bromosalicylidene derivatives are summarized in Table III. The signs of the Cotton effects near 255 and 325 nm are in accord with those predicted by the salicylidenimino chirality rule,[14] positive for all derivatives with the *S* configuration, negative for *R*. The more intense Cotton effects observed for (*R*)-**7a** result from reinforcement of the spectroscopic moments of the two para substituents on the benzene ring producing a larger transition moment along the attachment bond for the ^1L_a transition.

These results validate the application of the salicylidenimino chirality rule to polysubstituted arylalkylamines. Thus the assignment of the *S* configuration to the nonstimulant, anorectic agent (+)-fenfluramine [(+)-*N*-ethyl-α-(*m*-trifluoromethylbenzyl)ethylamine] [(*S*)-**11a**], made in part on the basis of the CD spectrum of the *N*-salicylidene derivative of (+)-norfenfluramine [(*S*)-**11b**],[25] is confirmed. The configurational assignment made on the same basis for the stereoisomers of the psychotomimetic amine α-(2,5-dimethoxy-4-methylbenzyl)ethylamine[26] (**12**) is also confirmed.



(*S*)-**11a**, R = C_2H_5 **12**
(*S*)-**11b**, R = H

Experimental Section

Hydrochlorides were prepared by treatment of potassium hydroxide dried ether solutions of the free bases with hydrogen chloride. Amines were obtained from the salts by treatment of the latter with 10% sodium hydroxide solution, extraction into ether, and drying over potassium hydroxide. Melting points were taken in sealed capillary tubes and are corrected. Optical rotations at the sodium D line were measured using a visual polarimeter and a 1-dm tube. Proton magnetic resonance (^1H NMR) spectra were determined with a Jeol MH-100 spectrometer and chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane. Isotropic electronic absorption (EA) spectra were measured with a Cary Model 14 spectrometer with the normal variable slit. Circular dichroism (CD) spectra were measured with a Cary Model 60 spectropolarimeter equipped with a CD Model 6001 accessory, and the slit was programmed for a spectral band width of 1.5 nm. A Varian Aerograph Model 90-P instrument fitted with a 5 ft × 0.25 in. 5% SE-30 column was used for GLC analyses (140°). Microanalyses were done by Galbraith Laboratories, Inc., Knoxville, Tenn.

(±)-*o*-Chloroamphetamine Hydrochloride [(±)-5a]. 1-(2-Chlorophenyl)-2-nitropropene[27] (**10a**, 65.1 g, 0.329 mol), prepared by the published procedure,[19] was reduced with excess $LiAlH_4$ in ether as described previously.[19] The resulting amine, (±)-**5b**, was

converted to the hydrochloride (±)-**5a** (46.1 g, 68%), recrystallized from acetone–ether, mp 182–183° (lit.[20] mp 175–176°).

(*R*)-(−)-*o*-Chloroamphetamine Hydrochloride [(*R*)-5a]. A solution of sodium L-*N*-acetylleucinate prepared from L-*N*-acetylleucine (7.35 g, 42.4 mmol) and sodium hydroxide (1.70 g, 42.5 mmol) in water (125 ml) was added dropwise to a stirred solution of (±)-**5a** (15 g, 73 mmol) in water (125 ml). It was necessary to concentrate the resulting solution to ca. 100 ml to obtain a crystalline salt (6 g) which was recrystallized twice from water to constant specific rotation, $[\alpha]^{25}D$ −31° (*c* 1.63, H_2O). Optically pure (*R*)-**5a** obtained therefrom had mp 171–172°; $[\alpha]^{25}D$ −26° (*c* 1.96, H_2O) [lit.[20] mp 175–176°; $[\alpha]^{25}D$ +9.0° (*c* 3.78, H_2O) for (*S*)-**5a**].

Hydrogenolysis of (*R*)-(−)-*o*-Chloroamphetamine Hydrochloride [(*R*)-5a]. A mixture of (*R*)-**5b** (0.32 g), absolute ethanol (12.5 ml), glacial acetic acid (2.5 ml), and 10% palladium on carbon (0.53 g) was stirred under hydrogen until uptake ceased (2.5 hr). The catalyst was removed by filtration, the filtrate was evaporated to near dryness and made strongly alkaline with 10% sodium hydroxide, and the amine was extracted into ether. GLC analysis showed in addition to ether a single peak identical in retention time (0.9 min) with authentic (*R*)-**8b** and no trace of (*R*)-**5b** (retention time 2.3 min). The hydrochloride had $[\alpha]^{25}D$ −24° (*c* 8.97, H_2O) [lit.[18] $[\alpha]^{25}D$ +21.6° (*c* 9.0, H_2O) for (*S*)-**8a**].

(*R*)-(−)-*N*-(5-Bromosalicylidene)-*o*-chloroamphetamine [(*R*)-5c] prepared from equimolar amounts of (*R*)-**5b** and 5-bromosalicylaldehyde was an oil which after drying for 48 hr at room temperature (0.05 mm) had $[\alpha]^{25}D$ −255° (*c* 1.06, absolute C_2H_5OH).

(±)-*m*-Chloroamphetamine Hydrochloride [(±)-6a]. 1-(3-Chlorophenyl)-2-nitropropene (**10b**), prepared in a similar manner to **10a**, had bp 98° (0.01 mm) [lit.[28] bp 101.5–102° (0.2 mm)]. Reduction of **10b** with excess $LiAlH_4$ in ether gave (±)-**6b**, bp 63–73° (0.5 mm). The hydrochloride (±)-**6a**, recrystallized from acetonitrile–methanol, had mp 158–160°.

Anal. Calcd for $C_9H_{13}Cl_2N$: C, 52.44; H, 6.36; Cl, 34.40. Found: C, 52.46; H, 6.39; Cl, 34.46.

(*S*)-(+)-*m*-Chloroamphetamine Hydrochloride [(*S*)-6a]. A solution of (−)-dibenzoyltartaric acid monohydrate (21.5 g, 0.057 mol) in 95% ethanol (120 ml) was added dropwise to a stirred solution of (±)-**6b** (18.2 g, 0.107 mol) in absolute ethanol (125 ml). The precipitated salt was collected, recrystallized twice from 80% aqueous ethanol, and treated with 10% sodium hydroxide to yield partially racemic (*R*)-**6b**, $[\alpha]^{25}D$ −18° (*c* 4.05, CH_3OH) [lit.[21] $[\alpha]^{20}D$ −17° (*c* 2, CH_3OH)]. Hydrochloride (*R*)-**6a** had $[\alpha]^{25}D$ −16° (*c* 1.98, H_2O).

Evaporation of the filtrate from the original precipitation of the dibenzoyltartrate salt above followed by treatment with 10% sodium hydroxide yielded partially racemic (*S*)-**6b** (3.86 g, 2.27 mmol). It was dissolved in absolute ethanol (20 ml) and treated as above with a solution of (+)-dibenzoyltartaric acid monohydrate (6.40 g, 1.70 mmol) in 95% ethanol (40 ml). The precipitated salt was collected, recrystallized from 80% aqueous ethanol, and treated with 10% sodium hydroxide to give (*S*)-**6b**. Hydrochloride (*S*)-**6a** had mp 165–166°, $[\alpha]^{25}D$ +21° (*c* 2.10, H_2O).

Hydrogenolysis of Partially Racemic (*R*)-(−)-*m*-Chloroamphetamine Hydrochloride [(*R*)-6a]. To a solution of partially resolved (*R*)-**6a** (219 mg), $[\alpha]^{25}D$ −16°, in water (9 ml) was added platinum oxide (110 mg) and concentrated hydrochloric acid (3 drops). The mixture was stirred under hydrogen until uptake ceased (20 hr). The catalyst was removed by filtration and the filtrate was evaporated to dryness. The white, crystalline residue of partially racemic (*R*)-**8a** had, after drying for 12 hr at 60° (0.1 mm), $[\alpha]^{25}D$ −11° (*c* 9.03, H_2O) [lit.[18] $[\alpha]^{25}D$ +21.6° (*c* 9.0, H_2O) for (*S*)-**8a**]. GLC analysis of the amine obtained from this hydrochloride showed only **8b**.

(*S*)-(+)-*N*-(5-Bromosalicylidene)-*m*-chloroamphetamine [(*S*)-6c], prepared from equimolar amounts of (*S*)-**6b** and 5-bromosalicylaldehyde in methanol, had mp 92–93°, $[\alpha]^{25}D$ +228° (*c* 0.95, absolute C_2H_5OH).

Anal. Calcd for $C_{16}H_{15}BrClNO$: C, 54.49; H, 4.29. Found: C, 54.20; H, 4.15.

(*S*)-*N*-Methyl-*m*-chloroamphetamine Hydrochloride [(*S*)-6d]. (*S*)-*N*-Carbobenzoxy-*m*-chloroamphetamine [(*S*)-**6f**], prepared in 90% yield by the procedure described below for (±)-**7f**, was treated with excess $LiAlH_4$ in ether as described below for the preparation of (±)-**7d** to give crude (*S*)-**6d** (83%), recrystallized from acetone, mp 140–141°, $[\alpha]^{25}D$ +13° (*c* 1.90, H_2O).

Anal. Calcd for $C_{10}H_{15}Cl_2N$: C, 54.56; H, 6.87. Found: C, 54.78; H, 6.90.

(*S*)-*N,N*-Dimethyl-*m*-chloroamphetamine Hydrochloride [(*S*)-6e]. Optically pure (*S*)-**6b** was subjected to Eschweiler–Clarke methylation as described below for (±)-**7b** to give crude (*S*)-**6e**, recrystallized from acetone, mp 161–162°, $[\alpha]^{25}D$ +10° (*c* 2.02, H_2O).

Anal. Calcd for $C_{11}H_{17}Cl_2N$: C, 56.42; H, 7.32. Found: C, 56.34; H, 7.10.

(*S*)-(+)- and *R*-(−)-*p*-Chloroamphetamine hydrochloride [(*S*)- and (*R*)-7a] had $[\alpha]^{25}D$ +22° (*c* 2.01, H_2O) and $[\alpha]^{25}D$ −22° (*c* 2.16, H_2O), respectively [lit.[16] $[\alpha]^{25}D$ +21° (*c* 2.02, H_2O) and $[\alpha]^{25}D$ −22° (*c* 1.90, H_2O) for (*S*)- and (*R*)-**7a**, respectively]; (*S*)-**7a** had $[\alpha]^{25}D$ −8.6° (*c* 2.10, *i*-PrOH).

(±)-, (*S*)-(+)-, and (*R*)-(−)-*N*-Carbobenzoxy-*p*-chloroamphetamine [(±)-, (*S*)-, and (*R*)-7f]. To a stirred, ice-cooled solution of (±)-**7b** (790 mg, 4.7 mmol) in pyridine (2 ml) was added dropwise during 30 min carbobenzoxy chloride (1.54 g, 9.03 mmol). The ice bath was removed and stirring was continued for 1.5 hr before water was added. The resulting mixture was extracted with ether, and the ether solution was washed with 2 *N* hydrochloric acid until the aqueous phase remained acidic, then with aqueous sodium bicarbonate and two portions of water. Removal of ether from the dried ($MgSO_4$) extract yielded crystalline (±)-**7f** (1.05 g, 74%). A sample recrystallized from carbon tetrachloride was homogeneous to TLC (silica gel HF-254, 9:1 benzene–ethyl acetate, R_f 0.7) and had mp 83–84°; ^1H NMR ($CDCl_3$) δ 1.08 (d, 3, *J* = 7 Hz), 2.70 (m, 2), 3.94 (m, 1, $CHCH_3$), 4.58 (m, 1, NH), 5.00 (s, 2, $OCH_2C_6H_5$), 6.9–7.4 ppm (m, 9).

Anal. Calcd for $C_{17}H_{18}ClNO_2$: C, 67.21; H, 5.97; N, 4.61. Found: C, 66.73; H, 5.96; N, 4.81.

(*S*)-**7f** and (*R*)-**7f**, prepared in a similar manner from (*S*)-**7b** and (*R*)-**7b**, had mp 186–188°; $[\alpha]^{25}D$ +22° (*c* 2.20, CH_3OH) and $[\alpha]^{25}D$ −23° (*c* 2.00, CH_3OH), respectively.

(±)-, (*S*)-(+)-, and (*R*)-(−)-*N*-Methyl-*p*-chloroamphetamine Hydrochloride [(±)-7d, (*S*)-7d, and (*R*)-7d]. A suspension of (±)-**7f** (602 mg, 1.98 mmol) in ether (15 ml) was ice cooled and stirred while excess $LiAlH_4$ was added in small portions. The mixture was stirred for 15 hr at room temperature, then cooled while water was added. The suspension was filtered, and the filtrate was extracted with 1 *N* hydrochloric acid (5 ml). Evaporation of the aqueous layer, trituration of the crystalline residue with acetone, and drying at 60° (0.1 mm) gave (±)-**7d** (345 mg, 79%): mp 136–138° (lit.[29] mp 133°); ^1H NMR (D_2O) δ 1.12 (d, 3, *J* = 7 Hz), 2.64 (s, 3), 2.84 (m, 2), 3.37 (m, 1), 7.0–7.3 ppm (m, 4).

Treatment of (*S*)-**7f** and (*R*)-**7f** in a similar manner gave (*S*)-**7d** and (*R*)-**7d**, which after recrystallization from acetone–methanol had mp 180–181°; $[\alpha]^{25}D$ +16° (*c* 1.22, H_2O) and $[\alpha]^{25}D$ −16° (*c* 1.20, H_2O), respectively.

(±)-, (*S*)-(+)-, and (*R*)-(−)-*N,N*-Dimethyl-*p*-chloroamphetamine Hydrochloride [(±)-, (*S*)-, and (*R*)-7e]. A mixture of (±)-**7b** (370 mg, 2.18 mmol), 90% formic acid (0.8 g, 16 mmol), and 37% aqueous formaldehyde (0.7 ml) was heated for 14 hr at 90–95°. The mixture was cooled, mixed with 6 *N* hydrochloric acid (1 ml), and evaporated to dryness. The residue was washed with small portions of acetone and dried at 60° (0.1 mm), yielding (±)-**7e** (425 mg, 83%): mp 207–208° dec; ^1H NMR (D_2O) δ 1.18 (d, 3, *J* = 7 Hz), 2.84 (s, 3), 2.87 (s, 3), 2.92 (m, 2), 3.60 (m, 1), 7.1–7.4 ppm (m, 4).

Anal. Calcd for $C_{11}H_{17}Cl_2N$: C, 56.42; H, 7.32; N, 5.98. Found: C, 56.54; H, 7.32; N, 5.93.

Treatment of (*S*)-**7b** and (*R*)-**7b** in a similar manner gave (*S*)-**7e** and (*R*)-**7e**, mp 220–221° dec; $[\alpha]^{25}D$ +11° (*c* 2.09, H_2O) and $[\alpha]^{25}D$ −9.3° (*c* 2.05, H_2O), respectively.

Acknowledgment. We thank Mr. Charles D. Mount for the preparation of racemic **5a** and **6a**.

Registry No.—(±)-**5a**, 35334-29-3; (*R*)-**5a**, 54676-31-2; (*R*)-**5b**, 54676-32-3; (*R*)-**5c**, 54643-56-0; (±)-**6a**, 35378-15-5; (*R*)-**6a**, 54712-19-5; (*S*)-**6a**, 54676-33-4; (±)-**6b**, 2486-97-7; (*S*)-**6b**, 54676-34-5; (*S*)-**6c**, 54643-57-1; (*S*)-**6d**, 54643-58-2; (*S*)-**6e**, 54643-59-3; (*S*)-**6f**, 54643-60-6; (*R*)-**7a**, 16064-31-6; (*S*)-**7a**, 16064-30-5; (±)-**7b**, 2275-84-5; (*R*)-**7b**, 405-47-0; (*S*)-**7b**, 405-46-9; (*R*)-**7c**, 52372-24-4; (±)-**7d**, 30572-91-9; (*R*)-**7d**, 24359-23-7; (*S*)-**7d**, 156-11-6; (±)-**7e**, 54643-61-7; (*R*)-**7e**, 54712-53-7; (*S*)-**7e**, 54676-35-6; (±)-**7f**, 54643-62-8; (*R*)-**7f**, 54676-36-7; (*S*)-**7f**, 54676-37-8; (*R*)-**8a**, 41820-21-7; (*S*)-**8a**, 1462-73-3; (*S*)-**8b**, 51-64-9; (*S*)-**8c**, 52372-25-5; **10b**, 19394-34-4; sodium *N*-acetyl-L-leucinate, 54643-63-9; 5-bromosalicylaldehyde, 1761-61-1; (−)-dibenzoyltartaric acid, 2743-38-6; (+)-dibenzoyltartaric acid, 17026-42-5.

References and Notes

(1) Part XVIII: H. E. Smith, R. K. Orr, and F.-M. Chen, *J. Am. Chem. Soc.*, in press.

(2) Supported by U. S. Public Health Service Grant MH-11468 and U. S. Army Medical Research and Development Command Contract DADA 17-73-C-3130 and presented in part at the 26th Southeastern Regional Meeting of the American Chemical Society, Norfolk, Va., Oct 1974, Abstract 270.
(3) (a) Vanderbilt University; (b) Tennessee State University.
(4) J. H. Brewster and J. G. Buta, *J. Am. Chem. Soc.*, **88**, 2233 (1966).
(5) G. G. DeAngelis and W. C. Wildman, *Tetrahedron*, **25**, 5099 (1969).
(6) H. E. Smith and T. C. Willis, *J. Am. Chem. Soc.*, **93**, 2282 (1971).
(7) G. Snatzke, M. Kajtár, and F. Werner-Zamojska, *Tetrahedron*, **28**, 281 (1972).
(8) J. R. Platt, *J. Chem. Phys.*, **19**, 263 (1951).
(9) J. Petruska, *J. Chem. Phys.*, **34**, 1120 (1961).
(10) M. Legrand and R. Viennet, *Bull. Soc. Chim. Fr.*, 2798 (1966).
(11) J. Horwitz, E. H. Strickland, and C. Billups, *J. Am. Chem. Soc.*, **91**, 184 (1969).
(12) T. M. Hooker, Jr., and J. A. Schellman, *Biopolymers*, **9**, 1319 (1970).
(13) O. Korver, *Tetrahedron*, **26**, 5507 (1970).
(14) H. E. Smith, J. R. Neergaard, E. P. Burrows, and F.-M. Chen, *J. Am. Chem. Soc.*, **96**, 2908 (1974).
(15) J. A. Schellman, *Acc. Chem. Res.*, **1**, 144 (1968).
(16) H. E. Smith, E. P. Burrows, J. D. Miano, C. D. Mount, E. Sanders-Bush, and F. Sulser, *J. Med. Chem.*, **17**, 416 (1974).
(17) Signs in parentheses refer to rotatory power observed at the D line for the amine hydrochlorides in water and for the Schiff bases in absolute ethanol. It was noted earlier[18] that (*S*)-(+)-amphetamine hydrochloride is dextrorotatory in water and levorotatory in isopropyl alcohol. (*S*)-(+)-*p*-Chloroamphetamine hydrochloride shows similar behavior (see Experimental Section).
(18) H. E. Smith, M. E. Warren, Jr., and L. I. Katzin, *Tetrahedron*, **24**, 1327 (1968); **25**, 4648 (1969).
(19) G. F. Holland, C. J. Buck, and A. Weissman, *J. Med. Chem.*, **6**, 519 (1963).
(20) I. B. Johns and J. M. Burch, *J. Am. Chem. Soc.*, **60**, 919 (1938).
(21) A. Ilvespaa, M. Wilhelm, and A. Marxer, German Offen. 1,900,576 (1969); *Chem. Abstr.*, **72**, 31477b (1970).
(22) T. C. Aschner, U. S. Patent 2608583 (1952); *Chem. Abstr.*, **48**, 1416*h* (1954).
(23) F. R. Dollish, W. G. Fateley, and F. F. Bentley, "Characteristic Raman Frequencies of Organic Compounds". Wiley, New York, N.Y., 1974, pp 171, 175, 363, 375, and 381.
(24) O. E. Weigang, Jr., *J. Chem. Phys.*, **43**, 3609 (1965).
(25) A. H. Beckett and L. G. Brookes, *Tetrahedron*, **24**, 1283 (1968).
(26) S. B. Matin, P. S. Callery, J. S. Zweig, A. O'Brien, R. Rapoport, and N. Castagnoli, Jr., *J. Med. Chem.*, **17**, 877 (1974).
(27) M. B. Neher, E. W. Goldberg, and R. W. Fairchild, *J. Org. Chem.*, **26**, 5220 (1961).
(28) M. Koremura, H. Oku, T. Shono, and T. Nakanishi, *Takamine Kenkyusho Nempo*, **13**, 212 (1961); *Chem. Abstr.*, **57**, 16451*b* (1962).
(29) T. M. Patrick, Jr., E. T. McBee, and H. B. Hass, *J. Am. Chem. Soc.*, **68**, 1009 (1946).

Photochemistry and Radiation Chemistry of Sulfur-Containing Amino Acids. A New Reaction of the 1-Propenylthiyl Radicals[1]

Hiroyuki Nishimura* and Junya Mizutani

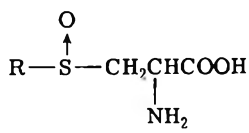
Department of Agricultural Chemistry, Hokkaido University, Sapporo, Japan

Received September 9, 1974

In connection with food-flavor deterioration caused by uv or γ irradiation, a new reaction of the 1-propenylthiyl radicals from *S*-(*cis*-1-propenyl)-L-cysteine irradiated by uv ray or γ-ray in oxygen-free aqueous solutions was investigated. The main products, formed via 1-propenylthiyl radicals, in uv photolysis were 1-propene-1-thiol, 2,4-dimethylthiophene, 3,4-dimethylthiophene, and 3-methylthiophene, while γ radiolysis yielded 1-propene-1-thiol, *n*-propyl 1-propenyl sulfide (cis and trans), and di-1-propenyl sulfide (cis,cis and cis,trans). Furthermore, cis–trans isomerization of 1-propenylthiyl radicals plays an important role in the formation of these products.

Sulfur-containing amino acids, such as *S*-alkyl-L-cysteine (alkyl: methyl, *n*-propyl, allyl, 1-propenyl), are found abundantly in *Allium*,[2] *Brassica*,[3] and *Phaseolus*[4] plants. These sulfoxides are also biologically active, i.e., they exhibit antihypercholesterolemic[5] and allithiamine effects.[6] Furthermore, since sulfur-containing amino acids are known to be highly sensitive to uv and γ irradiation, it is of interest to investigate the photolysis and radiolysis of these compounds.

We have studied the mechanism of formation of the major products when sulfoxide amino acids **1**, which are



1

$R = CH_3CH_2CH_2,\ CH_2{=}CHCH_2,\ CH_3CH{=}CH$

precursors of onion and garlic flavors, are irradiated by γ rays in an oxygen-free aqueous solution. This is of importance from the viewpoint of food irradiation.[7]

Recently, during studies on the uv photolysis and γ radiolysis of *S*-alkyl-L-cysteines (alkyl: *n*-propyl, allyl, 1-propenyl), we found that the major products formed from uv photolysis of *S*-*n*-propyl-L-cysteine (**2**) or *S*-allyl-L-cysteine (**3**) were approximately similar to those from γ radiolysis (Figure 1).[8] On the other hand, the uv photolysis of *S*-(*cis*-1-propenyl)-L-cysteine (**7**) proceeded quite differently from its γ radiolysis.

In this paper we report the identification of the products formed by uv photolysis and γ radiolysis of *S*-(*cis*-1-propenyl)-L-cysteine, one of the lachrymatory precursors in onions,[9] and suggest mechanistic schemes to rationalize the major products.

Results and Discussion

Identification of Products. Gas chromatograms of the volatile products from uv photolysis and γ radiolysis of *S*-(*cis*-1-propenyl)-L-cysteine are shown in Figure 2. Comparison of gas chromatographic retention time and mass spectrometric fragmentations with those of reference compounds permitted identification of the volatile compounds shown in Table I.

The major products of uv-irradiated *S*-(*cis*-1-propenyl)-L-cysteine were 1-propene-1-thiol, 2,4-dimethylthiophene, 3,4-dimethylthiophene, and 3-methylthiophene. Minor products were *n*-propyl 1-propenyl sulfides, di-1-propenyl sulfides, 2-methylthiophene, and 2,5- and 2,3-dimethylthiophenes.

The major products of γ radiolysis (10^4–10^6 rad) were 1-propene-1-thiol, *n*-propyl *cis*-1-propenyl sulfide, and *n*-propyl *trans*-di-1-propenyl sulfide. Minor products were *cis,cis*-di-1-propenyl sulfide and *cis,trans*-di-1-propenyl sulfide. No thiophene derivatives could be detected even by using a highly sensitive gas chromatograph and the combined GC–MS method.[10]

The mass spectral fragmentations of the main peaks in Figure 2 are summarized in Table II. Mass spectral fragmentations of 1-propene-1-thiol, *n*-propyl 1-propenyl sul-

Table I: Identification of Volatile Products from *S*-(*cis*-1-Propenyl)-L-cysteine Irradiated by Uv Ray or γ-Ray

Uv photolysis		γ radiolysis	
Peak no.	Compd	Peak no.	Compd
U_1	Propanal	γ_1	1-Propene-1-thiol
U_2	Propane-1-thiol	γ_2	*n*-Propyl *cis*-1-propenyl sulfide
U_3	1-Propene-1-thiol	γ_3	*n*-Propyl *trans*-1-propenyl sulfide
U_4	2-Methylthiophene	γ_4	*cis*,*cis*-di-1-Propenyl sulfide
U_5	3-Methylthiophene	γ_5	*cis*,*trans*-di-1-Propenyl sulfide
U_6	*n*-Propyl 1-propenyl sulfides[a]		
U_7	2,5-Dimethylthiophene		
U_8	2-Methyl-2-pentenal		
U_9	2,4-Dimethylthiophene		
U_{10}	(a) Di-1-propenyl sulfides[b]		
	(b) 2,3-Dimethylthiophene		
U_{11}	3,4-Dimethylthiophene		

[a] Mixture of cis and trans. [b] Mixture of cis,cis and cis,trans.

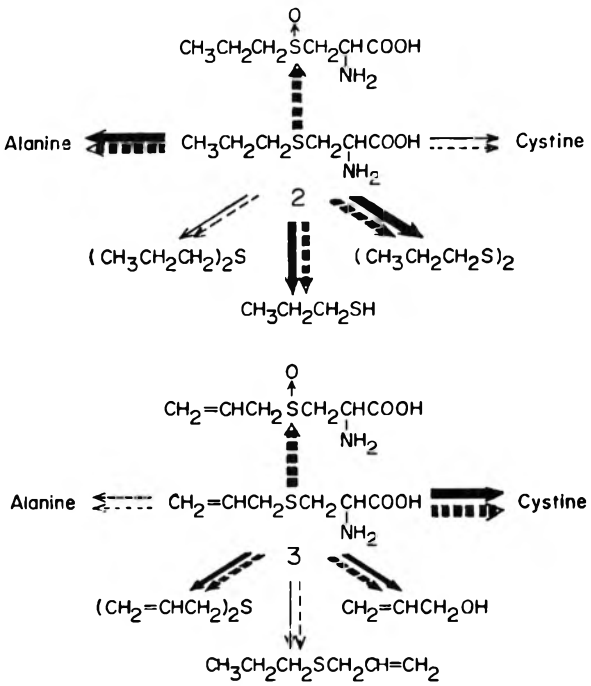


Figure 1. The products from *S*-*n*-propyl-L-cysteine (2) and *S*-allyl-L-cysteine (3) irradiated by uv ray (solid line) or γ-ray (dotted line) in oxygen-free aqueous solutions. Major products are represented with a thick line.

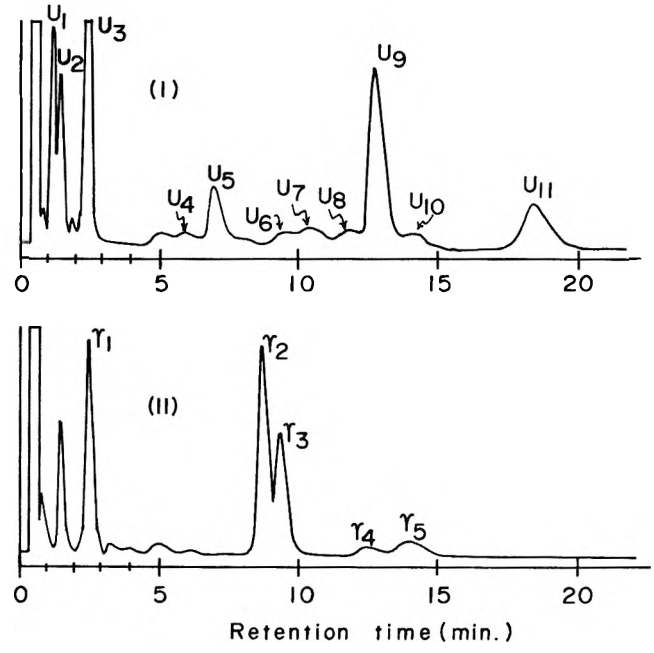


Figure 2. Gas–liquid chromatograms of head space vapor from *S*-(*cis*-1-propenyl)-L-cysteine irradiated in oxygen-free aqueous solutions: (I) uv ray, 20 m*M*, 2537 Å, 20 hr; (II) γ-ray, 20 m*M*, 1 × 10^6 rad.

fides, and di-1-propenyl sulfides have been rationalized on the basis of metastable ion peaks and distinguished the products from the isomeric allyl compounds.[11] Since the mass spectra of *cis*- and *trans*-1-propenyl sulfides did not differ, the geometrical isomers were characterized by ir and ^{1}H NMR.[12]

In Table II, the relative abundance of a fragment, mass 59 ($CH_3C{\equiv}S^+$), explains a significant difference between 2-methylthiophene and 3-methylthiophene. Although the base peak in the mass spectra of mono- and dimethylthiophenes is usually the (M − 1) ion, the base peak of 2,3-dimethylthiophene only is mass 97 ($M^+ - 15$). A significant difference among the mass spectra of 2,5-, 2,4-, and 3,4-dimethylthiophenes is the relative abundances of mass 59, i.e., 22.1, 8.9, and 4.5%, respectively (Table II).[13]

Among the ninhydrin-positive products of interest concerning the degradation mechanism, alanine (large) and cystine (trace), etc.,[14] were identified by comparing R_f values in two-dimensional thin layer chromatography[15] and gas chromatographic retention times[16] with those of reference compounds.

The formation of hydrogen sulfide was confirmed by lead tetraacetate and it was determined colorimetrically.[17] About 200 times more H_2S was produced by uv photolysis than by γ radiolysis.

Mechanism of Uv Photolysis. The oxygen-free neutral solutions of *S*-(*cis*-1-propenyl)-L-cysteine (2×10^{-2} mol/l.) dissolved in distilled water were irradiated for 0, 1, 2, 5, 10, 20, or 40 hr (2537 Å). The correlation between irradiation time and the yield of products is shown in Figure 3. Since alanine was produced in considerable quantity even at an early stage of uv irradiation, it seems that *S*-(*cis*-1-propenyl)-L-cysteine (7) is cleaved in the initial step to give 1-propenylthiyl radicals and 2-amino-2-carboxyethyl radical **9**. In the electron spin resonance (ESR) spectrum (77 K) of *S*-(*cis*-1-propenyl)-L-cysteine irradiated in aqueous system, an anisotropic signal (g_1 = 2.002, g_2 = 2.025, g_3 = 2.052) was observed in good agreement with reference alkylthiyl radicals (Figure 4).[18] This indicates that thiophene derivatives are produced via 1-propenylthiyl radicals as follows.

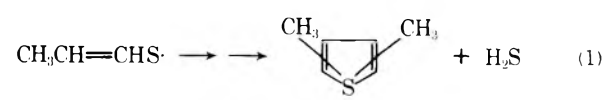


Table II: Mass Spectral Fragmentations of the Volatile Products from Uv Photolysis and γ Radiolysis of *S*-(*cis*-1-Propenyl)-L-cysteine

m/e	A[a]	B[b]	C[c]	D[d]	E[e]	F[f]	G[g]	H[h]	I[i]	J[j]	K[k]
39	54.3	17.0	11.4	13.3	23.6	20.3	22.9	65.1	50.0	77.7	91.9
40	8.6	2.0	1.1	1.9	3.9	3.5	4.0	17.2	5.5	5.0	5.5
41	100.0	1.5	1.1	2.4	5.8	8.2	11.5	94.3	91.8	89.2	97.4
42	8.6			1.1	1.1	1.1	1.2	5.7	4.5	3.3	4.8
43	1.4			1.1	1.1	1.1	2.3	32.5	30.9	4.1	4.1
44	4.3	3.1	2.0	1.0	2.2	1.7	1.9	8.9	1.8	1.7	2.1
45	71.4	21.6	26.8	14.5	31.4	25.5	35.1	82.7	81.8	89.3	98.7
46	18.6	2.5	2.2	1.2	2.1	1.6	2.5	14.9	12.7	8.3	8.2
47	14.6	3.0	2.3	1.8	2.3	1.6	2.5	21.2	20.0	14.9	16.4
48	1.7	1.4	1.0	1.2	1.0	1.1		1.6	1.4	1.6	0.7
49	1.4	3.5	3.0	2.0	1.1	1.7		1.6	1.4	0.8	0.7
50		4.0	7.8	8.1	4.5	10.2	6.3				
51		5.1	6.5	11.2	5.6	13.2	8.0				
52		1.8	3.5	3.5	2.3	4.0	2.2				
53		14.2	8.6	8.5	5.0	10.5	7.5	9.0	9.5	14.9	13.7
54		1.8	1.7	1.1	1.1	1.3	1.1	0.8	0.9	2.5	2.7
55				1.3	2.0	2.0	2.3	0.8	1.8	14.5	13.0
56					1.6	1.1	4.2				
57	5.7			4.4	2.0	5.0	1.8	1.6	1.8	8.3	4.1
58	8.6	5.0	6.6	7.9	3.8	11.2	4.5	3.2	6.4	9.9	9.6
59	18.6	6.2	2.3	22.1	8.9	14.0	4.5	16.3	16.8	23.2	28.8
60	1.4	1.4	1.1	1.7	1.4	1.8	1.3	1.6	1.8	3.3	5.5
61	1.4	2.5	2.0	1.8	2.0	1.9	1.8	1.6	1.8	3.3	10.3
62		2.5	2.0	1.4	3.8	1.9	1.8				
63		2.7	2.8	2.0	5.0	2.7	3.7				
64				1.1	1.1	1.0	1.1				
65		1.5	2.3	1.5	3.0	3.5	4.0				
67										10.7	16.8
68	1.2									1.7	2.7
69	5.7	7.9	8.4	7.1	8.0	8.2	10.5			12.4	13.7
70	1.4	2.5	2.3	2.1	3.3	3.5	4.1			1.6	1.4
71	5.7	3.8	6.0	7.0	9.5	5.0	9.5	11.2	10.0	26.4	30.8
72	1.4	1.2		1.2	2.8	1.1	2.2	10.2	9.1	25.6	31.5
73	22.9	1.2			1.4	1.1	1.1	29.2	29.1	33.1	32.9
74	82.9 (P)							100.0	100.0	12.4	16.5
75	5.7							10.9	10.7		
76	5.7							8.3	6.9		
77				13.8	17.0	13.3	12.5				
78				7.7	7.8	8.0	5.2				
79				4.1	5.5	3.9	5.3			14.9	13.7
80										1.6	2.7
81		1.3	1.4							16.5	21.9
82		1.5	1.4							2.5	7.5
83		1.3		2.0	1.2	1.4	1.1			1.7	2.1
84				2.0	1.8	3.9	1.3				
85				3.1	2.0	7.0	2.0	4.9	3.6	31.4	41.1
86								0.8	0.5	3.3	5.5
87								40.6	35.4	2.5	4.1
88								2.4	1.8		
89								2.5	1.8		
97		100.0	100.0	61.7	53.0	100.0	49.3			13.2	5.5
98		52.0 (P)	50.0 (P)		4.0	7.5	4.3			2.5	2.1
99		5.9	5.8		3.2	4.5	3.5			93.5	83.6
100		3.0	2.9							6.6	6.2
101								3.3	1.8	7.4	5.5
111				100.0	100.0	74.6	100.0				
112				75.7 (P)	76.7 (P)	77.5 (P)	73.7 (P)				
113				10.6	10.7	10.3	10.1			6.6	10.3
114				4.5	4.5	4.6	4.3			100.0 P	100.0 P
115										7.4	9.6
116								55.3 (P)	57.7 (P)	5.8	8.9
117								4.9	5.5		
118								4.1	4.1		

[a] 1-Propene-1-thiol. [b] 2-Methylthiophene. [c] 3-Methylthiophene. [d] 2,5-Dimethylthiophene. [e] 2,4-Dimethylthiophene. [f] 2,3-Dimethylthiophene. [g] 3,4-Dimethylthiophene. [h] *n*-Propyl *cis*-1-propenyl sulfide. [i] *n*-Propyl *trans*-1-propenyl sulfide. [j] *cis,cis*-Di-1-propenyl sulfide. [k] *cis,trans*-Di-1-propenyl sulfide.

As shown in Figure 3, the yield of each thiophene derivative, hydrogen sulfide, 1-propene-1-thiol, alanine, and sulfides increased approximately in parallel with irradiation time to the extent of 0–5 hr, respectively.

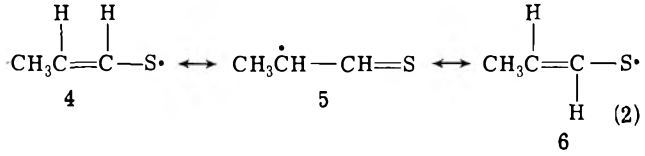
Couture and Lablache-Combier reported the isomerization of 2-methylthiophene to 3-methylthiophene by uv irradiation and suggested an isomerization mechanism.[19] Therefore there is a possibility that each dimethylthiophene is produced by methyl scrambling on the thiophene ring. Only trace amounts of isomerization products were obtained from 2,4-dimethylthiophene and 3,4-dimethylthiophene irradiated for 20–40 hr in aqueous solutions, respectively.

The dimethylthiophenes might also be produced by photocyclization of di-1-propenyl sulfides from uv-irradiated **7**. However, 2,4-dimethylthiophene or 3,4-dimethylthiophene could not be detected even by gas chromatography (FID).[20]

In addition, Block and Corey have reported that β,β′-diphenyldivinyl sulfide undergoes photocyclization to give *trans*-2,3-diphenyl-5-thiabicyclo[2.1.0]pentane and 2,3-dihydro-3,4-diphenylthiophene.[21] However, no cyclization products of this type were obtained from **7** or the di-1-propenyl sulfides.

From the above results, each dimethylthiophene must be produced independently, *via* 1-propenylthiyl radicals (Figure 4).

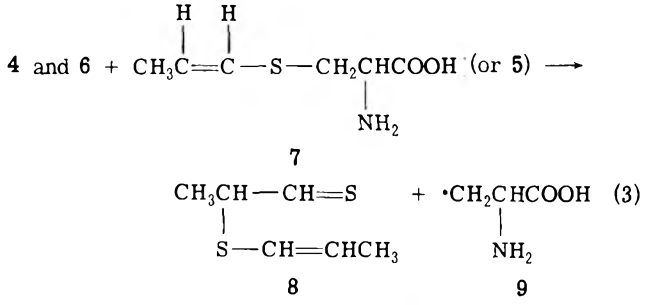
1-Propenylthiyl radicals exist as a resonance hybrid (eq 2), since cis–trans isomerization of the 1-propenylthiyl radicals has been found in the case of γ radiolysis.[1b,22]



(2)

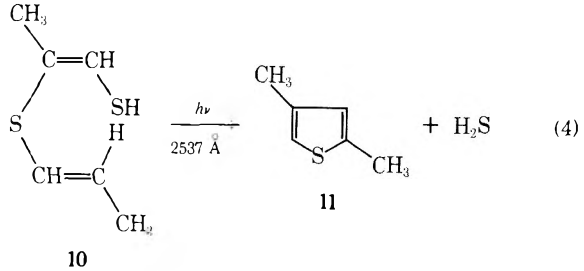
A reasonable tentative mechanism for dimethylthiophene formation is as follows.

1-Propenylthiyl radicals (**4** and **6**) react with **7** or alkyl radical **5** to produce unstable dimeric thioaldehyde **8**. **8** via



(3)

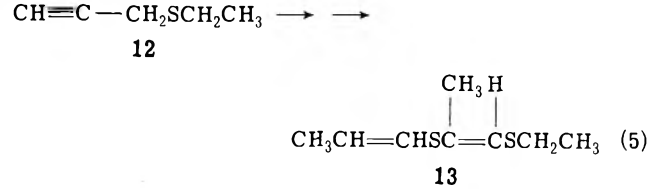
a [1,3]-prototropic shift gives the alkenethiol **10** and the immediate elimination of hydrogen sulfide then leads to stable 2,4-dimethylthiophene (**11**). Therefore, we tried to



(4)

prepare alkenethiol **10** to determine whether 2,4-dimethylthiophene could indeed be obtained by its irradiation.

First, 5-methyl-3,6-dithia-4,7-nonadiene (**13**) was prepared from ethyl 2-propynyl sulfide (**12**) in about 45% yield. Lithium alkenethiolate, which was prepared by reaction of **13** with lithium in liquid ammonia, gave **10** in low



(5)

yield by treatment with sulfuric acid.[23] A small amount of 2,4-dimethylthiophene was also produced, probably by partial decomposition during the acid hydrolysis and solvent extraction. Thereupon **10** was irradiated by uv ray and the products were characterized by combined GC–MS.[10] The major products were 2,4-dimethylthiophene, hydrogen sulfide, and 1-propene-1-thiol; other thiophene derivatives were produced only in trace amounts. Although the intermediates **8** or **10** could not be isolated at room temperature, the above evidence indicates that **10** might be an intermediate in the formation of 2,4-dimethylthiophene.

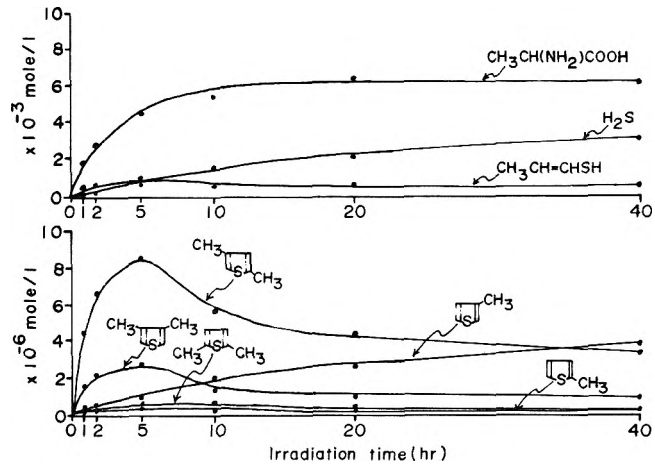


Figure 3. Correlation between irradiation time and products from *S*-(*cis*-1-propenyl)-L-cysteine irradiated in oxygen-free aqueous solutions.

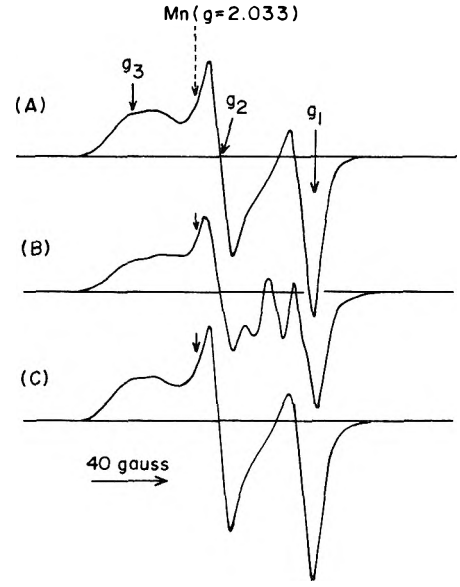


Figure 4. Electron spin resonance spectra of *S*-(*cis*-1-propenyl)-L-cysteine (A, B) and *n*-propyl 1-propenyl sulfide (C) irradiated by uv ray (2537 Å, 10 hr) at 77 K: (A) recorded in 8 hr after irradiation; (B) recorded in 10 min after irradiation; (C) recorded in 2 hr after irradiation. $g_1 = 2.002$, $g_2 = 2.025$, $g_3 = 2.052$.

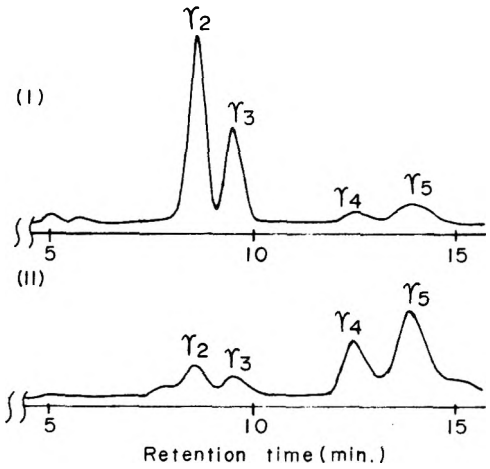
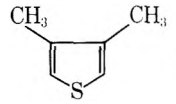


Figure 5. Gas–liquid chromatograms of head space vapor from (I) 2×10^{-2} mol/l. of *S*-(*cis*-1-propenyl)-L-cysteine and (II) mixture of 2×10^{-2} mol/l. of *S*-(*cis*-1-propenyl)-L-cysteine and 1×10^{-2} mol/l. of NaCN irradiated by γ-ray (1×10^6 rad).

Similarly alkyl radical **5** attacks **7** or another radical **5** to produce unstable bisthioaldehyde **14**, which gives dithiol **15** via a [1,3]-prototropic shift. Immediate elimination of hydrogen sulfide from **15** then leads to stable 3,4-dimethylthiophene (**16**).

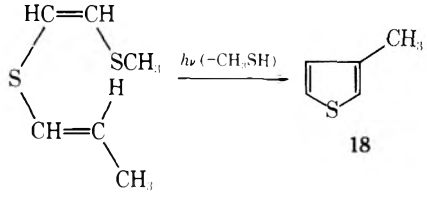
$$\underset{\text{CH}_3\text{CHCH=S}}{\overset{\text{CH}_3\text{CHCH=S}}{\mid}} \xrightarrow{\text{[1,3] shift}} \underset{\text{CH}_3\text{C=CHSH}}{\overset{\text{CH}_3\text{C=CHSH}}{\mid}} \xrightarrow{h\nu\,(-\text{H}_2\text{S})} \quad (6)$$

14 **15**



16

The amount of 3-methylthiophene produced after 20-hr irradiation was 20 times the amount of 2-methylthiophene, as shown in Figure 3. 3-Methylthiophene (**18**) is probably produced through intermediate **17** formed by a [1,3]-methyl shift in the thioaldehyde **8** (eq 7).[24]



(7)

17 **18**

The trace amounts of 2,5-dimethylthiophene and 2,3-dimethylthiophene may have been produced by methyl scrambling on the thiophene ring.

Further confirmation of the intermediates and other evidence for the suggested mechanism will be presented elsewhere.

Mechanism of γ Radiolysis. Some *trans*-1-propenyl sulfides were found from **7** irradiated by γ-ray with 1×10^6 rad (see Table I). These trans products must have been produced via cis–trans isomerization of the 1-propenylthiyl radicals[25] (eq 2).

In recent years, photochemical[26] and radiation-chemical[27] cis–trans isomerizations of olefins have been much investigated in organic solvents and in gaseous systems. However, radiation-induced cis–trans isomerization has not been investigated in aqueous systems in spite of its importance for animal and plant organisms.

The yield of alanine from **7** is considerably greater than

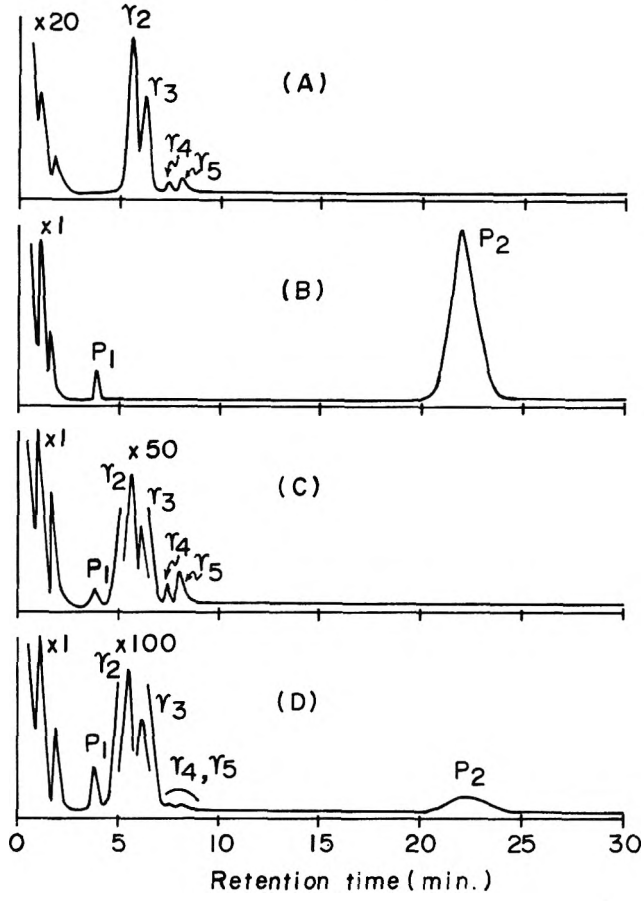


Figure 6. Gas–liquid chromatograms of the mixture of *S*-(*cis*-1-propenyl)-L-cysteine (PeCS) and *S*-*n*-propyl-L-cysteine (PCS) irradiated by γ-ray: (A) 1×10^{-2} mol/l. of PeCS, (B) 1×10^{-3} mol/l. of PCS, (C) mixture of 1×10^{-1} mol/l. of PeCS and 1×10^{-3} mol/l. of PCS, (D) mixture of 1×10^{-2} mol/l. of PeCS and 5×10^{-3} mol/l. of PCS.

that of cystine, in analogy with the case of uv photolysis. This fact indicates that the S–C (alanine moiety) bond in **7** is easily cleaved by γ irradiation.

The radiation-induced decomposition of water in the absence of oxygen proceeds as follows.

$$\text{H}_2\text{O} \longrightarrow \cdot\text{H},\ e_{aq},\ \cdot\text{OH},\ \text{H}_3\text{O}^+,\ \text{H}_2,\ \text{H}_2\text{O}_2 \quad (8)$$

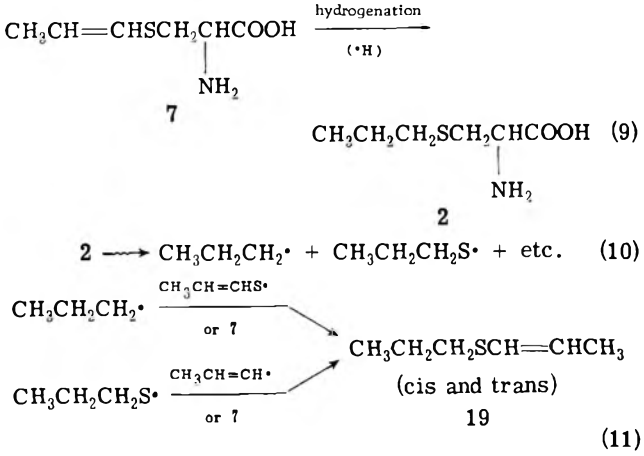
[28]

In order to elucidate the mechanism of γ radiolysis of **7**, it was irradiated after several scavengers had been added. The yield of alanine decreased with increasing concentration of N_2O (specific scavenger for e_{aq})[29] and increased with increasing concentration of KBr (specific scavenger for ·OH).[30] Therefore it is considered that **7** reacts with e_{aq} to produce alanine.

With increasing concentration of NaCN (H radical scavenger)[31] in irradiated **7**, both γ_2 and γ_3 decreased. Both γ_4 and γ_5 increased (Figure 5). This evidence indicates that H radicals from γ radiolysis of water contribute to the formation of *n*-propyl 1-propenyl sulfide (cis and trans).

At first we inferred that di-1-propenyl sulfides (**20** and **21**) reacted with two H radicals to produce *n*-propyl 1-propenyl sulfides **19**, but **19** could not be detected in the volatile products formed from **20** or **21** irradiated in an oxygen-free aqueous solution. Therefore we added various concentrations of **2** to aqueous solutions of **7** and irradiated the mixture in an oxygen-free aqueous solution (Figure 6). Di-*n*-propyl sulfide (P_1) and di-*n*-propyl disulfide (P_2) formed by γ radiolysis of 1×10^{-3} mol/l. of *S*-*n*-propyl-L-cysteine[32] could be detected in the same concentration as before (B in Figure 6). Disulfide (P_2) was not produced from the

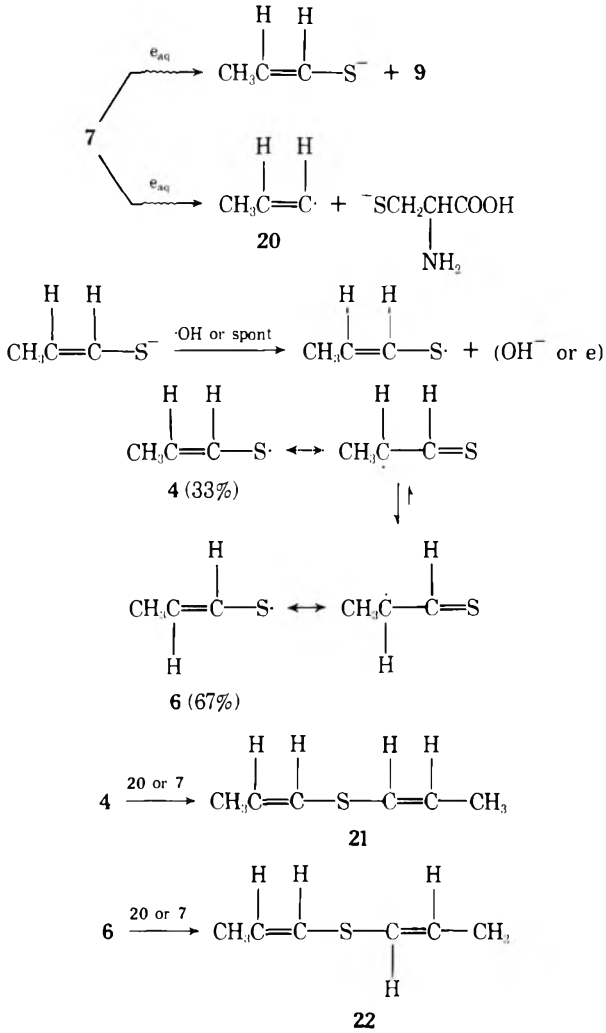
mixture of 2×10^{-2} mol/l. of **7** and 1×10^{-3} mol/l. of **2** (C in Figure 6).[33] On the other hand, the amount of *n*-propyl 1-propenyl sulfides (γ_2 and γ_3) increased steeply. At higher concentration of **2** (5×10^{-3} mol/l.), disulfide (P_2) was barely detected (D in Figure 6). These facts indicate that **7** is hydrogenated by H radicals from the γ radiolysis of water to produce **2**, and *n*-propyl radicals from irradiated **2** attack 1-propenylthiyl radicals or **7** to produce *n*-propyl 1-propenyl sulfides **19** as follows.



When irradiated to the extent of 10^4–10^6 rad, **7** gave di-1-propenyl sulfides (**21** and **22**) in the ratio of cis,cis:cis,trans (γ_4:γ_5) of 33:67. Although radiation-induced cis–trans isomerization of olefins in organic solvents has been observed frequently,[26] authentic cis isomer irradiated in an oxygen-free aqueous solution was not converted to trans isomer. Since the 1-propenyl radical is assumed to react with retention of stereochemistry,[34] the proportion of *cis*- and *trans*-1-propenylthiyl radicals (**4** and **6**) must be 33:67 (%).

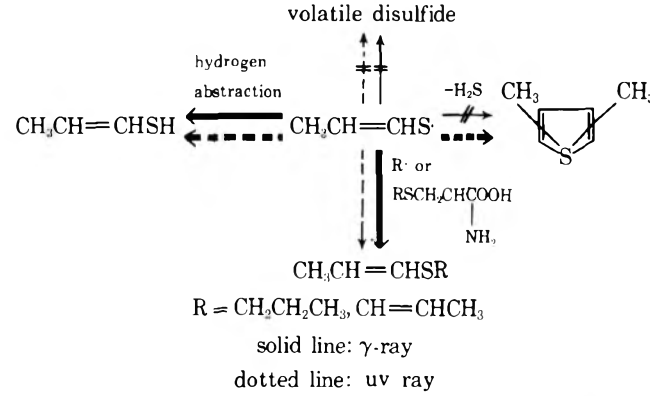
On the basis of the above results and evidence, we suggest that cis–trans isomerization of the 1-propenylthiyl radicals proceeds as shown in Chart I.

Chart I



Conclusions

In the case of γ radiolysis in aqueous systems, such chemical species as hydrated electrons (e_{aq}), hydroxyl radicals (·OH), etc. (eq 8), are produced in the first stage and attack the solute in the second stage. In uv photolysis, the solute is directly excited and decomposed. In spite of this basic difference, the major products from uv photolysis of **2** or **3** were approximately similar to those from γ radiolysis (Figure 1). However, the uv photolysis of *S*-(*cis*-1-propenyl)-L-cysteine was significantly different from its γ radiolysis. In spite of the formation of 1-propenylthiyl radicals from both uv photolysis and γ radiolysis of *S*-(*cis*-1-propenyl)-L-cysteine, thiophene derivatives were mainly produced in uv photolysis, while 1-propenyl-containing sulfides were mainly produced in γ radiolysis (Table I). Also, about 200 times more H_2S was produced by uv photolysis than by γ radiolysis. The main products via 1-propenylthiyl radicals are summarized as follows.



Furthermore, from alkenethiol **10**, 2,4-dimethylthiophene was obtained by uv photolysis but not by γ radiolysis, and instead of thiophenes, small amounts of 1-propene-1-thiol and di-1-propenyl sulfides were obtained by γ radiolysis (5×10^5 rad)[35] of **10** (about 2×10^{-2} mol/l.).

The intermediates, thioaldehyde **8** and **10**, etc., might be the key compounds in explaining the difference between uv photolysis and γ radiolysis of *S*-(*cis*-1-propenyl)-L-cysteine.

Experimental Section

General Instrumentation. The method of GC–MS combination was preferred to obtain the mass spectral data of trace amounts of products. A Watson-Biemann helium separator[10] was used between the gas chromatograph (Hitachi Model K-53 GLC) and the mass spectrometer (Hitachi Model RMS-4). The operating parameters were as follows: gas chromatograph, 1 m × 3 mm i.d. stainless steel column packed with 20% Reoplex 400 on 60–80 mesh acid-washed C-22, flow rate (helium carrier gas) of 25 ml/min, temperature 80°, injection port temperature 150°; mass spectrometer, ion source temperature 200°, ion source pressure 2×10^{-6} mm, target current 60 μA, total emission 80 μA, ionizing voltage 80 eV, accelerating voltage 3 kV. To purify the authentic compounds, a preparative gas chromatograph (Varian Aerograph 90-P) was used. To obtain the small amounts of products, a FID gas chromatograph (Yanagimoto GCG 550PF), in which a splitter was inserted, was also used. Infrared spectra were measured in KBr pellets with a Hitachi EPI-S2 infrared spectrometer. ^{1}H NMR spectral

data were obtained from a Hitachi R-22 apparatus (90 MHz). ESR spectra were taken at 77 K with X-band spectrometers (JeOL P-10).

Uv Irradiation. The oxygen-free neutral solutions of sulfur-containing amino acids (2×10^{-2} mol/l.) dissolved in triply distilled water were placed in stoppered quartz tubes. They were irradiated for 0, 1, 2, 5, 10, 20, or 40 hr at room temperature using a 50-W low-pressure mercury lamp, Ushio UL1-5BQ (2537 Å).

γ Irradiation. Irradiation was carried out by exposure to γ rays from cobalt-60 of 3 kCi at a dose rate of 6.24×10^4 rad/hr at room temperature. The oxygen-free neutral solutions of sulfur-containing amino acids (5×10^{-3} to 2×10^{-2} mol/l.) in triply distilled water were placed in stoppered Pyrex tubes and irradiated to the extent of 10^4–10^6 rad.

Irradiations in the presence of N_2O (specific scavenger for e_{aq}),[28] KBr (specific scavenger for ·OH),[29] or NaCN (H radical scavenger)[30] were also done for studies on the formation mechanism.

Separation and Identification of the Irradiation Products. In both the uv photolysis and γ radiolysis, volatile products from irradiated *S*-(*cis*-1-propenyl)-L-cysteine (5 l. of solution) were distilled off by passing through nitrogen gas as a carrier at approximately 80°, and absorbed into about 5 ml of isopentane trap cooled with Dry Ice–ethanol.

The volatile products were characterized by the combined GC–MS method and the products were further confirmed by comparing with the gas chromatographic retention time and mass spectra of the respective reference compounds.

Two-dimensional thin layer chromatography of ninhydrin-positive products from irradiated *S*-(*cis*-1-propenyl)-L-cysteine was carried out on Avicel SF (microcrystalline cellulose) by using (1) 1-butanol–acetic acid–water (4:1:1 v/v) and phenol–water (4:1 v/v) or (2) 1-butanol–acetic acid–water (63:10:27 v/v) and phenol–acetic acid–water (7:1:2 v/v) as solvent systems and the chromatograms were colored with ninhydrin reagent. Amino acids produced by irradiation were converted into *N*-trifluoroacetylamino acid *n*-butyl esters and were determined by using a FID gas chromatograph (Hitachi K-53).

***S*-*n*-Propyl-L-cysteine (2) and *S*-Allyl-L-cysteine (3).** The synthetic procedure is a modification of the method of du Vigneaud et al.[36] in preparing *S*-methyl-L-cysteine from L-cystine.

S-*n*-propyl-L-cysteine (2): mp 210–212° dec; ir (KBr) 2965–2860, 2580, 2120 (NH_3^+), and 1580 cm^{-1} (COO^-); mass spectrum *m/e* (rel intensity) 163 (M^+, 12.4), 118 (21.7), 90 (40.3), 89 (100), 74 (31.0), 61 (46.5), 47 (65.1), and 43 (89.9); ^1H NMR (D_2O–NaOD) δ 0.90 (3 H, t, J = 7.0 Hz, CH_3), 1.55 (2 H, m, CH_2), 2.50 (2 H, t, J = 7.2 Hz, SCH_2 at *n*-propyl), 2.75–2.85 (2 H, dd, J = 6.2 Hz, SCH_2 at C-β), and 3.45 (1 H, dd, J = 6.2 Hz, CH at C-α).

Anal. Calcd for $C_6H_{13}NO_2S$: C, 44.16; H, 8.03; N, 8.58. Found: C, 44.09; H, 7.99; N, 8.60.

S-Allyl-L-cysteine (3): mp 208–210° dec; ir (KBr) 3020–2870, 2590, 2120 (NH_3^+), 1580 (COO^-), and 990 and 918 cm^{-1} (allyl double bond); mass spectrum *m/e* (rel intensity) 161 (M^+, 14.2), 116 (8.4), 88 (55.8), 87 (100), 74 (90.0), 45 (46.8), 41 (87.6), and 39 (32.4); ^1H NMR (D_2O–NaOD) δ 2.61–2.71 (2 H, dd, J = 6.2 Hz, SCH_2 at C-β), 3.10 (2 H, d, J = 7.0 Hz, SCH_2 at allyl), 3.26 (1 H, dd, J = 6.2 Hz, CH at C-α), 5.01–5.22 (2 H, dd, J = 17.0 and 10.0 Hz, vinylic CH_2), and 5.71 (1 H, m, vinylic CH).

Anal. Calcd for $C_6H_{11}NO_2S$: C, 44.71; H, 6.88; N, 8.69. Found: C, 44.52; H, 6.81; N, 8.60.

***S*-(*cis*-1-Propenyl)-L-cysteine (7).** This compound was prepared by the synthetic procedure of Carson and Wong[37] from *S*-allyl-L-cysteine with potassium *tert*-butoxide in dimethyl sulfoxide: mp 179–180° dec; ir (KBr) 2970, 2840, 2580, 2100 (NH_3^+), and 1580 (COO^-), no absorption at 990 and 918 (allyl double bond) and at 967 cm^{-1} (trans isomer); mass spectrum *m/e* (rel intensity) 161 (M^+, 32.1), 116 (16.0), 88 (72.8), 87 (100), 74 (71.2), 59 (48.8), 45 (71.2), 41 (40.8), and 39 (44.0); ^1H NMR (D_2O–NaOD) δ 1.62 (3 H, d, J = 6.1 Hz, CH_3 at 1-propenyl), 2.85–2.95 (2 H, dd, J = 6.9 Hz, SCH_2 at C-β), 3.36 (1 H, dd, J = 6.9 Hz, CH at C-α), 5.67 (1 H, m, CH at 1-propenyl), and 5.98 (1 H, d, J = 9.0 Hz, SCH at 1-propenyl).

Anal. Calcd for $C_6H_{11}NO_2S$: C, 44.71; H, 6.88; N, 8.69. Found: C, 44.70; H, 6.81; N, 8.66.

The mass spectral fragmentations of such sulfur-containing amino acids as *S*-alkyl-L-cysteines were reported previously.[38]

Di-*n*-propyl Sulfide. Di-*n*-propyl sulfide was prepared from *n*-propyl bromide according to the method of Shriner et al.[39] in preparing dibenzyl sulfide from benzyl chloride with sodium sulfide. The product was distilled at atmospheric pressure: bp 141°; yield 82%; ir (film) 2990, 2890 (methyl C–H stretching vibration), 2960 (CH_2), and 1460 cm^{-1} (C–H); mass spectrum *m/e* (rel intensity) 118 (M^+, 95.2), 89 (100), 76 (81.2), 61 (63.5), 47 (62.3), and 43 (77.6).

Anal. Calcd for $C_6H_{14}S$: C, 60.98; H, 11.94. Found: C, 61.10; H, 11.92.

Diallyl Sulfide. Diallyl sulfide was also prepared by the above-mentioned method: bp 139°; yield 71%; ir (film) 1645 (double bond) and 990 and 913 cm^{-1} (allyl double bond); mass spectrum *m/e* (rel intensity) 114 (M^+, 30.5), 99 (30.8), 73 (78.3), 72 (42.5), 45 (91.2), 41 (100), and 39 (68.2).

Anal. Calcd for $C_6H_{10}S$: C, 63.13; H, 8.83. Found: C, 63.30; H, 8.75.

Di-1-propenyl Sulfides (21 and 22). This compounds were prepared by the method of Tarbell and Lovett,[40] bp 146–150°, yield 42%. *cis,cis*- and *cis,trans*-di-1-propenyl sulfides were purified by using the preparative gas chromatograph.

cis,cis-Di-1-propenyl sulfide (21): ir (film) 1720, 1610 (double bond), 932 (1-propenyl double bond), and 660 cm^{-1} (cis double bond); mass spectrum *m/e* (rel intensity) 114 (M^+, 100), 99 (93.5), 73 (33.1), 45 (89.3), 41 (89.2), and 39 (77.7); ^1H NMR (CCl_4) δ 1.66 (6 H, dd, J = 6.9 and 1.9 Hz, CH_3), 5.54 (2 H, m, CH at 1-propenyl), and 5.94 (2 H, m, J = 9.5 and 1.9 Hz, SCH at 1-propenyl).

Anal. Calcd for $C_6H_{10}S$: C, 63.13; H, 8.83. Found: C, 63.20; H, 8.80.

cis,trans-Di-1-propenyl sulfide (22): ir (film) 1680, 1610 (double bond), 962 (trans double bond), 932 (1-propenyl double bond), and 660 cm^{-1} (cis double bond); mass spectrum *m/e* (rel intensity) 114 (M^+, 100), 99 (83.6), 73 (32.9), 45 (98.7), 41 (97.4), and 39 (91.9); ^1H NMR (CCl_4) δ 1.60–1.75 (6 H, m, CH_3), 5.47–5.76 (2 H, m, CH at 1-propenyl), 5.90 (1 H, m, J = 17.2 and 1.9 Hz, SCH at trans double bond), and 5.96 (1 H, m, J = 9.5 and 1.9 Hz, SCH at cis double bond).

Anal. Calcd for $C_6H_{10}S$: C, 63.13; H, 8.83. Found: C, 63.21; H, 8.79.

***n*-Propyl Allyl Sulfide.** The synthetic procedure is a modification of the method of Kirner and Richter[41] in preparing α-furfuryl ethyl sulfide from furfuryl mercaptide with ethyl bromide. The product was obtained by distillation: bp 140°; yield 78%; ir (film) 2990, 2890 (methyl C–H stretching vibration), 1645 (double bond), and 989 and 912 cm^{-1} (allyl double bond); mass spectrum *m/e* (rel intensity) 116 (M^+, 34.7), 87 (30.2), 74 (63.1), 73 (20.7), 45 (51.8), 43 (20.3), 41 (100), and 39 (49.1).

Anal. Calcd for $C_6H_{12}S$: C, 62.04; H, 10.41. Found: C, 61.90; H, 10.39.

***n*-Propyl 1-Propenyl Sulfides (19).** This compound was prepared by the reaction of *n*-propyl allyl sulfide with sodium methoxide in absolute methanol, bp 139–141°, yield 55%. Cis and trans isomers were purified by the gas chromatograph.

n-Propyl *cis*-1-propenyl sulfide: ir (film) 1612 (double bond) and 936 and 665 cm^{-1} (cis double bond); mass spectrum *m/e* (rel intensity) 116 (M^+, 55.3), 87 (40.6), 74 (100), 73 (29.2), 45 (82.7), 43 (32.5), 41 (94.3), and 39 (65.1); ^1H NMR (CCl_4) δ 0.96 (3 H, t, J = 7.0 Hz, CH_3 at *n*-propyl), 1.56 (2 H, m, CH_2), 2.48 (2 H, t, J = 7.2 Hz, SCH_2 at *n*-propyl), 1.70 (3 H, d, J = 6.1 Hz, CH_3 at 1-propenyl), 5.27–5.72 (1 H, m, CH at 1-propenyl), and 5.78 (1 H, d, J = 9.9 Hz, SCH at 1-propenyl).

Anal. Calcd for $C_6H_{12}S$: C, 62.04; H, 10.41. Found: C, 61.95; H, 10.38.

n-Propyl *trans*-1-propenyl sulfide: ir (film) 1610 (double bond) and 960 cm^{-1} (trans double bond); mass spectrum *m/e* (rel intensity) 116 (M^+, 57.7), 87 (35.4), 74 (100), 73 (29.1), 45 (81.8), 43 (30.9), 41 (91.8), and 39 (50.0); ^1H NMR (CCl_4) δ 0.96 (3 H, t, J = 7.0 Hz, CH_3 at *n*-propyl), 1.56 (2 H, m, CH_2), 1.70 (3 H, d, J = 6.1 Hz, CH_3 at 1-propenyl), 2.48 (2 H, t, J = 7.2 Hz, SCH_2 at *n*-propyl), 5.27–5.72 (1 H, m, CH at 1-propenyl), and 5.82 (1 H, d, J = 15.2 Hz, SCH at 1-propenyl).

Anal. Calcd for $C_6H_{12}S$: C, 62.04; H, 10.41. Found: C, 62.10; H, 10.39.

Di-*n*-propyl Disulfide. This compound was prepared by the application of a synthetic procedure of *p,p'*-dinitrophenyl disulfide[42] from *p*-nitrophenyl chloride with Na_2S_2: bp 195°; yield 75%; ir (film) 2990, 2890 (methyl C–H), and 600–800 cm^{-1} (C–S); mass spectrum *m/e* (rel intensity) 150 (M^+, 28.0), 108 (23.6), 66 (10.9), 43 (100), 41 (44.5) and 39 (20.0).

Anal. Calcd for $C_6H_{14}S_2$: C, 47.98; H, 9.40. Found: C, 48.02; H, 9.39.

Diallyl Disulfide. This compound was also derived from allyl bromide by the above-mentioned method: bp 173°; yield 55%; ir (film) 1645 (double bond) and 989 and 915 cm^{-1} (allyl double bond); mass spectrum *m/e* (rel intensity) 146 (M^+, 71.5), 113

(22.0), 105 (40.8), 81 (72.5), 73 (62.9), 45 (81.2), 41 (100), and 39 (89.8).

Anal. Calcd for $C_6H_{10}S_2$: C, 49.31; H, 6.90. Found: C, 49.43; H, 7.04.

1-Propene-1-thiol. This compound was prepared by the synthetic procedure of Brandsma:[23] bp 63–70°; yield 21%; mass spectrum *m/e* (rel intensity) 74 (M^+, 82.9), 59 (18.6), 47 (14.6), 45 (71.4), 41 (100), and 39 (54.3).

Anal. Calcd for C_3H_6S: C, 48.64; H, 8.16. Found: C, 48.55; H, 8.05.

2-Methyl-2-pentenal. This compound was prepared by the synthetic procedure of Paquin:[43] bp 137–138°; yield 32%; mass spectrum *m/e* (rel intensity) 98 (M^+, 68.8), 83 (25.5), 69 (50.8), 55 (52.0), 41 (100), and 39 (38.5).

Anal. Calcd for $C_6H_{10}O$: C, 73.43; H, 10.27. Found: C, 73.39; H, 10.30.

Ethyl 2-Propynyl Sulfide (12). This compound was prepared by the reaction of propargyl bromide (119 g, 1 mol) with sodium ethanethiolate (84g, 1 mol) in 200 ml of absolute ethanol: bp 29–30° (15 mm); yield 75%; ir (film) 3220 (terminal acetylenic bond) and 2100–2120 cm^{-1} (C≡C); mass spectrum *m/e* (rel intensity) 100 (M^+, 56.7), 85 (35.5), 72 (61.1), 71 (78.9), 45 (100), and 39 (66.4); ^1H NMR (CCl_4) δ 1.23 (3 H, t, J = 7.0 Hz, CH_3), 2.04 (1 H, t, J = 1.2 Hz, CH), 2.60 (2 H, q, J = 7.0 Hz, CH_2 at ethyl), and 3.12 (2 H, d, J = 1.2 Hz, CH_2 at 2-propynyl).

Anal. Calcd for C_5H_8S: C, 59.98; H, 8.05. Found: C, 59.87; H, 8.06.

Isomerization of 2-Propynyl Sulfide to 1-Propynyl Sulfide. Isomerization was carried out by the method of Pourcelot et al.[44] The product was obtained by distillation: bp 35° (18 mm); yield 68%; ir (film) 2200 (C≡C), no absorption at 3220 cm^{-1} (terminal acetylenic bond); mass spectrum *m/e* (rel intensity) 100 (M^+, 84.3), 85 (15.5), 72 (90.2), 71 (100), 45 (66.4), and 39 (23.8); ^1H NMR (CCl_4) δ 1.32 (3 H, t, J = 7.0 Hz, CH_3 at ethyl), 1.90 (3 H, s, CH_3 at 1-propynyl), and 2.58 (2 H, q, J = 7.0 Hz, CH_2).

Anal. Calcd for C_6H_6S: C, 59.98; H, 8.05. Found: C, 59.90; H, 8.14.

5-Methyl-3,6-dithia-4,7-nonadiene (13). The synthetic procedure is a modification of the method of Schuijl and Brandsma.[45] To 200 ml of absolute ethanol was added 5 g of sodium. When the sodium disappeared, the solution was cooled to room temperature and successively 2-propene-1-thiol (14.8 g, 0.2 mol) and ethyl 1-propynyl sulfide (20 g, 0.2 mol) were added with cooling. The mixture was refluxed for 3 hr. 5-Methyl-3,6-dithia-4,8-nonadiene and **13** were detected by GLC. Sodium ethoxide (0.1 mol) was added to the mixture and was heated under reflux for 15 hr. Working up was carried out by pouring the reaction mixture onto 500 g of crushed ice and subsequently extracting three times with ether. The product was obtained by distillation and was purified by the gas chromatograph: yield 65%; ir (film) 1619 and 1580 (double bond), 965 (trans double bond), and 936 cm^{-1} (1-propenyl double bond); mass spectrum *m/e* (rel intensity) 174 (M^+, 74.2), 145 (24.6), 130 (18.9), 113 (100), 73 (36.0), 59 (90.8), 45 (91.5), 41 (33.6), and 39 (54.5); ^1H NMR (CCl_4) δ 1.25 (3 H, t, J = 6.4 Hz, CH_3 at ethyl), 1.68–1.73 (3 H, dd, CH_3 at 1-propenyl), 1.95 (3 H, d, J = 1.7 Hz, $SCCH_3$), 2.59 (2 H, q, J = 6.4 Hz, CH_2), 5.54–5.90 (1 H, m, CH at 1-propenyl), 5.89 (1 H, q, J = 1.7 Hz, SCH at vinyl), and 6.01 (1 H, m, J = 16.3 Hz, SCH at 1-propenyl).

Anal. Calcd for $C_8H_{14}S_2$: C, 55.16; H, 8.10. Found: C, 55.09; H, 8.03.

2-(1-Propenylthio)-1-propene-1-thiol (10). The same procedure as for 1-propene-1-thiol was used. The product was purified by using the preparative gas chromatograph: yield 7%; mass spectrum *m/e* (rel intensity) 146 (M^+, 66.3), 131 (40.7), 113 (52.3), 74 (64.0), 73 (63.2), 59 (76.7), 45 (100), 41 (82.6), and 39 (45.3).

Anal. Calcd for $C_6H_{10}S_2$: C, 49.31; H, 6.90. Found: C, 49.28; H, 6.88.

Synthesis of Authentic Thiophene Derivatives. 2-Methylthiophene. A mixture of levulinic acid (25 g, 0.22 mol) and phosphorus trisulfide (22 g, 0.14 mol) was heated. A vigorous reaction took place. As soon as the reaction had subsided, the product was distilled from the reaction mixture. The crude distillate was purified by using the preparative gas chromatograph: bp 112–113°; yield 14.2% (lit.[46] 15%); ir (film) 845, 815, and 750 cm^{-1} (thiophene ring); mass spectrum *m/e* (rel intensity) 98 (M^+, 52.0), 97 (100), 59 (6.2), 45 (21.6), and 39 (17.0); ^1H NMR (CCl_4) δ 2.47 (3 H, s, CH_3), 6.72 (1 H, m, C-3), 6.85 (1 H, dd, C-4), and 7.02 (1 H, dd, C-5).

Anal. Calcd for C_5H_6S: C, 61.23; H, 6.12; S, 32.65. Found: C, 61.41; H, 6.39; S, 32.14.

3-Methylthiophene was obtained as a by-product in preparation of 2,4- or 3,4-dimethylthiophene. 3-Methylthiophene was purified by using the gas chromatograph: ir (film) 850 and 760 cm^{-1} (thiophene ring); mass spectrum *m/e* (rel intensity) 98 (M^+, 50.0), 97 (100), 59 (2.3), 45 (26.8), and 39 (11.4); ^1H NMR (CCl_4) δ 2.19 (3 H, s, CH_3), 6.68 (1 H, d, J = 4.0 Hz, C-4), 6.73 (1 H, s, C-2), and 7.02 (1 H, d, J = 4.0 Hz, C-5).

2,5-Dimethylthiophene. A mixture of 2,5-hexanedione (25 g, 0.22 mol) and phosphorus trisulfide (22 g, 0.14 mol) was heated for 1 hr. The product was distilled from the reaction mixture: bp 134–135°; yield 50% (lit.[47] 50–60%); ir (film) 790 cm^{-1} (thiophene ring); mass spectrum *m/e* (rel intensity) 112 (M^+, 75.7), 111 (100), 97 (61.7), 59 (22.1), 45 (14.5), and 39 (13.3); ^1H NMR (CCl_4) δ 2.37 (6 H, s, CH_3) and 6.40 (2 H, s, C-3 and C-4).

Anal. Calcd for C_6H_8S: C, 64.27; H, 7.19; S, 28.54. Found: C, 64.73; H, 7.22; S, 28.48.

2,4-Dimethylthiophene. Ethyl 2-methyl-3-ethoxycarbonyl-4-oxopentanoate was prepared by condensation of ethyl acetoacetate and 2-bromopropionate: bp 123° (6 mm); yield 52%; ir (film) 1735 (ester) and 1715 cm^{-1} (carbonyl). Hydrolysis of this ester with concentrated hydrochloric acid gave 2-methyl-4-oxopentanoic acid: ir (film) 1715 (carbonyl) and 1710 cm^{-1} (COOH). A mixture of 2-methyl-4-oxopentanoic acid (24 g, 0.19 mol) and phosphorus trisulfide (22 g, 0.14 mol) was heated in carbon dioxide. The product was distilled from the reaction mixture and was purified by using the gas chromatograph: bp 137–138°; yield 33.8% (lit.[48] 34%); ir (film) 850, 820, and 760 cm^{-1} (thiophene ring); mass spectrum *m/e* (rel intensity) 112 (M^+, 76.6), 111 (100), 97 (53.0), 59 (8.9), 45 (31.4), and 39 (23.6); ^1H NMR (CCl_4) δ 2.07 (3 H, s, 4-CH_3), 2.34 (3 H, s, 2-CH_3), 6.34 (1 H, s, C-3), and 6.40 (1 H, s, C-5).

Anal. Calcd for C_6H_8S: C, 64.27; H, 7.19; S, 28.54. Found: C, 64.15; H, 7.23; S, 28.66.

2,3-Dimethylthiophene. Ethyl 3-methyl-3-ethoxycarbonyl-4-oxopentanoate was prepared by condensation of ethyl 2-methyl-3-oxobutanonate and ethyl bromoacetate, bp 102° (3 mm), yield 50%. Hydrolysis with concentrated hydrochloric acid gave 3-methyl-4-oxopentanoic acid. A mixture of 3-methyl-4-oxopentanoic acid (18 g, 0.14 mol) and phosphorus trisulfide (15 g, 0.1 mol) was heated for 1 hr. The product was obtained by distillation: bp 138–140°; yield 3% (lit.[49] 20%); mass spectrum *m/e* (rel intensity) 112 (M^+, 77.5), 111 (74.6), 97 (100), 59 (14.0), 45 (25.5), and 39 (20.3).

3,4-Dimethylthiophene. Diethyl 2,3-dimethyl-2-cyanosuccinate was prepared by condensation of ethyl 2-bromopropionate and ethyl 2-cyanopropionate: bp 125° (6 mm); yield 66%; ir (film) 2300 (CN) and 1736 cm^{-1} (ester). Hydrolysis of this ester with 6 *N* hydrochloric acid gave 2,3-dimethylsuccinic acid as a crystal, mp 191.2°. A mixture of the sodium salt of 2,3-dimethylsuccinic acid (19 g, 0.1 mol) and phosphorus trisulfide (19 g, 0.12 mol) was subjected to dry distillation in a stream of carbon dioxide. The crude distillate was purified by using the gas chromatograph: bp 144–146°; yield 26.8% (lit.[50] 21–22%); ir (film) 860 and 780 cm^{-1} (thiophene ring); mass spectrum *m/e* (rel intensity) 112 (M^+, 63.7), 111 (100), 97 (49.3), 59 (3.79), 45 (35.1), and 39 (22.9); ^1H NMR (CCl_4) δ 2.07 (6 H, s, CH_3) and 6.72 (2 H, s, C-2 and C-5).

Anal. Calcd for C_6H_8S: C, 64.27; H, 7.19; S, 28.54. Found: C, 64.56; H, 7.54; S, 28.45.

Acknowledgment. This work was partly supported by the Mishima Kaiun Memorial Foundation. We are indebted to Professor J. Soma of the Faculty of Engineering, Hokkaido University, for helpful advice on the ESR measurements, and also to Misses H. Kakizaki, T. Ohara, and A. Maeda of the Faculty of Pharmaceutical Sciences for elementary analyses. Cordial thanks are due to Mr. T. Hanzawa, a graduate student of our laboratory, for synthesis of thiophene derivatives. We are grateful to Mr. H. Campbell and Miss M. Nagaya of the IAY language laboratory for revising the manuscript.

Registry No.—**2**, 1115-93-1; **3**, 21593-77-1; **7**, 7683-75-2; **10**, 54677-58-6; **11**, 638-00-6; **12**, 7310-92-1; **13**, 54677-59-7; **16**, 632-15-5; **18**, 616-44-4; *cis*-**19**, 37981-34-3; *trans*-**19**, 37981-35-4; **21**, 37981-36-5; **22**, 37981-37-6; di-*n*-propyl sulfide, 111-47-7; diallyl sulfide, 292-88-1; *n*-propyl allyl sulfide, 27817-67-0; di-*n*-propyl disulfide, 629-19-6; diallyl disulfide, 2179-579; 1-propene-1-thiol, 925-89-3; 2-methyl-2-pentenal, 623-36-9; propargyl bromide, 106-96-7; sodium ethanethiolate, 811-51-8; 2-propynyl sulfide, 13702-09-5; 1-propynyl sulfide, 14453-81-7; 2-methylthiophene, 554-14-3; levulinic acid, 123-76-2; 2,5-dimethylthiophene, 638-02-8; 2,5-hex-

anedione, 110-13-4; ethyl 2-methyl-3-ethoxycarbonyl-4-oxopentanoate, 1113-77-5; ethyl acetoacetate, 141-97-9; ethyl 2-bromopropionate, 535-11-5; 2-methyl-4-oxopentanoic acid, 6641-83-4; 2,3-dimethylthiophene, 632-16-6; ethyl 3-methyl-3-ethoxycarbonyl-4-oxopentanoate, 13668-05-8; ethyl 2-methyl-3-oxobutanoate, 609-14-3; ethyl bromoacetate, 105-36-2; 3-methyl-4-oxopentanoic acid, 6628-79-1; diethyl 2,3-dimethyl-2-cyanosuccinate, 54677-60-0; 2,3-dimethylsuccinic acid, 13545-04-5; ethyl 2-cyanopropionate, 1572-99-2.

References and Notes

(1) Preliminary communications: (a) for the uv photolysis, see H. Nishimura, T. Hanzawa, and J. Mizutani, *Tetrahedron Lett.*, 343 (1973); (b) for the γ radiolysis, see H. Nishimura and J. Mizutani, *J. Chem. Soc., Chem. Commun.*, 738 (1972).

(2) E. J. Matikkala and A. I. Virtanen, *Acta Chem. Scand.*, **16**, 2461 (1962); M. Sugii, T. Suzuki, and S. Nagasawa, *Chem. Pharm. Bull.*, **11**, 548 (1963).

(3) R. L. M. Synge and J. C. Wood, *Biochem. J.*, **64**, 252 (1956).

(4) J. F. Thompson, C. J. Morris, and R. M. Zacharius, *Nature (London)*, **178**, 593 (1956); H. Rinderknecht, D. Thomas, and S. Aslin, *Helv. Chim. Acta*, **41**, 1 (1958).

(5) M. Fujiwara, Y. Itokawa, H. Uchino, and K. Inoue, *Experientia*, **28**, 254 (1972).

(6) Yurugi et al. reported the biological activity of allithiamine from the reaction between thiamine and diallyl thiosulfinate from *S*-allyl-L-cysteine sulfoxide with C–S lyase: S. Yurugi, T. Matsukawa, and M. Togashi, *J. Pharm. Soc. Jpn.*, **74**, 1017 (1955).

(7) H. Nishimura, S. Kawakishi, and M. Namiki, *Agric. Biol. Chem.*, **34**, 609 (1970); H. Nishimura, J. Mizutani, Y. Obata, and M. Namiki, *Tetrahedron*, **27**, 307 (1971); H. Nishimura and J. Mizutani, *Agric. Biol. Chem.*, **37**, 213, 1749 (1973).

(8) Unpublished data. Further detailed data will be presented elsewhere.

(9) Brodnitz and Pascale isolated a lachrymator from a raw onion extract by means of preparative gas chromatography and identified the isolate as thiopropanal *S*-oxide: M. H. Brodnitz and J. V. Pascale, *J. Agric. Food Chem.*, **19**, 269 (1971). The naturally occurring lachrymatory precursor is the trans isomer: C. G. Spare and A. I. Virtanen, *Acta Chem. Scand.*, **15**, 1280 (1961); J. F. Carson, R. E. Lundin, and T. M. Lukes, *J. Org. Chem.*, **31**, 1634 (1966).

(10) A Watson-Biemann helium separator was used between the gas chromatograph (Hitachi K-53) and the mass spectrometer (Hitachi RMS-4): J. T. Watson and K. Biemann, *Anal. Chem.*, **37**, 844 (1965).

(11) The proportions of the amounts of the fragment ion, *m/e* 45 ($CH{\equiv}S^+$), 47 ($CH_2{=}S^+H$), 59 ($C_2H_3S^+$), 73 ($CH_3CH{=}CHS^+$), etc., per the total ion, or the relative abundances of these fragments, explain the significant differences between 1-propenyl- and allyl-containing sulfur compounds: H. Nishimura, S. Koike, and J. Mizutani, *Agric. Biol. Chem.*, **37**, 1219 (1973).

(12) In ir spectra, *n*-propyl *cis*-1-propenyl sulfide has the characteristic absorptions at 936 and 665 cm^{-1}, and trans isomer has the absorptions at 960 cm^{-1}. Infrared spectra of di-1-propenyl sulfides have already been reported by Price and Snyder [the characteristic absorption at 660 (cis) and 965 cm^{-1} (trans)]: C. C. Price and W. H. Snyder, *J. Org. Chem.*, **27**, 4639 (1962). In ^1H NMR spectra of 1-propenyl sulfides, the coupling constant of the cis double bond is J = 9.5–9.9 Hz in the 5.9-ppm region, and that of the trans isomer is J = 15.2–17.2 Hz (see Experimental Section).

(13) The mass 59 peak is large (over 15% of the base peak) when methyl groups are in both the 2 and 5 positions, intermediate (6–15% of the base peak) when one methyl group is in the 2 position, and small (less than 5% of the base peak) when both the 2 and 5 positions are unoccupied: I. W. Kinney, Jr., and G. L. Cook, *Anal. Chem.*, **24**, 1391 (1952).

(14) As other products, *S*-(1-propenyl)cysteine sulfoxide, serine, and glycine were produced in γ radiolysis, and glycine in uv photolysis.

(15) As solvent systems, (1) 1-butanol–acetic acid–water (4:1:1 v/v) and phenol–water (4:1 v/v) or (2) 1-butanol–acetic acid–water (63:10:27 v/v) and phenol–acetic acid–water (7:1:2 v/v).

(16) Amino acids produced by irradiation were converted into *N*-trifluoroacetylamino acid *n*-butyl esters and examined by gas–liquid chromatography (FID).

(17) Hydrogen sulfide was determined by the method of Brenner et al. The concentration of Methylene Blue, which is formed by the reaction of hydrogen sulfide with *p*-aminodimethylaniline and ferric chloride, was measured colorimetrically: M. M. Bremmer, J. L. Owades, and R. Glyzniak, *Am. Brew.*, **87**, 29 (1954).

(18) Y. Kurita and W. Gordy, *J. Chem. Phys.*, **34**, 282 (1961); T. Henriksen and T. Sanner, *Acta Chem. Scand.*, **20**, 2888 (1966).

(19) A. Couture and A. Lablache-Combier, *Chem. Commun.*, 524 (1969); *Tetrahedron*, **27**, 1059 (1971).

(20) Wynberg and coworkers reported that a number of phenylthioethenes underwent a cyclization reaction to give benzo[*b*]thiophenes but di-1-propenyl sulfide gave no detectable amounts of cyclization products: S. H. Groen, R. M. Kellogg, J. Buter, and H. Wynberg, *J. Org. Chem.*, **33**, 2218 (1968).

(21) E. Block and E. J. Corey, *J. Org. Chem.*, **34**, 896 (1969).

(22) The details will be mentioned later in this paper.

(23) Alkenethiol was synthesized according to the method of Brandsma: L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, **89**, 593 (1970).

(24) Although there is another possibility that **18** is produced through the methyl elimination of **11** or **16**, the yield of **18** formed from **11** or **16** was trace.

(25) By the measurement of the ESR spectrum, such 1-propenylthiyl radicals as found in the case of uv photolysis (Figure 4) were also detected in the γ radiolysis of *S*-(*cis*-1-propenyl)-L-cysteine.

(26) J. A. Barltrop and J. Wills, *Tetrahedron Lett.*, 4987 (1968); M. J. Turro, *Photochem. Photobiol.*, **9**, 555 (1969); S. Warwell, H. P. Hemmerich, and F. Asinger, *Angew. Chem., Int. Ed. Engl.*, **10**, 281 (1971).

(27) M. A. Golub, *J. Am. Chem. Soc.*, **81**, 54 (1959); K. Sugimoto, W. Ando, and S. Oae, *Bull. Chem. Soc. Jpn.*, **38**, 224 (1965).

(28) Bielski and Allen have reported the G values for γ-ray-induced decomposition of pure water: G_H = 0.55, $G_{e_{aq}}$ = 2.76, G_{OH} = 2.74, G_{H_2} = 0.40, $G_{H_2O_2}$ = 1.00. B. H. J. Bielski and A. O. Allen, *Int. J. Radiat. Phys. Chem.*, **1**, 153 (1969).

(29) J. P. Keene, *Radiat. Res.*, **22**, 1 (1964).

(30) A. O. Allen, *Radiat. Res., Suppl.*, **4**, 54 (1964).

(31) M. Anbar and P. Neta, *Int. J. Appl. Radiat. Isot.*, **16**, 227 (1965).

(32) The 1×10^{-3} mol/l. of *S*-*n*-propyl-L-cysteine is enough concentration to be detected on the thin layer chromatogram (ninhydrin positive).

(33) Despite no detection of disulfide (P_2), di-*n*-propyl sulfide (P_1) was found on the chromatogram. This fact may indicate that the reaction of *n*-propylthiyl radicals with 1-propenyl radicals or **7** is considerably faster than the dimerization of *n*-propylthiyl radicals.

(34) M. S. Liu, S. Soloway, D. K. Wedegaertner, and J. A. Kampmeier, *J. Am. Chem. Soc.*, **93**, 3809 (1971).

(35) More than 90% of alkenethiol was decomposed and large amounts of precipitates which seem to be polymers were produced.

(36) V. du Vigneaud, H. S. Loring, and H. A. Craft, *J. Biol. Chem.*, **105**, 481 (1934).

(37) J. F. Carson and F. F. Wong, *Chem. Ind. (London)*, 1764 (1963).

(38) H. Nishimura, S. Tahara, H. Okuyama, and J. Mizutani, *Tetrahedron*, **28**, 4503 (1972).

(39) R. L. Shriner, H. C. Struck, and W. J. Jorison, *J. Am. Chem. Soc.*, **52**, 2060 (1930).

(40) D. S. Tarbell and W. E. Lovett, *J. Am. Chem. Soc.*, **78**, 2259 (1956).

(41) W. R. Kirner and G. H. Richter, *J. Am. Chem. Soc.*, **51**, 3131 (1929).

(42) M. T. Bogert and A. Stull, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, p 220.

(43) A. M. Paquin, *Chem. Ber.*, **82**, 316 (1949).

(44) G. Pourcelot, P. Cadiot, and A. Willemart, *C. R. Acad. Sci.*, **252**, 1630 (1961).

(45) P. J. W. Schuijl and L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, **87**, 929 (1968).

(46) W. Kues and C. Paal, *Ber.*, **19**, 555 (1886).

(47) C. Paal, *Ber.*, **18**, 2251 (1885).

(48) I. J. Rinkes, *Recl. Trav. Chim. Pays-Bas*, **52**, 1052 (1933).

(49) C. Paal and A. Puschel, *Ber.*, **20**, 2557 (1887); W. Grunewald, *ibid.*, **20**, 2585 (1887).

(50) N. Zelinsky, *Ber.*, **21**, 1835 (1888).

Intramolecular Isomerizations of 5-Phenyl-5-(3-aminopropyl)barbituric Acids

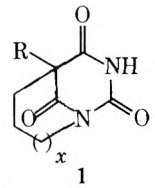
Edward E. Smissman† and Peter J. Wirth*[1]

Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66045

Received January 10, 1975

In an attempt to prepare the N-alkylated rigid analog of phenobarbital **1** from 5-phenyl-5-(3-bromopropyl)barbituric acid (**6**) an unexpected intramolecular isomerization occurred. Treatment of **6** with ammonium hydroxide yielded 3-phenyl-3-allophanyl-2-piperidone (**10**), which was further hydrolyzed to 3-phenyl-2-piperidone (**8**). In a similar manner 5-phenyl-5-(2-hydroxypropyl)barbituric acid (**14**) underwent a similar intramolecular isomerization to yield α-phenyl-α-allophanyl-γ-valerolactone (**17**).

As part of a continuing study on the steric requirements for selective central nervous system depression, attempts have been made to develop general synthetic routes to bridged barbituric acids **1**, to be investigated as antiepileptic agents.

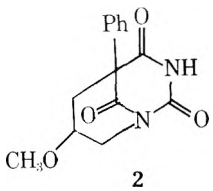


1

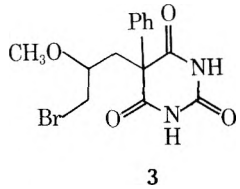
R = alkyl, aryl

x = 0, 1, 2

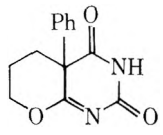
Although attempts to prepare such ring systems have met with great difficulty, one such barbituric acid, 5-phenyl-7-methoxy-2,4,9-triketo-1,3-diazabicyclo[3.3.1]nonane (**2**), has been prepared.[2] Its synthesis was accomplished via an intramolecular imide attack on the primary bromide function of 5-phenyl-5-(2-methoxy-3-bromopropyl)barbituric acid (**3**).



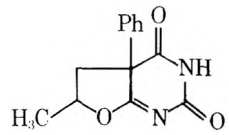
2



3



4



5

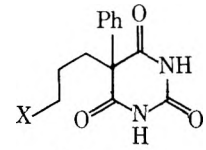
This procedure did not prove to be a general method for the desired compounds, since similar intramolecular alkylations of 5-phenyl-5-(3-halopropyl)- and 5-(2-halopropyl)-barbituric acids yielded the O-alkylated pyrano- and furopyrimidines **4** and **5**, rather than the N-alkylated systems.[3]

Taylor and McKillop[4] have reported exclusive C-alkylation when the thallous salts of 1,3-dicarbonyl compounds were heated with alkyl halides. In an attempt to extend this selectivity to our systems, it was hoped that the thallous salt of **6** could give the barbiturate **1** by intramolecular displacement by the imide nitrogen at N-1 of a proper side-chain substituent.

Kornblum and coworkers[5] have reported the importance of solvent in determining the ratios of C-alkylation to O-alkylation in the alkylation of ambident anions. Higher ratios of C-alkylated products were obtained when the alkylations were performed in fluoro alcohols or water.

With these facts in mind, it was hoped that heating the thallous salt of **6** in an aqueous benzene solvent system would yield the desired N-alkylated product **1** in preference to the O-alkylated pyranopyrimidine **4**.

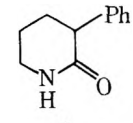
The thallous salt of 5-phenyl-5-(3-bromopropyl)barbituric acid (**6**) was prepared by the addition of thallium ethoxide in anhydrous dimethoxyethane (DME) to a solution of **6** in DME. However, when the thallous salt of **6** was refluxed in a 50:50 water–benzene solvent system, 5-phenyl-5-(3-hydroxypropyl)barbituric acid (**7**) and a colorless gum



6, X = Br

7, X = OH

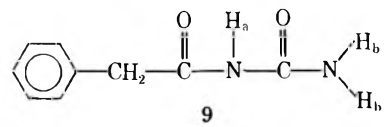
were obtained. Formation of **7** may have resulted either from direct solvent attack on **6** during reflux or from hydrolysis of the O-alkylated intermediate **4** during purification. The gum, although not completely purified, exhibited R_f values very similar to those of **6** in numerous TLC solvent systems. Treatment of the gum with ammonium hydroxide at 150° led to the formation of 3-phenyl-2-piperidone (**8**), the expected hydrolysis product of **1**. However,



8

treatment of an authentic sample of **6** under identical conditions also yielded **8** in excellent yield.

In an attempt to isolate intermediates in the formation of **8**, **6** was treated with ammonium hydroxide at 50°, affording a product which was insoluble in dilute acid but soluble in dilute base. The ir spectrum showed three sharp carbonyl absorptions at 1650, 1690, and 1720 cm^{-1} in addition to NH absorptions at 3400, 3350, and 3250 cm^{-1}. The NMR spectrum (DMSO-d_6) showed the presence of one imide proton at δ 10.04 and H_a in phenylacetylurea **9** occurs at δ 10.10. In both compounds the aromatic region integrates for seven protons and in **9** the H_b protons fall under

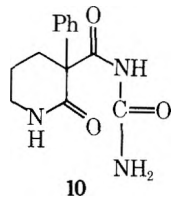


9

the aromatic protons. These data, therefore, suggested the presence of the allophanyl moiety, –CONHCONH$_2$. Warm-

† Deceased, July 14, 1974.

ing with dilute acid or treatment with nitrous acid converted the product to **8**. From these data the product isolated was 3-phenyl-3-allophanyl-2-piperidone (**10**).

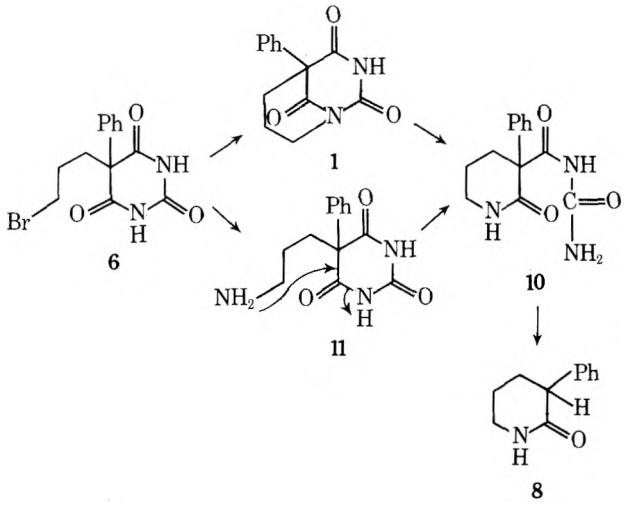


10

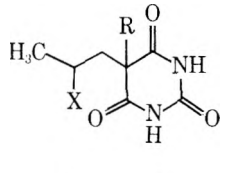
Therefore, the formation of **8** from **6** can be envisioned to occur by either of two pathways.

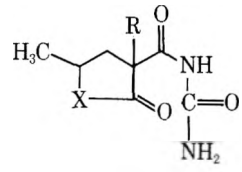
Pathway 1. Treatment of **6** with ammonium hydroxide leads to the abstraction of the imide proton followed by N-alkylation to give **1**. Compound **1** is then opened to **10**, which is further hydrolyzed to **8**.

Pathway 2. Alternatively, treatment of **6** with ammonium hydroxide leads, not to proton abstraction, but to the ammonolysis of **6** to yield the primary amine **11**. The primary amino function attacks the C-6 (C-4) carbonyl of the barbiturate ring in a neighboring group with ring opening to yield **10**, which is further hydrolyzed to **8**.



Bobranski and coworkers[6] have reported that 5-allyl-5-(2-hydroxypropyl)barbituric acid (**12**) undergoes a similar type of intramolecular isomerization to yield α-allyl-α-allophanyl-γ-valerolactone (**15**).

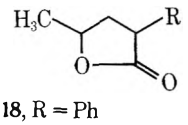




	X	R
12	OH	$CH_2CH{=}CH_2$
13	NH_2	$CH_2CH{=}CH_2$
14	OH	Ph

	X	R
15	O	$CH_2CH{=}CH_2$
16	NH	$CH_2CH{=}CH_2$
17	O	Ph

We similarly found that treatment of 5-phenyl-5-(2-hydroxypropyl)barbituric acid (**14**) with a catalytic amount of ammonium hydroxide yielded α-phenyl-α-allophanyl-γ-valerolactone (**17**). Hydrolysis of **17** under acidic conditions afforded α-phenyl-γ-valerolactone (**18**).

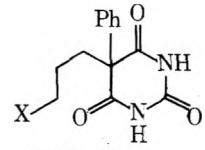


18, R = Ph

19, R = $CH_2CH{=}CH_2$

The amino derivative, 5-allyl-5-(2-aminopropyl)barbituric acid (**13**), however, failed to undergo such an isomerization to α-allophanyl-α-allyl-γ-valerolactam (**16**) and only α-allyl-γ-valerolactone (**19**) was formed.[7]

An attempt was made to obtain 5-phenyl-5-(3-aminopropyl)barbituric acid (**11**) by the reaction of **6** with gaseous ammonia under various conditions;[8] however, no identifiable products were obtained. An alternate approach to **11** involved the conversion of **6** to 5-phenyl-5-(3-azidopropyl)barbituric acid (**20**). Hydrogenation of **20** yielded the primary amine **11**. Treatment of **11** with ammonium hydroxide led to the formation of **10**.



20, X = N_3

21, X = $N(C_2H_5)_2$

In a similar manner, treatment of **6** with diethylamine afforded 5-phenyl-5-(3-diethylaminopropyl)barbituric acid (**21**), whereas addition of aqueous methylamine to **6** yielded a mixture of oils.

These results, although not eliminating pathway 1, suggest that treatment of **6** with ammonium hydroxide leads to the formation of **11**, which then isomerizes to **10** (pathway 2).

Experimental Section[9]

Treatment of 5-Phenyl-5-(3-bromopropyl)barbituric Acid (6) with Ammonium Hydroxide in the Autoclave. A suspension of 5-phenyl-5-(3-bromopropyl)barbituric acid (**6**, 5.0 g, 0.0154 mol) in 50 ml of concentrated NH_4OH (58%) was heated in a steel autoclave at 160° for 24 hr. The autoclave was allowed to cool to room temperature and opened, and the contents were filtered. Recrystallization of the solids from acetone yielded 2.0 g (0.0114 mol, 74%) of 3-phenyl-2-piperidone (**8**) as white needles, mp 169–171° (lit.[10] mp 170.0–170.5°). The ir spectrum of **8** was completely superimposable on the ir spectrum of an authentic sample of 3-phenyl-2-piperidone prepared by an alternate route.[10] Anal. Calcd for $C_{11}H_{13}NO$: C, 75.39; H, 7.47; N, 7.99. Found: C, 75.67; H, 7.62; N, 7.83.

3-Phenyl-3-allophanyl-2-piperidone (10). A suspension of 5-phenyl-5-(3-bromopropyl)barbituric acid (**6**, 15.0 g, 0.046 mol) in 150 ml of concentrated NH_4OH (58%) was heated on a steam bath for 1 hr. The reaction mixture was cooled to room temperature and filtered to yield 7.10 g (0.027 mol, 59%) of a white, crystalline solid. Recrystallization from CH_3OH yielded **10** as pure white needles: mp 220–221°; NMR (trifluoroacetic acid, 1% TMS) (detection of imide and lactam nitrogen H was made in DMSO-d_6) δ 1.40–1.80 (m, 2, $-CH_2\mathbf{CH_2}CH_2-$), 2.20–2.60 (m, 2, $-CH_2-$), 3.20–3.60 (m, 2, $-\mathbf{CH_2}NH$), 7.16 (singlet superimposed and broad singlet, 7, aromatic and $-NH_2$), 8.43 (br s, 1, $-CH_2CO\mathbf{N}H-$), 10.04 (s, 1, $-CONH-CO-$).

Anal. Calcd for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.78; N, 16.08. Found: C, 59.97; H, 5.74; N, 16.25.

5-Phenyl-5-(3-azidopropyl)barbituric Acid (20). Sodium azide (19.5 g, 0.30 mol) and 5-phenyl-5-(3-bromopropyl)barbituric acid (**6**, 52.0 g, 0.16 mol) were dissolved in a mixture of 600 ml of acetone and 400 ml of H_2O. The reaction mixture was heated at reflux for 18 hr, cooled to room temperature, and filtered. The filtrate was concentrated in vacuo to yield a slightly yellow solid. The solid was filtered, washed with water, and air dried to yield 43.2 g (0.15 mol, 94%) of the desired product **20**. Recrystallization from 95% EtOH yielded small, white crystals: mp 183–184°; NMR (DMSO-d_6–$CDCl_3$, 1% TMS) δ 1.30–1.83 (m, 2, $-CH_2-$), 2.16–2.60 (m, 2, $-CH_2-$), 3.13–3.37 (t, 2, $-CH_2\mathbf{CH_2}N_3$), 7.33 (s, 5, aromatic), 10.00–10.60 (br s, 2, imide H); ir (KBr) 3230, 3110, 2110, 1700, 1425, 1360, 830 cm^{-1}.

Anal. Calcd for $C_{13}H_{13}N_5O_3$: C, 54.35; H, 4.56; N, 24.38. Found: C, 54.70; H, 4.65; N, 24.31.

5-Phenyl-5-(3-aminopropyl)barbituric Acid Hydrochloride (11). A solution of 5-phenyl-5-(3-azidopropyl)barbituric acid (**20**,

21.3 g, 0.074 mol) in 160 ml of glacial acetic acid and 40 ml of dimethoxyethane (DME) was added to a suspension of 2 g of prereduced platinum oxide (Pt_2O) in 20 ml of HOAc in a Parr shaker hydrogenation apparatus. The azide was hydrogenated at an initial pressure of 50 psi at room temperature for 12 hr. The catalyst was filtered and the solvents were removed in vacuo to leave a clear, viscous oil. The oil was dissolved in 150 ml of anhydrous CH_3OH and saturated with gaseous HCl at 0–10°. Concentration of the solvents in vacuo yielded a pale, amorphous solid which was filtered, washed with Et_2O, and dried to yield 17.0 g (0.057 mol, 77%) of **11**. Recrystallization from CH_3OH–$CHCl_3$ yielded a white, amorphous powder: mp 262–263° dec; NMR (DMSO-d_6–$CDCl_3$, 1% TMS) δ 1.32–2.01 (m, 2, $-CH_2-$), 2.08–2.52 (m, 2, $-CH_2-$), 2.65–3.41 (m, 2, $-CH_2N^+$), 3.95 (s, 2.2, $-NH_3^+$, disappears with addition of D_2O), 7.32 (s, 5, aromatic), 11.42 (s, 2, imide H); ir (KBr) 3300–2900, 1710, 1405, 1345 cm^{-1}.

Treatment of 3-Phenyl-3-allophanyl-2-piperidone (10) with Nitrous Acid. Sodium nitrite (5 g) in 50 ml of water was added in a dropwise manner to a cooled solution (0–10°) of **10** (2.0 g, 0.0076 mol) in 200 ml of CH_3OH and 75 ml of concentrated HCl. With each addition a fine white precipitate formed in addition to the copious evolution of gas. After addition had been completed the reaction mixture was warmed to 80° for 15 min, cooled to room temperature, and filtered. A white, crystalline solid (0.8 g), mp 218–220°, was obtained whose ir spectrum was identical with that of the starting material **10**. Concentration of the CH_3OH solution in vacuo yielded a solid residue. This solid was dissolved in hot acetone and the solvent was allowed to slowly evaporate to yield an additional 0.7 g of **10**. Further evaporation of the solvent yielded 0.20 g (0.0011 mol, 15%), mp 170–171°, of a white, crystalline solid whose NMR and ir spectra were completely superimposable on those of an authentic sample of 3-phenyl-2-piperidone (**8**).

α-Allophanyl-α-phenyl-γ-valerolactone (17). To a solution of 5-phenyl-5-(2-hydroxypropyl)barbituric acid (**14**, 10.0 g, 0.038 mol) in 100 ml of CH_3OH was added 1 ml of concentrated NH_4OH (58%) and the resulting solution was heated at reflux for 2 hr. Removal of the solvent in vacuo yielded a white, crystalline solid. Recrystallization from CH_3OH yielded 5.10 g (0.019 mol, 51%) of **17** as pure white cubes: mp 167–169°; NMR (DMSO-d_6–$CDCl_3$, 1% TMS) δ 1.40–1.50 (d, 3, J = 6 Hz, CH_3CHO-), 2.70–2.90 (m, 2, $-CH_2-$), 4.13–4.80 (m, 1, CH_3CHO-), 7.43 (s, 7, aromatic and NH_2), 9.10 (s, 1, $-CONHCO-$); ir (KBr) 3420, 3230, 1755, 1725, 1700, 1590, 1375, 1190, 1215 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.64; H, 5.55; N, 10.78.

α-Phenyl-γ-valerolactone (18). To 50 ml of aqueous 5% hydrochloric acid (HCl) was added 5.1 g (0.019 mol) of α-allophanyl-α-phenyl-γ-valerolactone (**17**). The reaction mixture was heated to reflux for 4 hr, cooled to room temperature, extracted with 3 × 50 ml of diethyl ether, and dried ($MgSO_4$), and the solvent was removed in vacuo to yield 3.5 g of an oil–solid mixture. Filtration and distillation of the oil under reduced pressure yielded 2.30 g (0.013 mol, 68%) of **18** as a clear, colorless liquid: bp 146–147° (2 mm); NMR ($CDCl_3$, 1% TMS) δ 1.43–1.53 (dd, 3, J = 6 Hz, CH_3CHOCH_2-), 1.90–3.00 (m, 2, $-CH_2-$), 3.55–4.03 (m, 1, $-CH_2-CHPh$), 4.33–4.97 (m, 1, CH_3CHO), 7.33 (s, 5, aromatic); ir (neat) 1770, 1170 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.73; H, 7.25.

Treatment of 5-Phenyl-5-(3-aminopropyl)barbituric Acid Hydrochloride (11) with Ammonium Hydroxide. A solution of 2.0 g (0.0067 mol) of 5-phenyl-5-(3-aminopropyl)barbituric acid hydrochloride (**11**) in 10 ml of concentrated NH_4OH (58%) was heated on a steam bath for 1 hr. The reaction mixture was allowed to cool to room temperature, during which time a gummy residue formed. The aqueous phase was made acidic with 10% HCl and decanted, and the solids were collected. Recrystallization of the solids from CH_3OH yielded 0.85 g (0.0032 mol, 48%) of 3-phenyl-3-allophanyl-2-piperidone (**10**) as pure white needles, mp 219–221°. The ir spectrum of the product was completely superimposable on the ir spectrum of an authentic sample of **10** prepared by an alternate route.

5-Phenyl-5-(3-diethylaminopropyl)barbituric Acid (21). A solution of 5-phenyl-5-(3-bromopropyl)barbituric acid (**6**, 6.50 g, 0.020 mol) in 200 ml of 50% aqueous diethylamine was heated to reflux for 1 hr. Removal of excess volatile components yielded a milky white solution. Careful acidification (aqueous 10% HCl) of the aqueous solution to pH 6–7 yielded 2.70 g (0.012 mol, 60%) of a white solid. Recrystallization from CH_3OH yielded **21** as very fine, white needles: mp 256–257° dec; NMR (trifluoroacetic acid, 1% TMS) δ 1.30–1.60 (t, 6, $-NCH_2CH_3$). 1.73–2.23 (m, 2, $-CH_2-$), 3.10–3.60 (m, 6, $-NCH_2-$) 7.37 (s, 5, aromatic); ir (KBr) 3250, 3450, 1690, 1600, 1410, 1380, 1445, 1290, 1260 cm^{-1}.

Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.13; H, 7.30; N, 13.37.

Acknowledgment. The authors wish to acknowledge the support of this work by the National Institutes of Health (Grant GM 01341).

Registry No.—**6**, 25860-47-3; **8**, 51551-56-5; **10**, 54832-99-4; **11**, 54833-00-0; **14**, 25860-53-1; **17**, 54833-01-1; **18**, 40923-67-9; **20**, 54833-02-2; **21**, 54833-03-3; ammonium hydroxide, 1336-21-6; sodium nitrite, 7632-00-0; diethylamine, 109-89-7; sodium azide, 26628-22-8.

References and Notes

(1) Taken in part from the dissertation presented by P. J. Wirth, Aug 1974, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.
(2) E. E. Smissman, R. A. Robinson, J. B. Carr, and A. J. Matuszak, *J. Org. Chem.*, **35**, 3821 (1970).
(3) E. E. Smissman, R. A. Robinson, and A. J. Matuszak, *J. Org. Chem.*, **35**, 3822 (1970).
(4) E. C. Taylor and A. McKillop, *Acc. Chem. Res.*, **3**, 338 (1970).
(5) N. Kornblum, P. J. Berrigan, and W. J. LeNoble, *J. Am. Chem. Soc.*, **85**, 1141 (1963).
(6) (a) B. Bobranski, D. Prelicz, L. Syper, and R. Wojtowski, *Rocz. Chem.*, **37**, 395 (1963); (b) *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **8**, 475 (1960).
(7) M. Konieczny, *Arch. Immunol. Ther. Exp.*, **15**, 920 (1967).
(8) G. S. Skinner, A. Stoker, and G. Spiller, *J. Am. Chem. Soc.*, **69**, 3083 (1947).
(9) Infrared spectra were obtained on a Beckman IR-33 spectrophotometer. Nuclear magnetic resonance spectra were obtained using Varian A-60A and T-60 spectrometers. Elemental analyses were determined on a Hewlett-Packard 185 C, H, N analyzer at the University of Kansas. Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected.
(10) R. K. Hill, C. E. Glassick, and L. J. Fliedner, *J. Am. Chem. Soc.*, **81**, 737 (1959).

Intramolecular Catalysis. VIII. Effects on the Acetylation of the 7α-Hydroxyl Group of Steroids. A ^{1}H Nuclear Magnetic Resonance Rate Method[1]

James F. Baker and R. T. Blickenstaff*

Veterans Administration Hospital and Biochemistry Department, Indiana University School of Medicine, Indianapolis, Indiana 46202

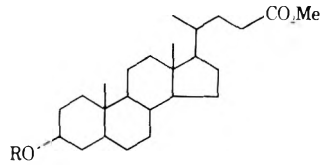
Received January 31, 1975

Analogs of methyl 7α-hydroxycholanoate were synthesized, and acetylation rates were determined by a new ^{1}H NMR method. Substituents at C-3 include α-acetoxy, α-tosyloxy, α-mesyloxy, α-succinoyloxy, α-p-nitrobenzoyloxy, α-dimethylamino, β-chloro, oxo, ethylenedioxy, and ethylenedithio. Substituents at C-12 include α-hydroxy and α-methoxy. The 3 esters were prepared by selective esterifications, the 3α-dimethylamino derivative by the Leuckart reaction on the corresponding 3-oxo compound, and the 12α-methoxy derivative by the action of methyl fluorosulfonate on methyl cholate 3,7-diacetate. Acetylations were carried out in NMR sample tubes, and rates were determined by measuring the relative intensities of angular methyl peaks, which shifted slightly on acetylation of the particular steroid. Most of the groups at C-3 afforded slight catalysis of 7α-hydroxyl acetylation. The 12α-hydroxyl was most effective, and the absence of catalysis by a 12α-methoxyl group points toward protonation in the rate-determining step.

The 7α-hydroxyl group of methyl cholate 3-acetate (**13a**) was shown to be more reactive toward acetic anhydride than that of methyl 7α-hydroxy-5β-cholan-24-oate (**3a**) by comparing their 24-hr yields.[2] This was explained in terms of enhancement of 7α-hydroxyl reactivity by both the 3α-acetoxy group and the 12α-hydroxyl group, and these effects were shown to be intramolecular.[3] Reactivity of the 7α-hydroxyl was found not to be influenced by the type of side chain attached at C-17.[4] 3-Oxo, 3-chloro, and 3-tosyloxy groups were shown to enhance 12α-hydroxyl reactivity,[4] but the influence of these groups on the 7α-hydroxyl has not been studied. Methods for the determination of acetylation rates of these hydroxy steroids have been developed utilizing GLC,[3] uv,[3] ^{14}C,[5] and optical rotation.[6] In the present work a rate method employing ^{1}H nuclear magnetic resonance is applied to the study of the effects of substituents at C-3 and at C-12 on 7α-hydroxyl reactivity.

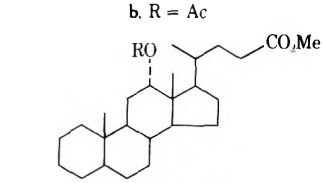
^{1}H nuclear magnetic resonance has been employed in the kinetic study of the esterification of methanol with acetic anhydride; measurements were based on the intensity of the singlet arising from the methoxyl group of the methyl acetate produced.[7] In the present method, we employed singlets arising from the angular methyl groups, whose chemical shifts are known to be influenced profoundly by substituents on the steroid ring system.[8] In particular, the 3α-acetoxy group exerts a 0.025-ppm downfield shift on the C-19 methyl resonance of 5β steroids in deuteriochloroform, while the 3α-hydroxyl exerts only a 0.008-ppm downfield shift.[8] In theory it should be possible to observe the progress of acetylation of a 3α-hydroxyl group by noting the gradual disappearance of the C-19 methyl resonance and the concomitant appearance of a new resonance about 0.02 ppm further downfield in such solutions. In practice, it was found possible to follow acetylations of the 3α-, 7α-, and 12α-hydroxyls by following shifts of either the C-18 or C-19 methyl resonances on samples dissolved in pyridine. Instead of a downfield shift, *upfield* shifts of 0.02–0.04 ppm of both methyl resonances were observed, the reversal most likely being related to complexing between steroid and solvent molecules.[9] While this is not a large separation, it is easily adequate in this case because of the sharpness of the angular methyl singlet resonances. Acetylations were carried out in the NMR sample tubes, and quantitation of the two methyl resonance peaks for either C-18 or C-19 methyl during acetylation permitted calculation of the second-order rate constants.

Most of the preparations of compounds for this study

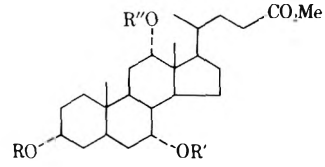


1a, R = H
b, R = Ac

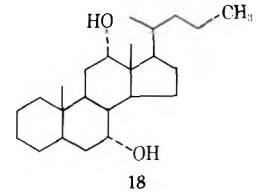
	R	R′	R″
3a	H	H	H
3b	H	H	Ac
4a	H	AcO	H
4b	H	AcO	Ac
5a	O		H
6a	OCH_2CH_2O		H
6b	OCH_2CH_2O		Ac
7a	H	CH_3SO_2	H
7b	H	CH_3SO_2	Ac
8a	H	$C_7H_7SO_2$	H
8b	H	$C_7H_7SO_2$	Ac
9a	H	$CH_2CO_2CH_2CO_2H$	H
9b	H	$CH_2CO_2CH_2CO_2H$	Ac
10a	Cl	H	H
10b	Cl	H	Ac
11a	Me_2N	H	H
11b	Me_2N	H	CHO
12a	H	Me_2N	H
12b	H	Me_2N	Ac



2a, R = H
b, R = Ac



	R	R′	R″
13a	Ac	H	H
13b	Ac	Ac	H
13c	Ac	Ac	Ac
13d	$O_2NC_6H_4CO_2$	H	H
14a	Ac	Ac	CH_3
14b	H	H	CH_3
14c	Ac	H	CH_3
15	O=	H	H
16	SCH_2CH_2S	H	H
17a	Ac	Ac	O=
17b	Ac	H	O=



18

were straightforward and are listed in Table I. Methyl 3α-dimethylamino-7α-hydroxy-5β-cholan-24-oate (**12a**) was prepared by the Leuckart reaction on the corresponding 3 ketone (**5a**),[22] and was separated from other minor products by chromatography on basic alumina followed by preparative TLC on silica gel. One minor component with a higher R_f (than **12a**) is tentatively presumed to be the 3 epimer (**11a**), as it exhibits a six-proton singlet at 2.27 ppm (dimethylamino), while **12a** exhibits the same at 2.38 ppm. This is completely consistent with the methyl dimethylamino-12α-hydroxy-5β-cholan-24-oates,[4] in which the faster moving 3β epimer has a 2.21- and the slower moving 3α epimer a 2.29-ppm resonance. The methyl cholate 3-*p*-nitro-

Table I
Synthesis of the 7α-Hydroxy Steroids[a]

Compd	Yield, %	Mp, °C (lit. value)	Ir absorption, selected bands, cm^{-1}	^1H NMR spectral assignments, δ
1a Methyl 3α-hydroxy-5β-cholan-24-oate	81	130–132[b] (lit.[10] 125–128)	3610 (OH), 1721 (C=O), 1106, 1010, 725	3.69 (s, 3 H, ester Me), 0.95 (s, 3 H, 19-Me), 0.64 (s, 3 H, 18-Me)
1b Methyl 3α-acetoxy-5β-cholan-24-oate[c]		135–136[b] (lit.[11] 133–135)	1736 (C=O), 1252 (acetate C–O), 1172, 1022	4.74 (broad m, 1 H, 3β-H), 3.69 (s 3 H, ester Me), 2.02 (s, 3 H, acetate Me), 0.94 (s, 3 H, 19-Me), 0.65 (s, 3 H, 18-Me)
2a Methyl 12α-hydroxy-5β-cholan-24-oate[d]		120.7–122.7[e] (lit.[12] 119–120)	3559 (OH), 1715 (C=O), 1205, 1174	4.15 (broad, 1 H, 12β-H), 3.62 (s, 3 H, ester Me), 0.92 (s, 3 H, 19-Me), 0.71 (s, 3 H, 18-Me)
2b Methyl 12α-acetoxy-5β-cholan-24-oate[f]		95–96[b] (lit.[10] 95–97)	1754 (C=O), 1247 (acetate C–O), 1168, 1031	5.25 (broad, 1 H, 12β-H), 3.65 (s, 3 H, ester Me), 2.14 (s, 3 H, acetate Me), 0.89 (s, 3 H, 19-Me), 0.66 (s, 3 H, 18-Me)
3a Methyl 7α-hydroxy-5β-cholan-24-oate[d]		80–81[b] (lit.[2] 75–79)	3584 (OH), 1724 (C=O) 1106	3.86 (broad, 1 H, 7β-H), 3.68 (s, 3 H, ester Me), 0.91 (s, 3 H, 19-Me), 0.65 (s, 3 H, 18-Me)
3b Methyl 7α-acetoxy-5β-cholan-24-oate		96–97[b] (lit.[2] 95–96)	1745 (C=O), 1242 (acetate C–O), 1157, 1017	4.86 (broad, 1 H, 7β-H), 3.67 (s, 3 H, ester Me), 2.03 (s, 3 H, acetate Me), 0.89 (s, 3 H, 19-Me), 0.64 (s, 3 H, 18-Me)
4a Methyl 3α-acetoxy-7α-hydroxy-5β-cholan-24-oate[g,h]	39	59–61[i] (lit.[13] 54–62)	3536 (OH), 1727 and 1715 (C=O), 1242 (acetate C–O), 1153, 971	4.56 (broad, 1 H, 3β-H), 3.86 (broad, 1 H, 7β-H), 3.68 (s, 3 H, ester Me), 2.00 (s, 3 H, acetate Me), 0.91 (s, 3 H, 19-Me), 0.66 (s, 3 H, 18-Me)
4b Methyl 3α,7α-diacetoxy-5β-cholan-24-oate[g]		131–132[j] (lit.[14] 128–130)	1730 (C=O), 1245 (acetate C–O), 1064, 1021, 969, 940	4.93 (broad, 1 H, 7β-H), 4.56 (broad, 1 H, 3β-H), 3.70 (s, 3 H, ester Me), 2.06 (s, 3 H, acetate Me), 2.03 (s, 3 H, acetate Me), 0.93 (s, 3 H, 19-Me), 0.67 (s, 3 H, 18-Me)
5a Methyl 7α-hydroxy-3-oxo-5β-cholan-24-oate[k]	41	122–124[b] (lit.[15] 128–129)	3521 (OH), 1739 (ester C=O), 1700 (keto	3.92 (broad, 1 H, 7β-H), 3.68 (s, 3 H, ester Me),

Table I
(Continued)

Compd	Yield, %	Mp, °C (lit. value)	Ir absorption, selected bands, cm^{-1}	^1H NMR spectral assignments, δ
			C=O), 1250, 1100	1.02 (s, 3 H, 19-Me), 0.71 (s, 3 H, 18-Me)
6a Methyl 3,3-ethylenedioxy-7α-hydroxy-5β-cholan-24-oate	42	114–116[b]	3636 (OH), 1736 (C=O), 1212, 1160, 1096	4.02 (broad s, 1 H, 7β-H), 3.88 (s, 4 H, ketal), 3.65 (s, 3 H, ester Me), 0.99 (s, 3 H, 19-Me), 0.66 (s, 3 H, 18-Me)
6b Methyl 7α-acetoxy 3,3-ethylenedioxy-5β-cholan-24-oate[c]		84–85[b]	1733 (C=O), 1238 (acetate C–O), 1220, 1099	5.05 (broad s, 1 H, 7β-H), 3.87 (s, 4 H, ketal), 3.64 (s, 3 H, ester Me), 2.00 (s, 3 H, acetate Me), 0.95 (s, 3 H, 19-Me), 0.60 (s, 3 H, 18-Me)
7a Methyl 7α-hydroxy-3α-methanesulfonoxy-5β-cholan-24-oate	23	133–134[l]	3545 (OH), 1721 (C=O), 1175 (SO_3), 920	4.51 (broad, 1 H, 3β-H), 3.84 (broad, 1 H, 7β-H), 3.69 (s, 3 H, ester Me), 3.01 (s, mesylate Me), 0.93 (s, 3 H, 19-Me), 0.67 (s, 3 H, 18-Me)
7b Methyl 7α-acetoxy-3α-methanesulfonoxy-5β-cholan-24-oate[c]		130–131[l]	1724 (C=O), 1238 (acetate C–O), 1223, 1167 (SO_3), 938	4.92 (broad, 1 H, 7β-H), 4.52 (broad, 1 H, 3β-H), 3.70 (s, 3 H, ester Me), 3.04 (s, 3 H, mesylate Me), 2.08 (s, 3 H, acetate Me), 0.96 (s, 3 H, 19-Me), 0.70 (s, 3 H, 18-Me)
8a Methyl 7α-hydroxy-3α-*p*-toluenesulfonoxy-5β-cholan-24-oate	76	129–131[e] (lit.[3] 128.5–129°)	3584 (OH), 1727 (C=O), 1170 (SO_3), 923, 868, 677	7.82 (d, 2 H, aromatic), 7.32 (d, 2 H, aromatic), 4.33 (broad, 1 H, 3β-H), 3.83 (broad, 1 H, 7β-H), 3.67 (s, 3 H, ester Me), 2.45 (s, 3 H, tosylate Me), 0.87 (s, 3 H, 19-Me), 0.64 (s, 3 H, 18-Me)
8b Methyl 7α-acetoxy-3α-*p*-toluenesulfonoxy-5β-cholan-24-oate		166–167[l]	1724 (C=O), 1227 (acetate C–O), 1174 (SO_3), 930	7.82 (d, 2 H, tosylate aromatic), 7.33 (d, 2 H, tosylate aromatic), 4.82 (broad, 1 H, 7β-H), 4.33 (broad, 1 H, 3β-H), 3.66 (s, 3 H, ester Me), 2.45 (s, 3 H, tosylate Me), 2.00 (s, 3 H,

Table I
(Continued)

Compd	Yield, %	Mp, °C (lit. value)	Ir absorption, selected bands, cm^{-1}	^1H NMR spectral assignments, δ
				acetate Me), 0.87 (s, 3 H, 19-Me), 0.63 (s, 3 H, 18-Me)
10a Methyl 3β-chloro-7α-hydroxy-5β-cholan-24-oate[m]	83	140–141[j]	3636 (OH), 1724 (C=O), 1105, 706	4.56 (broad, 1 H, 3α-H), 3.87 (broad, 1 H, 7β-H), 3.67 (s, 3 H, ester Me), 0.97 (s, 19-Me), 0.67 (s, 3 H, 18-Me)
10b Methyl 7α-acetoxy-3β-chloro-5β-cholan-24-oate[c]		150–152[j]	1721 (C=O), 1239 (acetate C–O), 1010, 700	4.90 (broad, 1 H, 7β-H), 4.56 (broad, 1 H, 3α-H), 3.66 (s, 3 H, ester Me), 2.02 (s, 3 H, acetate Me), 0.97 (s, 3 H, 19-Me), 0.60 (s, 3 H, 18-Me)
13a Methyl 3α-acetoxy-7α,12α-dihydroxy-5β-cholan-24-oate[g]		153–155[l] (lit.[16] 149–150)	1720 (C=O), 1640, 1240 (acetate C–O), 1160, 1010, 670	4.56 (broad, 1 H, 3β-H), 3.96 (broad, 1 H, 12β-H), 3.86 (broad, 1 H, 7β-H), 3.68 (s, 3 H, ester Me), 2.00 (s, 3 H, acetate Me), 0.90 (s, 3 H, 19-Me), 0.69 (s, 3 H, 18-Me)
13b Methyl 3α,7α-diacetoxy-12α-hydroxy-5β-cholan-24-oate[c]	67	188–190[b] (lit.[17] 187–188)		4.90 (broad, 1 H, 7β-H), 4.56 (broad, 1 H, 3β-H), 4.00 (broad, 1 H, 12β-H), 3.67 (s, 3 H, ester Me), 2.06 (s, 3 H, acetate Me), 2.02 (s, 3 H, acetate Me), 0.92 (s, 3 H, 19-Me), 0.68 (s, 3 H, 18-Me)
13c Methyl 3α,7α,12α-triacetoxy-5β-cholan-24-oate[c]		108–109[b] (lit.[18] 90–91)		5.07 (broad, 1 H, 12β-H), 4.90 (broad, 1 H, 7β-H), 4.56 (broad, 1 H, 3β-H), 3.65 (s, 3 H, ester Me), 2.09 (s, 3 H, acetate Me), 2.05 (s, 3 H, acetate Me), 2.00 (s, 3 H, acetate Me), 0.87 (s, 3 H, 19-Me), 0.69 (s, 3 H, 18-Me)
15 7α,12α-Dihydroxy-3-oxo-5β-cholan-24-oate[k]	11	178–179[b] (lit.[19] 171–173)	3540 (OH), 1740 (ester C=O), 1700 (keto C=O), 1190, 1082, 1040, 982	4.04 (broad m, 2 H, 7β-H and 12β-H), 3.71 (s, 3 H, ester Me), 1.04 (s, 3 H, 19-Me), 0.76 (s, 3 H, 18-Me)

Table I
(Continued)

Compd	Yield, %	Mp, °C (lit. value)	Ir absorption, selected bands, cm^{-1}	^1H NMR spectral assignments, δ
16 Methyl 7α,12α-dihydroxy-3,3-ethylenedithio-5β-cholan-24-oate	75	102–113[n]	3410 (OH), 1730 (C=O), 1192, 1166, 1066, 1030	4.02 (broad s, 1 H, 12β-H), 3.84 (broad s, 1 H, 7β-H), 3.70 (s, 3 H, ester Me), 3.28 (s, 4 H, thioketal), 0.94 (s, 3 H, 19-Me), 0.70 (s, 3 H, 18-Me)
17a Methyl 3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate[o]	87	183–184[l] (lit.[20] 179–181)	1752 (ester C=O), 1722 (keto C=O), 1252 (acetate C–O), 1070, 1031	5.04 (s, 1 H, 7β-H), 4.60 (broad m, 1 H, 3β-H), 3.68 (s, 3 H, ester Me), 2.04 (s, 6 H, acetate Me's), 1.03 (s, 6 H, C-18 and C-19 Me's), 0.82 (d, 3 H, 21-Me)
17b Methyl 3α-Acetoxy-7α-hydroxy-12-oxo-5β-cholan-24-oate[p]	42	194–195[b] (lit.[21] 194–195)	3436 (OH), 1727 and 1692 (C=O), 1258 (acetate C–O), 1085, 1032, 978	

[a] Satisfactory analytical data (±0.3% for C, H, S, Cl) were reported for **6a, 6b, 7b, 10a, 10b,** and **16**; **7a** was identified by its spectra and by analysis of its acetate **7b**. [b] Recrystallized from methanol–water. [c] Prepared with acetic anhydride and pyridine. [d] Prepared by hydrogenation of the Δ^3 olefin. [e] Recrystallized from methanol. [f] Prepared with acetic acid, acetic anhydride, and *p*-toluenesulfonic acid. [g] Prepared with acetic anhydride in benzene. [h] Separated from the diacetate by chromatography on alumina. [i] Recrystallized from acetone–petroleum ether. [j] Recrystallized from acetone–water. [k] Prepared with aluminum isopropoxide and acetone. [l] Recrystallized from ether. [m] Prepared with pyridinium chloride and **8a**. [n] Did not crystallize from solution; obtained as an amorphous powder. [o] Prepared by oxidation of **13b** with sodium dichromate in acetic acid. [p] Prepared by hydrolysis of **17b**, then methanolic HCl, then acetic anhydride, benzene, and THF.

benzoate (**13d**)[3] and 5β-cholane-7α,12α-diol (**18**)[4] are the samples described earlier. After several unsuccessful attempts to alkylate the hydroxyl of methyl cholate 3,7-diacetate (**13b**),[23] methyl 3α,7α-diacetoxy-12α-methoxy-5β-cholan-24-oate (**14a**) was prepared from **13b** and methyl fluorosulfonate.[24] Alkaline hydrolysis gave the dihydroxy acid, which was not purified, but was converted to the methyl ester (**14b**). Selective acetylations of the 3α-hydroxyl were carried out by treating the steroid with acetic anhydride in benzene (**4a, 13a**) or THF (**14c**). In the case of **4a**, some of the diacetate was also produced.

Comparisons of acetylation rates of the 3α-, 7α-, and 12α-hydroxyls with each other by this method, and with other methods previously reported.[3,5] are given in Table II. Again the 12α-hydroxyl reacts about 1.4 times as fast as the 7α-hydroxyl, and the 3α-hydroxyl is many times as fast. These rates are faster than those obtained by the other two methods, owing in part to the higher temperature in the sample well of the NMR instrument (35° vs. 25°).

The effects of substituents on the acetylation rate of the 7α-hydroxyl are indicated by the rate constants listed in Table III. It can be seen that the 3α-tosyloxy (**8a**), 3α-mesyloxy (**7a**), 3β-chloro (**10a**), 3α-acetoxy (**4a**), 3-oxo (**5a**), and 3α-succinoyloxy (**9a**) groups are all mildly enhancing, and the 3α-dimethylamino (**12a**) somewhat more so (2.4 times H). By far the largest effects are observed for those compounds containing a 12α-hydroxyl group in addition to the 3 substituent. Methyl cholate 3-acetate (**13a**) exhibits a rate constant 9.3 times that of methyl 7α-hydroxy-5β-cholan-24-oate (**3a**), and 5.7 times that of methyl chenodeoxycholate 3-acetate (**4a**), illustrating the added effect of the 12α-hydroxyl group. The combination of 3-ethylenedithio

Table II
Acetylation Rates[a]

Compd	^1H NMR,[b] $k_2 \times 10^6$	GLC,[c] $k_2 \times 10^6$	^{14}C,[d] $k_2 \times 10^6$
1a Methyl 3α-hydroxy-5β-cholan-24-oate	82.1 (44.8)[b]	55.6 (69)	37.8 (95)
2a Methyl 12α-hydroxy-5β-cholan-24-oate	2.47 (1.35)	1.12 (1.38)	0.58 (1.5)
3a Methyl 7α-hydroxy-5β-cholan-24-oate	1.83 (1.00)	0.81 (1.00)	0.39 (1.0)

[a] Rate constants are expressed in M^{-1} sec^{-1}; figures in parentheses are relative rates. [b] Obtained at 35°, the temperature of the sample well. [c] Reference 3. [d] Reference 5.

and 12α-hydroxy is the most effective, giving a rate constant 14.6 times that of **3a**.

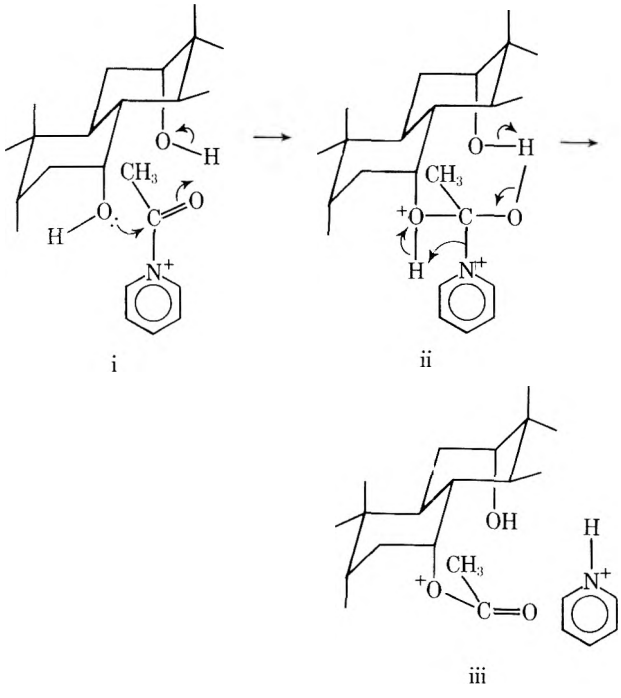
The mechanism of rate enhancement by the 3 substituents is not known, but a clue to the role of the 12α-hydroxyl is obtained by comparing methyl 3α,7α-dihydroxy-12α-methoxy-5β-cholan-24-oate 3-acetate (**14c**) with methyl cholate 3-acetate (**13a**). The hydroxyl and methoxyl groups have similar steric and inductive effects, so this large difference in rate constant (factor of 15) would appear to be related to the ability of the hydroxyl to contribute a proton. A plausible mechanism would employ protonation of

Table III
Acetylation Rates of 7α-Hydroxy Steroids

Compd	$k_2 \times 10^6$, M^{-1} sec^{-1}
14c Methyl 3α-acetoxy-7α-hydroxy-12α-methoxy-5β-cholan-24-oate	1.03 ± 0.11
6a Methyl 3,3-ethylenedioxy-7α-hydroxy-5β-cholan-24-oate	1.49 ±0.17
3a Methyl 7α-hydroxy-5β-cholan-24-oate	1.83 ± 0.03
8a Methyl 7α-hydroxy-3α-*p*-toluenesulfonoxy-5β-cholan-24-oate	2.37 ± 0.21
7a Methyl 7α-hydroxy-3α-methanesulfonoxy-5β-cholan-24-oate	2.63 ± 0.05
10a Methyl 3β-chloro-7α-hydroxy-5β-cholan-24-oate	2.71 ± 0.13
4a Methyl 3α-acetoxy-7α-hydroxy-5β-cholan-24-oate	2.90 ± 0.35
5a Methyl 7α-hydroxy-3-oxo-5β-cholan-24-oate	3.23 ± 0.05
9a Methyl 7α-hydroxy-3α-succinoyloxy-5β-cholan-24-oate	3.32 ± 0.20
12a Methyl 3α-dimethylamino-7α-hydroxy-5β-cholan-24-oate	4.47 ± 0.58
13a Methyl 3α-acetoxy-7α-12α-dihydroxy-5β-cholan-24-oate	17.00 ± 1.2
15 Methyl 7α,12α-dihydroxy-3-oxo-5β-cholan-24-oate	17.2 ± 1.9
18 5β-Cholane-7α,12α-diol	25.6 ± 1.1
13d Methyl 7α,12α-dihydroxy-3-*p*-nitrobenzoyloxy-5β-cholan-24-oate	26.2[a] ± 3.6
16 Methyl 7α,12α-dihydroxy-3,3-ethylenedithio-5β-cholan-24-oate	26.7 ± 1.1

[a] A rate constant of 31.3 × 10^{-6} M^{-1} sec^{-1} was obtained by the uv method.[3]

the acetyl pyridinium ion in production of the tetrahedral intermediate ii, which then collapses to product (iii) and pyridinium ion. With respect to substituents at C-3, there



i ii iii

is no obvious single mechanism by which all of the diverse groups used here [α-RSO_3, β-Cl, α-AcO, O=, α-HO_2C-$C_2H_4CO_2$, α-Me_2N, α-*p*-$O_2NC_6H_4CO_2$, and -$(CH_2S)_2$] can enhance acetylation of the 7α-hydroxyl; neither field effects nor inductive effects correlate with rates. Association between certain 3 substituents and the 7-hydroxyl is implied by the observation that upon acetylation appropriate resonances (acetate Me, mesylate Me, ketal and dithioketal methylenes) move downfield by 0.1–0.2 ppm. In the case of methyl 7α,12α-dihydroxy-3,3-ethylenedithio-5β-cholan-24-oate (**16**) this shift, rather than an angular methyl shift, was used to calculate the rate constant. These shifts are solvent dependent in the sense that they are substantially smaller (0.03) in deuteriochloroform.

The 7α,12α-dihydroxy steroids underwent a second upfield shift of the C-19 angular methyl representing acetylation of the 12-hydroxyl. These rates were calculated (Table IV) by assuming that the acetic anhydride concentration

Table IV
Acetylation Rates of 12α-Hydroxy Steroids

Compd	$k_2 \times 10^6$ M^{-1} sec^{-1}
18 5β-Cholane-7α,12α-diol	1.27 ± 0.14
13a Methyl 3α-acetoxy-7α,12α-dihydroxy-5β-cholan-24-oate	1.83 ± 0.12
13b Methyl 3α,7α-diacetoxy-12α-hydroxy-5β-cholan-24-oate	1.99 ± 0.23
13d Methyl 7α,12α-dihydroxy-3-*p*-nitrobenzoyloxy-5β-cholan-24-oate	2.74 ± 0.11
16 Methyl 7α,12α-dihydroxy-3,3-ethylenedithio-5β-cholan-24-oate	3.31 ± 0.29
15 Methyl 7α,12α-dihydroxy-3-oxo-5β-cholan-24-oate	3.70 ± 0.39

had been lowered by an amount equivalent to the steroid concentration (to accommodate that used in acetylation of the 7-hydroxyl). This method was validated by the finding of similar rate constants for the 12α-hydroxyls of methyl cholate 3-acetate (**13a**) and methyl cholate 3,7-diacetate (**13b**). The sequence differes in this series, suggesting that substituents at C-3 influence the 7- and 12-hydroxyls by different mechanisms.

Experimental Section[25]

Methyl 7α-Hydroxy-3α-succinoyloxy-5β-cholan-24-oate (9a). A solution of 2.00 g (4.93 mmol) of methyl chenodeoxycholate (**4a**) in 25 ml of benzene was dried by distilling 15 ml of the benzene. Succinic anhydride (2.00 g, 19.7 mmol) and chloroform (25 ml) were added and the resulting suspension was stirred at room temperature for 5 days. Washing the suspension with three 100-ml portions of H_2O, drying (Na_2SO_4), and evaporating produced a pale yellow syrup which was chromatographed from benzene solution on 70 g of Florisil. Elution with 7% MeOH in ether gave recovered **4a**, and elution with MeOH gave 1.34 g of a glass, mp 139–150°. Analysis implied contamination with succinic acid, which was removed by dissolving the glass in 25 ml of H_2O, acidifying, extracting with benzene (4 × 25 ml), drying (Na_2SO_4), and evaporating the benzene. Dissolving the residue in dilute NaOH, acidifying, adding MeOH to partially dissolve the resulting precipitate, and gradual cooling gave 758 mg of **9a**: mp 79–90°; ir 3546 (OH), 1721 (C=O), 1155, 1074, 1000, 973 cm^{-1}; NMR δ 4.60 (broad, 1 H, 3β-H), 3.88 (broad, 1 H, 7β-H), 3.69 (s, 3 H, ester Me), 2.62 (s, 4 H, succinate CH_2's), 0.92 (s, 3 H, 19-Me), 0.67 (s, 3 H, 18-Me).

Anal. Calcd for $C_{29}H_{46}O_7$: C, 68.74; H, 9.15. Found: C, 68.75; H, 9.23.

Methyl 3α-Dimethylamino-7α-hydroxy-5β-cholan-24-oate (12a). A solution of 2.06 g (5.0 mmol) of methyl 7α-hydroxy-3-oxo-5β-cholanoate (**5a**) and 1.0 ml of 97% HCO_2H in 2 ml of DMF was heated at reflux for 5.5 hr. Acidification with 20 ml of 1 *N* HCl,

dilution with 50 ml of H_2O, and neutralization with aqueous $NaHCO_3$, drying (Na_2SO_4), evaporating, and chromatographing the residue on basic Al_2O_3 (Brockman activity I) gave three oily fractions: A, eluted by Et_2O–C_6H_6 (1:9), 4% overall yield, presumed to be a 7-formate **11b** [NMR δ 8.11 (s, 1 H, formate H), 5.03 (s, 1 H, 7β-H), 2.21 (s, 6 H, amine Me's)]; B, eluted by Et_2O–C_6H_6 (1:4), 8% yield, presumed to be the 3β epimer **11a** [NMR s 2.27 (s, 6 H, amine Me's)]; C, eluted by Et_2O–C_6H_6 (4:1) and further purified by preparative TLC, 16% yield, **12a:** ir 3150–3400 (OH), 1730 (C=O), 1160, 980, 750 cm^{-1}; NMR δ 3.88 (broad, 1 H, 7β-H), 3.70 (s, 3 H, ester Me), 2.38 (s, 6 H, amine Me's), 0.94 (s, 3 H, 19-Me), 0.69 (s, 3 H, 18-Me). It was characterized as the hydrochloride, an amorphous solid from trituration in ether–petroleum ether, mp 262–265°.

Anal. Calcd for $C_{27}H_{48}O_3NCl$: C, 68.98; H, 10.38; N, 2.98; Cl, 7.54. Found: C, 68.71; H, 10.10; N, 3.01; Cl, 7.80.

The acetate (**12b**), prepared as usual and purified by chromatography on basic Al_2O_3, eluted by Et_2O–C_6H_6 (1:5) was an oil: ir 1272 (C=O), 1240 (acetate C=O), 1158, 1010, 670 cm^{-1}; NMR δ 4.91 (broad, 1 H, 7β-H), 3.68 (s, 3 H, ester Me), 2.30 (s, 6 H, amine Me's), 2.06 (s, 3 H, acetate Me), 0.93 (s, 3 H, 19-Me), 0.66 (s, 3 H, 18-Me).

Anal. Calcd for $C_{29}H_{49}O_4N$: C, 73.22; H, 10.38; N, 2.95. Found: C, 73.47; H, 10.21; N, 3.12.

Methyl 3α,7α-Diacetoxy-12α-methoxy-5β-cholan-24-oate (14a). A solution of 10.0 g (19.8 mmol) of methyl cholate 3,7-diacetate (**13b**) in 70 ml of benzene was dried by distilling 20 ml of the benzene. Methyl fluorosulfonate (25 ml) was added slowly to the benzene solution at room temperature. After 12 hr H_2O was added and the mixture was carefully neutralized with $NaHCO_3$. Extraction into ether, washing, and drying gave 5.3 g of a yellow oil whose benzene solution was chromatographed on Al_2O_3 (150 g). Following a forerun with 10% Et_2O in C_6H_6, 25–30% Et_2O in C_6H_6 eluted the product, which was rechromatographed twice to give 1.8 g (18%) of an oil: ir 1721 and 1704 (C=O), 1235 (acetate C–O), 1094 (ether C–O), 1020, 680 cm^{-1}; NMR δ 4.90 (broad, 1 H, 7β-H), 4.57 (broad, 1 H, 3β-H), 3.67 (s, 3 H, ester Me), 3.33 (s, 3 H, ether Me), 2.05 (s, 6 H, acetate Me's), 0.92 (s, 3 H, 19-Me), 0.70 (s, 3 H, 18-Me).

Anal. Calcd for $C_{30}H_{48}O_7$: C, 69.20; H, 9.29. Found: C, 69.42; H, 9.33.

Methyl 3α,7α-Dihydroxy-12α-methoxy-5β-cholan-24-oate (14b). Hydrolysis of **14a** with KOH in 90% MeOH at reflux for 20 hr, acidification, and extraction into $HCCl_3$ gave the acid, an oil, which was esterified in methanolic HCl to give **14b**, prisms out of MeOH–H_2O, 76%: mp 189–190°; ir 3247 (OH), 1757 (C=O), 1115, 1094 (ether C–O), 998 cm^{-1}; NMR δ 3.87 (broad, 1 H, 7β-H), 3.70 (s, 3 H, ester Me), 3.32 (s, 3 H, ether Me), 0.92 (s, 3 H, 19-Me), 0.70 (s, 3 H, 18-Me).

Anal. Calcd for $C_{26}H_{44}O_5$: C, 71.52; H, 10.16. Found: C, 71.32; H, 10.30.

Methyl 3α-Acetoxy-7α-hydroxy-12α-methoxy-5β-cholan-24-oate (14c). A solution of 1.23 g (2.82 mmol) of **14b** in 15 ml of anhydrous THF containing 5 ml of Ac_2O was kept at 60–65° for 10 hr. Pyridine (1 ml) and H_2O (50 ml) were added to the solution at room temperature. Extraction into ether, washing (dilute $NaHCO_3$ and H_2O), and drying gave 1.51 g of an oil. Chromatography on 50 g of Al_2O_3 and elution with Et_2O–C_6H_6 (1:3) to remove forerun, followed by elution with Et_2O, gave 620 mg (46%) of **14c**, an oil: ir 3540 (OH), 1720 and 1702 (C=O), 1240 (acetate C–O), 1090)ether C–O), 1068, 1020, 908, 730 cm^{-1}; NMR δ 4.57 (broad, 1 H, 3β-H), 3.85 (broad, 1 H, 7β-H), 3.69 (s, 3 H, ester Me), 3.32 (s, 3 H, ether Me), 2.04 (s, 3 H, acetate Me), 0.93 (s, 3 H, 19-Me), 0.70 (s, 3 H, 18-Me).

Anal. Calcd for $C_{28}H_{46}O_6$: C, 70.26; H, 9.69. Found: C, 70.42; H, 9.57.

Kinetic Runs. The steroid (0.370 mmol) was weighed into a 1-ml volumetric tube and dissolved in approximately 0.6 ml of pyridine (previously dried over molecular sieve). Acetic anhydride was weighed into a 3-ml volumetric tube and made up to the mark with anhydrous pyridine. At zero time, 0.20 ml of the Ac_2O solution was pipetted into the steroid solution, which was then immediately brought to the mark with anhydrous pyridine and mixed. The solution was transferred to a NMR sample tube, sealed with a cap and parafilm, and placed in a bath at 35 ± 1°. Periodically the tube was placed in the spectrometer and the spectrum from 5 to 0 ppm was traced. The time of the measurement was taken to be that time when the pen traced the particular methyl resonance of interest.

Peak heights of either the C-18 (usually) or C-19 methyl resonances for the alcohol and the acetate in each mixture were measured in millimeters from the spectrum base line. These peak heights were normalized by use of the peak height of an invariant resonance as an internal standard, usually the side-chain methyl resonance. Rate constants were calculated from these peak heights and starting concentrations using a program written in FORTRAN IV language for the CDC 6600 system and the standard rate expression

$$k = \frac{1}{t(b - a)} \ln \frac{a(b - x)}{b(a - x)}$$

where a = initial molar concentration of steroid, b = initial molar concentration of Ac_2O, and x = moles reacted at time t.

The computer calculated the second-order rate constant from a least-squares plot of log $(b - x)/(a - x)$ vs. t; data from a typical run are given in Table V.

Table V
Acetylation of Methyl 12α-Hydroxy-5β-cholan-24-oate[a]

Time, hr	ROH peak ht (corr)	ROAc peak ht (corr)	ROH, M	ROAc (x), M	Log (b - x)/(a - x)	% Reaction
8.4	107	16	0.320	0.049	1.156	13.2
21.9	85	36	0.260	0.109	1.305	29.6
33.6	72	41	0.235	0.134	1.380	36.4
45.5	75	61	0.203	0.166	1.491	45.1
58.2	67	71	0.179	0.190	1.587	51.4
68.8	62	82	0.159	0.210	1.684	56.9
103.0	46	93	0.122	0.247	1.909	67.1
130.6	41	96	0.109	0.260	1.999	70.4
166.5	38	106	0.097	0.272	2.106	73.8

[a] Initial molar concentrations: steroid, 0.369; Ac_2O, 1.067.

For the diols (**13a, 13d, 15, 16,** and **18**) there are two competing reactions occurring simultaneously, but preliminary work with methyl cholate 3-acetate (**13a**) indicated that the difference in rate between 7α-hydroxyl acetylation and 12α-hydroxyl acetylation was great enough that the two reactions could, as a good approximation, be considered sequential. Consequently, in calculating the rate constants for the 12-hydroxyl of these diols, it was assumed that the starting concentration of acetic anhydride was equal to the actual initial concentration minus the initial concentration of steroid. As a check of the value thus calculated in the case of methyl cholate 3-acetate (**13a**), runs were also carried out using the 3,7-diacetate (**13b**).

Each compound was run two to six times, the k_2's reported representing the mean for each compound.

Acknowledgment. Computations were performed at the Indiana University School of Medicine Research Computation Center and were supported in part by PHS Grant FR00162.

Registry No.—**1a,** 1249-75-8; **1b,** 3253-69-8; **2a,** 1249-70-3; **2b,** 1919-68-2; **3a,** 28050-19-3; **3b,** 19684-60-7; **4a,** 19684-68-5; **4b,** 2616-71-9; **5a,** 14773-00-3; **6a,** 54852-40-3; **6b,** 54852-41-4; **7a,** 54852-42-5; **7b,** 54852-43-6; **8a,** 28192-93-0; **8b,** 54852-44-7; **9a,** 54852-45-8; **10a,** 54852-46-9; **10b,** 54852-47-0; **11a,** 54852-48-1; **11b,** 54852-49-2; **12a,** 54852-50-5; **12a** HCl, 54852-51-6; **12b,** 54852-52-7; **13a,** 7443-91-6; **13b,** 3749-87-9; **13c,** 6818-44-6; **13d,** 28192-79-2; **14a,** 54852-53-8; **14b,** 54852-54-9; **14c,** 54852-55-0; **15,** 14772-99-7; **16,** 54852-56-1; **17a,** 28535-81-1; **17b,** 54852-57-2; **18,** 3701-54-0; succinic anhydride, 108-30-5.

References and Notes

(1) Part VII: *Steroids*, **23**, 895 (1974). Part VIII taken from the Ph.D. Thesis of James F. Baker, Indiana University.
(2) R. T. Blickenstaff and B. Orwig, *J. Org. Chem.*, **34**, 1377 (1969).
(3) R. T. Blickenstaff, K. Atkinson, D. Breaux, E. Foster, Y. Kim, and G. C. Wolf, *J. Org. Chem.*, **36**, 1271 (1971).
(4) G. C. Wolf, E. L. Foster, and R. T. Blickenstaff, *J. Org. Chem.*, **38**, 1276 (1973).
(5) A. Sattar and R. T. Blickenstaff, *Steroids*, **17**, 357 (1971).
(6) R. T. Blickenstaff and K. Sophasan, *Tetrahedron*, **28**, 1945 (1972).
(7) H. Schmid, H. Sofer, and B. Mayerböck, *Monatsh. Chem.*, **99**, 463 (1968).

(8) N. S. Bhacca and D. H. Williams, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, p 13.
(9) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Am. Chem. Soc.*, **90**, 5480 (1968).
(10) F. C. Chang, R. T. Blickenstaff, A. Feldstein, J. R. Gray, G. S. McCaleb, and D. H. Sprunt, *J. Am. Chem. Soc.*, **79**, 2164 (1957).
(11) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **26**, 536 (1943).
(12) J. Barnett and T. Reichstein, *Helv. Chim. Acta*, **21**, 926 (1938).
(13) E. Hauser, E. Baumgartner, and K. Meyer, *Helv. Chim. Acta*, **43**, 1595 (1960).
(14) Y. Sato and N. Ikekawa, *J. Org. Chem.*, **24**, 1367 (1959).
(15) H. B. Kagan and J. Jaques, *Bull. Soc. Chim. Fr*, 699 (1957).
(16) P. A. Plattner and H. Hauser, *Helv. Chim. Acta*, **27**, 748 (1944).
(17) L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, **72**, 5530 (1950).
(18) W. S. Knowles, J. Fried, and R. C. Elderfield, *J. Org. Chem.*, **7**, 383 (1942).
(19) A. S. Jones, M. Webb, and F. Smith, *J. Chem. Soc.*, 2164 (1949).
(20) L. F. Fieser, S. Rajagopalan, E. Wilson, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 4133 (1951).
(21) E. Berner, A. Lardon, and T. Reichstein, *Helv. Chim. Acta*, **30**, 1542 (1947).
(22) 3α-Amines were obtained by the Leuckart reaction also in the 5β-pregnane series: J. J. Panouse et al., *Bull. Soc. Chim. Fr.*, 1753 (1963).
(23) Attempted alkylation with $(CH_3)_2SO_4$ or CH_3I and strong bases gave no detectable reaction. Treatment with diazomethane and a Lewis acid provided, surprisingly, in each case, a high yield of the oxidation product, methyl 3α,7α-diacetoxy-12-oxo-5β-cholan-24-oate (**17a**).
(24) M. G. Ahmed, R. W. Alder, G. H. James, M. L. Sinnott, and M. C. Whiting, *Chem. Commun.*, 1533 (1968).
(25) Melting points were determined on a Thomas-Hoover melting point apparatus and are corrected. Infrared spectra were recorded from smears or Nujol mulls on a Perkin-Elmer 247 spectrophotometer. Nuclear magnetic resonance spectra were obtained in deuteriochloroform on a Varian T-60 spectrophotometer. Elemental microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Application of the Wittig Reaction to the Synthesis of Steroidal Side Chains. Possibility of 3β-Phenoxy Formation as a Secondary Reaction

Jean Pierre Schmit, Marcel Piraux,* and Jean François Pilette

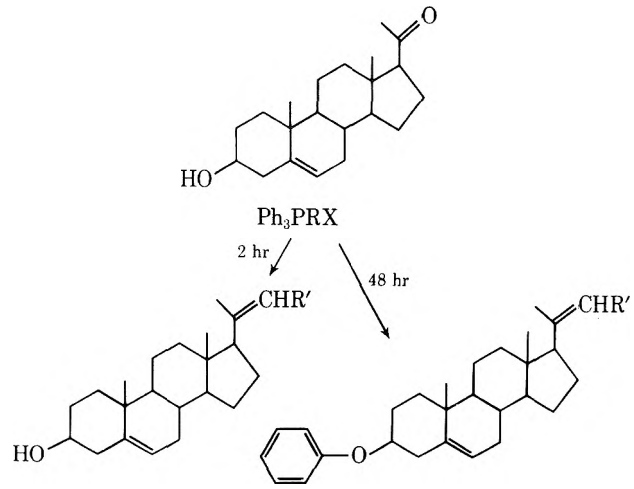
Department of Pharmacognosy and Natural Products Chemistry, Catholic University of Louvain, 1348 Louvain-la-Neuve, Belgium

Received September 18, 1974

The Wittig reaction of various alkylidenephosphoranes with Δ^5-pregnen-3β-ol-20-one has been studied. The formations of 3β-phenoxy derivatives in a secondary reaction is demonstrated.

With the available methods for the synthesis of side-chain steroids from C-20 and C-21 compounds, one obtains stereoisemeric 20-hydroxy compounds as an intermediate.[1] The latter, on being dehydrated at C-20 and then catalytically hydrogenated, yield a mixture of the two possible isomers. The dehydration of a 20-hydroxy intermediate in principle could give five different olefins: two $\Delta^{17(20)}$-dehydro compounds, the corresponding $\Delta^{20(21)}$ isomer, and two $\Delta^{20(22)}$ isomers.[2,3,4] The isomerism difficulty was partially resolved by Sondheimer and Mechoulam[5], who described the synthesis of $\Delta^{5,20(21)}$-cholestadien-3β-ol acetate by use of the Wittig reaction on 21-nor-20-ketocholesteryl acetate followed by hydrogenation. Subsequently, the Wittig reaction was applied, principally with triphenylphosphine methylene reagent,[6] to various keto steroids. In order to develop a simple route to various unambiguous isomeric side chain steroids, we investigated the Wittig reaction with Δ^5-pregnen-3β-ol-20-one (pregnenolone).

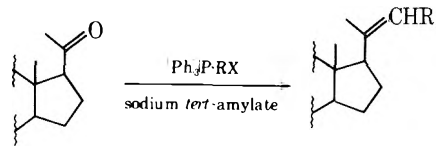
In the first study, isopentylidenephosphorane as the Wittig reagent in the presence of sodium *tert*-amylate[7] as base in benzene solution was found to give the $\Delta^{5,20(22)}$-cholestadien-3β-ol. Thin layer chromatography on Kieselgel with benzene as eluent revealed two products. The faster moving material, with a 0.9 R_f, was present in very low yield after the usual Wittig reaction time. The slower moving component, with a 0.6 R_f, isolated in 80% yield, was found to be the desired $\Delta^{5,20(22)}$-cholestadien-3β-ol. The fast-moving compound, which was initially present in negligible quantities, became the predominant compound with a longer reaction time. The ir spectrum of this secondary product shows the presence of bands at 1598, 1584, 1241, 760, and 694 cm^{-1}. NMR spectroscopy revealed two multiplets appearing respectively at 6.92 and 7.28 ppm. In comparison with the cholesterol the 3β proton was shifted 0.5 ppm to higher field and the 19 methyl peak was shifted 0.02 ppm to lower field. Protons H-6 and H-22 exhibited no observable shift change. Finally, mass spectroscopy gives a molecular ion at 76 units above the expected mass and a base peak 93 units lower than the molecular ion. All of these data support the replacement of the 3β-hydroxyl group by a 3β-phenoxy group in the minor product.



We have also carried out this reaction in the presence of cholesterol and triphenylphosphonium salt and obtained, in either benzene or toluene as solvent, 3β-phenoxycholesterol in high yield. As expected, no substitution occured when the phosphonium salt was absent.

The normal acetylated 20(22) condensation product was then selectively hydrogenated[8] in dioxane, in the presence of acetic acid and platinum oxide as catalyst, to give (80% yield) a product which was identical with the natural product in its spectroscopic properties, melting point, and specific rotation, $[\alpha]^{20}D$ −39.5° ($CHCl_3$). No other hydrogenated product was isolated. This selectivity results from two principal reasons. First, the Wittig reaction on pregnenolone gives a single condensation product (TLC proof and precise melting point, 124.5 ± 0.5°), which was found to be the 20(22) *E* isomer as evidenced by its 18-methyl NMR

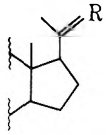
Table I



Phosphorane R	Registry no.	Products R'	3β-Acetate[c] Yield, %	3β-Acetate[c] Mp, °C	3β-Phenoxy[b,d] Mp, °C
CH_3	3487-44-3	H	87	130.5 ± 0.5	
C_2H_5	1754-88-7	CH_3	75	155 ± 1	105 ± 1
C_3H_7	16666-78-7	C_2H_5	82		106 ± 1
C_4H_9	3728-50-5	C_3H_7	79	111.5 ± 0.5	95 ± 1
C_4H_9-i[a]	21960-27-0	C_3H_7-i[a]	67	109 ± 1	
C_5H_{11}	29541-98-8	C_4H_9	73	115.5 ± 0.5	82 ± 1
C_5H_{11}-i[a]	39110-24-2	C_4H_9	84	126 ± 1	98.5 ± 0.5
C_6H_{13}	16666-79-8	C_5H_{11}	78	104.5 ± 0.5	60 ± 1
C_6H_{13}-i[a]	54517-55-4	C_5H_{11}-i[a]	80	124.5 ± 0.5	96 ± 1

[a] Isoterminal group. [b] 3β-Phenoxycholesterol: mp 151 ± 1°. Yields of 3β-phenoxy compounds are about 85% after 48 hr of reaction time. [c] Registry no. are, respectively, 38388-16-8, 54517-67-8, 54548-86-6, 54517-66-7, 54517-65-6, 54517-64-5, 54517-63-4, 54548-85-5. [d] Registry no. are, respectively, 54517-62-3, 54517-61-2, 54517-60-1, 54517-59-8, 54517-58-7, 54517-57-6, 54517-56-5.

Table II



R	Side chain 20(22) effect[b] 18-Me	21-Me	22-H
$=CH_2$	0.59	1.76	4.72 + 4.86
$=CHCH_3$	0.55	1.63	5.27
$=CHC_2H_5$	0.55	1.63	5.26
$=CHC_3H_7$	0.55	1.63	5.20
$=CHC_3H_7$-i[a]	0.55	1.63	5.20
$=CHC_4H_9$	0.55	1.63	5.20
$=CHC_4H_9$-i[a]	0.55	1.63	5.20
$=CHC_5H_{11}$	0.55	1.63	5.20
$=CHC_5H_{11}$-i[a]	0.55	1.63	5.20
Cholesterol	0.68	0.92	

[a] Isoterminal group. [b] All shifts are given in parts per million relative to TMS.

shift.[9] This result is probably due to the fact that the ratio of geometric isomers in the olefinic product appears to be controlled by a combination of steric factors in the reactants and by environmental factors.[10] In a nonpolar solvent such as benzene, the reactants probably approach in the first step of the reaction, to give the threo form as an intermediate which possesses maximum electrostatic attraction and minimum nonbonded interaction between the eclipsed substituents, and the thermodynamically more stable *E* isomer predominates after cis elimination in the second reaction step.

Second, with consideration for the steric hindrance of the condensation product, we have made a mathematical computer model[11] of the product and, on varying the two dihedral angles [PHI (1) 17–17–20–22 and PHI (2) 20–22–23–24], have found two preferential conformations: the first with PHI (1) = 170° and PHI (2) oscillating between 70 and 310° and the second with PHI (1) = 320° and the same PHI (2) as the first. We must note an energetic predominance of the 320° PHI (1) position, which corresponds to an α-21-methyl. Examination of the model also shows that on steric grounds only the α side is capable of being absorbed on the catalyst surface, near the 20(22) olefinic bond. Further, rotation of the side chain during the hydrogenation is sterically improbable. Reaction of pregnenolone with a series of different phosphoranes for 2 hr gave only the expected addition product, whereas extension of the time to 48 hr resulted in formation of the 3β-phenoxy derivatives (Table I). The NMR spectra of the products exhibit an important shift of about 0.7 ppm toward low field for the 21-methyl and a 0.12-ppm shift toward high field for the 18-methyl, when compared with compounds having a saturated side chain. A broad one-proton triplet at 5.2 ppm corresponds to the H-22 proton. 3β-Acetates exhibit a singlet at 1.03 ppm (19-methyl) and a broad multiplet centered at about 4.6 ppm (H-3) whereas in 3β-phenoxy compounds the 19-methyl peak appears at 1.05 ppm and the 3 H proton multiplet is centered at 4.1 ppm (Table II).

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on KBr disks, with a Beckman IR-12 double beam spectrophotometer. NMR spectra were measured in $CDCl_3$ solution, with Me_4Si as reference at room temperature, on a 60-MHz EM-360 Varian NMR spectrometer and at 100 MHz on an XL-100 Varian NMR spectrometer with external H_2O lock.

$\Delta^{5,20(22)}$-Cholestadien-3β-ol Acetate (Typical Reaction). Isopentylidenephosphorane (17.8 mmol) in 12 ml (1.5 mol) of sodium *tert*-amylate was refluxed under nitrogen during 15 min. To the dark-red solution was quickly added 3.2 mmol of pregnenolone in 15 ml of hot benzene solution. The combined solution was gently refluxed for 2 hr. The solution was cooled, filtered over crushed ice, acidified with 2 *N* hydrochloric acid, and extracted with ether. The organic layer was washed with water and dried over anhydrous Na_2SO_4 and the ether was evaporated. The residue was acetylated by being allowed to stand overnight with 20 ml of pyridine and 20 ml of acetic anhydride. Extraction with ether in the usual way led to a product which was isolated by preparative thin layer chromatography (2-mm thickness Kieselgel, Merck), yield 80%, mp 124.5 ± 0.5°. The analytical sample was obtained by crystallization from methanol. All the other Wittig condensation products were obtained as described above.

Cholesterol Acetate from $\Delta^{5,20(22)}$-Cholestadien-3β-ol Acetate. The diene (1 g, 2.3 mmol) of 50 ml of pure dioxane and 1 ml of glacial acetic acid was hydrogenated in the presence of 0.1 g of reduced platinum oxide, at room temperature and atmospheric pressure, until the theoretical quantity of hydrogen was absorbed. The filtered solution was diluted with water, extracted with ether, washed with water, and dried over anhydrous Na_2SO_4. After the ether was removed, the crude product was recrystallized in CH_3OH–$CHCl_3$ (1:1) solution, isolated 1.88 mmol, yield 80.5%, $[\alpha]^{20}D$ −31.5° ($CHCl_3$).

Registry No.—Pregnenolone, 145-13-1.

References and Notes

(1) (a) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952); (b) R. B. Woodward, F. Sondheimer, and D. Taub, *ibid.*, **73**, 3548 (1951); (c) H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann, and R. Robinson, *J. Chem. Soc.*, 361 (1953); (d) P. Kurath and M. Cabezzuto, *J. Am. Chem. Soc.*, **78**, 3527 (1956).
(2) V. Petrow and L. A. Stuart-Webb, *J. Chem. Soc.*, 4675 (1956).
(3) D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).
(4) A. Mijares, D. I. Cargill, J. A. Glusel, and S. Lieberman, *J. Org. Chem.*, **32**, 810 (1967).
(5) F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **80**, 3087 (1958); **79**, 5029 (1957).
(6) J. P. Dusza and W. Bergmann, *J. Org. Chem.*, **25**, 79 (1960); *Org. React.*, **14**, 368 (1960).
(7) J. M. Conia and J. C. Limasset, *Bull. Soc. Chim. Fr.*, **6**, 1936 (1967).
(8) E. B. Hershberg, E. P. Oliveto, C. Gerald, and L. Johnson, *J. Am. Chem. Soc.*, **73**, 5073 (1951).
(9) M. Gut, Personal communication. By comparison with the two NMR spectra of the *E* and *Z* products, obtained by dehydration of the 22-hydroxy derivative.
(10) R. L. Reeves, "The Chemistry of the Carbonyl Group", Interscience, New York, N.Y., 1966, Chapter 12.
(11) M. H. J. Koch, COMOL: a computer program for the calculation of the conformational energy of organic molecules (based on the concepts introduced by Westheimer, personal communication).

Total Synthesis of (±)-6,7-Didehydroaspidospermine

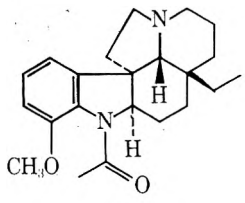
Sol S. Klioze*[1] and Frank P. Darmory

Department of Chemistry, Columbia University, New York, New York 10027

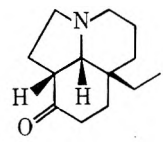
Received December 11, 1974

The total synthesis of the indole alkaloid derivative (±)-6,7-didehydroaspidospermine (**5**) by a Fischer indole approach is described. The cyclization precursor **4** was prepared in a stepwise fashion from ethyl 2-formylbutyrate via the key intermediates **10**, **14**, **16**, **21**, and **6**. Upon heating in acetic acid the o-methoxyphenylhydrazone of **4** was cyclized to indolenine **27**, which on reduction and acetylation afforded (±)-6,7-didehydroaspidospermine (**5**).

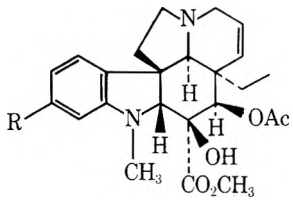
Some years ago a total synthesis of the indole alkaloid aspidospermine (**1**) was developed in these laboratories by Stork and Dolfini.[2,3] This synthesis possessed as its main feature the construction of tricyclic amino ketone **2** and the subsequent Fischer indole cyclization of its o-methoxyphenylhydrazone. We became intrigued with the possibility that this approach might be extended to provide a route to 6,7-didehydro indole alkaloids, e.g., the pharmacologically important alkaloids vindoline (**3a**)[4] and vindorosine (**3b**).[5]



1

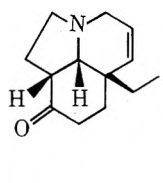


2

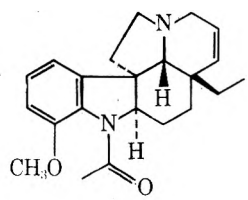


3a, R = OCH_3
b, R = H

We wish to report here a synthesis of the required unsaturated tricyclic amino ketone **4** and its subsequent conversion into (±)-6,7-didehydroaspidospermine (**5**).

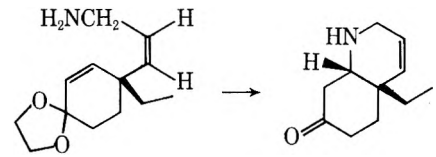


4



5

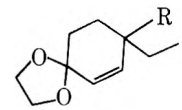
The synthetic plan involved construction of the necessary bicyclic amino ketone **6** by the hydrolysis and subsequent cyclization of ketal cis-allylic amine **7**. The third ring



7 **6**

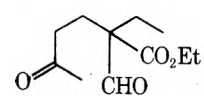
of unsaturated tricyclic amino ketone **4** could then be introduced in the same manner used in the preparation of the saturated analog **2**.[2]

It was decided to build up the cis-allylic amine chain of **7** in a stepwise manner from ketal ester **8**. Michael addition

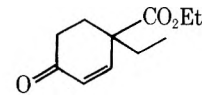


8, R = CO_2Et
11, R = CH_2OH
12, R = CHO
13, R = CH=CHCl
14, R = C≡CH
15, R = C≡CCH_2OH

of ethyl 2-formylbutyrate[6] to methyl vinyl ketone gave adduct **9**, which was cyclized with piperidine acetate–acetic acid in refluxing benzene[7] to afford cyclohexenone ester **10**



9



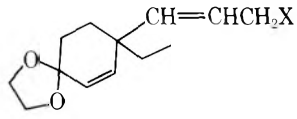
10

in 73% yield. Ketalization gave a quantitative yield of the desired ketal ester **8**.

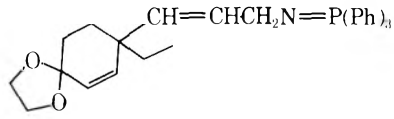
The ketal ester **8** was then reduced with lithium aluminum hydride (ether, 0°, 4 hr) to give ketal alcohol **11** in 57%

yield.[8] Oxidation with pyridine–sulfur trioxide complex in dimethyl sulfoxide–triethylamine[9] afforded ketal aldehyde **12** in 85% yield. The chain was subsequently extended one carbon by condensing ketal aldehyde **12** with chloromethylenetriphenylphosphorane[10] in refluxing tetrahydrofuran to produce ketal chloroolefin **13** in 97% yield. Dehydrohalogenation proceeded smoothly upon treatment of **13** with potassium *tert*-butoxide in 1:1 glyme–hexamethylphosphoramide at 25°, affording a 91% yield of ketal acetylene **14.**

The terminal carbon of the required chain was introduced by treatment of a glyme solution of the lithium acetylide of ketal acetylene **14** with excess monomeric formaldehyde to provide ketal propargyl alcohol **15** in 97% yield. Partial catalytic hydrogenation (PtO_2, ethyl acetate containing triethylamine) afforded a 99% yield of ketal allylic alcohol **16** as an approximately 3:1 mixture of cis to trans isomers.[11] Separation of these isomers was postponed to a later stage in the synthesis.



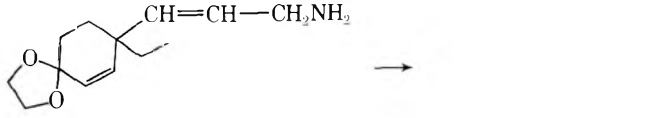
16, X = OH
17, X = N_3
18, X = OMs, Cl



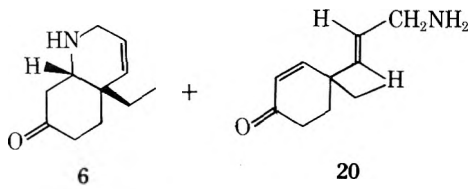
19

This mixture of allylic alcohols **16** was transformed into ketal allylic azide **17** in 88% yield by conversion into mesylate–chloride mixture **18** (MeLi, benzene, 15°, methanesulfonyl chloride) followed by nucleophilic displacement with sodium azide in aqueous dimethyl sulfoxide. Reduction of ketal allylic azide **17** to the corresponding amine initially caused some difficulty. Treatment of **17** with sodium borohydride both in ethanol at room temperature and 2-propanol at reflux failed to effect any reduction. In an alternative procedure **17** was smoothly converted to ketal phosphinimine **19** by refluxing with triphenylphosphine in benzene.[12] Hydrolysis and cyclization did afford a mixture of bicyclic amino ketone **6** and trans-allylic amine enone **20.** Unfortunately, the large amounts of triphenylphosphine oxide produced during the hydrolysis made separation of amines **6** and **20** very tedious.

This problem was eventually surmounted by reducing azide **17** with aluminum amalgam.[13] Thus stirring **17** with aluminum amalgam in 12:1:1 ether–methanol–water afforded an 81% yield of ketal allylic amine **21** (an approximately 3:1 mixture of ketal cis-allylic amine **7** and its corresponding trans isomer). Hydrolysis and cyclization proceeded in the anticipated manner to give the required bicyclic amino ketone **6** in 29% overall yield from ketal propargyl alcohol **15** after chromatography on activity IV neutral alumina to remove the undesired trans-allylic amine enone **20.**

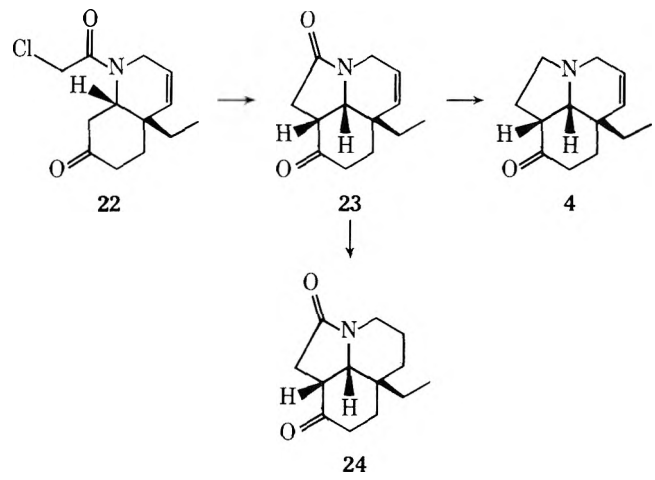


21



6 **20**

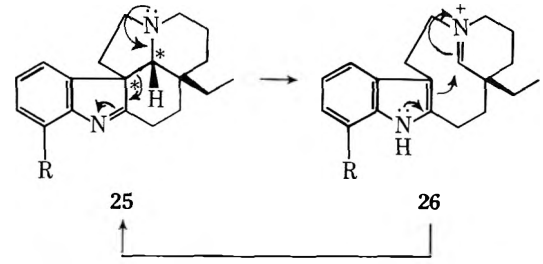
The third ring of **4** was now introduced in a manner identical with that used in the aspidospermine synthesis.[2] Chloroacetylation of **6** afforded chloroacetylamide **22** in 92% yield. Cyclization with potassium *tert*-butoxide in refluxing benzene gave the keto lactam **23** in 28% yield after repeated chromatography on silica gel. The stereochemistry of this intermediate was established as all-cis on the basis of its reduction to the Stork–Dolfini saturated keto lactam **24** (mp and mmp 114–115°) which Ban[14] had determined to possess the all-cis configuration. Ketalization and reduction with lithium aluminum hydride followed by deketalization proceeded in high overall yield to complete the preparation of tricyclic amino ketone **4.**



22 **23** **4**

24

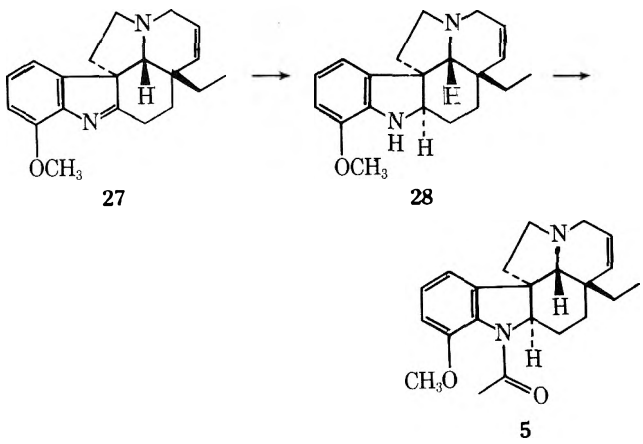
With amino ketone **4** in hand, one was ready to perform the crucial Fischer indole synthesis. It is worthy of note that, although **4** possesses the all-cis configuration necessary to produce a pentacyclic alkaloid precursor having the same relative stereochemical relationships as those present in aspidospermine and related natural products, the three configurational isomers of **4** should also lead to this same final stereochemistry. Stork pointed out that the indolenine **25** formed during the Fischer indole cyclization was generated under conditions which would lead to equilibration at the two centers marked by asterisks via a reverse Mannich reaction.[2] This equilibration proceeds through



25 **26**

the open form **26,** which can conceivably reclose to give any of the possible stereoisomers. However, the reversible nature of this tautomerization dictates that the eventual product possess the thermodynamically most stable arrangement, which in this case turns out to be the natural one.[15]

Fischer indole cyclization of the *o*-methoxyphenylhydrazone of amino ketone **4** was effected in refluxing acetic acid. The resulting indolenine **27** was reduced with lithium aluminum hydride to indoline **28.** Evaporative distillation followed by acetylation with acetic anhydride–sodium acetate gave a crude material from which crystalline (±)-6,7-didehydroaspidospermine (**5,** mp 190–191°) could be readi-



27 28 5

ly obtained. This material afforded (±)-aspidospermine (1), identical in all respects with that prepared by Stork and Dolfini,[2] on catalytic hydrogenation with palladium on charcoal in acetic acid.

It is hoped that a suitable adaptation of this approach will provide a viable route to the more complex, pharmacologically interesting 6,7-didehydro indole alkaloids.

Experimental Section

Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill., or Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Absorptions are in microns using a polystyrene standard. Nuclear magnetic resonance spectra were taken on Varian Model A-60A or T-60 spectrometers using deuteriochloroform as solvent. Signals are reported in parts per million (δ) relative to an internal tetramethylsilane standard. (Notation: s, d, t, etc., refer to singlet, doublet, triplet, etc., and br refers to a broad peak.) Mass spectra were recorded on a Hitachi Perkin-Elmer Model RMU-6D mass spectrometer. Ethereal solvents were distilled from lithium aluminum hydride; dimethyl sulfoxide, *tert*-butyl alcohol, and hexamethylphosphoramide were distilled from calcium hydride. Triethylamine was distilled from barium oxide. Column materials for chromatography were normally 60–100 mesh. The phrase "worked up in the usual manner", as applied to an organic extract, refers to drying over anhydrous sodium sulfate followed by evaporation in vacuo.

Ethyl 2-Formylbutyrate. A. Ethyl 2-formylbutyrate was prepared in 15.6% yield by condensing ethyl butyrate (406 g, 3.50 mol) with ethyl formate (260 g, 3.50 mol) in ether employing sodium hydride as the base, bp 76–80° (25 mm) [lit.[16] bp 64–66° (16 mm)].

B. A solution of 5.06 g (0.05 mol) of diisopropylamine in 50 ml of dry THF was treated with 21.3 ml (0.05 mol) of 2.35 *M n*-butyllithium in hexane at room temperature under nitrogen. The resultant pale yellow solution was cooled to −78°, at which time a solution of 5.81 g (0.05 mol) of ethyl butyrate in 15 ml of dry THF was added. Stirring was continued for 0.5 hr at −78°, after which 11.1 g (0.15 mol, 12.2 ml) of ethyl formate was added by syringe. The resultant mixture was allowed to warm to room temperature and stirred for 3 hr under nitrogen. After the addition of 9 g (0.15 mol, 8.55 ml) of acetic acid, the reaction mixture was diluted with 350 ml of ether and washed with water (2 × 100 ml) and saturated aqueous $NaHCO_3$ solution (100 ml). Work-up in the usual manner gave 7.29 g of an orange oil, which was distilled to afford 4.30 g (60%) of ethyl 2-formylbutyrate as a colorless liquid: bp 76–81° (23 mm); ir (film) 2.95, 5.80, 6.00, 6.20 μ; NMR δ 1.04 (t, J = 7 Hz, 3 H), 1.35 (t, J = 7 Hz, 3 H), 1.7–2.5 (m, 2 H), 3.22 (t of d, J_1 = 7, J_2 = 2 Hz, 0.5 H), 4.28 (q, J = 7 Hz, 2 H), 7.02 (d, J = 12 Hz, 0.5 H), 9.76 (d, J = 2 Hz, 0.5 H), 11.41 (d, J = 12 Hz, 0.5 H).

4-Ethyl-4-carboethoxycyclohex-2-enone (10). The cyclohexenone ester **10** was prepared according to the general procedure of Plieninger and coworkers[7]. Treatment of ethyl 2-formylbutyrate with methyl vinyl ketone in *tert*-butyl alcohol containing a catalytic amount of potassium *tert*-butoxide gave Michael adduct **9** as a nearly colorless oil: ir (film) 5.72, 5.80 μ; NMR δ 0.88 (t, J = 7 Hz, 3 H), 1.28 (t, J = 7 Hz, 3 H), 1.5–2.7 (m, 6 H), 2.11 (s, 3 H), 4.25 (q, J = 7 Hz, 2 H), 9.8 (s, 1 H). Cyclization of this material by refluxing in benzene with piperidinium acetate and acetic acid with azeotropic removal of water afforded after distillation a 73% yield of cyclohexenone ester **10**: bp 92–95° (0.25 mm); ir (film) 5.79, 5.91 μ; NMR δ 0.88 (t, J = 7 Hz, 3 H), 1.28 (t, J = 7 Hz, 3 H), 1.5–2.7 (m, 6 H), 4.25 (q, J = 7 Hz, 2 H), 5.98 and 6.95 (AB quartet, J = 10 Hz, 2 H).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.14; H, 8.26.

8-Ethyl-8-carboethoxy-1,4-dioxaspiro[4,5]-6-decene (8). Ketal ester 8 was prepared from cyclohexenone ester **10** using standard ketalization conditions (ethylene glycol, a catalytic amount of *p*-toluenesulfonic acid, and benzene at reflux with a Dean-Stark trap). From 37 g (0.189 mol) of **10** was obtained a nearly quantitative yield of ketal ester **8** as a pale yellow oil, which was used in subsequent experiments without further purification: ir (film) 5.80, 6.03 μ (weak); NMR δ 0.87 (t, J = 7 Hz, 3 H), 1.23 (t, J = 7 Hz, 3 H), 1.45–2.5 (m, 6 H), 3.96 (s, 4 H), 4.15 (q, J = 7 Hz, 2 H), 5.62 and 5.94 (AB quartet, J = 10 Hz, 2 H).

8-Ethyl-8-hydroxymethyl-1,4-dioxaspiro[4,5]-6-decene (11). To a suspension of 4.75 g (0.125 mol) of $LiAlH_4$ in 275 ml of anhydrous ether was added dropwise with stirring at 0° under nitrogen a solution of 34.75 g (0.144 mol) of ketal ester **8** in 75 ml of anhydrous ether. The reaction mixture was then stirred for 4 hr at 0° under nitrogen. Excess $LiAlH_4$ was decomposed by cautious dropwise addition of ethyl acetate and then saturated aqueous sodium sulfate at 0°. The precipitate was filtered off and washed repeatedly with ether. The combined filtrate and washings were evaporated in vacuo and distilled to afford 16.17 g (57%) of ketal alcohol **11** as a viscous, colorless liquid: bp 112–116° (0.25 mm); ir (film) 2.98, 6.05 μ; NMR δ 0.87 (t, J = 7 Hz, 3 H), 1.1–2.0 (m, 6 H), 2.19 (br s, 1 H), 3.41 (slightly broadened s, 2 H), 3.96 (s, 4 H), 5.65 (s, 2 H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.54; H, 9.11.

8-Ethyl-8-formyl-1,4-dioxaspiro[4,5]-6-decene (12). The ketal alcohol **11** was oxidized according to the general procedure of Parikh and Doering.[9]

To a solution of 16.10 g (81.3 mmol) of ketal alcohol in 160 ml of dry triethylamine and 160 ml of dry dimethyl sulfoxide (distilled from calcium hydride) was added a solution of 40 g (252 mmole) of pyridine–sulfur trioxide complex[17] in 240 ml of dry dimethyl sulfoxide. The mixture was stirred overnight at room temperature under nitrogen, diluted with 2 l. of ether, and washed with water (4 × 1000 ml). Work-up in the usual manner followed by distillation afforded 13.43 g (85%) of slightly yellow ketal aldehyde **12**: bp 93–97° (0.25 mm); ir (film) 3.40, 3.50, 3.68, 5.79, 6.01 μ; NMR δ 0.87 (t, J = 7 Hz, 3 H), 1.3–2.3 (m, 6 H), 3.98 (s, 4 H), 5.82 (s, 2 H), 9.47 (s, 1 H).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.12; H, 8.36.

Chloromethyltriphenylphosphonium Chloride. Chloromethyltriphenylphosphonium chloride was prepared in 82% yield according to the procedure of Wittig and Schlosser[18] from triphenylphosphine and paraformaldehyde.

8-Ethyl-8-chlorovinyl-1,4-dioxaspiro[4,5]-6-decene (13). The ketal aldehyde **12** was condensed with chloromethylenetriphenylphosphorane according to the general procedure described by Seyferth and coworkers.[10]

To a suspension of 34.7 g (100 mmol) of chloromethyltriphenylphosphonium chloride in 425 ml of dry THF was added 45 ml (100 mmol) of 2.24 *M* phenyllithium in 70:30 benzene–ether in a nitrogen atmosphere. The deep red mixture was allowed to stir at room temperature for 0.5 hr, after which a solution of 10.70 g (54.5 mmol) of ketal aldehyde in 75 ml of dry THF was added dropwise with stirring. The mixture was then refluxed overnight under nitrogen. The cooled reaction mixture was poured into 1.9 l. of 1:1 ether–hexane, washed with water (3 × 850 ml), and worked up in the usual manner. The residue was chromatographed on 80 g of Florisil (60–100 mesh) with 1:5 ether–hexane as eluent. The eluate was evaporated in vacuo and distilled to afford 12.04 g (97%) of colorless ketal chloroolefin **13**: bp 97–102° (0.40 mm); ir (film) 3.38, 3.48, 6.04, 6.14, 6.19, 10.54 μ; NMR δ 0.88 (t, J = 7 Hz, 3 H), 1.2–2.0 (m, 6 H), 3.95 (s, 4 H), 5.4–6.2 (m, 4 H).

8-Ethyl-8-ethynyl-1,4-dioxaspiro[4,5]-6-decene (14). To a solution of 12.0 g (52.5 mmol) of ketal chloroolefin 13 in 135 ml of dry glyme and 135 ml of dry hexamethylphosphoramide was added 30 g (267 mmole) of potassium *tert*-butoxide. The mixture was stirred overnight at room temperature under nitrogen, diluted with 1.8 l. of ether, and washed extensively with water (5 × 900 ml) to remove all the HMPA. Work-up in the usual manner and distil-

lation afforded 9.16 g (91%) of colorless ketal acetylene **14**: bp 75–79° (0.35 mm); ir (film) 3.08, 4.73, 6.03 μ; NMR δ 1.02 (t, J = 7 Hz, 3 H), 1.15–2.05 (m, 6 H), 2.13 (s, 1 H), 3.94 (s, 4 H), 5.50 and 5.78 (AB quartet, J = 10 Hz, 2 H).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.03; H, 8.56.

8-Ethyl-8-hydroxymethylethynyl-1,4-dioxaspiro[4,5]-6-decene (15). Ketal propargyl alcohol **15** was obtained in 97% yield by treating the lithium acetylide prepared from 7.50 g (39 mmol) of ketal acetylene **14** and methyllithium in glyme with excess monomeric formaldehyde: ir (film) 2.97, 4.48, 6.02 μ; NMR δ 1.00 (t, J = 7 Hz, 3 H), 1.15–2.2 (m, 6 H), 2.81 (br s, 1 H), 3.98 (s, 4 H), 4.22 (s, 2 H), 5.50 and 5.77 (AB quartet, J = 10 Hz, 2 H).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.10; H, 8.19.

8-Ethyl-8-hydroxymethylvinyl-1,4-dioxaspiro[4,5]-6-decene (16). A solution of 6.669 g (30 mmol) of ketal propargyl alcohol **15** in 125 ml of ethyl acetate containing 9 ml of triethylamine was hydrogenated at atmospheric pressure using 300 mg of 84% platinum oxide as catalyst. After 30 mmol of hydrogen (745 ml plus allowance for catalyst) was absorbed, the reaction was discontinued. The solution was filtered with the aid of filter cel and evaporated in vacuo to afford 6.65 (99%) of ketal allylic alcohol **16** (approximately 3:1, cis/trans) as an orange oil: ir (film) 2.96, 6.04 μ; NMR δ 0.83 (skewed t, 3 H), 1.05–2.0 (m, 6 H), 2.82 (s, 1 H), 3.98 (s, 6 H), 5.1–6.1 (m, 4 H).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.88; H, 8.95.

Bicyclic Ether Ketone i. Ketal allylic alcohol **16** (112.2 mg, 0.5 mmol) was hydrolyzed with 5 ml of 1 N hydrochloric acid (30 min). Standard work-up procedures afforded 83 mg of pale yellow oil. Investigation of the ir and NMR spectra of this material indicated that it was an approximately 3:1 mixture of bicyclic ether ketone i and trans-allylic alcohol enone ii, respectively.

8-Ethyl-8-azidomethylvinyl-1,4-dioxaspiro[4,5]-6-decene (17). To a solution of 6.66 g (29.7 mmol) of allylic alcohol **16** in 300 ml of dry benzene at 15° was added 20 ml (32 mmol) of 1.6 M methyllithium in ether. The solution was stirred at 15° under nitrogen for 5 min, after which 3.0 ml (38.4 mmol) of methanesulfonyl chloride was added. This mixture was then stirred overnight at room temperature under nitrogen and poured into 600 ml of 5% aqueous NaOH solution. The mixture was extracted with 1 l. of ether, washed with water (2 × 500 ml), and worked up in the usual manner to give 7.68 g of an approximately 3:1 mixture of ketal allylic mesylate and ketal allylic chloride **18** as a light orange oil: ir (film) no OH, 6.04, 7.37 μ; NMR δ 2.93 (CH_3SO_2–), 3.87 (–CH_2OMs), 3.95 (ketal), 4.80 (–CH_2Cl). Integration indicates that the mesylate:chloride ratio is approximately 3:1.

To a solution of 7.67 g of allylic mesylate–chloride mixture from the previous experiment in 250 ml of dimethyl sulfoxide and 50 ml of water was added 16 g (246 mmol) of sodium azide. The resulting solution was stirred overnight at room temperature under nitrogen, poured into 1200 ml of ether, and washed with water (3 × 500 ml). Work-up in the usual manner gave 6.53 g (88%) of ketal allylic azide **17** as a yellow oil: ir (film) 4.76, 6.04 μ; NMR δ 0.87 (skewed t, J = 7 Hz, 3 H), 1.03–2.10 (m, 6 H), 3.95 (s, 6 H), 5.30–6.00 (m, 4 H).

Ketal Phosphinimine 19. To a solution of 770 mg (3.10 mmol) of ketal allylic azide **17** in 50 ml of dry benzene was added 960 mg (3.66 mmol) of triphenylphosphine. The resulting solution was refluxed overnight under nitrogen, after which the solvent was removed in vacuo to give a quantitative yield of ketal phosphinimine **19** as a viscous yellow oil: ir (film) no azide, 6.30 (weak), 6.80 (strong), 7.00 μ (strong).

8-Ethyl-8-aminomethylvinyl-1,4-dioxaspiro[4,5]-6-decene (21). To aluminum–mercury amalgam prepared from 7.02 g (260 mmol) of aluminum turnings according to the procedure of Wislicenus and Kaufmann[19] under 60 ml of ether was added a solution of 6.52 g (26.2 mmol) of allylic azide **17** in 300 ml of ether. To this suspension was added 30 ml of methanol and 30 ml of water. The resulting mixture was stirred rapidly for 20 hr at room temperature under nitrogen, during which time a cloudy gray precipitate was formed. The mixture was then filtered, the precipitate being washed extensively with ether. The combined ether solutions were washed with 500 ml of water and worked up in the usual manner to afford 4.73 g (81%) of ketal allylic amine **21** as a yellow oil (an approximately 3:1 mixture of ketal cis-allylic amine **7** and its corresponding trans isomer): ir (film) 3.01, 6.07, 6.23 μ; NMR δ 0.87 (skewed t, J = 7 Hz, 3 H), 1.05–2.20 (m, 8 H), 3.95 (s, 6 H), 5.00–6.10 (m, 4 H).

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48. Found: C, 69.76; H, 9.30.

4a-Ethyl-2,4a,5,6,8,8a-hexahydro-7(1*H*)-quinolone (6). A solution of 4.50 g (20.2 mmol) of ketal allylic amine **21** dissolved in 400 ml of 1 N hydrochloric acid and 30 ml of methanol was stirred for 1 hr at room temperature under nitrogen and then made basic with 10% aqueous NaOH. After standing for 10 min, the mixture was extracted with ether (2 × 600 ml). Work-up in the usual manner gave 3.06 g of an orange oil which was shown by ir to be an approximately 3:1 mixture of bicyclic amino ketone **6** and trans-allylic amine enone **20**: ir (film) 3.05, 5.84 (strong), 5.96 μ (medium).

This mixture was chromatographed on 110 g of Woelm neutral alumina (activity IV). Elution with 250 ml of 40% ether–benzene gave first a small amount of a nonbasic enone followed by 1.55 g (29% overall yield from ketal propargyl alcohol **15**) of hexahydroquinolone **6**. If elution was continued with the same solvent trans-allylic amine enone **20** could be obtained. The chromatography was followed by ir: ir (film) 3.05, 3.45, 5.84, 6.05 μ; NMR δ 0.92 (skewed t, J = 7 Hz, 3 H), 1.05–3.0 (m, 9 H), 3.13 (t, J = 5 Hz, 1 H), 3.38 (br s, 2 H), 5.61 and 5.72 (AB quartet, J = 2.5 Hz, 2 H); MS m/e 179 (M^+), 150, 124, 108.

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56. Found: C, 73.91; H, 9.52.

***N*-Chloroacetyl-4a-ethyl-2,4a,5,6,8,8a-hexahydro-7(1*H*)-quinolone (22).** To a solution of 1.07 g (5.97 mmol) of hexahydroquinolone **6** and 605 mg (5.97 mmol) of triethylamine in 80 ml of dry methylene chloride at 0° under nitrogen was added dropwise with stirring a solution of 675 mg (5.97 mmol) of chloroacetyl chloride in 20 ml of dry methylene chloride. After the addition was complete, the reaction mixture was stirred for 1.5 hr at room temperature under nitrogen. The mixture was diluted with 350 ml of methylene chloride and washed with 1 N hydrochloric acid (150 ml), 5% aqueous potassium carbonate solution (150 ml), and water (150 ml). Work-up in the usual manner gave 1.58 g of viscous brown oil. Chromatography on 25 g of silica gel using 1:1 ether–benzene as eluent afforded 1.41 g (92%) of bicyclic chloroacetyl amide **22** as an orange gum: ir (film) 5.82, 6.06 μ; NMR δ 0.9 (skewed t, 3 H), 1.1–2.8 (m, 9 H), 4.10 (br s, 4 H), 5.81 (br s, 2 H).

6a-Ethyl-4,6a,7,8,9a,9b-hexahydro-9*H*-pyrrolo[3,2,1-*ij*]quinoline-2,9(1*H*)-dione (23). A solution of 3.00 g (11.75 mmol) of chloroacetyl amide **22** in 120 ml of dry benzene containing 1.54 g (13.75 mmol) of potassium *tert*-butoxide was refluxed under nitrogen for 26 hr, after which most of the benzene was removed in vacuo. The residue was taken up in 1 l. of methylene chloride, washed with 5% aqueous NaOH (400 ml) and water (500 ml), and worked up in the usual manner to give 2.40 g of an orange foam. This foam was chromatographed on 60 g of silica gel. After elution with 125 ml of 4:1 ether–benzene and 200 ml of ether, to remove any nonpolar by-products and unreacted starting material, a fraction containing the desired tricyclic keto lactam **23** was eluted with 1 l. of 2% methanol–methylene chloride. Evaporation of this fraction in vacuo gave 998 mg of viscous orange gum. As this material was contaminated with a small amount of very polar impurities, it was carefully rechromatographed on 27 g of silica gel using 2% methanol–methylene chloride as eluent. This second chromatography afforded 725 mg (28%) of tricyclic keto lactam **23** as a pale yellow, viscous oil, which was homogeneous on TLC (silica gel G, 2% MeOH–CH_2Cl_2): ir (film) 5.87, 5.93 μ; NMR δ 1.00 (split t, J = 7 Hz, 3 H), 1.30–2.2 (m, 4 H), 2.2–3.3 (m, 4 H), 3.44 (dd, J_1 = 7, J_2 = 2 Hz, 1 H), 3.6–4.07 (m, 2 H), 4.10–4.38 (m, 1 H), 5.72 (s, 2 H); MS m/e 219 (M^+), 190.

High-resolution mass spectrum: Anal. Calcd for $C_{13}H_{17}NO_2$: 219.1259. Found: 219.1259.

6a-Ethyl-1,2,4,6a,7,8,9a,9b-octahydro-9*H*-pyrrolo[3,2,1-*ij*]-quinolin-9-one (4). A solution of 186.8 mg (0.852 mmol) of tricyclic keto lactam **23** and 0.20 ml (3.6 mmol) of ethylene glycol in 30 ml of benzene containing 15 mg of *p*-toluenesulfonic acid monohydrate was refluxed for 19 hr under nitrogen, the water of reaction being removed with a Dean-Stark trap containing molecular sieves. A few drops of triethylamine were added, and the mixture was diluted with 30 ml of benzene and washed with saturated aqueous $NaHCO_3$ solution (2 × 20 ml). Work-up in the usual manner afforded 200 mg (90%) of tricyclic lactam ketal as a viscous orange oil: ir (film) 5.90, 6.03 μ; NMR δ 0.92 (skewed t, 3 H), 1.1–2.0 (m, 4 H), 2.1–2.7 (m, 4 H), 3.0–3.8 (m, 3 H), 3.8–4.2 (m, 1 H), 3.97 (s, 4 H), 5.68 (s, 2 H).

To a suspension of 57 mg (1.5 mmol) of $LiAlH_4$ in 10 ml of dry ether was added dropwise with stirring at room temperature under nitrogen a solution of 197 mg (0.75 mmol) of tricyclic lactam ketal in 5 ml of dry ether. The mixture was then stirred for 3 hr at room

temperature under nitrogen, after which excess $LiAlH_4$ was decomposed by cautious dropwise addition of saturated aqueous sodium sulfate solution at 0°. The precipitate was filtered off and washed with ether. The combined ethereal solutions were evaporated in vacuo to afford 178 mg (95%) of tricyclic amino ketal as a pale yellow gum: ir (film) 3.45, 3.50, Bohlmann bands, 3.61, 3.68 μ; NMR δ 0.90 (skewed t, 3 H), 1.1–2.7 (m, 8 H), 3.0–3.7 (m, 4 H), 3.97 (m, 6 H), 5.60 (br s, 2 H).

To a solution of 177 mg (0.710 mmol) of tricyclic amino ketal in 1.5 ml of methanol was added 3 ml of water and 1.5 ml of concentrated hydrochloric acid. The resulting solution was stirred overnight at room temperature under nitrogen. The mixture was basified with 10% aqueous NaOH and extracted with ether (2 × 60 ml). The combined ether extracts were worked up in the usual manner to afford 142 mg (97%) of crude tricyclic amino ketone **4** as a yellow gum. This gum could be purified by evaporative distillation to give colorless tricyclic amino ketone **4**: bp 120–130° (0.15 mm); ir (film) Bohlmann hands 3.60, 3.68, 5.85 μ; NMR δ 0.90 (skewed t, 3 H), 1.1–3.6 (m, 12 H), 3.95 (br s, 2 H), 5.62 (m, 2 H); MS *m/e* 205 (M^+).

High-resolution mass spectrum: Anal. Calcd for $C_{13}H_{19}NO$: 205.1467. Found: 205.1467.

6a-Ethyl-4,5,6,6a,7,8,9a,9b-octahydro-9*H*-pyrrolo[3,2,1-*ij*]-quinoline-2,9(1*H*)-dione (24). A solution of 355 mg (1.62 mmol) of tricyclic keto lactam **23** in 25 ml of 95% ethanol was hydrogenated at atmospheric pressure using 35 mg of 10% palladium on carbon as catalyst. After 5 hr the theoretical amount of hydrogen (39.6 ml) had been absorbed. The reaction mixture was filtered with the aid of Celite and evaporated in vacuo to afford 346 mg (96%) of saturated tricyclic keto lactam **24** as a viscous yellow oil which had ir and NMR spectra and thin layer properties (silica gel G, 2% MeOH–CH_2Cl_2) identical with those of the Stork–Dolfini saturated tricyclic keto lactam.[2] A small amount of material (53.5 mg) prepared in this manner was chromatographed on 1 g of silica gel with 2% methanol–methylene chloride. When the solvent was removed in vacuo and the residue triturated with ether, 33 mg of white crystalline saturated tricyclic keto lactam **24** was obtained: mp 114–115° (lit.[2] mp 113–116°); mmp 114–115°; ir (film) 5.86, 5.92 μ; NMR δ 0.97 (t, J = 7 Hz, 3 H), 1.10–3.0 (m, 11 H), 3.08 (d, J = 5 Hz, 1 H), 3.45 (dd, J_1 = 2, J_2 = 6 Hz, 2 H), 4.00 (br d, J = 13 Hz, 2 H).

***o*-Methoxyphenylhydrazine.** *o*-Methoxyphenylhydrazine was prepared in 54% yield according to the procedure of Bergmann and Hoffmann[20] by the reduction of diazotized o-anisidine with stannous chloride: mp 38–40° (lit.[20] mp 43°); NMR δ 3.78 (s, 3 H), 4.10 (br s, 3 H), 6.6–6.95 (m, 4 H).

(±)-6,7-Didehydroaspidospermine (5). Tricyclic amino ketone **4** (142 mg, 0.69 mmol) was dissolved in 5 ml of ether with 95.5 mg (0.69 mmol) of *o*-methoxyphenylhydrazine. Two drops of acetic acid was added as catalyst and the solution was stirred for 13 hr at room temperature under nitrogen. The solvent was then removed in vacuo to afford the *o*-methoxyphenylhydrazone of amino ketone **4**: viscous orange oil; ir (film) 3.05, 3.64, 3 69, 6.24, 6.63 μ.

The crude tricyclic *o*-methoxyphenylhydrazone was dissolved in 5 ml of glacial acetic acid and heated at reflux for 45 min under nitrogen. The solvent was removed in vacuo to give the crude pentacyclic indolenine **27** as a dark brown oil.

To a suspension of 228 mg (6 mmol) of $LiAlH_4$ in 8 ml of dry ether was added dropwise with stirring at 0° under nitrogen a solution of crude pentacyclic indolenine **27** in 8 ml of 1:1 ether–glyme. This mixture was stirred overnight at room temperature under nitrogen, after which excess $LiAlH_4$ was decomposed by cautious dropwise addition of saturated aqueous sodium sulfate solution at 0°. The precipitate was filtered off and washed repeatedly with ether. The combined ethereal solutions were evaporated in vacuo to afford 197 mg of a brown oil. Evaporative distillation gave two fractions: I, bp 90–150° (0.22 mm), 15 mg; II, bp 140–160° (0.22 mm), 112.4 mg.

The higher boiling fraction, II, was treated with 1 ml of acetic anhydride and 75 mg of anhydrous sodium acetate for 2 hr at room temperature under nitrogen. The acetic anhydride was removed in vacuo and the residue was diluted with 60 ml of benzene and washed with saturated aqueous sodium bicarbonate solution (2 × 25 ml) and water (20 ml). Work-up in the usual manner gave a viscous yellow oil which afforded 21 mg (9%) of crystalline (±)-6,7-didehydroaspidospermine (**5**), mp 190–191°, on trituration with ether. This material had an ir spectrum similar to that of (±)-aspidospermine with some subtle differences in the fingerprint region: ir (KBr) 3.64, 6.09, 6.29, 6.72, 6.90, 7.24 μ; NMR δ 2.20 (s, 3 H), 3.90 (s, 3 H), 5.63 (sharp m, 2 H).

High-resolution mass spectrum: Anal. Calcd for $C_{22}H_{28}N_2O_2$: 352.2151. Found: 352.2150.

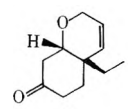
Hydrogenation of **5** in the presence of Pd on charcoal in acetic acid afforded (±)-aspidospermine (**1**) identical in all respects with that prepared by Stork and Dolfini.[2]

Acknowledgments. The authors wish to thank Professor Gilbert Stork for the guidance and encouragement he supplied during the progress of this investigation. Financial support from the National Institutes of Health and National Science Foundation (in the form of grants to Professor Stork) is gratefully acknowledged.

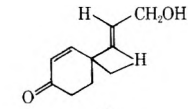
Registry No.—i, 54788-77-1; ii, 54788-78-2; **4**, 54788-79-3; **4** *o*-methoxyphenylhydrazone, 54788-80-6; **4** ketal analog, 54788-81-7; **5**, 54788-82-8; **6**, 54788-83-9; **7**, 54788-84-0; **7** trans analog, 54788-85-1; **8**, 54788-86-2; **9**, 54788-87-3; **10**, 54788-88-4; **11**, 54788-89-5; **12**, 54788-90-8; **13**, 54788-91-9; **14**, 54788-92-0; **15**, 54788-93-1; *cis*-**16**, 54788-94-2; *trans*-**16**, 54788-95-3; **17**, 54788-96-4; 18-Cl, 54788-97-5; 18-OMe, 54788-98-6; **19**, 54788-99-7; **20**, 54789-00-3; **22**, 54789-01-4; **23**, 54789-02-5; **23** ketal analog, 54789-03-6; **24**, 54831-17-3; **27**, 54789-04-7; **28**, 54789-05-8; ethyl 2-formylbutyrate, 36873-42-4; ethyl butyrate, 105-54-4; ethyl formate, 109-94-4; chloromethyltriphenylphosphonium chloride, 5293-84-5; *o*-methoxyphenylhydrazine, 18312-46-4.

References and Notes

(1) Address correspondence to this author at Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J. 08876.
(2) G. Stork and J. E. Dolfini, *J. Am. Chem. Soc.*, **85**, 2872 (1963); G. Stork, *Pure Appl. Chem.*, **9**, 131 (1964).
(3) For other syntheses of aspidospermine or the related alkaloid aspidospermidine see (a) Y. Ban, Y. Sato, I. Inoue, M. Nagai, T. Oishi, M. Terashima, O. Yonemitsu, and Y. Kanaoka, *Tetrahedron Lett.*, 2261 (1965); (b) M. Kuehne and C. Bayha, *ibid.*, 1311 (1966); (c) J. P. Kutney, N. Abdurahman, P. Le Quesne, E. Piers, and I. Vlattas, *J. Am. Chem. Soc.*, **88**, 3656 (1966); (d) J. Harley-Mason and M. Kaplan, *Chem. Commun.*, 915 (1967).
(4) N. Neuss, I. S. Johnson, J. G. Armstrong, and C. J. Jansen, *Adv. Chemother.*, **1**, 133 (1964).
(5) B. K. Moza, J. Trojanek, V. Hanus, and L. Dolejs, *Collect. Czech. Chem. Commun.*, **29**, 1913 (1964), and references cited therein. During the course of this work an elegant total synthesis of vindorosine (**3b**) was reported by Büchi and coworkers: G. Büchi, K. E. Matsumoto, and H. Nisimura, *J. Am. Chem. Soc.*, **93**, 3299 (1971).
(6) Ethyl 2-formylbutyrate was first prepared in 16% yield by refluxing ethyl butyrate and ethyl formate with sodium hydride in ether. However, it was later found that this conversion could be effected in 60% yield by treating ethyl butyrate with lithium diisopropylamide in tetrahydrofuran at −78° and treating the resulting anion with excess ethyl formate.
(7) Cf. H. Plieninger, L. Arnold, and W. Hoffmann, *Ber.*, **98**, 1399 (1965).
(8) The somewhat lower than usual yield for a conversion of this type was caused by a certain proportion of reductive fragmentation of the dioxalane, which could not be diminished even by performing the reduction at −78°.
(9) J. Parikh and W. von E. Doering, *J. Am. Chem. Soc.*, **89**, 5505 (1967).
(10) D. Seyferth, S. O. Grim, and T. O. Read, *J. Am. Chem. Soc.*, 83, 1617 (1961).
(11) This ratio was determined by hydrolysis of **16** followed by careful examination of the ir and NMR spectra of the resulting mixture of i and ii. An



i



ii

extensive investigation of a number of catalysts and reaction conditions failed to improve on this isomer ratio. One possible explanation of these results is that the hydroxyl was bound tightly to the catalyst surface, thereby facilitating the subsequent isomerization of the initially formed cis olefin.
(12) H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919); H. Staudinger and E. Hauser, *ibid.*, **4**, 861, 873, 887, (1921).
(13) Cf. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. I, Wiley, New York, N.Y., 1967, p 20. This conversion is, to our knowledge, the first report of the reduction of an azide to an amine using aluminum amalgam. Further investigation of the scope of this mild reductive procedure is planned.
(14) Y. Ban, I. Iijima, I. Inoue, M. Akagi, and T. Oishi, *Tetrahedron Lett.*, 2976 (1969).
(15) Recently Inoue and Ban reported that the less stable kinetic product could be obtained by performing the Fischer indole cyclization in formic acid: I. inoue and Y. Ban, *J. Chem. Soc. C*, 602 (1970).
(16) L. Legrand and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 79 (1955).
(17) P. Baumgarten, *Ber.*, **59**, 1166 (1926); J. Rubinfeld, Ph.D. Thesis, Columbia University, 1960, p 68.
(18) G. Wittig and H. Schlosser, *Chem. Ber.*, **94**, 1373 (1961).
(19) H. Wislicenus and L. Kaufmann, *Ber.*, **28**, 1323 (1895).
(20) E. D. Bergmann and E. Hoffmann, *J. Chem. Soc.*, 2827 (1962).

Synthesis of (Z)-6-Heneicosen-11-one. Douglas Fir Tussock Moth Sex Attractant

Ronald G. Smith* and G. Doyle Daves, Jr.

Department of Chemistry, Oregon Graduate Center, Beaverton, Oregon 97005

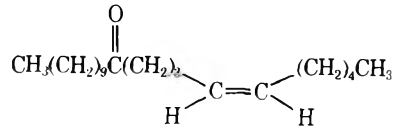
Gary E. Daterman

Pacific Northwest Forest and Range Experiment Station, Forest Service, U.S. Department of Agriculture, Corvallis, Oregon 97331

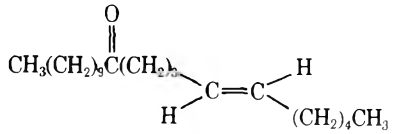
Received November 29, 1974

The syntheses of (Z)-6-heneicosen-11-one, the principal component of the sex attractant of the Douglas fir tussock moth, and the corresponding E isomer are described. The stereochemistries of the products were determined by selective reductions of the common intermediate, 6-heneicosyn-11-ol. The lower limits of isomeric purity of the products, determined by gas chromatographic analysis of the corresponding epoxides, was >97 and >98% for the Z and E isomers, respectively.

Chemical and spectroscopic studies of the sex attractant of the Doublas fir tussock moth (*Orgyia pseudotsugata*), a severe defoliator of firs in western North America, have led to the isolation and identification of (Z)-6-heneicosen-11-one (1) which is highly attractive in laboratory and field tests.[1] In the course of this work it became necessary to synthesize both 1 and the corresponding E isomer, 2, to establish the stereochemistry of the natural attractant and to provide synthetic material for entomological testing.

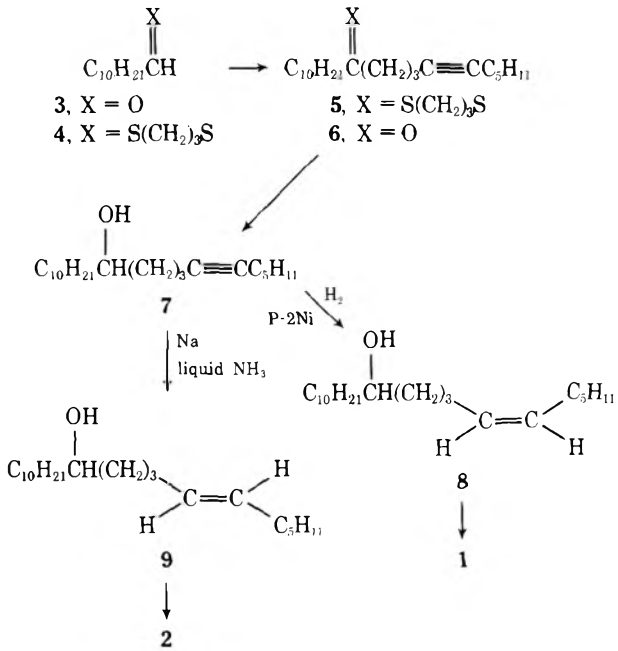


1



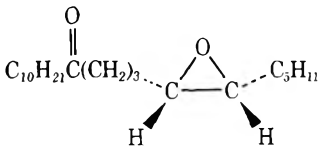
2

Synthesis. Both 1 and 2 were prepared from the acetylenic ketone 6. Synthesis of 6 was accomplished by initial conversion of undecanal to the dithiane 4 and alkylation of the corresponding dithianyl anion[2] (prepared by treatment of 4 with butyllithium) with 1-chloro-4-decyne to yield 5,

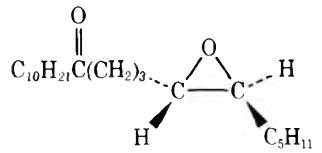


which was hydrolyzed, restoring the carbonyl group. Conversion of 6 to the isomeric olefins, 1 and 2, involved initial reduction of the carbonyl to obtain the acetylenic alcohol, 7, which was subjected to the appropriate stereospecific method of acetylene reduction. Catalytic reduction of 7 using P-2 nickel poisoned with ethylenediamine[3] yielded the Z olefinic alcohol 8 whereas the isomeric E olefinic alcohol was prepared by treatment of 7 with sodium in liquid ammonia.[4] Finally, reoxidation of the isomeric alcohols (8 and 9) yielded the corresponding ketones 1 and 2.

Stereochemical Analysis. The stereochemistries of the Z and E olefinic ketones, 1 and 2, were confirmed by infrared spectroscopy. The spectrum of 2 exhibited a sharp band at 10.4 μ (absent in the spectrum of 1), characteristic of E-disubstituted olefins.[5] Since stereochemical purity is critical for the function of several known insect pheromones,[6,7] it was necessary to obtain a quantitative measure of isomeric purity in the products 1 and 2. Gas–liquid chromatographic (GLC) separation of the stereoisomers 1 and 2 was unsuccessful using a variety of polar phases in packed columns.[8] In previous instances where direct GLC separation of E and Z isomers of long-chain monounsaturated olefins was difficult, analysis was achieved by examination of the corresponding epoxides.[6,9] The results in the present case are similar. Ketones 1 and 2 were readily epoxidized using *m*-chloroperbenzoic acid and GLC conditions were found which gave near-baseline separation of the two isomeric epoxides, 10 and 11 (see Figure 1a). Using this meth-



10



11

od the Z isomer (10) was shown to be >97% pure (Figure 1b) and the E isomer (11) was >98% pure (Figure 1c). These numbers represent lower limits of stereochemical purity of the ketones 1 and 2, since any isomerization occurring during the epoxidation reaction or work-up procedure would result in lower isomeric purity in the corresponding epoxides.

Experimental Section

Melting ranges were taken with a Thomas-Kofler micro hot stage. NMR spectra were obtained in CCl_4 (Me_4Si internal standard) using a Varian HA-100 spectrometer, infrared spectra were recorded on a Perkin-Elmer 337, and mass spectra were measured using either a CEC 21-110B or Du Pont 21-491B spectrometer. Analyses were by the Heterocyclic Chemical Corp., Harrisonville,

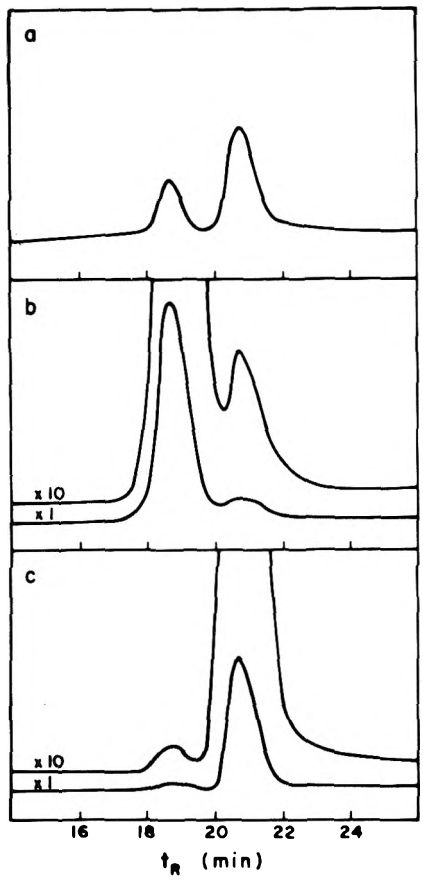


Figure 1. Gas chromatographs of epoxidation products derived from (a) a 1:2 mixture of **1** and **2**, (b) **1**, and (c) **2**.

Mo. Chromatographic separations were achieved with benzene on an alumina (activity III) column (40 × 2 cm) using the dry-column method.[10] Gas–liquid chromatographic (GLC) analyses (other than the stereochemical determinations) were obtained using a Varian 1200 gas chromatograph equipped with a 4 ft × 0.25 in. column of 3% Dexsil 300 on 80/100 Chromosorb W, AW-DMCS.

2-*n*-Decyl-1,3-dithiane (4). Using a procedure similar to that of Fieser,[11] 10 ml of boron trifluoride etherate was slowly added to a flask containing 51 g (0.3 mol) of undecanal (Chemical Samples Co.) and 32.4 g (0.3 mol) of 1,3-propanedithiol. After stirring for 1 hr the resulting two-phase mixture was added to 100 ml of water and extracted with two 50-ml portions of benzene. The combined benzene extracts were washed with four 50-ml portions of 3% aqueous sodium hydroxide and one 50-ml portion of water before drying over anhydrous magnesium sulfate. Evaporation of the solvent left 81 g of light-yellow liquid. Distillation at 125–128° (0.01 mm) gave 76.5 g (98%) of **4** as a colorless liquid: NMR δ 2.78 (m, 4 H, $-SCH_2$), 3.95 (t, 1 H, –SCH); mass spectrum (70 eV) *m/e* (rel intensity) 260 (44, $M^{\cdot+}$), 185 (33, $C_{10}H_{21}C{\equiv}S^+$), 119 (100, –S–C^+H–S–).

Anal. Calc'd. for $C_{14}H_{28}S_2$: C, 64.61; H, 10.77. Found: C, 64.59; H, 11.01.

11-Propylenedithio-6-heneicosyne (5). Following the procedure described by Corey,[12] 92 ml of 2.0 *M* *n*-butyllithium (in hexane) was added to a solution of 40.0 g (154 mmol) of **4** in 300 ml of freshly distilled (over CaH_2) tetrahydrofuran, cooled to −20°. This solution was stirred under nitrogen for 1.5 hr before adding 31.6 g (184 mmol) of 1-chloro-4-decyne[13] (Chemical Samples Co.). After sitrring for an additional 3 hr at −20° the reaction solution was allowed to stand for 60 hr at −10°. The reaction solution was added to a solution of 20 ml of acetic acid in 200 ml of water and extracted with four 75-ml portions of hexane. The combined hexane extracts were washed with three portions of 100 ml of saturated aqueous sodium bicarbonate solution and dried over anhydrous magnesium sulfate, and the solvent was evaporated to leave 52.0 g of a yellow liquid containing (by GLC) 10% unreacted starting material **4**. A sample of this product was purified by distillation at 176–178° (0.01 mm) to give a colorless liquid: NMR δ 2.78 (m, 4 H, $-SCH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 396 (21, $M^{\cdot+}$), 363 [10, $(M - SH)^+$], 321 [83, $(M - CH_2CH_2CH_2SH)^+$], 290 [65, $(M - HSCH_2CH_2CH_2SH)^{\cdot+}$], 259 [54, $(M - C_{10}H_{17})^+$], 119 (100, –S–C^+H–S–).

Anal. Calcd for $C_{24}H_{44}S_2$: C, 72.73; H, 11.11. Found: C, 72.88; H, 11.33.

6-Heneicosyn-11-one (6). A 30.9-g (78 mmol) sample of **5** (undistilled) was hydrolyzed by the method of Narasaka et al.[14] using 24.8 g (0.312 mol) of cupric oxide and 26.6 g (0.156 mol) of cupric chloride dihydrate in 500 ml of acetone and 5 ml of water. From this reaction was isolated 21.5 g (90%) of **6** as a light yellow liquid, bp 164–167° (0.01 mm), which slowly crystallized to a waxy solid: ir (melt) 5.84 μ (C=O); NMR δ 2.00–2.23 (m, 4 H, $C{\equiv}CCH_2$), 2.25–2.60 (m, 4 H, $CH_2C{=}O$); mass spectrum (70 eV) *m/e* (rel intensity 306 (100, $M^{\cdot+}$), 169 [74, $(M - C_{10}H_{17})^+$], 165 [20, $(M - C_{10}H_{21})^+$], 122 [42, $(C_5H_{11}C{\equiv}CCH{=}CH_2)^{\cdot+}$].

Anal. Calcd for $C_{21}H_{38}O$: C, 82.35; H, 12.42. Found: C, 82.41; H, 12.51.

6-Heneicosyn-11-ol (7). A solution of 1.33 g (35 mmol) of lithium aluminum hydride in 300 ml of anhydrous ether was prepared under nitrogen. To this stirred solution was added a solution of 21.0 g (69 mmol) of **6** in 50 ml of anhydrous ether. Stirring was continued for 1.5 hr before destroying excess hydride with slow addition of 5% aqueous sodium hydroxide. The mixture was filtered, the filtrate was dried over anhydrous magnesium sulfate, and the solvent was evaporated to produce 17.3 g of a yellow liquid. Separation by column chromatography afforded 14.2 g (67%) of GLC-pure **7** as a colorless liquid: bp 150–152° (0.01 mm); ir (neat) 3.01 μ (broad, –OH); NMR δ 1.98–2.25 (m, 4 H, $C{\equiv}CCH_2$), 3.52 (*m*, 1 H, CHO); mass spectrum (70 eV) *m/e* (rel intensity) 308 (1, $M^{\cdot+}$), 290 [1, $(M - H_2O)^{\cdot+}$], 167 (100, $C_{10}H_{17}CH{=}^+OH$).

Anal. Calcd for $C_{21}H_{40}O$: C, 81.82; H, 12.99. Found: C, 81.69; H, 13.02.

(*Z*)-6-Heneicosen-11-ol (8). A 1.0-g (3.25 mmol) sample of **7** was catalytically hydrogenated using P-2 nickel poisoned with ethylenediamine as described by Brown and Ahuja.[3] Upon filtration and evaporation of solvent, the isolated product, **8**, weighed 0.90 g (89%): ir (neat) 3.01 μ (broad, –OH), no band at 10.4 μ (*E*-disubstituted olefin); NMR δ 2.00 (m, 4 H, allylic), 3.46 (m, 1 H, CHO), 5.30 (m, 2 H, vinyl); mass spectrum (70 eV) *m/e* (rel intensity) 310 (1, $M^{\cdot+}$), 292 [2, $(M - H_2O)^{\cdot+}$], 124 (100, $(C_5H_{11}CH{=}CHCH{=}CH_2)^{\cdot+}$].

Anal. Calcd for $C_{21}H_{42}O$: C, 81.28; H, 13.63. Found: C, 81.09; H, 13.81.

(*Z*)-6-Heneicosen-11-one (1). Using the procedure described by Ratcliffe and Rodehorst,[15] a 0.615-g (2.0 mmol) sample of **8** was oxidized by addition to a stirred mixture of 1.8 g (18 mmol) of chromium trioxide and 2.85 g (36 mmol) of pyridine in 50 ml of methylene chloride. The worked up product[15] was chromatographed to obtain 0.53 g (86%) of **1** as a colorless liquid: ir (neat) 5.82 μ (sharp, C=O), no C–H band at 10.4 μ (*E*-disubstituted olefin); NMR δ 2.00 (m, 4 H, allylic), 2.30 (t, 4 H, $-CH_2C{=}O$), 5.29 (m, 2 H, vinyl); mass spectrum (70 eV) *m/e* (rel intensity) 308 (5, $M^{\cdot+}$), 197 [25, $C_{10}H_{21}CO^+(CH_2)_2$–], 169 (29, $C_{10}H_{21}C{\equiv}O^+$), 167 (23, $C_{10}H_{19}C{\equiv}O^+$], 124 [100, $(C_5H_{11}CH{=}CHCH{=}CH_2)^{\cdot+}$].

Anal. Calcd for $C_{21}H_{40}O$: C, 81.82; H, 12.99. Found: C, 81.90; H, 13.18.

(*E*)-6-Heneicosen-11-ol (9). A solution of 5.0 g (16.0 mmol) of **7** in 75 ml of anhydrous ether was added to a solution of about 0.95 g of metallic sodium in 250 ml of liquid ammonia.[4] Vigorous stirring was required for 43 hr before quenching with 5 ml of a saturated aqueous ammonium chloride solution. The ammonia was evaporated and the remaining residue was added to 50 ml of hexane, extracted with two 50-ml portions of water, dried over anhydrous magnesium sulfate, and filtered, and the hexane was evaporated to yield 4.7 g (95%) of **9**: mp 40–42°; ir (melt) 3.04 μ (broad, –OH), 10.4 μ (sharp, C–H bending for *E*-disubstituted alkene); NMR δ 1.85–2.30 (m, 5 H, allylic H and hydroxyl H), 3.50 (m, 1 H, CHO), 5.36 (m, 2 H, vinyl); mass spectrum (70 eV) *m/e* (rel intensity) 310 (1.3, $M^{\cdot+}$), 124 [100, $(C_5H_{11}CH{=}CHCH{=}CH_2)^{\cdot+}$].

Anal. Calcd for $C_{21}H_{42}O$: C, 81.28; H, 13.63. Found: C, 81.03; H, 13.81.

(*E*)-6-Heneicosen-11-one (2). A 3.0-g (10 mmol) sample of **9** was oxidized as described for the *Z* isomer to obtain 2.2 g (71%) of **2** as a white solid: mp 36–38°; ir (melt) 5.89 μ (C=O), 10.41 μ (sharp, C–H bending for *E*-disubstituted alkene); NMR δ 1.95 (m, 4 H, allylic), 2.26 (t, 4 H, $CH_2C{=}O$), 5.30 (m, 2 H, vinyl); mass spectrum (70 eV) *m/e* (rel intensity) 308 (25, $M^{\cdot+}$), 197 [28, $C_{10}H_{21}CO^+(CH_2)_2$–], 169 (68, $C_{10}H_{21}C{\equiv}O^+$), 167 (25, $C_{10}H_{19}C{\equiv}O^+$ 124 [100, $(C_5H_{11}CH{=}CHCH{=}CH_2)^{\cdot+}$].

Anal. Calcd for $C_{21}H_{40}O$: C, 81.82; H, 12.99. Found: C, 81.71; H, 13.19.

***cis*-Heneicosan-6,7-epoxy-11-one (10).** To a 0.45-g (1.46 mmol) sample of **1** dissolved in 20 ml of methylene chloride was added 0.504 g (2.92 mmol) of *m*-chloroperbenzoic acid which was stirred into solution before refrigerating at 5° for 15 hr.

The reaction mixture was transferred to a separatory funnel, 1.0 ml of dimethyl sulfide was added to destroy excess peracid, and the mixture was extracted with three 20-ml portions of saturated aqueous sodium bicarbonate solution and one 20-ml portion of water. The clear solution was dried over anhydrous magnesium sulfate and filtered, and the methylene chloride was removed. A 5-mg sample of this product was dissolved in methylene chloride for isomeric analysis. The remaining material was chromatographed, decolorized with activated charcoal, and recrystallized once from benzene–hexane to yield 0.23 g (48%) of **10**: mp 29–36°; ir (CCl_4 solution) 5.84 μ (C=O); NMR δ 2.35 (m, 4 H, CH_2C=O), 2.70 (m, 2 H, CHO); mass spectrum (70 eV) *m/e* (rel intensity) 324 (19, $M^{\cdot+}$), 169 (42, $C_{10}H_{21}C{\equiv}O^+$), 156 [100, $(C_5H_{11}\overline{CHCHO}CH_2CH_2CH_2 + H)^{\cdot+}$].

Anal. Calcd for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42. Found: C, 78.05; H, 12.33.

***trans*-Heneicosan-6,7-epoxy-11-one (11).** A 1.0-g (3.24 mmol) sample of **2** was epoxidized with 1.12 g (6.48 mmol) of *m*-chloroperbenzoic acid using the same procedure as described for the *Z* isomer. Isomeric analysis of this product was performed on a 5-mg sample before column chromatography and recrystallization from benzene–hexane. The remainder of the product, after one recrystallization, weighed 0.54 g (51%): mp 92–97°; ir (CCl_4 solution) 5.82 μ (C=O); NMR δ 2.30 (m, 4 H, CH_2C=O), 2.46 (m, 2 H, CHO); mass spectrum (70 eV) *m/e* (rel intensity) 324 (19, $M^{\cdot+}$), 169 (42, $C_{10}H_{21}C{\equiv}O^+$), 156 [100, $(C_5H_{11}\overline{CHCHO}CH_2CH_2CH_2 + H)^{\cdot+}$].

Anal. Calcd for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42. Found: C, 77.51; H, 12.42.

Stereochemical Analyses. Samples of **10**, **11**, and a 1:2 mixture of **10** and **11** (all in methylene chloride solutions) were examined using a Varian 2700 gas chromatograph equipped with dual flame ionization detectors and a 12 ft × 0.125 in. stainless steel column packed with 10% Apolar 10C on 100/120 mesh Gas-Chrom Q (Applied Science Laboratories). After conditioning overnight at 260° the column was set isothermally at 165°. At this temperature the two isomers, **10** and **11**, were eluted at 19 and 21 min, respectively,[16] with near-baseline resolution (see Figure 1a). The detector output was recorded on two channels of a Gould Brush 260 recorder, the two channels differing in sensitivity by a factor of 10. This made it possible to measure and compare the peak areas of both isomers from a single injection. Duplicate runs were made for each isomer. Measurements of peak areas using peak height and width at half height show the *Z* isomer to be 97.60 and 97.63% pure and the *E* isomer to be 98.42 and 98.49% pure. Calculations using (1) a planimeter and (2) weights of cut-out peaks from photocopies of chromatograms gave values which do not differ by more than 0.3%.

Acknowledgment. Financial assistance was provided by U.S. Forest Service Pacific Northwest Forest and Range Experiment Station, Northwest Forest Pest Action Council, and State of Washington, Department of Natural Resources.

Registry No.—**1**, 54844-65-4; **2**, 54844-66-5; **4**, 54844-67-6; **5**, 54844-68-7; **6**, 54844-69-8; **7**, 54844-70-1; **8**, 54844-72-2; **9**, 54844-72-3; **10**, 54844-73-4; **11**, 54844-74-5; undecanal, 112-44-7; 1,3-propanedithiol, 109-80-8.

References and Notes

(1) R. G. Smith, G. E. Daterman, and G. D. Daves, Jr., *Science*, **188**, 63 (1975).
(2) For a recent paper describing the synthesis and utility of 1,3-dithianes as alkylating agents, see D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975).
(3) C. A. Brown and V. K. Ahuja, *J. Chem. Soc., Chem. Commun.*, 553 (1973).
(4) J. D. Warthen, Jr., and M. Jacobson, *Synthesis*, 616 (1973).
(5) D. J. Pasto and C. R. Johnson, "Organic Structure Determination", Prentice-Hall, Englewood Cliffs, N.J., 1969, p 115.
(6) R. G. Smith, G. E. Daterman, G. D. Daves, Jr., K. D. McMurtrey, and W. L. Roelofs, *J. Insect Physiol.*, **20**, 661 (1974).
(7) J. A. Klun, O. L. Chapman, K. C. Mattes, P. W. Wojtkowski, M. Beroza, and P. E. Sonnett, *Science*, **181**, 661 (1973).
(8) Only a partial separation of **1** and **2** was achieved using a 50-ft SCOT column coated with DEGS and operated at 180°. We thank Dr. Iain Weatherston, Canadian Forestry Service, Sault Ste. Marie, Ontario, for this result.
(9) L. M. McDonough and D. A. George, *J. Chromatogr. Sci.*, **8**, 158 (1970).
(10) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, **48**, 2026 (1967).
(11) L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).
(12) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075 (1965).
(13) F. D. Gunstone and M. Lie Ken Jie, *Chem. Phys. Lipids*, **4**, 1 (1970).
(14) K. Narasaka, T. Sakashita, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **45**, 3724 (1972).
(15) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
(16) The GLC retention times of a *Z* olefin and its epoxide are typically greater than those of the corresponding *E* isomers.[6,9] The reverse order in the present case is unexplained.

Fungal Extractives. IX.[1a] Synthesis of the Velleral Skeleton[1b] and a Total Synthesis of Pyrovellerolactone

Jan Froborg, Göran Magnusson,* and Svante Thorén

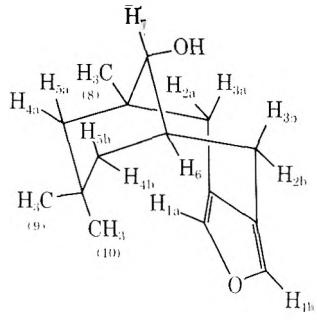
Organic Chemistry 2, Chemical Center, The Lund Institute of Technology, Box 740, S-220 07 Lund 7, Sweden

Received December 17, 1974

A synthetic route to the skeleton of the hydroazulenic sesquiterpene velleral (**1**) (from *Lactarius vellereus* and *L. Pergamenus;* Russulaceae, basidiomycetes) is described. The key intermediate 2,2,4-trimethylfuro[6,7-c]perhydroazulene (**13**) was transformed to the maleic anhydride derivative **18** by anodic oxidation of the furan ring to the corresponding 2,5-dihydroxy-2,5-dihydrofuran **17** followed by Jones oxidation. Two crystalline maleimides (**22** and **23**) were prepared for X-ray analysis by reaction of **18** with *p*-bromoaniline and **13** with *N*-(*p*-bromophenyl)maleimide. A Eu(fod)$_3$-induced chemical shift analysis was used to determine the stereostructure of 1,8,8-trimethylfuro[3,4-c]bicyclo[4.3.1]decan-10-ol (**7**). Hydrogenation of velleral gave a stereoisomer of **13**. A molecular force field calculation was used to determine the most stable conformer of a model precursor to **13**. A total synthesis of pyrovellerolactone (**3**) was accomplished using a new method for the preparation of lactones from furans (electrochemical oxidation followed by hydrolysis).

During the last few years we have reported seven new sesquiterpenes from basidiomycetes of the genus *Lactarius*. Of these, isovelleral[1c] has the same basic skeleton as marasmic acid,[2] which has been the object of synthetic work by other groups;[3,4] lactaral,[5] a 4-substituted furan-3-aldehyde with a previously unknown carbon skeleton, has recently been synthesized by us;[6] the remaining five sesquiterpenes [velleral (**1**),[7] vellerolactone (**2**),[8,9] pyrovellerolactone (**3**),[8,9] and two furan alcohols[10]) have a hydroazulenic skeleton with a *gem*-dimethyl-substituted cyclopentane

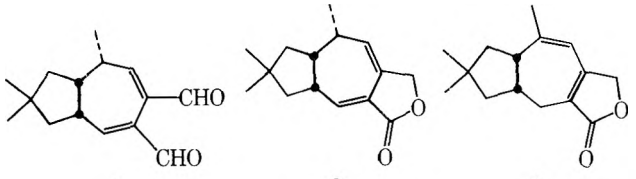
Table I
Eu(fod)$_3$-Induced Proton Chemical Shifts for 7 in Its Most Probable Conformation



Proton no.	Induced shift, Hz: Obsd[a]	Induced shift, Hz: Calcd[17]
1a	22	19
1b	22	20
2a	58	47
2b	48	41
3a	112	109
3b	124	124
4a	20[b]	32
4b	20[b]	36
5a	20[b]	17
5b	20[b]	30
6	90	89
7	240	241
8	69	96
9	18	14
10	12	5

[a] Sample containing 0.115 mol of Eu(fod)$_3$/mol of 7; $CDCl_3$ solution. [b] Average value; no unequivocal assignment could be made for protons 4 and 5.

ring. Three further sesquiterpenes of this type (all of basidiomycete origin) have been reported by other workers.[11-13]



1 velleral; 2 vellerolactone[a]; 3 pyrovellerolactone[a]

[a] We suggest these names for the previously unnamed lactones 2 and 3.

Syntheses of hydroazulenic sesquiterpenes have been concerned mainly with compounds containing guaiane-type skeletons;[14] no synthesis has hitherto been reported of a hydroazulenic compound containing the *gem*-dimethyl-substituted cyclopentane ring of velleral.

We now report an attempted synthesis of velleral, which has given a stereoisomer of a velleral derivative, and a total synthesis of pyrovellerolactone. As a primary synthetic goal we endeavored to prepare a furan derivative such as the velleral derivative **24** since we considered that this would be a suitable precursor to velleral because of the inherent functionality of the furan ring, and moreover the terpenes described in ref 10 and 13 have a furan ring in the same position. The product obtained was in fact the stereoisomer **13**.

The present synthesis (outlined in Scheme I) includes a solvolytic ring-contraction step following the general procedure used by Marshall and Partridge for their synthesis of bulnesol.[15] The synthesis starts with cycloalkylation of the enol acetate **4** with furan **5**, giving the ketone **6** in almost quantitative yield.[16] This compound was reduced with lithium aluminum hydride to give the alcohol **7** as the sole product.

Table II
Product Composition[a] for the Reaction

8 $\xrightarrow{0.5\ M\ \text{RCOONa in RCOOH}}$ 9-12

Compd	R = CH_3	$(CH_3)_3C$	$(CH_3CH_2)_3C$	$(CH_3)_2CH(CH_2)_2CH$
9	25	48	53	43
10	26	20	15	20
11	25	15	15	17
12	24	17	17	20

[a] Determined from NMR integrals (%).

To determine the stereostructure of **7**, a lanthanide-induced chemical shift (LIS) analysis [Eu(fod)$_3$] was performed [LIS vs. amount of Eu(fod)$_3$ added gave almost linear plots for all protons]. However, the local symmetry in the molecule prevented a simple interpretation of the LIS experiment. This problem was circumvented by making a double-resonance experiment on the NMR sample containing the maximum amount of Eu(fod)$_3$. On irradiation of the methylene protons showing the largest LIS (H_2 and H_3 in Table I) there was a significant simplification of the signals in the furan region, indicating coupling. This was not observed on irradiation of H_4 and H_5. Thus the hydroxyl group in **7** should be situated closer to the methylene protons α to the furan ring (H_2 and H_3) than to the other methylene protons in the molecule. To prove the stereostructure of **7** unequivocally, a theoretical calculation was made of the induced chemical shifts for the two possible diastereomers (two conformers of each) using the newly developed LISRIT computer program.[17] The conformer shown in Table I had the best (lowest) agreement factor[18] (8%). The other three conformers could thus be rejected with high statistical significance[19] (>99.5%). The observed and calculated LIS's are shown in Table I for the most probable conformer.

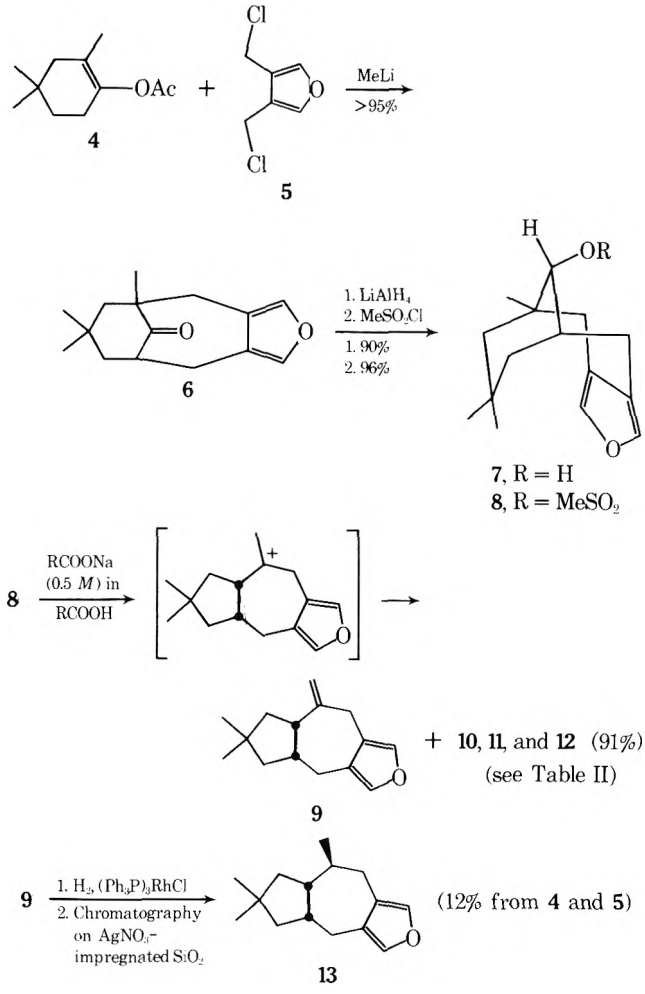
The alcohol **7** was converted to the mesylate **8** with mesyl chloride in pyridine.[15] Solvolytic ring contraction of **8** in a carboxylic acid–sodium carboxylate mixture (for specific details, see Table II) gave a mixture of isomeric furan olefins (**9–12**) presumably via (for **9–11**) the carbenium ion shown in Scheme I. The composition of the olefin mixture could be modified somewhat by choosing as base in the solvolysis step a sodium carboxylate of greater or lesser hindrance, as is shown in Table II. Although not generally appreciated in preparative work, it appears that the base used for removal of a proton from a carbenium ion is not unimportant and should be chosen with care.

In the preliminary planning of the synthesis we assumed that hydrogenation of the olefin mixture **9–11** would give

only a single saturated furan derivative by attack of hydrogen on the less hindered side of the double bonds, and thus would give a compound with the same stereostructure as in velleral (1). The best catalyst reported that allows the furan ring to be retained under hydrogenation conditions is palladium on strontium carbonate.[20] Nevertheless, even with this there was significant attack on the furan ring before complete saturation of the olefinic linkages was achieved and the product was a complex mixture difficult to separate. However, homogeneous phase hydrogenation with tris(triphenylphosphine)chlororhodium[21] as catalyst permitted a selective reduction of the exocyclic methylene of 9 without affecting the furan ring and also left the double bonds of 10, 11, and 12 unreduced. Chromatography on silver nitrate impregnated silica gave a single saturated furan derivative (13) free of olefinic material. To summarize, 13 could be prepared from 4 and 5 in 12% total yield without purification of the intermediates 6–12 (Scheme I).

Compound 13 has a stereostructure different from that of velleral (see Scheme IV, compounds 13 and 24). Catalytic hydrogenation can usually be expected to occur from the less hindered side, which would imply in the present case that the puckered conformation of 9 (cf. Figure 1) is unexpectedly the most stable and thus hydrogen will add on the side trans to the bridgehead hydrogens. To investigate the stabilities of the two conformers of 9, a theoretical calculation of the internal strain energies was performed using the BIGSTRN computer program (molecular force field calculation) described by Andose, Mislow, Engler, and Schleyer.[22,23] Since the program did not accommodate furan ring parameters, the calculation was made on a cyclopentene model compound (Figure 1; the cyclopentene ring was "frozen" in furan geometry). This gave an energy difference of ca. 3 kcal/mol between 14 and 15 (14 with lowest energy), suggesting an equilibrium in solution (strictly

Scheme I



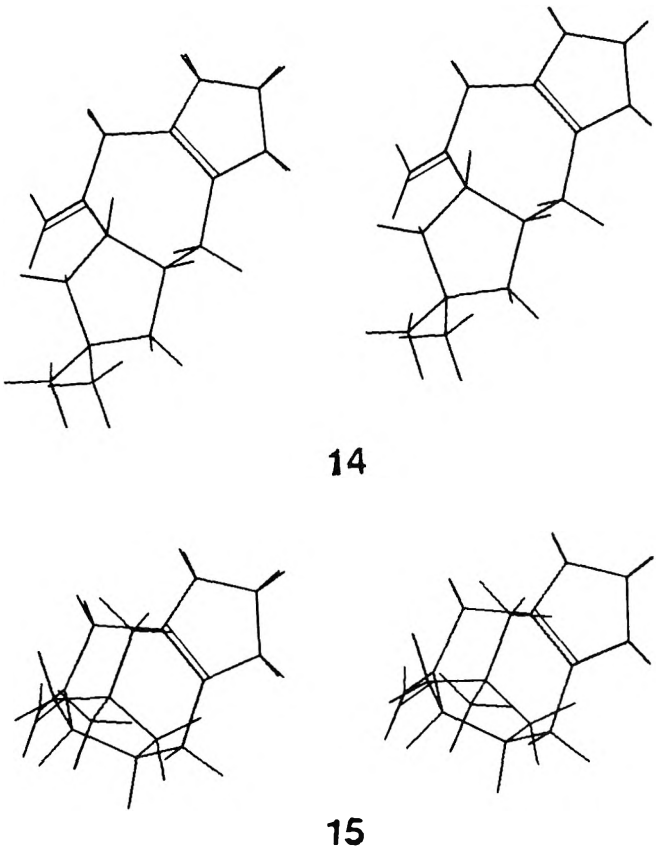
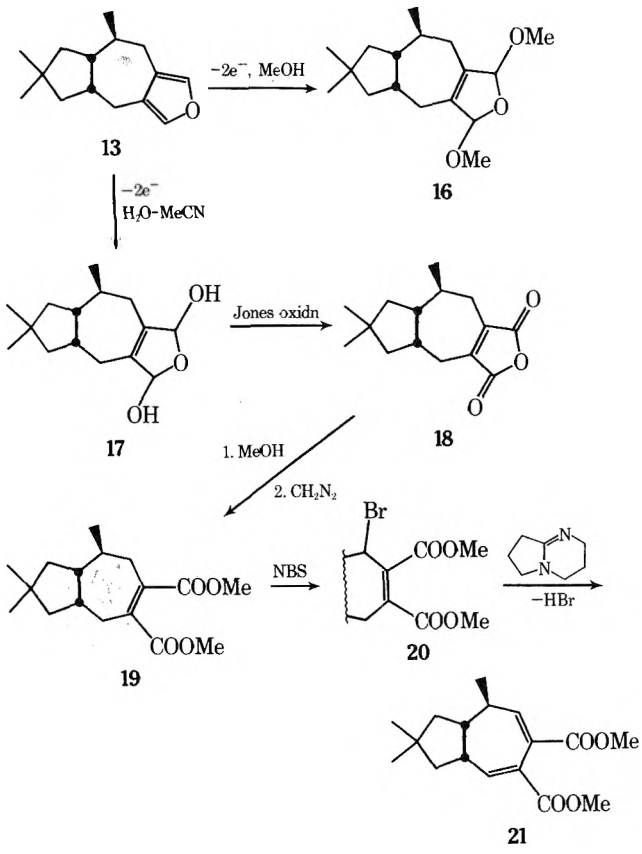


Figure 1. Stereoplots of the planar (14) and puckered (15) conformers of the cyclopentene model of 9.

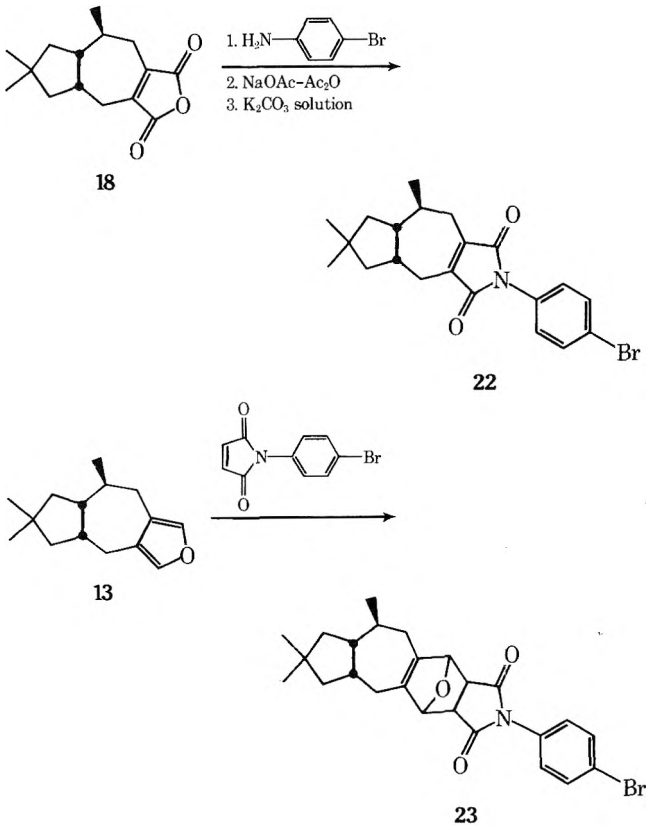
speaking in a gaseous phase) with the planar conformer (14) predominant. Thus it seems that only the minor component of the equilibrium mixture forms an effective substrate–catalyst complex[24] (this conclusion is supported by space-filling models and by the slow hydrogenation). Stereoplots (computer drawn[25]) of 14 and 15 are shown in Figure 1.

It seemed that the diene dialdehyde system of velleral (1) might be best prepared from 13 via a maleic derivative (e.g., dialdehyde or diester) using an allylic bromination–1,4-elimination sequence. The relative instability of maleic dialdehydes[26] made us focus on maleic acid derivatives, which should be accessible from 2,5-dimethoxy-2,5-dihydrofurans (cf. 16) by hydrolysis, followed by oxidation. However, this route gave mixtures containing much polymeric material (discussed in ref 27). We were thus forced to find a new procedure for the preparation of maleic acid derivatives from 3,4-disubstituted furans. Electrochemical oxidation to 2,5-dihydroxy-2,5-dihydrofurans[27] followed by Jones oxidation works well and this was used (Scheme II) for the preparation of anhydride 18 (13 to 18, ca. 80%). Methanolysis of 18 followed by diazomethane treatment gave the maleic diester 19, which could be brominated with *N*-bromosuccinimide, giving a mixture, presumably of the four isomeric monobromo derivatives 20. Treatment of 20 with 1,5-diazabicyclo[4.3.0]non-5-ene[28] gave the diester 21 (tentative structure; NMR two vinyl proton signals with J = 5.6 and 2.8 Hz, no allylic CH_3; uv λ_{max} 208 and 243 nm; no M^+, only $M^+ - 2$; for 25, $M^+ - 2$ = 24% of M^+; for 19, $M^+ - 2$ = 68% and $M^+ - 4$ = 108% of M^+) containing the basic unsaturated system of velleral. Attempts to reduce 21

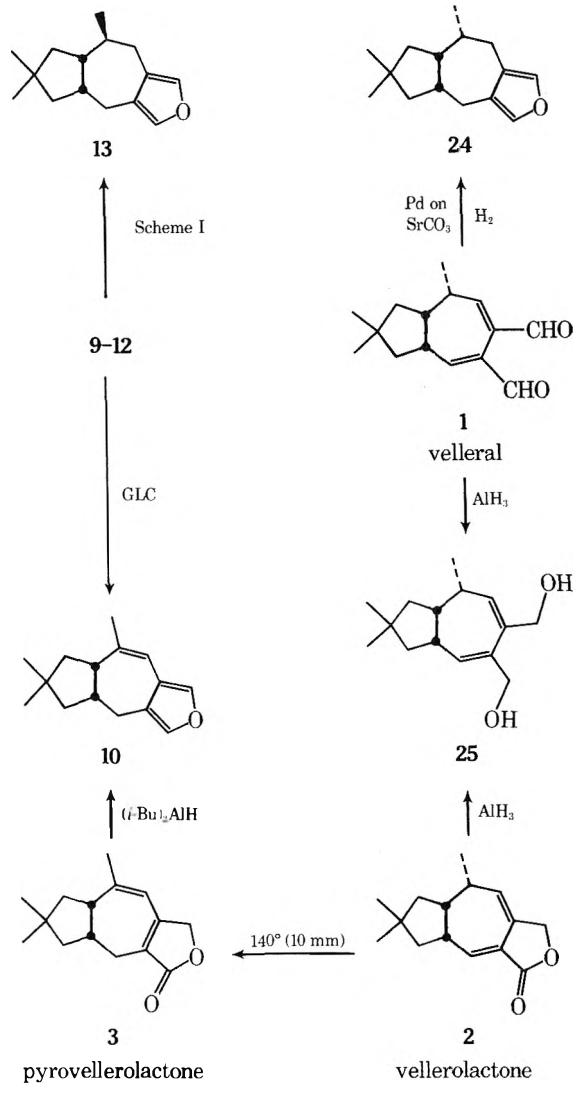
Scheme II



Scheme III



Scheme IV

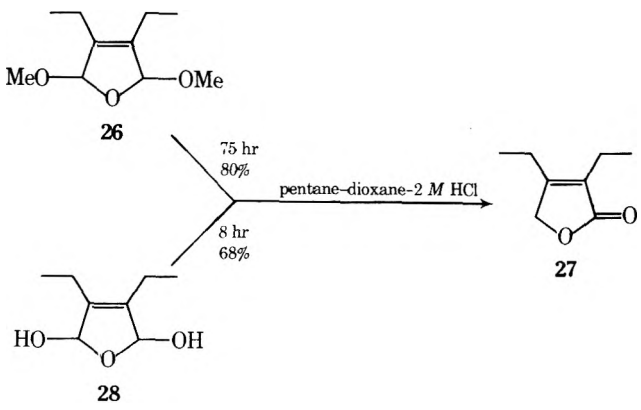


to the velleral dialdehyde system have so far been unsuccessful.

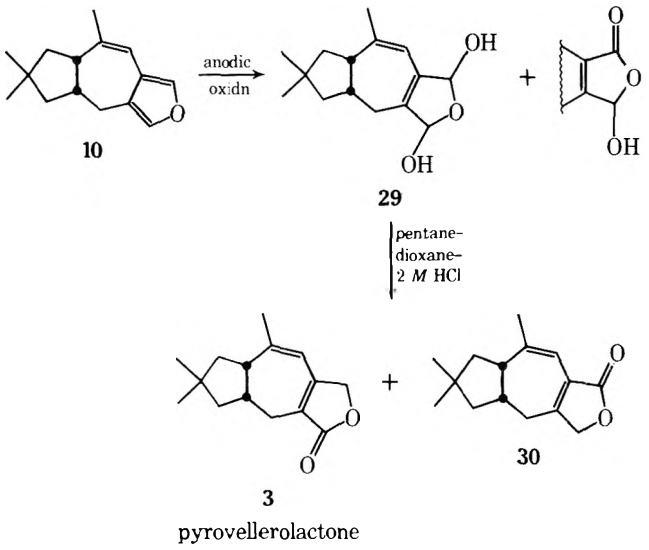
At this stage of the synthesis we succeeded in preparing the furan **24** by hydrogenation of velleral for comparison with furan **13**. Spectroscopic data (ir, NMR) showed small but significant differences, indicating that **13** had instead the stereostructure shown (MS practically identical). Two heavy-atom derivatives (**22** and **23**, Scheme III) were prepared[30,35,36] in order to settle the stereostructure of **13**, and thus of velleral, unequivocally by X-ray analysis.[29] Unfortunately, the crystals were thin leaflets rather unsuitable for single-crystal diffractometry. However, these two reactions offer convenient routes to heavy-atom derivatives of furans (cf. Scheme III) which may be useful elsewhere.

The unreduced mixture of olefins (**10–12** plus traces of **9**; separable by VPC on a 50-m OV-17 capillary column), obtained from the hydrogenation after removal of the dihydro compound **13**, was difficult to separate on a preparative scale. The synthetic component **10** was identical with semisynthetic **10** obtained by diisobutylaluminum hydride reduction (Scheme IV) of pyrovellerolactone (**3**) [same R_f values in VPC, identical mass spectra (VPC–MS) and ^{1}H NMR spectra (most of the signals from **10** were assigned previously in an independent analysis of the NMR spectra of the two olefin mixtures **10** plus **12** and **9–12**)]. The synthetic compounds **10** and **13** must have a cis ring junction because of the mechanism for solvolysis[15] of mesylate **8**. Velleral and vellerolactone have already been shown to have the same stereostructure [AlH_3 reduction to the same diol (**25**)[9]]. Vellerolactone has been transformed to pyrovellerolactone by heating[8] [140° (ca. 10 mm); presumably a 1,5-sigmatropic, suprafacial hydride shift]. These chemical transformations clearly show that velleral, vellerolactone,

Scheme V



Scheme VI



and pyrovellerolactone all have the *gem*-dimethylcyclopentane ring cis fused to the cycloheptadiene system. The difference between **13** and **24** must thus lie in the methyl group stereoarrangement. In velleral and vellerolactone this methyl group has been shown by NMR[7,9] to be trans to the bridgehead protons. It is hoped to obtain further confirmation by X-ray analysis (see above).

Synthesis of Pyrovellerolactone. A convenient method for the preparation of α,β-unsaturated γ-lactones was found during attempts to prepare maleic dialdehydes from 2,5-dimethoxy-2,5-dihydrofurans (cf. **16**). Mild hydrolysis in a two-phase system (pentane–dioxane–2 *M* HCl) was used in order to keep the concentration of the expected dialdehyde low in the acid phase and thereby avoid some side reactions (e.g., polymer formation[27,31]). On testing a model compound (**26**) we found, however, that this gave exclusive formation of the α,β-unsaturated γ-lactone **27** (NMR for crude and distilled material almost identical). Compound **16** gave under the same conditions a good yield (ca. 70%) of lactones. Since the hydrolysis of the methoxy compound was slow (more than 3 days for compound **26**) we tried the same hydrolysis conditions on the 2,5-dihydroxy-2,5-dihydrofuran **28**.[27] This gave lactone **27** after 8 hr reaction time (Scheme V).

Having a method for the conversion of furans into lactones, we saw the possibility of making a total synthesis of (racemic) pyrovellerolactone (**3**) from the unsaturated furan **10**. This was obtained in pure form (optically active) by diisobutylaluminum hydride reduction of pyrovellerolactone (and in mixture with **12** by reverse-phase chromatography with silver fluoroborate eluent[32,33] of the furan mixture **9–12**). Anodic oxidation of **10** (from **3**) according to the method described earlier[27] gave a mixture of the 2,5-dihydroxy-2,5-dihydrofuran **29**, some lactol (presumably by further oxidation of **29**; ir ν 3420, 1740 cm^{-1}) and unreacted furan **10**. Hydrolysis of **29**, followed by chromatography, gave pyrovellerolactone (**3**) and apparently some (ca. 10%) of the isomeric lactone **30** (Scheme VI). The synthetic pyrovellerolactone was shown to be identical with the natural compound (R_f values in VPC and TLC, mass, ir, uv, and NMR spectra).

Experimental Section

NMR spectra were run on Varian T-60 and XL-100 instruments in $CDCl_3$ with Me_4Si as internal standard. Ir spectra were run as liquid films unless otherwise stated. Melting points are uncorrected.

1,8,8-Trimethylfuro[3,4-*c*]bicyclo[4,3,1]decan-10-ol (7). The ketone **6**[16] (28.4 g, 0.12 mol, crude product) in dry ether (500 ml) was added dropwise to a suspension of lithium aluminum hydride (13.7 g, 0.36 mol) in dry ether (700 ml) at 0° with mechanical stirring. After 1 hr, water (27 ml), sodium sulfate (5 g), and sodium hydroxide solution (10%, 22 ml) were added and stirring was continued for 1 hr to granulate the precipitated aluminum salts. Filtration and evaporation gave almost pure alcohol **7** (25.7 g, 90%). Recrystallization from hexane gave an analytical sample: mp 89.5–90.0°; ir (KBr) ν 3440 (OH), 1052, 1030, 873 (furan), 788 cm^{-1}; NMR δ 7.15 (2 H, s, H_{1a}, H_{1b}), 4.40 (1 H, t, broad, J = 6.0 Hz; with D_2O, d, J = 7.0 Hz, H_7), 3.03 (1 H, d, broad, J = 15.0 Hz, H_{3b}), 2.97 (1 H, d, J = 15.0 Hz, H_{3a}), 2.37 (1 H, m, H_6), 2.18 (1 H, d of d, J = 15.0 and 4.5 Hz, H_{2b}), 1.98 (1 H, d, J = 15.0 Hz, H_{2a}), 1.20–2.0 (4 H, m, H_4 and H_5), 1.19 (3 H, s, H_8), 1.09, 0.70 ppm (3 H each, s, H_{10} and H_9) [for proton numbering, see Table I; coupling constants from Eu(fod)$_3$-shifted sample]; mass spectrum *m/e* (rel intensity) 234 (M$^+$, 34, $C_{15}H_{22}O_2$), 216 (100, base peak), 201 (91).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.9; H, 9.5. Found: C, 76.5; H, 9.4.

1,8,8-Trimethylfuro[3,4-*c*]bicyclo[4.3.1]dec-10-yl Mesylate (8). The alcohol **7** (4.52 g, 19.3 mmol, crude product) in dry pyridine (70 ml) was cooled to 0°. Methanesulfonyl chloride (2.50 g, 22 mmol) in dry pyridine (25 ml) was added dropwise with stirring and the ice bath was removed. After 24 hr the reaction mixture was poured onto ice (150 g). Extraction with ether (4 × 75 ml), drying of the ether phase (Na_2SO_4), and evaporation gave almost pure mesylate **8** (5.78 g, 96%, spontaneous crystallization). Recrystallization from hexane gave an analytical sample: mp 104.5–105.5°; ir (KBr) ν 3019 (furan), 1346, 1335, 1170 (sulfonate), 942, 876 (furan), 797 cm^{-1}; NMR δ 7.15 (2 H, m, furan H), 5.47 (1 H, d, J = 7.0 Hz, OCH), 3.07 (3 H, s, SO_3CH_3), 1.22, 1.16, 0.73 ppm (3 H each, s, CCH_3); mass spectrum *m/e* (rel intensity) 312 (M$^+$, 2, $C_{16}H_{24}O_4S$), 216 (37), 201 (29), 86 (64), 84 (100, base peak).

Anal. Calcd for $C_{16}H_{24}O_4S$: C, 61.6; H, 7.7; S, 10.3. Found: C, 61.7; H, 7.7; S, 10.2.

Olefin Mixture (9–12). The mesylate **8** (4.00 g, 12.8 mmol, crude product) was heated in pivalic acid containing sodium pivalate (0.5 *M*, 50 ml) at 150° for ca. 30 min. The reaction was followed by TLC (SiO_2–toluene). The reaction mixture was cooled, made alkaline with sodium hydroxide solution (2 *M*, 350 ml), extracted with ether (3 × 100 ml), dried (Na_2SO_4), and evaporated. This gave (see Table II) the olefin mixture **9–12** (2.53 g, 91%): NMR in accord; mass spectrum *m/e* (rel intensity) 216 (M$^+$, 100, base peak, $C_{15}H_{20}O$), 201 (53).

2,2,4-Trimethylfuro[6,7-*c*]perhydroazulene (13). The olefin mixture **9–12** (3.00 g, 13.9 mmol, crude product) was dissolved in ethanol (100 ml) in a dropping funnel with a pressure equilibration tube. This was mounted on a flask containing tris(triphenylphosphine)chlororhodium[21] (100 mg) in benzene (300 ml). The apparatus was evacuated and refilled with H_2 five times and then saturated with H_2 for 30 min, giving a yellow solution. The olefin solution was added in one lot and hydrogenation was continued until the exocyclic methylene compound **9** was consumed (ca. 30 hr). The other olefins did not react. Evaporation, extraction into hexane, filtration through alumina to remove catalyst, and reevaporation gave a mixture of furan **13** and unreduced olefins (2.8 g). Chromatography on silver nitrate impregnated silica (10%, 25 g, hexane) gave **13** (725 mg, 24%). Distillation gave an analytical sample: bp 71–73° (0.2 mm); n^{22}D 1.5113; ir ν 3150 (furan), 1388, 1371 (*gem*-dimethyl), 1045, 893 (furan), 775 cm^{-1}; NMR δ 7.06 (2 H, m, furan

H), 2.40–2.75 (4 H, m, furan CH_2), 1.05 (3 H, d, J = 7.0 Hz; $CHCH_3$), 0.98, 0.93 ppm (3 H each, s, CCH_3); ^{13}C NMR spectrum was in accord with a single substance of structure **13**; mass spectrum m/e (rel intensity) 218 (M^+, 87, $C_{15}H_{22}O$), 203 (15), 123 (100, base peak), 94 (68).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.5; H, 10.2. Found: C, 82.6; H, 10.1.

Elution of the column with ether gave compounds **10–12** containing traces of unreduced **9**.

2,2,4-Trimethyl(2,5-dimethoxy-2,5-dihydrofuro)[6,7-*c*]perhydroazulene (16). The furan **13** (720 mg, 3.3 mmol) was oxidized electrochemically[34] in methanol (40 ml) with boron trifluoride etherate (0.3 ml) as supporting electrolyte at −20° (Pt anode, Ni cathode, no diaphragm, constant current, 100 mA). After 1.5 times the theoretical reaction time, sodium methoxide in methanol (0.2 *M*, 15 ml) was added and the reaction mixture was evaporated. The residue was partitioned between ether (50 ml) and saturated sodium bicarbonate solution (20 ml) and the water phase was extracted with ether (2 × 15 ml). Drying, evaporation, and distillation gave a mixture of the cis and trans dimethoxydihydrofurans **16** (805 mg, 87%): bp 105–107° (0.2 mm); $n^{25}D$ 1.4892; ir ν 1467, 1388, 1369 (*gem*-dimethyl), 1198, 1100, 990, 957 cm^{-1}; NMR δ 5.64, 5.35 (2 H together, s, CH_3OCH), 3.36 ppm (6 H, s, OCH_3).

Anal. Calcd for $C_{17}H_{28}O_3$: mol wt, 280.2038. Found: mol wt, 280.2040 (M^+).

2,2,4-Trimethyl(2,5-dihydroxy-2,5-dihydrofuro)[6,7-*c*]perhydroazulene (17). The furan **13** (1040 mg, 4.56 mmol) was oxidized electrochemically as described in a previous paper.[27] After the theoretical reaction time (147 min) the reaction mixture was evaporated and the residue was partitioned between water and ether. The water phase was extracted with ether and the extract was dried (Na_2SO_4) and evaporated to give the dihydroxydihydrofuran **17** (1058 mg, 88%): ir ν 3380 (OH), 1387, 1372 (*gem*-dimethyl), 738 cm^{-1}; NMR δ 5.97, 5.86, 5.53, 5.43 ppm (2 H together, s, broad, HOCH).

2,2,4-Trimethyl-4,5-dihydro-1,3,8*H*-azulene-6,7-dicarboxylic Anhydride (18). The dihydroxydihydrofuran **17** (1058 mg, crude product) was dissolved in acetone (40 ml) and cooled with ice. Jones reagent [2.4 ml (10 g of CrO_3, 30 ml of H_2O, and 8.5 ml of concentrated H_2SO_4] was added dropwise with stirring (continued for 30 min). The precipitated chromium salts were filtered off and washed with acetone and the filtrate was evaporated. The residue was partitioned between water and ether, and the water phase was extracted with ether. The ether phases were dried (Na_2SO_4) and evaporated. The residue was dissolved in methylene chloride and treated with molecular sieve (Linde 3A) overnight. Filtration and evaporation gave the crude anhydride **18** (957 mg, 81%). An analytical sample was prepared by distillation [viscous oil which crystallized on cooling; bp 105–108° (0.2 mm); $n^{22}D$ 1.5129; ir ν 1857, 1780 (anhydride), 1385, 1370 (*gem*-dimethyl), 1280, 1260, 898, 730, 719, 707 cm^{-1}] followed by recrystallization from hexane: mp 120–121°; NMR δ 2.20–2.80 (4 H, m, $=CCH_2$), 1.10 (3 H, d, J = 6.0 Hz, $CHCH_3$), 1.01, 0.97 ppm (3 H each, s; CCH_3); mass spectrum m/e (rel intensity) 248 (M^+, 44, $C_{15}H_{20}O_3$), 233 (100, base peak).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.6; H, 8.1. Found: C, 72.4; H, 8.3.

2,2,4-Trimethyl-4,5-dihydro-1,3,8*H*-6,7-bis(methoxycarbonyl)azulene (19). The crude anhydride **18** (700 mg) was refluxed in methanol (15 ml) for 15 hr. Excess diazomethane (ca. 30 mmol) in ether was added to the methanol solution at 0°. After 15 min, acetic acid was added to destroy residual diazomethane. Evaporation gave crude (NMR 75% purity) dimethyl ester **19**. Chromatography on silica (60 g, CH_2Cl_2) gave pure **19** (486 mg, 50% from furan **13**). Distillation gave an analytical sample: bp 114–115° (0.07 mm); $n^{22}D$ 1.4959; ir ν 1735 (C=O), 1660 (C=C), 1387, 1370 cm^{-1} (*gem*-dimethyl); NMR δ 3.77 (6 H, s, OCH_3), 2.00–2.60 (4 H, m, $=CCH_2$). 1.06 (3 H, d, J = 6.0 Hz, $CHCH_3$), 1.00, 0.98 ppm (3 H each, s, CCH_3); mass spectrum m/e (rel intensity) 294 (M^+, 1, $C_{17}H_{26}O_4$), 262 (52), 158 (39), 139 (100, base peak).

Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.4; H, 8.9. Found: C, 69.5; H, 9.1.

Bromo Diester 20. The maleic ester **19** (470 mg) was dissolved in dry carbon tetrachloride (15 ml) and added to *N*-bromosuccinimide (425 mg, recrystallized and dried over P_2O_5) and azoisobutyronitrile (20 mg). The mixture was heated at 80° until the NBS had been consumed (ca. 1 hr). Cooling, removal of precipitated succinimide, and evaporation gave a mixture of brominated products. These were separated by preparative TLC (SiO_2, CH_2Cl_2) into three bands: R_f 0.55, 20 mg (dibrominated product); R_f 0.43, 385 mg (monobrominated product); R_f 0.30, 120 mg (starting material) [NMR (R_f 0.43) δ 4.80–5.45 (1 H, m, BrCH), 3.80 (6 H, s, OCH_3), 1.05, 0.93 ppm (3 H each, s, CCH_3); mass spectra of the three groups of compounds showed the isotopic distribution and fragmentation pattern expected].

2,2,4-Trimethyl-1,3,4*H*-6,7-bis(methoxycarbonyl)azulene (21). The bromo diester **20** (60 mg, 0.16 mmol) was dissolved in dry benzene (2 ml) and cooled with ice. 1,5-Diazabicyclo[4.3.0]non-5-ene[28] (20 mg, 0.16 mmol) in benzene (1 ml) was added dropwise with stirring (N_2). After 5 min (a white precipitate had formed) the reaction mixture was poured onto ice-cold sulfuric acid (2 *M*, 10 ml) and extracted with ether. Drying (Na_2SO_4) and evaporation gave almost pure diene diester **21** as a colorless oil (31 mg, 66%): uv λ_{max} (EtOH) 208 nm (ϵ 23,800), 243 (10,900); ir ν 1735 cm^{-1}; NMR δ 6.94 (1 H, d, broad, J = 5.6 Hz, =CH), 6.67 (1 H, d, broad, J = 2.8 Hz, =CH), 3.77 (6 H, s, OCH_3), 0.92 ppm (6 H, s, CCH_3); mass spectrum m/e (rel intensity) 290 (M^+ − 2, 38), 275 (25), 259 (52), 234 (54), 231 (55), 203 (100, base peak).

2,2,4-Trimethyl-4,5-dihydro-1,3,8*H*-6,7-dicarboximido(4-bromophenyl)azulene (22). The anhydride **18** (160 mg, 0.64 mmol) and *p*-bromoaniline (111 mg, 0.64 mmol) were dissolved in dry ether (10 ml) and stirred at room temperature (15 hr, a white precipitate was formed).[35] The ether was evaporated and the residue was heated (100°, 10 min) with acetic anhydride (10 ml) and sodium acetate (80 mg). The resulting yellow solution was cooled, poured into water, and extracted with ether. Drying (Na_2SO_4), evaporation, and chromatography (SiO_2–CH_2Cl_2) gave a yellow oil (**22** and the corresponding isomaleimide) (172 mg) which was treated with potassium carbonate solution[36] (44%, 15 ml) and dimethoxyethane (3 ml) for 2 hr. Extraction with ether, drying, evaporation, and sublimation (0.1 mm) gave pure **22** (90 mg, 35%): mp 168–169°; ir (KBr) ν 3110, 1780, 1716, 1498, 1385, 1080, 820, 722 cm^{-1}; NMR δ 7.10–7.70 (4 H, m, phenyl H), 2.30–2.60 (4 H, m, $=CCH_2$), 1.10 (3 H, d, J = 7.0 Hz, $CHCH_3$), 1.03, 0.98 ppm (3 H each, s, CCH_3); mass spectrum m/e (rel intensity) 401, 403 (M^+, 100, base peak, $C_{21}H_{24}NO_2Br$), 386, 388 (6), 278, 280 (91), 265, 267 (9). Recrystallization from ethanol gave crystals for X-ray analysis.

Anal. Calcd for $C_{21}H_{24}NO_2Br$: mol wt, 401.0990 and 403.0971. Found: mol wt, 401.0968 and 403.0978 (M^+).

***N*-(*p*-Bromophenyl)maleimide** was prepared by the method described for *N*-phenylmaleimide,[35] yield 70% (crude product). Recrystallization from cyclohexane gave an analytical sample: mp 118–120°; ir (KBr) ν 3100, 1728, 1500, 1408, 1392, 1155, 1070, 833, 710, 687 cm^{-1}; NMR δ 7.10–7.70 (4 H, m, phenyl H), 6.82 ppm (2 H, s, =CH); mass spectrum m/e 251, 253 (M^+, base peak, $C_{10}H_6NO_2Br$).

Diels–Alder Adduct 23. The furan **13** (50 mg, 0.23 mmol) and *N*-(*p*-bromophenyl)maleimide (40 mg, 0.16 mmol) were dissolved in ether (1.5 ml) and left at room temperature for 6 days.[30] A white precipitate (**23**, either or both of the two possible exo forms may be present, zero coupling) was formed which was filtered off and washed with cold ether, yield 55 mg (73%). Recrystallization from ethanol gave an analytical sample: mp 183–184°; ir (KBr) ν 1790, 1720, 1500, 1390, 1190, 1078, 871 cm^{-1}; NMR δ 7.00–7.65 (4 H, m, phenyl H), 5.07 (2 H, s, OCH), 2.94 ppm (2 H, s, COCH); the mass spectrum showed only furan **13** and *N*-(*p*-bromophenyl)maleimide (retro Diels–Alder reaction).

Anal. Calcd for $C_{25}H_{28}BrNO_3$: C, 63.8; H, 6.0. Found: C, 64.1; H, 6.0.

2,2,4-Trimethylfuro[6,7-*c*]perhydroazulene (24). Velleral (**1**, 70 mg) was dissolved in ethyl acetate (3 ml) and palladium on strontium carbonate[20] (3%, 15 mg) was added. Hydrogenation (1 atm, 2 equiv H_2 uptake) followed by column chromatography (SiO_2–hexane) gave the furan **24** (8 mg, 12%): $[\alpha]^{22}D$ + 39.1° (*c* 0.68, $CHCl_3$); ir ν 3150 (furan), 1390, 1375 (*gem*-dimethyl), 1058, 884 (furan), 783 cm^{-1}; NMR δ 7.12 (2 H, m, furan H), 2.30–2.65 (4 H, m, furan CH_2), 1.08, 1.00 ppm (3 H each, s, CCH_3); mass spectrum practically identical with that of furan **13**.

Anal. Calcd for $C_{15}H_{22}O$: mol wt, 218.1671. Found: mol wt, 218.1685 (M^+).

2,2,4-Trimethylfuro[6,7-*c*]-1,3,8*H*-azulene (10). Pyrovellerolactone (**3**, 440 mg, 1.9 mmol) was dissolved in dry ether (25 ml) and cooled with ice (magnetic stirring, N_2 atmosphere). Diisobutylaluminum hydride (2.5 mmol) in ether (2 ml) was added dropwise (syringe). After 60 min (0°) the reaction mixture was added with stirring to ice-cold hydrochloric acid (2 *M*, 10 ml) under nitrogen. The ether phase was washed with sodium bicarbonate solution and water, dried (Na_2SO_4), and evaporated. The residue (450 mg) was chromatographed (SiO_2–CH_2Cl_2), giving the furan **10** (210 mg, 51%): $[\alpha]^{22}D$ − 111.9° (c 0.90, $CHCl_3$); ir ν 3145 (furan), 1390, 1370 (*gem*-dimethyl), 1050, 885 (furan), 780 cm^{-1}; NMR δ 7.05, 7.16 (1 H each, s, broad, furan H), 6.05 (1 H, s, broad, =CH), 2.52 (2 H, s, broad, furan CH_2), 1.84 (3 H, d, J = 1.0 Hz, $=CCH_3$), 1.07,

1.02 ppm (3 H each, s, CCH_3); mass spectrum *m/e* (rel intensity) 216 (M^+, 100, base peak, $C_{15}H_{20}O$), 201 (50), 187 (20), 173 (11), 145 (32), 131 (35).

Conventional column and thin layer chromatography (SiO_2, $AgNO_3$-impregnated SiO_2) of the furan mixture **9–12** (after hydrogenation and isolation of **13**) did not give any separation of the four compounds. However, a reversed phase partition chromatography method (using a $AgBF_4$ solution as eluent) described by Wickberg and Westfelt[32,33] gave partial separation both on thin layer and column chromatography. R_f values (TLC) for the compounds follow: **9**, 0.8; **10** and **12**, 0.33; and **11**, 0.22. Compounds **10** and **12** could thus be isolated free of other material. Compounds **9–12** could be separated by VPC (OV-17, 50-m capillary column, 180°). Attempted preparative VPC (10% Reoplex 400 on Gas-Chrom Q, 60–80 mesh, 160°, 6-m steel column) was unsuccessful owing to aerosol formation and destruction on the column.

3,4-Diethyl-2,5-dimethoxy-2,5-dihydrofuran (26) was prepared from 3,4-diethylfuran[27] by the same method as for the synthesis of **16** (1.2 times the theoretical reaction time): yield 53%; bp 90–93° (11 mm); $n^{22}D$ 1.4462; ir ν 1470, 1200, 1100, 997, 930, 910, 862, 808 cm^{-1}; NMR δ 5.74, 5.45 (2 H, s, MeOC**H**), 3.38 (6 H, s, OCH_3), 2.18 (4 H, q, broad, J = 7.0 Hz, CH_2), 1.05 ppm (6 H, t, J = 7.0 Hz, $CH_2C\mathbf{H}_3$); mass spectrum *m/e* (rel intensity) 186 (M^+, 18, $C_{10}H_{18}O_3$), 155 (100, base peak).

2,3-Diethyl-2-penten-5-olide (27). The 2,5-dimethoxy-2,5-dihydrofuran **26** or the 2,5-dihydroxy-2,5-dihydrofuran **28**[27] (ca. 200 mg) was stirred in pentane–dioxane–2 *M* HCl (20:3:3 ml) for 75 or 8 hr, respectively. Extraction with ether, drying (Na_2SO_4), evaporation, and distillation gave the lactone **27**: yield 80% (from **26**) and 68% (from **28**); bp 51–52° (0.2 mm); $n^{21}D$ 1.4695; ir ν 1756, 1678, 1465 cm^{-1}; NMR δ 4.70 (2 H, s, OCH_2), 2.50 (2 H, q, J = 7.0 Hz, $=CCH_2$), 2.32 (2 H, q, J = 7.0 Hz, $=CCH_2$), 1.17 (3 H, t, J = 7.0 Hz, CH_3), 1.10 ppm (3 H, t, J = 7.0 Hz, CH_3); mass spectrum *m/e* (rel intensity) 140 (M^+, 100, base peak, $C_8H_{12}O_2$), 125 (26), 111 (74).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.6; H, 8.6; mol wt, 140.0836. Found: C, 68.0; H, 8.6; mol wt, 140.0832 (M^+).

Pyrovellerolactone (3).[8,9] The furan **10** (170 mg) was oxidized electrolytically,[27] giving a mixture of the 2,5-dihydroxy-2,5-dihydrofuran **29** with other material as a yellow oil. This was stirred in pentane–dioxane–2 *M* HCl (20:3:3 ml) for 15 hr. Standard work-up and chromatography (SiO_2–CH_2Cl_2) gave pyrovellerolactone (**3**) and some (ca. 10%) of, presumably, an isomer (**30**) in a total yield of 25 mg (14%). Compounds **3** and **30** were separated by VPC (GE SF-96, 50-m capillary column, 220°), **3** showing the same retention time as the natural compound. Identity was further shown by ir, NMR, uv, and mass spectrometry.

Acknowledgments. We thank Professor Börje Wickberg for stimulating discussions, Dr. Christer Svensson for X-ray data, Dr. Peter Stilbs for guidance in computer calculations, Dr. Torbjörn Drakenberg for running numerous NMR spectra, Dr. Sigfrid Svensson for running the high-resolution mass spectra, and Professor Kurt Mislow for making the BIGSTRN computer program available to us. The cost of the Varian XL-100 NMR instrument was defrayed by a grant from the Knut and Alice Wallenberg Foundation. This work was in part supported by the Swedish Natural Science Research Council.

Registry No.—**1**, 50656-61-6; **3**, 51276-29-0; (±)-**3**, 54823-66-4; **6**, 50388-42-6; **7**, 54823-67-5; **8**, 54823-68-6; **9**, 54823-69-7; **10**, 54823-70-0; (±)-**10**, 54823-71-1; **11**, 54823-72-2; **12**, 54823-73-3; **13**, 54823-74-4; **16**, 54823-75-5; **17**, 54823-76-6; **18**, 54823-77-7; **19**, 54823-78-8; **20**, 54823-79-9; **21**, 54823-80-2; **22**, 54823-81-3; **23**, 54823-82-4; **24**, 54868-47-2; **26**, 54823-83-5; **27**, 54823-84-6; **28**, 54823-85-7; **29**, 54823-86-8; methanesulfonyl chloride, 124-63-0; *N*-bromosuccinimide, 128-08-5; *p*-bromoaniline, 106-40-1; *N*-(*p*-bromophenyl)maleimide, 13380-67-1; 3,4-diethylfuran, 53059-82-8.

References and Notes

(1) (a) Part VIII: see ref 10. (b) Presented at 15:e Nordiska Kemistmötet, Tammerfors, Finland, June 1974. (c) G. Magnusson, S. Thorén and B. Wickberg, *Tetrahedron Lett.*, 1105 (1972).
(2) J. J. Dugan, P. de Mayo, M. Nisbet, J. R. Robinson, and M. Anchel, *J. Am. Chem. Soc.*, **88**, 2838 (1966).
(3) D. Helmlinger, P. de Mayo, M. Nye, L. Westfelt, and R. B. Yeats, *Tetrahedron Lett.*, 349 (1970).
(4) S. R. Wilson and R. B. Turner, *J. Org. Chem.*, **38**, 2870 (1973).
(5) G. Magnusson and S. Thorén, *Tetrahedron*, **30**, 1431 (1974).
(6) J. Froborg, G. Magnusson and S. Thorén, *Acta Chem. Scand, Ser. B*, **28**, 265 (1974).
(7) G. Magnusson, S. Thorén, and T. Drakenberg, *Tetrahedron*, **29**, 1621 (1973).
(8) G. Magnusson and S. Thorén, *Acta Chem. Scand.*, **27**, 1573 (1973).
(9) G. Magnusson and S. Thorén, *Acta Chem. Scand.*, **27**, 2396 (1973).
(10) G. Magnusson, S. Thorén, J. Dahmén, and K. Leander, *Acta Chem. Scand., Ser. B*, **28**, 841 (1974).
(11) W. M. Daniewski and M. Kocòr, *Bull. Acad. Pol. Sci., Ser. Chim.*, **19**, 553 (1971).
(12) W. M. Daniewski, B. Zóltowska, and M. Kocòr, *Bull. Acad. Pol. Sci., Ser. Chim.*, **21**, 785 (1973).
(13) S. Nozoe, H. Matsumoto, and S. Urano, *Tetrahedron Lett.*, 3125 (1971).
(14) C. H. Heathcock in J. ApSimon, Ed., "The Total Synthesis of Natural Products", Vol. 2, Wiley-Interscience, New York, N.Y., 1974. For a fuller account of syntheses of nonbridged hydroazulenes, see also G. Magnusson, Dissertation, Lund, Sweden, 1975.
(15) J. A. Marshall and J. J. Partridge, *Tetrahedron*, **25**, 2159 (1969).
(16) J. Froborg, G. Magnusson, and S. Thorén, *J. Org. Chem.*, **39**, 848 (1974).
(17) P. Stilbs, *Chem. Scr.*, **7**, 59 (1975).
(18) R. E. Davis and M. R. Willcott, III, *J. Am. Chem. Soc.*, **94**, 1744 (1972).
(19) W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).
(20) R. J. Rallings and J. C. Smith, *J. Chem. Soc.*, 618 (1953).
(21) J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1711 (1966).
(22) E. M. Engler, J. D. Andose, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **95**, 8005 (1973).
(23) J. D. Andose and K. Mislow, *J. Am. Chem. Soc.*, **96**, 2168 (1974).
(24) F. H. Jardine, J. A. Osborn, and G. Wilkinson, *J. Chem. Soc. A*, 1574 (1967).
(25) Program written by P. Stilbs, Physical Chemistry 2, Chemical Center, Lund, Sweden.
(26) D. L. Hufford, D. S. Tarbell, and T. R. Koszalka, *J. Am. Chem. Soc.*, **74**, 3014 (1952).
(27) J. Froborg, G. Magnusson, and S. Thorén, *J. Org. Chem.*, **40**, 122 (1975).
(28) H. Oediger, F. Möller, and K. Eiter, *Synthesis*, 591 (1972).
(29) X-Ray work was performed by Dr. Christer Svensson, Inorganic Chemistry 2, Chemical Center, Lund, Sweden.
(30) H. Kwart and I. Burchuk, *J. Am. Chem. Soc.*, **74**, 3094 (1952).
(31) J. A. Hirsch and A. J. Szur, *J. Heterocycl. Chem.*, **9**, 523 (1972).
(32) B. Wickberg, *J. Org. Chem.*, **27**, 4652 (1962).
(33) L. Westfelt and B. Wickberg, *Ark. Kemi*, **26**, 545 (1967).
(34) N. Elming, *Adv. Org. Chem.* **2**, 67 (1960).
(35) M. P. Cava, A. A. Deana, K. Muth, and M. J. Mitchell, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 944.
(36) R. Pummerer and G. Dorfmüller, *Ber.*, **45**, 292 (1912).

Synthesis of (−)-Acorone and Related Spirocyclic Sesquiterpenes[1]

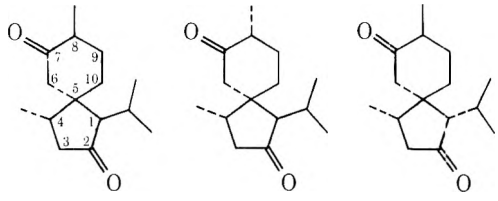
John N. Marx* and Lewis R. Norman[2]

Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

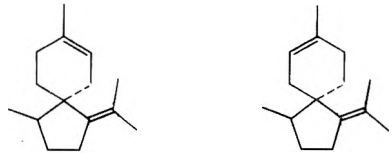
Received November 26, 1974

Total syntheses for four acorane sesquiterpenes, β-acoradiene (4), δ-acoradiene (5), and the enantiomers (27 and 28) of acorone (1) and isoacorone (2), are described. The synthetic route involves conversion of (*R*)-pulegone (11) into 3-methyl-2-carbethoxycyclopentanone (8) by improvement of literature procedures, then conversion of this into (*R*)-3-methyl-2-methylenecyclopentanone (17) by the sequence ketalization, reduction, deketalization, and dehydration. A Diels–Alder reaction between 17 and isoprene gave four adducts 18–21. The para:meta ratio in this reaction was improved from 2:1 to 24:1 by the use of $SnCl_4$ catalysis, which gave a ratio of products of 69:27:3:1. Structures were assigned to the various isomers on the basis of the known steric and electronic requirements in the Diels–Alder reaction. The major ketones 18 and 19 were purified by preparative high-pressure liquid chromatography. Treatment of 18 with isopropyllithium and then $SOCl_2$ gave γ-acoradiene (4) and its endocyclic isomer 23, whereas 19 led to δ-acoradiene (5) and its isomer 25. Hydroboration of 25 followed by Jones oxidation gave an equilibrium mixture of (−)-acorone (27), the enantiomer of natural acorone (1), and (+)-isoacorone (28), the enantiomer of natural isoacorone (2).

Acorone (1), isolated from the oil of Sweet Flag, *Acorus calamus L.*, is the best known member of a small group of spirocyclic sesquiterpenes having the acorane skeleton.[3] Other members include isoacorone (2), cryptoacorone (3), and acorenone from the same source,[3] as well as acorenone B from *Bothriochoa intermedia*,[4] two unnamed dienes from *Vetiveria zizanoides*,[5] and α-acorenol, β-acorenol, α-acoradiene, β-acoradiene, γ-acoradiene (4), and δ-acoradiene (5) from *Juniperus rigida*.[5] α-Alaskene, isolated from alaska cedar, *Chamecyparis nootkatensis*, was shown to be identical with γ-acoradiene, but β-alaskene from the same source was shown to be enantiomeric to δ-acoradiene.[6]



1 2 3



4 5

The absolute stereochemistry of acorone was assigned on the basis of ORD studies and X-ray of a derivative,[8] whereas that of γ-acoradiene follows[6,7] from its acid-catalyzed cyclization to α-edrene, whose absolute stereochemistry has been determined independently. Stereochemical assignments of other compounds in the series rest on chemical interconversions and on an X-ray study of acorenone B.

Successful syntheses of several members of the acorane class have been reported recently. An intermediate in a biogenetic-like synthesis of racemic α-cedrene by Crandall and Lawton[9] has the structure later assigned to α-acorenol.[6] A total synthesis of an unnamed diene by Kaiser and Naegeli[5] was reported as part of its structure proof. Total synthesis of optically active α-acorenol and β-acorenol has been accomplished.[10] Several other types of synthetic entries into this class have been reported,[11–13] though some[12,13] have not led to any natural products. Pinder's[12] attempted synthesis of acorone failed only at the penultimate step.

We report here full details of formal total syntheses of optically active β-acoradiene (4) and δ-acoradiene (5),[1] as well as syntheses of the enantiomeric forms of acorone (1) and isoacorone (2) from the same precursors. Since the acoradienes have the opposite absolute stereochemistry from the acorones, using the C-4 methyl as the point of reference, both natural series cannot be derived from the same precursors. The present synthesis uses a Diels–Alder reaction as the key step to generate the spirocyclic center and to establish the relative stereochemistry at C-4 and C-5. Since our starting material is pulegone (11), with absolute stereochemistry at the methyl known to be *R*,[14] the synthesis also establishes the absolute stereochemistry at C-4 and C-5 and collaborates the previous stereochemical assignments for both the acoradienes and the acorones.

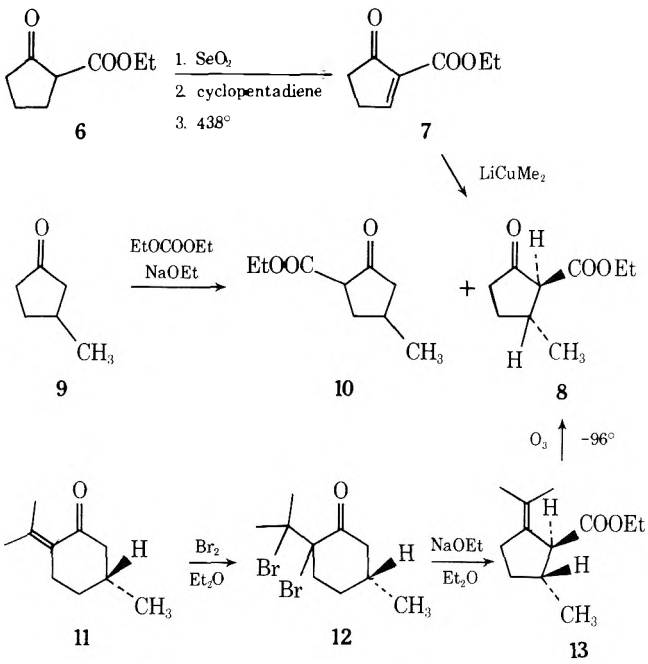
The starting material chosen was 3-methyl-2-carbethoxycyclopentanone (8). Although the compound has been synthesized from pulegone (11),[15] the overall reported yield was ca. 5% and some rather difficult separations were required; so we initially turned to other potential routes to the compound.

Selenium dioxide oxidation of 2-carbethoxycyclopentanone (see Chart I) gave up to 50% yields of 2-carbethoxycyclopent-2-enone (7).[16] However, evidently because of the great polarity of the chromophore in the molecule, it polymerized too rapidly for purification, and so was purified by trapping as a mixture of Diels–Alder adducts with cyclopentadiene and regenerating by pyrolysis.[16] The pure compound, which is also a potentially valuable intermediate for other syntheses, reacted smoothly with lithium dimethylcopper at −80° to give racemic 3-methyl-2-carbethoxycyclopentanone (8). However, this route to 8 was judged impractical for its use as starting material in a total synthesis.

Another approach investigated briefly was to condense 3-methylcyclopentanone (9) with diethyl carbonate. This gave, as expected, both 8 and 10 in the ratio 40:60.[16] While the two could be separated by VPC, no method applicable to large-scale work could be found for this separation.

We then turned to improving the yield of 8 from pulegone (11). Bromination of pulegone at −10° in ether gave mostly the dibromide 12, although the product was always contaminated with some unreacted pulegone and doubtlessly products of further bromination. The crude product was added to NaOEt in ether at 25°, giving, after simple distillation, a mixture of 85% ethyl pulegenate (13) and 15% unreacted pulegone. Wolinsky[17] reports similar yields, following a very careful distillation. In our hands, spinning band distillation was unsatisfactory for the separation, but

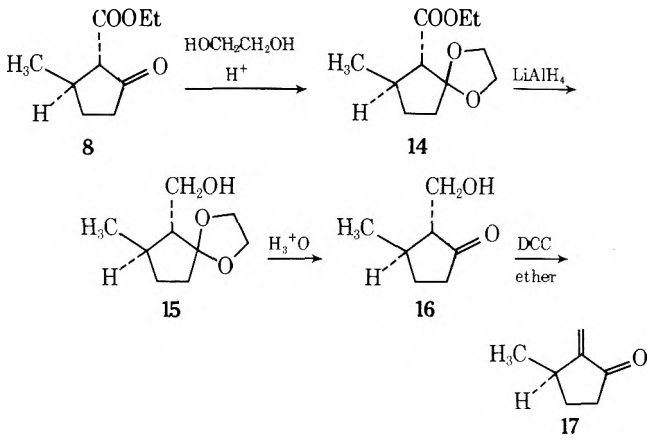
Chart I



selectively converting pulegone into its semicarbazone and extraction with pentane gave ethyl pulegenate (**13**) with no detectable impurities. Ozonolysis at −90° in ethyl acetate then gave the desired 3-methyl-2-carbethoxycyclopentanone (**8**) in 85% yield. The overall yield from pulegone was 57%.

3-Methyl-2-carbethoxycyclopentanone was converted into its ethylene ketal **14** (Chart II) by standard procedures

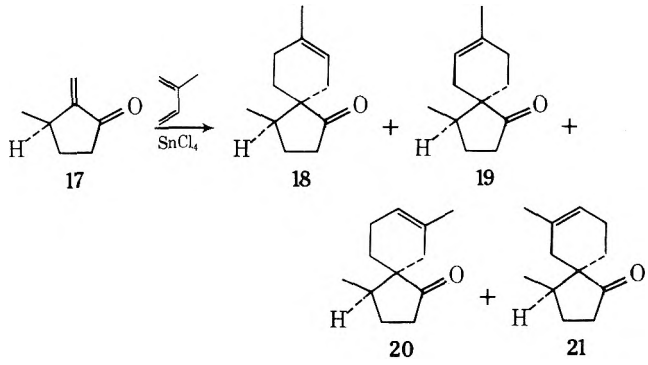
Chart II



(87%). This compound was then reduced smoothly by $LiAlH_4$ to the corresponding alcohol **15** (86%). The ketal group could then be removed by treatment of **15** with 3 *N* HCl for 2 min at 25° to give the keto alcohol **16** (96%). Dehydration of this with dicyclohexylcarbodiimide (DCC)[18] gave the rather easily polymerized (*R*)-3-methyl-2-methylenecyclopentanone (**17**, 67%). Other reaction sequences to convert **15** into **17**, including combined deketalization and dehydration by acid and elimination sequences on the derived tosylate, all gave very low yields of **17** because of polymerization which occurred under the acidic or basic conditions used.

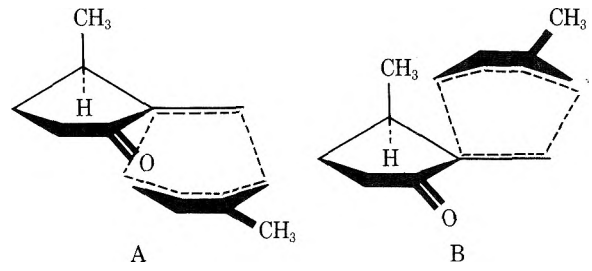
Heating **17** and an excess of isoprene in a sealed tube at 100° for 1 hr gave a mixture of four adducts in a 45:25:20:10 ratio. These are assigned the structures **18**, **19**, **20**, and **21** (Chart III), respectively, on the basis of the following considerations.

Chart III



When the reaction was run in the presence of 0.2 equiv of $SnCl_4$, the reaction proceeded at room temperature and the same four products were found in a ratio of 69:27:3:1. Thus, the first two products must be products of "para" orientation in the addition of isoprene to **17** and the last two must be products of "meta" orientation, since such orientation is controlled by electronic factors, with "para" orientation favored,[19] and Lewis acid catalysis increases this selectivity.[20-22] In the present case, the ratio of "para" to "meta" products was enhanced from 2:1 to 24:1 by the use of the $SnCl_4$.

Consideration of the transition states A and B for the Diels–Alder reaction which determine the stereochemistry

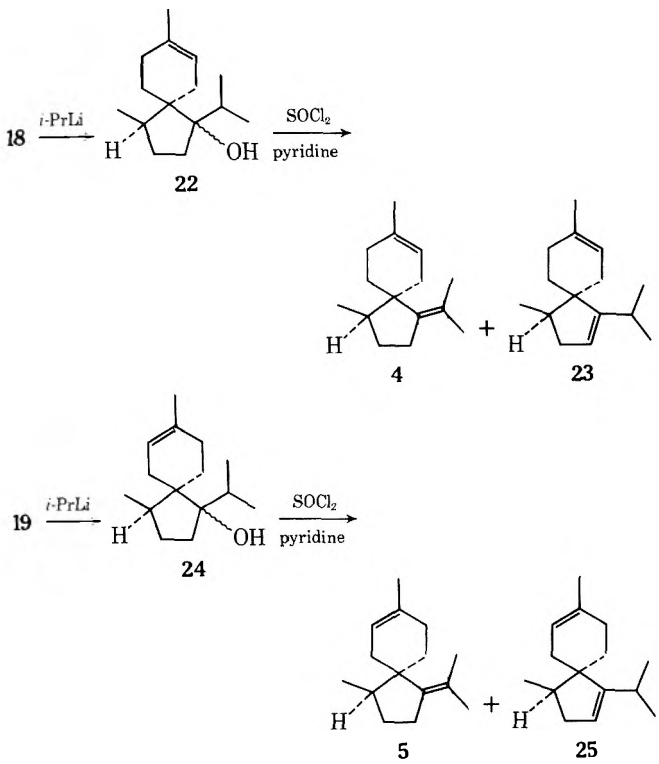


found in the two major isomers reveals that the enone chromatophore and cyclopentane ring of **17** are essentially planar, with only the methyl group partially blocking one face. Since the orientation in the Diels-Alder reaction is well known to be strongly influenced by steric effects,[19] one can predict with confidence that transition state A, in which the isoprene attacks on the opposite fact from the methyl group, would be favored. This would lead to the *S* absolute configuration at the spiro center (C-5), giving rise to **18**, which has the stereochemistry postulated for γ-acoradiene. The lesser major product must be **19**, derived from transition state B, and thus have the *R* configuration at that center, the same as in δ-acoradiene.

The ketones **18**–**21** were only partially separated by VPC under any conditions tried, but were well separated by preparative high-pressure liquid chromatography (0.375 in. × 4 ft Corasil C-18 column, 77% H_2O and 23% acetone). The major product, **18**, was then treated with isopropyllithium in ether (Chart IV). This process gave a 1:1 mixture of recovered ketone **18** and the tertiary alcohol **22**, presumably as a mixture of stereoisomers. The unreacted ketone was shown to result from competing enolization (gas evolution, deuterium incorporation on quenching with D_2O).

Dehydration of the alcohol **22** with thionyl chloride in pyridine gave a mixture of two dienes in a 72:28 ratio. These were readily separated by preparative VPC (40 ft × 0.125 in. SE-30 at 172°). The major product had spectral properties consistent with the endocyclic isomer **23**, whereas the lesser one, $[\alpha]_D$ −82°, was identical by VPC and all

Chart IV



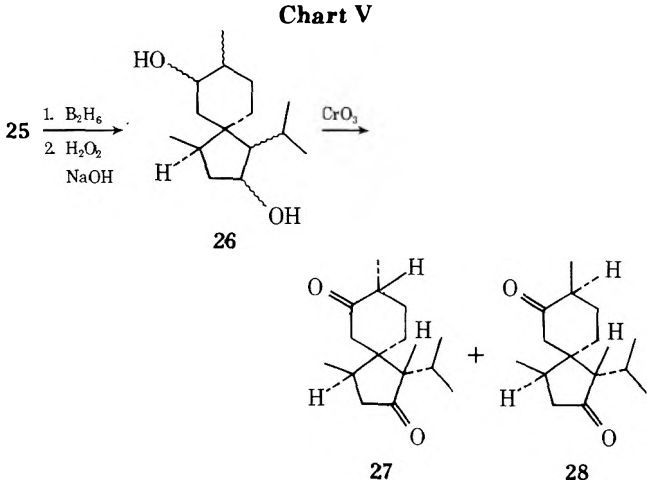
spectral comparisons (MS, NMR, ir) with an authentic sample of α-alaskene[23] [identical with γ-acoradiene (4)] (lit.[6] [α]D −66°,[6] −88° [7]), and was cyclized to α-cedrene with formic acid as reported.[6,7]

In like manner, ketone **19** was treated with isopropyllithium and the resulting alcohol **24** dehydrated to a 70:30 mixture of the endocyclic diene **25** and the exocyclic isomer, [α]D +14°, which was found to be identical by all criteria (except sign of its optical rotation) with an authentic sample of β-alaskene[23] and its rotation matches that reported[6] ([α]D +16°) for its enantiomer, δ-acoradiene. This completes the synthesis of these two natural products[1] and confirms their relative and absolute stereochemistry.

When the above dehydration of the tertiary alcohols **22** or **24** was carried out with $POCl_3$ in pyridine, more vigorous conditions were necessary, and only the endocyclic dienes **23** or **25** were formed. Attempts to convert either **18** or **19** directly into the natural exocyclic dienes **4** or **5** via a Wittig reaction gave back only the starting ketones, even under very forcing conditions.

Hydroboration–oxidation of the endocyclic diene **25** gave a mixture of alcohols **26** (Chart V), which was oxidized with

Chart V



chromic acid (Jones reagent) to a ca. 1:1 mixture of two diketones. This ratio was changed to 70:30 when the mixture was subjected to epimerization conditions with sodium methoxide.

Since the stereochemistry at C-4 and C-5 has been assigned in **25** on the basis of the Diels–Alder reaction and since the stereochemistry adjacent to the ketones is controlled by thermodynamic considerations, these two products can be assigned structures **27** and **28**, respectively. These formulas represent the enantiomers of natural acorone (**1**) and isoacorone (**2**), respectively.[3] The equilibrium mixture of acorone–isoacorone is reported[3] to be 70:30.

The two diketones were separated very cleanly by preparative liquid chromatography (Porasil T, 0.125 in. × 2 ft, 10% $CHCl_3$–90% hexane). The major one, [α]D −133°, mp 96.0–97.5°, was identical in all respects except sign of optical rotation with an authentic sample[23] of natural (+)-acorone [mp 96.0–97.5° (lit.[3] [α]D + 139°, mp 98.5–99°)]. The minor one, [α]D +90°, mp 94.0–95.5°, was identical in all respects except sign of optical rotation with an authentic sample[23] of natural (−)-isoacorone [mp 94.0–95.5° (lit.[3] [α]D −92°, mp 97.0–98.0°)]. Since the optical rotations have the expected opposite signs from the natural products, the stereochemical reasoning given above shows that the relative and absolute stereochemistry assigned to acorone and isoacorone is confirmed.

Experimental Section

General. All routine NMR spectra were run on a Varian A-60 spectrometer in 25–50% CCl_4 solutions unless otherwise stated. NMR spectra of small samples or for higher resolution were run on a Varian XL-100 as 10% deuteriochloroform solutions. All NMR chemical shifts are reported in δ units downfield from internal reference Me_4Si. Infrared spectra were obtained with a Perkin-Elmer Model 457 in CCl_4 solution or as a thin film. All melting points are uncorrected and were determined after at least one recrystallization and drying at 0.1 Torr. Melting points were obtained in open capillaries for abundant samples on a Laboratory Device's Mel-Temp or with an Arthur H. Thomas Hot-Stage apparatus for smaller quantities.

Thin layer chromatography was done on silica gel using Eastman Chromagram sheets 6060 with fluorescent indicator and were visualized with I_2 vapors or a short-wave ultraviolet lamp. Silica gel, 60–200 mesh, high purity, from W. H. Curtin and Co. was used for all column chromatography. Columns were packed as a slurry using the first eluting solvent as the packing solvent. High-pressure liquid chromatography was done with a Waters Associates ALC-100 liquid chromatograph. Either a Beckman GC-45 or Aerograph Hy-Fi 600-C was used for analytical gas chromatography with helium flow rates of 20 ml min^{-1}. A Varian Aerograph 1520 was used for preparative gas chromatography with helium flow rates of 120 ml min^{-1}. All preparative GLC samples were collected manually.

Optical rotations were determined with a Perkin-Elmer 141 polarimeter using the sodium D line and several other wavelengths from a built-in Hg lamp. The cell path length was 1.00 dm and the concentrations used gave experimental values of 0.1–5.0°.

Elemental analyses were done commercially by Chemalytics, Inc., Tempe, Ariz.

Ethyl 5-Isopropyl-2-methylcyclopentanecarboxylate (Ethyl Pulegenate, 13). The following is an improvement of the method described by Yates.[15] To a 2-l. round-bottom flask was added 152.23 g (1.00 mol) of pulegone, 25 g of anhydrous powdered $NaHCO_3$, and 1 l. of anhydrous reagent-grade ether. The mixture was cooled and stirred under N_2 in an ice–salt bath; then 159 g (1.00 mol) of Br_2 was added dropwise over a 30-min period. The mixture was then filtered and added to a cooled EtOH–NaOEt mixture which had been prepared from refluxing 50.6 g (2.2 mol) of Na in 1 l. of dry [$Mg(OEt)_2$] ethanol. This mixture was cooled in ice and the solid NaOEt cake was slowly broken up with a spatula, causing an exothermic reaction. All refluxing subsided after 1 hr. The mixture was stirred overnight, then 2 l. of 5% aqueous HCl and 0.5 l. of ether was added. The aqueous layer was reextracted with ether and the combined extracts were washed and dried, giving 189.4 g of brown oil, which was shown to consist of 85% ethyl

pulegenate and 15% pulegone by GLC (0.125 in. × 3 ft, 3.8% SE-30 at 110°). This oil was added to a warm solution containing 75 g of semicarbazide hydrochloride, 75 g of NaOAc, and 600 ml of H_2O; then enough boiling ethanol (600 ml) was added to give a clear solution. After refluxing for 2.5 hr and then stirring at 25° overnight, the mixture was treated with 2 l. of H_2O and 0.5 l. of petroleum ether. The water layer was extracted twice with 250-ml portions of petroleum ether, the combined extracts were washed and dried, and the solvent was removed, yielding a brown oil. Distillation gave pure (99+% by GLC) ethyl pulegenate, 131.6 g (67%), bp 83–85° (1.0 mm). All physical and spectral properties were in complete accord with those reported by Yates.[15]

2-Carbethoxy-3-methylcyclopentanone (8) by Ozonolysis of 13. Ethyl pulegenate (24.0 g, 0.123 mol) was dissolved in 100 ml of reagent ethyl acetate and cooled to −90° with isopropyl alcohol–liquid nitrogen. Ozonized oxygen (about 0.4 mmol of O_3/min as determined by bubbling into KI solution and titrating liberated KI with thiosulfate solution) was bubbled through this solution, with periodic addition of liquid nitrogen to maintain the cooling bath. The ethyl acetate was then removed at reduced pressure, and the resultant greenish, glassy ozonide mixture was dissolved in 150 ml of glacial acetic acid. The solution was cooled in ice, 45 g of powdered zinc was added, and the solution was stirred for 30 min and then filtered. Neutralizing the acetic acid of this solution with aqueous sodium bicarbonate, ether extraction, drying, solvent removal, and distilling gave 18.55 g (85%) of clear oil, bp 72–74° (0.1 mm), which was 100% pure by GC analysis. The ir and NMR spectra are in complete accord with those of the corresponding product prepared from $Li(CH_3)_2Cu$ and **7**.[16] The optical rotation was $[\alpha]^{25}D$ +66.9° (lit. +78° for the methyl ester[24]) and semicarbazone mp 124–128° (EtOH–H_2O). Anal. Calcd for $C_{10}H_{17}N_3O_3$: C, 52.85; H, 7.54. Found: C, 52.91; H, 7.67.

Ethylene Ketal of 2-Carbethoxy-3-methylcyclopentanone (14). A mixture of 18.80 g (0.11 mol) of 2-carbethoxy-3-methylcyclopentanone (**8**) 150 ml of reagent benzene, and about 25 mg of *p*-toluenesulfonic acid was treated with 20 ml of ethylene glycol and refluxed for 6 hr into a Dean-Stark trap, then for 3 hr into a large Soxhlet extractor filled with anhydrous $MgSO_4$. The solution was then cooled, 100 ml of ether was added, and the solution was washed with saturated brine. Drying, solvent removal, and distilling gave 20.68 g (87%) of clear, colorless oil: bp 84–87° (1.0 mm); NMR 1.03 (d, J = 6 Hz, 3 H), 1.15 (t, J = 7 Hz, 3 H), 1.6–2.1 (m, 4 H), 2.3–2.6 (m, 2 H), 3.84 (m, 4 H, $-OCH_2CH_2O-$), 4.11 ppm (q, J = 7 Hz, 2 H); ir (film) 1752 (C=O, ketone), 1721 cm^{-1} (C=O, ester). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.96; H, 8.53.

Ethylene Ketal of 2-Hydroxymethyl-3-methylcyclopentanone (15). A mixture containing 200 ml of dry ether and 4.55 g of $LiAlH_4$ was treated, dropwise, with 50 ml of an ether solution containing 34.5 g (0.16 mol) of **14**. After stirring at 25° for 30 min, the mixture was treated, carefully, with 0.42 ml of H_2O, then 0.42 ml of 15% NaOH, and then 1.5 ml of H_2O, then filtered, and the solvent was removed. Distillation gave 23.76 g (86%) of **15** as a colorless oil: bp 60–63° (0.1 mm); $[\alpha]^{25}D$ −14.8°; NMR 1.04 (d, 3 H, $-CH_3$), 1.66 (m, 6 H, ring H), 2.74 (t, J = 6 Hz, 1 H, OH), 3.57 (d of d, J = 6 and 3 Hz, 2 H, $-CH_2OH$), 3.87 ppm (s, 4 H, $-OCH_2CH_2O-$); ir 3440 (m, OH), 2960 and 2880 cm^{-1} (s, CH). Numerous attempts to make a crystalline derivative failed. High-resolution mass spectrum: calcd for $C_9H_{16}O_3$, 172.1099; found, 172.1101. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.55; H, 9.79.

2-Hydroxymethyl-3-methylcyclopentanone (16). To 11.16 g (64 mmol) of ketal alcohol **15** was added 111 ml of 3 *N* HCl and the homogeneous solution was stirred for 2.0 min (±5 sec), then quenched by pouring into 200 ml of saturated brine. Quickly extracting twice with chloroform, drying the combined extracts, and removal of the solvent gave 8.13 g (98%) of **16**: NMR 1.17 (d, J = 6 Hz, 3 H, $-CH_3$), 1.4–2.4 (complex absorption, 6 H), 3.40 (s, 1 H, OH), 3.72 ppm (d of d, J = 5 and 3 Hz, 2 H, $-CH_2OH$); ir 3460 (br, OH), 2965, 2940, 2880 (m, CH), 1735 cm^{-1} (s, C=O). No solid derivatives could be obtained from this compound.

3-Methyl-2-methylencyclopentanone (17). The following method was adapted from a similar one given by Alexandre and Rouessac.[18] A dry ($LiAlH_4$) 70-ml ether solution of **16** (8.13 g, 63 mmol) was treated with 19.7 g of dicyclohexylcarbodiimide (DCC) and 50 mg of Cu_2Cl_2. After refluxing for 2.2 hr, the solid precipitate of dicyclohexylurea was removed by filtration and the filtrate was evaporated at the aspirator. The resulting oily, green residue was rapidly distilled by heating the distillation pot with a hot air gun, and the distillate receiver was cooled in a Dry Ice–acetone bath, giving 4.68 g (67%) of **17** as a clear, colorless, pungent-smelling oil: bp 33–34° (0.1 mm); NMR 1.15 (d, 3 H), 1.8–2.8 (complex absorption, 5 H), 4.89 (d of d, J = 1 and 3 Hz, 1 H), 5.58 ppm (d of d, J = 1 and 3 Hz, 1 H); ir (film) 2980 (m, CH), 1732 (s, C=O), 1641 cm^{-1} (m, C=C); $[\alpha]^{25}D$ 53.5° (213 mg ml^{-1} in EtOH). This material could be stored without polymerization in dilute ether solution at −10°. The semicarbazide adduct (probably not a simple semicarbazone, but this was not investigated because of its insolubility in NMR solvents) had mp 177.5–179° (MeOH). Anal. Calcd for $C_8H_{13}N_3O$: C, 57.46; H, 7.80. Found: C, 57.79; H, 8.06.

4,8-Dimethylspiro[4.5]dec-8-en-1-one, Isomers 18, 19, 20, and 21. Diels–Alder Reactions of 17 and Isoprene. Distilled, dried ($MgSO_4$) isoprene (2 ml) was added to 245 mg (2.22 mmol) of 3-methyl-2-methylenecyclopentanone (**17**) in a 20-mm Pyrex tube, which was cooled to −78° and sealed. After heating to 105° for 1.0 hr, the tube was cooled (−78°) and opened, and the contents were chromatographed on silica gel, eluted with 90% petroleum ether–10% ether. All materials eluting with this solvent system were combined (the solvent was removed) and distilled through a short path at 0.1 mm, yield 161 mg (40%). The expected four adducts **18–21** were only partially separated by VPC, but were well resolved by high-pressure liquid chromatography (77% H_2O, 23% acetone on Corasil C-18 reverse phase, 2 ft × 0.125 in. column) into four peaks with retention times of 32, 38, 44, and 47 min in a ratio of 25:45:10:20, respectively. The two major isomers were characterized from the $SnCl_4$-catalyzed reaction described below.

A mixture of 6.45 g (58 mmol) of 3-methyl-2-methylenecyclopentanone (**17**), 30 ml of isoprene, and 4.10 g (0.2 equiv) of $SnCl_4 \cdot 5H_2O$ was mixed and stirred for 2.5 days. Working up and distilling as above gave 4.95 g (48%) of clear oil, bp 60–66° (0.1 mm). Analysis by liquid chromatography as above gave the same four compounds in a ratio of 27:69:1:3 in their order of elution. By use of a preparative column (4 ft × 0.375 in. Corasil C-18 column), there was obtained, using multiple injections, 1.18 g of the first component, which was identified by reasoning given in the text as **19** and 1.92 g of the second component, identified as **18**. The two minor isomers were not characterized further, but are assigned structures **21** and **20**, respectively, on the basis of their relative amounts.

Compound **18** had NMR 0.96 (d, 3 H), 1.38 (br s, 3 H), 1.3–2.2 (complex, 11 H), 5.30 ppm (br s, 1 H); ir 1735 cm^{-1}. A small sample was further purified by distillation at 0.1 mm in a capillary tube. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.44; H, 10.09.

Compound **19** had NMR 0.94 (d, 3 H), 1.39 (br s, 3 H), 1.3–2.2 (complex, 11 H), 5.24 ppm (br s, 1 H); ir 1735 cm^{-1}. A small sample was distilled as above. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.99; H, 10.02.

1-Isopropyl-4,8-dimethylspiro[4.5]dec-8-en-1-ol (Isomers 22 and 24). A dry ($LiAlH_4$) 15-ml pentane solution at 25° containing 23 mmol of isopropyllithium (15 ml of 1.6 *M* commercial solution) was treated, dropwise, with a dry pentane (10 ml) solution containing 1.25 g of **18** (gas evolution) and stirred for 15 min. Careful addition of water followed by drying and evaporation of the pentane layer gave 1.26 g of clear, colorless oil. NMR analysis of this oil indicated it to be about 50% isomeric alcohols **22** and 50% starting material as judged by the relative integration of the vinyl H (5.2–5.4, broad s) and saturated methyl group signals (0.9, m). Column chromatography on silica gel gave 0.52 g of alcohol **22** in the 10% ether–90% benzene fractions and 0.66 g of recovered **18** (slightly contaminated with **22**) in the 15% ether–85% benzene fractions. Alcohol **22** had NMR 0.9 (9 H, Me signals), 1.3–2.3 (complex), 1.62 (br s, 3 H), 5.31 ppm (br s, 1 H); ir 3630 and 3500 cm^{-1}.

In like manner, 1.02 g of compound **19** was treated with excess isopropyllithium. After work-up, it was resubmitted to the reaction conditions two more times. This multiple process gave an estimated 8:1 mixture of alcohol **24** to ketone **19**. Chromatography as above gave 0.76 g of alcohol **24**, with spectra virtually identical with those given by alcohol **22**.

γ-Acoradiene (4) and Endocyclic Isomer 23. To a solution of 0.50 g of alcohol **22** in 5 ml of dry pyridine was added 0.26 g of $SOCl_2$ and the mixture was stirred for 10 min at 25°, then poured into 5% HCl and extracted with ether. The product was filtered through a short column of silica gel with petroleum ether, yield 0.37 g of hydrocarbon material. GLC analysis (40 ft × 0.125 in., 3% SE-30 at 172°) gave two peaks eluting in 68 and 93 min in a ratio of 72:28. Collection from a preparative column (20 ft × 0.375 in., 30% SE-30 at 250°) gave 130 mg of the first component, which was identified as endocyclic diene **23**: 100-MHz NMR 0.80 (d, J = 7 Hz, 3 H), 1.01 (d, J = 7 Hz, 6 H), 1.2–2.5 (complex, 10 H), 1.61 (br s, 3 H), 5.30 (br s, 2 H). Collection of the second peak gave 50 mg of

a compound which was identical with γ-acoradiene (α-alaskene, **4**). It had $[\alpha]^{25}D$ −82° (lit. −66[6] and −88° [7]); 100-MHz NMR 0.88 (d, J = 7 Hz, $-CH_3$), 1.2–2.3 (complex absorption), 1.60–1.75 (multiplet with intense peak maxima at 1.63, 1.69, 1.70, and 1.71), 5.25–5.30 ppm (broad s, C=CH); ir (film) 2840–3020 (complex, CH), 1432–1455 (broad), and medium, sharp peaks at 1375, 1312, 1192, 1138, 1050, 950, 800, and 788 cm^{-1}; high-resolution mass spectrum of P^+, 204.1822 (calcd for $C_{15}H_{24}$, 204.1878). The NMR and ir spectra of **4** were compared to those of α-alaskene[23] and found identical. Also, **4** was stirred as a hexane solution heterogeneously with 98% formic acid at 25° for 24 hr as suggested for converting α-alaskene to α-cedrene,[7] and the resulting major product was identical with natural α-cedrene[23] by GLC comparisons.

δ-Acoradiene (5) and Endocyclic Isomer 25. A solution of 0.21 g of alcohol **24** in 2 ml of dry pyridine was dehydrated with 0.11 g of $SOCl_2$ as for **23**. GLC analysis as before showed two olefins eluting at 68 and 88 min in the ratio 70:30. These were collected by the same preparative method. The first one, 50 mg, was identified as the endocyclic diene **25**, which could be better prepared by $POCl_3$ dehydration of **24**, as described below. The second one, 18 mg, was identified as δ-acoradiene (**5**). It had $[\alpha]^{25}D$ +14° (lit. +16° [6]); 100-MHz NMR 0.82 (d, J = 7 Hz, CH_3), 1.1–2.3 (complex absorption), 1.50–1.70 (m with intense peak maxima at 1.59 and 1.68), 5.30–5.40 ppm (broad s, vinyl H); ir (film) 2840–3000 (complex, CH), 1435–1460 (broad), and medium, sharp peaks at 1380, 1260, 1006, 906, 800, and 733 cm^{-1}; high resolution mass spectrum, P^+ 204.1918 (calcd for $C_{15}H_{24}$, 204.1878). The ir and NMR spectra are identical with ones furnished for β-alaskene.[23] Also, the sample was compared to an authentic sample of β-alaskene[23] and found identical (retention time and peak enhancement) using 3% SE-30 (40 ft × 0.125 in., 160°).

A solution of 0.53 g of alcohol **24** and 0.53 g of $POCl_3$ in 5 ml of pyridine was heated at 92° for 27 hr. Work-up as before gave 0.40 g of diene material which was shown by VPC to be only the endocyclic isomer **25**: 100-MHz NMR 0.80 (d, J = 7 Hz, 3 H), 1.00 (d, J = 7 Hz, 6 H), 1.1–2.5 (m, 10 H), 1.6 (br s, 3 H), 5.32 (br s, 2 H). A sample was purified by distillation in a capillary at 0.1 mm. Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 87.92; H, 11.77.

4,8-Dimethyl-1-isopropylspiro[4.5]deca-2,7-diols (26). A solution of 0.40 g of diene **25** in 20 ml of dry THF (from $LiAlH_4$) was treated with 8 ml of 1.0 M BH_3 in THF (Aldrich) and stirred at 25° for 2 hr. Then H_2O was added, followed by 5 ml of 15% NaOH and 5 ml of 30% H_2O_2. The mixture was stirred for 1 hr, 20 ml of ether and 20 ml of H_2O were added, and the organic layer was washed with brine. Drying and removal of the solvents gave 0.35 g of colorless oil, presumed to be the isomeric mixture of alcohols **26**. This was supported by ir (film), 3200–3600 cm^{-1} (broad, OH), and NMR, no absorption of vinyl H at 5.2–5.4 ppm. The mixture was used in the next reaction without further purification.

(−)-Acorone (27) and (+)-Isoacorone (28). The total crude diol mixture **26** was dissolved in 20 ml of reagent acetone and treated dropwise with ca. 4 ml of Jones reagent until a permanent orange color remained. To the mixture was then added 5 ml of H_2O and 10 ml of ether, and the organic layer was washed with brine, dried, and evaporated, yielding 0.37 g of viscous oil, showing ir 1715 (cyclohexanone) and 1739 cm^{-1} (cyclopentanone) chromatophores. Analytical GLC analysis of this oil showed minor unidentified components and a major peak at 94 min (13% Carbowax 20M, 18 ft × 0.125 in. at 240°) which correspond to authentic samples of acorone (**1**) and isoacorone (**2**) (supplied[23] as a mixture, originally thought to be a pure compound, "neoacorone" [3]). Analysis by high-pressure liquid chromatography (Porasil T, 2 ft × 0.125 in., 10% $CHCl_3$–90% hexane) gave separation into two approximately equal-sized peaks eluting in 52.5 and 65 min, using an elution rate of 5.5 ml/min. Combination of all eluents collected for each peak gave 57 and 63 mg, respectively. Crystallization of the former component from n-hexane gave 27 mg, $[\alpha]^{25}D$ +90°, mp 94.0–95.5°, of material identical, except for sign of rotation, with authentic (−)-isoacorone (mp 94.0–95.5° for a sample isolated in the same way from "neoacorone",[23] lit.[3] $[\alpha]^{25}D$ −92°, mp 97–98°), mass spectrum, 236.1759 (calcd, 236.1776). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.21; H, 10.29. The second component, $[\alpha]^{25}D$ −133°, mp 96.0–97.5°, was identical, except for sign of rotation, with an authentic sample[23] of (+)-acorone [mp 96.0–97.5° (lit.[3] $[\alpha]^{25}D$ +139°, mp 98.5–99°], mass spectrum, 236.1762 (calcd, 236.1776). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.33; H, 10.33.

Acknowledgment. Financial support by the Robert A. Welch Foundation is gratefully acknowledged. L.R.N. thanks the National Science Foundation for a Traineeship, administered by Texas Tech University.

Registry No.—**4**, 28400-12-6; **5**, 28400-13-7; **8**, 52475-64-6; **8** semicarbazone, 54688-99-2; **13**, 54712-95-7; **14**, 52475-65-7; **15**, 52475-66-8; **16**, 52475-67-9; **17**, 52599-97-0; **17** semicarbazone, 52475-68-0; **18**, 52475-69-1; **19**, 52521-52-5; **22** α-OH, 54712-96-8; **22** β-OH, 54712-97-9; **23**, 54712-98-0; **24**, 54688-97-0; **25**, 54712-99-1; **26**, 54688-98-1; **27**, 54713-00-7; **28**, 54713-01-8; pulegone, 89-82-7; isoprene, 78-79-5.

References and Notes

(1) Portions of this work were reported at the 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug 29, 1973, and the 29th Southwest Regional Meeting of the American Chemical Society, El Paso, Tex., Dec 5, 1973. A preliminary account of a portion of this work has been published: J. N. Marx and L. R. Norman, *Tetrahedron Lett.*, 4375 (1973).
(2) National Science Foundation Trainee, 1970–1973.
(3) (a) F. Sorm and V. Herout, *Collect. Czech. Chem. Commun.*, **13**, 202 (1948); (b) *ibid.*, **14**, 753 (1949); (c) V. Sykora, V. Herout, J. Pliva, and F. Sorm, *Chem. Listy*, **51**, 1704 (1957); (d) *Chem. Ind. (London)*, 1231 (1956); (e) J. Vrkoc, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **27**, 2709 (1962); (f) J. Vrkoc, J. Jonas, V. Herout, and F. Sorm, *ibid.*, **29**, 539 (1964).
(4) R. J. McClure, K. S. Schorno, J. A. Bertrand, and L. H. Zalkow, *Chem. Commun.*, 1135 (1968).
(5) R. Kaiser and P. Naegeli, *Tetrahedron Lett.*, 2009, 2013 (1972).
(6) (a) B. Tomita and Y. Hirose, *Tetrahedron Lett.*, 143 (1970); (b) B. Tomita, T. Isono, and Y. Hirose, *ibid.*, 1371 (1970).
(7) (a) N. H. Anderson and D. D. Syrdal, *Tetrahedron Lett.*, 2277 (1970); (b) *ibid.*, 899 (1972).
(8) C. W. McEachan, A. T. McPhail, and G. A. Sim, *J. Chem. Soc. C*, 579 (1966).
(9) (a) T. G. Crandall and R. G. Lawton, *J. Am. Chem. Soc.*, **91**, 2127 (1969); see also (b) E. J. Corey, N. N. Girotra, and C. T. Mathew, *ibid.*, **91**, 1557 (1969).
(10) J. C. Guest, C. L. Hughes, R. Ramage, and R. Sattar, *J. Chem. Soc., Chem. Commun.*, 527 (1973).
(11) (a) W. Oppolzer, *Helv. Chim. Acta*, **56**, 1812 (1973); (b) T. R. Kasturi and M. Thomas, *Indian J. Chem.*, 777 (1972).
(12) A. R. Pinder, S. J. Price, and R. M. Rice, *J. Org. Chem.*, **37**, 2202 (1972).
(13) (a) J. M. Conia, M. P. Drouet, and J. Gore, *Tetrahedron*, **27**, 2481 (1971); (b) G. L. Lange, H. M. Campbell, and E. Neidert, *J. Org. Chem.*, **38**, 2117 (1973); (c) D. K. Banerjee and G. Subrahmanyam, *Synthesis*, 213 (1973).
(14) Cf. E. J. Eisenbraum and S. M. McElvain, *J. Am. Chem. Soc.*, **77**, 3383 (1955).
(15) P. Yates, M. J. Jorgenson, and P. Singh, *J. Am. Chem. Soc.*, **91**, 4739 (1969), and references cited therein.
(16) J. N. Marx, L. R. Norman, and J. H. Cox, *J. Org. Chem.*, **37**, 4489 (1972).
(17) J. Wolinsky and D. Chan, *J. Org. Chem.*, **30**, 41 (1965).
(18) C. Alexandre and F. Rouessac, *Bull. Soc. Chim. Fr.*, 1837 (1971).
(19) Cf. J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967).
(20) K. L. Williamson and Y. F. L. Hsu, *J. Am. Chem. Soc.*, **92**, 7385 (1970).
(21) A. Tanaka, H. Uda, and A. Yoshikoshi, *Chem. Commun.*, 188 (1967).
(22) K. N. Houk and R. W. Strozier, *J. Am. Chem. Soc.*, **95**, 4094 (1973).
(23) We wish to thank Dr. Niels H. Anderson of the University of Washington for generous samples of α-alaskene, β-alaskene, α-cedrene, acorone, and neoacorone and also for comparison spectra of α- and β-alaskene.
(24) C. Lucas, J. C. N. Ma, J. A. McClosky, and R. E. Wolf, *Tetrahedron*, **20**, 1789 (1964).

Naturally Occurring Terpenes. Synthesis of (+)- and (±)-14,15-Bisnor-8α-hydroxylabd-11(*E*)-en-13-one, (+)-Drimane-8,11-diol, and (−)-Drimenol

S. William Pelletier,* Stevan Lajšić, Yasuo Ohtsuka, and Zoltan Djarmati

Natural Products Laboratory, Department of Chemistry, University of Georgia, Athens, Georgia 30602

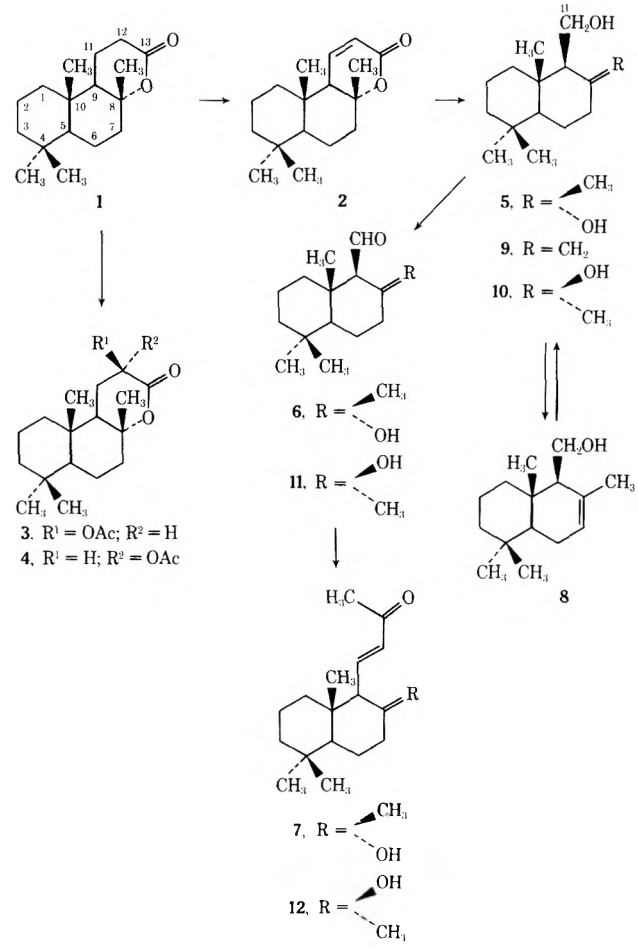
Received December 18, 1974

This paper reports a simple method of degradation of the readily available labdane group of diterpenoids to drimanic sesquiterpenes. The synthesis of (+)-drimane-8,11-diol (**5**), the (+) and (±) forms of 14,15-bisnor-8α-hydroxylabd-11(*E*)-en-13-one (**7**), (±)-8-epimeric hydroxy α,β-unsaturated ketone (**12**), and (−)-drimenol (**8**) is described. Treatment of (+)-ambreinolide (**1**) with $Pb(OAc)_4$ in boiling benzene for 120 hr gave compounds **2** (12%), **3** (22%), and **4** 27%). Treatment of **1** with DDQ in boiling *p*-dioxane for 48 hr afforded **2** (40%). Ozonolysis of **2** in methylene chloride at −70°, followed by treatment with Red-Al, gave (+)-**5** (85%). Oxidation of the latter with CrO_3–pyridine gave aldehyde (+)-**6** (50%). Treatment of (+)-**6** with sodium diethyl 2-oxopropylphosphonate in THF gave (+)-**7** (40%). A parallel series of reactions starting with (±)-ambreinolide (**1**) gave (±)-**2**, (±)-**5**, (±)-**6**, and (±)-**7**. Treatment of (+)-**5** with Ac_2O overnight gave a monoacetate which was dehydrated with $POCl_3$–pyridine at 0–5° to give a mixture of isomeric acetates. Basic hydrolysis of the latter gave a mixture of alcohols **8** and **9**. From this mixture (−)-dimenol (**8**) was isolated by preparative TLC. Treatment of (±)-drimenol (**8**) with *m*-chloroperbenzoic acid in methylene chloride at 0–5° gave a mixture of α and β epoxides. Reduction of the β epoxide with $LiAlH_4$ in THF gave diol **10**. Oxidation of **10** with CrO_3–pyridine gave **11**, which on treatment with sodium diethyl 2-oxopropylphosphonate in THF gave ketone **12** (30%).

Chirkova and coworkers have reported the isolation of (±)-14,15-bisnor-8α-hydroxylabd-11(*E*)-en-13-one (**7**) as a new bisnorditerpene hydroxy ketone from *Abies sibirica* Ledb (the oleoresin of the Siberian fir).[1] Recently, Hlubucek et al.[2] reported the isolation of the (+) isomer of this same compound, along with driman-8-ol, and drimane-8,11-diol (**5**) from the medium-volatile, neutral fraction of an extract of sun-cured *Nicotina Tabacum* L. Russian investigators have suggested that (+)-**7** is probably a diterpenoid autooxidation product of Δ^{13}-*cis*- and Δ^{1}-*trans*-neoabienol.[3] We wish to report a simple method of degradation of the readily available labdane group of diterpenoids (e.g., manool and sclareol) to drimanic sesquiterpenes. The synthesis of (+)-drimane-8,11-diol (**5**), and (+) and (±) forms of **7** from (+)- and (±)-ambreinolide, respectively, has been accomplished. Incidental to this work is the synthesis of the (±)-8-epimeric hydroxy α,β-unsaturated ketone **12** and (−)-drimenol (**8**).

The starting material for this synthesis was (+)-ambreinolide (**1**) obtained from manool.[4,5] When (+)-ambreinolide (**1**) was treated with 4 mol of lead tetraacetate[6] in boiling benzene, a very slow reaction occurred, and after 120 hr all starting material was consumed. A careful chromatographic separation of the oily product afforded three components: the unsaturated ambreinolide **2** (12%) and the epimeric acetoxy lactones **3** (22%) and **4** (27%). The structures for the acetoxy lactones were assigned on the basis of a comparison of the ^{13}C NMR shift values with the corresponding values of related steroidal acetoxy lactones.[7] Treatment of (+)-ambreinolide (**1**) with DDQ in boiling *p*-dioxane for 48 hr afforded compound **2** in much higher yield (40%). Exhaustive ozonolysis of the unsaturated (+)-ambreinolide **2** in dry methylene chloride at −70°, after evaporation, afforded an amorphous product which was dissolved in benzene and treated with Red-Al.[8] Work-up in the usual manner gave (+)-drimane-8,11-diol (**5**) in a nearly quantitative yield. The (+)-diol **5** was oxidized with CrO_3–pyridine complex in dry methylene chloride to aldehyde **6** in a yield of 50%. This aldehyde was allowed to react at −20° to room temperature with sodium diethyl 2-oxopropylphosphonate[9] in tetrahydrofuran to give the (+)-hydroxy α,β-unsaturated ketone **7** in a yield of 40%, mp 120–121°, $[\alpha]^{18}D$ +13.2°. The physical properties of the product **7** correspond with the reported data[2] for this compound.

The starting material for the synthesis of racemic hydroxy α,β-unsaturated ketone **7** was (±)-ambreinolide (**1**)



obtained from nerolidol.[10] Treatment of (±)-ambreinolide with DDQ (under conditions similar to those used in the case of (+)-ambreinolide) afforded (±) compound **2**. Ozonolysis of (±) compound **2**, followed by reduction with Red-

Al,[8] yielded (±)-drimane-8,11-diol **5** (87%). (±)-Diol (**5**) was oxidized with CrO_3–pyridine complex to the corresponding hydroxy aldehyde **6** in yields of 40–50%. Treatment of (±) compound **6** with sodium diethyl 2-oxopropylphosphonate in tetrahydrofuran at room temperature overnight and then at 50° for 2 hr gave the (±)-hydroxy α,β-unsaturated ketone **7**, mp 126.5–128° (lit.[1] mp 126°). The ir, NMR, and mass spectra of the product, (±) compound **7**, correspond exactly with reported data for this compound.[1]

(+)-Drimane-8,11-diol (**5**) was used as the starting material for synthesis of (−)-drimenol (**8**).[11] When (+)-diol **5** in pyridine was treated with acetic anhydride at room temperature overnight, the monoacetate was obtained in nearly quantitative yield. The latter was readily dehydrated with phosphorus oxychloride in pyridine at 0–5° to give a mixture of isomeric acetates (endo and exo double bond). Basic hydrolysis of the isomeric acetates yielded a mixture of alcohols **8** and **9**. From this mixture (−)-drimenol (**8**) was isolated by preparative TLC over silica gel in 40% yield, mp 95–96°, $[\alpha]^{19}D$ −20.0° (lit.[12b] mp 96–97°, $[\alpha]^{20}D$ −20°). The ir, NMR, and mass spectra of the product **8** correspond exactly with reported data for this compound.[12]

The starting material for synthesis of (±)-14,15-bisnor-8β-hydroxylabd-11(*E*)-en-13-one (**12**) was (±)-drimenol (**8**) obtained from β-ionone.[13] When 11-acetoxydrim-7-ene (drimenol acetate) was treated with *m*-chloroperbenzoic acid in methylene chloride at −30° for 3 days[2] the α epoxide was obtained in an excellent yield, formed by preferential attack from the sterically less hindered α side. However, treatment of (±)-drimenol (**8**) with the same peracid in methylene chloride at 0–5° (in the refrigerator) overnight afforded two epoxides (α and β) in a ratio of about 1:1, which could be separated by preparative TLC over silica gel. Reduction of the β epoxide (the less polar) with $LiAlH_4$ in boiling tetrahydrofuran gave diol **10**. Treatment of (±)-8β,11-diol **10** with CrO_3–pyridine complex in methylene chloride under the same conditions as used for (±)-8α,11-diol **5** afforded the hydroxy aldehyde **11**. The latter was treated with sodium diethyl 2-oxopropylphosphonate in tetrahydrofuran to give 8β-hydroxy α,β-unsaturated ketone **12** in 30% yield.

Experimental Section

All melting points were taken on a Büchi melting point apparatus and are uncorrected. Infrared (ir) spectra were determined in KBr or as film, with Perkin-Elmer Model 137 Infracord and Model 237B spectrometers. Mass spectra were taken with a Hitachi Perkin-Elmer RMU-6D2-s spectrometer operating with an ionization energy of 70 eV. The temperature of the ion source was about 200°. NMR spectra were taken in deuteriochloroform, with a Varian A-60 spectrometer. Ozonolysis was carried out using a Welsbach T-408 ozonator.

Oxidation of (+)-Ambreinolide by Means of Lead Tetraacetate (LTA). (+)-Ambreinolide (**1**, 3.0 g) was dissolved in 50 ml of anhydrous benzene and 6.0 g of LTA was added. The reaction mixture was stirred at reflux temperature for 2 days, when 6.0 g more of LTA was added; the heating and stirring were continued until all LTA had reacted (120 hr). The reaction mixture was diluted with ether, lead diacetate was collected, and the solution was washed with water, dried, and evaporated to dryness. The oily residue (4.2 g) was chromatographed on a column of 250 g of silica gel. Elution with hexane–ether (95:5) afforded 430 mg (12%) of unsaturated ambreinolide **2**: mp 193–194°; $[\alpha]^{25}D$ + 5.1° (*c* 2.0, chloroform); ν_{max} (KBr) 1720, 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.85, 0.93 (3 H, s, and 6 H, s, C-4 and C-10 CH_3), 1.46 (3 H, s, C-8 CH_3), 2.56 (1 H, dd, J = 3, 3 Hz, C-9 H), 6.23 (1 H, dd, J = 3, 10 Hz, C-12 H), 7.06 (1 H, dd, J = 3, 10 Hz, C-11 H).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.94; H, 9.99.

Elution with hexane–ether (9:1) afforded 800 mg (22%) of 12β-acetoxyambreinolide (**3**) and 980 mg (27%) of 12α-acetoxyambreinolide (**4**). The characteristics of acetoxy lactones **3** and **4** are as follows.

Acetoxy lactone **3**: mp 157–158°; $[\alpha]^{28}D$ +44.5° (*c* 2.0, chloroform); ν_{max} (KBr) 1760, 1750, 1225 cm^{-1}; NMR ($CDCl_3$) δ 0.85, 0.88, 0.93 (3 H, s, each, C-4 and C-10 CH_3), 1.53 (3 H, s, C-8 CH_3), 2.21 (3 H, s, C-12β $OCOCH_3$), 5.20–5.55 (1 H, m, C-12α H).

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.94; H, 9.43.

Acetoxy lactone **4**: mp 154–155°; $[\alpha]^{25}D$ +74.1° (*c* 2.0, chloroform); ν_{max} (KBr) 1765, 1745, 1250 cm^{-1}; NMR ($CDCl_3$) δ 0.85, 0.93 (3 H, s, and 6 H, s, C-4 and C-10 CH_3), 1.50 (3 H, s, C-8 CH_3), 2.22 (3 H, s, C-12α $OCOCH_3$), 5.68 (1 H, ABX q, $J_1 + J_2$ = 16 Hz, C-12β H).

Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 70.76; H, 9.39.

(+)- and (±)-Δ[11]-Ambreinolide (2). A solution of (+)-ambreinolide (**1**, 2.0 g) and DDQ (3.0 g) in 60 ml of dry *p*-dioxane was refluxed for 48 hr. The reaction mixture was diluted with ether, the precipitated solid was collected, and the solution washed with water, aqueous Na_2CO_3, and water, dried, and evaporated to dryness. The yellow solid residue (3.5 g) was chromatographed on activity III neutral alumina (100 g). Elution with hexane–ether (9:1) afforded 950 mg of material, which on crystallization from EtOAc yielded Δ[11]-ambreinolide (795 mg, 40%), mp 192–195°, and identical (ir and TLC) with the sample isolated from the (+)-ambreinolide–LTA reaction mixture.

Treatment of (±)-ambreinolide (1.5 g) with DDQ under conditions similar to those used in the case of (+)-ambreinolide afforded (±)-Δ[11]-ambreinolide (**2**) in a yield of 38% (565 mg), mp 212°.

(+)- and (±)-Drimane-8,11-diol (5). (+)-Δ[11]-Ambreinolide (**2**, 600 mg) in dry methylene chloride (75 ml) was treated with ozonized oxygen at −70° until the solution was blue (30 min). Evaporation afforded an amorphous product which was dissolved in benzene (50 ml) and treated with Red-Al.[8] The excess hydride was decomposed with dilute HCl (5%) and the mixture was extracted with ether. The combined extracts were washed with water, 5% aqueous $NaHCO_3$, and water, dried ($MgSO_4$), and evaporated. The residue (520 mg) was a colorless oil that crystallized from hexane (380 mg). After several recrystallizations the product **5** consisted of colorless prisms, mp 127–128°, $[\alpha]^{26}D$ +4.2° (*c* 1.3, chloroform). The ir, NMR, and mass spectra of the product **5** correspond exactly with data reported for this compound.[2]

The mother liquor was evaporated to dryness and purified by preparative TLC to give 83 mg of a product melting at 85–86°. This product has an identical NMR spectrum and specific rotation with the product melting at 127–128°, and appears to be a different crystalline form. Thus, the total yield of the (+)-drimane-8,11-diol (**5**) is 85%.

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.93; H, 11.76.

Exhaustive ozonolysis of (±)-Δ[11]-ambreinolide (500 mg), followed by reduction with Red-Al,[8] yielded (±)-drimane-8,11-diol (**5**, 87%), mp 100–101.5°.

(+)- and (±)-14,15-Bisnor-8α-hydroxylabd-11(*E*)-en-13-one (7). A solution of (+)-drimane-8,11-diol (**5**, 200 mg) in methylene chloride (4 ml) was treated for 30 min at room temperature with CrO_3–pyridine complex prepared from CrO_3 (750 mg), pyridine (1.28 ml), and methylene chloride (13 ml) at 5°. The reaction mixture was filtered through a short column of silica gel and washed with ether–methylene chloride. Evaporation of the solvent gave an oil, which was purified by preparative TLC on silica gel (50% hexane–ether) to give 100 mg of hydroxy aldehyde **6**: ν_{max} (film) 3500, 3420, 1725 cm^{-1}; NMR ($CDCl_3$) δ 0.85, 0.90 (3 H, s, each, C-4 CH_3), 1.13 (3 H, s, C-10 CH_3), 1.40 (3 H, s, C-8 CH_3), 2.08 (1 H, d, J = 2.0 Hz, C-9 H), 10.32 (1 H, d, J = 2.0 Hz, C-11 H). The aldehyde was used in the next step without further purification.

A mixture of $NaNH_2$ (140 mg) and diethyl 2-oxopropylphosphonate (170 mg) in tetrahydrofuran (6.0 ml) was stirred at 0° until the evolution of NH_3 has ceased. To the cold mixture (−10°) was added dropwise a solution of the above aldehyde **6** (100 mg) in tetrahydrofuran (6.0 ml). The reaction mixture was stirred at room temperature overnight, poured into ice–water, and extracted with ether. The extract was washed with water and dried over Na_2SO_4. Removal of the solvent gave an oil, which was chromatographed by preparative TLC on silica gel (50% hexane–ether) to separate a crystalline enone **7** (45 mg). Recrystallization from ether–hexane gave colorless needles: mp 120–121°; $[\alpha]^{18}D$ +13.2° (*c* 0.7, chloroform); ν_{max} (KBr) 3430, 1665, 1630 cm^{-1}; NMR ($CDCl_3$) δ 0.82, 0.88 (3 H, s, each, C-4 CH_3), 0.99 (3 H, s, C-10 CH_3), 1.26 (3 H, s,

C-8 CH_3), 2.25 (3 H, s, $COCH_3$), 6.14 (1 H, d, J = 16.0 Hz, C-12 H), 6.81 (1 H, dd, J = 16.0, 10.0 Hz, C-11 H).

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.48; H, 10.94.

Treatment of (±)-drimane-8,11-diol (**5**, 174 mg) with CrO_3–pyridine complex under conditions similar to those used in the case of (+)-diol **5** afforded (±)-hydroxy aldehyde **6** (80 mg).

The (±)-hydroxy aldehyde (65 mg) in tetrahydrofuran (4.9 ml) was added dropwise at −5° to the suspension of sodium diethyl 2-oxopropylphosphonate in tetrahydrofuran prepared as described above. The reaction mixture was stirred at room temperature overnight and then at 50° for 2 hr. The mixture was treated as described for the condensation of (+)-hydroxy aldehyde. The crystalline compound (30 mg) obtained was recrystallized from ether–hexane to give colorless needles, mp 126.5–128°, whose physical constants (melting point, ir and NMR spectra, R_f value of TLC) were identical with those of the (+)-hydroxy enone **7**.

(−)-Drimenol (8). A solution of (+)-drimane-8,11-diol (**5**, 200 mg) in pyridine (1 ml) and acetic anhydride (1 ml) was allowed to stand overnight at room temperature, then poured into iced $NaHCO_3$ solution. The solution was extracted with ether and the ether layer was washed with dilute HCl and saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. On removal of the solvent, an oily monoacetate was obtained, ν_{max} (film) 3500, 1750, 1250 cm^{-1}, which without purification was dehydrated.

To a solution of the monoacetate (215 mg) in pyridine (3.0 ml) at 0° was added phosphorus oxychloride (0.5 ml) and the resulting solution was stored overnight at 0–5°. The cold mixture was poured onto about 30 g of crushed ice and the resulting solution was extracted three times with ether. The ethereal solution was washed with water, dilute HCl, saturated aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude oil (160 mg) which showed two distinct spots on TLC. The product was dissolved in 2% methanolic potassium hydroxide (20 ml) and stirred overnight at room temperature. The methanolic solution was evaporated to dryness, the residue was dissolved in water, and the aqueous solution was extracted with ether. Evaporation of ether left a gum (120 mg). Separation on a 2-mm thick 200 × 200 mm silica gel plate afforded the less polar compound **8** (52 mg) as an oil that crystallized from hexane: mp 95–96°; $[\alpha]^{19}D$ −20.0° (c 1.3, chloroform); ν_{max} (KBr) 3300 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (9 H, s, C-4 and C-10 CH_3), 1.80 (3 H, s, C-8 CH_3), 3.70–3.86 (2 H, m, C-11 H_2), 5.70 (1 H, m, C-7 H).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.78. Found: C, 81.29; H, 11.94.

The more polar compound **9** was isolated as an oil: NMR ($CDCl_3$) δ 0.75, 0.85, 0.90 (3 H, s, each, C-4 and C-10 CH_3), 3.89–4.05 (2 H, m, C-11 H_2), 4.84, 5.16 (1 H, br, each, C-8=CH_2).

Epoxidation of (±)-Dimenol (8). A solution of (±)-drimenol (**8**, 990 mg) and m-chloroperbenzoic acid (800 mg) in methylene chloride (30 ml) was allowed to stand for 17 hr in a refrigerator. The reaction mixture was diluted with ether, washed with saturated aqueous $KHCO_3$ and water, and dried over Na_2SO_4. Evaporation of the solvent gave a colorless oil (1133 mg) which was chromatographed on silica gel (preparative TLC, 80% hexane–ether) to give two epoxides in a ratio of about 1:1. The less polar product (452 mg), the β epoxide, ν_{max} (film) 3430 cm^{-1}, NMR ($CDCl_3$) δ 0.86, 0.91 (3 H, s, and 6 H, s, C-4 and C-10 CH_3), 1.46 (3 H, s, C-8 CH_3), 3.0 (1 H, m, C-7α H), 3.90 (2 H, d, J = 4.5 Hz, C-11 H_2), 2.97 (1 H, br, OH), was used in the next step without further purification. The more polar product (442 mg) crystallized from ether–hexane to give colorless prisms, mp 94–96°, ν_{max} (film) 3420 cm^{-1}, NMR ($CDCl_3$) δ 0.76, 0.86 (3 H, s, and 6 H, s, C-4 and C-10 CH_3), 1.48 (3 H, s, C-8 CH_3), 2.98 (1 H, dd, J = 2, 2 Hz, C-7β H), 3.09 (1 H, br, OH), whose melting point was identical with that of α-epoxydrimenol reported by Appel and coworkers[12a] (mp 96–97°).

(±)-Drimane-8β,11-diol (10). A mixture of 7β,8β-epoxydriman-11-ol (315 mg) and $LiAlH_4$ (160 mg) in tetrahydrofuran (47 ml) was heated under reflux for 16 hr with stirring. The reaction mixture was treated with water to decompose excess $LiAlH_4$, washed with dilute HCl and water, and dried over Na_2SO_4. Evaporation of the solvent gave a crystalline residue (316 mg) which was recrystallized from ether–hexane to afford 268 mg of drimane-8β,11-diol (**10**) as colorless prisms, mp 133.8–134.5°, ν_{max} (KBr) 3280 cm^{-1}, NMR ($CDCl_3$) δ 0.87 (6 H, s, C-4 CH_3), 1.23 (3 H, s, C-10 CH_3), 1.33 (3 H, s, C-8 CH_3), 4.06 (2 H, d, J = 3 Hz, C-11 H_2), ca. 3.00 (1 H, br, OH), whose physical constants (melting point and ir spectra) were identical with those of drimane-8β,11-diol reported by Stadler and coworkers[13c] (mp 133°).

(±)-14,15-Bisnor-8β-hydroxylabd-11(E)-en-13-one (12). A solution of (±)-drimane-8β,11-diol (**10**, 120 mg) in methylene chloride (2.0 ml) was oxidized for 60 min at room temperature with CrO_3–pyridine complex prepared from CrO_3 (500 mg), pyridine (0.85 ml), and methylene chloride (8.5 ml) at 5°. The mixture was treated as described for the oxidation of (+)-drimane-8α,11-diol (**5**) to give hydroxy aldehyde **11** (50 mg) as an oil, ν_{max} (CCl_4) 3540, 1705 cm^{-1}, NMR ($CDCl_3$) δ 0.86, 0.90 (3 H, s, each, C-4 CH_3), 1.17, 1.20 (3 H, s, each, C-8 and C-10 CH_3), 2.12 (1 H, d, J = 2.6 Hz, C-9 H), 10.10 (1 H, d, J = 2.6 Hz, C-11 H), which was used in the next step without further purification.

A solution of hydroxy aldehyde **11** (50 mg) in tetrahydrofuran (3.0 ml) was added dropwise to a cold mixture (−5°) of sodium diethyl 2-oxopropylphosphonate in tetrahydrofuran prepared from 35 mg of $NaNH_2$ and 160 mg of diethyl 2-oxopropylphosphonate in 5 ml of tetrahydrofuran as described above. The mixture was stirred at room temperature overnight and at 40° for 1 hr and then treated as described for the synthesis of (+)-hydroxyenone **7**. The resulting crystalline compound (**12**, 18 mg) was recrystallized from ether–hexane to give colorless prisms: mp 153–153.8°; ν_{max} (KBr) 3420, 1670 (shoulder), 1660, 1635 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (6 H, s, C-4 CH_3), 1.02, 1.10 (3 H, s, each, C-8 and C-10 CH_3), 2.27 (3 H, s, $COCH_3$), 5.98 (1 H, d, J = 16.5 Hz, C-12 H), 6.96 (1 H, dd, J = 16.5, 10.2 Hz, C-11 H).

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.71; H, 10.65.

Registry No.—(+)-**1**, 468-84-8; (+)-**2**, 52811-58-2; (±)-**2**, 54656-74-5; **3**, 54632-03-0; **4**, 54656-75-6; (+)-**5**, 52617-99-9; (±)-**5**, 54656-76-7; (+)-**6**, 52618-00-5; (±)-**6**, 54656-77-8; (+)-**7**, 42569-64-2; (−)-**8**, 468-68-8; (±)-**8**, 54750-55-9; **9**, 54632-04-1; (±)-**10**, 54656-78-9; (±)-**11**, 54656-79-0; (±)-**12**, 54656-80-3.

References and Notes

(1) M. A. Chirkova, A. K. Dzizenko, and V. A. Pentegova, *Khim. Prir. Soedin.*, **3**, 86 (1967).
(2) J. R. Hlubucek, A. J. Aasen, S. O. Almqvist, and C. R. Enzell, *Acta Chem. Scand.*, **B28**, 131, 289 (1974).
(3) P. F. Vlad, M. N. Koltsa, and A. G. Russo, *Zh. Obshch. Khim.*, **43**, 646 (1973).
(4) H. R. Schenk, H. Gutmann, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **35**, 817 (1952).
(5) R. C. Cambie, K. N. Joblin, and A. F. Preston, *Aust. J. Chem.*, **24**, 2365 (1971).
(6) M. Stefanović, Z. Djarmati, and M. Gašić, *Tetrahedron Lett.*, 2769 (1970).
(7) M. Stefanović, Z. Djarmati, and M. Gašić, *Bull. Soc. Chim., Beograd*, **37**, 373 (1972). (8) 70% solution of sodium bis(2-methoxyethoxy)aluminum hydride in benzene.
(9) K. Sasaki, *Bull. Chem. Soc. Jpn.*, **39**, 2703 (1966).
(10) P. Dietrich and E. Lederer, *Helv. Chim. Acta*, **35**, 1148 (1952).
(11) For synthesis of (±)-drimenol see (a) A. Caliezi and H. Schinz, *Helv. Chim. Acta*, **32**, 2556 (1949); **33**, 1129 (1950); **35**, 1637 (1952); (b) E. E. van Tamelen, A. Storni, E. J. Hessler, and M. Schwartz, *J. Am. Chem. Soc.*, **85**, 3295 (1963); E. Wenkert and D. P. Strike, *ibid.*, **86**, 2044 (1964); (c) E. E. van Tamelen and E. J. Hessler, *Chem. Commun.*, 411 (1966); see also ref 13c.
(12) (a) H. H. Appel, C. J. W. Brooks, and K. H. Overton, *J. Chem. Soc.*, 3322 (1959); (b) S. Huneck, *Z. Naturforsch. B*, **22**, 462 (1967).
(13) (a) S. Kanno, T. Kato and Y. Kitahara, *Chem. Commun.*, 1257 (1967); (b) G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.*, **77**, 5068 (1955); (c) P. A. Stadler, A. Eschenmoser, H. Schinz, and G. Stork, *Helv. Chim. Acta*, **40**, 2191 (1957).

Synthesis of Substituted 5,6-Dihydro-2*H*-pyran-2-ones. Propiolic Acid Dianion as a Reactive Three-Carbon Nucleophile

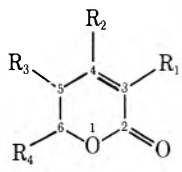
Robert M. Carlson,* A. R. Oyler, and J. R. Peterson

Department of Chemistry, University of Minnesota, Duluth, Minnesota 55812

Received January 21, 1975

Substituted 5,6-dihydro-2*H*-pyran-2-ones of four basic structural types (I–IV) were synthesized by addition reactions to derivatives of δ-hydroxyacetylenic acids **3**. The acetylenic acids were, in turn, obtained by the reaction of the propiolic acid dianion with epoxides. The addition of methanol, hydrogen, and dialkylcuprates generated three types of dihydropyrones related to biologically active compounds, while the subsequent alkylation or acylation of the vinyl anion derived from dialkylcuprate addition provided a route to the fourth structural type possessing substitution at C-3.

The 5,6-dihydro-α-pyrone ring system represents an intriguing goal for the development of new methods for polyketide synthesis, since there are many compounds of this structural type which show a wide variety of biological responses, including antibacterial and antifungal activity. These biologically active compounds can be classified by their characteristic substitution patterns at C-3 and C-4 as illustrated by the kava lactones,[1] pestalotin,[2a,b] and fungal lactone LL-P880β[3] (type I, **1**, R_1 = H; R_2 = OCH_3); phoma-

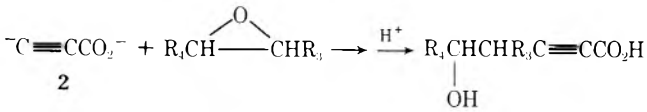


1

lactone,[4] asperline,[5] boronolide,[6] massiolactone,[7] isoranunculin,[8] parasorbic acid,[9] rubratoxins A and B,[10] goniothalamin,[11] and psilotin[12] (type II, **1**, R_1 = R_2 = H); dioscorine[13] (type III, **1**, R_1 = H; R_2 = CH_3); and the withanolides[14] (type IV, **1**, R_1 = CH_3 or CH_2OH, R_2 = CH_3).

The route to the dihydropyrone system that is presented herein employs the dianion (**2**) of propiolic acid as a stable three-carbon nucleophile[15] that will add in a regiospecific fashion to the less substituted (hindered) end of unsymmetrical epoxides (Table I). Subsequently, the resulting δ-hydroxyacetylenic acid system **3** is subjected to such selective processes as conjugate addition or reduction to generate the various substitution types I–IV (Scheme I).

Table I
Epoxide Addition Reactions

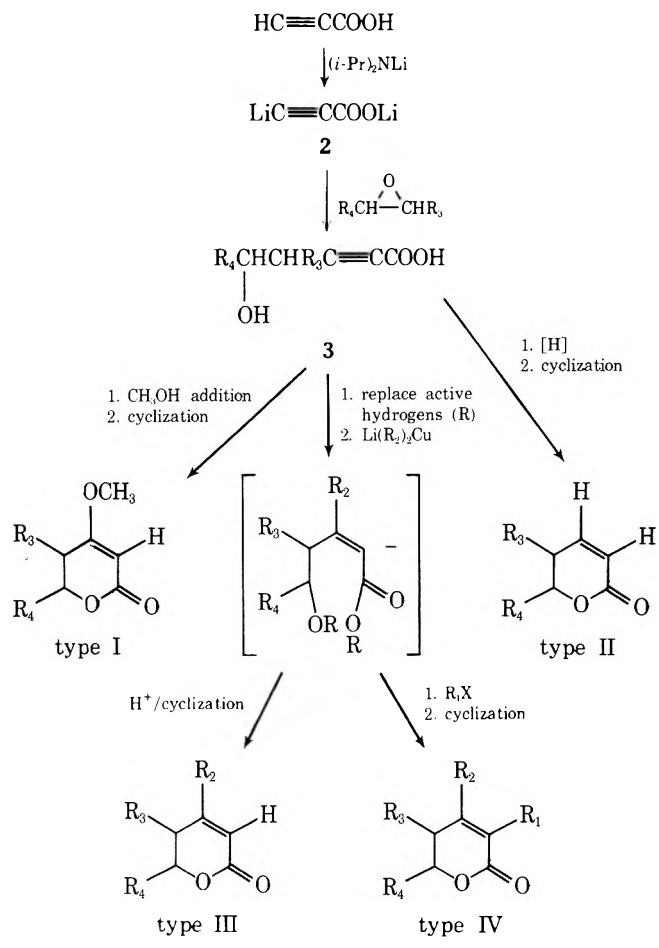


2 **3**

R_4	R_3	Reaction time, days	% yield[a]
C_6H_5[b]	H	2	48
C_2H_5	H	3	46
C_5H_{11}[c]	H	2	40
C_6H_{13}	H	3	40
$C_6H_5CH_2O$ | C_4H_9CH-	H	3	47
CH_2=$CHCH_2OCH_2$–	H	5	41
–$CH_2CH_2CH_2CH_2$–		17	30

[a] Determined by NMR of crude product mixture. [b] Previously prepared; see ref 19. [c] V. Lamberti, W. T. Weller, and J. Schagt, *Recl. Trav. Chim. Pays-Bas*, **86**, 504 (1967).

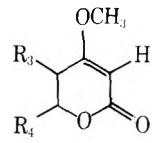
Scheme I

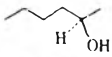
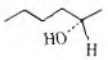


Results and Discussion

A. The Propiolic Acid Dianion. The propiolic acid dianion[15] (**2**) is generated at −45° with lithium diisopropylamide in a 1:1 THF–HMPA solvent system (3 mol of HMPA/mol of propiolic acid), which is necessary to maintain a solution throughout the dianion generation–addition sequence. The dianion **2** is allowed to react with an epoxide at room temperature for ca. 2–3 days to form the hydroxyacetylenic acid **3**. Reactions carried out without HMPA resulted in the formation of little or no addition product **3**. These results parallel the finding[16] that 1–3 mol of HMPA/mol of acid solubilize the dianions of aliphatic acids and accelerate their rate of alkylation in producing α-branched

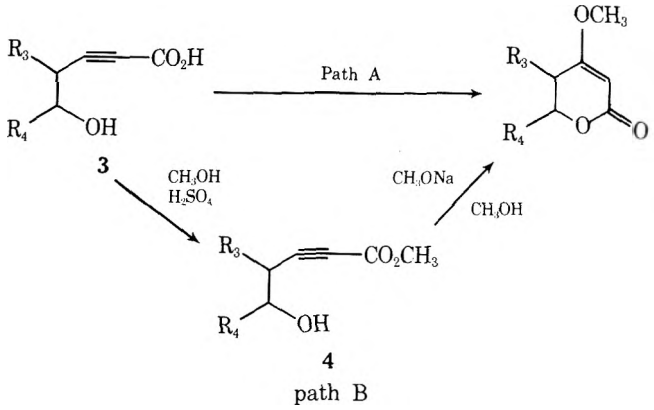
Table II
Type I Pyrones[h]



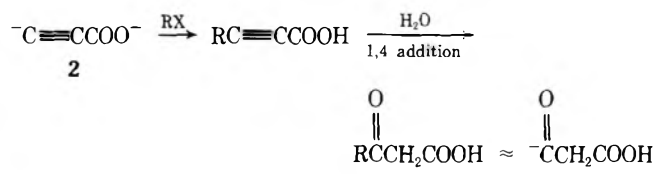
R_4	R_3	Path	% crude yield	Mp, °C	Bp, °C (mmHg)	NMR, δ, ppm ($CDCl_3$)	Registry no.
C_6H_5	H	A	51	144.5–145.5[a]		*b*	54814-58-3
C_2H_5	H	A	65	55.0–55.5		*b*	54814-59-4
C_5H_{11}	H	A	74		105 (0.08)[c]	0.9 (t, 3 H), 1.4 (m, 8 H), 2.4 (m, 2 H), 3.72 (s, 3 H), 5.17 (s, 1 H)	54814-60-7
C_6H_{13}	H	A	79	39.2–40.0		*b*	54814-61-8
$-CH_2CH_2CH_2CH_2-$		A	75	71.0–71.5		*b*	54620-72-3
$CH_2{=}CHCH_2OCH_2-$	H	B	32	49.0–49.7		2.5 (m, 2 H), 3.65 (d, 2 H), 3.72 (s, 3 H), 4.06 (m, 2 H), 4.5 (m, 1 H), 5.25 (m, 2 H), 5.75 (m, 1 H)	54814-62-9
	H	B	82[d]	81–82[e]		*g*	54814-63-0
	H	B	82[d]	71–72[f]		*g*	

[a] Lit.[19] mp 146–147°. [b] See ref 15. [c] Bath temperature. [d] Based on yield of benzyl ether diastereomers prior to cleavage and separation. See ref 15. [e] Lit.[22] mp 82°. [f] Lit.[22] mp 72°. [g] See ref 2. [h] Satisfactory elemental analyses were reported for all new compounds listed in the table.

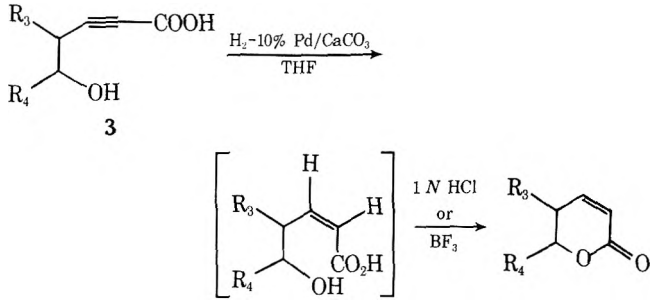
Scheme II



Scheme III



Scheme IV



acids. However, the addition of large quantities of HMPA in a reaction that proceeds for 2–3 days at room temperature raises the possibility of a competing process, whereby the propiolic acid dianion abstracts a proton from HMPA in a fashion analogous to that reported for other alkyllithiums.[17] This competing process may account for the formation of only moderate yields of the desired hydroxyacetylenic acid **3**. The thermal stability of the acetylide **2** should be contrasted with acetylides generated from propiolic acid esters,[18] which decompose at temperatures above −50°. Attempts to add these latter acetylides to epoxides at temperatures below −50° failed.

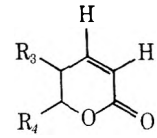
B. Type I Pyrones. Type I pyrones (Table II) were prepared either by the acid-catalyzed addition of methanol to the hydroxyacetylenic acid **3**[15] (path A, Scheme II) or by the base-catalyzed addition of methanol to the hydroxyacetylenic ester **4**[15,20] (path B, Scheme II). The latter two-step pathway was used only for the preparation of acid-sensitive pyrones such as pestalotin.[15,2a] As described previously,[15] this synthesis of type I pyrones represents an example of nucleophilic acyl substitution,[21] i.e., an acyl acetate equivalent (Scheme III).

C. Type II Pyrones. The semihydrogenation with 5% $Pd/BaSO_4$ of hydroxyacetylenic acids **3** obtained by alternate procedures has been reported[19,23] to form, after distillation, type II pyrones. In the present work, the synthetic scheme was modified slightly to use the less active $Pd/CaCO_3$ catalyst[24] and to effect ring closure with 1 *N* HCl or BF_3 (Scheme IV, Table III). Preparation of a type II pyrone **5** containing an exocyclic double bond is possible (Scheme V, Table III), but it is necessary to partially poison the $Pd/CaCO_3$ catalyst with quinoline.[25]

D. Type III Pyrones. The preparation of type III pyrones was carried out as outlined in Scheme VI by conjugate addition of dialkylcopper–lithium reagents[28] to either the hydroxyacetylenic acids[29] **3** or the corresponding bis(trimethylsilyl) derivatives[30,31] **7** (Table IV).

E. Type IV Pyrones. Preparation of tetrasubstituted olefins by conjugate addition of dialkylcopper–lithium reagents to α,β-acetylenic esters and subsequent reaction of the resulting intermediate with iodine[30] or methyl iodide[34]

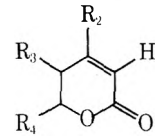
Table III
Type II Pyrones



R_4	R_3	% crude yield	Mp, °C	Bp, °C (mmHg)[b]	NMR, δ, ppm ($CDCl_3$)	Registry no.
C_6H_5	H	75	59–60[a]		2.5 (m, 2 H), 5.3 (t, J = 8 Hz, 1 H), 6.0 (m, J = 10, 1.75 Hz, 1 H), 6.85 (m, 1 H), 7.35 (s, 5 H)	4660-17-7
C_2H_5	H[g]	72		50–55 (0.1)	1.0 (t, 3 H), 1.7 (m, 2 H), 2.35 (m, 2 H), 4.3 (m, 1 H), 6.0 (m, J = 10, 1.5 Hz, 1 H), 6.9 (m, 1 H)	19895-35-3
C_5H_{11}	H	60		70–80 (0.1)[c]	0.9 (t, 3 H), 1.4 (br m, 8 H), 2.4 (m, 2 H), 4.4 (m, 1 H), 6.1 (m, J = 10, 1.5 Hz, 1 H), 7.0 (m, 1 H)	54814-64-1
C_6H_{13}	H[e]	78		80–85 (0.06)[d]	0.9 (t, 3 H), 1.4 (br m, 10 H), 2.35 (m, 2 H), 4.35 (m, 1 H), 6.0 (m, J = 10, 1.5 Hz, 1 H), 6.95 (m, 1 H)	2833-19-4
$-CH_2CH_2CH_2CH_2-$[g]		57	53.0–53.5		1.0–2.5 (br m, 9 H), 3.9 (m, 1 H), 5.85 (dd, J = 10.5, 2.5 Hz, 1 H), 6.65 (m, J = 10 Hz, 1 H)	19895-36-4
$CH_2{=}CHCH_2OCH_2-$	H[g]	*e*		70–85 (0.1)	2.5 (m, 2 H), 3.7 (d, J = 5 Hz, 2 H), 4.1 (d, J = 5 Hz, 2 H), 4.65 (m, 1 H), 5.3 (m, 2 H), 6.0 (m, 2 H), 7.0 (m, 1 H)	54814-65-2
$CH_3CH_2CH_2OCH_2-$	H[f]	*e*			0.8 (t, 3 H), 1.5 (m, 2 H), 2.5 (m, 2 H), 3.4 (d, J = 7.5 Hz, 2 H), 3.7 (d, J = 5 Hz, 2 H), 4.6 (m, 1 H), 6.0 (m, J = 10 Hz, 1 H), 6.9 (m, 1 H)	54814-66-3

[a] Lit.[19] mp 59°. [b] Bath temperature. [c] Lit.[26] bp 85–86° (0.07 mm). [d] Lit.[27] bp 106–109° (0.1 mm Hg). [e] Overall yield 43%, using modified quinoline containing catalyst; NMR of product mixture is consistent with 80:20 mixture of the two lactones 5 and 6 (see text). Lactones were separated by preparative HPLC. [f] Corroborated by mass spectral analysis. [g] A satisfactory elemental analysis was reported for this compound.

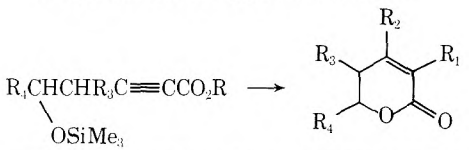
Table IV
Type III Pyrones



R_4	R_3	R_2	Path	% crude yield	Mp, °C	Bp, °C (mmHg)	NMR, δ, ppm ($CDCl_3$)	Registry no.
C_6H_5	H	CH_3	C	70	60.0–61.0[a]		2.02 (s, 3 H), 2.55 (m, 2 H), 5.4 (m, 1 H), 5.95 (m, 1 H), 7.4 (s, 5 H)	29643-79-6
C_2H_5	H	CH_3	C	70		60[b] (0.2)	0.9 (t, 3 H), 1.7 (m, 2 H), 1.9 (m, 3 H), 2.2 (m, 2 H), 4.25 (m, 1 H), 5.7 (m, 1 H)	54814-67-4
C_2H_5	H	CH_3[g]	D	63[c]		60[b] (0.2)	Same as above	
C_6H_{13}	H	CH_3[g]	C	65		100–120[b] (0.18)	0.9 (t, 3 H), 1.2 (m, 10 H), 1.9 (s, 3 H), 2.18 (m, 2 H), 4.3 (m, 1 H), 5.7 (m, 1 H)	54814-68-5
C_6H_{13}	H	CH_3	D	71[c]			Same as above	
CH_2CH_2-[d] CH_2CH_2-		CH_3[g]	C	88	65.8–66.2		0.9–2.4 (brm), 1.95 (m), 4.0 (m, 1 H), 5.9 (m, 1 H)	29681-61-6
C_6H_5[f]	H	C_4H_9	C	63		150 (0.17)[e]	0.9 (m, 3 H), 1.4 (brm, 4 H), 2.2 (m, 2 H), 2.55 (m, 2 H), 5.4 (m, 1 H), 5.9 (m, 1 H), 7.45 (s, 5 H)	54814-69-6

[a] Lit.[32] mp 61–62°. [b] Bath temperature. [c] Based on starting ester. [d] Previously reported (ref 33). [e] Decomposed. [f] Corroborated by mass spectral analysis. [g] A satisfactory elemental analysis was reported for this compound.

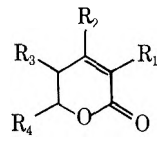
Table V
Preparation of Type IV Pyrones[a]



R_4	R_3	R	R_2	R_1	X	% yield	Mp, °C	Bp, °C (mmHg)	NMR, δ, ppm (CDCl3)	Registry no.
C_6H_5	H	$SiMe_3$	CH_3	CH_3	I	58	97.0–97.5		1.95 (s, 6 H), 2.5 (m, 2 H), 5.3 (m, 1 H), 7.4 (s, 5 H)	54814-70-9
C_6H_5	H	$SiMe_3$	CH_3	I	I	51	85.5–86.0		2.22 (s, 3 H), 2.7 (m, 2 H), 5.4 (m, 1 H), 7.4 (s, 5 H)	54832-64-3
C_6H_5	H	CH_3	CH_3	Ac	Cl	72	95.0–95.4		2.1 (s, 3 H), 2.49 (s, 3 H), 2.6 (m, 2 H), 5.4 (m, 1 H), 7.45 (s, 5 H)	54814-71-0
C_6H_5	H	CH_3	CH_3	$EtOCH_2$–	Cl	62[b]			1.15 (t, 3 H), 2.1 (s, 3 H), 2.5 (m, 2 H), 3.5 (q, 2 H), 4.25 (s, 2 H), 5.3 (m, 1 H), 7.4 (s, 5 H)	54814-72-1
C_6H_5	H	CH_3	CH_3	CH_3S	SCH_3	62	97.5–98		2.21 (s, 3 H), 2.31 (s, 3 H), 2.65 (m, 2 H), 5.35 (m, 1 H), 7.4 (s, 5 H)	54814-73-2
C_6H_5	H	$SiMe_3$	CH_3	$SiMe_3$	See text	See text	76.5–77		0.3 (s, 9 H), 2.1 (s, 3 H), 2.45 (m, 2 H), 5.2 (m, 1 H), 7.35 (s, 5 H)	54814-74-3
C_6H_{13}	H	$SiMe_3$	CH_3	I	I	72	41.5–42.5		0.9 (t, 3 H), 1.3 (br, 10 H), 2.2 (s, 3 H), 2.5 (m, 2 H), 4.4 (m, 1 H)	54814-75-4
OCH_2– $CH_2CH{=}CH_2$	H	CH_3	CH_3	$CH_2{=}CHCH_2$–	Br	85		120–130 (0.05)	1.95 (s, 3 H), 2.4 (m, 2 H), 3.1 (d, 2 H), 3.6 (d, 2 H), 4.0 (d, 2 H), 4.5 (m, 1 H), 5.1 (m, 4 H), 5.75 (m, 2 H)	54814-76-5

[a] Satisfactory elemental analyses were reported for all compounds listed in the table, unless otherwise noted. [b] Mass spectral analysis only.

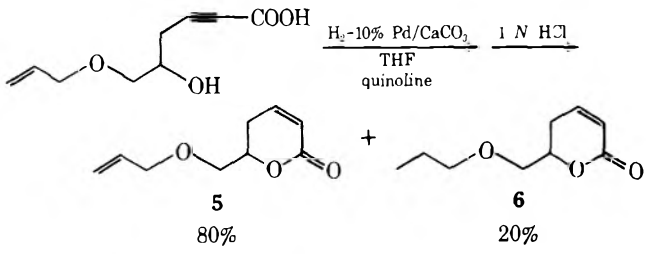
Table VI
Kirby-Bauer[36] Test Results[a]



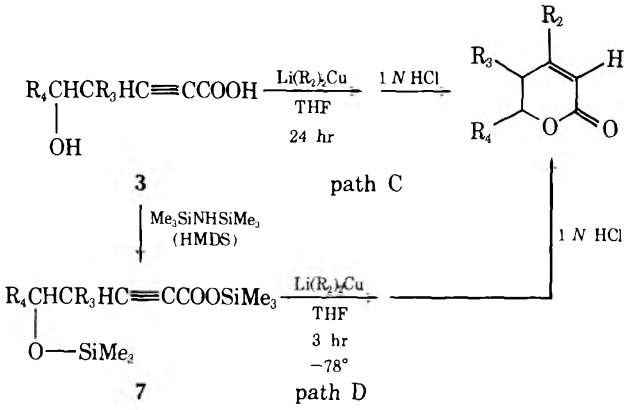
Type	R_4	R_3	R_2	R_1	Inhibition zone, mm					
					S. aureus			*E. coli*		
					100 μg	200 μg	300 μg	100 μg	200 μg	300 μg
I	C_5H_{11}	H	OCH_3	H		7	8–9			
I	$-CH_2CH_2CH_2CH_2-$		OCH_3	H			15			23
II	C_6H_5	H	H	H		8	10		6	9
II	C_5H_{11}	H	H	H			16		8	10
II	$-CH_2CH_2CH_2CH_2-$		H	H			16		9	18
II	C_6H_{13}	H	H	H			12			

[a] Sample of (−)-pestalotin was graciously provided by Lederle Laboratories.[2] This sample, as well as the synthetic *dl* material, gave a negative response by the Kirby-Bauer test above.

Scheme V



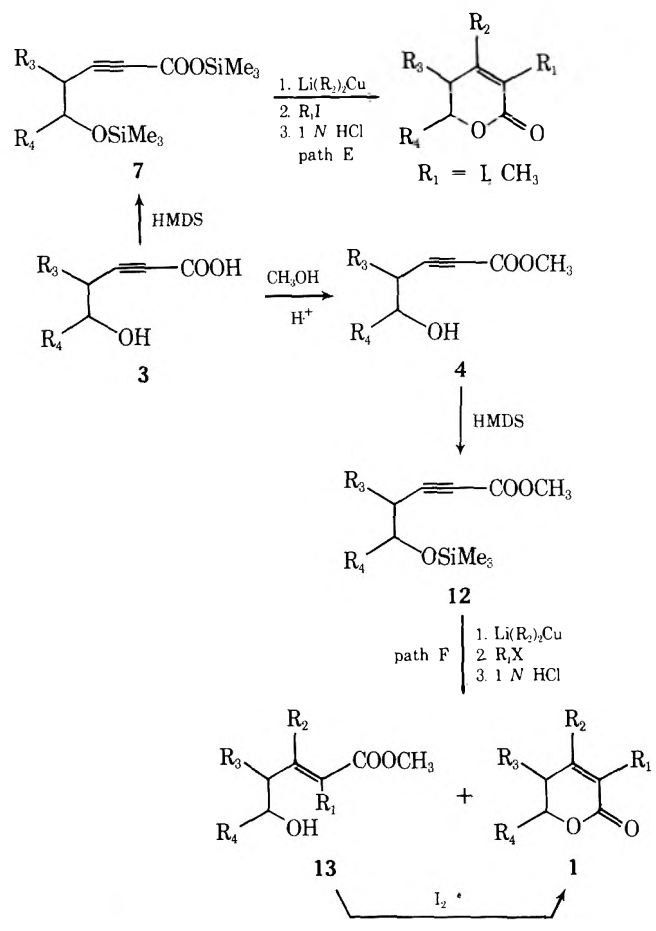
Scheme VI



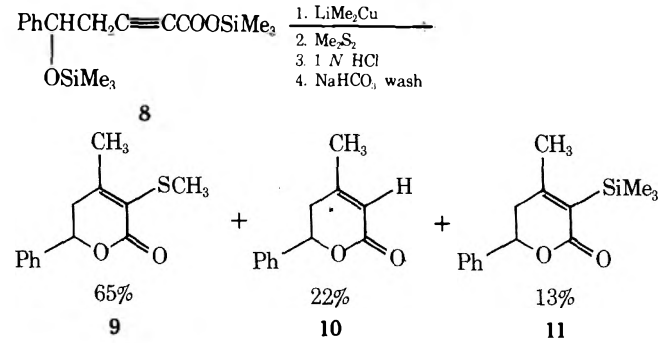
has been reported. However, attempts to react this intermediate with other electrophiles such as trimethylchlorosilane, acetic anhydride, or hexadeuterioacetone failed.[34] In contrast to these latter findings, we have found that this synthetic scheme can be extended to include a wide variety of electrophilic reagents as exemplified by the synthesis of the type IV pyrones described below.

The bis(trimethylsilyl) compound 7 provided a suitable starting point for the preparation of 3-methyl- and 3-iodopyrones (Scheme VII). However, when less reactive electrophiles were used, significant amounts of 3-unsubstituted and 3-trimethylsilylpyrones[35] were isolated in addition to the desired 3-substituted pyrones. For example, a reaction starting with the ester 8 and using dimethyl disulfide as the electrophile produced a 45% yield of a mixture of three pyrones, **9**, **10**, and **11**, in a ratio of 65:22:13 (Scheme VIII). This ratio was determined by comparison of the NMR spectrum and analytical liquid chromatograph of the mix-

Scheme VII



Scheme VIII



ture with those of the pure compounds, whose isolation is described elsewhere in this work.

These difficulties encountered with less reactive electrophiles were alleviated by using the trimethylsilyl methyl ester **12**. Thus, addition of dimethylcopper–lithium to **12** ($R_4 = C_6H_5$; $R_3 = H$) and treatment of the resulting intermediate with acetyl chloride gave a 1:1 mixture of the desired lactone **1** ($R_4 = C_6H_5$; $R_3 = H$; $R_2 = CH_3$; $R_1 = CH_3C{=}O$) and the uncyclized ester **13** ($R_4 = C_6H_5$; $R_3 = H$; $R_2 = CH_3$; $R_1 = CH_3C{=}O$), plus some minor unidentified compounds. Treatment of the mixture with a catalytic amount of iodine led to isomerization and ring closure of the ester to the desired pyrone **1** in an overall yield of 72% (Scheme VII). Similarly, for all the other electrophiles except I_2 or MeI listed in Table V, mixtures of lactones and uncyclized esters were obtained and treated with iodine to produce good yields of types IV pyrones.

F. Biological Testing. All pyrones prepared in this work were tested for antibacterial activity against. *E. coli* and *S. aureus* using the Kirby–Bauer method[36] (Table VI).

Experimental Section

General. Melting points (uncorrected) were obtained on a Thomas-Hoover capillary apparatus. Infrared spectra were taken on a Beckman IR-33. NMR spectra were obtained with a Varian A-60D instrument using Me_4Si as internal standard. Analytical liquid chromatographs were obtained on Waters Associates equipment, including refractive index and ultraviolet detectors, and two 28-mm Micro Porasil columns. The flow rate was 3 ml/min and 1:1 ether–hexane was used in most cases. For preparative work three 56-mm Porasil A columns were sometimes substituted and a flow rate of 9.9 ml/min was used. The propiolic acid was used as received from Farchan and Aldrich Chemical Co. The alkyllithiums were obtained from Alfa Products. The THF (Baker Analyzed, <0.003% H_2O) was maintained under nitrogen in a septum-capped bottle from which the solvent was removed by syringe. The HMPA (Aldrich) was stored in a septum-capped bottle under nitrogen over 4-Å sieves for several weeks before use. The cuprous iodide was Fisher Certified. The acetyl chloride (Baker Analyzed) was distilled from pyridine to remove traces of HCl. All reactions involving organometallic reactants were carried out under nitrogen in septum-capped flasks with introduction of reagents via syringe. Elemental analyses were performed by Robertson Laboratories, Florham Park, N.J. Mass spectra were run on a Varian CH5 by Mr. Douglas Kuehl, National Water Quality Laboratory, Duluth, Minn.

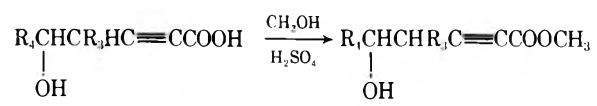
Preparation of Hydroxyacetylenic Acid 3. The procedure previously reported was employed.[15] In nearly all cases the crude product mixture (mostly hydroxyacetylenic acid **3** and ether) was used directly in subsequent reactions.

Preparation of Hydroxyacetylenic Methyl Ester 4. The δ-hydroxyacetylenic acid **3** (0.01 mol) was treated with 20 ml of a 1% sulfuric acid solution in methanol for 1–2 days. The reaction was saturated with solid sodium bicarbonate, filtered, and concentrated. The residue was diluted with ether and the organic layer was washed with saturated sodium bicarbonate solution and brine. After drying over magnesium sulfate, the ether was evaporated to yield the ester **4**, which was used without further purification. Yield data are presented in Table VII.

Preparation of Type I Pyrones. The previously described procedures[15] were used. The crude products were purified when necessary by preparative liquid chromatography before recrystallization or distillation (Table II).

General Procedure for Preparation of Type II Pyrones. The hydroxyactylenic acid **3** (0.007 mol) with ca. 0.1 g of 10% Pd/$CaCO_3$ in 15 ml of THF was allowed to take up ca. 85% of the theoretical amount of hydrogen. The reaction mixture was then poured into 1 *N* HCl[37] and stirred for 1–2 hr. The mixture was extracted with ether and the combined ether extracts were washed with saturated sodium bicarbonate solution and brine. After drying over magnesium sulfate, the ether was evaporated to give crude lactone, which was purified, if necessary, by preparative liquid chromatography before recrystallization or distillation (Table III). For the preparation of pyrone **5**, with an exocyclic double bond, the amount of catalyst was decreased to 0.02 g and 50% by weight of quinoline was added (see text).

Table VII
δ-Hydroxyacetylenic Esters 4

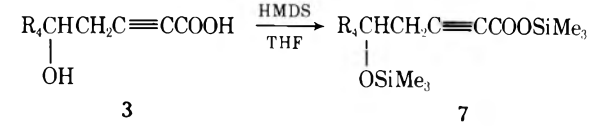


3 **4**

R_4	R_3	% yield
C_6H_5[a]	H	90
C_2H_5	H	70
C_5H_{11}	H	62
C_6H_{13}	H	80
$C_4H_9CHOCH_2C_6H_5$	H	90
$CH_2{=}CHCH_2OCH_2-$	H	79
$-CH_2CH_2CH_2CH_2-$		85

[a] See ref 19.

Table VIII
Preparation of Bis(trimethylsilyl) Compounds 7



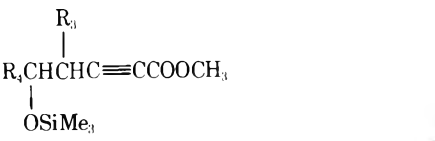
3 **7**

R_4	% yield after distillation	Bp, °C (mmHg)	NMR, δ, ppm ($CDCl_3$)
C_6H_5	67	95–125 (0.30)	0.10 (s, 9 H), 0.31 (s, 9 H), 2.65 (d, J = 6 Hz, 2 H), 4.90 (t, J = 6 Hz, 1 H), 7.35 (s, 5 H)
C_2H_5	81	81–89 (0.25)	0.11 (s, 9 H), 0.29 (s, 9 H), 0.90 (t, 3 H), 2.55 (m, 2 H), 2.45 (d, 2 H), 3.80 (m, 1 H)
C_6H_{13}	60	111–119 (0.25)	0.12 (s, 9 H), 0.30 (s, 9 H), 0.89 (t, 3 H), 1.3 (m, 10 H), 2.42 (d, 2 H), 3.8 (m, 1 H)
$CH_2{=}CHCH_2OCH_2-$	67	80–110 (0.14)	0.13 (s, 9 H), 0.30 (s, 9 H), 2.5 (m, 2 H), 3.45 (d, 2 H), 4.0 (m, 3 H), 5.25 (m, 2 H), 5.8 (m, 1 H)

General Procedure for the Preparation of Bis(trimethylsilyl) Compounds 7. The hydroxyacetylenic acid **3** (1 equiv), hexamethyldisilazane (HMDS, ca. 4 equiv), and enough THF to effect solution were refluxed for 24–48 hr. The THF and excess HMDS were removed in vacuo and the product was distilled (Table VIII).

General Procedure for Preparation of Type III Pyrones. From Hydroxyacetylenic Acids 3. The cuprous iodide (0.014 mol, 3.05 equiv) was slurried in 40 ml of THF under N_2 at 0°. Dropwise addition of 0.028 mol (6.10 equiv) of methyllithium (1.65 *M* in ether) formed a clear, colorless solution which was stirred for 5 min at 0°[38] and then cooled to −78°. The hydroxyacetylenic acid **3** (0.0046 mol, 1.0 equiv) dissolved in 5 ml of THF was then added. The Dry Ice–acetone bath was packed with Dry Ice and allowed to slowly come to room temperature overnight. The reaction mixture was poured into 250 ml of vigorously stirred 1 *N* HCl, and after stirring for 1 hr the mixture was extracted with ether. The combined ether extracts were washed with a saturated solution of sodium bicarbonate and brine. After drying over magnesium sulfate the ether was evaporated to give crude lactone, which was purified, if necessary, by preparative liquid chromatography before recrystallization or distillation (Table IV). For bis(trimethylsilyl)

Table IX
Trimethylsilyl Methyl Esters 12



R_4	R_3	% yield after distillation	Bp, °C (mmHg)[a]	NMR, δ, ppm ($CDCl_3$)
C_6H_5	H	74	110–120 (0.35)	0.07 (s, 9 H), 2.66 (d, J = 6 Hz, 2 H), 3.71 (s, 3 H), 4.9 (t, J = 6 Hz, 1 H), 7.33 (s, 5 H)
C_6H_{13}	H	68	92–100 (0.20)	0.16 (s, 9 H), 0.91 (t, 3 H), 1.30 (m, 10 H), 2.50 (d, 2 H), 3.80 (s, 3 H), 3.88 (m, 1 H)
CH_2=$CHCH_2OCH_2$–	H	83	95 (0.25)	0.17 (s, 9 H), 2.55 (m, 2 H), 3.40 (d, 2 H), 3.72 (s, 3 H), 4.0 (m, 3 H), 5.25 (m, 2 H), 5.75 (m, 1 H)

[a] Bath temperature.

compounds **7**, the above procedure was modified to use only 1.1 equiv of cuprous iodide and 2.2 equiv of methyllithium and a reaction time of only 3 hr at −78° before work-up.

General Procedure for the Preparation of Trimethylsilyl Methyl Esters 12. The hydroxyacetylenic ester **4** (1 equiv), HMDS (ca. 4 equiv), and enough THF to effect solution were refluxed for 24–48 hr. The THF and excess HMDS were removed in vacuo and the product **12** was distilled (Table IX).

General Procedure for the Preparation of Type IV Pyrones. The bis(trimethylsilyl) compound **7** or the trimethylsilyl methyl ester **12** was treated with 1.1 equiv of dialkylcopper–lithium reagent in THF as described above for type III pyrones. After stirring for 3 hr at −78°, 2.2 equiv of HMPA was added to the nonhomogeneous reaction mixture to form a solution, followed by the electrophile (2.2 equiv). The Dry Ice–acetone bath was packed with Dry Ice and allowed to gradually warm to room temperature. After stirring for 24 hr after the electrophile addition, the reaction mixture was poured into 1 *N* HCl and stirred for 1 hr. The aqueous mixture was extracted with ether and the combined ether extracts were dried over magnesium sulfate and evaporated. The mixture obtained (see text) was refluxed with 0.1 equiv of iodine in THF for 0.5 hr.[39] The mixture was diluted with ether, washed with a 10% sodium sulfite solution, and dried over magnesium sulfate. Evaporation of the ether gave crude lactone, which was purified, if necessary, by preparative liquid chromatography prior to recrystallization or distillation (Table V).

Biological Testing. The technique used for determining the susceptibility of *Escherichia coli*[40] and *Staphylococcus aureus* was described by Difco.[41] The disks containing the agent were prepared by the application of the test compound via syringe onto 6-mm paper disks[42] and allowing approximately 15 min for the solvent to air dry. The Petri dishes[43] could easily accommodate four disks in an outer ring, three containing the agent at a concentration of 100–200–300 μg per disk. The fourth disk was a prepared standard[44] and the final disk was a blank. All zones were read to the nearest millimeter following 16–24 hr of incubation (Table VI).

Acknowledgments. We wish to express our appreciation to Mr. Kevin H. Costley for the development of the screening program and to the National Institute of Allergy and Infectious Disease for overall support of this research (2R01-AI-10597).

Registry No.—**2**, 54620-69-8; **3** (R^3 = H; R^4 = CH_2=$CHCH_2OCH_2$), 54814-77-6; **3** (R^3 = C_6H_5; R^4 = H), 54814-78-7; **3** (R^3 = C_2H_5; R^4 = H), 54814-79-8; **3** (R^3 = C_5H_{11}; R^4 = H), 27003-14-1; **3** (R^3 = C_6H_{13}; R^4 = H), 54814-80-1; **3** (R^3 = R^4 = $CH_2CH_2CH_2CH_2$), 54814-81-2; **3** (R^3 = H; R^4 = C_6H_5), 54814-82-3; **3** (R^3 = H; R^4 = C_2H_5), 54814-83-4; **3** (R^3 = H, R^4 = C_5H_{11}), 16400-66-1; **3** (R^3 = H; R^4 = C_6H_{13}), 54814-84-5; **3** (R^3 = H; R^4 = $CH_3CH_2CH_2OCH_2$), 54814-85-6; **4** (R^3 = CH_2=$CHCH_2OCH_2$; R^4 = H), 54814-86-7; **4** (R^3 = $CH(OH)CH_2CH_2CH_2CH_3$; R^4 = H), 54814-87-8; **7** (R^4 = C_6H_5), 54814-88-9; **7** (R^4 = C_2H_5), 54814-89-0; **7** (R^4 = C_6H_{13}), 54814-90-3; **7** (R^4 = CH_2=$CHCH_2OCH_2$), 54814-91-4; **12** (R^3 = H; R^4 = C_6H_5), 54814-92-5; **12** (R^3 = H; R^4 = C_6H_{13}), 54814-93-6; **12** (R^3 = H; R^4 = CH_2=$CHCH_2OCH_2$), 54814-94-7; $Li(CH_3)_2Cu$, 15681-48-8; $Li(Bu)_2Cu$, 24406-16-4; I_2, 7553-56-2; MeI, 74-88-4.

References and Notes

(1) M. Klohs, "The Chemistry of Kava", USPHS Publication No. 1645, 1967, pp 126–140; H. Achenbach and W. Regel, *Chem. Ber.*, **106**, 2648 (1973), and references cited therein.
(2) (a) G. Ellestad, W. J. McGahren, and M. P. Kunstmann, *J. Org. Chem.*, **37**, 2045 (1972); (b) Y. Kimura, K. Karagiri, and S. Tamura, *Tetrahedron Lett.*, 3137 (1971).
(3) W. J. McGahren, G. A. Ellestad, G. O. Morton, and M. P. Kunstmann, *J. Org. Chem.*, **38**, 3542 (1973).
(4) I. Yamamoto, H. Suide, T. Hemmi, and Y. Yamano, *Takeda Kenkyusho Ho*, **29**, 1 (1970), *Chem. Abstr.*, **73**, 52347 (1970); R. H. Evans, G. A. Ellestad, and M. P. Kunstmann, *Tetrahedron Lett.*, 1791 (1969).
(5) S. D. Miller and W. B. Turner, *J. Chem. Soc. C*, 2242 (1967); A. D. Argoudelis and J. F. Zieserl, *Tetrahedron Lett.*, 1969 (1966).
(6) N. C. Franca and J. Polonsky, *C. R. Acad. Sci., Ser. C*, **273**, 439 (1971).
(7) G. W. K. Cavill, D. V. Clark, and F. B. Whitfield, *Aust. J. Chem.*, **21**, 2819 (1968).
(8) R. Tschesche, K. Wilmar, G. Wueff, and G. Snatzke, *Chem. Ber.*, **105**, 290 (1972).
(9) A. E. Stafford, D. R. Black, W. F. Haddon, and A. C. Waiss, *J. Sci. Food Agric.*, **23**, 771 (1972), and references cited therein.
(10) M. O. Moss, F. V. Robinson, A. B. Wood, H. M. Paisley, and J. Feeney, *Nature (London)*, **220**, 767 (1968); M. O. Moss, A. B. Wood, and F. V. Robinson, *Tetrahedron Lett.*, 367 (1969).
(11) K. Jewers, J. B. Davis, J. Dougan, and A. H. Manchanda, *Phytochemistry*, **11**, 2025 (1972); T. R. Govindachari and P. C. Parthasarathy, *Tetrahedron Lett.*, 3401 (1971).
(12) A. G. McInnes, S. Yoshida, and G. H. N. Towers, *Tetrahedron Lett.*, 2939 (1965).
(13) C. B. Page and A. R. Pinder, *J. Chem. Soc.*, 4811 (1964).
(14) I. Kirkson, E. Glotter, A. Abraham, and D. Lavie, *Tetrahedron Lett.*, 2209 (1970).
(15) R. M. Carlson and A. R. Oyler, *Tetrahedron Lett.*, 2615 (1974).
(16) P. E. Pfeffer, L. S. Silbert, and J. M. Chirinko, *J. Org. Chem.*, **37**, 451 (1972).
(17) A. G. Abatjoglou and E. L. Eliel, *J. Org. Chem.*, **39**, 3042 (1974).
(18) E. J. Corey, C. U. Kim, R. H. Chen, and M. Takeda, *J. Am. Chem. Soc.*, **94**, 4395 (1972).
(19) H. Henbest and E. R. Jones, *J. Chem. Soc.*, 3628 (1950).
(20) E. R. Jones and M. C. Whiting, *J. Chem. Soc.*, 1423 (1949).
(21) D. Seebach and M. Kolb, *Chem. Ind (London)* **17**, 687 (1974); J. E. Baldwin, G. A. Höfle, and O. W. Lever, Jr., *J. Am. Chem. Soc.*, **96**, 7125 (1974); R. M. Carlson and J. L. Isidor, *Tetrahedron Lett.*, 4819 (1973).
(22) D. Seebach and H. Meyer, *Angew. Chem., Int. Ed. Engl.*, **13**, 77 (1974).
(23) V. Lamberti, W. T. Weller, and J. C. Schogt, *Recl. Trav. Chim Pay-Bas*, **86**, 504 (1967); A. Nabuhara, *Agric. Biol. Chem.*, **32**, 1016 (1968).
(24) H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 3.
(25) D. J. Cram and N. L. Allinger, *J. Am. Chem. Soc.*, **78**, 2518 (1956).
(26) L. Crombie, *J. Chem. Soc.*, 2535 (1955).
(27) S. Dolezal, *Collect. Czech. Chem. Commun.*, **30**, 2638 (1965).
(28) G. Posner, *Org. React.*, **19**, 1 (1972).
(29) J. Klein and R. M. Turkel, *J. Am. Chem. Soc.*, **91**, 6186 (1969).
(30) E. J. Corey and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, **91**, 1851 (1969).
(31) E. J. Corey, C. U. Kim, R. H. Chen, and M. Takeda, *J. Am. Chem. Soc.*, **94**, 4395 (1972).
(32) M. Girard and D. Molho, *Bull. Soc. Chim. Fr.*, 2652 (1970).
(33) M. Tada, T. Kakubo, and T. Sato, *Bull. Chem. Soc. Jpn.*, **43**, 2162 (1970).
(34) J. B. Siddall, M. Biskup, and J. G. Fried, *J. Am. Chem. Soc.*, **91**, 1853 (1969).
(35) 5,6-Dihydro-4-methyl-6-phenyl-3-trimethylsilyl-2*H*-pyran-2-one was isolated from one of these reactions and purified (Table V).
(36) A. W. Bauer, W. M. Kirby, J. Sherris, and M. Turck, *Am. J. Clin. Pathol.*, **45**, 493 (1966).
(37) Alternatively, BF_3-Et_2O or 1 *N* HCl in THF can be used.
(38) Di-*n*-butylcopper lithium was prepared by adding *n*-BuLi (2 *M* in hexane) to the CuI at −45° and stirring for 5 min.
(39) For type IV pyrone **1** (R_4 = C_6H_5; R_3 = H; R_2 = CH_3; R_1 = SCH_3), 1.3 equiv of iodine and a reflux time of 1.5 hr was required.
(40) Difco Bactrol Disks, *Staphylococcus aureus and Escherichia coli.*
(41) "Quality Control in Bacteriology with Bactrol Disks", Difco Technical Information, Feb 1973.
(42) Eaton-Dikeman No. 301–85.
(43) Fisher 100 × 15 mm sterilized, disposable plastic Petri dishes.
(44) Erythromycin, Difco Dispens-O-Disc (15 μg).

Rearrangements of 2-Pyrones and Pyran-2-thiones Involving 1,5-Sigmatropic Hydrogen Shifts

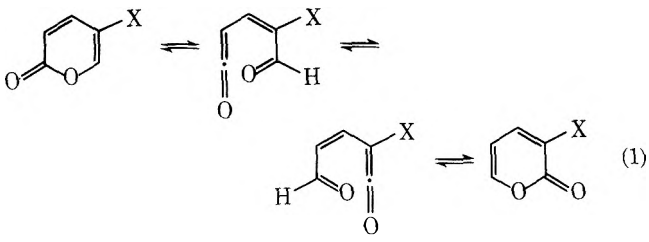
W. H. Pirkle* and W. V. Turner

School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

Received January 3, 1975

At elevated temperatures, 2-pyrones bearing hydrogen in the 6 position reversibly exchange substituents between the 3 and 5 positions. Evidence is presented from oxygen-18 labeling experiments that the "migrations" actually occur via reversible electrocyclic ring opening to ketene aldehydes which undergo reversible [1,5] sigmatropic shifts of the aldehydic hydrogen. Pyran-2-thiones undergo similar rearrangements and quantitatively afford thiapyran-2-ones. These rearrangements are blocked by the presence of a methyl group in the 6 position.

In a preliminary report,[1] the migration of substituents between the 3 and 5 positions of 2-pyrones during gas-phase pyrolysis was rationalized by invoking reversible electrocyclic ring opening to ketene aldehydes which undergo reversible [1,5] sigmatropic shifts of the aldehydic hydrogen (eq 1). In view of the obvious synthetic utility of



(1)

the reaction and the possible relevence of the postulated mechanistic sequence to a prior mass spectrometric study of isotopically labeled pyrones,[2,3] the results of an investigation of the synthetic scope and mechanism of the rearrangement are presently reported.

The reaction sequence of eq 1 is a priori reasonable since ketene aldehydes related to the hypothesized intermediates have been shown to arise photochemically from 2-pyrone,[4-7] and thermally to reclose very rapidly ($t_{1/2}$ 0.92 μsec at 45.7°). Moreover, thermal sigmatropic shifts of order [1,5] are well-established reactions.[8]

However, one need not rely upon these analogies, satisfying though they may be, since the postulated reaction sequence lends itself to experimental verification in several ways. For example, the carbonyl oxygen of a 5-substituted isomer should become the pyran ring oxygen on rearrangement to the 3-substituted isomer. Similarly, if the sulfur analogs of 2-pyrone also undergo the rearrangement, a pyran-2-thione should, on rearrangement, give a thiapyran-2-one, with an accompanying exchange of the 3 and 5 substituents. Finally, one expects that when a substituent having a lower migratory aptitude than hydrogen occupies the 6 position, it will impede the rearrangement.

Table I lists a number of substituted 2-pyrones which were pyrolyzed to determine the scope of the rearrangement. Previously unreported ^{1}H NMR data for the compounds prepared in this study are shown in Table II.

Pyrones bearing hydrogen in the 6 position and having bromine, methyl, methoxy, or acetoxy substituents in the 3 or 5 positions rearrange readily to give an equilibrium mixture of the 3- and 5-substituted isomers. Coumalyl chloride (2-pyrone-5-carbonyl chloride) does not appear to rearrange, presumably because the equilibrium for carbonyl-substituted 2-pyrones greatly favors the 5-substituted isomer. Note that 3-carbethoxy-2-pyrone rearranges completely (>99% by GLC) to ethyl coumalate, the 5-substituted isomer.[9]

Table I
Pyrolyses of 2-Pyrones

Registry no.	Compd pyrolyzed	Product	Temp, °C	% rearrangement
19978-33-7	5-Bromo-2-pyrone[b]	3-Bromo-2-pyrone[b]	490	53–54[a]
51270-32-7	5-Methyl-2-pyrone	3-Methyl-2-pyrone	650	76[c]
	3-Methoxy-2-pyrone[d]	5-Methoxy-2-pyrone	550	14[e]
51270-29-2	3-Acetoxy-2-pyrone	5-Acetoxy-2-pyrone[f]	550	33[e]
54657-80-6	3-Trifluoroacetoxy-2-pyrone	5-Trifluoroacetoxy-2-pyrone[g]	550	30[e]
	3-Carbethoxy-2-pyrone[i,j]	Ethyl coumalate[h]	540	>99
	Coumalyl chloride[k]		575	0
54657-81-7	5-Carbethoxy-6-methyl-2-pyrone	*l*	650	0
3385-34-0	4,6-Dimethyl-5-carbethoxy-2-pyrone		550	0
		m	650	0
	Pyran-2-thione[n]	Thiapyran-2-one	370	30[e]
			620	100
51270-31-6	4-Methylpyran-2-thione	4-Methylthiapyran-2-one	500	100
54657-82-8	5-Bromopyran-2-thione	3-Bromothiapyran-2-one	480	100
	4,6-Dimethylpyran-2-thione[n]		700	0

[a] Equilibrium value. [b] Reference 18. [c] After two passes through the pyrolysis tube; the first gave 72% rearrangement. [d] R. H. Wiley and C. H. Jarboe, *J. Am. Chem. Soc.*, 78, 2398 (1956). [e] Not an equilibrium value. [f] Some 3-hydroxy-2-pyrone also resulted. [g] Not isolated. Identified by ^{1}H NMR spectrum. [h] Some decarbethoxylation to 2-pyrone occurred. [i] T. B. Windholz, L. H. Peterson, and G. J. Kent, *J. Org. Chem.*, 28, 1443 (1963). [j] Reference 9. [k] J. Fried and R. C. Elderfield, *J. Org. Chem.*, 6, 566 (1941). [l] 6-Methyl-2-pyrone and 6-methylcoumalic acid were produced. [m] Complete decarbethoxylation to 4,6-dimethyl-2-pyrone occurred. [n] R. Mayer and P. Fischer, *Chem. Ber.*, 95, 1307 (1962).

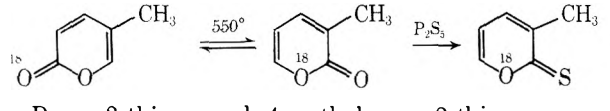
Table II
^{1}H NMR Spectra of 2-Pyrones Prepared in This Study

Registry no.	Compd	Chemical shift, δ[a] H-3	H-4	H-5	H-6	Others	Coupling constants, Hz $J_{3,4}$	$J_{3,5}$	$J_{3,6}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$	Others
31678-73-6	3-Methyl-2-pyrone		7.13	6.15	7.36	2.00 (CH_3)				6.6	2.2	5.4	~1.5 ($J_{3',4}$)
	5-Methyl-2-pyrone	6.31	7.34		7.36	2.00 (CH_3)	9.5		1.3		2.5		1.2 ($J_{5',6}$)
4394-76-7	6-Methyl-2-pyrone	~6	6.40	~6		2.3 (CH_3)	9			6.5			
22682-15-1	4-Methyl-6-chloro-2-pyrone	6.02		6.18		219 (CH_3)		1.2					1.3 ($J_{3,4'}$)
51270-28-1	3-Methoxy-2-pyrone		6.6	6.25	7.12	3.8 (CH_3)				7	1.6	5	
54657-83-9	5-Methoxy-2-pyrone[b]		7.33			3.68 (CH_3)	10				3		
496-64-0	3-Hydroxy-2-pyrone		6.7	6.2	7.15	6.0 (OH)				7.2	1.7	5.2	
	3-Acetoxy-2-pyrone		7.2	6.27	6.45	2.3				6.9	1.9	5.1	
54657-84-0	5-Acetoxy-2-pyrone	6.31	7.22		7.58	2.3 (CH_3)	10		1		3		
	3-Trifluoroacetoxy-2-pyrone		7.5	6.5	7.5					7.2	1.8	5.2	
54657-85-1	5-Trifluoroacetoxy-2-pyrone[c]	6.50	~7.5		7.95		10		1		3		
1008-44-2	3-Carbethoxy-2-pyrone		8.20	6.45	7.78	1.31 (CH_3) 4.25 (CH_2)	9.5			6.8	2.3	4.9	
25683-10-7	5-Carboxy-6-methyl-2-pyrone[d]	6.45	8.06			2.76 (CH_3)	9.5						
	5-Carbethoxy-6-methyl-2-pyrone	6.12	7.79			2.63 (6-CH_3) 1.36 (CH_3) 4.28 (CH_2)	9.5						
23639-33-0	Pyran-2-thione	7.20	7.13	6.55	7.86		9.2	1.7	1.3	6.2	1.7	5.2	
54657-86-2	3-Methylpyran-2-thione		7.10	6.44	7.75	2.30 (CH_3)				6.9	1.8	5.0	1.1 ($J_{3,4'}$), 0.8 ($J_{3',6}$) 0.3 ($J_{3',5}$)
	4-Methylpyran-2-thione	7.05		6.38	7.72	2.06 (CH_3)		1.7	1.0			5.1	1.0 ($J_{3,4'}$)
54657-87-3	4,6-Dimethylpyran-2-thione	6.97		6.20		2.07 (4-CH_3) 2.32 (6-CH_3)							1.2 ($J_{3,4'}$), ~0.5 ($J_{5,6'}$)
	5-Bromopyran-2-thione[e]	6.65	6.00		6.78		8.7		1.0		2.2		
6788-51-8	Thiapyran-2-one	6.48	7.53	6.95	7.78		10.4	0.6	1.0	7.0	2.0	9.2	
51270-30-5	4-Methylthiapyran-2-one	6.32		6.77	7.55	2.24 (CH_3)		0.9	~1			9.5	1.2 ($J_{3,4'}$)
54657-88-4	3-Bromothiapyran-2-one		7.48	6.65	7.85					7.4	1.9	9.0	
54657-89-5	5-Bromothiapyran-2-thione	7.14	6.98		7.45		10.5		1.0		2.2		

[a] Typically, spectra were obtained at 60 MHz in $CDCl_3$. When spectral complexity necessitated, solvent variation and/or use of a 220-MHz spectrometer enabled complete spectral assignments to be made. [b] This compound was not isolated, and the remaining protons were obscured by other components in the mixture. [c] Not isolated. [d] Run in $CDCl_3$–CF_3COOH (2:1). [e] Run in C_6D_6.

At elevated temperatures, several of the substituted 2-pyrones undergo fragmentation reactions. Thus, those bearing carbethoxy groups undergo partial decarbethoxylation or loss of ethylene. Similarly, a small fraction of 3-acetoxy-2-pyrone cracks to 3-hydroxy-2-pyrone.[10] However, most of the pyrones investigated can be recovered in high yield. Typically, the 3 and 5 isomers are readily separated by liquid or gas chromatography.

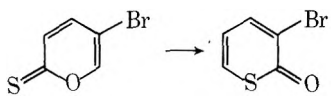
Further evidence for the rearrangement pathway of eq 1 was obtained by following an oxygen-18 label through the rearrangement. Oxygen-18-labeled 5-methyl-2-pyrone was prepared by hydrolysis of 2-ethoxy-5-methylpyrylium fluoroborate with 30% oxygen-18-enriched water. The label is expected to be exclusively in the carbonyl, since in the case of 2-pyrone labeled in the same manner, all label is lost on conversion of the enriched pyrone to pyran-2-thione.[3] The mixed 3-methyl- and 5-methyl-2-pyrones resulting from pyrolysis of the labeled sample at 550° were separated by liquid chromatography and examined by mass spectrometry. Before pyrolysis, the 5-methyl-2-pyrone contained 27.0 ± 0.5% oxygen-18; after pyrolysis, 27.4 ± 0.8%. The 3-methyl-2-pyrone resulting from the pyrolysis retains the label (26.4 ± 1.0%), as does the 3-methylpyran-2-thione prepared from it (27.1 ± 0.9%). This result is consistent with initial labeling occuring exclusively in the carbonyl, followed by a rearrangement which entails the shift of the oxygen label (eq 2).



(2)

Pyran-2-thione and 4-methylpyran-2-thione rearrange completely to the isomers having sulfur in the ring. Pyran-2-thione isomerizes more readily than any other compound studied, being 30% converted in a single pass through a 370° tube. Indeed, this isomerization is so facile that it occurs extensively during attempted gas chromatography at 160° (150° injector). Rearrangement of 4-methylpyran-2-thione to 4-methylthiapyran-2-one is complete (by ^{1}H NMR) in one pass at 500°. The quantitative rearrangement of the preceding pyran-2-thiones to thiapyran-2-one is readily understandable in view of the destabilization of a

thiocarbonyl group relative to its carbonyl isomer.[11] The rearrangement of pyran-2-thiones to thiapyran-2-ones is accompanied by exchange of the substituents in the 3 and 5 positions. 5-Bromopyran-2-thione rearranges completely to 3-bromothiapyran-2-one (eq 3).



(3)

In contrast to the facile rearrangement of pyran-2-thione, 4-methylpyran-2-thione, and 5-bromopyran-2-thione, 4,6-dimethylpyran-2-thione is unreactive even at 700°. Apparently, the methyl group in the 6 position impedes the rearrangement, a view consistent with the paucity of reports of [1,5] sigmatropic shifts of methyl groups.[12]

The ability to interchange substituents between the 3 and 5 positions of the 2-pyrone ring is of obvious synthetic application. Since most 2-pyrones are available only by multistep reaction sequences, this rearrangement can, in many cases, provide a second isomeric pyrone with little additional effort and offers additional flexibility in the initial synthetic approach, since in a number of instances, either of the isomers may be utilized. The reaction also makes thiapyran-2-ones readily available, since pyran-2-thiones are generally obtainable by the action of P_2S_5 on 2-pyrones. The usual method of obtaining thiapyran-2-ones starts from the dithiopyrones, which are generally prepared from enamines and carbon disulfide.[13,14] This earlier method gives limited control over substituents, two of which, arising from two molecules of enamine, must be the same. In the context of these rearrangements, it should be recalled that it has recently been shown possible to exchange substituents between the 4 and 6 positions of 2-pyrone by photolysis in sulfuric acid.[15]

Experimental Section

Pyrolyses of 2-pyrones were carried out by sublimation or distillation (0.1–1 Torr) through a hot Vycor tube (370–700°) packed with Pyrex helices (Table I). Isomeric composition of the product mixtures was determined by ^{1}H NMR spectroscopy and/or GLC. The 5- and 3-substituted isomers are readily distinguished by ^{1}H NMR, since there are two large vicinal coupling constants (ca. 7 and 5 Hz) in the 3-substituted isomers and only one (ca. 10 Hz) in the 5-substituted isomers.[16] The isomeric sulfur analogs are also readily distinguishable; the pyran-2-thiones are brilliant orange whereas the thiapyran-2-ones are almost colorless. Consistencies in the ^{1}H NMR spectra of the sulfur analogs were also observed. Substitution of a sulfur for the carbonyl oxygen results in a downfield shift of H-3 of about 0.8–1.0 ppm,[17] but in no significant changes in the proton coupling constants. Replacing the ring oxygen with sulfur, however, shifts H-5 downfield by 0.4–0.5 ppm and also increases $J_{5,6}$ to 9.0–9.5 Hz. As in the 2-pyrones, the substitution pattern in the sulfur analogs is revealed by the number of large vicinal coupling constants. In addition, most of the new pyrones isolated were examined by mass spectrometry. All gave appropriate molecular ions.

5-Bromopyran-2-thione. A solution of 5-bromo-2-pyrone[18] (2.0 g) in 30 ml of benzene was heated under reflux with 2.54 g of P_2S_5. At 24-hr intervals, the solution was decanted from the P_2S_5 residue onto similar amounts of fresh P_2S_5. After 4 days the solution was chromatographed on 100 g of silica gel with benzene.

The first colored band gave 0.03 g of red crystalline material which, after sublimation at 50° (5 Torr), melted at 163° dec. The ^{1}H NMR spectrum (Table II) is appropriate for 5-bromothiapyran-2-thione. The mass spectrum has base peaks at *m/e* 162 and 164 (M − CS) and molecular ions at *m/e* 206 and 208 ($C_5H_3BrS_2$).

The second colored band afforded 0.2 g of orange crystals melting at 122–126° dec after sublimation [50° (5 Torr)]. The ^{1}H NMR spectrum (Table II) is consistent with that expected for 5-bromopyran-2-thione. The mass spectrum has the molecular ions at *m/e* 190 and 192 (C_5H_3BrOS) as the base peaks, with prominent ions at *m/e* 146 and 148 (M − CS) and *m/e* 162 and 164 (M − CO). On standing under nitrogen but exposed to light, this material is partially converted into an insoluble, high-melting, nonvolatile solid. The mass spectrum of 5-bromopyran-2-thione thus stored shows, in addition to the expected peaks, weak "triplets" at *m/e* 380, 382, and 384, indicative that a dimerization has occurred.

A third chromatographic fraction afforded 1.6 g of unreacted 5-bromo-2-pyrone.

3-Acetoxy-2-pyrone.[19] A solution of 3-hydroxy-2-pyrone (0.25 g) in 10 ml of acetyl chloride was heated under reflux, until after 5 hr ^{1}H NMR showed that acetylation was complete. The excess acetyl chloride was removed under vacuum, and the residual oil was subjected to molecular distillation at 0.1 Torr. After recrystallization from cold diethyl ether, the 3-acetoxy-2-pyrone melts at 34–36°.

3-Trifluoroacetoxy-2-pyrone. A solution of 3-hydroxy-2-pyrone (1.0 g) in ca. 5 g of trifluoroacetic anhydride was allowed to stand at 25° for 18 hr, after which time ^{1}H NMR showed that no 3-hydroxy-2-pyrone remained. The solvent was removed under vacuum to leave an oil which contained a trace of trifluoroacetic acid. The 3-trifluoroacetoxy-2-pyrone was pyrolyzed without further work-up to avoid hydrolysis.

2-Ethoxy-5-methylpyrylium Fluoroborate. To a mixture of 5-methyl-2-pyrone (0.33 g) and triethyloxonium fluoroborate[20] (0.65 g) was added 0.65 g of methylene chloride, and the homogeneous mixture was allowed to stand for 18 hr. After removal of the solvent, ^{1}H NMR showed about 85% conversion of the pyrone to the salt. The mixture was redissolved in 2 g of methylene chloride and allowed to stand for 24 hr, by which time alkylation of the pyrone was about 90% complete by ^{1}H NMR. Addition of 20 ml of ether caused separation of the salt as a dark brown oil. Repeated washing with ether afforded noncrystalline 2-ethoxy-5-methylpyrylium fluoroborate which, by ^{1}H NMR, contained only a trace of 5-methyl-2-pyrone and triethyloxonium fluoroborate: ^{1}H NMR (CH_2Cl_2) δ 1.55 (t, J = 7 Hz, 3 H, CH_3), 2.32 (d, J = 1 Hz, 3 H, CH_3), 4.88 (q, J = 7 Hz, 2 H, CH_2), 7.35 (dd, J = 9, 1 Hz, H-3), 8.40 (m, H-6), 8.51 (dd, J = 9, 2 Hz, H-4).

5-Methyl-2-pyrone (C=^{18}O). To the preceding oxonium salt was added 0.18 g of water containing 30.0% oxygen-18. After 2 hr at 25°, the mixture was taken into ether and treated at 0° for 3 hr with 2 g of $NaHCO_3$. It was then filtered; the $NaHCO_3$ was washed with more ether. The ether was removed under vacuum to leave 0.28 g of brown oily 5-methyl-2-pyrone which showed no impurities by ^{1}H NMR and which (by mass spectrometry) contained 27.0 ± 0.5% oxygen-18.

Pyrolysis of 5-Methyl-2-pyrone (C=^{18}O). The labeled 5-methyl-2-pyrone (0.28 g) was pyrolyzed at 450° to afford 0.22 g of pyrolysate. The 3-methyl- and 5-methyl-2-pyrone were separated chromatographically (silica gel, methylene chloride), the former being eluted first. ^{1}H NMR verified the completeness of separation. Mass spectrometry indicated isotope enrichments of 26.4 ± 1.0% in the 3-methyl-2-pyrone and 27.4 ± 0.8% in the 5-methyl-2-pyrone.

3-Methylpyran-2-thione. The aforementioned labeled 3-methyl was converted to the thione by the method used to prepare 5-bromopyran-2-thione and was chromatographed on silica with chloroform. The initially eluted yellow material was identified as 3-methylpyran-2-thione by ^{1}H NMR. Further elution gave unreacted 3-methyl-2-pyrone. The thione was examined by mass spectrometry and found to contain 27.1 ± 0.9% oxygen-18 enrichment.

Preparation of 4-Methyl-6-chloro-2-pyrone.[19] Over 15 min, 88 g of PCl_5 was added to a slurry of 50.6 g of 3-methylglutaconic anhydride[21] in 100 ml of $POCl_3$. Hydrogen chloride was evolved, and the anhydride dissolved to give a dark red solution. After 1 hr at 95°, ^{1}H NMR showed ca. 75% conversion. More PCl_5 (20 g) was added, and the heating was continued. After 1 hr, no anhydride could be detected by ^{1}H NMR. The $POCl_3$ was removed under vacuum and the crude material was distilled at 135° (~20 Torr) to give 4-methyl-6-chloro-2-pyrone as an oil which crystallized on cooling.

Preparation of 4-Methyl-2-pyrone.[19] Zinc dust (30 g) was added slowly to a solution of 4-methyl-6-chloro-2-pyrone (15.2 g) in 75 ml of acetic acid, held at 0°. The mixture was stirred at 25° overnight, then filtered under nitrogen. The zinc was washed with ether, and the combined filtrates were concentrated under vacuum. The residual oil was stirred with ice and neutralized with Na_2CO_3. After filtration of the precipitated zinc salts, the aqueous filtrate was extracted three times with several times its own volume of ether to afford, on solvent removal, 10.5 g of 4-methyl-2-pyrone as a yellow oil showing no impurities by ^{1}H NMR. This material was distilled at 115° (6 Torr).

4-Methylpyran-2-thione.[19] Using the previously described

P_2S_5 method, 4-methyl-2-pyrone (2.0 g) afforded 2.4 g of pasty yellow crystals which were chromatographed on silica gel with a mixture of pentane and methylene chloride. The heart cut of the yellow band gave 1.75 g of yellow solid which afforded 1.0 g of 4-methylpyran-2-thione, mp 70–71°, after recrystallization from cyclohexane–benzene.

Preparation of Methyl 4-Formylpentanoate. The enamine from pyrrolidine and propionaldehyde[22] (230 g) was added to freshly distilled, neat methyl acrylate (195 g). A yellow color and an exothermic reaction ensued. The temperature was kept below 40° by cooling, and, after 1 hr, the colorless mixture was heated on a steam bath for several hours.

A portion of the reaction mixture (27 g), while chilled in ice, was treated with 11.5 ml of concentrated hydrochloric acid. After 2 hr, this mixture was extracted twice with ether and the combined extracts were washed with water and saturated sodium chloride solution, dried over Drierite, and concentrated under vacuum to leave methyl 4-formylpentanoate (84%) as a colorless oil: ^{1}H NMR (CCl_4) δ 9.21 (1 H, d, J = 1.5 Hz, CHO), 3.64 (3 H, s, OCH_3), 1.5–2.6 (5 H, m, aliphatic), 1.12 (3 H, d, J = 7 Hz, CH_3); dinitrophenylhydrazine mp 90.5–91.5° (ethanol).

Preparation of 4-Formylpentanoic Acid. The preceding methyl ester (257 g) was hydrolyzed by treatment at 25° with a solution of 232 g of K_2CO_3 in 1 l. of water with subsequent addition of 500 ml of methanol. It is necessary to make the ester basic before methanol is added, to avoid formation of the dimethyl acetal. After 12 hr at 25°, the desired acid was isolated by removal of the methanol under vacuum and ether extraction of the acidified hydrolysis mixture. Evaporation of the ether afforded 195 g of crude acid (84%). A portion of this acid was purified by distillation [110° (3 Torr)]: ^{1}H NMR (CCl_4) δ 10.45 [1 H, s, COOH), 8.96 (1 H, s, CHO), 1.4–2.8 (5 H, m, aliphatic), 1.16 (3 H, d, J = 7 Hz, CH_3); dinitrophenylhydrazone mp 167.5–169° (ethanol). Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.12; H, 7.65.

Preparation of 5-Methyl-3,4-dihydro-2-pyrone. The procedure of Pettit et al.[23] was followed, using 15.7 g of 4-formylpentanoic acid. The crude 5-methyl-3,4-dihydro-2-pyrone was obtained as a colorless oil (64%) and was purified by distillation [75° (5 Torr)]: ^{1}H NMR (220 MHz, CCl_4) δ 6.3 (1 H, dt, J = 1.5, 1.5 Hz, vinyl), 2.55 (2 H, br t, J = 7.5 Hz, CH_2CO), 2.30 (2 H, br t, J = 7.5 Hz, allylic CH_2), 1.68 (3 H, dt, J = 1.5, 0.9 Hz, CH_3). Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.23; H, 7.16.

Preparation of 5-Methyl-2-pyrone.[19] The dihydropyrone (2.25 g) was brominated with *N*-bromosuccinimide as described by Pettit et al.[23] and dehydrobrominated with 1,5-diazabicyclo-[4.3.0]non-5-ene. On distillation, 5-methyl-2-pyrone was obtained in 40% yield.

Registry No.—P_2S_5, 1314-80-3; acetyl chloride, 75-36-5; trifluoroacetic anhydride, 407-25-0; 2-ethoxy-5-methylpyrylium fluoroborate, 54657-91-9; triethyloxonium fluoroborate 368-39-8; 3-methylglutaconic anhydride, 54657-92-0; 4-methyl-2-pyrone, 22682-12-8; methyl 4-formylpentanoate, 40630-06-6; methyl 4-formylpentanoate 2,4-DNP, 54657-93-1; pyrrolidine and propionaldehyde enamine, 13937-88-7; 4-formylpentanoic acid, 3619-43-0; 4-formylpentanoic acid 2,4-DNP, 3770-62-5; 5-methyl-3,4-dihydro-2-pyrone, 54657-94-2.

References and Notes

(1) W. H. Pirkle, H. Seto, and W. V. Turner, *J. Am. Chem. Soc.*, **92**, 6984 (1970).
(2) W. H. Pirkle and M. Dines, *J. Am. Chem. Soc.*, **90**, 2318 (1968), have described these labeled 2-pyrones.
(3) W. H. Pirkle and W. V. Turner, *J. Org. Chem.*, **40**, 1644 (1975).
(4) W. H. Pirkle and L. H. McKendry, *J. Am. Chem. Soc.*, **91**, 1179 (1969).
(5) O. L. Chapman, C. L. McIntosh, and J. Pacansky, *J. Am. Chem. Soc.*, **95**, 244 (1973).
(6) R. G. S. Pong and J. S. Shirk, *J. Am. Chem. Soc.*, **95**, 248 (1973).
(7) A. Krantz, *J. Am. Chem. Soc.*, 96, 4992 (1974).
(8) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, N.Y., 1970, p 123.
(9) This result has been independently reported: C. R. Engel, A. F. de Krassny, A. Belanger, and G. Dionne, *Can. J. Chem.*, **51**, 3263 (1973).
(10) Isolation of 3-hydroxy-2-pyrone from this pyrolysis is somewhat puzzling, since 3-hydroxy-2-pyrone itself is completely converted under similar conditions to noncondensable products (−78°, 1 Torr). However, it is perhaps relevant to the latter fragmentation that hydrolysis of a mixture of 3- and 5-trifluoroacetoxy-2-pyrone affords a mixture containing 3-hydroxy-2-pyrone and a number of other components, none of which has a ^{1}H NMR spectrum judged to be appropriate for 5-hydroxy-2-pyrone.
(11) P. Beak, D. S. Mueller, and J. Lee, *J. Am. Chem. Soc.*, **96**, 3867 (1974).
(12) R. B. Woodward and R. Hoffmann (ref 8, p 123n) refer to only one dubious example.
(13) R. Mayer, W. Broy, and R. Zahradnik, *Adv. Heterocycl. Chem.*, **8**, 219 (1967).
(14) Although dithiopyrones may also be prepared from 2-pyrones by conversion to pyran-2-thiones followed by reaction with potassium sulfide, hydrolysis of dithiopyrones to thiapyran-2-ones typically proceeds in low yield.[13]
(15) J. W. Pavlik and E. L. Clennan, *J. Am. Chem. Soc.*, **95**, 1697 (1973).
(16) W. H. Pirkle and M. Dines, *J. Heterocycl. Chem.*, **6**, 1 (1969).
(17) Similar downfield shifts of H-3 of pyridthiones relative to those of H-3 of pyridones have been observed by W. E. Stewart and T. H. Siddall, *J. Phys. Chem.*, **74**, 2027 (1970), and attributed to increased magnetic anisotropy of thione over carbonyl. However, in the pyridthiones, consistent downfield shifts of H-5 and H-6 were also observed.
(18) W. H. Pirkle and M. Dines, *J. Org. Chem.*, **34**, 2239 (1969).
(19) Cmr data for this compound are found in W. V. Turner and W. H. Pirkle, *J. Org. Chem.*, **39**, 1935 (1974).
(20) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).
(21) C. T. Bedford, J. M. Forrester, and T. Money, *Can. J. Chem.*, **48**, 2645 (1970).
(22) G. Opitz, H. Helmann, and H. W. Schubert, *Justus Liebigs Ann. Chem.*, **623**, 112 (1959).
(23) G. R. Pettit, D. C. Fessler, K. D. Paull, P. Hofer, and J. C. Knight, *J. Org. Chem.*, **35**, 1398 (1970).

Halomethyl Metal Compounds. 75. Organomercury Reagents for Room Temperature Dihalocarbene Generation[1]

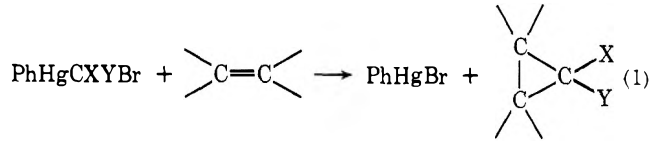
Dietmar Seyferth* and Carol K. Haas[2]

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

Received November 22, 1974

The new organomercury reagents $PhHgCCl_2I$, PhHgCClBrI, and $PhHgCBr_2I$ were prepared and found to be effective divalent carbon transfer agents. They react with carbenophiles within 1–4 days at room temperature and within minutes at 80°. The reasons for their high reactivity are discussed.

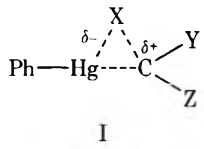
Phenyl(bromodichloromethyl)mercury, phenyl(dibromochloromethyl)mercury, and phenyl(tribromomethyl)mercury react with a wide variety of carbenophiles (e.g., eq 1, which shows their reaction with an olefin).[3,4] At 80°, these reactions are rapid and go to completion within 2 hr. At lower temperatures, the rates are correspondingly slower. These reactions proceed even at room temperature, but 16–18 days are required in order to obtain high product yields.[5]



X, Y
Cl, Cl
Cl, Br
Br, Br

The advantages of these organomercury reagents are that they release dihalocarbenes under neutral conditions by a direct carbene extrusion mechanism, without intervention of other intermediates such as the trihalomethyl anion,[6] and that their divalent carbon transfer reactions proceed in high yield because carbene-diverting side reactions do not intrude with most carbenophiles.

The transition state which is believed to be involved in the carbene extrusion step is I,[6] i.e., a concerted process in-



I

volving intramolecular nucleophilic attack by X at mercury and heterolytic Hg–C and C–X bond fission to give PhHgX and the carbene CYZ. Consequently, if all other factors are held constant in I, one might expect that the carbene extrusion reactivity would change as X was varied in the order I > Br > Cl, since this is the well-known order of halide ion nucleophilicity and since the C–X bond energies increase in the order C–I < C–Br < C–Cl. In earlier work we had found $PhHgCCl_3$ (PhHgCl eliminated) to be a much less reactive dichlorocarbene source than $PhHgCCl_2Br$ (PhHgBr eliminated),[3,4] so a phenyl(trihalomethyl)mercury compound whose decomposition would involve phenylmercuric iodide elimination would be expected to be rather more reactive than an analogous one in which the decomposition proceeded by way of phenylmercuric bromide elimination. Accordingly, we decided to investigate the synthesis, thermal stability, and preparative utility of mercurials of the type PhHgCXYI (X = Cl, Br).

Results and Discussion

Our general procedure for the preparation of $PhHgCCl_2Br$ (eq 2)[7] has been adapted, with minor varia-

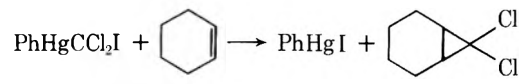
$$PhHgCl + Me_3COK + HCCl_2Br \xrightarrow{THF,\ -25^\circ} PhHgCCl_2Br + Me_3COH + KCl \quad (2)$$

tions, to the synthesis of many other organomercurials.[4] This procedure also could be applied successfully to the preparation of $PhHgCCl_2I$, PhHgCClBrI, and $PhHgCBr_2I$, but some modifications were required in view of the very limited stability of these reagents.

Several attempts to prepare phenyl(iododichloromethyl)mercury from phenylmercuric chloride in THF according to the published[7] procedure failed; phenylmercuric iodide was the only organomercury product isolated. Its isolation, together with the observation of the yellow color of the CCl_2I^- anion during the addition of $CHCl_2I$ to the PhHgCl–Me_3COK mixture and its apparent discharge on reaction with phenylmercuric chloride, suggested that the desired mercurial was being formed but that it was too reactive under the conditions of work-up to allow isolation. Consequently, in subsequent reactions, lower reaction temperatures were used, a minimum quantity of reaction solvent mixture was used, and all extraction solvents were chilled to 0° before use; in addition, all steps of the synthesis were carried out with maximum dispatch. In the successful preparation of $PhHgCCl_2I$, the iododichloromethane was added to the slurry of phenylmercuric chloride and potassium *tert*-butoxide in a minimum amount of 1:1 THF–diethyl ether at −70°. Immediately upon completion of the addition the work-up procedure was initiated and the desired organomercury reagent was obtained consistently in about 50% yield. An analytically pure sample could be obtained, but the extreme reactivity of phenyl(iododichloromethyl)mercury makes its complete purification extremely difficult and inefficient. The attempt to recrystallize this material slowly always results in some decomposition to phenylmercuric iodide. For practical purposes it is better to filter a solution of the crude product in dichloromethane into pentane which has been chilled to −78° and collect the solid which precipitates. The microcrystalline yellow solid thus obtained has a purity of 75–90%, as determined by its reaction with cyclohexene. In this synthesis it is essential that all operations, in particular the removal of solvents from the reaction mixture, be carried out *as quickly as possible.*

The application of this modified method to the synthesis of phenyl(iodobromochloromethyl)mercury and phenyl(iododibromomethyl)mercury also proved successful. Both mercury compounds also are yellow, microcrystalline, and very reactive solids. All three of the new reagents prepared were found to be stable for several weeks at 0° as the dry solid; they also are stable toward oxygen. However, care must be taken to avoid contamination of these materials with traces of oxygen-containing solvents such as THF, diethyl ether, acetone, methanol, or ethanol. When traces of any of these are present, the solid mercurials will invariably undergo exothermic and complete decomposition. Such a catalytic decomposition even occurred with a sample of $PhHgCCl_2I$ which was being stored at 0° in the refrigerator in a flask that had been rinsed with acetone but apparently still contained traces of the rinse liquid. The exact nature of this decomposition is not known; it is not effected by atmospheric oxygen or by light and is in accord with the observed lower stability of halomethylmercurials in ether solvents when compared to hydrocarbon solvents. Presumably an exothermic chemical reaction of the mercurial with the oxygen-containing solvent is involved which generates a "hot spot" in the solid sample and provides the activation energy for further (rapid) decomposition. Moistening of these mercurials with hexane, benzene, or dichloromethane did not result in such decomposition. A similar phenomenon has been observed with phenyl(fluorodibromomethyl)mercury, which is another reactive, "room temperature" dihalocarbene precursor.[8]

As expected, phenyl(iododichloromethyl)mercury is a very reactive dichlorocarbene transfer reagent. When this mercurial was stirred with an excess of cyclohexene in benzene solution at room temperature, the yellow color of the mercury compound was discharged completely within 24 hr, while white phenylmercuric iodide precipitated. 7,7-Dichloronorcarane was formed in 89% yield during this time (eq 3). A similar transfer of CCl_2 to cyclohexene was



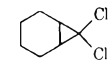
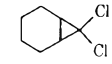
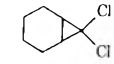
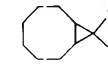
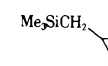
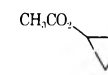
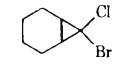
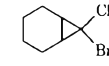
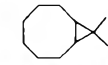
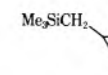
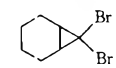
(3)

found to occur *within seconds* at 80°. Indeed, a 71% yield of 7,7-dichloronorcarane could be obtained by stirring a solution of $PhHgCCl_2I$ with cyclohexene at 0° for 8 days. A comparison of similar CCl_2 transfer to cyclohexene at 80° and at room temperature using $PhHgCCl_2Br$ (vide supra) shows the dramatic effect of changing the halogen atom X in $PhHgCCl_2X$ from Br to I.

The transfer of dichlorocarbene from $PhHgCCl_2I$ to other carbenophiles could be effected in high yield within 24 hr at room temperature; these results are included in Table I. Again, the progress of these reactions could be followed by noting the gradual disappearance of the yellow color of the reagent. In no cases were any organic iodine products observed.

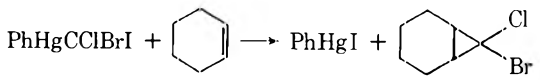
Phenyl(iodobromochloromethyl)mercury served as a

Table I
Divalent Carbon Transfer Reactions of Phenyl(iododihalomethyl)mercury Compounds

Mercury reagent[a] (mmol)	Carbenophile (mmol)	Ml of benzene	Reaction time	Reaction temp, °C	Product (% yield)	PhHgI, % yield
$PhHgCCl_2I$ (10.5)[c]	 (30)[d]	15	24 hr	25	 (89)	92
$PhHgCCl_2I$ (10)	 (30)	25	<1 min	80	 (85)	94
$PhHgCCl_2I$ (7.5)	 (30)	15	8 days	0	 (71)	80
$PhHgCCl_2I$ (7.3)	 (30)[e]	15	24 hr	25	 (93)	93
$PhHgCCl_2I$ (9.8)	$Me_3SiCH_2CH{=}CH_2$ (30)[f]	15	24 hr	25	 (95)	88
$PhHgCCl_2I$ (10)	$CH_3CO_2CH{=}CH_2$ (30)[g]	15	24 hr	25	 (38)	72
$PhHgCCl_2I$ (7.1)	Et_3SiH (30)	15	24 hr	25	Et_3SiCCl_2H (83)	82
PhHgCClBrI (10)[h]	 (30)	20	4 days	25	 (75)[b]	80
PhHgCClBrI (10)	 (30)	50	<10 min	80	 (81)[b]	82
PhHgCClBrI (10)	 (30)	20	4 days	25	 (83)[b]	87
PhHgCClBrI (10)	$Me_3SiCH_2CH{=}CH_2$ (30)	20	4 days	25	 (78)[b]	80
PhHgCClBrI (10)	Et_3SiH (30)[i]	20	4 days	25	$Et_3SiCHBrCl$ (60)	84
$PhHgCBr_2I$ (10.4)[j]	 (30)	20	7 days	25	 (65)	70

[a] Number of millimoles of active reagent in sample used (usually 70–90% purity). [b] Mixture of isomers. [c] Registry no., 33441-85-9. [d] Registry no., 110-83-8. [e] Registry no., 931-88-4. [f] Registry no., 762-72-1. [g] Registry no., 108-05-4. [h] Registry no., 35349-96-3. [i] Registry no., 617-86-7. [j] Registry no., 54724-58-2.

source of chlorobromocarbene at room temperature. However, a reaction time of 4 days was required with cyclohexene in benzene solution before the yellow color of the mercury reagent had disappeared and thin layer chromatography[3] indicated that the starting material had been consumed. Again, exclusive elimination of phenylmercuric iodide appeared to be occurring, since only chlorobromocarbene-derived products were obtained (eq 4). Transfer of



(4)

CClBr from this mercurial was complete within minutes at 80°.

The divalent carbon transfer reactivity of phenyl(iododibromomethyl)mercury, which could not be obtained analytically pure, was investigated only briefly. A solution of this compound and cyclohexene in benzene required stirring for 7 days at room temperature before TLC indicated that the starting material had been consumed. Thus $PhHgCBr_2I$ is only about two times more reactive than $PhHgCBr_3$. Furthermore, the product yields obtained with $PhHgCBr_2I$ unaccountably were not high (60–65%), so no advantage can be gained by using this reagent.

All of the dihalocarbene transfer reactions effected with these new reagents are summarized in Table I.

A comparison of the periods of time required for complete decomposition at room temperature of various phenyl(trihalomethyl)mercury reagents in the presence of the same carbene trap, cyclohexene, is given in Table II. In all

Table II
Times Required for Decomposition in Benzene Solution in the Presence of Cyclohexene at Room Temperature

Compd	Registry no. (X = Br)	X = Br[5]	X = I
$PhHgCCl_2X$	3294-58-4	18 days	24 hr
PhHgCClBrX	3294-59-5	16 days	4 days
$PhHgCBr_2X$	3294-60-8	15 days	7 days

cases substitution of an iodine for a bromine as the eliminated halide results in increased thermal lability. This is entirely in accord with the ideas discussed in the introduction.

The variation of decomposition rate among the various iodine-containing mercurials possibly can be rationalized in terms of the ability of the other halogen substituents to stabilize the carbene center. Thus chlorine provides better p_π–p_π stabilization at the incipient carbene center than does bromine. Our other studies[9] have provided evidence that the stability of the extruded carbene is an important factor in determining the effectiveness of a halomethylmercury compound; the more stable the carbene formed, the faster its rate of extrusion.

The lack of practical utility of $PhHgCBr_2I$ already has been noted. Another factor which is of some importance as far as the application of these new reagents in synthesis is concerned is the availability of the required haloforms. The preparation of dibromoiodomethane and chlorobromoiodomethane is cumbersome and this immediately detracts

from any potential attractiveness of $PhHgCBr_2I$ and PhHgCClBrI. On the other hand, the preparation of dichloroiodomethane is not difficult. However, in spite of this fact and in spite of the attractive synthetic applicability of $PhHgCCl_2I$ as described above, this reagent cannot be recommended as a "routine" CCl_2 source. Its handling requires the greatest care in view of its thermal lability and its ready catalytic decomposition by various common solvents. Prudence dictates that its synthesis and storage be carried out on a relatively modest scale—no more than about 0.25 mol. As a result, for room-temperature applications the less reactive but equally reliable[5] and much more easily prepared and handled $PhHgCCl_2Br$ will be preferable.[10]

Experimental Section

General Comments. All reactions were carried out in flame-dried glassware under an atmosphere of prepurified nitrogen. Tetrahydrofuran (THF), benzene, and hexane (all reagent grade) were distilled from sodium benzophenone ketyl before use.

Infrared spectra were recorded using a Perkin-Elmer 257 or 457A grating infrared spectrophotometer, NMR spectra using a Varian Associates T60 or a Perkin-Elmer Hitachi R-20B spectrometer. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Chloroform (δ 7.27 ppm) and dichloromethane (δ 5.30 ppm) also were used as internal standards.

Gas chromatography (GLC) was used routinely for isolation of pure samples, for determination of purity, and for yield determinations using an appropriate internal standard. All columns were packed with acid-washed dimethyldichlorosilane-treated Chromosorb W.

Preparation of Haloforms. Iododichloromethane was prepared by a modification of the procedure of Soroos and Hinkamp[11] for the preparation of iodoform. In this case a large excess (1200 ml) of chloroform was treated with iodomethane (400 g) and a catalytic amount of aluminum chloride (30 g) at reflux until evolution of chloromethane ceased. In this manner, $CHCl_2I$ could be prepared in 54% yield on up to a 7-mol scale with no difficulty. Iodobromochloromethane and iododibromomethane were prepared by treatment of dibromochloromethane and bromoform, respectively, with sodium methoxide in the presence of sodium iodide by the method of Hine and Prossner.[12] In both cases, the yields were low and careful fractional distillation was required to separate product and starting material. All three haloforms are very sensitive toward light.

An alternate procedure for the preparation of iododibromomethane was developed which involves the iodination of $CHBr_2MgCl$. This has the advantage of making the isolation of the product easier, since no bromoform remains in the reaction mixture.

Into a 2-l. flask equipped with mechanical stirrer, addition funnel, pentane thermometer, and nitrogen inlet were placed 69 ml (0.8 mol) of bromoform and 500 ml of THF. The solution was cooled to −80° and 0.8 mol of isopropylmagnesium bromide was added over a 1-hr period, while the temperature was kept below −70°. In portions, 200 g (0.8 mol) of iodine was added over a 10-min period via a transfer tube. The reaction mixture at −70° was stirred for 6 hr and subsequently was hydrolyzed with ca. 100 ml of saturated ammonium chloride solution and filtered to remove the precipitated magnesium salts. The organic layer was reduced in volume to 400 ml by rotary evaporation and the remaining brown liquid was washed with several portions of 1 *M* sodium thiosulfate solution totaling 400 ml in volume. The residue was trap-to-trap distilled (50°, 0.2 mm); the distillate was washed with 100 ml of 1 *M* thiosulfate solution, which removed all the remaining brown color. Redistillation (10-cm Vigreux column) yielded 50 g (25%) of iododibromomethane, bp 62° (2.8 mm), $n^{25}D$ 1.6807.

Preparation of Phenyl(iododichloromethyl)mercury. Into a 1-l. flask equipped with mechanical stirrer, pressure-equalizing dropping funnel, pentane thermometer, and nitrogen inlet were placed 50.0 g (0.16 mol) of phenylmercuric chloride and 150 ml of diethyl ether. To this slurry, chilled to −55°, was added, over a 5-min period, 25 g (0.22 mol) of potassium *tert*-butoxide (M. S. A.) in 120 ml of THF. The resulting mixture was stirred at −55° for a 15-min period, during which time most of the mercuric halide dissolved. To this was added, over a 10-min period, keeping the temperature below −55°, 40.0 g (0.18 mol) of iododichloromethane. After 3 min of additional stirring, the solvents were removed rapidly in vacuo from the dark yellow-green reaction mixture. To the colored solids were added 75 ml of water and 600 ml of chilled (ca. 0°) methylene chloride. The methylene chloride layer was decanted through a paper towel into a chilled flask (ca. −70°). The water layer was extracted with two 100-ml portions of methylene chloride. The filtered organic layers were combined and the solvent was removed rapidly on a rotary evaporator. The yellow solid was dissolved in 200 ml of chilled methylene chloride and the solution was filtered into 600 ml of pentane chilled in a Dry Ice–acetone bath. After 3 min, 40 g (52%) of the mercurial was collected by filtration as a yellow, microcrystalline solid. Evaporation of the mother liquor to 150 ml produced another 5 g (6%) of the desired material. The solid was identified as phenyl(iododichloromethyl)mercury on the basis of the following: mp 72° (instant decomposition); ir (CCl_4) 3030 m, 3025 m, 1805 w, 1630 m, 1573 w, 1480 m, 1433 s, 1330 w, 1300 w, 1065 w, 1030 m, 1003 m, 915 w, 850 w, 735 m, 700 s, 633 cm^{-1} m; NMR ($CDCl_3$) δ 7.30 (s, 5, C_6H_5).

Anal. Calcd for $C_7H_5Cl_2IHg$: C, 17.24; H, 1.03; I, 26.04. Found: C, 17.09; H, 1.08; I, 25.72. (Calcd for C_6H_5HgI: C, 17.80; H, 1.25; I, 31.37.)

Thermal Analysis of Phenyl(iododichloromethyl)mercury. Into a tared 50-ml flask with magnetic stir bar were placed 1.498 g of the crude title mercurial and 2 ml of cyclohexene. The mercurial solution was stirred at 40° for 12 hr, during which time PhHgI was precipitated. All volatile materials (cyclohexene and 7,7-dichloronorcarane by GLC) were removed by evacuation (40°, 0.07 mm) for 5 hr and the flask was reweighed. A 0.2170-g weight loss was noted. Calculations as follows indicated a sample purity of 86%: 0.2170 g of dichlorocarbene formed/0.0829 g/mol of dichlorocarbene = 2.62 mmol of carbene in sample; 2.62 mmol × 487.5 mg of $PhHgCCl_2I$/mmol = 1280 mg of $PhHgCCl_2I$ in sample; 1.280 g of $PhHgCCl_2I$/1.498 g of sample = 86% pure by weight.

Catalytic Solvent-Induced Decomposition of Phenyl(iododichloromethyl)mercury. Into a 10-ml erlenmeyer flask was placed ca. 0.2 g of the title mercurial. Two drops of the appropriate solvent was placed directly onto the solid. When acetone, THF, methanol, ethanol, or ether was used, after 10 sec had elapsed, decomposition accompanied by emission of white fumes abruptly commenced. When hexane, benzene, methylene chloride, chloroform, or water was employed, no such decomposition ensued; the mercurial remained unchanged. Similar results were obtained in flasks flushed with argon or air, or in flasks exposed to or shielded from the light.

Preparation of Phenyl(iodobromochloromethyl)mercury. Into a 1-l. flask equipped with mechanical stirrer, addition funnel, pentane thermometer, and nitrogen inlet were placed 50 g (0.16 mol) of phenylmercuric chloride and 150 ml of anhydrous diethyl ether. To this slurry, chilled to −65°, was added over a 3-min period 25 g (0.22 mol) of potassium *tert*-butoxide (M. S. A.) in 120 ml of THF. This mixture was stirred at −65° for 15 min. To this was added over a 10-min period, while the temperature was kept below −60°, 44 g (0.18 mol) of freshly distilled iodobromochloromethane. After the solvents had been removed from the deep orange solution at reduced pressure, 800 ml of chilled methylene chloride and 75 ml of cold water were added to the remaining solids. The yellow organic layer was rapidly filtered into a flask chilled to −70°. After removal of the methylene chloride, the solid residue was dissolved in 150 ml of methylene chloride and the solution was filtered into 600 ml of hexane chilled to −70°. After 5 min of chilling, 61 g of yellow, microcrystalline phenyl(iodobromochloromethyl)mercury was filtered with suction. The mother liquor was reduced in volume to 200 ml and an additional 4 g of solid was collected to give a total yield of 76%. The dry mercurial was stored in the freezer. A twice recrystallized sample melted at 78° with decomposition: ir (Nujol mull) 1500 w, 1435 m, 1370 m, 1025 w, 1000 w, 735 s, 720 s, 695 m, 660 w, 635 cm^{-1} m; NMR ($CDCl_3$) δ 7.32 (s, 5, C_6H_5).

Anal. Calcd for $C_7H_5BrClIHg$: C, 15.80; H, 0.95; I, 23.86; Hg, 37.70. Found: C, 15.62; H, 0.87; I, 23.74; Hg, 38.06.

Preparation of Phenyl(iododibromomethyl)mercury. To a slurry of 50 g (0.16 mol) of phenylmercuric chloride in 120 ml of diethyl ether chilled to −70° was added a solution of 25 g (0.22 mol) of potassium *tert*-butoxide (M. S. A.) in 100 ml of THF over a period of 5 min. This slurry was stirred for 1 hr, and then 60 g (0.20 mol) of iododibromomethane was added over a 7-min period while the temperature was maintained below −60°. The solvents were removed at reduced pressure from the yellow-orange solution, and the remaining solid was treated with 600 ml of chilled methylene chloride and 50 ml of water. The solvents were removed quickly from the filtered, orange organic layer. The remaining solid was dissolved in 150 ml of methylene chloride and filtered into 600 ml

of hexane chilled to −70°. After the filtrate had been chilled for 5 min, 45 g (49%) of a yellow, microcrystalline solid was removed by filtration. Satisfactory elemental analysis on a twice recrystallized sample of mp 85° dec was not obtained but the spectral data support the assignment of structure as phenyl(iododibromomethyl)-mercury. Similar features to those for $PhHgCCl_2I$ and PhHgCClBrI are seen in the infrared spectrum. TLC indicates that only one compound is present: ir (Nujol mull) 3060 w, 2857 m, 1523 w, 1475 m, 1460 m, 1258 w, 1058 w, 1021 w, 1012 w, 992 w, 908 w, 798 w, 728 s, 693 cm^{-1} s; NMR ($CDCl_3$) δ 7.38 (s, 5, C_6H_5).

Anal. Calcd for $C_7H_5Br_2IHg$: C, 14.58; H, 0.88. Found: C, 11.91; H, 0.98.

Several attempts were made to recrystallize this mercurial more slowly. While this was occasionally successful, several times a dark red color appeared as phenylmercuric halide was rapidly deposited. Once this decomposition commenced, none of the desired mercurial could be recovered.

Reaction of Phenyl(iododichloromethyl)mercury with Cyclohexene at Room Temperature. Into a 50-ml flask equipped with thermometer and nitrogen inlet were placed 2.46 g (30 mmol) of cyclohexene (distilled from $LiAlH_4$), 6.0 g of 86% pure (10.5 mmol of active reagent) title mercurial, and 15 ml of benzene. The solution was stirred for 24 hr, during which time the yellow color of the mercurial was discharged and white phenylmercuric iodide precipitated. TLC monitoring confirmed that the starting material had been consumed by the end of this period. The mixture was filtered to give 4.72 g (92%, corrected for starting mercurial purity) of phenylmercuric iodide, mp 264° (lit.[13] mp 269°). The clear filtrate was trap-to-trap distilled (40°, 0.05 mm) into a liquid nitrogen chilled receiver. GLC analysis (10% UC-W98, 120°) using dodecane as the internal standard indicated an 89% yield of 7,7-dichloronorcarane. The product was identified by comparison of its GLC retention time and the infrared spectrum of a GLC-collected sample (20% UC-W98, 140°) with those of authentic material.

Reaction of Phenyl(iododichloromethyl)mercury with Cyclohexene at 0°. Into a 50-ml flask were placed 2.46 g (30 mmol) of cyclohexene, 4.88 g of 75% pure (7.5 mmol) phenyl(iododichloromethyl)mercury, and 15 ml of benzene. The yellow solution was stirred for 8 days at 0°, during which time the yellow color of the mercurial gradually disappeared. Filtration yielded 80% of phenylmercuric iodide, mp 260°. Trap-to-trap distillation and GLC yield analysis as above showed the presence of a 71% yield of 7,7-dichloronorcarane.

Reaction of Phenyl(iododichloromethyl)mercury with Cyclohexene at 80°. Into a 50-ml flask equipped with thermometer, reflux condenser, pressure-equalizing dropping funnel, and nitrogen inlet were placed 2.56 g (30 mmol) of cyclohexene and 3 ml of benzene. The olefin solution was heated to reflux, and then a solution of 5.7 g (10 mmol) of 86% pure title mercurial in 20 ml of benzene was added over a period of 3 min. The yellow color of the mercurial was completely discharged within 10 sec of its addition. After the reaction mixture was cooled, 4.63 g (94%) of phenylmercuric iodide, mp 260°, was collected by filtration. Trap-to-trap distillation and yield analysis, as above, showed an 85% yield of 7,7-dichloronorcarane.

Reaction of Phenyl(iodobromochloromethyl)mercury with Cyclohexene at 80°. Into a 50-ml flask equipped with thermometer, reflux condenser, pressure-equalizing dropping funnel, and nitrogen inlet were placed 2.46 g (30 mmol) of cyclohexene and 3 ml of benzene. To the refluxing olefin was added 5.3 g (10 mmol) of the title mercurial in 20 ml of benzene over a period of 4 min. The yellow color of the mercurial was completely discharged within 3 min of its addition. After the reaction mixture had been cooled, 3.3 g (82%) of phenylmercuric iodide, mp 255°, was collected by filtration. GLC analysis of the distilled filtrate (as above) showed an 81% yield of 7-bromo-7-chloronorcarane.

Reaction of Phenyl(iododibromomethyl)mercury with Cyclohexene at Room Temperature. In a 50-ml flask 2.86 g (30 mmol) of cyclohexene (distilled from $LiAlH_4$), 6.0 g (10.4 mmol) of the title mercurial, and 20 ml of benzene were stirred for 7 days at room temperature, during which time the dark yellow-orange color of the mercurial became less intense. TLC monitoring of the reaction indicated that the starting mercurial had been consumed by the end of this period. Filtration yielded 2.5 g (70%) of white phenylmercuric iodide, mp 255°. GLC analysis (column A, 140°, dodecane) of the trap-to-trap distillate (60°, 0.05 mm) indicated a 65% yield of 7,7-dibromonorcarane. Spectral data on a GLC-collected sample agreed with those for authentic material.

All other reactions listed in Table I were carried out using these general procedures at the temperatures indicated. In all reactions carried out, samples of the dihalocyclopropane or the triethyl(dihalomethyl)silane produced were isolated by GLC and their identities were confirmed by comparison of their GLC retention times and ir spectra with those of authentic samples from our previous studies with $PhHgCCl_2Br$, $PhHgCClBr_2$, and $PhHgCBr_3$.[3,14-16]

Acknowledgments. The authors are grateful to the U.S. Air Force Office of Scientific Research (NC)-AFSC (Grant AF-AFOSR-72-2204) for generous support of this research and to M & T Chemicals, Inc., for gifts of chemicals.

Registry No.—Iododichloromethane, 594-04-7; iodobromochloromethane, 34970-00-8; iododibromomethane, 593-94-2; $CHBr_2MgCl$, 17609-20-0; phenylmercuric chloride, 100-51-6.

References and Notes

(1) Part 74: D. Seyferth, G. J. Murphy, R. L. Lambert, Jr., and R. E. Mammarella, *J. Organomet. Chem.*, **90**, 173 (1975).
(2) National Science Foundation Graduate Fellow, 1970–1973; Sloan Research Trainee, 1973–1974.
(3) D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y.-P. Mui, H. D. Simmons, Jr., A. J.-H. Treiber, and S. R. Dowd, *J. Am. Chem. Soc.*, **87**, 4259 (1965).
(4) D. Seyferth, *Acc. Chem. Res.*, **5**, 65 (1972).
(5) D. Seyferth and H. Shih, *Organomet. Chem. Synth.*, **1**, 415 (1972).
(6) (a) D. Seyferth, J. Y.-P. Mui, and J. M. Burlitch, *J. Am. Chem. Soc.*, **89**, 4953 (1967); (b) D. Seyferth, J. Y.-P. Mui, and R. Damrauer, *ibid.*, **90**, 6182 (1968).
(7) D. Seyferth and R. L. Lambert, Jr., *J. Organomet. Chem.*, **16**, 21 (1969).
(8) D. Seyferth and S. P. Hopper, *J. Organomet. Chem.*, **51**, 77 (1973).
(9) Discussed in summary form in ref 8 and in D. Seyferth and R. A. Woodruff, *J. Organomet. Chem.*, **71**, 335 (1974).
(10) If the olefinic carbenophile contains no functional groups that are very base sensitive or if it is not one which can intercept a trihalomethyl anion, then the phase transfer catalysis procedure can, of course, be applied to dihalocyclopropane preparation at around room temperature. For a review see E. V. Dehmlow, *Angew. Chem.*, **86**, 187 (1974).
(11) H. Soroos and J. B. Hinkamp, *J. Am. Chem. Soc.*, **67**, 1642 (1945).
(12) J. Hine and F. P. Prosser, *J. Am. Chem. Soc.*, **80**, 4282 (1958).
(13) A. N. Nesmejanow, *Ber.*, **62**, 1013 (1929).
(14) D. Seyferth, J. M. Burlitch, H. Dertouzos, and H. D. Simmons, Jr., *J. Organomet. Chem.*, **7**, 405 (1967).
(15) D. Seyferth, S. P. Hopper, and T. F. Jula, *J. Organomet. Chem.*, **17**, 193 (1969).
(16) D. Seyferth and S. P. Hopper, *J. Organomet. Chem.*, **23**, 99 (1970).

Oxidative Cleavage by Lead(IV). II. The Role of Oxidant Modification in the Mechanism of the Base-Catalyzed Decarboxylation of Mandelic Acid by Lead Tetraacetate[1]

Y. Pocker* and Brian C. Davis[2]

Department of Chemistry, University of Washington, Seattle, Washington 98195

Received August 12, 1974

The oxidative decarboxylation of mandelic acid by lead tetraacetate (LTA) in acetic acid solvent is strongly catalyzed by a variety of Lewis bases, such as water, methanol, DMF, and acetate ion. The rate of cleavage, v_{obsd}, consists of two terms, one representing the uncatalyzed reaction, v_0, and the second the base-catalyzed reaction, v_b. The dependence of v_b on [MeOH] suggests that reaction pathways involving both one and two molecules of methanol in the transition state are important. Below 3 *M* addend the dependence of v_b on [MeOH] is most important, whereas in the region 3–8 *M*, $[MeOH]^2$ dependence predominates. With added water v_b is similarly dependent on $[H_2O]$ and $[H_2O]^2$, with the term involving $[H_2O]^2$ making the greatest contribution over the concentration range studied. Catalysis by alkali metal acetates is more effective than that afforded by methanol or water, and follows the order KOAc > NaOAc > LiOAc. The kinetic order in the above acetates is close to, but less than, one, suggesting that both free and ion-paired acetate ions are involved in catalysis. Rate enhancement with added amines appears to arise from oxidant modification, not only through the generated acetate, but also through the free amine. For all cases studied oxidant modification seems to provide a more important channel for base catalysis than proton removal.

The oxidative cleavages of 2-hydroxycarboxylic acids by lead tetraacetate (LTA) are rapid, clean, and relatively free from side reactions. The reaction kinetics are well defined and indicate a concerted reaction pathway.[3] Thus general salt and substituent effects are minor, and with inert cosolvents there is little rate dependence on solvent composition save for an inverse dependence on acetic acid concentration, due to the preequilibrium displacement of two acetate moieties as the dimer $(HOAc)_2$.[3] Free radicals cannot be detected by the usual trapping reagents, except under quite extreme conditions.[3] Consequently, these cleavage reactions seemed particularly appropriate for an investigation of Lewis base catalysis in Pb(IV) oxidations. Not only is the kinetic behavior of these reactions in mixed solvents well characterized, but their concerted nature precludes an array of accompanying homolytic or heterolytic side reactions.[4]

Lead tetraacetate is claimed to be octacoordinate in its ground state.[6,7] Certainly all eight acetate oxygens appear to be bonded to the lead, as indicated by the absence of a carbonyl band in the ir spectrum of LTA.[6,8] Further, low molar conductivity shows that LTA has little salt character, whether in acetic acid,[9] dimethyl sulfoxide,[7b] or pyridine.[7b] The most often postulated preequilibrium intermediates for LTA oxidations are Pb(IV) complexes with electron-donating substrates, where displacement of one or more of the acetate ligands is complete. Certainly the isolation and characterization of $Pb(OAc)_2(OMe)(OH)$ from wet methanol[10] tends to confirm this hypothesis, as do the kinetic results of Pocker and Davis.[3] Furthermore, Partch and Monthony[7b] have isolated $Pb(OAc)_4(C_5H_5N)$ from a solution of LTA in benzene and pyridine, showing that in certain cases coordination may take place without the complete displacement of an acetate. We have found that formation of Lewis base–LTA complexes of some kind is indicated by color development when $Pb(OAc)_4$ is added to neat methanol, acetone, acetonitrile, nitrobenzene, nitromethane, DMSO, DMF, pyridine, 2,4- and 2,6-lutidine, and triethylamine. This color disappears in methanol on addition of as little as 5% acetic acid without loss of titratable oxidant.

Two possible mechanisms for base catalysis of LTA oxidations have received the greatest attention. In one, the base is assumed to coordinate with the Pb(IV), transforming it into a much more powerful oxidant; in the other, the base is cast in the role of a proton acceptor in the rate-determining step. The oxidant modification pathway has been postulated by Partch[7b,11] for the acceleration of alcohol oxidation by LTA, by Criegee and Buchner[12] in cyclohexanediol cleavages, by Starnes[13] in the formation of hemiketal acetates from triarylmethanols, by Kochi[14a,b] for lead tetracarboxylate decompositions, and by Benson et al. in the LTA oxidations of Co(II),[15a] Ce(III),[15b] and *tert*-butyl hydroperoxide.[15c] On the other hand, that bases function as proton acceptors has been suggested by Norman[16] for the decomposition of LTA in acetic acid, and by Grob[17] for the Pb(IV) decarboxylation of dicarboxylic acids.

The present study examines in some detail the Lewis base catalysis of mandelic acid cleavage by lead tetraacetate. This is a particularly appropriate system for elucidating the relative importance of oxidant modification and proton removal because the amount and stoichiometry of catalysis can be easily determined without being obscured by accompanying side reactions.

Experimental Section

Materials. All kinetic studies were performed with solvent acetic acid of minimum melting point 16.58°.[3,18] Reagent-grade benzene was shaken with Drierite, stored over sodium wire, and distilled just before use. Freshly opened acrylonitrile was distilled immediately before use, as was reagent-grade acetic anhydride (bp 139–140°). Ethyl lactate was carefully fractionated. The middle cut (about ⅓ of the total volume) was again fractionated just before use, keeping only the constant-boiling fraction, bp 153–154° (lit. bp 154.5°).[19] *N,N*-Dimethylformamide (DMF) was purified in the same manner after drying overnight over anhydrous $MgSO_4$ (bp 152.5–153°). 1,4-Dioxane was purified as described by Vogel.[20] 2,6-Lutidine, 2,4-lutidine, and triethylamine were each dried overnight over anhydrous potassium carbonate and then carefully fractionated. Absolute methanol was prepared by the method of Vogel.[21] Reagent-grade ethylene glycol was fractionated and the middle third of the distillate dried for 24 hr over anhydrous sodium sulfate. This cut was then carefully refractionated just before use (bp 197–198°).[22] The refractive indices and boiling points of all the solvents used matched literature values.

Lead tetraacetate was purified as in the previous study.[23,3] Real concentrations of LTA in solution were determined either spectrophotometrically or titrimetrically rather than by weight of solid oxidant added. Anhydrous reagent-grade sodium and potassium acetate were dried under reduced pressure at 80° for 24 hr. Reagent grade $LiOAc \cdot 2H_2O$ was heated in acetic acid with 2 equiv of

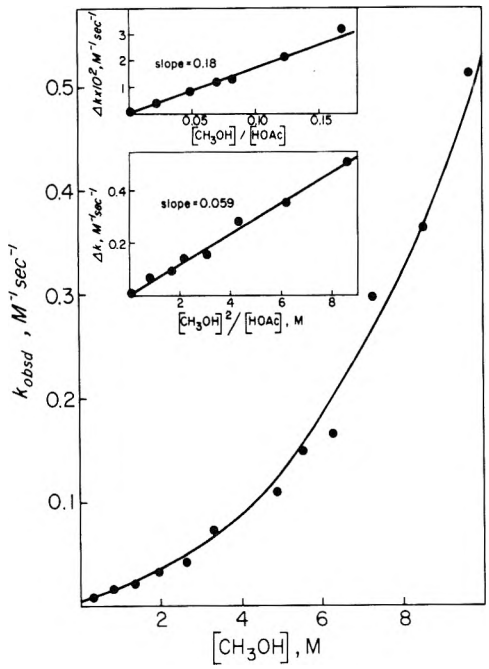


Figure 1. Effect of added methanol on mandelic acid cleavage by lead tetraacetate in acetic acid at 25.0°. Points are experimental and the solid line is calculated from $k_{obsd} = k_0 + k_A[MeOH]/[HOAc] + k_B[MeOH]^2/[HOAc]$, where $k_0 = 9.8 \times 10^{-3}$ M^{-1} sec^{-1}, $k_A^{MeOH} = 0.13$ M^{-1} sec^{-1}, and $k_B^{MeOH} = 0.043$ M^{-2} sec^{-1}. Upper insert: a plot of Δk vs. $[CH_3OH]/[HOAc]$ where $\Delta k = k_{obsd} - k_0$. Lower insert: a plot of Δk vs. $[CH_3OH]^2/[HOAc]$ at higher methanol concentrations.

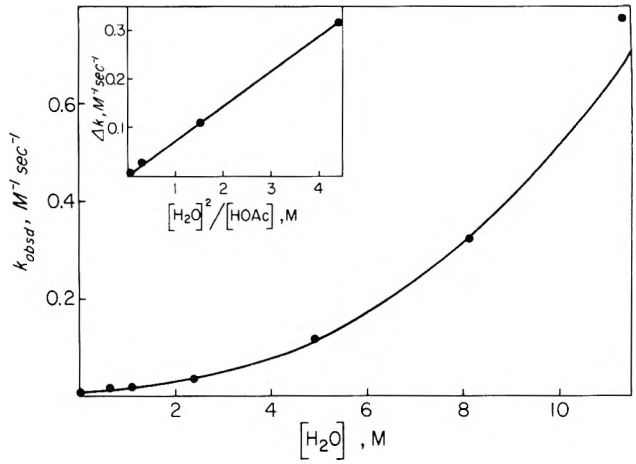


Figure 2. Effect of added water on mandelic acid cleavage by lead tetraacetate in acetic acid at 25.0°. Points are experimental and the solid line is calculated from $k_{obsd} = k_0 + k_A[H_2O]/[HOAc] + k_B[H_2O]^2/[HOAc]$, where $k_0 = 9.8 \times 10^{-3}$ M^{-1} sec^{-1}, $k_A^{H_2O} = 0.065$ M^{-1} sec^{-1}, and $k_B^{H_2O} = 0.060$ M^{-2} sec^{-1}. Insert: a plot of Δk vs. $[H_2O]^2/[HOAc]$, where $\Delta k = k_{obsd} - k_0$.

acetic anhydride. Control runs indicated that rate contributions from the acetic anhydride added were negligible. Benzoin was recrystallized several times from hot methanol (mp 136–137°), as was methyl mandelate (mp 54–55°) from hot heptane. Benzopinacol was synthesized by the method of Pocker and Ronald[18] and recrystallized four times from benzene–ligroin.[24]

Kinetic Measurements. All rates were monitored from 2 to 5 half-lives. Infinities were taken after 10 half-lives. Spectrophotometric rates were determined by following the disappearance of Pb(IV) absorption at various wavelengths between 300 and 330 nm,[3] using a high-speed Gilford multiple sample recording spectrophotometer, Model 2000, fitted with a thermostatted immersion sample compartment. Control runs indicated that no significant loss of Pb(IV) absorbance occurred due to possible thermal or photochemical decompositions of LTA under the conditions employed in this study. In any given run, independent of the Lewis base used, the kinetics of oxidation were first order in mandelic acid and first order in Pb(IV) oxidant; i.e., base catalysis does not change dependence on oxidant or substrate.

Further, control experiments were carried out to determine absorbance changes due to addend oxidation and catalysis of LTA decomposition. Also as indicated, solutions of LTA in triethylamine, 2,4- and 2,6-lutidine, methanol, ethanol, acetonitrile, dimethyl sulfoxide, DMF, nitrobenzene, and nitromethane are highly colored, but decolorize with added acetic acid. Consequently, with none of the added compounds was the absorbance of the LTA–acetic acid–addend solution any higher than would have been expected for LTA alone. However, significant rates of Pb(IV) absorbance loss were noted with added *N,N*-dimethylformamide (DMF) and ethylene glycol. Corrections were made for these side effects in the rate constants reported here for these two cosolvents.

To better understand the interaction of LTA and methanol catalyst, a parallel study of methanol oxidation by LTA in methanol solvent was undertaken.[25] Using Criegee's titration method for [Pb(IV)] determination,[6,10,12] changes in the absorptions of the highly colored LTA–methanol solutions were found to be linear with [Pb(IV)]. Rates of methanol oxidation were followed both titrimetrically and spectrophotometrically. The effect of added acetic acid on this oxidation was also examined. In mixed MeOH–HOAc solvents no color formation was noted with 5% or more acetic acid, and the decrease in Pb(IV) absorbance could be monitored directly. To investigate product catalysis, formaldehyde, produced by warming paraldehyde, was bubbled through methanol and subjected to LTA oxidation. The concentration of formaldehyde was titrimetrically assayed by the method of Buchi.[26]

Product identification for the methanol oxidation was made by injecting samples of the raw reaction mixture directly into a Carbowax column mounted in a Model 5750 Hewlett-Packard research gas chromatograph with a flame ionization detector. Retention times for the reaction mixture were compared with those for a mixture of acetic acid, methanol, formaldehyde, methyl acetate, and methyl formate. Additionally each of these compounds was used in turn to spike the reaction mixture. Identification could then be confirmed by the relative increase in corresponding peak areas. An isothermal oven temperature of 53° was maintained for all VPC product studies.

Results

The base-catalyzed cleavage of mandelic acid (MA) by lead tetraacetate in anhydrous acetic acid was investigated in the presence of several Lewis bases (Table I). When the cleavage is carried out in the presence of methanol, water, DMF, ethylene glycol, and acrylonitrile, a far greater rate enhancement occurs than could be explained by the dilution of acetic acid solvent; e.g., in solvent mixtures containing 25% (v/v) acetic acid the oxidative fission of mandelic acid with added water occurs 63 times faster than that with added benzene (Table I). A detailed examination of MA oxidation with different acetic acid–methanol solvent mixtures reveals that catalysis rates are dependent on both [MeOH] and $[MeOH]^2$. As can be seen from Figure 1, an expression of the type $k_{obsd} = k_0 + k_A[MeOH]/[HOAc] + k_B[MeOH]^2/[HOAc]$ fits the experimental data well for $k_A^{MeOH} = 0.13$ M^{-1} sec^{-1} and $k_B^{MeOH} = 0.043$ M^{-2} sec^{-1}. It is interesting that plots of Δk vs. [MeOH]/[HOAc] and log Δk vs. log ([MeOH]/[HOAc]) are very nearly linear up to 3 M addend with slopes of 0.18 M^{-1} sec^{-1} and 0.99, respectively.[27] Further, Δk vs. $[MeOH]^2/[HOAc]$ and log Δk vs. log ($[MeOH]^2[HOAc]$) plots are also linear with respective slopes 0.059 M^{-1} sec^{-1} and 1.0 with 3 M < [MeOH] < 8 M.[25] Catalysis by added water follows a similar pattern with the calculated curve for $k_{obsd} = k_0 + k_A^{H_2O}[H_2O]/[HOAc] + k_B^{H_2O}[H_2O]^2/[HOAc]$ closely fitting the experimental points with $k_A^{H_2O} = 0.065$ M^{-1} sec^{-1} and $k_B^{H_2O} = 0.060$ M^{-2} sec^{-1} (Figure 2). However, water catalysis is predominantly dependent on the $[H_2O]^2$ term for most of the concentration range studied. A plot of log Δk vs. log ($[H_2O]^2/[HOAc]$) is linear for 1 M < $[H_2O]$ < 11 M with slope 0.92. The slope of the Δk vs. $[H_2O]^2/[HOAc]$ plot shown in Figure 2 is 0.070 M^{-2} sec^{-1}.

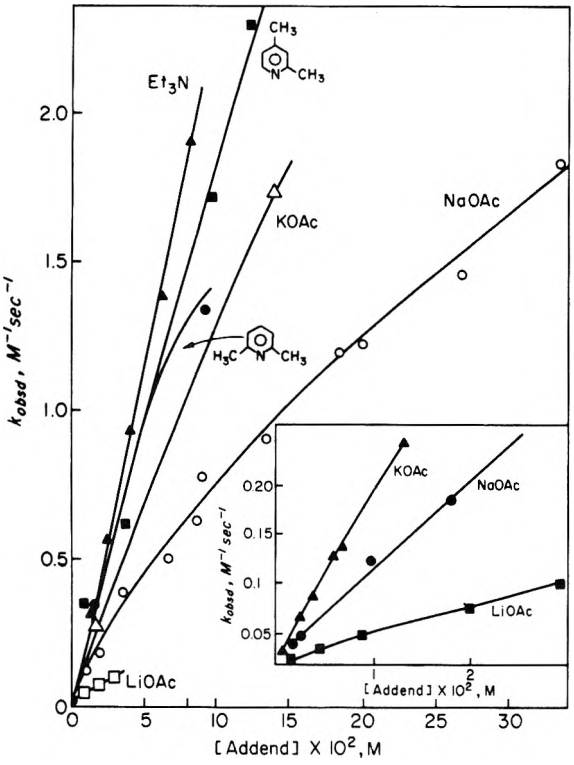


Figure 3. The effect of added acetates and amines on the rate of mandelic acid oxidation by lead tetraacetate in acetic acid at 25°. Addends: ▲, triethylamine; ■, 2,4-lutidine; ●, 2,6-lutidine; △, potassium acetate; ○, sodium acetate; □, lithium acetate. Insert: an expansion of the smaller [addend], lower rate constant portion of the figure. Addend: ▲, potassium acetate; ●, sodium acetate; ■, lithium acetate.

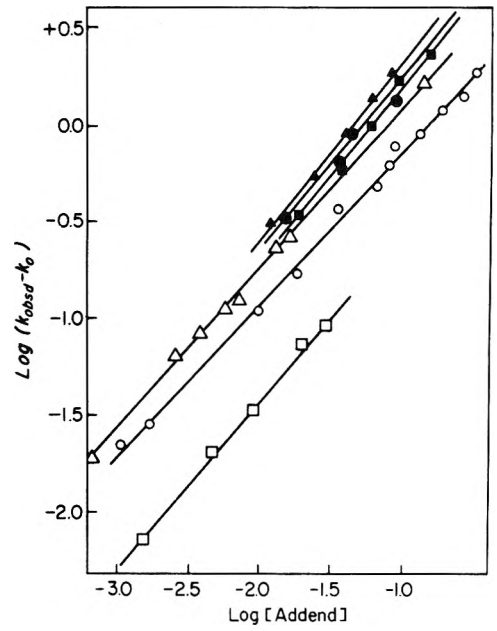


Figure 4. Determination of reaction order in addend for acetate catalysis of mandelic acid cleavage by lead tetraacetate in acetic acid at 25°. Addend: □, lithium acetate; ○, sodium acetate; △, potassium acetate; ■, acetate generated by adding 2,6-lutidine; ▲, acetate generated by adding 2,4-lutidine; ●, acetate generated by adding triethylamine.

The rate increases observed in water–acetic acid and methanol–acetic acid mixtures are much greater than those observed with cosolvent benzene or dioxane. Even acetonitrile (up to 6 M) and acetic anhydride (up to 4 M) lead to about the same amount of rate enhancement as does added benzene,[3] each exhibiting an inverse dependence on [HOAc]. With such cosolvent catalysis, which is directly attributable to the dilution of acetic acid, the quantity k_{obsd}[HOAc] should remain small and relatively constant. Considering the drastic change in the composition of the solvent, the mandelic acid oxidation with added benzene approximates this condition quite well (Table I). However, addition of either acrylonitrile or DMF leads to a much larger rate enhancement than could be explained by solvent dilution. Only nonlinear kinetics were observed with added DMF.

Catalysis by acetate salts is dramatic (Table II), especially in comparison to the minor effects noted with added $LiClO_4$.[4] However, the amount of catalysis observed with a given molarity of added salt was greater for potassium acetate than for sodium acetate; similarly, sodium acetate was catalytically more efficient than lithium acetate (Figure 3). The initial slopes of Δk vs. [acetate], taken from Figure 3, are as follows: KOAc, 15 M^{-2} sec^{-1}; NaOAc, 11 M^{-2} sec^{-1}; LiOAc, 4.2 M^{-2} sec^{-1}. Plots of log Δk vs. log [salt] were straight for all of the above acetates and had slopes between 0.5 and 1.0: KOAc, 0.85; NaOAc, 0.70; LiOAc, 0.92 (Figure 4).

Plots of log Δk vs. log [amine] were also straight with slopes of 0.88, 1.0, and 0.97 for added 2,6-lutidine, 2,4-lutidine, and triethylamine, respectively (Figure 4). With amine-generated acetate catalysis, plots of addend concentrations vs. observed rates were more nearly linear (Figure 3), with added amines catalytically more efficient than acetate salts. Initial slopes: added Et_3N, 22.7 M^{-2} sec^{-1}; added lutidines, 18.5 M^{-2} sec^{-1}.

The effect of adding both methanol and water to the same run was very interesting. The k_{obsd} for mandelic acid oxidation with 2.25 M added methanol is 0.0379 M^{-1} sec^{-1} and that for 3.30 M added water is 0.0645 M^{-1} sec^{-1}. The sum of these extrapolated[28] rate constants is 0.102 M^{-1} sec^{-1}, while k_{obsd} for the above amounts of methanol and water added simultaneously is 0.105 M^{-1} sec^{-1}. In contrast, added simultaneously, methanol and sodium acetate lead to an observed rate increase which is much more than additive. Thus, with 7.28 M MeOH in acetic acid, k_{obsd} = 0.299 M^{-1} sec^{-1}, and with 0.184 M NaOAc, k_{obsd} = 1.19 M^{-1} sec^{-1}; however, when both of the above addends were present together in the same amounts, k_{obsd} = 20.7 M^{-1} sec^{-1}.

Addition of ethylene glycol, a bidentate reagent, is especially interesting, allowing the investigation of possible autocatalysis in glycol cleavage. The second-order rate constant for ethylene glycol oxidation in acetic acid at 25° (k_{obsd} = 2.49 × 10^{-3} M^{-1} sec^{-1}) agrees well with that reported by Cordner and Pausacker.[29] To avoid the necessity for corrections due to changes in acetic acid concentration, only small amounts of ethylene glycol were added. Under these conditions the sum of pseudo-first-order rate constants for uncatalyzed mandelic acid oxidation and the uncatalyzed ethylene glycol cleavage is nearly the same as the overall pseudo-first-order rate constant for the mixture (Table I).

A parallel study was also conducted to more fully understand the LTA oxidation of methanol, the addend most extensively employed in this study.[25] Addition of LTA to pure methanol gave highly colored brown-red solutions, whose absorbances were proportional to the concentration of lead tetraacetate (determined titrimetrically). The rate of methanol oxidation, i.e., Pb(IV) disappearance, is the same whether the absorption of the LTA–methanol complex is spectrophotometrically monitored or the concentration of Pb(IV) is titrimetrically followed. However, in pure methanol solvent these rates appeared constant only to

Table I
Cosolvent Rate Enhancement of Lead Tetraacetate Oxidations in Acetic Acid

Cosolvent	*M*	[HOAc], *M*	$k_{obsd} \times 10^2$, M^{-1} sec^{-1} [a]	k_{obsd}/k_0 [c]	k_{obsd}[HOAc], [c] sec^{-1}
		Mandelic Acid Cleavage			
CH_3OH	0.357	17.2	1.35	1.38	0.232
	0.820	16.9	1.78	1.82	0.301
	1.06	16.7	2.14	2.18	0.357
	1.34	16.5	2.27	2.32	0.375
	1.98	16.1	3.10[d]	3.16	0.499
	2.64	15.6	4.21	4.29	0.656
	3.35	14.9	7.13[d]	7.28	1.08
	4.87	14.1	10.1	10.3	1.42
	5.40	13.6	15.0	15.3	2.04
	6.30	13.1	16.5	16.9	2.16
	7.28	12.3	29.9	30.5	3.68
	8.48	11.5	36.6	37.4	4.21
	9.60	10.7	52.5	53.6	5.62
	10.8	9.87	90.4	92.2	8.92
	13.8	7.75	242	247	18.8
	14.3	7.35	410	418	30.1
	16.8	5.66	1160	1180	65.7
$HOCH_2CH_2OH$	0.160	17.4	2.88	2.94	0.501
	0.209	17.3	3.50	3.57	0.605
	0.286	17.2	3.76	3.84	0.646
	0.388	17.1	5.37	5.48	0.918
	0.515	17.0	7.13	7.28	1.21
	0.771	16.7	10.7	10.9	1.79
	1.68	15.8	47.6	48.6	7.51
C_6H_6	1.86	14.6	1.79[d]	1.82	0.266
	2.78	13.1	2.06[d]	2.10	0.270
	4.66	10.2	2.54[d]	2.59	0.259
	6.00	8.1	3.76[d]	3.84	0.296
	6.22	6.9	4.08[d]	4.17	0.282
CCl_4	1.73	14.6	2.12[d]	2.16	0.310
CH_3OH and H_2O	2.25 3.30	14.9	10.5	10.7	1.56
H_2O	0.638	17.3	1.66	1.69	0.287
	1.09	17.1	1.83	1.87	0.313
	2.38	16.8	3.66[d]	3.73	0.615
	4.91	15.9	11.5[d]	11.6	1.81
	8.13	14.9	32.2	32.9	4.80
	11.3	13.9	77.5	79.1	10.8
	16.1	12.4	248	254	30.8
$(CH_3)_2NCHO$	0.369	17.0	3.56	3.63	0.605
(DMF)	0.727	16.5	12.1[b]	12.4	2.00
	1.21	15.8	17.3[b]	7.7	2.80
	1.92	14.9	103[b,d]	105	15.6
	1.89	12.6	1.38	1.41	0.174
	3.77	11.8	2.14	2.18	0.252
	5.64	9.04	3.77	3.85	0.341
$CH_2{=}CHCN$	4.78	12.0	8.95	9.13	1.07
CH_3CN	1.68	16.0	1.26[d]	1.29	0.202
	2.78	14.9	1.41[d]	1.44	0.210
	4.45	13.4	2.10[d]	2.14	0.281
	5.56	12.4	2.58[d]	2.63	0.320
	6.02	12.0	2.72[d]	2.78	0.326
	8.33	9.86	4.07[d]	4.16	0.401
	11.1	7.36	9.09[d]	9.28	0.670
$(CH_3CO)_2O$	3.21	12.0	2.12[d]	2.16	0.254
	3.97	10.9	2.95[d]	3.01	0.322
	4.86	9.47	4.72[d]	4.82	0.447
	6.52	6.56	7.60[d]	7.75	0.499
$CH_3COOC_2H_5$	1.71	14.6	1.98	2.02	0.289

Table I
(Continued)

Cosolvent	M	[HOAc], M	$k_{obsd} \times 10^2$, M^{-1} sec^{-1} [a]	k_{obsd}/k_0 [c]	k_{obsd}[HOAc], [c] sec^{-1}
		Benzopinacol Cleavage[e]			
		17.5	16.7	1.0	2.89
C_6H_6	1.41	15.3	18.7	1.12	2.86
	3.52	12.0	24.0	1.44	2.87
	6.34	7.65	30.8	1.84	2.36
		Benzoin Oxidation[f]			
		17.5	1.87	1.0	0.327
CH_3OH	6.70	12.7	12.3	6.58	1.56
		Methyl Mandelate Cleavage[g]			
		17.5	0.018	1.0	0.00315
CH_3OH	7.65	12.0	0.377	2.10	0.00452
	15.4	6.57	0.402	22.3	0.00264
	20.8	2.92	0.195	108	0.0569
		Methanol Oxidation[h]			
CH_3OH	7.60	13.5	0.000110		0.00148
	15.2	6.73	0.000420		0.00282
	19.0	4.04	0.000973		0.00762
	24.7	0.00	0.00185		0.00
CH_3OD	(solvent, >99% d_1)	0.00	0.0012		0.00
CH_3OD	(solvent, >99% d_1)	0.00	0.00048		0.00
		Ethyl Lactate Oxidation[i]			
		17.5	0.0181	1.0	0.00317
C_6H_6	1.79	11.9	0.0287	1.59	0.00342
	3.58	9.15	0.0346	1.91	0.00317
	5.37	6.40	0.0495	2.73	0.00317
$CH_2{=}CHCN$	2.40	12.0	0.0260	1.44	0.00312
	7.20	6.39	0.0301	1.66	0.00192
CH_3OH	1.58	13.6	0.0274	1.51	0.00372
	3.16	12.5	0.0466	2.58	0.00582
	4.74	4.74	0.0596	3.30	0.0283
	6.32	6.32	0.0892	4.93	0.0564
H_2O	1.72	14.2	0.0283	1.56	0.00400
	3.44	13.6	0.0443	2.45	0.00646
	6.88	12.5	0.0962	5.31	0.0120

[a] At 25.0°; k_{obsd} are average values of the spectrophotometric second-order rate constants obtained under the specified conditions; $k_{obsd} = k_x/$[mandelic acid] where k_x is the rate coefficient monitored under pseudo-first-order conditions. [b] Corrected for addend oxidation by lead tetraacetate. Such oxidation is negligible in undesignated cases. [c] In pure acetic acid ([HOAc] = 17.5 M), the rate constant for mandelic acid oxidation, k_0, is 9.80×10^{-3} M^{-1} sec^{-1} and k_0[HOAc] = 0.173 sec^{-1}. Rate enhancements are caused not only by acetic acid dilution (ref 3) but also, in some cases, by direct addend catalysis: $\Delta k = k_{obsd} - k_0 = k_A$[addend]/[HOAc] + k_B[addend]^2/[HOAc]. [d] Data taken from ref 3. [e] Cleavage product benzophenone; $k_{obsd} = k_x/$[benzopinacol]. [f] Product benzil (i.e., no cleavage); $k_{obsd} = k_x/$[benzoin]. [g] Cleavage product benzaldehyde; $k_{obsd} = k_x/$[methyl mandelate]. [h] Oxidation products formaldehyde and methyl formate; $k_{obsd} = k_x/[CH_3OH]$. [i] Cleavage product acetaldehyde; $k_{obsd} = k_x/$[ethyl lactate].

25% reaction, with rate increase occurring thereafter. Addition of acetic acid leads to more linear kinetics. Under these conditions methanol oxidation rates appear to be inversely proportional to acetic acid concentrations. Addition of even small amounts (5–10%) of acetic acid results in rapid loss of Pb(IV)–methanol absorbance at 370 nm ($\epsilon_{complex}$ = 1830), and the resultant spectrum is virtually that of LTA in pure acetic acid.

Solvent deuterium isotope effects were also determined. With methanol-d_1, k_{CH_3OH}/k_{CH_3OD} = 1.5, but with methanol-d_4, k_{CH_3OH}/k_{CD_3OD} = 3.8 (Table I). When methanolic solutions containing formaldehyde (the expected product of methanol oxidation) are oxidized by LTA, both the spectrophotometric and the titrimetric rates are faster than expected. However, the rapid rate of absorbance change is even greater than that which could be explained by increased oxidation rates. Product studies using VPC show that both formaldehyde and methyl formate are produced. Traces of methyl acetate were also detected.

Discussion

Two fundamental base- (B) catalyzed pathways can be envisaged for the concerted cleavage of mandelic acid by lead tetraacetate. Scheme I visualizes that this oxidative decarboxylation is channeled through certain Pb(IV) complexes, **1**, which are more reactive than $Pb(OAc)_4$ itself. Such carriers of Pb(IV) arise from the complexation of certain Lewis bases with LTA. The second pathway, Scheme II, consists of a proton removal which could be synchronous as below, or stepwise with the formation of carboxylate anion. The inverse dependence of the base-catalyzed reactions studied on acetic acid concentration, $v_b \propto [(CH_3COOH)_2]^{-1}$, favors Scheme I over either case of Scheme II.[30]

Table II
Amine and Acetate Salts Rate Enhancement of Lead Tetraacetate Oxidations in Acetic Acid

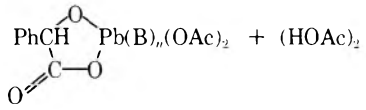
Addend	$M \times 10^2$	$k_{obsd} \times 10^2$, M^{-1} sec^{-1} [a]	k_{obsd}/k_0 [b]	Addend	$M \times 10^2$	$k_{obsd} \times 10^2$, M^{-1} sec^{-1} [a]	k_{obsd}/k_0 [b]
			Mandelic Acid Cleavage				
LiOAc	0.156	1.96	2.00	2,6-Lutidine	1.56	34.3	35.0
	0.472	3.26	3.33		3.71	63.0	64.3
	0.893	4.61	4.71		4.30	92.0	94.0
	2.00	7.13	7.28		9.22	133	136
	2.94	9.87	10.1				
NaOAc	0.105	3.50	3.57	2,4-Lutidine	1.85	35.0	35.7
	0.167	4.07	4.15		3.70	61.7	63.0
	0.973	12.0	12.2		6.17	103	105
	1.80	17.8	18.2		9.25	172	175
	3.59	38.6	39.4		12.3	229	234
	6.65	49.2	50.2				
	8.50	62.5	63.8				
	8.90	77.7	79.3	Triethylamine	1.23	31.3[c]	31.9
	13.3	90.0	91.8		2.46	56.6	57.8
	18.4	119	121		4.11	92.7	94.6
	19.9	122	124		6.17	138	141
	26.8	142	145		8.23	190	194
	33.5	183	187				
KOAc	0.0658	3.10	3.16	NaOAc and	18.2		
	0.249	6.39	6.52	MeOH	728	2070	2110
	0.385	8.68	8.85	([HOAc] = 12.3 M)			
	0.576	12.6	12.9				
	0.676	13.5	13.8				
	1.33	24.1	24.6				
	1.67	27.6[c]	28.2				
	13.9	176	180				

[a] At 25.0°, average second-order rate constants; individual $k_{obsd} = k_x/[\text{mandelic acid}]$, where k_x is the slope of $-\ln(A_t - A_\infty)$ vs. time for rates monitored spectrophotometrically under pseudo-first-order conditions. [b] $k_0 = 9.80 \times 10^{-3}\ M^{-1}$ sec^{-1}; k_0 is the rate constant for mandelic acid oxidation in pure acetic acid with no added catalyst. [c] Data taken from ref 3.

Scheme I

$$Pb(OAc)_4 + nB \rightleftharpoons (B)_nPb(OAc)_4$$
1

$$PhCH(OH)COOH + 1 \rightleftharpoons PhCHOPb(B)_n(OAc)_3 + 1/2(HOAc)_2 \rightleftharpoons$$
COOH
2

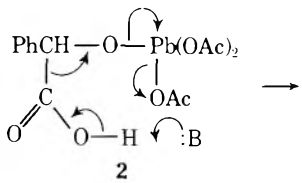


3

$$3 \xrightarrow{rds} PhCHO + CO_2 + Pb(OAc)_2 + nB$$

Scheme II

$$PhCH(OH)COOH + Pb(OAc)_4 \rightleftharpoons 2 + 1/2(HOAc)_2$$



2

$$PhCHO + Pb(OAc)_2 + CO_2 + \overset{+}{B}H, {}^{-}OAc$$

Rate enhancement by addition of either water or methanol clearly involves moieties containing both one and two molecules of addend. Indeed, catalysis involving two molecules of water seems to make the major contribution for most of the concentration range studied (insert, Figure 2). With added methanol the transition state in which one molecule of addend is involved makes the major contribution at low concentration ([MeOH] < 3 M); the primary catalytic contributor at higher concentration (3 M < [MeOH] < 8 M) appears to be a species in which two molecules of addend are important (see insert, Figure 1). It is instructive to compare the rate constants calculated to give the best curve fit for methanol and water catalysis, respectively.

	k_A, M^{-1} sec^{-1}	k_B, M^{-2} sec^{-1}
Methanol	0.13	0.043
Water	0.065	0.060

Further, there is good agreement between these constants and the slopes of the inserts in Figures 1 and 2. As expected, each slope is somewhat higher than the corresponding catalytic rate constant, because it contains contributions from other order terms.

It should also be noted that the inverse dependence on acetic acid concentration is identical for catalyzed and uncatalyzed cleavage of mandelic acid. This is exactly as would be expected if the catalytic species were a complex between base and Pb(IV) without complete displacement of an acetate moiety. Actual reaction would then involve displacement of acetate by substrate, giving the same rate dependence as in the uncatalyzed case ($v \propto [(HOAc)_2]^{-1}$). When ethylene glycol is present during the mandelic acid cleavage, both compounds are oxidized at the rate expected

for the concentration employed, independent of the presence of the other. Apparently both of these bidentate reagents coordinate to the Pb(IV) such that they displace an acetate moiety and are then cleaved so efficiently that they fail to act as oxidation catalysts for each other.

This bidentate nature may also be important in the oxidation of formaldehyde methyl hemiacetal in methanol solvent. When $Pb(OAc)_4$ is added to methanol, complex formation is indicated by a dark brown-red color. Changes in absorbance corresponded to changes in [LTA] during the oxidation of methanol to formaldehyde. However, after about 30% reaction the rate of apparent oxidation, spectrophotometrically measured, accelerated. Thereafter, it was found that the addition of a methanol solution of formaldehyde, mainly present as the hemiacetal, caused rapid decolorization of a freshly prepared solution of LTA in methanol, which did not correspond, titrimetrically, to loss of Pb(IV). Thus it seems that bidentate CH_3OCH_2OH can successfully compete with a much larger concentration of methanol for Pb(IV). With this addition the real oxidation rate, measured titrimetrically, also increases, with oxidation in the new complex giving methyl formate.[25] That oxidant modification takes place during methanol oxidation is indicated by the intense color of CH_3OH–LTA solutions, which disappears with even 5% acetic acid without loss of oxidant, and by the $Pb(OAc)_2(OCH_3)(OH)$ isolated by Criegee et al.[10] from wet methanol.

Further indications of oxidant modification by alcohols include the observations that log k_{obsd} vs. vol % methanol plots were parallel for LTA cleavage of several glycols[12] and that k_{obsd} is linearly dependent on ethanol concentration in the alcohol catalysis of *tert*-butyl hydroperoxide decomposition by LTA.[15] Similarly, in mandelic acid cleavage the total rate is the sum of uncatalyzed and catalyzed hydroxy acid cleavage, i.e., $k_{obsd} = k_0 + \Delta k$.

All of the above evidence seems to imply that only a small percentage of catalytically effective modified oxidant is produced. The independence of catalyzed and uncatalyzed rates is also observed in acetate catalysis, both with respect to added salts and with those generated by the addition of amines. In this connection, Criegee has shown by solubility measurements that added acetate ion modifies LTA to produce new complexes in acetic acid.[6] Further, Benson and Sutcliffe[15] found that lead migrates to the anode in acetic acid solutions containing both sodium acetate and LTA, whereas no such migration was seen in the absence of acetate salt.

Initially all k_{obsd} vs. [acetate salt] plots are nearly linear (Figure 3). A comparison of the $k_{obsd}[HOAc]_0/[\text{acetate salt}]$ with k_A for water and methanol, respectively, emphasizes the greater catalytic efficiency of acetate catalysis: water, 0.065 M^{-1} sec^{-1}; methanol, 0.13 M^{-1} sec^{-1}; LiOAc, 73.5 M^{-1} sec^{-1}; NaOAc, 193 M^{-1} sec^{-1}; KOAc, 263 M^{-1} sec^{-1}. However, as [addend] increases, catalytic efficiency decreases for all acetate-producing catalysts except 2,4-lutidine and triethylamine. The log $(k_{obsd} - k_0)$ vs. log [salt] plots for mandelic acid cleavage are straight but with slopes slightly less than one for added LiOAc, NaOAc, KOAc, and 2,6-lutidine; however, slopes of one are observed with added 2,4-lutidine and triethylamine. The key to the understanding of this acetate catalysis in acetic acid is the great range of electrostatic forces in this solvent.[31] Thus, it is known that salts do exist in acetic acid essentially as ion pairs, in equilibrium with small proportions of free ions, triplet ions, and perhaps also quadruplets.[32] If only free acetate were the catalytic agent, a dependence of k_{obsd} on $[\text{salt}]^{1/2}$ would have been observed; however, if acetate salt ion pairs were responsible for the catalysis, the log–log plots would have yielded a slope of unity. Clearly, the concurrent catalytic action of the prevalent ion pairs and the more efficient, but less abundant, free ions would result in the observed fractional order. Indeed, the relative catalytic efficiency, KOAc > NaOAc > LiOAc, parallels the order of dissociation of ion pairs into free ions found by Kolthoff and Bruckenstein,[32] K^+OAc^- > Na^+OAc^- > Li^+OAc^-.[33] However, amine catalysis is more difficult to analyze. Thus in addition to free acetate and amine-H^+, OAc^- ion pairs one has to consider catalytically significant concentrations of remaining free amine (e.g., pyridine + HOAc ⇌ pyridine-H^+OAc^-, $K_B^{Py} = 5.4$[32b]). Such contributing catalysis by free amine has been shown by other workers, who actually isolated a pyridine · $Pb(OAc)_4$ complex.[7b]

It is interesting that when mandelic acid was cleaved in a solvent containing 7.28 *M* methanol, 0.182 *M* NaOAc, and 12.3 *M* HOAc, the observed rate constant was 14 times greater than the sum of rate constants for identical quantities of each catalyst independently added. A similar instance was reported by Criegee[12] where mixed water–potassium acetate catalysis of *cis*-cyclohexanediol cleavage was 2.7 times faster than the sum of rate constants for independent addition.

The addition of DMF to the reaction mixture results in rate increases, H_2O < DMF < $CH_3CO_2^-$. However, neither k_{obsd} vs. [DMF] nor log k_{obsd} vs. log [DMF] plots were linear for this addend. Nevertheless, it is interesting to note that DMF exerts a profound effect on LTA oxidations either by virtue of its bidentate nature or possibly because small but catalytically significant amounts of $DMFH^+OAc^-$ are formed in these solutions.[34] Acrylonitrile causes a ninefold increase in rate, when added in the same concentration that only produces a two- to three-fold rate increase with added acetonitrile. This effect might also arise via a bidentate interaction with Pb(IV).

It is attractive to attribute most of the observed catalysis to the production of a more reactive oxidant. Certainly oxidant modification does take place. Further, this study has shown that the catalytic portion of the observed rate is inversely proportional to $[(HOAc)_2]$, as would be expected from Scheme I, not $[(HOAc)_2]^{1/2}$, as Scheme II would have predicted. Analogously, Criegee[12] has shown that the relative amounts of Lewis base catalysis in glycol cleavage reactions are independent of the nature of the diol, as would accord with a catalytic mechanism involving oxidant modification. Similar conclusions have been reached by Benson and Sutcliffe[15] for a variety of Pb(IV) oxidations of metal ions and hydroperoxides. Finally, the apparent order of catalytic efficiency parallels the ability of the various addends to donate an electron pair to Pb(IV).

Registry No.—LTA, 546-67-8; mandelic acid, 90-64-2; methanol, 67-56-1; 1,2-ethanediol, 107-21-1; benzene, 71-43-2; carbon tetrachloride, 56-23-5; water, 7732-18-5; dimethylformamide, 68-12-2; *p*-dioxane, 123-91-1; acrylonitrile, 107-13-1; acetonitrile, 75-05-8; acetic anhydride, 108-24-7; ethyl acetate, 141-78-6; benzopinacol, 464-72-2; benzoin, 119-53-9; methyl mandelate, 771-90-4; ethyl lactate, 97-64-3; methanol-*d*, 1455-13-6; methanol-d_4, 811-98-3; lithium acetate, 546-89-4; sodium acetate, 127-09-3; potassium acetate, 127-08-2; 2,6-lutidine, 108-48-5; 2,4-lutidine, 108-47-4; triethylamine, 121-44-8.

References and Notes

(1) This work was supported in part by a Public Health Service Grant from the National Institute of Arthritis and Metabolic Diseases. Taken in part from the Ph.D. Dissertation of B. C. Davis, University of Washington, 1972.
(2) National Science Foundation Predoctoral Fellow, 1968–1971.
(3) Y. Pocker and B. C. Davis, *J. Am. Chem. Soc.*, **95**, 6216 (1973).
(4) Extensive controls (ref 3 and subsequent experiments) exclude both ionic and free-radical mechanisms. Minor salt effects (with 2.5 *M* added

$LiClO_4$, k_{salt}/k_0 = 1.2), small substituent effects ($k_{C_6H_5C(Me)OHCO_2H}$: $k_{C_6H_5CHOHCO_2H}$:$k_{p\text{-}CH_3C_6H_4CHOHCO_2H}$ = 0.91:1.0:1.2), and relative insensitivity to solvent polarity (small and parallel rate changes with cosolvents, acetic anhydride, acetonitrile, and benzene) argue against pathways involving rate-determining ionization.[3] Furthermore, none of the observations indicating a free-radical pathway for the decarboxylation of monofunctional carboxylic acids, (1) induction times and sigmoidal rate profile with time, (2) very strong inhibition by oxygen in every case, (3) increased rates with uv illumination, and (4) radical trapping, were observed during mandelic acid cleavage by $Pb(OAc)_4$ in acetic acid solvent. Parallel runs using degassed samples in an oxygen-free atmosphere had virtually identical rates with those exposed to the atmosphere; also, bubbling air through a degassed sample did not change the rate of oxidative cleavage. Decarboxylations of pivalic, phenylacetic, and acetic acids all yielded free radicals which were trapped by acrylonitrile. In contrast, no radicals could be detected during the cleavage of mandelic acid under identical conditions. Similarly, Trahanovsky[5] differentiated between free-radical and non-free-radical mechanisms for glycol cleavage by Ce^{IV} and $Pb(OAc)_4$, respectively, by trapping radicals with acrylamide during the cerium(IV) oxidation. None could be detected during the lead tetraacetate cleavage.

(5) W. S. Trahanovsky, L. H. Young, and M. H. Bierman, *J. Org. Chem.*, **34**, 869 (1969).
(6) R. Criegee, "Oxidations with Lead Tetraacetate", Oxidation in Organic Chemistry, Part A, K. Wiberg, Ed., Academic Press, New York, N.Y., 1965, p 281.
(7) (a) B. Kamenar, *Acta Crystallogr., Sect. A*, **16**, 34 (1963); (b) R. Partch and J. Monthony, *Tetrahedron Lett.*, 4427 (1967).
(8) F. R. Preuss and J. Janshen, *Arch. Pharm. (Weinheim)*, **295**, 284 (1965).
(9) A. W. Davidson, W. C. Lanning, and M. Zeller, *J. Am. Chem. Soc.*, **64**, 1523 (1942).
(10) R. Criegee, L. Kraft, and B. Rank, *Justus Liebigs Ann. Chem.*, **507**, 159 (1933).
(11) R. E. Partch, *Tetrahedron Lett.*, 3071 (1964).
(12) R. Criegee and E. Buchner, *Ber.*, **73**, 563 (1940).
(13) W. H. Starnes, Jr., *J. Am. Chem. Soc.*, **90**, 1807 (1968).
(14) (a) J. K. Kochi, *J. Am. Chem. Soc.*, **87**, 3609 (1965); (b) J. K. Kochi, *J. Org. Chem.*, **30**, 3265 (1965).
(15) (a) D. Benson, P. J. Proll, L. H. Sutcliffe, and J. Walkley, *Discuss. Faraday Soc.*, **29**, 60 (1960); (b) D. Benson and L. H. Sutcliffe, *Trans. Faraday Soc.*, **55**, 246 (1960); (c) D. Benson and L. H. Sutcliffe, *ibid.*, **55**, 2107 (1959).
(16) R. O. C. Norman, *J. Chem. Soc. B*, 781 (1969).
(17) C. A. Grob, M. Ohta, and A. Weiss, *Angew. Chem.*, **70**, 343 (1958).
(18) Y. Pocker and B. P. Ronald, *J. Am. Chem. Soc.*, **92**, 3385 (1970).
(19) J. A. Riddick and W. B. Bunger, "Organic Solvents, Techniques of Chemistry", Vol. 2, 3rd ed, Wiley-Interscience, New York, N.Y., 1970.
(20) A. I. Vogel, "A Textbook of Practical Organic Chemistry Including Qualitative Analysis", 3rd ed, Wiley, New York, N.Y., 1964, pp. 177.
(21) Reference 20, p 169.
(22) C. P. Smyth and W. S. Walls, *J. Am. Chem. Soc.*, **53**, 527 (1931).
(23) R. O. C. Norman, *J. Chem. Soc. B*, 184 (1968).
(24) Y. Pocker and B. P. Ronald, *J. Org. Chem.*, **35**, 3362 (1970).
(25) Y. Pocker and B. C. Davis, *J. Chem. Soc., Chem. Commun.*, 803 (1974).
(26) J. Buchi, *Pharm. Acta Helv.*, **6**, 1 (1931).
(27) Rate constant for the catalytic portion, $\Delta k = k_{obsd} - k_0$, where k_{obsd} is the experimentally determined second-order rate constant and k_0 is the constant for mandelic acid cleavage in the absence of catalyst; k_0 = $9.80 \times 10^{-3}\ M^{-1}\ sec^{-1}$.
(28) These rate constants were extrapolated from the data in Table I and Figures 1 and 2, correcting to the solvent dilution found when both addends are present, i.e., [HOAc] = 14.9 *M*.
(29) J. P. Cordner and K. H. Pausacker, *J. Chem. Soc.*, 102 (1953).
(30) All the evidence so far cited indicates that the oxidative cleavage of mandelic acid by $(B)_nPb(OAc)_4$ occurs via a more or less concerted pathway in which the rate-determining step apparently involves the decomposition of the cyclic intermediate **3**. In Scheme I, we depicted intermediate **3** as being formed from **2** ≡ $PhCH(COOH)OPb(OAc)_3(B)_n$; however, none of the above observations would preclude its formation from **2′** ≡ $PhCH(OH)COOPb(OAc)_3(B)_n$. Similarly, in the reaction pathway depicted in Scheme II, intermediate **2** ≡ $PhCH(COOH)OPb(OAc)_3$ could be replaced by **2′** ≡ $PhCH(OH)COOPb(OAc)_3$. At the same time, the importance of a free hydroxyl group in the substrate is made apparent by the fact that whereas 1,2-diols, 2-hydroxy acids, 2-hydroxy esters, and benzoin are oxidized by LTA, 2-keto acids, mandelic acetate, and benzil are not.[3]
(31) (a) E. D. Hughes, C. K. Ingold, S. F. Mok, S. Patai, and Y. Pocker, *J. Chem. Soc.*, 1265 (1957); (b) Y. Pocker, *Proc. Chem. Soc., London*, 226 (1959).
(32) (a) I. M. Kolthoff and S. Bruckenstein, *J. Am. Chem. Soc.*, **78**, 1 (1956); (b) S. Bruckenstein and I. M. Kolthoff, *ibid.*, **78**, 10 (1956); (c) I. M. Kolthoff, *Experientia, Suppl.*, V, 33 (1956).
(33) Clearly, it should be recognized that even more complex equilibria may play a significant part in catalysis; e.g., efficiency among acetate salts may also be related to the relative abilities of $(M^+)^n[Pb(OAc)_{4+n}^{-n}]$ ion pairs to form Pb(IV)–mandelic acid intermediates. Further, changing $\Delta k/[addend]$ with greater catalyst concentration could be related not only to the number of addend molecules in the activated complex, but also to the amount of aggregation into even larger species. Norman[16] has isolated a salt from a mixture of NaOAc and LTA in pyridine and acetic acid containing two lead and ten acetate moieties, and Kolthoff and Bruckenstein[32a] have reported that KOAc and pyridine in HOAc begin to form ionic aggregates above 0.04–0.05 *M* addend.
(34) R. C. Paul and B. R. Sreenathan, *Indian J. Chem.*, **4**, 348 (1966).

A Reexamination of the Equilibrium Addition of Bisulfite and Sulfite Ions to Benzaldehyde

Fritz C. Kokesh* and Robert E. Hall

Guelph-Waterloo Centre for Graduate Work in Chemistry, University of Guelph, Guelph, Ontario, Canada N1G 2W1

Received October 25, 1974

The equilibrium constants for the addition of "bisulfite ion" to benzaldehyde were determined at 21° and μ = 1.0 *M* over the pH range 3.55–12.62. A spectrophotometric method was employed. The pH dependence of these observed constants was used to obtain values fo! the equilibrium constants for the reaction of benzaldehyde with HSO_3^- and SO_3^{2-}, and for the acidity constant of the benzaldehyde–HSO_3^- adduct. A comparison of our results with the earlier reports of Stewart and Donnally suggests that the titration method used by these workers yielded inaccurate equilibrium constants at pH's >8. The effect of our equilibrium results on the kinetic scheme and parameters for the reaction of benzaldehyde and bisulfite ion is also discussed.

Some time ago Stewart and Donnally[1] reported a study of the equilibria for the reaction of bisulfite ion[2] and benzaldehyde over the pH range 0–13 in which they determined the extent of reaction by titration of unreacted bisulfite ion with iodine. We became interested in reexamining this reaction because in the above study the observed dependence of the equilibrium constant vs. pH led to the claim that at the more basic pH's hydroxide ion was adding to a measurable extent to the carbonyl group of benzaldehyde. Using Stewart and Donnally's value for the equilibrium constant for the addition of hydroxide ion to benzaldehyde, $10^{1.4}\ M^{-1}$,[1c,3] together with an estimate of the pK_a of benzaldehyde hydrate of $10^{-12.7}\ M$,[4] one can calculate that in aqueous solution the ratio of hydrated to unhydrated benzaldehyde should be about 1.0, which is contrary to the known lack of hydration of this compound.[5] Recently, Greenzaid[5] and Zuman[6] have determined that the equilibrium constant for the addition of hydroxide ion to benzaldehyde is in fact only $10^{-0.9}\ M^{-1}$. Thus either Stewart and Donnally's determination of the observed equilibrium constant[1b] for the addition of bisulfite ion to benzaldehyde at high pH is in error, or their interpretation of the observed behavior is in error.

Similarly, the work of Stewart and Donnally[1c] led to a value for the pK_a of $PhCH(OH)SO_3^-$ of 9.5, while Taft[7] and "σ^I"[10] correlations lead to estimates of this pK_a as 11.7

and 13.8, respectively. The discrepancies are rather large to be totally a failure of the methods of estimation. Green and Hine[12] also have noted recently that the pK_a of 9.5 seems low.

Experimental Section

Reagents and Solutions. Benzaldehyde (J. T. Baker "N.F.") was redistilled at atmospheric pressure under nitrogen and stored under nitrogen in small vials at −15°. Samples of benzaldehyde stored in this way showed no signs of oxidation (as evidenced by the formation of crystals of benzoic acid inside or around the cap) for about 3 weeks. A ^1H NMR spectrum of neat freshly distilled benzaldehyde showed that there was at most 0.1% benzoic acid in the sample.

Stock solutions of benzaldehyde about 0.03 or 0.06 *M* in 95% ethanol as solvent were prepared by syringing 35 or 70 μl of benzaldehyde into a tared 10-ml volumetric flask that contained 1–2 ml of ethanol, reweighing the flask, and diluting to the mark with ethanol. Using solutions prepared by accurately syringing aliquots of these stock solutions into known volumes of cyclohexane, the molar extinction coefficient of benzaldehyde at 242 nm was measured as 14,540 cm^2/mol (lit.[13] 14,500). In 0.10 *M* phosphate buffer, pH 7.18, μ = 1.0 *M* with KCl, benzaldehyde showed a slight deviation from Beer's law with ϵ^{250} decreasing from 1.387×10^4 at 1.125×10^{-5} *M* to 1.335×10^4 at 7.836×10^{-5} *M*. In a separate experiment, the addition of a fixed volume of benzaldehyde stock solution to aliquots of the various buffers used for the equilibrium experiments (vide infra) showed that ϵ^{250} was independent of pH and the nature of the buffer. If care was taken to exclude O_2, benzaldehyde stock solutions were stable at −15° for up to 1 week, as shown by the fact that the absorbance at 250 nm of samples prepared by mixing a fixed volume of stock solution to a fixed volume of buffer were constant over this length of time.

Stock solutions of sodium sulfite 0.05–0.10 *M* were prepared from Fisher "Certified A. C. S." anhydrous Na_2SO_3 and degassed distilled water containing 5% (v/v) ethanol[14] and were stored under nitrogen at 4°. Standardization was carried out by addition with stirring of an aliquot of the Na_2SO_3 to an excess of standard I_2–KI solution followed by back titration of the excess I_2 with standard sodium thiosulfate solution.[15] All operations were done under a nitrogen atmosphere. Although this standardization is described in numerous texts, it is not usually mentioned that efficient stirring during the addition of the sulfite solution to the iodine solution is extremely important. Without rapid stirring we obtained erratic results that probably resulted from the fact that the stoichiometry of the reaction between iodine and sulfite is pH dependent and the desired reaction $I_3^- + SO_3^{2-} + H_2O \rightarrow 3I^- + SO_4^{2-} + 2H^+$ is obtained only at acid pH's. Stock solutions of 0.125 *M* K_2SO_3 (μ = 1.0 *M* withKCl) were prepared from reagent-grade chemicals and standardized as above. These solutions were used at pH 11.90 and 12.62.

Buffer solutions were prepared from Fisher Certified reagents and degassed distilled water. Following any necessary dilutions (*c.f.* Equilibrium Studies) the buffers consisted of pH 3.55, 0.63 *M* acetic acid–sodium acetate; pH 5.27, 0.60 *M* acetic acid–sodium acetate; pH 6.78 and 7.46, 0.80 *M* NaH_2PO_4–Na_2HPO_4; pH 8.14, 9.08, and 10.24, 0.10 *M* boric acid–sodium borate. At pH 11.11 and above, potassium hydroxide of an appropriate concentration was prepared using a carbonate-free J. T. Baker "Dilut-it" concentrate. All buffers were brought to ionic strength 1.0 *M* with KCl. Buffer solutions were stored at 4° under nitrogen.

Standard hydrochloric acid solutions were prepared from "Dilut-it" concentrate.

Equilibrium Studies. For equilibrium determinations at or above pH 9.08, 2.0 ml of buffer solution was pipetted into a 25-ml erlenmeyer flask, *n* ml of sodium sulfite stock solution was added, then 8 − *n* ml of water. The solution was thoroughly mixed and a 1.0-ml aliquot was transferred to a 0.5-cm path length quartz cuvette with a Teflon stopper. At or below pH 8.14, 3.0 ml of buffer was pipetted directly into a 1.0-cm path length quartz cuvette with a Teflon stopper, and 10–70 μl of stock sulfite solution was added from a 100-μl Hamilton syringe. The accuracy and precision of this syringing technique were checked by doing several dilutions of acidic dichromate solutions and monitoring the final dichromate concentration at 257 nm, an absorption maximum. This control showed that delivery of 40-μl aliquots was reproducible within less than 1%, and that with volumes up to 70 μl the accuracy of this dilution was comparable to that achieved using ordinary volumetric techniques. At all pH's flasks and cuvettes were flushed with nitrogen. The cells were placed in the temperature-controlled cell holder of the spectrophotometer and allowed at least 10 min to equilibrate to temperature.[16] The absorbance at 250 nm of the buffer + sulfite solution was measured vs. air, and then an aliquot (constant in a "run" but varying from 2 to 4 μl) of benzaldehyde stock solution was added to the cell and the solution was well mixed. The cell was returned to the spectrophotometer and the absorbance at 250 nm was read after 10 min or after the absorbance became constant. Following equilibration the pH of the reaction solution was remeasured; in all cases the addition of benzaldehyde caused no measureable pH change.

Potentiometric Titrations. Duplicate titrations of 25.0-ml aliquots of 0.1159 *M* Na_2SO_3 (μ = 1.0 *M* with KCl) with 0.1000 *M* HCl, duplicate titrations of 20.0-ml aliquots of 0.0772 *M* Na_2SO_3 (μ = 1.0 *M* with KCl) with 0.1000 *M* HCl that was 0.90 *M* in KCl, and a single titration of a 20.0-ml aliquot of 0.0166 *M* Na_2SO_3 (μ = 1.0 *M* with KCl) with 0.0100 *M* HCl were performed using a reaction vessel thermostated at 21°. The observed pH–volume HCl points were used to calculate an apparent pK_a according to the equation $pK_a = pH - \log([SO_3^{2-}]/[HSO_3^-])$, where the concentrations of SO_3^{2-} and HSO_3^- are calculated from mass and charge balance assuming $[H^+] = 10^{-pH}$. The pK_a's calculated in this way were 6.59–6.64 for $[SO_3^{2-}]/[HSO_3^-]$ ratios of 0.2–20.

Instrumentation. Absorbance measurements were made on a Pye-Unicam SP1700 visible-uv spectrophotometer that was equipped with a circulating water-type thermostable cell holder connected to a Lauda K4R thermostat that was operated at 21.0 ± 0.3°. Absorbance readings were taken directly from the digital readout, which has a precision of 0.001 absorbance units. At higher absorbances, where meter fluctuations exceeded ±0.001, 20–50 instantaneous readings were averaged to obtain the true absorbance. The linearity of the absorbance readout was checked in two ways. First we showed that the absorbances at 250 nm of acidic potassium dichromate solutions were linear with dichromate concentrations. Secondly, during the determination of K_{obsd} at pH 12.6, we found that if after we measured the absorbance of a solution of sulfite we placed in the sample beam an additional cell containing a dichromate solution, then the increase in absorbance was nearly independent of the absorbance of the sulfite, decreasing from 1.073 at no sulfite to 1.040 when the absorbance due to sulfite was 1.2. In this same interval of sulfite concentrations, the increase in absorbance caused by addition of constant volume aliquots of benzaldehyde stock solution decreased from 1.053–1.083 to 0.934–0.937.

The pH measurements were made with a Radiometer Model 26 pH meter equipped with a Radiometer GK2321C combination pH electrode that was calibrated using Fisher and Radiometer standard buffers.

Results

The equilibrium constant for the formation of benzaldehyde bisulfite at any given pH was obtained by adding a known amount of benzaldehyde to buffers that contained known concentrations of bisulfite ion, which was always in a large molar excess. Under these conditions the assumption that the free aldehyde but not the adduct absorbs leads to eq 1

$$\frac{1}{\Delta A} = \frac{K_{obsd}[\text{bisulfite}]_{total}}{\epsilon_B[\text{benzaldehyde}]_{total}} + \frac{1}{\epsilon_B[\text{benzaldehyde}]_{total}} \quad (1)$$

where ΔA is the increase in absorbance caused by addition of the benzaldehyde, K_{obsd} is the observed equilibrium constant for adduct formation (defined below), ϵ_B is the molar extinction coefficient of benzaldehyde, and the remaining terms are total concentrations. Plots of $1/\Delta A$ vs. $[\text{bisulfite}]_{total}$ were made for a five-to-eight-fold charge in $[\text{bisulfite}]_{total}$ and at two separate toal aldehyde concentrations at most pH's. All such plots were linear (and therefore showed no evidence of bisulfite oxidation during sample preparation or analysis) and gave intercepts on the $1/\Delta A$ axis in agreement with the extinction coefficient of benzaldehyde that was determined independently. Plots of the absorbance (vs. air) of the buffered solutions of bisulfite ion were approximately linear at all pH's studied. Using the apparent extinction coefficient of bisulfite ion at any

Table I
Values of Log K_{obsd} vs. pH at 21° and μ = 1.0 M

pH	Log K_{obsd}	$[Benzaldehyde]_{total} \times 10^5$	$[Bisulfite]_{total} \times 10^3$	No. of points
0.081	2.300	9.86	2.64	5
3.55	3.796	9.86	2.64	6
3.55	3.806	4.93	2.64	6
5.27	3.803	8.52	2.60	6
5.27	3.871	4.26	2.60	6
6.78	3.721	9.86	2.64	6
6.78	3.704	4.93	2.64	6
7.46	3.082	8.52	2.60	6
7.46	3.003	4.26	2.60	6
8.14	2.549	9.86	2.64	6
8.14	2.581	4.93	2.64	6
9.08	1.549	12.78	79.7	7
9.08	1.509	6.39	79.7	7
10.24	0.541	15.98	91.1	6
10.24	0.539	12.78	91.1	5
10.70	0.236	~16.6	98.2	7
11.11	−0.0567	14.80	69.5	5
11.71	0.0056	12.78	79.7	6
11.90	0.3175	~16.6	99.5[a]	5
12.62	0.1178	~16.6	99.5[a]	12

[a] Prepared from potassium sulfite.

pH together with the relative total concentrations of benzaldehyde and bisulfite ion, it can be shown that when benzaldehyde is added to bisulfite solution, the decrease in absorption due to bisulfite caused by the conversion of bisulfite ion to adduct is negligible compared to the increase, ΔA, caused by the benzaldehyde.

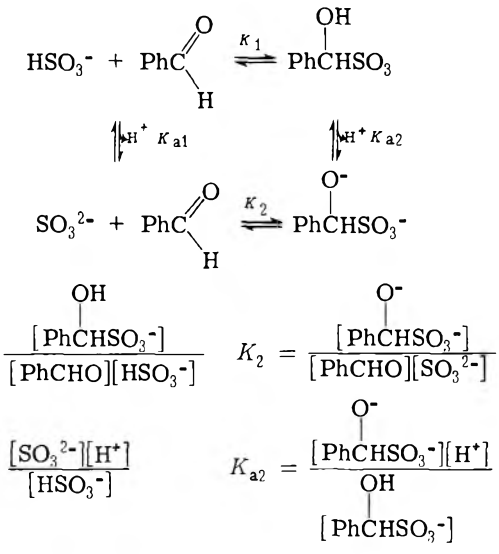
The logarithms of the observed equilibrium constant, K_{obsd} vs. pH are listed in Table I and plotted in Figure 1.

$$K_{obsd} = \frac{[\text{benzaldehyde bisulfite}]_{total}}{[\text{benzaldehyde}]_{total}[\text{bisulfite}]_{total}} \quad (2)$$

Also shown in Figure 1 are the values of K_{obsd} vs. pH reported by Stewart and Donnally.[1b] Although both sets of determinations were done at 21°, ours were done at constant ionic strength of 1.0 M, while those of Stewart and Donnally were at an ionic strength of about 0.1 M.

The pH dependence of K_{obsd} can be understood in terms of the pH-independent equilibrium constants for the reactions shown in Scheme I. Except for a single measurement

Scheme I



$$K_1 = \frac{[PhCH(OH)SO_3^-]}{[PhCHO][HSO_3^-]} \qquad K_2 = \frac{[PhCH(O^-)SO_3^-]}{[PhCHO][SO_3^{2-}]}$$

$$K_{a1} = \frac{[SO_3^{2-}][H^+]}{[HSO_3^-]} \qquad K_{a2} = \frac{[PhCH(O^-)SO_3^-][H^+]}{[PhCH(OH)SO_3^-]}$$

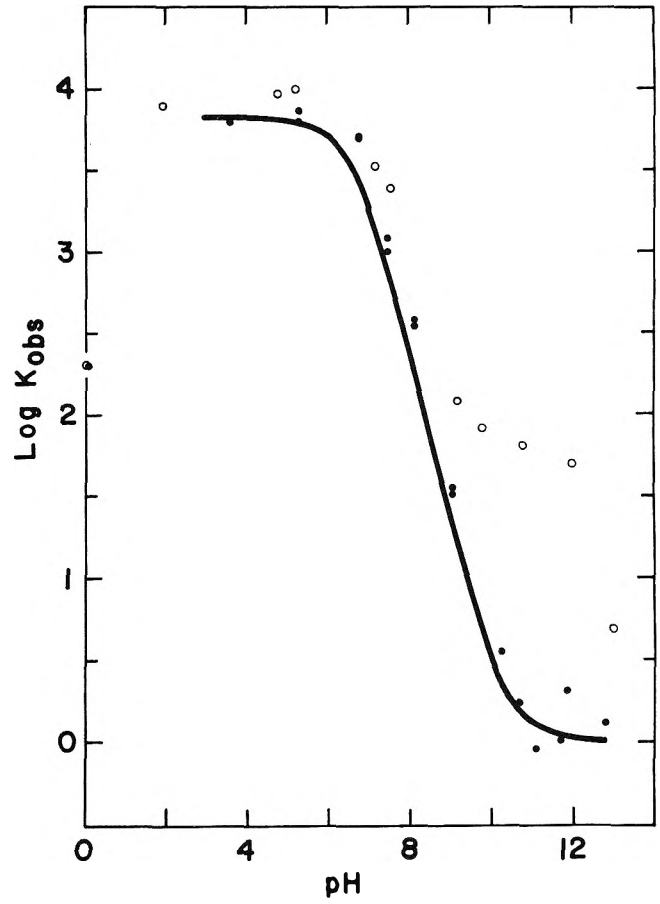


Figure 1. Log K_{obsd} for benzaldehyde bisulfite formation at 21° *vs.* pH: ●, our data; ○, data of Stewart and Donnally.[1b]

of K_{obsd} at pH 0.08, we studied the reaction of benzaldehyde and bisulfite ion above pH 3.55 only, and, therefore Scheme I does not include the conjugate acids of either HSO_3^- or the adduct of benzaldehyde with HSO_3^-. Of course, only three of the four constants are independent, and $K_2 = K_1K_{a2}/K_{a1}$. In terms of the scheme, the pH-dependent constant K_{obsd} can be expressed

$$K_{obsd} = K_1 \frac{1 + K_{a2}/[H^+]}{1 + K_{a1}/[H^+]} \quad (3)$$

Between pH's 3.55 and 5.27 K_{obsd} is pH independent, as would be expected if $K_{a1} \ll [H^+] \gg K_{a2}$. Using $K_1 = K_{obsd} = 6400\ M^{-1}$ obtained from this pH range, $K_{a1} = 2.40 \times 10^{-7}\ M$ that was obtained by potentiometric titration of $Na_2SO_3^{2-}$ with HCl at 21°, and μ = 1.0 M (with KCl), we chose K_{a2} to minimize the sum of the squares of the *fractional* deviations.

$$\Sigma\left(\frac{K_{obsd_i} - K_{calcd_i}}{K_{obsd_i}}\right)^2 = \text{minimum} \quad (4)$$

$$K_{a2} = \frac{\Sigma(1/(K_{obsd_i}(K_{a1} + [H^+]_i)))}{K_1\Sigma(1/(K_{obsd_i}(K_{a1} + [H^+]_i))^2)} - \frac{\Sigma([H^+]_i/(K_{obsd_i}(K_{a1} + [H^+]_i))^2)}{K_1\Sigma(1/(K_{obsd_i}(K_{a1} + [H^+]_i))^2)} \quad (5)$$

The procedure yielded $K_{a2} = 3.95 \times 10^{-11}\ M$, from which $K_2 = K_1K_{a2}/K_{a1} = 1.05\ M^{-1}$. The resultant fit of the data to eq 2 is shown by the calculated line in Figure 1, and has an average fractional deviation of 0.1. The fit can be significantly improved if K_{a1} is treated as a variable; the fit is then optimized with $K_{a1} = 1.48 \times 10^{-7}\ M$ and the sum

of the fraction deviations is cut by a factor of 2. We then obtain $K_{a2} = 2.11 \times 10^{-11}$ M and $K_2 = 9.12 \times 10^{-1}$ M^{-1}.

Discussion

At pH's below 8, the observed equilibrium constants for formation of benzaldehyde bisulfite determined here by a spectrophotometric method substantially agree with those determined by Stewart and Donnally by a titration method, and the small deviations between the two sets of data are probably due to differences in the ionic strength. However, above pH 8 the values of K_{obsd} obtained in this study are 3–100 times smaller than those obtained earlier. In order to discuss the differences in the equilibrium constants determined by the two methods, it is useful to summarize the titration procedure.

Stewart and Donnally's method consisted of allowing benzaldehyde and bisulfite ion to equilibrate in a solution that also contained HCl, a buffer, or NaOH to maintain pH. The reaction mixture was then rapidly added to a stirred "quenching solution" containing sufficient HCl so that the final pH was about 2 and an excess (with respect to bisulfite ion) of iodine. Free bisulfite ion but not benzaldehyde bisulfite is oxidized by iodine, and at pH 2 the dissociation of the adduct is slow. The excess iodine was then quickly back-titrated with thiosulfate solution, and a small empirical correction was applied for the amount of dissociation of the adduct during the time of the back titration. This solution was then neutralized with bicarbonate and titrated with iodine. Because the dissociation of benzaldehyde bisulfite is rapid at neutral pH (and in spite of the fact that the equilibrium formation of adduct is favored at neutral pH) this titration determined the amount of bisulfite ion that had been present as adduct. There is, therefore, sufficient information to calculate the value of the equilibrium constant.

The method requires, of course, that the amount of benzaldehyde bisulfite is unaffected by the quenching process. For the quenching of basic solutions where lowering the pH would initially make the equilibrium constant for adduct formation more favorable, the reaction of iodine with bisulfite ion must be fast relative to the reaction of benzaldehyde with bisulfite ion, and the decrease of the pH to 2 must be rapid so that as bisulfite is removed by iodine oxidation adduct does not dissociate. Only the slow removal of bisulfite ion would give equilibrium constants that are too large.

To test the efficiency of the quenching process, Stewart and Donnally performed a control experiment in which 200 ml of a solution containing 0.05 mol of sodium hydroxide and 0.0015 mol of sodium sulfite was added to 300 ml of a rapidly stirred solution containing 0.10 mol of hydrochloric acid, 0.0015 mol of benzaldehyde, and 0.004 mol of iodine. Back-titration with thiosulfate showed that 5×10^{-6} mol of adduct had been formed during the quenching, which was reported to be within experimental error of zero. This amount of adduct formed in an equilibration mixture of 0.003 M benzaldehyde and bisulfite ion would correspond to an equilibrium constant for adduct formation of $10^{-0.26}$ M^{-1}. Based on this control the titration method seems to be suited to obtain equilibrium constants as small as those obtained by the spectrophotometric method.

We believe, however, that our spectrophotometrically determined values for the equilibrium constant are to be preferred at high pH's. Green and Hine[12] determined the equilibrium constant for the addition of bisulfite ion to isobutyraldehyde using both the spectrophotometric and titration methods, and report that above pH 10 the titration method gives values larger than those by the spectrophotometric method. They attribute these differences to the failure of the quenching procedure even when they used 5 N HCl at 0°. We do not understand the precise reasons for the failure of the quenching procedure, but it may be related to the apparent pH dependence of the stoichiometry of the oxidation of bisulfite ion by iodine. Since Stewart and Donnally performed control experiments for a sodium hydroxide solution, which they used to measure the equilibrium constant at pH 13, but did not perform controls with any of the buffered solutions used at lower pH's, it seems possible that the decrease in K_{obsd} that they observed at pH 13 and attributed to an addition of hydroxide ion to benzaldehyde may be only an experimental artifact arising from the fact that the quenching procedure is even less efficient with buffered solutions than it is with a sodium hydroxide solution. We have no current plans to investigate the quenching procedure.

In deriving eq 1, which gives a satisfactory fit to our experimental data, we assumed that the benzaldehyde–bisulfite adduct does not absorb at 250 nm. Jencks[18] made a similar assumption in studying the addition of bisulfite ion to p-chlorobenzaldehyde. Sousa and Margerum[19] have claimed that from the spectra of concentrated solutions of benzaldehyde and sulfite ion, in which almost all of the aldehyde was converted to adduct, they have obtained the absorption spectrum of the adduct. However, they do not seem to have considered the possibility that the spectrum obtained was that of an impurity of the aldehyde.

The value of $K_1 = 6.4 \times 10^3$ M observed here is similar to $K_{obsd} = 6.25 \times 10^3$ M at pH 4.0, 25° in 1.5 M acetic acid buffer reported by Geneste, Lamaty, and Rogue,[20] who used a titration technique.

The only other reports of the study of the equilibrium for the reaction of bisulfite ion and benzaldehyde are those of Gubareva,[21] who used a titration like that of Stewart and Donnally, and Sousa and Margerum,[19] who used a spectrophotometric method like that described here. However, in both of these studies the pH of the solutions—indeed, the fact that the solutions were buffered—is not reported, so that a comprison of the reported equilibrium constants with our results is difficult.

Although we have not studied the kinetics of the reaction of benzaldehyde and bisulfite ion, our equilibrium results necessitate some minor changes in the kinetic scheme and parameters reported by Stewart and Donnally.[1c] First of all, our equilibrium study detects no drop of the equilibrium constant for benzaldehyde bisulfite formation near pH 12 like that reported earlier. Therefore, pH's of 8–12.6, where the ratio SO_3^{2-}/HSO_3^- is large, the rate of adduct formation should be independent of pH and need not decrease at the upper pH's of this range as predicted previously. According to Greenzaid[5] and Zuman,[6] at pH 12.6 1% of the aldehyde exists as the hydroxide ion adduct. Therefore, as the pH is raised above 12.6 a decrease in rate will become apparent as benzaldehyde is converted to an adduct that is probably unreactive toward SO_3^{2-}.

Also, because Stewart and Donnally's evaluation of the rate constant for the decomposition of the benzaldehyde–SO_3^{2-} adduct requires the value of K_{a2}. Using $K_{a2} = 3.95 \times 10^{-11}$ M, we calculate that the rate constant for the first-order decomposition of this species is 3.23×10^3 sec^{-1} rather than 1.80×10^2 sec^{-1}. Thus the rate of addition and loss of SO_3^{2-} from benzaldehyde is as fast as that from isobutyraldehyde,[12] and one would expect comparable problems with the quenching method.

Acknowledgment. The authors wish to thank Drs. L. R. Green and J. Hine for a prepublication copy of their paper.

Registry No.—Benzaldehyde, 100-52-7; bisulfite, 15181-46-1; sulfite, 14265-45-3; sulfurous acid, 7782-99-2; benzaldehyde bisulfite monosodium salt, 4657-72-9.

References and Notes

(1) (a) T. D. Stewart and L. H. Donnally, *J. Am. Chem. Soc.*, **54**, 2333 (1932); (b) *ibid.*, **54**, 3555 (1932); (c) *ibid.*, **54**, 3559 (1932).

(2) Throughout this paper the term "bisulfite ion" will be used to refer to the mixture of SO_3^{2-}, HSO_3^-, H_2SO_3, and dissolved SO_2 regardless of the pH of the solution. Similarly, the adduct will be called benzaldehyde bisulfite.

(3) Reference 1c actually reports that "K_c" = $([PhCH(OH)O^-][H_3O^+])/[PhCHO] = 10^{-12.7}$ *M* at 21°. Therefore, the equilibrium constant for the addition of hydroxide is $[PhCH(OH)O^-]/([PhCHO][OH^-]) = K_c/K_w = 10^{1.4}\ M^{-1}$ at 21°.

(4) From a Taft correlation of alcohol acidities in aqueous solution at 25°: F. C. Kokesh, Ph.D. Dissertation, The Ohio State University, 1969. $pK_a^{chem}(R_1R_2CHOH) = -1.47(\sigma^*_{R_1} + \sigma^*_{R_2}) + 16.59$, where $\sigma^*_{OH} = 1.28$.

(5) P. Greenzaid, *J. Org. Chem.*, **38**, 3164 (1973).

(6) W. J. Bover and P. Zuman, *J. Chem. Soc., Perkin Trans. 1*, 786 (1973); *J. Am. Chem. Soc.*, **95**, 2531 (1973).

(7) The correlation is that noted in ref 4. The necessary value of $\sigma^*_{SO_3^-}$ was estimated as $(2.8)^2 \times \sigma^*_{CH_2CH_2SO_3^-}$, where the latter constant was obtained from Hall's[8] Taft correlation of the pK_a's of primary ammonium ions, and King's[9] value for the pK_a (at 25°) of $H_3N^+CH_2CH_2SO_3^-$ = 9.061.

(8) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957).

(9) E. J. King, *J. Am. Chem. Soc.*, **15**, 2204 (1953).

(10) From a σ^I correlation of alcohol acidities in aqueous solution at 25°: F. C. Kokesh, Ph.D. Dissertation, The Ohio State University, 1969. $pK_a^{chem}(R_1R_2CHOH) = -7.19(\sigma_{R_1}{}^I + \sigma_{R_2}{}^I) + 15.42$, where $\sigma^I_{SO_3^-} = 0.13$.[11]

(11) M. Charton, *J. Org. Chem.*, **29**, 1222 (1964).

(12) L. R. Green and J. Hine, *J. Org. Chem.*, **39**, 3896 (1974).

(13) W. F. Forbes and J. J. J. Myron, *Can. J. Chem.*, **39**, 2452 (1961).

(14) I. M. Kolthoff and R. Belcher, "Volumetric Analysis", Vol. 3, Interscience, New York, N.Y., 1957, pp 383–384.

(15) L. C. Schroeter, "Sulfur Dioxide", Pergamon Press, Elmsford, N.Y., 1966, p 169.

(16) At the higher pH's, the absorbance of sulfite solutions is extremely temperature dependent,[17] so that benzaldehyde was not added until the absorbance reading was constant, as shown by a strip-chart recorder.

(17) D. P. Ames and J. E. Willard, *J. Am. Chem. Soc.*, **75**, 3267 (1953).

(18) E. G. Sander and W. P. Jencks, *J. Am. Chem. Soc.*, **90**, 6154 (1968).

(19) J. A. Sousa and J. D. Margerum, *J. Am. Chem. Soc.*, **82**, 3013 (1960).

(20) P. Geneste, G. Lamaty, and J. Rogue, *Recl. Trav. Chim. Pay-Bas*, **91**, 188 (1972).

(21) M. A. Gubareva, *J. Gen. Chem. USSR*, **17**, 2259 (1947); *Chem. Abstr.*, **42**, 4820*a* (1948).

Notes

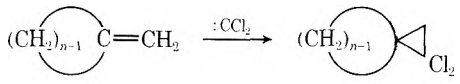
Relative Reactivities in the Addition of Dichlorocarbene to Methylenecycloalkanes

Ellis V. Couch[1] and John A. Landgrebe*

Department of Chemistry, University of Kansas, Lawrence, Kansas 66045

Received October 30, 1974

In spite of the multitude of olefins which have been subjected to attack by dichlorocarbene,[2] data have been lacking for the relative rates of addition of these species to simple methylenecycloalkanes. We now report these values for olefins 1 (n = 4–6) under a variety of conditions as summarized in Table I. The products were the dichlorospiroalkanes 2, which were isolated and characterized (see Experimental Section). Rate constant ratios were determined by

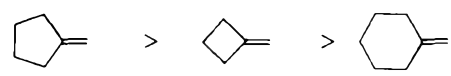


1 2

a, $n = 4$
b, $n = 5$
c, $n = 6$

VPC procedures described previously.[3] As anticipated, the data of Table I do not show large variations with changes in the mode of generation of the carbene, the solvent, or the temperature.[4,5]

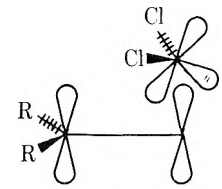
Using data at 25° for the generation of $:CCl_2$ from ethyl trichloroacetate and sodium methoxide in pentane, one obtains the following relative reactivities among olefins **1a–c.**



1b > **1a** > **1c**

2.44 + 0.02 1.53 + 0.1 1.00

Theoretical studies suggest that the transition state for the addition of $:CCl_2$ to an unsymmetrical olefin should resemble **3** and should represent a relatively early stage of the bond formation process.[6] The p orbital of the divalent carbon is in the same plane occupied by the π bond of the methylenecycloalkane. If one recognizes that the preferred



3

direction of attack of $:CCl_2$ on **1c** is equatorial,[7] the already small dihedral angle between the exocyclic carbon–carbon bond and the α-equatorial hydrogens in **1c**[8] should decrease slightly so as to produce an increase in torsional strain as this olefin approaches the transition state. Similar changes in torsional strain for **1a** and **1b** should be small and ought to favor the transition state from **1a** relative to that from **1b.**

Changes in bond angle strain on going from ground state to transition state should involve those normally anticipated for the formation of a three-membered ring for **1c** but are more difficult to access for **1a** and **1b** because of the

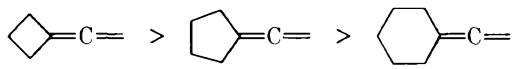
Table I
Data Summary for Competitive Addition of Dichlorocarbene to Methylenecycloalkanes

Olefin in competition with 1b	Carbene source	Solvent	Temp, °C	Time, hr	No of runs	K_{1b}/K[a]
1c	Cl_3CO_2Et	Pentane	0	2	1	2.30
1c	Cl_3CO_2Et	Pentane	0–25[b]	2	3	2.48 ± 0.30
1c	Cl_3CO_2Et	Pentane	0	36	2	2.36 ± 0.09
1c	Cl_3CO_2Et	Pentane	25	2	2	2.44 ± 0.02
1c	Cl_3CO_2Et	Benzene	25	2	2	2.09 ± 0.10
1c	PhHgCClBr	Benzene	60	36	2	2.16 ± 0.05
1a	Cl_3CO_2Et	Pentane	25	2	4	1.59 ± 0.12

[a] Errors expressed as ± one-half of the range. [b] Reagents mixed at 0° followed by removal of ice bath.

lack of adequate structural and thermodynamic data on spirohexanes and spiro[2.4]heptanes. If an increase in bond angle strain in the transition state is greater for **1a** than for **1b**, then a combination of bond angle and torsional strain arguments might explain the observed reactivity sequence. If one examines nonbonded steric interactions between the chlorines and the α hydrogens of the ring in models of each transition state, the interactions appear to diminish in the order **1b** > **1a** > **1c** and cannot explain the observed reactivities. Without further data the observed results for **1a** vs. **1b** cannot be satisfactorily evaluated.

It is interesting to note that in the addition of $:CCl_2$ (from chloroform and potassium *tert*-butoxide, −8 to −10°) to allenes **4a–c** the order of reactivity for **4a** and **4b** is the reverse of that observed for **1a** and **1b**.[11] Unfortu-



4a	4b	4c
2.49	2.09	1.00

nately, the lack of relative reactivity data between compounds **1** and **4** precludes detailed comparisons between these series. The greater reactivity of $:CCl_2$ toward 1-methyleneindan compared to 1-methylenetetralin[12] is consistent with our observations for **1b** and **1c** and can be explained by considering differences in the increased torsional strain on going to the transition states.[13] Greater reactivity of **1b** relative to **1c** has also been noted for olefin reduction by diimide[14] and for epoxidation with peracids.[15] However, in the latter study the rate of epoxidation of **1a** was slower than that of either **1b** or **1c**.

Experimental Section

Elemental analyses were performed by the Department of Medicinal Chemistry at the University of Kansas or by Galbraith Laboratories, Inc., Knoxville, Tenn., unless otherwise noted. Melting points and boiling points (capillary) are uncorrected. Infrared spectra were obtained from a Beckman IR-8 instrument with a 1604-cm^{-1} (polystyrene vs. air) reference standard. Analyses of halides by VPC were performed with an F & M Model 700 instrument (thermal conductivity detector) and the following columns: 20% QF-1 on 30–60 Chromosorb P (15 ft × 0.25 in.); 20% Carbowax 20M on 30–60 Chromosorb P (12 ft × 0.25 in.); 20% tris(cyanoethoxy)propane on 30–60 Chromosorb P (12 ft × 0.25 in.); 15% SE-30 on 30–60 Chromosorb W (10 ft × 0.25 in.); and 10% OV-210 on 80–100 Gas Chrom Q (6 ft × 0.125 in. glass column). Area measurements were performed with a disk integrator. A Varian A-60 or A-60A spectrometer was used to determine NMR spectra of compounds as solutions in carbon tetrachloride containing 3–6% tetramethylsilane.

Methylenecyclobutane (1a), bp 40.5–41.5° (lit.[16] bp 41.5–42°), was prepared from pentaerythrityl tetrabromide in 68% yield by the method of Roberts.[16]

Methylenecyclopentane (1b) was prepared from *tert*-butyl β-hydroxycyclopentaneacetate by the method of Vilkos and Abraham[17] in 83% yield, bp 75–76° (lit.[17] bp 77–78°). Ir and NMR spectra concurred with those already reported.[17,18] The desired olefin was also obtained from pyrolysis of cyclopentylmethyl acetate. However, a Wittig reaction between cyclopentanone and methyltriphenylphosphonium bromide in DMSO[19] produced a significant amount of benzene which forms an azeotrope with **1b**.

Methylenecyclohexane (1c) was prepared in 70% yield by a Wittig reaction between cyclohexanone and methyltriphenylphosphonium bromide in DMSO,[19] bp 100° (lit.[19,20] bp 98°).

1,1-Dichlorospiro[2.3]hexane (2a) was prepared by the general method of Parham[21] from methylenecyclobutane, sodium methoxide, and ethyl trichloroacetate in 47% yield: bp 153°; ir (CS_2) 3000 (s), 2950 (sh), 2860 (sh), 1420, 1245, 1200 (w), 1063 (s), 1030 (s), 1014 (s), 932 (w), 916 (w), 866, 781 (s), 747 cm^{-1} (s); NMR (CCl_4) broad absorption τ 7.0–8.1 (6 H, cyclobutyl CH_2), singlet 8.65 (2 H, cyclopropyl CH_2).

Anal. Calcd for $C_6H_8Cl_2$: C, 47.71; H, 5.34. Found: C, 47.67; H, 5.42.

1,1-Dichlorospiro[2.4]heptane (2b) was prepared as described for **1a** in 39.6% yield: bp 181°; ir (CS_2) 2975 (s), 2870 (sh), 1430, 1308 (w), 1242 (w), 1070, 1040, 1028 (doublet), 1000 (w), 963 (w), 850 (w), 758 cm^{-1} (s); NMR (CCl_4) broad absorption τ 7.5–8.6 (8 H, cyclopentyl CH_2), singlet 8.66 (2 H, cyclopropyl CH_2).

Anal. Calcd for $C_7H_{10}Cl_2$: C, 50.94; H, 6.11. Found: C, 50.73; H, 6.34.

1,1-Dichlorospiro[2.5]octane (2c) was prepared as described for **1a** in 53% yield: bp 200° [lit.[22] bp 79–80° (13 mm)]; ir (CS_2) 3005 (w, sh), 2960 (sh), 2935 (s), 2860 (s), 1420, 1275, 1210, 1150 (w), 1125 (w), 1100 (w), 1036 (s), 1021 (sh), 955, 921 (w), 891 (w), 845, 754 (s), 729 (w), 653 cm^{-1} (w); NMR (CCl_4) broad singlet τ 8.38 (10 H, cyclohexyl CH_2) singlet 8.86 (2 H, cyclopropyl CH_2).

Anal. Calcd for $C_8H_{12}Cl_2$: C, 53.65; H, 6.75. Found: C, 53.54; H, 6.85.

Competitive Addition of Dichlorocarbene to Methylenecycloalkanes. Parham Method.[21] For reaction times and temperatures of various runs, see Table I. As a representative procedure cold methylenecyclopentane (4.1 g, 50 mmol) and methylenecyclohexane (4.8 g, 50 mmol) were weighed carefully into a tared 25-ml flask which contained pentane (5 ml, olefin-free, stored over Na wire). This solution was added to a 50-ml, round-bottomed flask in which sodium methoxide (0.81 g, 15 mmol) and pentane (5 ml) were being stirred magnetically. Ethyl trichloroacetate (0.952 g, 5 mmol) was added dropwise and the mixture was stirred for the specified time.

The reaction mixture was filtered and the residual solid was rinsed with pentane; the filtrate was dried ($CaSO_4$), and the pentane and other volatile compounds were removed over a period of 10 min under aspirator vacuum with no external heating. (The product ratio in one case did not change during an additional 20 min under vacuum.)

When the above procedure was carried out at 25° for 2 hr or at 0° for 36 hr, or when other pairs of olefins were used, the amount of each olefin was 25 mmol. In still another modification of the procedure pentane was replaced with benzene. Methylenecyclobutane and methylenecyclopentane were always kept cold during the weighing process.

Seyferth Method.[23] A solution of 25 mmol each of the olefins in benzene (5 ml) was added to a 50-ml round-bottomed flask containing phenyl(bromodichloromethyl)mercury (2.2 g, 5 mmol) in benzene (5 ml). The tightly stoppered flask was stirred magnetically at 60° (oil bath) for 36 hr, sufficient time for complete decomposition of the mercurial.[24]

Analysis of Products. The high-boiling portion of the crude reaction mixture from any pair of the olefins, **1a, 1b,** and **1c,** was injected directly into the VPC (15% QF-1 on 30–60 mesh Chromo-

sorb P, 8 ft or 10% SE-30 on 60–80 Chromosorb P, silanized with dimethyldichlorosilane, 9 ft) and the quotients of the peak areas from four or more injections were observed as apparent values of the rate constant quotient, k_1/k_2. A detector sensitivity factor was determined with a standard mixture. Each observed rate constant quotient was corrected for detector sensitivity and the corrected values were averaged for each competition.

Acknowledgment. Partial support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, is hereby acknowledged. One of the authors (J.A.L.) expresses gratitude to the Department of Chemistry of the University of California, Berkeley, Calif., for providing facilities and secretarial support during the preparation of the manuscript.

Registry No.—**1a,** 1120-56-5; **1b,** 1528-30-9; **1c,** 1192-37-6; **2a,** 54788-75-9; **2b,** 54788-76-0; **2c,** 15997-13-4; dichlorocarbene, 1605-72-7; cyclohexanone, 108-94-1; methyltriphenylphosphonium bromide, 1779-49-3; ethyl trichloroacetate, 515-84-4; phenyl(bromodichloromethyl)mercury, 3294-58-4.

References and Notes

(1) Taken from the Ph.D. Dissertation of E. V. Couch.
(2) (a) R. A. Moss, "Carbenes", Vol. I, M. Jones, Jr., and R. A. Moss, Ed., Wiley-Interscience, New York, N.Y., 1973, Chapter 2; (b) W. Kirmse, "Carbene Chemistry", 2nd ed, Academic Press, New York, N.Y., 1971, Chapter 8.
(3) E. V. Couch and J. A. Landgrebe, *J. Org. Chem.*, **37,** 1251 (1972).
(4) Reference 2a, p 287.
(5) P. S. Skell and M. S. Cholod, *J. Am. Chem. Soc.*, **91,** 7131 (1969).
(6) (a) R. Hoffman, D. M. Hayes, and P. S. Skell, *J. Phys. Chem.*, **76,** 664 (1972); (b) R. Hoffman, *J. Am. Chem. Soc.*, **90,** 1475 (1968).
(7) E. V. Couch, J. A. Landgrebe, and E. T. Castaneda, *J. Org. Chem.*, **40,** 1529 (1975).
(8) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83,** 4013 (1961).
(9) The torsional strain discussed by Cherest and Felkin[10] for attack of reagents at the carbonyl carbon in cyclohexanones should be minimal for a reaction in which attack is near the terminal carbon in a methylenecyclohexane.
(10) M. Cherest and H. Felkin, *Tetrahedron Lett.*, 2205 (1968).
(11) A. Bezaguet and M. Bertrand, *C. R. Acad. Sci., Ser. C,* **262,** 428 (1966).
(12) I. H. Sadler, *J. Chem. Soc. B,* 1024 (1969).
(13) The author[12] attributes the greater reactivity of 1-methyleneindan to "relief of conformational strain upon formation of the transition state".
(14) E. W. Garbish, Jr., S. M. Schildcrout, D. B. Patterson, and C. M. Sprecher, *J. Am. Chem. Soc.*, **87,** 2932 (1965).
(15) A. Endo, M. Saito, Y. Wada, and Y. Fushizaki, *Nippon Kagaku Zasshi,* **85,** 797 (1964); *Chem. Abstr.*, **63,** 455*b* (1965); *Nippon Kagaku Zasshi,* **86,** 108 (1965); *Chem. Abstr.*, **63,** 455*d* (1965).
(16) J. D. Roberts and C. W. Sauers, *J. Am. Chem. Soc.*, **71,** 3925 (1949).
(17) M. Vilkas and W. Abraham, *Bull Soc. Chim. Fr.*, 1196 (1960).
(18) "NMR Spectra Catalog", Varian Associates, Palo Alto, Calif., 1962, No. 132.
(19) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28,** 1128 (1963).
(20) F. Sorm and J. Beranek, *Chem. Listy,* **47,** 708 (1953).
(21) W. E. Parham and E. E. Schweizer, *J. Org. Chem.*, **24,** 1733 (1959).
(22) P. Weyersthal, D. Klamann, C. Finger, F. Nerdel, and J. Buddrus, *Chem. Ber.*, **100,** 1858 (1967).
(23) D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y.-P. Mui, H. D. Simmons, Jr., A.-J. H. Treiber, and S. R. Dowd, *J. Am. Chem. Soc.*, **87,** 4259 (1965).
(24) D. Seyferth, J.-P. Mui, and J. M. Burlitch, *J. Am. Chem. Soc.*, **89,** 4953 (1967).

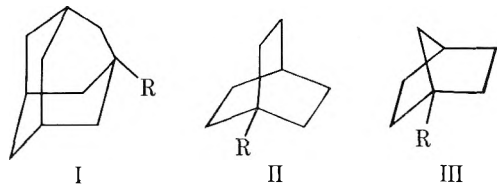
Aspects of Direct Bridgehead Methylation

Ernest W. Della* and Tony K. Bradshaw

School of Physical Sciences, The Flinders University of South Australia, Bedford Park, S.A. 5042, Australia

Received December 2, 1974

We recently required a method of synthesizing the hydrocarbons (I–III, R = CH_3) via direct quaternization of the readily available tertiary bromides. One attractive route appeared to be coupling of the appropriate halide with Grignard reagents. Despite several, largely unsuccessful, attempts[1,2] at direct alkylation of bridgehead halides,



I II III

Schleyer and coworkers[3] recently described the preparation of 1-methyladamantane in high yield by treatment of 1-bromoadamantane with methylmagnesium bromide (molar ratio 1:3) in ether contained in a pressure bottle heated to 100°. These workers further reported that methylmagnesium iodide can also be used, and suggested that the method may be applicable to related alicyclic compounds.

We repeated the experiments outlined by von Schleyer's group and similarly obtained the desired product (I, R = CH_3) in high yield (Table I). However, we found that use of methylmagnesium iodide under the same conditions gave a 3:1 mixture of 1-methyladamantane and adamantane, which are difficult to separate by VPC but which could easily be detected and analyzed by NMR (^{13}C and proton). In an attempt to apply this method to the other bridgehead bromides (II and III, R = Br) we found that longer reaction times were necessary in order to convert bicyclooctyl bromide into the methyl derivative (II, R = CH_3). Use of methylmagnesium iodide led to extensive reduction of the halide and afforded the hydrocarbons (II, R = CH_3 and R = H) in essentially equal proportions. Accordingly, this route to 1-methylbicyclo[2.2.2]octane is very attractive if methylmagnesium bromide is used as the coupling reagent.[4] As indicated in Table I, prolonged heating of 1-bromobicyclo[2.2.1]heptane in ether at 100° gave only a trace (5%) of the coupled product (III, R = CH_3), the remainder of the product being starting material. Obviously, under these conditions the coupling reaction is extremely slow, and the Grignard reagent preferentially reacts with the solvent (as confirmed by conducting a "blank" experiment).

As a possible alternative to the synthesis of 1-methylbicyclo[2.2.1]heptane, the lithio derivative (III, R = Li) was heated with methyl iodide in ether (and also hexane). The product was found to consist entirely of 1-iodobicyclo-[2.2.1]heptane arising from simple halogen–metal exchange (eq 1) in which the position of equilibrium lies almost completely to the right. Similar treatment of 1-bicyclo-

[2.2.1]heptylmagnesium halide, whose preparation has recently been successfully performed[5] and which was not expected to undergo exchange, yielded only bicyclo[2.2.1]heptane.

The use of trimethylaluminum in the quaternization of tertiary acyclic halides has been shown[6] to be widely applicable and proceeds without the intervention to any appreciable extent of unwanted side reactions. In any case, although coupling of this kind involving bridgehead halides has not previously been reported, it seemed reasonable that in the systems under examination here, competing reactions, such as elimination, would be highly unlikely. The solvent found to be most appropriate in the study[7] of the acyclic halides was methyl chloride, in which coupling occurs rapidly at very low temperatures.

Accordingly, we treated the bromides (I–III, R = Br)

Table I
Coupling Reactions of the Bridgehead Bromides

Compd	Reagent	Molar ratio reagent/compd	Temp, °C	Reaction time, hr	Product, % Coupling	Reduction	Halide
I (R = Br)	CH_3MgBr[a]	3.0	100	1	76		
I (R = Br)	CH_3MgI[a]	1.5	95	1	69	22	9[c]
I (R = Br)	CH_3MgI[a]	1.5	110	3	72	28	
I (R = Br)	$(CH_3)_3Al$[b]	1.0	−70	0.5	82	8	
II (R = Br)	CH_3MgBr[a]	3.0	95	18	82		18[d]
II (R = Br)	CH_3MgI[a]	2.0	110	18	46	44	8[e]
II (R = Br)	$(CH_3)_3Al$[b]	1.0	−70	0.5	98	≤2	
III(R = Br)	CH_3MgBr[a]	3.0	110	18	≤5		95[f]
III (R = Br)	$(CH_3)_3Al$[b]	1.0	100	24			100[f]

[a] In ether solution. [b] In CH_2Cl_2 solution. [c] 1-Iodoadamantane. [d] 1-Bromobicyclo[2.2.2]octane. [e] 1-Iodobicyclo[2.2.2]octane. [f] 1-Bromobicyclo[2.2.1]heptane.

with trimethylaluminum in methylene chloride. The results are summarized in Table I.

Both 1-bromoadamantane and 1-bromobicyclo[2.2.2]octane reacted rapidly, even at −70°, and at that temperature methylation was complete in 15 min. The products were obtained in excellent yield, and although 1-methyladamantane was contaminated with a small quantity of reduction product, 1-methylbicyclo[2.2.2]octane was obtained almost completely pure. Unfortunately, 1-bromobicyclo[2.2.1]heptane again proved to be inert and was unaffected by trimethylaluminum even when heated at 100° for 24 hr.

Experimental Section

1-Bromoadamantane, purchased from Koch-Light Laboratories Ltd., was recrystallized and sublimed. 1-Bromobicyclo[2.2.2]octane was synthesised from 2-methoxybuta-1,3-diene,[8] following the route described by Morita and coworkers.[9] 1-Bromobicyclo-[2.2.1]heptane was prepared from 1-carboxybicycloheptane[10] using dibromomethane as solvent in the Cristol–Firth modification[11] of the Hunsdiecker reaction. All reactions described below were performed under an atmosphere of nitrogen.

Methylation with Grignard Reagents. 1-Bromoadamantane. The procedure adopted was that outlined by von Schleyer and coworkers,[3] except that, in order to effect complete consumption of substrate, it was found necessary to heat the reaction for longer periods than specified (Table I). The identity of the products was established by comparison of their spectral properties with those of authentic specimens.

1-Bromobicyclo[2.2.2]octane. The reactions were performed as for 1-bromoadamantane, except that the period of heating was extended to 18 hr. The results are displayed in Table I. VPC analysis (10 ft × 0.125 in. 10% QF-1 at 40°) cleanly separated 1-methylbicyclo[2.2.2]octane and bicyclo[2.2.2]octane, whose physical properties were consistent with those reported.

1-Bromobicyclo[2.2.1]heptane. A. A 3 *M* solution of methylmagnesium bromide in ether (2.8 ml) and 1-bromobicyclo-[2.2.1]heptane (0.5 g) were heated at 110° for 18 hr. After work-up (no residual Grignard reagent detected) the product was analyzed by VPC–mass spectrometry and shown to consist of 5% of 1-methylbicycloheptane (*m/e* 110) and 95% of 1-bromobicycloheptane. When the bromide (1.0 g) in cyclohexane (10 ml) was converted into the lithio derivative[12] and treated with methyl iodide (0.8 g) in ether (10 ml) for 2 hr at 35°, the product isolated after work-up consisted solely of 1-iodobicyclo[2.2.1]heptane (VPC and spectral analysis).

B. Following the reported procedure[5] for the preparation of the 1-bicyclo[2.2.1]heptyl Grignard reagent, anhydrous magnesium chloride (1.71 g, 0.018 mol), freshly cut potassium (1.33 g, 0.034 g-atom), predried potassium iodide (2.82 g, 0.017 mol), and anhydrous THF (40 ml) were placed in a flame-dried 100-ml three-necked flask equipped with a magnetic follower, condenser, and septum, and protected under a nitrogen atmosphere. The stirred solution was boiled under reflux for 3 hr, after which 1-bromobicyclo[2.2.1]heptane (1.75 g, 0.01 mol) in THF (3 ml) was injected and the mixture was heated at 67° for 6 hr, when VPC analysis of an aliquot quenched with dilute HCl indicated that all the bromide had been consumed. Methyl iodide (2.84 g, 0.02 mol) was added to the cooled mixture, which was stirred for 3 hr at room temperature. No alkylation was evident (VPC). The mixture was heated at 65° for 5 hr, cooled to 0°, and treated with gaseous CO_2. After the usual work-up, the product was isolated and shown (VPC–mass spectrometry) to be bicyclo[2.2.1]heptane. Neither the 1-methyl nor the 1-carboxy derivative was detected. Similar results were obtained when the reaction mixture was heated in a pressure bottle.

Methylation with Trimethylaluminum. General Procedure.[13] Trimethylaluminum (1.1 g, 0.015 mol) was added to dry methylene chloride (10 ml) in a 100-ml two-necked flask equipped with a stirring bar, condenser, and septum, and the stirred solution was maintained at −70° under a nitrogen atmosphere. The bridgehead bromide (0.015 mol) in methylene chloride (5 ml) was injected and the mixture was allowed to warm to 0° over 0.5 hr. After excess trimethylaluminum had been destroyed by careful addition of methanol, the mixture was washed with 5% HCl (3 × 10 ml) and water (2 × 10 ml), and then dried ($MgSO_4$). Solvent was removed through an 3-in. column packed with helices and the residue was analyzed by NMR and VPC–mass spectrometry. The products were purified by sublimation and recrystallization.

Both 1-bromoadamantane and 1-bromobicyclo[2.2.2]octane reacted rapidly under the conditions specified above and the products obtained are shown in Table I. A small-scale run (sealed NMR tube) monitored by NMR indicated that reaction was complete in 15 min at −70°.

1-Bromobicyclo[2.2.1]heptane was unaffected under these conditions or when the reaction mixture was heated in a bomb at 100° for 24 hr. At the higher temperature the only noticeable reaction was that between trimethylaluminum and the solvent.

Registry No.—I (R = Br), 768-90-1; II (R = Br), 7697-09-8; III (R = Br), 13474-70-9; methyl bromide, 74-83-9; methyl iodide, 74-88-4; trimethylaluminum, 75-24-1.

References and Notes

(1) S. Landa and S. Hála, *Collect. Czech. Chem. Commun.*, **24**, 93 (1959).
(2) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances", Prentice-Hall, Englewood Cliffs, N.J., 1954, Chapter XVI.
(3) E. Ōsawa, Z. Majerski, and P. v. R. Schleyer, *J. Org. Chem.*, **36**, 205 (1971).
(4) It is not clear why von Schleyer and coworkers[3] did not detect the product of reduction (adamantane) when 1-bromoadamantane was treated with CH_3MgI. The inconsistency between our results and theirs may simply be related to the purity of the magnesium—trace quantities of, e.g., transition metals could easily account for the observed differences.
(5) R. D. Rieke and S. E. Bales, *J. Am. Chem. Soc.*, **96**, 1775 (1974).
(6) J. P. Kennedy, *J. Org. Chem.*, **35**, 532 (1970).
(7) J. P. Kennedy, N. V. Desai, and S. Sivaram, *J. Am. Chem. Soc.*, **95**, 6386 (1973).
(8) L. J. Dolby and K. S. Marshall, *Org. Prep. Proced.*, **1**, 229 (1969).
(9) (a) K. Morita and T. Kobayashi, *J. Org. Chem.*, **31**, 229 (1966); (b) Z. Suzuki and K. Morita, *ibid.*, **32**, 31 (1967).
(10) W. R. Boehme, *J. Am. Chem. Soc.*, **81**, 2762 (1959).
(11) S. J. Cristol and W. C. Firth, *J. Org. Chem.*, **26**, 280 (1961).
(12) R. L. Bixler and C. Niemann, *J. Org. Chem.*, **23**, 742 (1958).
(13) Although aluminum alkyls and alkyl halides may react violently,[14] reactions in which the halide is added to trimethylaluminum at low temperature normally proceed safely.[6,14]
(14) D. B. Miller, *J. Org. Chem.*, **31**, 908 (1966).

Lactone Cleavage with Triphenylphosphine Dibromide[1a,b]

Edward E. Smissman,† Hanan N. Alkaysi, and Mary Weir Creese*

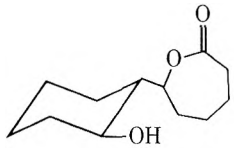
Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045

Received December 10, 1974

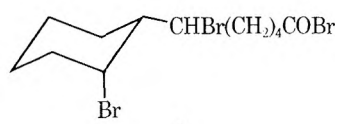
The cleavage of carbon–oxygen bonds with the adduct of triphenylphosphine and bromine (or chlorine) has been known for some time,[2-5] and the stereochemistry and the mechanism of the reaction have been investigated for the conversion of alcohols (e.g., the neopentyl[6] and norbornanol[7,8] systems) to halides.

The early studies of Horner and coworkers[2] established that ketones, aldehydes, and acids, as well as alcohols, could be converted into the corresponding halides by these reagents, and Bestmann and Mott[4] demonstrated that anhydrides followed a similar route; later Anderson and coworkers[9] reported the corresponding cleavage of ethers, and Burton and Koppes[10,11] showed that carboxylic esters and lactones were cleaved to acid halides.

When looking for a mild reagent to convert lactones of the type **1** to the corresponding halides, **2**, we investigated

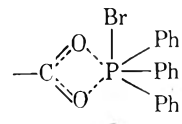


1

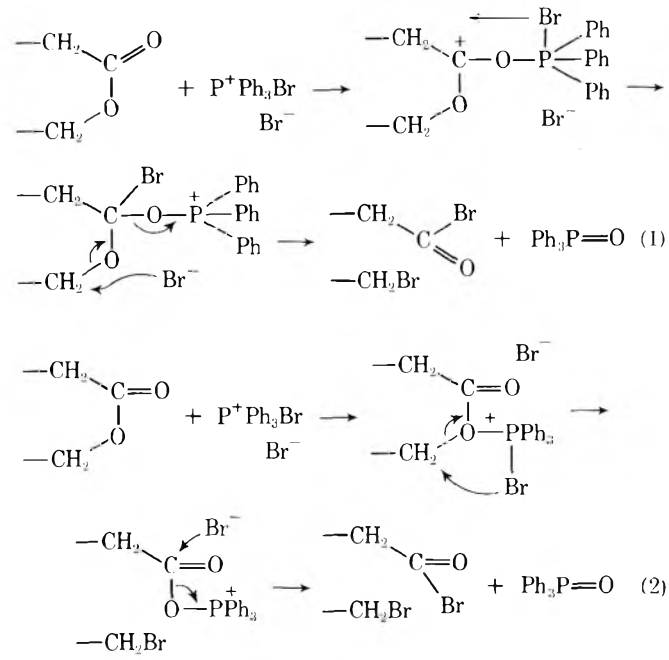


2

the Ph_3PBr_2 ring opening of the series of lactones listed in Table I. The expected products were obtained in every case, though yields were low, usually because of polymerization and tar formation.[12]

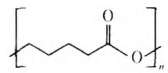


3



While the reaction of acids, acid anhydrides, esters, and lactones with triphenylphosphine dihalide might be expected to follow the same general mechanistic path as that of the C–O bond cleavage in alcohols, the presence of both a carbonyl and an ester oxygen affords the attacking agent a choice of possible sites (pathways 1 and 2), and, in the case of acids in particular, a transition state, or intermediate, of the form **3** might also be envisioned.

Table I

Lactone	Registry no.	Reaction conditions	Product	Yield, %	Registry no.
	96-48-0	100°, 12 hr	$Br(CH_2)_3COOCH_3$	27	4897-84-1
	504-31-4	110°, 12 hr	$Br(CH_2)_4COOCH_3$	30	5454-83-1
	26499-05-8	82°, 12 hr	$Br(CH_2)_4COOCH_3$	50	
	502-44-3	a. 82°, 12 hr b. 110°, 12 hr	$Br(CH_2)_5COOCH_3$ $Br(CH_2)_5COOCH_3$	34 34	14273-90-6
	539-87-7	110°, 12 hr	$Br(CH_2)_6COOCH_3$	27	54049-24-0

The general procedure was to add the lactone, which was itself prepared from the corresponding ketone by Baeyer–Villiger oxidation with trifluoroperacetic acid, to a preformed suspension of Ph_3PBr_2 in dry acetonitrile. The mixture was then heated for 8–12 hr under nitrogen. Subsequent addition of dry methanol to the mixture converted the acid halide to the methyl ester. The product was purified by chromatography on alumina, followed by distillation, and the identity was established by ir and NMR spectral analysis and elemental analysis.

† Deceased, July 14, 1974.

Experimental Section

General Procedure[13] for the Preparation of the Lactones. ε-Caprolactone. Trifluoroacetic anhydride (27.2 g, 0.13 mol) was added dropwise to an ice-cold suspension of 4.5 ml (0.12 mol) of 90% H_2O_2 in 25 ml of dry, freshly distilled methylene chloride and the mixture was stirred for 30 min. The resulting peroxytrifluoroacetic acid solution was then added dropwise to a vigorously stirred suspension of 30 g of anhydrous Na_2HPO_4 in 100 ml of dry methylene chloride, at 0°, containing 17.6 g (0.18 mol) of cyclohexanone. The mixture was stirred under N_2 for 3–4 hr, after which period water was added, and the aqueous phase was extracted four times with methylene chloride. The combined methylene chloride

extracts were washed twice with 70-ml portions of saturated Na_2CO_3 (aqueous) and dried ($MgSO_4$), and the solvent was removed, leaving a colorless oil, bp 58–59° (0.1 mm) [lit.[14] bp 108° (2.5 mm)] which gave one spot on a thin layer chromatogram, and whose ir and NMR spectra were as expected.

General Procedure for Triphenylphosphine Dibromide Cleavage of Lactones. To 52.4 g (0.2 mol) of triphenylphosphine in 200 ml of dry, freshly distilled acetonitrile under N_2 was added dropwise 32 g (0.2 mol) of bromine. The mixture was stirred at 0° throughout the addition, and the stirring was continued for 30 min thereafter. The lactone (22.8 g, 0.2 mol) in acetonitrile was then added dropwise, and the mixture was stirred under reflux for 10 hr, during which time it changed color to dark brown. After cooling, 20 ml of anhydrous methanol was added and the stirring was continued for a further 30 min. Removal of the solvent left a dark, viscous residue, which was dissolved in ether–benzene. This solution was washed several times with water and then dried ($MgSO_4$). The solvents were removed, and the dark residue thus produced was passed through a 14 × 2 in. dry alumina column, benzene being used as eluent. Examination of the column under uv light allowed identification of the fluorescent $Ph_3P{=}O$ band. The faster moving bromomethyl ester band appeared lower down, and methylene chloride extraction of the bottom section of the column gave a relatively pure sample of the expected ester, which was then distilled. A thin layer chromatogram showed one spot. Anal. Calcd for $Br(CH_2)_5COOCH_3$: C, 40.19; H, 6.22. Found: C, 39.91; H, 6.02. Ir 1730 cm^{-1} (ester C=O); NMR ($CDCl_3$) δ 1.8 [m, 6, $-(CH_2-)_3$], 2.3 (t, 2, $-CH_2COOCH_3$), 3.4 (t, 2, $-CH_2Br$), 3.7 (s, 3, ester CH_3). This is consistent with literature reports [Sadtler NMR spectrum no. 4566M and ir spectrum no. 32825 for $Br(CH_2)_4COOEt$].

Registry No.—Triphenylphosphine dibromide, 1034-39-5.

References and Notes

(1) (a) Taken in part from the Ph.D. Dissertation submitted by H.N.A. to the University of Kansas, Feb 1973. (b) This work was supported by a Training Grant (GM 1341) and a Research Grant (NS 9399), National Institutes of Health.
(2) L. Horner, H. Oediger, and H. Hoffmann, *Justus Liebigs Ann. Chem.*, **626**, 26 (1959).
(3) G. A. Wiley, R. L. Herskowitz, B. M. Rein, and B. C. Chang, *J. Am. Chem. Soc.*, **86**, 964 (1966).
(4) H. J. Bestmann and L. Mott, *Justus Liebigs Ann. Chem.*, **693**, 132 (1966).
(5) L. E. Barstow and V. J. Hruby, *J. Org. Chem.*, **36**, 1305 (1971).
(6) R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, **36**, 403 (1971).
(7) J. P. Schaefer and D/ S. Weinberg, *J. Org. Chem.*, **30**, 2635 (1965).
(8) J. P. Schaefer and D. S. Weinberg, *J. Org. Chem.*, **30**, 2639 (1965).
(9) A. G. Anderson, Jr., and F. J. Freenor, *J. Org. Chem.*, **37**, 627 (1972).
(10) D. J. Burton, University of Iowa, private communication, 1970.
(11) D. J. Burton and W. M. Koppes, *J. Chem. Soc., Chem. Commun.*, 425 (1973).
(12) The possibility of some accompanying elimination cannot be ruled out.
(13) E. E. Smissman and J. R. J. Sorenson, *J. Pharm. Sci.*, **54**, 324 (1965).
(14) P. S. Starcher and B. Phillips, *J. Am. Chem. Soc.*, **80**, 4079 (1958).

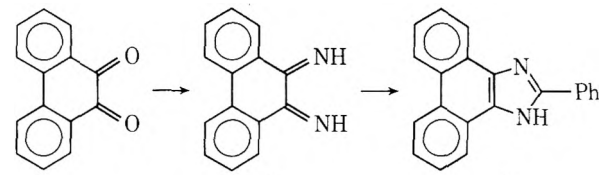
Reaction of Phenanthrenequinone with Ammonium Acetate

Ivan Lantos[1]

American Cyanamid Company, Organic Chemicals Research Division, Bound Brook, New Jersey

Received November 18, 1974

One of the synthetic methods available for the preparation of 2-aryl-1*H*-phenanthro[9,10-*d*]imidazoles is the condensation of phenanthrenequinones with an aromatic aldehyde in the presence of excess ammonium acetate in glacial acetic acid. This reaction has been suggested to proceed via diimine **1**, which condenses with the aldehyde forming a labile adduct that yields imidazole **2** after a facile proton shift and ring closure. From the condensation of phenanthrenequinone and ammonium acetate, Day et al.[2,3] isolated a base-soluble compound which was considered to be the intermediate **1**; it was indicated that this product was converted to **2** by reaction with benzaldehyde in base.

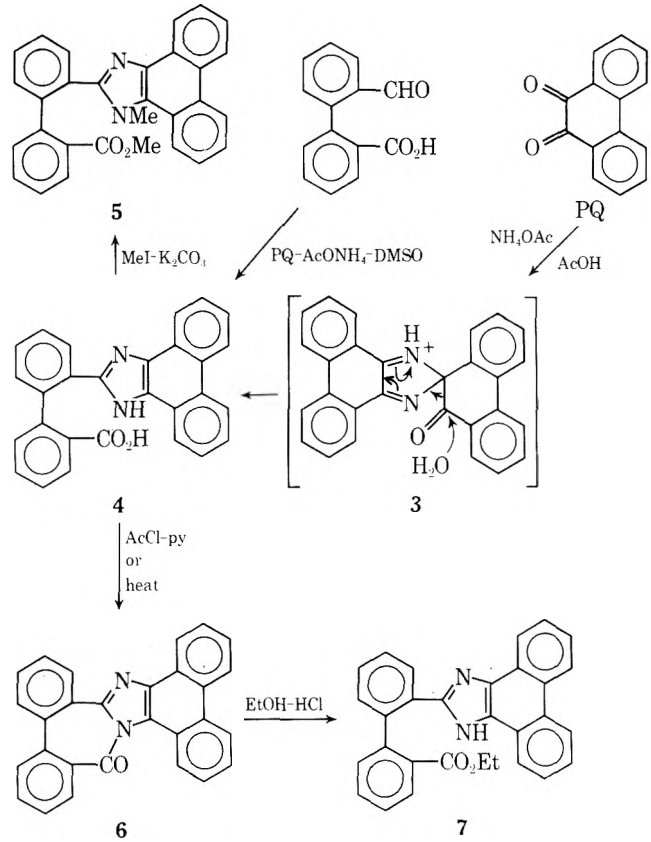


1 **2**

In a reexamination of this reaction, we found that condensation of the quinone, ammonium acetate, and benzaldehyde indeed leads to the imidazole **2**. We also obtained a crystalline product, apparently the same as that described by Day et al., from the reaction of the quinone with ammonium acetate. This substance, however, did not furnish **2** on treatment with benzaldehyde.

The quinone–ammonium acetate product was base soluble; acidification caused the compound to reprecipitate unchanged (under these conditions, hydrolysis of **1** would be expected). The uv, ir, NMR, and high-resolution mass spectra together with the chemical transformations shown in Scheme I leave little doubt that the compound is correctly formulated as 2′-(1*H*-phenanthro[9,10-*d*]imidazol-2-yl)-2-biphenylcarboxylic acid (**4**). Acid **4** could be dimethylated with methyl iodide in alkaline DMSO solution or in refluxing acetone and potassium carbonate to yield the *N*-methyl methyl ester **5**. Vacuum sublimation of **4** or reaction with acetyl chloride gave the dehydration product **6**. On refluxing in ethanolic hydrochloric acid, **6** was converted to the ester **7**. Structure **4** was further substantiated by independent synthesis. Condensation reactions aimed at the formation of aromatic phenanthroimidazoles (*cf.* **2**) showed much improved yields when the quinone, aromatic aldehyde, and ammonium acetate were allowed to react in DMSO instead of the glacial acetic acid employed pre-

Scheme I



viously. No reaction between the quinone and ammonium acetate was observed in this solvent, however; essentially quantitative conversion to **4** was observed when diphenaldehydic acid was added to the reaction mixture. We interpret this result not only as support for our proposed structure **4**, but also as an indication for an acid-catalyzed mechanism of formation.

It appears likely that spiro intermediate **3**, which is first formed, undergoes an acid-catalyzed stereoelectronically favored realignment involving the cleavage of the C_9–C_{10} bond and leading to the formation of **4**.

Experimental Section

All melting points were uncorrected. Unless otherwise stated, NMR, uv, and ir spectra were obtained in DMSO-d_6, absolute ethanol solutions, and Nujol mulls, respectively. Molecular formulae were arrived at by computer analysis of the high-resolution mass spectra. NMR positions are reported in τ units relative to Me_4Si standard.

2-Phenyl-1*H*-phenanthro[9,10-*d*]imidazole (2). Phenanthrenequinone (4.0 g, 0.02 mol), benzaldehyde (2.0 g, 0.02 mol), and ammonium acetate (15.0 g, 0.2 mol) were mixed with thorough stirring in DMSO (50 ml). The mixture was heated to 95° with continued stirring for 0.5 hr. The solution was cooled and diluted with water (250 ml), and the precipitate was filtered. Recrystallization of the solid from 2-butanone yielded 5.0 g of product, mp 318–320°; picrate mp 292–294° (lit.[2] mp 314, 289–290°, respectively); uv λ_{max} 362 nm (ϵ 12,500), 348 (13,500), 326 (23,000), 312 (22,000), 260 (56,000).

2′-(1*H*-Phenanthro[9,10-*d*]imidazol-2-yl)-2-biphenylcarboxylic Acid (4). Phenanthrenequinone (10.0 g, 0.045 mol) and ammonium acetate (75 g, 1.0 mol) were refluxed in glacial acetic acid (150 ml) for 1 hr. The solution was cooled and the crystalline precipitate was filtered and dried. Purification was effected by crystallization once from acetic acid and twice from cellosolve, giving 8.0 g of crystalline material, mp 320–322° (lit.[2] mp 290–292°; the crystalline compound obtained from acetic acid had mp 286–285°). Purification of material from other runs was accomplished by dissolving the crude compound in alcoholic potassium hydroxide solutions.

Anal. Calcd for $C_{28}N_{18}N_2O_2{\cdot}H_2O$: C, 77.75; H, 4.66; N, 6.47. Found: C, 77.95; H, 4.98; N, 6.47.

The molecular water of crystallization could not be liberated by drying at 140° for 2.5 days at 6 mmHg pressure: picrate mp 307–309°; ir 3300–2800 (COO–H–N), 1660–1570 cm^{-1} (COO^- and NH, NH_2^+); hydrochloride 1670 cm^{-1} (CO); NMR 3.80 (s, D_2O exchanged), 1.10 (s, D_2O exchanged), 1.10–3.18 ppm (complex m, 16 H); uv 358 nm (ϵ 5,500), 340 (5,500), 306 (17,500), 286 (18,000), 258 (61,000).

The compound was also prepared by the following method. Phenanthrenequinone (1.0 g, 0.005 mol), diphenaldehydic acid[5] (1.10 g, 0.005 mol), and ammonium acetate (10 g, 0.13 mol) were heated in DMSO (25 ml) for 1 hr at 100°. The solution was allowed to cool and diluted with water to a final volume of 100 ml. After acidification of the solution with dilute hydrochloric acid, the precipitated compound was purified as above.

10H-Dibenzo[*f,h*]phenanthro[9,10-*b*]imidazo[1,2-*a*]azepin-10-one (6). Compound **4** (2 g, 0.005 mol) was dissolved in pyridine (25 ml) and the solution was cooled in an ice bath. Acetyl chloride (1.5 ml) was added and the solution was allowed to warm to ambient temperature. The reaction was allowed to proceed with stirring for an additional 2 hr and was diluted with water to 60 ml. The solid precipitate was collected and crystallized from 2-butanone, yielding 1.5 g of compound: mp 260–261°; ir 1710 cm^{-1} (CO); NMR 1.10–3.16 ppm (complex m); uv 360 nm (ϵ 11,250), 345 (12,2), 300 (35,000); MS *m/e* 396 ($C_{28}H_{16}N_2O$), 367 ($C_{27}H_{15}N_2$), 183 ($C_{11}H_7N_2O$), 163 ($C_{13}H_7$).

Anal. Calcd for $C_{28}H_{16}N_2O$: C, 84.83; H, 4.07; N, 7.07. Found: C, 84.38; H, 4.23; N, 7.25.

Ethyl 2′-(1*H*-Phenanthro[9,10-*d*]imidazo-2-yl)-2-biphenylcarboxylate (7). Compound **6** (0.5 g) was refluxed in a solution of ethanol (40 ml) and concentrated hydrochloric acid (10 ml) for 3 hr. The solution was cooled, diluted with water to 100 ml; and neutralized with Na_2CO_3. The product (0.25 g) was crystallized from ethanol: mp 185°; ir 1690 cm^{-1} (CO); NMR 1.17–3.0 (complex m, 16 H), 5.80 (q, J = 7 Hz, 2 H), 8.99 ppm (t, J = 7 Hz, 3 H); MS *m/e* 442 ($C_{30}H_{22}N_2O_2$), 396 (P – C_2H_5OH), 368 (P – $CO_2C_2H_5$), 184 ($C_{11}H_8N_2O$), 183 ($C_{11}H_7N_2O$); uv 358 nm (ϵ 6,000), 340 (7,000), 300 (17,000), 258 (56,700).

Methyl 2′-(1-Methyl-1*H*-phenanthro[9,10-*d*]imidazol-2-yl)-2-biphenylcarboxylate (5). Compound **4** (1 g) was refluxed with methyl iodide (2 ml) and potassium carbonate (1 g) in 50 ml of acetone and 2.5 ml of water for 20 hr, diluted with water to twice the original volume, and extracted with chloroform (3 × 50 ml). The organic extract was dried, evaporated to almost dryness, and crystallized from 1-butanol: mp 190–192°; ir 1705 cm^{-1} (CO); NMR 0.74–3.34 (complex m, 16 H), 6.05 (s, 3 H), 6.28 ppm (s, 3 H); uv 354 nm (ϵ 4500), 338 (4500), 306 (13,500), 284 (18,500), 254 (63,000); MS *m/e* 442 ($C_{30}H_{22}N_2O_2$), 383 (P – CO_2CH_3), 368 (P – CH_3, CO_2CH_3), 183 ($C_{11}H_7N_2O$).

Anal. Calcd for $C_{30}H_{22}N_2O_2$: C, 81.43; H, 5.01; N, 6.33. Found: C, 80.98; H, 4.82; N, 6.41.

Acknowledgment. The author wishes to express his gratitude to Drs. R. A. Coleman and R. K. Madison, and to his personal friend J. J. Leavitt for the many useful discussions and continued help. Thanks are extended to Dr. T. Mead for the mass spectra and to Dr. J. Gove for the NMR spectra.

Registry No.—**2**, 6931-31-3; **2** picrate, 54774-64-0; **4**, 54774-65-1; **4** picrate, 54774-66-2; **5**, 54774-67-3; **6**, 32005-25-7; **7**, 54774-68-4; ammonium acetate, 631-61-8; phenanthrenequinone 84-11-7.

References and Notes

(1) Address correspondence to Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pa. 19101.
(2) E. A. Steck and A. R. Day, *J. Am. Chem. Soc.*, **65**, 452 (1943).
(3) G. McCoy and A. R. Day, *J. Am. Chem. Soc.*, **65**, 2159 (1943).
(4) See Experimental Section for spectroscopic details.
(5) P. S. Bailey and R. E. Erickson, *Org. Syn.*, **41**, 46 (1961).

Acid-Catalyzed Epoxide Cleavage of 3,4-Epoxytricyclo[4.2.2.0^{2,5}]deca-7-ene[1]

Tadashi Sasaki,* Ken Kanematsu, and Akihiro Kondo

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Chikusa, Nagoya 464, Japan

Received January 16, 1975

With a hope of providing a synthetic entry for new carbon-skeleton construction and further additional data for understanding the transannular reactions of tricyclo[4.2.2.0^{2,5}]deca-3,7-diene derivatives **1** and **2** (1:1 adducts of cyclooctatetraene with maleic anhydride and methyl maleate) with electrophiles,[2-4] we have investigated the reactions of **1** and **2** with *m*-chloroperbenzoic acid and the acid-catalyzed cleavage of the resulting epoxide derivatives.[5]

Reaction of **1** with *m*-chloroperbenzoic acid gave a monoepoxide product **3**.[6] Similar reaction of **2** gave **4**[6] together with a trace amount of unknown compound **5**. The NMR spectrum of **5** exhibits signals at δ 1.93 (4 H, m), 2.68 (4 H, m), 3.02 (4 H, s), 3.18 (4 H, m), 3.60 (12 H, s), and 6.50 (4 H, t) suggesting the presence of two cyclohexene moieties, and also the syn or anti dimer of **4** (Chart I).

Treatment of the epoxide **4** with hydrogen chloride in methanol at 0° gave compound **6** in an almost quantitative yield. The yields of **6** under various acidic conditions are summarized in Table I.

Similar treatment of **3** with the acid under various conditions gave a complex mixture, which we were unsuccessful in further purifying.

The NMR spectrum of **6** exhibits a methine proton at δ 4.75 (dd) adjacent to a lactone moiety, a sharp singlet at δ 4.06 (1 H) adjacent to a hydroxyl group, and one methoxyl group at δ 3.68 (3 H, s), but lack of olefinic protons. The

Chart I

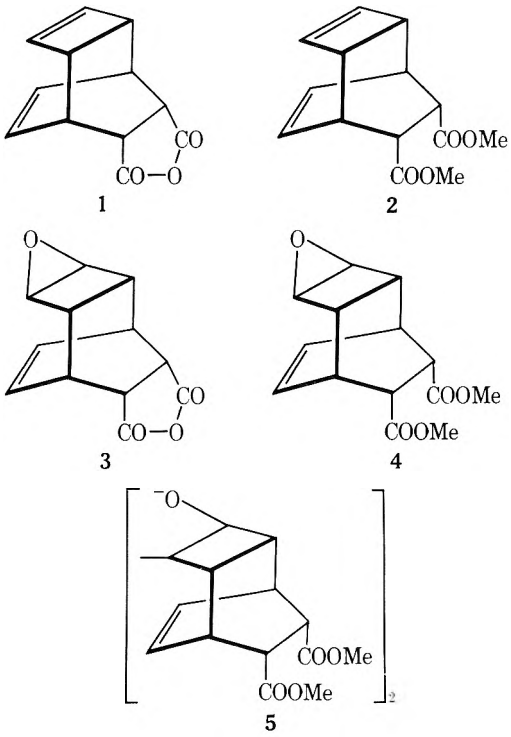


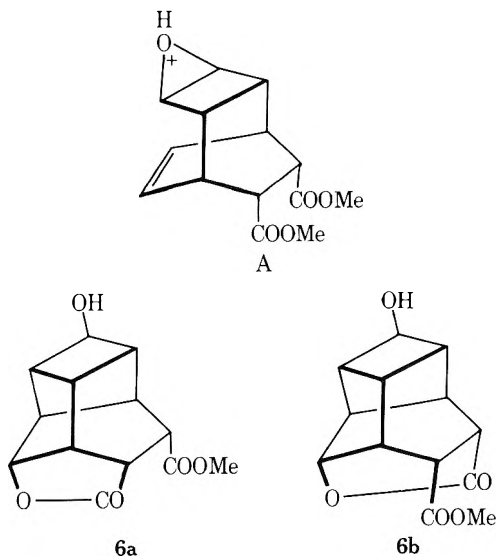
Table I
Acid-Catalyzed Cleavage Reaction of 4

Reagent	Solvent	Product 6 yield, %
HCl[a]	MeOH	Quantitative
Concd HCl	None	56.5
45% HBr	None	28
BF_3	AcOH	17.5

[a] In methanol saturated with dry hydrogen chloride.

spectral patterns of **6** are very similar to that of the halolactonization products.[2] Thus, the formation mechanism of **6** could be explained to proceed by an initial produced bridged protonated oxide (A) followed by ring opening to cause the transannular cross cyclization affording the lactonization product **6a** or **6b** (see Chart II). However, it is difficult to establish the structure of **6** from its ir data, since the spectrum in the solid state shows only one broad

Chart II



carbonyl band at 1740 cm^{-1}, but in chloroform two absorptions at 1775 and 1750 cm^{-1}. Therefore, the final determination of the structure was accomplished by the chemical transformations.

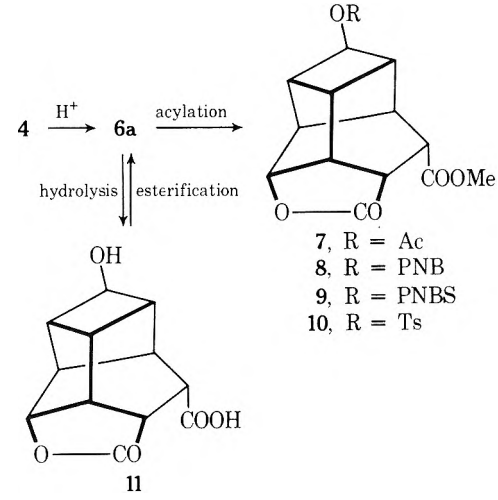
Acetylation of **6** with acetic anhydride in the presence or the absence of pyridine afforded compound **7**. The ir spectrum of **7** in the solid state shows carbonyl absorptions at 1790 cm^{-1} attributable to a five-membered lactone and at 1740 cm^{-1} due to acetoxyl and ester carbonyl groups. Similar treatments of **6** with *p*-nitrobenzoyl chloride, *p*-nitrobenzenesulfonyl chloride, and tosyl chloride in pyridine at room temperature gave the acylated compounds, **8**, **9**, and **10**, respectively. The ir spectra of these compounds in KBr exhibit lactone absorptions in the regions of 1770–1765 cm^{-1} as shown in Table II, suggesting the presence of a five-membered lactone moiety and at least the absence of a six-membered lactone group.

Table II
Carbonyl Absorptions of Acylated Compounds by Ir

Compd	Ir (KBr), C=O, cm^{-1}	
	Lactone	Ester
7	1790	1740
8	1765	1750, 1720
9	1770	1730
10	1770	1740

Furthermore, hydrolysis of **6** with 50% sulfuric acid or 10% aqueous sodium hydroxide at room temperature afforded compound **11** (Scheme I), which shows a lactone ab-

Scheme I



sorption at 1775 cm^{-1} suggesting the presence of a five-membered ring. Esterification of **11** with methanol in sulfuric acid or diazomethane in ether gave **6** exclusively. Thus, the structure **6** was established to be **6a**. From these data, it is pointed out that no skeletal rearrangement (relactonization) from the six-membered ring to the five-membered lactone moiety has occurred during the chemical conversions even under both acidic and basic conditions. By contrast, all attempted base-catlayzed cleavage of the epoxides **3** and **4** was unsuccessful, although many examples of the ring-opening reactions of epoxide derivatives with nucleophilic reagents have been reported.[7]

Experimental Section

The melting points were measured with Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were per-

formed on a Perkin-Elmer 240 elemental analyzer. The NMR spectra were taken with a Jeol C-60-XL recording spectrometer with tetramethylsilane as an internal standard and the chemical shifts are expressed in δ values. The ir spectra were taken with a Jasco Model IRA-1 grating infrared spectrophotometer.

Epoxidation of 1. A solution of 1 (200 mg) and *m*-chloroperbenzoic acid (170 mg) in chloroform (20 ml) was stirred for 24 hr at room temperature. Then chloroform (30 ml) was added to the reaction mixture and the solution was washed with a saturated sodium bicarbonate solution followed by water (20 ml). Drying over anhydrous sodium sulfate followed by evaporation of the chloroform solution gave 3 (100 mg): mp 209–211°; ir (KBr) 1860, 1840, and 1780 cm^{-1} (anhydride); NMR ($CDCl_3$) δ 6.30 (2 H, t, J = 4.5 Hz), 3.55 (2 H, d, J = 2.3 Hz), 3.35 (2 H, m), 3.04 (2 H, t, J = 1.5 Hz), and 2.43 (2 H, m).

Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.07; H, 4.72.

Epoxidation of 2. A solution of 2 (1.0 g) and *m*-chloroperbenzoic acid (700 mg) in chloroform (30 ml) was stirred for 24 hr at room temperature. Work-up as described above and evaporation of the solvent followed by silica gel chromatography using chloroform gave 4 (800 mg) and 5 (20 mg).

4: mp 83–84° (*n*-hexane); ir (KBr) 1740 and 1720 cm^{-1}; NMR ($CDCl_3$) δ 6.28 (2 H, t, J = 4.5 Hz), 3.55 (6 H, s, COOMe-2), 3.50 (2 H, m), 3.00 (2 H, m), 2.86 (2 H, s), and 2.30 (2 H, m); MS *m/e* 264 (M^+) and 233 (M − 31).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.90; H, 6.04.

5: mp 263–265° (benzene–*n*-hexane); ir (KBr) 1740 cm^{-1}; NMR ($CDCl_3$) δ 6.50 (4 H, t), 3.60 (12 H, s), 3.18 (4 H, m), 3.02 (4 H, s), 2.68 (4 H, m), and 1.93 (4 H, m); MS *m/e* 528 (M^+) and 497 (M − 31).

Anal. Calcd for $C_{28}H_{32}O_{10}\cdot C_6H_6$: C, 67.31; H, 6.31. Found: C, 67.25; H, 6.24.

Acid-Catalyzed Reaction of 4. General Procedure. A solution of 4 in acidic condition was kept at 0° or room temperature for 2 days. After evaporation of the solvent, the residue was recrystallized from benzene to give **6**: mp 167–169°; ir (KBr) 3400 and 1740 cm^{-1}; NMR ($CDCl_3$) δ 4.75 (1 H, dd, J = 3.0 and 6.75 Hz), 4.06 (1 H, s), 3.68 (3 H, s, COOMe), 3.58 (1 H, m), 3.18 (1 H, dd, J = 4.5 and 6.75 Hz), 2.3–2.9 (6 H, m), 2.20 (broad s, 1 H, exchangeable by D_2O).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.62; H, 5.94.

The yields of **6** under various conditions are summarized in Table I.

Acetylation of 6. A. A solution of **6** (300 mg) in acetic anhydride (15 ml) was refluxed for 6 hr. After evaporation of the solvent, the residue was recrystallized from benzene–*n*-hexane to give **7** (345 mg); mp 158–159°; ir (KBr) 1790 and 1720 cm^{-1}; NMR ($CDCl_3$) δ 4.77 (1 H, dd, J = 3.0 and 8.0 Hz), 4.57 (1 H, s), 3.70 (3 H, s, COOMe), 3.40 (1 H, m), 3.20 (1 H, t, J = 5.0 Hz), 3.50–3.85 (6 H, m), and 2.10 (3 H, s, $COCH_3$).

Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found: C, 61.90; H, 5.52.

B. A solution of **6** (100 mg) in acetic anhydride (0.7 ml) and pyridine (2 ml) was kept at room temperature for 3 days. The reaction mixture was added with water and then extracted with chloroform. The extract was washed with dilute hydrochloric acid followed by aqueous sodium bicarbonate and finally with water. Evaporation of the solvent gave **7** (90 mg).

Reaction of 6 with *p*-Nitrobenzoyl Chloride. A solution of **6** (240 mg) and *p*-nitrobenzoyl chloride (360 mg) in pyridine (10 ml) was stirred for 2 hr at room temperature. Work-up as described above gave **8** (370 mg): mp 200–203° (benzene–chloroform); ir (KBr) 1765, 1750, 1720, 1530, and 1350 cm^{-1}; NMR ($CDCl_3$) δ 4.85 (1 H, s), 4.80 (1 H, dd, J = 3.0 and 8.0 Hz), 3.65 (3 H, s, COOMe), 3.50 (1 H, m), 3.23 (1 H, t, J = 5.0 Hz), 2.5–3.0 (6 H, m), 8.08 (2 H, d, J = 10.0 Hz), and 8.28 (2 H, d, J = 10.0 Hz).

Anal. Calcd for $C_{20}H_{17}O_8N$: C, 60.15; H, 4.29; N, 3.51. Found: C, 60.17; H, 4.32; N, 3.31.

Reaction of 6 with *p*-Nitrobenzenesulfonyl Chloride. A solution of **6** (250 mg) and *p*-nitrobenzenesulfonyl chloride (340 mg) in pyridine (10 ml) was stirred for 1 day at room temperature. Work-up gave **9** (401 mg): mp 202–203° (benzene–*n*-hexane); ir (KBr) 1770, 1730, 1540, 1370, and 1350 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}O_9NS$: C, 52.52; H, 3.93; N, 3.21. Found: C, 52.47; H, 3.99; N, 3.12.

Reaction of 6 with Tosyl Chloride. A solution of **6** (80 mg) and tosyl chloride (100 mg) in pyridine (10 ml) was stirred for 2 days at room temperature. Work-up gave **10** (139 mg): mp 138–140° (benzene–*n*-hexane); ir (KBr) 1770, 1740, 1360, and 1180 cm^{-1}.

Anal. Calcd for $C_{20}H_{20}SO_7$: C, 59.39; H, 5.00. Found: C, 59.45; H, 5.08.

Hydrolysis of 6. A. A solution of **6** (300 mg) in 50% sulfuric acid (20 ml) was kept at 90° for 5 hr. After neutralization with 10% sodium hydroxide followed by acidification with 10% hydrochloric acid, the solvent was evaporated under reduced pressure. The resulting residue was extracted with hot acetone. Evaporation of the solvent gave **11** (178 mg); mp 220–222° (acetone–benzene); ir (KBr) 1775, 1710, and 3400 cm^{-1}.

Anal. Calcd for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 61.16; H, 5.17.

B. A suspension of **6** (970 mg) in 10% sodium hydroxide (20 ml) was stirred for 2 hr at room temperature. After acidification with hydrochloric acid followed by evaporation of the solvent, the resulting residue was extracted with acetone. Evaporation of the solvent gave **11** (806 mg).

Esterification of 11. A. A solution of **11** (400 mg) in methanol (10 ml) and a trace amount of sulfuric acid was refluxed for 4 hr. After evaporation of the solvent, the reaction mixture was added to water and the product was extracted with chloroform. Drying with sodium sulfate followed by evaporation of the solvent gave **6** (430 mg).

B. To a suspension of **11** (200 mg) in ether (20 ml), an excess of diazomethane in ether (50 ml) was added. The reaction mixture was stirred for 1 day. The resulting residue was recrystallized from benzene to give **6** (210 mg).

Registry No.—**1**, 51447-09-7; **2**, 35211-83-7; **3**, 54712-51-5; **4**, 54677-36-0; **5**, 54773-74-9; **6**, 54677-37-1; **7**, 54677-38-2; **8**, 54677-39-3; **9**, 54677-40-6; **10**, 54677-41-7; **11**, 54677-42-8; *m*-chloroperbenzoic acid, 937-14-4; *p*-nitrobenzoyl chloride, 122-04-3; *p*-nitrobenzenesulfonyl chloride, 98-74-8; tosyl chloride, 98-59-9.

References and Notes

(1) Molecular Design. XXII. Part XXI of this series: T. Sasaki, K. Kanematsu, and T. Kataoka, *J. Org. Chem.*, **40**, 1201 (1975).
(2) T. Sasaki, K. Kanematsu, and A. Kondo, *J. Org. Chem.*, **39**, 2246 (1974).
(3) T. Sasaki, K. Kanematsu, A. Kondo, and Y. Nishitani, *J. Org. Chem.*, **39**, 3569 (1974).
(4) T. Sasaki, K. Kanematsu, and A. Kondo, *Tetrahedron*, in press.
(5) Recently bromination of acid-catalyzed cleavage of epoxide was discussed from a point of intermediacy of cation: B. Giese, *Chem. Ber.*, **107**, 868 (1974).
(6) (a) W. Reppe, O. Schlichting, K. Klager, and T. Toepel, *Justus Liebigs Ann. Chem.*, **560**, 1 (1948); (b) A. C. Cope, P. T. Moore, and W. R. Moore, *J. Am. Chem. Soc.*, **80**, 5504 (1958).
(7) J. G. Buchanan and H. Z. Sable in "Selective Organic Transformations", Vol. 2, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N.Y., 1972, p 8.

Specific Oxygen-18 Labeling and Mass Spectral Fragmentation of 2-Pyrone. CO vs. CS Loss on Fragmentation of Sulfur Analogs of 2-Pyrones

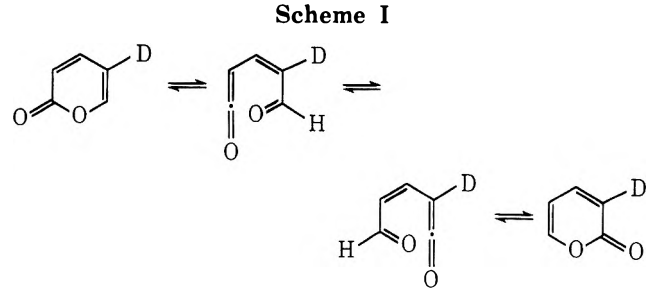
W. H. Pirkle* and W. V. Turner

School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

Received January 3, 1975

The discovery of a pyrolytic 2-pyrone (1) rearrangement[1] (Scheme I) which renders the 3 and 5 positions equivalent

Scheme I

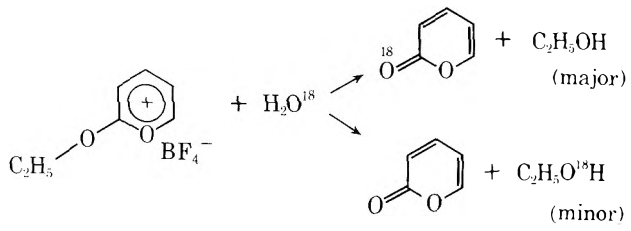


while maintaining the uniqueness of the 4 and 6 positions suggested a possible explanation for the previously observed[2] mass spectral deuterium distributions among the fragments from the four monodeuterated 2-pyrones. These distributions indicate that, at some stage, the 3 and 5 positions of **1** become equivalent, while the 4 and 6 positions remain unique. Whether the equivalence stems from ion symmetry or dynamic scrambling could not be ascertained, nor could it be determined whether it is attained in the $C_5H_4O_2$ molecular ion(s) or the C_4H_4O daughter ion(s). Because the thermal rearrangement scrambles the two oxygen atoms as well as the 3 and 5 positions of **1**,[3] it should be possible to learn whether a similar rearrangement is operative during electron impact induced fragmentation simply by noting the isotopic distribution among the fragments of 2-pyrone labeled specifically with oxygen-18.

Results and Discussion

Labeling of 2-pyrone with oxygen-18 was accomplished by hydrolysis of 2-ethoxypyrylium fluoroborate[4] with oxygen-18-enriched water (Scheme II). The extent of labeling

Scheme II



was determined by mass spectrometry. To minimize the possibility that thermal scrambling in the spectrometer inlet system might precede fragmentation, the labeled samples were adsorbed onto charcoal and directly loaded into the direct oven lock inlet system, which was maintained at 20°. The ion source temperature was 150°. Because M + 1 and M + 2 peaks were slightly larger in the spectrum of unlabeled 2-pyrone than was predicted on the basis of natural isotopic abundances, the oxygen-18 enrichment was found by subtracting the intensities of ions at *m/e* 98 and 100 in the spectrum of unlabeled 2-pyrone from those of labeled 2-pyrone.

Labeled 2-pyrone thus prepared with 30.0% oxygen-18-enriched water contains 24.5% oxygen-18 (Table I). No doubly labeled pyrone is observed. The oxygen-18 is incorporated selectively into the carbonyl group, since conversion of a portion of the labeled pyrone into pyran-2-thione (P_2S_5 in benzene)[5] removes at least 99.5% of the label (Table II). Incomplete labeling (i.e., 24.5/30.0) may be explained either by imperfect exclusion of atmospheric moisture or by partial hydrolysis of the ethyl group. Sib et al.[6] have recently shown that nucleophiles may attack alkoxypyryllium salts at either the ring or the alkyl group, as shown in the minor route of Scheme II.

Table I
Mass Spectra of 2-Pyrone and Oxygen-18-Labeled 2-Pyrone

m/e	Relative ion intensities: Labeled	Relative ion intensities: Unlabeled	Corrected ion intensities[a] (normalized)
	M⁺ Region[b]		
96	100	100	75.5
98	32.2 ± 0.5	0.68 ± 0.01	24.5 ± 0.3
100	0.21 ± 0.02	>0.01	
	M − CO Region[c]		
68	100	100	95.7
70	5.02 ± 0.07	0.65 ± 0.11	4.30 ± 0.09
72	0.09 ± 0.01	0.51 ± 0.03	

[a] Intensities of ions at *m/e* 98, 100, 70, and 72 for unlabeled 2-pyrone were subtracted from intensities of those ions for the labeled 2-pyrone. In addition, an isotropic correction at *m/e* 100 was based on the intensity of the ion at *m/e* 98. [b] Average of five scans at 10 eV. [c] Average of five scans at 70 eV.

Table II
Mass Spectra of 2-Pyran-2-thione

m/e	From labeled 2-pyrone[a]	Expected for C_5H_4OS
112	100	100
114	4.83 ± 0.03	4.78

[a] Containing ca. 25% oxygen-18. Average of three scans with 10-eV electrons.

To determine the extent of ^{18}O retention after decarbonylation of the molecular ion of labeled **1**, the ion intensities at *m/e* 68 of the labeled and unlabeled spectra were normalized to 100, and the intensities of the ions at *m/e* 70 and 72 of the latter were subtracted from the former. Under the same spectrometer conditions, which completely scramble the deuterium label in either 3- or 5-monodeuterated 2-pyrone, only 17.5% of the oxygen label is retained after decarbonylation of the molecular ion.[7] Hence, the two oxygens could have equilibrated in no more than 35% of the molecular ions and a rearrangement similar to that shown in Scheme I is thus ruled out as the principle source of deuterium scrambling. The actual extent of deuterium scrambling occurring via a Scheme I type mechanism may be considerably less; the molecular ion of ^{18}O-labeled **1** may lose unlabeled CO by some alternative process. However, in this regard, it should be noted that Johnstone et al.[8] examined the mass spectra of 4′-methyl-3,4,5′,6′-pyranocoumarin having both carbonyl carbons ^{13}C labeled and found that the first two (of four) sequential decarbonylations proceed with loss of the ^{13}C labels. No competing loss of unlabeled carbonyl was reported. In this instance, the presence of substituents in the 6 position of both pyrone rings presumably would prevent a Scheme I like rearrangement (see ref 3).

Mass spectra of several sulfur analogs of 2-pyrones suggest that a mechanism similar to that of Scheme I may play a role in fragmentation of their molecular ions. Table III shows the ratios of loss of CS to loss of CO for eight of these compounds. The numbers reflect intensities of the M − CS and M − CO ions and may, because of further frag-

Table III
Ratio of Loss of CS to Loss of CO in Sulfur Analogs of 2-Pyrones

Compd	M − CS/M − CO[a]
Thiapyran-2-one	0.01
4-Methylthiapyran-2-one	0.03
4,6-Dimethylpyran-2-thione	100
4-Methoxy-6-methylpyran-2-thione	>73[b]
Pyran-2-thione	0.69
5-Bromopyran-2-thione	0.40
3-Methylpyran-2-thione	0.37
4-Methylpyran-2-thione	0.95

[a] At 70 eV. [b] At 10 eV. Reference 10.

mentation, not represent the true ratios of loss of CS and CO. Nevertheless, the trend is obvious and invites the hypothesis that the more stable isomers,[9] thiapyran-2-one and 4-methylthiapyran-2-one, having sulfur in the ring, do not rearrange and lose solely CO. However, 4,6-dimethylpyran-2-thione, which cannot rearrange by the thermal mechanism because of the blocking methyl group in position 6 (see ref 3), loses CS almost exclusively. By analogy, 4-methoxy-6-methylpyran-2-thione is expected to lose only CS. This occurs predominately (98.6%).[10] Intermediate in behavior are the molecular ions of pyran-2-thione, 5-bromopyran-2-thione, 3-methylpyran-2-thione, and 4-methylpyran-2-thione, which, by this criterion, appear to rearrange substantially prior to fragmentation.

The simplest rationalization of the preceding results is that decarbonylation is several times faster than the rearrangement sequence for 2-pyrone molecular ions but several times slower for thio-2-pyrone molecular ions unless the rearrangement of the latter is blocked by a substituent in position 6. The failure of 2-pyrone to scramble the oxygen label requires the operation of some alternate process to scramble the 3 and 5 deuteriums. Whether this deuterium scrambling occurs before or after decarbonylation is unknown nor is it known whether it occurs via a symmetric ion or through dynamic scrambling. Hence, speculation on the source of the deuterium scrambling is presently unwarranted.

Experimental Section

Oxygen-18-Labeled 2-Pyrone. 2-Ethoxypyrylium fluoroborate[4] (0.17 g) was added to 0.07 g of water containing 30.0% oxygen-18 and 41.2% deuterium. After 3 hr at room temperature and 18 hr of storage at −20°, the sample was distilled at 80° (7 Torr). ^{1}H NMR showed the resulting pale yellow oil to be 2-pyrone, water, and ca. 1% of an ethoxyl-containing impurity. The sample was dissolved in methylene chloride and dried over anhydrous potassium carbonate. Vacuum evaporation of the solvent afforded 2-pyrone with an impurity with a significant ion at *m/e* 66. The impurity was removed by liquid chromatography on silica, eluting with 50:50 methylene chloride–pentane, to give 2-pyrone containing 24.5% oxygen-18 (Table I).

To assess the limits of acid-catalyzed exchange, an attempt was made to label 2-pyrone by HCl-catalyzed exchange with water containing 30.0% oxygen-18 (pH ca. 2). This experiment gave no oxygen-18 incorporation either after 32 days at room temperature or after 1 hr in a steam bath.

Acknowledgment. Mass spectrometric analyses were performed by Mr. J. Wrona on a Varian MAT CH-5 spectrometer. The mass spectral data processing equipment was provided by NIH Grants CA 11388 and GM 16864, from the National Cancer Institute and the National Institute of General Medical Sciences, respectively.

Registry No.—2-Pyrone, 504-31-4; 2-pyrone-2-thione, 23639-33-0.

References and Notes

(1) W. H. Pirkle, H. Seto, and W. V. Turner, *J. Am. Chem. Soc.*, **92**, 6984 (1970).
(2) W. H. Pirkle and M. Dines, *J. Am. Chem. Soc.*, **90**, 2318 (1968).
(3) W. H. Pirkle and W. V. Turner, *J. Org. Chem.*, **40**, 1617 (1975).
(4) M. Dines, Ph.D. Thesis, University of Illinois, 1968.
(5) R. Mayer and P. Fischer, *Chem. Ber.*, **95**, 139U (1962).
(6) S. Sib and M. Simalty, *Tetrahedron Lett.*, 3661 (1973).
(7) At lower ionization voltages, the extent of label loss is slightly greater (e.g., 85% at 10 eV). Mass spectra (70 eV) of similarly labeled 3-methyl-2-pyrone and 5-methyl-2-pyrone[3] indicate that as much as 71 and 66% rearrangement, respectively, may have taken place in these compounds prior to decarbonylation.
(8) R. A. Johnstone, B. J. Millard, F. M. Dean, and A. W. Hill, *J. Chem. Soc. C*, 1712 (1966).
(9) P. Beak, D. S. Mueller, and J. Lee, *J. Am. Chem. Soc.*, **96**, 3867 (1974).
(10) P. Beak, personal communication.

Methyl Hyponitrite

G. David Mendenhall* and L. W. Cary

Stanford Research Institute, Menlo Park, California 94025

Received January 6, 1975

Several of the lower molecular weight alkyl hyponitrites were synthesized by Partington and Shah,[1] Zorn,[2a] and Holden and Kutschke.[2b] The parent member of the series has been mentioned in the patent literature[3] but apparently has not been synthesized, probably because safety considerations outweighed the need. Methyl hyponitrite is an attractive, low-temperature source of methoxy radicals, and we were interested in the compound for use in connection with studies of gas-phase reactions leading to photochemical smog.

Reaction of silver hyponitrite[4] with excess methyl bromide at 0° according to Traylor's procedure[5] gave a solution that was fractionated at low pressure and temperature to remove methyl bromide. Methyl hyponitrite was obtained as a colorless, fragrant liquid at 25° that formed ice-like crystals when condensed from the gas phase onto the walls of a tube at −196°.

The ester was prepared twice without incident. A third preparation of ca. 1 g, however, exploded violently during a *second* bulb-to-bulb distillation from an 8-mm tube. The glass was pulverized into dust so fine that no damage was done to the vacuum system, although the operator sustained superficial cuts from particles that penetrated clothing.[6]

We suspected that "bumping" of the boiling liquid caused the detonation, but a 0.5-g sample in a wide, shallow-bottomed tube later exploded as it was being frozen in a Dewar flask containing liquid nitrogen. Since there was no obvious reason in this case, handling of the neat ester appears to be exceptionally unpredictable. Our experience is in accord with highly disparate accounts in the literature concerning the stability of lower alkyl hyponitrites.

A modified preparation with mineral oil as a diluent proceeded without incident. The ester was handled as a gas and cocondensed with excess 1,4-cyclohexadiene. The resulting solution was diluted with benzene-d_6. Portions were transferred to two NMR tubes for product study. The tubes were degassed and sealed off. One was placed in a bath at 100° for 5 min; a signal at δ 3.06 (CH_3OH) was the only resonance observed other than those from 1,4-cyclohexadiene (δ 2.6 and 5.8) and benzene (δ 7.2). The latter was initially present as an impurity, although it was also an expected product from H abstraction.

A second tube containing 0.9 ± 0.2 *M* hyponitrite was placed in a preheated ^{1}H NMR probe at 70°. The area of the resonance at δ 3.5 decreased 88% in 50 min, with $t_{1/2}$ 17 ± 5 min.

The area of the methanol product signal was only half of the original methyl area in the ester. We cannot account for the difference, since signals from dimethyl peroxide (δ 3.6) or low-field resonance from CH_2O were not observed. The absence of the former is consistent with a value of $k_{\text{disproportionation}}/k_{\text{recombination}} = 9.3$ reported in the gas phase,[7] and also with the small yield of di-*tert*-butyl peroxide observed from di-*tert*-butyl hyponitrite by Kiefer and Traylor[5] and by Neuman and Bussey.[8]

From group additivity[9] we estimate $\Delta H°_{f,g} \cong 70$ kcal/mol for the hyponitrite, and an enthalpy change for the reaction

$$CH_3ON{=}NOCH_3(l) \rightarrow N_2(g) + CH_3OH(g) + CH_2O(g)$$

* Address correspondence to this author at Battelle-Columbus Laboratories, Columbus, Ohio 43201.

of −139 kcal/mol, or about 1.5 kcal/g of ester. This value is comparable to that for a number of explosives and is consistent with the observed properties. The exothermicity also exceeds singlet and triplet energies of formaldehyde and other carbonyl compounds.[10] We will report our observations of solution chemiluminescence from hyponitrites later.

Experimental Section

Dry silver hyponitrite (2 g) was added at 0° to stirred methyl bromide (10 ml) that had been purified by bubbling through concentrated sulfuric acid and condensing at −78°. After 5 hr, the mixture was filtered. The excess methyl bromide was allowed to distil off at 25°; the remaining liquid was further concentrated on a vacuum line by warming repeatedly from −196° and removing vapor portionwise at low temperature. In later runs, mineral oil (1 ml/g $Ag_2N_2O_2$) was added before concentration. The fractionation was followed by means of a capillary bleed leading to a quadrupole mass spectrometer (Finnigan Model 4000). Methyl bromide displayed intense signals at *m/e* 79 and 81. Pure methyl hyponitrite froze to a white solid below 0°: ^1H NMR (C_6D_6) δ 3.52 ($J_{^{13}C-H}$ = 145.3 Hz); ^{13}C NMR (C_6D_6) δ 60.1 ppm downfield from internal TMS; mass spectrum (70 eV) principal *m/e* 90, 59, 31, 30, 29, 28, 15. In pure benzene-d_6 the ^1H NMR signal of the hyponitrite decreased 50% after 1 week at 25°. For the product study in 1,4-cyclohexadiene, the hyponitrite at 2 Torr pressure was diluted with diene to a total pressure of 6 Torr, and the mixture was condensed out at −196° and removed from the vacuum line. The magnetic resonance experiments were determined with a Varian XL-100 NMR spectrometer.

Acknowledgment. This work was supported, in part, by Environmental Protection Agency Grant R 802288.

Registry No.—Silver hyponitrite, 7784-04-5; methyl bromide, 74-83-9; methyl hyponitrite, 29128-41-4.

References and Notes

(1) J. R. Partington and C. C. Shah, *J. Chem. Soc.*, 2589 (1932).
(2) (a) Z. Zorn, *Ber.*, **11**, 1630 (1878); (b) H. W. Holden and K. O. Kutschke, *Can. J. Chem.*, **39**, 1552 (1961).
(3) (a) L. Seed, British Patent 796,728; (b) I. Marshall, I. Harris, and K. B. Garrett, British Patent 618,168.
(4) G. D. Mendenhall, *J. Am. Chem. Soc.*, **96**, 5000 (1974).
(5) H. Kiefer and T. G. Traylor, *Tetrahedron Lett.*, 6163 (1966); *J. Am. Chem. Soc.*, **89**, 6667 (1967).
(6) With respect to a recent letter [*Chem. Eng. News*, 5 (June 17, 1974)], we wish to add that the synthetic work was carried out by the principal author.
(7) J. Heicklen and H. S. Johnson, *J. Am. Chem. Soc.*, **84**, 4030 (1962).
(8) R. C. Neumann, Jr., and R. J. Bussey, *J. Am. Chem. Soc.*, **92**, 2440 (1970).
(9) S. W. Benson, "Thermochemical Kinetics", Wiley, New York, N.Y., 1968.
(10) N. J. Turro, "Molecular Photochemistry", W. A. Benjamin, New York, N.Y., 1967.

Testing Proposed Reaction Mechanisms with Compounds Bound to Solid Supports

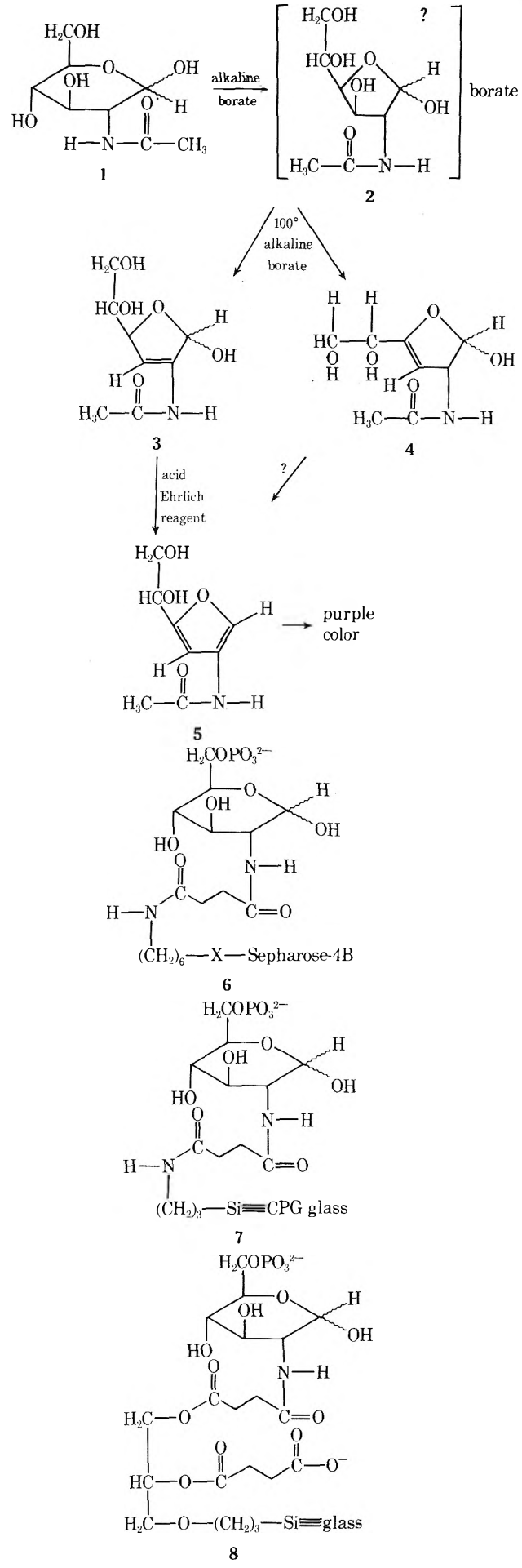
Robert L. Benson

Department of Entomology, Washington State University, Pullman, Washington 99163

Received December 2, 1974

During a sequence of reactions, the fate of a functional group or side chain may be difficult to determine, particularly if one of the intermediates or the product is unstable. Determining the fate of various parts of a molecule may be facilitated if the compound can be bound to a solid support through the part of interest. This paper illustrates the value of this approach by following the fate of an *N*-acyl group through a sequence of reactions.

Scheme I



The Morgan–Elson[1] assay for 2-acylamido-2-deoxy-D-hexose sugars 1 and their 6-phosphate esters involves two main steps[2] (see Scheme I). In step A, heating the sugar with borate buffer at alkaline pH may produce a furanose–borate complex 2. This is followed by dehydration to form a 2,3-anhydro sugar derivative[2] 3 and perhaps a 4,5-anhydro sugar derivative[3] 4. In step B, treatment with Ehrlich reagent (*p*-*N*,*N*-dimethylaminobenzaldehyde in HCl–glacial acetic acid) dehydrates the monoanhydro sugars above to furan derivatives[2,3] 5 and complexes them with Ehrlich reagent, resulting in a purple color with absorption maxima at 550 and 590 nm.

It has been proposed that in the course of the Morgan–Elson reaction the *N*-acyl group of 2-acylamido-2-deoxy-D-hexose sugars may be eliminated during some stage of color development[2,3] because of differential behavior of *N*-acyl and *N*-alkyl hexosamines.

"These results show that, under the conditions of the Morgan–Elson procedure, a wide variety of *N*-acyl groups facilitates chromogen formation (possibly by binding the lone electron pair on the nitrogen atom during the β-elimination process) but that they do not affect the color formed by subsequent reaction with [*p*-*N*,*N*-dimethylaminobenzaldehyde]. *N*-Alkyl substituents, on the other hand, which do little to promote chromogen formation, have a marked effect upon the final color. This suggests that acyl, but not alkyl, groups are eliminated during the color development."[2]

The chromogens produced during the Morgan–Elson reaction are the monoanhydro sugars and furan derivatives mentioned above and seen in Scheme I.[2,3] These compounds do retain the acetamido group of the starting *N*-acetylhexosamine, so that if the *N*-acyl group is eliminated during color development, it probably occurs after the dehydration steps.

The hypothesis that the *N*-acyl group is eliminated has been tested using an *N*-acylhexosamine bound to a solid support via the other end of the *N*-acyl side chain. "*N*-Succinylglucosamine 6-phosphate Sepharose-4B" (6) and "*N*-succinylglucosamine 6-phosphate CPG-Glass" (7) were synthesized from 2-amino-2-deoxy-D-glucose 6-phosphate and succinylated solid supports using the water-soluble carbodiimide procedure.[4,5]

The Sepharose-4B 6 and the CPG-Glass 7 derivatives were subjected to a modified Morgan–Elson procedure,[6] and the typical purple color appeared in both the soluble and nonsoluble phases. Beads were placed in small columns and rinsed with borate buffer–Ehrlich reagent mix equivalent to the normal blank used in the quantitative assay. The soluble color was quickly removed, and the other color in the beads remained attached.

In order to determine the step during which chromogen is released from the Sepharose-4B solid support and the relative amounts of color remaining attached and released, the following experiment was performed. A sample of 0.4 ml of Sepharose derivative 6 was boiled in borate buffer (step A) and cooled. The sample containing the beads was placed on a small column and washed with the appropriate borate buffer while 0.7-ml fractions of the effluent were collected. The Sepharose beads were recovered from the column, and both the beads and fractions were treated with Ehrlich reagent (step B). The absorbance of the various fractions was measured at 585 nm and compared to standards of *N*-acetylglucosamine.

The above experiment could have several possible results. If color appeared in the washings of the Sepharose derivative subjected to the borate boiling above (step A), this would suggest that some of the "*N*-succinylglucosamine-6-P" and/or derivatives with longer side chains had been solubilized during the alkali heating step. If color did not appear after treatment of these fractions with Ehrlich reagent, this would suggest release of the chromogen during a later stage.

Next, if Ehrlich reagent treatment of the recovered Sepharose beads produced only insoluble color, this would suggest that the *N*-succinyl bridge of 6 remains attached to glucosamine-6-P during the entire Morgan–Elson reaction. On the other hand, if this treatment produced either both soluble and insoluble color, or just soluble color, the result would be ambiguous because any of several bonds could be cleaved.

The results of the experiment were straightforward. The early washings from the beads produced color upon treatment with Ehrlich reagent, and accounted for about 137 (16%) of the original 880 nmol of N-succinylglucosamine-6-P attached to the starting material. Compounds covalently bound to Sepharose and glass beads are released in appreciable amounts at pH 8–10 at 4° during an 18-hr period;[7] therefore it is reasonable to expect that 9 min at 100° will also cause release. Consistent with this, treatment of the recovered Sepharose beads with Ehrlich reagent produced only insoluble color, suggesting that the *N*-succinyl group is not eliminated during color development with Ehrlich reagent. However, these experiments do not eliminate the possibility of an internal rearrangement during the Morgan–Elson reaction.

Possible release of soluble factors important to the reaction was tested by running part of the reaction under flow conditions on a column. The CPG-Glass derivative 7 was heated in borate buffer (step A) and then placed in a small column and rinsed with borate buffer. During step B, color developed in the beads on column under flow conditions using borate buffer–Ehrlich reagent mix. This suggests that no soluble factors necessary to the reaction are produced during heating in borate buffer (step A) or during treatment with Ehrlich reagent. The colored pigment is probably not physically trapped because it remains attached to the glass after grinding with a mortar and pestle.

The necessity of the side arm remaining intact for the production of insoluble color by the action of the Morgan–Elson reaction has been tested by including a linkage which is labile to one of the conditions of the sequence. Fully acetylated glucosamine (1,3,4,6-tetra-*O*-acetyl-2-acetamido-2-deoxy-D-glucose, α and β anomers) is Morgan–Elson positive[3] owing to *O*-deacetylation during step A. An ester linkage included in the side chain of a derivative similar to 7 should be labile to alkaline hydrolysis and cause all of the color to be soluble after subjection to the Morgan–Elson procedure. A compound with an ester linkage was synthesized[8] with structure 8, and upon assaying it by the Morgan–Elson procedure, all of the color appeared in the soluble phase. Thus, cleavage of the ester linkage in the side arm brings about release of the purple pigment.

Finally, it was possible that the purple color bound to the solid support, especially Sepharose, might be linked through some unspecified covalent bonds formed during the harsh conditions of the Morgan–Elson reaction. To examine this possibility, we subjected 0.4 ml of aminohexyl-Sepharose-4B and 1 μmol of 2-succinamido-2-deoxy-D-glucose-6-phosphoric acid[9] to the Morgan–Elson procedure. The resulting purple color was quickly removed when the beads were placed in a small column and washed with appropriate borate buffer–Ehrlich reagent mix, eliminating the possibility of an unspecified covalent linkage formed after solubilization of *N*-succinylglucosamine-6-P.

These results suggest that the *N*-acyl group is not elimi-

nated during the Morgan–Elson reaction, and any mechanism proposed for this reaction should take this into account. Because the colored products of the Morgan–Elson reaction are unstable and disappear in a few hours, I have not attempted to identify the colored compounds bound to solid supports. These experiments represent one example of an approach to elucidating reaction mechanisms. In cases where the product may be removed from the solid support and its structure identified, this method will lead to useful models of reaction mechanisms.

Acknowledgment. This work was supported by USPHS Grant AI-10360 and by the Washington State University College of Agriculture Research Center, Project 0056, Scientific Paper No. 4341.

Registry No.—7 (minus support group), 54814-95-8; 8 (minus support group), 54814-96-9.

References and Notes

(1) W. T. J. Morgan and L. A. Elson, *Biochem. J.*, **28**, 988 (1934); J. L. Reissig, J. L. Strominger, and L. F. Leloir, *J. Biol. Chem.*, **217**, 959 (1955).
(2) D. H. Leaback and P. G. Walker, *Biochim. Biophys. Acta*, **74**, 297 (1963).
(3) D. Horton in R. W. Jeanloz, Ed., "The Amino Sugars", Vol. 1A, Academic Press, New York, N.Y., 1969, p 13.
(4) P. Cuatrecasas, *J. Biol. Chem.*, **245**, 3059 (1970). Sepharose-4B (Pharmacia Fine Chemicals) was purchased through Sigma Chemical Co., and structure **6** was synthesized according to Cuatrecasas. CPG/carboxyl succinylated controlled pore glass (550-Å pores) (Corning Glass Works) was purchased through Pierce Chemical Co., and 2-amino-2-deoxy-D-glucose 6-phosphate was added according to Cuatrecasas, resulting in structure **7**.
(5) The purpose of synthesizing these compounds is for affinity chromatography of glucosamine phosphate isomerase (E.C. 5.3.1.10) which is activated allosterically by 2-acetamido-2-deoxy-D-glucose 6-phosphate. The 2-succinamido-2-deoxy-D-glucose-6-P moiety mimics the physiological activator, binding the enzyme to the immobile Sepharose phase via the allosteric site. Subsequently, the enzyme can be eluted with a basic gradient: R. L. Benson, *Fed. Proc., Fdd. Am. Soc. Exp. Biol.*, **33**, 1477 (1974).
(6) R. L. Benson and S. Friedman, *J. Biol. Chem.*, **245**, 2219 (1970); S. Friedman and R. L. Benson, *Methods Enzymol.*, in press.
(7) M. S. Yong, *Science*, **182**, 157 (1973).
(8) From Pierce Chemical, Corning Glass Works product Glycophase-G/CPG-1500 was purchased and succinylated with pure succinyl chloride. The 2-amino-2-deoxy-D-glucose 6-phosphate was attached by the water-soluble carbodiimide method to produce what is probably a mixture of structures, one of which is **8**.
(9) J. J. Distler, J. M. Merrick, and S. Roseman, *J. Biol. Chem.*, **230**, 497 (1958). Succinic anhydride was substituted for the acetic anhydride used to produce *N*-acetylglucosamine-6-phosphoric acid from glucosamine 6-phosphate by these authors. Data on the resulting *N*-succinylglucosamine-6-phosphoric acid will be published at a later date.

Asymmetric Decarboxylation of Ethylphenylmalonic Acid in a Cholesteric Liquid Crystal Solvent

Lawrence Verbit,* Thomas R. Halbert, and Richard B. Patterson

Department of Chemistry,
State University of New York at Binghamton,
Binghamton, New York 13901

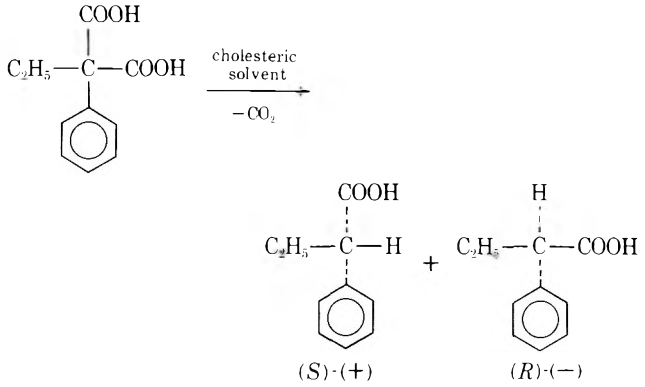
Received October 9, 1974

In connection with our interest in liquid crystals,[1] we have been investigating the use of cholesteric liquid crystals as chiral media for asymmetric reactions. Cholesteric or twisted-nematic phases occur in many derivatives of steroids, most commonly cholesterol, as well as in some nonsteroidal compounds. Common features of molecules which exhibit cholesteric mesomorphism are that they are relatively rigid, have a molecular length considerably greater than their breadth, and are, without exception, chiral. The model of the cholesteric phase is that of a layered nematic liquid twisted about an axis at right angles to the molecular layers. Along the direction of the twist axis a gradual change in molecular orientation within the layers occurs, imparting a helical macrostructure to the liquid. Thus, in contrast to the more usual optically active solvents, cholesteric liquid crystals appear particularly attractive as solvents for asymmetric reactions, since they possess not only molecular chirality but also an overall macrochirality owing to the helical arrangement of the mesophase.

Previous asymmetric reactions in isotropic chiral media have been reviewed by Morrison and Mosher.[2] Generally, stereoselectivities are in the range of 5–10%. The only report pertinent to the present work is a recent communication of the use of a cholesteric liquid crystal solvent for the Claisen rearrangement of methylallyl *p*-tolyl ether.[3] The methylallylphenol rearrangement product exhibited optical activity but the absolute configuration and optical purity of the phenol are unknown.

In this report we describe the results of the asymmetric decarboxylation of ethylphenylmalonic acid in the liquid crystal phase of cholesteryl benzoate (Chart I) and in the isotropic chiral solvent, bornyl acetate.

Chart I



Ethylphenylmalonic acid is an achiral molecule but contains two prochiral ligands. The carboxyl group at the top of the structure in Chart I is the pro-*R* ligand, since preferential loss of this group would yield the (*R*)-(−) enantiomer of 2-phenylbutanoic acid. The other carboxyl group is then the pro-*S* one.

A solution containing 10 mol % of the malonic acid in cholesteryl benzoate (2 g in 50 g) was smoothly decarboxylated by heating at 160° for 2 hr.[4] Vacuum distillation of the reaction mixture afforded 1.6 g of 2-phenylbutyric acid (80% yield), which was shown by a combination of TLC and VPC to be free of contaminants. Determination of the rotation utilizing a photoelectric polarimeter gave $[\alpha]^{27}D$ −14.2° (c 1.3, absolute EtOH). Based on the highest reported rotation for 2-phenylbutanoic acid of $[\alpha]^{25}D$ 78.5° (absolute EtOH),[5] the phenylbutanoic acid formed in this asymmetric decarboxylation has a minimum optical purity of 18%. This value is based on the assumption that the 20% of unrecovered acid has the same enantiomeric composition as the distilled material. If it does not, the stereoselectivity would be different from the observed 59:41 ratio. However, stability experiments involving the distillation of optically active and racemic 2-phenylbutanoic acid gave material having unchanged rotation in the former case and zero rotation in the latter case.

In contrast to the 18% enantiomeric excess found in the ordered cholesteric solvent, decarboxylation of ethylphenylmalonic acid in bornyl acetate, an isotropic chiral solvent, yielded 2-phenylbutanoic acid which was essentially racemic.

The stereoselectivity in the present asymmetric decarboxylation is relatively high compared to typical asymmet-

ric reactions in isotropic chiral media.[2] Our results indicate that for the system studied, a chiral environment due only to molecular chirality is not sufficient for a significant asymmetric bias to occur. One predicts that a preponderance of (*S*)-(+)-2-phenylbutanoic acid would result by use of a cholesteric mesophase having chirality opposite to that used here and that a shorter helical pitch of the mesophase would result in increased optical purity. While the nature of the diastereomeric solute–solvent interaction is not known, we note a certain parallel to the induced circular dichroism phenomenon[6] in which achiral molecules become optically active when dissolved in a cholesteric mesophase. The induced circular dichroism presumably results in part from a particularly strong interaction between the solute and solvent molecules. Work on other asymmetric reactions in chiral liquid crystal solvents is in progress.

Experimental Section

NMR spectra were measured on a Varian A-60 instrument with internal Me_4Si as standard. The vapor phase chromatograph was a Hewlett-Packard Model 5750 with FID, modified for on-column injection. Optical rotations were measured on a Jasco photoelectric spectropolarimeter. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Temperatures are corrected.

Ethylphenylmalonic acid. Freshly distilled (152–155°, 1 Torr) diethyl ethylphenylmalonate (Eastman, 44.0 g, 0.166 mol) was dissolved in 100 ml of 95% ethanol and a solution of KOH (19.0 g, 0.34 mol) in 20 ml of water was added. The reaction mixture was stirred vigorously at 28° for 20 hr. The solvent was then removed by vacuum distillation and the remaining solid was dried in a vacuum desiccator. The solid was washed well with ether (150 ml). The remaining solid (33.5 g) was placed in 150 ml of ether and acidified with 6 *M* hydrochloric acid (ice bath) to the Congo Red point. Water (55 ml) was added and the mixture was stirred vigorously until all the solid had dissolved. The ether layer was separated, dried (anhydrous sodium sulfate), and filtered, and the ether was removed on a rotary evaporator. The remaining material was recrystallized from pentane followed by a second recrystallization from ether–ligroin (bp 30–60°) to afford ethylphenylmalonic acid (21.7 g, 63%): mp 158–161° dec; NMR (methyl ethyl ketone) δ 6.5–7.0 (aryl H's), 10.45 (singlet, carboxyl protons).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.15; H, 5.70.

Asymmetric Synthesis of 2-Phenylbutanoic Acid. Cholesteryl benzoate (50 g), prepared as described in ref 1 [crystal-cholesteric point 150.2°, cholesteric–isotropic point 178.0°, $[\alpha]^{27}D$ −20.8° (c 1.72, heptane)], was intimately mixed with 2.0 g of ethylphenylmalonic acid and the mixture was heated for 2 hr at 160° under a nitrogen atmosphere. The reaction flask was then attached to an 18-in. Teflon spinning band column and 1.6 g of 2-phenylbutanoic acid was collected at 95–97° (0.1 mm). The sample was examined for the presence of steroidal and other impurities by TLC on silica gel GF 254 [developing solvent ethyl acetate–heptane (1.6:1)] and by VPC on 1 m × 4 mm stainless steel columns packed with OV-1, 3% on 100/120 Gas Chrom Q and on 2 m × 4 mm copper columns packed with 10% Carbowax 20M on 100/120 Chromosorb W. No contaminants were observed under these conditions. Elemental analysis of 2-phenylbutanoic acid gave the following results.

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.40; H, 7.68.

Measurement of the optical rotation yielded $[\alpha]^{27}D$ −14.2° (*c* 1.3, absolute ethanol) [lit.[5] $[\alpha]^{25}D$ 78.5° (absolute ethanol)].

Decarboxylation of ethylphenylmalonic acid in bornyl acetate [Aldrich Chemical Co., $[\alpha]^{27}D$ −38.0° (neat)] under the conditions described above led to 2-phenylbutanoic acid which exhibited no optical rotation.

Registry No.—Ethylphenylmalonic acid, 1636-25-5; diethylethylphenyl malonate, 76-67-5; 2-phenylbutanoic acid, 938-79-4; cholesteryl benzoate, 604-32-0.

References and Notes

(1) L. Verbit, *J. Chem. Educ.*, **49**, 46 (1972).
(2) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., Chapter 10.
(3) F. D. Saeva, P. E. Sharpe, and G. R. Olin, *J. Am. Chem. Soc.*, **97**, 204 (1975).
(4) At this concentration the binary mixture is cholesteric between 149 and 166°.
(5) C. Aaron, D. Dull, J. L. Schmiegel, D. Jaeger, Y. Ohashi, and H. S. Mosher, *J. Org. Chem.*, **32**, 2979 (1967). The rotation of 2-phenylbutanoic acid is strongly solvent dependent: A. Horeau and A. Nouaille, *Tetrahedron Lett.*, 1939 (1971).
(6) F. D. Saeva in "Liquid Crystals and Ordered Fluids", J. F. Johnson and R. S. Porter, Ed., Plenum Press, New York, N.Y., 1974, p 581.

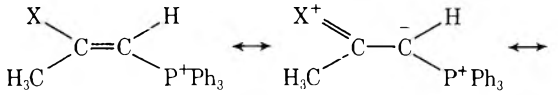
Electronic Structure of β-Vinyl Substituted Phosphonium Salts by Carbon-13 Nuclear Magnetic Resonance

Thomas A. Albright, Susan V. DeVoe, Walter J. Freeman, and Edward E. Schweizer*

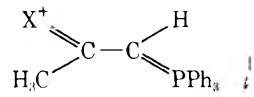
Department of Chemistry, University of Delaware, Newark, Delaware 19711

Received December 17, 1974

We have previously examined the ^{13}C NMR for a large variety of triphenylphosphonium salts and ylides.[1] The focus of the current work is directed toward β-vinyl substituted phosphonium salts having the general structure shown below, where X = Me, NHR, OEt, and the counter-



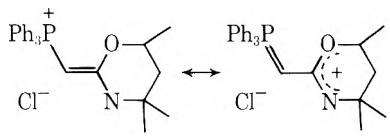
1a 1b



1c

anion Br^- or Cl^-. One would expect that when X possesses unshared pairs of electrons, the resonance form **1b** should be a large contributor to the total electronic structure. In addition, there is also the possibility of the transfer of excess charge from the π system into empty d orbitals[2] on phosphorus. This latter interaction is illustrated by resonance form **1c**. It is expected that when X = CH_3 charge polarization via hyperconjugation[3] may contribute to **1b**. However, this effect should be of smaller magnitude than that previously described for X = –N̈– or –Ö–.

Support for the contribution of resonance forms **1b** and **1c** has been recently published by Trefonas.[4] In this study the X-ray structure of a related phosphonium salt, **2**, was examined. The shortened P–C, C–O, and C–N bond lengths and a long C=C bond compared to model compounds was claimed to be a result of the intervention of resonance structure **2b**.

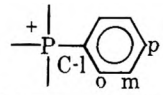


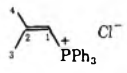
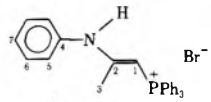
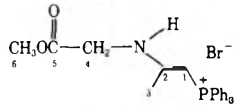
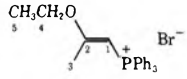
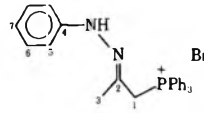
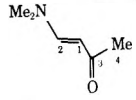
2a 2b

Results and Discussion

The ^{13}C chemical shifts and ^{31}P–^{13}C nuclear spin couplings of vinyltriphenylphosphonium salts and related compounds are reported in Tables I and II, respectively. The assignments of the carbons were made by the use of single frequency off-resonance decoupling and comparisons to model analogs. The assignments of the cis and trans methyl carbons in 2-methylpropenyltriphenylphosphonium chloride (**3**) were discussed previously.[1] The stereochemistry about the carbon–carbon double bond was

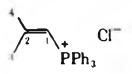
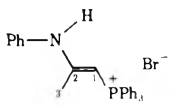
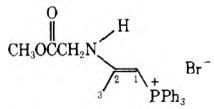
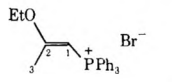
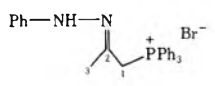
Table I
Carbon Chemical Shifts of Phosphonium Salts and Their Analogs[a]



Registry no.	Compd	No.	^{13}C chemical shift, ppm 1	2	3	4	5	6	7	C-1	O	M	P
42855-48-1		3	102.4	172.0	24.8	29.9				119.4	133.2	130.6	134.8
54774-75-3		4	60.8	163.2	21.4	138.4	124.1	129.5	125.8	122.6	133.0	130.1	134.0
54774-76-4		5	57.7	*	21.2	44.5	169.3	52.0		*	133.0	130.0	134.0
54774-77-5		6	76.5	178.9	20.6	66.1	14.0			120.9	133.0	130.0	134.2
5477-78-6		7	31.3	136.5	17.8	145.5	112.2	128.2	118.5	119.8	133.5	129.8	134.2
21477-76-9		8[b]	98.4	194.6	154.4	28.2							
109-92-2		9[c]	84.6	152.9									

[a] The chemical shifts are referenced to internal Me_4Si. The numbering system of the triphenylphosphonium group is as shown. An asterisk indicates that the resonance was obscured by another peak or too weak to be observed. All compounds were run in $CDCl_3$ except **5**, in which the solvent was DMSO-d_6. [b] L. Kozerski and J. Dubrowksi, *Org. Magn. Reson.*, **5**, 459 (1973). [c] G. E. Maciel, *J. Phys. Chem.*, **69**, 1947 (1965).

Table II
^{31}P–^{13}C Coupling Constants for the Phosphonium Salts[a]

Compd	No.	^{31}P–^{13}C Coupling, Hz 1	2	3	4	C-1	O	M	P
	3	89.4	1.2	7.7	18.6	89.5	10.6	12.8	2.4
	4	120.2		4.3		90.3	10.4	12.9	
	5	120.2	*	4.9		*	10.4	12.2	
	6	96.4	3.0	12.2		92.2	11.0	13.4	3.0
	7	53.7	9.8	6.0		87.9	9.8	12.2	

[a] The numbering system is identical with that used in Table I. The digital resolution was ±0.6 Hz. No coupling from phosphorus was observed beyond the carbons numbered.

uniquely determined as the *E* form (as shown). This was done on the basis of the similarity of the three bonded cis ^{31}P–^{13}C nuclear spin coupling in **3** for carbon 3 compared to that found for the triphenylphosphonium salts **4–6**. The ^{13}C chemical shift for the cis methyl carbon in **3**, 24.8 ppm, is also much closer to that observed in compounds **4–6**, 21.4–20.6 ppm, than that observed for the trans methyl group in **3**, 29.9 ppm.

We wish to point out that carbon-1 in compounds **4–6** is found at unusually high fields for vinyl carbons. To our knowledge carbon-1 in **5** represents the most shielded vinyl carbon, 57.7 ppm, reported in the literature with the exception of conjugated carbanions.[5] This is consistent with the influence of resonance form **1b**. This suggestion is supported by a consideration of the ^{13}C NMR of the enamine **8**,[6] which is analogous to the β-amino vinyltriphenylphosphon-

ium salts, **4** and **5**. Increased electron density on carbon-1 for analogs of **8** was found by CNDO/2 calculations, which is in complete agreement with the carbon chemical shifts.[7] The decreased shielding of carbon-1 in the conjugated enamine **8** compared to **4** or **5** is undoubtedly a consequence of delocalization of the charge into the acetyl group in **8**. It should be noted that carbon-1 in the 2-ethoxyvinyltriphenylphosphonium bromide (**6**) is deshielded by 18.8–15.7 ppm compared to the carbon-1 resonances for **4** and **5**. This is consistent with the notion that delocalization into a π system becomes increasingly inhibited when the atom possessing the unshared pair of electrons becomes more electronegative. That carbon-1 in **6** is shielded by 8.1 ppm from carbon-1 in ethoxyethane (**9**) is probably a result of the combined electronic changes induced into the π system by the substitution of the additional methyl group in **6** and steric differences between **6** and **9**. It should be noted at this point that the accumulation of electron density on carbon-1 for **4** and **5** does not rule out the intervention of resonance structure **1c**, since the diffuseness of the d orbitals[2] will still leave most of the electron density concentrated near carbon-1.

The hydrazone substituted methylenetriphenylphosphonium salt, **7**, a tautomer of the enaminophosphonium salts, **4** and **5**, exhibits no unusual behavior when comparing the ^{13}C chemical shifts and ^{13}C–^{31}P couplings to simple saturated phosphonium salts.[1] It is seen in Table II that the coupling of phosphorus to carbon-1 increases from 53.7 Hz in **7** to 89.4 Hz in **3**. This increase is typical on going from an sp^3 to an sp^2 hybridized carbon as described previously.[1] The β-amino vinyl substituted phosphonium salts have a $^1J(^{31}P$–$^{13}C)$ which is 30.8 Hz larger for carbon-1 than their equivalently hybridized analog, **3**. However, the electron density on carbon-1 is increased in **4** and **5** compared to **3** and if effective nuclear charge considerations[8] are valid in this situation, there should be a decrease in the magnitude of $^1J(^{31}P$–$^{13}C)$. A similar dramatic increase in $^1J_{P-C}$ was found on going from a phosphonium salt to a ylide.[1,9] It was rationalized[1] that this is a consequence of electron density being transfered from the carbon bearing the formal negative charge to phosphorus, presumably via d orbitals. Therefore, the inclusion of resonance structure **1c** should cause $^1J(^{31}P$–$^{13}C)$ for carbon-1 to increase. This infers that electron density on C-1 is being transferred to a greater extent onto phosphorus in **4** and **5** than in **3**. In keeping with this argument the slightly increased $^1J(^{31}P$–$^{13}C)$ coupling of carbon-1 of **6** compared to **3** (ΔHz = 7.0) is justified, since the contribution of **1b** is diminished for **6** owing to the greater electronegativity of oxygen (the contribution of **1c** must also diminish).

Further evidence for the contribution of resonance structure **1c** is given by the slight, but definite, decrease in the shielding of the C-1 phenyl carbons in **4** and **6** compared to **3** (3.2 and 1.5 ppm, respectively). This effect was also noted in going from a phosphonium salt to an ylide, albeit the differences were greater (11.5–15.9 ppm)[1].

The extent of hyperconjugative interaction of the methyl group in **3** is difficult to ascertain. Comparison of $^1J(^{31}P$–$^{13}C)$ of carbon-1 in **3** vs. vinyltriphenylphosphonium bromide reveals an increase of only 9.1 Hz;[1] however, steric differences are also likely to make changes in the magnitude of the coupling. Thus, the additional contribution of resonance structure **1c** for **3** by hyperconjugation must be small.

The electronic description of β-amino and alkoxyvinylphosphonium salts presented here is intriguing. These compounds, by virtue of the delocalization of electrons on nitrogen or oxygen onto d orbitals on phosphorus, seem to represent, electronically, a median between a "normal" phosphonium salt and a carbon–phosphorus ylide. An examination of the synthetic utility of these compounds is under active investigation.

Experimental Section

Spectra were obtained on a Bruker HFX-90 spectrometer equipped for Fourier transform pulsed NMR with a Nicolet 1085 data system. The ^{13}C data were taken at an operating frequency of 22.63 MHz. The ^{13}C chemical shifts are reported as referenced to internal Me_4Si. All samples were run in approximately 0.05 *M* solutions of $CDCl_3$ or DMSO-d_6 (as indicated in footnote *a*, Table I) at 28° with broad band ^1H decoupling. The preparation of the phosphonium salts will be reported elsewhere.

Acknowledgment. Support from the University of Delaware is greatly appreciated.

References and Notes

(1) T. A. Albright, W. J. Freeman, and E. E. Schweizer, *J. Am. Chem. Soc.*, **97**, 2942, 2946 (1975).
(2) There also exists the possibility of a hybrid combination of empty 3d and 4p orbitals which could provide energetically more favorable overlap. This remains a matter for theoretical chemists to sort out. For recent reviews on the importance of d orbitals for chemical bonding, see C. A. Coulson, *Nature (London)*, **221**, 1106 (1969); K. A. R. Mitchell, *Chem. Rev.*, **69**, 157 (1967); R. S. Mulliken and B. Liu, *J. Am. Chem. Soc.*, **93**, 6738 (1971).
(3) See, for example, L. Libit and R. Hoffmann, *J. AM/ Chem. Soc.*, **96**, 1370 (1974), and references cited therein.
(4) L. M. Trefonas and J. W. Brown, *J. Heterocycl. Chem.*, **9**, 985 (1972).
(5) R. B. Bates et al., *J. Am. Chem. Soc.*, **95**, 926 (1973).
(6) L. Kozerski and J. Dabrowski, *Org. Magn. Reson.*, **5**, 459 (1973).
(7) J. Dabrowski, K. Kamienska-Trela, and A. J. Sadlej, *J. Mol. Struct.*, **12**, 185 (1972); J. Dabrowski, K. Kamienska-Trela, and L. Kozerski, *Org. Magn. Reson.*, **6**, 43 (1973).
(8) D. M. Grant and W. M. Litchman, *J. Am. Chem. Soc*, **87**, 3994 (1965); and J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, pp 324–325 and 377–378.
(9) G. A. Gray, *J. Am. Chem. Soc.*, **95**, 7736 (1973).

Photosensitized Oxygenation of *trans,trans*-1-Methylcyclodeca-1,6-diene. A Regiospecific Hydroperoxidation with Singlet Oxygen

Sung-Kee Chung and A. Ian Scott*

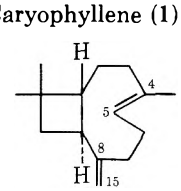
Department of Chemistry, Yale University, New Haven, Connecticut 06520

Received January 20, 1975

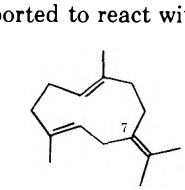
The reactive species of dye-sensitized photooxygenation is presumably singlet oxygen,[1] which is known to react with olefins and conjugated dienes in three ways, namely "ene" reaction, Diels–Alder reaction, and 1,2-dioxetane formation.[1,2] In principle, nonconjugated dienes can react with singlet oxygen to give either the transannular cycloaddition product when the geometry is favorable[3] or the "ene" products, a mixture of allylic hydroperoxides.[2]

The hydroperoxidation of olefins with singlet oxygen is an important synthetic method for the preparation of allylic hydroperoxides and allylic alcohols. Although this hydroperoxidation is generally believed to occur faster with tri- and tetrasubstituted olefins than with di- or monosubstituted ones, there are only a few literature reports in which a completely regiospecific hydroperoxidation of a double bond was actually observed within the molecule.[4]

(−)-Caryophyllene (**1**) was reported to react with singlet



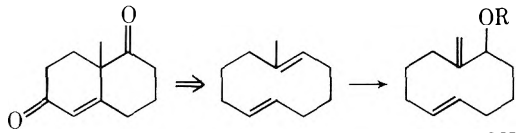
1



2

oxygen at the trisubstituted double bond (C-4,5) faster than at the exocyclic double bond (C-8,15), thus exclusively generating 4-methylene-5-hydroperoxy derivative.[4a] Germacrene (2) was reported to react with singlet oxygen at the isopropylidene double bond much faster than the endocyclic double bonds, giving specifically the 7-hydroperoxy derivative.[4b]

We have studied the dye-sensitized photooxygenation of *trans,trans*-1-methylcyclodeca-1,6-diene (4), because it has two transannularly interacting double bonds which are suitable for a cycloaddition reaction, and because the two double bonds have different substitution patterns which are capable of revealing the regiospecificity of the "ene" reaction. The diene 4 was readily synthesized from 9-methyloctalin-1,6-dione (3) according to literature procedures.[5] A methanol solution of 4 was irradiated in the presence of Methylene Blue at 10° for 4.5 hr while pure oxygen was bubbled through. The disappearance of 4 was monitored by taking aliquots and analyzing them on TLC. A single produce **5a** isolated in 55% yield showed a positive peroxide test with starch–iodine and gave an alcohol **5b** upon reduction with aqueous methanolic sodium sulfite.



3 4 5a, R = OH
b, R = H

Analysis by TLC, GC, and NMR spectrum clearly indicated that alcohol **5b** was homogenous and free from other possible isomers. A thorough search for the transannular cycloaddition products proved futile. It is interesting to note that the hydroperoxidation is completely regiospecific in spite of the fact that four other positions are also available for the "ene" reaction. A qualitative reactivity order of the double bonds toward the singlet oxygen "ene" reaction appears to be the following: isopropylidene > endocyclic trisubstituted olefin > endocyclic disubstituted olefin > isopropenyl > *exo*-methylene.[4] Although there is no straightforward explanation for the exclusive formation of the *exo*-methylene *sec*-hydroperoxide over the other possible endocyclic *tert*-hydroperoxide products, the observed regiospecificity should be of considerable value in synthetic design.[6]

Experimental Section

The NMR spectra were recorded on a Jeol JNM-MH 100 spectrometer. Ir spectra were recorded on a Perkin-Elmer Model 421 grating spectrophotometer. Mass spectral data were obtained on a Hitachi RMU-6 spectrometer. Gas chromatograms were run on a Varian Model 2700 using the columns 5 ft × 0.125 in, 10% OV-101 on Anakrom C.D. and 5 ft × 0.125 in, 10% FFAP on Anakrom C.D. Microanalysis was performed by Dr. R. C. Rittner at Olin Laboratory, New Haven, Conn.

***trans,trans*-1-Methylcyclodeca-1,6-diene (4)** was prepared from 1-methyloctalin-1,6 dione (3)[7] according to literature procedures[5] in ca. 35% overall yield: NMR ($CDCl_3$) δ 1.0–2.0 (m, 4 H), 1.64 (s, 3 H), 2.0–2.6 (m, 8 H), 5.0–5.5 (m, 3 H).

2-Methylenecyclodeca-*trans*-6,7-enol (5b). A solution of diene 4 (266 mg, 1.77 mmol) and Methylene Blue (10 mg) in methanol (20 ml) at 10° was irradiated with a 275-W sun lamp while pure oxygen was bubbled through the solution. After 4.5 hr, the solution was poured into cold water and extracted with ether. The extract was washed thoroughly with water, dried (Na_2SO_4), and evaporated at room temperature to give crude hydroperoxide **5a**. Pure **5a** (oil, 180 mg, 55% yield) was obtained by a thick layer chromatography (2 mm SiO_2, developed in 40% ether in hexane): NMR ($CDCl_3$) δ 1.0–2.4 (m, 12 H), 4.36 (hr, 1 H), 5.18 (s, 1 H), 5.28 (s, 1 H), 5.42 (m, 2 H).

Stirring a solution of **5a** in methanol (20 ml) and 10% sodium sulfite in water (20 ml) for 5 hr at room temperature, followed by an extractive work-up with ether, gave pure alcohol **5b** in quantitative yield: oil, homogeneous by TLC (SiO_2) and GC (OV 101, 140°); ir 3600, 3080, 3030, 1640, 1448, 1345, 980, 910 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.4 (m, 12 H), 4.08 (br, 1 H), 4.98 (s, 1 H) 5.18 (s, 1 H), 5.36 (m, 2 H); MS *m/e* 166 (M^+), 148, 134, 124, 120.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.52; H, 10.84. Found: C, 79.33; H, 10.77

Acknowledgment. We wish to thank the National Science Foundation (Grant GP33505X) for support of this work.

Registry No.—**3**, 20007-72-1; **4**, 13304-33-1; **5a**, 54814-44-7; **5b**, 54814-45-8.

References and Notes

(1) C. S. Foote, *Acc. Chem. Res.*, **1**, 104 (1968); R. P. Wayne, *Adv. Photochem.*, **7**, 311 (1969).
(2) K. Gollnick, *Adv. Photochem.*, **6**, 1 (1968); W. R. Adams, "Oxidation", Vol. 2, R. L. Augustine and D. J. Trecker, Ed., Marcel Dekker, New York, N.Y., 1971, p 65, excellent review of these reactions.
(3) T. Matsuura, A. Horinaka, H. Yoshida, and Y. Butsugan, *Tetrahedron*, **27**, 3095 (1971); C. J. Sih and C. A. Takeguchi, "The Prostaglandins", P. W. Ramwell, Ed., Plenum Press, New York, N.Y., 1973.
(4) (a) K. Gollnick and G. Schade, *Tetrahedron Lett.*, 689 (1968); (b) T. W. Sam and J. K. Sutherland, *J. Chem. Soc., Chem. Commun.*, 424 (1972); (c) F. Bellesia, U. M. Pagnoni, and R. Trave, *Tetrahedron Lett.*, 1245 (1974); (d) E. Klein and W. Rojahn, *Tetrahedron*, **21**, 2173 (1965).
(5) J. A. Marshall and G. L. Bundy, *J. Am. Chem. Soc.*, **88**, 4291 (1966); J. A. Marshall, *Synthesis*, 229 (1971).
(6) A referee has pointed out that an explanation for the absence of the endocyclic *tert*-hydroperoxide probably lies in the preferred crown conformation of the cyclodecadiene ring, where none of the *sec*-allylic protons have the optimal 90° angle between them and the plane of the double bond for the "ene" reaction to readily occur.
(7) Purchased from Aldrich Chemical Co.

Synthesis of Three Substituted Aminochloropropanes

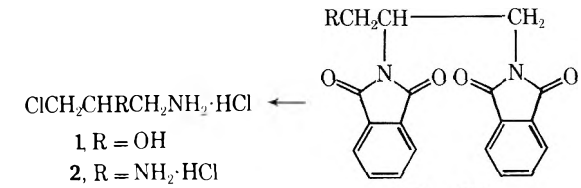
Rolf Paul,* Richard P. Williams, and Elliott Cohen

Metabolic Disease Therapy Research Section, Lederle Laboratories, Division of American Cyanamid Company, Pearl River, New York 10965

Received October 25, 1974

In the course of a study of male antifertility agents it became necessary to synthesize several aminochloropropanes. Because of the proximity of mutually interactive functional groups in such molecules, the instability of the products was a problem that had to be overcome. One of these, 1-amino-3-chloro-2-propanol hydrochloride (1), had very interesting properties and its pharmacology has been reported elsewhere.[1,2]

The synthesis of 1,2-diamino-3-chloropropane dihydrochloride (2) has been reported by Philippi[3] via the following sequence. 2,3-Dibromopropanol on fusion with potassium phthalimide gave 2,3-bisphthalimidopropanol (3).



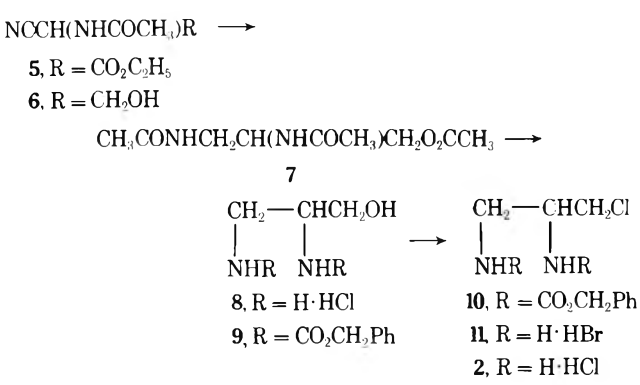
$ClCH_2CHRCH_2NH_2 \cdot HCl$ ←

1, R = OH
2, R = $NH_2 \cdot HCl$

3, R = OH
4, R = Cl

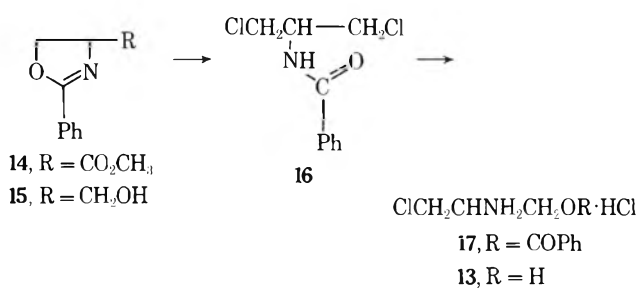
Phosphorus pentachloride converted **3** to **4**, which gave **2** on hydrolysis. Although part of the sequence has been repeated in the literature[4] but without proof of structure of the products, in our hands dehydrobromination occurred on the first step, yielding phthalimide and potassium bro-

mide as the only recovered solids. If epibromohydrin were formed during the hydrogen bromide elimination and not permitted to escape, there would be a danger of getting 1,3-bisphthalimido-2-propanol.[5] A less equivocal path was adopted by us wherein ethyl acetamidocyanoacetate (**5**) was reduced to the alcohol **6** with sodium borohydride. Hydrogenation over Raney nickel in acetic anhydride gave **7**.



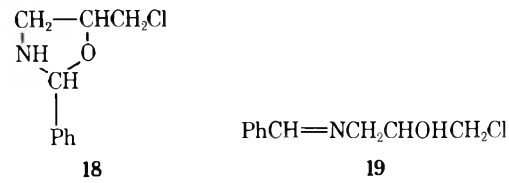
This triacetate had been previously reported,[4] via the phthalimido approach discussed above, but ours had a different melting point. Attempts at a selective hydrolysis of the ester linkage of **7** failed and it was totally hydrolyzed to **8**. Carbobenzoxylation of **8** gave **9** while triphenylphosphine–carbon tetrachloride converted that alcohol to the chloride **10**. Hydrogen bromide in acetic acid on **10** gave **11**, whose structure was confirmed by NMR. After two precipitations from concentrated hydrochloric acid–ethanol, **11** was converted to **2**, demonstrating that the covalent chloride had not been displaced during the hydrogen bromide treatment. The melting point of our **2**, 220–223°, was close to that cited by Philippi, 218–219°. On the other hand, Gabriel[6] prepared 1,3-diamino-2-chloropropane dihydrochloride by the following scheme. 1,3-Dichloro-2-propanol and potassium phthalimide gave 1,3-bisphthalimido-2-propanol; next phosphorus pentachloride and then hydrolysis gave 1,3-diamino-2-chloropropane dihydrochloride (**12**). Even if epichlorohydrin were an intermediate, this scheme would give the structure Gabriel assigned to it. Since Gabriel's melting point was 216°, Philippi's compound could also be, and probably is, **12**.

The second aminochloropropane prepared was 2-amino-3-chloropropanol hydrochloride (**13**). Methyl 2-phenyl-2-oxazoline-4-carboxylate[7] (**14**) was reduced with sodium borohydride to the alcohol **15**. Thionyl chloride converted the alcohol to a chloride and opened the ring to give *N*-2-(1,3-dichloropropyl)benzamide (**16**). Treatment with dilute hydrochloric acid gave **17** via anchimeric assistance, while further reaction of **17** with concentrated hydrochloric acid gave the desired **13**. In the course of a different synthesis



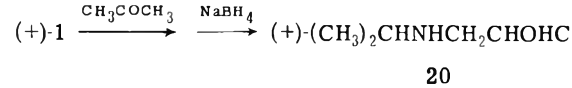
that had one step in common with ours, Berger et al.[8] prepared **16** in low yield and also noted its conversion to **17** by the anchimeric effect.

Finally we wanted to obtain the two enantiomers of our active compound **1**. There are a number of syntheses of racemic **1** in the literature;[9] however, the yields are poor and they do not lend themselves to large scale-ups. Carter and Bhattacharyya[10] reported the reaction of epichlorohydrin with concentrated ammonium hydroxide and benzaldehyde to give **18** in 67% yield. Their structure was based on an



earlier assignment by Bergmann.[11] On preparing **18** and taking an ir spectrum, an imine band was seen at 6.08 μ, indicating that Carter and Bhattacharyya's and Bergmann's compound was probably the Schiff base **19**. Hydrolysis of **19** gave **1** in high yield, thus achieving a simple two-step preparation. Originally we resolved **1** using dibenzoyl-*d*-tartaric acid,[1] but a better resolution was achieved with (+)-10-camphorsulfonic acid.

To determine the absolute configuration of (+)-**1**, it was converted to the free base and condensed with acetone to form a Schiff base, which was reduced without purification to **20**. Dukes and Smith[12] had previously determined the



absolute configuration of **20**; thus (+)-**1** had the *R* configuration.

Experimental Section

Melting points were determined with a standardized Mel-Temp apparatus. NMR spectra were recorded on a Varian HA-100.

2-Acetamido-3-hydroxypropionitrile[13] **(6).** To a stirred slurry of 100 g (0.59 mol) of ethyl acetamidocyanoacetate (**5**) in 1 l. of ethanol was added 60 g (1.59 mol) of $NaBH_4$ over a 20-min period. Occasional cooling was used to maintain a 50–55° temperature throughout the addition. Then the reaction was stirred at ambient temperature for 3 hr and cooled in an ice bath and 132 ml of 12 *N* HCl in 500 ml of ethanol was added over a 20-min period. An inorganic precipitate was filtered off and the filtrate was concentrated under vacuum. Three portions of ethanol were added, followed by concentration under vacuum each time to remove water. The residue was leached with 800 ml of acetone and the insolubles were discarded. Concentrating the acetone solution left an oil which on seeding gave 66.5 g of orange crystals. Recrystallization from ethanol gave 28.5 g (38%) of solid, mp 108–110°.

This reaction proved to be erratic and in 13 runs yields varied from 0 to 51%.

An analytical sample was recrystallized twice from ethanol to give mp 111–112°.

Anal. Calcd for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.87. Found: C, 46.92; H, 6.14; N, 22.14.

2,3-Bis(acetamido)propyl Acetate (7). 2-Acetamido-3-hydroxypropionitrile (33.5 g, 0.26 mol), 18.0 g of Raney Ni (prewashed with ethanol three times and then with acetic anhydride three times), 61 g of anhydrous sodium acetate, and 280 ml of acetic anhydride were hydrogenated in a Parr shaker in two portions at 33–40°. When the theoretical amount of hydrogen had been taken up, the mixture was filtered and the filtrate was concentrated under vacuum to give a yellow oil. On crystallization from ethyl acetate–benzene–ether, 48 g of oily crystals, mp 90–95°, were obtained. Recrystallizations from ethyl acetate gave 26 g (46%) of colorless crystals: mp 130–132°; NMR (DMSO-d_6) 2-NAc (6 H) δ 1.85 (s), OAc (3 H) 2.04 (s), CH_2N (2 H) 3.19 (m), CHN and CH_2O (3 H) 4.00 (m), 2-NH (2 H) 7.84 (m).

An analytical sample was recrystallized twice from benzene–cyclohexane to give mp 132–133° (lit.[4] mp 146° for a compound claimed, but not proven, to be **7**).

Anal. Calcd for $C_9H_{16}N_2O_4$: C, 49.99; H, 7.46; N, 12.96. Found: C, 49.88; H, 7.47; N, 13.04.

2,3-Diaminopropanol Dihydrochloride (8). After 130 g (0.60 mol) of **7** was refluxed in 1.3 l. of 6 *N* HCl for 45 min, the solution

was permitted to stand overnight. It was next concentrated at 70° (25 mm) to dryness and the residue was slurried with ethanol. Upon standing, crystals were collected, 70 g (71%), mp 162–163°, and recrystallized from aqueous ethanol to obtain 50 g (51%) of light tan crystals, mp 184–186°.

Anal. Calcd for $C_3H_{12}Cl_2N_2O$: C, 22.10; H, 7.42; Cl, 43.49; N, 17.18. Found: C, 22.09; H, 7.51; Cl, 43.30; N, 17.28.

***N,N'*-Dicarbobenzoxy-2,3-diaminopropanol (9)** was prepared by a method of Bergmann and Zervas,[14] yield 62%, mp 109–110° (ethanol).

Anal. Calcd for $C_{19}H_{22}N_2O_5$: C, 63.67; H, 6.19; N, 7.82. Found: C, 63.50; H, 6.09; N, 7.65.

***N,N'*-Dicarbobenzoxy-1,2-diamino-3-chloropropane (10).** A solution of 36.0 g (0.10 mol) of *N,N'*-dicarbobenzoxy-2,3-diaminopropanol in 170 ml of alumina-dried chloroform and 112 ml of carbon tetrachloride was warmed while 53.5 g (0.2 mol) of triphenylphosphine was added. After the exothermic reaction subsided, the solution was refluxed for 2 hr. The solvent was removed under vacuum, and the resulting yellow oil was taken up in 1 l. of hot 60% aqueous ethanol. Seeding and cooling to 0° gave 27.5 g (73%) of colorless crystals, mp 119–120°. A sample was recrystallized from ethanol for analysis, mp 120–121°.

Anal. Calcd for $C_{19}H_{21}ClN_2O_4$: C, 60.55; H, 5.62; Cl, 9.41; N, 7.44. Found: C, 60.51; H, 5.64; Cl, 9.28; N, 7.39.

1,2-Diamino-3-chloropropane Dihydrobromide (11) and Dihydrochloride (2). *N,N'*-Dicarbobenzoxy-1,2-diamino-3-chloropropane (**10**, 30 g, 0.08 mol) was dissolved in 300 ml of glacial acetic acid and saturated with HBr at 0°. After standing for 1 hr, the precipitate which had formed was collected, washed with ether, and air dried to give 19 g (81%) of **11**, mp 210–212° dec. A NMR spectrum confirmed the structure: CH_2N^+ (2 H) δ 3.23 (d), J = 6 Hz, CHN^+ (1 H) 3.96 (m), CH_2Cl (2 H) 4.08 (m), 2-NH_3^+ (6 H) 8.49 (s).

Anal. Calcd for $C_3H_{11}Br_2ClN_2$: C, 13.32; H, 4.10; Br, 59.10; Cl, 13.11; N, 10.36. Found: C, 13.58; H, 4.13; Br, 58.79; Cl, 12.57; N, 10.72.

To ensure that the covalent chlorine had not been lost, the 19 g of hydrobromide **11** was dissolved in 210 ml of warm 12 *N* HCl, filtered, and diluted with 800 ml of ethanol. Cooling overnight gave 13 g of damp crystals, mp 219–222° dec, which were dissolved in 100 ml of hot 12 *N* HCl and diluted with 300 ml of ethanol. Again cooling gave a precipitate which was collected and dried to obtain 11.5 g (79%) of colorless, crystalline **2**, mp 220–223° dec.

Anal. Calcd for $C_3H_{11}Cl_3N_2$: C, 19.85; H, 6.11; Cl, 58.60; N, 15.44. Found: C, 19.72; H, 6.13; Cl, 58.67; N, 15.52.

2-Phenyl-4-hydroxymethyl-2-oxazoline (15). A solution of 50.0 g (0.24 mol) of methyl 2-phenyl-2-oxazoline-4-carboxylate[7] in 670 ml of ethanol was cooled to 5–10° while 33.4 g (0.88 mol) of $NaBH_4$ was added portionwise. After stirring at room temperature for 1.5 hr, 85 ml of water was added and stirring was continued for 1.5 hr more. The reaction was then diluted to 3 l. with water, saturated with salt, and extracted three times with 500 ml of ether. On combining the extracts, they were dried ($MgSO_4$) and concentrated to give 42.2 g (99%) of colorless crystals, mp 85–87°, whose NMR agreed with the structure.

A sample was recrystallized for analysis from ethyl acetate–cyclohexane, mp 83–86°.

Anal. Calcd for $C_{10}H_{11}NO_2 \cdot {}^1/_4C_2H_5OH$: C, 66.82; H, 6.68; N, 7.42. Found: C, 66.89; H, 6.30; N, 7.78.

***N*-2-(1,3-Dichloropropyl)benzamide (16).** Over a 10-min period, 24.0 g (0.135 mol) of **15** was added to 120 ml of $SOCl_2$ at 5° with stirring. After stirring for 30 min at room temperature, the mixture was refluxed for 1 hr. Next the mixture was concentrated under vacuum, ethanol was added, and the mixture was reconcentrated to flush out excess $SOCl_2$. A gray solid was obtained which was recrystallized from benzene–hexane to give 18.7 g (65%) of **16**, mp 107–108°. Recrystallizing a sample for analysis from the same system gave mp 112–113°. The structure was confirmed by NMR.

Anal. Calcd for $C_{10}H_{11}NOCl_2$: C, 51.74; H, 4.78; Cl, 30.55; N, 6.04. Found: C, 51.71; H, 4.79; Cl, 31.38; N, 5.92.

1-Chloro-2-amino-3-propyl Benzoate Hydrochloride (17). After a solution of 18.0 g (0.078 mol) of *N*-2-(1,3-dichloropropyl)benzamide (**16**) in 455 ml of 50% ethanol–water and 23.1 ml of 12 *N* HCl was refluxed for 30 min, the solvent was removed under vacuum. The residue was flushed with ethanol to give 18 g (92%) of colorless crystals, mp 180–182°. Recrystallization from ethanol gave 14 g of crystals (72%), mp 190–191° (lit.[8] mp 184–185°), which were identified by NMR.

Anal. Calcd for $C_{10}H_{13}Cl_2NO_2$: C, 48.02; H, 5.24; Cl, 28.35; N, 5.60. Found: C, 47.94; H, 5.38; Cl, 28.53; N, 5.59.

2-Amino-3-chloropropanol Hydrochloride (13). 1-Chloro-2-amino-3-propyl benzoate hydrochloride (**17**, 7.0 g, 0.028 mol) was dissolved in 245 ml of 6 *N* HCl preheated to 85°. After stirring and maintaining the temperature for 10 min, the solution was refluxed for 0.5 hr. Then the solution was chilled in ice and extracted four times with 400-ml portions of ether. On concentrating the aqueous layer under vacuum at 60°, a yellow oil was obtained, which was flushed several times with ethanol. Three days under high vacuum left 1.88 g of intractable oil which would not give a correct analysis but whose structure was confirmed by NMR: CHN^+ (1 H) δ 3.46 (m), CH_2O (2 H) 3.71 (d), CH_2Cl (2 H) 3.93 (d), OH (1 H) 4.92 (s), NH_3^+ (3 H) 8.56 (s).

(±)-1-Amino-3-chloro-2-propanol Hydrochloride (1). (±)-1-Benzalimino-3-chloro-2-propanol[10] (6.3 g, 0.032 mol) was stirred with 30 ml of 2 *N* HCl for 1 hr. After the mixture was extracted with three 10-ml portions of benzene to remove the benzaldehyde, the aqueous portion was concentrated at 40° (25 mm) to obtain an oil. Flushing with ethanol gave crystals which were collected, washed with ether, and dried to give 4.6 g (98%) of product, mp 101–102° (lit.[9a] mp 103–104°).

Resolution of (±)-1-Amino-3-chloro-2-propanol Using (+)-10-Camphorsulfonic Acid. A solution of 584 g (4.00 mol) of (±)-1-amino-3-chloro-2-propanol hydrochloride in 1 l. of methanol at 40° was neutralized with a second solution of 392 g (4.00 mol) of potassium acetate in 1.3 l. of methanol. After cooling, 1.1 l. of ether was added and the precipitate was filtered off. Then the filtrate was concentrated under vacuum and 930 g (4.00 mol) of (+)-10-camphorsulfonic acid in 1.0 l. of ethanol was added. Cooling and seeding with (−)-1-amino-3-chloro-2-propanol (+)-10-camphorsulfonic acid salt gave the first precipitate. A fractional crystallization from ethanol was then carried out. As the (−)-amine salt became pure, the rotation approached $[\alpha]^{25}D$ +5.2°, mp 118–119°, while pure (+)-1-amino-3-chloro-2-propanol (+)-10-camphorsulfonate had $[\alpha]^{25}D$ +23.1°, mp 118–120°.

Anal. Calcd for $C_{13}H_{24}ClNO_5S$ [(−)-1 salt]: C, 45.67; H, 7.08; Cl, 10.37; N, 4.10; S, 9.38; Found: C, 45.78; H, 7.07; Cl, 10.67; N, 4.12; S, 9.19.

Apparently the solubility of the salts was so similar that whichever one was in excess would come out of the mother liquor. To convert back to the hydrochloride salt, the camphorsulfonate was slurried in 5 ml of tetrahydrofuran/g of salt while HCl was bubbled in until about 20% excess (by weight) had been added. The solution was then cooled to 0° and 5 ml of ether/g of salt was added. The hydrochloride from (−)-1-amino-3-chloro-2-propanol (+)-camphorsulfonic acid salt, $[\alpha]^{25}D$ +5.23° (c 2, water), was pure in one recrystallization at 1 g/7 ml ethanol–HCl, with constants of mp 144–146°, $[\alpha]^{25}D$ −23.6° (*c* 2.18, water). Yields up to 69% were obtained.

(+)-1-Chloro-3-isopropylamino-2-propanol hydrochloride (20) was prepared from (+)-1 and acetone following the general procedure of Billman and Diesing[15] to give the free base of **20**, bp 40° (0.1 mm), which was immediately converted to the hydrochloride, yield 39%, mp 105–107°. A sample was recrystallized for analysis and rotation from 2-propanol–ether–HCl(g), mp 107–108.5°, $[\alpha]^{25}D$ +33.6° (c 2.3, ethanol) [lit.[11] mp 106°, $[\alpha]^{25}D$ +25.9° (c 2, ethanol)]. The structure was confirmed by NMR.

Anal. Calcd for $C_6H_{15}Cl_2NO$: C, 38.31; H, 8.04; Cl, 37.70; N, 7.45. Found: C, 38.58; H, 8.13; Cl, 37.28; N, 7.21.

Acknowledgments. Microanalyses were performed by Mr. L. M. Brancone and staff. Spectra and rotations were determined by Mr. W. Fulmor and staff, while Mr. G. O. Morton interpreted the NMR spectra.

Registry No.—(±)-1 HCl, 34839-12-8; (−)-1 HCl, 54798-66-2; (−)-1 (+)-10-camphorsulfonic acid salt, 54798-67-3; (+)-1 (+)-10-camphorsulfonic acid salt, 54868-32-5; **2**, 54798-68-4; **5**, 4977-62-2; **6**, 54832-65-4; **7**, 54798-69-5; **8**, 52393-59-6; **9**, 54798-70-8; **10**, 54798-71-9; **11**, 54798-72-0; **13**, 54798-73-1; **14**, 55044-06-9; **15**, 15263-48-6; **16**, 23546-99-8; **17**, 23551-84-0; (±)-**19**, 54798-75-3; **20** HCl, 54831-47-9; **20** free base, 54831-48-0; (+)-10-camphorsulfonic acid, 3144-16-9.

References and Notes

(1) R. Paul, R. P. Williams, and E. Cohen, *Contraception*, **9**, 451 (1974).
(2) J. A. Coppola and R. J. Saldarini, *Contraception*, **9**, 459 (1974).
(3) E. Philippi, R. Seka, and L. Ableindinger, *Justus Liebig's Ann. Chem.*, **433**, 94 (1923).
(4) J. Staněk and J. Průšová, *Chem. Listy*, **46**, 491 (1952).
(5) In an analogous experiment, 2,3-dibromopropanol, succinimide, and po-

tassium carbonate were refluxed in ethanol for 24 hr. 1,3-Bis(succinimido)-2-propanol was obtained in good yield. Acid hydrolysis of the bisimide gave 1,3-diamino-2-propanol, a known compound.[6b] An authentic sample, as the hydrochloride, had the same ir as ours and gave no depression on taking a mixture melting point.
(6) (a) S. Gabriel and W. Michels, *Ber.*, **25**, 3056 (1892); (b) S. Gabriel, *ibid.*, **22**, 224 (1889).
(7) M. Bergmann and A. Mickeley, *Hoppe-Seyler's Z. Physiol. Chem.*, **140**, 128 (1924); E. M. Fry, *J. Org. Chem.*, **14**, 887 (1949).
(8) J. Berger, K. Günther, and J. Vogel, *J. Prakt. Chem.*, **311**, 15 (1969).
(9) (a) S. Gabriel and H. Ohle, *Ber.*, **50**, 819 (1917); (b) H. J. Roth, *Arch. Pharm. (Weinheim, Ger.)*, **292**, 76 (1959); (c) E. Cherbuliez, B. Baehler, A. Yazgi, and J. Rabinowitz, *Helv. Chim. Acta*, **43**, 1158 (1960), to name a few.
(10) H. E. Carter and P. K. Bhattacharyya, *J. Am. Chem. Soc.*, **75**, 2503 (1953).
(11) M. Bergmann, E. Brand, and F. Weinmann, *Hoppe-Seyler's Z. Physiol. Chem.*, **131**, 1 (1923).
(12) M. Dukes and L. H. Smith, *J. Med. Chem.*, **14**, 326 (1971).
(13) Prepared as an unisolated intermediate by L. Berlinguet, *Can. J. Chem.*, **33**, 1119 (1955).
(14) M. Bergmann and L. Zervas, *Chem. Ber.*, **65**, 1192 (1932).
(15) J. H. Billman and A. C. Diesing, *J. Org. Chem.*, **22**, 1068 (1957).

Total Synthesis of (±)-4-Deoxydamsin. Structure Correlation of Pseudoguaianolide Sesquiterpenes

James A. Marshall* and William R. Snyder

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received December 2, 1974

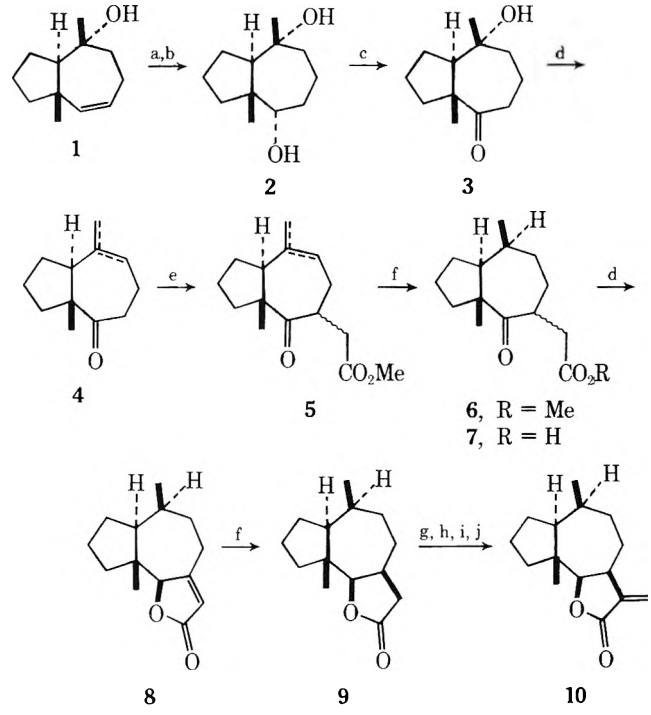
The pseudoguaianolides are a widespread class of nonisoprenoid hydroazulene lactones containing an array of functional and chiral centers which challenge present-day synthesis methodology and design.[1] Initial structure assignments based on chemical degradations erroneously classified these natural products as guaiazulene derivatives.[2] Their identity as a separate family of rearranged "pseudo" guaiazulenes was revealed by nuclear magnetic resonance (NMR), which showed the presence of a quaternary methyl grouping.[3] Stereochemical details were subsequently elucidated by NMR studies and single-crystal X-ray analysis.[1]

Despite the increasing variety of reported synthetic approaches to hydroazulenes, none of the pseudoguaianolides have yet been synthesized.[4,5] Attempts to date have failed to develop the necessary stereochemical control of the cycloheptane substituents.[5] In this report we describe a scheme for construction of the pseudoguaianolide skeleton with complete stereochemical control of the five commonly encountered chiral centers.

Our synthetic plan centered about the hydroazulenol **1**, an intermediate which we prepared via 1,6-cyclodecadienol solvolysis.[6] This intermediate with its propitious arrangement of substituents and functional groups seemed well suited for further elaboration to a pseudoguaianolide derivative for several reasons. Foremost, the rigidity imposed upon the hydroazulene system by the trans ring fusion simplifies conformational analysis, thus permitting realistic stereochemical predictions. In addition, the angular methyl grouping serves as a stereochemical directing group for the introduction of proximate chiral centers. The only real disadvantage of hydroazulenol **1** as a pseudoguaianolide precursor is its lack of functionality in the cyclopentane ring. Thus we could not expect to prepare the natural sesquiterpenes, at least initially. Nonetheless we felt that the aforementioned stereochemical problems were of sufficient intrinsic interest to justify work on the synthesis of 4-deoxypseudoguaianolides.

Our first objective was to incorporate a properly oriented fused γ-butyrolactone at the double bond position of hydroazulenol **1** (Chart I). Toward this end the double bond

Chart I[a]



1 2 3 4 5 6, R = Me 7, R = H 8 9 10

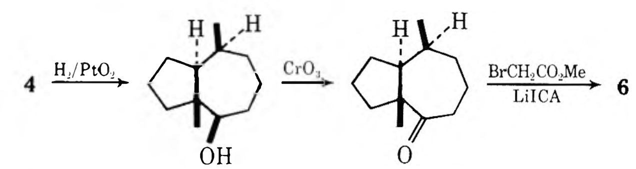
[a] a, *m*-$ClC_6H_4CO_3H$; b, $LiAlH_4$; c, H_2CrO_4, acetone; d, Ac_2O, NaOAc; e, LiICA, $BrCH_2CO_2Me$; f, H_2/PtO_2; g, NaH, HCO_2Et; h, $NaBH_4$; i, TsCl; j, C_5H_5N.

was epoxidized with *m*-chloroperoxybenzoic acid and the crude epoxide was reduced with lithium aluminum hydride to the diol **2**. Oxidation with Jones reagent[7] afforded the desired ketone intermediate **3**. However, attempted alkylation of the corresponding enolate with methyl bromoacetate proceeded poorly. Thinking that steric factors might be responsible for this result, we decided to examine the alkylation of unsaturated ketones related to ketol **3**.

Dehydration with thionyl chloride in pyridine led to a mixture of three double-bond isomers (25% exo, 60% trisubstituted, and 15% tetrasubstituted). However with acetic anhydride–sodium acetate only the trisubstituted (**4**) and exo olefins (60:40) were formed. Previous results have indicated that the dehydration of tertiary alcohols with sodium acetate–acetic anhydride proceeds via the acetate, which subsequently undergoes a pyrolytic cis elimination.[8] Accordingly, the isolation of only the trisubstituted olefin **4** and the corresponding exo isomer is unexpected. However, molecular models show that eclipsing of a tertiary acetate carbonyl grouping with the ring fusion hydrogen introduces severe steric strain in the transition state leading to the tetrasubstituted olefin. The corresponding transition states leading to olefin **4** and its exo isomer appear relatively strain free. Thus steric factors may block this elimination pathway.

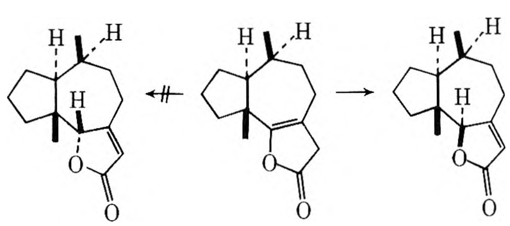
Alkylation of unsaturated ketone **4** (40% exo isomer) with methyl bromoacetate afforded the keto esters **5** as an apparent mixture of epimers and double-bond isomers in high yield. Hydrogenation of this mixture gave the saturated keto ester **6** as an epimeric mixture. Keto ester **6** could also be prepared by reordering these steps. However, this variation suffered from two drawbacks. In the first place, hydrogenation of enone **4** took place at the ketone carbonyl

as well as the double bond to give the alcohol **11**, apparently a single isomer. Secondly, the related ketone **12** obtained through Jones oxidation[7] gave an impure product in low yield upon alkylation with methyl bromoacetate. Presumably, the additional trigonal centers present in the enolate derived from unsaturated ketone **4** ameliorate the steric congestion of the seven-membered ring, thereby providing a less hindered avenue of approach for the alkylating agent.



11 **12**

The NMR spectra indicated that keto ester **6** and the corresponding acid **7** were stereochemically nonhomogeneous. Since enone **4** was found to give a single C-2 epimer upon catalytic hydrogenation, we presumed that the unsaturated keto ester **5** would behave analogously. Therefore, the epimeric center of ester **5** and acid **6** would most likely be at C-5. Our plan was to introduce unsaturation at this center and utilize the steric directing effect of the angular methyl grouping to attain the desired contrathermodynamic stereochemical orientation of the ester side chain through catalytic hydrogenation. Accordingly, the keto acid **7** was heated with sodium acetate–acetic anhydride to give the butenolide **8**, apparently a single stereoisomer according to spectral properties, as the sole reaction product. This precedented conversion[9] must proceed via the enol lactone **13**, which undergoes subsequent double-bond isomerization. The isomerization could conceivably be subject to kinetic or thermodynamic control. Kinetic protonation would expectedly lead to the observed butenolide isomer **8** on steric grounds, since the angular methyl grouping would block protonation or proton transfer leading to the alternative epimer **8a**. Molecular models indicate that butenolide **8** has fewer nonbonded interactions than the epimer **8a**. Thus an equilibrium isomerization process would likewise favor the syn isomer **8**.

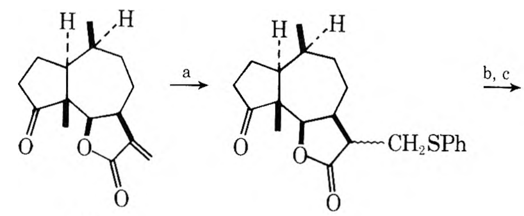


8a **13** **8**

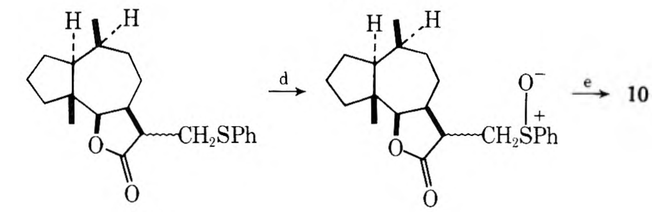
Hydrogenation of butenolide **8** afforded, as expected, the cis lactone **9**, which displayed a sharp doublet in its NMR spectrum characteristic of cis-fused pseudoguaianolide lactone carbinyl hydrogens.[1] As previously noted, the angular methyl grouping should direct the stereochemistry of double-bond hydrogenation.

To complete the synthesis we employed the sequence of Minato and Horibe to introduce the α-methylene functionality to lactone **9**.[10] The resulting methylene lactone **10** showed NMR spectral patterns extremely similar to those of damsin (**14**), a naturally occurring pseudoguaianolide.[11] An authentic comparison sample of this lactone was obtained via the selective degradation of natural damsin according to the scheme outlined in Chart II. Addition of thiophenol[12] afforded the adduct **15**, which was condensed with p-toluenesulfonylhydrazine and then reduced with sodium cyanoborohydride to give the deoxy derivative **16**.[13]

Chart II[a]



14 **15**



16 **17**

[a] a, PhSH; b, TsNHNH$_2$; c, NaBH$_3$CN; d, m-ClC$_6$H$_4$CO$_3$H; e, heat, CH$_3$Ph.

Oxidation to the sulfoxide **17** and pyrolysis in toluene[14] afforded 4-deoxydamsin (**10**), identical with the synthetic material according to spectral and chromatographic criteria.

Experimental Section[15]

***t*-2,*t*-7-Dimethyl-*r*-1-*H*-bicyclo[5.3.0]decane-*c*-2,*c*-6-diol (2).** To a solution of 1.41 g (7.82 mmol) of hydroazulenol **1** in 175 ml of chloroform at 0° was added a solution of 5.90 g (34.2 mmol) of m-chloroperoxybenzoic acid in 200 ml of chloroform dropwise over 1 hr. Stirring was continued for 14 hr at 0°. The mixture was washed with cold 10% aqueous sodium hydroxide and saturated brine. The chloroform was removed under reduced pressure and the residue was distilled, affording 1.46 g (95%) of colorless oil: bp 110–120° (bath temperature) (0.1 mm); λ_{max} (film) 2.96 μ (OH); δ_{TMS} (CDCl$_3$) 3.34–2.79 (H-5, H-6 multiplet), 1.12 (C-2 CH$_3$), 1.00 ppm (C-7 CH$_3$).

The analytical sample was secured through preparative layer chromatography on silica gel using benzene as the eluent followed by short-path distillation.

Anal. Calcd for C$_{12}$H$_{20}$O$_2$: C, 73.43; H, 10.27. Found: C, 73.33; H, 10.27.

The epoxide was reduced along the lines of Henbest and Wilson.[16] To a stirred mixture of 0.46 g (12.1 mmol) of lithium aluminum hydride in 150 ml of tetrahydrofuran (THF) at room temperature was added a solution of 1.19 g (6.07 mmol) of epoxide in 50 ml of THF. The mixture was heated at reflux for 3 hr, cooled, and carefully treated with water and 15% sodium hydroxide solution. Ether was added, the mixture was filtered, and the solvent was removed under reduced pressure to give 1.20 g (100%) of solid diol **2**: λ_{max} (melt) 3.05 μ; δ_{TMS} (CDCl$_3$) 3.68 (H-6 multiplet), 1.20 (C-2 CH$_3$), 0.95 ppm (C-7 CH$_3$).

The analytical sample, mp 152–153°, was secured by recrystallization from ether–ethyl acetate.

Anal. Calcd for C$_{12}$H$_{22}$O$_2$: C, 72.68; H, 11.18. Found: C, 72.60; H, 11.26.

***c*-2-Hydroxy-*t*-2,*t*-7-dimethyl-*r*-1-*H*-bicyclo[5.3.0]decan-6-one (3).** To a solution of 139 mg (0.70 mmol) of diol **2** in 4.0 ml of acetone at 0° was added 0.20 ml of Jones reagent[7] dropwise over 2.0 min. After stirring for 15 min at 0°, the reaction mixture was quenched by the addition of 0.10 ml of 2-propanol. The reaction mixture was poured into brine, and the product was isolated with ethyl acetate, affording 118 mg (86%) of a colorless oil which crystallized on standing (mp 80–81°). Recrystallization from ether gave analytically pure material: λ_{max} (KBr) 2.92, 5.96 μ; δ_{TMS} (CDCl$_3$) 1.25 (C-2 CH$_3$), 1.08 ppm (C-7 CH$_3$).

Anal. Calcd for C$_{12}$H$_{20}$O$_2$: C, 73.43; H, 10.27. Found: C, 73.41; H, 10.30.

***t*-7-Methyl-2-methylene-*r*-1-*H*-bicyclo[5.3.0]decan-6-one and 2,*t*-7-Dimethyl-*r*-1-*H*-bicyclo[5.3.0]dec-2-en-6-one (4).** A solution of 132 mg (0.67 mmol) of ketol **3**, 600 mg of sodium acetate, and 4.0 ml of freshly distilled acetic anhydride was heated at

reflux for 12 hr. The solution was cooled to 0° and quenched with 2.0 ml of methanol. After stirring for 1.5 hr at 0°, the solution was poured into water and the product mixture was isolated with ether. The combined ether layers were carefully washed with saturated sodium bicarbonate solution and then with saturated brine. Short-path distillation (oven temperature 90–110°, 0.05 mm) afforded 118 mg (99%) of a colorless oil: λ_{max} (film) 5.90, 6.08 μ; δ_{TMS} (CCl_4) 5.70 (t, J = 5.6 Hz, endocyclic vinyl H), 4.90 and 4.74 (exo CH_2 vinyl H's), 1.67 (vinyl CH_3), 0.97 ppm (C-7 CH_3).

Integration of the NMR spectrum indicated a 40:60 mixture of exocyclic and endocyclic olefin isomers.

Methyl (*t*-7-Methyl-2-methylene-6-oxo-*r*-1-*H*-bicyclo[5.3.0]dec-5-yl)acetate and Methyl (2,*t*-7-Dimethyl-6-oxo-*r*-1-*H*-bicyclo[5.3.0]dec-2-en-5-yl)acetate (5). The procedures developed by Rathke[17] and Schlessinger[18] were modified. To a solution of 0.29 ml (1.60 mmol) of *N*-isopropylcyclohexylamine in 4.0 ml of tetrahydrofuran at −78° was added 0.80 ml (1.60 mmol) of 2.0 *M* *n*-butyllithium–hexane solution dropwise over 2.0 min. The solution was stirred for 30 min at −78°, at which time a solution of 267 mg (1.50 mmol) of keto olefin mixture **4** in 1.0 ml of tetrahydrofuran was introduced The reaction mixture was stirred for an additional 30 min at −78°. A solution of 245 mg (1.60 mmol) of methyl bromoacetate, 0.28 ml (1.60 mmol) of hexamethylphosphoramide, and 1.0 ml of tetrahydrofuran was then introduced dropwise and the reaction temperature was allowed to reach room temperature over 1.0 hr. The reaction mixture was poured into dilute hydrochloric acid and the products were isolated with ether. Short-path distillation (oven temperature 110–130°, 0.05 mm) afforded 330 mg (88%) of a colorless oil: λ_{max} (film) 5.75, 5.88, 6.08 μ; δ_{TMS} (CCl_4) 5.27 (t, J = 5.6 Hz, endocyclic vinyl H), 4.98 and 4.85 (exo CH_2 vinyl H's), 3.56 (OCH_3), 1.05 and 0.97 ppm (C-7 CH_3).

Methyl (*t*-2,*t*-7-Dimethyl-6-oxo-*r*-1-*H*-bicyclo[5.3.0]dec-5-yl)acetate (6). A suspension of 330 mg (1.32 mmol) of olefin mixture **5** and 50 mg of platinum oxide in 7.0 ml of absolute methanol was hydrogenated at room temperature and atmospheric pressure. After 2.0 hr the uptake of hydrogen ceased, the reaction mixture was filtered, and the solvent was removed by distillation at reduced pressure. Short-path distillation (oven temperature 110–130°, 0.05 mm) afforded 290 mg (88%) of a colorless oil: λ_{max} (film) 5.76, 5.90 μ; δ_{TMS} (CCl_4) 3.60 (OCH_3), 2.58 (m, C-5 methine), 2.30 (d, J = 6.0 Hz, acetate CH_2), 1.10 (C-7 CH_3), 0.97 ppm (d, J = 6.2 Hz, C-2 CH_3).

The keto ester was saponified without further purification.

(*t*-2,*t*-7-Dimethyl-6-oxo-*r*-1-*H*-bicyclo[5.3.0]dec-5-yl)acetic Acid (7). A solution of 280 mg (1.11 mmol) of keto ester **6** and 300 mg of potassium hydroxide in 6.0 ml of methanol was heated at reflux for 2.0 hr. The solution was cooled, poured into water, and washed with ether. The aqueous layer was carefully acidified with concentrated hydrochloric acid and the product was isolated with ether. The crude product crystallized on standing, affording 225 mg (85%) of white, crystalline product (mp 130–132°). Recrystallization from ether gave analytically pure material: λ_{max} (film) 3.20–3.80, 5.80, 5.92 μ; δ_{TMS} ($CDCl_3$) 9.66 (CO_2H), 3.45 (m, C-5 methine), 2.66 and 2.36 (doublets, J = 4.8 and 8.0 Hz, respectively, CH_2CO_2H), 1.08 (C-7 CH_3), 1.23 and 0.90 ppm (doublets, J = 6.5 Hz, C-2 CH_3).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.59; H, 9.30.

(*t*-6-Hydroxy-*t*-2,*t*-7-dimethyl-*r*-1-*H*-bicyclo[5.3.0]dec-5-ylidene)acetic Acid γ-Lactone (8). The procedure of Minato and Nagasaki[9] was employed. A mixture of 115 mg (0.484 mmol) of keto acid **7** and 200 mg of sodium acetate in 4.0 ml of acetic anhydride was heated at reflux for 2.0 hr. The mixture was cooled to 0° and 2.0 ml of methanol was added. After stirring for 1.5 hr at 0°, the solution was poured into water and the product was isolated with ether. The combined ether layers were carefully washed with saturated sodium bicarbonate solution and then with saturated brine. Distillation of the ether at reduced pressure afforded 91 mg (86%) of pale yellow oil which crystallized on standing (mp 71–73°). An analytical sample was secured by preparative thin layer chromatography using 50% ether–petroleum ether (R_f 0.20–0.45) and short-path distillation (oven temperature 120–130°, 0.10 mm): λ_{max} (film) 5.68, 6.12 μ; δ_{TMS} (CCl_4) 5.68 (vinyl H), 4.56 (C-6 methine), 2.66 (m, allylic CH_2), 0.97 (d, J = 6.4 Hz, C-2 CH_3), 0.72 ppm (C-7 CH_3).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.18; H, 8.98.

(*t*-6-Hydroxy-*t*-2,*t*-7-dimethyl-*r*-1-*H*-bicyclo[5.3.0]dec-*t*-5-yl)acetic Acid γ-Lactone (9). A suspension of 873 mg (3.97 mmol) of butenolide **8** and 100 mg of platinum oxide in 20 ml of absolute ethanol was hydrogenated at room temperature and atmospheric pressure. After 6.5 hr the uptake of hydrogen ceased, the reaction mixture was filtered, and the solvent was removed by distillation at reduced pressure. Short-path distillation (oven temperature 120–130°, 0.05 mm) afforded 782 mg (89%) of colorless oil. An analytical sample was secured by preparative thin layer chromatography using 50% ether–petroleum ether and short-path distillation (as above): λ_{max} (film) 5.63 μ; δ_{TMS} (CCl_4) 4.18 (d, J = 8.5 Hz, C-6 methine), 2.37 and 2.20 (doublets, J = 9.0 and 6.0 Hz, respectively, acetate CH_2), 1.00 (d, J = 6.2 Hz, C-2 CH_3), 0.97 ppm (C-7 CH_3).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63, H, 9.98. Found: C, 75.43; H, 10.15.

(±)-4-Deoxydamsin (10). The procedure of Minato and Horibe[10] was employed. To a suspension of 42 mg (1.75 mmol) of sodium hydride in 4.0 ml of ether at 0° was added at solution of 319 mg (1.44 mmol) of lactone **9** and 0.17 ml (2.00 mmol) of ethyl formate in 4.0 ml of ether dropwise over 2.0 min. The solution was stirred for 1.0 hr at 0°. The cooling bath was removed and the solution was stirred for an additional 12 hr at room temperature. The solution was poured into dilute hydrochloric acid and the product was isolated with ether, affording 342 mg (95%) of a yellow gum. No further purification of this product was attempted.

To a solution of 50 mg (1.31 mmol) of sodium borohydride in 3.0 ml of absolute methanol was added a solution of 342 mg (1.37 mmol) of the above α-formyl-γ-butyrolactone in 2.0 ml of absolute methanol. The solution was stirred for 1.0 hr at room temperature and poured into dilute hydrochloric acid, and the product was isolated with ether, affording 342 mg (99%) of a viscous yellow oil. No further purification of this product was attempted.

A solution of 342 mg (1.35 mmol) of the above β′-hydroxy-γ-butyrolactone and 315 mg (1.65 mmol) of *p*-toluenesulfonyl chloride in 4.0 ml of freshly distilled pyridine was stirred for 20 hr at 0°. The solution was poured into water and extracted with four portions of ether. The combined ether extracts were washed with dilute hydrochloric acid until the washes were acidic to litmus paper. The crude product, 372 mg (68%), was a brown, viscous oil: λ_{max} [film ($CDCl_3$)] 5.66, 6.24 μ; δ_{TMS} ($CDCl_3$) 7.48 (AB, J_{AB} = 7 Hz, $\Delta\nu_{AB}$ = 27 Hz, aromatic H's), 4.40–3.60 (m, C-6 methine and C-13 methylene), 2.40 ($ArCH_3$), 1.00 (d, J = 6.2 Hz, C-10 CH_3), 0.97 ppm (C-5 CH_3).

A solution of 372 mg (0.92 mmol) of the above tosylate in 5.0 ml of pyridine was heated at reflux for 5.0 hr. The solution was cooled and poured into water and the product was isolated with ether, affording 215 mg (100%) of a yellow oil. Short-path distillation (oven temperature 120–140°, 0.10 mm) and preparative thin layer chromatography on silica gel using 30% ether–benzene (R_f 0.55) afforded a white, crystalline product which was recrystallized from petroleum ether to give analytically pure material (mp 87–88°): λ_{max} (KBr) 3.38, 3.48, 5.70, 6.02, 7.85, 8.76, 10.04, 10.24, 10.60, 12.16 μ; δ_{TMS} ($CDCl_3$) 6.15 and 5.40 (doublets, J = 3.0 Hz, vinyl H's), 4.30 (d, J = 8.2 Hz, C-6 methine), 0.97 (d, J = 6.4 Hz, C-10 CH_3), 0.82 ppm (C-5 CH_3); MS *m/e* 234 (M^+), 219, 206, 177, 163.

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.74; H, 9.49.

4-Deoxydamsin (10) from Degradation of Damsin (14). The procedure of Romo and coworkers[12] was modified. A solution of 566 mg (2.28 mmol) of damsin, 0.54 ml (5.36 mmol) of thiophenol, and 0.30 ml of triethylamine in 15 ml of benzene was stirred at room temperature for 10 hr. The solution was diluted with ether and washed with two portions of 10% sodium hydroxide followed by two portions of saturated brine. Filtration of the crude product mixture through a 15-ml column of silica gel using benzene afforded 199 mg of nonpolar aromatic impurities. Elution with ether afforded 519 mg (64%) of the desired adduct **15**: δ_{TMS} ($CDCl_3$) 7.20 (m, aromatic H's), 4.30 (d, J = 8.2 Hz, C-6 methine), 3.50–3.10 (m, C-13 methylene), 1.10 (d, J = 6.4 Hz, C-10 CH_3), 1.00 ppm (C-5 CH_3). No further purification of this compound was attempted.

A solution of 519 mg (1.45 mmol) of the above thioether **15** and 372 mg (2.00 mmol) of *p*-toluenesulfonylhydrazide in 20 ml of absolute methanol was heated at reflux for 5.5 hr. The reaction mixture was poured into water and the product was isolated with ether, affording 708 mg (93%) of a white foam.

This material was reduced according to the procedure of Hutchins, Maryanoff, and Milewski.[13]

To a solution of 708 mg (1.35 mmol) of the tosylhydrazone in 3.5 ml of dimethylformamide and 3.5 ml of freshly distilled sulfolane was added 20 mg of *p*-toluenesulfonic acid and 340 mg (5.40 mmol) of sodium cyanoborohydride. The solution was heated at 100° for 6 hr, cooled, and diluted with water. The product was isolated with

ether, affording 504 mg of crude material containing some unreacted starting material. The desired thioether **16** was isolated by column chromatography on silica gel using 30% ether–benzene.

To a solution of 367 mg (1.07 mmol) of chromatographed thioether **16** in 5 ml of methylene chloride at 0° was added a solution of 190 mg (1.10 mmoles) of *m*-chloroperoxybenzoic acid in 5 ml of methylene chloride dropwise over 2.0 min. The solution was stirred for 2.0 hr at 0° and the solvent was removed by distillation at reduced pressure. The residue was taken up in ether and washed with two portions of saturated sodium bicarbonate solution to give the crude sulfoxide **17** as a white foam (276 mg).

This material was directly converted to the methylene lactone **10** according to the procedure of Trost and Salzmann.[14] A solution of 276 mg (0.77 mmol) of crude sulfoxide **17** in 8.0 ml of toluene was heated at reflux for 4.0 hr. The solution was cooled, diluted with ether, and washed with two portions of saturated sodium bicarbonate solution to afford 175 mg (98%) of crude product. Preparative thin layer chromatography on silica gel using 5% ether–benzene gave 4-deoxydamsin (R_f 0.39) as a white, crystalline solid: mp 108–110°; λ_{max} (melt) 3.38, 3.48, 5.70, 6.02, 7.85, 8.76, 10.04, 10.24, 10.60, 12.16 μ; δ_{TMS} ($CDCl_3$) 6.15 and 5.40 (doublets, J = 3.0 Hz, vinyl H's), 4.30 (d, J = 8.2 Hz, C-6 methine), 0.97 (d, J = 6.4 Hz, C-10 CH_3), 0.82 ppm (C-5 CH_3).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.65; H, 9.61.

Acknowledgments. Support for this project through a research grant (RO1 CA 11089) from the National Institutes of Health is gratefully acknowledged. We are indebted to Professor Tom Mabry and Mr. Eloy Rodríguez for a generous sample of *Ambrosia ambrosioides* extract.

Registry No.—**1**, 54798-48-0; 1 epoxide, 54798-49-1; **2**, 54798-50-4; **3**, 54798-51-5; *exo*-**4**, 54798-52-6; *endo*-**4**, 54798-53-7; *exo*-**5** epimer A, 54798-54-8; *exo*-**5** epimer B, 54798-55-9; *endo*-**5** epimer A, 54798-56-0; *endo*-**5** epimer B, 54798-65-1; **6** epimer A, 54910-30-4; **6** epimer B, 54809-86-8; **7** epimer A, 54798-63-9; **7** epimer B, 54798-64-0; **8**, 54798-58-2; **9**, 54798-60-6; **9** α-tosylate, 54798-61-7; (±)-**10**, 54798-59-3; (*S*)-**10**, 54831-46-8; **14**, 1216-42-8; **15**, 54798-57-1; **16**, 54798-62-8; *m*-chloroperoxybenzoic acid, 937-14-4; methyl bromoacetate, 96-32-2; *p*-toluenesulfonyl chloride, 98-59-9; thiophenol, 108-98-5.

References and Notes

(1) H. Yoshioka, T. J. Mabry, and B. N. Timmermann, "Sesquiterpene Lactones", University of Tokyo Press, Tokyo, 1973.
(2) Cf. T. Nozoe and S. Itō, *Prog. Chem. Org. Nat. Prod.*, **19**, 61–76 (1962).
(3) W. Herz, H. Wantanabe, M. Miyazaki, and Y. Kishida, *J. Am. Chem. Soc.*, **84**, 2601 (1962); J. Romo and A. Romo de Vivar, *Prog. Chem. Org. Nat. Prod.*, **25**, 90 (1967).
(4) Cf. J. A. Marshall, *Synthesis*, 517 (1972).
(5) J. B. Hendrickson, C. Ganter, D. Dorman, and H. Link, *Tetrahedron Lett.*, 2235 (1968); R. A. Kretchmer and W. M. Schafer, *J. Org. Chem.*, **38**, 95 (1973).
(6) J. A. Marshall, W. F. Huffman, and J. A. Ruth, *J. Am. Chem. Soc.*, **94**, 4691 (1972).
(7) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 142.
(8) J. A. Marshall and J. J. Partridge, *Tetrahedron*, **25**, 2159 (1969). A small amount of the acetate derivative of tertiary alcohol **3** was isolated in preliminary experiments.
(9) H. Minato and T. Nagasaki, *Chem. Commun.*, 377 (1965).
(10) H. Minato and I. Horibe, *J. Chem. Soc. C*, 1575 (1967).
(11) M. Suchy, V. Herout, and F. Šorm, *Collect. Czech. Chem. Commun.*, **28**, 2257 (1963).
(12) J. Romo, A. Romo de Vivar, A. Vélez, and E. Urbina, *Can. J. Chem.*, **46**, 1535 (1968).
(13) R. O. Hutchins, B. E. Maryanoff, and C. A. Milewski, *J. Am. Chem. Soc.*, **93**, 1793 (1971).
(14) B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.*, **95**, 6840 (1973).
(15) Reactions were conducted under an argon atmosphere using the apparatus described by W. S. Johnson and W. P. Schneider ("Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 132). Reaction products were isolated by the addition of water and extraction with the specified solvent. The combined extracts were washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed from the filtered solutions on a rotary evaporator. Short-path distillations were carried out on a Büchi Kugelrohrofen using bulb-to-bulb apparatus. Stereochemical designations of substituents in bicyclic compounds are indicated by c (cis) and *t* (trans) relative to a reference substituent *r*.
(16) H. B. Henbest and R. A. L. Wilson, Jr., *J. Chem. Soc.*, 3289 (1956).
(17) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 2318 (1971).
(18) R. J. Cregge, J. L. Herrmann, C. S. Lee, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 2425 (1973).

Use of the Azido Group in the Synthesis of 5′ Terminal Aminodeoxythymidine Oligonucleotides[1]

William S. Mungall, Geoffrey L. Greene, George A. Heavner, and Robert L. Letsinger*

Department of Chemistry and Department of Biochemistry and Molecular Biology, Northwestern University, Evanston, Illinois 60201

Received December 27, 1974

Phosphoramidate analogs of oligonucleotides possess unique features which have interesting implications in nucleic acid chemistry.[2,3] In extending the synthetic methodology for this class of compounds we have explored the utility of the azido group as a synthon for a terminal amino group in an oligonucleotide. The formation of aminonucleosides by catalytic reduction of azidonucleosides is well known; representative examples include the preparation of 5′-amino-5′-deoxythymidine,[4] 2′-amino-2′-deoxyuridine,[5] and 5′-amino-2′,5′-dideoxyadenosine.[6] In addition, 5′-amino-5′-deoxythymidine 3′-phosphate and 3′-amino-3′-deoxythymidine 5′-phosphate have been obtained by catalytic hydrogenation of the corresponding azidonucleotides.[7]

As target compounds for study we selected di- and tetranucleotide analogs **2** and **4**. The synthetic scheme, outlined in Chart I, utilized the condensation procedure employed previously for preparation of some thymidylyl phosphoramidate analogs.[2]

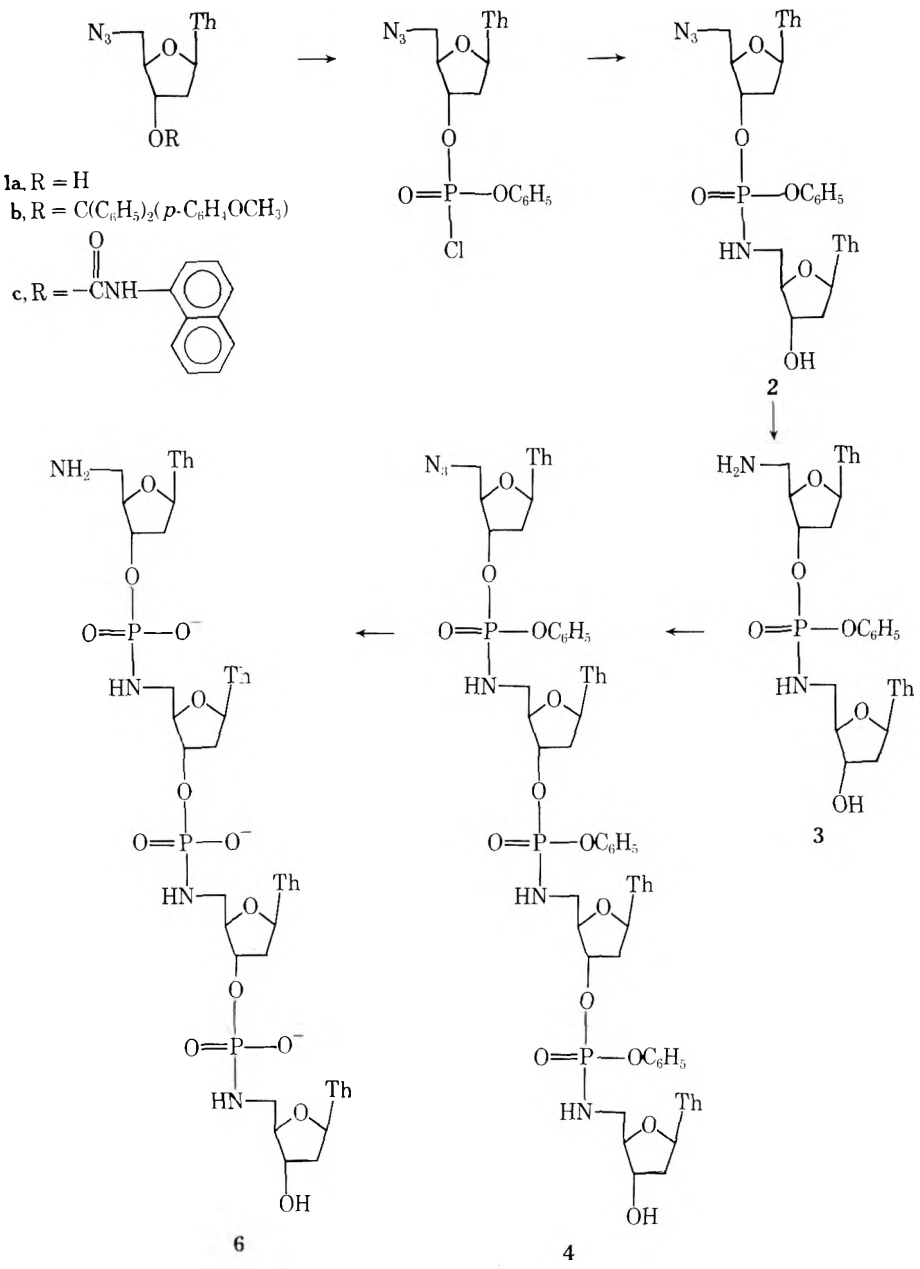
5′-Azido-5′-deoxythymidine (**1a**) reacted smoothly with phenyl phosphorodichloridate in pyridine to give an active phosphorylated intermediate, which on treatment with 5′-amino-5′-deoxythymidine afforded the desired azidodinucleoside phosphate analog, **2**, in good yield. In contrast to the facile catalytic hydrogenation of **1a**, however, the reduction of **2** with hydrogen over a platinum catalyst was sluggish. Under conditions where **1a** was converted to the aminodeoxythymidine in high yield (90% isolated), little reduction of **2** was achieved. When the time of reaction was increased fivefold (to 2.5 hr), **2** was partially reduced, and the desired amino derivative (**3**) was isolated in 54% yield.

Repetition of the synthetic sequence with **2** in place of **1a** and **3** in place of 5′-amino-5′-deoxythymidine gave compound **4**. This tetranucleotide derivative, however, proved to be resistant to hydrogenation with palladium and platinum catalysts under all conditions that were explored. The decrease in susceptibility to catalytic reduction for the series **1a**, **2**, **4** correlates with increasing steric bulk at the 3′-O position.

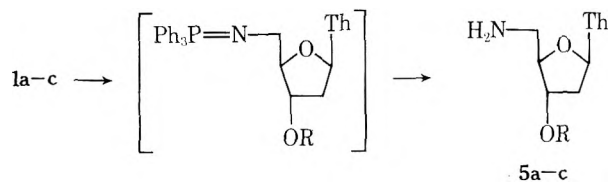
Of the other methods available for converting azides to amines, the most promising for application in the nucleotide field appeared to be that utilizing triphenylphosphine, first described by Staudinger and Hauser.[8] Thus, methyl and ethyl azide are converted by triphenylphosphine to phosphinimines, which are reported to hydrolyze on exposure to moisture to triphenylphosphine oxide and the corresponding amines. Other workers have used alkali (refluxing 2% alcoholic potassium hydroxide)[9] and strong acid (hot 40% hydrogen bromide in acetic acid)[10] to liberate substituted alkylamines from phosphinimines. The conversion of an azido sugar, tetraacetyl-β-D-glucosyl azide, to a triphenylphosphinimine has also been reported.[11]

Experiments with model nucleosides, 5′-azido-5′-deoxythymidine (**1a**), 3′-*O*-mono-*p*-methoxytrityl-5′-azido-5′-deoxythymidine (**1b**), and 3′-*O*-α-naphthylcarbamoyl-5′-azido-5′-deoxythymidine (**1c**), indeed showed that the triphenylphosphine hydrolytic sequence constitutes a convenient preparative technique for this class of compounds. The aminonucleoside (**5a–c**) was isolated in high yield

Chart I



(88–90%) in each case. The reactions are easily scaled up, and a bulky group at the 3′-O position (methoxytrityl or α-



napthylcarbamoyl) does not interfere. In contrast to the phosphinimines derived from the simple alkyl azides, the intermediates obtained from the azidonucleosides are relatively stable in water. They hydrolyze cleanly to the aminonucleosides, however, on treatment with ammonium hydroxide or aqueous sodium hydroxide at room temperature. Indeed, the amine can be obtained directly by treating the azide with a solution containing both triphenylphosphine and ammonium hydroxide in pyridine.

Treatment of compound **4** with triphenylphosphine in pyridine, followed by hydrolysis with aqueous sodium hydroxide, yielded the aminotetranucleoside triphosphate, **6**, with no observable products of side reactions. Furthermore, **2** could be converted to **3** by the action of triphenylphosphine and ammonium hydroxide, demonstrating that reduction of a terminal azido function can be achieved under conditions where a phenoxy group masking an internucleotide phosphoramidate link is stable. These experiments therefore indicate that a procedure utilizing a terminal azido group and reduction of the azide with triphenylphosphine offers an attractive route for synthesis of an oligonucleotide terminated with an amino group.

Experimental Section

The equipment and general procedures were the same as described in ref 1 (part XIX). The chromatographic solvents were: A, *i*-C_3H_7OH–NH_4OH–H_2O (7:1:2); F, *n*-C_3H_7OH–NH_4OH–H_2O (55:10:35). Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Phenyl Ester of 5′-Azido-5′-deoxythymidylyl-(3′–5′)-5′-amino-5′-deoxythymidine (2). Dry 5′-azido-5′-deoxythymidine (801 mg, 3 mmol) in dioxane (30 ml) was stirred with phenyl phosphorodichloridate (0.48 ml, 3 mmol) and pyridine (0.48 ml, 6 mmol) for 48 hr at room temperature. Triethylamine (0.84 ml, 6 mmol) and a solution of 5′-amino-5′-deoxythymidine (850 mg, 3.7 mmol) in dioxane (240 ml) were then added. The mixture was stirred for 30 min and then cooled with an ice bath. Aqueous sodi-

Table I
Chromatographic and Electrophoretic Values[a]

Compd	R_f (solvent A)	R_f (solvent F)	R_m[b]
$d(N_3)T$	0.7	0.9	−0.1
$d(N_3)Tp$	0.2	0.7	+1.0
$d(N_3)Tp(NH)T$	0.4	0.7	+0.3
$d(N_3)Tp(NH)Tp(NH)Tp(NH)T$	0.03	0.4	+0.7
$d(NH_2)T$	0.5	0.7	−0.7
$d(NH_2)Tp$	0.09	0.5	+0.45
$d(NH_2)Tp(NH)T$	0.1	0.6	−0.1
$d(NH_2)Tp(NH)Tp(NH)Tp(NH)T$	0.02	0.3	+0.5
dT	0.6	0.8	−0.1
dTp	0.1	0.5	+1.0
dTp(NH)T	0.3	0.6	+0.35
dTp(NH)Tp(NH)Tp(NH)T	0.02	0.4	+0.7

[a] Other identifying characteristics are: (1) all amino derivatives give a positive ninhydrin test; (2) on silica gel TLC in ethyl acetate R_f for dT is 0.1; none of the 5′-amino derivatives or the compounds bearing charged phosphoryl groups moved on TLC under these conditions. [b] Electrophoretic migration relative to d_pT at pH 7.2.

um hydroxide (10 ml, 0.5 *M*) was added, and the mixture was filtered immediately to remove the precipitated salts. The filtrate was concentrated to a syrup at reduced pressure, and, after addition of water (20 ml), the mixture was extracted twice with ethyl acetate (300, 100 ml). The organic extract was dried over sodium sulfate, evaporated at reduced pressure, and chromatographed on a silica gel column (4 × 50 cm) with 1.5 l. of ethyl acetate [which removed azidodeoxythymidine, 203 mg, 0.76 mmol, R_f (EtOAc) 0.37] followed by 1 l. of tetrahydrofuran. Concentration of the fractions and precipitation with hexane afforded 1.41 g [96% yield based on unrecovered $d(N_3)T$; 71% based on initial $d(N_3)T$] of **2**: mp 120–123° (softening at 115°); λ_{max} 264 nm (ε 18,000); λ_{min} 234 nm (ε 4500); principal infrared bands at 3.2, 4.8, 5.9, 6.8, and 7.9 μ; homogeneous on TLC, R_f (EtOAc) 0.04; R_f (THF) 0.55.

Anal. Calcd for $C_{26}H_{31}N_8O_{10}P$: C, 48.30; H, 4.83; N, 17.33. Found: C, 48.29; H, 4.89; N, 16.76.

For further characterization this product was hydrolyzed with 0.1 *M* aqueous sodium hydroxide (6 hr, 23°). A single nucleotidic product was observed on paper chromatography in solvent A (R_f 0.40). Elution with water and lyophilization afforded $d(N_3)T_p(NH)T$ as a white powder, R_f (F) 0.68 and R_m 0.29. This product hydrolyzed quantitatively to $d(N_3)T_p$ and $d(NH_2)T$ (**5a**) on treatment with aqueous acetic acid. In addition it was quantitatively cleaved by snake venom phosphodiesterase and by spleen phosphodiesterase under the standard conditions to give $d(N_3)T$ + $d(NH_2)T$ and $d(N_3)T_p$ + $d(NH_2)T$, respectively (see Table I for properties of the hydrolytic products).

Catalytic Reduction of Azide 2 to Amine 3. A solution of azide **2** (500 mg, 0.77 mmol) in 100 ml of absolute ethanol was shaken with platinum oxide catalyst (150 mg) for 1.5 hr under 30 psi pressure of hydrogen. An additional 100 mg of the catalyst was added and the hydrogenation was continued for another 1 hr. Analysis by TLC showed two spots, attributable to **3** [R_f (THF) 0.1, positive ninhydrin test] and unreduced starting material [R_f (THF) 0.7]. Filtration, concentration, and chromatography on silica gel (2 × 30 cm). Elution successively with tetrahydrofuran (500 ml), 1:9 ethanol–tetrahydrofuran (100 ml), and 3:7 ethanol–tetrahydrofuran (200 ml) afforded 258 mg (54%) of **3** (precipitated by addition of hexane to fractions homogeneous by TLC): mp 135–138° with softening at 128°; λ_{max} 265 nm (ε 18,000); λ_{min} 234 nm (ε 4100); principal infrared bands at 3.0, 3.2, 5.9, 6.8, and 7.9 μ; R_m −0.4 relative to dpT; R_f (F) 0.8; R_f (A) 0.5.

Anal. Calcd for $C_{26}H_{33}N_6O_{10}P{\cdot}H_2O$: C, 48.90; H, 5.52; N, 13.16. Found: C, 48.70; H, 5.34; N, 12.92.

Hydrolysis of **3** with 0.1 *M* sodium hydroxide in 50% aqueous dioxane (6 hr at room temperature), neutralization, and chromatography on paper with solvent A yielded a single nucleotidic product, $d(NH_2)Tp(NH)T$, identical in electrophoretic and chromatographic properties (Table I) with $d(NH_2)Tp$-(NH)T prepared previously by a different route.[2]

$d(N_3)Tp_{(Ph)}(NH)Tp_{(Ph)}(NH)Tp_{(Ph)}(NH)T$ (4). Compound **2** (200 mg, 0.31 mmol), dried by evaporation of three 1-ml portions of pyridine, was dissolved in dioxane (6 ml) and treated with phenyl phosphorodichloridate (0.050 ml, 0.31 mmol) and pyridine (0.050 ml, 0.62 mmol) for 65 hr. Triethylamine (0.087 ml, 0.62 mmol) and a solution of **3** (120 mg, 0.21 mmol) in 40 ml of dioxane were added and stirring was continued for 2 hr. Aqueous 0.5 *M* sodium hydroxide (1 ml) was added (15 min) and the resulting solution was concentrated to a syrup at reduced pressure. Chromatography on a silica gel column (3 × 32 cm) with ethyl acetate (100 ml), ethyl acetate–tetrahydrofuran (1:1, 250 ml; 1:3, 250 ml), and tetrahydrofuran (500 ml), followed by precipitation by addition of hexane to the fractions, afforded three substances insoluble in hexane: unreacted **2** (11 mg, 6%), compound **4** (149 mg, 44%), and a product tentatively identified as phenyl-phosphorylated **2** [$d(N_3)Tp_{(Ph)}(NH)Tp_{(Ph)}$; R_m 0.21 relative to d_pT on paper electrophoresis at pH 7.2]. An analytical sample of **4**, obtained by rechromatography and reprecipitation with hexane, melted at 144–148° (softening at 141°).

Anal. Calcd for $C_{58}H_{67}N_{14}P_3O_{22}{\cdot}H_2O$: C, 48.94; H, 4.74; N, 13.81. Found: C, 49.10; H, 4.84; N, 13.22.

Characterization of 4. The phenyl protecting groups were removed from **4** by treatment with 0.1 *M* aqueous sodium hydroxide for 6 hr in the usual manner.[2] After neutralization with dilute acid, paper chromatography in solvent F showed a single nucleotidic product (R_f 0.35). This product, $d(N_3)T_p(NH)T_p(NH)T_p(NH)T$, was eluted with water and isolated by lyophilization. In preparation for hydrolytic degradation it was further purified by rechromatography on paper with solvent A and by paper electrophoresis (pH 7.2; R_m 0.7 relative to d_pT). This material was hydrolyzed by aqueous acetic acid and by snake venom phosphodiesterase.[2] The products were separated by paper chromatography in solvent A, and the relative quantities were determined by eluting the materials from the paper and measuring the absorbance at 260 nm. In conformity with the assigned structure, the substance was completely degraded in each case. The venom degradation afforded two products, $d(N_3)T$ and $d(NH_2)T$ (1.03 and 3.3 optical density units, respectively), and the acid hydrolysis yielded $d(N_3)T$, $d(NH)T_p$, and $d(NH_2)T$ (1.4:2.1:1.2 optical density units, respectively). These substances were characterized by their electrophoretic and chromatographic behavior (Table I).

5′-Amino-5′-deoxythymidine (5a). 5′-Azido-5′-deoxythymidine (5.00 g, 18.7 mmol) and triphenylphosphine (8.00 g, 30.5 mmol) were dissolved in 15 ml of pyridine and kept at room temperature for 1 hr. Concentrated ammonium hydroxide was then added and the solution was allowed to stand for an additional 2 hr. Pyridine was removed at reduced pressure, water was added, and triphenylphosphine and triphenylphosphine oxide were removed by filtration. The filtrate was extracted with benzene and with ether to remove residual triphenylphosphine and then concentrated to dryness. Recrystallization of the solid residue from ethanol afforded 4.1 g (90%) of 5′-amino-5′-deoxythymidine, mp 178–180°, mmp with a sample prepared by catalytic hydrogenation, 178–180°. The chromatographic properties [R_f (CH_3OH) 0.26] and the infrared spectrum were identical with those for the authentic sample.

5′-Amino-5′-deoxy-3′-*O*-naphthylcarbamoylthymidine (5c). Naphthyl isocyanate (1.4 ml, 10 mmol) was added to 5′-azido-5′-deoxythymidine (0.53 g, 2 mmol, dried by distillation of anhydrous pyridine) in pyridine (20 ml). After 1 hr the product was precipitated by addition of 1 l. of hexane. The precipitate was collected by centrifugation, washed with hexane, redissolved in pyridine (8 ml), and again precipitated with hexane (400 ml). The product (**1c**) weighed 0.85 g (98%); R_f (THF) 0.63; principal infrared bands at 3.0, 3.25, 4.75, 5.9, and 6.5 μ.

For reduction of the azido function, **1c** (0.217 g, 0.5 mmol) was treated with triphenylphosphine (0.26 g, 1 mmol) in pyridine (1 ml) for 1 hr, followed by addition of concentrated ammonium hydroxide (0.4 ml). After 8 hr the solution was concentrated to a gum and anhydrous pyridine was evaporated twice from the residue to remove water. The gum was then taken up in a small volume of pyridine and added slowly to 1:1 hexane–cyclohexane (350 ml). The resulting white precipitate was collected by centrifugation, washed, and crystallized from ethanol to give 0.184 g (88% from **1c**) of **5c**, mp 207–210°, R_f (THF) 0.50, R_f (EtOAc) 0.03. An analytical sample obtained by recrystallization from ethanol melted at 211–212°; λ_{max} (EtOH) 270 nm (ε 13,000), λ_{min} 244 nm (ε 6400); principal infrared bands at 2.9, 3.25, 5.8, 6.0, 6.45, and 8.15 μ.

Anal. Calcd for $C_{21}H_{22}N_4O_5$: C, 61.45; H, 5.40; N, 13.65. Found: C, 61.43; H, 5.45; N, 13.55.

5′-Amino-5′-deoxy-3′-*O*-mono-*p*-methoxytritylthymidine (5b). 5′-Azido-5′-deoxythymidine was converted to the 3′-*O*-mono-*p*-methoxytrityl ether by reaction with mono-*p*-methoxytrityl

chloride essentially as described for preparation of related nucleoside derivatives.[12] Compound **1b** was obtained in 85% yield as a white solid melting at 93–98°; λ_{max} (EtOH) 266 nm (ϵ 11,500), λ_{min} 250 nm (ϵ 9650).

Anal. Calcd for $C_{30}H_{29}N_5O_5$: C, 66.78; H, 5.42; N, 12.98. Found C, 66.35; H, 5.27; N, 13.28.

Compound **1b** (0.27 g, 0.5 mmol) and triphenylphosphine (0.26 g, 1 mmol) were dissolved in pyridine (0.6 ml) at 0°. Concentrated ammonium hydroxide (0.4 ml) was added and the solution was allowed to warm to room temperature. After 2 hr TLC revealed that the azide had reacted completely but the phosphinimine had only partially hydrolyzed to the amine [R_f (CH_2Cl_2–THF 1:1) 0.35 for **1b** and 0.20 for the phosphinimine]. Additional pyridine–ammonia (1 ml, 6:4 v/v) was added and the mixture was allowed to stand overnight, at which time the reaction was complete by the TLC test. Work-up as described for **1c** yielded 0.23 g (88%) of compound **5b**. This sample [R_f (EtOAc) 0.01] contained traces of material with R_f 0 (ninhydrin positive) and R_f 0.47 (positive to perchloric acid spray). Thick layer chromatography on silica gel yielded a pure sample (softened at 100°, completely melted at 114°), λ_{max} (EtOH) 265 nm (ϵ 11,100), λ_{min} 250 nm (ϵ 9190).

Anal. Calcd for $C_{30}H_{31}N_3O_5$: C, 70.16; H, 6.08; N, 8.18. Found: C, 69.89; H, 5.82; N, 8.15.

d(NH$_2$)T$_p$(NH)T$_p$(NH)T$_p$(NH)T (6). A solution of **4** (16 mg, 0.015 mmol) and triphenylphosphine (43 mg, 0.16 mmol) in pyridine (0.5 ml) was stirred at 25° for 1.5 hr, mixed with water (0.5 ml), and stirred for an additional 2 hr. The solvent was evaporated under reduced pressure, aqueous sodium hydroxide (1.0 ml, 0.2 *M*) was added, and the mixture was stirred overnight. Following extraction with methylene chloride (5 × 2 ml) a small portion of the aqueous layer was analyzed by paper electrophoresis at pH 7.2. A strong spot was observed under ultraviolet light at R_m −0.51 (relative to d$_p$T), and it was ninhydrin positive; the only other nucleotidic material appeared as a very faint spot (ninhydrin negative) at R_m 0.73, corresponding to a trace of unreacted **4**. The reaction product was separated from the major portion of the solution by chromatography on paper with solvent F. Elution with water, conversion to the triethylammonium salt, and lyophilization afforded 18 mg of **6**, R_f (F) 0.33. Hydrolysis of an aliquot with 80% aqueous acetic acid (15 min on steam bath) yielded d(NH$_2$)T and d(NH$_2$)T$_p$ (see Table I for properties) in a ratio of 1:2.8.

Reduction of Azide 2 to Amine 3 with Triphenylphosphine. Compound **2** (10 mg, 0.015 mmol) was added to a solution of triphenylphosphine (10 mg, 0.04 mmol) in pyridine (0.1 ml) and 50% saturated methanolic ammonia (0.1 ml). After 72 hr the solution was concentrated under reduced pressure, and the residue was dissolved in methanol and spotted on Whatman 3MM paper. Development in solvent A yielded **3** as a spot at R_f 0.56 (visualized under uv light, ninhydrin positive). The product was eluted from the paper with tetrahydrofuran and was precipitated from the tetrahydrofuran with hexane. On drying to constant weight, 7.5 mg (78%) of **3** was obtained, mp 139–141° (with softening at 130°). It was identical with **3** (prepared independently by catalytic reduction) on TLC [R_f (THF) 0.12], paper chromatography with solvent A, and paper electrophoresis (R_m −0.4 relative to d$_p$T, pH 7.2, 0.05 *M* sodium phosphate buffer).

Acknowledgment. This research was supported by the National Institute of General Medical Sciences of the National Institutes of Health (Grant GM 10265).

Registry No.—**1a,** 19316-85-9; **1b,** 54814-97-0; **1c,** 54814-98-1; **2,** 54814-99-2; **2** phenyl phosphorylated, 54815-00-8; **3,** 54815-01-9; **4,** 54815-02-0; **5a,** 25152-20-9; **5b,** 54815-03-1; **5c,** 54815-04-2; **6,** 54815-05-3; phenyl phosphorodichloridate, 770-12-7; naphthyl isocyanate, 86-84-0; mono-*p*-methoxytrityl chloride, 14470-28-1; triphenylphosphine, 603-35-0.

References and Notes

(1) Part XX in series on Nucleotide Chemistry. Part XIX: W. S. Mungall, G. L. Greene, P. S. Miller, and R. L. Letsinger, *Nucleic Acids Res.*, **1**, 615 (1974).
(2) R. L. Letsinger and W. S. Mungall, *J. Org. Chem.*, **35**, 3800 (1970).
(3) R. L. Letsinger, J. S. Wilkes, and L. B. Dumas, *J. Am. Chem. Soc.*, **94**, 292 (1972).
(4) J. P. Horwitz, A. J. Thompson, J. A. Urbansk, and J. Chua, *J. Org. Chem.*, **27**, 3045 (1972).
(5) D. Wagner, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, **36**, 250 (1971).
(6) M. G. Stout, M. J. Robins, R. K. Olsen, and R. K. Robins, *J. Med. Chem.* **12**, 658 (1969).
(7) R. P. Glinski, M. S. Khan, R. L. Kalamas, and C. L. Stevens, *Chem. Commun.*, 915 (1970).
(8) H. Staudinger and E. Hauser, *Helv. Chim. Acta*, **4**, 21 (1921).
(9) H. Zimmer and G. Singh, *J. Org. Chem.*, **28**, 483 (1963).
(10) L. Horner and A. Gross, *Justus Liebigs Ann. Chem.*, **591**, 117 (1955).
(11) A. Messmer, I. Pinter, and F. Szegö, *Angew. Chem.*, **76**, 227 (1964).
(12) K. K. Ogilvie and R. L. Letsinger, *J. Org. Chem.*, **32**, 2365 (1967).

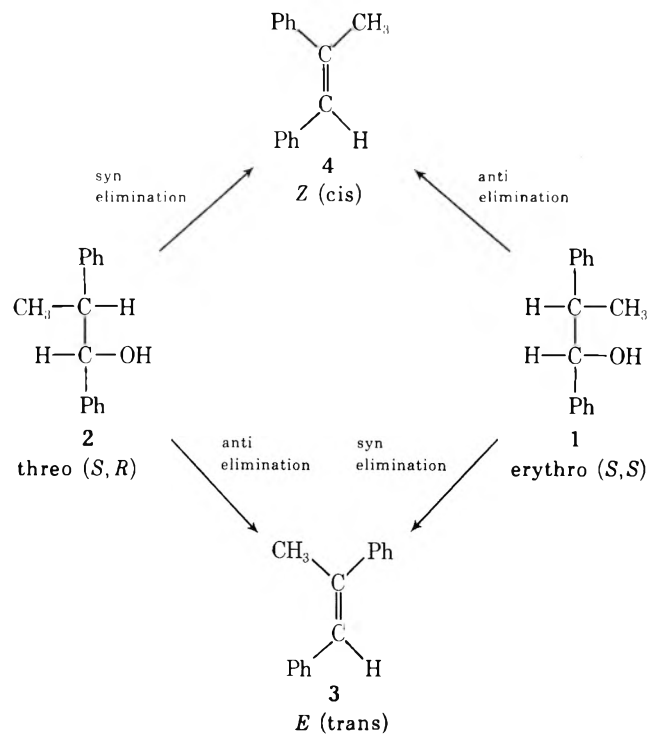
Dehydration of *erythro*- and *threo*-1,2-Diphenyl-1-propanol with Iodine, *p*-Toluenesulfonic Acid, and Methyltriphenoxyphosphonium Iodide

Wilkins Reeve* and Ruth M. Doherty

Department of Chemistry, University of Maryland, College Park, Maryland 20742

Received November 12, 1974

Iodine has long been used as a catalyst for the dehydration of secondary alcohols,[1,2] including diacetone alcohol,[1,3] and tertiary alcohols,[1,2] including pinacols.[1,4] Little is known about why iodine has this remarkable catalytic activity and nothing is known about the stereochemistry of iodine-catalyzed dehydrations. We have studied the dehydration of the erythro (**1**) and threo (**2**) isomers of 1,2-diphenyl-1-propanol to determine the stereochemistry of the reaction.



We have found these dehydrations to be essentially nonstereospecific. In both cases the reaction proceeded initially with about 55% anti-periplanar elimination. This was followed by equilibration to the equilibrium mixture consisting of 72% *E*- (**3**) and 28% *Z*-α-methylstilbene (**4**). The threo alcohol (**2**) dehydrated more rapidly than its erythro isomer.

The *p*-toluenesulfonic acid (PTSA) catalyzed dehydration of **1** and **2** in refluxing *p*-xylene was also found to proceed initially in a nonstereospecific manner followed by equilibration of **3** and **4** on longer heating. As with the iodine-catalyzed reaction, the threo alcohol dehydrated more rapidly than the erythro isomer. With both iodine and PTSA our results are consistent with the formation with a common intermediate carbonium ion, but are insufficient

to prove this mechanism. Manas and Villa[2] have demonstrated the absence of a common intermediate carbonium ion in a related case. These authors dehydrated *erythro*- and *threo*-2,3-diphenyl-2-butanol (**5**) using either iodine or PTSA in refluxing benzene, and obtained *cis*- and *trans*-α,α'-dimethylstilbene (**6**) and 2,3-diphenyl-1-butene (**7**) in the following amounts: from *erythro*-**5** with iodine, 62% *cis*-**6**, 27% *trans*-**6**, and 11% **7**; from *threo*-**5** with iodine, 10% *cis*-**6**, 4% *trans*-**6**, and 86% **7**; from *erythro*-**5** with PTSA, 41% *cis*-**6**, 18% *trans*-**6**, and 41% **7**; from *threo*-**5** with PTSA, 48% *cis*-**6**, 50% *trans*-**6**, and 2% **7**. The different product distribution from the erythro and threo compound rules out a common intermediate.

Recently, Hutchins et al.[5] have pointed out the usefulness of methyltriphenoxyphosphonium iodide in hexamethylphosphoramide (HMPA) for the selective dehydration of secondary alcohols; so it seemed desirable to try this reagent with alcohols **1** and **2** to determine the stereoselectivity of this method of preparing olefins. The reaction is believed to involve the initial replacement of the hydroxyl group by iodine with inversion, followed by dehydroiodination induced by the HMPA solvent and iodide ion.[5] We find the mixture of olefins to be formed almost quantitatively and to consist of 64–72% of the less stable *Z* olefin, irrespective of the stereochemistry of the starting alcohol. This strongly suggests that some common intermediate is involved in the reaction. Equilibration is probably occurring at the intermediate iodide stage, since Hutchins et al.[5] observed equilibration at this stage in the dehydration of *cis*-4-*tert*-butylcyclohexanol. These authors also studied the dehydration of 1,2-diphenylethanol (which does not exist in diastereoisomeric forms), and found that it formed (99%) the more stable (*E*)-stilbene. This demonstrates that the more stable olefin is formed by this reaction sequence when structural features allow both possibilities. With our alcohols, the predominate *Z* olefin is formed from the erythro iodide, assuming anti-periplanar elimination. The threo alcohol forms the erythro iodide, and the threo alcohol therefore is expected to form the larger amount of the *Z* olefin, as observed, if complete equilibration is not attained at the iodide stage. In any event, the reaction is partially stereoselective.

Cram[6] first studied the equilibration of olefins **3** and **4** and concluded, on the basis of uv spectra, that the equilibrium mixture contained at least 98% of the *E* isomer (**3**). Manas and Vila[2] isomerized **3** with PTSA, analyzed the products by GLC, and concluded that the equilibrium mixture consisted of 79% of **3**. We used PTSA to equilibrate the olefins by refluxing **3** and **4** in *p*-xylene for up to 44 hr. The equilibrium composition was approached from each side and found by GLC to be 70–73% *E* (**3**) with the balance being the *Z* isomer (**4**).

Our work has demonstrated that (1) the dehydration of alcohols **1** and **2** with either iodine or PTSA is essentially nonstereospecific; (2) the new reagent for selectively dehydrating secondary alcohols, methyltriphenoxyphosphonium iodide, is not stereospecific; the same olefin mixture rich in the less stable *Z* isomer (70%) is obtained from either the erythro or threo alcohols **1** or **2**.

Experimental Section

Melting points are corrected. The infrared spectra were determined with a Perkin-Elmer Model 337 spectrophotometer; the ultraviolet spectra with a Cary 15; and the NMR spectra with a Varian Model A-60. Chemical shift values are expressed as δ values (parts per million) downfield from tetramethylsilane internal standard. GLC analyses were carried out on a Hewlett-Packard Model 5750 research chromatograph with a disk integrator.

***threo*-1,2-Diphenyl-1-propanol (2)** was prepared by Cram's method[7] starting with 12 g of magnesium, 78 g of bromobenzene, and 54 g of technical 2-phenylpropionaldehyde which had been freshly distilled, bp 72–73° (6.6 mm). This gave 71 g (70%) of a colorless oil, bp 112–118° (7–8 mm). The product was further purified by conversion to the *p*-nitrobenzoate, which was crystallized seven times from ethyl acetate, mp 143–144°.[7] The ester was hydrolyzed to give the alcohol by refluxing the ester (25 g) in methanol (50 ml) and water (50 ml) with sodium hydroxide (3.1 g) for 12 hr: bp 136–138° (1.5 mm) [lit.[7] bp 136–137° (1–2 mm)]; ir identical with literature spectrum;[8a] NMR (CCl_4) δ 4.52 (d, 1, J = 6 Hz, >CHOH), 2.90 (m, 1, >C**H**CH_3), 2.30 (s, 1, –OH), 1.18 (d, 3, J = 7 Hz, –CH_3).

***erythro*-1,2-Diphenyl-1-propanol (1).** 1,2-Diphenyl-1-propanone was first prepared by a chromic acid oxidation of **2**.[7] The crude ketone was hydrogenated over W-2 Raney nickel at 100° and 70 atm pressure. NMR analysis showed nine parts of **1** to one part of **2** in the product. Crystallization from "isooctane" gave crystals: mp 48–49° (lit.[7] mp 50–51°); ir identical with literature value;[8b] NMR (CCl_4) δ 7.10 (m, 10, Ph), 4.43 (d, 1, J = 8 Hz, CHOH), 2.87 (m, 1, >C**H**CH_3), 2.20 (s, 1, –OH), 1.00 (d, 3, J = 7 Hz, –CH_3).

***(E)*-α-Methylstilbene (3).** A pure sample, mp 80–81° (lit.[7] mp 81–82°), was prepared by the low-temperature pyrolysis of the methyl xanthate of **1** according to Cram's method:[7] uv max (95% C_2H_5OH) 274 nm (ϵ 20,400) [lit.[7] 273 nm (ϵ 19,900)]; ir identical with literature;[8c] NMR (CCl_4) δ 7.25 (m, 10, Ph), 6.75 (broad d, 1, >CH–), 2.42 (d, 3, J = 1.5 Hz, –CH_3).

***(Z)*-α-Methylstilbene (4).** We could not obtain **4** by the preceding procedure starting with **2**; our modified procedure follows. Five grams of **2** was dissolved in 60 ml of toluene and 25 ml of the toluene was distilled off. Metallic potassium (0.75 g) was added and the mixture was refluxed for 1 hr. Carbon disulfide (3.5 g) was added, and the mixture was heated with stirring for 10 hr. Methyl iodide (8 g) was added and the solution was refluxed for an additional 2.5 hr. At the end of this time the mixture was shaken with 100 ml of 1:1 water–ether. The ether layer was washed with three 35-ml portions of water and the solvents were removed under water-pump pressure, leaving a yellow-orange oil. This was heated to around 180° at water-pump pressure to pyrolyze the xanthate and distil off the olefin. The portion that distilled was a pale yellow oil (1.6 g), which could not be induced to crystallize. Injection of a sample of the oil in a F & M Model 300 GLC chromatograph (silicon gum rubber column at 160°) revealed three major peaks with retention times of 8.7, 11.9 (**4**), and 21.9 (**3**) min in the ratio 20:35:45. The properties of the GLC-purified **3** follow: ir, identical with literature;[8d] NMR (CCl_4) δ 7.00 (m, 10, Ph), 6.40 (broad d, 1, >CH–), 2.13 (d, 3, J = 1.5 Hz, –CH_3). The uv spectrum was obtained on another sample known from GLC analysis to be 85% **4** and 15% **3**: uv max (95% C_2H_5OH) 263 nm (ϵ 11,800) [lit.[7] 262 nm (ϵ 11,700)].

General Procedure Using Iodine. In a 50-ml round-bottom flask were placed 5–50 mg of iodine, 200 mg of **1** or **2**, and 10 ml of *p*-xylene. This mixture was heated at reflux for 1 hr and then allowed to cool. Sodium thiosulfate solution (10 ml) was added to the solution, and the mixture was stirred for 5 min. The layers were separated and the organic layer was concentrated on a rotary evaporator to a yellow oil. This was chromatographed on 30 g of silica gel (Brinckman, 70–325 mesh), using cyclohexane as the el-

Table I
Dehydration of 1,2-Diphenyl-1-propanol

Stereoisomer	Reagent (mg catalyst/g alcohol)	Time, hr	% yield of 3 + 4	Composition of mixture	
				% *E* (3)	% *Z* (4)
1	Iodine[a] (250)	1	19	43	57
1	Iodine[a] (260)	3	95	73	27
2	Iodine[a] (250)	1	82	54	46
2	Iodine[a] (240)	3	83	70	30
2	Iodine[b] (21)	1	50	45	55
1	PTSA[a] (44)	3	95	53	47
2	PTSA[a] (44)	3	95	72	28
1	MTPI[c]	1	95	36	64
2	MTPI[c]	1	95	28	72

[a] In refluxing *p*-xylene at 138°. [b] No solvent; temperature was 150°. [c] Followed procedure of ref 5; the methyltriphenoxyphosphonium iodide in excess was heated with the alcohol at 80° in hexamethylphosphoramide for 1 hr.

uent. The cyclohexane was removed from each fraction at water-pump pressure, and the residues were weighed. The fractions were as follows. Fraction 1 (70 ml) contained no olefins and was discarded. Fraction 2 (450 ml) contained 150 mg of the two olefins and no starting material. Fraction 3 (100 ml) contained neither olefins nor starting alcohol and was discarded. Fraction 4 (200 ml) contained 58 mg of material, primarily the starting alcohol and no olefins. Samples of fractions 2 and 4, dissolved in a little cyclohexane, were analyzed by GLC (silicon gum rubber column at 180°). The *Z* olefin had a retention time of 7.8 min while the *E* olefin had a retention time of 13.6 min. The results are tabulated in Table I.

General Procedure Using PTSA. Compound 2 (250 mg), 12 mg of PTSA monohydrate, and 5 ml of *p*-xylene were heated with refluxing for 3 hr. The mixture was allowed to cool to room temperature and washed with 20% sodium carbonate solution and water. After removal of the solvent the NMR spectrum showed no indication of starting alcohol. Accordingly, the chromatography on silica gel was omitted. The olefin mixture was analyzed by GLC as before and the results are in Table I.

General Procedure Using Methyltriphenoxyphosphonium Iodide. This followed ref 5. Compound 2 (296 mg), 1.86 g of methyltriphenoxyphosphonium iodide, and 9 ml of dry hexamethylphosphoramide (dried over calcium hydride and stored over molecular sieves 4A) were heated in an oil bath at 80° for 1 hr. The reaction mixture was poured over 20 ml of 10% potassium hydroxide solution and extracted with four 10-ml portions of cyclohexane. These were washed with water and dried ($MgSO_4$), the solvent was removed, and the oil was analyzed by NMR and GLC. The results are in Table I.

Equilibration of 3 and 4. Olefin 3 (315 mg) was refluxed with 13 mg of PTSA monohydrate in 10 ml of *p*-xylene. Samples were removed for analysis of the *E* and *Z* olefins from time to time, and injected directly into the GLC. The results were as follows (hr, % 3): 0, 100; 0.5, 88; 1.0, 79; 3.0, 78; 20, 73.

The experiment was repeated with 109 mg of 4 (containing 15% of 3) and 6 mg of PTSA in 4 ml of refluxing *p*-xylene. The results were as follows (hr, % 3): 0, 15; 0.5, 17; 1.0, 21; 1.5, 39; 2.0, 44; 4.0, 50; 24.0, 61; 44, 70.

Registry No.—1, 7693-84-7; 2, 7693-85-8; 3, 833-81-8; 4, 1017-22-7; iodine, 7553-56-2; *p*-toluenesulfonic acid, 104-15-4; methyltriphenoxyphosphonium iodide, 17579-99-6; triphenoxymethyliodophosphorane, 4167-91-3.

References and Notes

(1) H. Hibbert, *J. Am. Chem. Soc.*, **37**, 1748 (1915).
(2) M. J. Manas and J. P. Vila, *An. Quim.*, **65**, 37 (1969).
(3) J. B. Conant and N. Tuttle, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, p 345.
(4) W. Reeve and D. M. Reichel, *J. Org. Chem.*, **37**, 68 (1972).
(5) R. O. Hutchins, M. G. Hutchins, and C. A. Milewski, *J. Org. Chem.*, **37**, 4190 (1972).
(6) D. J. Cram, F. D. Greene, and C. H. Dupuy, *J. Am. Chem. Soc.*, **78**, 790 (1956).
(7) D. J. Cram and F. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).
(8) Sadtler Standard Spectra, Sadtler Research Laboratory, Philadelphia, Pa.: (a) no. 1948; (b) no. 1940; (c) no. 2081; (d) no. 1932.

Selective Oxidation of Allylic Alcohols with Chromic Acid

Kenn E. Harding,* Leslie M. May, and Kevin F. Dick

Department of Chemistry, Texas A&M University, College Station, Texas 77843.

Received January 17, 1975

Although examples of synthesis of aldehydes by oxidation of primary alcohols with chromic acid reagents are in the literature, many reviews and advanced texts[1] suggest that other reagents (chromic anhydride–pyridine, activated manganese dioxide) or special conditions (removal of aldehyde as it is formed) are necessary for effecting this conversion in high yields. This note demonstrates that primary allylic alcohols can be converted to the corresponding α,β-unsaturated aldehydes in high yield using chromic acid in acetone (Jones reagent).[2]

In other synthetic work[3] we had observed that some α,β-unsaturated aldehydes were inert to normal conditions for Jones oxidation. Although an extensive investigation of the reaction did not seem warranted, we have examined the behavior of some simple primary allylic alcohols upon treatment with Jones reagent.

The oxidation of cinnamyl alcohol to cinnamaldehyde has frequently been cited as an illustration of the utility of the chromic anhydride–pyridine complex.[1a,c] Holum[4] obtained cinnamaldehyde in 87% yield using the complex. We found that simple oxidation with Jones reagent gave the aldehyde in an 84% yield.[5]

Geraniol and nerol were used as examples of simple terpenoid primary allylic alcohols. Treatment of these alcohols with Jones reagent gave aldehydes in high yield. Geraniol was converted into aldehyde in a 91% yield. However, GLC investigation showed that a small amount of isomerization of the double bond had occurred. The GLC data indicated that the product consisted of about 96% geranial and 4% neral. Oxidation of 95% nerol gave aldehyde in 84% yield, and GLC indicated that isomerization had occurred to the extent of about 8%. Thus the oxidation with Jones reagent does have the disadvantage of causing some loss of double-bond stereochemistry in these two cases.

Oxidation of benzyl alcohol to benzaldehyde with Jones reagent also proceeded in good yield, although this reaction appeared more sensitive to experimental variations than the other oxidations. Thus benzaldehyde was obtained in 76% yield using Jones reagent.

These results demonstrate that oxidation of allylic or benzylic alcohols to the corresponding aldehydes occurs using the simple Jones oxidation procedure without the need to use large amounts of expensive activated manganese dioxide or to use a chromic acid–pyridine reagent.

Experimental Section

Proton NMR spectra were recorded on a Varian T-60 spectrometer employing tetramethylsilane as an internal standard and CCl_4 as a solvent. The ir spectra were recorded on a Beckman IR-8 spectrophotometer. GLC analyses were performed on a Hewlett-Packard 700 gas chromatograph using an SE-30 column (6 ft × 0.1875 in., 10% on Chromosorb W) and a Carbowax 20M column (6 ft × 0.1875 in., 10% on Chromosorb W).

The products from the oxidations were identified by comparison of the ir and NMR spectra with spectra of authentic samples or with spectra recorded in the literature.

Jones Oxidation of Cinnamyl Alcohol. A solution of 500 mg (3.72 mmol) of cinnamyl alcohol and 10 ml of reagent-grade acetone was placed in a 50-ml round-bottom flask under nitrogen and cooled to 0° (ice–water bath). To the magnetically stirred solution was added dropwise a solution consisting of 2 ml of 8 *N* Jones reagent and 18 ml of reagent acetone. The Jones solution was added over a period of ca. 20 min until an orange tint persisted in the reaction mixture. Isopropyl alcohol was then added dropwise to destroy excess Jones reagent, as indicated by the reappearance of a deep green color. The reaction mixture was then extracted twice with ether, and the combined ether extracts were washed (water, sodium bicarbonate, and brine), dried over anhydrous magnesium sulfate, and concentrated. Evaporative distillation (0.1 mm, 100°) yielded 420 mg (2.96 mmol, 84%) of a cinnamon-smelling, pale yellow oil (>92% pure by GLC) identified as cinnamaldehyde by comparison of the ir and NMR spectra with literature spectra.

Jones Oxidation of Geraniol. A solution of 500 mg (3.24 mmol) of 99+% geraniol and 10 ml of reagent-grade acetone was placed in a 50-ml round-bottom flask and cooled to 0° (ice–water bath). This solution was treated with Jones reagent in the manner described above. Evaporative distillation of the crude product (0.1 mm, 100°) yielded 450 mg (2.92 mmol, 91%) of a light yellow oil having a citrus odor. GLC (Carbowax) showed 96% geranial and 4% neral as the only significant (>94%) components. The ir and NMR

spectra were consistent with those of an authentic sample of geranial, obtained from GLC separation of citral.

Jones Oxidation of Nerol. A solution of 500 mg (3.24 mmol) of 95% nerol and 10 ml of reagent-grade acetone was placed in a 50-ml round-bottom flask and cooled to 0° (ice–water bath). Oxidation as described for cinnamyl alcohol gave material which upon evaporative distillation (0.1 mm, 100°) yielded 420 mg (2.72 mmol, 84%) of a pale yellow oil having a citrus odor. GLC (Carbowax) showed a 7:1 ratio (87.5%) of neral to geranial as the only significant (97%) components. The NMR and ir spectra were consistent with those of an authentic sample of neral, obtained from GLC separation of citral.

Jones Oxidation of Benzyl Alcohol. A solution of 500 mg (4.63 mmol) of benzyl alcohol and 10 ml of reagent-grade acetone was placed in a 50-ml round-bottom flask and cooled to 0° (ice–water bath). Oxidation in the same manner gave material which upon evaporative distillation (water aspirator pressure, 100°) yielded 380 mg (3.52 mmol, 76%) of a clear oil (>99% pure by GLC) identified by ir and NMR as benzaldehyde.

Acknowledgments. We thank the Robert A. Welch Foundation and the National Cancer Institute (PHS Research Grant CA 15736) for support of this research.

Registry No.—Cinnamyl alcohol, 104-54-1; cinnamaldehyde, 104-55-2; geraniol, 106-24-1; geranial, 141-27-5; neral, 106-26-3; nerol, 106-25-2; benzyl alcohol, 100-51-6; benzaldehyde, 100-52-7; chromic acid, 7738-94-5.

References and Notes

(1) (a) H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 270; (b) W. Carruthers, "Modern Methods of Organic Synthesis", Cambridge University Press, New York, N.Y., 1971, p 245; (c) K. L. Rinehart, Jr., "Oxidation and Reduction of Organic Compounds", Prentice-Hall, Englewood Cliffs, N.J., 1973, pp 70–71; (d) R. O. C. Norman, "Principles of Organic Synthesis", Methuen, London, 1968, p 518; (e) C. A. Buehler and D. E. Pearson, "Survey of Organic Syntheses", Wiley-Interscience, New York, N.Y., 1970, pp 545–549; (f) L. J. Chinn, "Selection of Oxidants in Synthesis", Marcel Dekker, New York, N.Y., 1971, pp 41–43.

(2) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(3) K. E. Harding and R. C. Ligon, *Synth. Commun.*, **4**, 297 (1974); K. E. Harding and R. C. Ligon, unpublished observations.

(4) J. R. Holum, *J. Org. Chem.*, **26**, 4814 (1961).

(5) A recent communication has described oxidation of cinnamyl alcohol in 85% yield using sodium dichromate and sulfuric acid in dimethyl sulfoxide: Y. S. Rao and R. Filler, *J. Org. Chem.*, **39**, 3304 (1974).

220-MHz Nuclear Magnetic Resonance Spectra of Bicyclo[3.2.1]octan-6-ones

William C. Agosta* and Steven Wolff*

Laboratories of The Rockefeller University, New York, New York 10021

Received December 2, 1974

Over the past few years we have accumulated a number of substituted bicyclo[3.2.1]octan-6-ones, both as substrates and as products in diverse photochemical investigations. Examination of the 220-MHz NMR spectra of these compounds has permitted consistent assignments for the various low-field proton resonances in each case, and these results are presented here. Other investigators have previously underscored the advantages and value of NMR studies of this bicyclic ring system,[1] and indeed our results allow worthwhile comparisons with the large store of information now on hand for norbornanes.[2] Furthermore, they permit generalizations which should facilitate future determinations of structure and stereochemistry for related bicyclooctanes.

Synthesis of most of these ketones has been described in earlier work,[3] and details of the preparation of the epimeric methoxy ketones **15** and **16** are given at the end of the present article. The remaining new compounds, **5–7**, are formed on photolysis of appropriate cyclopentenones,[4] and their preparation and other data defining their structures will be reported in a forthcoming publication.

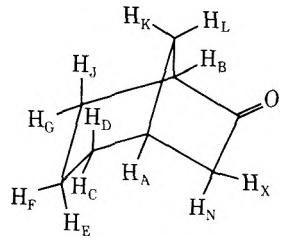
The methyl and low-field resonances of the 220-MHz NMR spectra of these 16 bicyclooctanones are collected in Table I. For comparison the completely interpreted spectrum[3] of the closely related oxabicyclic ketone **17** is also presented.

Typically the lowest field signals in the simple alkylated ketones of this series are those of the bridgehead positions at C(1) and C(5), H_A and H_B, respectively, with H_A the farther downfield (compare, for example, **1**, **2**, and **4**). The positions of these protons closely parallel those of the bridgehead hydrogens of norbornanone (**18**): C(4) H, δ 2.57, 2.61, and C(1) H, 2.39, 2.41 ppm.[2b,5] Interestingly, these effects do not appear in bicyclo[2.2.2]octanone (**19**); here the two bridgehead protons at C(1) and C(4), along with the C(3) methylene protons, all appear at 2.15 ppm ($W_{1/2}$ = 5 Hz).[5] The bridgehead proton more distant from the carbonyl both in norbornanones and in bicyclo[3.2.1]octan-6-ones then appears downfield from the bridgehead proton adjacent to the carbonyl. The reason for this is not known with certainty; for norbornanones it has been suggested[5] that excess s character and abnormal polarizability in the bridgehead bonding orbital may be responsible. In this regard it is noteworthy that in the bicyclo[3.2.1]octanones a qualitatively similar low-field shift is also seen for methyl groups at the distant bridgehead position. For example, the C(1) methyl of **2** appears well downfield from the C(5) methyl of **4** (1.13 vs. 0.936 ppm).

The next two signals upfield are those of the endo and exo protons at C(7), H_N and H_X. These are characterized by two, and occasionally three, coupling constants. First, the geminal coupling is typically 18 Hz (J_{NX}). Second, H_X shows a vicinal coupling constant (J_{XA}) of 6–7 Hz, while the corresponding interaction for H_N is not seen or else is small (J_{NA} = 0–1 Hz). Finally, there are long-range splittings over four bonds; H_N couples with H_K in all cases (J_{NK} = 3–4 Hz),[6] and H_X occasionally does so with H_D (J_{XD} = 0–0.5 Hz). All these interactions are analogous to those well documented in norbornanes, although the range of values observed is slightly different in some cases. Thus, in norbornanes the vicinal coupling constant corresponding to J_{XA} is a little smaller (3–4 Hz[2]), and the long-range coupling constant corresponding to J_{XD} is a little larger (1–1.5 Hz[2]). The noted difference in vicinal coupling constants between the two systems would appear primarily attributable to the increase in the dihedral angle involving H_A and H_X on passing from the bicyclo[3.2.1]octane to the bicyclo[2.2.1]heptane skeleton. The high value of the geminal coupling in the bicyclooctanes (J_{NX} = 18 Hz) is due largely to the effect of the carbonyl group. There is good evidence[7] that adjacent π bonds can enhance geminal coupling if the geometry is appropriate, and models indicate that the rigid geometry of the five-membered ring here should lead to a maximum contribution from the carbon–oxygen double bond to the value of J_{NX}.

H_N and H_X appear at about 2.0 ppm, with the exact position of each influenced by substitution not only at the adjacent bridgehead position but also at C(2) and C(3). The difference in chemical shift between these protons is usually 0.2 ppm or less. For these reasons assignment of the two signals to one or the other of the C(7) protons is based on the magnitude of the observed vicinal and long-range coupling constants, as discussed above, and not on the chemical shifts of these protons. In the ketones bearing hydrogen at C(1), H_X appears at lower field in six of the nine exam-

Table I
NMR Spectra of Bicyclo[3.2.1]octan-6-ones



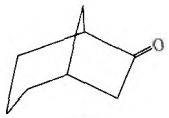
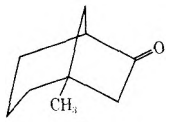
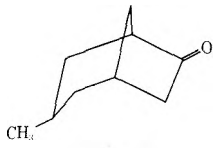
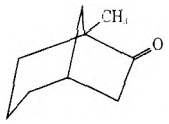
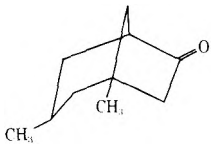
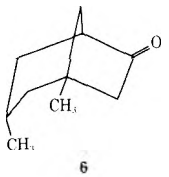
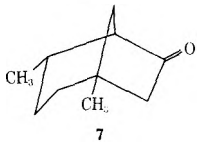
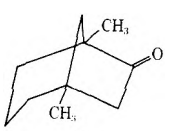
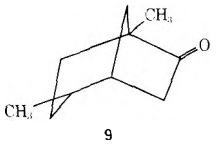
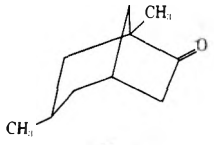
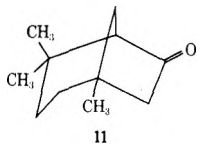
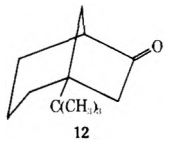
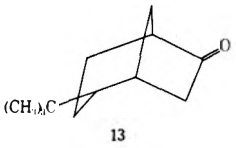
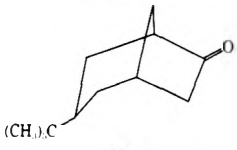
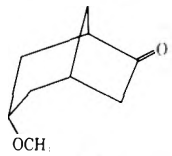
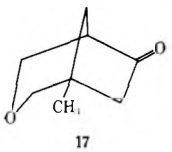
Compd	Chemical shifts, δ, and coupling constants, Hz					
	H_A	H_B	H_N	H_X	C(1)CH_3	Other
 1	2.57, br	2.23, br	1.96, dd J_{NK} = 3 J_{NX} = 18	2.16, dd J_{XA} = 7 J_{XN} = 18		
 2		2.33, br	1.98, dd J_{NK} = 3 J_{NX} = 18	1.83, dd J_{XD} = 0.5 J_{XN} = 18	1.13, s	
 3	2.54, br	2.23, br	1.95, dd J_{NK} = 3 J_{NX} = 18	2.12, ddd J_{XD} = 0.5 J_{XA} = 7 J_{XN} = 18		C(3) CH_3: 0.900, d J = 6
 4	2.50, br		2.00, dd J_{NK} = 3.5 J_{NX} = 18	2.19, dd J_{XA} = 7 J_{XN} = 18		C(5) CH_3: 0.936, s
 5		2.33, br	1.98, dd J_{NK} = 4 J_{NX} = 18	1.80, dd J_{XD} = 0.5 J_{XA} = 18	1.12, s	C(3) CH_3: 0.905, d J = 7
 6		2.29, br	2.18, dd J_{NK} = 3 J_{NX} = 18	1.73, d J_{XN} = 18	1.14, s	C(3) CH_3: 1.01, d J = 7
 7		2.09, br	1.93, dd J_{NK} = 4 J_{NX} = 18	1.81, d J_{XN} = 18	1.14, s	C(4) CH_3: 0.927, d J = 7
 8			2.01, dd J_{NK} = 4 J_{NX} = 18	1.85, d J_{XN} = 18	1.12, s	C(5) CH_3: 0.945, s
 9	2.19, br		2.09, dd J_{NK} = 4 J_{NX} = 18	1.98, dd J_{XA} = 7 J_{XN} = 18		C(2) CH_3: 0.891, d J = 6 C(5) CH_3: 0.927, s

Table I (*Continued*)

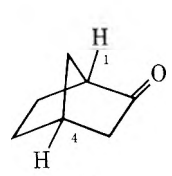
Compd	Chemical shifts, δ, and coupling constants, Hz					
	H_A	H_B	H_N	H_X	$C(1)CH_3$	Other
 10	2.47, br		2.00, ddd J_{NA} = 0.5 J_{NK} = 4 J_{NX} = 18	2.15, dd J_{XA} = 7 J_{XN} = 18		C(3) CH_3: 0.886, d J = 6 C(5) CH_3: 0.935, s
 11		~1.82	1.92, dd J_{NK} = 4 J_{NX} = 18	1.74, dd J_{XD} = 0.5 J_{XN} = 18	1.13, s	C(4) CH_3: 0.932, s C(4) CH_3: 0.986, s
 12		2.34, br	1.80, dd J_{NK} = 3 J_{NX} = 18	2.09, dd J_{XD} = 0.5 J_{XN} = 18		$C(CH_3)_3$: 0.91, s
 13	2.63, br	2.19, br	2.16, dd J_{NK} = 3 J_{NK} = 18	2.02, dd J_{XA} = 6 J_{XN} = 18		$C(CH_3)_3$: 0.89, s
 14	2.58, br	2.26, br	1.94, ddd J_{NA} = 0.5 J_{NK} = 3.5 J_{NX} = 18	2.11, dd J_{XA} = 6.5 J_{XN} = 18		$C(CH_3)_3$: 0.84, s
 15	2.63, br	2.34, br	1.98, ddd J_{NA} = 1 J_{NK} = 3 J_{NX} = 18	2.12, dd J_{XA} = 6 J_{XN} = 18		H_E: 3.31, m OCH_3: 3.21, s
 16	2.52, br	2.14, br	2.47, dd J_{NK} = 3 J_{NX} = 17	~1.93		H_F: 3.45, m OCH_3: 3.14, s
 17		2.26, br	2.18, dd J_{NK} = 3 J_{NX} = 17	1.96, d J_{XN} = 17	1.07, s	H_C: 3.53, dd J_{CD} = 11 J_{CL} = 3 H_D: 3.44, d J_{DC} = 11 H_G: 3.98, ddd J_{GJ} = 10 J_{GB} = 2 J_{GL} = 3 H_J: 3.47, d J_{JG} = 10 H_K: 1.74, dd J_{KN} = 3 J_{KL} = 13 H_L: 1.89, br

ples.[8] In the exceptional cases (**9**, **13**, and **16**) there is endo substitution at either C(2) or C(3), placing a substituent rather close in space to C(7). Interestingly, substitution of a methyl group at C(1) causes a sizable upfield shift of H_X but not H_N, with the result that in all six C(1)-methyl compounds H_N appears at lower field than H_X. In contrast to these observations, it has been known for some years that in norbornanes an exo proton appears reliably at lower field than the corresponding endo proton, and that this is true whether the adjacent bridgehead bears hydrogen or methyl.[9]

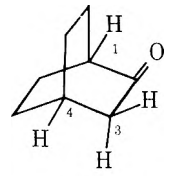
In six of the ketones the three-carbon bridge [C(2)–C(4)]

of the cyclohexane ring bears a single methyl group. It is noteworthy that the one axial methyl in this series (in **6**) exhibits the expected[10] downfield shift relative to the five equatorial ones (δ_{ax} = 1.01, δ_{eq} = 0.90 ± 0.03 ppm).

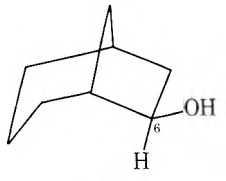
Preparative Experiments. The methoxy ketones **15** and **16** were prepared from hydroxy ketal **22**.[11] Reaction of this alcohol with methyl iodide and base gave the methoxy ketal, which was hydrolyzed to **15** in dilute acid. For **16** the configuration of the hydroxyl group of **22** was inverted through oxidation to **23** as previously described,[11] followed by reduction to **24**. We found lithium tri-*sec*-butyl hydride[12] to be highly stereoselective in this reduction, with no detectable amount (<2%) of **22** accompanying formation of **24**. Etherification and subsequent hydrolysis of **24** following the procedures noted above then gave **16**.



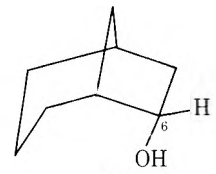
18



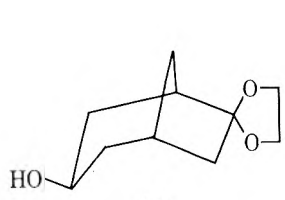
19



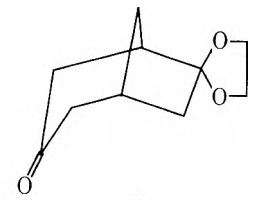
20



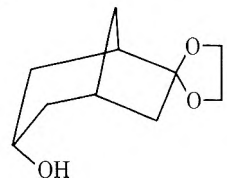
21



22



23



24

Experimental Section

Materials and Equipment. All VPC was carried out with a 10 ft × 0.375 in. aluminum column containing DEGS (30%) absorbed on 45/60 Chromosorb W in a Varian Aerograph Model A-90-P3. The column oven was operated at 145–175° and the helium carrier gas flow rate was 120–150 ml/min. NMR spectra were recorded for dilute CCl_4 solutions using a Varian HR-220 (220-MHz) spectrometer. Ir spectra were obtained for CCl_4 solutions with a Perkin-Elmer Model 237B spectrometer. Mass spectra were obtained on a Du Pont 21-492 double-focusing mass spectrometer with a resolution of 10^4, and the results were processed with a AEI DS-30 data system. Boiling points are uncorrected; all products were obtained as colorless oils.

***exo*-3-Methoxybicyclo[3.2.1]octan-6-one (15).** Hydroxy ketal **22** (184 mg, 1 mmol) was methylated using NaH and methyl iodide in dimethyl sulfoxide as previously described for the synthesis of 4-methyl-4-methoxymethylcyclopentanone ethylene ketal.[3] Deketalization was effected by vigorous stirring of the crude ether with 5 ml of 10% HCl for 1 hr at room temperature. The reaction mixture was poured into brine and extracted three times with pentane. The combined pentane extracts were washed with brine, saturated $NaHCO_3$, and brine and dried over $MgSO_4$. Removal of the pentane by distillation through a Vigreux column yielded a residue which was distilled bulb-to-bulb (120°, 12 mm) to afford 144 mg of oil. The major component of this crude product was purified by preparative VPC and identified as **15:** ir 2980 (m), 2895 (w), 2850 (w), 1742 (s), 1400 (w), 1098 (s), 1058 (m), 975 cm^{-1} (w); NMR δ 3.31 (seven-line m, 1 H), 3.21 (s, 3 H), 2.63 (br m, 1 H), 2.34 (br m, 1 H), 2.30–1.82 (br m, 3 H), 2.12 (dd, J = 6, 18 Hz, 1 H), 1.98 (ddd, J = 1, 3, 18 Hz, 1 H), 1.67 (dd, J = 3, 12 Hz, 1 H), 1.46 (m, 1 H), 1.33 (ddd, J = 2, 11, 11 Hz, 1 H); mass spectrum *m/e* 154.1005 (M^+, calcd for $C_9H_{14}O_2$, 154.0993).

***endo*-3-Methoxybicyclo[3.2.1]octan-6-one (16).** An anhydrous tetrahydrofuran solution (5 ml) of keto ketal **23** (338 mg), obtained from **22** by the method of Monti,[11] was added to lithium tri-*sec*-butylborohydride (4.65 ml of a 1 *M* solution) at −78° under a nitrogen atmosphere. After stirring at this temperature for 3 hr, the reaction mixture was warmed to room temperature and oxidized with 3 *M* aqueous NaOH (3 ml) and 30% H_2O_2 (5 ml). The mixture was poured into water and extracted three times with ether. The organic phases were combined, washed with brine, and dried. Removal of solvents in vacuo gave 542 mg of a viscous oil. Without further attempt to remove 2-butanol, the crude hydroxy ketal was methylated and worked up as described for **15** above. Hydrolysis of the ketal by vigorous stirring with 5 ml of 3% H_2SO_4 for 1 hr at room temperature and extractive work-up with pentane yielded impure **16**. This was distilled bulb-to-bulb (135°, 12 mm) to give 184 mg of an oil which was purified by preparative VPC. There was no evidence of **15** in the distilled material. The major component was collected and identified as **16:** ir 2980 (s), 2900 (m), 2850 (w), 1745 (s), 1360 (m), 1260 (m), 1148 (m), 1082 (s), 962 (m), 880 cm^{-1} (m); NMR δ 3.45 (br, 1 H), 3.14 (s, 3 H), 2.52 (br, 1 H), 2.47 (dd, J = 3, 17 Hz, 1 H), 2.38–1.54 (br m, 7 H), 1.93 (d, J = 17 Hz, 1 H); mass spectrum *m/e* 154.0998 (M^+, calcd for $C_9H_{14}O_2$, 154.0993).

Acknowledgments. The NMR spectra were obtained on an instrument at The Rockefeller University and operated by a consortium supported in part by NSF Grant GB-43257. We thank Miss Luz Catan for technical assistance and The Rockefeller University Mass Spectrometry Laboratory for mass spectra.

Registry No.—**1**, 6553-12-4; **2**, 54277-28-0; **3**, 54277-29-1; **4**, 20608-68-8; **5**, 54831-14-0; **6**, 54831-15-1; **7**, 54831-16-2; **8**, 38857-63-5; **9**, 54788-70-4; **10**, 54788-71-5; **11**, 33315-89-8; **12**, 54277-32-6; **13**, 54788-72-6; **14**, 54277-33-7; **15**, 54788-73-7; **16**, 54788-74-8; **17**, 39921-29-4; **22**, 31444-22-1; **23**, 31444-23-2.

References and Notes

(1) C. W. Jefford and K. C. Ramey, *Tetrahedron*, **24**, 2927 (1968).
(2) For leading references, see (a) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Oxford, 1969; (b) J. L. Marshall and S. R. Walter, *J. Am. Chem. Soc.*, **96**, 6358 (1974).
(3) **1**, K. B. Wiberg and B. A. Hess, Jr., *J. Org. Chem.*, **31**, 2250 (1966); **2–4**, **9**, **12–14**, W. C. Agosta and S. Wolff, *ibid.*, **40**, 1027 (1975); **8**, **10**, S. Wolff and W. C. Agosta, *ibid.*, **38**, 1694 (1973); **11** and **17**, S. Wolff, W. L. Schreiber, A. B. Smith, III, and W. C. Agosta, *J. Am. Chem. Soc.*, **94**, 7797 (1972).
(4) S. Wolff, unpublished work in this laboratory; similar photochemical reactions lead to **11** and **17** (see ref 3).
(5) D. G. Farnum and G. Mehta, *J. Am. Chem. Soc.*, **91**, 3256 (1969).
(6) Direct evidence for J_{NK} is seen in labeled **17**, in which H_K is replaced by deuterium. In this compound H_N appears as a simple doublet, J_{NX} = 17 Hz: S. Wolff and W. C. Agosta, *J. Chem. Soc., Chem. Commun.*, 502 (1973).
(7) M. Barfield and D. M. Grant, *J. Am. Chem. Soc.*, **85**, 1899 (1963). For examples involving cyclic ketones, see N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, pp 57–61.
(8) In the spectra of *exo*- and *endo*-bicyclo[3.2.1]bicyclooctan-6-ol (**20** and **21**), as well as the derived acetates and tosylates, the C(6) proton also appears at lower field when exo: R. A. Appleton, J. C. Fairlee, R. McCrindle, and W. Parker, *J. Chem. Soc. C*, 1716 (1968).
(9) J. I. Musher, *Mol. Phys.*, **6**, 93 (1963); W. D. Kumler, J. N. Shoolery, and F. V. Brutcher, Jr., *J. Am. Chem. Soc.*, **80**, 2533 (1958); T. J. Flautt and W. F. Erman, *ibid.*, **85**, 3212 (1963); K. Tori, Y. Hamashima, and A. Takamizawa, *Chem. Pharm. Bull.*, **12**, 924 (1964); P. V. Demarco, D. Doddrell and E. Wenkert, *Chem. Commun.*, 1418 (1969).
(10) A. Segre and J. I. Musher, *J. Am. Chem. Soc.*, **89**, 706 (1967); D. K. Dalling and D. M. Grant, *ibid.*, **89**, 6612 (1967).
(11) S. A. Monti and S.-S. Yuan, *J. Org. Chem.*, **36**, 3350 (1971). We thank Professor Monti for a generous gift of **22**.
(12) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972).

Solid Phase Phosphorus Reagents. Conversion of Alcohols to Alkyl Chlorides[1]

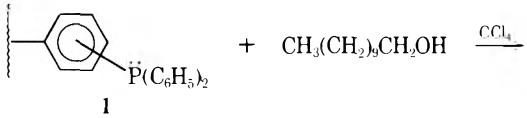
Steven L. Regen* and Dan P. Lee

Department of Chemistry, Marquette University, Milwaukee, Wisconsin 53233

Received February 6, 1975

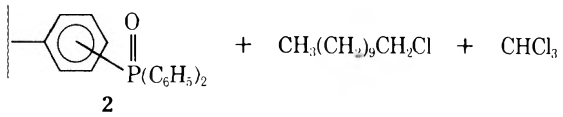
The reaction of triphenylphosphine with primary and secondary alcohols in carbon tetrachloride constitutes a mild and efficient method for conversion of the alcohols into the corresponding alkyl chlorides.[2]

We wish to describe a modification of the above reaction which requires only a filtration and evaporation process for product isolation. Our method is based upon the use of the polystyryl-diphenylphosphine resin 1 as the phosphorus reagent.[3,4] The convenience afforded by the use of 1 is demonstrated by the conversion of 1-undecanol to 1-chloroundecane. After heating a carbon tetrachloride solution of 1-undecanol for 2 hr at 80° in the presence of an excess of 1, the oxidized phosphine polymer, 2, was filtered. Solvent containing chloroform was then removed under reduced pressure, leaving a 99% isolated yield of 1-chloroundecane as a colorless liquid which was spectroscopically identical with an authentic sample.



1

polystyryl-diphenylphosphine-2% divinylbenezene



2

Further examples of the use of 1 are illustrated in Table I. Heitz has recently reported that polymeric phosphine oxides similar to 2 can be readily reduced to the phosphine form with trichlorosilane.[5] We have found the reduction of 2 to 1 feasible using similar procedures.

The advantages of this method for the conversion of alcohols to alkyl chlorides lie in its simplicity, its ability to be carried out under neutral pH, and its facile regeneration of the polymer reagent.

Experimental Section[6]

General Methods. Unless stated otherwise, all reagents were obtained commercially and were used without further purification. Cross-linked polystyrene beads (2% divinylbenzene, 200–400 mesh) were obtained from Bio-Rad Laboratories and were used without further purification. Chlorodiphenylphosphine (Aldrich Chemical Co.) was distilled before use. Trichlorosilane (Aldrich Chemical Co.) was used without purification. Tetrahydrofuran and benzene were dried by distillation from sodium and benzophenone under a nitrogen atmosphere. Carbon tetrachloride (spectrophotometric grade, Aldrich Chemical Co.) was dried by passage through a short column of alumina. All glassware was oven dried (100°) prior to use. Elemental analyses were performed by Midwest Microlab, Indianapolis, Ind.

Bromination of Cross-Linked Polystyrene. Cross-linked polystyrene (2% divinylbenzene, 200–400 mesh) was brominated employing a procedure identical with that described by Relles.[4] Elemental analysis indicated that 71% of the phenyl rings contained bromine (Anal. Found: Br, 35.53).

Polystyryl-diphenylphosphine (1). Lithium wire (9.8 g, 1.4 mol, cut into 0.25-in. lengths) was placed in a 500-ml round-bottomed flask equipped with a No-Air stopper and a Teflon-coated magnetic stirring bar. The flask was thoroughly degassed under a stream of nitrogen and a dry solution of 100 g (0.55 mol) of chlorodiphenylphosphine in 250 ml of tetrahydrofuran was added via forced siphon through a stainless steel cannula under a nitrogen atmosphere. The mixture was stirred for 12 hr at room temperature, and the liquid phase was transferred via cannula into a 500-ml round-bottomed flask equipped with a No-Air stopper and Teflon-coated magnetic stirring bar which contained a degassed mixture of 50 g of 2% cross-linked brominated polystyrene (71% ring substitution) preswelled in 250 ml of tetrahydrofuran. The mixture was stirred for 24 hr at room temperature, hydrolyzed with degassed acetone–water (3:1), and filtered, and the resin was then washed with water, acetone, chloroform, benzene, and anhydrous ether. The polymer beads were dried under vacuum (6 hr, 100°, 0.05 mm). Elemental analysis indicated that 79% of the phenyl rings of the polymer backbone contained diphenylphosphine groups (Anal. Found: P, 9.87).[7,8]

General Procedure for Small-Scale Reactions. Procedures similar to that described for the conversion of 1-octanol to 1-chlorooctane were followed for all of the small-scale reactions described in Table I. A mixture of 65 mg (0.5 mmol) of 1-octanol, 200 mg (0.64 mmol of phosphorus) of 1, 2 ml of carbon tetrachloride, and an internal standard were placed in a 5-ml round-bottomed flask equipped with a reflux condenser and a Teflon-coated magnetic stirring bar. The flask was maintained under a nitrogen atmosphere, and was placed in an oil bath (80°) for 2 hr, withdrawn, and cooled. The liquid phase was analyzed by GLC using a Carbowax on Chromosorb P column.

Conversion of 1-Undecanol to 1-Chloroundecane. A mixture of 3.10 g (18 mmol) of 1-undecanol, 10.0 g (32 mmol of phosphorus) of 1, and 50 ml of carbon tetrachloride was placed in a 100-ml round-bottomed flask equipped with a reflux condenser and a Teflon-coated magnetic stirring bar. The flask was maintained under a nitrogen atmosphere and was placed in an oil bath (80°) for 2 hr, withdrawn, cooled to room temperature, and filtered. The resin was washed with 75 ml of carbon tetrachloride and the combined filtrate was concentrated by rotary evaporation, leaving a colorless liquid which was found to be 1-chloroundecane (3.42 g, 99%) having NMR and ir spectra indistinguishable from those of an authentic sample.

Regeneration of 1 from 2. Polymer 2 (5.0 g, 16 mmol of phosphorus) was placed in a 100-ml round-bottomed flask equipped with a No-Air stopper and Teflon-coated magnetic stirring bar. A solution of trichlorosilane (13.0 g, 96 mmol) in 20 ml of benzene was added to the flask via syringe followed by 7.2 g (71 mmol) of triethylamine while stirring in an ice–water bath. The flask was fitted with a reflux condenser and heated for 170 hr at 80°. The mixture was filtered and the beads were washed successively with benzene and tetrahydrofuran. The beads were then added to 250 ml of

Table I
Conversion of Alcohols to Alkyl Chlorides[a]

Alcohol	Registry no.	Alkyl Chloride	Registry no.	Yield,[b] %
1-Decanol	112-30-1	1-Chlorodecane	1002-69-3	89
1-Undecanol	112-42-5	1-Chloroundecane	2473-03-2	80 (99)[c]
1-Dodecanol	112-53-8	1-Chlorododecane	112-52-7	71
1-Octanol	111-87-5	1-Chlorooctane	111-85-3	90
Benzyl alcohol	100-51-6	Benzyl chloride	100-44-7	99
Cyclohexanol	108-93-0	Chlorocyclohexane	542-18-7	60
Cycloheptanol	502-41-0	Chlorocycloheptane	2453-46-5	92

[a] Unless noted otherwise, reactions were carried out using procedures similar to that described for the chlorination of 1-octanol. [b] Yields based on the alcohol were obtained by GLC. [c] Isolated yield from a large-scale reaction.

a 20% sodium hydroxide solution, stirred for 4 hr at room temperature, filtered, and added to 500 ml of 0.5 *N* sodium hydroxide in tetrahydrofuran. After stirring for an additional 4 hr, the resin was filtered, washed with tetrahydrofuran, and dried under vacuum (6 hr, 100°, 0.1 mm). Reaction of regenerated **1** with 1-undecanol using the small-scale procedure produced a 76% yield of 1-chloroundecane.

Acknowledgment. We are grateful to Professor Heitz for communicating valuable experimental procedures to us prior to publication.

Registry No.—Polystyrene, 9003-53-6; chlorodiphenylphosphine, 1079-66-9.

References and Notes

(1) Supported by the Research Corporation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Marquette University Committee on Research.
(2) J. B. Lee and T. J. Nolan, *Can. J. Chem.* **44**, 1331 (1966); J. Hooz and S. S. H. Gilani, *ibid.*, **46**, 86 (1968).
(3) Similar solid-phase techniques have been successfully applied to Wittig reagents for the facile removal of triphenylphosphine oxide: W. Heitz and R. Michels, *Angew. Chem., Int. Ed. Engl.* **11**, 298 (1972); S. V. McKinley and J. V. Rakshys, Jr., *J. Chem. Soc., Chem. Commun.*, 134 (1972); F. Camps, J. Castells, J. Font, and F. Vela, *Tetrahedron Lett.*, 1715 (1971).
(4) Relles has recently reported the preparation of certain polymer-supported trisubstituted phosphine dichlorides. Although such reagents are capable of converting alcohols to alkyl chlorides, they necessarily liberate hydrogen chloride: H. M. Relles and R. W. Schluenz, *J. Am. Chem. Soc.*, **96**, 6469 (1974).
(5) W. Heitz and R. Michels, *Justus Liebigs Ann. Chem.*, 227 (1973).
(6) All ^{1}H NMR spectra were recorded using a Varian A-60 spectrometer. Product mixtures were analyzed by GLC on a Hewlett-Packard Model 5711A flame ionization instrument.
(7) Phosphorus analyses for such samples were usually high and were not lowered by extensive washing.
(8) In order to determine the number of reactive phosphine sites along the polymer backbone, we treated **1** with 2 equiv of benzyl alcohol (based upon phosphorus content) using the procedure described for the small-scale reactions. Analysis of the benzyl chloride produced indicated that 100% of the phosphorus present was active in the halogenation reaction.

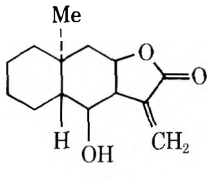
Oxygenated α-Methylene-γ-butyrolactones[1]

Paul A. Grieco,*[2] Nebojsa Marinovic, and Masaaki Miyashita

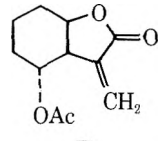
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received December 26, 1974

Synthetic efforts to date[3] have concentrated on the construction of α-methylene-γ-butyrolactones with almost no attention being devoted to the homoallylic oxygenated α-methylene-γ-butyrolactones. Two recent publications have reported syntheses of the oxygenated α-methylene lactones I[4] and II.[5] Interest in such oxygenated α-methylene lactones stems from recent studies[6] which have demonstrated that the presence of a lipophilic, conjugated ester or halo ester situated homoallylic to the exocyclic double bond of many naturally occurring α-methylene-γ-butyrolactones contributes to the enhancement of cytotoxic activity. Such oxygenated α-methylene lactone structural types are commonly found fused to six-, seven-, and ten-membered rings.[3]



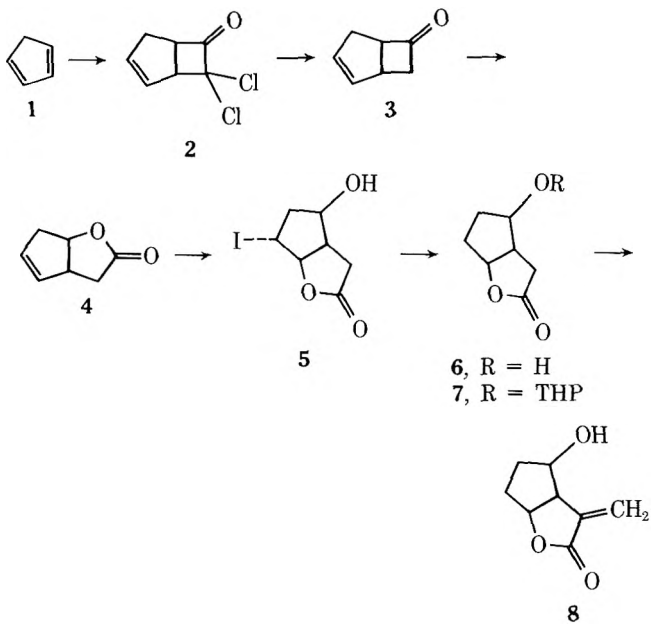
I



II

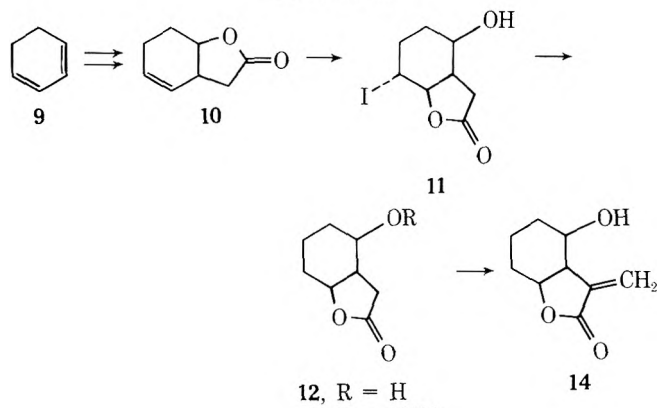
We wish to detail here a method for the construction of oxygenated α-methylene-γ-butyrolactones fused to five- and six-membered rings of type I. The method is applicable to other ring systems as well.[7] As illustrated in Scheme I, the approach involves the position-specific addition of dichloroketene[8] to an appropriate diene followed by dechlorination. Baeyer–Villiger oxidation results in formation of an olefinic γ-butyrolactone, which when subjected to the conditions of saponification and subsequent iodolactonization results in formation of the oxygenated γ-butyrolactone structural unit. Deiodination is cleanly carried out on the free hydroxy lactone followed by methylenation of the γ-lactone ring.

Scheme I



Addition of dichloroketene to cyclopentadiene followed by dechlorination and Baeyer–Villiger oxidation as previously described[9] results in the formation of the bicyclic lactone **4**. Saponification of **4** in water followed by neutralization with carbon dioxide and treatment with potassium triiodide at 5° causes iodolactonization with formation of **5** (95%). Deiodination of **5** using tributyltin hydride (initiation with azobisisobutyronitrile) in benzene at an elevated temperature affords hydroxy lactone **6** (91%). Protection of the free hydroxyl of **6** as its tetrahydropyranyl ether **7** followed by methylenation employing the α-hydroxymethylation procedure for lactone enolates[10] produces the oxygenated α-methylene-γ-butyrolactone **8**. During the elimination (anhydrous pyridine, ca. 130°) of the mesylate derived from the hydroxymethylated derivative of lactone **7**, simultaneous formation of the α-methylene unit and cleavage of the tetrahydropyranyl ether occur.[11]

Scheme II



The application of this sequence of reactions to the synthesis of **14** was also realized (Scheme II). Transformation of cyclohexadiene (**9**) to the bicyclic lactone **10** was carried out in ca. 70% overall yield by addition of dichloroketene followed by dechlorination and Baeyer–Villiger oxidation.[12] Conversion of **10** to the iodolactone **11** via the iodolactonization reaction (95%) and subsequent deiodination (99%) affords the oxygenated γ-butyrolactone **12**. Tetrahydropyranylation of **12** (98%) followed by α-hydroxymethylation (74%), mesylation (99%), and elimination (83%) affords directly the oxygenated α-methylene-γ-butrolactone **14**.

Experimental Section

Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting and boiling points are uncorrected. The following spectrometers were used: nuclear magnetic resonance (NMR), Varian T-60 and A-60D (in δ units, with Me_4Si as internal reference in CCl_4 unless stated otherwise); infrared (ir), Perkin-Elmer Model 247 and Beckman IR-8; mass spectrometer (MS), LKB-9000.

***cis,cis*-2,5-Dihydroxy-*trans*-3-iodocyclopentylacetic Acid Lactone (5).** Lactone **4** (1.00 g, 8.08 mmol) was dissolved in an aqueous solution of sodium hydroxide (880 mg in 40 ml of water). After ca. 20 min the resulting homogeneous solution was cooled to 0° and carbon dioxide was introduced for ca. 15 min until pH 7 was reached. A solution of potassium iodide (12.0 g, 72 mmol) and iodine (6.10 g, 24 mmol) in water (20 ml) was added all at once to the neutralized solution cooled to 0°. The reaction was allowed to stir for 24 hr at 0–5°. The reaction was quenched by the addition of methylene chloride and solid sodium sulfite. The resulting decolorized solution was saturated with potassium sodium tartrate and extracted exhaustively with methylene chloride. The combined organic layers were washed with saturated brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Passage of the crude iodolactone through a short column of silica gel (benzene) afforded 2.05 g (95%) of **5** which was homogeneous by TLC [benzene–ethyl acetate (1:1)]: ir ($CHCl_3$) 3425, 1755 cm^{-1}; NMR ($CDCl_3$) 5.02 (m, 1 H), 4.38 ppm (m, 2 H).

***cis,cis*-2,5-Dihydroxycyclopentylacetic Acid Lactone (6).** To a solution of iodolactone **5** (1.42 g, 5.32 mmol) in 60 ml of dry benzene heated to 50° was added 2.56 g (8.78 mmol) of freshly prepared tri-*n*-butyltin hydride[13] and 65 mg of azobisisobutyronitrile. The mixture was stirred at 50° for 1 hr. Removal of the benzene on a rotary evaporator afforded the crude hydroxylactone **6**, which was purified by passage through a column of silica gel (40 g). Elution with benzene–ethyl acetate gave 688 mg (91%) of pure **6**: ir (film) 3450, 1755 cm^{-1}; NMR ($CDCl_3$) 4.90 (m, 1 H, CHOCO–), 4.25 ppm (m, 1 H, CHOH); MS *m/e* 142.

Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.17; H, 7.16.

***cis*-2-Hydroxy-*cis*-5-tetrahydropyranyloxycyclopentylacetic Acid Lactone (7).** A solution of hydroxylactone **6** (500 mg, 3.52 mmol) and dihydropyran (443 mg, 5.28 mmol) in dry methylene chloride (8.0 ml) containing *p*-toluenesulfonic acid (2.5 mg) was stirred at 0° for 25 min. The reaction was quenched by the addition of six drops of pyridine. The mixture was diluted with methylene chloride and washed with brine and the resulting organic phase was dried over anhydrous magnesium sulfate. Concentration of the organic layer in vacuo afforded the crude product (**7**), which was passed through a short column of silica gel, affording 790 mg (99%) of pure **7** as a colorless oil. An analytical sample was prepared by distillation [114° (0.14 mmHg)].

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.83; H, 7.82.

2-(*cis,cis*-2,5-Dihydroxycyclopentyl)propenoic Acid Lactone (8). A solution of lactone **7** (468 mg, 2.07 mmol) in 3.0 ml of anhydrous THF (freshly distilled from lithium aluminum hydride) was added dropwise via a mechanically driven syringe over a period of 40 min to a cooled (−78°) solution of lithium diisopropylamide (LDA) in anhydrous THF [prepared from diisopropylamine (333 mg, 3.3 mmol) and 2.0 ml of 1.51 *M* *n*-butyllithium in 8.0 ml of THF]. After enolate formation was complete, the reaction mixture was warmed to −23° and the lactone enolate was trapped with formaldehyde. Paraformaldehyde (700 mg, dried over P_2O_5 under vacuum) was depolymerized at 150–160° and the monomeric formaldehyde was carried by a stream of nitrogen (flow rate 200 ml/min) into the reaction vessel. The reaction was terminated 40 min after complete depolymerization by addition of a saturated solution of ammonium chloride. The product was extracted with ethyl acetate. The combined organic extracts were washed with water, saturated sodium bicarbonate, and saturated brine. Drying over anhydrous magnesium sulfate followed by removal of the solvent on a rotary evaporator afforded 526 mg (99%) of crude hydroxymethyl lactone. After purification by column chromatography on silica gel (32 g) using ethyl acetate–benzene there was obtained 414 mg (78%) of pure α-hydroxymethyl lactone [ir (film) 3430, 1760 cm^{-1}].

To a solution of the above α-hydroxymethyl lactone (280 mg, 1.09 mmol) in 5.0 ml of dry pyridine cooled to 0° was added methanesulfonyl chloride (229 mg, 2.0 mmol). After 15 hr at 5°, the reaction mixture was warmed to room temperature and the solvent was removed in vacuo (high vacuum pump). The product was dissolved in ethyl acetate and was washed with brine (saturated). Concentration of the dried (magnesium sulfate) organic phase yielded 331 mg (90%) of crude mesylate (homogeneous on TLC analysis) which was immediately used in the next reaction.

A solution of crude mesylate (320 mg, 0.96 mmol) in 5.0 ml of dry pyridine was refluxed for 6 hr (bath temperature 130°). After removal of pyridine in vacuo (high vacuum pump), the resulting residue was taken up in ethyl acetate and washed with saturated brine. Concentration of the dried (magnesium sulfate) organic layer followed by removal of solvent on a rotary evaporator afforded 145 mg (99%) of crude **8**. Purification by column chromatography on silica gel yielded 103 mg (70%) of pure crystalline hydroxy-α-methylene lactone **8**: mp 79.5° (benzene–ethyl acetate); ir (KBr) 3344, 3003, 1740, 1661 cm^{-1}; NMR ($CDCl_3$) 6.38 (d, J = 2.5 Hz, 1 H), 5.78; (d, J = 2.5 Hz, 1 H), 4.94 (m, 1 H, –CHOCO), 4.25 (m, 1 H, –CHOH), 3.42 (m, 1 H, –CHC=), 2.58 ppm (s, 1 H, OH); MS *m/e* 152.

Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.10; H, 6.42.

In addition, chromatography yielded 9 mg (6%) of the THP ether of **8**.

***cis,cis*-2,6-Dihydroxy-*trans*-3-iodocyclohexylacetic Acid Lactone (11).** Lactone **10** (544 mg, 4.0 mmol) was dissolved in 15.0 ml of water containing 432 mg (10.8 mmol) of sodium hydroxide. After stirring at room temperature for 15 min, the homogeneous solution was cooled to 0° and the excess base was neutralized with carbon dioxide until pH 7 was reached (approximately 10 min). To the cooled, neutralized solution was added a solution of potassium iodide (5.98 g, 36 mmol) and iodine (3.05 g, 12.0 mmol) in 7.5 ml of water. After stirring at 0–5° for 23 hr, methylene chloride was added to the reaction mixture followed by solid sodium sulfite to decolorize the solution. The aqueous layer was saturated with potassium sodium tartrate and then extracted four times with methylene chloride. The combined organic layers were washed with aqueous sodium thiosulfate solution, water, and saturated brine. Removal of the solvent in vacuo gave 1.17 g of a colorless oil which crystallized on standing. Recrystallization from benzene–ethyl acetate gave 1.07 g (95.5%) of hydroxy iodolactone **11**: mp 95–97° dec; NMR ($CDCl_3$) 4.61 (m, 1 H), 4.38 (m, 1 H), 4.10 ppm (m, 1 H).

Anal. Calcd for $C_8H_{11}IO_3$: C, 34.06; H, 3.93. Found: C, 34.18; H, 4.03.

***cis,cis*-2,6-Dihydroxycyclohexylacetic Acid Lactone (12).** To a solution of iodolactone **11** (392 mg, 1.40 mmol) in 6.0 ml of dry benzene warmed to 50° was added tri-*n*-butyltin hydride[13] (610 mg, 2.10 mmol) and azobisisobutyronitrile (3.0 mg). The mixture was stirred at 50° for 40 min. Removal of the solvent in vacuo gave an oil which was chromatographed on silica gel (14.0 g). Benzene–ether (3:1) eluted the hydroxylactone **12** (219 mg, 99%) as a colorless oil: ir ($CHCl_3$) 3610, 3450, 1762 cm^{-1}; NMR ($CDCl_3$) 4.58 (m, 1 H, –CHOCO), 3.98 ppm (m, 1 H, CHOH). An analytical sample was prepared by distillation [115° (bath temperature) (0.35 mmHg].

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.31; H, 7.60.

***cis*-2-Hydroxy-*cis*-6-tetrahydropyranyloxycyclohexylacetic Acid Lactone (13).** A solution of hydroxylactone **12** (234 mg, 1.5 mmol), *p*-toluenesulfonic acid (5 mg), and dihydropyran (189 mg, 2.25 mmol) in 7.0 ml of dry methylene chloride was stirred for 40 min at 0°. The reaction was quenched by the addition of 5 drops of pyridine and then washed with saturated brine. Removal of the solvent in vacuo gave 414 mg of crude THP ether which was chromatographed on silica gel (25 g). Elution with benzene–ether (8:1) afforded the THP ether **13** (355 mg, 99%) as a colorless oil. An analytical sample was prepared by distillation [125–130° (bath temperature) (0.4 mmHg)].

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.12; H, 8.56.

2-(*cis,cis*-2,6-Dihydroxycyclohexyl)propenoic Acid Lactone (14). A solution of lactone **13** (240 mg, 1.0 mmol) in 4.0 ml of dry THF was added slowly over a period of 1 hr to a cooled (−78°) solution of LDA under nitrogen. LDA was prepared from diisopropylamine (131 mg, 1.30 mmol) and *n*-butyllithium (0.81 ml of 1.6 *M* solution in hexane) in THF (3.5 ml) cooled to −78°. After enolate formation was complete, the reaction mixture was warmed to −30° and formaldehyde was passed into the reaction vessel via a stream of nitrogen (flow rate 200 ml/min) by heating paraformaldehyde (450 mg, 15.0 mmol) at 155° until depolymerization was complete. Stirring was continued for an additional 1.5 hr. The reaction was quenched by the addition of saturated aqueous ammonium chloride. The solvent was removed under reduced pressure on a rotary evaporator and the remaining residue was dissolved in methylene chloride (40 ml). The organic solution was washed with water and saturated brine. Evaporation of the solvent in vacuo gave an oil (381 mg) which was chromatographed on silica gel (13 g). Benzene–ether (15:1) eluted pure hydroxymethylated lactone (200 mg, 74%). In addition 30 mg of starting lactone was recovered.

A solution of the above pure hydroxymethylated lactones (189 mg, 0.7 mmol) and methanesulfonyl chloride (96.6 mg, 0.84 mmol) in dry pyridine (3.0 ml) was stirred at 3° for 16 hr. The solvent was evaporated in vacuo and the residue was dissolved in ethyl acetate. The organic solution was washed with brine and dried (magnesium sulfate). Removal of the solvent afforded 250 mg (100%) of mesylate which was homogeneous by TLC analysis.

A solution of the crude mesylate (244 mg, 0.7 mmol) in 4.0 ml of dry pyridine was heated at 135° (bath temperature) under nitrogen. After 6 hr, the solvent was evaporated in vacuo (high vacuum pump). The residue was dissolved in methylene chloride and was washed with saturated brine. After drying and removal of the solvent, there was obtained 126 mg of an oil which was chromatographed on silica gel (6 g). Benzene–ether (20:1) eluted the THP ether of lactone **14** (40 mg, 23%). Benzene–ether (15:1) eluted the oxygenated α-methylene lactone **14** (71 mg, 60%): ir (film) 3450, 1760, 1668 cm^{-1}; NMR ($CDCl_3$) 6.24 (d, J = 2 Hz, 1 H, $=CH_2$), 5.92 (d, J = 2 Hz, 1 H, $=CH_2$), 4.62 (m, 1 H, CHOCO–), 4.08 (m, 1 H, –CHOH), 3.22 (m, 1 H, –CHC=)]. An analytical sample was prepared by distillation [115° (bath temperature) (0.35 mmHg)].

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.19; H, 7.26.

A solution of the THP ether of lactone **14** (40 mg, 0.16 mmol) in 2.0 ml of methanol containing *p*-toluenesulfonic acid (1.0 mg) was stirred at room temperature for 6 hr. The reaction was quenched with pyridine (2 drops). The solvent was evaporated in vacuo, affording 29 mg of an oil which was through a short column of silica gel. Elution with benzene–ether (1:1) yielded pure oxygenated α-methylene lactone **14** (27 mg, 100%).

Acknowledgment. This investigation was supported by a Public Health Service Research Grant (RO1 CA 13689-03) from the National Cancer Institute and in part by Eli Lilly and Co. We thank F. Okuniewicz for mass spectral data and Ljiljana Marinovic for experimental assistance.

Registry No.—**4**, 26054-46-6; **5**, 54911-58-9; **6**, 54911-59-0; **7**, 54911-60-3; **8**, 54911-61-4; **10**, 34896-02-1; **11**, 54911-62-5; **12**, 54911-63-6; **13**, 54911-64-7; **14**, 54911-65-8; 2-hydroxy-5-tetrahydropyranyloxycyclopentylacetic acid α-methylhydroxy lactone, 54911-66-9; 2-hydroxy-5-tetrahydropyranyloxycyclopentylacetic acid α-methylhydroxymesylate lactone, 54911-67-0; 2-hydroxy-6-tetrahydropyranyloxycyclohexylacetic acid α-methylhydroxy lactone, 54911-68-1; 2-hydroxy-6-tetrahydropyranyloxycyclohexylacetic acid α-methylhydroxymesylate lactone, 54911-69-2.

References and Notes

(1) α-Methylene Lactones. Part IX. For the previous paper in this series see P. A. Grieco and M. Miyashita, *J. Org. Chem.*, **40**, 1181 (1975).
(2) Fellow of the Alfred P. Sloan Foundation, 1974–1976.
(3) For a recent review on α-methylene lactone synthesis see P. A. Grieco, *Synthesis*, 67 (1975).
(4) P. A. Grieco and K. Hiroi, *Tetrahedron Lett.*, 3467 (1974).
(5) F. E. Ziegler, A. F. Marino, O. A. C. Petroff, and W. L. Stadt, *Tetrahedron Lett.*, 2035 (1974).
(6) J. L. Hartwell and B. J. Abbott, *Adv. Pharmacol. Chemother.*, **7**, 117 (1969); K.-H. Lee, E.-S. Huang, C. Piantadosi, J. S. Pagno, and T. A. Geissman, *Cancer Res.*, **31**, 1649 (1971); S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971); K.-H. Lee, R. Meck, C. Piantadosi, and E.-S. Huang, *J. Med. Chem.*, **16**, 299 (1973).
(7) P. A. Grieco and N. Marinovic, unpublished results.
(8) H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain, and E. J. Gaughan, *J. Am. Chem. Soc.*, **87**, 5257 (1965); L. Ghosez, R. Montaigne, and P. Mollet, *Tetrahedron Lett.*, 135 (1966).
(9) P. A. Grieco, *J. Org. Chem.*, **37**, 2363 (1972); E. J. Corey, Z. Arnold, and J. Hutton, *Tetrahedron Lett.*, 307 (1970).
(10) P. A. Grieco and K. Hirol, *J. Chem. Soc., Chem. Commun.*, 1317 (1972).
(11) We have observed that tetrahydropyranyl ethers can be efficiently cleaved in pyridine with either methanesulfonic acid (i) or *p*-toluenesulfonic acid (ii). For example, treatment of **13** with i (2.0 equiv) in pyridine for 6 hr at 135° results in a 91% yield of **12**. Utilization of ii under identical conditions affords **12** in 82% yield. Heating in pyridine for 6 hr at 135° without added i or ii results in complete recovery of starting material. We have also found that **13** can be quantitatively cleaved with a catalytic amount of pyridinium *p*-toluenesulfonate in absolute ethanol at 55° for 3 hr.
(12) E. J. Corey and T. Ravindranathan, *Tetrahedron Lett.*, 4753 (1971).
(13) H. G. Kuivila and O. F. Beumel, Jr., *J. Am. Chem. Soc.*, **83**, 1246 (1961).

Reaction of Benzoins with Hexamethylphosphoric Triamide. A Convenient Synthesis of 2,3,5,6-Tetraarylpyridines[1]

Richard S. Monson* and Adina Baraze

Department of Chemistry, California State University, Hayward, California 94542

Received February 11, 1975

In the course of our investigation[2] on the reaction between hexamethylphosphoric triamide (HMPT) and benzyl alcohols to give *N,N*-dimethylbenzylamines, we treated benzoin (**1a**) with HMPT in an attempt to prepare the corresponding α-dimethylaminodeoxybenzoin (**2**). After a 30-min reflux, the solution was subjected to a water work-up and an 18% yield of 2,3,5,6-tetraphenylpyridine (**3a**) was isolated (Scheme I). The identity of the product was verified by comparison with a sample prepared by the published method.[3]

The reaction of benzoin with ammonium acetate in acetic acid to give 2,3,5,6-tetraphenylpyrazine is well known,[4a] but the conversion of benzoins to substituted pyridines requires the incorporation at the 4 position of one additional carbon atom whose source is not immediately apparent, although a related reaction of simple ketones has been the

Scheme I

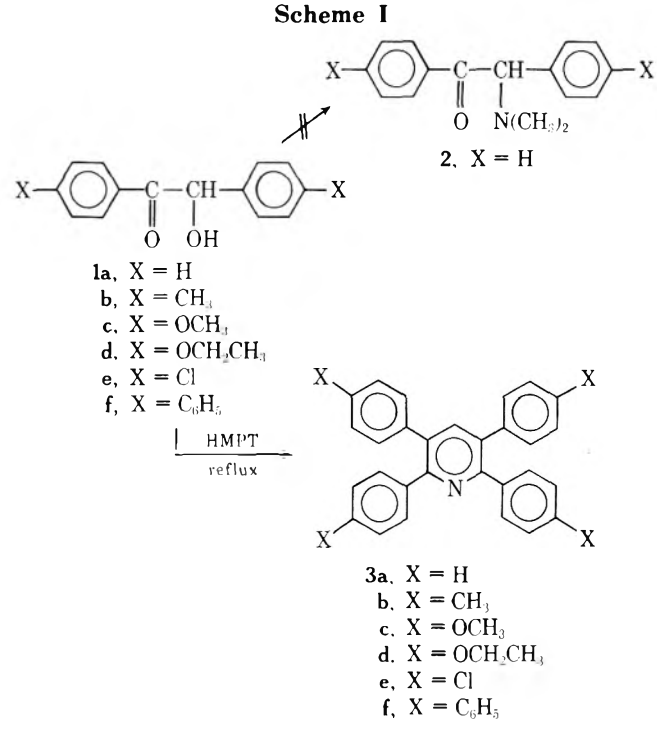


Table I
Tetraarylpyridines (3) from the Reaction of Benzoins with Refluxing HMPT

Benzoin	Reflux time, min	Product	Yield, %	Mp, °C	Anal., % Calcd	Anal., % Found
1a	30	3a	18	238–239[a]		
1b	40	3b	18	278	C, 90.2; H, 6.6; N, 3.2	C, 90.1; H, 6.7; N, 3.2
1c	60	3c	10	259–260	C, 78.7; H, 5.7; N, 2.8	C, 78.9; H, 5.9; N, 3.1
1d	60	3d	19	250	C, 79.4; H, 6.6; N, 2.5	C, 79.2; H, 6.6; N, 2.7
1e	15	3e	16	285–286	C, 66.8; H, 3.3; N, 2.7	C, 66.9; H, 3.3; N, 2.8
1f	30	3f	18	>350	C, 92.5; H, 5.4; N, 2.0	C, 92.3; H, 5.2; N, 2.3

[a] Lit.[5] mp 240–241°.

subject of some speculation.[4b] In any case, an investigation of the scope of the reaction seemed appropriate, since a convenient synthesis of these tetraarylpyridines is not available.

The reaction of substituted benzoins with refluxing HMPT proved to be quite general. A variety of 4,4′-disubstituted benzoins (1) underwent the conversion to the corresponding tetraarylpyridines (3) smoothly in yields ranging from 10 to 19%, as shown in Table I. One merely heats the benzoin in an excess of HMPT until the pot temperature just exceeds 245°. The solution at this point is usually a clear dark orange. After the work-up, the crude reaction product weighs about 50% more than the starting benzoin. Infrared examination of this product indicates the presence of the product pyridine, some unreacted benzoin (<10%), and organophosphorus compounds, although a detailed characterization of the components of this mixture has not been carried out. Tetraphenylpyrazine was not found in the crude reaction product from benzoin by comparison with the spectrum of an authentic sample.[4] Treatment of the crude reaction product with ethanol results in the rapid precipitation of the tetraarylpyridine, which is easily isolated by filtration.

If the reaction mixture is heated much above 245°, considerable darkening occurs, and the yield of tetraarylpyridine is diminished. A shorter reflux period results in much unreacted benzoin with organophosphorus compounds being the major products detectable by infrared.

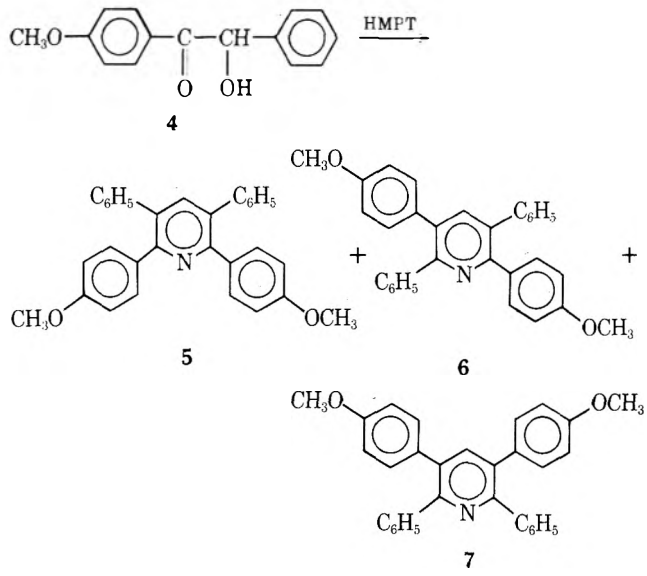
α-Pyridoin, tropolone, and α-hydroxyacetophenone all failed to give isolable products. These latter compounds are apparently sensitive to hot HMPT and decompose well below the reflux temperature. 2-Hydroxycyclohexanone reacted rapidly with refluxing HMPT, affording 2-dimethylaminocyclohexanone in 59% yield.

The reaction between 4-methoxybenzoin (4) and HMPT (45-min reflux) gave a 16% yield of product which after two recrystallizations from ethanol–benzene had a melting point of 178–194°. Its spectral properties and elemental analysis were consistent with a di(*p*-methoxyphenyl)diphenylpyridine, but its melting point suggested that it was a mixture, possibly arising as shown in Scheme II. Column chromatography (neutral alumina) of the mixture afforded three sharp-melting fractions, as well as small amounts of lower melting intermediate fractions. The melting points of the three fractions (in order of elution) follow: A, 212–214°; B, 220–221°; C, 197–198°.

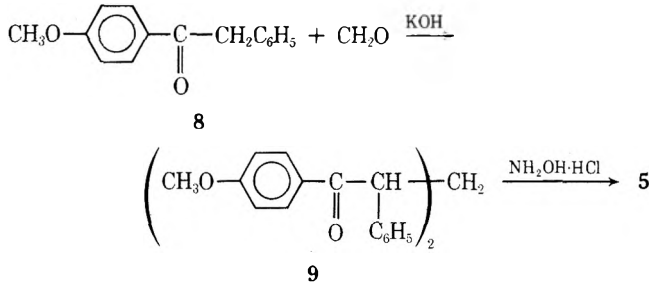
In order to clarify these results, we undertook the synthesis of authentic **5** by an unambiguous route employing as the starting material benzyl *p*-methoxyphenyl ketone (8). The procedure was adapted from the published synthesis of **3a**[3] (Scheme III). The melting point of **5** proved to be 203–204°, and its ir and NMR spectra were virtually identical with those of the unchromatographed products of Scheme II.

Mixture melting points of authentic **5** with the chromatographic fractions A, B, and C gave the following results: A + **5**, mmp 180–200°; B + **5**, mmp 175–190°; C + **5**, mmp 198–203°. These results suggest that fraction C is identical with authentic **5** and that the product of the reaction of 4-methoxybenzoin with HMPT is indeed the mixture of compounds shown in Scheme II.

Scheme II



Scheme III



It appears, therefore, that the reaction proceeds through a symmetrical intermediate, and that for synthetic purposes, the reaction will give unambiguous products only when the starting benzoin is symmetrically substituted. Based on the fact that the dimethylamino group substitutes for hydroxyl in 2-hydroxycyclohexanone and in benzyl alcohols,[2] and on the fact that enamines are known to be produced by the reaction of ketones with HMPT,[6] we are led to suggest that the symmetrical intermediate is an enediamine such as $ArC(NMe_2)=C(NMe)_2Ar$.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are corrected. Infrared spectra were taken on a Perkin-Elmer Model 337 spectrophotometer. NMR spectra were recorded on a

Jeolco Model C-60 spectrometer with Me_4Si as internal standard. Microanalyses were performed by Chemical Analytical Services, University of California, Berkeley, Calif. Commercial HMPT was distilled before use, bp 120–122° (21 mm). Other compounds not described below were commercially available and were used without further purification.

Benzoins (1). Conventional procedures[7] were employed for the synthesis of the benzoins listed in Table I as well as 4-methoxybenzoin (**4**). 4,4'-Dichlorobenzoin could not be crystallized and was oxidized with nitric acid to the corresponding benzil.[8] Reduction of this benzil with sodium dithionite[9] afforded the expected 4,4'-dichlorobenzoin.

2,3,5,6-Tetraarylpyridines (3). General Procedure. The benzoin (0.05 mol) was refluxed with 35 ml of HMPT until the pot temperature just exceeded 245° (15–60 min as shown in Table I). After cooling, the clear, dark orange reaction mixture was poured into 150 ml of cold water and the resulting mixture was saturated with sodium chloride. This mixture was extracted three times with benzene. The benzene solution was washed twice with brine, dried (anhydrous sodium sulfate), and reduced in volume on a rotary evaporator, leaving a residue of oil and crystals. Ethanol (100 ml) was added to the residue and the solution was heated briefly on a steam bath. Crystallization followed upon cooling. The product was recrystallized from ethanol–benzene. For example, benzoin (**1a**, 10.6 g, 0.05 mol) treated as above affords 15.05 g of crude reaction product as a dark orange oil. The ir spectrum (film) of the oil shows bands at 5.96 (benzoin C=O), 7.04 (tetraphenylpyridine), and 7.6–8.0 μ (organophosphorus P=O). Addition of ethanol at room temperature followed by standing for several hours afforded 1.73 g (18%) of **3a** as a light yellow solid. Recrystallization from ethanol–benzene gave white product of the reported melting point.

Reaction of 2-Hydroxycyclohexanone with HMPT. 2-Hydroxycyclohexanone (0.05 mol) was refluxed with 35 ml of HMPT. Ten minutes after the onset of reflux, a volatile material had formed which was distilled from the reaction vessel. Water (200 ml) was added to the reaction vessel and distillation was continued until no more organic material steam distilled. The distillate was extracted with ether, the ethereal solution was dried (anhydrous sodium sulfate), and the ether was evaporated, affording 2-dimethylaminocyclohexanone in 59% yield. The ir and NMR spectra of the product were identical with those of an authentic sample. The picrate melted at 110–113° (lit.[10] mp 113–114°).

Reaction of 4-Methoxybenzoin (4) with HMPT. 4-Methoxybenzoin (**4**) was refluxed with HMPT and worked up in the same manner as described above. The product, after two recrystallizations from ethanol–benzene, had mp 178–194°. The ir and NMR spectra of the product were virtually identical with those of authentic **5**.

Anal. Calcd for $C_{31}H_{25}O_2N_2$: C, 84.0; H, 5.6; N, 3.1. Found: C, 83.7; H, 5.7; N, 3.1.

The product was chromatographed on neutral alumina. Petroleum ether–benzene (3:7) as eluent gave fractions A and B, and petroleum ether–benzene (1:4) gave fraction C. Small amounts of intermediate materials having depressed melting points were also obtained.

1,3-Di(*p*-methoxybenzoyl)-1,3-diphenylpropane (9). This compound was prepared by the method used by Carpenter[3] for an analogous compound. Thus, benzyl *p*-methoxyphenyl ketone[11] (**8**) was treated with aqueous formaldehyde and potassium hydroxide in ethanol at room temperature to give crude **9** in 63% yield. The product was recrystallized twice from ethanol: mp 150–151°; ir (film) 5.99 and 6.26 μ.

Anal. Calcd for $C_{31}H_{28}O_4$: C, 80.2; H, 6.0. Found: C, 80.3; H, 6.1.

2,6-Di(*p*-methoxyphenyl)-3,5-diphenylpyridine (5). This compound was prepared by the method used by Carpenter[3] for an analogous compound. Thus, **9** (1.0 g) and hydroxylamine hydrochloride (0.35 g) were dissolved in 40 ml of absolute ethanol and heated in a closed tube at 150° for 21 hr. Upon cooling, the mixture yielded 0.29 g of crude **5** which was recrystallized from benzene–ethanol: mp 203–204°; ir (film) 6.23 and 6.35 μ; NMR (CCl_4) δ 4.04 (s, 6, CH_3O), 7.02 (d, 4, J = 9 Hz), 7.61 (m, 11), 7.86 (d, 4, J = 9 Hz).

Anal. Calcd for $C_{31}H_{25}O_2N_2$: C, 84.0; H, 5.6; N, 3.1. Found: C, 84.0; H, 5.7; N, 3.1.

Registry No.—**1a**, 119-53-9; **1b**, 1218-89-9; **1c**, 119-52-8; **1d**, 53458-15-4; **1e**, 4254-20-0; **1f**, 5623-25-6; **3a**, 24301-97-1; **3b**, 54932-37-5; **3c**, 54932-38-6; **3d**, 54932-39-7; **3e**, 54932-40-0; **3f**, 54932-41-1; **4**, 4254-17-5; **5**, 54932-42-2; **8**, 1023-17-2; **9**, 54932-43-3; 2-hydroxycyclohexanone, 533-60-8; hexamethylphosphoric triamide, 680-31-9; 2-dimethylaminocyclohexanone, 6970-60-1; 2-dimethylaminocyclohexanone piciate, 54932-44-4.

References and Notes

(1) Previous papers in this series on reactions in HMPT are (a) R. S. Monson and A. Baraze, *Tetrahedron*, in press; (b) R. S. Monson and B. M. Broline, *Can. J. Chem.*, **51**, 942 (1973), and references cited therein.
(2) R. S. Monson and D. N. Priest, *Chem. Commun.*, 1018 (1971).
(3) H. Carpenter, *Justus Liebigs Ann. Chem.*, **302**, 223 (1898).
(4) (a) D. Davidson, M. Weiss, and M. Jelling, *J. Org. Chem.*, **2**, 328 (1937). (b) cf. ref 1a and 6c; see also G. R. Newkome and D. L. Fishel, *J. Org. Chem.*, **37**, 1329 (1972).
(5) V. J. Traynelis and R. H. Ode, *J. Org. Chem.*, **35**, 2207 (1970).
(6) (a) E. B. Pederson and S.-O. Lawesson, *Tetrahedron*, **30**, 875 (1974); (b) S. Arimatsu, R. Yamaguchi, and M. Kawanisi, *Bull. Chem. Soc. Jpn.*, **47**, 1553 (1974); (c) R. S. Monson, D. N. Priest, and J. C. Ullrey, *Tetrahedron Lett.*, 929 (1972).
(7) W. S. Ide and J. S. Buck, *Org. React.*, **4**, 269 (1948).
(8) R. Adams and C. S. Marvel, *Org. Syn.*, **1**, 25 (1921).
(9) T. van Es and O. G. Backegerg, *J. Chem. Soc.*, 1371 (1963).
(10) M. Mousserson, J. Jullien, and Y. Jolchine, *Bull. Soc. Chim. Fr.*, 757 (1952).
(11) J. S. Buck and W. S. Ide, *J. Am. Chem. Soc.*, **54**, 3012 (1932).

Identification of C-22 Epimers in Steroids by Carbon-13 Nuclear Magnetic Resonance Spectroscopy[1a]

Yves Letourneux,[1b] Qui Khuong-Huu,[1b] Marcel Gut,[1c] and Gabor Lukacs*[1b]

Institut de Chimie des Substances Naturelles du Centre National de la Recherche Scientifique, 91190 Gif/Yvette, France, and Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts 01545

Received December 16, 1974

A recent communication reported a ^1H NMR analytical method to identify (20*R*,22*R*)- and (20*R*,22*S*)-dihydroxy steroidal isomers.[2] However, the same study indicated that ^1H NMR spectroscopy failed to differentiate (22*R*)- and (22*S*)-hydroxy cholesterols.[2]

We wish to report the utility of ^{13}C NMR in this case and provide an easy method to determine the absolute configuration at C-22 of steroids substituted at this center and having the cholestane side chain.

Noise and single frequency decoupled ^{13}C NMR spectra were recorded for the (22*R*)- and (22*S*)-substituted cholesterol derivatives[3,4] **2–7** and for cholesteryl benzoate **1**. Application of chemical shift rules[5] as well as previous analysis of the ^{13}C NMR spectrum of cholesterol[6] led to the signal assignments shown in Table I.

Compared to the respective resonance positions in the spectrum of **1**, C-22, C-20, and C-23 are deshielded while C-17, C-21, and C-24 are shielded in all the compounds studied. These chemical shift variations are easily understood from the qualitative point of view as a consequence of α, β, and γ effects.[5,7] However, inspection of Table I indicates that the magnitude of the β effects is totally different for the 22*S* and 22*R* compounds. Considering the spectra of **2**, **3**, **5**, and **6**, the average β effect on C-20 is 4.1 and 6.8 ppm in the *S* and *R* series, respectively. On the chemical shift of C-23 an even more pronounced difference is observed between the two series. The β effect in this case is

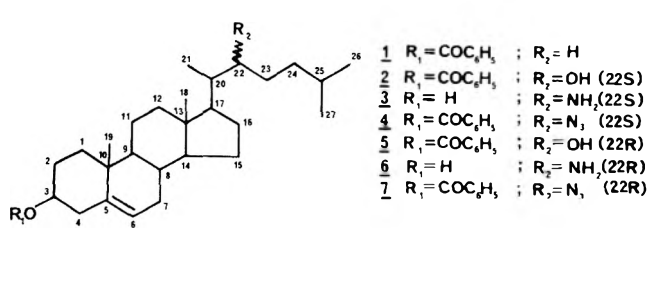


Table I
^{13}C Chemical Shift [a]

Compd	C-17	C-18	C-20	C-21	C-22	C-23	C-24	C-25	C-26	C-27
1	56.3	11.9	35.8	18.8	36.3	23.9	39.6	28.0	22.6	22.8
2	52.6	11.8	40.3	11.6	73.8	33.3	35.7	27.8	22.6	22.6
3	52.9	11.8	39.5	11.3	52.9	34.2	36.2	27.6	22.6	22.6
4	53.2	11.8	40.5	12.7	66.5	30.5	36.1	28.1	22.6	22.6
5	53.2	11.9	42.6	12.5	74.0	27.5	36.1	27.9	22.5	22.9
6	53.3	11.8	42.7	12.3	53.3	27.6	36.6	28.2	22.3	23.0
7	52.8	11.8	40.1	13.5	66.9	25.4	36.7	28.0	22.4	22.9

[a] ^{13}C NMR spectra were recorded (at room temperature) in 0.3 *M* $CDCl_3$ solution on a Bruker HX-90E Fourier transform spectrometer at 22.63 MHz. Chemical shifts (±0.1 ppm) are given with respect to Me_4Si used as an internal standard. Resonance positions of the following carbons were only slightly affected by the structural changes of the side chain: C-1 (δ 38.2 ± 0.1); C-2 (δ 28.0 ± 0.2); C-3 (δ 74.5 ± 0.1); C-4 (δ 37.0 ± 0.1); C-5 (δ 139.7 ± 0.2); C-6 (δ 122.6 ± 0.1); C-7 (δ 31.9 ± 0.1); C-8 (δ 31.9 ± 0.1); C-9 (δ 50.0 ± 0.1); C-10 (δ 36.6 ± 0.1); C-11 (δ 21.1 ± 0.1); C-12 (δ 39.8 ± 0.1); C-13 (δ 42.3 ± 0.2); C-14 (δ 56.4 ± 0.3); C-15 (δ 24.2 ± 0.2); C-16 (δ 28.1 ± 0.2); C-19 (δ 19.4 ± 0.1); CO (δ 165.9 ± 0.1); substituted aromatic carbon (δ 132.6 ± 0.1) para carbon (δ 130.8 ± 0.1); specific assignment for the ortho and meta carbons cannot be made (δ 129.5 ± 0.1 and 128.2 ± 0.1). The (22*S*)- and (22*R*)-amino compounds **3** and **6** were examined with a free hydroxyl group at C-3. Chemical shifts for these two compounds from C-1 to C-16 and C-19 were identical with those published previously.[6] In the spectrum of (22*S*)-hydroxycholesterol-20,22,23,23-d_4 the 40.3-, 73.8-, and 33.3-ppm signals of **2** were not detectable, while the A- and B-ring carbons showed resonances which were identical with those observed in the spectra of **3** and **6**.

greater for the *S* than for the *R* compounds (average value 9.8 and 3.6 ppm). Small differences are also observed for the γ carbons C-21 and C-24 of the respective isomers; these signals appear slightly downfield in the *R* compared to the *S* compounds.[11] Similar stereochemical effects on the chemical shifts of the aliphatic β- and γ-carbon resonances have been reported in C-15 epimeric prostaglandins.[10]

The interpretation of the magnitude of the observed effects is not easy; however, these results seem to be structurally diagnostic and may be helpful for stereochemical assignments of C-22 epimers in steroids.

Acknowledgment. The authors are indebted to Dr. Kazuo Tori, Shionogi Research Laboratory, for stimulating discussions.

Registry No.—**1**, 604-32-0; **2**, 17954-95-9; **3**, 50921-62-5; **4**, 50921-61-4; **5**, 17954-94-8; **6**, 50921-65-8; **7**, 50921-64-7.

References and Notes

(1) (a) Résonance Magnétique Nucléaire du ^{13}C de Produits Naturels et Apparentés. XXII. For Part XVIII, see K. Tori, T. Komeno, M. Sangaré, B. Septe, B. Delpech, A. Ahond, and G. Lukacs, *Tetrahedron Lett.*, 1157 (1974). (b) Institut de Chimie des Substances Naturelles du Centre National de la Recherche Scientifique. (c) Worcester Foundation for Experimental Biology.
(2) T. A. Wittstruck, *J. Org. Chem.*, **38**, 1426 (1973). The (20*R*,22*R*)- and (20*R*,22*S*)-dihydroxy steroids described in the cited paper were mistakenly called 20*S*,22*R* and 20*S*,22*S* isomers.
(3) E. P. Burrows, G. H. Hornby, and E. Caspi, *J. Org. Chem.*, **34**, 103 (1969).
(4) Q. Khuong-Huu, Y. Letourneux, M. Gut, and R. Goutarel, *J. Org. Chem.*, **39**, 1065 (1974).
(5) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(6) (a) H. J. Reich, M. Jautelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, *J. Am. Chem. Soc.*, **91**, 7445 (1969); (b) H. Eggert and C. Djerassi, *J. Org. Chem.*, **38**, 3788 (1973).
(7) In azido compounds the β nitrogen of the azide has a normal γ effect: A. Pancrazi, I. Kaboré, Q. Khuong-Huu, and G. Lukacs, unpublished results. In view of this observation on many model compounds, C-20 and C-23 of **7** are more shielded than the same carbons of **5** and **6**. While the C-23 shift of **4** is easy to interpret, the C-20 resonance of **4** is not understood at the present time.
(8) G. Lukacs and C. R. Bennett, *Bull. Soc. Chim. Fr.*, 3996 (1972).
(9) (a) H. Hikino and Y. Hikino, *Prog. Chem. Org. Nat. Prod.*, **28**, 256 (1970); (b) K. Nakanishi, *Pure Appl. Chem.*, **25**, 167 (1971).
(10) G. F. Cooper and J. E. Fried, *Proc. Natl. Acad. Sci. U.S.*, **70**, 1579 (1973).
(11) Reported chemical shift values in pyridine solution for C-20 (41.9 ppm) and C-23 (25.3 ppm) of α-ecdysone[8] are in agreement with the known *R* configuration[9] at C-22 of the hydroxyl group of this natural product. As a result of the γ effect on C-23 of the C-25 hydroxyl group of α-ecdysone, the C-23 shift of this compound is expected to be shielded by about 3 ppm[5] with respect to the resonance position of C-23 in **5**.

An Intermolecular Alkyl-Transfer Reaction of Tetraorganoborate Anions with Acyl Halides. A Novel Method for Moderating the Carbanion Reactivity

Summary: Lithium tetraorganoborate complexes, readily formed by the reaction of organolithiums with organoboranes, react smoothly with acyl halides to produce the corresponding ketones in high yields without concomitant formation of carbinols, thereby providing a novel method for moderating the carbanion reactivity.

Sir: We wish to report an *intermolecular* alkyl-transfer reaction of tetraorganoborate complexes, which provides a novel method for moderating the carbanion reactivity.

Trigonal organoboron compounds, i.e., organoboranes, function as electrophiles in a variety of reactions[1] but seldom as nucleophiles. Thus organoboranes are usually inert toward typical organic electrophiles, such as alkyl halides, carbonyl derivatives,[2] and epoxides, under ionic reaction conditions. One way of converting an organoborane into a nucleophilic species would be to form the corresponding borate anion or "ate" complex.[3] Surprisingly, relatively little is known as to the *intermolecular* alkyl-transfer ability of the borate anions,[3,4] although the highly nucleophilic nature of the hydridic hydrogens of borate anions has been amply demonstrated.[5]

We have found that lithium tetraorganoborates, such as lithium tetra-*n*-butylborate (**1**), react smoothly at 25° with acyl halides, such as benzoyl chloride and valeryl chloride, to form the corresponding ketones (eq 1). To our knowledge, such a clean-cut *intermolecular* alkyl-transfer reaction of tetraorganoborate anions under mild reaction conditions has not been reported. Since lithium tetra-*n*-butylborate does not react at any noticeable rate under the same reaction conditions with methyl iodide, benzyl chloride,[4a] ethyl benzoate, and cyclohexenone,[6] the reaction shown by eq 1 provides a potentially highly "chemospecific"[7] route to "mixed" ketones.[8]

$$LiBRR'_3 + R''COX \longrightarrow RCOR'' + BR'_3 \quad (1)$$

R and R′ = alkyl; R″ = alkyl or aryl; X = Cl or Br

Significantly, the reaction is not complicated by the formation of the corresponding carbinols. The reaction of Grignard reagents or organolithiums with acyl halides usually produces predominantly the carbinols,[9] and trialkylboranes do not react with the acyl halides under comparable conditions. It is, therefore, unlikely that the reaction involves the predissociation of **2** into the alkyllithium and the trialkylborane. We tentatively conclude that the borate complex **2** is the actual reacting species. The relative reactivities of benzoyl halides are in the order PhCOBr > PhCOCl ≫ PhCOF, suggesting that the ionization of acyl halides is probably not significant.

There are a few salient features which are worth noting. First, in the reaction of "mixed" tetraalkylborate complexes containing primary and secondary alkyl groups, the primary group is transferred nearly exclusively regardless of statistical factors (eq 2). This is true even when the primary group is derived from the trialkylborane moiety (entry 5, Table I). Second, in the reaction shown in eq 2, the organoborane added is recovered quantitatively (>95% by GLC). Thus, the reaction may be viewed as *an organoborane-moderated reaction* of an organolithium with an acyl halide. Such a moderation not only diverts the reaction course (from carbinol formation to ketone formation) but renders the new reaction highly "chemospecific" (eq 3, entries 7, 8, 10, 12, 13). In our hands, the reaction of 3-carbomethoxypropionyl chloride with either **3**[10] or the reagent derived from **3** and cuprous chloride or iodide (3/CuX = 1 or 2) did not provide the desired product in any appreciable yield (<5%).[11] Third, the moderation of carbanion reac-

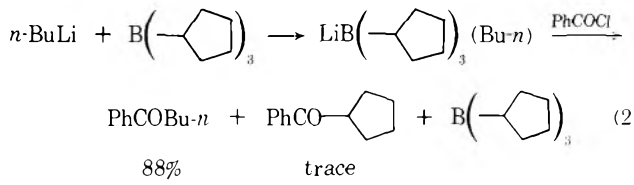
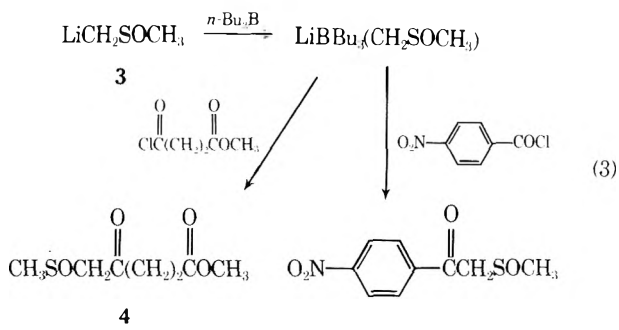


Table I
Preparation of Ketones by the Reaction of Lithium Tetraorganoborates with Acyl Halides

$$LiBRR'_3 + R''COX \xrightarrow[25°]{THF\text{–}hexane} RCOR'' + BR'_3$$

Entry	R	R′	R″	X	Product[a]	Yield,[b] %
1	n-C_4H_9	n-C_4H_9	Ph	Cl	n-C_4H_9COPh	80
2	n-C_4H_9	n-C_4H_9	Ph	Br	n-C_4H_9COPh	65
3	n-C_4H_9	n-C_4H_9	Ph	F	n-C_4H_9COPh	4
4	n-C_4H_9	c-C_5H_9	Ph	Cl	n-C_4H_9COPh	89
5	n-C_4H_9	c	Ph	Cl	n-C_4H_9COPh	57
6	n-C_4H_9	n-C_4H_9	n-C_4H_9	Cl	n-$C_4H_9COC_4H_9$-n	53
7	n-C_4H_9	n-C_4H_9	$CH_2{=}CH(CH_2)_8$	Cl	n-$C_4H_9CO(CH_2)_8CH{=}CH_2$	69
8	n-C_4H_9	c-C_5H_9	$MeOOC(CH_2)_2$	Cl	n-$C_4H_9CO(CH_2)_2COOMe$	76
9	$PhCH_2$	n-C_4H_9	Ph	Cl	$PhCH_2COPh$	88
10	$PhCH_2$	n-C_4H_9	p-IPh	Cl	$PhCH_2COPhI$-p	(72)[d]
11	CH_3SOCH_2	n-C_4H_9	Ph	Cl	CH_3SOCH_2COPh	(51)
12	CH_3SOCH_2	n-C_4H_9	$MeOOC(CH_2)_2$	Cl	$CH_3SOCH_2CO(CH_2)_2COOME$	(61)
13	CH_3SOCH_2	n-C_4H_9	p-NO_2Ph	Cl	$CO_3SOCH_2COPhNO_2$-p	(55)[e]

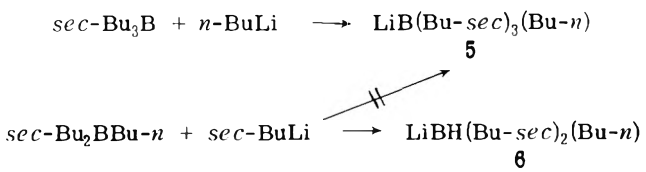
[a] All products gave satisfactory ^1H NMR and ir spectra. All new products yielded correct analytical data. [b] By GLC. The numbers in parentheses are isolated yields. [c] $BR'_3 = B(C_4H_9\text{-}n)_2(C_4H_9\text{-}sec)$. The borate complex was obtained by the reaction of tri-*n*-butylborane and *sec*-butyllithium. [d] Mp 99–100°. [e] Mp 44–45°.



(3)

tivity by organoboranes appears a broadly applicable principle as demonstrated by the data in Table I. The data in Table I also indicate that the relative transferability increases in the order secondary alkyl, primary alkyl, and benzyl (or methylsulfinylmethyl), which appears inversely proportional to their basicity.

A few limitations have been observed. First, tetraorganoborate anions containing alkynyl[12] and thioalkoxymethyl[13] groups undergo predominantly *intramolecular* alkyl-transfer reactions with acyl halides. We have found that, although arylborate anions undergo an intramolecular alkyl-transfer reaction with certain alkylating reagents,[14] their reaction with acyl halides involves a clean intermolecular alkyl transfer.[15] Second, although no difficulty exists in the preparation of lithium tri-*sec*-butylmono-*n*-butylborate (**5**) as a thermally stable product (at least for 1 week at 25°) from tri-*sec*-butylborane and *n*-butyllithium, the same borate anion cannot be obtained in high yield by the reaction of di-*sec*-butylmono-*n*-butylborane[16] and *sec*-butyllithium, the major product in this case being the corresponding trialkylborohydride[17] **6** [ir (THF) broad band centered at 2000 cm^{-1}] formed in 80% yield (hydride analysis).[18] Clearly, the difficulty is kinetic rather than thermodynamic.



The following procedure for the preparation of methyl 4-oxooctanoate is representative. All operations are carried out under nitrogen. To a dry 250-ml flask with a septum inlet, a reflux condenser, and a stirring bar were introduced sequentially 10.9 g (50 mmol) of tricyclopentylborane in THF (~50 ml), 20.8 ml (50 mmol) of 2.40 *M* n-butyllithium in hexane (0°, 1 hr), and 7.52 g (50 mmol) of 3-carbomethoxypropionyl chloride (0°, 30 min, then 40–45°, 24 hr). After evaporation of the volatile compounds, distillation provided 6.54 g (76%) of methyl 4-oxooctanoate:[19] bp 57–61° (0.25 mm); $n^{22}D$ 1.4372; ^1H NMR (CCl_4, Me_4Si) δ 0.91 (t, J = 6.5 Hz, 3 H), 1.1–1.8 (m, 4 H), 2.3–2.8 (m, 6 H), 3.63 (s, 3 H) ppm; ir (neat) 1720, 1210, 1160 cm^{-1}. The residue was extracted with petroleum ether. After evaporation, 9.3 g (85%) of tricyclopentylborane was recovered as a crystalline compound.[20]

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, Research Corporation, and Syracuse University for financial support.

References and Notes

(1) (a) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972; (b) G. M. L. Cragg, "Organoboranes in Organic Synthesis", Marcel Dekker, New York, N.Y., 1973.
(2) (a) Organoboranes undergo conjugate addition reactions with α,β-unsaturated carbonyl compounds by a free-radical mechanism: G. W. Kabalka, H. C. Brown, A. Suzuki, S. Honma, A. Arase, and M. Itoh, *J. Am. Chem. Soc.*, **92**, 710 (1970), and references cited therein. (b) Allylic organoboranes react with carbonyl compounds to form corresponding carbinols: B. M. Mikhailov, *Organomet. Chem. Rev., Sect. A*, **8**, 1 (1972).
(3) (a) W. Tochtermann, *Angew Chem. Int. Ed. Engl.*, **5**, 351 (1966); (b) G. Wittig, *Quart. Rev.*, **20**, 191 (1966).
(4) (a) The reaction of lithium tetra-*n*-butylborate with benzyl chloride at 125° produces among other products *n*-pentylbenzene in 5% yield: H. Jaeger and G. Hesse, *Chem. Ber.*, **95**, 345 (1962). (b) Certain potassium tetraarylborate complexes react with bromoferrocene in the presence of cuprous bromide at 130° to form arylferrocenes. Although unclear, arylcoppers appear to be the actual reacting species: A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozal, *Dokl. Akad. Nauk SSSR*, **154**, 158 (1964), and references therein.
(5) (a) For an extensive review, see E. Schenker, "Newer Methods of Preparative Organic Chemistry", Vol. IV, W. Foerst, Ed., Verlag Chemie GmbH, Weinheim/Bergstr., 1968, pp 196–335. (b) For recent results with trialkylborohydrides, see H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972), and references cited therein.
(6) We have recently reported that **1** does not react with ethyl acrylate at 25°: E. Negishi and T. Yoshida, *J. Am. Chem. Soc.*, **95**, 6837 (1973).
(7) For the definition of this term, see B. M. Trost and T. N. Satzmann, *J. Am. Chem. Soc.*, **95**, 6840 (1973).
(8) A few chemospecific methods for the conversion of acyl halides to ketones have been reported recently: (a) J. P. Collman, S. R. Winter, and D. R. Clark, *J. Am. Chem. Soc.*, **94**, 1788 (1972); (b) G. Posner, C. E. Whitten, and P. E. McFarland, *ibid.*, **94**, 5106 (1972); (c) L. S. Hegedus, S. M. Lo, and D. E. Bloss, *ibid.*, **95**, 3040 (1973).
(9) See, for example, M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances", Prentice-Hall, Englewood Cliffs, N.J., 1954.
(10) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
(11) For other syntheses of β-keto sulfoxides, see S. Iriuchijima, K. Maniwa, and G. Tsuchihashi, *J. Am. Chem. Soc.*, **97**, 596 (1975), and references cited therein.
(12) (a) P. Binger, G. Benedikt, G. W. Rotermund, and R. Köster, *Justus Liebigs Ann. Chem.*, **717**, 21 (1968); (b) M. Naruse, T. Tomita, K. Utimoto, and H. Nozaki, *Tetrahedron Lett.*, 351 (1971).
(13) E. Negishi, T. Yoshida, A. Silveira, Jr., and B. L. Chiou, *J. Org. Chem.*, **40**, 814 (1975).
(14) E. Negishi and R. E. Merrill, *Chem. Commun.*, 860 (1974).
(15) E. Negishi, A. Abramovitch, and R. E. Merrill, *Chem. Commun.*, 138 (1975).
(16) Prepared from methoxydi-sec-butylborane and 1-butene under the influence of lithium aluminum hydride: H. C. Brown, E. Negishi, and S. K. Gupta, *J. Am. Chem. Soc.*, **92**, 6648 (1970).
(17) An analogous trialkylborohydride formation has been reported: E. J. Corey, S. M. Albonico, V. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Am. Chem. Soc.*, **93**, 1491 (1971).
(18) On treatment of the product mixture with aqueous hydrochloric acid, di-sec-butylmono-*n*-butylborane was regenerated in 91% yield (GLC).
(19) J. Cason, *J. Am. Chem. Soc.*, **68**, 2078 (1946).
(20) In cases where the recovery of the trialkylborane is not required, the alkaline hydrogen peroxide oxidation of the reaction mixture is generally the most convenient and dependable method for removing the trialkylborane by-product. We have also achieved the recovery of trialkylboranes by selective crystallization or extraction in this and other cases.

Department of Chemistry
Syracuse University
Syracuse, New York 13210

Ei-ichi Negishi*
Kuen-Wai Chiu
Takao Yosida

Received February 18, 1975

Counterion Effect in the Hofmann–Martius Rearrangement of a Quaternary Anilinium Ion[1]

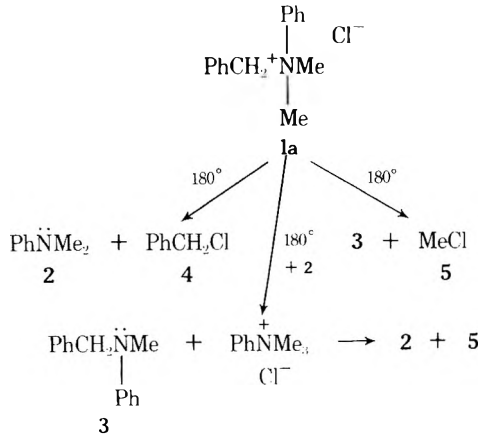
Summary: Thermolysis of *N*-benzyl-*N*,*N*-dimethylanilinium iodide (**1b**) gave "monomeric" and cross-alkylated Hofmann–Martius amines with relatively minor amounts of *N*,*N*-dimethylaniline (**2**). The chloride of the same cation (**1a**) gave only retro-Menschutkin products.

Sir: The majority of the studies on the Hofmann–Martius rearrangement of N-substituted anilines dates back to preinstrumental times and, therefore, even in work of excellent quality, some data are necessarily not complete or very accurate, either qualitatively or quantitatively. Mechanistic conclusions also seem in need of a deep revision. Moreover, practically nothing is known about the relative reactivities of quaternary anilinium ions, the migratory aptitudes of different N substituents, and the effect of the counterion.[2] In this context, we wish to report the dramatic

effect of the counterion change on the course of the thermolysis of the two halides **1a** (Cl) and **1b** (I) of the *N*-benzyl-*N*,*N*-dimethylanilinium ion.

When the chloride **1a** was heated at 175–180° without solvent, 90% of the salt reacted in 30 min to give the products arising from the two possible retro-Menschutkin reactions, namely *N*,*N*-dimethylaniline (**2**) and *N*-benzyl-*N*-methylaniline (**3**), as free bases together with the corresponding alkyl chlorides, benzyl chloride (**4**) and chloromethane (**5**). Amine **3** is in much larger amount than amine **2**, a fact which has a simple explanation in the operation of the Le Chatelier principle.

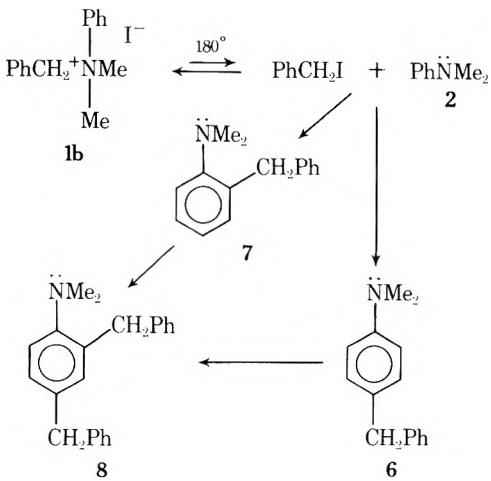
Scheme I



The reaction between **1a** and the *N*,*N*-dimethylaniline (**2**) being formed in the reaction may be an important source of **3**. In fact, independent experiments showed that *N*,*N*-dimethylaniline (**2**) reacts with the *N*-benzyl-*N*,*N*-dimethylanilinium cation to yield **3** at 180°.

The behavior of the iodide **1b** in the same experimental conditions was completely different, giving some amine **2** (~20%), no **3**, but three rearranged products: *p*-benzyl-*N*,*N*-dimethylaniline (**6**), o-benzyl-*N*,*N*-dimethylaniline (**7**), and *o*,*p*-dibenzyl-*N*,*N*-dimethylaniline (**8**). Products **6** and **7** were definitively different from all the Stevens and Sommelet isomers previously identified in the reaction of both **1a** and **1b** with strong bases.[3] The unequivocal identification of the reaction products from the thermolysis of **1b** was reached on the basis of gas chromatographic properties on widely different stationary phases (Carbowax 20M–KOH, silicones, etc.), mass spectrometry (electron impact at 70 and 15 eV), and spectroscopic characteristics (infrared and ^{1}H nuclear magnetic resonance on separated samples). Independent syntheses, which will be reported at a later time, confirmed the identifications.

Scheme II



The ortho/para ratio (~0.35) and the presence of the polyalkylated amine **8** does not suggest the operation of a radical mechanism recently advanced,[4] but rather indicates the possibility of a two-stage process: a predissociation (retro-Menschutkin, a reversible reaction, when no gaseous product is removed from the reacting mixture), followed by direct ring alkylation. Further study of these reactions is in progress.

References and Notes

(1) This work was supported in part by CNR Grant No. 7200124/03.
(2) G. F. Grillot, in "Mechanisms of Molecular Migrations", S. B. Thyagarajan, Ed., Wiley, New York, N.Y., 1971.
(3) A. G. Giumanini, *Chem. Ind. (London)*, 1140 (1967); A. R. Lepley and A. G. Giumanini, *J. Org. Chem.*, **36**, 1217 (1971); A. G. Giumanini and L. Plessi, *Chim. Ind. (Milan)*, **56**, 268 (1974).
(4) D. A. Archer, H. Booth, and R. D. Stangroom, *J. Chem. Soc. C*, 2276 (1970).
(5) Chemistry student.

Centro di Gascromatografia–Spettrometria di Massa and Istituto Chimico G. Ciamician
University of Bologna
40126 Bologna, Italy

Angelo G. Giumanini*
Sergio Roveri[5]
Dario Del Mazza[5]

Received March 10, 1975

The Reaction of Superoxide with Alkyl Halides and Tosylates[1]

Summary: Alcohols are the major end product resulting from the reaction of alkyl halides and tosylates with an *excess* of potassium superoxide in an extraordinarily rapid process in which the carbon–oxygen bond-forming step proceeds with *inversion* of configuration.

Sir: The perspicacious observations of Fridovich and McCord[2] have led to the realization that superoxide is a common by-product produced by virtually all aerobic organisms. Moreover, recent studies suggest that superoxide may be involved in certain biological disorders and defense mechanisms.[3] Despite its apparent importance, much of the basic chemistry of superoxide remains ill-defined.[4] Of singular importance to the understanding of the reactivity of superoxide is a clarification of the ability of $O_2\cdot^-$ to act as either a one-electron reducing agent[6,7] or as a possible nucleophile. We have undertaken to answer this question by examining the reaction of superoxide with a particular class of electrophilic substrates, viz., alkyl halides and tosylates.

In a typical experiment, 1-bromooctane (0.644 g, 3.33 mmol) was added to a vigorously stirred mixture of powdered potassium superoxide[8] (0.710 g, 10.0 mmol) and 18-crown-6 ether[9] (0.264 g, 1.0 mmol) in dry DMSO (20 ml) at 25°.[10] The resulting mixture was allowed to stir for 75 min, then cautiously treated with 10 ml of water saturated with sodium chloride, and finally extracted with three 30-ml portions of petroleum ether. GLC analysis of the combined extracts indicated the presence of 1-octanol (63%), 1-octene (1%), and 1-octanal (12%). Results obtained on similar treatment of other representative substrates are given in Table I.

This sequence seems applicable to the production of alcohols from primary and secondary halides and tosylates; in our hands tertiary halides gave poor yields of alcohols

Table I
Reaction of Potassium Superoxide with Various Organic Halides and Tosylates[a]

Substrate	Products (%)[b]	Rel reactivity[c]
1-$C_8H_{17}I$	1-Octanol (46) 1-Octene (3) 1-Octanal (11)	4.5
2-$C_8H_{17}I$	2-Octanol (48) Octenes[d] (48) 2-Octanone (<1)	3.3
1-$C_8H_{17}Br$[e]	1-Octanol (63) 1-Octene (<1) 1-Octanal (12)	1.0
2-$C_8H_{17}Br$	2-Octanol (51) Octenes[d] (34) 2-Octanone (<1)	0.98
$CH_3(CH_2)_2C(CH_3)_2Br$	2-Methyl-2-pentanol (20) 2-Methylpentenes (30)	0.90
1-$C_8H_{17}Cl$	1-Octanol (34) 1-Octene (~1) 1-Octanal (5)	0.089
2-$C_8H_{17}Cl$	2-Octanol (36) Octenes[d] (12) 2-Octanone (<1)	0.020
1-$C_8H_{17}OTs$	1-Octanol (75) 1-Octene (<1) 1-Octanal (1)	1.0
2-$C_8H_{17}OTs$	2-Octanol (75) Octenes[d] (23) 2-Octanone (<1)	*f*
$C_6H_5CH_2Cl$	Benzyl alcohol (41) Benzaldehyde (6)	2.9

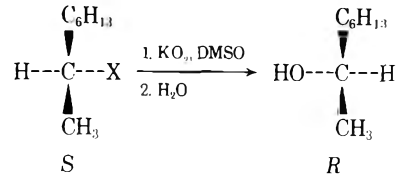
[a] Unless otherwise indicated, all reactions were carried out by adding 3.33 mmol of halide or tosylate to a vigorously stirred mixture of KO_2 (10.0 mmol) and 18-crown-6 ether (1.0 mmol) in dry DMSO (20 ml) at ambient temperature. Reaction time varied from 75 min for the alkyl bromides, iodides, tosylates, and benzyl chloride to 3 hr for the alkyl chlorides. Yields did not improve with increased reaction time. [b] Yields are based on alkyl halide or tosylate and were determined by GLC analysis using the internal standard procedure. [c] Reactivities were determined relative to 1-bromooctane (1.00) by the standard competitive technique of allowing a mixture of a designated standard (1-bromooctane) and one additional substrate to react with a limited amount of potassium superoxide and determining the amount of unreacted starting substrates. [d] No attempts were made to distinguish possible octene isomers. [e] Repetition of this reaction using HMPA as solvent required an extended reaction time (17 hr) and yielded 1-octanol (55%), 1-octene (<1%), and 1-octanal (5%). Reaction in benzene also required longer reaction times (~20 hr) and produced lower yields of 1-octanol (29%), 1-octene (<1%), and 1-octanal (<1%). [f] Not determined.

while phenyl halides showed no significant reactivity. Optimum alcohol yields were obtained at superoxide to alkyl halide ratios of ≥3. Reaction was accompanied by an initially moderate to vigorous evolution of oxygen[11] which abated with time but otherwise continued throughout the course of the reaction. Finally, somewhat lower yields of alcohol were obtained when reactions were carried out in the absence of a macrocyclic polyether while the use of HMPA or benzene as solvent required longer reaction time, producing similar products but in diminished yields.

Our understanding of the details of this reaction is still incomplete. In this context, however, several specific points deserve brief comment. First, the organic groups bonded to the halogen and the nature of the leaving group exert an influence on the course of the reaction that is consistent with a mechanism for carbon-oxygen bond formation which involves a SN2 displacement at carbon.[12] Specifically, the observed substrate reactivity is benzyl > primary > secondary > tertiary > aryl and I > Br > Cl.

Second, substitution is predominant with primary halides; however, substantial elimination occurs with secondary systems whereas elimination is the predominant process observed from the reaction with the tertiary halide 2-bromo-2-methylpentane. These facts parallel similar observations involving the reactions of other nucleophiles with alkyl halides.[13]

Third, consistent with this conclusion is the fact that carbon–oxygen bond formation in at least two instances takes place with predominant *inversion* of configuration at the chiral center. Reaction of the tosylate of (+)-(*S*)-2-octanol (α^{20}_{589} +7.97°, optical purity 99.4%) with potassium superoxide produced (−)-(*R*)-2-octanol (α^{20}_{589} −7.71°) corresponding to an optical purity and overall stereoselectivity of 97%. Similar reaction with (−)-(*R*)-2-bromooctane[14] afforded (+)-(*S*)-2-octanol in 90% optical purity (95% net inversion).



Finally, we have carried out a comparison of the reactivity of potassium superoxide and potassium iodide toward a selected electrophilic substrate, viz., 1-bromooctane. The half-life for the reaction of 1-bromooctane (0.5 *M*) with potassium iodide (0.5 *M*) in dry DMSO containing 18-crown-6 ether (0.05 *M*) was ~20 hr.[15] By comparison, the reaction of potassium superoxide with 1-bromooctane under equivalent conditions has a half-life of ~*45 sec*.

These results exclude as a principal reaction pathway leading to the production of the carbon–oxygen bond, a mechanism involving a one-electron transfer process since such a step would necessarily produce an alkyl radical which, in turn, would lead to products with loss of stereochemistry. The observed substitution reaction can in these instances be viewed as involving the direct displacement of halide at carbon by superoxide radical anion. The nature of the subsequent intermediates involved in this reaction sequence remain unclear although peroxo compounds are certainly reasonable possibilities. Further speculation on the details of the subsequent reactions that occur must be deferred until a clearer understanding of the nature of the intermediates in this reaction can be delineated.

Acknowledgment. The experimental assistance of Mr. Richard Sweet in the initial course of this investigation is gratefully acknowledged.

References and Notes

(1) Supported by the Research Corporation, Rutgers Research Council, Charles and Johanna Busch Memorial Fund, and Biomedical Sciences Support Grant.
(2) J. M. McCord and I. Fridovich, *J. Biol. Chem.*, **243**, 5733 (1968); J. M. McCord, B. B. Keele, Jr., and I. Fridovich, *Proc. Nat. Acad. Sci. U. S.*, **68**, 1024 (1971); B. B. Keele, Jr., J. M. McCord, and I. Fridovich, *J. Biol. Chem.*, **246**, 2875 (1971); I. Fridovich, *Acc. Chem. Res.*, **5**, 321 (1972), and references therein.
(3) J. M. McCord, *Science*, **185**, 529 (1974); J. T. Curnutte, D. M. Whitten, and B. M. Babior, *New Eng. J. Med.*, **290**, 593 (1974); A. P. Autor, *Life Sci.*, **14**, 1309 (1974); J. D. Crapo and D. F. Tierney, *Am. J. Physiol.*, **226**, 1401 (1974); F. J. Yost and I. Fridovich, *Arch. Biochem. Biophys.*, **161**, 395 (1974); I. Fridovich, *New Eng. J. Med.*, **290**, 624 (1974).
(4) Chronopotentiometric and cyclic voltametric studies of the reaction of electrochemically generated superoxide with several alkyl halides have been reported.[5]
(5) M. V. Merritt and D. T. Sawyer, *J. Org. Chem.*, **35**, 2157 (1970); R.

Dietz, A. E. J. Forno, B. E. Larcombe, and M. E. Peover, *J. Chem. Soc. B*, 816 (1970).
(6) J. S. Valentine and A. B. Curtis, *J. Am. Chem. Soc.*, **97**, 224 (1975).
(7) R. Poupko and I. Rosenthal, *J. Phys. Chem.*, **77**, 1722 (1973).
(8) Using a mortar and pestle and working in a glove bag under an atmosphere of dry nitrogen, lumps of potassium superoxide, purchased from K & K Chemicals, were ground to a fine consistency before use.
(9) G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, *J. Org. Chem.*, **39**, 2445 (1974).
(10) Relatively stable solutions containing substantial concentrations (~0.2 *M*) of potassium superoxide can be obtained in dry DMSO in the presence of a macrocyclic polyether.[6]
(11) Identified by GLC analysis.
(12) A. Streitwieser, Jr., "Solvolytic Displacement Reactions", McGraw-Hill, New York, N.Y., 1962 pp. 29–31.
(13) F. L. Cook, C. W. Bowers, and C. L. Liotta, *J. Org. Chem.*, **39**, 3416 (1974), and references therein.
(14) J. San Filippo, Jr., and L. J. Romano, *J. Org. Chem.*, **40**, 1514 (1975). Optical rotations were determined on neat liquids (GLC pure) in a 1-cm cell using a Perkin-Elmer Model 141 spectropolarimeter. Experimental and literature values are corrected to $l = 1$ dm.
(15) Determined by the disappearance of 1-bromooctane.

School of Chemistry **Joseph San Filippo, Jr.***
Rutgers University **Chuen-Ing Chern**
New Brunswick, New Jersey
08903

Department of Chemistry **Joan S. Valentine***
Douglass College
Rutgers University
New Brunswick, New Jersey
08903

Received February 2, 1975

Superoxide Chemistry. A Convenient Synthesis of Dialkyl Peroxides

Summary: A convenient synthesis of dialkyl peroxides from the reaction of alkyl bromides or alkyl sulfonate esters with potassium superoxide, the latter solubilized in benzene by crown ethers, is described.

Sir: The chemistry of the superoxide radical anion, $O_2\cdot^-$, in organic systems has been studied very little. On a synthetic scale, superoxide is available to the chemist from two sources, either as the alkali metal salts, potassium superoxide (KO_2) and sodium superoxide (NaO_2), or from the electrochemical reduction of oxygen to $O_2\cdot^-$ (eq 1).[1] The use of

$$O_2 + e \rightleftharpoons O_2\cdot^- \qquad -0.75\ \text{V (SCE)} \quad (1)$$

$$RBr + O_2\cdot^- \longrightarrow \tfrac{1}{2}ROOR + Br^- + \tfrac{1}{2}O_2 \quad (2)$$

the alkali metal salts in organic reactions has not been fruitful owing to the lack of solubility of these salts in many organic systems.[2] The electrochemical method is experimentally more complex, but it has been used on a limited scale for several organic reactions.[1d,3] Two groups reported in 1970 that electrochemically generated superoxide will react with alkyl halides to form dialkyl peroxides according to eq 2.[4,5]

In view of the recently reported solubilization of KO_2 in dimethyl sulfoxide with the aid of dicyclohexyl-18-crown-6,[6] we wish to report our observations on the solubilization of KO_2 by crown ethers in various other aprotic solvents, including benzene, tetrahydrofuran, and dimethylformamide.[7] Using this method we have developed a convenient synthesis of dialkyl peroxides from various alkyl bromides and alkyl sulfonate esters (i.e., mesylates and tosylates). The following simple procedure can be used for this synthesis.

Potassium superoxide[8] (0.0050 mol) was weighed directly into a dry flask containing a magnetic stirring bar and was immediately covered with dry benzene (15 ml). The alkyl bromide or alkyl sulfonate ester (0.0050 mol) and dicyclohexyl-18-crown-6 (0.0050 mol) were then added to the flask. The pieces of KO_2 were carefully crushed with a heavy glass rod. The resulting mixture was protected from moisture with a $CaCl_2$ drying tube and was stirred vigorously. The reaction may be followed by VPC or TLC[10] and occasionally requires additional KO_2 to reach completion. The reaction was usually complete within 3 to 6 hr at room temperature. The reaction may be worked up by pouring it into saturated aqueous sodium chloride solution (50 ml) and extracting with methylene chloride or benzene.[12] The product can be isolated by chromatography on silica gel using, for example, benzene as the eluent.

Table I
The Reactions of Alkyl Bromides and Sulfonate Esters with KO_2 in the Presence of Crown Ethers[a]

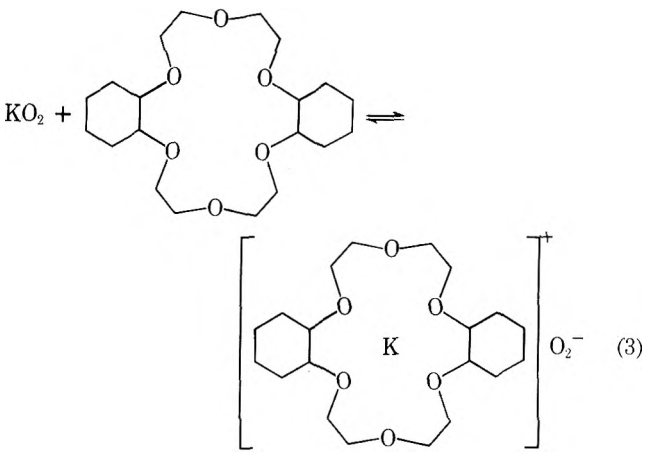
Substrate (R–X)	Products, % Peroxide (ROOR)	Alcohol (ROH)	Olefins[b]
n-C_5H_{11}–Br	53[c]		
n-C_6H_{13}–Br	54[c]		
n-C_7H_{15}–Br	56[c]		
n-$C_{16}H_{33}$–Br	44[d]	21	
n-$C_{18}H_{37}$–Br	77[e]	21	
n-$C_{18}H_{37}$–Br[f]	61	18	
c-C_6H_{11}–Br			67
c-C_5H_9–Br	42[e]		24
$C_6H_{13}CH(CH_3)$–Br	55[e]		37[g]
n-$C_{18}H_{37}$–OTos[h]	50	42	
n-$C_{18}H_{37}$–OMs[d]	46	40	
$C_6H_{13}CH(CH_3)$–OTos[i]	52	13	16[g]
$C_6H_{13}CH(CH_3)$–OMs[j]	44	19	14[g]

[a] Dicyclohexyl-18-crown-6 used except where noted otherwise. [b] VPC analyses for olefins were carried out using an F & M Scientific Model 5750 research chromatograph equipped with a flame ionization detector. A 3-ft stainless steel column packed with 26.6% Carbowax 20M on Gas-Chrom Z was used with a helium flow rate of 35–40 cc/min. The column was programmed for 4 min at 90° and then to increase 8° per minute to 225°. [c] Reference 16. [d] S. Wawzonek, P. D. Klimstra, and R. E. Kallio, *J. Org. Chem.*, **25**, 621 (1960). [e] Satisfactory analytical data has been obtained for this compound. [f] 18-Crown-6 was used in this experiment. [g] A mixture of 1-octene, *cis*-2-octene, and *trans*-2-octene was found. [h] V. C. Sekera and C. S. Marvel, *J. Am. Chem. Soc.*, **55**, 345 (1933). [i] A. Streitwieser, Jr., T. D. Walsh, and J. R. Wolfe, *ibid.*, **87**, 3682 (1965). [j] H. A. Weiner and R. A. Sneen, *ibid.*, **87**, 287 (1965).

Using this procedure, we have obtained the results summarized in Table I. Yields of peroxides and alcohols were determined from isolation of the products, whereas the yields of olefinic products were determined by VPC. In addition to these results we offer the following observations and comments on these reactions.

By analogy to recent reports of the solubilization of various inorganic salts in organic media by the crown ethers,[7] we assume that the equilibrium shown in eq 3 is responsible for the solubilization of KO_2. The dicyclohexyl-18-crown-6 used in these experiments was a mixture of stereoisomers. A stoichiometric quantity of crown ether was used in all the reactions reported in Table I. In a similar experiment, using only 0.1 equiv of crown ether relative to KO_2, 1-bromohexane was converted to di-*n*-hexyl peroxide in 50% yield. The reaction time was somewhat longer than when a full equivalent of crown ether was used. 18-Crown-6 and dibenzo-18-crown-6 also were effective in solubilizing KO_2 in benzene, although the latter was itself sparingly soluble in this solvent.

The formation of dialkyl peroxides by eq 2 was proposed by Dietz et al.[5] to occur stepwise according to eq 4–6. Sum-

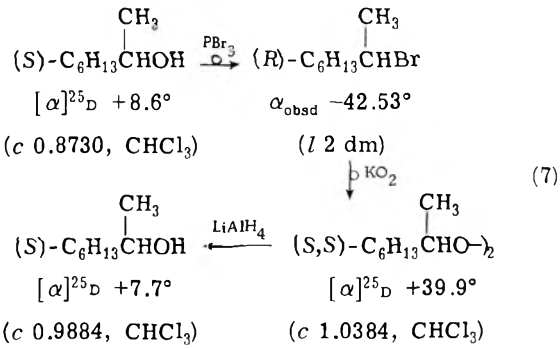


$$O_2^{\cdot-} + RBr \longrightarrow ROO^{\cdot} + Br^- \quad (4)$$

$$ROO^{\cdot} + O_2^{\cdot-} \longrightarrow ROO^- + O_2 \quad (5)$$

$$ROO^- + RBr \longrightarrow ROOR + Br^- \quad (6)$$

mation of these equations gives eq 2. Two displacements of bromide are seen in these equations and it was suggested[5] that these occurred by SN2 mechanisms. We have examined the stereochemistry of the reaction as outlined below.



The entire three-step reaction sequence (7) proceeds with a net 94% retention of configuration. Since the first step is known to proceed with complete inversion at the asymmetric carbon[13] and the last step[14] proceeds with retention of configuration, we conclude that the conversion of 2-bromooctane to di-2-octyl peroxide must occur with inversion at the asymmetric carbon. This result is consistent with the SN2 mechanism postulated for the reaction steps depicted in eq 4 and 6.

The yields of primary dialkyl peroxides obtained by the present method are comparable with, and in some cases better than, those reported for the generally used methods of peroxide synthesis.[15] Yields of secondary dialkyl peroxides, except for the cyclohexyl example, are better than those obtained by other methods. The procedure is considerably simpler than the generally used method of displacement of mesylates with alkaline hydrogen peroxide.[16]

The formation of alcohols as significant by-products in these reactions is not completely understood as yet and remains under investigation.

References and Notes

(1) (a) M. E. Peover and B. S. White, *Chem. Commun.*, 183 (1965); (b) D. L. Maricle and W. G. Hodgson, *Anal. Chem.*, **37**, 1562 (1965); (c) D. T. Sawyer and J. L. Roberts, Jr., *J. Electroanal. Chem.*, **12**, 90 (1966); (d) J. M. McCord and I. Fridovich, *J. Biol. Chem.*, **244**, 6049 (1969).

(2) A. LeBerre and Y. Berguer, *Bull. Soc. Chim. Fr.*, 2363, 2368 (1966).

(3) (a) E. A. Mayeda and A. J. Bard, *J. Am. Chem. Soc.*, **95**, 6223 (1973); (b) *ibid.*, **96**, 4023 (1974).

(4) M. V. Merritt and D. T. Sawyer, *J. Org. Chem.*, **35**, 2157 (1970).

(5) R. Dietz, A. E. J. Forno, B. E. Larcombe, and M. E. Peover, *J. Chem. Soc. B*, 816 (1970).

(6) J. S. Valentine and A. B. Curtis, *J. Am. Chem. Soc.*, **97**, 224 (1975).

(7) Recent references to the use of crown ethers to solubilize inorganic salts in organic media: (a) C. J. Pederson, *J. Am. Chem. Soc.*, **89**, 7017 (1967); (b) D. J. Cram and J. M. Cram, *Science*, **183**, 803 (1974); (c) B. Dietrich, J. M. Lehn, and J. Simon, *Angew. Chem., Int. Ed. Engl.*, **13**, 406 (1974); (d) C. L. Liotta, H. P. Harris, M. McDermott, T. Gonzalez, and K. Smith, *Tetrahedron Lett.*, 2417 (1974); (e) C. L. Liotta, and H. P. Harris, *J. Am. Chem. Soc.*, **96**, 2250 (1974); F. L. Cook, C. W. Bowers, and C. L. Liotta, *J. Org. Chem.*, **39**, 3416 (1974); (f) D. J. Sam and H. E. Simmons, *J. Am. Chem. Soc.*, **96**, 2252 (1974); (g) H. D. Durst, *Tetrahedron Lett.*, 2421 (1974); (h) J. W. Zubrick, B. I. Dunbar, and H. D. Drust, *ibid.*, 71 (1975).

(8) Supplied by the Ventron Corporation, Beverly, Mass. 01915, as small chunks of a caked yellow powder. Potassium superoxide reacts rapidly with water, producing peroxide, hydroxide, and oxygen according to the eq I.[5] Care should be taken to avoid reaction of large quantities of KO_2

$$2KO_2 + H_2O \longrightarrow 2K^+ + OH^- + OOH^- + O_2 \quad (I)$$

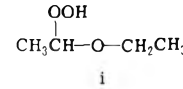
with water in the presence of organic materials. Precautions similar to those used with hydrogen peroxide are recommended.[9] In the present experiments, excessive contact with atmospheric moisture was avoided by using larger pieces of the solid and quickly covering them with dry solvent. More rigorous anhydrous conditions could be attained in a dry-box.

(9) "Kirk-Othmer Encyclopedia of Chemical Technology", Vol. 14, 2nd ed, Wiley, New York, N.Y., 1967, pp 748–749, 762–764.

(10) Peroxides and hydroperoxides can be visualized on silica gel tlc plates by spraying with a freshly prepared (remains effective for about 1 day) solution of ammonium thiocyanate (0.625 g), concentrated sulfuric acid (0.125 ml), and ferrous ammonium sulfate [$FeSO_4 \cdot (NH_4)_2SO_4$, 0.875 g] in water (12.5 ml).[11] With this spray, peroxidic materials give a rust-red-colored spot.

(11) R. D. Mair and R. T. Hall, in "Organic Peroxides", Vol. II, D. Swern, Ed., Wiley-Interscience, New York, N.Y., 1971, pp 553–560.

(12) Extraction of several reactions with ether resulted in formation of a peroxidic product tentatively considered to have structure i. Since i is an



i

intermediate in the formation of the potentially explosive polymeric ether peroxides [A. Rieche, *Angew. Chem.*, **70**, 251 (1958)], use of ether should be avoided until the nature of i is clarified.

(13) H. R. Hudson, *Synthesis*, 112 (1969).

(14) (a) M. Matic and D. A. Sutton, *J. Chem. Soc.*, 2679 (1952); (b) G. A. Russell, *J. Am. Chem. Soc.*, **75**, 5011 (1953).

(15) R. Hiatt, in "Organic Peroxides", Vol. III, D. Swern, Ed., Wiley-Interscience, New York, N.Y., 1972, pp 1–66.

(16) F. Welch, H. R. Williams, and H. S. Mosher, *J. Am. Chem. Soc.*, **77**, 551 (1955).

Experimental Chemistry Research **Roy A. Johnson***
The Upjohn Company **Eldon G. Nidy**
Kalamazoo, Michigan 49001

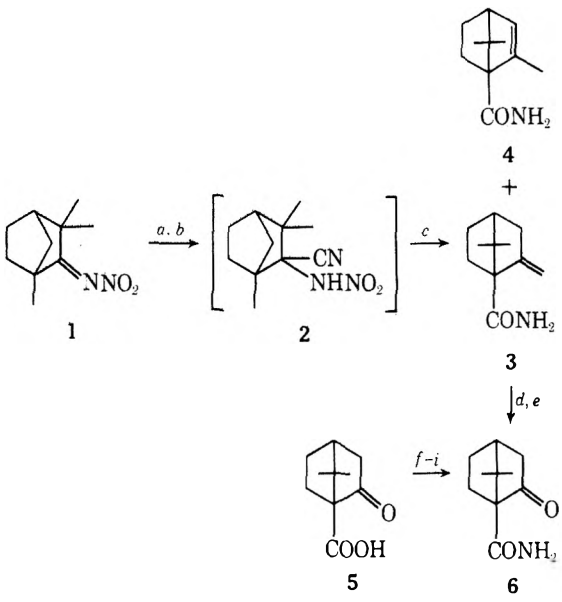
Received February 27, 1975

Reaction of Nitrimines with Cyanide Ions

Summary: The nitrimines of fenchone, menthone, camphor, and benzophenone were treated with KCN in aqueous methanol to give unstable cyanonitramine intermediates which decompose with the loss of N_2O to afford α-fenchene-1-carboxamide, ρ-menth-3-ene-3-carboxamide, camphene-1-carboxamide, and α-methoxydiphenylacetamide, respectively.

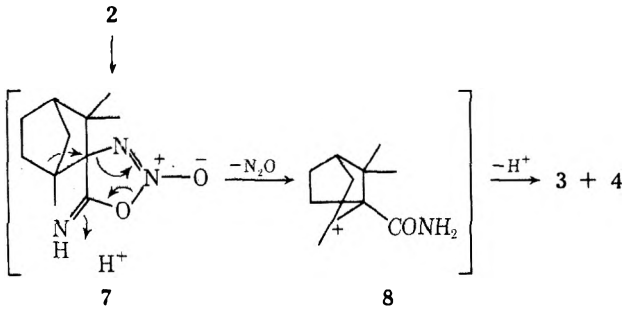
Sir: The reaction of fenchone nitrimine (1) with cyanide ion was reported by Passerini to afford a mixture of isomeric fenchone cyanohydrins.[1] We have reinvestigated this reaction duplicating the conditions of Passerini and have found that the products actually isolated are the rearranged amides 3 and 4 formed in 80% yield in a ratio of 85:15, respectively. The structure of the major product 3 was deduced from the spectral data [NMR ($CDCl_3$) δ 1.05 (s, 3 H), 1.10 (s, 3 H), 4.91 (m, 1 H), 5.07 (m, 1 H); ir ($CHCl_3$) 3520, 3400, 1665, 895 cm^{-1}] and by conversion to ketopinic amide (6) which was prepared independently from ketopinic acid (5)[2] as shown in Scheme I.

Scheme I



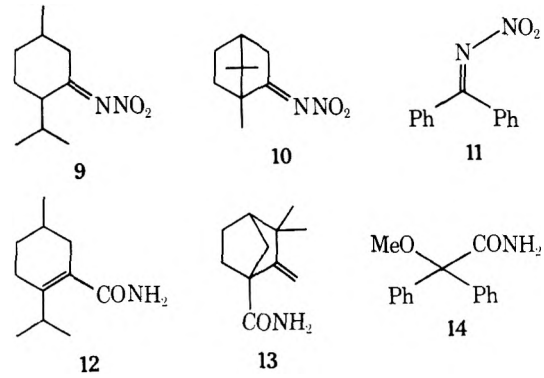
[a] KCN/MeOH, room temperature. [b] HOAc. [c] $CHCl_3$, reflux 20 min. [d] O_3/MeOH, −60°. [e] Me_2S/MeOH. [f] $SOCl_2$/benzene, reflux 45 min. [g] NH_4OH/MeOH, room temperature, 30 min. [h] O_3/MeOH, −60°. [i] Me_2S/MeOH.

When the above reaction was conducted at room temperature in aqueous methanol for 20 min, acidification of the reaction mixture gave an unstable crystalline cyanonitramine intermediate **2** (mp 81–83° dec) in virtually quantitative yield which gradually decomposed at 25° with gas evolution to afford the same mixture of amides **3** and **4** cited above. The structure of **2** (exclusive of stereochemistry) was assigned on the basis of the spectral data:[3] NMR ($CDCl_3$) δ 1.08, 1.40, 1.47 (s, 3 H each); ir ($CHCl_3$) 3360, 2240, 1585, 1330 cm^{-1}. Since the decomposition of the cyanonitramine **2** takes place readily in inert solvents, the formation of the amide products suggests an internal transfer of oxygen from the nitro group to the nitrile via the intermediate **7**. Loss of N_2O, accompanied by rearrangement



of the carbon skeleton, and finally loss of a proton account for the products observed.

To demonstrate the synthetic potential of this unusual transformation, the nitrimines of menthone (**9**),[4] camphor (**10**),[4] and benzophenone (**11**)[5] were treated with cyanide ion to afford the amides **12**,[6] **13**,[7] and **14**,[8] respectively.[9] In



each case, the formation of a cyanonitramine adduct analogous to **7** followed by elimination of N_2O as depicted above can be invoked to explain the formation of the products. The fact that skeletal rearrangement, loss of an adjacent proton to generate an olefin, and the capture of an external nucleophile were observed variants provides additional evidence in support of the ionic mechanism proposed.

Since the above reactions proceed under mild conditions (MeOH, room temperature) to afford the amides in 50–85% isolated yield, the synthetic utility of this reaction is being further investigated, and will be reported in a later paper.

References and Notes

(1) M. Passerini, *Gazz. Chim. Ital.*, **55**, 559 (1925).
(2) P. D. Bartlett and L. H. Knox, "Organic Syntheses" Collect. Vol. V, Wiley, New York, N.Y., 1973, p 689.
(3) The instability of the cyanonitramine precluded combustion analysis.
(4) J. Houben and E. Pfankuch, *Chem. Ber.*, **60B**, 586 (1927).
(5) L. Horner, L. Hochenberger, and W. Kirmse, *Chem. Ber.*, **94**, 290 (1961).
(6) Mp 140–144°; ir ($CHCl_3$) 3520, 3400, 1665, 1580 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (d, 6 H, J = 7.0 Hz, superimposed over d, 3 H), 3.0 (septet, 1 H, J = 7.0 Hz), 1.2–2.5 (m, 7 H), 6.5 (br, 2 H); uv (95% EtOH) 207 nm (ε 4900).
(7) Mp 206–208° (lit.[4] mp 208°); ir (CH_2Cl_2) 3545, 3420, 1675, 1585, 1380, 885 cm^{-1}; NMR (CCl_4) of corresponding nitrile (prepared by *p*-toluenesulfonyl chloride/pyridine dehydration) δ 1.12 (s, 6 H), 1.48–2.32 (m, 7 H), 4.80 (s, 1 H), 5.15 (s, 1 H).
(8) Mp 147–149°. Compared with an authentic sample: D. A. Petgunin and M. S. Kodyrera, *Zh. Obshch. Khim.*, **33** (3), 755 (1961), who report mp 146–148°.
(9) The cyanonitramine intermediates were too unstable to permit isolation.

Department of Chemistry
State University of New York
at Binghamton
Binghamton, New York 13901

P. J. Kocienski*
M. Kirkup

Received March 11, 1975

A New ACS Audio Course

Principles of Heterocyclic Chemistry

Parts I & II

Taught by Professor Edward C. Taylor, 1974 recipient of the ACS Award for Creative Work in Synthetic Organic Chemistry, this course comprises the first half (which is complete by itself) of a comprehensive four-part introduction to the immense field of organic heterocycles. The course consists of twelve audiotape cassettes (playing time—11.4 hrs.) and a 223-page integrated reference manual.

Professor Taylor avoids the traditional treatment of cataloging reactions and properties in favor of discussing the relationships between structure and chemical and physical properties, the chemical consequences of heteroatom introduction, and the differences between heterocyclic and homocyclic compounds. He discusses five-membered (pi-excessive) heterocycles such as pyrroles, furans, and thiophenes, and six-membered (pi-deficient) heterocycles in depth. Specific topics include electrophilic substitution and nucleophilic addition reactions, the introduction and modification of substituent groups, various ring-opening, ring-transformation, and rearrangement reactions, the chemical and biochemical consequences of covalent hydration, and the chemistry of N-oxides and hetarynes. Numerous questions, and discussions of their solutions, are interspersed throughout the course. Listeners should be familiar with basic organic chemistry.

Dr. Taylor, A. Barton Hepburn Professor of Organic Chemistry and Chairman of the Chemistry Department of Princeton University, is one of the world's leading authorities on the subject of heterocyclic chemistry. Professor Taylor serves as a consultant to several firms; is a member of the editorial boards of four journals; has published several books and over 250 articles; and is editor of the series *Advances in Organic Chemistry* and co-editor of the series, *The Chemistry of Heterocyclic Compounds* and *General Heterocyclic Chemistry*.

Like all ACS Audio Courses, PRINCIPLES OF HETEROCYCLIC CHEMISTRY can be used effectively by one person for individual study or by groups in classroom situations. (Only one copy of the course is necessary for use by a group, but every participant will need a copy of the course manual.)

Other ACS Audio Courses: Technical Writing • Chemical Abstracts • Orbital Symmetry • Gas Chromatography • Liquid Chromatography • Gel Permeation Chromatography • Infrared Spectra • Patent Practice • Marketing • Acids/Bases • Fluorescence/Phosphoresence • Organic Synthesis • R&D Management • NMR • Raman Spectroscopy • Ion-Selective Electrodes • Crystalline Polymers • Organometallic Compounds • Business Aspects of Chemistry • Organic Photochemistry • Organofluorine Chemistry

Fill out and mail to:
Department of Educational Activities
American Chemical Society
1155 Sixteenth Street, N.W.
Washington, D.C. 20036

Please send me the following. I understand that I may return all purchases within 10 days if not completely satisfied.

_____ complete unit(s) of the ACS Audio Course, *Principles of Heterocyclic Chemistry—I & II,* at $195 per unit.

_____ extra copies of the course manual (1-9 copies, $13.00 each; 10-49, 11.50 each; 50 or more, 10.50 each).

_____ your catalog describing the 24 ACS Audio Courses now available.

Note: Payment must accompany orders of $25 or less. Please allow five weeks for delivery.

Name and Title _____

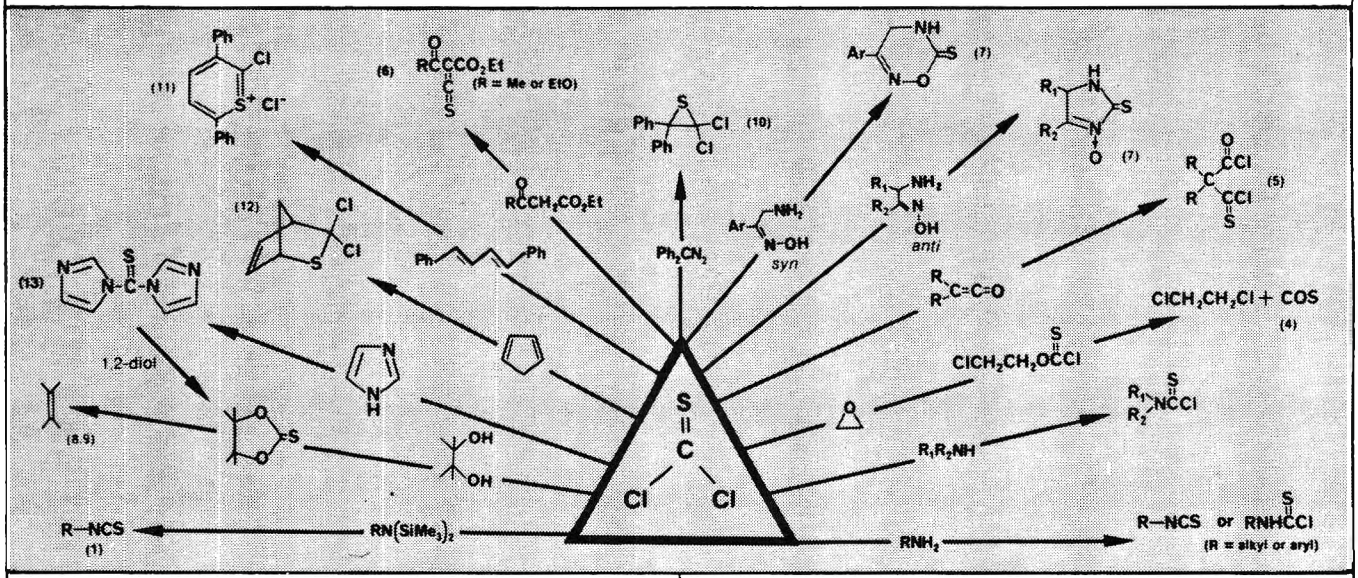
Organization _____

Address _____

City, State, ZIP _____ Phone _____

Thiophosgene

- Synthesis of isothiocyanates, thiocarbonyl compounds, heterocycles
- Stereospecific Corey-Winter alkene synthesis



THIOPHOSGENE reacts with alcohols, phenols, mercaptans, thiophenols, and various amines to give products which vary depending on the reaction conditions and the starting materials. For instance, **aromatic amines** give thiocarbamoyl chlorides in anhydrous ether, but afford isothiocyanates and/or thioureas in an aqueous medium or upon heating the reaction mixture. **Primary aliphatic amines** give isothiocyanates with great ease, whereas **secondary aliphatic amines** lead to thiocarbamoyl chlorides. Other amines, such as silylated amines,[1] hydrazines, hydrazides and semicarbazides behave similarly.

Thiophosgene reacts with **aromatic diazoketones** to produce various interesting products including some heterocycles.[2,3] It also reacts with **epoxides**,[4] **ketenes**[5] and **activated methylenes.**[6] A Friedel-Crafts reaction on benzene produces thiobenzophenone.[6]

Thiophosgene leads to a great variety of heterocycles, especially with substrates containing either two amino, hydroxyl or mercapto groups, or any combination thereof at 1,2- or 1,3-positions.[7] The **thionocarbonates derived from 1,2-diols** undergo *cis*-elimination to yield olefins when heated with trialkyl phosphites.[8] This constitutes a useful, **stereospecific synthesis of olefins** from 1,2-diols. A non-stereospecific conversion of **thionocarbonates** to olefins can also be achieved *via* an alkylation-reduction sequence.[9] Reactions of thiophosgene with diazo compounds[10] and Diels-Alder additions with 1,3-dienes afford sulfur-containing heterocycles.[11,12]

For additional reactions involving **thiophosgene**, please send for data sheet.

References:

1) G. Barnikow and W. Abraham, *Z. Chem.*, **8**, 335 (1968)
2) W. Ried and B.M. Beck, *Ann. Chem.*, **673**, 124 (1964).
3) T. Bacchetti, A. Alemagna, and B. Danieli, *Tetrahedron Lett.*, 3569 (1964).
4) J.I. Jones, *J. Chem.Soc.*, 2735 (1957).
5) J.C. Martin and P.G. Gott, *Def. Publ., U.S. Pat. Off. 877,022; Chem. Abstr.*, 73, P76690c (1970).
6) H. Bergreen, *Ber.*, **21**, 337 (1888).
7) H. Gnichtel, S. Exner, H. Bierbüsse, and M. Alterdinger, *Chem. Ber.*, **104**, 1512 (1971).
8) E.J. Corey and R.A.E. Winter, *J. Amer. Chem. Soc.*, **85**, 2677 (1963); E.J. Corey, F.A. Carey, and R.A.E. Winter, *ibid.*, **87**, 934 (1965).
9) E. Vedejs and E.S.C. Wu, *J. Org. Chem.*, **39**, 3641 (1974).
10) H. Staudinger and I. Siegwart, *Helv. Chim. Acta*, **3**, 840 (1920).
11) G. Laban and R. Mayer, *Z. Chem.*, **7**, 227 (1967).
12) W.J. Middleton, *J. Org. Chem.*, **30**, 1390 (1965); C.R. Johnson, J.E. Keiser, and J.C. Sharp, *ibid.*, **34**, 860 (1969).
13) H.A. Staab and G. Walther, *Ann. Chem.*, **657**, 98 (1962); T.L. Nagabhushan, *Can. J. Chem.*, **48**, 383 (1970).

11,515-0 **Thiophosgene** ..... **11.5g†** **$10.80**
25g $18.35; 100g $48.30

†Decimole unit

Aldrich Chemical Company, Inc.

Craftsmen in Chemistry

Corporate Offices:
Aldrich Chemical Co., Inc.
940 W. Saint Paul Ave.
Milwaukee, Wisconsin 53233

In Great Britain:
Aldrich Chemical Co., Ltd.
264 Water Rd., Wembley, Middx.
HAO 1PY, England

In Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium

In Germany:
EGA-Chemie KG
7924 Steinheim am Albuch
Germany