VOLUME 43 APRIL 28, 1978 NUMBER 9 JOCEAH

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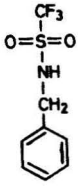
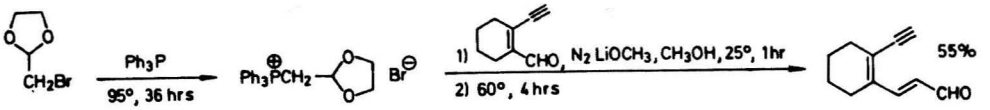
13960 N-Benzyl trifluoromethanesulfonamide purum MP 45-47 (N-Benzyl-triflamide) — 5 g sFr. 32.— US$ 16.00
$CF_3SO_2NHC_7H_7$ $C_8H_8F_3NO_2S$ MW 239.22



Reagent for a new "Gabriel" synthesis of primary amines. — 25 g sFr. 135.— US$ 62.50
J.B. Hendrickson et al., Tetrahedron (1975) 31, 2517

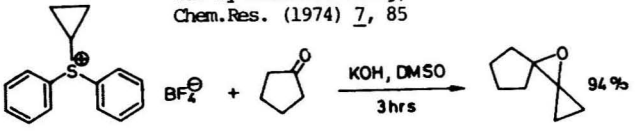
17618 2-Bromomethyl-1,3-dioxolane pract. BP_{12} 65-67°; n_D^{20} 1.4798 — 1 lt ≈ 1.61 kg — 25 ml sFr. 18.— US$ 9.00
$C_4H_7BrO_2$ MW 167.02

Useful synthon for the preparation of α,β-unsaturated aldehydes: T.M. Cresp, M.V. Sargent, P. Vogel, J.Chem.Soc.Perkin I (1974) 39; — 100 ml sFr. 65.— US$ 32.50
synthon, for the preparation of 1,4-dialdenyde monoacetals: J.F. Le Borgne, Th. Cuvigny, M. Larchevêque, H. Normant, Tetrahedron Lett. (1976) 1379

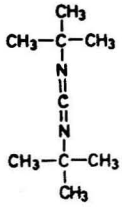


29950 Cyclopropyldiphenylsulfonium tetrafluoroborate pract. MP 135-137° — 1 g sFr. 65.— US$ 32.50
$CH_2CH_2CHS(C_6H_5)_2(BF_4)$ $C_{15}H_{15}BF_4S$ MW 314.15

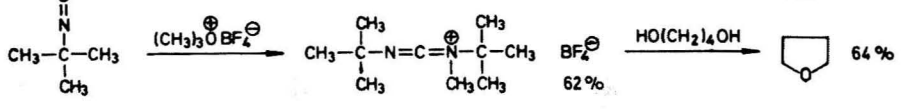
Excellent reagent for the spiroannelation of carbonyl compounds. The ylide derived from this salt effects many different synthetic transformations: M.J. Bogdanowicz, B.M. Trost, Org.Synth. (1974) 54, 27; B.M. Trost, Pure and Appl.Chem. (1975) 43, 563-585; B.M. Trost in "Organic Sulphur Chemistry", ed. by D.J.M.Stirling, Butterworths, London (1975) 237-263; B.M. Trost, Acc. Chem.Res. (1974) 7, 85



34640 N,N'-Di-tert-butylcarbodiimide purum >99% (GLC); BP_{12} 48-50°; n_D^{20} 1.4298; 1 lt ≈ 0.80 kg — 5 ml sFr. 37.— US$ 18.50
$(CH_3)_3C:N:C(CH_3)_3$ $C_9H_{18}N$ MW 140.25

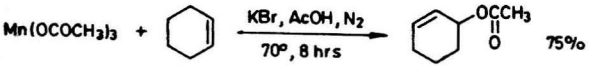


Synthon; dehydrating reagent; starting material for the preparation of N,N'-di-tert-butyl-N-methylcarbodiimidium tetrafluoroborate, a potent agent to effect molecular dehydrations: K. Hartke et al., Liebigs Ann.Chem. (1972) 762, 167; R.C. Schnur, E.E. van Tamelen, J.Am.Chem.Soc. (1975) 97, 464



63538 Manganese (III) acetate pract. (Manganic acetate) — 50 g sFr. 50.— US$ 25.00
$Mn(OCOCH_3)_3.2H_2O$ $C_6H_9MnO_6.2H_2O$ MW 268.10

Reagent for the oxidation of olefins and aromatic hydrocarbons: L. Fieser M. Fieser, "Reagents for Organic Synthesis", 2, 263, 4, 318, 6, 355; John Wiley and Sons, Inc.; J.R. Gilmore, J.M. Mellor, J.Chem.Soc. (C) (1971) 2355



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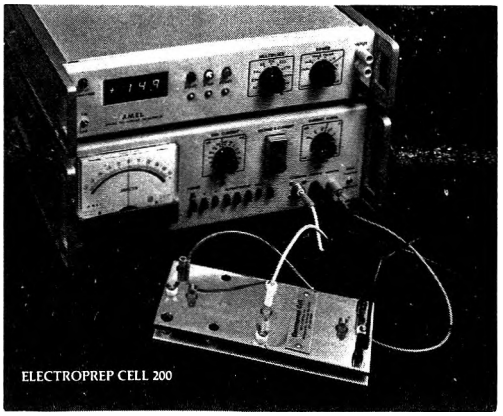

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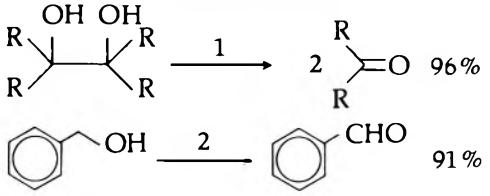
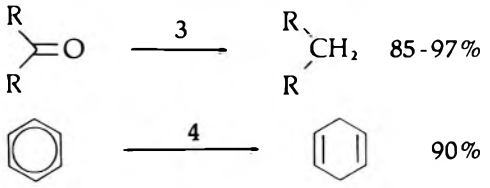


REDUCTIONS



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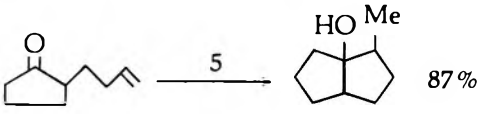

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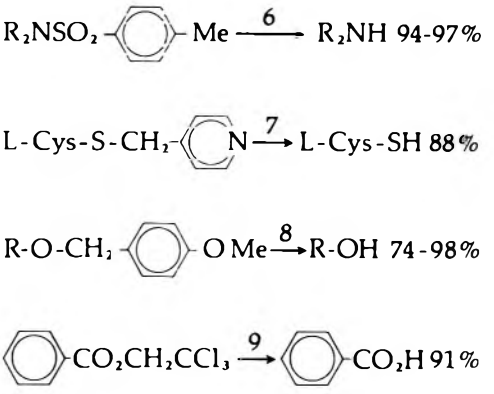
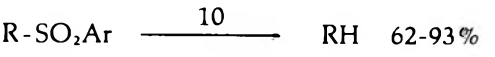
DEPROTECTIONS



DESULFONATIONS



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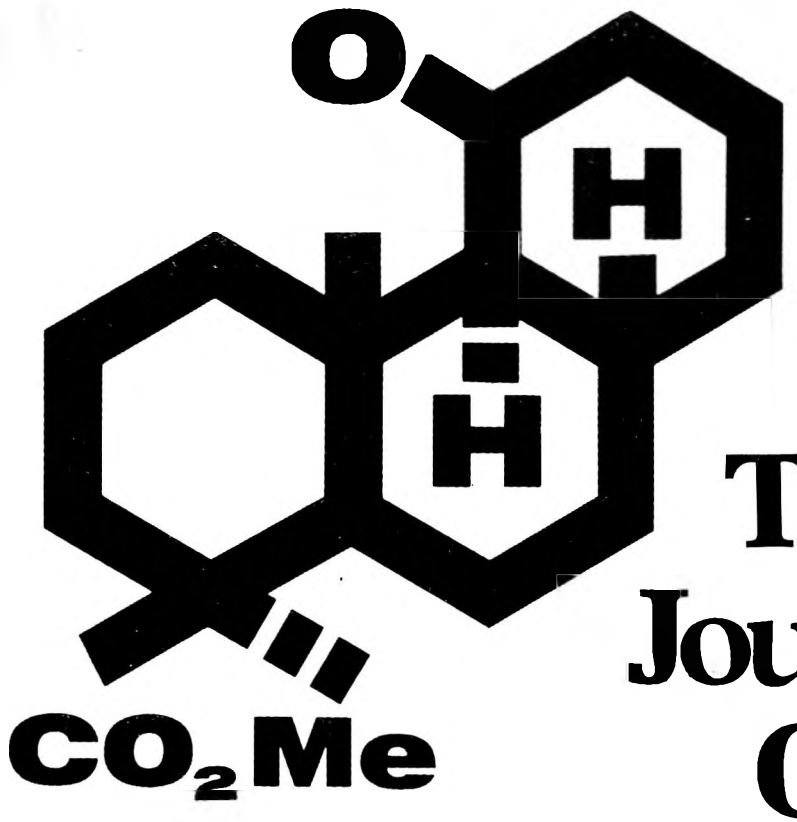
JOCEAH 43(9) 1627–1842 (1978)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry®

VOLUME 43, NUMBER 9 APRIL 28, 1978

Martha L. Casey,* Robert C. Paulick, and Howard W. Whitlock	1627	Carbon-13 Nuclear Magnetic Resonance Study of the Biosynthesis of Daunomycin and Islandicin
Ulf-H. Dolling,* Alan W. Douglas, Edward J. J. Grabowski, Erwin F. Schoenewaldt, Paul Sohar, and Meyer Sletzinger	1634	Synthesis and Resolution of 3-Fluoro-D,L-alanine-*2-d*: A Selective Deuteration via Reductive Amination with Sodium Borodeuteride
M. Brawner Floyd	1641	Prostaglandins and Congeners. 18. Synthesis of Cyclopentenolone Precursors to Prostaglandins from 2,5-Dihydro-2,5-dimethoxyfurans
Charles R. Frihart, Aaron M. Feinberg, and Koji Nakanishi*	1644	Synthesis of 4,9-Dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-*a*]purine and the "Y" Base from *Saccharomyces cerevisiae* Phenylalanine Transfer RNA
James K. Whitesell* and Randall S. Matthews	1650	Studies in the Total Synthesis of Mono- and Sesquiterpenes. 3. Genipic Acid
Antonio Mouriño and William H. Okamura*	1653 ■	Studies on Vitamin D (Calciferol) and Its Analogues. 14. On the 10,19-Dihydrovitamins Related to Vitamin D_2 Including Dihydrotachysterol$_2$
Clinton E. Browne, Thomas K. Dobbs, Stephen S. Hecht, and Edmund J. Eisenbraun*	1656	Stereochemical Assignment of (*E*)- and (*Z*)-2-(1-Naphthyl)-1-phenylpropene and Their Photocyclization to 5-Methylchrysene
Kazushi Arata, James O. Bledsoe, Jr.,* and Kozo Tanabe*	1660	Isomerization of 2- and 3-Carene Oxides over Solid Acids and Bases
Albert Padwa,* Steven Nahm, and Eisuke Sato	1664	Intramolecular 1,3-Dipolar Cycloaddition Reactions of Alkenyl-Substituted Nitrile Imines
Saroj K. Vohra, George W. Harrington, and Daniel Swern*	1671	Reversible Interconversion of *N*-Nitroso(2-methylamino)acetonitrile and 3-Methyl-5-amino-1,2,3-oxadiazolium Chloride and Related Reactions
H. C. van der Plas,* A. van Veldhuizen, M. Wozniak, and P. Smit	1673 ■	Nuclear Magnetic Resonance Studies on σ Adducts of Heterocyclic Systems with Nucleophiles. 18. Proton and Carbon-13 Nuclear Magnetic Resonance Investigations on σ-Adduct Formation between 1,*X*-Naphthyridines and Some Methyl-1,8-naphthyridines with Potassium Amide in Liquid Ammonia
Keitaro Senga,* Misuzu Ichiba, and Sadao Nishigaki	1677	Synthesis and Properties of [1,2,3]Thiadiazolo[4,5-*d*]pyrimidine Derivatives Including Their Mesoionic Compounds. A New Class of Heterocycles
Miwako Mori, Katsumi Chiba, and Yoshio Ban*	1684	Reactions and Syntheses with Organometallic Compounds. 7. Synthesis of Benzolactams by Palladium-Catalyzed Amidation
James E. Bittell* and John L. Speier	1687	Synthesis of Thiols and Polysulfides from Alkyl Halides, Hydrogen Sulfide, Ammonia, and Sulfur
T. Hori and K. B. Sharpless*	1689	Synthetic Applications of Arylselenenic and Arylseleninic Acids. Conversion of Olefins to Allylic Alcohols and Epoxides
Hans J. Reich,* Susan Wollowitz, John E. Trend, Flora Chow, and Daniel F. Wendelborn	1697	Syn Elimination of Alkyl Selenoxides. Side Reactions Involving Selenenic Acids. Structural and Solvent Effects on Rates

Richard D. Gandour,* Valentino J. Stella, Mark Coyne, Richard L. Schowen, and Emilio A. Icaza	1705	Secondary Isotope Effects in Intramolecular Catalysis. Mono-*p*-bromophenyl Succinate Hydrolysis
Herbert C. Brown* and M. Ravindranathan	1709	Structural Effects in Solvolytic Reactions. 25. Solvolysis of Aryl(2-norbornyl)methylcarbinyl *p*-Nitrobenzoates. Search for a Special Stereoelectronic Effect with the Tool of Increasing Electron Demand
John A. Zoltewicz* and John K. O'Halloran	1713	Model Studies of Thiamin Catalysis. Comparison of the Effects of Heteroatoms at Annular Positions on Side-Chain Kinetic Acidity
John A. Zoltewicz* and Larry S. Helmick	1718	Model Studies of Thiamin Catalysis. Steric Inhibition of Deprotonation of a Hydroxyethyl Side Chain
Sanford Slae and Robert Shapiro*	1721	Kinetics and Mechanism of the Deamination of 1-Methyl-5,6-dihydrocytosine
Ralph J. De Pasquale	1727	An Approach to the Synthesis of *F*-Tertiary Amines
Douglas E. Applequist* and James H. Klug	1729	Energies of the Cycloalkyl and 1-Methylcycloalkyl Free Radical by the Decarbonylation Method
Hideyuki Matsumoto,* Taichi Nakano, Keizo Takasu, and Yoichiro Nagai	1734	Radical Reactions in the Coordination Sphere. 4. Addition of Carbon Tetrachloride to *cis*-Cyclooctene Catalyzed by Dichlorotris(triphenylphosphine)ruthenium(II)
Vincenzo Malatesta and Michael Cocivera*	1737	Flow Nuclear Magnetic Resonance Measurement of Nucleophilic Addition to Pyruvate Anion
George A. Olah* and Daniel J. Donovan	1743	The Search for Stable Nitrenium Ions: Protonation of Benzoquinone Monooximes in Superacids and the Study of Their Structure by Proton and Carbon-13 Nuclear Magnetic Resonance Spectroscopy
Dorit Ayalon Chass, Duang Buddhasukh, and Philip D. Magnus*	1750	Studies on Terpenes. 5. Synthesis of (+)-Hinesol and (+)-10-Epihinesol
Stanley J. Cristol,* Dean P. Stull, and Thomas E. McEntee. Jr.	1756	Photochemical Transformations. 21. Photochemical and Thermal Methanolyses of Two Epimeric Bridged Polycyclic Bromides
Yoshiro Ogata,* Yasuhiko Sawaki, and Hideo Shimizu	1760	Rates and Scope of the Oxidative Carbon–Carbon Cleavage of Epoxides by Alkaline Hydrogen Peroxide
F. G. Bordwell* and Frederick J. Cornforth	1763	Application of the Hammett Equation to Equilibrium Acidities of Meta- and Para-Substituted Acetophenones
Nancy K. Wilson* and Robert D. Zehr	1768	Substituent Effects and Additivity in the Carbon-13 Nuclear Magnetic Resonance Spectra of Chlorinated Naphthalenes and Their Chlorinated Naphthol Metabolites
Alfred Hassner,* Harold W. Pinnick, and Jay M. Ansell	1774	Synthetic Approaches to α-Methylene γ-Lactones via Cycloadditions of Ketenes
Xavier Creary	1777	Addition of Carbenes to 1,1-Dimethylallene. Formation and Rearrangement of Substituted Methylenecyclopropanes
Donald R. Paulson,* L. Scott Gilliam, Virgil O. Terry, Susanne M. Farr, Earl J. Parker, Franklin Y. N. Tang, Rudiger Ullman, and George E. Ribar	1783	Hydrogenation of 2,5-Diacetoxy-2,5-dimethyl-3-hexyne over Palladium
John Solodar	1787	Asymmetric and Regioselective Hydrogenation of Piperitenone by Homogeneous Rhodium Complexes
Giampaolo Giacomelli, Rita Menicagli, Anna Maria Caporusso, and Luciano Lardicci*	1790	Alkylmetal Asymmetric Reduction. 9. Asymmetric Reduction of Alkyl Phenyl Ketones by Sterically Hindered Chiral Organoaluminum Compounds
Bruce E. Leach	1794	Alumina-Catalyzed Ipso Attack in Electrophilic Aromatic Substitution: Methylation of 2,6-Xylenol to 2,3,6-Trimethylphenol
Franklin A. Davis* and Paul A. Mancinelli	1797	Chemistry of the Sulfur–Nitrogen Bond. 13. A New Synthesis of *N*-Alkylidenearenesulfenamides (Sulfenimines): Alkylation of Sulfenamide Enolate Equivalents
John E. McMurry* and William Choy	1800	On the Mechanism of the Thermal Isomerization of 1,2-Diolates. Is the Pinacol Coupling Reaction Reversible?



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John A. Hyatt	1808	Octopus Molecules in the Cyclotriveratrylene Series

NOTES

J. O. Stoffer,* D. R. Strait, D. L. Filger, E. T. Lloyd, and C. Crain	1812	A Novel Method for Direct Measurement of the pK_a's of Weakly Acidic Hydrocarbons
C. David Johnson	1814	Use of the Tool of Increasing Electron Demand in Determination of the Status of the Yukawa–Tsuno (YT) Equation
Ryuichi Ueoka, Kazuo Shimamoto, Yoshimasa Maezato, and Katsutoshi Ohkubo*	1815	Hydrophobic Forces in Selective Hydrolyses of Nonionic *p*-Nitrophenyl Ester and Anionic 3-Nitro-4-acyloxybenzoic Acid Substrates by Hydroxamic Acids
Jean Khazarian, Serge Geribaldi, Louis Ferrero, Michel Rouillard, and Marcel Azzaro*	1817	A Method for β-C-Acylation and β-Alkylation of α,β-Unsaturated Ketones
Richard P. Szajewski	1819	Concerning the Reductive Alkylation of Epoxy Ketones
James H. Babler,* Nancy Casey Malek, and Michael J. Coghlan	1821	Selective Hydrolysis of α,β- and β,γ-Unsaturated Ketals: a Method for Deconjugation of β,β-Disubstituted α,β-Unsaturated Ketones
Steven P. Schmidt and Gary B. Schuster*	1823	Photolysis of o-Phenylene Oxalate. A High-Yield Photodecarbonylation Reaction
Ronald H. Rynbrandt* and Doris P. Balgoyen	1824	Synthesis and Thermal Decomposition of 1-Methyl-1*H*,3*H*-1,2-benzisothiazole 1-Oxide Hydrochloride
Reinhard Richter* and George H. Temme	1825	Base-Catalyzed Cis–Trans Isomerization of Bis(4-benzylideneaminocyclohexyl)methane
Gerald J. Boudreaux, Ernest I. Becker,* and Byron H. Arison	1827	Intramolecular Aldol Condensation of 2,2′-Dimethylbenzil
Enrico Mincione	1829	Hydroboration of Carbonyl Compounds with Borane–Methyl Sulfide
Herman O. Krabbenhoft	1830	Correlation of σ^+ and σ^- Substituent Constants with Carbon-13 Shieldings of β Carbons of Para-Substituted β,β-Dichlorostyrenes
Roger S. Macomber	1832	Epoxidation of Allenic Phosphonic Acids. Intramolecular Trapping of Allene Oxides
Alan A. Millard and Michael W. Rathke*	1834	Procedure for the Permethylation of Ketones Using Potassium Hydride and Methyl Iodide
H. Harry Szmant* and Raghunath Nanjundiah	1835	Thiol–Olefin Cooxidation Reaction. 6. A New Convenient Route to 1-Substituted Indenes. Indenone as Dienophile in Diels–Alder Reactions
Glen A. Russell,* V. Malatesta, and R. A. Blankespoor	1837	Radical Anions of Substituted Cyclobutene-1,2-diones
Gary L. Grunewald* and Wayne J. Brouillette	1839	An Ethoxycarbonyl Migration from an Amide Nitrogen to Oxygen

COMMUNICATIONS

Philip E. Sonnet	1841	Conversion of Epoxides to Olefins with Trifluoroacetyl Iodide and Sodium Iodide

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

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

AUTHOR INDEX

Ansell, J. M., 1774
Applequist, D. E., 1729
Arata, K., 1660
Arison, B. H., 1827
Azzaro, M., 1817

Babler, J. H., 1821
Balgoyen, D. P., 1824
Ban, Y., 1684
Becker, E. I., 1827
Bittell, J. E., 1687
Blankespoor, R. A., 1837
Bledsoe, J. O., Jr., 1660
Bordwell, F. G., 1763
Boudreaux, G. J., 1827
Brouillette, W. J., 1839
Brown, H. C., 1709
Browne, C. E., 1656
Buddhasukh, D., 1750

Caporusso, A. M., 1790
Casey, M. L., 1627
Chass, D. A., 1750
Chiba, K., 1684
Chow, F., 1697
Choy, W., 1800
Cocivera, M., 1737
Coghlan, M. J., 1821
Cornforth, F. J., 1763
Coyne, M., 1705
Crain, C., 1812
Creary, X., 1777
Cristol, S. J., 1756

Davis, F. A., 1797
De Pasquale, R. J., 1727
Dobbs, T. K., 1656
Dolling, U.-H., 1634
Donovan, D. J., 1743
Douglas, A. W., 1634

Eisenbraun, E. J., 1656

Farr, S. M., 1783
Feinberg, A. M., 1644
Ferrero, L., 1817
Filger, D. L., 1812
Floyd, M. B., 1641
Frihart, C. R., 1644

Gandour, R. D., 1705
Geribaldi, S., 1817
Giacomelli, G., 1790
Gilliam, L. S., 1783
Grabowski, E. J. J., 1634
Grunewald, G. L., 1839

Harrington, G. W., 1671
Hassner, A., 1774
Hecht, S. S., 1656
Helmick, L. S., 1718
Hirakawa, K., 1804
Hori, T., 1689
Hyatt, J. A., 1808

Icaza, E. A., 1705
Ichiba, M., 1677

Johnson, C. D., 1814

Khazarian, J., 1817
Klug, J. H., 1729
Krabbenhoft, H. O., 1830

Lardicci, L., 1790
Leach, B. E., 1794
Lloyd, E. T., 1812

Macomber, R. S., 1832
Maezato, Y., 1815
Magnus, P. D., 1750
Malatesta, V., 1737, 1837
Malek, N. C., 1821
Mancinelli, P. A., 1797
Matsumoto, H., 1734
Matthews, R. S., 1650
McEntee, T. E., Jr., 1756
McMurry, J. E., 1800
Menicagli, R., 1790
Millard, A. A., 1834
Mincione, E., 1829
Mori, M., 1684
Mouriño, A., 1653

Nagai, Y., 1734
Nahm, S., 1664
Nakanishi, K., 1644
Nakano, T., 1734
Nakazawa, S., 1804
Nanjundiah, R., 1835
Nishigaki, S., 1677

O'Halloran, J. K., 1713
Ogata, Y., 1760
Ohkubo, K., 1815
Okamura, W. H., 1653
Olah, G. A., 1743

Padwa, A., 1664
Parker, E. J., 1783
Paulick, R. C., 1627
Paulson, D. R., 1783
Pinnick, H. W., 1774

Rathke, M. W., 1834
Ravindranathan, M., 1709
Reich, H. J., 1697
Ribar, G. E., 1783
Richter, R., 1825
Rouillard, M., 1817
Russell, G. A., 1837
Rynbrandt, R. H., 1824

Sato, E., 1664
Sawaki, Y., 1760
Schmidt, S. P., 1823
Schoenewaldt, E. F., 1634
Schowen, R. L., 1705
Schuster, G. B., 1823
Senga, K., 1677
Shapiro, R., 1721
Sharpless, K. B., 1389
Shimamoto, K., 1815
Shimizu, H., 1760
Slae, S., 1721
Sletzinger, M., 1634
Smit, P., 1673
Sohar, P., 1634
Solodar, J., 1787
Sonnett, P. E., 1841
Speier, J. L., 1687
Stella, V. J., 1705
Stoffer, J. O., 1812
Strait, D. R., 1812
Stull, D. P., 1756
Swern, D., 1671
Szajewski, R. P., 1819
Szmant, H. H., 1835

Takasu, K., 1734
Tanabe, K., 1660
Tang, F. Y. N., 1783
Temme, G. H., 1825
Terry, V. O., 1783
Trend, J. E., 1697

Ueoka, R., 1815
Ullman, R., 1783

van der Plas, H. C., 1673
van Veldhuizen, A., 1673
Vohra, S. K., 1671

Wendelborn, D. F., 1697
Whitesell, J. K., 1650
Whitlock, H. W., 1627
Wilson, N. K., 1768
Wollowitz, S., 1697
Wozniak, M., 1673

Zehr, R. D., 1768
Zoltewicz, J. A., 1713, 1718

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Carbon-13 Nuclear Magnetic Resonance Study of the Biosynthesis of Daunomycin and Islandicin

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The biosynthesis of daunomycin (**1a**) and islandicin (**2a**) has been studied, utilizing both sodium [1-^{13}C]- and [2-^{13}C]acetate and sodium [1,2-^{13}C]acetate. The results establish the biosynthetic scheme for both compounds and indicate a pathway more complicated than a simple acetate connectivity pattern in the biosynthesis of daunomycin. The assignment of the ^{13}C resonance frequencies in the two compounds was based partially on a study of the ^{13}C frequencies in a series of diacetoxyanthraquinones.

Introduction

A ^{13}C nuclear magnetic resonance study using $^{13}CH_3{}^{13}CO_2Na$ was used to establish the connectivity pattern in the biosynthesis of the polyketide antibiotic daunomycin (**1a**) and the related compound islandicin (**2a**). Both daunomycin (**1a**) and adriamycin (**1b**) demonstrate therapeutic activity in the treatment of leukemias, especially acute lymphocytic leukemia in children. Adriamycin is a particularly potent anticancer antibiotic showing, in addition, chemotherapeutic effectiveness against many solid tumors.[1] The fluorescent properties of daunomycin had made possible the observance of the molecule's penetration into the cell and its fixation in the nuclear structure. It has been shown to bind strongly to DNA and current thinking regards its primary effect as one of interfering with template DNA function.[1]

A number of plausible connectivity patterns for daunomycin are possible (Figure 1) via an acetate–polymalonate biosynthetic route (a or b). We have applied the Tanabe[2] technique to this biosynthetic problem and have obtained results that are consistent with only route a, a propionate "starter" and nine successive malonate condensations with loss of the terminal carboxyl.[3]

This result for daunomycin is strikingly different from that determined for the similar polyketide islandicin (**2a**) which was originally considered a biosynthetic prototype for daunomycin and adriamycin. Gatenbeck[4] had established using $CH_3{}^{14}CO_2Na$ that islandicin is biosynthesized from a polyketide precursor, with the labeling pattern indicated in Figure 2, but this pattern could arise from one of two possible foldings of the polyketide chain (Figure 2). In this case, we have demonstrated that islandicin is biosynthesized via configuration a of Figure 2.

Results and Discussion

We have previously described the method used by Tanabe[2] and ourselves[6] of employing [1,2-^{13}C]acetate of high isotopic purity, which enables one to trace acetate incorporation patterns on a two-carbon basis and detect skeletal rearrangements and cleavages without integration of the carbon spectrum. We have also described[6] how excellent carbon spectra of anthraquinone and naphthaquinone type molecules can be obtained when these compounds are acetylated to increase their solubility in $CDCl_3$ and render them compatible with the tris(acetylacetonato)chromium(III)($Cr(acac)_3$) T_1 suppressor technique.[7] The use of this technique assures that all peaks, including the easily saturated quarternary carbons, are visible when minimal pulse delays (2–3 s) are employed, and that all peaks are distinct and of comparable height, which is crucial to the studies using monolabeled acetate. For ^{13}C NMR analysis, islandicin was converted to its corresponding triacetate (**2b**) and daunomycin was hydrolyzed and acetylated with the formation of daunomycinone tetraacetate (Figure 3). The spectra of islandicin triacetate and daunomycinone tetraacetate are shown in Figures 4 and 5, respectively.

Culture and Isolation. Islandicin was first isolated in purified form by Howard and Raistrick[8] when they sought to determine the coloring matter in *Penicillium islandicum* Sopp. This fungus was first discovered and named by Sopp[9] in 1912 when he isolated the organism from a moldy specimen of Skyr, a soured milk peculiar to Iceland. Islandicin is just one of several hydroxyanthraquinones produced by the organism and isolated and identified by Howard and Raistrick.

Since our initial attempts to reproduce the culture conditions of Howard and Raistrick[8] gave variable yields of islandicin, we decided to employ a Czapek–Dox–agar medium for the organism. The use of these agar plates provided a small, reasonably uniform surface on which the mold could grow and to which the potential precursors could be added.

Instead of the multiple extraction and recrystallization steps utilized by the initial authors, our much simpler isolation procedure involved only chromatography of the crude extract and sublimation of the islandicin-containing fractions. The major contaminant in these fractions was iridoskyrin, an is-

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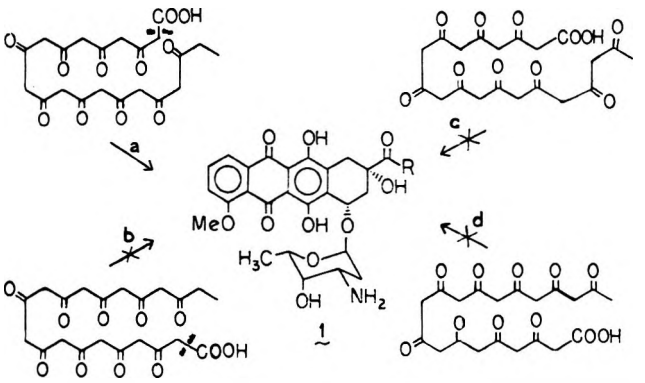


Figure 1. Plausible acetate connectivity patterns for the biosynthesis of daunomycin: **1a**, R = CH_3 (daunomycin); **1b**, R = CH_2OH (adriamycin).

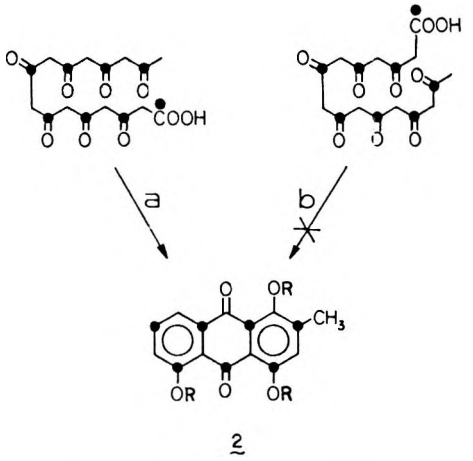


Figure 2. Acetate connectivity patterns for the biosynthesis of islandicin (**2a**, R = H). Islandicin triacetate (**2b**, R = $COCH_3$) was used for NMR analysis. Both indicated foldings of the polyketide chain would result in the labeling pattern observed by Gatenbeck using $CH_3{}^{14}CO_2Na$ (indicated with ●).

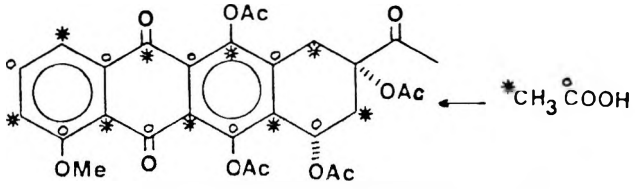


Figure 3. The labeling pattern established by the incorporations of sodium [1-^{13}C]- and [2-^{13}C]acetate into daunomycin.

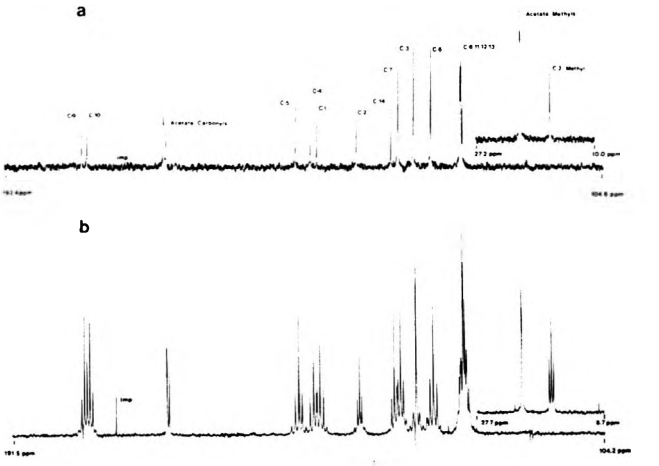


Figure 4. Proton noise-decoupled FT ^{13}C NMR spectrum of islandicin triacetate (20K transients, 3.0 s pulse delay): (a) from ^{13}C natural abundance (73 mg + 15 mg $Cr(acac)_3$); (b) from $^{13}CH_3{}^{13}CO_2Na$ enrichment (152 mg + 40 mg $Cr(acac)_3$).

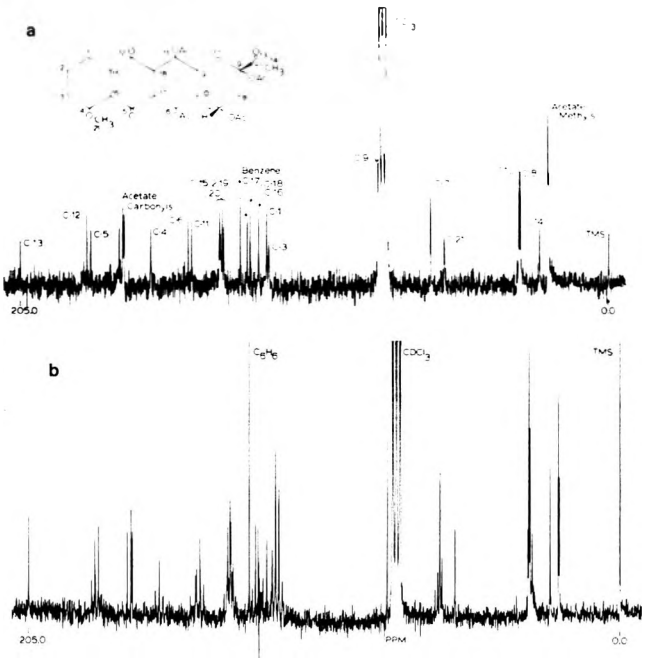


Figure 5. Proton noise-decoupled FT ^{13}C NMR spectrum of daunomycinone tetraacetate (11K transients, 1.27 s pulse delay): (a) from ^{13}C natural abundance (135 mg + 45 mg of $Cr(acac)_3$); (b) from $^{13}CH_3{}^{13}CO_2Na$ enrichment (30 mg + 6 mg of $Cr(acac)_3$).

landicin dimer, which could be recovered unchanged from the sublimation vessel. The yield of this material (<5% of the amount of islandicin isolated) was too low to warrant ^{13}C NMR analysis.

Daunomycin was first reported by Grien et al.[10] when they isolated this metabolite from the bacterium *Streptomyces peucetius*. Elucidation of the daunomycin structure was facilitated by its resemblance to several anthracyclines which have also demonstrated antibiotic activity.

Yields of daunomycin from submerged fermentations of *S. peucetius* have been reported[10] as high as 70 μg/mL, but this figure was based solely on spectral data. Actual isolation of the hydrochloride salt produced yields in the vicinity of 15 μg/mL, and this method of precipitating the material is not conducive to the small-scale fermentation necessary for ^{13}C incorporation studies.

Consequently, experimentation was directed toward elucidating the biosynthesis of daunomycinone (Figure 3), the aglycone portion of the molecule, which is much more adaptable to isolation and purification (chromatography) techniques than the glycoside itself. Both the aglycone and glycoside have been found in the mycelial extracts, and it was felt that acidic hydrolysis of the crude extract would liberate the aglycone portion of daunomycin while leaving the daunomycinone already formed unchanged. This procedure proved successful and yields of 25–30 μg/mL of daunomycinone were obtained.

The preparation of the tetraacetate has already been described,[11b] but in our hands the reaction also produced small amounts of the triacetate which had to be separated chromatographically. The triacetate could be recycled to produce more of the tetraacetate, but the reaction never effected complete conversion. Longer reaction times resulted in the formation of increasing amounts of low R_f material and a darkening of the reaction solution, so the reaction times were shortened and the recycling process used. This method rou-

Table I. Chemical-Shift Assignments for Carbons of Anthraquinone and Diacetoxyanthraquinones

Registry no.	Compd	Carbon no.	Obsd chemical shift[a]	Predicted/calcd chemical shift[b]
84-65-1	Anthraquinone	1, 4, 5, 8	127.3	126.4[c]
		2, 3, 6, 7	134.1	133.9[d]
		9, 10	183.1	184.9[e]
		11, 12, 13, 14	133.7	131.9[e]
2289-36-3	1,4-Diacetoxyanthraquinone	1, 4	148.3	148.0
		2, 3	131.0	129.0
		5, 8	127.0	127.3
		6, 7	134.2	134.1
		9, 10	181.5	183.1[g]
		11, 12	126.2	126.8[h]
		13, 14	133.4	133.7[h]
1747-93-9	1,5-Diacetoxyanthraquinone[f]	1, 5	150.1	150.3
		2, 6	129.7	127.7[i]
		3, 7	135.1	135.4
		4, 8	125.8	125.0
		9, 10	181.1	183.1[g]
		11, 13	124.4	127.3[h,i]
1963-82-2	1,8-Diacetoxyanthraquinone[f]	1, 8	150.1	150.3
		2, 7	130.3	127.7[h]
		3, 6	134.7	135.4
		4, 8	125.5	125.0
		9	181.0	181.1–181.5[j]
		10	182.0	183.1
		11, 14	125.7	127.3[h,i]
		12, 13	134.5	135.0[h]
1629-51-2	1,2-Diacetoxyanthraquinone	1	142.2	143.9
		2	148.5	150.7
		3	128.8	129.0
		4	126.6	126.3
		5, 8	127.3, 127.1	127.3
		6, 7	134.4, 134.2	134.1
		9	181.5	181.5[k]
		10	181.7	182.0[k]
		11	126.5	128.6[k,i]
		12, 13, 14	134.3, 132.7, 132.4	132.7–133.7[h]
		Acetate carbonyls	168.4, 167.7	
		Acetate methyls	20.8, 20.7	

[a] Chemical shifts were measured in $CDCl_3$ in ppm relative to internal Me_4Si. [b] The chemical shifts observed in anthraquinone formed the basis for the predicted/calculated chemical shifts of the diacetoxyanthraquinones, which were obtained by adding the substituent effect parameters for –OAc[12] to the basic anthraquinone shifts. 1,4-Naphthoquinone provided the model for the predicted shifts of 9,10-anthraquinone. [c] Broad doublet in undecoupled spectrum (J_{CH} = 163.7 Hz) with further long-range coupling apparent. [d] Doublet of doublets in undecoupled spectrum (J_{CH} = 162.8 Hz, J_{CCH} = 8.3 Hz). [e] Broad singlet in undecoupled spectrum. [f] The chemical shift of the acetate carbons are not separately recorded because they are consistent and characteristic; carbonyl carbon shift 169.3–169.5 ppm and methyl carbon shift 21.2 ppm. [g] Some upfield shift relative to anthraquinone expected due to the peri acetoxy group. [h] Sharp singlet in off-resonance experiments. For other carbons, signal appears as a broad singlet or multiplet. [i] The discrepancy between observed and calculated shifts was greatest for carbons ortho to an acetoxy substituent. [j] Predicted shift based on 1,4- and 1,5-diacetoxyanthraquinone. [k] Predicted shift of C-9 based on 1,4- model and of C-10 on 1,8- model; however, these two assignments could be interchanged.

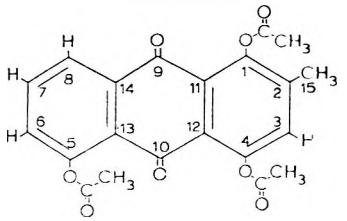
tinely gave yields of 60–70% of tetraacetate suitable for ^{13}C NMR analysis.

Chemical-Shift Assignment. Accurate chemical-shift assignment of each carbon of islandicin and daunomycin was essential in establishing which pairs of carbons originate from the same molecule of acetate, a prerequisite to determining the biosynthetic pathway. Because the literature had very few examples of model compounds for anthraquinone-type molecules, we undertook the determination of the ^{13}C chemical shifts of a series of model diacetoxy 1.4-anthraquinones (Table I), relating the proton and carbon chemical shifts to facilitate single-frequency decoupling experiments in daunomycin.

Diacetoxyanthraquinones. The basic method for assigning these chemical shifts was to compare a predicted/calculated chemical shift with the observed shift; the former was determined by adding parameters for ^{13}C substituent effects[12,13] to the chemical shifts observed for anthraquinone itself (Table I). Since these substituent effect parameters were determined for benzene, some systematic deviations from the calculated shifts were observed, in particular, the shifts of carbons ortho to an acetoxy group. For these ortho carbons, observed and calculated shifts agreed only to within 3 ppm, while for the other carbons agreement was almost always within 1 ppm. In addition to calculated shifts, other standard methods, mainly off-resonance decoupling, were useful in making the assignments detailed in Table I.

Islandicin Triacetate (2b). No single diacetoxyanthraquinone proved to be a "best model" for predicting the chemical shifts in islandicin triacetate (which, in turn, became the model for many of the carbons in daunomycinone tetraacetate). As might be expected, some carbons were best predicted from one model and some from another. Therefore, Table II gives a range of calculated chemical shifts for each carbon. The range represents the spread of values based on calculations using four model compounds; anthraquinone itself and 1,4-, 1,5-, and 1,8-diacetoxyanthraquinone. Obviously, the observed chemical shift could be even more closely matched by choosing a different "best model" for each indi-

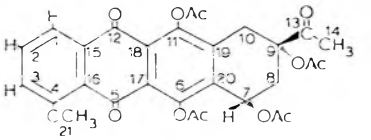
Table II. Chemical Shift Assignments for the Carbons of Islandicin Triacetate (tabulated by the numbering system shown below)



Carbon no.	Obsd chemical shift[a]	Predicted/calcd chemical shift[b]
1	146.4	148.5–149.0[c]
2	140.6	137.9–140.5
3	132.2	129.0–131.7
4	147.4	148.0–148.8[d]
5	149.6	150.0–150.3[d]
6	129.7	127.7–130.3
7	134.6	134.7–135.5[e]
8	125.3	124.6–125.8[f]
9	181.2	181.1–181.5[g]
10	180.4	181.0–181.1[g]
11	125.4	126.1–128.6[f,h]
12	125.1	123.3–126.5[f,h,i]
13	125.3	124.3–127.3[f,h,i]
14	135.5	134.5–136.0[c]
Acetate carbonyls		168.8–169.1
Acetate methyls		20.9–21.0

[a] Chemial shifts were measured in $CDCl_3$ in ppm relative to internal Me_4Si. [b] The chemical shifts observed in four model compounds, anthraquinone itself and 1,4-, 1,5-, and 1,8-diacetoxyanthraquinone, formed the basis for the range of predicted/calculated chemical shifts. As appropriate, substituent effect parameters[12,13] were added to the basic model compound shifts to obtain the predicted chemical shifts. [c] This carbon is distinguished from C-4 and C-5 on the basis of its derivation from the methyl carbon of acetate, while C-4 and C-5 are derived from the carbonyl carbon. [d] Calculated chemical shifts based on any one of the model compounds predict that C-4 will be at higher field than C-5. [e] C-7 distinguished from C-14 by off-resonance experiments where C-14 appears as a sharp singlet. [f] C-11, C-12 and C-13 distinguished from C-8 by off-resonance experiments where all except C-8 appear as a singlet. [g] Predicted chemical shift of C-9 is based on 1,4- and 1,5-diacetoxyanthraquinone, and of C-10 on 1,5- and 1,8-diaceoxyanthraquinone. These carbons distinguished primarily on the basis of singly labeled acetate studies which show C-9 as derived from the acetate methyl carbon and C-10 from the acetate carbonyl carbon. [h] C-11 distinguished from C-12 and C-13 by monolabeling experiments which show the former as derived from the carbonyl carbon of acetate and the latter two as derived from the acetate methyl. [i] C-12 distinguished from C-13 by experiments using doubly labeled acetate which clearly indicate that carbon at 125.1 ppm is coupled to C-4, while the carbon at 125.3 ppm is coupled to C-10 which, given the other data, is only internally consistent with the assignments given.

Table III. Chemical Shift Assignments for the Carbons of Daunomycinone Tetraacetate (tabulated by the numbering system shown below)



Carbon no.	Obsd chemical shift[a]	Predicted/calcd chemical shift[b]
1	119.3	118.4–119.6[c]
2	134.1	134.1–135.1[c]
3	118.3	118.6–119.7[c]
4	159.7	157.5–158.7
5	180.6	180.4[d]
6	146.7	147.4[d]
7	62.1	*c*
8	30.9	*c*
9	80.4	~81.2[e]
10	31.3	~29.3–38.5[c,f]
11	145.1	146.4[d]
12	182.0	181.2[d]
13	205.0	~205.0[g]
14	24.0	*c*
15	135.8	133.7–134.7
16	122.3	118.2–119.3
17	126.2	125.1[h]
18	125.2	125.4[h]
19	134.7	*h*
20	134.2	*h*
21	57.0	54.7[c,i]

[a] Chemical shifts were measured in $CDCl_3$ in ppm relative to internal Me_4Si. [b] The chemical shifts observed in the four model anthraquinones used to predict islandicin shifts (see Table II, *b*) also formed the basis for the predicted/calculated shifts of carbons 1–4 and carbons 15 and 16 of daunomycinone tetraacetate, while islandicin itself provided this basis for carbons 5, 6, 11, 12, 17, and 18. As appropriate, substituent effect parameters[12,13] were added to the basic model compound shifts to obtain the predicted chemical shifts. [c] Assignment of C-1, C-2, C-3, C-7, C-8, C-10, C-14, and C-21 was confirmed by single-frequency decoupling experiments. (H-1 = 7.70 ppm, H-2 = 7.59 ppm, H-3 = 7.24 ppm, H-7 = 6.34 ppm, H-8 protons, which are obscured, are best decoupled by irradiation at 2.40 ppm, H-10 is an AB quartet centered at 3.10 ppm, H-14 = 2.42 ppm, H-21 = 3.96 ppm.) The assignment of the proton spectrum was based on the previously reported assignments for daunomycinone[11a,f] and *N*-acetyldaunomycin.[11d] [d] The use of islandicin triacetate as a model predicts the given chemical shifts for C-5 vs. C-12 and for C-6 vs. C-11, but these assignments were also confirmed by the experiments using singly labeled acetate. [e] Predicted shift based on the model 1-acetoxy-1-methylcyclohexane: J. B. Stothers, ref 12, p 168. [f] Predicted shift range based on the shift of the carbon of alkylbenzenes: J. B. Stothers, ref 12, p 98. [g] Predicted shift based on acetone. [h] The pair C-17 and C-18 and the pair C-19 and C-20 were distinguished on the basis on the singly labeled acetate experiments. [i] Predicted shift based on anisole.

vidual islandicin carbon, but the range of values seems to be a less subjective approach in general, although as recorded in Table II, specific models were used in a few cases.

In addition to the standard carbon assignment technique, the islandicin assignments depended extensively on single-labeling experiments. The labeling pattern observed by Gatenbeck (Figure 2) and confirmed by experiments using sodium [1-^{13}C]- and [2-^{13}C]acetate establishes whether a given carbon is derived from the methyl or carbonyl carbon of acetate. Once most of the chemical-shift assignments have been made, one can use the results of the singly labeled acetate experiments to distingush between pairs of carbons, for example C-9 and C-10, which are close in chemical shift. Definitive assignment in such cases is easily made on the basis of the observed labeling pattern.

The doubly labeled acetate experiment permits final assignments of some carbons; C-12 and C-13 were assigned on the basis of their observed coupling to another carbon of known chemical shift. (The use of the doubly labeled results in making this assignment leads to completely internally consistent results.)

Daunomycinone Tetraacetate (Figure 3). Islandicin was the obvious basic model compound for predicting/calculating chemical shifts for C-5, 6, 11, 12, 17, and 18 of daunomycinone, and predicted values agree within 1.3 ppm with observed

Table IV. The Enrichment Levels at Various Carbons of Islandicin Triacetate from Sodium [1-^{13}C]- and [2-^{13}C]Acetate

Carbon	Peak intensity[a] Natural abundance	From [1-^{13}C]-NaOAc	From [2-^{13}C]-NaOAc
Acetate methyls (2 or 3)	1.00	1.00	1.00
C-1	0.39	0.26	1.10
C-2	0.38	0.76	0.30
C-3	0.79	0.60	2.04
C-4	0.50	1.08	0.41
C-5	0.43	1.05	0.39
C-6	0.77	0.52	2.15
C-7	0.65	1.73	0.52
C-8[b]	0.80	1.04	2.85
C-9	0.34	0.18	0.71
C-10	0.34	0.56	0.23
C-11[b]	0.80	1.04	2.85
C-12	0.39	0.30	0.84
C-13[b]	0.80	1.04	2.85
C-14	0.43	0.78	0.36
C-2 methyl	0.49	0.44	1.55

[a] Peak intensities were standardized to the peak representing two of three acetate methyls. The peak for the third methyl, being a partial shoulder, was not a suitable standard. [b] The peak at 125.3–125.4 ppm contains the resonances for C-8, C-11, and C-13. Since two of these are derived from the acetate methyl (C-8, -13) and one from the acetate carbonyl (C-11), the greatest enhancement is observed in islandicin grown from [2-^{13}C]acetate.

Table V. The Enrichment Levels at the Various Carbons of Daunomycinone Tetraacetate from Sodium [1-^{13}C]- and [2-^{13}C]Acetate

Carbon	Peak intensity[a] Natural abundance	From [1-^{13}C]-NaOAc	From [2-^{13}C]-NaOAc
C-1	1.68	1.00	3.89
C-2	1.07	2.31	1.02
C-3	0.97	0.76	3.10
C-4	1.21	1.84	0.68
C-5	1.21	1.71	1.02
C-6	1.39	1.53	0.91
C-7	2.21	3.25	1.70
C-8	2.54	1.12	5.61
C-9	2.60	1.04	2.00
C-10	2.57	1.31	6.20
C-11	1.43	0.86	2.96
C-12	1.43	0.71	2.87
C-13	1.07	0.55	1.05
C-14	1.25	0.73	2.28
C-15	1.50	1.98	0.75
C-16	1.36	0.90	2.82
C-17	1.50	0.64	2.60
C-18	1.68	1.84	0.84
C-19	1.82	1.84	1.04
C-20	1.32	0.51	2.34
C-21	1.00	1.00	1.00

[a] Peak intensities were standardized to the methoxy carbon.

values (Table III). The shifts for C-1, 2, 3, 4, 15, and 16 were calculated from anthraquinone and appropriate substituent effect parameters as described above. The remaining carbons were assigned from various other models as indicated in Table III.

Since the predicted ^{13}C shifts for C-1 and C-3 were very close, the assignment of these carbons rests on single-frequency experiments (H-1 at 7.70 ppm and H-3 at 7.24 ppm), which were definitive due to the adequate difference in proton chemical shift. Single frequency experiments also distinguished C-8 and C-10 (by irradiation of the AB quartet for C-10 at 3.10 ppm).

The following pairs of carbons, which were not definitively distinguishable on the basis of chemical shift, were assigned from the results of the experiments using singly labeled acetate: C-5 and C-12, C-6 and C-11, C-17 and C-18, and C-19 and C-20 (see results in Table V).

Incorporation of Singly Labeled Acetates. Islandicin Triacetate. In order to confirm the acetate labeling pattern in islandicin observed by Gatenbeck[4] using $CH_3{}^{14}CO_2Na$, *P. islandicum* was cultured separately in the presence of sodium [1-^{13}C]- and [2-^{13}C]acetate (both 91% isotopic purity). In each case, the resulting islandicin was chemically acetylated for ^{13}C NMR analysis. Because conditions had been established[6] under which all of the carbon signals of the unlabeled islandicin were within a factor of 2.5 of the same peak height, the spectra of the singly labeled islandicin triacetates were easily analyzed. The results of these labeling experiments are summarized in Table IV, and clearly show that the labeling pattern in islandicin is as shown in Figure 2. Seven carbons originate from the carbonyl carbon of acetate (C-2, 4, 5, 7, 10, 11, and 14) and eight from the methyl carbon (C-1, 3, 6, 8, 9, 12, 13, and 15), indicating that one decarboxylation is involved in the biosynthesis.

Table IV also shows that the incorporation level of [1-^{13}C]acetate about three times the natural abundance level. The variation in the apparent incorporation level between carbons is due partly to the insufficient resolution of the computer on the Brucker WH-270 spectrometer, which possesses a 16 384 digit capacity for the real part of the spectrum. At the required spectral width of 13 500 Hz, the resolution is 0.92 Hz/point, while most of the carbon peaks were observed to be 2–3 Hz wide, so that highly accurate peak height/peak area definition could not be expected (although it is somewhat better than the 1.38 Hz/point resolution available with the XL-100 spectrometer, used for the daunomycinone tetraacetate spectra).

A further obvious cause for relative peak height variation between samples is intrinsic differences in carbon relaxation times. These differences could be caused by different sample concentrations, different $Cr(acac)_3$ concentrations (although a contant molar ratio was used throughout), and/or instrumental variation in spite of standard settings.

Daunomycinone Tetraacetate. Since there were no reports of the acetate labeling pattern in daunomycin, single labeled acetate studies were of special interest. Using a method analogous to that described for islandicin, *S. peucetius* was cultured separately in the presence of [1-^{13}C]- and [2-^{13}C]acetate, acetylated, and observed under established ^{13}C NMR conditions. A molar ratio of 0.55 $Cr(acac)_3$ to daunomycinone tetraacetate was found to optimize the peak height of the carbonyl and quarternary carbons, although some line broadening of the methoxyl carbon occurred at the high absolute $Cr(acac)_3$ concentration used in studying the unlabeled sample. (To shorten observation times, a high concentration of both sample and $Cr(acac)_3$ was used in this case.)

The results of the [1-^{13}C]- and [2-^{13}C]acetate experiments are presented in Table V. Appreciable incorporation of [1-^{13}C]acetate was observed at carbons 2, 4, 5, 6, 7, 15, 18, and 19, while [2-^{13}C]acetate incorporation was observed at carbons 1, 3, 8, 10, 11, 12, 16, 17, and 20. Signals of enriched carbons generally appear two or three times more intense than the natural abundance level, with incorporations of the [2-^{13}C]-acetate being slightly greater than that of the [1-^{13}C]acetate. However, because the peak intensities are relative to the methoxyl carbon, which showed appreciable line broadening

Table VI. ^{13}C–^{13}C Coupling Constants for [1,2-^{13}C]Acetate-Enriched Islandicin Triacetate

Coupled carbons	J, Hz	Coupled carbons	J, Hz
C(2)–C(15)	44.3	C(7)–C(8)	56.4
C(15)–C(2)	44.4	C(8)–C(7)	55.5
C(4)–C(12)	71.2	C(14)–C(9)	53.7
C(12)–C(4)	72.1	C(9)–C(14)	54.6
C(10)–C(13)	56.4	C(11)–C(1)	73.1
C(13)–C(10)	56.4	C(1)–C(11)	74.0
C(5)–C(6)	70.2		
C(6)–C(5)	70.3		

Table VII. ^{13}C–^{13}C Coupling Constants for [1,2-^{13}C]Acetate-Enriched Daunomycinone Tetraacetate

Coupled carbons	J, Hz	Coupled carbons	J, Hz
C(1)–C(15)	53.1	C(6)–C(20)	~70
C(15)–C(1)	a	C(20)–C(6)	a
C(2)–C(3)	a	C(7)–C(8)	37.8
C(3)–C(2)	62.4	C(8)–C(7)	37.2
C(4)–C(16)	70.1	C(11)–C(19)	~63
C(16)–C(4)	70.3	C(19)–C(11)	a
C(5)–C(17)	54.3	C(12)–C(18)	~55
C(17)–C(5)	55.3	C(18)–C(12)	a

[a] In these cases either overlap was too extensive or signal intensity too weak to measure the values.

only in the high concentration unlabeled sample, a comparison of the peak intensities for the two labeled samples (run at approximately the same concentrations) proved, in most cases, the best measure of incorporation.

Peak intensity variation due to insufficient computer points and/or other factors (see islandicin discussion) was again a problem,[14] particularly in regard to C-13 and C-14, which together with C-9 are key to the "propionate starter" interpretation. While C-14 shows some [2-^{13}C]acetate incorporation, a careful comparison of spectra indicated that incorporation was probably not as extensive as observed for the other [2-^{13}C]acetate derived carbons, a result which is more evident in relation to C-9. (This result is expected if C-14 is derived from propionate which has, in turn, been derived from labeled acetate.) Unfortunately, C-13 showed an abnormally undefined peak height in the spectrum of the [1-^{13}C]acetate derived sample. Expansion of the C-13 signal in this particular spectrum showed that no computer point had fallen near the top of the peak, which is particularly narrow, so that its true peak height was not established. Conclusions, therefore, are based on other key carbons.

To summarize the results, it is clear that the biosynthesis of daunomycin does not conform to a "classical" acetate–polymalonate pathway (Figure 1, pathway c or d). In particular the carboxyl and methyl derived carbons are opposite from those predicted by these two routes; the three-carbon-fragment, carbons 9, 13, 14, is apparently not directly acetate derived at all, and there is one more methyl-derived carbon than there are carboxyl-derived carbons.

Incorporation of Doubly Labeled Acetate. We have previously described the expected appearance of ^{13}C NMR spectra when a low level (1–2% on a per acetate unit) of exogenous [1,2-^{13}C]acetate has been incorporated into the compound under observation.[3] At sites where incorporation has occurred, carbons appear either as singlets, if a decarboxylation or skeletal rearrangement has occurred resulting in the loss of one carbon from the double labeled acetate molecule, or as triplets. Triplets occur because the doublet due to ^{13}C–^{13}C coupling (arising, or course, when doubly labeled acetate is incorporated), is approximately the same height as the central singlet due to unlabeled material.

Islandicin Triacetate. In the 67-MHz spectrum of islandicin triacetate grown from [1,2-^{13}C]acetate (Figure 4b), 14 of the 15 nucleus carbon atoms appear as distinct triplets (although three overlap at ~125.3 ppm), while C-3 is a distinct singlet. Therefore, the islandicin skeleton is derived from eight acetate units with one decarboxylation occurring during the biosynthesis. The observed coupling pattern (reported in Table VI), together with the distinct singlet for C-3, unequivocally establish the folding pattern a in Figure 2 as the biosynthetic pathway. Obviously pattern b would predict a different coupling pattern and a singlet for C-1 rather than C-3. Numerous other possibilities are also ruled out.

Close inspection of the enriched sample spectrum (Figure 4b) shows that most peaks, in particular C-3, have associated with them small symmetrically placed satellite pairs. These are of the expected intensity for multiply labeled species and apparently represent neither incursion of alternate biosynthetic pathways nor machine anomalies. We conclude this for the following reasons: (a) the C-1 resonance shows this effect and should not were configuration b operable, since the configuration would result in a singlet for this resonance; (b) the acetate carbonyl and methyl resonances do not show this effect (they probably would if the cause were machine anomalies); and (c) the C-2 methyl does not show this effect because it can have only one enriched neighboring carbon.

While it is thus unlikely that these satellite peaks arise from an alternative biosynthetic pathway, there are several ways in which multiple labeled species can arise. (1) The inherent probability of incorporation of labeled acetate at adjacent positions at this level of incorporation. In this case, the calculated satellite peak height at the observed incorporation level is ~3–4% of the main peak, while the observed satellites are larger than this (~8% of main peak), seemingly too large to be accounted for by this alternative. (2) The presence of a substantial preformed pool of islandicin at the time of initiation of feeding. This would give rise to an enhanced intensity of the satellite peaks over that expected on the basis of average acetate incorporation. No perceptible islandicin is formed at the time of initial pulsing, but any committed biosynthetic precursor (e.g., a polyketide) would give the same effect. (3) A lag period after initial pulsing during which exogenous acetate is not incorporated but islandicin is formed.

All of these are possible, but in the absence of accurate integration, possibilities 2 and 3 above, which predict an enhanced intensity of the satellite peaks, can only be suggested.

To summarize, these results demonstrate unequivocally that of the two pathways a and b (Figure 2), the former is correct.

Daunomycinone Tetraacetate. Analysis of the ^{13}C NMR spectrum of daunomycinone tetraacetate derived from [1,2-^{13}C]acetate (Figure 5b) in conjunction with the singly labeled acetate results permitted the following strong conclusions. First, the carbon fragment (C-9, C-13, C-14) is either not acetate derived or is derived by a process that entails both dilution of the isotope (relative to the other carbons in the molecule) and loss of the integrity of the added two-carbon acetate fragments. Second, while the coupling of all carbon pairs was not evident (Table VII), enough couplings could be measured (and enough chemical-shift assignments firmly established) to specifically implicate pathway a in Figure 1. Specific considerations were the following. (a) Because C-7 and C-8 appear to be derived from the same acetate unit, while C-10 is a singlet, pathway a is uniquely required. Although this conclusion could be reversed (pathway b) if the assignments of C-8 and C-10 were reversed, while C-19 and C-10 as well as C-7 and C-20 were coupled, this seems unlikely on the basis of single-frequency decoupling experiments (C-8 vs. C-10) and other pairings which implicate pathway a (see below). (b) The

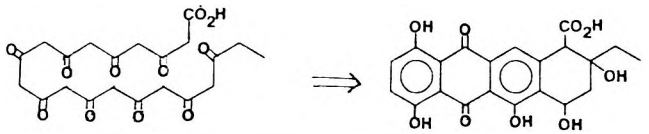


Figure 6. Proposed biosynthetic pathway for rutilantinone.

coupling of C-5 to C-17 and of C-4 to C-16 was apparent, firmly establishing that each of these pairs is derived from the same acetate unit. (c) A distinct 55-Hz coupling can be measured for C-12, presumably due to coupling to C-18; only one satellite peak is visible for C-18. However C-18 is not coupled to C-11, and postulating coupling to C-17 would require a most esoteric connectivity pattern. The elimination process confirms that C-12 and C-18 are derived from the same acetate unit. (d) C-3 appears with a satellite doublet (J = 68 Hz) and since it cannot be coupled to C-4 (whose coupling to C-16 is established), it must be coupled to C-2, although the splitting of C-2 is immersed in the 135-ppm complex and could not be determined. Even if the assignment of C-1 and C-3 were reversed, C-3 still cannot be coupled to C-4; it must be coupled to C-2. (The assignment reversal was considered because the carbon shifts are very close; however, the corresponding protons are separated by 0.44 ppm, enough to use single-frequency decoupling to establish that C-3 is coupled to the higher field aromatic proton.)

The small symmetrically placed satellite pairs (3–4% of mean peak in the islandicin triacetate spectrum, Figure 4b) were not observed in the daunomycin tetraacetate spectrum. However, the signal/noise level was much less favorable in the latter case which may have precluded their observation.

Taken together, the above results are uniquely consistent with pathway a (Figure 1) and show an acetate connectivity pattern both strikingly different from that determined for islandicin and strikingly similar to that proposed some time ago for metabolite rutilantinone (Figure 6),[15] wherein the three-carbon fragment corresponding to carbons 19, 13, and 14 was shown to be propionate derived. In the latter compound, sodium [1-^{14}C]propionate was used to demonstrate the involvement of a propionate "starter" in the polyketide synthesis.

Experimental Section

Carbon spectra for islandicin triacetate were obtained on a Bruker WH 270 spectrometer at 67.92 MHz. The computer associated with this instrument yielded 16K data points in the real transformed spectrum. Carbon spectra for the substituted anthraquinones and daunomycinone tetraacetate were obtained on a Varian XL-100-15 spectrometer operating at 25.16 MHz. Its computer yielded 4K data points in the real transformed spectrum. Chemical shifts are in parts per million relative to internal tetramethylsilane and $Cr(acac)_3$ was used as a relaxation agent in all experiments. Standard techniques were used for single frequency, broad band noise, and off-resonance decoupling experiments.

Islandicin Experimental. Organism. *Penicillium islandicum* Sopp was obtained from the American Type Culture Collection (strain no. 10127) and maintained on malt extract agar (Balkeslee).[16] This medium produced abundant sporulation.

Culture Conditions. Medium Preparation. Czapek–Dox–2% agar was prepared in the following manner. To 1 L of distilled water were added the following: 50 g of glucose (Mallinckrodt), 2.0 g of $NaNO_3$ (MCB), 1.0 g of KH_2PO_4 (Mallinckrodt), 0.5 g of KCl (Mallinckrodt), 0.5 g of $MgSO_4 \cdot 7H_2O$ (Baker), 0.01 g of $FeSO_4 \cdot 7H_2O$ (Allied), and 20 g of Bacto agar (Difco). This molten solution was sterilized and then poured into sterile petri dishes. Each petri dish received approximately 30–40 mL of the medium.

Inoculation and Growth Conditions. *P. islandicum* spores from a culture which was at least 3 weeks old were scraped from the agar (Blakeslee malt extract) surface and spread over the fresh Czapek–Dox medium. The new cultures were allowed to grow 22–23 days at 20–24 °C. At this point the agar plates were removed from the petri dishes and dried in an oven.

Isolation of Islandicin. The dried agar mats were ground to a powder and exhaustively extracted with Skellysolve A to remove lipid material. This process also extracted some islandicin and other pigments, but the islandicin could be isolated from this extract by basic extraction and chromatography. The mycelial powder was then extracted with chloroform, a process which removed a substantial amount of colored pigments. This extract was chromatographed (silica gel/benzene) to yield islandicin and its dimer, iridoskyrin; the islandicin could be purified by sublimation at temperatures not exceeding 180 °C. The iridoskyrin could be recovered unchanged from the sublimation vessel. The islandicin is recrystallized from chloroform.

Preparation of Sodium Acetate Solutions. Sodium [2-^{14}C]acetate (2.0 mCi/mmol, 2.1 mg) was dissolved in 100 mL of water and cold sodium acetate was added to bring the concentration up to the desired level (4.0, 5.0, 6.0, 8.0 mg/mL). The solutions were sterilized and the radioactivity was determined on a Packard Tri-Carb Model 3375 counter in Aquasol (New England Nuclear) solution. Sodium [1-^{13}C]-, [2-^{13}C]-, and [1,2-^{13}C]acetate solutions were prepared analogously from 90% [^{13}C]acetates (Merck) with added [2-^{14}C]acetate as tracer.

Addition of Sodium Acetate. Solutions (0.5 mL) of known sodium acetate concentration were added daily to the cultures starting at day 7 and continuing through day 16 of the growth period. The yield of islandicin and the percent incorporation of [^{14}C]acetate as a function of acetate concentration are as shown.

Acetate added per 12 cultures, mmol	Islandicin produced per 12 cultures, mmol	% incorporation of added acetate
2.93	0.186	1.76
3.66	0.181	2.32
4.19	0.209	2.75
5.63	0.208	3.72

Islandicin Triacetate. Recrystallized islandicin (51.8 mg; 0.192 mmol) was placed in a small test tube along with 1.5 mL (17.3 mmol) of pyridine and the mixture heated to 110 °C. Acetic anhydride (1.5 mL; 15.9 mmol) was then added and the mixture was stirred and warmed intermittently over a 90-min period. The yellow solution was then quenched in ice water and stirred for 15 min, and the resultant precipitate was filtered, washed, and dried in vacuo. The crude product (86.6 mg) was sublimed [175 °C (0.1 Torr)] to yield 83.2 mg (0.185 mmol; 96%) of the purified islandicin triacetate, mp 207.5–208 °C (lit. 208 °C). The material could be recrystallized from methanol to give pale yellow needles: NMR (100 MHz; $CDCl_3$) δ 2.30 (3 H, s) (this methyl group shows a reduced peak height, although the 1.5-Hz coupling to the proton at 7.30 ppm was not observable), 2.42 (6 H, s), 2.49 (3 H, s), 7.30 (1 H, q, J = 1.5 Hz), 7.38 (1 H, dd, J = 1.5, 7.5 Hz), 7.75 (1 H, t, J = 7.5 Hz), 8.13 (1 H, dd, J = 1.5, 7.5 Hz); IR (KBr) ν 1791, 1779, 1685, 1602, 1385, 1342, 1271, 1212, 1191, 1036, 921, 910, 822 cm^{-1}; UV–vis $\lambda_{max}(CH_3OH)$ 342 (ϵ 6470), 270 (ϵ 34 200 sh), 250 nm (ϵ 36 800); MS m/e 354 (3), 312 (31.5), 270 (100).

Counting Protocol. Radioactivity of sodium [^{14}C]acetate (New England Nuclear) was determined by counting in Aquasol. Radioactive islandicin (100 mg) was dissolved in 50 mL of chloroform. A 50 μL aliquot was added to 5 mL of toluene-based scintillation fluid (5 g of PPO, 0.066 g of POPOP/L of toluene) and counted. Self-quenching was corrected for by means of a concentration–count plot.

Daunomycin Experimental. Organism. *Streptomyces peucetius* was obtained from the American Type Culture Collection (strain no. 21354) and was maintained on a malt extract agar at 20–24 °C (Hesseltire[17]).

Culture Conditons. Vegetative Medium Preparation. To 1 L of distilled water were added: 3.0 g of yeast extract (Difco), 3.0 g of malt extract (Difco), 5.0 g of Bacto peptone (Difco), and 10.0 g of dextrose (Mallinckrodt). To each of several small shake flasks was added 40 mL of this medium, and the flasks were subsequently sterilized.

Productive Medium Preparation. To 790 mL of tap water was added 10 mL of an ion solution containing Zn^{2+} (10^{-4} M), Cu^{2+}, Mn^{2+}, Co^{2+} (all 10^{-5} M), and Mo^{2+} (10^{-6} M). To this solution were added the following: 15.0 g of dry yeast (Red Star), 2.0 g of NaCl (Merck), 1.0 g of KH_2PO_4, 1.0 g of $CaCO_3$ (Allied), 0.1 g of $MgSO_4 \cdot 7H_2O$, and 0.01 g of $FeSO_4 \cdot 7H_2O$. This solution was divided equally among four 2-L *creased* flasks and sterilized. Dextrose solutions were prepared separately by dissolving 10-g portions of dextrose in 50-mL aliquots of distilled water and sterilizing prior to use.

Inoculation and Growth Conditions. *S. peucetius* mycelia were

scraped from an agar surface and added to the vegetative media. Mycelia between 9 and 12 days old proved most viable for production of the metabolite. The vegetative cultures were grown on a rotary shaker at 28 °C for 45 h. The vegetative mycelia thus prepared served as inocula for the productive media prepared above. Dextrose solutions were added separately. Cultures were grown on a rotary shaker for 120 h.

Isolation of Daunomycinone. The culture broth from the shake flasks was centrifuged with Celite at 0 °C and the solids were extracted several times with a 3:1 mixture of acetone/0.5 N HCl. The aqueous acetone solution was neutralized and the acetone removed in vacuo. The aqueous suspension remaining was immediately hydrolyzed with 0.5 N HCl (1 h; 90 °C) and the resultant suspension extracted with chloroform.

The chloroform extracts were pooled, concentrated, and chromatographed (silica gel; 1% methanol/chloroform) to yield 25–30 mg of daunomycinone from 1 L of broth. The daunomycinone thus obtained was not purified further.

Preparation of Sodium [^{13}C]Acetate Solutions and Pulsing Conditions. In 18 mL of distilled water was dissolved 1.8 g of sodium [^{13}C]acetate (1-^{13}C, 2-^{13}C, and 1,2-^{13}C for the three experiments). The solutions were sterilized and added daily to growing cultures of *S. peucetius*. Additions commenced 45 h after inoculation and continued at 12-h intervals through the 108th hour of the growth period. Each pulse consisted of a 0.5-mL aliquot of the solution and this ensured that the concentration of acetate would be <200 mg/L.

Daunomycinone Tetraacetate. The chromatographed daunomycinone (32 mg; 0.08 mmol) was dissolved in 1.0 mL (12.4 mmol) of pyridine. Acetic anhydride (1.5 mL; 15.0 mmol) was then added and the mixture was stirred at 60 °C for 3 h. The solution was quenched in ice water and extracted with chloroform. The crude product, a mixture of tri- and tetraacetates, was chromatographed on silica gel (5% methanol/benzene) to yield 31.1 mg (0.055 mmol; 68%) of the tetraacetate. This was used for the ^{13}C NMR experiments without additional purification; NMR (100 MHz; $CDCl_3$) δ 2.01 (6 H, s), 2.22 (3 H, s), 2.42 (3 H, s), 2.48 (3 H, s), 3.10 (1 H, AB quartet, J = 18 Hz), 3.96 (3 H, s), 6.34 (1 H, bd), 7.24 (1 H, dd, J = 7.5, 2 Hz), 7.59 (1 H, t, J = 7.5 Hz), 7.70 (1 H, dd, J = 7.5, 2 Hz) (The multiplet expected for H-8 is obscured by the resonances in the 2.0–2.6-ppm range, but shows in the integration.); IR (KBr) 1781, 1746, 1681, 1590, 1375, 1242, 1192, 1077, 1019 cm^{-1}; UV–vis λ_{max}(MeOH) 375 (ϵ 5960), 252 (ϵ 30 200); MS *m/e* 488 (2), 362 (50), 60 (61), 44 (42).

Registry No.—**1a**, 20830-81-3; **2a**, 476-56-2; **2b**, 18713-46-7; daunomycinone, 21794-55-8; daunomycinone tetraacetate, 32384-96-6.

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Synthesis and Resolution of 3-Fluoro-D,L-alanine-*2-d:* A Selective Deuteration via Reductive Amination with Sodium Borodeuteride

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3-Fluoro-D,L-alanine-2-*d* (**11**) is synthesized in aqueous (protio) ammonia from lithium fluoropyruvate (**3**) via reductive amination with sodium borodeuteride with complete retention of isotopic purity. Fluoropyruvate salts (**5**) equilibrate in 13, 6.5, and 4 M aqueous ammonia to 95:5, 85:15, and 80:20 mixtures of 3-fluoro-2,2-diaminopropionate (**8**) and 3-fluoro-2-amino-2-hydroxypropionate (**6**), respectively. The reduction of these mixtures with sodium borodeuteride to **11** and 3-fluoro-2-hydroxypropionic-2-*d* acid (**10**), a side product, is studied in detail. A mechanistic scheme is proposed in which the rate-limiting step for the formation of **10** is the reequilibration of **8** to **5**, and for the formation of **11** it is the reduction of 3-fluoro-2-iminopropionate (**7**) with sodium borodeuteride. The yield of **11** is maximized with respect to an efficient use of sodium borodeuteride. Racemic **11** is resolved via the *N*-carbobenzoxy derivative with quinine and by a continuous resolution via preferential crystallization of the benzenesulfonate salt.

3-Fluoro-D-alanine-*2-d* in combination with the 2,4-pentanedione enamine of cycloserine, sodium salt, constitutes a novel, uniquely synergistic, bactericidal antimicrobial with an unusually broad spectrum.[1] The first synthesis of 3-fluoro-D,L-alanine by fluorination of 2-phenyl-4-chloromethylene-5-azlactone, followed by hydrolysis, hydrogenation, and saponification was reported by Yuan et al.[2] Later, Lettré and Wölcke obtained the racemic amino acid by α-bromination and subsequent ammonolysis of 3-fluoropropionic acid.[3] However, neither approach can introduce deuterium selectively into the α position. Photofluorination of D-alanine-2-*d* with CF_3OF in liquid HF at −78 °C produced the first 3-flu-

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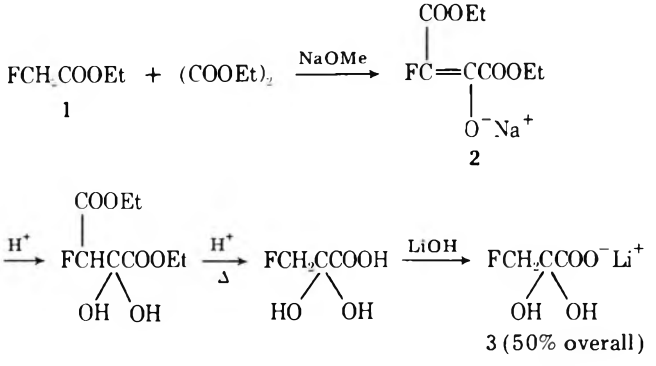
oro-D-alanine-2-*d*.[4] This process has been the only known synthesis, and its limitations in the production of larger quantities are obvious. We wish to report the reductive amination of fluoropyruvate salts in aqueous ammonia to 3-fluoro-D,L-alanine-2-*d* and the resolution of the racemate.

Although the reduction of Schiff bases with sodium borohydride,[5] sodium cyanohydroborate ($NaBH_3CN$),[6] and sulfurated borohydrides[7] is well established, this is, to our knowledge, the first report of the use of sodium borodeuteride in protio aqueous ammonia for the synthesis of isotopically pure α-deuterio amino acids. In this instance, the fluorine presents an additional synthetic hazard since the instability of the fluorine bond in Schiff base derivatives of fluoropyruvic acid to chemical and electrolytic reductions has been reported.[8] The synthesis of α-amino acids from α-keto acids in alcoholic or aqueous ammonia by catalytic hydrogenation was reported by Knoop and Oesterlin.[9] However, the synthesis of alanine from pyruvic acid failed.[9] We found that fluoropyruvic acid under similar conditions substantially defluorinated and produced alanine.

Results and Discussion

The synthesis of 3-fluoro-D-alanine-2-*d* comprises four steps: (1) synthesis of lithium fluoropyruvate, (2) its equilibration with aqueous ammonia, (3) reduction with $NaBD_4$, and (4) resolution of 3-fluoro-D,L-alanine-2-*d*.

1. Synthesis of Lithium Fluoropyruvate. Fluoropyruvic acid was prepared according to the literature procedures[10] from ethyl fluoroacetate (**1**). After hydrolysis of the intermediate ethyl ethoxallylfluoroacetate sodium salt (**2**), fluoropyruvate is conveniently isolated by precipitation of the highly insoluble lithium fluoropyruvate monohydrate (**3**). This isolation procedure avoids the low yield distillation of the acid.[10] Impurities such as oxalic acid and chloropyruvic acid can be removed by precipitation as the calcium salt and by an aqueous bicarbonate wash, respectively.[11,12] However, their removal is not essential for the subsequent steps.

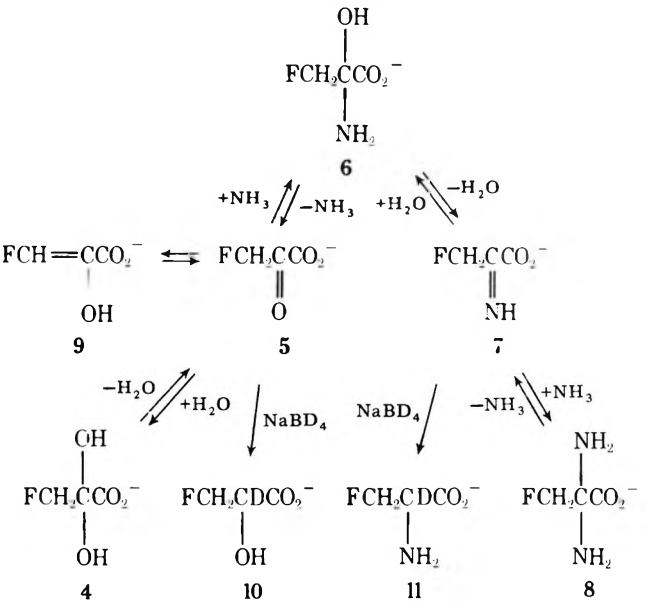


1 2 3 (50% overall)

2. Equilibration of Fluoropyruvate with Aqueous Ammonia. The proton NMR spectrum of lithium fluoropyruvate in D_2O shows two FCH_2 groups: one adjacent to an sp^3 carbon at 4.43 ppm (downfield from DSS; d, J_{HF} = 47 Hz), consistent with the *gem*-diol **4** (Scheme I), and the second adjacent to an sp^2 carbon at 5.45 ppm (d, J_{HF} = 46 Hz), consistent with the keto species **5**. The ratio of **4** to **5** in D_2O is 7:1. This ratio is pH dependent, with lower pH values favoring the keto form **5**. The spectrum of sodium fluoropyruvate in D_2O shows essentially only the diol species **4**. This is in contrast to pyruvate which shows a *gem*-diol to keto ratio of 1:19 in water at pH 7.[13] In the solid state, neither lithium pyruvate monohydrate nor sodium (or lithium) fluoropyruvate monohydrate shows a carbonyl frequency in the infrared spectrum (KBr).

A priori, a complex equilibrium mixture of fluoropyruvate in aqueous ammonia can be expected. As shown in Scheme I, diol **4** can equilibrate by the loss and addition of H_2O or NH_3

Scheme I. Equilibration and Reduction of Fluoropyruvate in Aqueous Ammonia



with the ketone **5**, aminal **6**, imine **7**, and diamine **8** species. However, when fluoropyruvate is dissolved in 13 M ammonium hydroxide, initially only one species is observed at 4.47 ppm (J_{HF} = 46 Hz). With time the intensity of the doublet decreases and only one new doublet arises at 4.42 ppm (J_{HF} = 46 Hz).

These two equilibrating species were identified by ^{13}C NMR. The proton-decoupled ^{13}C NMR spectrum of sodium fluoropyruvate in D_2O shows the C_3 carbon absorption at 86.1 ppm ($^1J_{CF}$ = 171 Hz), C_2 at 93.5 ppm ($^2J_{CF}$ = 22 Hz), and C_1 (carboxyl) at 176.1 ppm ($^3J_{CF}$ = 2 Hz). During the equilibration in 13 M ammonium hydroxide, two sets of signals are observed: that of an initial species with C_3 at 87.6 ppm ($^1J_{CF}$ = 172 Hz), C_2 at 83.5 ppm ($^2J_{CF}$ = 19 Hz), and C_1 (carboxyl) at 176.8 ppm ($^3J_{CF}$ = 3 Hz); and that of the new species with C_3 at 88.9 ppm ($^1J_{CF}$ = 173 Hz), C_2 at 70.1 ppm ($^2J_{CF}$ = 19 Hz), and C_1 (carboxyl) at 178.6 ppm ($^3J_{CF}$ = 3 Hz). The large chemical shift differences between the diol C_2 and the equilibrating initial and final C_2 carbon types suggest the equilibrating species to be the aminal **6** and the diamine **8**.[14] *gem*-Diol **4** was not detected.

To determine the structure of the intermediate unequivocally, sodium fluoropyruvate was equilibrated in 95% enriched ammonium-^{15}N hydroxide (12 M). The predicted diamine intermediate **8** is expected to show the $^{13}C_2$ doublet split into triplets by two neighboring ^{15}N's, whereas the aminal **6** would show the $^{13}C_2$ doublet split only into a doublet. The ^{13}C spectrum of the equilibrated solution shows the C_2 carbon of the dominant species at 70.1 ppm split by ^{19}F into a doublet and by ^{15}N into a triplet ($^2J_{CF}$ = 19 Hz, $^1J_{C-^{15}N}$ = 5 Hz). The C_3 carbon at 88.9 ppm shows similar splitting ($^1J_{CF}$ = 173 Hz, $^2J_{C-^{15}N}$ = 3 Hz). These data clearly identify the initial and final equilibrating species as the aminal **6** and the diamine **8**, respectively.

Concomitant with the above equilibration of **6** to **8** is the slow enolization to **9**. During the equilibration of a 0.59 M solution of lithium fluoropyruvate in 26% ND_3/D_2O for 90 min at 37 °C, the β protons slowly exchanged and the signal intensity (vs. an internal standard) decreased by approximately 35%. Subsequent reduction, isolation, and demonstration of deuterium incorporation into the β position verified the exchange and excluded decomposition as the cause of the decrease in signal intensity.

This enolization is considerably slower than that of the chloropyruvate. The high stability of the fluoropyruvate to

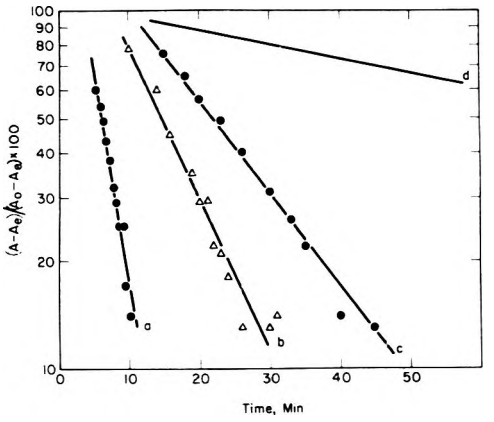


Figure 1. Semilog plot of disappearance of **6** (A = concentration at time t, A_e = concentration at equilibrium, and initial concentration, 0.59 M) in aqueous ammonia. (a) 13 M NH_3, 37 °C, 1.0 equiv of NH_4Cl; slope = −0.1264, $t_{1/2}$ = 2.4 min. (b) 6.5 M NH_3, 37 °C; slope = −0.0423, $t_{1/2}$ = 7.1 min. (c) 13 M NH_3, 37 °C; slope = −0.0259, $t_{1/2}$ = 11.6 min. (d) 13 M NH_3, 20 °C; slope = −0.00385, $t_{1/2}$ = 78 min (line extrapolated from measurements taken between 60 and 220 min).

these reaction conditions is in contrast to the instability of the chloro and bromo analogues.[12]

The equilibration of **6** and **8** in the aqueous ammonia system can be followed quantitatively by proton NMR spectroscopy. Treatment of the rate data as an equilibrium (**6** ⇌ **8**) shows that the equilibration follows pseudo-first-order kinetics. Semilog plots of $(A - A_e)/(A_0 - A_e)$ (A = concentration of **6** at time t, A_e = concentration at equilibrium, and A_0 = initial concentration) vs. time give straight lines (see Figure 1). The data are summarized in Table I. The lithium and sodium salts of **4** give identical results. At 37 °C in 13 M ammonia the half-life is 11.6 min and the equilibrium ratio of diamine **8** to aminal **6** at t = infinity is 95:5. Lowering the temperature to 20 °C increases the half-life to 78 min but does not alter the final equilibrium ratio. In 6.5 M ammonia the half-life decreases to 7.1 min and the final equilibrium ratio is lowered to 85:15. However, the use of the free acid (generation of NH_4^+) or addition of NH_4Cl catalyzes the equilibration substantially. The presence of 1 equiv of ammonium chloride decreases the half-life of **6** from 11.6 to 2.4 min at 37 °C. The ammonium ion acts as an acid catalyst and enhances the addition of NH_3.

3. Reduction with $NaBD_4$: (a) Isotopic Purity. Reduction of fluoropyruvic acid with sodium borodeuteride in liquid ammonia provided **11** in 64% yield but with only 80% isotopic purity. When the sodium fluoropyruvate was equilibrated and reduced in aqueous ammonia with NH_4Cl catalysis, **11** had 96% isotopic purity, which represented a small but significant scrambling of the deuterium label. The scrambling was attributed to the presence of the NH_4^+ ions which, acting as an acid catalyst, exchanged the deuterium of $NaBD_4$ prior to the reduction. The difference in isotopic purity of both runs is enhanced by the considerably slower reduction in liquid ammonia, thereby providing ample time for exchange. In a control experiment, sodium borodeuteride, 2 N in 13 M aqueous ammonia at ambient temperature, slowly exchanged deuterium with the solvent system as observed by a small increase in the proton NMR absorptions of $NaBH_4$ after 70 h. However, the rate of exchange was so small that it had no significant effect on the faster reduction. Attempts to measure the rate of exchange in the presence of ammonium chloride were hampered by the rapid decomposition of sodium borodeuteride. $NaBD_3CN$ has also been reported to exchange with the solvent system in a more acidic medium.[6]

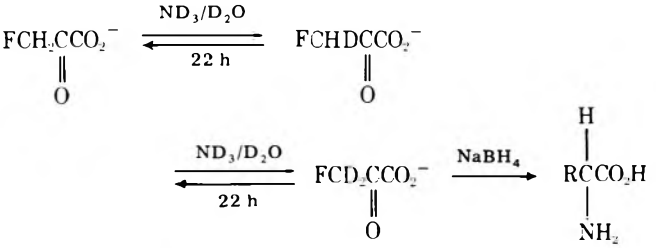
Equilibration of lithium or sodium fluoropyruvate in aqueous ammonia in the absence of added ammonium ions

Table I. Equilibration of 0.59 N $FCH_2C(OH)_2CO_2X$ in Aqueous Ammonia

X	Registry no.	$[NH_3]$, M	Temp. °C	Half-life, min	Ratio 8/6 (t = ∞)
Li		13	20	78	95:5
Li		13	37	11.2	95:5
Li[a]		13	37	2.4	95:5
Na	65120-54-9	13	37	11.6	95:5
Li	60079-40-5	6.5	37	7.1	85:15
Li		4.0	37	*b*	80:20

[a] Addition of 1 equiv of NH_4Cl. [b] Not measured.

followed by borodeuteride reduction afforded **11** with no dilution of the deuterium at the α-carbon. No deuterium was detected at the β-carbon. Conversely, equilibration of lithium fluoropyruvate with ND_3/D_2O followed by borohydride reduction yielded 3-fluoroalanine with extensive deuteration on the β-carbon (by slow enolization and exchange of the fluoropyruvate and/or its imine), but with no detectable deuterium on the α-carbon.



R = FCH_2 (32%), FCHD (40%), and FCD_2 (28%)

(b) Kinetics. The species **5** and **7** (Scheme I) in the equilibrated solution can be reduced by sodium borodeuteride to 3-fluoro-2-hydroxypropionic-2-*d* acid (**10**) and 3-fluoro-D,L-alanine-2-*d* (**11**), respectively. It is apparent from Scheme I that the ratio of **10** to **11** in the final product mixture may depend on the relative rates of reduction of **5** to **10** and **7** to **11** and/or on the rate of reequilibration of **8**, **7**, and **5**. To gain some insight into the reaction and to maximize the yield and the efficient use of $NaBD_4$ the reduction was examined with respect to the concentrations of $NaBD_4$, ammonia, diamine **8**, and added salts (catalytic effects). The reaction progress was conveniently followed by proton NMR spectroscopy. The only components observed after the addition of $NaBD_4$ to an equilibrated solution were **8**, **10**, and **11** (the latter two presumably as their boron complexes). A graph of typical results is presented in Figure 2.

Effect of $NaBD_4$ Concentration. The initially present **6** was always reduced to **10** within the time period needed to take the first spectrum, whereas the disappearance of **8** was slower and could be measured. Formation of **11** increased markedly with higher concentrations of $NaBD_4$ (Figure 3; Table II, runs 1, 2, and 3), whereas the rate of formation of **10** decreased (Figure 4). If, for example, only 1 equiv of $NaBD_4$ was used, the slow reduction permitted large amounts of **8** to reequilibrate to **5** prior to reduction. These results are consistent with the following scheme: a rapid preequilibrium exists between **8** and **7**. Subsequently, the rate-limiting step for the formation of **11** is the bimolecular reduction of **7** to **11**, whereas the rate of formation of **10** is limited by the pseudo-first-order conversion of **7** to **5**.

Effect of Ammonia Concentration. In 26 M aqueous ammonia (under pressure) no reduction with $NaBH_4$ was observed. If the ammonia concentration was reduced from 13 to 6.5 M, the initial ratio of **8** to **6** was less favorable but a substantially higher reduction rate of **7** to **11** allowed less of **7** to reequilibrate to **5**, even though the rate of equilibration

Table II. Reduction of Fluoropyruvate with $NaBD_4$ in Aqueous NH_3 at 37 °C[a]

Run	$[FCH_2COCO_2Li \cdot H_2O]$, M[c]	$NaBD_4$, equiv	$[NH_3]$, M	NMR yield, %[b] 11	10	8
1	0.59	1.14	13	26	51	23
2	0.59	2.28	13	45	55	0
3	0.59	4.55	13	76	24	0
4	0.59	1.14	6.5	36	45	19
5	0.59[d]	1.14	6.5	40	41	19
6	0.59	2.28	6.5	63	37	0
7	0.67[e]	2.0	6.5	69	31	0
8	0.67[e,f]	2.0	6.5	72	28	0
9	0.67[e,g]	2.0	6.5	71	29	0
10	0.59[h]	1.7	4.0	65	35	0
11	0.29[i]	2.28	6.5	43	57	0

[a] Fluoropyruvate was completely equilibrated in solution prior to reduction. [b] Relative yields, normalized to 100%; **11**, **10**, and **8** were the only detectable reaction components; isolated yields were usually within 5% of the NMR yields. [c] Based on the assayed purity of fluoropyruvate. [d] LiCl added (1.14 equiv). [e] Sodium fluoropyruvate. [f] NaCl added (2.0 equiv). [g] LiCl added (2.0 equiv). [h] LiCl added (2.3 equiv).

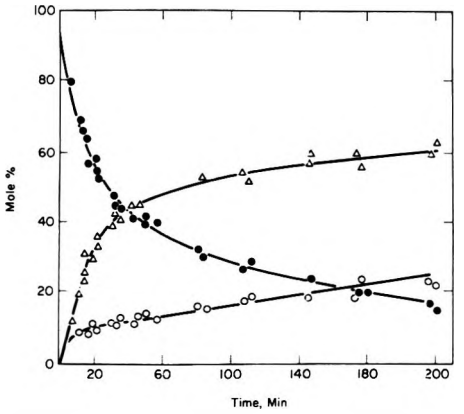


Figure 2. Reduction of an equilibrated solution of **3** in 13 M ammonia at 37 °C with 4.55 equiv of $NaBD_4$: ● = **8**, △ = **11**, and ○ = **10**.

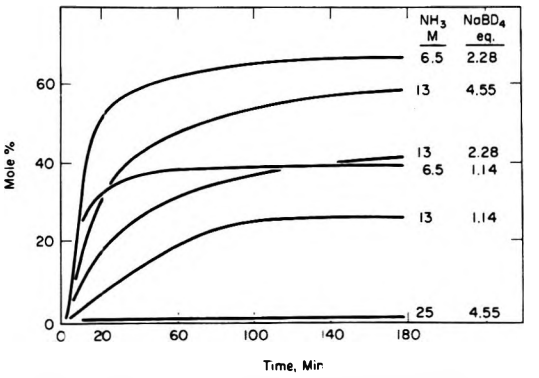


Figure 3. Formation of **11** during the reduction of equilibrated solutions of **3** with $NaBD_4$ at 37 °C. The reaction in 25 M ammonia was run under pressure with 4.55 equiv of $NaBH_4$.

increased slightly (vide supra). The net effect was a higher yield of **11** than in 13 M ammonia (Table II, runs 1, 2, and 4, 6). The reduction of imines and ketones is pH dependent,[5a] and therefore the decrease in the ammonia concentration from 13 to 6.5 M, which lowered the pH by approximately one unit, increased the imine reduction rate but apparently had a smaller effect on the reequilibration of **7** to **5**.

Effect of Concentration of 8, Salt, and Temperature. Most reduction studies were run at a standard concentration of 0.59 M fluoropyruvate (Table II). As expected from the above discussion, a decrease in concentration of **4** to 0.3 M (6.5 M NH_3, 2.3 equiv of $NaBD_4$) decreased the yield of **11** from 63 to 43% (Table II, runs 6 and 11), concomitant with an increase in the yield of **10**. On the other hand, with increasing concentrations a more rapid polymerization and/or decomposition of the equilibrating fluoropyruvate solution was noticed. Thus, solutions of 1 M concentrations rapidly turned dark. Addition of lithium chloride or sodium chloride (sodium fluoropyruvate as starting material) had little effect on the yield (runs 7, 8, and 9). This is in agreement with previous reports on aqueous $NaBH_4$ reductions.[15] Reactions in the presence of ammonium ions (NH_4Cl) were not studied further because of the marked increase in $NaBD_4$ decomposition and loss of the deuterium label. The effect of temperature on the reduction was briefly examined. At 20 °C both the reduction of **7** to **11** and the reequilibration of **7** to **5** (Table I) in 13 M ammonia are slower than at 37 °C.

(c) Comparison between $NaBD_4$ and $NaBH_4$. All of the considerations described for borodeuteride apply to borohydride, but the reaction rates are more favorable for the amino

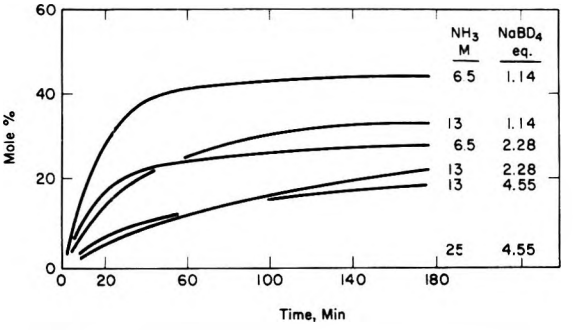


Figure 4. Formation of **10** during the reduction of equilibrated solutions of **3** with $NaBD_4$ at 37 °C. The reaction in 25 M ammonia was run under pressure with 4.55 equiv of $NaBH_4$, and **10** was not detectable.

acid synthesis with borohydride. The rate of hydrolysis of $NaBD_4$ in aqueous systems is greater than that of $NaBH_4$,[16] while the rate of reduction of the imine **7** is slower with $NaBD_4$. The slower reduction provides more time for decomposition of $NaBD_4$ and more time for reequilibration to **5**. The comparative result shown in Figure 5 is striking.

The implication for the synthesis of the protio analogue is clear: a large excess of $NaBH_4$ will essentially quench the equilibrium mixture. Thus, an equilibrated solution (13 N NH_3, 0.67 M fluoropyruvate) was reduced with 5.5 equiv of borohydride to an isolated yield of 88% of 3-fluoro-D,L-alanine.

The high cost of sodium borodeuteride does not permit the

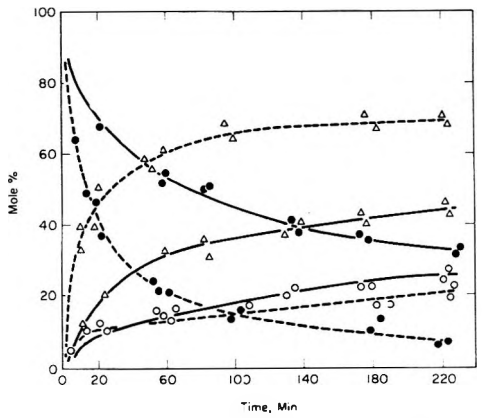


Figure 5. Comparison between $NaBD_4$ (–) and $NaBH_4$ (- - -) reductions (2.28 equiv) of equilibrated 0.59 M solutions of **3** in 13 M NH_3 at 37 °C: ● = **8**, △ = 3-fluoroalanine, and ○ = 3-fluorolactic acid (H and D).

luxury of the high excess of reducing agent as described above. Considering the data obtained from the equilibration and reduction studies, the following procedure uses $NaBD_4$ efficiently: lithium fluoropyruvate is equilibrated, at 0.67 M, with 13 M NH_4OH at 37 °C for 1.5 h (obtaining 95% conversion to **8**). The solution is cooled to 10 °C (effectively freezing the equilibrium) and treated with 1.7 equiv of $NaBD_4$. Under vacuum and with vigorous N_2 sparging, the ammonia is purged from the reaction mixture and the solution is allowed to warm from 10 to 30 °C over a 3-h period. In the ammonia-poor system the reduction proceeds rapidly, even at these temperatures. A crude yield of 70% is obtained, and after recrystallization 56% (overall) of pure **11** is obtained. The only impurities in the crude material were small amounts of alanine and serine.

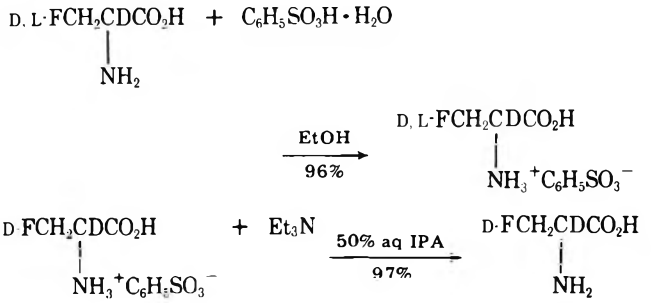
4. Resolution. Two resolutions of 3-fluoro-D,L-alanine-2-*d* were developed:[17] (a) a chemical resolution of carbobenzoxy-3-fluoroalanine-2-*d* with quinine, and (b) a continuous resolution via preferential crystallization of the benzenesulfonate salts of D- and L-3-fluoroalanine-2-*d*.[18,19]

(a) Quinine Resolution. 3-Fluoro-D,L-alanine-2-*d* was acylated under Schotten–Baumann conditions to the *N*-carbobenzoxy derivative (*N*-Cbz).[20] The *N*-Cbz-3-fluoro-D-alanine-2-*d* quinine salt crystallized from ethanol, ethyl acetate, or acetonitrile in almost complete optical purity. One recrystallization usually brought the optical purity to 99%. The L salt was crystallized from the mother liquors by the addition of acetone. After liberation of the acid, catalytic hydrogenolysis (5% Pd/C, EtOH) generated the 3-fluoro-D-alanine-2-*d* with complete retention of the label in an overall yield of 50% of theory.

(b) Continuous Resolution. A basic prerequisite for a continuous resolution by preferential crystallization is that the D,L form be a racemic mixture and not a racemic compound. The D or L isomer, therefore, will not dissolve in solutions saturated with respect to the racemic material. The first resolution based on this principle was reported by Gernez in 1866.[21] Resolutions of optical isomers by crystallization have been reviewed.[22]

3-Fluoro-D,L-alanine-2-*d* itself is a racemic compound and therefore not suitable for a continuous resolution. The benzenesulfonate salt of the D,L amino acid, however, has been found to be a racemic mixture by x-ray crystallography.[23]

The racemic salt was readily prepared from the amino acid and an excess of benzenesulfonic acid in 95% ethanol. The salt was crystallized by concentration and replacement of solvent by 1-propanol. After the resolution the amino acid was crystallized from 50% aqueous 2-propanol (IPA) by neutralization with triethylamine. Solubility and stability studies suggested 1-propanol as the solvent of choice with a solubility of 40 mg/mL at room temperature and a 16.8% supersaturation value obtainable by saturating at 28 °C and crystallizing at 23 °C.[23]



The optical purity of the resolved benzenesulfonate salt was usually 99+%. The insolubility of the optically pure salt in a solution saturated with respect to D,L permits a highly efficient purification by "slurry" in a calculated volume of 1-propanol. Occasionally, optically impure products were restored to optical purity by overnight slurrying, with recoveries of 93–99% of the theoretically obtainable pure isomer. The isomeric purity of regenerated 3-fluoro-D-alanine-2-*d* was 99.995% as measured by an enzymatic assay.[24] On a 13-kg scale the yield of optically pure 3-fluoro-D-alanine-2-*d* from benzenesulfonate salt was 85% of theory.

Experimental Section

Proton NMR spectra were measured on a Varian A-60 spectrometer, and chemical shifts are reported in parts per million downfield from 3-(trimethylsilyl)propanesulfonic acid sodium salt (TSP) or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS). Carbon-13 spectra were obtained with a Varian CFT-20 or XL-100 instrument, and chemical shifts were measured with dioxane as an internal standard set at 67.4 ppm relative to Me_4Si.

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Optical rotations were obtained on a Carl Zeiss photoelectric precision polarimeter (LEP A1). The rotations of $[\alpha]_D$ were obtained by extrapolation: $[\alpha]_D = [\alpha]_{546}/[1 + 1.3727([\alpha]_{546} - [\alpha]_{578})/[\alpha]_{578}]$. Mass spectra were recorded with a LKB-900 instrument and interpreted by Jack L. Smith. The isotopic purity of 3-fluoroalanine-2-*d* at C_2 and C_3 was determined by comparison of the intensity ratio *I m/e* 134:135:136 (M − 117 = M − $COOSi(CH_3)_3$) with that of *I m/e* 218:219 (M − CH_2F, − CHDF, − CD_2F) using unlabeled 3-fluoroalanine as a reference. Amino acid analyses were carried out on a Spinco-Beckman automatic amino acid analyzer. Sodium fluoropyruvate monohydrate was purchased from Calbiochem. $NaBD_4$ (98.5–99% D), ND_3/D_2O, and $^{15}NH_3$ were obtained from Merck Sharp and Dohme Canada Ltd. Ethyl fluoroacetate[25] was purchased from Fike Chemical, Inc. TLC analyses were carried out on Quanta Q1F silica gel plates with *n*-BuOH/HCO_2H/H_2O (78:14:8) (alanine, R_f 0.27; fluoroalanine, R_f 0.16; serine, R_f 0.10).

Lithium Fluoropyruvate Hydrate (3). A 2-L flask equipped with a stirrer, thermometer, N_2 inlet, dropping funnel, and condenser was charged with 440 mL of anhydrous ethyl ether and 54 g (1 mol) of fresh sodium methoxide in a N_2 atmosphere. To the well-stirred suspension was added 204 mL (1.5 mol) of freshly distilled diethyl oxalate dropwise over 0.5 h. A slight exotherm (T = 34 °C) was noted, but no cooling was required. Ethyl fluoroacetate[25] (106.1 g, 1 mol) was added to the almost clear yellow solution over a period of 2.5 h. A precipitate of the ethyl ethoxallylfluoroacetate sodium salt appeared near the midpoint of the addition. After aging overnight the mixture was filtered, and the product was washed with 2 × 800 mL of ether and 200 mL of hexane and dried in the air, yield 138 g (60.5%).

A mixture of 400 mL of ethyl ether and 240 mL of 5 N HCl was chilled to −15 to −20 °C in a flask equipped with good mechanical stirring, a powder funnel, thermometer, and N_2 inlet. With good stirring under a N_2 atmosphere, 138 g of sodium enolate, free of lumps, was added in a steady stream such that the temperature did not rise above −15 °C. (Too strenuous cooling may freeze the aqueous layer in the flask.) When addition was complete, the mixture was warmed to room temperature, diluted with 250 mL of water, and heated at atmospheric pressure to distill out the ether. Heating and distillation was continued until the flask temperature reached 102–105 °C. After

refluxing for 4 h, the resulting solution was cooled to room temperature, stirred with 6 g of Darco G-60, and filtered through (acid prewashed) Supercel using a minimum of water as wash. The filtrate was neutralized (ice cooling, pH meter) by addition of solid $LiOH·H_2O$ (ca. 47 g) to a final pH of 6.0–6.5. The slurry was aged at 0–5 °C overnight and filtered, and the filter cake was washed with a minimum amount of cold water and then with 2 × 200 mL of methanol and 2 × 200 mL of acetone. The product was air-dried, yield 56 g (70%). The lithium fluoropyruvate monohydrate thus obtained was approximately 80% pure, the major impurities being lithium oxalate and lithium chloropyruvate. The purity was assayed by NMR spectroscopy in 3.5 N HCl with DSS as an internal standard.

Fluoropyruvic Acid. Lithium fluoropyruvate monohydrate (16.5 g, 0.127 mol) was dissolved in 700 mL of water, passed through 100 mL of Dowex W50-X8 (H^+), and eluted with water. The acidic fractions were concentrated on a rotary evaporator (20 mm; bath temperature, 30–40 °C) to an oil. The oil was dissolved in 400 mL of ether/CH_2Cl_2 (1:1). After concentration to a semisolid, the flushing was repeated to yield 15.3 g (91%) of a waxy solid containing 19.6% water as measured by Karl Fischer analysis. Anhydrous fluoropyruvic acid (which is extremely hygroscopic) may be obtained by freeze-drying of an aqueous solution of the acid, but this operation is accompanied by substantial losses due to sublimation.

3-Fluoro-D,L-alanine-2-*d*. Lithium fluoropyruvate hydrate (26 g, 0.2 mol) was added with good agitation to 300 mL of 13 M aqueous ammonia (0.67 N in pyruvate) at room temperature. The slurry was equilibrated at 37 °C for 1.5 h to a clear yellow solution, cooled to 10 °C, and treated with 3.57 g (0.085 mol, 1.7 equiv) of $NaBD_4$. Under vacuum and with vigorous N_2 sparging, the ammonia was purged from the reaction mixture as the bath was allowed to warm from 10 to 30 °C over a 3-h period. Residual ammonia was removed by concentration on a rotary evaporator. The solution was chilled in an ice bath, stirred, and acidified by the addition of ca. 165 mL of 2.5 N HCl (0.41 mol). The acidified solution was stirred at room temperature with 1.3 g of Darco G-60 for 15 min, filtered, and passed through a column of 400 mL of Dowex 50W-X8 (H^+). The column was washed with water until the eluate was neutral. The initial fractions contained **10**,[26] which was identified by its NMR spectrum. The amino acid **11** was eluted with 0.5 N NH_4OH. The ninhydrin-active fractions were combined and freeze-dried to give 15 g (70%) of crude **11** containing small amounts of deuterated alanine (<0.5%) and serine (1.1%). The product recrystallized from 70 mL of H_2O at 60 °C by the addition of preheated 2-propanol (ca. 50 mL), aging in an ice bath for 2 h, and filtering, and it was washed with 2 × 20 mL of cold 90% aqueous 2-propanol, 2 × 10 mL of 2-propanol, and hexane. The product was dried to a constant weight in vacuo at 50–60 °C, yield 12.0 g (80% recovery). The ^1H and ^{19}F NMR spectra were identical with the reported spectra of 3-fluoro-D-alanine-2-*d*.[4a] The mass spectrum showed an isotopic purity of 99%. No deuterium was detectable at C_3. Anal. Calcd for $C_3H_5DFNO_2$: C, 33.34; H, 5.60; N, 12.96; F, 17.58. Found: C, 33.55; H, 5.68; N, 13.09; F, 17.64.

NMR Studies: (a) Equilibrations. Aqueous ammonia of the desired concentration was pipetted onto the weighed amounts of fluoropyruvate and salts. As soon as the solid was dissolved, the solution was filtered through a glass wool plug into an NMR tube. This procedure usually took about 2–3 min, and the first spectrum was obtained within 5 min. The reaction rates were measured by peak heights normalized relative to an internal standard (TSP).

(b) Reductions. Fully equilibrated stock solutions of fluoropyruvate and ammonia were prepared. Aliquots were pipetted onto $NaBD_4$ (or $NaBH_4$) and, where desired, salts. Further preparation and measurements were carried out as above (a).

Reduction in Liquid Ammonia. Fluoropyruvic acid (0.34 g, 3.2 mmol) was added to 40 mL of liquid ammonia in a glass-lined bomb. To the colorless solution 70 mg (1.67 mmol) of $NaBD_4$ was added. After shaking for 40 h at room temperature, the ammonia was evaporated with a slow stream of nitrogen. The residue was taken up in 10 mL of MeOH and concentrated to dryness. The solid was dissolved in 4 mL of 1 N HCl containing 10 g of ice. After dilution to 50 mL, **11** was isolated by ion exchange on Dowex 50W-X8 as described above. Freeze-drying yielded 0.22 g (64%) of **11**, which contained by mass spectral analysis 20% of the protio analogue.

Reduction in ND_3/D_2O with $NaBH_4$. Lithium fluoropyruvate monohydrate (35 mg, 0.269 mmol) was dissolved in 0.50 mL of 26% ND_3/D_2O (TSP as an internal standard). The equilibration was followed by NMR spectroscopy (37 °C). During the first 1.5 h the signal intensity (relative to TSP) of the β protons decreased by 35% due to exchange. The solution was allowed to stand at room temperature for 20 h. The mixture was reduced with 7.8 mg (0.206 mmol, 3 equiv) of $NaBH_4$ at 37 °C. After the reduction was completed (20 min by NMR spectroscopy), the solution was acidified with DCl and diluted with H_2O to ~30 mL. 3-Fluoroalanine was again isolated by ion exchange and freeze-drying, yield 19 mg (66%). Mass spectral analysis showed no deuterium in the α position but 40% mono- and 28% dideuteration in the β position.

3-Fluoro-D,L-alanine-^{15}N. Ammonia-^{15}N (100 mL, 4.46 mmol, 95.9 atom % ^{15}N) was condensed at liquid nitrogen temperature, 0.37 mL of H_2O was added, and the solid was allowed to warm to 0 °C. In this solution 32 mg (0.22 mmol) of sodium fluoropyruvate monohydrate was dissolved and equilibrated. The intermediate diamine **8** was observed by ^{13}C NMR spectroscopy (see Results and Discussion). After reduction with 5 equiv of $NaBH_4$ and usual work up (see above), 8 mg (34%) of 3-fluoro-D,L-alanine-^{15}N was isolated and identified by its ^{13}C NMR spectrum: carboxyl C_1 at 171.4 ppm ($^3J_{CF}$ = 6.0 Hz), C_2 at 55.8 ppm ($^2J_{CF}$ = 19.8 Hz, $J_{C-^{15}N}$ = 6.4 Hz), and C_3 at 82.9 ppm ($^1J_{CF}$ = 169 Hz)

***N*-Carbobenzoxy-3-fluoro-D,L-alanine-2-*d*.**[20] A 500-mL three-neck round-bottom flask fitted with a mechanical stirrer, pH probe, and two dropping funnels, one for benzyl chloroformate and the other for 2.5 N NaOH, was charged with 10.7 g (0.10 mol) of **11** in 107 mL of H_2O. The reaction mixture was cooled to 0–5 °C, and pH was adjusted to 10.5–11.0 with approximately 30 mL of 2.5 N NaOH, and 33.2 g (0.198 mol) of benzyl chloroformate was added over a period of 1 h, keeping the pH between 10.5–11.0 by the addition of NaOH (60 mL was required). After the pH drift ceased, the aqueous solution was extracted with 2 × 100 mL of ethyl acetate, acidified to pH 2 in the cold with 2.5 N HCl (39.3 mL), and extracted with 3 × 100 mL of ethyl acetate. The combined ethyl acetate solutions were dried over $MgSO_4$, filtered, and concentrated to dryness. The crude material was dissolved in 3 L of CCl_4 at reflux. After concentration to 250 mL, the crystallized product was filtered off, washed with CCl_4, and dried overnight at 0.1 mm over P_2O_5: yield 23.4 g (97%); mp 112–113 °C. The NMR spectrum was identical with that of an authentic sample.[20]

Resolution with Quinine. *N*-Cbz-3-fluoro-D,L-alanine-2-*d* (3.62 g, 15 mmol) and quinine (4.87 g, 15 mmol) were dissolved in 6 mL of warm ethanol[27] and allowed to crystallize slowly overnight. The crystals were filtered, washed with cold ethanol, and dried at 65 °C (0.1 mm) to give 2.65 g (62%) with mp 144–145 °C. This material was dissolved in 3 mL of hot ethanol, concentrated slightly, and allowed to crystallize (ice cooling). After filtration, washing, and drying, 2.32 g (55%), mp 150–151 °C, was isolated. The quinine salt was distributed between 20 mL of 1 N HCl and 30 mL of ethyl acetate; the organic phase was washed with 3 × 15 mL of 0.5 N HCl. The organic solution was dried over $MgSO_4$ and concentrated to dryness. Recrystallization from 12 mL of wet CCl_4 yielded 912 mg (50%) of the *N*-Cbz derivative with $[\alpha]^{20}_D$ −4.35° (*c* 11, EtOH). The reference compound prepared from authentic 3-fluoro-D-alanine-2-*d*[20] showed a rotation of $[\alpha]^{20}_D$ −4.46° (*c* 11, EtOH).

Hydrogenolysis as described below on a larger scale yielded 390 mg (96%) of 3-fluoro-D-alanine-2-*d* with a rotation of $[\alpha]^{20}_D$ −10.16° (*c* 6, 1.0 N HCl). A reference sample[20] had, under identical conditions, a rotation of $[\alpha]^{20}_D$ −10.4° (lit. $[\alpha]^{20}_D$ −10.0°,[4a] $[\alpha]^{25}_D$ −10.4°[17]). The ^1H NMR spectrum agreed with the reported one.[4a] Anal. Calcd for $C_3H_5DFNO_2$: C, 33.34; N, 12.96; F, 17.58. Found: C, 33.21; N, 12.75; F, 17.85.

Hydrogenolysis of *N*-Carbobenzoxy-3-fluoro-D-alanine-2-*d*. Resolved *N*-Cbz-3-fluoro-D-alanine-2-*d* (22.34 g, 0.092 mol) was hydrogenated for 3 h in 150 mL of MeOH over 2 g of 10% Pd/C at 40 psig and ambient temperature. The mixture was diluted with 250 mL of H_2O and partially concentrated in vacuo. After filtration the filtrate was evaporated to dryness. The white crystalline mass was triturated with 2-propanol, filtered off, washed with hexane, and air-dried: yield 9.31 g (93.5%); $[\alpha]^{20}_D$ −10.36° (*c* 6, 1.0 N HCl). The product gave satisfactory analyses.

3-Fluoro-D,L-alanine-2-*d* Benzenesulfonate. To a solution of benzenesulfonic acid hydrate (363 g, 2.06 mol, 110% of theory) in 3 L of 95% ethanol was added **11** (201.87 g, 1.87 mol). An additional 1.7 L of 95% ethanol was added as needed to effect solution at room temperature. The clear brownish solution was decolorized by stirring with 53 g of activated charcoal for 1 h. After filtration (Supercel) and washing with 95% ethanol, the pale yellow filtrate was concentrated in vacuo at an internal temperature of ≤25 °C to a heavy crystalline slurry of a total volume of 900 mL. The slurry was stirred as 900 mL of ethyl ether was added over 0.5 h. After stirring for an additional hour, the mixture was filtered and washed with 500 mL of 3:1 ether/ethanol and then with 500 mL of ether. The filtrate and washings were removed, and the cake was further washed liberally with hexane. This first crop, after air-drying, weighed 420.35 g (84.5%).

The mother liquor and washings were combined and concentrated in vacuo (internal temperature ≤25 °C) to a volume of ca. 250 mL.

1-Propanol (250 mL) was added, and the mixture was reconcentrated to 250 mL. This flushing (to remove H_2O) was repeated. To the heavy crystalline slurry 250 mL of ethyl ether was added. The mixture was filtered, and the cake was washed with 400 mL of 3:1 ether/1-propanol, then with 250-mL of ethyl ether, and then liberally with hexane. Air-drying provided an additional 57.07 g (11.5%; total yield 96%) of product: ^1H NMR (D_2O) 7.7 (m, 5 H), 4.99 ppm (ABX pattern, J_{HF} = 46 Hz, 2 H). Anal. Calcd for $C_9H_{11}DNFSO_5$: C, 40.60; H, 4.54; N, 5.26; F, 7.14; S, 12.04. Found: C, 40.74; h, 4.63; N, 5.05; F, 7.42; S, 12.03.

Continuous Resolution.[28] A stirred saturated solution (1-propanol) of 3-fluoro-D,L-alanine-2-*d* benzenesulfonate salt with excess suspended salt was maintained at 28 °C in a dissolver. The solution was drawn through filter candles by a pump and pushed through a gas disengagement device, a pressure relief valve, a flow meter, a pressure gauge, and a heat exchanger to lower the temperature to that of the crystallizer (e.g., 23 °C). The solution was jetted into the L-seeded column, which was maintained as a fluidized bed. The supernatant liquid was rewarmed in a heat exchanger, passed through a filter, recooled to the crystallizer temperature, jetted into the D-seeded column, and recycled to the dissolver through a prewarmer.

At the end of the crystal growth period, the L and D isomers were filtered, washed with a minimum of 1-propanol and hexane, and dried at RT (20 mm). In a typical run with a temperature differential of 5 °C, corresponding to 16.8% supersaturation, a flow rate of 400–600 mL/min, a growth period of 8.4 h, and 100 g of seed of each isomer (80–140 mesh), a net yield of 323 g of D isomer and 330 g of L isomer was obtained. ^1H NMR (D or L isomer) (37% DCl) 7.7 ppm (m, 5 H), 5.1 (J_{HF} = 46 Hz, 2 H). Isotopic purity by mass spectral analysis: D isomer, 98.6% D; L isomer, 98.6% D. Optical purity ($CuSO_4$ buffer; see below): D isomer, $[\alpha]^{20}_{436}$ +68.4°; L isomer, $[\alpha]^{20}_{436}$ −68.7°. Anal. Calcd for $C_9H_{11}DNFSO_5$: C, 40.60; H, 4.54; N, 5.26; F, 7.14; S, 12.04. Found: (D isomer) C, 40.67; H, 4.67; N, 5.49; F, 7.41; S, 12.08; ash, none. Found: (L isomer) C, 40.42; H, 4.54; N, 5.25; F, 6.88; S, 12.22; ash, none.

3-Fluoro-D-alanine-2-*d*: Reversal of the Benzenesulfonate. The benzenesulfonate salt of 3-fluoro-D-alanine-2-*d* (10.0 g, 37.6 mol) was dissolved with stirring in 30 mL of 50% aqueous 2-propanol at room temperature. The clear colorless solution was cooled with stirring in an ice bath and treated dropwise with triethylamine (3.81 g, 37.6 mol). The slurry was stirred in the cold for 0.5 h, filtered, and washed with 50 mL of cold 2-propanol/water (9:1), 50 mL of 2-propanol, and then liberally with hexane. The product was vacuum-dried at room temperature, yield 3.84 g (97%). The ^1H and ^{19}F NMR spectra were identical with those reported previously.[4e] Isotopic purity by mass spectral analysis: 98.8% D. Optical purity: $[\alpha]^{20}_D$ −10.4° (*c* 6, 1.0 N HCl). Spinco analysis: 9.36 μmol/mg; no other amino acids were detected. Titration (NaOH) 100%, equivalent weight 108.1. Anal. Calcd for $C_3H_5DFNO_2$: C, 33.34; H, 5.60; N, 12.96. Found: C, 33.28; H, 5.56; N, 12.84.

3-Fluoro-L-alanine 2-*d* was regenerated by the same procedure. The ^1H and ^{19}F NMR spectra were identical to those of the D isomer. Isotopic purity by mass spectra analysis: 99.0% D. Optical purity: $[\alpha]^{20}_D$ +10.4° (*c* 6, 1.0 N HCl). Spinco analysis: 9.34 μmol/mg; trace of alanine and ammonia, but no other amino acids were detected. Titration (NaOH) 99.9%, equivalent weight 108.0. Anal. Calcd for $C_3H_5DFNO_2$: C, 33.34; H, 5.60; N, 12.96. Found: C, 33.42; H, 5.65; N, 12.74.

Purification of 3-Fluoro-D-alanine-2-*d* Benzenesulfonate via 1-Propanol Slurry. The slurry was based on a solubility of 36 mg for the racemic salt in 1 mL of 1-propanol at 23 °C. The effectiveness of the method was demonstrated by the slurry of an optically impure sample. A slurry of 66.9 g (optical purity 64.6%) of 3-fluoro-D-alanine-2-*d* benzenesulfonate in 707 mL (calcd 658 mL) of 1-propanol was stirred overnight at 23 °C. After filtration, washing with a minimum of 1-propanol and hexane, and drying, 42.7 g of material was recovered (98.8% of theory): $[\alpha]_{365}$ +122.5°; enzymatic assay, isomeric purity >99.995%.

The optical rotations were measured in copper sulfate/acetic acid/sodium acetate buffer solutions (4.0 g of anhydrous NaOAc, 10.0 mL of glacial acetic acid, and 13.5 g of $CuSO_4$ in 100 mL of aqueous solution). The specific rotations for the optically pure compound **11**, $[\alpha]_{365}$ +310.8° (*c* 1), $[\alpha]_{405}$ +217.5°, and $[\alpha]_{436}$ +174.0°, and the benzenesulfonate salt of **11** (24.75 mg/mL of solution), $[\alpha]_{365}$ +122.5°, $[\alpha]_{405}$ +85.6°, and $[\alpha]_{436}$ +68.5°, are within a reproducibility of ±0.5.

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Registry No.—**10**, 65120-55-0; D,L-**11**, 59189-03-6; diethyl oxalate, 95-92-1; ethyl fluoroacetate, 459-72-3; ethyl ethoxallylfluoroacetate Na salt, 7582-61-8; fluoropyruvic acid, 433-48-7; *N*-Cbz-3-fluoro-D,L-alanine-2-*d*, 65120-56-1; benzyl chloroformate, 201-53-1; quinine, 130-95-0; *N*-Cbz-3-fluoro-D-alanine-2-*d* quinine salt, 65120-58-3; *N*-Cbz-3-fluoro-D-alanine-2-*d*, 65120-57-2; 3-fluoro-D,L-alanine-2-*d* benzenesulfonate, 59189-04-7; 3-fluoro-D-alanine-2-*d* benzenesulfonate, 59189-07-0; 3-fluoro-L-alanine-2-*d* benzenesulfonate, 59189-06-9; 3-fluoro-D-alanine-2-*d*, 35523-45-6; 3-fluoro-L-alanine-2-*d*, 59189-05-8; **5**, 59769-04-9; **6**, 65120-59-4; **8**, 65120-60-7; 3-fluoro-D,L-alanine-^{15}N, 65149-95-3.

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(23) Solubility and stability studies were carried out by Dr. G. B. Smith. X ray analyses were performed by Dr. J. A. McCauley.

(24) The enzymatic assay was developed by F. M. Kahan and H. Kropp, who kindly supplied us with the experimental details.

(25) *Caution!* Ethyl fluoroacetate is very toxic. The LD_{50} for man is 2–3 mg/kg; it may be absorbed through the skin and by inhalation. All operations should be conducted with gloves in a well-ventilated hood.

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Prostaglandins and Congeners. 18. Synthesis of Cyclopentenolone Precursors to Prostaglandins from 2,5-Dihydro-2,5-dimethoxyfurans

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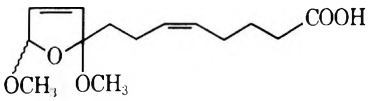
A synthesis of cyclopentenolone **1**, a useful prostaglandin precursor, from 2,5-dihydro-2,5-dimethoxyfuran (DHDMF) intermediates is described. A sequential hydrolysis–aldol cyclization under mildly acidic conditions was found to be a useful procedure for conversion of DHDMF derivatives such as **2** to cyclopentenolones with the pattern of functionality exemplified by **4**. The latter compound was isomerized in dilute sulfuric acid to **1**. The preparation of the requisite precursors to **1** and some of its derivatives are discussed.

Several synthetic schemes for the preparation of cyclopentenolone **1** have been reported.[2] We wish to report a six-stage synthesis of this useful prostaglandin precursor from readily available materials which proceeds in an overall yield of ca. 20%.

The method is dependent on the previously observed rearrangement of cyclopentenolones of type **4** to the thermodynamically favored isomer of type **1**.[3] Since **4** was in principle the product of aldol cyclization of *cis*-enedione **3**, we sought a synthesis of the latter compound or a suitable derivative. It was found that 2,5-dihydro-2,5-dimethoxyfuran **2** fulfilled this synthetic objective and that these dihydrofuran (DHDMF) derivatives[4] represent useful general precursors to cyclopentenolones.[5]



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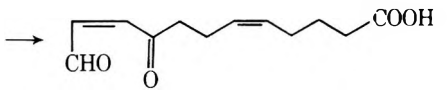

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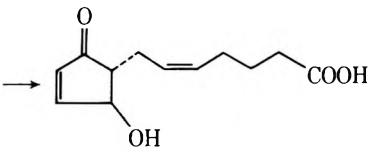

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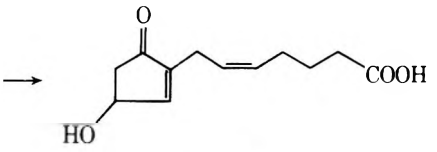
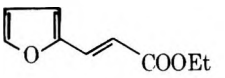


1

Hydrogenation of ethyl β-(2-furyl)acrylate (**5**) using Raney nickel in ethanol afforded the propionate **6** in 90–95% yield if ammonium hydroxide was added to suppress ring reduction. Oxidative methoxylation[4] of **6** with bromine in methanol gave in ca. 85% yield the dihydrofuran **7** which contains the desired latent functionality. Treatment of **7** with diisobutylaluminum hydride in toluene at −75 °C followed by careful neutral workup and distillation gave the aldehyde **8** in 91% yield. Condensation of **8** with ylid salt **9**[6] in dimethyl sulfoxide (Me_2SO) gave the required **2** in 80–85% yield.

Our attempts to convert **2** to *cis*-enedione **3** were only partly successful, since in all cases the corresponding *trans*-enedione was also formed and the isolation was inconvenient.[7] It was decided therefore to combine the hydrolysis of the DHDMF



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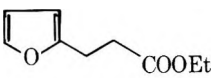
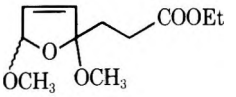


6



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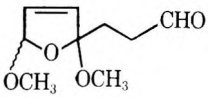

8

$Ph_3P{=}CH(CH_2)_3COONa$

9

function with the aldol cyclization step in a one-pot procedure. After evaluation of several buffer systems including chloroacetate, formate, and acetate, it was found that the weakly acidic (pH ca. 5.5–6.5) system derived from 0.1 M **2**, 0.2 M NaH_2PO_4, and 0.1 M Na_2HPO_4 in boiling aqueous dioxane resulted in the desired sequential conversion to **3** and **4**. While formation of the trans isomer of **3** was not suppressed, the desired **4** was formed in ca. 50–55% yield.

Since the isomerization represented by the conversion of **4** to **1** may be a consequence of hydration–dehydration, we examined the feasibility of equilibration under acid catalysis. Control experiments demonstrated that the desired conversion occurred cleanly in ca. 1 N H_2SO_4 in aqueous dioxane at reflux temperature. This finding allowed a further simplifying modification in our scheme. When the conversion (**2** → **3** → **4**) is complete, as demonstrated by chromatographic (TLC) and spectral (NMR) examination of an aliquot, the solution containing crude **4** may be treated with sulfuric acid and the sequence to give the desired **1** may be completed. This procedure has routinely resulted in a one-pot conversion of **2** to **1** in an overall yield of 45–55%, after appropriate workup and chromatography.

Work in these laboratories has shown that the bis(trimethylsilyl) [$(Me_3Si)_2$] derivative **12** is a useful blocked precursor to prostaglandins via the conjugate addition reaction with organocuprate reagents.[8] When crude **1** obtained from the above sequence was subjected to silylation by a mixture of hexamethyldisilazine and chlorotrimethylsilane in pyridine, the resulting **12** was obtained directly in 45–55% overall yield from **2** by simple Kugelrohr distillation in excellent purity. The sequence reported here therefore has the advantage of requiring no chromatographic purification.

Since we were interested in the introduction of other groups than hydroxy on the cyclopentenone ring, acid-catalyzed equilibration of **1** in methanol was examined. After reaction in methanolic sulfuric acid (1 N) for a period of time somewhat greater than that required for the concomitant Fisher esterification, the ether **13** was produced cleanly in 78% yield.

For preparation of the methyl ester **14** of cyclopentenolone **1**, the following modification proved useful. The crude reac-

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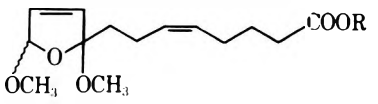
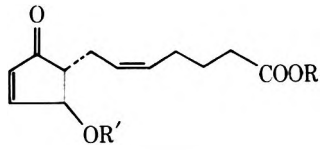
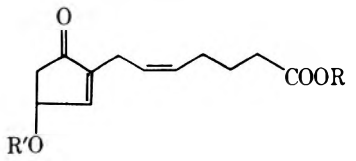
tion mixture containing the sodium salt of **2** in Me_2SO was treated with excess iodomethane at room temperature to give



2, R = H
10, R = Me



4, R = R′ = H
11, R = Me; R′ = Me_3Si



1, R = R′ = H
12, R = R′ = Me_3Si
13, R = R′ = Me
14, R = Me; R′ = H

10 in 82% yield (from **8**). A system which employed 0.1 M **10**, 0.1 M NaH_2PO_4, and 0.03 M sodium acetate in 2:1 dioxane–water at reflux temperature served to convert **10** to **11** in 45% yield after silylation and distillation. Removal of the Me_3Si function and subsequent isomerization using the chloral–triethylamine system provides **14**.[2d]

Experimental Section

Boiling points are uncorrected. NMR spectra were recorded at 100 MHz on a Varian HA-100 spectrometer in deuteriochloroform solution with chemical shifts reported in δ units downfield from internal tetramethylsilane. Mass spectra were recorded on an AEI MS-9 mass spectrometer. Elemental compositions were determined at resolution $M/\Delta M$ = 10 000 by the peak matching method using perfluorokerosene as the standard. For TLC on silica gel plates, two systems were employed: 30:20:1 heptane–ethyl acetate–acetate acid (system A) and 100:1 ethyl acetate–acetic acid (system B). Spots were visualized with 2,4-dinitrophenylhydrazine spray.

Hydrogenation of 5. A solution of 21.6 g (0.13 mol) of **5**[9] in 260 mL of ethanol and 8.75 mL (0.13 mol) of concentrated ammonium hydroxide was hydrogenated on a Parr shaker in the presence of 3 mL of catalyst (No. 28 Raney active nickel washed with water to neutrality and then with ethanol). When hydrogen uptake ceased (ca. 8 h; 105% of theory for 1 mol uptake) the catalyst was filtered and washed with ethanol.

Solutions from two such runs were combined and concentrated in the presence of toluene chaser. The residue was distilled to give 42.8 g (89%) of propionate **6** as a colorless liquid, bp 87–88.5 °C (8 mm) (lit.[9] bp 94–95 °C (10 mm)).

Dimethoxy Ester 7. To a mechanically stirred solution of 42.5 g (252 mmol) of furano ester **6** in 750 mL of methanol at −25 °C was added 53 g (500 mmol) of sodium carbonate. To the stirred mixture was added a solution of 40.5 g (253 mmol) of bromine in 250 mL of methanol during 2.5 h at −25 to −22 °C. Decolorization was rapid throughout the addition, after which the stirred mixture was brought to 25 °C during 10 min and maintained at that temperature for 20 min to ensure solvolysis of intermediate bromo compounds. The mixture was filtered, and the filtrate was partitioned with brine and ether. The ether extract was washed with brine and dried over magnesium sulfate. Evaporation and distillation through a 6 in. Vigreux column gave 48.9 g (84%) of light yellow liquid, bp 78–84 °C (0.2 mm): NMR δ 3.10, 3.18, 3.44, and 3.49 (methoxy singlets for two diastereomers), 4.12 (q, 2, CH_2O), 5.44 and 5.72 (broad s, 1, OCHO for each of two diastereomers); MS 229.1069 [calcd for $C_{11}H_{17}O_5$ (M − H), 229.1075].

Dimethoxyaldehyde 8. To a mechanically stirred solution of 48.9 g (212 mmol) of ester **7** in 800 mL of toluene was added 263 mL of 0.89 M diisobutylaluminum hydride in toluene during 90 min at −75 °C. After stirring an additional 30 min at −75 °C, the solution was treated dropwise with 5 mL of methanol during 10 min. While maintaining the above cooling, the solution was treated with 100 mL of water during 15 min, warmed to 0 °C during 15 min, and stirred at 0–5 °C for 15 min (ice bath; hydrolysis is exothermic at this stage). The mixture was saturated with sodium sulfate and filtered through Celite with the aid of ethyl acetate. The organic phase of the filtrate was separated, washed successively with water and brine, dried briefly over magnesium sulfate, and filtered. The filtrate was treated with ca. 0.1 mL of pyridine and ca. 15 mg of hydroquinone and concentrated.

The residue was short-path distilled to give 35.87 g (91%) of light yellow liquid: bp 76–78 °C (0.25 mm, bath 110 °C); NMR δ 3.12, 3.20, 3.46, and 3.51 (methoxy singlets for two diastereomers), 5.40 and 5.75 (broad s, 1, OCHO for two diastereomers), and 9.73 (m, 1, CHO); MS 185.0804 [calcd for $C_9H_{13}O_4$ (M − H), 185.0814].

Dimethoxy Acid 2. A stirred suspension of sodium hydride [prepared by washing 18.5 g (440 mmol) of 57% dispersion free of mineral oil with 3 × 120 mL of petroleum ether] in 220 mL of dry Me_2SO was heated to 65 °C while monitoring hydrogen evolution and maintained at that temperature for 45 min. The cloudy, light-grey solution was cooled to 17 °C and treated during 15 min with a solution of 98 g (221 mmol) of 4-carboxybutyltriphenylphosphonium bromide in 370 mL of Me_2SO while cooling at 20–25 °C. The red solution was stirred for 15 min at 25 °C, cooled to 17 °C, and treated during 20 min with a solution of 35.8 g (192 mmol) of aldehyde **8** in 150 mL of Me_2SO, while cooling at 17–20 °C. After the addition the solution was stirred at 20–23 °C for 60 min. The solution was concentrated by distillation of Me_2SO under high vacuum (bath 55°), and the resulting residue was treated with 800 mL of water and 2.3 g (22 mmol) of sodium carbonate. The mixture (pH ca. 11) was extracted with ethyl acetate to remove triphenylphosphine oxide.

The aqueous phase was carefully acidified to pH 6 by addition of a 4 M NaH_2PO_4 solution, saturated with sodium chloride, and extracted with 4 × 500 mL of 3:2 ether–petroleum ether. The combined extracts were filtered, washed with brine, dried over magnesium sulfate briefly, filtered, and concentrated to give 43.6 g (85%) of light amber oil. TLC (system A): two green spots, R_f 0.45 and 0.41, for product epimers; NMR δ 3.14, 3.21, 3.48, and 3.52 (methoxy singlets for two epimers), and 5.4 (m, 2, cis-CH=CH); MS 270.1456 (calcd for $C_{14}H_{22}O_5$, 270.1467).

Dimethoxy Ester 10. The dimethoxyaldehyde **8** (49.3 g, 264 mmol) was submitted to the above Wittig reaction with the appropriate scale of materials. After completion of the 60-min reaction period, the solution containing the crude sodium salt of **2** was treated during 10 min with 112 g (790 mmol) of iodomethane while cooling at 30–35 °C. The solution was stirred at room temperature for 18 h and the bulk of the Me_2SO and excess iodomethane were removed in vacuo. The resulting sludge was treated with 700 mL of water. The product was extracted from the mixture of solid triphenylphosphine oxide and solution into several portions of petroleum ether. The extract was washed successively with saturated $NaHCO_3$, water, and brine and dried over potassium carbonate. After concentration to ca. 250 mL, the extract was cooled to 5 °C and filtered. The filtrate was concentrated to give 61.5 g (82%) of light orange liquid: NMR δ 3.11, 3.20, 3.45, and 3.51 (methoxy acetal singlets for two epimers), and 3.66 (methyl ester). Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.58; H, 8.45.

Cyclopentenolone 4. To a stirred solution of 2.70 g (10 mmol) of dimethoxy acid **2** and ca. 10 mg of hydroquinone in 25 mL of peroxide-free 3:2 (v/v) dioxane–water was added 25 mL of phosphate buffer (0.4 M NaH_2PO_4, 0.2 M Na_2HPO_4). After heating to reflux temperature during 20 min, the solution was maintained at that temperature until reaction was complete according to the criteria below. To follow the course of reaction, 2-mL aliquots were withdrawn and partitioned with EtOAc–brine. The EtOAc phase was evaporated and spotted for TLC (System A); when reaction was complete, spots for **2** were absent. Also absent was a green spot, R_f 0.30, corresponding to *cis*-enedione **3**. The indicated products were the *trans*-enedione corresponding to **3** (orange spot, R_f 0.35) and cyclopentenolone **4** (light orange spot, R_f 0.13). The NMR spectra of aliquots were also useful in observing the conversion.[10]

After 90 min at reflux, the solution was cooled, saturated with sodium chloride, acidified with 3 mL of 4 N HCl, and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated. The residue was subjected to dry column chromatography on Woelm Act. III silica gel with System B to afford 1.09 g (49%) of amber oil: NMR δ 4.70 (broad s, 1, CHOH), 6.11 (d of d, 1, COCH=C), and 7.55 (d of d, 1, COC=CH). In addition the spectrum showed resonances due to 5–10% of cyclopentenolone **1** (see below).

Cyclopentenolone Trimethylsilyl Ether 11. A stirred solution of 5.69 g (20 mmol) of dimethoxy ester **10**, 2.65 g (19.2 mmol) of $NaH_2PO_4 \cdot H_2O$, 525 mg (6.4 mmol) of anhydrous sodium acetate, and 20 mg of hydroquinone in 135 mL of peroxide-free dioxane and 68 mL of water was heated at reflux temperature for 27 h. The solution was cooled, saturated with sodium chloride, and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated.

To a stirred solution of the residue (5.0 g) in 20 mL of pyridine at 0 °C was added 5.0 mL (ca. 24 mmol) of hexamethyldisilazane, followed during 2 min by 2.5 mL (ca. 20 mmol) of chlorotrimethylsilane. The mixture was stirred at ambient temperature for 3 h. Volatile matter was removed in vacuo (bath 30 °C), and the resulting residue was slurried with dry petroluem ether. After filtration, the filtrate (ca. 200 mL) was concentrated to 50 mL and filtered. The filtrate was concentrated, and the residue was distilled on a Kugelrohr apparatus (0.02 mm, air bath 130 °C) to give 2.80 g (45%) of light yellow liquid: NMR δ 0.18 (s, 9, trimethylsilyl ether), 3.65 (s, 3, CH_3OOC), 4.70 (broad s, 1, CHO), 6.25 (dd, 1, COCH=C), 7.51 (dd, 1, COC=CH). Anal. Calcd for $C_{16}H_{26}SiO_4$: C, 61.90; H, 8.44. Found: C, 61.67; H, 8.52.

Telescoped Procedure. Preparation of Cyclopentenolone 1. To a mechanically stirred, refluxing mixture of 1300 mL of peroxide-free 3:2 (v/v) dioxane–water and 1300 mL of phosphate buffer [prepared by dissolving 138 g (1.00 mol) of $NaH_2PO_4 \cdot H_2O$ and 70.9 g (0.50 mol) of Na_2HPO_4 in water and diluting to 2500 mL] was added 100 mg of hydroquinone, followed by dropwise addition of neat dimethoxy acid **2** (70.4 g, 260 mmol) during 2 h. After an additional 45-min reflux period the hydrolysis–cyclization was complete by the criteria above for the preparation of cyclopentenolone **4**.

The stirred solution was cooled to 50 °C and treated dropwise with 170 mL (ca. 312 g, 3.12 mol) of concentrated H_2SO_4 during 10 min. The dark solution was stirred at 65 °C for 18 h. The NMR spectrum of an aliquot worked up as below showed the conversion of **4** to **1** to be complete. The solution was cooled, saturated with sodium chloride, and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated to give 68 g of dark oil.

A 64-g portion of the crude was dissolved in 50 mL of 100:5:2 $CHCl_3$–THF–HOAc and subjected to chromatography on 1250 g of Davison No. 923 silica gel (deactivated with 5% water). Elution was carried out with chloroform progressively enriched in THF to ratio 100:14:2 $CHCl_3$–THF–HOAc, followed by ether, followed by ether progressively enriched in acetone (to 10%). Fractions which contained cyclopentenolone **1** (R_f 0.45 on TLC with system B) were combined to give 12.1 g (21%) of one-spot material and 22.0 g (38%) of material with minor contamination. With the above TLC system, isomer **4** (R_f 0.47) is not effectively separated from **1**.

Cyclopentenolone **1**: NMR δ 2.95 (m, doubly allylic CH_2), 4.95 (m, 1, CHOH), 5.56 (broad t, *cis*-CH=CH), and 7.20 (broad s, CO-C=CH).

Other chromatography systems are probably as good or better than the above (cf. purification of **4**). The conditions above for rearrangement of **4** to **1** are ca. 2 N sulfuric acid. An equally effective procedure is to make the reaction solution ca. 1 N in sulfuric acid and carry out the rearrangement at reflux temperature for 16–24 h.

$(Me_3Si)_2$ Derivative 12. To a stirred solution of 76 g of crude **1** [prepared as described above from 82.0 g (440 mmol) of aldehyde **8**] in 625 mL of pyridine at 10 °C was added 124 mL (ca. 900 mmol) of hexamethyldisilazane followed by 105 mL (ca. 900 mmol) of chlorotrimethylsilane. The mixture was stirred at ambient temperature for 3 h. The volatile matter was evaporated under vacuum (bath 40 °C), and the resulting residue was slurried with 300 mL of hexane, treated with charcoal, and filtered. The filtrate was concentrated to give 101 g of dark oil, which was distilled on a Kugelrohr apparatus (0.03 mm, air bath 155 °C) to give 55.2 g of light amber liquid (36% overall yield from aldehyde **8**): NMR δ 0.18 (s, 9, trimethylsilyl ether), 0.28 (s, 9, trimethylsilyl ester), 4.93 (m, 1, CHO), 7.16 (m, 1, COC=CH). Anal. Calcd for $C_{18}H_{32}Si_2O_4$: C, 58.65; H, 8.75. Found: C, 58.89; H, 8.69.

Methyl Ether–Methyl Ester 13. To a stirred solution of 6.28 g (27.8 mmol) of hydroxy acid **1** in 280 mL of methanol was added 7.6 mL (ca. 140 mmol) of concentrated H_2SO_4. The solution was stirred under reflux for 40 h, at which point the resonance at δ 4.95 in **1** was completely replaced by a resonance at 4.48 in the NMR spectrum of a worked up aliquot. The solution was cooled, treated cautiously with 7.4 g (70 mmol) of sodium carbonate, and concentrated. The residue was partitioned with ether and brine. The ether phase was washed with brine, dried over magnesium sulfate, and concentrated. The residue was short-path distilled to give 5.45 g (78%) of light yellow liquid: bp 130–134 °C (0.05 mm); NMR δ 3.41 (methyl ether), 3.66 (methyl ester), and 4.48 (m, 1, CHO). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.28; H, 8.38.

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Registry No.—**1**, 52419-12-2; *cis*-**2**, 65377-96-0; *trans*-**2**, 65377-97-1; *trans*-**3**, 65338-45-6; **4**, 65377-98-2; **5**, 623-20-1; **6**, 10031-90-0; *cis*-**7**, 65338-46-7; *trans*-**7**, 65338-47-8; *cis*-**8**, 65338-48-9; *trans*-**8**, 65338-49-0; *cis*-**10**, 65338-50-3; *trans*-**10**, 65377-99-3; **11**, 65338-51-4; **12**, 62555-09-3; **13**, 65378-00-9; 4-carboxybutyltriphenylphosphonium bromide, 17814-85-6.

References and Notes

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Synthesis of 4,9-Dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-*a*]purine and the "Y" Base from *Saccharomyces cerevisiae* Phenylalanine Transfer RNA

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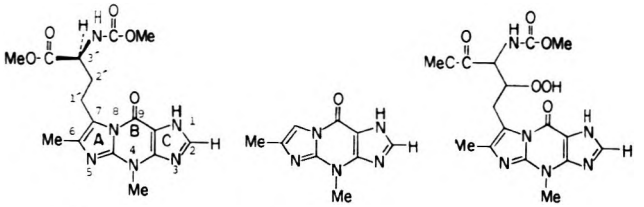
An efficient synthesis of the "Y" base compounds has been developed using 7-benzyl-3-methylguanine as the key intermediate. A study of the regioselectivity of the alkylation of this intermediate, plus the high yields in this synthesis, confirms the proposed structure for the fluorescent bases isolated from the phenylalanine transfer RNA of *Torulopsis utilis* and *Saccharomyces cerevisiae*.

Because of their distinctive physical properties and/or because of their ability to be selectively altered, the modified nucleosides occurring in transfer RNA (tRNA) have been used to study the tertiary structure of tRNA and its interactions with other molecules.[1] Some of the most distinctive of these modified nucleosides are the "Y" type compounds,[2] which are still the only nucleic acid bases possessing a condensed tricyclic skeleton. Y bases have been isolated from the phenylalanine tRNA of several eukaryotic species, including *Saccharomyces cerevisiae*,[3] wheat germ,[4] beef liver,[5] rat liver,[6] and *Torulopsis utilis*,[7] but at least one eukaryotic species does not possess Y bases in its phenylalanine tRNA.[8] In contrast to most other modified nucleosides, the Y compounds have been of special interest because of their intense fluorescence.[9]



1 $Y_{S.C.}$ 2 $Y_{T.U.}$ 3 $Y_{L.}$

To date the structures of three Y bases have been determined. The planar structure of the Y base **1** isolated from $tRNA^{Phe}$ of *S. cerevisiae* was determined by comparing its spectroscopic data obtained with 300 μg of sample with various synthetic models[10] and was subsequently "confirmed" by a "synthesis" in which the yield of the last step was 2%.[11] The absolute configuration of the side chain was established as *S* by a microozonolysis of Y base which yielded dimethyl (*S*)-2-methylcarbamoylglutarate.[11] The structures of the *Torulopsis utilis* Y base **2**[7] and the Y base isolated from mammalian liver[12] and *Lupinus luteus* **3**,[13] which contains the rare hydroperoxide function, were determined by correlation (and by the synthesis of Y_{TU} **2**[7]). The possible presence of Y bases other than **1–3** have also been reported.[14] Interestingly, the $tRNA^{Phe}$ isolated from brain tumor has been shown to be deficient in the Y bases.[15,16]

The structure of the Y nucleosides, however, still remains to be proven unambiguously by synthesis. It has been proposed to be the 3-β-D-ribofuranoside[17] because the synthetic Y_{TU}-1-β-D-ribofuranoside resisted hydrolysis by 2 N hydrochloric acid at 37 °C, which was in contrast to the well-known lability of Y nucleosides to mild acid.[18] On the other hand, Reese and Whittall[19] synthesized a 3,4-cyclo-β-D-ribofuranoside and found it to be acid resistant; they have thus suggested the possibility that the Y nucleosides could be 2′-deoxyribonucleosides. The skeleton of the Y_{SC} nucleoside has been shown to be biosynthesized from guanine,[20,21] whereas the side chain is apparently derived from methionine.[22]

Since it is difficult to isolate more than a few hundred micrograms of these bases from natural sources, an efficient synthesis of these compounds is necessary in order to study their chemical and physical properties. This paper discusses our synthetic studies on these naturally occurring modified bases.

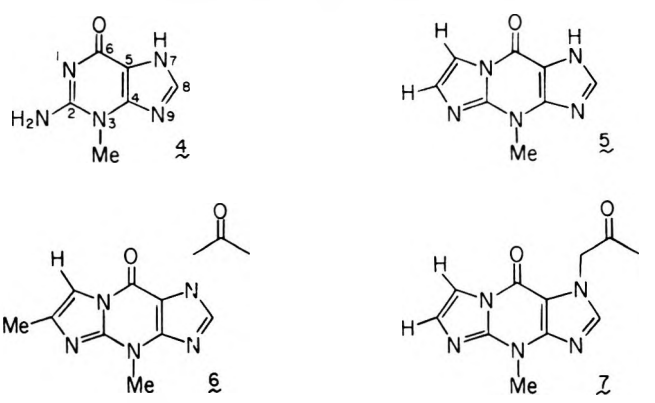
Results and Discussion

Our goal was to develop an efficient synthesis of the simplest of the naturally occurring Y bases, **2**, with the expectation that this route could be used for the syntheses of other bases such as **1** and **3**. Noting the vigorous conditions needed to form the B and C rings, it seemed that the best route involved building ring A onto the preformed 3-methylguanine nucleus. The necessary 3-methylguanine (**4**) was prepared by several modifications of the literature procedure,[23,24] which resulted in an increase of overall yield from 3 to 35%.

It seemed reasonable to form the A ring by causing an α-bromo ketone to react with 3-methylguanine (**4**). After this work had commenced, it was reported that chloroacetaldehyde reacts well with adenosines and cytosines under acidic conditions (pH 3.5–4.5) to form tricyclic and dicyclic compounds, respectively, but no detectable reaction occurred with guanines under these conditions.[25,26] More recently, Leonard and co-workers have reported that under slightly higher pHs (6.4) chloroacetaldehyde also reacts with guanosine to give a linear tricyclic compound possessing basically the Y base nucleus, i.e., 1,N^2-ethenoguanine (hydrogens instead of the two methyls in structure **2**); this compound, however, is only weakly fluorescent.[27]

Reaction of α-Bromo Ketones with 3-Methylguanine. The alkylation–condensation reaction of an appropriate α-bromo ketone with 3-methylguanine is the only published synthesis of **1** and **2**,[7,11] but this was not a satisfactory route because of the side reactions, poor solubility properties of 3-methylguanine, etc.[28]

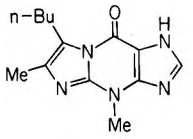
Although 3-methylguanine is completely insoluble in most solvents, it is slightly soluble in dimethylformamide and dimethylacetamide. It is more soluble in dimethyl sulfoxide, water (pH >8), and ethanol (pH >8), but these solvents cause substantial decomposition of the α-bromo ketone. To exem-



4 5 6 7

plify the side reactions encountered, the condensation of α-bromo ketone with **4** at 100 °C in DMF with diethylaniline as the base yielded not only the desired **2**, but also the desmethyl derivative **5** and the dialkylation compounds **6** and **7**. It is conceivable that compound **5** results from the reaction of 3-methylguanine with α,α′dibromoacetone formed from the disproportionation of α-bromoacetone followed by loss of formaldehyde. As would be expected, position 7 of the guanine competes with position 1 as the site of alkylation as shown by the formations of **6**, **7**, and 3-methyl-7-(2-oxopropyl)guanine. The side products **5** and **7** can be eliminated and the yield of the desired **2** raised to 25% by using water (pH 10) as the solvent, but these conditions can not be used for synthesis of the Y_{SC}, since the ester and carbamate groups are unstable in base.

When a secondary bromide is used in place of a primary bromide, other side products are formed; e.g., **9** is formed in



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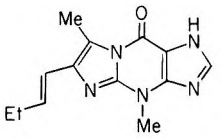
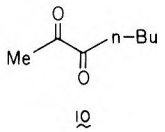


9



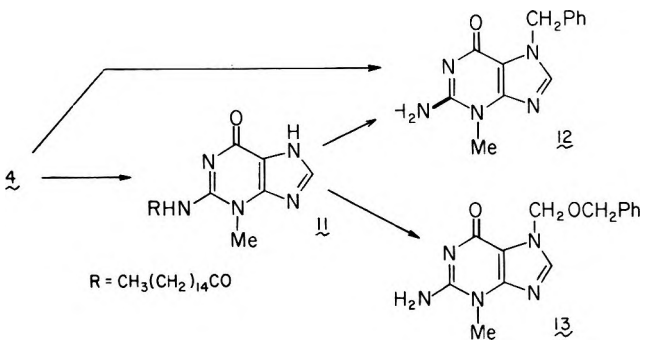
10

addition to **8** and **5** when 3-methylguanine is caused to react with 3-bromo-2-heptanone. Product **9** is most likely formed by oxidation of the α-bromo ketone to the diketone **10** (especially in dimethyl sulfoxide) followed by its cyclization with 3-methylguanine (**4**).[29]

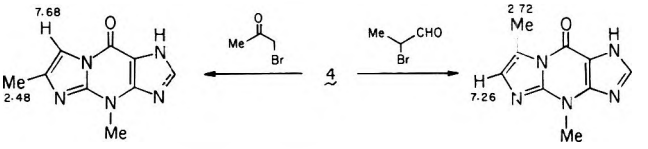
Because of the poor yields of the desired tricyclics and the multitude of products, protection of the 7 position of the 3-methylguanine is desirable to prevent alkylation of this position by the α-bromo ketone and also to make the guanine more soluble. A benzyl group was considered to be most suitable for protection in view of its regioselective attachment at the 7 position rather than the N^2 or 1 positions, its stability during the cyclization reaction, and its ease of removal even in the presence of the carbamate and ester groups of **1**.[30]

Protection of 3-Methylguanine. The desired alkylation of the 7 position of **4** was not accomplished as readily as expected. When the preformed anion of **4** (NaH in DMF) is stirred with benzyl chloride, only unreacted 3-methylguanine is recovered (>85%) after heating the mixture at 60 °C for 24 h. The same results are obtained even when the more reactive benzyl chloromethyl ether is used as the alkylating reagent. This unreactivity is in contrast to the alkylation of the anion of guanine with alkyl chloride at room temperature in DMF.[31]

On the other hand, prior protection of the 2-amino group by reacting 3-methylguanine with palmitoyl chloride in pyridine[32] to yield 3-methyl-N^2-palmitoylguanine (**11**) allowed the alkylation at N-7 to take place. In this case, reaction of **11** with potassium carbonate and benzyl chloride or benzyl chloromethyl ether followed by treatment with ammonium



Scheme I

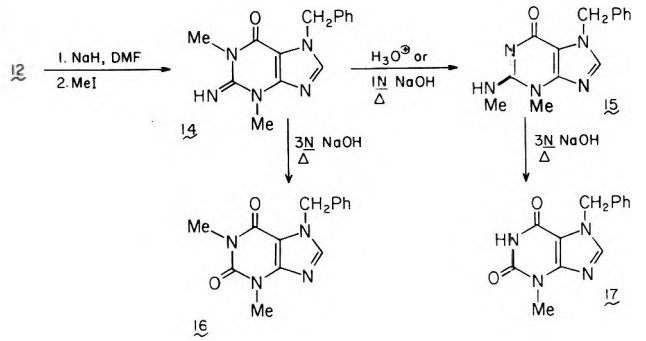


hydroxide yielded **12** and **13**, respectively. Since **11** is alkylated readily compared to **4**, the difficulty of alkylating **4** must be due to electronic rather than steric factors. Thus usage of a more reactive alkylating agent such as benzyl bromide results in direct alkylation of **4** to give **12** in good yield.

Alkylation of 7-Benzyl-3-methylguanine. The next step is the formation of the second imidazole ring by cyclization between the 1 and N^2 positions of the guanine. As with the unprotected 3-methylguanine, this can be carried out by using an α-bromo ketone. Since the orientation of the two reactive carbons of the α-bromo ketone with respect to the guanine is dependent on whether the 1 or N^2 position of the guanine is alkylated in the initial step, the site of alkylation (1 or N^2) must be determined. For the 7- or 9-substituted guanines, it is well known that alkylation under basic conditions occurs predominantly at the 1 position,[23] but it is necessary to verify that **12** is alkylated with the same regioselectivity for that position.

In connection with the verification of the substitution at the 6 and 7 positions of the tricyclic, the original structural assignment for these positions should be mentioned.[10] From the ^1H NMR spectra of a number of model compounds, it was found that the methyl groups at the 6 and 7 positions were at ~2.3 and 2.6 ppm; namely, there was a chemical shift difference of 0.3 ppm. It was rationalized that the methyl protons at the 7 position should be further downfield due to the anisotropic effect of the 9-carbonyl. A similar argument was used in the structural studies of the Y_{Tu} base **2**.[7] This rationalization could be questioned since there is a lack of proper model compounds for the prediction of the chemical shift at this position, but the synthesis of a number of model compounds supported the assigned structure.[34] The ^1H NMR data obtained from the synthesis of **2**[7] and its structural isomer as shown in Scheme I supports this assignment as long as alkylation takes place at the 1 position of 3-methylguanine.

To prove this point, we studied the alkylation of the anion of **12**. Employment of conditions similar to those for the synthesis of the tricyclics, but replacement of methyl iodide for the α-bromo ketone, produces a single benzyldimethylguanine (as determined by thin-layer chromatography and ^1H NMR) plus a small amount of unreacted 3-methylguanine. It was originally planned to identify the structure of the dimethyl derivative (either **14** or **15**) by hydrolysis to the xanthine derivative (**16** or **17**, respectively). Upon acid hydrolysis

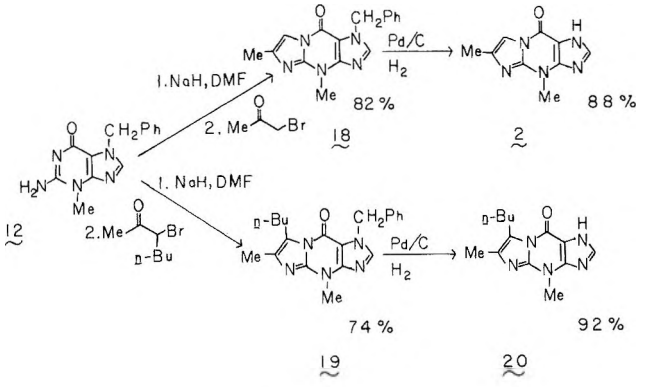


conditions (1 N HCl, 100 °C, 24 h; concentrated HCl, 100 °C, 24 h; 5 N H_2SO_4, 100 °C 24 h; 1 N HNO_3, 100 °C, 24 h) the compound was converted into another isomer, but neither isomer would hydrolyze to the xanthine derivative.[35] Unlike

the original dimethylguanine, which had two singlets at 3.42 and 3.26 ppm for the methyl groups, the rearranged compound **15** had one singlet at 3.42 ppm and one doublet at 2.74 ppm (J = 4 Hz, coupled to a single amino proton). These ^{1}H NMR data indicate that the expected guanine **14** is formed originally, but that it rearranges to the isomer **15**.[36]

Compound **14** is also converted to **15** by aqueous base,[36] but if the conditions are vigorous enough (3 N NaOH, 100 °C) **14** can be hydrolyzed to **16** before an appreciable amount of rearrangement to **15** takes place. In a similar manner **15** can be hydrolyzed to **17**. Since both **16** and **17** have been synthesized in a different manner previously,[37-40] we have verified the assigned structures for **14** and **15** and the regioselectivity of alkylation at the 1 position.

When α-bromoacetone is caused to react with the anion of **12** under the same conditions as those used with methyl iodide, a single fluorescent compound **18** was produced in 82% yield. The reaction proceeded almost as well with a secondary bromide (3-bromo-2-heptanone) to give **19** in 74% yield. The



isolated tricyclics were judged to be a single isomer in each case on the basis of the ^{1}H NMR spectra and thin-layer chromatography on silica gel in several solvent systems. Since both the α-bromo ketone and methyl iodide are completely regioselective and **14** does not rearrange to **15** under the reaction conditions, the tricyclic structures should be **18** and **19** and not any structural isomers. The ^{1}H NMR signals of the C–Me groups in **18** (2.22 ppm) and **19** (2.10 ppm), which are at chemical shifts for methyls not "peri" to the carbonyl, also corroborate these structures.

Debenzylation of Imidazo[1,2-*a*]purines. In determining hydrogenation conditions for the removal of the benzyl protecting group from **18** to yield the desired tricyclic **2**, two possible complications have to be considered, namely, the hydrogenation of the 6,7 double bond and alteration of the ester or carbamate portion of **1** under some acidic conditions.[30] Since the hydrogenation reaction proved to be much more difficult than expected, our results are described somewhat in detail.

The benzyl tricyclic compound **19** remained unchanged when its methanolic solution was stirred with 10% Pd/C under 1 atm of H_2 for 24 h. With 10% Pd/C in methanol, some debenzylation was possible when acetic acid (1–20% by volume) was added to the mixture, but this method yielded three other fluorescent compounds in about equal amounts as compared to the desired **20**. Addition of 1 N aqueous HCl along with 10% Pd/C to a methanolic solution of **19** caused clean reduction to **20**, but the rate was very slow. The above results were not improved by using the normally more readily reducible benzyloxymethyl derivative in place of the benzyl derivative.

In contrast to the other conditions, usage of 5% acetic acid and a few drops of 1 N HCl in methanol or 2-propanol with 10% Pd/C and 1 atm of H_2 led to the rapid reduction of **19** to the desired **20** in 92% yield. This method was equally successful in transforming **18** into **2**. It should be noted that under these conditions the fluorescent compound was completely destroyed if too much oxygen was present either during the reduction or in the workup until all the acetic acid was removed.

In summary, the use of the benzyl protecting group at the 7 position of 3-methylguanine allows it to be converted to the "Y" bases **2** and **20** in overall yields of approximately 60%. This synthesis establishes the structure of the "Y_T" base and hence the skeleton of the other related "Y" bases.

Synthesis of the Y Base from *Saccharomyces cerevisiae*. Although the synthesis of the Y compounds via the route described above gave good yields for simple Y compounds, e.g., **2** and **20**, a number of problems arose in using this synthesis for making the more complicated molecule Y_{SC} **1**. One of the problems was that the reported synthesis of **23** was lengthy;[11] in addition, this synthesis did not allow a ready route to the optically active compound.

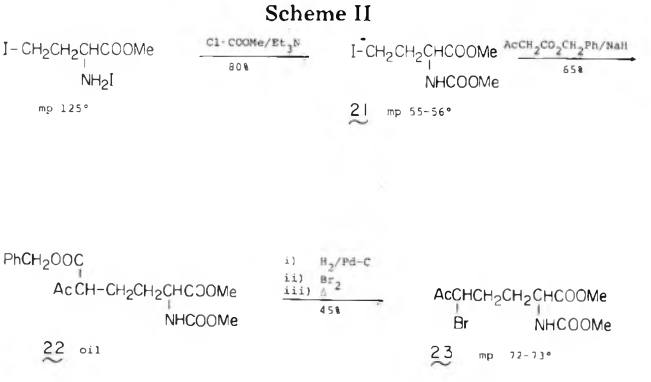
We therefore considered a number of alternative routes where the tricyclic system would be constructed first, and then the amino acid side chain would be added. The advantage of this route was that a derivatized L-homoserine could be used to yield the optically active naturally occurring **1**.[42] Unfortunately, the three attempted routes failed because of the instability or reactivity of the tricyclic heterocyclic system.[42,43]

It has been reported that **23** reacts with 3-methylguanine directly to give **1**; however, the yield was only 2% based on purine and using 3 equiv of **23**.[11] In addition, a number of other fluorescent compounds were formed and had to be separated by silica gel chromatography. The synthesis of **23** is given in Scheme II and the Experimental Section.

It was expected that the use of 7-benzyl-3-methylguanine should give a much cleaner reaction and higher yields of the desired Y base. Using 1 equiv of **23** in place of bromoacetone gave a 6% yield of 1-benzyl-Y_{SC} and no other fluorescent products were produced. Increasing the reaction time, bromo ketone addition time, and reaction temperature did not increase the product yield. The major problem was a decomposition of the bromo ketone by an internal cyclization process. It had been previously noted that the yield of tricyclic bases could be increased at higher temperatures in a dimethylformamide–tetrahydrofuran (1:3, v/v) mixture when the bromo ketone was exceptionally unstable.[43] These conditions did not give an increased yield in the case of cyclization with **23**. In all cases, most of the 7-benzyl-3-methylguanine did not react and was recovered.

The low tricyclic yield with **23** cannot be attributed to steric hindrance since other secondary bromo ketones, such as 2-bromo-2-heptanone, reacted readily. The internal cyclization of **23** is apparently more facile than the alkylation of the purine system. The reaction of potassium *tert*-butoxide, methylmagnesium bromide, or triethylamine instead of sodium hydride with 7-benzyl-3-methylguanine (**12**) prior to the addition of **23** did not improve the yield of 1-benzyl-Y_{SC}. However, it was finally found that reaction of **12** with 1 equiv of **23**

Scheme II



in DMF at 50 °C with 5 equiv of *N,N*-diethylaniline gave a 20% yield of 1-benzyl-Y_{SC}.

This product could be converted to Y_{SC} under the same conditions that converted 1-benzyl-Y_{TU} to Y_{TU}. Therefore, the synthesis of Y_{SC} described here has been considerably improved from that previously reported.[11] These synthetic studies also chemically corroborate the structures forwarded for the Y bases.

Experimental Section

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Jasco (Model 13A-1) or a Perkin-Elmer (Model 621) grating infrared spectrophotometer. The peaks are given in reciprocal centimeters with polystyrene film as the standard. Ultraviolet spectra were recorded on a Cary 14 recording spectrophotometer. Fluorescence measurements were conducted on a Perkin-Elmer MPF-2A spectrophotofluorimeter fitted with a xenon lamp and are uncorrected using 310 nm as excitation wavelength for the emission spectra. Proton magnetic resonance spectra (^{1}H NMR) were recorded on Varian A-60A, T-60, or HA-100 spectrometers. Chemical shifts are in δ units with respect to tetramethylsilane as the internal standard and $(CD_3)_2SO$ as the solvent unless otherwise specified. Low-resolution mass spectra were recorded on a Jeol JMA-07 spectrometer and high-resolution spectra on a DuPont CEC 21-110B with PFK as the standard for peak matching. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Analytical and preparative thin-layer chromatography plates were made using Merck silica gel G. The preparative plates were prewashed with methanol and the desired bands were eluted from the plates using the same solvent as for developing the plates. Column chromatography was done on Merck silica gel 60 and at room temperature. The dimethylformamide was stirred with potassium hydroxide pellets and then distilled from CaH prior to use. All other organic solvents were distilled and stored over molecular sieves.

2,6-Diamino-1,4-dihydro-1-methyl-4-pyrimidone. The procedure of Roth et al.[24] was followed until the purification of the crude pyrimidone. Instead of purification as the sulfate salt, the free base was purified in the following manner. To a 75 °C solution (120 mL of water/10 g of pyrimidone) was added 40% aqueous sodium hydroxide until the solution had cleared. Addition of charcoal, followed by filtration through Celite and acidification to pH 6, yielded a white precipitate, which when filtered and dried weighed 200 g (65% yield): mp 284 °C.

2,6-Diamino-1,4-dihydro-1-methyl-5-nitroso-4-pyrimidone. To a solution at 40 °C of 25 g of 2,6-diamino-1,4-dihydro-1-methyl-4-pyrimidone, 28 g of sodium nitrite, and 8 g of sodium hydroxide in 3 L of water, glacial acetic acid was slowly added until pH 6 was reached. If precipitation occurred before the solution turned a deep magenta, aqueous sodium hydroxide was added until the precipitate dissolved and then the solution was reacidified. After a red precipitate started to form, the pH was adjusted to 5 with acetic acid. The solution stayed at room temperature for 4 h and was then filtered. After dissolving the red solid in water by adding 40% aqueous sodium hydroxide, the solution was filtered, washed with water and acetone, and dried to yield 22 g (70%): mp >300 °C.

1,4-Dihydro-1-methyl-2,5,6-triamino-4-pyrimidone Sulfate. The triaminopyrimidone sulfate was prepared according to the procedure of Roth et al.[24] except for the following simplification. After the addition of the sodium dithionite, the hot yellow solution was filtered and 6 N sulfuric acid was added until pH 1 was reached. After cooling, the solid was removed by filtration and dried to yield 12.9 g (86%): mp >300 °C.

3-Methylguanine (4). The triaminopyrimidone sulfate was converted to 3-methylguanine according to the procedure of Townsend and Robins,[23] except that the product was recrystallized from hot water with a charcoal treatment and then recrystallyzed twice more from hot water to yield white crystals in 89% yield: mp >300 °C; ^{1}H NMR δ 4.50 (s, 3), 8.08 (br, 2), 8.63 (s, 1).

7-Benzyl-3-methylguanine (12). 3-Methylguanine (0.32 g, 2 mmol) was dissolved in 100 mL of DMF through which nitrogen was bubbled for 1 h. After adding sodium hydride (96 mg of a 50% oil dispersion, 2 mmol), the solution was stirred for 3 h before adding the benzyl bromide (0.34 g, 2 mmol). After stirring for 18 h, silica gel (0.3 g) was added and the DMF was removed in vacuo. The solid was placed on top of a 100-g silica gel column, which was then washed with 300 mL of chloroform to remove unreacted benzyl bromide. Finally, 800 mL of chloroform–methanol (9:1, v/v) was used to elute the product. Recrystallization twice from methanol yielded 0.43 g (85%) of white needles: mp 269–270 °C; ^{1}H NMR δ 3.50 (s, 3), 5.50 (s, 2), 6.89 (br s, 2), 7.28 (s, 5), 8.18 (s, 1); UV λ_{max} (H_2O, pH 1) 245 (ϵ 9300), 267 (11 900); (pH 7) 248 (8100), 268 (10 400); (pH 12) 242 (9 100), 265 (11 500).

Anal. Calcd for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43. Found: C, 60.94; H, 5.17; N, 27.14.

7-Benzyl-1,3-dimethylguanine (14). To a solution of 12 (128 mg, 0.5 mmol) in DMF (50 mL), which was deoxygenated under a flow of nitrogen, was added sodium hydride (24 mg of a 50% oil dispersion, 0.5 mmol). After stirring for 3 h, methyl iodide (70 mg, 0.5 mmol) was added and the mixture was stirred for 15 h. After removing the DMF in vacuo, the solid was stirred in benzene and then removed by filtration. Rapid recrystallization from water yielded 120 mg (89%) of a white solid: mp 175 °C; ^{1}H NMR δ 3.26 (s, 3), 3.42 (s, 3), 4.4 (br, 1), 5.45 (s, 2), 7.35 (s, 5), and 8.10 (s, 1). The facile rearrangement of this compound to **15** precluded obtaining an elemental analysis of this material.

7-Benzyl-N^2,3-dimethylguanine (15). A solution of **14** (114 mg, 0.4 mmol) was stirred in 1 N NaOH (5 mL) for 4 h. After neutralization with 1 N HCl and cooling, the mixture was filtered to yield 88 mg (85%) of a white solid: mp 235 °C; ^{1}H NMR δ 2.74 (d, 3, J = 4 Hz), 3.43 (s, 3), 5.43, (s, 2), 6.84 (br, 1), 7.20 (s, 5), 7.90 (s, 1); UV λ_{max} (H_2O, pH 1) 238 (ϵ 9200), 262 (11 400); (pH 7) 240 (9400), 261 (11 800); (pH 12) 236 (9200), 265 (11 700).

Anal. Calcd for $C_{14}H_{15}N_5O$: C, 62.44; H, 5.61; N, 26.01. Found: C, 62.27; H, 5.53; N, 25.95.

7-Benzyl-1,3-dimethylxanthine (16). To a refluxing solution of 3 N NaOH (5 mL) was added 7-benzyl-1,3-dimethylguanine (**14**; 114 mg, 0.4 mmol). After refluxing for 1 h, the solution was neutralized with glacial acetic acid. After cooling in a refrigerator, the product was removed by filtration. Purification by silica gel chromatography yielded 80 mg (74%) of the desired xanthine plus 9 mg (9%) of 7-benzyl-3-methylxanthine (**17**), which is derived by rearrangement prior to hydrolysis. The 7-benzyl-1,3-dimethylxanthine had: mp 157 °C (lit. mp 158 °C);[38-40] ^{1}H NMR (Me_2SO–TFA) δ 3.15 (s, 3), 3.36 (s, 3), 5.43 (s, 2), 7.25 (s, 5), 8.03 (s, 1).

7-Benzyl-3-methylxanthine (17). To a solution of 3 N NaOH (5 mL) was added 114 mg of 7-benzyl-N^2,3-dimethylguanine (0.4 mmol). After refluxing for 2 h, the solution was neutralized with glacial acetic acid. After cooling in a refrigerator, the product was removed by filtration and recrystallized from methanol to yield 84 mg (82%): mp 271 °C (lit. mp 273 °C);[38] ^{1}H NMR (Me_2SO–TFA) δ 3.38, (s, 3), 5.43 (s, 2), 7.25 (s, 5), 8.08 (s, 1).

1-Benzyl-4,9-dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-*a*]purine (18). After bubbling nitrogen through a solution of 7-benzyl-3-methylguanine (255 mg, 1 mmol) in DMF (50 mL), sodium hydride (48 mg of a 50% oil dispersion, 1 mmol) was added and the mixture was stirred for 2 h. Then bromoacetone (150 mg, 1.1 mmol) in DMF (10 mL) was added and the mixture was stirred an additional 18 h under nitrogen. (Cooling the solution below room temperature when adding the bromoacetone results in a much lower yield of the tricyclic.) After adding 1 g of silica gel, the DMF was removed in vacuo and the solid was placed on top of a 30-g silica gel column. The only fluorescent band to long wavelength UV light that eluted with 2-propanol–ethyl acetate (2:8, v/v) was recrystallized from methanol to yield 121 mg (82%) of white crystals: mp 205–206 °C; ^{1}H NMR δ 2.22 (d, 3, J = 1 Hz), 3.78 (s, 3), 5.57 (s, 2), 7.34 (s, 5), 7.3 (1), 8.40 (s, 1); UV λ_{max} (90% MeOH, pH 1) 229 (ϵ 39 200), 232 (39 000), 282 (10 100); (pH 7) 229 (3500), 233 (38 000), 266 (7000), 304 (6600); (pH 12) 227 (33 000), 230 (36 100), 265 (6800), 306 (7600).

Anal. Calcd for $C_{16}H_{15}N_5O$: C, 64.04; H, 5.37; N, 24.90. Found: C, 64.15; H, 5.17; N, 24.80.

4,9-Dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-*a*]purine (2). The benzyl tricyclic **19** (29 mg, 0.1 mmol) and 10% Pd/C (30 mg) were added to distilled propanol (50 mL) containing acetic acid (3 mL) and 0.1 N aqueous HCl (3 drops). After flushing the flask at least four times (evacuation, followed by hydrogen) to remove almost all the oxygen present, the mixture was stirred under 1 atm of hydrogen for 6 h. The mixture was rapidly filtered and taken to dryness in vacuo. The residue was purified by preparative silica gel TLC using 2-propanol–ethyl acetate (2:8, v/v). Since the R_f of the product varied depending on impurities that were present, the product band was the main fluorescent one under long wavelength UV light. Recrystallization from methanol yielded 18 mg (88%) of white solid: mp 280 °C; ^{1}H NMR δ 2.23 (d, 3, J = 1 Hz), 3.81 (s, 3), 7.36 (q, 1, J = 1 Hz), 7.75 (s, 1); UV λ_{max} (H_2O, pH 6.8) 230 (ϵ 34 000), 265 (6400), 304 (6900); (H_2O, pH 1.3) 227 (38 160), 231 (38 000), 282 (10 400); (H_2O, pH 11.6) 230 (39 200), 273 (10 400), 300 (10 680); MS 203 (M^+).

Anal. Calcd for $C_9H_9N_5O$: C, 53.20; H, 4.47; N, 34.46. Found: C, 52.96; H, 4.62; N, 34.70.

1-Benzyl-7-butyl-4,9-dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-a]purine (19). After bubbling nitrogen through a solution of 7-benzyl-3-methylguanine (255 mg, 1 mmol) in DMF (50 mL), sodium hydride (48 mg of a 50% oil dispersion, 1 mmol) was added and the mixture was stirred for 2 h. Then 3-bromo-2-heptanone (212 mg, 1.1 mmol) in DMF (10 mL) was added and the mixture was stirred an additional 18 h under nitrogen. After adding 1 g of silica gel, the DMF was removed in vacuo and the solid was placed on top of a 30-g silica gel column. The fluorescent band to long wavelength UV lamp that eluted with 2-propanol–ethyl acetate (1:9, v/v) was recrystallized from methanol to yield 237 mg (74%): mp 164–166 °C; ^{1}H NMR δ 0.84 (m, 3), 1.33 (m, 4), 2.10 (s, 3), 2.92 (m, 2), 3.70 (s, 3), 5.58 (s, 2), 7.34 (s, 5), 8.35 (s, 1); UV λ_{max} (10% aqueous MeOH, pH 1.0) 230 (ϵ 36 100), 284 (7600); (10% aqueous MeOH, pH 6.5) 229 (29 500), 265 (6100), 315 (5200); (10% aqueous MeOH, pH 11) 230 (28 000), 266 (6200), 313 (4900).

Anal. Calcd for $C_{20}H_{23}N_5O$: C, 68.75; H, 6.63; N, 20.04. Found: C, 68.66; H, 6.57; N, 20.16.

7-Butyl-4,9-dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-a]purine (20). The benzyl tricyclic **19** (66 mg, 0.2 mmol) and 10% Pd/C (60 mg) were added to distilled 2-propanol (50 mL) containing acetic acid (3 mL) and 0.1 N aqueous HCl (3 drops). After flushing the reaction mixture at least four times (evacuation, followed by hydrogen) to remove almost all the oxygen present, the mixture was stirred under 1 atm of hydrogen for 6 h. The mixture was then rapidly filtered and taken to dryness in vacuo. The residue was purified by preparative silica gel TLC using 2-propanol–ethyl acetate (2:8, v/v). Since the R_f of the product varied depending on impurities that were present, the product band was the main fluorescent one under long wavelength UV light. Recrystallization from methanol yielded 45 mg (92%) of a white solid: mp 276–278 °C; ^{1}H NMR δ 0.97 (t, 3), 1.58 (m, 4), 2.28 (s, 3), 3.16 (t, 2), 4.00 (s, 3), 7.89 (s, 1); UV λ_{max} (10% aqueous MeOH, pH 2.1) 232 (ϵ 31 100), 283 (7600); (10% aqueous MeOH, pH 6.2) 231 (27 000), 265 (6200), 310 (5700); (10% aqueous MeOH, pH 9.4) 233 (29 000), 273 (6300), 303 (7050).

Anal. Calcd for $C_{13}H_{17}N_5O$: C, 60.21; H, 6.60; N, 27.01, Found: C, 60.21; H, 6.57; N, 26.97.

Methyl 2-Carbomethoxyamino-4-iodobutyrate (21). To a suspension of methyl 2-amino-4-iodobutyrate hydriodide[44] (50 g, 0.18 mol) in dry ether (300 mL) at 0 °C, methyl chloroformate (25.40 g, 1.5 mol) and triethylamine (36.43 g, 2.0 mol) were added while the suspension was stirred with a mechanical stirrer. After 4 h at 0 °C, the mixture was stirred overnight at room temperature. Unreacted methyl chloroformate was decomposed by the addition of 100 mL of ice water. After separating the layers, the aqueous fraction was extracted with ether and the combined ethereal fractions were washed with 0.1 N aqueous sodium thiosulfate and saturated aqueous sodium chloride. After drying the ether solution over sodium sulfate and filtration, the ether was removed in vacuo. Chromatography of the residue on 500 g of silica gel gave the desired product as the only material that eluted with 1 L of ether–hexane (2:8). The yield was 46.5 g (85%): mp 58–59 °C; ^{1}H NMR ($CDCl_3$) δ 2.34 (m, 3), 3.20 (t, 2, J = 8 Hz), 3.73 (s, 3), 3.79 (s, 3), 4.40 (m, 1), 5.75 (brd, 1, J = 8 Hz); IR (KBr) 3318, 1733, 1717, 1693, 1538, 591 cm^{-1}.

Exact mass. Calcd for $C_7H_{12}INO_4$: 420.9770. Found: 420.9765.

Methyl 5-Carbobenzyloxy-2-carbomethoxyamino-6-oxo-1-heptanoate (22). To a suspension of sodium hydride (4.2 g of a 57% oil dispersion, 0.1 mol) in dioxane (150 mL), benzyl acetoacetate (19.1 g, 0.1 mol) in 100 mL of benzene was slowly added. After stirring for 1 h, methyl 2-methylcarbamoyl-4-iodobutyrate (**21**; 25.0 g, 0.08 mol) in 50 mL of benzene was added. The solution was refluxed for 24 h while mixing with a mechanical stirrer. After cooling, the mixture was filtered and the solid was washed with dioxane. The filtrate was reduced to an oil in vacuo and then suspended in water. After adjusting the pH to 5 with 1 N HCl, the aqueous mixture was extracted with chloroform. The chloroform solution was dried with magnesium sulfate, filtered, and concentrated to an oil in vacuo. The oil was chromatographed on silica gel (200-fold ratio of silica gel to compound) and eluted with chloroform until all the benzyl acetoacetate had come off. The solvent was then changed to a 50:1 mixture of chloroform–acetone to separate the product **22** from the iodobutyrate **21**. Combining the pure fractions and rechromatography of the impure fractions yielded 19 g (55–65%) of the desired triester **22** as an oil. If the oil was colored, it was treated with 10% Pd/C (activated charcoal does not work) until the oil was colorless: ^{1}H NMR ($CDCl_3$) δ 1.84 (m, 4), 2.16 (s, 3), 3.47 (m, 1), 3.69 (s, 3), 3.72 (s, 3), 4.36 (m, 1), 4.46 (brd, 1, J = 8 Hz), 5.20 (s, 2), 7.40 (s, 5); IR (liquid film) 3360, 2955, 1716, 1523 cm^{-1}.

Exact mass. Calcd for $C_{18}H_{23}NO_7$: 365.1474. Found: 365.1480.

Methyl 2-Carbomethoxyamino-6-oxoheptanoate. To a solution of **22** (10 g, 27 mmol) in methanol, 10% Pd/C (2 g) was added and the mixture was reduced under 1 atm of hydrogen. If the **22** was colored, the catalyst became poisoned and no reduction would take place. After the uptake of 600 mL of hydrogen, the mixture was filtered through Celite and the methanol was removed in vacuo while keeping the solution cold. The residue was partitioned between ether and 1 N aqueous sodium bicarbonate. After separating the layers, the aqueous fraction was extracted with chloroform. After drying and filtering, the chloroform solution was concentrated in vacuo and decarboxylated at 0.5 mm and room temperature for 24 h to yield 5.2 g of the debenzylated acid (83%), a viscous oil: ^{1}H NMR ($CDCl_3$) δ 1.72 (m, 4), 2.18 (s, 3), 2.50 (t, 2), 3.77 (s, 3), and 3.83 (s, 3); IR (liquid film) 3330, 1742, 1710 cm^{-1}.

Exact mass. Calcd for $C_{10}H_{17}NO_5$: 231.1106. Found: 231.1112.

The acid could be isolated by recrystallizing in the cold the residue from the chloroform extraction, but it underwent decarboxylation at room temperature to the title heptanoate: ^{1}H NMR ($CDCl_3$) δ 1.86 (m, 4), 2.18 (s, 3), 3.45 (m, 1), 3.69 (s, 3), 4.38 (m, 1), 4.49 (brd, 1, J = 8 Hz).

Methyl 5-Bromo-2-carbomethoxyamino-6-oxoheptanoate (23). Method A. To a solution of the above acid (5 g, 18 mmol) in methanol (25 mL) and chloroform (25 mL), bromine (3.2 g, 20 mmol) was added over a 4-h period at 0 °C. After the bromine had reacted, water (10 mL) was added and the mixture was heated to 55 °C to cause the decarboxylation. Alternatively, nitrogen was bubbled through the solution to remove the HBr; the solvent was removed in vacuo and the oil was decarboxylated at 0.5 mm for 18 h. In either case, after decarboxylation the bromo ketone was extracted into chloroform from the neutralized aqueous mixture. After drying with magnesium sulfate and filtering, the chloroform was removed in vacuo to yield 4 g of an oil. Repeated column chromatography on silica gel using chloroform–acetone (90:10, v/v) as eluting solvent was needed to separate the desired 5-bromo compound from the undesired 7-bromo and the unbrominated compounds. The purified oil could then be crystallized from ether–hexane to yield a white solid: mp 73 °C; ^{1}H NMR ($CDCl_3$) δ 2.02 (m, 2), 2.38 (s, 3), 3.78 (s, 3), 4.39 (m, 1), 5.40 (brd, 1); IR (KBr pellet) 3330, 1745, 1710, 1690, 1540, 639 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}BrNO_5$: C, 38.72; H, 5.19; N, 4.51. Found: C, 38.82; H, 5.32; N, 4.45.

Method B. To a solution of methyl 2-carbomethoxyamino-6-oxoheptanoate (4.6 g, 18 mmol) in methanol (25 mL) and chloroform (25 mL), bromine (3.2 g 20 mmol) was added over a 4-h period at 0 °C. After the bromine had reacted the solution was extracted with 10% aqueous NaCl. The chloroform fraction was worked up as above and yielded similar amounts of unbrominated, monobrominated (5- and 7-bromo), and dibrominated compounds.

Dimethyl α-(Carboxyamino)-1-benzyl-4,9-dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2-a]purine-7-butyrate (or (or 1-benzyl-Y_{SC} base). After bubbling nitrogen through a solution of 7-benzyl-3-methylguanine (255 mg, 1 mmol) and purified *N,N*-diethylaniline (745 mg, 5 mmol) in dry DMF, the solution was stirred at 50 °C while methyl 5-bromo-2-carbomethoxyamino-6-oxoheptanoate (310 mg, 1 mmol) in dry DMF (5 mL) was added over 8 h. The reaction was stirred at 50 °C an additional 10 h. After adding silica gel (2 g), the solvent was removed in vacuo. The solid was placed atop a 50-g silica gel column which was first eluted with 500 mL of benzene. Then elution with 2-propanol–ethyl acetate (2:8, v/v) gave a single fluorescent band (to long wavelength UV lamp). This material was then rechromatographed on silica gel TLC plates using 2-propanol–ethyl acetate (2:8, v/v). The major fluorescent band (R_f varied) was isolated and recrystalyzed from methanol to yield 93 mg of crystals (20%): ^{1}NMR ($CDCl_3$) δ 2.12 (m, 2), 2.26 (s, 3), 3.20 (m, 2), 3.67 (s, 3), 3.70 (s, 3), 3.90 (s, 3) 4.40 (m, 1), 5.58 (s, 2), 7.36 (s, 5), 8.35 (s, 1); UV (MeOH) 237 (ϵ 24 100), 261 (4900), 313 (3200) nm.

Exact mass Calcd for $C_{23}H_{26}N_6O_5$: 466.1963. Found: 466.1958.

Dimethyl (±)-α-(Carboxyamino)-4,9-dihydro-4,6-dimethyl-9-oxo-1*H*-imidazo[1,2a]purine-7-butyrate (or Y_{SC} base, 1). The 1-benzyl-Y_{SC} base (47 mg, 0.1 mmol) and 10% Pd/C were added to distilled 2-propanol (50 mL) containing acetic acid (3 mL) and 0.1 N aqueous HCl (3 drops). After flushing the reaction mixture at least four times (evacuation, followed by hydrogen) to remove almost all the oxygen present, the mixture was stirred under 1 atm of hydrogen for 6 h. The mixture was then rapidly filtered and taken to dryness in vacuo. The residue was purified by preparative silica gel TLC (20 × 40 cm plate) using 2-propanol–ethyl acetate (2:8, v/v) and then recrystallized from methanol to yield 32 mg (85%) of a white solid. The spectral properties of this racemic compound were identical with those reported in the literature.

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Registry No.—**1,** 35693-53-9; 1 benzyl derivative, 65120-77-6; **2,** 33359-03-4; **4,** 2958-98-7; **12,** 65120-78-7; **14,** 65120-79-8; **15,** 65120-80-1; **16,** 1807-85-8; **17,** 56025-86-6; **18,** 65120-81-2; **19,** 65138-60-5; **20,** 35693-54-0; **21,** 65120-82-3; **22,** 65120-83-4; **22** dibenzyl derivative, 65120-84-5; **23,** 65120-85-6; **23,** 7-bromo derivative, 65120-86-7; **23,** dibromo derivative, 65120-87-8; 2,6-diamino-1,4-dihydro-1-methyl-4-pyrimidone, 51093-34-6; 2,6-diamino-1,4-dihydro-1-methyl-5-nitroso-4-pyrimidone, 58160-46-6; 1,4-dihydro-1-methyl-2,5,6-triamino-4-pyrimidone sulfate, 65120-88-9; benzyl bromide, 100-39-0; methyl iodide, 74-88-4; bromoacetone, 598-31-2; 3-bromo-2-heptanone, 51134-59-9; methyl 2-amino-4-iodobutyrate hydriodide, 65166-01-0; methyl chloroformate, 79-22-1; benzyl acetoacetate, 5396-89-4.

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Studies in the Total Synthesis of Mono- and Sesquiterpenes. 3.[1] Genipic Acid

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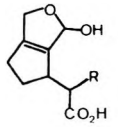
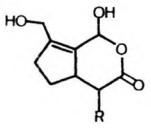
Several pathways for the synthesis of genipic acid (**1a**) were explored. Specifically, the epoxyolefin **7** was converted to the penultimate intermediates **6**, **11**, and **12** by short sequences. In no case were conditions found that could be used to transform these compounds into the novel, unsaturated bicyclo[3.3.0]lactol system evident in genipic acid.

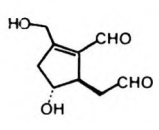
A period of 13 years has passed since W. H. Tallent proposed structures **1a** and **1b** for genipic acid and genipinic acid, respectively.[2] It is curious that during that period no communications have appeared detailing synthetic efforts directed at this fascinating pair, since, in addition to significant antibiotic activity, these iridoid terpenes are endowed with a highly unusual unsaturated lactol moiety.[3] Though the information obtained for these molecules seems consistent only with the suggested structures, it is troublesome that those factors favoring lactol formation from γ-hydroxyaldehydes are here more than sufficient to compensate for what must be considerable strain in the lactol form.[4] It is conceivable that these acids exist in the alternative, lactol–lactone forms **2a** and **2b**, which would be consistent with the lack of aldehydic absorption observed in the ^1H NMR of the natural products. However, genipic acid was converted with diazomethane to a methyl derivative that exhibited methyl absorption at δ 3.70, but still lacked aldehydic absorption. It thus appears that, at least in methyl genipate, the unsaturated lactol function does exist. A recent communication detailing some of the chemistry of the acubin aglycone only casts more confusion on the matter as the dialdehyde **3** refused to be converted into any lactol form.[5]



1a: R = H
b: R = CO_2CH_3



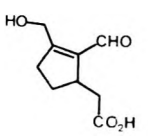
2a: R = H
b: R = CO_2CH_3



3

For some time, we have been developing methods for synthesizing cyclopentanoid terpenes of the iridoid class from the more readily available bicyclo[3.3.0]octane derivatives. A glance at the ring opened form of genipic acid (**4**) reveals that the cyclopentene ring bears three consecutive side chains, each at a progressively higher oxidation state. Thus, the major synthetic challenge is the assemblage of these chains at the correct levels of oxidation, either by unique introduction of each or by appropriate differentiation.

The propitious unsaturated ketone **5**[6] is a natural starting point for elaboration to genipic acid, since cleavage of the al-



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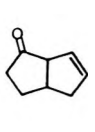
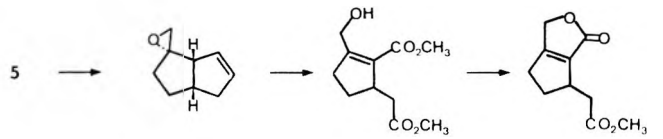


5

kene linkage would afford the adjacent two and one carbon side chains, and conversion of the carbonyl functionality to a hydroxymethyl substituent would complete the carbon skeleton. In the event, the ketone **5** was transformed into the lactone ester **6** by the sequence illustrated in Scheme I. The

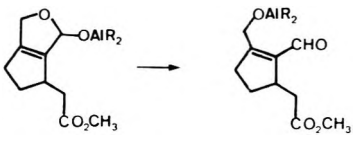
Scheme I



7 **8** **6**

epoxide **7**[7] was prepared in 60% yield using Corey's dimethylsulfonium methylide reagent,[8] though varying quantities of the starting ketone **5** tenaciously failed to react even with large excesses of the ylide, rapid stirring during addition, or dilution of the ketone in dimethyl sulfoxide prior to addition.[9] Ozonolytic cleavage of epoxide **7** followed by alkaline silver oxide oxidation[10] of the ozonide to the diacid followed by diazomethane esterification produced the diester alcohol **8** in 40% overall yield. Lactonization of **8** using Amberlyst-15[11] as an acid catalyst in refluxing benzene afforded in moderate yield the lactone **6** in which the central, lactone carboxyl carbon would appear to be ideally situated for selective, partial reduction to the aldehyde stage.

However, we were totally thwarted in our efforts to form methyl genipate from lactone **6**. Diisobutylaluminum hydride reduction[12] failed to produce any detectable quantity of methyl genipate over many attempts under a variety of conditions. Changing the solvent from toluene to methylene chloride or THF, varying the temperature from −100 to −78 to −30 to +25 to +110 °C, and adjusting the ratio of hydride to lactone from the desired 1:1 to a large deficiency of reducing agent all failed to alter the apparent course of the reaction–overreduction. This failure can perhaps be rationalized by assuming that the intermediate from addition of the first hydride does indeed possess considerable strain and thus opens to the aldehyde **9** at a rate considerably faster than the initial reduction.



9

Other reducing agents, including 9-BBN,[13] diborane,[14] sodium borohydride,[15] and Red-Al,[16] were tried, all with equally dismal results. An attempted in situ methylation with Magic Methyl (CH_3OSO_2F)[17] followed by Red-Al reduction failed to produce any of the anticipated methyl lactolide.

Our inability to accomplish a controlled reduction of the lactone **6** prompted us to turn to the alternative approach wherein the olefin would be cleaved with ozone as before, but left at the dialdehyde stage with a subsequent selective oxidation of the two-carbon aldehyde providing the carboxyl carbon of genipic acid. In fact, zinc and acetic acid reduction of the ozonide from epoxyolefin **7** served to open the epoxide

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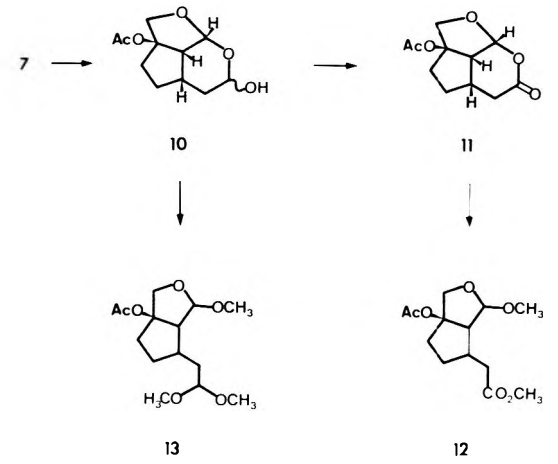
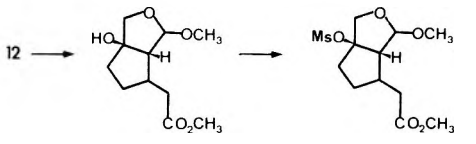


10 11 13 12

function as well, affording the cyclic form of the dialdehyde (**10**) in moderate yield. The selective oxidation now became a trivial matter; pyridinium chlorochromate[18] produced the crystalline lactone acetate **11** in good yield. Having now assembled the three chains each at the appropriate oxidation level, we had only the apparently simple tasks of removing acetic acid and opening the lactone ring.

Unfortunately, elimination of the elements of acetic acid could be effected neither thermally (450–600 °C) nor with acid catalysis (aprotic boron trifloride etherate or trifluoroacetic acid, or aqueous acid) without concomitant destruction of the product(s) thus formed. The only identifiable material obtained from reactions run under any of these conditions was the starting lactone acetate. On the other hand, the lactone ring in **11** was smoothly cleaved with *p*-toluenesulfonic acid in methanol, providing the acetate–lactolide ester **12**. Alternatively, a similar array (**13**) was obtained from lactol **10** under the same conditions. As before, neither of these acetates produced volatile products from vapor phase thermolysis in the range 350–600 °C.

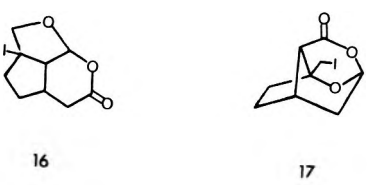
In order to obtain a functionality which might serve as a precursor to the double bond under more gentle conditions than those required for the acetates **11–13**, the tertiary alcohol **14** was prepared in 70% overall yield by the sequence potassium carbonate–methanol and then diazomethane. Here again, no identifiable products were obtained from the treatment of **14** with phosphorus oxychloride or thionyl chloride in pyridine,[19] or with aqueous acid. Though the xanthate of **14** could not be obtained, the mesylate **15** was



14 15

formed smoothly.[20] No identifiable products were obtained from reaction of **15** with either 1,5-diazabicyclcundecene or potassium *tert*-butoxide under conditions sufficiently vigorous to cause disappearance of the starting material.

Still seeking a more labile leaving group, we rationalized that the acetoxy function in the lactol acetate **10** had resulted from a first-order-like opening of the epoxide to the cation and subsequent trapping. Hence, the iodide **16** might be obtainable if potassium iodide, fortuitously present as the reductant for the ozonide,[21] would compete successfully for the cation. In fact, a tricyclic iodide was produced as the result of potassium iodide–acetic acid reduction of the ozonide of olefin **5**, and subsequent oxidation afforded a lactone with ^{1}H NMR spectra quite similar to that of the acetate lactone **11**. However, the presence in the ^{13}C NMR of a triplet at δ 10.1, consistent with the presence of a $-CH_2-I$ structural unit, suggested the alternative lactone **17**, which would be the ultimate result of a second-order-like nucleophilic opening by iodide at the less hindered position of the epoxide. The suggested arrangement in **17** was firmly established by a three-dimensional x-ray analysis on a single crystal.[22] It is clear that the tricyclic lactol precursor to iodolactone **17** exposes the wrong aldehyde to further oxidation and thus in the lactone the oxidation levels of the carboxylic and aldehydic carbons are the reverse of those in genipic acid.



16 17

The repeated failure of several penultimate intermediates to suffer conversion to genipic acid led us to direct our synthetic efforts elsewhere.

Experimental Section

Procedure. Dry tetrahydrofuran (THF) was distilled immediately before use from a deep red mixture containing lithium aluminum hydride and triphenylmethane, while dry ether was distilled from a deep blue solution resulting from benzophenone and sodium. Dimethyl sulfoxide was dried by extended contact (several days) with molecular sieves. Drying of organic layers resulting from aqueous extractions was accomplished with 4A sieves. All reactions were routinely run under a nitrogen atmosphere.

Proton spectra were recorded on a Varian HA-100 using deuteriochloroform solutions and are reported on the δ scale relative to internal tetramethylsilane. Infrared spectra were obtained using a Perkin-Elmer 237B.

Elemental microanalyses were done by Chemalytics, Inc., Tempe, Ariz.

Methyl (2-Keto-3-oxabicyclo[3.3.0]oct-$\Delta^{1,5}$-en-8-yl)acetate (6). A solution of 0.662 g (2.90 mmol) of diester **8** and 0.60 g of dry Amberlyst-15 in 30 mL of benzene was refluxed for 45 min, cooled, and then the resin was removed by filtration. Concentration of the yellow solution followed by purification by preparative thin layer chromatography on silica gel with 1:1 ethyl acetate–cyclohexane afforded 0.36 g (63%) of lactone: IR (CH_2Cl_2) 1755, 1735 cm^{-1}; NMR δ 1.6–3.3 (m, 7 H), 2.45 (s, 3 H), 4.08–4.18 (m, 2 H); HRMS Calcd for $C_{10}H_{12}O_4$: 196.0736. Found: 196.0733.

8-Methyl-8a,9-oxidobicyclo[3.3.0]oct-2-ene (7). A solution of 144 mmol of dimsyl anion prepared from 0.607 g of 57% sodium hydride dispersion (twice pentane washed) in 72 mL of dry DMSO was diluted with an equal volume of dry THF and cooled in an ice–salt bath. A solution of 2.94 g (144 mmol) of trimethylsulfonium iodide in 12 mL of DMSO was then added rapidly with stirring followed after 1 min by 1.5 g (123 mmol) of ketone added neat over 1 min. After 5 min the cooling bath was removed and stirring was continued for 1 h. The reaction was diluted with three volumes of water and the product extracted with three 50-mL portions of pentane. The combined organic layers were dried and concentrated, affording 1.4 g of crude product containing from 10 to 40% of the starting ketone. Recycling this mixture using a 20% excess of the ylide necessary for the remaining ketone afforded essentially pure epoxide after distillation (bp 82–85 °C (20 mmHg)): NMR δ 1.72 (d, 2 H, J = 6 Hz), 1.2–2.1 (m, 3 H), 2.85 (s, 2 H), 2.5–3.2 (m, 3 H), 5.5 (m, 1 H), 5.75 (m, 1 H). Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.12; H, 8.97.

Methyl (2-Carbomethoxyl-3-hydroxymethylcyclopent-2-enyl)acetate (8). One equivalent of ozone was passed into a solution of 0.564 g (4.15 mmol) of epoxide **7** in 40 mL of dichloromethane at −78 °C. This solution was then concentrated and the resulting white foam (0.79 g) was taken up in 21 mL of ethanol. With stirring, first a solution of 3.04 g (17.9 mmol) of silver nitrate in 4 mL of water and then 2.48 g (30 mmol) of 87% potassium hydroxide in 42 mL of water was added. After 2 h the silver salts were removed by filtration and washed with 65 mL of water. The combined aqueous solutions were extracted twice with 50-mL portions of ether and then acidified to pH 2 with 2.0 N hydrochloric acid. Extraction with ten 25-mL portions of ethyl acetate followed by drying and concentration of the combined organic layers afforded 0.644 g of crude diacid. This material was dissolved in ether and treated with excess diazomethane. Concentration of the ether solution and purification of the resulting material

by preparative layer chromatography on silica gel with 1:1 ethyl acetate–cyclohexane afforded 0.378 g (40%) of pure diester: IR (CH_2Cl_2) 1740, 1710; NMR δ 1.5–4.0 (m, 8 H), 3.70 (s, 3 H), 3.79 (s, 3 H), 4.4–4.6 (m, 2 H). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.65; H, 6.79.

4β-Acetoxy-9-hydroxy-2,10-dioxatricyclo[5.3.1.0^{4,11}]undecane (10). The crude ozonide from 0.49 g of epoxide **7** obtained as described above was treated with 0.235 g (2 equiv) of zinc dust in 25 mL of glacial acetic acid for 3 h, with stirring at room temperature. Most of the solvent was then removed on the vacuum pump. The residue was taken up in 25 mL of methylene chloride and extracted with 25 mL of 1.0 N aqueous sodium bicarbonate. The aqueous layer was extracted with three 25-mL portions of methylene chloride which were combined with the original organic layer and concentrated to 0.38 g of crude lactol, purified by preparative layer chromatography on silica gel (1:3 ethyl acetate–cyclohexane) affording 0.14 g of **10:** NMR δ 1.1–2.8 (m, 8 H), 2.05 (s, 3 H), 4.0–4.2 (m, 2 H), 4.3–4.6 (m, 1 H), 5.3–5.7 (m, 2 H); IR (CH_2Cl_2) 3575 (broad), 2950 (broad), 1740, 1357, 1240 cm^{-1}.

4β-Acetoxy-9-keto-2,10-dioxatricyclo[5.3.1.0^{4,11}]undecane (11). A solution of the crude lactol **10** from 3.85 g (23.6 mmol) of epoxide **7** in 100 mL of methylene chloride was added all at once to a stirred suspension of 5 g (24 mmol) of pyridinium chlorochromate in 50 mL of the same solvent. After 2 h the reaction mixture was diluted with 200 mL of ether and filtered through a short column of activity IV alumina. The column was washed with 50 mL of additional ether and the combined organic layers were concentrated to 2.9 g of crude lactone. Column chromatography (silica gel, 3:1 cyclohexane–ethyl acetate) afforded a fraction (1.2 g) which could be crystallized from ethyl acetate to 0.8 g (15% overall) with mp 124–125 °C: IR (CH_2Cl_2) 1745 cm^{-1} (broad); NMR δ 1.2–3.0 (m, 7 H), 2.06 (s, 3 H), 3.25 (d, d, J = 6, 9 Hz, 1 H), 3.97 and 4.4 (AB q, J = 10 Hz, 2 H), 5.88 (d, J = 6 Hz, 1H). Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.45; H, 6.04.

Methyl (1β-Acetoxy-4β-methoxy-3-oxabicyclo[3.3.0]octan-6α-yl)acetate (12). A mixture of 0.488 g (2.2 mmol) of lactone **11** and 0.100 g of *p*-toluenesulfonic acid in 20 mL of dry methanol was stirred for 2 days. The mixture was then diluted with 100 mL of aqueous 1 N sodium bicarbonate and extracted with three 25-mL portions of dichloromethane. The combined organic layers were dried and concentrated to 0.583 g (100%) of essentially pure ester **12:** IR (CH_2Cl_2) 1745 cm^{-1} (broad); NMR δ 1.2–2.8 (m, 8 H), 2.04 (s, 3 H), 3.34 (s, 3 H), 3.72 (s, 3 H), 4.03 and 4.25 (AB q, J = 10 Hz, 2 H), 4.80 (s, 1 H); MS, no molecular ion, m/e 257 (m − 15), 241 (m − 31 = MeO), 199 (base peak). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.32; H, 7.21.

Methyl (1β-Hydroxy-4β-methoxy-3-oxabicyclo[3.3.0]octan-6α-yl)acetate (14). Acetate **12** (0.583 g, 2.14 mmol) was stirred in 25 mL of 4:1 methanol–water containing 0.592 g (4.3 mmol) of potassium carbonate for 12 h. The solution was then diluted with water, acidified with 2 N hydrochloric acid, and extracted with three 50-mL portions of ethyl acetate. The combined organic layers were dried and concentrated, and the residue was taken up in ether and treated with excess diazomethane. Removal of the solvent afforded 386 mg (78%) of essentially pure alcohol **14:** IR (CH_2Cl_2) 3560 (broad), 2940 (broad), 1735, 1190, 1090, 1025 cm^{-1}; NMR ($CDCl_3$) 1.2–3.0 (m, 8 H), 3.45 (s, 3 H), 3.70 (s, 3 H), 3.80 and 3.95 (AB q, J = 9 Hz, 2 H), 4.80 (s, 1 H).

Methyl (1β-Methanesulfonyloxy-4β-methoxy-3-oxabicyclo[3.3.0]octan-6α-yl)acetate (15). To a stirred solution of 180 mg (0.78 mmol) of alcohol **14** and 0.83 mL (6.0 mmol) of triethylamine in 15 mL of dichloromethane at −5 °C was added dropwise 0.33 mL of methanesulfonyl chloride in 10 mL of the same solvent. After 15 min, the solution was extracted with 10 mL of water, 10 mL of 2 N hydrochloric acid, and then 10 mL of 1 N aqueous sodium bicarbonate. Concentration afforded 250 mg (100%) of essentially pure mesylate **15,** used without further purification: NMR δ 1.2–3.4 (m, 8 H), 3.05 (s, 3 H), 3.35 (s, 3 H), 3.70 (s, 3 H), 4.05 and 4.35 (AB q, J = 10 Hz, 2 H), 4.8 (bs, 1 H).

3-Iodomethyl-8-keto-2,9-dioxatricyclo[4.3.1.0^{3,7}]decane (17). A solution of 0.760 g (4.1 mmol) of the crude ozonide from epoxide **7** in 10 mL of glacial acetic acid was treated with 1.37 g (8.2 mmol) of potassium iodide. The resulting dark red solution was stirred 1 h, and then the color was discharged with 10% aqueous sodium bisulfite. The solvents were removed with the vacuum pump, and the residue was partitioned between dichloromethane and 1 N sodium bicarbonate. The aqueous layer was extracted with two additional portions of dichloromethane and the combined organic layers were concentrated to yield 0.808 g of crude lactol: IR (CH_2Cl_2) 3550 (broad), 2925 (broad), 1115, 1060, 1035, 960 cm^{-1}. All of the above was oxidized with pyridinium chlorochromate as described above for the conversion of lactol **10** to lactone **11.** The crude material (0.60 g, 50% overall) was quite pure and could be crystallized from ethyl acetate–hexane to afford an analytical sample with mp 61–61.5 °C: IR (CH_2Cl_2) 1760 cm^{-1}; NMR δ 1.6–2.5 (m, 6 H), 2.6–3.92 (m, 2 H) 3.28 and 3.39 (ABq, J = 10 Hz, 2 H), 5.65–5.75 (m, 1 H). Anal. Calcd for $C_9H_{11}O_3I$: C, 36.76; H, 3.77; I, 43.15. Found: C, 36.66; H, 3.67; I, 42.95.

Acknowledgment is gratefully made to the Robert A. Welch Foundation for financial support of this research.

Registry No.—**1a,** 6902-76-7; **5,** 56138-05-7; **6,** 65276-79-1; **7,** 65276-80-4; **8,** 65276-81-5; **10,** 65276-82-6; **11,** 65276-83-7; **12,** 65276-84-8; **14,** 65276-85-9; **15,** 65276-86-0; **16** lactol derivative, 65276-87-1; **17,** 65276-88-2; methanesulfonyl chloride, 124-63-0.

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(22) We are grateful to Professor R. E. Davis, University of Texas at Austin, for the execution of this structure determination.

Studies on Vitamin D (Calciferol) and Its Analogues. 14. On The 10,19-Dihydrovitamins Related to Vitamin D_2 Including Dihydrotachysterol$_2$[1,2]

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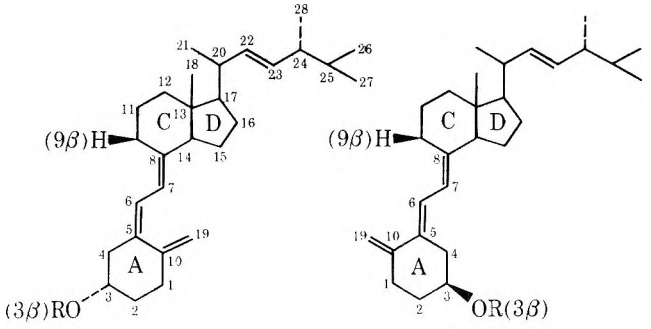
Received September 27, 1977

Vitamin D_2 (**1a**), its benzoate (**1b**), 5,6-*trans*-vitamin D_2 (**2a**), and its benzoate (**2b**) were each treated with 9-borabicyclo[3.3.1]nonane and then oxidized with basic hydrogen peroxide to afford the following pairs of stereoisomeric 10,19-dihydrovitamin D_2's: **3a–4a, 3b–4b, 5a–6a,** and **5b–6b,** respectively. Catalytic reduction of **1a** and **2a** afforded the stereoisomeric pairs **3d–4d** and **5d–6d,** respectively. The four benzoyloxy alcohols **3b–6b** were each individually converted to their *p*-toluenesulfonates **3c–6c,** respectively, and then each diester was subjected to lithium triethylborohydride reduction to afford **3d, 7, 5d,** and **8,** respectively. Finally, saponification of **4b** produced **4a** and **6b** gave **6a.** How these chemical transformations including spectral analyses definitively establish the absolute configurations of **3–6** is discussed. The relationship of **3d–6d** to the substances referred to in the old literature as DHT_2, DHV_2-II, DHV_2-III, DHV_2-IV, and DT-66 is also discussed.

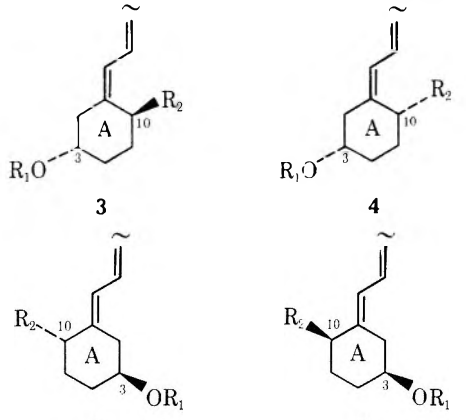
Vitamin D_2 (**1a,** ergocalciferol)[4] is utilized extensively as a dietary supplement in foods. Two of its analogues, (5*E*)-vitamin D_2 (**2a**)[5] and dihydrotachysterol$_2$ (**5d,** DHT_2),



1a, R = H
b, R = C_6H_5CO

2a, R = H
b, R = C_6H_5CO

have found clinical applications. In fact **5d** was marketed as early as 1934 under the trade name A. T. 10 by E. Merck (Darmstadt) as an antitetany agent.[6] This substance (**5d**) is one of the four possible stereoisomers (**3d–6d**) which could result from saturation of the 10,19 double bond of **1a** and **2a.** The corresponding stereoisomers in the natural vitamin D_3 series have recently been fully characterized[1b] by this laboratory, but there remained uncertainty in the identity of the 10,19-dihydrovitamins in the D_2 series referred to in the older literature as DHT_2, DHV_2-II, DHV_2-III, DHV_2-IV, and DT-66.[7,8] This paper not only describes the full stereo-



3 **4**

5 **6**

a, R_1 = H; R_2 = CH_2OH
b, R_1 = C_6H_5CO; R_2 = CH_2OH
c, R_1 = C_6H_5CO; R_2 = $CH_2OSO_2C_6H_4$-*p*-CH_3
d, R_1 = H; R_2 = CH_3

Scheme I. Chemical Transformations[a]

1a $\xrightarrow{a}$ (**3a,** 43%) + (**4a,** 43%)	(1)
2a $\xrightarrow{a}$ (**5a,** 33%) + (**6a,** 39%)	(2)
1b $\xrightarrow{a}$ (**4b,** 51%) + (**3b,** 33%)	(3)
2b $\xrightarrow{a}$ (**6b,** 39%) + (**5b,** 18%)	(4)
1a $\xrightarrow{b}$ (**3d,** 54%) + (**4d,** 35%)	(5)
2a $\xrightarrow{b}$ (**6d,** 25%) + (**5d,** 35%)	(6)
4b $\xrightarrow{c}$ **4a** (not **3a**)	(7)
6b $\xrightarrow{c}$ **6a** (not **5a**)	(8)
3b $\xrightarrow{d,e}$ **7**	(9)
3b $\xrightarrow{d,e}$ **3d** (not **4d**)	(10)
6b $\xrightarrow{d,e}$ **8**	(11)
5b $\xrightarrow{d,e}$ **5d** (not **6d**)	(12)

[a] The absolute yields of products are given in parentheses. The first product given of each pair in eq 1–6 corresponds to the less polar component obtained under the column chromatography conditions used for the separation. Reactions: (a) 9-BBN, HO^-/H_2O_2; (b) $H_2/C_6H_6/[(C_6H_5)_3P]_3$-RhCl; (c) KOH/CH_3OH; (d) *p*-TsCl, C_5H_5N; (e) $Li(CH_3CH_2)_3BH$.

structural characterization of **3d–6d** and related derivatives but also delineates improved synthetic procedures incorporating a strategy that should allow the convenient preparations of new 19-substituted dihydrovitamins with potential antagonist properties.[9]

Results and Discussion

The chemical transformations carried out in this study are outlined in Scheme I. The following observations are pertinent:

(1) Each of the reactions (catalytic hydrogenation[8] or hydroboration–oxidation[1b]) of **1** and **2** results in two and only two stereoisomeric products. Thus the stereochemical integrity of the $\Delta^{5,7}$-diene is retained in each case (eq 1–6).

(2) Equations 7, 8, 10, and 12 prove that members of each of the following triads possess the same relative stereochemistry: **3a–3b–3d, 4a–4b–4d, 5a–5b–5d,** and **6a–6b–6d.**

(3) Our earlier ^{1}H-NMR results[1b] in the vitamin D_3 series of dihydrovitamins lend considerable confidence on the basis of spectral comparisons to the C_{10} configurational assignments given to the four monoalcohols **3d–6d.** The transformations given in eq 9–12 now also provide definitive chemical evidence for these assignments. This requires, of course, that the structures of the cyclization products **7** and **8** are assigned correctly. Their spectral data (NMR, UV, MS) are certainly in line with the assigned structures and moreover this kind of

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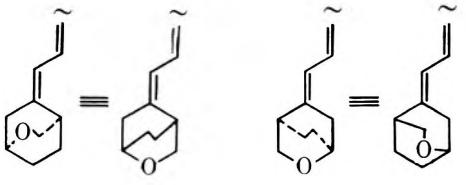
Table I. Chemical Shifts and Bandwidths of the $H_{3\alpha}$ Resonance

	Registry no.	$\tau_{H_{3\alpha}}$	$\sim W_{3\alpha}$, Hz
(5*Z*,7*E*-dienes)			
Trans (CH_3, OH), **3d**	65377-86-8	5.97	7.7
Cis (CH_3, OH), **4d**	65377-87-9	6.4	20
Trans (CH_2OH, OH), **3a**	75338-35-4	5.92	9
Cis (CH_2OH, OH), **4a**	65377-88-0	(6.2–6.6)[a]	*b*
Trans (CH_2OH, OBz), **3b**	65338-36-5	4.67	9
Cis (CH_2OH, OBz), **4b**	65377-89-1	5.0	23
Trans (CH_2OTs, OBz), **3c**	65338-37-6	~4.8	<12
Cis (CH_2OTs, OBz), **4c**	65377-90-4	5.08	23
(5*E*,7*E*-dienes)			
Trans (CH_3, OH), **5d**	67-96-9	6.4	24
Cis (CH_3, OH), **6d**	65377-91-5	6.15	14
rans (CH_2OH, OH), **5a**	65338-38-7	~6.2	*b*
Cis (CH_2OH, OH), **6a**	65377-92-6	~6.3	*b*
Trans (CH_2OH, OBz), **5b**	65338-39-8	~4.8	*b*
Cis (CH_2OH, OBz), **6b**	65377-93-7	~4.9	*b*
Trans (CH_2OTs, OBz), **5c**	65338-40-1	~4.95	>16.5
Cis (CH_2OTs, OBz), **6c**	65377-94-8	~4.95	≳13.5

[a] Includes resonances due to $2H_{19}$. [b] Not measurable.

cyclization is not only logical but also has analogy in the synthesis of the parent 2-oxabicyclo[2.2.2]octane.[10]



7 8

These results reveal that the stereochemistries assigned to **5a** and **6a** (in the vitamin D_3 series)[4] in the previous study[1b] were based on incorrect ^{1}H-NMR analyses.[11] The pertinent ^{1}H-NMR spectral characteristics are discussed in the next paragraph. We emphasize here that the assignments given in the previous paper *are correct*[1b] as a result of yet a second (transposition) error.[11]

Table I summarizes the chemical shifts and bandwidths for the resonance due to $H_{3\alpha}$ for dihydrovitamins **3–6**. For the (5*Z*,7*E*)-dienes derived from **1** it is evident that the trans isomers consistently exhibit their $H_{3\alpha}$ resonance at lower fields (more equatorial character)[12] than the cis isomers. Moreover, the bandwidth of this resonance is consistently smaller (more equatorial character) for the trans isomers than for the cis. Thus the chemical shifts and bandwidths support our earlier conformational analyses of these systems.[1b] For the (5*E*,7*E*)-dienes derived from **2**, the relative chemical shifts and bandwidths for the monoalcohols **5d** and **6d** are in line with their conformational properties (**5d** exhibits more axial 3α-H character than **6d**). The remaining derivatives (**5a–c** and **6a–c**) do not exhibit analogous results and the NMR data (Table I) therefore do not allow stereochemical assignments to be made. The chemical correlations (Scheme I) however establish the absolute configurations of **5a–c** and **6a–c**.

The final subject in this paper deals with the identity of DHT_2, DHV_2-II, DHV_2-III, DHV_2-IV, and DT_{66} referred to in the older literature. It is clear that DHT_2,[6a,e,f,h,i] DHV_2-II,[6c,d,g-i,k] and DHV_2-IV[6e,g,h,k,8] are **5d**, **3d**, and **4d**, respectively. As pointed out by von Werder,[6g] DT_{66}[6e] is probably impure DHT_2. It follows that DHV_2-III described by Schubert[6e,8] must have been **6d** or an impure sample of one of the other isomers. Our **6d** exhibited mp 108–110 °C (acetone) and $[\alpha]^{25}_D$ +60.4° (*c* 0.83, ethanol); Schubert's DHV_2-III[6e,8] exhibited mp 50–55 °C (90% methanol) and $[\alpha]_D$ +85° (0.8%, ethanol). From the literature descriptions[6] and from our own experience, it is quite apparent that these dihydrovitamins crystallize erratically and poorly if at all.[13] We made no further attempts to correlate our **6d** with Schubert's DHV_2-III. This study, however, does provide all four unsubstituted DHV's (**3d–6d**) of unequivocally established stereochemistry. We consider the chapter[6j] on the identities of the 10,19-dihydrovitamins of the vitamin D_2 series closed.

Experimental Section

General. Ultraviolet spectra (UV), ^{1}H nuclear magnetic resonance spectra (NMR), and mass spectra (MS) are summarized in Table II (see Supplementary Material paragraph): melting points (mp, uncorrected), Thomas-Hoover capillary apparatus. Dry tetrahydrofuran (THF), freshly distilled (nitrogen) from $LiAlH_4$; lbpe, redistilled 30–60 °C low-boiling petroleum ether; 9-BBN, 0.5 M solution of 9-borabicyclo[3.3.1]nonane in THF (Aldrich Chemical Co.); silica gel for column chromatography, Baker Analyzed reagent (60–200 mesh); alumina for chromatography, Woelm neutral grade III; silica gel G (EM reagents, type 60) for thin layer chromatography (TLC, 0.25 mm analytical plates); alumina for TLC (aluminum oxide G, EM reagents type 60/E). Crystalline vitamin D_2 and dihydrotachysterol$_2$ (DHT_2) were obtained as gifts from Philips-Duphar (Weesp, the Netherlands).

Vitamin D_2 Benzoate (1b). Vitamin D_2 (**1a**, 8.0 g, 16.5 mmol), dry pyridine (40 mL), benzoyl chloride (4.8 g, 4 mL, 38.5 mmol), 45 min (N_2). Standard workup, crystallization (acetone–95% ethanol): 9.06 g (90%); mp 88–90 °C; TLC (silica gel, isopropyl ether), **1a/1b** R_f 0.3/0.6.

5,6-*trans*-Vitamin D_2 (2a).[5] To a solution of **1a** (1 g) in dry ether (1 L) was added iodine (5 mL of a solution containing 20 mg of iodine in 100 mL of ether). After standing for 2.5 h at room temperature (fluorescent room lights), 3 drops of pyridine was added and then the mixture was concentrated under vacuum. The residue was chromatographed on a dry column of silica gel (50 g, pretreated with 4 drops of pyridine; 1.2-cm diameter column) using isopropyl ether (200 mL treated with 2 drops of pyridine). Yield after concentration was 70% (pure by NMR and TLC) of a foam: TLC (alumina, isopropyl ether), **1a/2a** R_f 0.22/0.44.

5,6-*trans*-Vitamin D_2 Benzoate (2b). The benzoate of **2a** was prepared by the method described above for converting **1a** to **1b** except that the reaction time was longer (~2 h) and the residual product after work up was passed through a short column of silica gel (5% ether–lbpe). The residual foam (~quantitative) was found to be pure by NMR and TLC (silica gel, benzene): **2a/2b** R_f 0.39/0.70.

19-Hydroxy-[10*S*(19)]-(3a) and 19-Hydroxy-[10*R*(19)]-dihydrovitamin D_2 (4a). A solution of 9-BBN (11 mL, 0.5 M, 5.5 mmol) in THF was added (syringe) to crystalline **1a** (1.0 g, 2.5 mmol) under nitrogen at room temperature with magnetic stirring. After 2 hr, the resulting clear solution was quenched (H_2O, 5 mL) and then allowed to stand for 15 min. The mixture was cooled (ice) and then aqueous NaOH (1.85 mL, 3 M) and H_2O_2 (1.85 mL, 30%) were added successively (syringe). The mixture was heated (55 °C, 1 h), cooled, and then worked up with pentane and water. The pentane layer afforded a residue which was chromatographed (90 g silica gel, 2 × 120 cm column, 60% ether–lbpe to 100% ether) to afford after thorough drying **3a** (445 mg, 43%; foam, mp 53–6 °C; crystallization from 90% ethanol, mp 66–70 °C) and **4a** (446 mg, 43%; foam, mp 56–60 °C; could not be crystallized). Each of the isomers was completely homogeneous to TLC (silica gel, 30% acetone–benzene: **3a**, R_f 0.36; **4a**, R_f 0.20). Spectroscopic data (Table II) and chemical correlations (below) established configurational assignments.

19-Hydroxy-[10*S*(19)]-(5a) and 19-Hydroxy-[10*R*(19)]-dihydro-(5*E*)-vitamin D_2 (6a). The procedure of the preceding experiment was followed using the following quantities of material: 5,6-*trans*-D_2 (**2a**, 0.68 g, 1.71 mmol) and 9-BBN in THF (7.6 mL, 0.5 M, 3.8 mmol); water (3 mL for quenching); aqueous NaOH (1.25 mL, 3 M) and 30% H_2O_2 (1.25 mL) for oxidation; pentane–water for workup. The residue from the pentane layer was carefully chromatographed (alumina, 1.5 × 70 cm column, 60% ether–lbpe to ether to 2% methanol–ether) to afford after thorough drying **5a** (232 mg, 33%; foam, double mp 52–60 and 121–123 °C; crystallization from isopropyl ether, mp 129–30 °C) and **6a** (275 mg, 39%; foam, mp 59–62 °C; could not be crystallized). TLC (ether, alumina; silica gel was ineffective) revealed that the materials were homogeneous: **5a** R_f 0.36 and **6a** R_f 0.32. Spectroscopic data (Table II) and, most importantly, the chemical correlations showed that **5a** is the trans isomer and **6a** is the cis isomer.

19-Hydroxy-[10*S*(19)]-(3b) and 19-Hydroxy-[10*R*(19)]-dihydrovitamin D_2 Benzoate (4b). The 9-BBN/THF solution (11.4 mmol, 22.8 mL, 0.5 M) was added (syringe 6 min) to D_2 benzoate (**1b**, 4.1 g, 8.2 mmol) under nitrogen. The resulting clear solution was stirred at ambient for 2 h and then the ice cooled reaction mixture was quenched with methanol (10.8 mL). After adding aqueous NaOH (1.92 mL, 6 M) and 30% H_2O_2 (3.84 mL) to the ice cooled mixture, the mixture was stirred at room temperature for 30 min. After work-up (pentane–water) and concentration, the resulting residue was chromatographed (160 g of silica gel, lbpe to 20% ether–lbpe) to afford an excellent separation of **4b** (2.14 g, 51%, mp 60–65 °C) and **3b** (1.39 g, 33%, mp 55–60 °C). Neither isomer could be crystallized although both proved to be homogeneous by TLC (silica gel, isopropyl ether): **4b** R_f 0.55 and **3b** R_f 0.40. Spectral (Table II) and chemical correlations established their stereochemistries.

19-Hydroxy-[10*S*(19)]-(5b) and 19-Hydroxy-[10*R*(19)]-dihydro-(5*E*)-vitamin D_2 Benzoate (6b). The procedure was essentially the same as that described in the preceding experiment except that the oxidation step was carried out for a longer reaction time (1 h at room temperature and then 0.5 h at 40 °C). The quantities of materials were as follows: 5,6-*trans*-D_2 benzoate (**2b**, 1.48 g, 2.94 mmol); 9-BBN/THF (8.2 mL, 4.10 mmol, 0.5 M); methanol (3 mL) quench; oxidation with aqueous NaOH (0.7 mL, 6 M) and 30% H_2O_2 (1.4 mL). After standard work-up (pentane–water), the residual product was chromatographed (85 g, 5% $AgNO_3$ impregnated silica gel, 2-cm diameter column, dry column method, chloroform) to afford after thorough drying **6b** (600 mg, 39%) and **5b** (270 mg, 18%). TLC ($AgNO_3$–silica gel, isopropyl ether) showed **6b** R_f 0.37 and **5b** R_f 0.25.

The less polar isomer was rechromatographed (silica gel, 40 g, 1.5-cm diameter column, lbpe to 30% ether–lbpe) to afford a white foam (540 mg, mp 54–58 °C). This substance was identified as the cis isomer **6b** by spectral (Table II) and chemical correlations.

The more polar isomer was similarly chromatographed to afford a colorless foam (mp 53–59 °C). It was characterized spectrally (Table II) and chemically as **5b**, the trans isomer.

Tosylation of the Hydroxybenzoates 3b, 4b, 5b, and 6b to the 3β-Benzoyloxy-19-*p*-toluenesulfonates 3c, 4c, 5c, and 6c. The procedure for **6c** is exemplary. A mixture of hydroxybenzoate isomer **6b** (150 mg, 0.29 mmol), *p*-toluenesulfonyl chloride (185 mg, 1.16 mmol, crystallized), and dry pyridine (1.5 mL, freshly distilled) was left under nitrogen in the refrigerator overnight. Ice water was added, the residual solid was gravity filtered several times, and then the product was rinsed thoroughly with water. The solid was taken up in ether and worked up conventionally to afford (after drying under high vacuum) **6c** as a solid (180 mg, 93%, mp ~50–56 °C) which could not be crystallized.

Tosylation of **5b: 5b** (133 mg, 0.26 mmol), *p*-toluenesulfonyl chloride (164 mg, 1.03 mmol), pyridine (1.3 mL); overnight (refrigerator); 174 mg (quantitative) of **5c** with mp ~50–58 °C. See Table II.

Tosylation of **4b: 4b** (300 mg, 0.58 mmol), *p*-toluenesulfonyl chloride (370 mg, 2.32 mmol), pyridine (2.5 mL); 6 h at room temperature; 367 mg (94%) of **4c** with mp ~50–57 °C. See Table II.

Tosylation of **3b: 3b** (300 mg, 0.58 mmol), *p*-toluenesulfonyl chloride (370 mg, 2.23 mmol), pyridine (2.5 mL); 4 h at room temperature; 389 mg (~quantitative) of **3c** with mp ~50–57 °C. See Table II.

Their spectral properties (Table II) were in accord with the structural assignments. These spectral data and the chemical correlations described below established their stereochemistries. Their TLC behavior was as follows: **3c/4c**, silica gel, 25% ether–lbpe, R_f 0.39/0.56; **5c/6c**, 10% $AgNO_3$–silica gel, 25% ether–lbpe, R_f 0.42/0.39.

Reduction of Benzoyloxytosylate 3c to [10*S*(19)]-Dihydrovitamin D_2 (3d). Lithium triethylborohydride/THF (1.05 mL, 1.05 mmol, 1.05 M, Aldrich)[14] was added (syringe) to **3c** (100 mg, 0.15 mmol) under nitrogen with ice cooling. The bath was removed and the solution was stirred at reflux for 2 h. Water (0.5 mL), aqueous NaOH (0.35 mL), and 30% H_2O_2 (0.35 mL) were added successively to the ice cooled solution and then the reaction mixture was refluxed for 0.5 h. The cooled reaction mixture was worked up with pentane–water by conventional methods. The vacuum dried solid residue **3d** (51 mg, 86%) proved homogeneous by NMR (Table II) and TLC. Crystallization (acetone) afforded material with mp 104–5 °C (lit. mp 102.5–106.5,[6d] 108 °C,[6g] liquid[6k]). The **3d** prepared in this way was identical[8] to that prepared by catalytic reduction of vitamin D_2 (see below).

Reduction of Benzoyloxytosylate 4c to the Ether 7. The cis isomer **4c** (100 mg, 0.15 mmol) was reduced essentially as described in the preceding experiment except the reaction was carried out at room temperature for 1 h, methanol (0.5 mL) was used instead of water to quench the excess hydride, and a conventional ether–water (instead of pentane–water) work-up was utilized. As described below for **6c**, it appears that the procedure of the preceding experiment is superior. The resulting residue from this experiment was chromatographed (silica gel, 20 g, 10% ether–lbpe) to afford after vacuum drying 35 mg (59%, oil) of a material assigned the cyclic ether structure **7** on the basis of spectral data (Table II).[11]

Reduction of Benzoyloxytosylate 5c to Dihydrotachysterol$_2$ (5d). The tosylate **5c** (135 mg, 0.20 mmol) was reduced with lithium triethylborohydride in precisely the same way as described for **3c** above to afford after chromatography (silica gel, 1 × 55 cm column, lbpe to 10% ether–lbpe) 21 mg (26%) of TLC (silica gel, benzene; comparison with authentic **5d**) pure **5d**. Crystallization (methanol) afforded material with mp 123–125 °C (authentic commercial specimen, mp 122–123.5 °C;[7] mmp 124–125 °C; lit. mp 128,[6g] 125–127,[6e] 131–133 °C[6h,i]). NMR data are summarized in Table II; $[\alpha]^{25}_D$ +90.4° (c 0.83 g/100 mL 95% EtOH).

Reduction of Benzoyloxytosylate 6c to the Ether 8. Using the procedure of the preceding section, **6c** (140 mg, 0.21 mmol) was reduced to afford after vacuum drying a TLC homogeneous substance (70 mg, 85%, oil) assigned the cyclic ether structure **8** on the basis of spectral data (Table II).

Saponification of 6b to the Diol 6a. The ester **6b** (40 mg) described above in a mixture of 5% KOH–CH_3OH (5 mL) and THF (1 mL) was refluxed under nitrogen for 2 h. Standard workup afforded material with properties (TLC–alumina/ether, NMR) identical to the diol isomer **6a** and clearly different from the diol isomer **5a** described earlier.

Saponification of 4b to the Diol 4a. The ester **4b** (40 mg) described earlier was saponified as in the preceding experiment to afford a substance identical (TLC-30% acetone in benzene/silica gel, NMR) to the diol cis isomer **4a** which is clearly different from trans isomer **3a**.

Catalytic Hydrogenation of Vitamin D_2 (1a) to [10*S*(19)]-(3d) and [10*R*(19)]-Dihydrovitamin D_2 (4d). Vitamin D_2 (**1a**, 350 mg, 0.88 mmol) and $[(C_6H_5)_3P]_3RhCl$ (87 mg) in benzene (40 mL, freshly distilled from potassium under nitrogen) were subjected to hydrogenation (1 atm) for 14 h at room temperature by which time hydrogen uptake had essentially ceased.[6k,8] Benzene was removed under vacuum and the residue was taken up in pentane. The latter was washed thoroughly with water, filtered, and then dried (Na_2SO_4). The filtered and concentrated organic phase left a residue (394 mg) which was chromatographed (dry column, 1.5 × 120 cm column of silica gel, 8 mL fractions, 30% ether–lbpe). Fractions 4–10 afforded TLC pure **3d** (190 mg, 54%). Fractions 11–25 were combined and concentrated to afford a residue which was rechromatographed (dry column, 1.5 × 70 cm silica gel, 6 mL fractions, 25% ether–lbpe): fractions 4–6 contained small amounts of **3d**; fractions 8–21 contained TLC pure **4d** (122 mg, 35%).

Crystallization (acetone) of **3d** afforded material with mp 100–102 °C. It proved to be identical (NMR, TLC, mp) to the trans isomer **3d** described earlier in this paper.

Crystallization (90% acetone–H_2O) of **4d** afforded material with mp 83.5–86 °C (lit.[6h,i] mp 85–7 °C from petroleum ether, mp 60–65[6h,i] or 61 °C[6k] from CH_3OH). The combined yield of TLC pure **3d** and **3d** was 89%. Spectral data (NMR) for both **3d** and **4d** are summarized in Table II. Their TLC behavior (**3d/4d**, R_f's) was as follows: isopropyl ether–silica gel (0.40, 0.33); isopropyl ether–5% $AgNO_3$ silica gel (0.35/0.50).

Catalytic Hydrogenation of 5,6-*trans*-Vitamin D_2 (2a) to [10*S*(19)]-, Dihydrotachysterol$_2$ (5d), and [10*R*(19)]-Dihydro-(5*E*)-vitamin D_2 (6d). The reduction (5,6-*trans*-D_2, **2a**, 639 mg; catalyst, 160 mg; benzene, 70 mL; overnight) and work-up (pentane–water) was carried out as described in the preceding section. Dry column chromatography (silica gel, 2.2 × 160 cm, 30% ether–lbpe) afforded TLC pure **6d** [160 mg, 25%; crystallization from acetone gave crystals with mp 108–110 °C, $[\alpha]^{25}_D$ +60.4° (c 0.83 g/100 mL 95% EtOH)] and impure **5d** (271 mg). Rechromatography of impure **5d** (alumina, 1.5 × 70 cm, 15% ether–lbpe to 75% ether–lbpe) afforded TLC pure **5d** (2.5 mg, 34%; crystallization from methanol gave mp 122.5–123.5 °C). Silica gel TLC using 25% ether–lbpe effectively resolved the two stereoisomers: **6d** R_f 0.22 and **5d** R_f 0.16.

The more polar isomer proved to be identical by TLC (alumina, 50% ether–lbpe; silica gel, isopropyl ether), mmp (122.5–123.5 °C), and NMR (Table II) to the dihydrotachysterol$_2$ (**5d**, mp 122–123 °C) prepared by reduction of **5c** described earlier. See earlier section for $[\alpha]^{25}_D$.

The less polar isomer is assigned stereostructure **6d** on the basis of its spectral characteristics (Table II, including a comparison of its NMR spectrum to that of the corresponding stereoisomer in the vitamin D_3 series[4] previously reported by this laboratory)[1b] and the

chemical correlations described above.

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Registry No.—**1a,** 50-14-6; **1b,** 65338-41-2; **2a,** 65377-95-9; **2b,** 65338-42-3; **7,** 65338-43-4; **8,** 65338-44-5; benzoyl chloride, 98-88-4; Ts-Cl, 98-59-9.

Supplementary Material Available: Table II giving the NMR, UV, and/or MS data for the 18 compounds **3–6, 7,** and 8 (5 pages). Ordering information is given on any current masthead page.

References and Notes

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(2) This study was supported by USPHS Grant AM-16595 and by a grant from the intramural Research Fund of the University of California, Riverside.
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(7) Commercial dihydrotachysterol$_2$ (**5d**) clearly has the stereostructure shown as determined by comparison of its 300 MHz ^{1}H-NMR spectrum with that of dihydrotachysterol$_3$ (vitamin D_3 side chain) (ref 1b).
(8) The two products (**3d** and **4d**) obtained by saturating the 10,19 double bond of vitamin D_2 have been labeled in our laboratory as DHV$_2$-II and DHV$_2$-III, respectively. Other workers (ref 6e,h,i,k) refer to **4d** as DHV$_2$-IV while our laboratory (see also ref 6g,j) labels **6d,** the C_{10} epimer of dihydrotachysterol$_2$ (**5d**), as DHV$_2$-IV. See footnote 17 of ref 1b. While this study was in progress, Barett et al. (ref 6k) reported the fact that catalytic reduction of **1a** results in only two products: DHV$_2$-II (**3d**) and DHV$_2$-IV (**4d** or what we call DHV$_2$-III).
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Stereochemical Assignment of (*E*)- and (*Z*)-2-(1-Naphthyl)-1-phenylpropene and Their Photocyclization to 5-Methylchrysene

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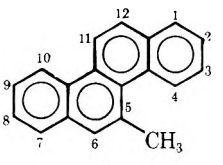
Dehydration of 2-(1-naphthyl)-1-phenyl-2-propanol (**3**) gave varying ratios of (*E*)-2-(1-naphthyl)-1-phenylpropene (**4**), (*Z*)-2-(1-naphthyl)-1-phenylpropene (**5**), and 2-(1-naphthyl)-3-phenylpropene (**6**), depending upon conditions and choice of reagent. Assignment of configuration to these alkenes by UV and ^{1}H NMR spectroscopy was equivocal, but unambiguous assignment was made through comparison of chemical shifts in the ^{1}H NMR spectra of the cis diols and the corresponding cyclic phenylboronates prepared from **4** and **5**. Photocyclization of **4** or **5** gave 5-methylchrysene (**1**), whereas **6** was inert.

The environmental carcinogen 5-methylchrysene (**1**), which occurs in the biologically active neutral subfractions of tobacco smoke, is more carcinogenic on mouse skin than any of the other monomethylchrysene isomers or chrysene itself.[2] The carcinogenic activity of **1** is comparable to that of benzo[*a*]pyrene.[3] 5-Methylchrysene is also more mutagenic towards *S. typhimurium* than the other monomethylchrysenes.[4]

Previous syntheses[2a,5] of **1** involved multistep routes and gave low yields, none exceeding 5%. In order to continue carcinogenicity studies of **1**, a more efficient synthesis was needed. Photocyclization of the appropriately substituted alkene[6] appeared to be a more suitable route. We now report a shorter and improved synthesis (20% yield) of **1** via UV irradiation of (*E*)- or (*Z*)-2-(1-naphthyl)-1-phenylpropene (**4** and **5**, respectively) in the presence of iodine and oxygen as shown in Scheme I.



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Treatment of 1-acetonaphthone with benzylmagnesium chloride gave **3** in 75% yield. Dehydration of **3** was performed under a variety of conditions in an attempt to control the ratio of the resulting alkenes.[7] In all cases, GC analyses[8] indicated the three products shown in Table I.

During dehydration of **3** in refluxing benzene with Amberlyst-15 (A-15) resin,[9] the ratio of alkenes **4/5/6** (48:9:43) remained fairly constant while alcohol **3** was still present. After **3** was consumed, the concentration of exo alkene **6** decreased rapidly with simultaneous increase of **4** to a maximum of 57%. Alkene **4** then slowly diminished as the concentration of **5** increased. After 36 h, the ratio **4/5/6** (54:45:1)[10] stabilized

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Table I. Acid-Catalyzed Dehydration of 3

Reagent and temp (°C)	Ratio of Alkenes 4	5	6
Amberlyst-15, C_6H_6 (80)	48[a]	9	43
	57[b]	30	13
	54[c]	45	1
Trifluoracetic acid (27)	83[d]	16	1
$POCl_3$, pyridine (0)	33[e]	5	62

[a] During dehydration of 3. [b] 2.5 h after disappearance of 3. [c] 36 h after disappearance of 3. [d] 0.5 h. [e] No change over 3 h.

and the concentration of 4 was only slightly favored. The kinetic formation of 4 and 6, particularly with trifluoroacetic acid, can be rationalized by examination of the presumably most stable conformation of the alcohol 3 and the resulting cation shown in Scheme II.

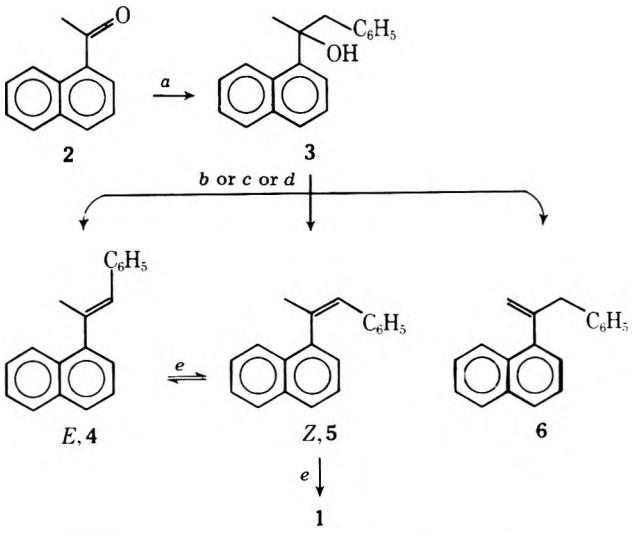
In the preferred conformation of alcohol 3, the phenyl and naphthyl groups are anti. Protonation of the hydroxyl followed by loss of water generates the cation which has two protons H_a and H_b correctly oriented for periplanar elimination[11] to 4 or 6.

The failure of the E alkene 4 to predominate to any great extent over the Z alkene 5 after prolonged exposure to equilibrating conditions should be noted. Although both 4 and 5 exhibit a steric interaction between the methyl group and the naphthalene *peri*-hydrogen,[12] the net result is to reduce the usual difference in stability between E and Z isomers.

Under nonequilibrating conditions, the dehydration of 3 using phosphorus oxychloride and excess pyridine at 0 °C favored formation of 6 (4/5/6; 6:1:12). This ratio did not change over 3 h at 0 °C. The preponderance of the thermodynamically less stable alkene 6 may be related to the ease of approach of base preceding elimination.[11]

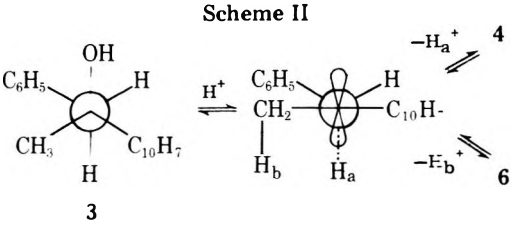
The alkenes 4, 5, and 6 were separated via picric acid with the picrate of 4, mp 94–95 °C, being the least soluble and most stable. Successive concentrations of the mother liquor gave the picrate of 6, which is less stable and dissociated on attempted recrystallization from ethanol. The Z alkene 5 did not form a picrate under these conditions and was isolated from the mother liquor. Dreiding models and NMR data, subsequently to be discussed, show that the naphthyl ring of the Z isomer of 5 is crowded (aryl–aryl interaction) compared to that of 4. This may explain the decreased stability of the picrate of 5.

Scheme I



[a] $C_6H_5CH_2MgCl$. [b] A-15, C_6H_6, Δ. [c] CF_3CO_2H. [d] $POCl_3$, pyridine. [e] $h\nu$, I_2, O_2, C_6H_6.

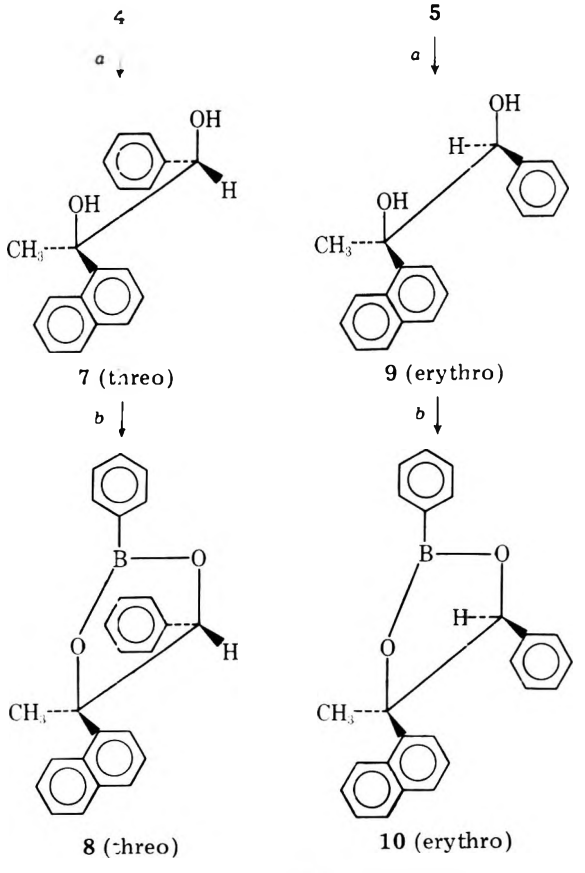
Scheme II



Attempts to assign configuration to the E and Z alkenes 4 and 5 using ^1H NMR and UV spectroscopy led to uncertain results. However, the assignment of configuration to 4 and 5 was achieved through ^1H-NMR studies of the diol and the phenylboronate derivatives of these alkenes.[13] The *threo*-2-(1-naphthyl)-1-phenylpropane-1,2-diol (7) was prepared by treatment of the E alkene 4 with osmium tetroxide and hydrolysis of the osmate with sodium sulfite. Analogously, the Z alkene 5 gave the erythro diol 9. Treatment of each of these diols (7 and 9) with phenylboronic acid gave the corresponding cyclic phenylboronates 8 and 10 respectively, as shown in Scheme III. The configurations used in Scheme III are an arbitrary selection for 7, 8, 9, and 10 and should not be considered as an absolute assignment.[14]

Assignments have previously been made for meso and racemic aryl containing diols[15] and their corresponding phenylboronates[13] based on chemical shifts in the ^1H-NMR spectra produced by anisotropic effects of the aromatic ring cis to a methyl group. The ^1H-NMR spectra of the phenylboronates have the advantage of showing enhanced methyl proton shifts relative to what is observed for the diols. Thus, this technique allows stereochemical assignment to E and Z alkenes 4 and 5, whereas other methods (NMR and UV) applied to these isomers failed to give unambiguous assignments. The ^1H-NMR data of the diols and phenylboronates are presented in

Scheme III



[a] OsO_4, pyridine, Et_2O; Na_2SO_3. [b] $C_6H_5B(OH)_2$.

Table II. ^{1}H NMR (δ) Data for Diols 7 and 9 and Phenylboronates 8 and 10

	Registry no.	Aromatic H	CH_3	H(C-1)	OH(C-1)	OH(C-2)
Threo diol (7)	65059-19-0	6.72–8.86	1.40	3.22	3.20	5.46
Erythro diol (9)	65059-20-3	7.00–8.80	1.66	2.38	2.28	5.34
Threo boronate (8)	65059-21-4	7.34–8.28	1.62	6.02		
Erythro boronate (10)	65059-22-5	6.70–8.20	2.10	5.88		

Table III. UV and ^{1}H-NMR (δ) Data of Alkenes 4, 5, and 6

	4[e]	5[f]	6[g]
UV (EtOH), nm	222.5 (4.79)	225 (4.87)	225 (4.77)
(log ϵ)	245[a] (4.15)	245[a] (4.28)	*b*
	282.5 (4.04)	285 (3.98)	282.5 (3.85)
^{1}H NMR (CCl_4)			
CH_3	2.30 (d, J = 1 Hz, 3)	2.24 (d, J = 1 Hz, 3)	CH_2 3.68 (s, 2)
Vinyl H	6.52 (s, 1)[c]	*d*	5.08 (d, J = 2 Hz, 1) 5.22 (d, J = 2 Hz, 1),
Aromatic H	7.00–8.02 (m, 12)	6.64–7.88 (m, 13)[d]	6.94–8.02 (m, 12)

[a] Shoulder. [b] No shoulder at 245. [c] Broad, but no discernible splitting. [d] The vinyl proton signal was buried within the aromatic proton resonances. [e] Registry no. 65059-23-6. [f] Registry no. 65085-71-4. [g] Registry no. 65059-24-7.

Table II. Infrared studies have also been used to establish the relative configuration of vicinal diols.[16]

In making the configurational assignments for the threo isomers relative to the erythro isomers (diols as well as the corresponding phenylboronates), the methyl proton resonances would be expected to appear at higher field because they lie within the shielding region of the phenyl ring.[13,15] The hydroxyl protons (in threo diol 7) should absorb at lower field because of an increased intramolecular hydrogen bonding, which decreases electron density on oxygen and deshields the hydroxyl protons.[15] The benzylic protons are deshielded in the threo isomers 7 and 8 relative to those of the erythro isomers 9 and 10 and opposite to that which is generally observed.[17] This effect may result from interaction of the methyl group with the *peri*-hydrogen of the naphthyl ring which causes rotation of the naphthyl ring and in turn deshielding of the benzylic proton in the threo isomers. In summary, these directional shifts are consistently observed in the spectra of the diol and phenylboronate derived from the *E* alkene, mp 36–37 °C. This allows assignment of stereochemistry to the diols 7 and 9, mp 102–104 and 109–110.5 °C, respectively, which in turn allows structural assignment of *E* and *Z* alkenes 4 and 5.

Attention is directed to this use of phenylboronic acid. Addition of an equimolar quantity of phenylboronic acid to a deuteriochloroform solution of 7 or 9 followed by 10 min of shaking and filtration through glass wool to remove water gave quantitative conversion to the cyclic phenylboronates 8 and 10. The locked orientation of substituents on these cyclic esters leads to enhanced chemical shifts in the ^{1}H-NMR spectra that are valuable for making diol configuration assignments.[13]

Considering the above stereochemical assignments, it is of interest to examine the ^{1}H-NMR and UV data obtained for 4, 5, and 6. The structure of the latter is conclusively established through the ^{1}H-NMR spectrum, which shows vinyl protons at δ 5.21 (broad d, J = 2 Hz) and δ 5.08 (d, J = 2 Hz) and two benzylic protons at δ 3.68 (s) as shown in Table III.

The similarity of the UV data from 4, 5, and 6 precluded satisfactory use as stated above in making structural assignments.[18] The similarities in the UV spectra of 4 and 5 result from steric interaction, as previously mentioned, between the *peri*-hydrogen of the naphthyl ring and the methyl group,[12] thus preventing coplanarity in the *E* as well as the *Z* isomer.

The ^{1}H-NMR data of 4 and 5 are unusual in that the vinyl proton resonance of the *E* isomer 4 appears at higher field than that of the *Z* isomer 5. Generally in 1,2-diarylethenes, these resonance positions are reversed, although exceptions are known.[19] The usual occurrence of vinyl protons at lower field in *E* isomers is attributed to the coplanarity of the aromatic ring and double bond.[19] This places the vinyl proton in the deshielding region of the aromatic ring. The nonplanarity of the naphthyl ring and alkene double bond in 4 causes the vinyl proton to lie above the naphthyl ring, i.e., in the shielding region, and hence its shift to higher field.[18] Some indication of the angle between the naphthyl ring and the alkene double bond may be seen in the shift of the naphthyl peri proton signal proximal to the methyl group, since an increased angle should lead to an upfield shift due to shielding by the double bond.[12] In 4, 5, 6, and 1, this appears as a discernible multiplet at δ 7.96, 7.90, 8.02, and 8.90, respectively. The assignments of 4 and 5 are further confirmed by the strong upfield shift of aromatic protons in the *Z* alkene 5, which is caused by the proximity of aromatic rings.[18]

Photocyclization of 4, 5, and 6 with periodic sampling and GC analysis[8] was conducted by irradiation of an air-saturated 0.01 M benzene solution of alkene containing iodine (0.001 M) at 3600 Å. After 7 h, the exo alkene 6 had failed to isomerize or cyclize and was recovered unchanged. No other products were detected by GC. The *E* and *Z* alkenes 4 and 5 both rapidly equilibrated to a fairly constant *E*/*Z* (4/5, 1:2–3) ratio but the formation of 5-methylchrysene (1) was initially faster as shown in Figure 1 when the *Z* alkene was used as starting material. The photocyclization of 4 and 5 is assumed to proceed by a mechanism similar to that for the photocyclization of stilbene.[20]

Preparative-scale photocyclization of 4 and 5 was most conveniently carried out on the mixture of alkenes obtained from acid-catalyzed dehydration. Attempts to increase the yield (29%) by using cupric chloride[21] or using a higher concentration of oxygen were unsuccessful and actually led to decreased yields. Dilution of the benzene solution of alkenes from 0.01 to 0.0025 M also failed to give a significant increase in yield.

The structure of the product from photocyclization was identified as 5-methylchrysene (1) by mp 117–117.5 °C (lit.[2a,5] mp 117 °C), mass spectrum,[2a] and ^{1}H NMR.[2a]

Experimental Section[22]

2-(1-Naphthyl)-1-phenyl-2-propanol (3). To the Grignard reagent prepared from 48.6 g (2.0 mol) of magnesium and 252 g (2.0 mol) of benzyl chloride in 500 mL of ether was added a solution of 314 g (1.85 mol) of purified 1-acetonaphthone (2) in 500 mL of ether at a rate sufficient to maintain reflux. The mixture was then heated at reflux an additional 0.5 h, cooled, treated with dilute hydrochloric acid, and then ether extracted. The ether extracts were washed with sodium bicarbonate solution, dried ($MgSO_4$), filtered, and concentrated. Recrystallization from a mixture of isohexane[22c] and benzene gave 365 g (75%) of 3: mp 74–85 °C dec; IR (KBr) 3150 (s), 800 (s), 740 (s), 700 (s), 695 (s), 680 cm^{-1} (s); ^{1}H NMR (CCl_4) δ 2.72 (s, 3, CH_3), 2.80 (s, 1, OH), 3.34, 3.66 (d of d, 2, $J_{HH'}$ = 13 Hz), 6.76–8.80 (m, 12, ArH); MS *m/e* (rel intensity) M^+ 262 (1), 172 (12), 171 (100), 127 (12),

91 (16). 43 (78). Anal. Calcd for $C_{19}H_{18}O$: C, 86.98; H, 6.91. Found: C, 87.00; H, 7.06.

Dehydration of 3 to (*E*)-2-(1-Naphthyl)-1-phenylpropene (4), (*Z*)-2-(1-Naphthyl)-1-phenylpropene (5), and 2-(1-Naphthyl)-3-phenylpropene (6). A. To a magnetically stirred flask containing 500 mL of benzene fitted with a Dean-Stark trap were added 50 g (0.191 mol) of **3** and 1 g of A-15 resin.[9] The mixture was heated at reflux temperature until **3** disappeared as shown by GC.[8] Filtration to remove resin, followed by distillation at 140–170 °C (0.3 mm), gave 39.3 g (84%) of alkenes **4/5/6** (2.5:1:2). Equilibration of the alkenes was carried out under similar conditions.

B. To 120 mL of trifluoroacetic acid was added 12.0 g (0.046 mol) of **3**. After stirring at 25 °C for 30 min, the mixture was diluted with water, extracted with isohexane,[22c] washed with sodium bicarbonate, and dried ($MgSO_4$). Filtration, concentration, and distillation gave 8.8 g (78%) of **4/5/6** (83:16:1).

C. To 50 mL of pyridine and 4.6 g (0.30 mol) of phosphorus oxychloride was added 6.6 g (0.025 mol) of **3** at 0 °C. The solution was stirred 3 h and then poured on ice. Extraction with isohexane[22c] and distillation gave 5.4 g (89%) of 4/5/6 (6.6 1:12.4).

Separation of Alkenes 4, 5, and 6. To a warm solution of 68.0 g of picric acid in 500 mL of 95% ethanol was added 48.8 g of a mixture of alkenes **4**, **5**, and **6**. After standing overnight, the picrate was filtered out. Two successive concentrations of the filtrate gave a second and third crop of picrates and mother liquor. The first crop of picrate (45 g) was recrystallized from ethanol to give 35 g of bright red picrate, mp 96–97 °C. Cleavage of this picrate by continuous extraction[23] with isohexane over Merck neutral alumina followed by recrystallization of the alkene from isohexane[22c] gave 13.5 g of (*E*)-2-(1-naphthyl)-1-phenylpropene (**4**): mp 36–37 °C; IR (NaCl) 915 (m), 860 (m), 800 (s), 775 (s), 750 (s), 705 (s), 695 cm^{-1} (s); ^1H NMR (CCl_4) δ 2.30 (d, J = 1 Hz, 3, CH_3), 6.52 (s, 1, vinyl H), 7.00–8.02 (m, 12, ArH); MS *m/e* (rel intensity) M^+ 244 (93), 230 (20), 229 (100), 166 (26), 165 (35), 152 (20); UV nm (log ϵ) 95% ethanol 222.5 (4.79), 245 (4.15), 282.5 (4.04). Anal. Calcd for $C_{19}H_{16}$: C, 93.06; H, 6.94. Found: C, 93.31; H, 6.58.

The second crop of picrate (25 g) was recrystallized from ethanol to give 10.2 g of a mixture consisting of picrates from **4** and **6**. The mother liquor was evaporated to give 15.4 g of the yellow picrate of **6**, mp 80–95 °C. Attempted recrystallization resulted in dissociation. The picrate was cleaved as above and the recovered hydrocarbon was recrystallized from isohexane[22c] to give 6.0 g of 2-(1-naphthyl)-3-phenylpropene (**6**): mp 26–27 °C; IR (NaCl) 900 (m), 795 (s), 775 (s), 745 (m), 695 (s) cm^{-1}; ^1H NMR (CCl_4) δ 3.68 (s, 2, CH_2), 5.08 (d, J = 2 Hz, 1, vinyl H), 5.22 (d, J = 2 Hz, 1, vinyl H), 6.94–8.02 (m, 12, ArH); MS *m/e* (rel intensity) M^+ 244 (37), 165 (11), 154 (32), 153 (8), 152 (100), 91 (26); UV nm (log ϵ) 95% ethanol 225 (4.77), 282.5 (3.85). Anal. Calcd for $C_{19}H_{16}$: C, 93.06; H, 6.94. Found: C, 93.06; H, 6.66.

The third crop of picrate (30.6 g) consisted of picrates of **4** and **6**. The mother liquor consisted of **5** and picric acid but no picrate could be isolated. The mixture was separated on alumina as above and recrystallized from isohexane[22c] to give 5.5 g of (*Z*)-2-(1-naphthyl)-1-phenylpropene (**5**): mp 27–28 °C; IR (NaCl) 915 (m), 860 (m), 800 (s), 775 (s), 690 cm^{-1} (s); ^1H NMR (CCl_4) δ 2.24 (d, J = 1 Hz, 3, CH_3), 6.64–7.88 (m, 13, vinyl H, ArH); MS *m/e* (rel intensity) M^+ 244 (100), 230 (19), 299 (100), 228 (26), 166 (17), 165 (27); UV nm (log ϵ) 95% ethanol 225 (4.87), 245 (4.28), 285 (3.98). Anal. Calcd for $C_{19}H_{16}$: C, 93.06; H, 6.94. Found: C, 93.30; H, 6.94.

***threo*-2-(1-Naphthyl)-1-phenyl-1,2-propanediol (7).** To a magnetically stirred solution of 1.0 g (3.93 mmol) of OsO_4 in 25 mL of ether and 2 mL of pyridine was added 960 mg (3.93 mmol) of **4** in 5 mL of ether. After 60 h, 70 mL of ethanol and 7.0 g of Na_2SO_3 in 12 mL of H_2O were added and the mixture was heated at reflux for 3 h. The solution was cooled and filtered through Dicalite, the Dicalite was rinsed with ethanol, and the filtrate was concentrated to a small volume under reduced pressure. The residue was extracted with ether and the extract was dried ($MgSO_4$), filtered, concentrated, and then recrystallized from isohexane[22c] to give 470 mg (43%) of **7**: mp 102–104 °C; IR (CCl_4) 3570 cm^{-1} (OH) (m); ^1H NMR (80 mg/0.5 mL of $CDCl_3$) δ 1.40 (s, 3, CH_3), 3.20 (s, 1, OH), 3.22 (s, 1, ArCH), 5.46 (s, 1, OH), 6.72–8.86 (m, 12, ArH); MS *m/e* (rel intensity) M^+ 278 (4), 171 (20), 170 (100), 154 (12), 126 (12). Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 81.66; H, 6.44.

Cyclic Boronate 8. The cyclic boronate **8** of **7** was prepared by adding 32 mg (0.328 mmol) of phenylboronic acid and 0.5 mL of $CDCl_3$ to 80 mg (0.328 mmol) of **7** in 0.5 mL of $CDCl_3$, shaking for 5 min, and filtering through glass wool. ^1H NMR ($CDCl_3$) δ 2.10 (s, 3, CH_3), 5.88 (s, 1, ArCH), 6.70–8.20 (m, 17, ArH).

***erythro*-2-(1-Naphthyl)-1-phenyl-1,2-propanediol (9).** The diol **9** was prepared as above using 865 mg (3.40 mmol) of OsO_4 and 830 mg (3.40 mmol) of **5**, giving 300 mg (32%) of **9**: mp 109–110.5 °C; IR (CCl_4) 3500 (m), 3450 cm^{-1} (OH) (m); ^1H NMR (80 mg/0.5 mL of $CDCl_3$) δ 1.66 (s, 3, CH_3), 2.28 (d, 1, OH), 2.38 (s, 1, ArCH), 5.34 (d, 1, OH), 7.00–8.80 (m, 12, ArH); MS *m/e* (rel intensity) M^+ 278 (2), 171 (29), 170 (100), 154 (9), 126 (12). Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 82.11; H, 6.60.

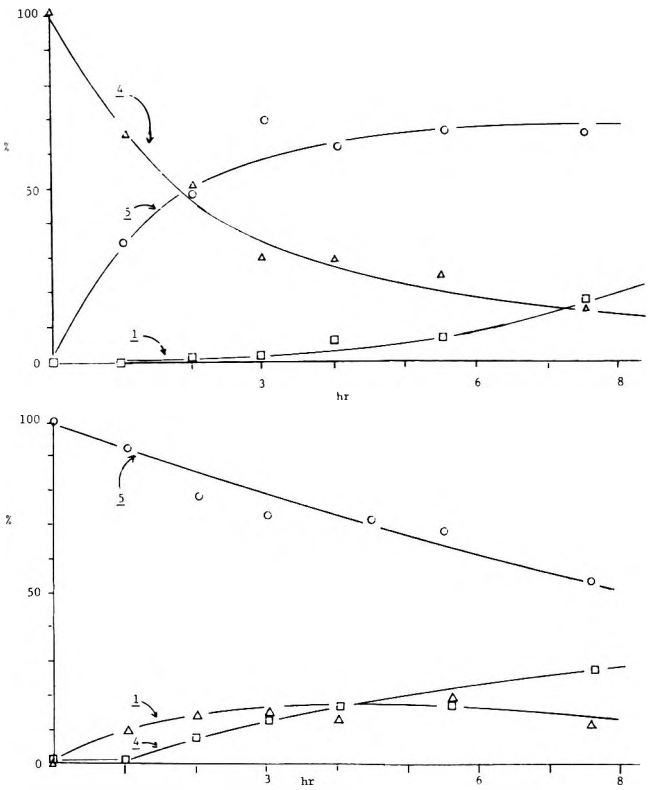


Figure 1. Photolysis of *E* and *Z* alkenes **4** and **5** (0.01 M) in benzene with I_2 (0.001 M) and saturated with O_2 reactor; (Rayonet reactor; irradiation at 3600 Å).

The cyclic boronate **10** of **9** was prepared as above; ^1H NMR ($CDCl_3$) δ 1.62 (s, 3, CH_3), 6.02 (s, 1, ArCH), 7.34–8.28 (m, 17, ArH).

5-Methylchrysene (1). To 15 L of benzene were added 12.2 g (50 mmol) of alkene mixture (**4/5/6**; 5.3:4.0:1.1) obtained by acid-catalyzed equilibration of **4**, **5**, and **6** and 0.64 g (5 mmol) of I_2. The solution was thoroughly mixed and a 3-L aliquot was transferred to a 5-L beaker. Air was bubbled through the aliquot for 30 min, the air bubbler was removed, and irradiation was begun (Hanovia, 450-W, medium-pressure, Hg lamp equipped with Corex filter). After 4 h the irradiation was stopped, the solution was removed, and the process was repeated until all 15 L were irradiated. After photolysis, the solvent was removed and the resulting oil was placed on a Soxhlet column[23] of Merck basic alumina and eluted for 24 h with isohexane.[22c] Subsequent concentration and crystallization yielded 3.6 g (29%) of 5-methylchrysene, mp 115–117 °C. A sample recrystallized from isohexane[22c] and benzene had mp 117–117.5 °C (lit.[5] mp 117 °C): ^1H NMR ($CDCl_3$) δ 3.15 (s, 3, CH_3), 7.40–7.80 (m, 8, ArH), 8.52–8.64 (m, 2, C-10 and C-11 protons), 8.82 (m, 1, C-4 proton); MS *m/e* (rel intensity) M^+ 242 (100), 241 (39), 240 (14), 239 (28), 120 (18), 119.5 (22); UV nm (log ϵ) 95% ethanol 271 (5.00), 286.5 (4.00), 300.5 (3.96), 312.5 (4.10), 326.5 (4.08).

The individual alkenes **4**, **5**, and **6** were irradiated at 3600 Å in quartz tubes in a Rayonet Reactor. Each alkene solution in benzene was 0.001 M in alkene, 0.001 M in I_2, and saturated with O_2. Samples were periodically removed and analyzed by GC.[8]

Registry No.—**1**, 3697-24-3; **2**, 1333-52-4; **3**, 65059-25-8; **4** picrate, 65059-26-9; **6** picrate, 65059-27-0; benzyl chloride, 100-44-7; picric acid, 88-89-1; phenylboronic acid, 98-80-6.

References and Notes

(1) (a) Support from Continental Oil Company (Summer, 1977) and from Texas Eastman Company (Eastman Kodak) is gratefully acknowledged; (b) Oklahoma State University; (c) Naylor Dana Institute.

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(9) Amberlyst-15 resin is a sulfonic acid resin available from Rohm and Haas Company, Philadelphia, Pa. We are grateful for a research sample.
(10) Beyond this reaction time, GC showed the appearance of three new products with slightly longer retention times. These new products are possibly cyclized materials. Use of *p*-toluenesulfonic acid in the place of A-15 decreased the reaction times but gave similar results.
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Isomerization of 2- and 3-Carene Oxides over Solid Acids and Bases[1]

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The reaction of 3-carene oxide catalyzed by solid acids and bases gave ten compounds and several unidentified products. The main products were carbonyl compounds (IV, VI, and VII) and allylic alcohols (IX and X) with a three-membered ring except for the case of H_2SO_4/SiO_2, which gave a large amount of III, V, and VIII. The carbonyl compounds were predominantly formed over SiO_2–Al_2O_3, Al_2O_3 A and $FeSO_4$, while the allylic alcohols were preferentially formed over Al_2O_3 C and TiO_2–ZrO_2. The reactivity of 2-carene oxide over solid acids and bases was exceedingly high in comparison with that of 3-carene oxide, and eight compounds and several unidentified products were observed. All the products were the three-membered ring-opened ones. The formation of allylic alcohols with the hydroxyl group rearranged to the 3 or 8 position was also observed. A large amount of III and XIII was formed. TiO_2–ZrO_2 showed 100% selectivity for the formation of XIII at 30 °C. It is significant that the breaking of the C(3)–O bond of oxygen is much more favorable with 3-carene oxide, while the C(2)–O bond is broken with 2-carene oxide.

Introduction

Among many studies on the rearrangement of α-pinene, limonene, caryophyllene and other terpene epoxides,[2–8] there are some studies dealing with the carene oxides. In the presence of zinc bromide, 3-carene oxide rearranged mainly to the ring-contracted aldehyde and to the ketones with retention of the three-membered ring.[9–11] Joshi and co-workers reported that passing the epoxide over active alumina yielded bicyclic unsaturated alcohols together with some by-products.[11] As for 2-carene oxide, allylic alcohols with the three-membered ring intact were predominantly formed with lithium diethylamide, a strong base,[12] while the three-membered ring was

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Table I. Isomerization of 3-Carene Oxide[d] at 80 °C for 75 min

Catalyst[a]	Catalyst amount, g	Conversion, %	Selectivity, %										
			I	II	III	IV	V	VI	VII	VIII	IX	X	Others
SiO_2–Al_2O_3[b]	0.16	100	1	2	9	52	1	11	14	0.2	1		10
H_2SO_4/SiO_2	0.24	100	2		24		15	10	4	23			23
H_2SO_4/SiO_2[c]	0.24	100	2	4	16	12	5	6	29	10	4	4	10
Al_2O_3 A	0.22	70	10	5	4	46		3	13		6	12	1
$FeSO_4$ (500 °C)	0.48	94	1	3	8	23		5	36		4	8	13
$FeSO_4$ (700 °C)	0.32	95	0.4	2	4	23		4	36	2	3	7	17
SiO_2–TiO_2	0.26	92	6	13	8	33		2	6		14	16	2
$NiSO_4$ (350 °C)	0.28	88	2	10	5	13		6	34		7	18	5
Al_2O_3 C	0.27	37	4	1	1	17		3	3		15	54	1
TiO_2	0.28	42	13	8	2	19		3	1		28	27	
TiO_2–ZrO_2[c]	0.24	61	12	10	2	11		1	2		41	19	2
Al_2O_3 B	0.20	76	11	3	0.4	29		2	5		7	42	2

[a] Figures in parentheses show calcination temperatures. [b] 10 min. [c] 90 °C. [d] Registry no.: 21218-11-1; I, 3479-89-8; II, 21195-59-5; III, 99-87-6; IV, 19534-12-4; V, 31507-62-7; VI, 43124-59-0; VII, 43124-60-3; VIII, 499-74-1; IX, 62532-46-1; X, 22626-38-6.

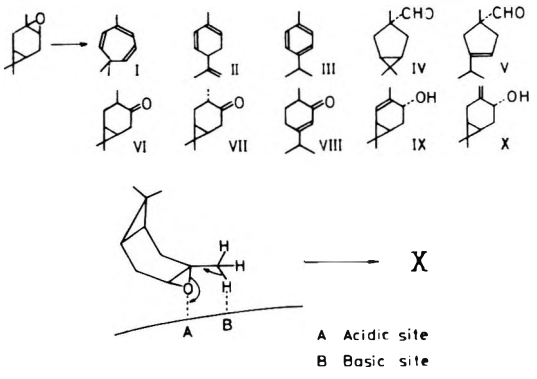
opened to the diene alcohol, *cis*-isolimonenol, on reaction with metatitanic acid.[13]

As part of a series on dealing with the rearrangement of epoxides over heterogeneous acid and base catalysts, we have already studied the *d*-limonene and carvomenthene oxides.[14-16] In order to examine the change in catalytic action due to the effect of the three-membered ring as a substituent group, we have now carried out the isomerization of the 2- and 3-carene oxides over several solid acid and base catalysts.

Results and Discussion

Isomerization of 3-Carene Oxide. The reaction of 3-carene oxide catalyzed by solid acid and base catalysts gave the following products: 3,7,7-trimethyltropilidene (I), 1,5,8(9)-*p*-menthatriene (II), *p*-cymene (III), 3,6,6-trimethylbicyclo[3.1.0]hexane-3-carboxaldehyde (IV), 1-methyl-1-formyl-3-isopropyl-3-cyclopentene (V), isocaranone (VI), caranone (VII), carvenone (VIII), *trans*-2-caren-4-ol (IX), *trans*-3(10)-caren-4-ol (X), and unidentified products.

The catalytic activity and selectivity of several solid acid and base catalysts in 75 min at 80 °C are shown in Table I. Catalysts were chosen from those studied in isomerizations of *d*-limonene[14,15] and carvomenthene[16] oxides on the basis of their activities and selectivities. SiO_2–Al_2O_3 and H_2SO_4/SiO_2 are most active for the isomerization. The high activity of SiO_2–Al_2O_3 is considered to be based on its high acidity on the surface.[17,18] The main products with various catalysts were carbonyl compounds (IV, VI, and VII) and allylic alcohols (IX and X) with a three-membered ring except for the case of H_2SO_4/SiO_2, which gave a large amount of III, V, and VIII. Carbonyl compounds were formed predominantly over



SiO_2–Al_2O_3, Al_2O_3 A and $FeSO_4$, while allylic alcohols were formed preferentially by Al_2O_3 C and TiO_2–ZrO_2, the selectivities being more than 60%.

Most of the products with H_2SO_4/SiO_2 resulted from opening of the three-membered ring. This is in contrast to the results with the other catalysts. It appears likely that sulfuric acid supported on SiO_2 partially dissolves in the medium and that cleavage of the epoxide and the cyclopropane rings is the result of acid catalysis. In the case of the other catalysts which gave products with the three-membered ring intact, it is thought that the oxygen atom of oxide is adsorbed on the catalyst surface without there being an interaction between the three-membered ring and the surface.

The formation of a large amount of cymene (III) and carvenone over H_2SO_4/SiO_2 was also observed in the isomerization of *d*-limonene oxide.[14] Cymene formation is interpreted as a Bronsted acid-catalyzed dehydration of the reactant to form II with a subsequent shift of the double bond of the isopropenyl group of II to the six-membered ring. Carvenone is probably formed from VI and VII.[19] Compound V was reported in the literature[11] to form by isomerization of 3-carene oxide with silica gel. Its formation is considered due to the very acidic H_2SO_4/SiO_2 catalyst which causes isomerization of the cyclopropane ring in compound IV.

In our previous paper,[20] it was concluded that strong acids on the catalyst surface cause preferential formation of carbonyl compounds. That aldehyde is formed in larger amount than ketone over SiO_2–Al_2O_3, Al_2O_3 A and SiO_2–TiO_2 is ascribed to the extremely high acid strength of these catalysts, as was explained previously.[16] As for the ketones, the more stable caranone (VII) rather than the less stable isocaranone (VI) was formed predominantly.

As discussed in a previous paper,[20] opening of the epoxide ring to form the allylic alcohol can be interpreted by an acid–base bifunctional mechanism, where an oxygen atom of the oxide is adsorbed on an acidic site of the catalyst surface, while a hydrogen atom of the methyl or methylene group is adsorbed on a basic site.

IX was formed predominantly over TiO_2–ZrO_2, while X was formed over Al_2O_3 B and C. TiO_2 produced the same amount of both. TiO_2–ZrO_2 is supposed to have acidic and basic properties which are different from those of the aluminas. It is of interest that Al_2O_3 A showed high selectivity for the formation of carbonyl compounds, while Al_2O_3 B and C yielded the allylic alcohols selectively. The reaction scheme over each catalyst is summarized in Scheme I.

Isomerization of 2-Carene Oxide. The products of the isomerization of 2-carene oxide were *p*-cymene (III), 1(7),2,8(9)-*p*-menthatriene (XI), α,*p*-dimethylstyrene (XII),

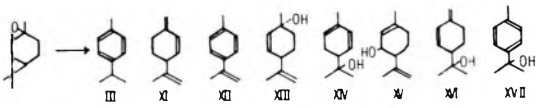


Table II. Isomerization of 2-Carene Oxide[f] at 80 °C for 10 min

Catalyst[a]	Catalyst amount, g	Conversion, %	Selectivity, % III	XI	XII	XIII	XIV	XV	XVI	XVII	Others
SiO_2–Al_2O_3	0.12	100	43	6	7		5				28
HCl/SiO_2	0.16	61	58		3	13	2			2	22
$NiSO_4$ (250 °C)[c]	0.35	51	21	4		24	5	4			32
Al_2O_3 A[b]	0.12	54	21			43	4	3	4		25
$FeSO_4$ (700 °C)	0.23	45	24	1		45	5				24
$FeSO_4$ (900 °C)[c]	0.21	4									
Al_2O_3 C	0.30	53	14	3		36	7	8			31
TiO_2–ZrO_2	0.19	77	11		2	75	4	2		3	3
TiO_2–ZrO_2[d]	0.25	20				100					
TiO_2–ZrO_2[b,e]	0.23	100	22		11	16		10		19	7
TiO_2 (500 °C)	0.19	55	21			49	3	2		4	21
TiO_2 (900 °C)[c]	0.32	4									
CaO[c]	0.10	2									

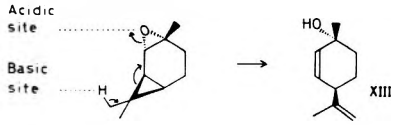
[a] Figures in parentheses show calcination temperatures. [b] With 0.5 mL of the epoxide in 2.5 mL of toluene. [c] 75 min. [d] 30 °C, 1 h. [e] 100 °C, 2 h. [f] Registry no.: 35071-29-5; XI, 65293-08-5; XII, 1195-32-0; XIII, 7212-40-0; XIV, 1686-20-0; *cis*-XV, 4017-76-9; *trans*-XV, 4017-77-0; XVI, 65293-09-6; XVII, 1197-01-9.

cis-2,8(9)-*p*-menthadien-1-ol (XIII), α-phellandren-8-ol (XIV), *cis*- and *trans*-1,8(9)-*p*-menthadien-3-ol (XV), α-phellandren-8-ol (XVI), *p*-cymen-8-ol (XVII), and unidentified materials.

Table II shows the catalytic activity and selectivity for the isomerization of 2-carene oxide at 80 °C in 10 min. The reactivity was exceedingly high in comparison with that of 3-carene oxide. However, since $FeSO_4$ and TiO_2 heat-treated at 900 °C or CaO, which has basic character,[21] were almost inactive, it appears that the reaction does not take place without a catalyst at 80 °C. The epoxide used was a mixture of 2- and 3-carene oxides (4:1), but the yields of the products formed from 3-carene oxide are excluded from the table. However, the conversion of 3-carene oxide was quite low except in the case of SiO_2–Al_2O_3, as is expected from the results in Table I.

All products resulted from opening of the cyclopropyl ring, in contrast with the observations on 3-carene oxide, though 2-carene oxide yields allylic alcohols corresponding to IX and X with retention of the cyclopropane ring on exposure to lithium diethylamide.[12] It is also remarkable that the cleavage of the C(3)–O bond is much more favorable for 3-carene oxide, while the C(2)–O bond is cleaved in 2-carene oxide.

Large amounts of III and XIII were produced. Cymene (III) is considered to be formed from XIII by acid-catalyzed dehydration through a stable tertiary carbonium ion. In accord with this, SiO_2–Al_2O_3 produced complete dehydration of XIII on its very strongly acidic sites,[17,18] as did the protonic acid, HCl/SiO_2. However, it is also possible that SiO_2–Al_2O_3 causes



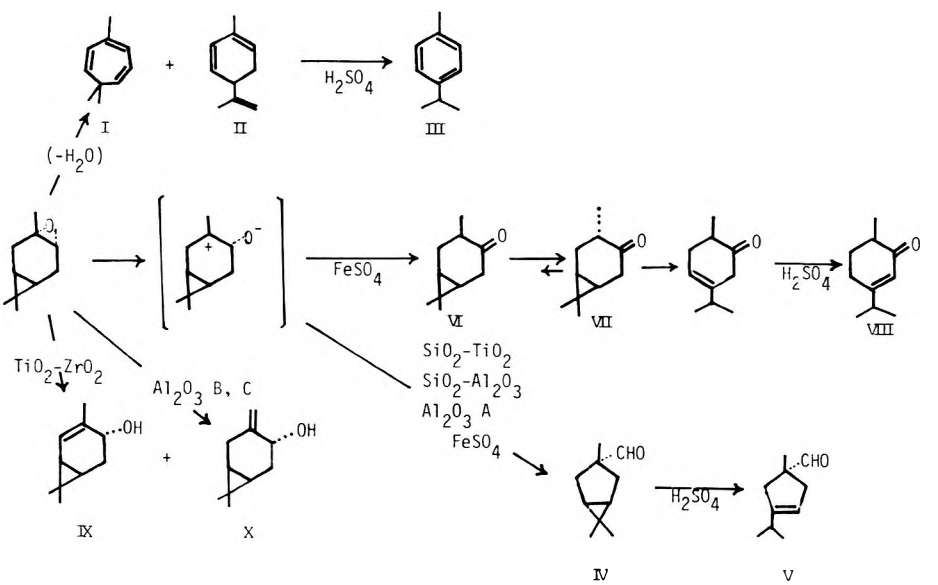
dehydration of the oxide to form cymene without forming XIII first.

The formation of XIII can be interpreted by taking into account the great stability of a cyclopropyl carbinyl cation.[22] Hence, cleavage of the β bond of oxygen, adsorbed on an acid site of the catalyst, is much more favorable, and is followed by opening of the cyclopropane ring.[23]

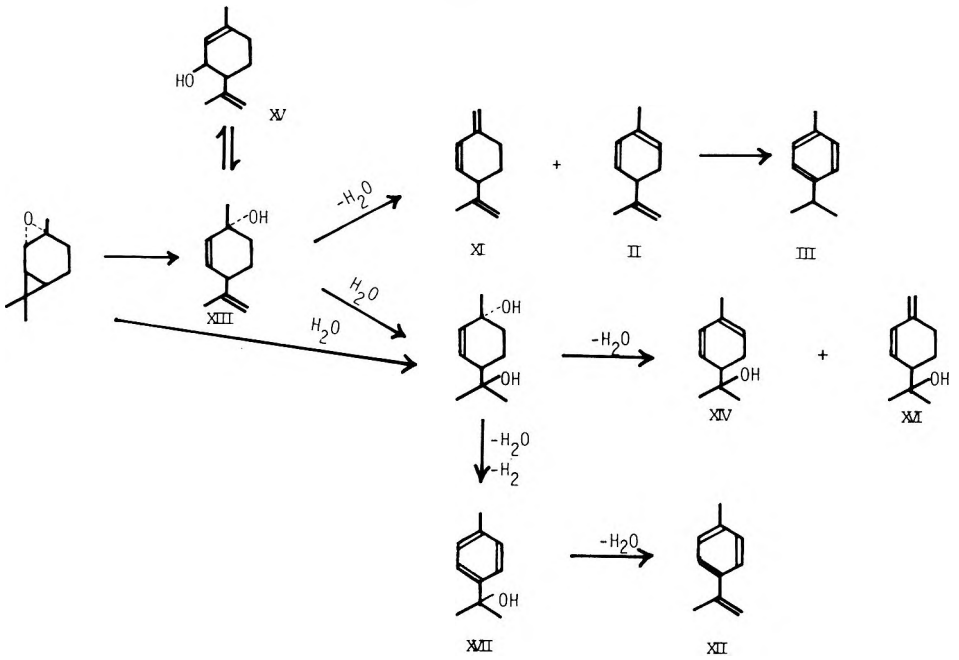
Abstraction of a hydrogen from C-9 by the basic site facilitates opening of the 3-ring by the push effect of the anion. This helps explain the high selectivity of TiO_2–ZrO_2 (75%), which is a remarkable catalyst for bifunctional catalytic action[16,20] for formation of XIII and gave 100% of XIII even at 30 °C.

The formation of allylic alcohols with a hydroxyl group in the 3 or 8 position of the cymene structure was observed. XV

Scheme I



Scheme II



consists of cis and trans forms and is certainly formed by isomerization of compound XIII. Compounds XIV and XVI were presumably formed by hydration of 2-carene oxide or XIII (H_2O being produced by cymene formation) and subsequent dehydration. XII and XVII are presumably formed via a dehydrogenation step on the basis of mechanistic considerations. A dehydrogenated product, carvone, was found in the isomerization of *d*-limonene oxide over TiO_2–ZrO_2 at 108 °C for 75 min.[15] This is similar to the present observations; that is, a considerable amount of XII and XVII was given by TiO_2–ZrO_2 under the severe conditions, at 100 °C for 2 h. Dehydrogenation is considered to take place on the basic sites of the TiO_2–ZrO_2 surface, but it is not clear of what stage dehydrogenation occurs. The reaction scheme for 2-carene epoxide is summarized in Scheme II.

Experimental Section

3-Carene oxide and 2-carene oxide (containing 20% 3-carene oxide) were supplied by the Organic Chemicals Group, SCM Corp., the latter material being purified to better than 96% by preparative gas–liquid chromatography (2-m column, 20% PEG). Toluene was purified by distillation over sodium metal.

Standard Reaction Procedure. The reaction was carried out at 80 °C in the presence of toluene as solvent. A mixture of 0.5 mL of the epoxide, 2.5 mL of toluene, and about 0.3 g of catalyst, ground to below 100 mesh, was stirred magnetically. In the case of 2-carene oxide, the mixture consisted of equal amounts of the reagents. At appropriate time intervals, a small amount of the sample was withdrawn with a 1-mL syringe, separated from catalyst by using a centrifuge, and analyzed by GLC (TCD detector) using a 3-m column of 20% polyethylene glycol 20M on Celite 545 SK (150 °C, He 1.0 kg/cm^2). Yields were based on epoxide and calculated by measurement of GLC peak areas (uncorrected).

Catalysts. SiO_2–Al_2O_3 [N361(L)(Al_2O_3; 15 wt %) from Nikki Chemical Co.] was calcined at 500 °C. SiO_2–TiO_2 (molar ratio 1:1) was prepared by coprecipitation of the mixed solution of ethyl orthosilicate and titanium tetrachloride with aqueous ammonia. The precipitate was aged over a water bath for 1 h, washed with distilled water until no chloride ion was detected, dried at 100 °C for 20 h, and calcined at 500 °C. H_2SO_4/SiO_2 was prepared as follows: 10 g of granular silica gel was immersed in 12 mL of 1 N H_2SO_4, evaporated, dried, and then calcined at 150 °C. HCl/SiO_2 was prepared by the same method. $FeSO_4$, $Fe_2(SO_4)_3$, and $NiSO_4$ were prepared by calcining their guaranteed hydrates. TiO_2 and TiO_2–ZrO_2 (molar ratio 1:1) were prepared by thermal decomposition, at 500 °C, of H_4TiO_4 and H_4TiO_4–$Zr(OH)_4$, respectively. These hydrogels were precipitated by heating a mixed aqueous solution of titanium tetrachloride, zirconium oxychloride, and excess urea on a boiling water bath, followed by washing thoroughly with distilled water until no chloride ions were detected in the filtrate and drying in air at 110 °C. Al_2O_3 A and B were Albes C and Albes FF, respectively, supplied from Showa Tansan Kaisha, Ltd., and Al_2O_3 C was KAT 6 of Nishio Chemical Co. All the aluminas were heat-treated at 500 °C before use. CaO was prepared by calcining its hydrates in air at 550 °C. All the catalysts were calcined in Pyrex glass tubes (quartz tubes for 900 °C) in air for 3 h and stored in sealed ampules until use.

Identification of Products. All reference materials for comparison of spectra were obtained from the Organic Chemicals Group, Division of SCM Corp., Jacksonville, Fla.

GLC component I (RRT = 0.37, the compound of RRT = 1 being the starting epoxide) was identified as 3,7,7-trimethyltropilidene.[24,25] An authentic sample was isolated from the reaction of 3-carene oxide with aluminum isopropoxide;[11,26] its spectral data were in agreement with the proposed structure.

Peaks IV and V (RRT = 0.81 and 1.15) had almost identical mass spectra, but there was one striking difference as can be seen by comparison of the mass spectra.

Catalyst	Peak	Mass spectra (8 most intense peaks) *m/e*
H_2SO_4/SiO_2	V	137, 81, 41, 152 (M^+), 109, 67, 43, 79
SiO_2–Al_2O_3	IV	109, 41, 81, 67, 43, 137, 39, 91

Compound IV had a base peak of 109, whereas compound V had a base peak of 137. 3-Carene oxide was reacted with 10% by weight of Davison (W. R. Grace Co.) silica–alumina catalyst at 60 °C, whereupon the temperature rose to 140 °C before the reaction mixture was cooled to room temperature. A pure compound having a retention time similar to that of IV was distilled from this reaction mixture (70 °C (10 mmHg); lit.[9] 70–72 °C (9 mmHg)). The IR, NMR, and mass spectra showed it to be 3,6,6-trimethylbicyclo[3.1.0]hexane-3-carboxaldehyde[9] [IR 1725 cm^{-1} aldehyde, 1035, 835 cm^{-1} cyclopropane; NMR δ 9.38 (s, 1, CHO), 1.02 (s, 11, $-CH_3$ and methine bridgehead protons), 2.4–2.0 and 1.5–1.07 ppm (m, 4, $>CH_2$); MS 109, 41, 81, 67, 137, 43, 123, 152 (M^+)]. Compound V is considered to be 1-methyl-1-formyl-3-isopropyl-3-cyclopentene. The base peak of 137 is explained by ready loss of one of two allylic methyl groups.

Compounds VI and VII (RRT = 1.51 and 1.68) were identified as 4-isocaranone and 4-caranone, respectively. Authentic samples were obtained as a mixture by reaction of 3-carene oxide with silica–alumina catalyst. The mixture showed a ketone band at 1704 cm^{-1} and a parent ion peak at *m/e* 152 in the IR and mass spectra, respectively. The two compounds were purified by preparative GLC; the NMR spectrum of the higher boiling isomer showed methyl signals at δ 0.91(s), 1.04(s), and 1.16 ppm(s); lit.[11] for isocaranone δ 0.86(s), 1.05(s), and 0.92(d) and 1.2 ppm(d). There was good NMR spectral agreement between the higher boiling compound and caranone (VII), but the purified lower boiling compound did not produce a good NMR

spectrum consistent with the structure of isocaranone; MS VI, 81, 67, 41, 69, 109, 108, 82; VII, 81, 67, 41, 82, 152, 55, 95

Compounds IX and X (RRT = 2.50 and 2.97) were identified as *trans*-2-caren-4-ol and *trans*-3(10)-caren-4-ol, respectively. An authentic sample of X was obtained by isomerization of 3-carene oxide over aluminum isopropoxide (AIP).[8]

Peak XIII (RRT = 2.13) was identified as *cis*-2,8,(9)-*p*-menthadien-1-ol by comparison of retention time and mass spectrum with those of an authentic sample prepared by isomerization of 2-carene oxide with metatitanic acid[13]: MS 134, 119, 91, 109, 79, 43, 41, 152 (M^+); reference 91, 119, 134, 41, 79, 77, 43, 152 (M^+).

Peaks XIV and XVI (RRT = 2.58 and 3.13) had nearly identical mass spectra. The base peak in the mass spectrum at *m/e* 59 (Me_2COH^+) suggested loss of the dimethylcarbinol ion. A fragment of *m/e* 94 ($C_7H_{10}^+$) together with the 59 fragment suggested structures of α- and β-phellandren-8-ol for the pair of isomers, XIV, and XVI, respectively. The IR and NMR spectra of the isolated compound XIV were consistent with those of an authentic sample [IR 3400, 1170, 1130 cm^{-1} tertiary alcohol; NMR δ 1.18 (s, 6, $>C(CH_3)_2$), 1.70 (s, 3, vinylic CH_3), 2.1–2.3 (m, 3, $>CH_2$ and $\geq CH$), 2.56 (s, 1, OH), 5.3–5.6 (broad, 1) and 5.79 ppm (d, 2) for vinylic protons]. The structure of XVI was only inferred because its mass spectrum was almost identical with that of compound XIV [MS XIV, 59, 79, 94, 91, 93, 119, 77, 134 ($M^+ - 18$); XVI, 59, 79, 94, 91, 43, 77, 119, 134 ($M^+ - 18$)].

GLC peaks II, III, VIII, XI, XII, XV, and XVII (RRT = 0.42, 0.55, 2.77, 0.46, 0.96, 3.03, and 4.13) were identified as 1,5,8(9)-*p*-menthatriene, *p*-cymene, carvenone, 1(7),2,8(9)-*p*-menthatriene, α,*p*-dimethylstyrene, a mixture of *cis*- and *trans*-1,8(9)-*p*-menthadien-3-ol and *p*-cymen-8-ol, respectively, by comparison of GLC retention times and mass spectra with reference materials.

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Intramolecular 1,3-Dipolar Cycloaddition Reactions of Alkenyl-Substituted Nitrile Imines[1]

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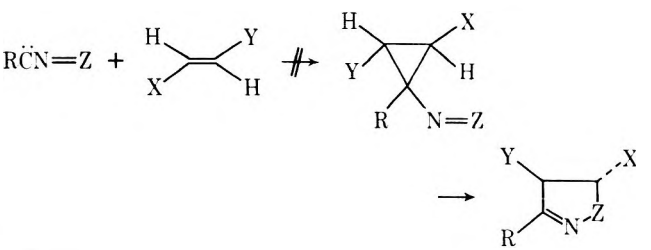
A series of nitrile imines bearing alkenyl substituents on the nitrogen atom of the 1,3 dipole were generated in situ by the photolysis of 2-alkenyl-5-phenyl-substituted tetrazoles or by the base treatment of 1-chlorohydrazones. Intramolecular 1,3-dipolar cycloaddition leading to substituted pyrazoles was the exclusive reaction observed. When the nitrile imine was generated in the presence of an active dipolarophile, bimolecular 1,3-dipolar cycloaddition occurred. Under these conditions, the intramolecular cycloaddition reaction is entirely suppressed. The mode of internal cycloaddition of the allyl-substituted nitrile imine is very different from that previously encountered in the closely related nitrile ylide system. With that system, intramolecular 1,1 cycloaddition was the predominant mode of reaction. Insight into the differences in chemical behavior of the two nitrilium betaines was obtained from molecular orbital calculations. These calculations show that the introduction of a nitrogen atom in the 1,3 dipole results in a significant flattening of the molecule. As the dipole becomes less bent it is less likely to undergo the 1,1-cycloaddition reaction.

The thermally induced addition of 1,3 dipoles to multiple bonds is an extremely versatile and important reaction.[2-4] Numerous possibilities for variation are available by changing the structure of both the dipolarophile and dipole. Some of the more interesting members of the 1,3-dipole family are the nitrilium betaines.[2] This class of 1,3 dipoles always contains nitrogen as the middle atom since only this element can supply an unshared electron pair while in the trivalent neutral state. Among the possible geometric forms of a nitrilium betaine, a carbene structure can be envisaged which makes conceivable a 1,1 cycloaddition of this 1,3 dipole. The possibility that

$$[\overset{-}{R}C{=}\overset{+}{N}{=}Z \leftrightarrow RC{\equiv}\overset{+}{N}\overset{-}{Z} \leftrightarrow R\overset{+}{C}{=}N\overset{-}{Z} \leftrightarrow RCN{=}Z]$$
$$Z = C, N, O$$

the 1,3-dipolar cycloaddition reaction of a nitrilium betaine with a dipolarophile actually proceeds via a 1,1 cycloaddition followed by ring expansion has been discounted by Huisgen and co-workers.[5] These workers were able to show that three-membered rings are not primary products in the cy-



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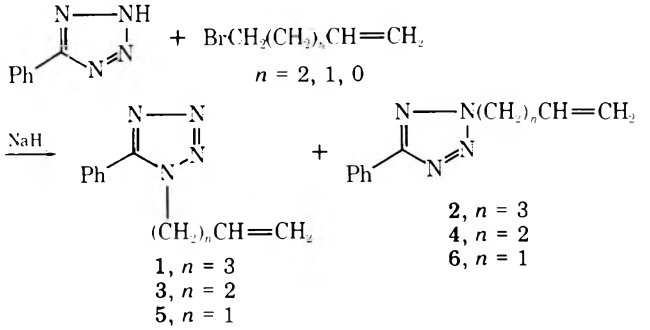
cloaddition reaction leading to five-membered heterocycles with nitrilium betaines.

Recent results from our laboratory have shown, however, that there are two pathways by which nitrile ylides can react with multiple π bonds.[6-9] The most frequently encountered path involves a "parallel-plane approach of addends" and can be considered to be an orbital symmetry-allowed [4 + 2] concerted process.[2] The other path, designated as 1,1 cycloaddition, operates only in certain intramolecular cases. It occurs when the p orbitals of the dipolarophile have been deliberately constrained to attack perpendicular to the nitrile ylide plane. Since our original report of this novel phenomenon appeared, a related intramolecular carbene type of 1,1 cycloaddition of a nitrilimine has been reported by Garanti and co-workers.[10] An analogous 1,1 cycloaddition of benzonitrile oxide has also been proposed to occur in the cycloaddition of benzonitrile oxide with several 4-arylideneisoxazol-5-ones.[11] As a further consequence of our interest in this area, we thought it worthwhile to determine whether additional examples of carbenoid activity of nitrilium betaines could be uncovered. In this paper we describe some of our efforts involving the generation and chemistry of a number of nitrilimines containing unsaturation several atoms away from the dipole center.

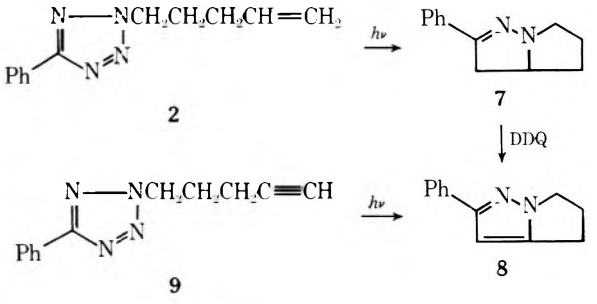
Results and Discussion

As our first model we chose to investigate the photochemistry of a series of 2-alkenyl-5-phenyl-substituted tetrazoles. The photolysis[12] and/or thermolysis[13] of 2,5-disubstituted tetrazoles represents a convenient method for the in situ generation of nitrilimines.[14] The same products are generally obtained from cycloaddition reactions with the products of tetrazole photolysis as from nitrilimines generated by the standard procedure of treating hydrazonyl chlorides with base.[15,16] The synthesis of these 2-alkenyl-5-phenyl-substituted tetrazoles was straightforward and involved the reaction of 5-phenyltetrazole with an appropriately substituted bromoalkene in the presence of base. Under these conditions a mixture of 1- and 2-alkenyl-substituted tetrazoles (ratio ca. 1:20) was obtained in good yield. Much work on the alkylation of tetrazoles has been carried out,[17-19] and in general it appears that electron-donating substituents at the 5 position favor alkylation at the N_1 position of tetrazole anions, while electron-withdrawing 5 substituents favor the 2 position.[20] The predominant formation of the 2-alkenyl-substituted tetrazoles (i.e., **2, 4,** and **6**) is perfectly consistent with the reported trends of tetrazole anion alkylation.[14]



The structural assignments were made on the basis of UV and NMR spectroscopy. Evidence has been obtained demonstrating that in a given pair of structural isomers the 2,5-disubstituted structure exhibits an absorption maximum at longer wavelengths than the 1,5-disubstituted isomer.[21] As expected, the UV spectra of tetrazoles **2, 4,** and **6** exhibited a maximum at 239 nm (ϵ ca. 17 000), while the maximum for the corresponding 1,5-disubstituted tetrazoles (i.e., **1, 3,** and **5**) was shifted to slightly shorter wavelength [232 nm (ϵ 9000)] and possessed a smaller extinction coefficient. Structural assignments were further strengthened by NMR measurements. Previous work in the literature has established that the phenyl protons of 5-phenyl-1-substituted tetrazoles appear as a singlet, while with the corresponding 2-substituted tetrazoles these protons appear as a multiplet with the ortho protons approximately 0.7 Hz downfield from the meta/para protons.[22] This was also the case with the above 1- and 2-alkenyl-substituted tetrazoles. The shielding of the meta/para protons with tetrazoles **2, 4,** and **6** can be attributed to an electron-donating resonance interaction between the two rings which is absent or greatly diminished owing to steric loss of coplanarity in the 1-alkenyl isomer. Similar effects have been observed for a series of related aryl azoles.[23]

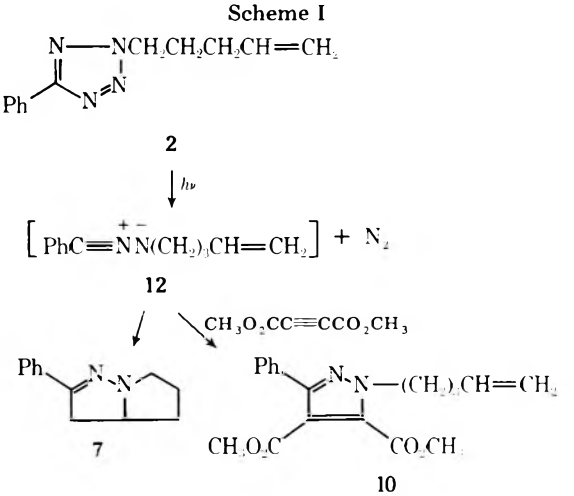
With the structural assignments of these 2,5-disubstituted tetrazoles firmly established, a detailed study of their photochemical behavior was undertaken. Irradiation of 2-(4-pentenyl)-5-phenyltetrazole (**2**) in benzene using a 450-W Hanovia immersion apparatus equipped with a Corex filter sleeve led to the complete consumption of reactant in 60 min. The only product obtained was 3a,4,5,6-tetrahydro-2-phenyl-3*H*-pyrrolo[1,2-*b*]pyrazole (**7**): NMR ($CDCl_3$, 60 MHz)



τ 8.04–8.90 (m, 4 H), 5.94–7.10 (m, 5 H), 2.70–2.87 (m, 3 H), 2.37–2.60 (m, 2 H). This structure was further supported by DDQ oxidation to 5,6-dihydro-2-phenyl-4*H*-pyrrolo[1,2-*b*]-pyrazole (**8**): NMR ($CDCl_3$, 60 MHz) τ 7.0–7.7 (m, 4 H), 5.87 (t, 2 H, J = 7.0 Hz), 3.75 (s, 1 H), 2.57–2.73 (m, 3 H), 2.17–2.37 (m, 2 H). Structure **8** was verified by an independent synthesis which involved the photolysis of 2-(4-pentynyl)-5-phenyltetrazole (**9**).

The formation of structure **7** (and/or **8**) could be completely suppressed when the irradiation of **2** (and/or **9**) was carried out in the presence of excess dimethyl acetylenedicarboxylate. The only product formed under these conditions was the expected 1,3-dipolar cycloadduct **10** (and/or **11**) (Scheme I). Similar results were obtained when methyl acrylate was used as the trapping reagent with tetrazole **9**. Clearly, nitrilimine **12** is an intermediate in these reactions, and **7** (or **8**) arises by

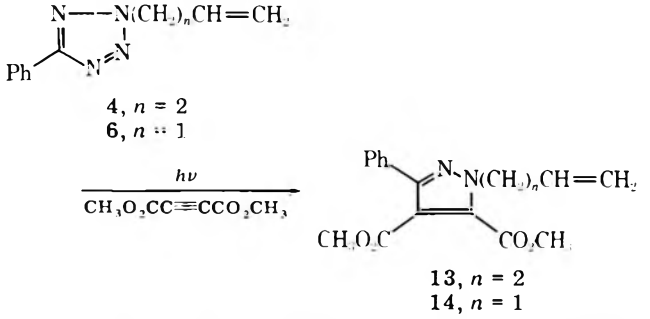
Scheme I



intramolecular 1,3-dipolar cycloaddition of the transient nitrilimine with the neighboring double bond (Scheme I).

A number of reports in the literature by Garanti and coworkers[24-26] have shown that nitrilimines undergo smooth intramolecular 1,3-dipolar cycloadditions.[27] In order for the intramolecular 1,3-dipolar cycloaddition reaction to proceed, two criteria must be met. First, the distance between the two reacting centers should be sufficiently short so that effective three-center overlap of the nitrilimine with the dipolarophile can occur. Secondly, the atoms of the dipole and dipolarophile should be arranged in such a way as to allow attainment of the "two-plane orientation approach."[2] These criteria are readily satisfied with the nitrilimine (i.e., **12**) generated from the irradiation of tetrazole **2**. The intramolecular cyclization reaction of nitrilimine **12** is also of interest in that it involves cycloaddition with an unactivated olefin, a substrate which is generally unreactive toward nitrilimines.[28] The facility with which the above cycloaddition proceeds suggests that an extremely favorable entropy term, relative to the intermolecular reaction, offsets the unfavorable electronic factor.

Whereas tetrazole **2** was smoothly converted to pyrazole **7** on irradiation, photolysis of the homologous tetrazoles **4** and **6** resulted in the formation of polymeric material. When the irradiation of these compounds was carried out in the presence of dimethyl acetylenedicarboxylate, however, the expected 1,3-dipolar cycloadducts **13** and **14** were obtained in good

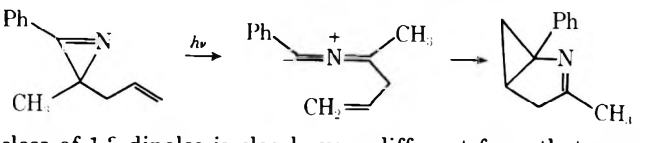


4, $n = 2$
6, $n = 1$

13, $n = 2$
14, $n = 1$

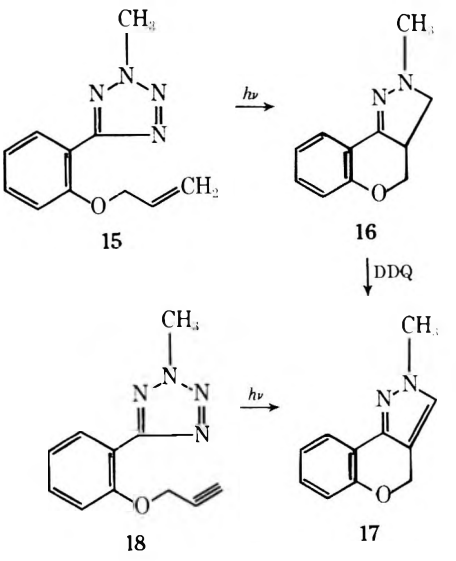
yield. All attempts to detect an intramolecular cycloadduct (1,3 or 1,1) from the nitrilimines derived from these tetrazoles failed. The isolation of cycloadducts **13** and **14** indicates that the expected nitrilimines are formed but that intramolecular cycloaddition does not occur. With the nitrilimines derived from tetrazole **4** or **6**, the methylene chain is not of sufficient length to allow the dipole and dipolarophile to approach each other in parallel planes. Consequently, intramolecular 1,3-dipolar cycloaddition does not occur. The situation here is very different from that observed with the 2-(4-pentenyl)tetrazole **2**. With tetrazole **2**, the transition state for cycloaddition allows easy attainment of the "parallel-plane approach," and consequently intramolecular 1,3-dipolar cycloaddition of the initially generated nitrilimine readily occurs.

While this analysis satisfactorily explains the absence of an intramolecular 1,3-dipolar cycloaddition with tetrazole **6**, it does not account for the absence of a 1,1 cycloadduct with the 2-allyl-substituted tetrazole.[29] Allyl-substituted nitrile ylides are known to undergo smooth 1,1 cycloaddition to give azabicyclo[3.1.0]hex-2-enes.[6-8] The situation with the nitrilimine



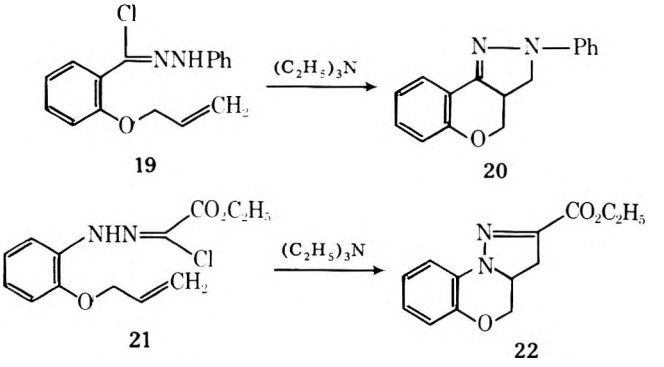
class of 1,3 dipoles is clearly very different from that previously encountered with the closely related nitrile ylide system. The nature of the Z atom of the nitrilium betaine seems to play an important role in controlling the intramolecular 1,1-cycloaddition reaction.

This contention was further supported by a study of the photolysis of 2-methyl-5-(o-allyloxyphenyl)tetrazole (**15**). Irradiation of tetrazole **15** in benzene afforded 2,3,3a,4-tetrahydro-2-methyl[*l*]benzopyrano[4,3-c]pyrazole (**16**) as the exclusive cycloadduct in 88% yield: NMR ($CDCl_3$, 60 MHz) τ 7.37–7.80 (m, 1 H), 7.12 (s, 3 H), 6.0–6.75 (m, 3 H), 5.27–5.57 (m, 1 H), 2.64–3.30 (m, 3 H), 2.20–2.44 (m, 1 H). The DDQ oxidation of **16** led to the corresponding dihydrobenzopyrano[4,3-*b*]pyrazole **17**, thus providing chemical support to the assigned structure. Compound **17** could also be independently prepared from the irradiation of (o-propargyloxyphenyl)tetrazole **18**.



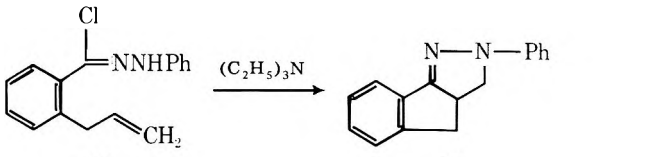
It should be noted that o-allyloxyphenyl-substituted nitrile ylides have previously been found to undergo both 1,1- and 1,3-cycloaddition reactions.[8] However, all attempts to detect a 1,1 cycloadduct from the irradiation of tetrazole **15** failed. The exclusive formation of a 1,3-dipolar cycloadduct from the nitrilimine derived from tetrazole **15** provides further evidence that the type of reaction entered into by these nitrilium betaines is strongly dependent on the nature of the Z atom of the 1,3 dipole.

Recent results in the literature have shown that significant differences in the reactivity of a 1,3 dipole can occur when it is generated in the ground state or in an excited state.[30] In order to determine whether the mode of intramolecular cycloaddition of these nitrilimines is related to the manner in which they are generated, we decided to investigate the base-induced chemistry of hydrazonyl chlorides **19** and **21**. Reaction of triethylamine with a benzene solution of **19** at 80 °C produces triethylammonium chloride and 2,3,3a,4-tetrahydro-2-phenyl[*l*]benzopyrano[4,3-c]pyrazole (**20**): mp 99–100 °C; NMR ($CDCl_3$, 60 MHz) τ 5.76–7.02 (m, 4 H), 5.40 (dd, 1 H, J = 10.0, 5.0 Hz), 2.6–3.3 (m, 8 H), 2.20 (m, 1 H)). A similar reaction of hydrazonyl chloride **21** with triethylamine afforded a 82% yield of 2-carboethoxy-3,3a-dihydro-4*H*-pyrazolo[5,1-c][1,4]benzoxazine (**22**) as the only detectable cycloadduct.[31]

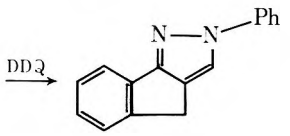


The close similarity in the behavior of all of these nitrilimines strongly suggests that the mode of internal cycloaddition is independent of the precursor used to generate the dipole.

We also studied the intramolecular dipolar cycloaddition reaction of the nitrilimine generated from the base treatment of 1-(*o*-allylphenyl)-*N*-(phenylhydrazidoyl) chloride (**23**). The

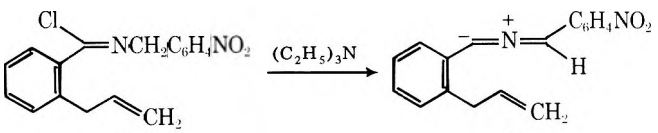


23 **24**

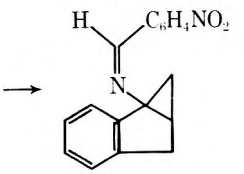


25

only product obtained in this reaction was 2,3,3a,4-tetrahydro-2-phenylindeno[1,2-c]pyrazole (**24**). This product was identified on the basis of its characteristic 270-MHz NMR spectrum ($CDCl_3$) which showed a set of doublet of doublets at τ 7.29 (1 H, J = 15.4, 7.3 Hz), 6.92 (1 H, J = 14.3, 9.6 Hz), and 6.74 (1 H, J = 15.4, 8.8 Hz), a multiplet centered at τ 6.39 (1 H), triplets at τ 5.71 (1 H, J = 9.6 Hz) and 3.24 (1 H, J = 6.0 Hz), and a multiplet for the aromatic protons at τ 2.30–3.00 (8 H). This structure was supported by its ready oxidation with DDQ to pyrazole **25**. The intramolecular cyclization of **23** is a particularly interesting case in that it proceeds exclusively in the 1,3 sense. The closely related nitrile ylide **27**,



26 **27**



28

generated from the base treatment of imidoyl chloride **26**, had previously been found to undergo exclusive 1,1 cycloaddition.[7]

A major aspect of interest requiring discussion involves the substantially different chemical behavior exhibited by these unsaturated nitrilium betaines toward intramolecular dipolar cycloaddition. In the present investigation, nitrilimines containing unsaturation four bonds away from the dipole center undergo cycloaddition exclusively in the 1,3 sense. The structurally related nitrile ylide systems, on the other hand, undergo both 1,1 and 1,3 cycloaddition. Since the geometry of approach of the dipole and dipolarophile centers with both systems is very similar, steric factors can not account for the divergent behavior observed. Insight into the difference in chemical behavior of the two nitrilium betaines can be gleaned from molecular orbital calculations. Recent ab initio LCAO–MO–SCF calculations by Houk and co-workers[32,33] have shown that nitrile ylides exist preferentially in the bent form with an HCN angle of 114–116°. These findings indicate that the most stable form of a nitrile ylide resembles a bent allenyl anion rather than a linear propargyl anion. The HOMO and second LUMO of the bent ylide bear a strong resemblance to the HOMO and LUMO of a singlet carbene. Carbenes are known to react readily with double bonds,[34] thereby providing good precedent for the formation of the 1,1 cycloadduct. This type of reaction will only occur when the alkene has been deliberately constrained to attack perpendicular to the CNC plane of the bent nitrile ylide.

Houk's group has also carried out optimizations on the geometry of the parent nitrilimine ($HC{\equiv}N^+NH^-$) and has found that the dipole is quite flexible. The STO-3G minimum suggests bent geometry with the bent form being favored by 2.2 kcal/mol over the linear form.[32] However, at the 4–31G level, the linear species was favored over the bent form by 3.9 kcal/mol [32,33] In contrast, the bent nitrile ylide has been calculated to be 11.1 kcal/mol (4–31G) more stable than the linear form. Thus, replacement of the C_3 carbon atom of the nitrile ylide with a nitrogen atom results in a significant straightening of the molecule. More recent calculations show that the introduction of a phenyl group at C_1 further straightens the dipole.[35] Clearly, the geometric features of the nitrile ylide and nitrilimine are significantly different. The increasing stability of the linear geometry relative to the bent form, as the electronegativity of the Z terminus increases ($RC{\equiv}N^+Z^-$), can be attributed to the fact that the linear structure places more negative charge on the Z atom and possesses less N–Z double-bond character. The valence bond structure, $RC{\equiv}N^+NR^-$, is a good representation of the electronic structure of the nitrilimine, whereas the ylide can best be described by the $R\bar{C}N{=}CR_2$ (carbene-like) designation. As the dipole becomes less bent it is less likely to undergo the 1,1-cycloaddition reaction. We believe that this explanation satisfactorily accounts for the propensity of these unsaturated nitrilimines to undergo intramolecular dipolar cycloaddition in the 1,3 sense.

We are continuing to explore the scope and mechanistic details of intramolecular nitrilimine cycloadditions and look forward to determining whether it will be possible to induce 1,1 cycloadditions of this dipole with related systems.

Experimental Section[36]

Preparation of 2-(4-Pentenyl)-5-phenyltetrazole (2). A 1.46-g sample of 5-phenyltetrazole[37] in 10 mL of dimethylformamide was added dropwise to an ice-cooled suspension containing 480 mg of sodium hydride in 3 mL of dimethylformamide. After the evolution of gas had ceased, 1.49 g of 5-bromo-1-pentene in 5 mL of dimethylformamide was added and the mixture was allowed to stir at 25 °C for 12 h. At the end of this time the mixture was poured onto 50 mL of ice water and extracted with benzene. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The resulting yellow oil was subjected to dry column chromatography using methylene chloride as the eluent. The first component eluted from the column contained 1.40 g (65%) of a colorless oil, bp 180–181 °C (0.1 mm), whose structure was assigned as 2-(4-pentenyl)-5-phenyltetrazole (**2**): IR (neat) 6.05, 6.55, 6.80, 6.90, 7.35, 8.32, 9.25, 9.50, 9.70, 10.85, 12.60, 13.65, 14.40 μm; UV (95% ethanol) 239 nm (ϵ 17 100); NMR ($CDCl_3$, 60 MHz) τ 7.73–7.93 (m, 4 H), 4.8–5.5 (m, 4 H), 4.0–4.6 (m, 1 H), 2.4–2.65 (m, 3 H), 1.80–2.0 (m, 2 H); MS *m/e* 214 (M^+), 186, 185, 158, 131, 129, 115, 77.

Anal. Calcd for $C_{12}H_{14}N_4$: C, 67.26; H, 6.59; N, 26.15. Found: C, 67.21; H, 6.66; N, 26.04.

The second component eluted from the column contained 70 mg (3%) of 1-(4-pentenyl)-5-phenyltetrazole (**1**) as a colorless oil: bp 165 °C (0.05 mm); IR (neat) 6.10, 6.55, 6.85, 7.15, 8.98, 9.25, 10.05, 10.85, 12.80, 13.60, 14.35 μm; UV (95% ethanol) 231 nm (ϵ 8950); NMR ($CDCl_3$, 60 MHz) τ 7.8–8.0 (m, 4 H), 4.8–5.65 (m, 4 H), 4.0–4.7 (m, 1 H), 2.37 (s, 5 H); MS *m/e* 214 (M^+), 118, 104, 83, 77, 68 (base).

Anal. Calcd for $C_{12}H_{14}N_4$: C, 67.26; H, 6.59; N, 26.15. Found: C, 67.43; H, 6.54; N, 26.32.

Irradiation of 2-(4-Pentenyl)-5-phenyltetrazole (2). A solution containing 214 mg of tetrazole **2** in 100 mL of benzene was irradiated through a Corex filter sleeve for 1 h. Removal of the solvent under reduced pressure left a pale yellow oil which was purified by thick-layer chromatography using a 3:1 methylene chloride/ethyl acetate mixture as the eluent. The major component (83 mg, 45%) was a clear oil, bp 135 °C (0.08 mm), and was identified as 3a,4,5,6-tetrahydro-2-phenyl-3*H*-pyrrolo[1,2-*b*]pyrazole (**7**) on the basis of the following

data: IR (neat) 6.28, 6.68, 6.90, 7.40, 8.45, 8.96, 9.15, 9.54, 10.25, 10.88, 13.10, 14.40 μm; UV (95% ethanol) 285 nm (ε 7600), 219 (6300); NMR ($CDCl_3$, 60 MHz) τ 8.04–8.90 (m, 4 H), 5.94–7.10 (m, 5 H), 2.70–2.87 (m, 3 H), 2.37–2.60 (m, 2 H); MS *m/e* 186 (M^+), 185, 131, 77.

Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.05. Found: C, 77.05; H, 7.71; N, 14.78.

The nitrilimine derived from the photolysis of tetrazole **2** could be trapped with dimethyl acetylenedicarboxylate. A solution containing 212 mg of tetrazole **2** and 1.42 g of dimethyl acetylenedicarboxylate in 120 mL of benzene was irradiated through a Corex filter sleeve for 8 h. The solvent was removed under reduced pressure, and the residual oil was purified by thick-layer chromatography using methylene chloride as the eluent. The major component isolated was a yellow oil which was distilled at 165 °C (0.04 mm) to give 1-(4-pentenyl)-3-phenyl-4,5-dicarbomethoxypyrazole (**10**) in 77% yield: IR (neat) 5.79, 6.58, 6.91, 8.00, 8.65, 9.10, 9.45, 10.80, 12.10, 12.55, 12.90, 14.30 μm; NMR ($CDCl_3$, 60 MHz) τ 7.86–8.20 (m, 4 H), 6.22 (s, 3 H), 6.13 (s, 3 H), 5.44–5.77 (m, 2 H), 4.84–5.20 (m, 2 H), 3.94–4.57 (m, 1 H), 2.30–2.84 (m, 5 H); UV (95% ethanol) 232 nm (ε 21 200); MS *m/e* 328 (M^+), 327 (base), 274, 273, 269, 129, 113, 77.

Preparation of 2-(4-Pentynyl)-5-phenyltetrazole (9). A 1.46-g sample of 5-phenyltetrazole in 10 mL of dimethylformamide was added dropwise to an ice-cooled suspension containing 480 mg of sodium hydride in 3 mL of dimethylformamide. After the evolution of gas had ceased, 1.03 g of 5-chloro-1-pentyne in 5 mL of dimethylformamide was added and the mixture was stirred at 80 °C for 3 h. At the end of this time the mixture was poured onto 50 mL of ice water and extracted with benzene. The benzene extracts were dried over magnesium sulfate and concentrated under reduced pressure. The resulting yellow oil was subjected to dry column chromatography using methylene chloride as the eluent. The first component eluted from the column contained 1.2 g (57%) of a colorless oil, bp 190 °C (0.5 mm), whose structure was assigned as 2-(4-pentynyl)-5-phenyltetrazole (**9**): IR (neat) 4.65, 6.50, 6.75, 6.85, 7.15 μm; UV (95% ethanol) 239 nm (ε 16 500); NMR ($CDCl_3$, 60 MHz) τ 7.50–7.98 (m, 5 H), 5.0–5.36 (m, 2 H), 2.50–2.64 (m, 3 H), 1.84–2.00 (m, 2 H); MS *m/e* 212 (M^+), 184, 183, 131, 128, 104 (base), 77.

Anal. Calcd for $C_{12}H_{12}N_4$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.68; H, 5.72; N, 26.53.

The second component isolated from the column contained 62 mg (3%) of 1-(4-pentynyl)-5-phenyltetrazole: IR (KBr) 4.50, 6.80, 6.95, 7.05, 7.20 μm; NMR ($CDCl_3$) τ 7.74–8.10 (m, 5 H), 5.18–5.42 (m, 2 H), 2.47 (broad s, 5 H); MS *m/e* 212 (M^+), 191, 189, 117, 105, 104, 103, 91, 78, 75 (base); UV (95% ethanol) 232 nm (ε 9000)

Anal. Calcd for $C_{12}H_{12}N_4$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.84; H, 5.82; N, 26.28.

Irradiation of 2-(4-Pentynyl)-5-phenyltetrazole (9). A solution containing 212 mg of tetrazole **9** in 120 mL of benzene was irradiated with a 450-W medium-pressure lamp through a Corex filter sleeve for 2.5 h. Removal of the solvent under reduced pressure left a yellow oil which was purified by thick-layer chromatography using methylene chloride as the eluent. The major component isolated (90 mg, 49%) was a colorless solid, mp 80–81 °C, whose structure was assigned as 5,6-dihydro-2-phenyl-4*H*-pyrrolo[1,2-*b*]pyrazole (**8**) on the basis of the following data: IR (KBr) 6.20, 6.45, 6.60, 6.85, 7.00, 7.20, 7.50, 7.60, 9.18, 9.60, 10.25, 12.45, 13.05, 14.55 μm; UV (95% ethanol) 254 nm (ε 18 200); NMR ($CDCl_3$, 60 MHz) τ 7.0–7.7 (m, 4 H), 5.87 (t, 2 H, *J* = 7.0 Hz), 3.75 (s, 1 H), 2.57–2.73 (m, 3 H), 2.17–2.37 (m, 2 H); MS *m/e* 184 (M^+ and base), 156, 124, 102, 95, 77.

Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.21; H, 6.50; N, 14.99.

The structure of this material was verified by the DDQ oxidation of pyrazole **7**. A mixture of 80 mg of **7** and 100 mg of DDQ in 5 mL of benzene was allowed to reflux for 24 h. Removal of the solvent under reduced pressure left a dark red residue which was subjected to thick-layer chromatography to give **8** in 85% yield. The spectroscopic properties of **8** prepared from the oxidation of **7** were identical with those obtained from the iradiation of tetrazole **9**.

The initially produced nitrilimine could be trapped by carrying out the irradiation of **9** in the presence of methyl acrylate or dimethyl acetylenedicarboxylate. A solution containing 212 mg of tetrazole **9** and 861 mg of methyl acrylate in 120 mL of benzene was irradiated through a Corex filter sleeve for 6 h. The solvent was then removed under reduced pressure, and the residual oil was purified by thick-layer chromatography using a 10:1 pentane/ethyl acetate mixture as the eluent. The major component was a colorless oil (190 mg, 68%), bp 180 °C (0.04 mm), whose structure was assigned as 1-(4-pentynyl)-3-phenyl-5-carbomethoxypyrazole on the basis of its spectral data: IR (KBr) 5.80, 6.50, 6.65, 6.80, 7.15, 7.95, 9.05, 10.40, 12.10, 13.05, 14.40 μm; UV (95% ethanol) 234 nm (ε 25 700); NMR ($CDCl_3$, 60 MHz) τ 7.80–8.16 (m, 5 H), 6.16 (s, 3 H), 5.25–5.46 (m, 2 H), 2.95 (s, 1 H), 2.45–2.85 (m, 3 H), 2.08–2.30 (m, 2 H); MS *m/e* 268 (M^+), 267 (base), 215, 183, 104.

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.76; H, 6.10; N, 10.41.

A similar trapping experiment with dimethyl acetylenedicarboxylate gave a 58% yield of 1-(4-pentynyl)-3-phenyl-4,5-dicarbomethoxypyrazole (**11**) as a crystalline solid: mp 82–83 °C; IR (KBr) 5.73, 6.55, 6.90, 7.25, 8.00, 8.70, 9.05, 12.15, 13.70, 14.15 μm; UV (95% ethanol) 232 nm (ε 22 700); NMR ($CDCl_3$, 60 MHz) τ 7.70–8.04 (m, 5 H), 6.18 (s, 3 H), 6.08 (s, 3 H), 5.46 (t, 2 H, *J* = 7.0 Hz), 2.20–2.70 (m, 5 H); MS *m/e* 326 (M^+), 325 (base), 273, 77.

Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.00; H, 5.52; N, 8.50.

Preparation and Irradiation of 2-(3-Butenyl)-5-phenyltetrazole (4). A 1.46-g sample of 5-phenyltetrazole in 10 mL of dimethylformamide was added dropwise to an ice-cooled suspension containing 480 mg of sodium hydride in 3 mL of dimethylformamide. After the evolution of gas had ceased, 1.35 g of 4-bromo-1-butene in 5 mL of dimethylformamide was added and the mixture was stirred at 25 °C for 12 h. At the end of this time the mixture was poured onto 50 mL of ice water and extracted with benzene. The benzene extracts were dried over magnesium sulfate, and the solvent was removed under reduced pressure to give an orange residue. The residue was subjected to dry column chromatography using methylene chloride as the eluent. The first component isolated from the column contained 1.17 g (59%) of a colorless oil, bp 165 °C (0.15 mm), whose structure was assigned as 2-(3-butenyl)-5-phenyltetrazole (**4**) on the basis of the following data: IR (neat) 6.05, 6.55, 6.85, 6.95, 7.30, 9.25, 9.50, 9.65, 9.95, 10.70, 12.60, 13.60, 14.40 μm; UV (95% ethanol) 238 nm (ε 15 900); NMR ($CDCl_3$, 60 MHz) τ 7.20 (g, 2 H, *J* = 7.0 Hz), 5.33 (t, 2 H, *J* = 7.0 Hz), 4.70–5.10 (m, 2 H), 3.67–4.50 (m, 1 H), 2.43–2.63 (m, 3 H), 1.80–1.97 (m, 2 H); MS *m/e* 200 (M^+), 131, 104 (base), 77.

Anal. Calcd for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98. Found: C, 65.99; H, 6.37; N, 28.11.

The second component isolated from the column contained 74 mg (4%) of 1-(3-butenyl)-5-phenyltetrazole (**3**) as a colorless oil: bp 180 °C (0.2 mm); IR (neat) 6.05, 6.50, 6.80, 7.10, 8.95, 10.05, 10.70, 12.75, 13.60, 14.40 μm; UV (95% ethanol) 231 nm (ε 10 400); NMR ($CDCl_3$, 60 MHz) τ 7.33 (q, 2 H, *J* = 7.0 Hz), 5.50 (t, 2 H, *J* = 7.0 Hz), 4.87–5.20 (m, 2 H), 3.97–4.60 (m, 1 H), 2.40 (s, 5 H); MS *m/e* 200 (M^+), 185, 144, 131, 119, 105, 78 (base).

Anal. Calcd for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98. Found: C, 66.12; H, 5.98; N, 28.26.

A solution containing 200 mg of tetrazole **4** and 1.42 g of dimethyl acetylenedicarboxylate in 120 mL of benzene was irradiated through a Corex filter sleeve for 4 h. Removal of the solvent left a yellow oil which was subjected to dry column chromatography (alumina) using chloroform as the eluent. The major component isolated contained 220 mg (70%) of a colorless oil, whose structure was assigned as 1-(3-butenyl)-3-phenyl-4,5-dicarbomethoxypyrazole (**13**) on the basis of the following data: IR (neat) 5.75, 6.05, 6.52, 6.90, 7.90, 8.65, 9.20, 9.50, 9.70, 10.75, 12.10, 12.60, 12.85, 14.30 μm; UV (95% ethanol) 234 nm (ε 22 100); NMR ($CDCl_3$, 60 MHz) τ 7.36 (q, 2 H, *J* = 7.0 Hz), 6.22 (s, 3 H), 6.12 (s, 3 H), 5.48 (t, 2 H, *J* = 7.0 Hz), 4.74–5.17 (m, 2 H), 3.64–4.54 (m, 1 H), 2.24–2.80 (m, 5 H); MS *m/e* 314 (M^+), 313, 273, 132, 131 (base), 104, 77.

Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77; N, 8.91. Found: C, 65.26; H, 5.95; N, 9.20.

Preparation and Irradiation of 2-Allyl-5-phenyltetrazole (6). To a solution containing 2.9 g of 5-phenyltetrazole in 100 mL of 95% ethanol was added 5.1 g of silver nitrate in 10 mL of water. After stirring for 20 min, a 14% aqueous ammonia solution was added and 5.2 g of a gray solid was collected by filtration. A 2.5-g sample of the above silver salt was suspended in 20 mL of chloroform, and 6.0 g of allyl bromide was added. The mixture was heated at reflux for 24 h, and the solid precipitate was filtered off. The filtrate was concentrated under reduced pressure, and the resulting oil was subjected to dry column chromatography using methylene chloride as the eluent. The initial component isolated from the column contained 1.3 g (70%) of a colorless liquid, bp 178 °C (0.14 mm), whose structure was assigned as 2-allyl-5-phenyltetrazole (**6**): IR (neat) 6.03, 6.50, 6.78, 6.90, 8.35, 9.30, 9.55, 9.70, 10.05, 10.70, 12.60, 13.55, 14.40 μm; UV (95% ethanol) 239 nm (ε 16 700); NMR ($CDCl_3$, 60 MHz) τ 3.50–3.90 (m, 4 H), 3.60–4.24 (m, 1 H), 2.50–2.70 (m, 3 H), 1.80–2.00 (m, 2 H); MS *m/e* 130, 129 (base), 128, 115, 77.

Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.74; H, 5.55; N, 29.94.

The second component isolated from the column contained 180 mg (10%) of 1-allyl-5-phenyltetrazole (**5**): IR (neat) 6.08, 6.20, 6.50, 6.80,

7.15, 7.60, 8.0, 8.95, 9.25, 10.05, 10.75, 12.70, 13.60, 14.35 μm; UV (95% ethanol) 231 nm (ε 10 500); NMR ($CDCl_3$, 60 MHz) τ 4.63–5.07 (m, 4 H), 3.57–4.23 (m, 1 H), 2.43 (m, 5 H); MS *m/e* 186 (M^+), 129 (base), 128, 115, 104, 103, 77.

Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.76; H, 5.40; N, 29.86.

A solution containing 186 mg of tetrazole **6** and 1.42 g of dimethyl acetylenedicarboxylate in 120 mL of benzene was irradiated through a Corex filter for 6 h. Removal of the solvent left a yellow oil which was purified by alumina chromatography using chloroform as the eluent. The major component isolated (195 mg, 66%) was a colorless oil whose structure was assigned as 1-allyl-3-phenyl-4,5-dicarbomethoxypyrazole (**14**) on the basis of the following data: bp 165 °C (0.03 mm); IR (neat) 5.73, 6.50, 6.85, 7.90, 8.65, 9.20, 9.55, 9.70, 12.10, 12.60, 12.90, 14.30 μm; UV (95% ethanol) 236 nm (ε 18 000); NMR ($CDCl_3$, 60 MHz) τ 6.20 (s, 3 H), 6.12 (s, 3 H), 4.67–5.03 (m, 4 H), 3.64–4.30 (m, 1 H), 2.24–2.84 (m, 5 H); MS *m/e* 300 (M^+), 270, 269, 268, 239, 182, 163 (base).

Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.19; H, 5.60; N, 9.48.

Preparation of 2-Methyl-5-(*o*-allyloxyphenyl)tetrazole (15). A mixture containing 10.1 g of 2-cyanophenol, 17.2 g of sodium azide, and 6.0 g of ammonium chloride in 50 mL of dimethylformamide was heated at reflux for 20 h. At the end of this time the reaction mixture was poured onto 300 mL of ice water and acidified with a 10% hydrochloric acid solution. The solid which formed was filtered off and recrystallized from ethanol/water to give 10.8 g (78%) of 5-(*o*-hydroxyphenyl)tetrazole, mp 224–225 °C.

A 1.62-g sample of the above tetrazole in 20 mL of dimethylformamide was added to an ice-cooled mixture containing 480 mg of sodium hydride in 3 mL of dimethylformamide. After the evolution of gas had ceased, 1.42 g of methyl iodide in 5 mL of dimethylformamide was added at 0 °C. The mixture was allowed to stir at 25 °C for 12 h and was then poured onto 50 mL of ice water. The solution was extracted with benzene, and the extracts were dried over magnesium sulfate and concentrated under reduced pressure. The resulting liquid was purified by dry column chromatography followed by distillation at 150 °C (0.1 mm) to give 756 mg (43%) of 2-methyl-5-(*o*-hydroxyphenyl)tetrazole as a crystalline solid: mp 59–60 °C; IR (neat) 3.05, 6.15, 6.30, 6.55, 6.83, 7.25, 8.05, 9.45, 9.60, 9.85, 11.90, 13.20, 13.80 μm; UV (95% ethanol) 295 nm (ε 5400), 241 (11 800); NMR ($CDCl_3$, 60 MHz) τ 5.58 (s, 3 H), 2.47–3.20 (m, 3 H), 1.99 (dd, 1 H, J = 7.0, 2.0 Hz), 0.38 (1 H, s); MS *m/e* 176 (M^+), 148, 119, 105, 77.

Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.74; H, 4.60; N, 32.13.

To a solution containing 706 mg of the above tetrazole in 10 mL of 95% ethanol was added 160 mg of sodium hydroxide in 5 mL of water followed by 605 mg of allyl bromide. The mixture was heated at 70 °C for 20 h and then poured onto 50 mL of ice water. The solution was extracted with benzene, and the benzene extracts were washed with a 10% sodium hydroxide solution and water and then dried over magnesium sulfate. Removal of the solvent left 662 mg (77%) of a colorless solid, mp 39–40 °C, whose structure was assigned as 2-methyl-5-(*o*-allyloxyphenyl)tetrazole (**15**): IR (KBr) 6.15, 6.25, 6.50, 6.70, 7.18, 7.79, 8.95, 9.50, 10.05, 10.70, 13.20, 13.80 μm; UV (95% ethanol) 288 nm (ε 4500), 235 (9900); NMR ($CDCl_3$, 60 MHz) τ 5.66 (s, 3 H), 5.27–5.47 (m, 2 H), 4.30–4.94 (m, 2 H), 3.60–4.24 (m, 1 H), 2.47–3.14 (m, 3 H), 2.05 (dd, 1 H, J = 7.0, 2.0 Hz); MS *m/e* 216 (M^+), 189, 188 (base), 145, 117, 115, 91, 77.

Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.09; H, 5.59; N, 25.91. Found: C, 61.26; H, 5.68; N, 26.04.

Irradiation of 2-Methyl-5-(*o*-allyloxyphenyl)tetrazole (15). A 216-mg sample of tetrazole **15** in 100 mL of benzene was irradiated through a Corex filter sleeve for 2 h. Removal of the solvent under reduced pressure left a yellow oil which was purified by thick-layer chromatography using a 5:2 methylene chloride/ethyl acetate mixture as the eluent. The major component contained 164 mg (88%) of a crystalline solid, mp 52–53 °C, whose structure was assigned as 2,3,3a,4-tetrahydro-2-methyl[*l*]benzopyrano[4,3-c]pyrazole (**16**) on the basis of the following data: IR (KBr) 6.22, 6.80, 6.90, 7.25, 7.65, 8.10, 8.25, 8.90, 9.05, 9.60, 9.90, 10.60, 11.95, 13.20 μm; UV (95% ethanol) 325 nm (ε 9950), 297 (6900); NMR ($CDCl_3$, 60 MHz) τ 7.37–7.80 (m, 1 H), 7.12 (s, 3 H), 6.0–6.75 (m, 3 H), 5.27–5.57 (m, 1 H), 2.64–3.30 (m, 3 H), 2.20–2.44 (m, 1 H); MS *m/e* 188 (M^+), 187 (base), 149, 115, 91.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 69.86; H, 6.18; N, 14.58.

Preparation of 2-Methyl-5-(*o*-propargyloxyphenyl)tetrazole (18). To a solution containing 560 mg of 2-methyl-5-(*o*-hydroxyphenyl)tetrazole in 10 mL of 95% ethanol was added 130 mg of sodium hydroxide in 5 mL of water followed by 454 mg of propargyl bromide. The mixture was heated at 70 °C for 20 h and then poured onto 50 mL of ice water. The solution was extracted with benzene, and the benzene extracts were washed with a 10% sodium hydroxide solution and water and then dried over magnesium sulfate. Removal of the solvent left a yellow oil which was purified by dry column chromatography to give 350 mg (51%) of 2-methyl-5-(*o*-propargyloxyphenyl)tetrazole (**18**) as a crystalline solid: mp 81–82 °C; IR (KBr) 4.78, 6.22, 6.32, 6.60, 6.78, 7.24, 7.90, 8.18, 9.04, 9.51, 9.65, 9.75, 10.80, 13.40, 13.75 μm; UV (95% ethanol) 287 nm (ε 3900), 236 (11 300); NMR ($CDCl_3$, 60 MHz) τ 7.50 (t, 2 H, J = 2.0 Hz), 5.62 (s, 3 H), 5.20 (d, 2 H, J = 2.0 Hz), 2.4–2.97 (m, 3 H), 1.94–2.17 (dd, 1 H, J = 7.0, 2.0 Hz); MS *m/e* 214 (M^+), 186 (base), 185, 115, 77.

Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.16. Found: C, 61.84; H, 4.76; N, 26.34.

Irradiation of 2-Methyl-5-(*o*-propargyloxyphenyl)tetrazole (18). A 150-mg sample of tetrazole **18** in 100 mL of benzene was irradiated through a Corex filter sleeve for 2 h. Removal of the solvent under reduced pressure left a yellow oil which was purified by thick-layer chromatography using a 5:1 mixture of methylene chloride/ethyl acetate as the eluent. The major component isolated (96 mg, 74%) was a crystalline solid, mp 122–123 °C, whose structure was assigned as 2,4-dihydro-2-methyl[*l*]benzopyrano[4,3-c]pyrazole (**17**) on the basis of the following data: IR (neat) 6.15, 6.30, 6.40, 6.85, 7.20, 8.20, 8.45, 9.10, 9.55, 10.20, 11.85, 13.20 μm; UV (95% ethanol) 298 nm (ε 6190), 263 (9000), 254 (9220); NMR ($CDCl_3$, 60 MHz) τ 6.15 (s, 3 H), 4.80 (s, 2 H), 2.20–3.27 (m, 4 H), 2.70 (s, 1 H); MS *m/e* 186 (M^+), 185 (base), 160.

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.82; H, 5.70; N, 14.85.

The structure of benzopyrano[4,3-c]pyrazole **17** was further confirmed by an independent synthesis involving the oxidation of 2,3,3a,4-tetrahydro-2-methyl[*l*]benzopyrano[4,3-c]pyrazole (**16**) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). A mixture of 70 mg of **16** and 100 mg of DDQ in 5 mL of benzene was allowed to reflux for 5 h. The solvent was removed under reduced pressure, and the dark residue was passed through a small neutral alumina column using benzene/chloroform as the eluent to give **17** as the major product. The infrared and NMR spectra of this compound were identical in all respects with those of a sample of **17** obtained from the irradiation of tetrazole **18**.

Preparation of *N*-(o-Allyloxybenzoyl)-*N'*-phenylhydrazine. A sample of o-(allyloxy)benzoic acid[38] was converted to the corresponding acid chloride by stirring with excess thionyl chloride at room temperature for 24 h. To a 6.1-g sample of this acid chloride in 100 mL of methylene chloride was added 1 equiv of sodium *p*-nitrophenoxide (prepared by the addition of sodium hydride to 4.3 g of *p*-nitrophenol in 100 mL of ether). The solution was allowed to reflux for 24 h. At the end of this time, 10 mL of 95% ethanol was added followed by water. The organic extracts were washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 6.5 g (71%) of *p*-nitrophenyl (o-allyloxy)benzoate, mp 62–63 °C. A mixture containing 3.27 g of the above *p*-nitrobenzoate and 2.36 g of phenylhydrazine in 150 mL of tetrahydrofuran was heated at reflux for 17 h. At the end of this time the mixture was taken up in ether and washed with water. The organic layer was extracted with a 10% sodium hydroxide solution, followed by a washing with a saturated sodium chloride solution. The extracts were dried over magnesium sulfate and concentrated under reduced pressure to 2.71 g of an orange oil. This material was purified by silica gel chromatography using a 1:1 ether/pentane mixture as the eluent. The major function contained 1.94 g (66%) of *N*-(*o*-allyloxybenzoyl)-*N'*-phenylhydrazine as a crystalline solid: mp 73–74 °C; IR (KBr) 2.94, 3.03, 5.99, 6.23, 6.68, 7.62, 7.99, 8.51, 8.96, 9.97, 10.61, 10.86, 13.20, 14.37 μm; NMR ($CDCl_3$, 60 MHz) τ 5.32 (d, 2 H, J = 6.0 Hz), 4.40–4.80 (m, 2 H), 3.6–4.24 (m, 1 H), 3.84 (broad s, 1 H, exchanged with D_2O), 2.4–3.2 (m, 8 H), 1.80 (dd, 1 H, J = 6.0, 2.0 Hz), 0.51 (broad s, 1 H, exchanged with D_2O).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.55; H, 6.02; N, 10.44.

Treatment of 1-(*o*-Allyloxyphenyl)-*N*-(phenylhydrazidoyl) Chloride with Triethylamine. To a solution containing 1.52 g of o-allyloxybenzoylphenylhydrazine in 50 mL of ether was added 1.30 g of phosphorus pentachloride. The mixture was heated at reflux for 14 h, and then 1.9 g of phenol was added to destroy the phosphorus oxychloride. The resulting mixture was concentrated under reduced pressure, and 50 mL of benzene was added. To the above mixture was added 2 mL of triethylamine, and the resulting mixture was allowed to reflux for 2 h. At the end of this time the mixture was washed with a 0.5 N hydrochloric acid solution and water and then dried over magnesium sulfate. Removal of the solvent under reduced pressure

left 4.8 g of an orange residue which was chromatographed on silica gel and recrystallized from ether/pentane to give 0.86 g (61%) of 2,3,3a,4-tetrahydro-2-phenyl[*l*]benzopyrano[4,3-*c*]pyrazole (**20**) as a crystalline solid: mp 99–100 °C; IR (KBr) 6.23, 6.64, 6.73, 6.85, 7.15, 7.27, 7.58, 8.08, 8.23, 8.85, 9.12, 9.33, 9.62, 9.83, 9.93, 10.53, 11.84, 13.42, 14.45 μm; NMR ($CDCl_3$, 60 MHz) τ 5.76–7.02 (m, 4 H), 5.40 (dd, 1 H, J = 10.0, 5.0 Hz), 2.6–3.3 (m, 8 H), 2.20 (m, 1 H); MS *m/e* 250 (M^+, base), 249, 91, 77; UV (95% ethanol) 363 nm (ε 17 400), 304 (4900), 255 (13 000).

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 77.06; H, 5.85; N, 11.33.

Preparation of Ethyl 2-[*o*-(Allyloxy)phenylhydrazono]-2-chloroacetate (21). To a mixture containing 8.79 g of *o*-allyloxyaniline[39] in 25 mL of a 3.0 N hydrochloride acid solution was added 1.18 g of sodium nitrite at 0 °C. After 15 min, solid sodium bicarbonate was added until the solution became basic and then 1.47 g of sodium acetate was added at 0 °C. To the above mixture was added 1.45 g of 2-chloroethyl acetoacetate, and the solution was allowed to stir at 25 °C for 90 min. The aqueous solution was extracted with ether, dried over magnesium sulfate, and concentrated under reduced pressure to give a dark oil. This material was passed through a column of neutral alumina to give 2.23 g (88%) of ethyl 2-[*o*-(allyloxy)phenylhydrazono]-2-chloroacetate (**21**): mp 41–42 °C (lit.[26] mp 42 °C); NMR ($CDCl_3$, 60 MHz) τ 8.62 (t, 3 H, J = 7.0 Hz), 5.60 (q, 2 H, J = 7.0 Hz), 5.40 (dt, 2 H, J = 5.0 Hz), 4.40–4.85 (m, 2 H), 3.6–4.23 (m, 1 H), 2.95–3.20 (m, 3 H), 2.40–2.60 (m, 1 H), 1.16 (broad s, 1 H).

Anal. Calcd for $C_{13}H_{15}N_2O_3Cl$: C, 55.23; H, 5.35; N, 9.91. Found: C, 55.29; H, 5.37; N, 9.97.

Treatment of Ethyl 2-[o-(Allyloxy)phenylhydrazono]-2-chloroacetate (21) with Triethylamine. To a solution containing 1.20 g of the above hydrazonochloroacetate **21** in 50 mL of benzene was added 2 mL of triethylamine. The solution was heated at reflux for 24 h, cooled, and taken up in ether. The organic layer was washed with a 0.5 N hydrochloric acid solution, dried over magnesium sulfate, and concentrated under reduced pressure to give 0.86 g (82%) of 2-carboethoxy-3,3a-dihydro-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (**22**) as pale yellow crystals: mp 105–106 °C (lit.[26] mp 101 °C); IR (KBr) 5.80, 6.40, 6.70, 6.85, 7.73, 8.08, 8.90, 9.13, 9.53, 9.88, 10.68, 11.91, 12.88, 13.40, 13.80 μm; NMR ($CDCl_3$, 100 MHz) τ 8.64 (t, 3 H, J = 6.0 Hz), 7.10 (dd, 1 H, J = 18.0, 6.5 Hz), 6.66 (dd, 1 H, J = 18.0, 11.5 Hz), 6.44 (t, 1 H, J = 12.0 Hz), 5.54–5.90 (m, 4 H), 2.96–3.10 (m, 3 H), 2.40–2.50 (m, 1 H); MS *m/e* 246 (M^+, base), 218, 173, 133, 118, 105, 78; UV (95% ethanol) 345 nm (ε 11 200), 240 (5000).

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.35; H, 5.75; N, 11.37.

Preparation of 1-(*o*-Allylphenyl)-*N*-(phenylhydrazidoyl) Chloride (23). To a solution containing 1.83 g of *o*-allylbenzoyl chloride in 50 mL of ether was added 1.1 g of phenylhydrazine at 0 °C. The reaction mixture was allowed to warm to room temperature, and then 50 mL of a 1.0 M sodium hydroxide solution was added. The ethereal layer was separated, washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 2.11 g (82%) of *N*-(o-allylbenzoyl)-*N'*-phenylhydrazine: mp 158–159 °C; IR (KBr) 3.02, 6.07, 6.26, 6.67, 6.96, 7.61, 8.06, 10.10, 10.82, 13.31, 14.50 μm; NMR ($CDCl_3$, 60 MHz) τ 6.39 (d, 2 H, J = 6.0 Hz), 4.76–5.18 (m, 2 H), 3.60–4.50 (m, 1 H), 2.4–3.4 (m, 6 H).

Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.18; H, 6.40; N, 11.12.

To a solution containing 550 mg of the above benzoylhydrazine in 30 mL of ether was added 420 mg of phosphorus pentachloride. The mixture was heated at reflux for 14 h. The solvent was partially removed under reduced pressure, and 575 mg of phenol in 30 mL of benzene was added in order to destroy excess phosphorus pentachloride. The mixture was heated at 70 °C for 2 h and concentrated under reduced pressure to give hydrazidoyl chloride **23** as a pale yellow oil which was immediately reacted with triethylamine. The IR spectrum of 23 contained signals at 6.23, 6.70, 6.90, 7.42, 7.85, 9.25, 9.60, 10.90, 13.05, and 13.25 μm.

Treatment of 1-(o-Allylphenyl)-*N*-(phenylhydrazidoyl) Chloride (23) with Triethylamine. To a 500-mg sample of the above hydrazidoyl chloride in 30 mL of benzene was added 2 mL of triethylamine. The mixture was heated at 70 °C for 10 h, extracted with ether, washed with a 0.5 N hydrochloric acid solution, and dried over magnesium sulfate. The solvent was concentrated under reduced pressure, and the crystalline residue was recrystallized from ether/pentane to give 280 mg (60%) of 2,3,3a,4-tetrahydro-2-phenylindeno[1,2-c]pyrazole (**24**): 172–173 °C; IR (KBr) 6.23, 6.65, 6.81, 7.23, 7.53, 7.91, 8.46, 8.54, 9.12, 9.47, 9.66, 9.95, 10.40, 10.81, 11.24, 12.02, 13.28, 13.65, 14.35 μm; UV (methanol) 345 nm (ε 15 100), 250 (13 800); NMR ($CDCl_3$, 270 MHz) τ 7.29 (dd, 1 H, J = 15.4, 7.3 Hz), 6.92 (dd, 1 H, J = 14.3, 9.6 Hz), 6.74 (dd, 1 H, J = 15.4, 8.8 Hz), 6.39 (m, 1 H), 5.71 (t, 1 H, J = 9.6 Hz), 3.24 (t, 1 H, J = 6.0 Hz), 2.70–3.0 (m, 7 H), 2.3–2.40 (m, 1 H); MS *m/e* 234 (M^+), 134, 133, 131, 120, 116, 105, 91, 77.

Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.04; H, 6.04; N, 11.93.

A 94-mg sample of the above compound in 15 mL of benzene which contained 100 mg of chloranil was allowed to reflux for 48 h. At the end of this time the reaction mixture was washed with a 5% sodium hydroxide solution. The organic layer was dried over magnesium sulfate, and the solvent was removed under reduced pressure to give 91 mg (98%) of 2,4-dihydro-2-phenylindeno[1,2-c]pyrazole (**25**) as a crystalline solid: mp 100–101 °C; IR (KBr) 6.28, 6.73, 6.88, 7.30, 9.17, 9.38, 9.60, 9.93, 10.53, 12.48, 13.02, 13.30, 13.68, 14.67 μm; NMR ($CDCl_3$, 60 MHz) τ 6.35 (s, 2 H), 2.0–2.9 (m, 10 H); MS *m/e* 232 (M^+, base), 218, 161, 155, 77.

Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 83.05; H, 5.27; N, 11.68.

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Registry No.—**1**, 65103-32-4; **2**, 65103-33-5; **3**, 65103-34-6; **4**, 65103-35-7; **5**, 65103-36-8; **6**, 65103-37-9; **7**, 65103-38-0; **8**, 23894-57-7; **9**, 65103-39-1; **10**, 65103-40-4; **11**, 65103-41-5; **13**, 65103-42-6; **14**, 65103-43-7; **15**, 65103-44-8; **16**, 65103-45-9; **17**, 65103-46-0; **18**, 65103-23-3; **19**, 65103-47-1; **20**, 65103-48-2; **21**, 61364-10-1; **22**, 61364-13-4; **23**, 65103-22-2; **24**, 2380-43-0; **25**, 65103-24-4; 5-phenyltetrazole, 18039-42-4; 5-bromo-1-pentene, 1119-51-3; dimethyl acetylenedicarboxylate, 762-42-5; 5-chloro-1-pentyne, 14267-92-6; 1-(4-pentynyl)-5-phenyltetrazole, 65103-25-5; methyl acrylate, 96-33-3; 1-(4-pentynyl)-3-phenyl-5-carbomethoxypyrazole, 65103-26-6; 4-bromo-1-butene, 5162-44-7; 5-phenyltetrazole silver salt, 65103-27-7; allyl bromide, 106-95-6; 5-(*o*-hydroxyphenyl)tetrazole, 51449-77-5; methyl iodide, 74-88-4; 2-methyl-5-(*o*-hydroxyphenyl)-tetrazole, 65103-28-8; propargyl bromide, 106-96-7; *N*-(*o*-allyloxybenzoyl)-*N'*-phenylhydrazine, 65103-29-9; *o*-(allyloxy)benzoic acid, 59086-52-1; *o*-allylbenzoyl chloride, 52542-42-4; β-nitrophenyl (*o*-allyloxy)benzoate, 65103-30-2; phenylhydrazine, 100-63-0; *o*-allyloxyaniline, 27096-64-6; *N*-(o-allylbenzoyl)-*N'*-phenylhydrazine, 65103-31-3.

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Reversible Interconversion of *N*-Nitroso(2-methylamino)acetonitrile and 3-Methyl-5-amino-1,2,3-oxadiazolium Chloride and Related Reactions[1]

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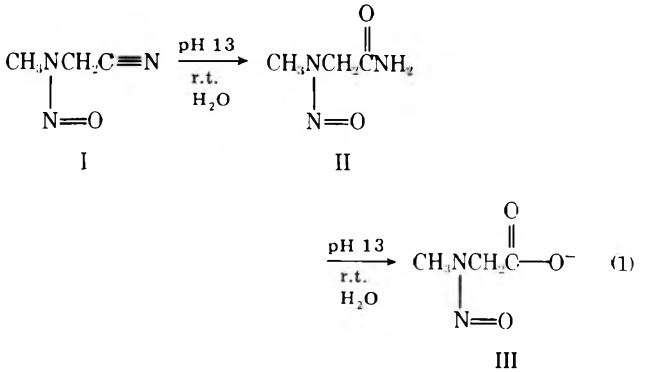
Reaction of *N*-nitroso(2-methylamino)acetonitrile (I) with gaseous hydrogen chloride in dry methanol, ethanol or ether is a fast reaction that yields 3-methyl-5-amino-1,2,3-oxadiazolium chloride (VI) virtually quantitatively. A pathway for the conversion of I to VI involving anchimeric assistance by the nitroso group is suggested. With aqueous base at pH 8–11, VI is reversibly converted to I, but at pH 11.5–14 VI is converted to *N*-nitrososarcosine (VII). Treatment of the homologous *N*-nitroso(3-methylamino)propionitrile (IV) with hydrogen chloride in methanol is a relatively slow reaction and does not yield a cyclic product; IV is denitrosated and converted to methyl (3-methylamino)propionate hydrochloride (VIII), with concomitant formation of ammonium chloride. The unnitrosated parent amine of I, methylcyanomethylamine hydrochloride (IX), on reaction with hydrogen chloride, behaves in the same manner as IV; products are methyl(2-methylamino)acetate hydrochloride (X) and ammonium chloride. A simple denitrosation procedure for *N*-nitrosamines derived from secondary amines is also described.

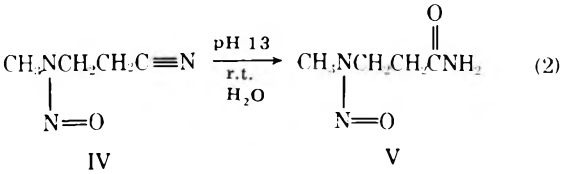
In an earlier paper,[3] we reported the unexpectedly rapid hydrolysis of *N*-nitroso(2-methylamino)acetonitrile (I) in aqueous alkaline solution under mild conditions (room temperature and pH 13) to a salt of *N*-nitrososarcosine (III) via the intermediate amide (II) (eq 1). The homologous *N*-nitrosamine, *N*-nitroso(3-methylamino)propionitrile (IV), was hydrolyzed to the amide (V) under similar conditions but at a rate only about 1/500 that of I (eq 2). These results, coupled with ^{18}O-labeling studies and determination of activation parameters, showed unequivocally that anchimeric assistance by the *N*-nitroso group plays the dominant role in the more rapid hydrolysis of I.



I II

(1)

III



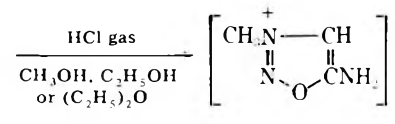
(2)

IV V

As part of our ongoing investigation of anchimeric effects of the *N*-nitroso group in conjunction with studies on structure–biological activity relationships in *N*-nitrosamines, we examined the behavior of I and IV with anhydrous hydrogen chloride in nonaqueous solvents—methanol, ethanol, and diethyl ether; the results of that study are reported here. During that investigation deuterium-exchange studies were conducted on starting materials and products with interesting results. Finally, a mild chemical denitrosation technique was developed for certain nitrosamines which should be useful in destroying carcinogenic or potentially carcinogenic nitrosamines.[4]

Results and Discussion

Treatment of I in dry methanol with hydrogen chloride gas for 1 h followed by solvent evaporation, washing with acetone, and recrystallization from ethanol yields 3-methyl-5-amino-1,2,3-oxadiazolium chloride (VI) in high to quantitative yield (eq 3). This compound had been prepared similarly in 1962 by Daeniker and Druey.[5] Similar results are obtained using ethanol or ether as solvent.



(3)

VI

mp 154–156 °C

Compound VI undergoes (a) typically *rapid* exchange of two protons by deuterium when D_2O is added to a Me_2SO-d_6 solution, (b) *slow* exchange of the vinyl proton when it remains in D_2O solution overnight, (c) complete reconversion to I on treatment with aqueous base at pH 8–11, and (d) complete

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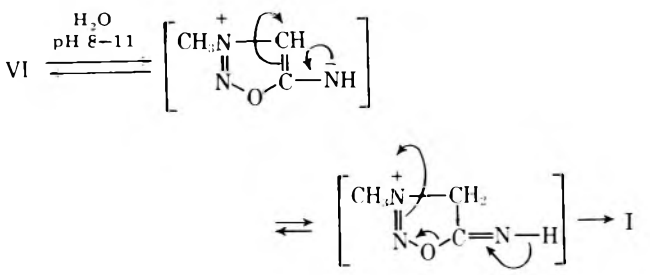
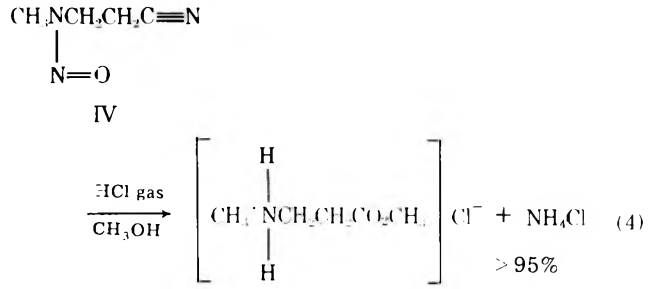
Scheme I



conversion to the sodium salt of *N*-nitrososarcosine (III) on treatment with aqueous base at pH 11.5–14. Acidification of III yields *N*-nitrososarcosine (VII). The slow exchange of the vinyl proton to yield VI-d_3 is characteristic of α protons in enols and enamines. Recoversion of VI to I at pH 8–11 is rationalized in Scheme I.

If VI is treated with NaOD–D_2O at pH 8 instead of with NaOH–H_2O, I-d_2 (both methylene protons replaced) is obtained instead of I. The pathway for the conversion of VI to III at pH 11.5–14 is assumed to occur via the intermediacy of I, and has already been explained.[3] Further, I rapidly undergoes exchange of its methylene protons by neutral D_2O whereas IV does not; this is a consequence of the higher acidity of the methylene protons in I.

A special feature of the conversion of I → VI by hydrogen chloride is the anchimeric assistance for the formation of a five-membered ring provided by the *N*-nitroso group. In contrast, reaction of *N*-nitroso(3-methylamino)propionitrile (IV), the next higher homologue of I, with hydrogen chloride gas in methanol under identical conditions does not yield a cyclic product. Compound IV undergoes denitrosation and the cyano group is transformed to the methyl ester. Products are methyl (3-methylamino)propionate hydrochloride (VIII) (75–95% yields) and ammonium chloride (>95% yield) (eq 4).



(4)

VIII, 75–95%

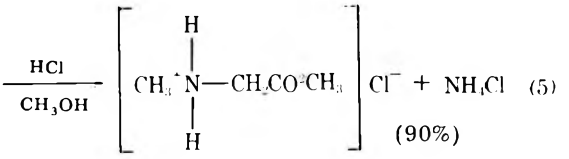
The additional methylene group that separates the *N*-nitroso and nitrile groups in IV is responsible for the difference in behavior of I and IV; cyclization requires the formation of a six-membered ring, a process that occurs less readily than five-membered ring formation. These results are consistent with our earlier studies and conclusions on the difference in reactivity of I and IV with aqueous base.[3]

To confirm the importance of the nitroso group in directing the reaction of I with hydrogen chloride to the cyclic product VI, the unnitrosated parent amine of I [methyl cyanomethylamine hydrochloride (IX)] was also treated with hydrogen chloride gas in methanol (eq 5). Compound IX was cleanly and rapidly converted to methyl (2-methylamino)acetate hydrochloride (X) (80%) and NH_4Cl (90%).

Denitrosation Studies. Literature methods for the destruction or deactivation of *N*-nitroso compounds are often time-consuming and complex, and results are irreproducible and equivocal.[6] These methods have been applied to nitrosoureas and nitrosamines of complex structure not related to the carcinogenic types of dialkylnitrosamines with which we are concerned. Reaction of I with hydrogen chloride gas in methanol, ethanol, or ether eliminates the nitroso function by cyclization within 30 min, the method is simple and requires no special apparatus or reagents, and products are easily isolated in pure form if desired. With IV however, denitrosation occurs, as already described, and since hydrogen chloride gas is bubbling through the solution, the nitrosonium ion is removed as a volatile species, nitrosyl chloride (see Experimental Section), requiring no scavengers and avoiding reversible renitrosation of the amine (or transnitrosation in mixtures of amines and *N*-nitrosamines[4]).

$CH_3NHCH_2CN \cdot HCl$

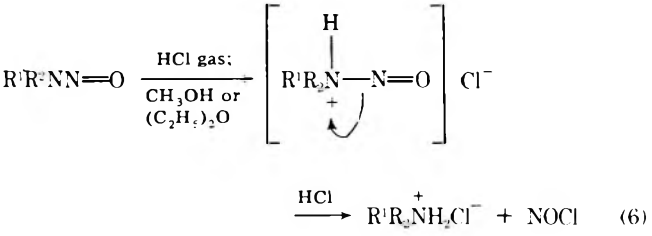
IX



(5)

X, 80%

Denitrosation of IV with hydrogen chloride prompted us to extend the technique to dimethyl-, diethyl-, dipropyl-, and dibutylnitrosamines and *N*-nitrososarcosine. In all of these cases, denitrosation occurs within 30 min; the products are hydrochlorides of the corresponding secondary amines. When the gases leaving the reaction flasks are passed through 2,3-dimethyl-2-butene in diethyl ether, a royal blue color develops in less than 10 min, a result typical of the reaction of nitrosyl chloride with the olefin.[7] The denitrosation technique is presumed to be general for *N*-nitrosamines unable to form rings by anchimeric assistance of the nitroso group (eq 6).



(6)

Experimental Section[8]

3-Methyl-5-amino-1,2,3-oxadiazolium Chloride (VI) from *N*-Nitroso(2-methylamino)acetonitrile (I) and Gaseous Hydrogen Chloride. This was prepared essentially by the method of Daeniker,[5] but instead of tetrahydrofuran as solvent, we used methanol, ethanol, or diethyl ether (90–92% yields).

NMR (Me_2SO-d_6): CH_3 (δ 1.36, s, 3 H); vinyl (5.53, s, 1 H); NH_2 (7.34, s, 2 H) (Me_2SO=O). Addition of 1 drop of D_2O to the solution caused virtually immediate disappearance of the two amino protons. In D_2O, only the signals of the methyl (δ −0.03) and vinyl (δ 2.94) protons (HOD=O) were observed. The signal of the vinyl proton decayed slowly and had completely disappeared overnight. IR: moderately strong absorption at 1680 cm^{-1} (C=N) and absence of absorption due to the C≡N group. UV: in ethanol, VI showed two maxima at λ 204 and 294 mμ,[5] shifted slightly in water at pH 2 to 200 and 292 mμ.

Reaction of VI with Aqueous Base. Compound VI (2.0 g, 15 mmol) was dissolved in H_2O (16 mL) and the solution was divided into two equal parts. Part 1 was adjusted to pH 8.5 with sodium hydroxide solution and stirred under a nitrogen atmosphere for 1 h. Evaporation of the water was followed by extraction of the residue with methylene chloride (4 × 10 mL) and filtration. Evaporation of the solvent from the combined extracts yielded I (0.68 g, 93%) as a yellow oil. The differential pulse polarogram in basic solution (pH ~10) showed a single well-defined peak (E_p = −1.25 V vs. SCE). Addition of authentic I to the solution gave an increase in peak height without any change in peak potential. NMR spectra of the yellow oil in Me_2SO-d_6 and D_2O were identical with those of an authentic sample of I.[3] An identical

study of pH 8.5 using NaOD–D_2O instead of NaOH–H_2O yielded I-d_2 (both methylene protons were replaced by deuterium).

Part 2 was adjusted to pH 13.5 with sodium hydroxide solution and stirred under a nitrogen atmosphere for 8 h. The pH was adjusted to 4.0 followed by evaporation to dryness. The residue was extracted with acetone (4 × 20 mL) and filtered. The combined acetone extracts were evaporated to dryness and the residual yellow oil was dissolved in methylene chloride (50 mL) and filtered. Evaporation of the filtrate yielded a yellow oil (0.8 g, 92%) identified by NMR, IR, and UV as VII.

Reaction of *N*-Nitroso(3-methylamino)propionitrile (IV) with Gaseous Hydrogen Chloride. Compound IV (5.0 g, 40 mmol) was dissolved in dry methanol (40 mL) and dry hydrogen chloride gas was passed through the solution for 2 h; a white precipitate formed. The reaction mixture was evaporated to half its volume under vacuum and the concentrate was cooled in a dry ice–acetone bath for 15 min. Filtration yielded a white solid identified as ammonium chloride (2.1 g, 89%) (sublimation temperature ca. 340 °C, evolution of NH_3 on treatment with NaOH). The filtrate was evaporated to dryness and washed with acetonitrile (3 × 50 mL). The second residue was also NH_4Cl (0.19 g, 8%); total yield of NH_4Cl, 97%. The combined acetonitrile washings were evaporated to dryness to yield a white powder (6.45 g, 95%) which was recrystallized from acetone–ethyl acetate. The resulting product, methyl (3-methylamino)propionate hydrochloride (VIII), was strongly hygroscopic, making it difficult to obtain an accurate or reproducible melting point or elemental analysis. Anal. Calcd for $C_5H_{12}O_2ClN$: C, 39.1; H, 7.82; N, 9.12; Cl, 23.1. Found: C, 37.6; H, 8.45; N, 9.42; Cl, 22.5.

NMR (Me_2SO-d_6): CH_3 (δ 0.04, s, 3 H); CH_2 (0.32, t, 2 H); CH_2 (0.62, t, 2 H); OCH_3 (1.17, s, 3 H); NH_2 (6.80, s, 2 H) (Me_2SO=O). Addition of 1 drop of D_2O to the solution caused the two proton signal due to NH_2 to disappear. IR: intense absorption at 1750 cm^{-1} (C=O) and weak absorption at 3000 cm^{-1} (NH_2).

Reaction of Methyl Cyanomethylamine Hydrochloride (IX) with Gaseous Hydrogen Chloride. This was conducted and worked up as described for IV. The yield of NH_4Cl was 90% and that of methyl (2-methylamino)acetate hydrochloride (X) was 80%. Compound X was also exceedingly hygroscopic. Anal. Calcd for $C_4H_{10}O_2ClN$: C, 34.4; H, 7.17; N, 10.0; Cl, 25.4. Found: C, 33.8; H, 7.07; H, 9.90; Cl, 25.7.

NMR (Me_2SO-d_6): CH_3 (δ 0.06, s, 3 H); OCH_3 (1.44, s, 3 H); CH_2 (1.62, s, 2 H); NH_2 (7.20, s, 2 H) (Me_2S=O = 0). Addition of 1 drop of D_2O to the solution caused the two proton signal due to NH_2 to disappear. IR: intense absorption at 1750 cm^{-1} (C=O) and weak absorption at 2900 cm^{-1} (NH_2).

Denitrosation of *N*-Nitrosamines. General Procedure. Dry hydrogen chloride gas was bubbled through a solution of *N*-nitrosamine (2.0 g) in dry methanol (25 mL) for about 30 min. The solution was evaporated to dryness under vacuum and the residue was washed with cold acetone (3 × 20 mL). The residue was the hydrochloride of the corresponding amine. Recrystallization from ethyl acetate, diethyl ether, or petroleum ether yielded the analytically pure salt identified by analysis and/or NMR.

Denitrosation of dimethyl-, diethyl-, dipropyl-, and dibutylnitrosamines yielded salts of the corresponding secondary amines. If the effluent gases were passed through an ether solution of 2,3-dimethyl-2-butene, a royal blue color developed within 10 min. I and IV also underwent denitrosation to yield VI and VIII, respectively, as already described.

Acknowledgment. This investigation was supported by Grants CA-18618, 12227, and 05280 from the National Cancer Institute, DHEW, and the Samuel S. Fels Fund.

Registry No.—I, 3684-91-7; IV, 60153-49-3; VI, 65103-49-3; VIII, 65103-50-6; IX, 25808-30-4; X, 13515-93-0.

References and Notes

(1) Presented at the 11th Middle Atlantic Regional Meeting, American Chemical Society Newark, Del., April 1977.
(2) Taken from the Ph.D. dissertation of S. K. Vohra, Temple University, 1977.
(3) S. K. Chang, G. W. Harrington, H. S. Veale, and D. Swern *J. Org. Chem.*, **41**, 3752 (1976).
(4) S. S. Singer, W. Lijinsky, and G. M. Singer, *Tetrahedron Lett.*, 1613 (1977).
(5) H. U. Daeniker and J. Druey, *Helv. Chim. Acta*, **45**, 2426 (1962); H. U. Daeniker, *ibid.*, **47**, 33 (1964).
(6) P. Quitt, R. O. Studer, and K. Vogler, *Helv. Chim. Acta*, **47**, 166 (1964); H. C. Stewart, *Aust. J. Chem.*, **22**, 2451 (1969); E. H. White, *J. Am. Chem. Soc.*, **77**, 6003 (1955).
(7) H. C. Hamann and D. Swern, *J. Am. Chem. Soc.*, **90**, 6481 (1968).
(8) Nitrosamines were prepared as described in ref 3 or purchased from Aldrich or Eastman. NMR spectra were recorded with a Varian XL-100 spectrometer using Me_4Si, HOD, or Me_2SO as internal standards. UV spectra were obtained using a Cary Model 14 spectrophotometer. IR spectra were obtained on a Perkin-Elmer 225 or Pye Unicam AP 1000 spectrophotometer. Differential pulse polarography was conducted as described in ref 3. All solvents and reagents were the finest obtainable. All work with nitrosamines was conducted on the smallest scale necessary to obtain the requisite information utilizing efficient hoods and maximum protection of personnel.

Nuclear Magnetic Resonance Studies on σ Adducts of Heterocyclic Systems with Nucleophiles. 18.[1] Proton and Carbon-13 Nuclear Magnetic Resonance Investigations on σ-Adduct Formation between 1,*X*-Naphthyridines and Some Methyl-1,8-naphthyridines with Potassium Amide in Liquid Ammonia

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1,5-, 1,6- and 1,8-naphthyridines dissolved in liquid ammonia containing potassium amide showed the H-2 and C-2 resonances at about 4 and 90 ppm higher field, respectively, than the H-2 and C-2 resonances observed in solutions of these naphthyridines in $CDCl_3$. It indicated that all three naphthyridines underwent addition of the amide ion to position 2, yielding a 2-amino-1,2-dihydro-1,*X*-naphthyridinide ion. The 1,7-naphthyridine showed a more complex reactivity pattern toward amide ions. Besides addition at C-2, addition at C-6 and at C-8 has been found. The relation of this study with that of the Chichibabin amination of the 1,*X*-naphthyridines is discussed. It was further proven that under the influence of the amide ion 2-methyl- and 4-methyl-1,8-naphthyridine only gave deprotonation of the methyl group and that 3-methyl-1,8-naphthyridine gave formation of the 2-amino-1,2-dihydro-3-methyl-1,8-naphthyridinide ion.

Recently there has been great interest in the study of the formation of the 1:1 σ adducts between azines and amide ions[2] and between azinium salts and liquid ammonia.[3,4] This is due to the fact that the many often surprising rearrangements which can take place in these systems[5-7] occur via the intermediacy of these σ adducts. NMR spectroscopy has been found to be a valuable tool for the detection of these adducts, since the newly formed tetrahedral center causes a consider-

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Table I. ^{1}H- and ^{13}C-NMR Data of the 1,*X*-Naphthyridines and Their 1:1 σ Adducts with Amide Ions

Compd	Registry no.	Solvent	^{1}H-NMR chemical shift (δ) H-2	H-3	H-4	H-5	H-6	H-7	H-8	^{13}C-NMR chemical shift (δ) C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1	254-79-5	$CDCl_3$	8.96	7.55	8.37		8.96	7.55	8.37	151.0	124.1	137.2		151.0	124.1	137.2	144.0	144.0
		NH_2^-/NH_3	4.85	5.27	*a*		6.65	*a*	*a*	65.8	121.3	127.4[b]		125.1	122.7	121.6[b]	151.2	137.3
		$\Delta\delta$	4.11	2.28			2.31			85.2	2.8	9.8		25.9	1.4	15.6	+7.2	6.7
2	253-72-5	$CDCl_3$	9.03	7.43	8.20	9.22		8.75	7.87	154.9	122.7	135.8	153.0		146.9	122.2	150.5	123.8
		NH_2^-/NH_3	5.05	5.19	6.23	7.15		7.20	5.82	66.1	120.0	124.6	146.1		146.6	112.2	156.2	114.0
		$\Delta\delta$	3.98	2.24	1.97	2.07		1.55	2.05	88.8	2.7	11.2	6.9		0.3	10.0	+5.7	9.8
3	253-69-0	$CDCl_3$	9.01	7.48	8.14	7.64	8.60		9.50	152.1	125.2	134.7	119.9	144.0		154.5	143.7	131.3
		NH_2^-/NH_3	4.98[c]	5.30[d]	*a*	*a*	4.51[e]		5.15[f]	66.0[c]	*a*	*a*	*a*	80.1[e]		71.0[f]	*a*	*a*
		$\Delta\delta$	4.03	2.18			4.09		4.35	86.1				63.9		83.5		
4	254-60-4	$CDCl_3$	9.15	7.51	8.21	8.21	7.51	9.15		153.8	122.3	137.3	137.3	122.3	153.8		156.6	123.1
		NH_2^-/NH_3	5.21	5.42	6.32	6.65	5.62	7.60		67.0	122.1	126.0	131.5	100.8	149.3		162.6	112.9
		$\Delta\delta$	3.94	2.09	1.89	1.56	1.89	1.55		86.8	0.2	11.3	5.8	21.5	4.5		+6.0	10.2

[a] These peaks could not be assigned. [b] The signals may be interchanged. [c] H-2 and C-2 in adduct **8**. [d] H-3 in adduct **8**. [e] H-6 and C-6 in adduct **9**. [f] H-8 and C-8 in adduct **10**.

able upfield shift. In the ^{1}H-NMR spectra upfield shifts of about 3–4 ppm are observed; in the ^{13}C-NMR spectra shifts as large as about 90 ppm are found.[2] The ^{1}H- and ^{13}C-NMR spectra of the parent 1,*X*-naphthyridines have been published,[8,9] but no ^{1}H and ^{13}C data of anionic 1:1 σ adducts, formed between the 1,*X*-naphthyridines and an amide ion, i.e., the aminodihydro-1,-*X*-naphthyridinide ions, are known. Information about the possible existence of these 1,*X*-naphthyridinide ions is of considerable interest, especially in relation to an earlier study on the Chichibabin amination of the 1,*X*-naphthyridines,[10] in which discrepancies were found between a reactivity order for amination in 1,7- and 1,8-naphthyridine, as calculated by the total π-electron density ground state data[10] and the one being experimentally established. Thus 1,7-naphthyridine on amination gave *only* the 8-amino product, while from calculations C-2 was predicted to have about the same reactivity as C-8. Similar discrepancies were also observed in the 1,6-naphthyridine series.

In order to establish which position(s) in the 1,*X*-naphthyridines is (are) vulnerable to attack by amide ions, we have carried out the NMR study on the σ-adduct formation of the parent 1,*X*-naphthyridines, **1–4**, with amide ions. Therefore the ^{1}H- and ^{13}C-NMR spectra of the 1,*X*-naphthyridines in both deuteriochloroform and liquid ammonia containing potassium amide were measured. The ^{1}H and ^{13}C chemical shift data and their assignments are summarized in Table I. The assignment of the proton chemical shifts in the ^{1}H-NMR spectrum of the σ adducts was based on the magnitude of the corresponding coupling constant and on the spectra obtained when deuterated 1,*X*-naphthyridines were used as substrate. The following deuterated compounds were prepared for this spectroscopic study: 2,6-dideuterio-1,5-naphthyridine, 5-deuterio-1,6-naphthyridine, 8-deuterio-1,7-naphthyridine, 2,6,8-trideuterio-1,7-naphthyridine, and 2,7-dideuterio-1,8-naphthyridine (see Experimental Section). The unambiguous assignment of the ^{13}C chemical shifts in the σ adducts was achieved by selective heteronuclear decoupling.

1,5- (1), 1,6- (2), and 1,8-Naphthyridine (4). On dissolving the naphthyridines **1, 2,** or **4** (see for the structures, Table I) in liquid ammonia containing potassium amide no trace of the parent compounds **1, 2,** and **4** could be detected in the NMR spectrum; only resonance signals indicating the presence of the anionic 1:1 σ adducts **5, 6,** or **7,** respectively, were found

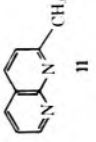
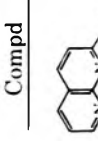
5

6

7

(see Table I). The adduct spectra showed a very uniform pattern in that the absorptions of all carbon and hydrogen atoms were shifted upfield, compared to the shieldings of the corresponding atoms in the compounds **1, 2,** and **4** in deuteriochloroform. The most striking upfield shifts are of H-2 (about 4 ppm) and of C-2 (about 85–90 ppm). These upfield shifts are ascribed to the rehybridization of C-2 ($sp^2 \rightarrow sp^3$) on adduct formation and are in excellent agreement with the shielding differences reported for chloropyrimidines[11] and substituted pteridines.[12] In accordance with the adduct formation is the change of the $J(C_2\text{–}H)$ of 180 Hz in the compounds **1, 2,** and **4** to 150 Hz in the adducts **5, 6,** and **7**.[11b,13] The results given in Table I further showed that from all the remaining carbon atoms, C-6 is the most shielded in both σ adducts **5** and **7,** reflecting a notable contribution of the para quinoid resonance structure in these naphthyridinides. The preferential attack of the nucleophilic amide ion on C-2 in the compounds **1, 2,** and **4** is in accordance with calculations on the total π-electron density of the several atoms in these systems, predicting that C-2 is the most favorable position for nucleophilic attack. It is further in good agreement with the Chichibabin amination of the 1,*X*-naphthyridines **2** and **4,** yielding exclusively the corresponding 2-amino compounds,[10] but not with the amination of the 1,5-naphthyridine (**1**) which has been reported to yield exclusively the 4-amino compound.[14] With **2** no σ adduct at C-5 has been observed despite the fact that above-mentioned calculations predicted that C-5 would have about the same total π-electron density as C-2. Our results indicate that calculations on ground state prop-

Table II. ^{1}H- and ^{13}C-NMR Data of 2-, 3-, and 4-Methyl-1,8-naphthyridines, the Conjugate Base of 2- and 4-Methyl-1,8-naphthyridines, and the Amide Adduct with 3-Methyl-1,8-naphthyridine

Compd	Registry no.	Solvent	^{1}H-NMR chemical shift (δ) H-2	H-3	H-4	H-5	H-6	H-7	H side chain	^{13}C-NMR chemical shift (δ) C-2	C-3	C-4	C-5	C-6	C-7	C-9	C-10	C side chain
 11	1569-16-0	$CDCl_3$		7.25	7.97	8.03	7.32	9.00	2.75	163.0	123.0	137.0[a]	136.8[a]	121.4	153.3	156.2	120.9	25.6
		NH_2NH_3		6.00	6.25	6.69	5.83	7.60	3.05	158.4	125.9	128.1	131.4	107.0	149.4	163.7	117.4	76.1
									3.30									
		Δδ		−1.25	−1.72	−1.34	−1.49	−1.40	+0.30	−4.6	+2.9	−8.9	−5.4	−14.4	−3.9	+7.5	−3.5	+50.5
									+0.55									
 12	14759-22-9	$CDCl_3$	8.98		7.94	8.12	7.45	9.07	2.55	155.5	131.9	135.6	136.6	122.2	152.6	155.0	122.5	18.4
		NH_2NH_3	5.02		6.00	6.55	5.59	7.48	1.90	71.4	130.5	121.8	129.9	101.0	148.1	162.2	113.8	21.0
		Δδ	−3.96		−1.94	−1.57	−1.86	−1.59	−0.65	−84.1	−1.4	−13.8	−6.7	−21.2	−4.5	+7.2	−8.7	+2.6
 13	1569-17-1	$CDCl_3$	8.87	7.15		8.17	7.35	9.01	2.56	153.1	122.7	145.9	133.4	121.7	153.0	156.2	122.7	17.6
		NH_2NH_3	6.72	5.35		7.70	6.42	8.02	3.52	145.7	104.5	145.2	131.3	112.2	149.3	162.7	119.1	74.7
									3.85									
		Δδ	−2.15	−1.80		−0.47	−0.93	−0.99	+0.96	−7.4	−18.2	−0.7	−2.1	−9.5	−3.7	+6.5	−3.6	+57.1
									+1.29									

[a] The signals may be interchanged.

erties can only be used with extreme caution as a method to predict a reactivity pattern. Moreover this argument is reinforced by the fact that it is unknown whether the σ-adduct formation involves a kinetically or thermodynamically controlled process.

1,7-Naphthyridine (3). The ^{1}H- and ^{13}C-NMR spectra of a solution of **3** in liquid ammonia, containing potassium amide, measured at −50 °C were found to be very complex (see both Figures 1 and 2). Although not all ^{1}H and ^{13}C resonance signals could be assigned, it is evident that no unreacted **3** is present

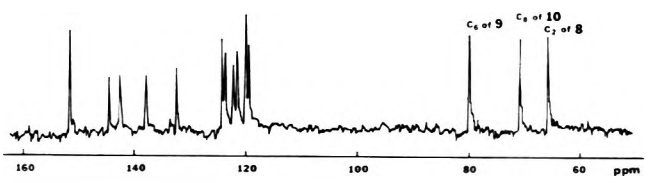


Figure 1. ^{13}C-NMR spectrum of 1,7-naphthyridine (**3**) in liquid ammonia, containing potassium amide.

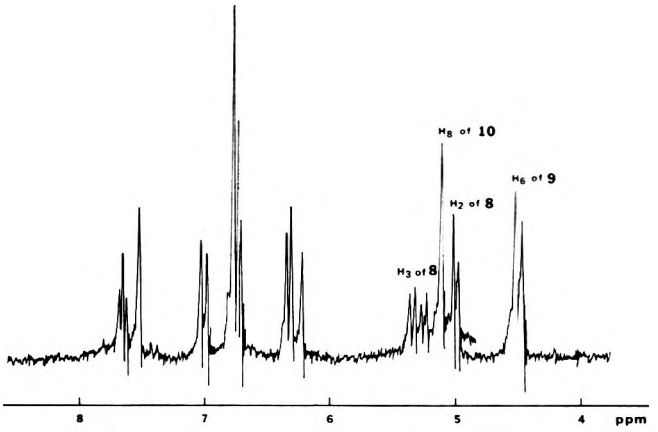
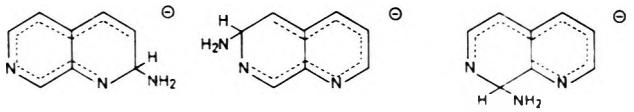


Figure 2. ^{1}H NMR spectrum of 1,7-naphthyridine (**3**) in liquid ammonia, containing potassium amide.

and that the high-field resonance absorptions must be ascribed to the presence of three anionic 1:1 σ adducts, i.e., the aminodihydro-1,7-naphthyridinide ions **8**, **9**, and **10**. From the



8 **9** **10**

^{1}H-NMR spectra the ratio in which these three σ adducts are formed is about 1:1:1.

Calculations of the total π-electron densities in the 1,7-naphthyridine (**3**) show[10] that the order of nucleophilic reactivity is C-2 > C-8 > C-4 > C-6. Our experiments nicely confirm the favored addition at C-2 and C-8. However, since the formation of an adduct was found at C-6 and not at C-4, it again indicates the unreliability of ground-state π-electron densities to predict reactivity patterns. Agreement between the experimental data and the results of the calculations may be considered as only fortuitous. It has been reported that adduct formation at C-4, besides C-6 and C-8, occurs with 2-chloro-1,7-naphthyridine.[15] Apparently the presence of the electron-attracting inductive effect of the chloro atom promotes the addition of the amide ion at C-4. Similar observations have been made in pyridine chemistry. 2-Bromopyridine does not give an adduct,[16] but 2-bromo-6-chloropyridine forms an adduct at C-4.[17] The fact that from the reaction mixture containing the three adducts **8**, **9**, and **10** only 8-amino-1,7-naphthyridine could be isolated is puzzling.[10] It might be possible that at the temperature which has been used for the Chichibabin amination (25 °C) only the adduct **10** is present. That the temperature can influence the regiospecificity of the addition has been observed with pteridines[12] and 1-methylpyrazinium ions.[4]

2-Methyl- (11), 3-methyl- (12), and 4-Methyl-1,8-naphthyridine (13). When the ^{1}H- and ^{13}C-NMR spectra of solutions of **11** and **13** in liquid ammonia, containing potassium amide, were measured, they were found to be quite different from the anionic σ adduct **7** (see Table II). The resonance of all ring hydrogen and carbon atoms has been shifted

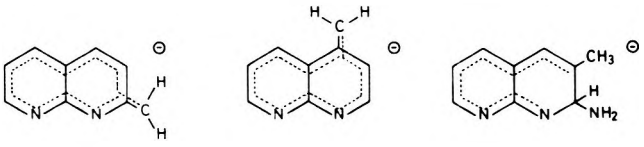
Table III. Results of Hydrogen/Deuterium Exchange in 1,*X*-Naphthyridines (1–4)

Starting material	Temp, °C	Time, h	Product	% deuterium (position) by ^{1}H-NMR data	Mass spectrum data
1,5-Naphthyridine (1)	220	24	2,6-Dideuterio-1,5-naphthyridine	88 (2 and 6)	0 D 1.2%; 1 D 19.7%; 2 D 78.2%; 3 D 0.7%; 4 D 0.2%
1,6-Naphthyridine (2)	170	12	5-Deuterio-1,6-naphthyridine	95 (5); 22 (2)	0 D 7.1%; 1 D 78.4%; 2 D 14.3%; 3 D 0.2%
1,7-Naphthyridine (3)	170	12	8-Deuterio-1,7-naphthyridine	90 (8)	0 D 9.6%; 1 D 79.7%; 2 D 10.5%; 3 D 0.2%
	220	24	2,6,8-Trideuterio-1,7-naphthyridine	87 (8); 67 (2); 53 (6); 25 (5)	0 D 0.04%; 1 D 1.5%; 2 D 18.7%; 3 D 51.2%; 4 D 28.0%; 5 D 0.5%
1,8-Naphthyridine (4)	220	24	2,7-Dideuterio-1,8-naphthyridine[a]	95 (2 and 7)	0 D 0.5%; 1 D 11.7%; 2 D 83.0%; 3 D 4.3%; 4 D 0.4%; 5 D 0.1%

[a] This compound was also prepared by oxidation of 2,7-dihydrazino-1,8-naphthyridine with a solution of cupric sulfate in deuterated water.[25]

upfield, but the magnitude of the upfield shift did not exceed 2 ppm in the ^{1}H-NMR spectra and 20 ppm in the ^{13}C-NMR spectrum. It is evident that *no* σ adduct is formed.

The downfield shift of the hydrogens ($\Delta\delta$ = 0.3–1.3 ppm) and C atom ($\Delta\delta$ = 50–57 ppm) of the substituent at C-2 or C-4 is remarkable. It strongly indicates the formation of the anions **14** and **15**, formed by deprotonation of the side chain in **11** and



14 **15** **16**

13, respectively. It is further of interest that both hydrogens of the substituent were split into a pair of doublets (J = 2–3 Hz). The coupling is due to the presence of a methylene group in which the free rotation around the C(methylene)–C-2 bond is absent causing a difference in chemical environment of the methylene protons. It indicates further that the charge formed in the side chain is delocalized over the heterocyclic rings. The relatively large upfield shift for C-6 in **14** and C-3 in **15** is in agreement with this charge delocalization. Amide-induced deprotonation of a methyl group α or γ to the ring nitrogen is well established and NMR data of the conjugated base of 4-methylpyrimidine,[18] 4-methyl-5-bromopyrimidine,[18] and 2-methylpyridine[19] are recorded.

As seen from Table II, 3-methyl-1,8-naphthyridine (**12**) surprisingly shows a completely different behavior. From the spectrum it became evident that the formation of the 1:1 σ adduct **16** is favored over deprotonation. The ^{1}H- and ^{13}C-NMR signals data are in agreement with those of **7**; H-2 and C-2 show considerable upfield shift to be expected for conversion of an sp^2 center into an sp^3 center.

Experimental Section

All carbon spectra were obtained with a Varian XL-100-15 spectrometer operating at 25.2 MHz. The spectrometer was equipped with a Varian Fourier transform unit. The pulse separation was chosen as 0–1.2 s. The spectral width was 5000 Hz (1.25 Hz/point). In $CDCl_3$ solutions ^{13}C chemical shifts were measured from internal Me_4Si, while in ammonia solutions ^{13}C chemical shifts were measured from internal $(CH_3)_3N$ and were converted to the Me_4Si scale by adding 47.5 ppm. The $CDCl_3$ solvent was used as field frequency lock; in case of liquid ammonia as solvent field frequency lock was based on the ^{19}F-NMR signal of a capillary of hexafluorobenzene position along the longitudinal axis of the 12 mm (o.d.) sample tubes employed. The probe temperature when measuring samples in liquid ammonia was −55 °C. Downfield shifts are indicated by a positive sign.

The ^{1}H-NMR spectra were recorded on a Jeol JNM C-60H spectrometer, using Me_4Si (δ = 0) as internal standard. In the case of adduct measurement the apparatus was equipped with a JES-VT-3 variable temperature controller. Spectra were obtained at temperatures between −40 and −60 °C. Trimethylamine was used as an internal standard (δ = 2.13 ppm). The procedure for measuring the NMR spectra in liquid ammonia, containing potassium amide, was performed as described before.[18]

Starting Materials. The following compounds were prepared according to the procedures described before: 1,5-naphthyridine (**1**),[20,22] 1,6-naphthyridine (**2**),[20,21] 1,7-naphthyridine (**3**),[22] 1,8-naphthyridine (**4**),[20,23] 2-methyl-1,8-naphthyridine (**11**),[20,23] 3-methyl-1,8-napthyridine (**12**),[24] and 4-methyl-1,8-naphthyridine (**13**).[23]

Deuterated 1,*X*-Naphthyridines. The deuterated 1,*X*-napthyridines were prepared by heating of the appropriate naphthyridine with deuterated water in a sealed tube at a temperature and for a period of time as given in Table III. It was not possible to obtain by this procedure a selective hydrogen/deuterium exchange on just one position.

Under the heading "product" in Table III only the compound that is formed in the largest amount is mentioned. The position of labeling was determined by ^{1}H-NMR spectroscopy and the amounts of deuterium present in the deuterated 1,*X*-napthyridines were established by mass spectrometry, using an AEI MS-902 instrument.

Registry No.—Ammonia, 7664-41-7.

Supplementary Material Available: NMR spectra of compounds **1**, **2**, **3**, and **4** in KNH_2–NH_3 (2 pages). Ordering information is given on any current masthead page.

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Synthesis and Properties of [1,2,3]Thiadiazolo[4,5-*d*]pyrimidine Derivatives Including Their Mesoionic Compounds. A New Class of Heterocycles[1]

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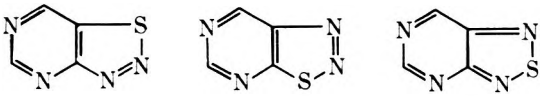
Treatment of 6-hydrazino-1,3-dimethyluracil (**1a**) with thionyl chloride gave 4,6-dimethyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**5a**), a new class of heterocycles. Reaction of 6-hydrazino-3-methyluracil (**8a**) with thionyl chloride afforded 6-methyl[1,2,3,5]thiatriazolino[5,4-c]pyrimidine-5,7(6*H*)-dione 1-oxide (**10a**), which was subsequently converted to 6-methyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5.7(4H,6H)-dione (**14a**) by a novel 1,3-sulfur migration. Treatment of 3-methyl-6-(1-methylhydrazino)uracil (**8d**) with thionyl chloride provided the mesoionic compound, *anhydro*-3,6-dimethyl-5-hydroxy[1,2,3]thiadiazolo[4,5-*d*]pyrimidinium-7(6*H*)-one hydroxide (**14d**), via the 1,3-sulfur migration of 3,6-dimethyl[1,2,3,5]thiatriazolino[5,4-c]pyrimidine-5,7(6*H*)-dione 1-oxide (**10d**). Several other thiadiazolo[4,5-*d*]pyrimidines including their mesoionic compounds were also synthesized. Thiation of **5a** with phosphorus pentasulfide in pyridine yielded 4,6-dimethyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidin-5(4*H*)-one-7(6*H*)-thione (**17**). Nucleophilic displacement of **17** with hydrazines furnished the corresponding 4,6-dimethyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidin-5(4*H*)-one 7(6*H*)-hydrazones (**18a–c**). The photolysis of **5a** in ethanol gave 1,3-dimethyl-5-mercaptouracil disulfide (**22**), while the thermolysis of **5a** in Dowtherm A yielded both 1,3,5,7-tetramethyl[1.4]dithiino[2,3-*d*;5,6-*e'*]dipyrimidine-2,6,8,10(1*H*,3*H*,5*H*,7*H*)-tetrone (**26**) and 1,3,5.7-tetramethylthiopheno[2,3-*d*;4,5-*e'*]dipyrimidine-2,6,8,9(1*H*,3*H*,5*H*,7*H*)-tetrone (**27**) probably via the thiirene intermediate **25**.

Although [1,2,3]thiadiazolo[5,4-*d*]pyrimidines (II)[2] and [1,2,5]thiadiazolo[3,4-*d*]pyrimidines (III)[3] have been extensively studied, primarily as potential purine and pteridine antagonists, nothing has been reported on the isomeric [1,2,3]thiadiazolo[4,5-*d*]pyrimidines (I). The present paper



I II III

describes the synthesis and properties of derivatives of I, including their mesoionic compounds. The derivatives of type I are of interest from a chemical as well as a biological point of view. Thus, they may be considered analogues of various biologically important bicyclic fused pyrimidines, e.g., purines, pyrazolo[3,4-*d*]pyrimidines, *v*-triazolo[4,5-*d*]pyrimidines (by virtue of the fusion of the five-membered ring to the pyrimidine nucleus), pteridines, pyrimido[5,4-e]-*as*-triazines, and pyrimido[4,5-*e*]-*as*-triazines (by the isoelectronic relationship between a sulfur atom and an ethylenic group[4]). Moreover, they may also be regarded as cyclic analogues of 5-mercaptopyrimidines[5] and 6-azopyrimidines,[6] which have been known to exhibit interesting biological activities.

Treatment of 1,3-dialkyl-6-hydrazinouracils (**1a**[7] and **1b**[8]) with excess thionyl chloride at room temperature (an exothermic reaction) for 30 min afforded good yields of the corresponding 4,6-dialkyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4H,6H)-diones (**5a** and **5b**), which were isolated by evaporation of the thionyl chloride and addition of water. The structures of these products were assigned by elemental analyses and spectral data. In particular, their UV spectra (see Table I) revealed the anticipated analogy with that of the known 6,8-dimethylpyrimido[4,5-c]pyridazine-5,7(6*H*,8*H*)-dione (**7**)[9] [λ_{max} (EtOH) 240 (log ϵ 3.98), 324 nm (3.56)].[4] Compounds **5a** and **5b** could also be obtained by similar treatment of 1,3-dialkyl-6-(1-methylhydrazino)uracils (**1c**[10] and **1d**) with thionyl chloride. When 6-hydrazino-1,3-dimethyl-2-thiouracil (**1e**) was used as a starting material, the product isolated was again **5a**. An analogous replacement of a sulfur by an oxygen has recently been reported on the reaction of 6-amino-1,3-diethyl-2-thiouracil with thionyl chloride–dimethylformamide mixture to give 5,7-diethyl-3-dimethylaminoisothiazolo[3,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione.[11] The reaction of **1a** or **1b** with thionyl chloride presumably proceeds by the initial formation of the sulfinyl chloride intermediate (**2a** or **2b**), followed by cyclization to the thiadiazoline *S*-oxide (**3a** or **3b**), and subsequent dehydration via the Pummerer reaction intermediate (**4a** or **4b**). A similar mechanism for the conversion of **3** to **5** via **4** has been speculated in the reaction of 6-substituted amino-1,3-dimethyluracils with thionyl chloride, leading to 4,6-dimethylthiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones.[12] In the case of **1c** or **1d** with thionyl chloride, the analogously formed Pummerer reaction intermediate (**4c** or **4d**) would undergo demethylation by the acid hydrolysis of the methylthiadiazolium chloride intermediate (**6c** or **6d**) during the workup (Scheme I).

The reaction of 3-alkyl-6-hydrazinouracils (**8a**,[13] **8b**, and **8c**) with excess thionyl chloride at room temperature (an exothermic reaction) for 30 min also provided the corresponding 6-alkyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (**14a**, **14b**, and **14c**). However, these reactions appeared to involve a strikingly different and unexpected mechanism with that of the foregoing. Namely, careful treatment of **8a** with thionyl chloride at 0 °C for 30 min gave relatively stable 6-methyl[1,2,3,5]thiatriazolino[5,4-*c*]-pyrimidine-5,7(6*H*)-dione 1-oxide (**10a**), probably via the

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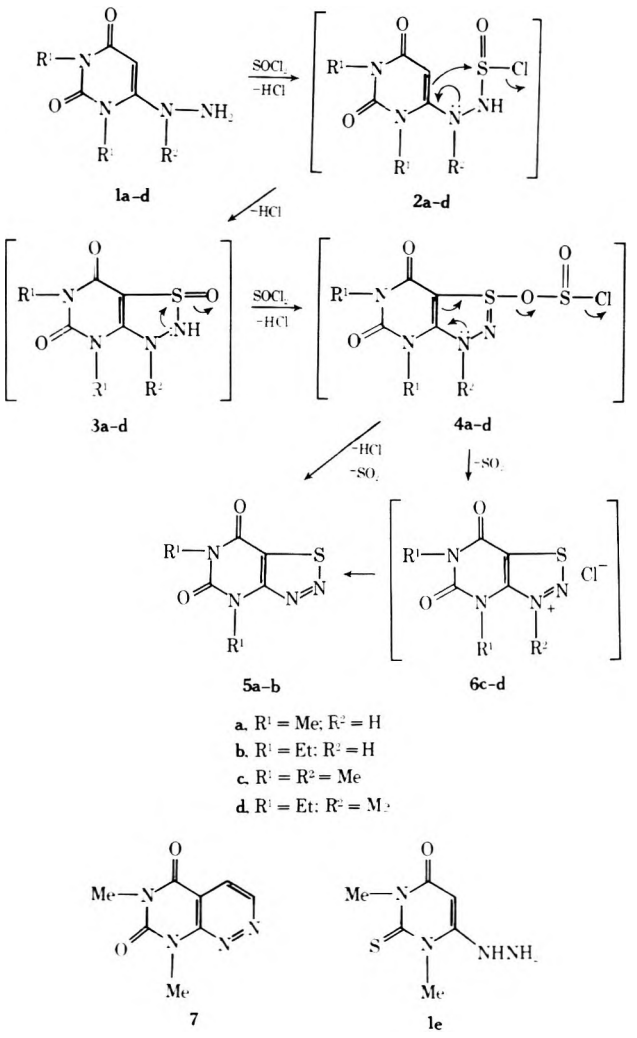
Table I. [1,2,3]Thiadiazolo[4,5-*d*]pyrimidines

Compd	Registry no.	Starting material	Registry no.	Yield, %	Mp,[a] °C	Formula[b]	NMR(Me_2SO-d_6), δ N-3	N-4	N-6	UV λ_{max} (EtOH), nm (log ε)	IR (Nujol), cm^{-1}
5a	60297-55-4	**1a**	40012-14-4	83	140–141	$C_6H_6N_4O_2S$		3.33 (s)	3.83 (s)	242 (3.81)	1715 (CO)
		1c	4318-53-0	78						327 (3.79)	
		1e	65150-59-6	63							
		14a		75							
5b	65150-55-2	**1b**	65150-60-9	92	81–82	$C_8H_{10}N_4O_2S$		1.25 (CH_3–, t)	1.40 (CH_3–, t)	240 (3.35)	1710 (CO)
		1d	65150-53-0	80				4.00 (–CH_2–, q)	4.08 (–CH_2–, q)	327 (3.37)	
14a	60297-58-7	**8a**	4318-55-2	82	235 dec	$C_5H_4N_4O_2S$		12.70 (br)[g]	3.26 (s)	250 (3.87)	1720 (CO)
		10a[c]	65150-61-0	52						320 (3.56)	3040–3200 (NH)
		10a[d]		90							
		14d		49							
14b	65150-57-4	**8b**	65150-54-1	47	142–144	$C_7H_8N_4O_2S$		11.33 (br)[g]	0.92 (CH_3–, t)	245 sh (3.46)	1720 (CO)
		14e		51					1.77 (–CH_2–, q)	275 (3.42)	3040–3200 (NH)
									4.20 (–CH_2–, q)	325 (3.44)	
14c	65150-58-5	**8c**	65150-56-3	72	179–181	$C_{11}H_8N_4O_2S$		9.63 (br)[g]	5.00 (–CH_2–, s)	230 sh (3.77)	1720 (CO)
		14f		35					7.30 (Ph, s)	260 (3.53)	3040–3200 (NH)
										398 (3.80)	
14d	60297-59-8	**8d**	42747-84-2	67	192–193	$C_6H_6N_4O_2S$	4.27 (s)		3.23 (s)	242 (5.22)	1690 (CO)
		10d	65150-64-3	71						300 (2.69)	
										405 (3.42)	
14e	65150-62-1	**8e**	65150-49-4	53	154–155	$C_8H_{10}N_4O_2S$	4.23 (s)		0.87 (CH_3–, t)	243 (3.68)	1680 (CO)
									1.53 (–CH_2–, q)	300 (2.27)	
									3.83 (–CH_2–, q)	410 (2.82)	
14f	65150-63-2	**8f**	52197-07-6	58	148–149	$C_{12}H_{11}N_4O_2S$	4.26 (s)		5.07 (–CH_2–, s)	245 (4.36)	1690 (CO)
									7.26 (Ph, s)	300 (2.69)	
										410 (3.59)	
14g	65150-52-9	**8g**	21236-98-6	90	294–295	$C_{11}H_8N_4O_2S$	7.66–8.33 (m)[e,f]		3.63 (s)[h]	225 (4.39)	1710 (CO)
										282 (4.42)	
17	65150-40-5	**5a**		82	159–160	$C_6H_6N_4OS_2$		3.73 (s)	3.83 (s)	250 (4.11)	1690 (CO)
										375 (4.03)	
18a	65150-42-7	**17**		85	229–230	$C_6H_8N_6OS$		3.31 (s)	3.66 (s)	245 sh (3.37)	1670 (CO)
									5.63 (s)[h]	325 (3.23)	3300 (NH)
18b	65150-43-8	**17**		84	135–136	$C_7H_{10}N_6OS$				243 sh (3.40)	1675 (CO)
										327 (3.26)	3220 (NH)
18c	65150-44-9	**17**		81	172–173	$C_{12}H_{12}N_6OS$				247 (3.74)	1690 (CO)
										325 (2.61)	3240 (NH)

[a] All compounds were recrystallized from EtOH. [b] All compounds were analyzed for C, H, and N within ±0.4%. [c] In the presence of thionyl chloride. [d] In the presence of EtOH. [e] Determined in CF_3COOD. [f] The chemical shift at position 2. [g] Exchangeable with D_2O. [h] The chemical shift of the extranuclear amino group.

sulfinyl chloride intermediate (**9a**), which upon refluxing in either thionyl chloride for 15 min or ethanol for a prolonged period resulted in the formation of **14a**. The structural assignment of **10a** was derived from its NMR and IR spectra: the presence of a singlet (δ 5.38) for position 4 and a sulfoxide absorption band (1090 cm^{-1}).[14] The formulation of **14a** was based on the close relationship of its UV spectrum to that of **5a** as well as its methylation to **5a** using methyl iodide in dimethylformamide containing potassium carbonate. The ring transformation of **10a** to **14a** involving a novel 1,3-sulfur migration can be best explained in terms of the initial ring opening of **10a** to the sulfinyl intermediate (**11a**), followed by intramolecular recyclization to the thiadiazolino[4,5-*d*]pyrimidine *S*-oxide (**12a**) (1,3-sulfur migration), and subsequent dehydration through the Pummerer reaction intermediate (**13a**). In the absence of thionyl chloride, **12a** would directly undergo dehydration to give **14a**. Attempts to isolate pure **10b** and **10c** in the reaction of **8b** or **8c** with thionyl chloride were unsuccessful, indicating that the stability of **10a** might arise from an electron-releasing character of the methyl group. The

Scheme I



isolation of **10a** is worthy of note as such a compound has rarely been isolated in the reaction of 2-hydrazinopyridine with thionyl chloride[15] (Scheme II).

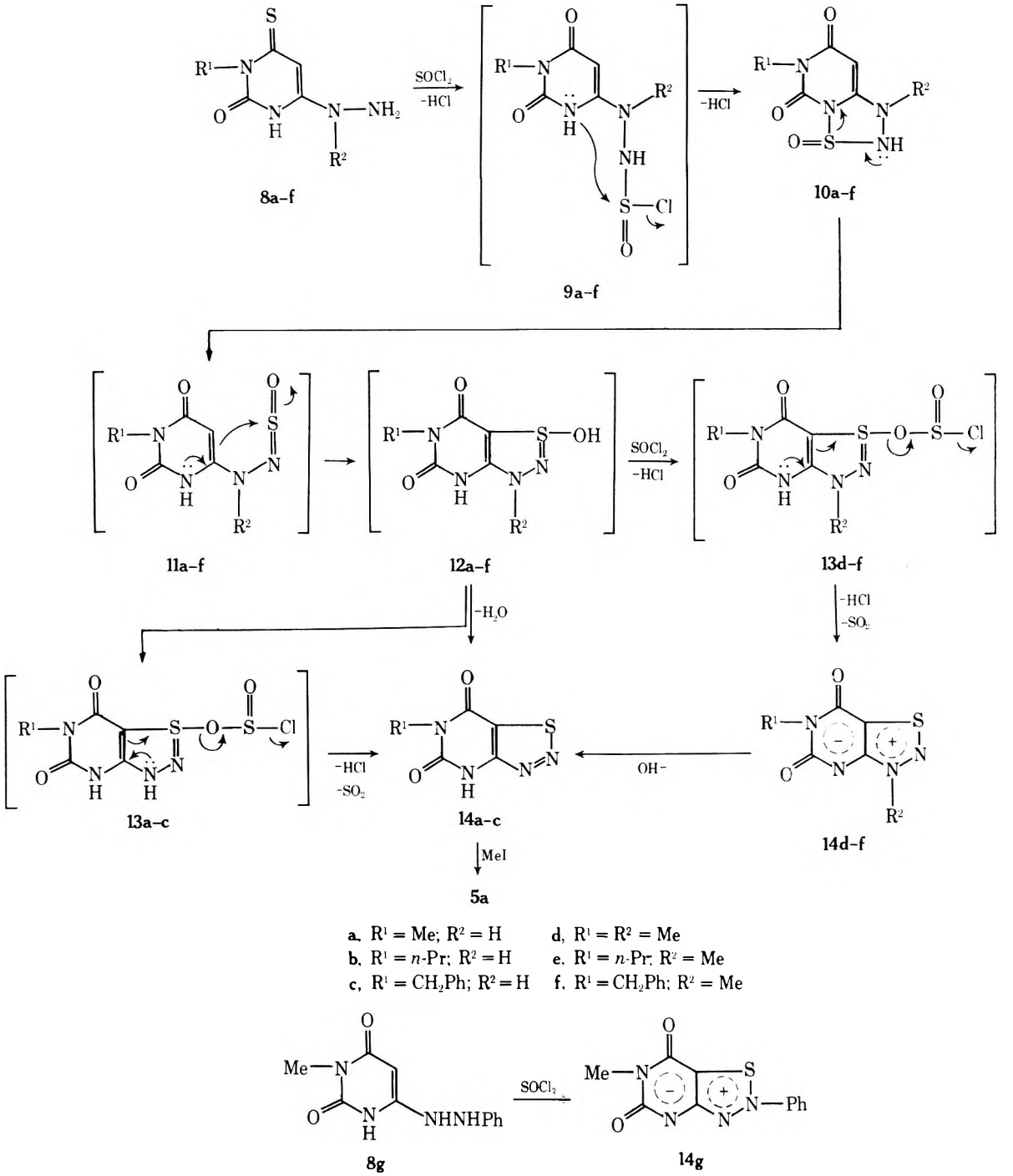
The reaction of hydrazinouracils with thionyl chloride described above could successfully be extended to the preparation of mesoionic [1,2,3]thiadiazolo[4,5-*d*]pyrimidines, a new class of mesoionic heterocycles. Namely, treatment of 3-methyl-6-(1-methylhydrazino)uracil (**8d**)[16] with thionyl chloride at 0 °C for 30 min gave 3,6-dimethyl[1,2,3,5]thiatriazolino[5,4-*c*]pyrimidine-5,7(6*H*)-dione 1-oxide (**10d**) [δ 5.32 (s, 1 H, C-4 H); 1100 cm^{-1} (SO)],[14] which upon refluxing in thionyl chloride for 15 min afforded the mesoionic compound, *anhydro*-3,6-dimethyl-5-hydroxy[1,2,3]thiadiazolo[4,5-*d*]pyrimidinium-7(6*H*)-one hydroxide (**14d**) in a good yield. Compound **14d** was also attained directly from **8d** by treatment with thionyl chloride at room temperature (an exothermic reaction). As depicted in Scheme II, the rearrangement of **10d** to **14d** accompanying 1,3-sulfur migration was envisioned as proceeding through the Pummerer reaction intermediate (**13d**). The thermal ring transformation observed on **10a** seems to be less favorable in the case of **10d**, since no reaction occurred even after refluxing **10d** in dioxane (bp 101 °C) for 1 h. In contrast with the reaction of **8d** with thionyl chloride giving **10d**, treatment of other 3-alkyl-6-(1-methylhydrazino)uracils (**8e** and **8f**[17]) with thionyl chloride directly gave the respective mesoionic compounds (**14e** and **14f**), and attempted isolation of the intermediates (**10e** and **10f**) was again unsuccessful. These findings are consistent with the observed instability of **10b** and **10c**. 3-Methyl-6-(2-phenylhydrazino)uracil (**8g**)[18] was also converted directly to *anhydro*-6-methyl-2-phenyl-5-hydroxy[1,2,3]thiadiazolo-[4,5-*d*]pyrimidinium-7(6*H*)-one hydroxide (**14g**). The characterization of the mesoionic compounds prepared was established by analytical and spectral data as well as their smooth conversion to **14a, 14b,** and **14c** by the action of 0.5% sodium hydroxide in the cases of **14d, 14e,** and **14f.**

We next investigated the chemical properties of **5a.** Compound **5a** was extremely stable against acid hydrolysis. Thus, heating **5a** with concentrated hydrochloric acid in a sealed tube at 100 °C for 8 h resulted in the quantitative recovery of **5a.** Similar stability was also noted in the mesoionic compounds. For example, refluxing **14d** in 10% hydrochloric acid for 1 h did not give any hydrolyzed products. On the contrary, alkaline hydrolysis of **5a** with 0.6% potassium hydroxide gave the unexpected 1,3-dimethylbarbituric acid (**15**)[7] in 20% yield as the only isolatable product[19] (Scheme III). Reduction of **5a** with Raney nickel in ethanol caused the dethiation and nitrogen–nitrogen double bond cleavage to give a 60% yield of 6-amino-1,3-dimethyluracil (**16**).[20] Thiation of **5a** with excess phosphorus pentasulfide in pyridine furnished 4,6-dimethyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidin-5(4*H*)-one-7(6*H*)-thione (**17**) in a good yield. The actual site of thiation was decided by the fact that heating **17** with saturated ethanolic ammonia in a sealed tube yields the known 6-amino-1,3-dimethyl-4-thiouracil (1,3-dimethyl-6-thiocytosine) (**19**).[21] The sulfur atom at position 7 of **17** was found to react with hydrazines in a sealed tube to provide the corresponding 4,6-dimethyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidin-5(4*H*)-one 7(6*H*)-hydrazones (**18a, 18b,** and **18c**). However, aniline did not give the expected product, presumably owing to its lower nucleophilicity than that of hydrazines.

In connection with recent interest in the possible involvement of thiirene intermediates in the photolysis and thermolyses of 1,2,3-thiadiazoles[22] and 1,2,3-benzothiadiazoles,[23] we also examined these reactions on **5a.** The irradiation of **5a** in ethanol by a high-pressure mercury lamp in a stream of nitrogen provided a 50% yield of symmetric 1,3-dimethyl-5-mercaptouracil disulfide (**22**). The disulfide **22** was readily characterized by the NMR spectrum and by its alternative synthesis consisting of the thermolysis of 1,3-dimethyl-5-mercaptouracil sulfide (**23**)[24] in Dowtherm A. A reasonable mechanism for the conversion of **5a** to **22** is that the initial formation of the diradical (**20a**) by the extrusion of nitrogen, followed by hydrogen abstraction from the solvent to give the thiyl radical (**21**), and subsequent dimerization. The thermolysis of **23** to **22** may also be explained by the participation of **21.** The structure of **22** was also supported by its thermal conversion to **23** in Dowtherm A (Scheme IV).

In contrast to the above results, the thermolysis of **5a** in Dowtherm A at 280 °C for 4 h surprisingly gave both 1,3,5,7-tetramethyl[1,4]dithiino[2,3-*d*;5,6-*e'*]dipyrimidine-2,6,8,10(1*H*,3*H*,5*H*,7*H*)-tetrone (**26**) and 1,3,5,7-tetramethylthiopheno[2,3-*d*;4,5-e']dipyrimidine-2,6,8,9-(1*H*,3*H*,5*H*,-7*H*)-tetrone (**27**) in 24 and 65% yield, respectively. Compound **27** was readily precipitated out from the reaction mixture and **26** was isolated by dilution of the filtrate with ethanol. When 5,7-dimethyl[1,2,3]thiadiazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**24**),[25] an isomer of **5a,** was treated under the same conditions, **27** was again obtained in 84% yield.[26] The NMR data and elemental analyses of **26** and **27** supported the structures indicated; however, these data could not unequivocally exclude the possibility of the isomeric structures **29** for **26** and **30** or **31** for **27.** Rigorous structural proofs of **26** and **27** were accomplished by the following evidences. Heating **26** in Dowtherm A under similar conditions afforded **27,** indicating that **26** is a precursor of **27.** Reduction of **27** with Raney nickel furnished symmetric 5,5'-di(1,3-dimethyl)uracil (**28**), whose NMR spectrum (CF_3COOD) showed two singlets (δ 3.10 and 3.17) as four *N*-methyl groups and a singlet (δ 7.43)

Scheme II



as two protons at position 6 and 6′. The close proximity of the latter chemical shift to the reported value (CF_3COOD, δ 7.34)[27] for position 6 of 1,3-dimethyluracil supported the validity of the structure of **27**. Additional evidence for the assignment of **27** was derived from the comparison of its UV spectrum with that of recently reported 1,3,5,7-tetraethylthiopheno[2,3-*d*;4,5-*e*′]dipyrimidine-2,6,8,9(1*H*,3*H*,5*H*,-7*H*)-tetrone (**32**),[28] which could alternately be prepared by the thermolysis of **5b**. We suggest that the formation of **27** from either **5a** or **24** involves the intermediacy of thiirene (**25**). Thus, the thermolysis of **5a** or **24** could give the respective diradicals (**20a** and **20b**), both of which cyclize to **25**. Subsequent ring opening of **25** would provide both diradicals **20a** and **20b**, respectively. Reaction of either **20a** with **20b** or **25** with **20b** could yield **26**. Thus formed **26** can then undergo ring contraction to give **27**. The conversion of 1,4-dithiins to thiophenes has been well documented[29] (Scheme V).

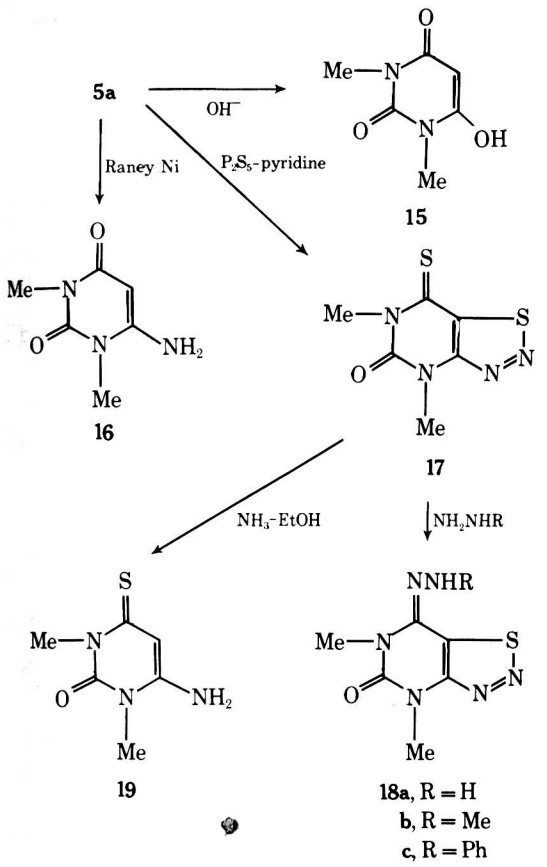
Experimental Section

Melting points were taken on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded on a Japan Spectroscopic Co., Ltd., spectrophotometer Model IR-E from samples mulled in Nujol. NMR spectra were determined at 60 MHz with a Varian T-60 spectrometer using tetramethylsilane as the internal standard. UV spectra were recorded on a Hitachi 124 spectrophotometer. Mass spectra were performed on a JMS D100 EI spectrometer by a direct inlet system at 75 eV. [1,2,3]Thiadiazolo[4,5-*d*]pyrimidine derivatives prepared are summarized in Table I.

Preparation of 1,3-Dialkyl-6-hydrazinouracils (1a–e) and 3-Alkyl-6-hydrazinouracils (8a–g). Compounds **1a**,[7] **1b**,[8] **1c**,[10] **8a**,[13] **8d**,[16] **8f**,[17] and **8g**[18] were prepared according to the reported procedures, and other uracils were obtained as follows.

1,3-Diethyl-6-(1-methylhydrazino)uracil (1d) and 6-(1-Methylhydrazino)-3-*n*-propyluracil (8e). A mixture of 6-chloro-1,3-diethyluracil[7] (0.426 g, 0.002 mol) or 6-chloro-3-*n*-propyluracil[30] (1.0 g, 0.005 mol) and methylhydrazine (1 mL) in EtOH (10 mL) was stirred at room temperature for 3 h. The reaction mixture was evap-

Scheme III

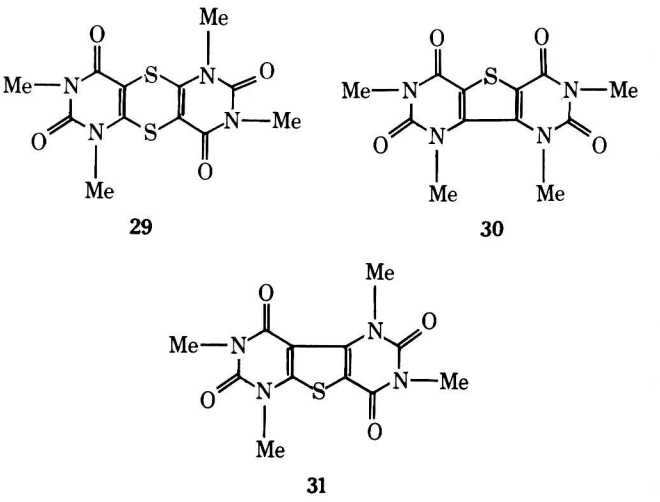


orated in vacuo and the residue was recrystallized from EtOH–H_2O to give the corresponding products.

Compound **1d** (0.26 g; 62%): mp 102–104 °C. Anal. Calcd for $C_6H_{16}N_4O_2$: C, 50.93; H, 7.60; N, 26.40. Found: C, 50.72; H, 7.59; N, 26.31

Compound **8e** (0.86 g; 85%): mp 119–120 °C. Anal. Calcd for $C_6H_{14}N_4O_2$: C, 48.47; H, 7.12; N, 28.27. Found: C, 48.51; H, 7.05; N, 28.15

6-Hydrazino-3-*n*-propyluracil (8b) and 3-Benzyl-6-hydrazinouracil (8c). A mixture of 6-chloro-3-*n*-propyluracil[13] (0.94 g, 0.005 mol) or 3-benzyl-6-chlorouracil[31] (0.6 g, 0.0025 mol) and 10% hydrazine hydrate (10 mL) was refluxed for 45 min. The reaction mixture



was evaporated in vacuo and the residue was covered with H_2O. The insoluble material was filtered and recrystallized from EtOH to give the corresponding products.

Compound **8b** (0.64 g; 62%): mp 242–243 °C. Anal. Calcd for $C_7H_{12}N_4O_2$: C, 45.64; H, 6.57; N, 30.43. Found: C, 45.33; H, 6.47; N, 30.48.

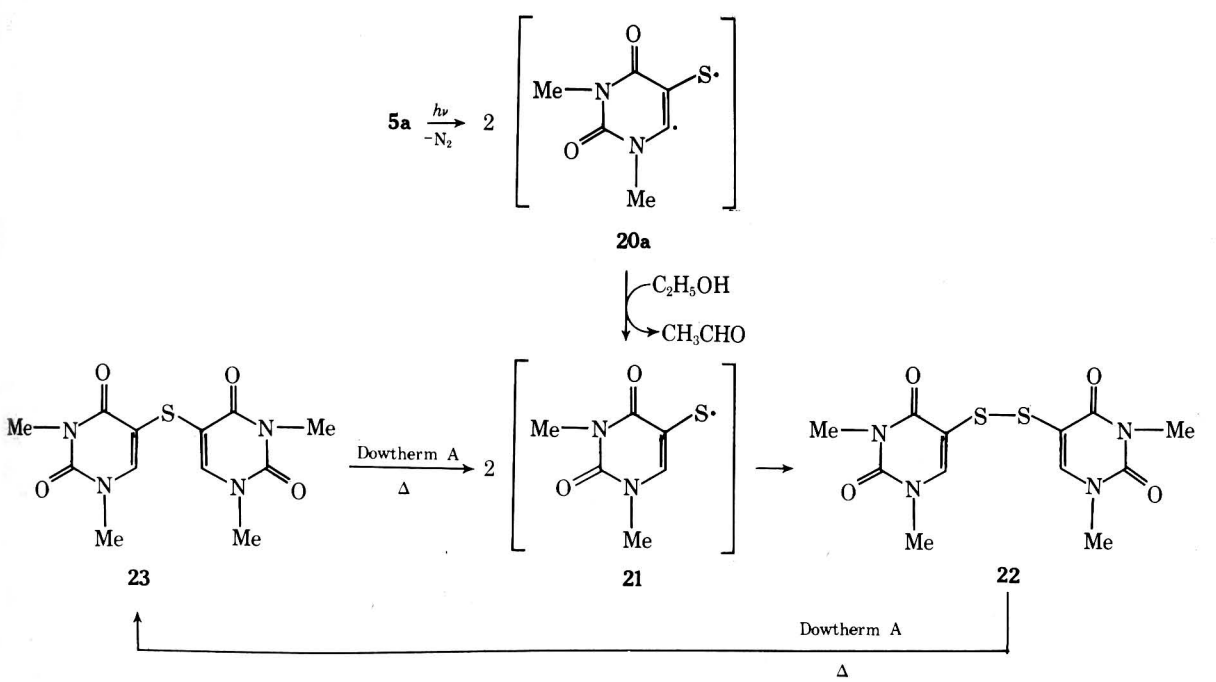
Compound **8c** (0.5 g; 90%): mp 212–213 °C. Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.13. Found: C, 56.83; H, 5.29; N, 24.34.

6-Hydrazino-1,3-dimethyl-2-thiouracil (1e). This compound was prepared by two steps starting with 1,3-dimethyl-2-thiobarbituric acid.[32] A mixture of 1,3-dimethyl-2-thiobarbituric acid (1.72 g, 0.01 mol) and $POCl_3$ (10 mL) containing H_2O (0.5 mL) was refluxed for 45 min. The excess $POCl_3$ was removed in vacuo and the residue (syrup) was poured onto ice–H_2O. The solution was extracted with $CHCl_3$ (three 30-mL portions) and dried (Na_2SO_4). The $CHCl_3$ extracts were evaporated in vacuo and the residue was recrystallized from EtOH to give 6-chloro-1,3-dimethyl-2-thiouracil (1 g; 53%): mp 189–191 °C. Anal. Calcd for $C_6H_7ClN_2OS$: C, 37.80; H, 3.71; N, 14.70. Found: C, 37.56; H, 3.77; N, 14.99.

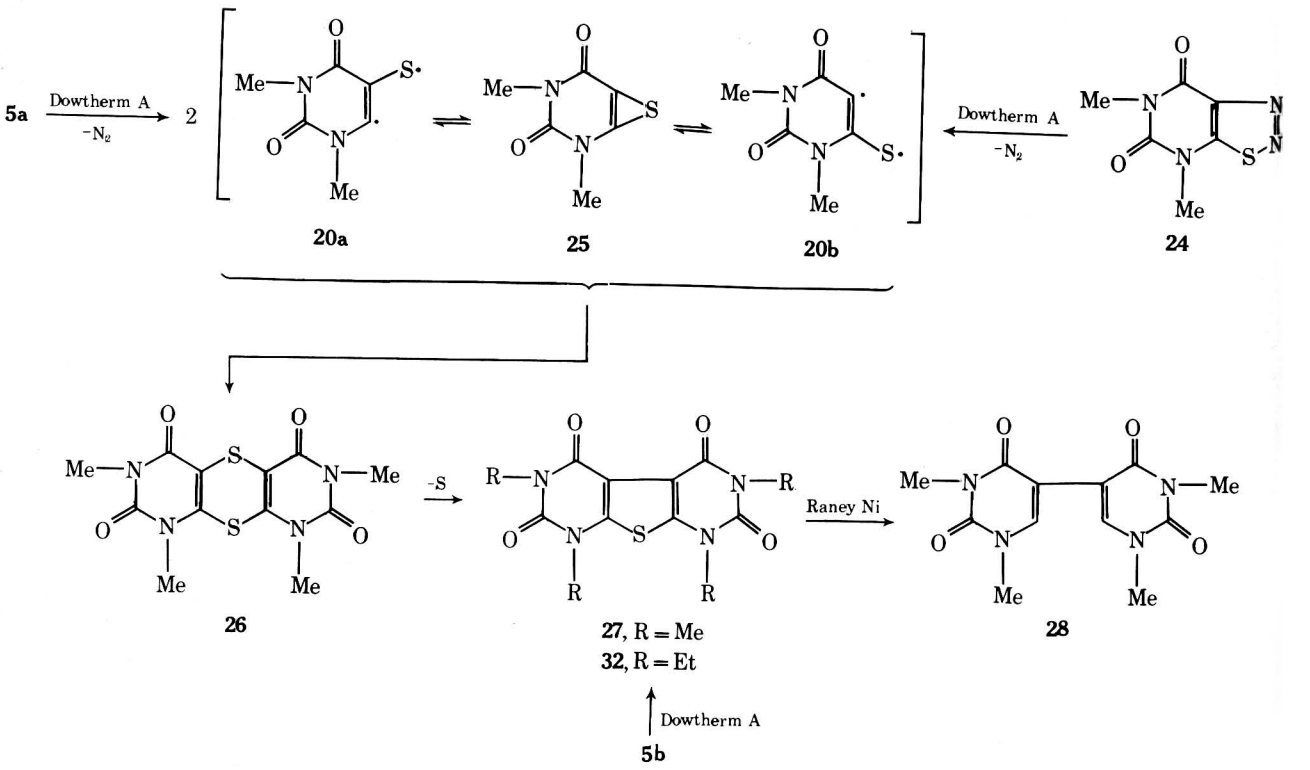
A mixture of the chlorouracil (0.38 g, 0.002 mol) and 10% hydrazine hydrate (5 mL) was treated as described in the preparation of **8b** and **8c** to give **1e** (0.21 g; 60%): mp 223–224 °C. Anal. Calcd for $C_6H_{10}N_4OS$: C, 38.69; H, 5.42; N, 30.09. Found: C, 38.70; H, 5.31; N, 30.00.

4,6-Dialkyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-diones (5a–b). Method A. A mixture of the appropriate hydrazinouracils **1a–d** (0.01 mol) and thionyl chloride (20 mL) was stirred

Scheme IV



Scheme V



at room temperature (an exothermic reaction) for 30 min. The resulting solution was evaporated in vacuo and the residue was covered with chilled H_2O. The insoluble material was filtered and recrystallized to give the corresponding **5**.

In complete analogy with the above results, treatment of **1e** with thionyl chloride afforded **5a**.

Method B. A mixture of 6-methyl[1,2,3]thiadiazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (**14a**) (0.184 g, 0.001 mol), methyl iodide (0.426 g, 0.003 mol), and K_2CO_3 (0.414 g, 0.003 mol) in DMF (10 mL) was refluxed for 2 h. The reaction mixture was evaporated in vacuo and the residue was covered with H_2O. The insoluble solid was filtered and recrystallized to give **5a**.

6-Alkyl[1,2,3]thiadiazolo[4,5-d]pyrimidine-5,7(4*H*,6*H*)-diones (14a–c). Method A. A mixture of the appropriate hydrazinouracils **8a–c** (0.001 mol) with thionyl chloride (2 mL) was stirred at room temperature (an exothermic reaction) for 30 min. The reaction mixture was treated as described in method A of **5a–b** to give the corresponding **14**.

Method B. A suspension of 6-methyl[1,2,3,5]thiatriazolino[5,4-*c*]pyrimidine-5,7(6*H*)-dione 1-oxide (**10a**) (0.2 g, 0.001 mol) and thionyl chloride (2 mL) was refluxed for 15 min. The reaction mixture was treated as described in method A of **5a–b** to give **14a**.

Method C. A mixture of **10a** (0.2 g, 0.001 mol) and EtOH (10 mL) was refluxed for 3 h. The reaction mixture was evaporated in vacuo and the residue was recrystallized to yield **14a**.

Method D. A suspension of the appropriate *anhydro*-6-alkyl-3-methyl-5-hydroxy[1,2,3]thiadiazolo[4,5-*d*]pyrimidinium-7(6*H*)-one hydroxide (**14d–e**) (0.001 mol) in 5% NaOH (5 mL) was heated at 95 °C for 10 min. The reaction mixture was neutralized with 5% HCl and extracted with $CHCl_3$ (three 10-mL portions). The $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated in vacuo. Recrystallization of the residue afforded the respective **14a–c**.

6-Methyl[1,2,3,5]thiatriazolino[5,4-c]pyrimidine-5,7(6*H*)-dione 1-Oxides (10a and 10d). To ice-cooled (0 °C) thionyl chloride (5 mL) was added **8a** or **8d** (0.001 mol) over a period of 5 min with good stirring, and the mixture was maintained at the same temperature for 30 min. The reaction mixture was rapidly evaporated in vacuo at room temperature and the residue was covered with ice–H_2O. The separated solid was recrystallized to give the corresponding pure products.

Compound **10a:** recrystallized from MeOH (1.35 g; 67%); mp 197–198 °C; IR 1090 (SO), 1720 (CO), 3160 cm^{-1} (NH); NMR (Me_2SO-d_6) δ 3.14 (s, 3 H, NCH_3), 5.38 (s, H, C-4 H), 12.50 (br, 2 H, N-2 H and N-3 H); MS *m/e* 202 (M^+); UV λ_{max} (EtOH) 260 (log ϵ 3.85), 400 nm (4.04). Anal. Calcd for $C_5H_6N_4O_3S$: C, 29.70; H, 2.97; N, 27.71. Found: C, 30.01; H, 3.01; N, 27.46.

Compound **10d:** recrystallized from EtOH (1.45 g; 67%); mp 202 °C; IR 1100 (SO), 1715 (CO), 3080 cm^{-1} (NH); NMR (Me_2SO-d_6) δ 3.10 (s, 3 H, NCH_3), 4.00 (s, 3 H, NCH_3), 5.32 (s, 1 H, C-4 H), 12.00 (br, 1 H, NH); MS *m/e* 216 (M^+); UV λ_{max} (EtOH) 265 (log ϵ 4.25), 343 nm (4.24). Anal. Calcd for $C_6H_8N_4O_3S$: C, 33.32; H, 3.74; N, 25.92. Found: C, 33.61; H, 3.72; N, 25.96.

***anhydro*-6-Alkyl-3-methyl-5-hydroxy[1,2,3]thiadiazolo-[4,5-*d*]pyrimidinium-7(6*H*)-one Hydroxides (14d–f) and *anhydro*-6-Methyl-2-phenyl-5-hydroxy[1,2,3]thiadiazolo[4,5-*d*]-pyrimidinium-7(6*H*)-one Hydroxide (14g). Method A.** A mixture of the appropriate **8d–g** (0.001 mol) and thionyl chloride (1 mL) was stirred at room temperature (an exothermic reaction) for 30 min. The reaction mixture was evaporated in vacuo and the residue was dissolved in chilled H_2O (30 mL). The solution was extracted with $CHCl_3$ (three 20-mL portions) and the $CHCl_3$ extracts were dried (Na_2SO_4). Evaporation of the extracts in vacuo and the recrystallization of the residue afforded the corresponding products **14d–g**.

Method B. A mixture of **10d** (0.216 g, 0.001 mol) and thionyl chloride (2 mL) was refluxed for 15 min. The reaction mixture was treated as described in method A to give **14d**.

1,3-Dimethylbarbituric Acid (15). A suspension of **5a** (0.198 g, 0.001 mol) in 0.6% KOH (5 mL) was heated at 95 °C for 3 h. The reaction mixture was neutralized with AcOH and the precipitated solid was filtered. Recrystallization from EtOH gave **15** (0.03 g, 20%), mp 123–124 °C, identical with an authentic sample.[7]

6-Amino-1,3-dimethyluracil (16). A mixture of **5a** (0.198 g, 0.001 mol) and Raney Ni (NDHT-90, 0.5 g) in EtOH (20 mL) was refluxed for 1 h. The reaction mixture was filtered and the filtrate was evaporated in vacuo. The residue was recrystallized from EtOH–DMF to give **16** (0.09 g, 60%), mp >300 °C, identical with an authentic sample.[20]

4,6-Dimethyl[1,2,3]thiadiazolo[4,5-d]pyrimidin-5(4*H*)-one-7(6*H*)-thione (17). A mixture of **5a** (1.98 g, 0.01 mol) and P_2S_5 (4.44 g, 0.02 mol) in pyridine (60 mL) was refluxed for 3 h. The reaction mixture was evaporated in vacuo and the residue was covered with hot H_2O. After cooling, the precipitates were filtered and recrystallized to give **17**.

4,6-Dimethyl[1,2,3]thiadiazolo[4,5-d]pyrimidin-5(4*H*)-one-7(6*H*)-Hydrazones (18a–c). A mixture of **17** (0.214 g, 0.001 mol) and the appropriate hydrazines (1 mL) in EtOH (5 mL) was heated in a sealed tube at 100 °C for 3 h. The precipitated crystals were filtered and recrystallized to give the corresponding products **18a–c**.

6-Amino-1,3-dimethyl-4-thiouracil (1,3-Dimethyl-6-thiocytosine; 19). A suspension of **17** (0.214 g, 0.001 mol) in saturated ethanolic NH_3 (10 mL) was heated in a sealed tube at 100 °C for 2 h. The precipitated solid was filtered and recrystallized from EtOH to

give **19** (0.16 g; 94%), mp 267 °C dec, identical with an authentic sample.[21]

1,3-Dimethyl-5-mercaptouracil Disulfide (22). Method A. A solution of **5a** (0.198 g, 0.001 mol) in EtOH (400 mL) was irradiated with a 100-W high-pressure mercury lamp surrounded by a H_2O-cooled Pyrex filter at 30 °C for 2 h in a stream of nitrogen. The reaction mixture was evaporated in vacuo and the residue was recrystallized from EtOH to give **22** (0.086 g; 50%): mp 243–245 °C; IR 1710 cm^{-1} (CO); NMR (CF_3COOD) δ 3.23 (s, 6 H, two NCH_3), 3.33 (s, 6 H, two NCH_3), 8.17 (s, 2 H, two C-6 H); MS *m/e* 342 (M^+); UV λ_{max} (EtOH) 220 sh (log ε 3.93), 285 nm (4.01). Anal. Calcd for $C_{12}H_{14}O_4N_4S_2$: C, 42.09; H, 4.13; N, 16.36. Found: C, 42.20; H, 4.28; N, 16.30.

Method B. A mixture of 1,3-dimethyl-5-mercaptouracil sulfide (**23**)[24] (0.3 g, 0.001 mol) and Dowtherm A (1 mL) was heated at 280 °C for 2 h. The reaction mixture was diluted with *n*-hexane (10 mL) and the precipitated crystals were filtered. Recrystallization of the crude product from EtOH afforded **22** (0.08 g; 24%), identical with the material prepared by method A.

1,3-Dimethyl-5-mercaptouracil Sulfide (23). A mixture of **22** (0.103 g, 0.003 mol) and Dowtherm A (1 mL) was heated at 270 °C for 5 h. The reaction mixture was treated as described in method B of **22** to give **23** (0.03 g; 32%), mp 288 °C, identical with an authentic sample.[24]

1,3,5,7-Tetramethyl[1,4]dithiino[2,3-d;5,6-e']dipyrimidine-2,6,8,10(1*H*,3*H*,5*H*,7*H*)-tetrone (26) and 1,3,5,7-Tetramethylthiopheno[2,3-d;4,5-e']dipyrimidine-2,6,8,9(1*H*,3*H*,5*H*,7*H*)-tetrone (27). A mixture of **5a** (1.0 g, 0.005 mol) and Dowtherm A (2 mL) was heated at 280 °C for 4 h. After standing overnight at room temperature, the precipitated solid was filtered and recrystallized from DMF to give **27** (0.5 g; 65%): mp >300 °C; IR 1705 cm^{-1} (CO); NMR (CF_3COOD) δ 3.13 (s, 6 H, two NCH_3), 3.26 (s, 6 H, two NCH_3); MS *m/e* 308 (M^+); UV λ_{max} (EtOH) 245 (log ε 2.95), 304 nm (2.80). Anal. Calcd for $C_{12}H_{12}N_4O_4S$: C, 46.80; H, 3.97; N, 18.40. Found: C, 46.75; H, 3.90; N, 18.18.

The filtrate which removed **27** was diluted with EtOH (5 mL) and the precipitated crystals were filtered. The crude product was recrystallized from DMF–EtOH to give **26** (0.2 g; 24%): mp >300 °C; IR 1710 cm^{-1} (CO); NMR (CF_3COOD) δ 3.53 (s, 6 H, two NCH_3), 3.86 (s, 6 H, two NCH_3); MS *m/e* 340 (M^+); UV λ_{max} (EtOH) 230 (log ε 3.64), 280 (3.27), 310 nm (2.98). Anal. Calcd for $C_{12}H_{12}N_4O_4S_2$: C, 42.57; H, 3.24; N, 16.53. Found: C, 42.35; H, 3.53; N, 16.47.

Compound **27** was also prepared by the thermolysis of 5,7-dimethyl[1,2,3]thiadiazolo[5,4-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**24**) (0.8 g, 0.004 mol) in Dowtherm A (3 mL) at 290 °C for 3 h in 81% yield (0.41 g).

5,5-Di(1,3-dimethyl)uracil (28). A suspension of **27** (0.3 g, 0.001 mol) and Raney Ni (NDHT-90, 1 g) in EtOH (30 mL) was refluxed with stirring for 30 min. The reaction mixture was filtered and the filtrate was evaporated in vacuo. The residue was recrystallized from EtOH to give **28** (0.26 g, 95%): mp 286 °C; IR 1690 cm^{-1} (CO); NMR (CF_3COOD) δ 3.10 (s, 6 H, two NCH_3), 3.17 (s, 6 H, two NCH_3), 7.43 (s, 2 H, two C-6 H); MS *m/e* 278 (M^+); UV λ_{max} (EtOH) 238 sh (log ε 3.77), 294 nm (3.89). Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.07; N, 20.14. Found: C, 51.78; H, 4.95; N, 19.76.

1,3,5,7-Tetraethylthiopheno[2,3-d;4,5-e']dipyrimidine-2,6,8,9(1*H*,3*H*,5*H*,7*H*)-tetrone (32). A mixture of **5b** (0.45 g, 0.002 mol) and Dowtherm A (0.2 mL) was heated at 250 °C for 2 h. The reaction mixture was diluted with *n*-hexane (10 mL) and the precipitated crystals were filtered. Recrystallization from EtOAc afforded **32** (0.2 g; 55%): mp 204–205 °C (lit.[28] mp 204–205 °C); IR 1710 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.22 (t, 6 H, two CH_3–), 1.40 (t, 6 H, two CH_3–), 4.02 (two q, 8 H, four $-CH_2-$); MS *m/e* 364 (M^+); UV λ_{max} (EtOH) 245 (log ε 3.94), 304 nm (3.91). Anal. Calcd for $C_{16}H_{20}N_4O_4S$: C, 52.72; H, 5.54; N, 15.38. Found: C, 52.75; H, 5.31; N, 15.33.

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Registry No.—**15,** 41949-07-9; **16,** 6642-31-5; **19,** 6506-84-9; **22,** 65150-45-0; **23,** 37737-50-1; **24,** 65150-48-3; **26,** 65150-46-1; **27,** 65150-47-2; **28,** 7033-42-3; **32,** 65150-50-7; 6-chloro-1,3-diethyluracil, 65150-41-6; 6-chloro-3-*n*-propyluracil, 50721-48-7; methylhydrazine, 60-34-4; 3-benzyl-6-chlorouracil, 5759-76-2; 1,3-dimethyl-2-thiobarbituric acid, 3158-63-2; 6-chloro-1,3-dimethyl-2-thiouracil, 65150-51-8; hydrazine, 302-01-2; phenylhydrazine, 100-63-0; 3-*n*-propylbarbituric acid, 5496-93-5.

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Reactions and Syntheses with Organometallic Compounds. 7. Synthesis of Benzolactams by Palladium-Catalyzed Amidation

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o-Bromoaminoalkylbenzene **5** was heated with a catalytic amount of $Pd(OAc)_2$–PPh_3 in the presence of n-Bu_3N in a carbon monoxide atmosphere to give five-, six-, and even seven-membered benzolactams, that is, isoindolinone, isoquinolinone, and benzazepinone derivatives, in good yields.

Low-valent metal complexes can be oxidatively inserted into aryl halides to afford aryl metal complexes; this process has been developed by us as a novel synthesis for heterocyclic compounds.[1] Aryl metal complexes (2, M = Ni or Pd; Scheme I), which were prepared from aryl halides (1, X = Br or Cl) and low-valent metal complexes such as $Ni(PPh_3)_n$ or $Pd(PPh_3)_n$, react with an internal double bond to give indole, oxindole,[1a] quinoline,[1c] isoquinoline,[1b] and benzazepine derivatives.[1c] It was thus anticipated that the acyl metal complex **7** could react with an internal amino group to produce the benzolactam **8**.

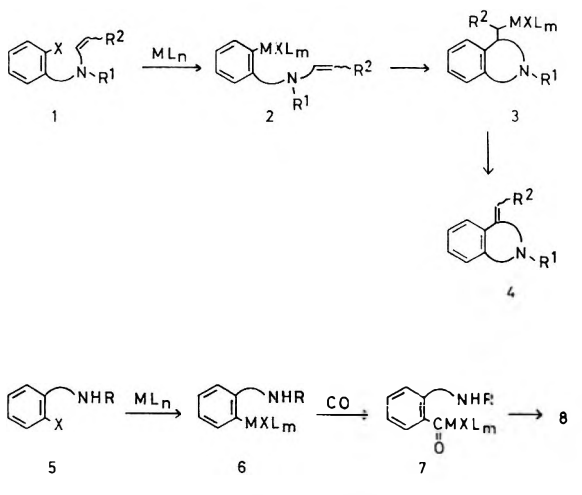
Carbonylation by means of transition metals is a useful process, but the reaction usually requires rather drastic conditions such as a high pressure of carbon monoxide and an elevated temperature.[2] However, Heck et al. reported the ingenious process of palladium-catalyzed carboalkoxylation and amidation under milder conditions at 100 °C or lower temperatures in an atmospheric pressure of carbon monoxide.[3]

$$ArX + R^1NH_2 + R^2{}_3N \xrightarrow[Pd(OAc)_2-PPh_3]{CO} ArCONHR^1 + R^2{}_3NH^+X^-$$

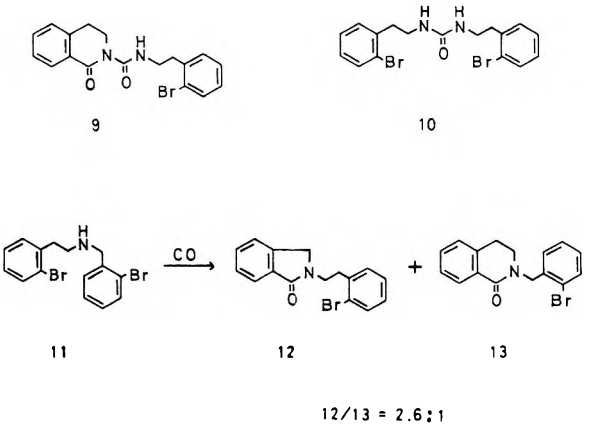
We now report a new and facile synthesis of benzolactams by utilization of this palladium-catalyzed amidation. Existing processes for these benzolactams **8** are lengthy and have serious practical limitations.

In a typical example, *N*-benzyl-*o*-bromobenzylamine (**5a**, Table I), n-Bu_3N, and a catalytic amount of $Pd(OAc)_2$ and PPh_3 were added to a reaction vessel connected to a balloon filled with carbon monoxide. The whole mixture was heated at 100 °C for 26 h, and a neutral substance was obtained in 63% yield. The melting point and all the spectral data of this compound indicated that the product was the expected *N*-benzylisoindolin-1-one (**8a**): mp 90–91 °C (lit.[4] mp 90–91 °C); IR ν 1680 cm^{-1}.

Scheme I



Scheme II



12/13 = 2.6:1

In a similar manner, *N*-benzyl-*o*-bromophenethylamine (**5b**) gave *N*-benzyl-1,2,3,4-tetrahydroisoquinolin-1-one (**8b**) in 65% yield. To test the suitability of a primary amine as a substrate, *o*-bromophenethylamine (**5c**) was submitted to this reaction to give 1,2,3,4-tetrahydroisoquinolin-1-one (**8c**) in 38% yield along with *N*-acylisoquinolinone **9** (7%) and the urea derivative **10** (15%) (Scheme II).

Moreover, o-bromo-*N*-(*o*′-bromobenzyl)phenethylamine (**11**) was an interesting substrate since it could cyclize to give a five- or six-membered ring. Thus, compound **11** furnished isoindolinone **12** and isoquinolinone **13** in a 2.6:1 ratio.

Subsequently, the possibility of generation of the seven-membered ring by this method was surveyed. The required precursor for **5d**, *N*-benzyl-3-(*o*-bromophenyl)propionylamide (**15**, R = CH_2Ph), was prepared by a procedure developed by Umino et al., who exploited a new reducing reagent from $NaBH_4$ and acetic acid (Scheme III).[5] This reagent reduced the amide group to the amine, leaving the bromo group on the aromatic ring intact. Compound **5d**, prepared by reduction of **15**, furnished *N*-benzyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (**8d**) in 63% yield. Compound **8d** was reduced with $LiAlH_4$ in tetrahydrofuran to give *N*-benzyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (**16**).[6] When the primary amine **5e** was used for the formation of the seven-membered ring, 2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (**8e**)[7] was also obtained in 41% yield.

Scheme III

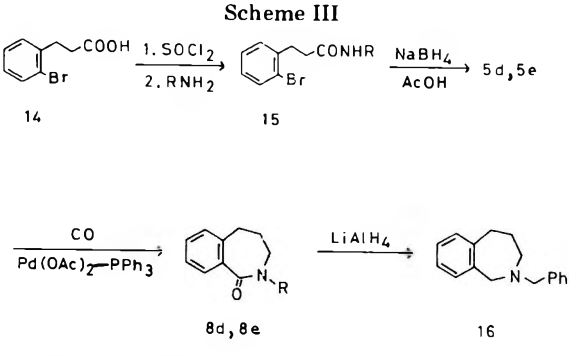


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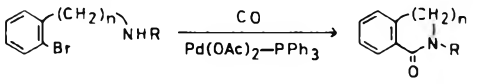
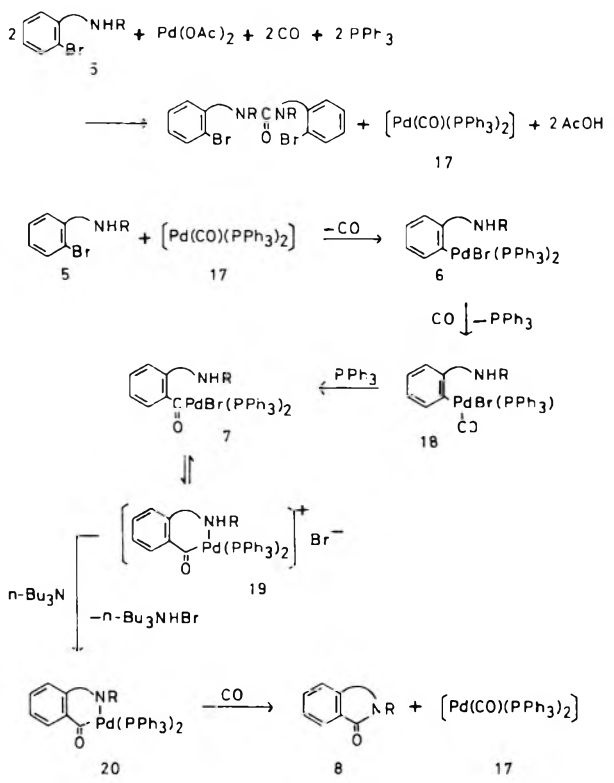
Table I. Reaction of o-Bromoaminoalkylbenzene 5 with Carbon Monoxide in the Presence of $Pd(OAc)_2$ and PPh_3



5a–e 8a–e

Run	Starting material	Registry no.	R	n	Product	Registry no.	Yield, %
1	**5a**	65185-56-0	CH_2Ph	1	**8a**	13380-32-0	63
2	**b**	65185-57-1	CH_2Ph	2	**b**	6772-61-8	65
3	**c**	65185-58-2	H	2	**c**	1196-38-9	38
4	**d**	65185-59-3	CH_2Ph	3	**d**	65185-61-7	63
5	**e**	65185-60-6	H	3	**e**	6729-50-6	41

Scheme IV



A plausible mechanism is shown in Scheme IV. It is already known that palladium acetate is converted to zerovalent palladium **17** by treating it with a primary or secondary amine and carbon monoxide.[8] The zerovalent palladium complex **17** could be inserted into o-bromoaminoalkylbenzene **5** to produce the arylpalladium complex **6** (M = Pd), which should coordinate with carbon monoxide. The migration of the aryl group to carbon monoxide affords the acylpalladium complex **7** (M = Pd), which must be in equilibrium with **19**. Hydrogen bromide is eliminated from **19** with n-Bu_3N to afford **20**, which is converted to the benzolactam **8**) and a zerovalent palladium complex **17** coordinated with carbon monoxide.

The reaction is a useful synthetic method for preparation of benzolactams because the procedure is very facile and the starting material is readily available. Moreover, only a catalytic amount of transition metal of low toxicity is required. The synthesis of natural products has been accomplished by an application of this palladium-catalyzed amidation, which will be published in a forthcoming paper.

Experimental Section

Melting points were measured with a hot stage microscope (Yanaco MP-J2) and with a melting point apparatus (Yamato MP-1) and are uncorrected. Spectra reported herein were measured on a Jasco IRA-2 diffraction grating infrared spectrophotometer, a Hitachi R-20B (NMR, 60 MHz), and a Hitachi RMU-7M double focusing mass spectrometer. The preparation of $Pd(OAc)_2$ was conducted by the method previously described,[9] and all solvents were purified by established procedures.

***N*-Benzyl-*o*-bromobenzylamine (5a).** A mixture of benzylamine (4.665 g, 43.5 mmol) and o-bromobenzaldehyde (8.042 g, 43.5 mmol) was stirred at room temperature for 1.5 h. Benzene was added to the reaction mixture, and the supernatant phase was separated and dried over Na_2SO_4. The solvent was removed, and the residue was dissolved in 30 mL of methanol. To this methanolic solution $NaBH_4$ (1.65 g, 43.5 mmol) was added with ice cooling, and the whole mixture was stirred at room temperature overnight. After the MeOH was removed, the residue was extracted with ether. The ether layer was washed with water and dried over Na_2SO_4, and the solvent was evaporated to give a pale yellow oil (10.731 g, 89%) of *N*-benzyl-o-bromobenzylamine (**5a**): MS *m/e* 277, 275 (M^+), 276, 274, 186, 184 ($M^+ - CH_2Ph$), 171, 169, 91; IR ν_{max} 3300, 1600, 1570 cm^{-1}; NMR ($CDCl_3$) δ 1.9 (s, 1 H, NH), 3.8 (s, 2 H), 3.9 (s, 2 H), 6.95–7.7 (m, 9 H, aromatic).

***o*-Bromophenethylamine (5c).** o-Bromo-β-nitrostyrene was synthesized according to the procedure for the preparation of β-nitrostyrene.[10] A solution of NaOH (908 mg) in 0.9 mL of H_2O was added to a solution of 4 g (21.6 mmol) of o-bromobenzaldehyde and 1.32 g (21.6 mmol) of nitromethane in MeOH (5 mL). After 15 min, the white precipitate which had formed was dissolved in water and the aqueous solution was added to excess hydrochloric acid to deposit the crude product, which was recrystallized from ethanol to give pale yellow pillars of o-bromo-β-nitrostyrene (2.916 g, 59%): mp 88–91 °C; IR ν_{max} (Nujol) 1630, 1580, 1520, 1340 cm^{-1}.

To a suspension of $LiAlH_4$ (1.06 g, 27.9 mmol) in ether (20 mL) was added 1.591 g (6.98 mmol) of o-bromo-β-nitrostyrene in ether (40 mL) with ice cooling. After the solution was stirred at the same temperature, the excess of $LiAlH_4$ was carefully destroyed with wet ether and then with water. The undissolved material was filtered off, and the filtrate was dried and evaporated to give 1.34 g of pale yellow oil. Chromatography on silica gel eluting with benzene–ethyl acetate–methanol (1:2:3) gave 867 mg (62.0%) of o-bromophenethylamine (**5c**): MS *m/e* 201, 199 (M^+), 200, 198, 171, 169, 120, 90; IR ν_{max} (film) 3370, 3270, 1565, 1470 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (brd s, 2 H), 2.95 (s, 4 H), 7.0–7.4 (m, 3 H, aromatic), 7.5–7.7 (m, 1 H).

***N*-Benzyl-*o*-bromophenethylamine (5b).** A mixture of o-bromophenethylamine (**5c**; 563 mg, 2.82 mmol) and benzaldehyde (300 mg, 2.82 mmol) was stirred at room temperature for 3 h. The Schiff base thus obtained was reduced with $NaBH_4$ (107 mg, 2.82 mmol) in methanol to give *N*-benzyl-o-bromophenethylamine (**5b**) as a pale yellow oil (674 mg, 83.0%): MS *m/e* 291, 289 (M^+), 290, 288 ($M^+ - 1$), 185, 183, 171, 169, 120, 91; NMR ($CDCl_3$) δ 1.6 (s, 1 H, NH), 2.85 (s, 4 H), 3.75 (s, 2 H), 6.8–7.6 (9 H, aromatic).

o-Bromo-*N*-(*o*′-bromobenzyl)phenethylamine (11). A mixture of benzaldehyde (550 mg, 2.98 mmol) and o-bromophenethylamine (**5c**; 595 mg, 2.98 mmol) was stirred at room temperature for 30 min. The product was reduced with $NaBH_4$ (113 mg, 2.98 mmol) to afford the amine **11** as a pale yellow oil (942 mg, 86.0%): MS *m/e* 290, 288 (M^+), 200, 198, 171, 169, 90; IR ν_{max} (film) 3300, 1590, 1565, 1465, 1440, 1020 cm^{-1}; NMR ($CDCl_3$) δ 1.75 (brd s, 1 H, NH), 2.9 (s, 4 H), 3.87 (s, 2 H), 6.85–7.65 (m, 8 H, aromatic).

3-(*o*-Bromophenyl)propylamine (5e). 3-(o-Bromophenyl)propionic acid (**14**; 650 mg, 2.84 mmol)[11] was added to 1.69 g of $SOCl_2$ (14.2 mmol), and the mixture was refluxed for 3 h. The excess $SOCl_2$ was removed under reduced pressure, and the residue was dissolved in anhydrous benzene (3 mL). The benzene solution was added to 5

mL of NH_4OH (25–28%) with ice cooling and stirred for 2 h. The solution was neutralized with 10% hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and the solvent was evaporated. The residual solid was recrystallized from *n*-hexane–ethyl acetate to give colorless plates of 3-(*o*-bromophenyl)propionylamide (**15**, R = H) (630 mg, 97%): mp 97–98 °C; IR ν_{max} (Nujol) 3470, 3330, 1670, 1620 cm^{-1}; NMR ($CDCl_3$) δ 2.3–2.7 (m, 2 H), 2.8–3.3 (m, 2 H), 5.3–6.0 (brd s, 2 H), 7.0–7.7 (4 H, aromatic).

A solution of acetic acid (633 mg, 10.5 mmol) in anhydrous dioxane (2 mL) was added to a solution of 3-(*o*-bromophenyl)propionylamide (**15**, R = H) (481 mg, 2.11 mmol) containing 401 mg (10.55 mmol) of $NaBH_4$ in anhydrous dioxane (5 mL) at 10 °C. After the whole mixture was refluxed for 9 h, dioxane was removed under reduced pressure. The residue was extracted with ether and washed with water. The ether layer was dried over $MgSO_4$, and the solvent was removed. Chromatography on alumina eluting with benzene–ethyl acetate–methanol (1:2:3) gave a colorless oil of 3-(*o*-bromophenyl)propylamine (**5e**; 155 mg, 34%): MS *m/e* 171, 169, 58; IR ν_{max} (film) 3350, 3270, 1565 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (s, 2 H), 1.5–2.1 (m, 1 H), 2.5–3.0 (m, 4 H), 7.0–7.7 (m, 4 H, aromatic).

***N*-Benzyl-3-(*o*-bromophenyl)propylamine (5d).** 3-(*o*-Bromophenyl)propionic acid (**14**; 1.60 g, 7.0 mmol) was dissolved in 2.54 mL (35.0 mmol) of $SOCl_2$ and refluxed for 4 h. After cooling, the excess $SOCl_2$ was removed under reduced pressure and the residue was dissolved in anhydrous benzene (10 mL). When 1.87 g (17.5 mmol) of benzylamine was added to its benzene solution, a white precipitate was deposited. After 2.5 h, water was added to the reaction mixture. The organic layer was separated from the aqueous layer, washed with 10% hydrochloric acid, and dried over $MgSO_4$. The solvent was removed, and the residual solid was recrystallized from ether–petroleum ether to give colorless needles (2.25 g, 99%) of *N*-benzyl-3-(*o*-bromophenyl)propionylamide (**15**, R = CH_2Ph): mp 70–73 °C; IR ν_{max} (Nujol) 3260, 1640, 1540 cm^{-1}; NMR ($CDCl_3$) δ 2.25–2.65 (m, 2 H), 2.7–3.2 (m, 2 H), 4.25 (d, J = 5 Hz, 2 H), 7.0–7.6 (m, 10 H, aromatic and NH).

A solution of acetic acid (1.16 g, 19.3 mmol) in anhydrous dioxane (5 mL) was added to a solution of *N*-benzyl-3-(*o*-bromophenyl)propionylamide (**15**, R = CH_2Ph) (1.227 g, 3.86 mmol) containing 732 mg of $NaBH_4$ (19.3 mmol) in anhydrous dioxane (10 mL) at 10 °C. After the whole mixture was refluxed for 2 h, dioxane was removed under reduced pressure. Water was added to the residue, and the solution was extracted with $CHCl_3$. The organic layer was extracted with 10% hydrochloric acid, and the acidic layer was made strongly basic with 10% NaOH. The basic solution was extracted with ether, and the ether layer was dried over $MgSO_4$. The solvent was removed and the residual oil purified by chromatography on silica gel eluting with *n*-hexane–ether (1:1). The first fraction was a colorless oil of an amine–borane complex (198 mg) of **5d**: IR ν_{max} (film) 2300–2400 cm^{-1}.

The second fraction was a pale yellow oil (743 mg, 63.1%) of *N*-benzyl-3-(*o*-bromophenyl)propylamine (**5d**): MS *m/e* 305, 303 (M^+), 224 (M^+ − Br), 198, 196, 171, 169, 120, 107, 91; IR ν_{max} (film) 3300, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.4 (s, 1 H, NH), 1.6–2.1 (m, 2 H), 2.70 (t, 2 H), 2.83 (t, 2 H), 3.80 (s, 2 H, NCH_2Ph), 7.0–7.7 (9 H, aromatic).

The amine–borane complex of **5d** was dissolved in 10% hydrochloric acid and MeOH (1:1; 10 mL), and the solution was refluxed for 2 h. After the MeOH was removed, the acidic layer was made basic with 10% NaOH and the basic solution was extracted with ether. The ether layer was dried over $MgSO_4$, and the solvent was removed to give a pale yellow oil (180 mg, 15.3%) of desired amine **5d**.

General Procedure for the Synthesis of Benzolactam. A mixture of *o*-haloaminoalkylbenzene **5** or **11** (1 equiv), *n*-Bu_3N (1.1 equiv), $Pd(OAc)_2$ (0.02 equiv), and PPh_3 (0.04 equiv) was added to a reaction vessel which was connected to a balloon filled with carbon monoxide and heated at 100 °C for 26 h. After cooling, ether was added to the solution and the ether layer was washed with 10% hydrochloric acid and dried over $MgSO_4$. The solvent was removed and the residue was purified by chromatography or recrystallization.

***N*-Benzylisoindolin-1-one (8a).** The crude product which was prepared from **5a** (336 mg, 1.22 mmol) by the general procedure was purified by chromatography on silica gel eluting with *n*-hexane–ether (1:2) to give 171 mg (63%) of colorless crystals of **8a**, which was recrystallized from *n*-hexane–ethyl acetate: mp 90–91 °C; MS *m/e* 223 (M^+), 132 (M^+ − CH_2Ph), 119, 91; IR ν_{max} (Nujol) 1680, 1620, 1600 cm^{-1}; NMR ($CDCl_3$) δ 4.3 (s, 2 H), 4.84 (s, 2 H), 7.4–7.6 (8 H, aromatic), 7.85–8.1 (m, 1 H, aromatic).

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.63; H, 5.88; N, 6.27. Found: C, 80.69; H, 5.89; N, 6.26.

Starting material **5a** (38 mg, 11%) was recovered from the reaction mixture.

***N*-Benzyl-1,2,3,4-tetrahydroisoquinolin-1-one (8b).** The crude product obtained from **5b** (423 mg, 1.46 mmol) was purified by chromatography on silica gel eluting with benzene–ether (1:1) to give a pale yellow oil (223 mg, 64.7%) of *N*-benzyl-1,2,3,4-tetrahydroisoquinolin-1-one (**8b**): MS *m/e* 237 (M^+), 146 (M^+ − CH_2Ph), 133, 118, 91; IR ν_{max} (film) 1640, 1600, 1580 cm^{-1}; NMR ($CDCl_3$) δ 2.8–3.1 (m, 2 H), 3.35–3.7 (s, 2 H, NCH_2Ph), 7.1–7.6 (m, 8 H, aromatic), 8.1–8.35 (m, 1 H, aromatic).

From the acidic extract was recovered 11 mg of the starting material.

1,2,3,4-Tetrahydroisoquinolin-1-one (8c). The crude product obtained from **5c** (408 mg, 2.04 mmol) according to the general procedure was purified by chromatography on silica gel eluting with benzene–ether (1:1) to give three products. The first fraction was a pale yellow oil of 1,2,3,4-tetrahydroisoquinolin-1-one (**8c**; 113 mg, 38%): MS *m/e* 147 (M^+), 118, 90; IR ν_{max} (film) 3250, 1660, 1600, 1580 cm^{-1}; NMR ($CDCl_3$) δ 2.95 (t, 2 H), 3.4–3.75 (m, 2 H), 7.05–8.0 (m, 4 H, aromatic), 7.95–8.15 (m, 1 H, aromatic).

The second fraction was colorless needles (63 mg, 15%) of *N,N'*-di(*o*-bromophenethyl)urea (**10**): mp 159–161 °C (from benzene); MS *m/e* 347, 345 (M^+ − Br), 257, 255, 171, 169; IR ν_{max} (Nujol) 3340, 1620, 1580 cm^{-1}; NMR (Me_2SO-d_6) δ 2.75–3.0 (m, 4 H), 3.1–3.35 (m, 4 H), 5.95 (m, 2 H), 7.05–7.75 (m, aromatic).

Anal. Calcd for $C_{17}H_{18}N_2OBr_2$: C, 47.91; H, 4.25; N, 6.57; Br, 37.50. Found: C, 47.92; H, 4.29; N, 6.56; Br, 37.11.

The last fraction was a brown oil of 2-[*N*-(*o'*-bromophenethyl)-carbamoyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**9**; 26 mg, 7%): MS *m/e* 227, 225, 171, 169, 147, 146, 118, 90; IR ν_{max} (film) 3270, 1695, 1650, 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.85–3.3 (m, 4 H), 3.45–3.9 (m, 2 H), 4.05–4.4 (m, 2 H), 7.0–7.8 (m, 7 H, aromatic), 8.05–8.3 (m, 1 H, aromatic), 9.65 (brd s, 1 H, NH).

The acidic extract of the reaction products was neutralized with K_2CO_3 and extracted with ether to give 30 mg (7%) of starting material **5b**.

The Reaction of *o*-Bromo-*N*-(*o'*-bromobenzyl)phenethylamine (11) with Carbon Monoxide. The crude product obtained from the preparation of **11** (428 mg, 1.16 mmol) was purified by chromatography on silica gel eluting with *n*-hexane–ether (1:1). The first fraction furnished colorless prisms (141 mg, 38.5%) of *N*-(*o'*-bromophenethyl)isoindolin-1-one (**12**), which were recrystallized from *n*-hexane–ethyl acetate: mp 105–108 °C; MS *m/e* 317, 315 (M^+), 236 (M^+ − Br), 171, 169, 146, 91; IR ν_{max} (Nujol) 1680, 1620, 1470 cm^{-1}; NMR ($CDCl_3$) δ 3.0–3.3 (m, 2 H), 3.75–4.1 (m, 2 H), 4.3 (s, 2 H), 6.9–7.7 (m, 7 H, aromatic), 7.8–8.0 (m, 1 H, aromatic).

Anal. Calcd for $C_{16}H_{14}NOBr$: C, 60.77; H, 4.47; N, 4.43; Br, 25.27. Found: C, 60.79; H, 4.51; N, 4.32; Br, 25.50.

The second fraction afforded colorless prisms (55 mg, 14.6%) of *N*-(*o'*-bromobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-one (**13**), which were recrystallized from *n*-hexane–ethyl acetate: mp 91–93 °C; MS *m/e* 317, 315 (M^+), 236 (M^+ − Br), 130, 118, 91, 90; IR ν_{max} (Nujol) 1650, 1600, 1580 cm^{-1}; NMR ($CDCl_3$) δ 2.85–3.2 (m, 2 H), 3.4–3.75 (m, 2 H), 4.95 (s, 2 H, NCH_2Ph), 7.0–7.75 (7 H, m, aromatic), 8.15–8.35 (m, 1 H, aromatic).

Anal. Calcd for $C_{16}H_{14}NOBr$: C, 60.77; H, 4.47; N, 4.43; Br, 25.27. Found: C, 60.88; H, 4.38; N, 4.34; Br, 25.55.

***N*-Benzyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one (8d).** The product obtained from the preparation of **5d** (397 mg, 1.31 mmol) was purified by chromatography on silica gel eluting with *n*-hexane–ether (1:1) to give colorless prisms which were recrystallized from *n*-hexane–ethyl acetate to afford **8d**: mp 82–85 °C; MS *m/e* 251 (M^+), 222, (M^+ − CH_2Ph), 147, 131, 91; IR ν_{max} (Nujol) 1630, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.5–2.0 (m, 2 H), 2.73 (t, J = 7 Hz, 2 H), 3.18 (t, J = 7 Hz, 2 H), 4.80 (s, 2 H), 7.0–7.6 (m, 8 H, aromatic), 7.7–7.95 (m, 1 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 29.2, 30.0, 45.4, 50.1, 126.9, 127.5, 128.3, 128.6, 130.8, 136.0, 137.4, 138.1, 171.3.

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.23; H, 6.83; N, 5.57. Found: C, 81.27; H, 6.81; N, 5.70.

***N*-Benzyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (16).** To a suspension of $LiAlH_4$ (8 mg) in tetrahydrofuran (3 mL) was added 28 mg (0.11 mmol) of **8d** in tetrahydrofuran (2 mL) at room temperature. After the reaction mixture was refluxed for 67 h, excess $LiAlH_4$ was destroyed with a small amount of water. Undissolved material was filtered off and washed with ether. The combined organic layer was dried over $MgSO_4$, and the solvent was removed to give a colorless oil (16 mg, 60.7%) of **16**: MS *m/e* 237 (M^+), 146, 117, 91; IR ν_{max} (film) 1600, 1500 cm^{-1}; NMR ($CDCl_3$) δ 1.55–2.0 (m, 2 H), 2.8–3.3 (m, 4 H), 3.55 (s, 2 H), 3.9 (s, 2 H, NCH_2Ph), 6.9–7.5 (m, 9 H, aromatic); **16** picrate, mp 132 °C (yellow plates from ethanol).[6]

Anal. Calcd for $C_{23}H_{22}N_4O_7$: C, 59.21; H, 4.76; N, 12.01. Found: C, 59.03; H, 4.63; N, 11.89.

2,3,4,5-Tetrahydro-1*H*-2-benzazepin-1-one (8e). The crude product obtained from the preparation of **5e** (143 mg, 0.668 mmol) was purified by preparative chromatography on silica gel eluting with benzene–ethyl acetate (1:2) to give colorless pillars (44 mg, 41%) which were recrystallized from ether–petroleum ether, furnishing **8e**: mp 100–104.5 °C; MS *m/e* 161 (M^+), 132, 131, 104, 77; IR ν_{max} (Nujol) 3250, 1660, 1600, 1460 cm^{-1}; NMR ($CDCl_3$) δ 1.75–2.3 (m, 2 H), 2.90 (t, J = 7 Hz, 2 H), 3.20 (t, J = 7 Hz, 2 H), 7.1–7.5 (m, 5 H, aromatic).

The acidic extract of the reaction mixture was made alkaline with K_2CO_3, and the basic solution was extracted with ether. The ether layer was dried over $MgSO_4$ and concentrated to give 14 mg (10%) of the starting material.

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Registry No.—**9**, 65185-62-8; **10**, 65185-63-9; **11**, 65185-64-0; **12**, 65185-65-1; **13**, 65185-66-2; **14**, 15115-58-9; **15** (R = H), 55223-26-2; **15** (R = CH_2Ph), 65185-67-3; **16**, 54311-89-6; **16** picrate, 54311-90-9; benzylamine, 100-46-9; *o*-bromobenzaldehyde, 6630-33-7; nitromethane, 75-52-5; *o*-bromo-β-nitrostyrene, 65185-68-4; benzaldehyde, 100-52-7; $Pd(OAc)_2$, 33571-36-7.

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Synthesis of Thiols and Polysulfides from Alkyl Halides, Hydrogen Sulfide, Ammonia, and Sulfur

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Alkyl thiols and silyl-substituted alkyl thiols have been synthesized from the corresponding alkyl halides by the action of hydrogen sulfide and ammonia or alkyl amines under autogenous pressures in methanol. Alkyl halides converted to thiols in greater than 90% yield include hexyl, dodecyl, benzyl, trimethoxysilylpropyl, and methyldimethoxysilylpropyl chlorides, and 1,2-dibromoethane. Exceptionally low yields (~1%) of dialkyl sulfides were observed. Cyclohexyl bromide gave chiefly cyclohexene with a low yield of thiol. Dialkyl disulfides and polysulfides were prepared from hexyl and trimethoxysilylpropyl chlorides by the action of hydrogen sulfide, sulfur, and ammonia.

The reaction of alkyl halides and alkali metal hydrogen sulfides to prepare alkyl thiols is well known and industrially important.[1,2] In some cases, this route gives an acceptable yield of thiol, although it always leads to formation of sulfides. Even with excess hydrogen sulfide under pressure the formation of sulfides is not completely suppressed. For example, the amount of sulfides formed from dihalides is usually such that dithiols are best prepared otherwise.[1]

The reaction of alkyl halides with hydrogen sulfide and ammonia was studied as a more economical route to anhydrous preparations of alkyl thiols than the use of relatively expensive anhydrous sodium hydrosulfide. The procedure was easily extended to the preparation of disulfides and mixtures of polysulfides by adding sulfur to the mixture of reagents.

Ammonia and hydrogen sulfide combine to form unstable salts, ammonium hydrosulfide and ammonium sulfide. While these salts have received little attention in recent literature, early reports indicate that ammonium sulfide melts at −18 °C and has a vapor pressure of 760 mm at 0 °C. The more stable ammonium hydrosulfide melts at 118 °C and has a vapor pressure of 80 mm at 0 °C.[3,4] The reaction of ammonium hydrosulfide with dihalides to prepare dithiols was reported in 1947 by Simpson.[5] The yields of dithiols were poor (10–47%) and no better than those obtained with sodium hydrosulfide, so the reaction apparently received no further study.

Dodecyl thiol, $(MeO)_3Si(CH_2)_3SH$ (**1**), and $(MeO)_2MeSi(CH_2)_3SH$ (**2**) were prepared in high yield by heating the corresponding chlorides in an autoclave with a 10–20% molar excess of hydrogen sulfide and ammonia. Normally 15–25% methanol was used as solvent. For example, thiol **1** was obtained in 88.3% isolated yield by heating the corresponding chloride with hydrogen sulfide and ammonia in a molar ratio of 1:1.2:1.2 for 18.5 h at 100 °C. The rate of reaction increased with greater excess ammonia. Thiol **2** was obtained in 90.3% yield after 4 h at 100 °C when the molar ratio of chloride, hydrogen sulfide, and ammonia was 1:1:1.8. With a large excess of ammonia the yield of $[(MeO)_2MeSi(CH_2)_3]_2S$ (**3**) was only 1%.

Very little alkylation of ammonia occurred. Only 1–2% of $(MeO)_2MeSi(CH_2)_3NH_2$ (**4**) was detected in the products. Amine **4** was separated by distillation. Some loss of thiol resulted from oxidation of the thiol by air to disulfide. Oxygen must be excluded as far as possible during the reaction and workup since ammonia and amines catalyze the oxidation of thiols.

Amines and hydrogen sulfide also reacted with alkyl halides to form thiols. Conversion of 1-chlorohexane to the corresponding thiol was 80% after 6 h at 95 °C in a sealed tube with a solution of hydrogen sulfide, triethylamine, and methanol. The yield of thiol was 99% with only 0.9% of sulfide.

1,2-Dibromoethane in a solution of dipropylamine, hydrogen sulfide, and methanol at room temperature and at-

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mospheric pressure gave a 95% yield of 1,2-ethanedithiol in 4 h. However, 1,4-dichlorobutane gave a nearly quantitative yield of tetrahydrothiophene.

Benzyl chloride in a solution of ammonia, hydrogen sulfide, and methanol at 0 °C formed chiefly thiol with dibenzyl sulfide in 6–10% yield as the only other product. Bromocyclohexane in solution with methanol, triethylamine, and hydrogen sulfide at 75 °C for 24 h gave cyclohexene and cyclohexyl thiol in a ratio of 2.5:1. Bromocyclohexane and potassium hydrosulfide also gave cyclohexene as the major product.[1]

This system produced less sulfide than has been observed when alkali hydrosulfides were used. The low yield of sulfide probably is a result of dissociation of ammonium sulfide according to eq 1.[3,4] Under the conditions of the reactions this dissociation may be nearly complete so that very little sulfide was present. Similarly, ammonium alkyl thiolate formation was not favored at the temperatures of reaction, so little sulfide resulted.

$$(NH_4)_2S \rightleftarrows NH_4SH + NH_3 \quad (1)$$

The preparation of disulfides from alkyl halides was accomplished by the use of sulfur in similar solutions. 3-Chloropropyltrimethoxysilane (**5**) with hydrogen sulfide, ammonia, and sulfur in a mole ratio of 2:1:4:1 after 2 h at 70 °C gave bis(trimethoxysilylpropyl) disulfide (**6**) in 95% yield with less than 2% of thiol **1** or bis(trimethoxysilylpropyl) sulfide (**7**). With 3 mol of sulfur the product was a mixture of polysulfides with an average rank of 3.4 in a di-/tri-/tetra-/pentasulfide ratio of 1:2.3:1.1:1.1.[6] As with alkali metal polysulfide solutions, the average rank of the resulting organic polysulfide is lower than the original solution.[7]

The mechanism of formation of polysulfides from alkyl chlorides in a mixture of excess ammonia, hydrogen sulfide, and sulfur has not been determined. The mechanism may involve rapid initial formation of ammonium polysulfides, which then react with the alkyl halides to form the organic polysulfides. Alternatively, alkyl thiols may be formed initially and then oxidized by sulfur to a mixture of polysulfides.[8]

Experimental Section

NMR spectra of carbon tetrachloride solutions were recorded on a Varian A-60-A or T-60 spectrometer. Gas–liquid chromatographic analysis were carried out on a S&M Model 720 gas chromatograph using 10% DC-200 (6 ft) on Chromasorb W and 5% DC-200 (8 ft) on Anakrum ABS columns. The thiol equivalent weights were determined by titration of aqueous ethanol solutions with a standard ethanolic iodine solution.

Preparation of Alkyl Thiols. General Procedure for Preparing Alkyl Thiols from Halides. A 3-L stainless steel Aminco rocking autoclave was evacuated (50 mm) and charged with weighed portions of NH_3 and H_2S. Alkyl halide and solvent were pumped into the autoclave which was maintained at 100 or 125 °C until 98% of the halide had reacted as determined by GLC. The pressure was released from the autoclave, and a volatile mixture of H_2S, NH_3, and solvent was trapped. The contents of the autoclave were filtered by nitrogen pressure through a coarse sintered glass filter. The filtrate and hexane washes of the filter cake were combined and distilled.

1-Dodecanethiol. Dodecyl chloride (819 g, 4.0 mol) in methanol (120 mL), NH_3 (78.4 g, 4.6 mol), and H_2S (171 g, 5.0 mol) was converted to the thiol in 22 h at 120 °C. The yield by GLC was 98%. The mixture of products was added to hexane (500 mL), washed free of salts with water, and distilled to obtain 655 g (81%) of 1-dodecanethiol: bp 120–125 °C (5 mm); n^{25} 1.4558 [lit.[2] bp 124 °C (5 mm), n^{25}_D 1.4558]. Thiol equiv wt calcd for $C_{12}H_{26}S$: 202.4. Found: 203.9

A high boiling residue (27 g, 3.3%) remained after distillation. The major component of the residue was identified by GLC as dodecyl disulfide.

3-Mercaptopropyltrimethoxysilane. Chloride **5** (938 g, 4.68 mol) in methanol (150 mL), NH_3 (95.9 g, 5.64 mol), and H_2S (192 g, 5.65 mol) gave by GLC a 97 area % yield of thiol in 18.5 h at 100 °C. The pressure at 100 °C was 195 psi, which decreased to 85 psi. The GLC area of bis(trimethoxysilylpropyl) sulfide was less than 1% in the product. Distillation afforded the thiol in 88.3% yield: bp 93–94 °C (10 mm); n^{25}_D 1.4412; d^{25}_4 1.0503; NMR (CCl_4) δ 3.42 (s, 9, CH_3O), 2.45 (t, CH_2S), 1.6 (m, 3, CH_2, SH), 0.67 (m, 2, CH_2Si). Thiol equiv wt calcd for $C_6H_{16}O_3SSi$: 196.3. Found: 196.4.

3-Mercaptopropylmethyldimethoxysilane. 3-Chloropropylmethyldimethoxysilane (593 g, 3.25 mol) in methanol (200 mL), NH_3 (100 g, 5.88 mol), and H_2S (127.5 g, 3.25 mol) gave by GLC a 99 area % yield of thiol in 4 h at 100 °C. The GLC area of sulfide **3** was 1% in the product. Distillation afforded the thiol **2** in 90.3% yield: bp 72–74 °C (4 mm); n^{25}_D 1.4478; d^{20}_4 0.996; mass spectrum, *m/e* (relative intensity) 165 (3.6), 148 (54.7), 133 (72), 105 (100). Thiol equiv wt calcd for $C_6H_{16}O_2SSi$: 180.3. Found: 183.9.

1-Hexanethiol. A mixture of *n*-hexyl chloride (3.49 g, 0.029 mol) and 15 mL of a 2.2 M H_2S (0.033 mol) solution in equal volumes of Et_3N and methanol was heated in a sealed glass tube at 75 °C for 6 h. Analysis by GLC indicated that the reaction was 80% complete with the products being 99.1% 1-hexanethiol and 0.9% dihexyl sulfide.

1,2-Ethanedithiol. 1,2-Dibromoethane (10.9 g, 0.058 mol) in a solution of dipropylamine (13.5 g, 0.133 mol) and methanol (10 mL) saturated with H_2S at room temperature precipitated Pr_2NH_2Br within minutes. After 4 h at room temperature, GLC showed only one product in 95% yield (based on methanol as an internal standard). About 200 mL of water was added to the mixture, and the product (more dense than water) was separated and dried over Na_2SO_4. The IR spectrum of the product was identical with the reported spectrum of 1,2-ethanedithiol: IR (neat) 2550 (S–H) and 693 (C–S) cm^{-1}.[9]

Benzyl Mercaptan. A solution of NH_3 (3.3 g, 0.19 mol) and methanol was saturated with H_2S at 0 °C. Benzyl chloride (20.9 g, 0.165 mol) was added to the solution at 0 °C while slowly bubbling H_2S through the solution. The reaction was complete in 1 h with benzyl mercaptan (92% GLC area) and dibenzyl sulfide (8% GLC area) as the only detectable products.

Cyclohexanethiol. An H_2S saturated solution of triethylamine (9.4 g, 0.093 mol), methanol (20 mL), and bromocyclohexane (13.2 g, 0.08 mol) was heated at 75 °C in sealed glass tubes for 24 h. Triethylamine hydrobromide precipitated from the solution. Cyclohexene and cyclohexanethiol were identified by coinjection on GLC with authentic samples. GLC analysis with methanol as the internal standard indicated that the products were cyclohexene and cyclohexanethiol in a ratio of 2.5:1.

Preparation of Alkyl Polysulfides. General Procedure for Preparing Alkyl Polysulfides from Halides. Polysulfides were prepared by the same general procedure as the thiols except that sulfur was added to the autoclave before it was evacuated. The pressure observed during the reactions was minimal (<150 psig). When the polysulfides were not stable to distillation, semiquantitative analyses were performed by NMR spectroscopy based on the relative areas of the methylene protons adjacent to the sulfur atoms as described by Grant and Van Wazer.[6]

Bis(trimethoxysilylpropyl) Disulfide. Chloride **5** (794 g, 4.0 mol) in methanol (187 mL), sulfur (64 g, 2.0 mol), H_2S (72 g, 2.1 mol), and NH_3 (135 g, 7.9 mol) reacted completely in 2 h at 70 °C. The filtrate and hexane washes of the NH_4Cl filter cake were stripped on a rotary evaporator to 50 °C at 20 mm to give 757 g (97%) of light yellow disulfide **6**: n^{25}_D 1.4662; NMR (CCl_4) δ 3.53 (s, 9, CH_3O), 2.67 (t, 2, CH_2S), 1.75 (m, 2, $-CH_2-$), 0.67 (t, 2, CH_2Si).

The product was identical with an authentic sample of disulfide **6** prepared from 3-mercaptopropyltrimethoxysilane by iodine oxidation.[10] The product contained 1.7 wt % of $(MeO)_3Si(CH_2)_3SH$ as determined by iodine titration. Sulfide **7** was not detected by NMR spectroscopy or GLC.

Bis(trimethoxysilylpropyl) Polysulfide. Chloride **5** (993, 5 mol) in methanol (250 mL), sulfur (240 g, 7.5 mol), H_2S (87 g, 2.56 mol), and NH_3 (119 g, 7.0 mol) reacted completely in 2.5 h at 70 °C. The filtrate and hexane washes of the NH_4Cl filter cake were stripped to 60 °C at 10 mm to give 1,074 g of a cloudy yellow mixture of polysulfides, $[(MeO)_3Si(CH_2)_3]_2S_x$: NMR (CCl_4) δ 3.52 (s, 9, CH_3O), 2.66 (t, 0.36, CH_2S_2), 2.86 (t, 0.84, CH_2S_3), 2.94 (t, 0.4, CH_2S_4), 2.98 (t, 0.4, CH_2S_5), 1.87 (m, 2, CH_2), 0.70 (m, 2, CH_2Si).

Anal. Calcd for $C_{12}H_{30}O_6S_3Si_2$: S, 22.7. Found: S, 22.0.

The product contained 0.15 wt % of thiol **1** as determined by iodine titration.

Dihexyl Disulfide. 1-Chlorohexane (362 g, 3 mol), methanol (250 mL), sulfur (48 g, 1.5 mol), H_2S (51 g, 1.5 mol), and ammonia (103 g, 6 mol) gave 95% conversion in 2 h at 70 °C. Dihexyl sulfide was not detected by GLC (<0.3%). The product was distilled to yield 293 g (87.6%) of dihexyl disulfide: bp 120–122 °C (1 mm); n^{25}_D 1.4864; d^{25}_4 0.9145.

Anal. Calcd for $C_{12}H_{26}S_2$: C, 61.5; H, 11.2; S, 27.4. Found: C, 61.6; H, 11.2; S, 27.3.

Registry No.—1, 4420-74-0; 2, 31001-77-1; 5, 2530-87-2; 6, 35112-74-4; 1-dodecanethiol, 112-55-0; dodecyl chloride, 112-52-7; dodecyl disulfide, 2757-37-1; 3-chloropropylmethyldimethoxysilane, 18171-19-2; 1-hexanethiol, 111-31-9; *n*-hexyl chloride, 544-10-5; 1,2-ethanedithiol, 540-63-6; 1,2-dibromoethane, 106-93-4; benzyl mercaptan, 100-53-8; benzyl chloride, 100-44-7; cyclohexanethiol, 1569-69-3; bromocyclohexane, 108-85-0; bis(trimethoxysilylpropyl) polysulfide, 40550-17-2; dihexyl disulfide, 10496-15-8; 1-chlorohexane, 544-10-5.

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Synthetic Applications of Arylselenenic and Arylseleninic Acids. Conversion of Olefins to Allylic Alcohols and Epoxides

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A new direct (one reaction vessel) route from olefins to rearranged allylic alcohols has been developed. It involves electrophilic addition of phenylselenenic acid (PhSeOH) to the olefin. The phenylselenenic acid is generated in situ by comproportionation of phenylseleninic acid ($PhSeO_2H$) and diphenyl diselenide (PhSeSePh). The addition of PhSeOH to trisubstituted olefins is highly regioselective. A new procedure for the oxidation/elimination of alkyl phenyl selenides is described. It employs *tert*-butyl hydroperoxide in place of hydrogen peroxide and avoids the secondary epoxidation process which can be a problem with the latter oxidant. Arylseleninic acids were found to be effective catalysts for the epoxidation of olefins with hydrogen peroxide. However, attempts to achieve asymmetric epoxidations by employing optically active arylseleninic acids as catalysts met with failure. A simple procedure for generating DMAC solutions of sodium selenocyanate by direct reaction of sodium cyanide with selenium metal is described. NaSeCN so generated is used in the preparation of *o*-nitrophenyl selenocyanate.

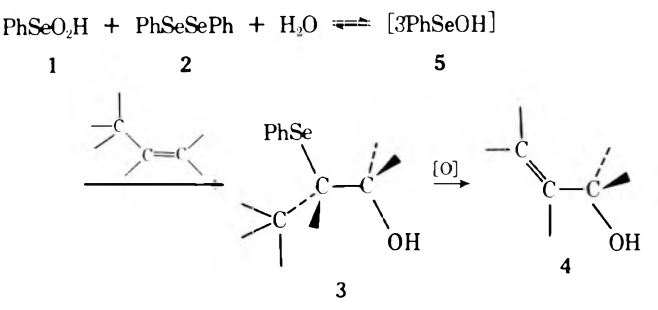
Olefins to Allylic Alcohols

We report here a new procedure for the conversion of an olefin to a rearranged allylic alcohol. The process involves addition of the olefin to a methylene chloride solution containing both phenylseleninic acid (**1**) and diphenyl diselenide (**2**). As shown in Scheme I a β-hydroxyphenyl selenide adduct **3** is produced,[2,3] and subsequent oxidation of this adduct, in the same reaction vessel, leads to the allylic alcohol **4** in good yield. The adduct **3** probably arises by electrophilic addition of phenylselenenic acid (**5**)[4] to the olefin.

The putative intermediate **5** is thought to be generated in situ by the redox reaction between seleninic acid **1** and diselenide **2**. Going from left to right, as shown in Scheme I, this process is formally a comproportionation. The equilibrium is apparently driven by capture of the selenenic acid **5** by the olefin.

The addition of aromatic selenenic acid derivatives (ArSeX) to olefins was discovered by Hölzle and Jenny.[5] Our group,[6] Reich's group,[7] and Clive[8] demonstrated the utility of such additions for synthesis of allylically functionalized alkenes.

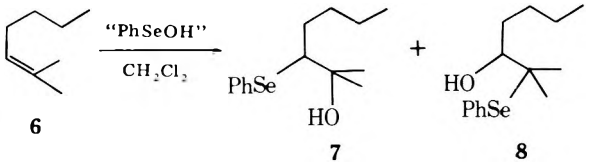
Scheme I



However, the direct addition of "PhSeOH" to olefins had not been accomplished.[9] In addition to producing allylic alcohols directly, the new procedure offers high regioselectivity (Table I, entries 4 and 5) in circumstances where the earlier reagents (e.g. CH_3CO_2SePh[6] and CF_3CO_2SePh[7,8]) afford almost 1:1 mixtures of regioisomers.

The general procedure employed for addition of "PhSeOH" to olefins calls for generation of phenylseleninic acid (**1**) in situ by addition of the appropriate (i.e., that required to generate an ~1:1 mixture of **1** and **2**) amount of 30% hydrogen peroxide to a methylene chloride solution of diphenyl diselenide (**2**).[10] When this initial oxidation is complete anhydrous $MgSO_4$ is added to sequester most of the excess water. The addition of $MgSO_4$ has two important, if unanticipated, effects on the course of the subsequent reaction with the olefin: (1) both the rates of formation and the yields of the adducts **3** are increased; (2) in the case of trisubstituted olefins the Markownikoff regioselectivity is complete (whereas when anhydrous $MgSO_4$ is omitted some of the anti-Markownikoff regioisomer is also formed). For example, as shown in Scheme II addition of "PhSeOH" to 2-methyl-2-heptene (**6**) in the presence of anhydrous $MgSO_4$ gave adduct **7** exclusively, whereas when

Scheme II



with $MgSO_4$ 100:0
without $MgSO_4$ 85:15

0022-3263/78/1943-1689$01.00/0

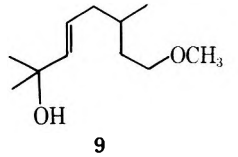
Table I. Olefins to Allylic Alcohols

Entry	Olefin	Registry no.	Allylic alcohol, % yield[a]
1	(*E*)-4-Octene	14850-23-8	(*E*)-3-Octen-5-ol, 88
2	(*Z*)-4-Octene	7642-15-1	(*E*)-3-Octen-5-ol, 84
3	Cyclooctene	931-88-4	**10**, 83
4	Citronellol methyl ether	55915-70-3	**9**, 87
5	1-Methylcyclohexene	591-49-1	**17**, 33[b]

[a] The reported yields are for pure substances isolated by distillation. [b] In this case anhydrous chloramine-T was used in place of TBHP for oxidation/elimination of the hydroxyselenide adduct **15**.

the addition was performed in the absence of $MgSO_4$ some of the regioisomer **8** was also produced.

The second stage of this transformation, which is carried out in the same reaction vessel, is the oxidation of the hydroxy selenide adduct **3** to the corresponding selenoxide. The selenoxide is thermally unstable and eliminates PhSeOH (**5**) producing the desired allylic alcohol product **4**. Hydrogen peroxide has been the reagent most commonly employed for the oxidation/elimination of alkyl aryl selenides. However, we and others have encountered side reactions, principally overoxidation, associated with the use of H_2O_2 for the oxidative removal of phenylseleno moieties from organic structures. In the present case when the hydroxy selenide adducts **3** were oxidized with excess H_2O_2 the allylic alcohol products were sometimes further transformed to the corresponding epoxy alcohols. For cyclooctene this was a serious complication, but for the other examples in Table I it was less of a problem. For example, allylic alcohol **9** produced from citronellol methyl



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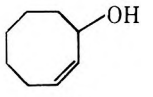

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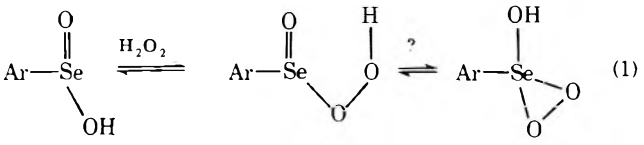
ether (entry 4) was very resistant to epoxidation. Even in the case of cyclooctene, allylic alcohol **10** could be isolated in good yield if only 2 molar equiv (based on diphenyl diselenide used) of H_2O_2 was employed. This is the calculated amount of H_2O_2 necessary to oxidize all the selenium(II) species to selenium(IV) species. However, under these conditions some diphenyl diselenide (**2**) always remains at the end of the reaction. This may be due in part to catalytic decomposition of some of the H_2O_2 by selenium species.[17] Separation of the yellow diselenide **2** from the allylic alcohol requires either a chromatography or a distillation. Thus convenience dictates the use of excess oxidant so that all the diphenyl diselenide is oxidized to phenylseleninic acid, which can be readily extracted into aqueous base.[11] We have found that *tert*-butyl hydroperoxide is an ideal oxidant for this purpose. It can be used in excess with no tendency for epoxidation of the olefinic products.

We have recently established the superiority of *tert*-butyl hydroperoxide over H_2O_2 for use in both OsO_4[12] and SeO_2[13] catalyzed oxidations of olefins. The success of this alkyl hydroperoxide in the present system is in keeping with its highly selective oxidizing properties. The presence of an alkyl group on one side of the peroxide linkage removes many of the reaction pathways which are open to H_2O_2. For example, the epoxidation process observed with H_2O_2 is almost certainly due to the formation of a peracid **12a** or its related cyclic peroxo isomer **12b** through the equilibrium given in eq 1.



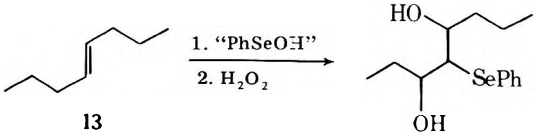
11 **12a** **12b** (1)

We have shown that seleninic acids undergo facile exchange with ^{18}O-labeled water.[14] Specifically, it was found that an allylic seleninic acid underwent oxygen exchange with $H_2{}^{18}O$ much more rapidly than it underwent 2,3-sigmatropic rearrangement to the allylic alcohol.

Several other advantages which accrue from the use of *tert*-butyl hydroperoxide (TBHP) in place of H_2O_2 as the oxidant are worth mentioning. Unlike H_2O_2, TBHP reveals no tendancy to cause oxidative removal of the selenium from the aromatic ring in the phenylseleninic acid (**1**) by-product. Thus the seleninic acid **1** is recovered in high yield and then readily reduced to regenerate the starting diphenyl diselenide (**2**). Following a typical allylic alcohol preparation which employed 23.4 g (75 mmol) of diphenyl diselenide (**2**), reduction of the aqueous phenylseleninic acid containing extracts afforded 21.9 g (93% recovery) of diselenide **2** (mp 60.3–61.1 °C). This crude diselenide was sufficiently pure for reuse, but could be further purified by recrystallization from hexane.

Our attempts to recover the diselenide **2** in cases where H_2O_2 has been the oxidant have been less successful. As reported previously,[6] in a sequence beginning with 29.5 g of diselenide **2** only 15 g (51% recovery) was recovered by reduction of the aqueous extracts. We feel these poorer recoveries with H_2O_2 are due, at least in part, to the oxidative destruction of phenylseleninic acid mentioned above.[18] In support of this contention is the observation that reduction of aqueous extracts containing phenylseleninic acid, which has been exposed to excess H_2O_2, often leads to production of red selenium metal, in addition to the desired yellow diselenide **2**. The extent of seleninic acid decomposition varies with the amount of excess H_2O_2 and the period of exposure.[22] The problem can be alleviated by using only 2 molar equiv (based on diphenyl diselenide used) of H_2O_2, but this leads to the aforementioned product contamination by diselenide **2**.

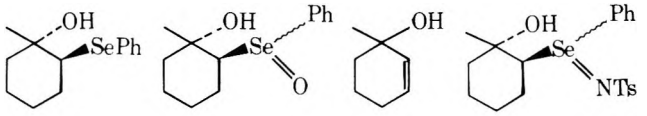
Both our group and Reich's[2,3] have encountered another important reason for the use of excess oxidant in the oxidation/elimination step. The initial product of syn elimination of an alkyl phenyl selenoxide is phenylselenenic acid (PhSeOH, **5**). As revealed in the present work and by Reich's recent results,[2,3] PhSeOH readily undergoes electrophilic addition to olefins. Thus it would be expected to add to the allylic alcohol being produced unless either disproportionation (Scheme I, **5** → **1** + **2**) or oxidation to phenylseleninic acid (**1**) occurred more rapidly. The presence of excess oxidant (H_2O_2 or TBHP) ensures rapid oxidation and prevents addition of PhSeOH to the product olefins. However, when excess oxidant is not utilized undesirable side reactions involving PhSeOH can be observed. This problem is more pronounced for some substrates than for others. For example, before it was found that excess TBHP could be used as the oxidant, we were trying to avoid the overoxidation problem (seleninic acid catalyzed epoxidation) by using only 2 molar equiv (based on diphenyl diselenide used) of H_2O_2. For 4-octene (**13**) this led to formation of substantial amounts of the diol selenide **14** (mp 77.9–78.6 °C, 48%). Diol **14** presumably arises by addition of



13 **14**

PhSeOH to the corresponding *E*-allylic alcohol. The addition seems to be regio- and stereoselective, since only one diastereomer was detected. However, the possibility that other isomers were present in small amounts was not rigorously excluded.

TBHP was highly successful as the oxidant for all the cases in Table I except for 1-methylcyclohexene (entry 5). In this case the selenoxide(s) **16** derived from the hydroxy selenide adduct **15** showed negligible tendency for elimination at room temperature. Even when the solvent was changed from CH_2Cl_2 to 1,2-dichloroethane, so that a reflux temperature of about 80 °C could be achieved, the yield of the desired allylic alcohol **17** was <10%. We had previously found[23] that the *p*-toluenesulfonylselenimide analogues of selenoxides elimi-



15 **16** **17** **18**

nate more readily than the selenoxides. Therefore the adduct **15**, which was isolated in 83% yield, was treated with 2 equiv of anhydrous chloramine-T in dichloroethane.[24] After stirring for several hours at room temperature the hydroxy selenide **15** had disappeared and two new compounds were apparent by TLC. Although these new substances were not isolated, they were presumably the two diastereomeric selenimides **18**. Probably due to the steric congestion in this system, even these selenimides were slow to undergo thermal elimination. However, after refluxing for 2 h allylic alcohol **17** and 1,2-epoxy-1-methylcyclohexane[25] were produced in a 2:1 ratio. Chromatography (to remove the epoxide) and distillation afforded allylic alcohol **17** in 40% yield from adduct **15** or in 33% yield based on the starting olefin. It is interesting to note that one (the less polar isomer on TLC) of the selenimides **18** disappeared more rapidly upon refluxing than the other. This observation parallels that of Jones, Mundy, and Whitehouse on the pyrolysis of a pair of sterically encumbered diastereomeric selenoxides.[26]

The general applicability of this new method (i.e., the use of 2 equiv of anhydrous chloramine-T in CH_2Cl_2 or $ClCH_2CH_2Cl$) for the oxidation/elimination of alkyl phenyl selenides has not been explored. However, it has an advantage over the phase-transfer procedure[23] utilizing chloramine-T in that there is no need to worry about separation of the phase-transfer agent (e.g. "Aliquat-336") from the products.

The other new procedure (i.e., TBHP in CH_2Cl_2) for oxidation/elimination of alkyl phenyl selenides has also not been investigated with regard to its general usefulness. However, we have made several observations worth mentioning here. The procedure offers no advantage over H_2O_2 for primary selenides. Only a trace of 1-dodecene is formed after exposure of 1-dodecyl phenyl selenide to excess TBHP in CH_2Cl_2 for 22 h. The problem does not lie in the rate of the oxidation step since TLC indicates that oxidation to the selenoxide is complete in 0.5–1 h. In the case of cyclododecyl phenyl selenide, exposure to TBHP in CH_2Cl_2 for 15 h at 25 °C resulted in formation of 92% cyclododecene (~1:1 mixture of *E* and *Z* isomers). By contrast, oxidation of cyclododecyl phenyl selenide with H_2O_2 in THF at 25 °C led rapidly (<1 h) to cyclododecene in 94% yield.[14] If this latter reaction mixture were allowed to stand for 15 h at 25 °C, then a substantial amount of epoxidation occurred (after 15 h: 58% cyclododecene and 38% cyclododecene oxide).[27] Since polar solvents such as THF disfavor epoxidation, one could anticipate that epoxidation would have been more of a complication had CH_2Cl_2 been the solvent. Actually, this problem of further epoxidation does not seem to exist for monosubstituted olefins and is only rarely experienced with disubstituted olefins. It is in cases involving tri- and especially tetrasubstituted olefins where further epoxidation is difficult to prevent if H_2O_2 is used as the oxidant.[20,21] It is in these latter circumstances that the use of TBHP for the oxidation/elimination step should provide special advantage. Baeyer–Villiger oxidation of certain ketones to lactones is another complication which has been encountered when H_2O_2 is employed as oxidant.[23,28] The use of TBHP as oxidant in such cases would be worth investigating.

As can be seen from the preceding discussion *tert*-butyl hydroperoxide (TBHP) should in many cases prove superior to hydrogen peroxide for the oxidation/elimination of alkyl phenyl selenides.[29] Because TBHP is a gentle oxidant, we generally use an excess to promote rapid completion of the desired oxidation. For example, in the present work 268 mmol were employed when 150 mmol is the theoretical amount required to convert all the selenium species to phenylseleninic acid (**1**). Since TBHP is not as sensitive[30] to catalytic decomposition by selenium species as is H_2O_2,[17] the excess oxidant remains at the end of the reaction. Moreover, TBHP is (unlike H_2O_2) more soluble in organic solvents than in water, and is therefore not removed by aqueous washes[31] during workup. There are a variety of ways of dealing with this excess TBHP. One approach is to perform a nonreductive workup and then remove it under vacuum (1 mm or better) at around 25–35 °C. However, for large-scale (>1 mol) reactions prior reduction is recommended. *Aqueous bisulfite has often been used for this purpose,*[12,32] *but we strongly recommend that this reductant be avoided whenever possible.* We have recently found that its use has a deleterious effect on isolated yields, especially when the desired products are epoxides[33] or allylic alcohols.[13] The effect is particularly severe if one attempts to distill the product of a large-scale (>1 mol) reaction; typically, the product will polymerize exothermically during attempted distillation. This complication is easily avoided by using dimethyl sulfide[34] (in the presence of a catalytic amount of acetic acid[35]) as the reductant in place of bisulfite. We now use this Me_2S procedure for all large-scale reductions of TBHP.[13]

In the present work aqueous ferrous sulfate is employed as the reducing agent. This method works well; reduction occurs more rapidly than with Me_2S and it has the added advantage of being odorless. However, we do not recommend use of this $Fe^{II}SO_4$ reduction technique for larger scale (>0.1 mol) reactions. Even though the reductions involve a two-phase (ether–water) system, the Fe^{II}/Fe^{III} couple is well known[36] to catalyze free-radical decomposition of alkyl hydroperoxides, suggesting obvious possibilities for trouble. If larger scale applications of this reduction technique were to be explored, it would seem advisable to employ inverse addition (i.e., slowly add the ethereal organic extract containing the TBHP to a well-stirred aqueous $FeSO_4$ solution).[37]

Olefins to Epoxides

There has been long-standing interest in discovering a means for direct use of H_2O_2 for epoxidation of olefins. An obvious approach is the in situ generation of carboxylic peracids. Unfortunately the exchange process between H_2O_2 and a carboxylic acid requires strong acid catalysis and is therefore incompatible with the desired epoxide products. For example, formic acid (a strong enough acid to catalyze its own exchange with H_2O_2) is often used for conversion of an olefin to a vicinal diol in the presence of H_2O_2; the intermediate epoxides cannot be isolated under these conditions.[38] Since there is a trend toward more facile exchange processes upon descending the rows in the periodic table, one finds that the in situ formation of peracids (**20a**, e.g. M = Se) and peroxides (**20b**, e.g. M = V,

Table II. Epoxidation of Cyclooctene

Entry	Catalyst[a]	Registry no.	Equiv of 30% H_2O_2	$MgSO_4$[b]	Time, h	Epoxide/olefin[c]
1	SeO_2 (control)		2	−	16	2:98
2	**1**	6996-92-5	2	−	16	65:35
3	**26**	65252-75-7	2.2	−	20	79:21
4	**26**		2.2	+	20	99.7:0.3
5	**24**	15001-52-2	2	−	16	0.4:99.6
6	**25**	65252-76-8	2	−	16	0.3:99.7
7	**27**	20753-53-1	2.2	−	16	40:60
8	**28**	33350-70-8	2.2	−	16	50:50
9	**22**	56790-59-1	2.2	−	20	91:9
10	**23**	65252-77-9	2.2	−	20	96:4
11	**23**		2.2	+	20	99.6:0.4

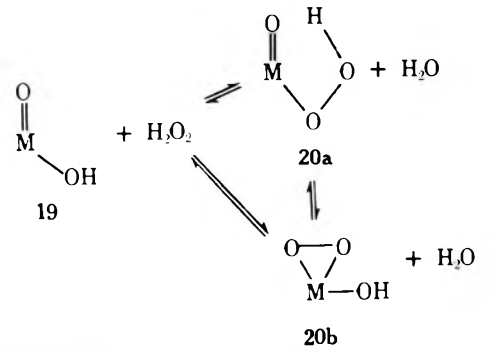
[a] In each case 10% of the seleninic acid catalyst was employed and the solvent was always CH_2Cl_2. [b] A + sign indicates that excess anhydrous $MgSO_4$ was added. [c] Indicates the GLC determined ratio of product to starting material; in all cases the mass balance is ~100%.

Table III. Epoxidation of Citronellol Methyl Ether

Entry	Catalyst[a]	Equiv of H_2O_2 (% strength)	$MgSO_4$	Time, h	Epoxide/olefin[b]
1	**22**	2 (30)	−	16	84:16
2	**22**	2 (30)	+	16	100:0
3	**22**	2 (98)	−	16	100:0
4	**23**	2 (30)	−	16	69:31
5	**23**	2 (30)	+	16	100:0

[a] In each case 1.0% of the seleninic acid catalyst was used. [b] Same as footnote *c* in Table II except that with this olefin the mass balances were only ~90%.

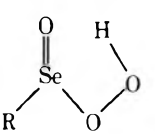
Scheme III



20b

Mo, W) occurs under very mild conditions[39] in the presence of H_2O_2 (Scheme III). In fact, the elements indicated above (V, Mo, W, Se) are among those which are known to be active catalysts for the epoxidation of olefins with H_2O_2.[40,42] However, these catalytic systems are very poor for the epoxidation of simple, isolated olefins.[40b,40c] Of particular interest for the present work are the reports in which SeO_2 was observed to catalyze epoxidation of olefins.

In his pioneering studies of allylic oxidation with SeO_2, Guillemonat had investigated the use of H_2O_2 as a source of the oxygen in the reaction.[41] However, the only products he obtained were vicinal diols and no allylic oxidation products. The formation of diols from olefins and SeO_2 in the presence of H_2O_2 was later studied as a reaction in its own right.[42] Tanaka eventually showed that epoxides were the initial products in this reaction, and that diols arose from ring opening under the usual reaction conditions.[43] Perselenious acid (**21a**) was proposed as the active epoxidizing species.



21a, R = OH
b, R = Ph

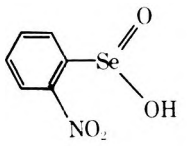
Very recently Grieco has reported epoxidation of olefins by H_2O_2 in the presence of a stoichiometric quantity of phenylseleninic acid (**1**).[21] He suggests that the corresponding peracid **21b** is the active reagent. We had discovered this same epoxidizing activity[16,18] in the course of our early[15] experiments on organoselenium reagents. It was further observed that stoichiometric use of the seleninic acid is not necessary, and that arylseleninic acids showed activity as phase-transfer catalysts for the epoxidation of olefins with H_2O_2.[18] However, the lifetime of the seleninic acid (**1**) itself as a catalyst was disappointing for the acid was being degraded to SeO_2 and presumably some oxidized organic fragment.[18] This decomposition process may be due to Baeyer–Villiger type rearrangement[19] of the peracid **12a** or its peroxo isomer **12b**.

Reich's group has also encountered these seleninic acid catalyzed epoxidations.[20] We report here those aspects of our results on this new epoxidation procedure which are most relevant to its preparative potential.

In addition to phenylseleninic acid (**1**), we have also investigated the seleninic acids **22–30** as epoxidation catalysts. With the exception of the alkyl seleninic acid **24** and *o*-hydroxycarbonylphenylseleninic acid (**25**), all of these compounds exhibited some activity as epoxidation catalysts (Table II). Methylene chloride is an especially good solvent for these epoxidations.

The results in Table II for the epoxidation of cyclooctene reveal the relative effectiveness of the various seleninic acid catalysts. The *o*-nitrophenylseleninic acid (**22**) and the 2,4-dinitrophenylseleninic acid (**23**) are clearly the best catalysts.[44] The presence of water has a deleterious effect on the epoxidation process.[45] Good results were obtained using 30% H_2O_2 and anhydrous $MgSO_4$ to scavenge the excess water.[46] High-strength (98%) H_2O_2 was also successful, but seemed less desirable from the point of view of both safety and convenience.

Table III gives results obtained using the nitroseleninic acids **22** and **23** as catalysts for the epoxidation of a trisubstituted olefin (citronellol methyl ether); in this case 1.0% catalyst was used. The combination of 30% H_2O_2 and anhy-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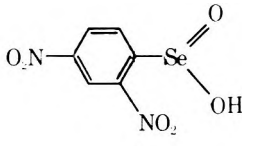
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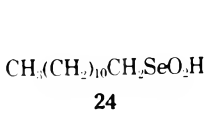
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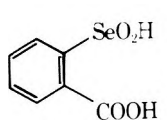
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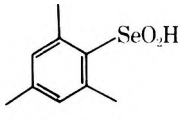
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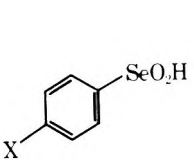
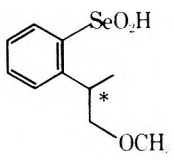

27, X = Cl
28, X = NO_2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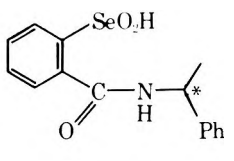

30

drous $MgSO_4$ works well (entries 2 and 5), but if 98% H_2O_2 is employed (entry 3) use of $MgSO_4$ is obviated.

In Table IV are shown the results of performing the catalytic epoxidation on a preparative scale. The yields given are for pure, distilled epoxides. Only for cyclooctene is the yield near quantitative. In the case of (*E*)-5-decene and 2-methyl-2-heptene the isolated yields are somewhat below the ~95% value that one would expect to be able to obtain by careful epoxidation of these olefins with carboxylic peracids. The simplicity of the procedure and the fact that H_2O_2 is less expensive than peracetic and perbenzoic acids (the most commonly used reagents for large scale laboratory epoxidations) are attractive aspects of these catalytic epoxidations.

It is always of interest to explore the behavior of a new epoxidizing reagent with olefinic alcohols. These substrates (especially allylic alcohols) are well known for undergoing highly selective epoxidations with both carboxylic peracids[47] and with alkyl hydroperoxides in the presence of vanadium and molybdenum catalysts.[32] As shown in Scheme IV epoxidation of 2-cyclohexen-1-ol (**31**) occurs almost randomly giving a 3:2 mixture of the *syn*- (**32**) and *anti*- (**33**) epoxy alcohols. This contrasts with the highly stereoselective syn epoxidation of **31** by carboxylic peracids[47] and by transition metal–alkyl hydroperoxide reagents.[32] Similarly, geraniol (**34**) affords a 2:1 mixture of epoxy alcohols **35** and **36.** This resembles the result with carboxylic peracids,[32a] but contrasts with the highly regioselective epoxidation (**34** → **36**) achieved with alkyl hydroperoxides in the presence of vanadium or molybdenum catalysts.[32a] This result differs somewhat from that of Grieco and co-workers using a stoichiometric quantity of phenylseleninic acid (**1**) and H_2O_2 in protic solvents.[21] They report a 5:1 mixture of epoxy alcohols **35** and **36.** This difference in regioselectivity probably arises from the difference in the seleninic acids and the solvents which were employed. In any case it appears that arylperoxyseleninic acids (**12a**) are unique[48] among epoxidizing agents in that they exhibit little, if any, regio- or stereoselectivity in epoxidations of allylic alcohols.

Scheme IV. Epoxidation of Allylic Alcohols

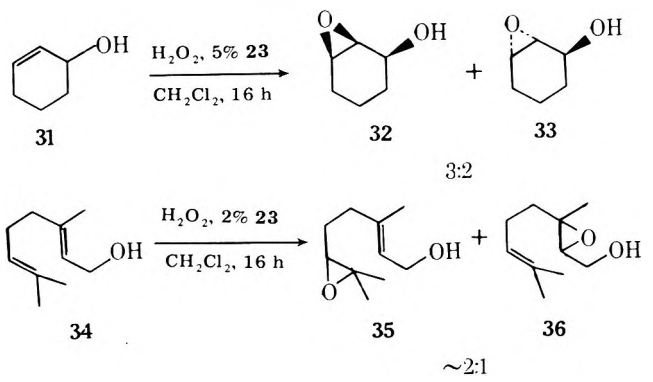


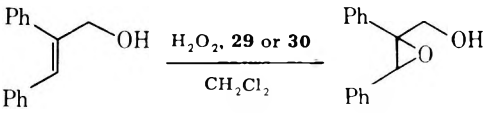
Table IV. Preparative Scale Epoxidations

Olefin	Registry no.	Catalyst (%)[a]	% yield[b] of epoxide
Cyclooctene		**23** (5)	95
(*E*)-5-Decene	7433-56-9	**22** (5)	90
2-Methyl-2-heptene	627-97-4	**22** (0.5)	81

[a] The figure in parentheses indicates the percentage of seleninic acid used. [b] The reported yields are for pure substances isolated by distillation.

In thinking of other possible unique features associated with these seleninic acid catalyzed epoxidations, it occurred to us that the putative active epoxidizing species, the arylperoxyseleninic acid **12a** or its peroxo isomer **12b,** was chiral.[49] Moreover, since the chirality resides at the selenium center this would place the asymmetry one atom closer to the site of oxygen transfer than can be achieved in chiral carboxylic peracids. Thus it seemed possible that chiral perseleninic acids might be superior to chiral percarboxylic acids[50] for the asymmetric epoxidation of olefins.

In order to test this idea the optically active seleninic acids **29** and **30** were synthesized.[51] The asymmetric centers in **29** and **30** are admittedly rather distant from the selenium; however, it was hoped that there would be considerable asymmetric induction in the exchange process (**11** ⇌ **12a**) leading to generation of the peroxyseleninic acid **12a.** Both seleninic acids **29** and **30** were effective epoxidation catalysts in CH_2Cl_2 in the presence of H_2O_2.[51] However, when the prochiral allylic alcohol **37** was epoxidized using either **29** or **30** as catalyst the resulting epoxy alcohol **38** was racemic.[51,52]



37 38 (racemic)

Summary

1. A new direct (one reaction vessel) route from olefins to rearranged allylic alcohols has been developed. The only other direct process for this transformation involves reaction with singlet oxygen. The reactivity of singlet oxygen toward most disubstituted olefins is poor.[53] Singlet oxygen is often not regioselective in reactions with trisubstituted olefins,[53] whereas the addition of "PhSeOH" to trisubstituted olefins is highly regioselective.

2. A new procedure using *tert*-butyl hydroperoxide for the oxidation/elimination of alkyl phenyl selenides is described. It avoids the secondary epoxidation process, which can be a problem when H_2O_2 is used as the oxidant. The use of *tert*-butyl hydroperoxide in place of H_2O_2 also leads to much better recoveries of diphenyl diselenide when the byproduct phenylseleninic acid is reduced. In the present work *tert*-butyl hydroperoxide has proved an ideal reagent for the oxidation/elimination of β-hydroxyalkyl phenyl selenides. Its general applicability to other types of alkyl phenyl selenides has not been established but would seem to merit attention. In particular, whenever tri- or tetrasubstituted olefins are present in the molecule (either initially or are being formed

as a result of the selenoxide elimination) the use of *tert*-butyl hydroperoxide instead of H_2O_2 should avoid the epoxidation processes to which these types of olefins are especially prone.

3. It has been independently discovered by four groups,[20,21] including our own,[16,18] that arylseleninic acids catalyze the epoxidation of olefins by H_2O_2. A convenient catalytic procedure for the epoxidation of di-, tri-, and tetrasubstituted[54] olefins has been developed. The best catalysts found to date are o-nitrophenylseleninic acid (**22**) and 2,4-dinitrophenylseleninic acid (**23**); 0.5–5% of the catalyst is generally employed. The best solvent is CH_2Cl_2. The best general procedure involves use of 30% H_2O_2 in the presence of excess anhydrous $MgSO_4$.

Experimental Section

Reagent grade methylene chloride was employed, and for all applications it was dried by storage over 4-Å molecular sieves. *All reactions* were performed under an atmosphere of dry nitrogen in order to exclude atmospheric moisture. If the use of more than 12–13 g of anhydrous magnesium sulfate was required, then it was found that a mechanical stirrer should be used in place of a magnetic stirrer. The 90% *tert*-butyl hydroperoxide was obtained either from Aldrich or from the Lucidol Division of the Pennwalt Corp. Melting points and boiling points are uncorrected.

Sources of Olefins. The cyclooctene obtained from Aldrich is about 95% pure; it contains 4 or 5% of a nonolefinic impurity. The citronellol methyl ether was prepared by methylation (NaH, CH_3I, DMF) of an old sample of Aldrich citronellol and was >95% pure. The citronellol now sold by Aldrich is of much lower (~70%) purity. The other olefins [1-methylcyclohexene, 2-methyl-2-heptene, (*E*)-4-octene, (*Z*)-4-octene, and (*E*)-5-decene] were obtained from Chemical Samples and are all 96–99% pure.

Sources of Organoselenium Reagents and Catalysts. Diphenyl diselenide (PhSeSePh, **21**) is available from Aldrich; however, the material used here was prepared according to our published procedure.[55] *This procedure*[55] *gives full experimental details for preparation of PhSeSePh on a 1-mol scale.*

The o-nitrophenylseleninic acid (**22**) is the most generally useful epoxidation catalyst and therefore full details for an improved preparation of the corresponding selenocyanate and diselenide are given below. It should be noted that only in the case of seleninic acids **1**[56] and **24**[57] were the seleninic acids themselves actually used as the catalysts. In all other instances the catalysts were added in the form of their diselenides. It is well known[56] that diselenides are oxidized to seleninic acids in the presence of hydrogen peroxide. The diselenides corresponding to seleninic acids **23**,[58] **25**,[59] **26**,[60] **27**,[55] and **28**[61] were prepared according to the cited literature procedures.[62]

A Simple Procedure for in Situ Generation of Sodium Selenocyanate. The method[63] commonly used for preparing pure potassium selenocyanate or sodium selenocyanate is not very appealing. Therefore we have developed a simple procedure[64] for generating a *N,N*-dimethylacetamide (DMAC) solution of KSeCN or NaSeCN which should in many cases obviate the need for preparing the pure substance: anhydrous DMAC (75 mL) was degassed by bubbling nitrogen through it for 15 min. The reaction vessel containing the DMAC was maintained under a positive pressure of nitrogen, and 7.90 g (0.10 mol) of powdered gray selenium metal and 5.24 g (95% pure, 0.102 mol) of sodium cyanide were added. The resulting suspension was stirred magnetically and heated in an oil bath (bath temperature at 110 °C) for 45 min until all the gray selenium metal disappeared, and a colorless solution contaminated with a little bit of white solid was obtained. After cooling, this solution of NaSeCN in DMAC was used as described below.

Similarly, KSeCN in DMAC solution (pale yellow solution contaminated with a little bit of white solid) can be prepared by heating a mixture of potassium cyanide and gray selenium metal in DMAC at 110 °C for 12 h. The pure crystalline KSeCN may be obtained by cooling the DMAC solution at 0 °C.

Preparation of o-Nitrophenyl Selenocyanate. According to the procedure of Bauer,[65a] o-nitroaniline (13.81 g, 0.10 mol), 39 mL of water, and 22 mL of concentrated hydrochloric acid are placed in a 250-mL two-neck flask equipped with a thermometer, a dropping funnel, and a magnetic stirrer.[65b] After the mixture was cooled to 2–3 °C in an ice–salt bath, a chilled solution of sodium nitrite (97% pure, 7.47 g, 0.105 mol) in 24 mL of water was added slowly maintaining the temperature at 2–3 °C. Stirring was then continued for 1 h at 2–3 °C. To this reaction mixture, 21 mL of chilled 25% aqueous sodium acetate solution was added dropwise until pH paper indicated a pH of about 4. The slightly brownish solution was filtered to remove traces of insoluble impurities and poured into a 1-L beaker surrounded by an ice–salt bath. The solution of NaSeCN (0.10 mol) in DMAC (see above) was cooled and then added dropwise to the reaction mixture in the beaker maintaining the temperature below 0 °C. The mixture was stirred with both a magnetic stirrer and a glass rod during the addition. The precipitated product was collected by filtration, washed with water, and dried to give 17.5 g of a dark yellow powder (mp 132–137 °C). This crude product was dissolved in 100 mL of chloroform and passed through a short plug of silica gel (40 g). Then 200 mL of chloroform was passed through the silica gel to ensure complete elution of the yellow o-nitrophenyl selenocyanate. Evaporation of the chloroform followed by recrystallization from acetone (120 mL) gave 11.37 g (50% yield) of orange-yellow crystals, mp 140–142 °C (lit.[65a] mp 142 °C). One gram of the crystals was recrystallized further from 20 mL of ethanol [the hot ethanol solution was treated with 40 mg of activated charcoal (Norit)] to give 0.91 g of yellow needles, mp 141.5–142.5 °C.

Preparation of Bis(o-nitrophenyl) Diselenide. The Source of the Seleninic Acid Catalyst 12. The o-nitrophenyl selenocyanate (10 g, 44 mmol) was added to a solution of 2.7 g (50 mmol) of sodium methoxide (Aldrich) in methanol (250 mL). The resulting light brown slurry was stirred under nitrogen for 3 h at room temperature. Water (200 mL) was added and the mixture was filtered. The solid was washed three times with water and dried to give 8.59 g (97%) of the diselenide as a light brown powder, mp 210–211 °C (lit.[61] mp 212–213 °C). It was this material which was used as the source of in situ generated, seleninic acid catalyst **22**.[62]

General Procedure for Olefin → Allylic Alcohol. Preparation of (*E*)-5-Octen-4-ol. To a magnetically stirred, ice-cooled solution of diphenyl diselenide (23.41 g, 75 mmol) in 250 mL of dry methylene chloride was slowly added 7.66 mL (8.50 g, 75 mmol) of chilled 30% hydrogen peroxide. After stirring vigorously for 30 min (white crystals deposit in 5–10 min), 12.5 g of powdered anhydrous magnesium sulfate was added and the mixture was stirred for an additional 30 min in the ice bath. The ice bath was removed. (*E*)-4-octene (5.61 g, 50 mmol) was added, and the mixture was stirred vigorously for 6 h at 24 °C. Chilled 90% *tert*-butyl hydroperoxide (30 mL, 268 mmol) was added to the reaction mixture which had been immersed in an ice bath; then, after removing the ice bath, the mixture was stirred for 20 h at 24 °C to give a pale orange solution with a lot of white precipitate. The white precipitate ($PhSeO_2H$ and hydrated $MgSO_4$) was filtered off (save for recovery of diphenyl diselenide) and washed with ether. The filtrate was concentrated (20 °C, aspirator) to give an oil. The oil was dissolved in 300 mL of ether and washed with 5% aqueous sodium carbonate (200 mL and then 100 mL, save), water (100 mL, save), 10% aqueous ferrous sulfate (200 mL and then 100 mL), water, saturated aqueous sodium hydrogen carbonate, water, and brine, successively. The ether extracts were dried over anhydrous magnesium sulfate. Concentration (20 °C, aspirator) gave an oil, which upon vacuum distillation gave 5.64 g (88%) of (*E*)-5-octen-4-ol, bp 58.5–59.5 °C (2.5 mm). NMR, IR, TLC, and GLC were identical with an authentic specimen.[15,16]

Following the same procedure (except that 20 h, instead of 6 h, was allowed for addition of "PhSeOH" to the olefin) (*Z*)-4-octene was converted to the same allylic alcohol [(*E*)-5-octen-4-ol] in 84% yield.

Preparation of Allylic Alcohol 9. In the case of citronellol methyl ether, the procedure was identical with that described for (*E*)-4-octene. The allylic alcohol **9** was obtained in 87% yield upon distillation, bp 76–77 °C (0.3 mm) [lit.[15,16] bp 77 °C (0.3 mm)]. NMR, IR, TLC, and GLC were identical with those for an authentic sample:[15,16] NMR ($CDCl_3$) δ 0.7–2.1 (m, 8 H, CH_2 and $CHCH_3$), 1.35 [s, 6 H, $C(CH_3)_2OH$], 3.35 (s, 3 H, OCH_3), 3.40 (t, 2 H, J = 6 Hz, OCH_2–), 5.65 (m, 2 H, =CH).

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.86; H, 11.80.

Preparation of Allylic Alcohol 10. In the case of cyclooctene the same (except that 20 h, instead of 6 h, was allowed for addition of "PhSeOH" to the olefin) procedure as described in detail for (*E*)-4-octene was employed. The allylic alcohol **10** was obtained in 83% yield following distillation, bp 78–79 °C (3 mm) [lit.[66] bp 74 °C (2 mm)]; this product was spectrally and chromatographically identical with the authentic sample.[15,16]

Preparation of 1-Methyl-2-cyclohexenol (17). The procedure for preparation of the hydroxy selenide of 1-methyl-1-cyclohexene was identical (10 mmol of olefin) with that described above for (*E*)-5-octen-4-ol, and the hydroxyselenide **15** was isolated by chroma-

tography on 40 g of silica gel. Elution with 2:1 CH_2Cl_2–hexane gave 2.25 g of the hydroxy selenide **15**, which was dissolved in dichloroethane. Then 3.8 g of anhydrous chloramine-T[67] (Aldrich) was added and the mixture was refluxed for 2 h. The products were extracted with 100 mL of ether and the extracts were washed with 200 mL of 1 N sodium hydroxide solution, water, and brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded an oil which was submitted to chromatography on silica gel. The epoxide byproduct was eluted with 5% ethyl acetate–hexane. Evaporation of the solvent gave 187 mg (16%) of 1,2-epoxy-1-methylcyclohexane, which was identified by comparison with an authentic sample. Further elution with 10% ethyl acetate–hexane followed by concentration gave an oil, which upon Kugelrohr distillation [80 °C (5 mm)] afforded 374 mg (33% based on olefin) of 1-methyl-2-cyclohexenol (**17**):[68] NMR (CCl_4) δ 1.20 (s, 3 H, CH_3), 1.5–2.2 (m, 6 H, CH_2), 2.72 (s, 1 H, OH), 5.59 (s, 2 H, olefinic).

Regeneration of Diselenide 2 by Reduction of the Reclaimed Seleninic Acid 1. In the foregoing description of the preparation of (*E*)-5-octen-4-ol it was noted that during the workup several of the washes (5% sodium carbonate washes and water washes) and a solid obtained by filtration were saved. This solid was added to the saved washes and 6 N hydrochloric acid was added to the resulting mixture until indicator paper revealed a pH of <3. Then 250 mL of a 10% sodium bisulfite solution was added which resulted in precipitation of a yellow solid (PhSeSePh). This suspension of diphenyl diselenide in water was extracted thrice with ether (300 mL, 100 mL, and finally 50 mL). In order to remove water and minor polar impurities, the combined ether extracts were passed quickly through a short plug of silica gel (50 g); then several small portions of ether were passed through the silica gel to ensure complete elution of the yellow diselenide. Evaporation of the ether afforded 21.9 g (93% recovery) of the diselenide **2**, mp 60.3–61.1 °C. This material was sufficiently pure for reuse. Recrystallization from hexane gave 19.42 g of yellow crystals, mp 60.8–61.8 °C; the mother liquid yielded a second crop (1.1 g, mp. 60.3–61.1 °C) of the diselenide.

Complications Resulting from Readdition of "PhSeOH" to the Allylic Alcohol Product. Formation of Diol Selenide 14. In the same manner as described above for preparation of (*E*)-5-octen-4-ol, 30% H_2O_2 (648 μL, 720 mg, 6.35 mmol) was added dropwise to a cooled and magnetically stirred solution of 1.98 g (6.35 mmol) of diphenyl diselenide in 22 mL of CH_2Cl_2. Powdered anhydrous magnesium sulfate (1.06 g) was then added and the mixture was stirred for an additional 30 min in the ice bath. (*E*)-4-Octene (475 mg, 4.23 mmol) was added and the suspension was stirred vigorously at room temperature for 15 h. The reaction mixture was cooled with an ice bath and any remaining anhydrous magnesium sulfate was hydrated by addition of 1.4 mL of water. Chilled 30% hydrogen peroxide (1.27 mL, 1.41 g, 12.5 mmol) was added dropwise, then the ice bath was removed and stirring was continued for 1 h at room temperature. The suspended solids were removed by filtration and washed with ether. The filtrate was concentrated to give an oil. The oil was dissolved in ether and washed with 5% aqueous sodium carbonate, water, and brine and dried ($MgSO_4$). Concentration afforded a solid which was recrystallized from hexane to give 608 mg (48%) of 4-phenylselenyl-3,5-dihydroxyoctane: mp 77.9–78.6 °C; NMR (90 MHz, $CDCl_3$) δ 3.28 (dd, 1 H, J_{AX} = 1.7 Hz, J_{BX} = 4.3 Hz, CHSePh), 3.8–4.3 (m, 2 H, C*H*OH), 7.3–7.7 (m, 5 H, aromatic).

Anal. Calcd for $C_{14}H_{22}O_2Se$: C, 55.81; H, 7.36. Found: C, 56.00; H, 7.23.

Epoxidation of Cyclooctene. Data in Table II. To a cooled, stirred reaction mixture containing cyclooctene (110 mg, 1 mmol) and the selenium catalyst (0.05 mmol of the diaryl diselenide or 0.1 mmol of selenium dioxide) in 2 mL of methylene chloride was added 204 μL (227 mg, 2.0 mmol) or 220 μL (244 mg, 2.15 mmol) of chilled 30% hydrogen peroxide. When anhydrous magnesium sulfate was used, 250 mg was added after addition of the 30% hydrogen peroxide. The ice bath was allowed to melt (~30 min) and the reaction mixture was stirred for 16 or 20 h at room temperature. Small aliquots of the reaction mixtures were dissolved in ethyl acetate and washed with 10% aqueous sodium carbonate and brine in preparation for the gas chromatographic analysis performed (temperature programming from 100 to 200 °C) on a 6 ft × 0.125 in. glass column packed with 10% UCW-98 on 80/100 mesh Gas Chrom Q.

Epoxidation of Citronellol Methyl Ether. Data in Table III. To the mixture of 170 mg (1 mmol) of citronellol methyl ether and 0.005 mmol of bis(o-nitrophenyl) diselenide or bis(2,4-dinitrophenyl) diselenide[58] in 2 mL of methylene chloride, 204 μL (227 mg, 2.0 mmol) of chilled 30% hydrogen peroxide or 49 μL (69 mg, 2.0 mmol) of 98% hydrogen peroxide was added while stirring in an ice bath. When anhydrous magnesium sulfate was employed, 250 mg was added after addition of the 30% hydrogen peroxide. The ice bath was allowed to melt (~30 min) and stirring was continued at room temperature for 16 h. Aliquots of the reaction mixtures were prepared for GLC analyses as described above for the cyclooctene experiments. The GLC analyses were performed at 120 °C on a 6 ft × 0.125 in. glass column packed with 3% OV-17 on 80/100 mesh Gas Chrom Q.

Preparative Scale Epoxidations. Cyclooctene → Cyclooctene Epoxide. To a 250 mL round-bottom flask equipped with a mechanical stirrer and a reflux condenser were added 11.48 g of cyclooctene (Aldrich, 96% pure, equivalent to 11.02 g, 0.1 mol), 1.23 g (2.5 mmol) of bis(2,4-dinitrophenyl) diselenide, 25 g of anhydrous magnesium sulfate, and 100 mL of methylene chloride. The resulting suspension was cooled in an ice bath and 20.4 mL (22.67 g, 0.2 mol) of chilled 30% hydrogen peroxide was added dropwise (~5 min) while stirring vigorously. The ice bath was removed and after about 30 min the reaction mixture began to reflux. This spontaneous refluxing continued for about 1 h and then the mixture was stirred at room temperature for an additional 18.5 h. The hydrated magnesium sulfate was filtered off and washed with ether. This filtrate was diluted with 500 mL of ether and washed with water, 10% sodium carbonate, water, and brine and then dried ($MgSO_4$). Concentration gave an oil which was distilled by Kugelrohr [80 °C (0.1 mm)] to give 0.35 g as the first fraction and 11.99 g (95%) of cyclooctene oxide as the second fraction. NMR, IR, TLC, and GLC were identical with an authentic sample (Aldrich).

(*E*)-5-Decene → (*E*)-5,6-Epoxydecane. A 100-mL two-neck round-bottom flask equipped with a magnetic stirrer, a reflux condenser, and an ice cooling bath was charged with 25 mL of methylene chloride, 3.51 g (25 mmol) of (*E*)-5-decene, 2.51 mg (0.63 mmol) of bis(o-nitrophenyl) diselenide, and 6.25 g of powered anhydrous magnesium sulfate. To this vigorously stirred suspension was added dropwise 5.11 mL (5.67 g, 50 mmol) of chilled 30% hydrogen peroxide. The mixture was allowed to warm to room temperature and heated at reflux for 8 h. GLC analysis at this point revealed that olefin (~10%) still remained. The mixture was cooled in an ice bath and 3.3 g of anhydrous magnesium sulfate was added, followed by dropwise addition of 3.51 mL (3.90 g, 25 mmol) of chilled 30% hydrogen peroxide. The reaction mixture was then refluxed for 16 h, at which time GLC analysis revealed that no olefin remained.[69] [*This modified procedure employing heating, additional hydrogen peroxide, and a longer reaction time is recommended for less reactive olefins* which are not completely epoxidized under the milder conditions described above for preparation of cyclooctene epoxide.] Workup as described for epoxidation of cyclooctene afforded 4.2 g of a yellow oil which was distilled to give 3.9 g (90%) of (*E*)-5,6-epoxydecane, bp 39–40 °C (0.05 mm). It was identical in all respects with an authentic sample prepared by epoxidation of (*E*)-5-decene with *m*-chloroperbenzoic acid.

2-Methyl-2-heptene → 2,3-Epoxy-2-methylheptane. A reaction mixture consisting of 5.71 g (50 mmol) of 2-methyl-2-heptene, 50.3 mg (0.125 mmol) of bis(o-nitrophenyl) diselenide (**22**), and 12.5 g of anhydrous magnesium sulfate in 50 mL of methylene chloride was magnetically stirred vigorously; the 100-mL round-bottom flask was also equipped with a reflux condenser. This suspension was cooled in an ice bath and 10.22 mL (11.34 g, 0.1 mol) of chilled 30% hydrogen peroxide was added dropwise over about 3 min. Then the cooling bath was removed and after about 2.5 h the reaction mixture began to reflux spontaneously. Refluxing continued for about 1 h and then the suspension was stirred at room temperature for an additional 16.5 h. Workup as described above for epoxidation of cyclooctene gave an oil which upon kugelrohr distillation [80 °C (0.1 mm)] afforded 5.27 g (81%) of 2,3-epoxy-2-methylheptane. It was spectrally and chromatographically identical with an authentic sample prepared by epoxidation of 2-methyl-2-heptene with *m*-chloroperbenzoic acid.

Epoxidation of Allylic Alcohol 31. A reagent solution was prepared by addition of chilled 30% hydogen peroxide (204 μL, 227 mg, 2.0 mmol) to a mixture of 12.3 mg (0.025 mmol) of bis(2,4-dinitrophenyl) diselenide in 2 mL of methylene chloride. The resulting mixture was stirred for 1 h at room temperature. To this reagent was added 98 mg (1 mmol) of 2-cyclohexenol (**31**) and stirring was continued for 16 h at room temperature. At this point GLC analysis (6 ft × 0.125 in. glass column, 10% UCW-98 on 80/100 mesh Gas Chrom Q) revealed a 3:2 mixture of the *syn*- (**32**) and *anti*- (**33**) epoxy alcohols. Epoxy alcohols **32** and **33** were identified by comparison with authentic samples prepared by epoxidation of cyclohexenol **31** with *m*-chloroperbenzoic acid.[47,32d] The *syn*-epoxy alcohol **32** has the shorter GLC retention time.

Epoxidation of Allylic Alcohol 34. Epoxidation of **34** was carried out as described for epoxidation of **31** except that less catalyst [4.9 mg (0.01 mmol) of bis(2,4-dinitrophenyl) diselenide for 1 mmol of allylic

alcohol **34**] was used. GLC analysis at 150 °C (6 ft × 0.125 in. glass column, 10% OV-101 on Supelcon AW-DMCS) showed a 2:1 mixture of epoxy alcohols **35** and **36**. Epoxy alcohols **35** and **36** were identified by comparison with authentic samples prepared by epoxidation of **34** with *m*-chloroperbenzoic acid.[32a]

Acknowledgment. We thank the National Institutes of Health (GM-21686), the National Science Foundation (CHE74-21260), and Hoffmann-La Roche, Inc., for support of this research. We are very grateful to Dr. Lian Ee Khoo (on leave from Universiti Sains Malaysia, Penang, Malaysia) for performing several of the important experiments described in the section on catalytic epoxidations.

Registry No.—**2,** 1666-13-3; **9,** 65252-78-0; **15,** 65252-79-1; **17,** 23758-27-2; *o*-nitrophenyl selenocyanate, 51694-22-5; PhSeOH, 5818-99-5; 4-phenylselenyl-3,5-dihydroxyoctane, 65252-80-4.

References and Notes

(1) Address correspondence to this author at the Department of Chemistry of Stanford University.
(2) As chance would have it, on the same day in which the experiments were performed which established that β-hydroxy selenides **3** resulted from reaction of olefins with solutions containing **1** and **2**, one of us (K.B.S.) learned in a phone conversation with Professor Hans Reich that he and his co-workers had also discovered this type of reactivity (see neighboring publication[3] in this issue).
(3) H. J. Reich, S. Wollowitz, J. E. Trend, F. Chow, and D. F. Wendelborn, *J. Org. Chem.*, following paper in this issue.
(4) The addition process could just as well involve other selenium(II) electrophiles such as i and ii:

PhSeOSe(O)Ph PhSeOSePh
i ii

(5) G. Hölzle and W. Jenny, *Helv. Chim. Acta*, **41,** 593 (1958).
(6) K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, 39, 429 (1974).
(7) H. J. Reich, *J. Org. Chem.*, **39,** 428 (1974).
(8) D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 100 (1974).
(9) (a) An intramolecular example of the addition of an arylselenenic acid to an olefin has been reported: H. J. Reich and J. E. Trend, *J. Org. Chem.*, **41,** 2503 (1976). (b) More recently it has been reported that reaction of cyclohexene with PhSeCN in THF–H_2O in the presence of a copper or nickel(II) halide gave *trans*-2-hydroxycyclohexyl phenyl selenide: A. Toshimitsu, S. Uemura, and M. Okano, *J. Chem. Soc., Chem. Commun.*, 166 (1977).
(10) In order to ensure complete reaction of the olefin we found it necessary to use 1.5 molar equiv of the diselenide **2** (i.e., enough diselenide to give rise to 3 molar equiv of "PhSeOH"). The disavantage of having to employ an excess of the selenium reagent is offset by the demonstration (see Experimental Section) that PhSeSePh (**2**) can be efficiently (>90%) recovered.
(11) The pK_a of phenylseleninic acid (**1**) is about 4.8 [J. D. McCullogh and E. S. Gould, *J. Am. Chem. Soc.*, **71,** 674 (1949)].
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(15) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **95,** 2697 (1973).
(16) R. F. Lauer, Ph.D. Thesis, Massachusetts Institute of Technology, 1974, p 102.
(17) Reich and co-workers have made some very interesting discoveries concerning the ability of selenium species to catalyze the dismutation of H_2O_2.[3]
(18) S. E. Dinizo, H. P. Jensen, R. F. Lauer, and K. B. Sharpless, unpublished results.
(19) However, decomposition pathways involving radical processes must also be considered. We have recently obtained evidence suggesting the involvement of radicals in the decomposition of allylic seleninyl peresters (M. A. Umbreit and K. B. Sharpless, unpublished results).
(20) (a) H. J. Reich, F. Chow and S. L. Peake, *Synthesis*, in press; (b) see also ref 3.
(21) P. A. Grieco, Y. Yokoyama, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, **42,** 2035 (1977); T. Kametani, H. Nemoto, and K. Fukumoto, *Heterocycles*, **6,** 1365 (1977).
(22) R. F. Lauer, H. P. Jensen, and K. B. Sharpless, unpublished results.
(23) K. B. Sharpless, K. M. Gordon, R. F. Lauer, D. W. Patrick, S. P. Singer, and M. W. Young, *Chem. Scr.*, **8A,** 9 (1975). A phase-transfer-catalyzed process for the oxidation/elimination of alkyl phenyl selenides utilizing chloramine-T was described. This same procedure was also reported to be effective for the generation of sulfilimines from sulfides. It was claimed that these were the first phase-transfer applications of chloramine-T. *This is wrong.* Oae and co-workers had much earlier reported the conversion of sulfides to sulfilimines with chloramine-T under phase-transfer conditions: K. Tsujihara, N. Furukawa, K. Oae, and S. Oae, *Bull. Chem. Soc. Jpn.*, **42,** 2631 (1969). Carl R. Johnson (private communication) has found that chloramine-T is effective for the oxidation of sulfides to sulfilimines in the absence of an aqueous phase provided a phase-transfer catalyst is present (i.e., solid–liquid PTC).
(24) This is preferable to the earlier[23] procedure in that a phase-transfer catalyst, which can be difficult to separate from the desired products, is not necessary. However, we have founc that secondary allylic alcohols are oxidized to α,β-unsaturated ketones under these conditions (T. Hori and K. B. Sharpless, unpublished results).
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(30) Phenylseleninic acid (**1**) has been reported to catalyze the decomposition of TBHP in refluxing benzene: D. T. Woodbridge, *J. Chem. Soc. B*, 50 (1966).
(31) TBHP (pK_a ~12–13) can be extracted from organic solutions with aqueous KOH, but in our experience this is not a very satisfactory method for its removal. Numerous alkaline washes are necessary and this can result in loss of water-soluble products. Emulsions were also a problem.
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(43) J. Itakura, H. Tanaka, and H. Ito, *Bull. Chem. Soc. Jpn.*, **42,** 1604–1608 (1969).
(44) Reich has also found that *o*-nitrophenylseleninic acid (**22**) is a very active catalyst.[20]
(45) The inhibition of the epoxidation process by coordinating and protic solvents is not surprising. Epoxidations by carboxylic peracids are well known to exhibit this same type of solvent sensitivity.
(46) Before adding the $MgSO_4$ the reactions are heterogenous (the presence of water droplets is apparent). To the extent that the arylseleninic acid catalyst is dissolved in these water droplets, the rate increase associated with addition of anhydrous $MgSO_4$ may be in part due to the increased catalyst concentration in the organic (CH_2Cl_2) phase caused by removal of the aqueous phase.
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(49) This conclusion is based on the reasonable assumption that the peracid **12a** has an approximately tetrahedral selenium center. A referee has pointed out that the epoxidizing species might be a hydrated peroxyseleninic acid [$ArSe(OH)_2OOH$] which, depending on the relative orientation of the substituents, may or may not be chiral at selenium. If one wishes to consider alternative structures for the active oxidant we feel that the cyclic peroxy species **12b** is a more likely candidate than the hydrate mentioned above. The only configurations of **12b** which are achiral at selenium are trigonal bipyramids with the peroxo unit equatorial and some combination of the aryl group, the lone pair, or the hydroxyl group in the two apical positions; such configurations would be highly disfavored by strain in the three-membered peroxo ring and by having at least one of the less electronegative substituents in the apical position.
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(52) For successful asymmetric epoxidations of allylic alcohol **37**, see R. C. Michaelson, R. E. Palermo, and K. B. Sharpless, *J. Am. Chem. Soc.*, **99,** 1990 (1977).
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catalyzed epoxidations.
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(62) Since for the most electronegatively substituted cases the diselenide is prepared from the corresponding selenocyanate, it would be advantageous to be able to use the selenocyanate itself as the catalyst. This possibility was briefly explored in the case of the *o*-nitrophenyl selenocyanate. It was found that the selenocyanate was rather slow to be oxidized by hydrogen peroxide to the seleninic acid; this gave rise to induction periods when it was used as the catalyst. However, if the methylene chloride solution of the selenocyanate catalyst was first treated with an equivalent amount (e.g., if 5% catalyst then 5% Ph_3P) of triphenylphosphine, no induction period was observed and the results were identical with those using the corresponding diselenide as the catalyst.
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(69) Preliminary results (L. E. Khoo and K. B. Sharpless, unpublished) indicate that most of the seleninic acid catalyst **22** is still present and active at the end of these reactions. This is suggested by the observation that one can effect epoxidation of cyclooctene by adding cyclooctene and fresh hydrogen peroxide and anhydrous magnesium sulfate to a crude reaction mixture in which the epoxidation of (*E*)-5-decene has just been completed.

Syn Elimination of Alkyl Selenoxides. Side Reactions Involving Selenenic Acids. Structural and Solvent Effects on Rates[1]

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The olefin-forming syn elimination of alkyl aryl selenoxides was examined. The formation of β-hydroxy selenides by addition of the elements of benzeneselenenic acid (PhSeOH) to olefin product was found to be a persistent side reaction unless an alkylamine was present during syn elimination. The selenium(II) electrophile is provided by a comproportionation (reverse disproportionation) of Ph_2Se_2 and $PhSeO_2H$. If an intramolecular reaction is possible (as for the decomposition of **1**) only an unhindered secondary amine will prevent the electrophilic addition to the double bond. The selenoxide syn elimination was shown to be irreversible for compound **1**. Alkyl aryl selenoxides react with dimethyl acetylenedicarboxylate to form ylides (e.g. **8**). Solvent and substitutent effects on the rates of selenoxide syn eliminations were measured. Protic solvents reduce the rate of syn elimination. Chloro and phenyl substituents at either the α or β position or alkyl at the α position accelerate the syn elimination, whereas β-alkyl and methoxy substituents retard it. Methyl aryl selenoxides were shown to catalytically decompose hydrogen peroxide, a widely used oxidant for selenides. Reaction conditions for optimizing rates and yields for selenoxide syn eliminations are proposed.

The selenoxide syn elimination has been shown to be a mild and selective procedure for olefin formation.[3,4] The reaction frequently provides high yields of clean products, but side reactions have been identified in certain cases. For example, some α-phenylselenino ketones in acidic media undergo seleno-Pummerer reactions leading to α-dicarbonyl compounds.[3a] Reactions of enols, enolates, and enamines with active selenium(II) electrophiles formed during syn eliminations have also given unwanted products in some systems.[3a,5] Alkyl selenoxide eliminations, however, have generally been assumed to be free of byproducts, although low yields particularly for primary alkyl selenoxides have occasionally been reported in the published literature[4c,6] as well as in private communications to the authors. Modifications of the selenide reagent[6a] and elimination reaction conditions[3b] have been proposed to improve yields for such compounds.

The scattered results available suggested that selenoxide decompositions were complex. It is clear in retrospect that the long delay in recognition of the selenoxide syn elimination was a consequence of alternate reaction pathways available during the thermolysis.[7] The work described here was initiated to identify side reactions which may be occurring, and to gather product and kinetic data which will serve as a guide to optimizing reaction conditions for synthetic applications of the syn elimination.

Thermolysis of 2,2-Dimethyl-2,3-dihydrobenzo[*b*]-selenophene Oxide (1). The selenoxide is obtained by ozonization of 2,2-dimethyl-2,3-dihydrobenzo[*b*]selenophene in CH_2Cl_2, $CHCl_3$, or CF_2HCl at −78 to −60 °C. NMR spectra of the selenoxide can be obtained if taken rapidly at ambient probe temperature or more leisurely at sub-zero probe temperatures. Complete decomposition takes a few hours in organic solvents at room temperature. In the ^1H NMR spectrum of the ozonization solutions are observed two methyl singlets assigned to the diastereotopic *gem*-dimethyl group and an AB quartet corresponding to the benzylic hydrogens. An IR absorption assigned to the seleninyl $\nu_{Se=O}$ stretch[8] can be observed. Undecomposed solutions of **1** when treated with aqueous potassium iodide are reduced to the starting selenide. Although **1** does not lend itself to mass analysis, the above physical and spectral parameters satisfactorily characterize the compound.

If **1** is allowed to decompose completely, preparative TLC affords an ~4:1 mixture of isomeric alcohols in 77% combined yield which were assigned structures **2** (major) and **3** (minor) (Scheme I) on the basis of their NMR spectra and mass spectral analysis. The *p*-nitrobenzoate of **2** was isolated and successfully analyzed for C and H. The ^1H NMR spectrum of **2** in benzene-d_6 shows two AB quartets corresponding to the benzylic (δ 2.70, 2.96; J_{AB} = 15.2 Hz) and hydroxymethyl protons (δ 3.29, 3.25; J_{AB} = 11.0 Hz). Assignments are based on the magnitude of the benzylic coupling constant typical of indane structures[9] and the ~1 ppm downfield shift of the hydroxymethyl protons in going to the *p*-nitrobenzoate of **2**.

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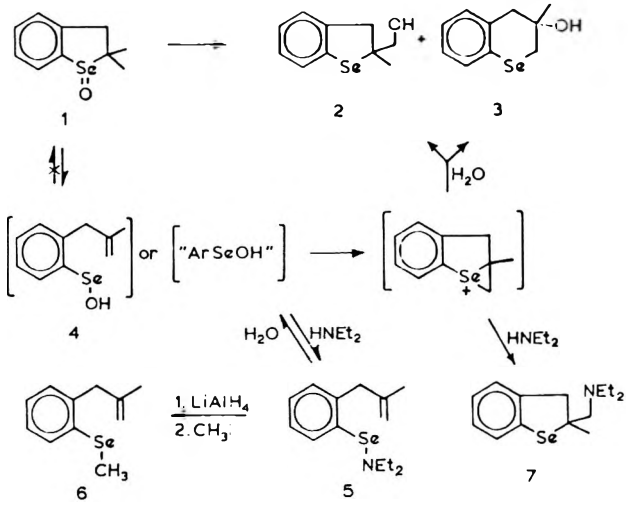
Scheme I



Spectral assignments for **3** are less secure, though they are tentatively assigned on the basis of the magnitude of J_{gem} characteristic of chroman compounds:[10] benzylic protons (δ 2.16 and 2.36; J_{AB} = 15.5 Hz) and methylene protons α to selenium (δ 2.47 and 2.65; J_{AB} = 11.0 Hz) in benzene-d_6. In $CDCl_3$ the hydroxymethyl protons of **2** and benzylic protons of **3** appear as apparent singlets. Selenium-77 (7.6% abundance) satellites (J_{SeCCH} = 12 Hz) observed for the methyl singlet of **2** and absent from that of the minor isomer serve to further differentiate the isomers and establish the structure of **2**.

Decomposing the selenoxide in the presence of triethylamine or acetic acid in methylene chloride or hydrochloric acid or sodium carbonate in aqueous solution does not significantly alter the product ratio; the major isomer always dominates in the range of 80–90%.

The thermal transformations of **1** are probably initiated by selenoxide syn elimination to selenenic acid **4**. To confirm the existence of ring-opened species along the reaction pathway to the alcohols, the selenoxide was decomposed in the presence of dialkylamines. Previous work has shown that selenenamides are isolable, though easily hydrolyzable compounds, and that they are formed when selenoxide syn eliminations are buffered with dialkylamines (eq 1).[5,11]

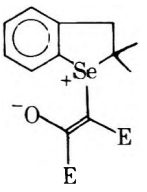
$$R'SeOH + HNR_2 \rightleftharpoons R'SeNR_2 + H_2O \qquad (1)$$

When **1** is decomposed in the presence of excess diethylamine, proton and carbon NMR resonances assignable to selenenamide **5** are observed. Little of the alcohols **2** and **3** is formed. Particularly informative are the ^{13}C resonances for a terminal vinyl carbon and a CH_2N carbon 10 ppm downfield from that of diethylamine having selenium satellites (J_{SeNC} = ~10 Hz). Attempts to isolate **5** by evaporation of solvent and excess diethylamine resulted in the formation of alcohols **2** and **3** apparently by forcing the equilibrium in eq 1 to revert in favor of selenenic acid leading to the alcohols **2** and **3**. Other results[5] had suggested that the diisopropylselenenamide might not be so labile; however, when a large excess of diisopropylamine is present during the decomposition of **1** only the alcohols can be observed, suggesting that the forward reaction in eq 1 does not successfully compete with the rearrangement of **4** to the alcohols when sterically bulky amines are used.

To obtain more concrete evidence for the selenenamide, a solution of **5** in diethylamine–ether was cleaved with excess lithium aluminum hydride at 0 °C and then treated with iodomethane. On workup a compound was isolated by TLC in 60% yield. Vinyl resonances (δ 4.60, 4.86) and a methyl singlet (δ 2.28) with selenium satellites (J_{SeCH} = 12.0 Hz) are observed in the ^1H NMR spectrum. The ^1H NMR and analytic data required the aryl methyl selenide **6**.

If a solution of **5** in diethylamine stands for a day at room temperature, the vinyl resonances in the ^1H NMR spectrum disappear and a complex mixture of products is formed from which can be isolated in 17% yield a compound with ^1H NMR and mass spectra consistent with structure **7**. Observable quantities of the ring-expanded diethylamino adduct corresponding to **3** are not formed, but the alcohols **2** and **3** are isolated in 18% yield in a 4:1 ratio.

The chemistry described above provided an opportunity to test the reversibility of the selenoxide syn elimination. It is reasonable to anticipate that selenenic acids react with olefins, since sulfoxide syn eliminations have been shown to be highly reversible both intra- and intermolecularly.[12] When selenoxide **1** was decomposed under different conditions in the presence of excess D_2O, *no* deuterium incorporation in either of the products **2** and **3** could be detected. Attempts to trap the selenenic acid **4** in an intermolecular reaction by thermolysis of **1** in the presence of dimethyl acetylene dicarboxylate (a process with much precedent in sulfur chemistry[12a,b,c]) led instead to the formation of the ylide **8** by direct



8

reaction of **1** with the acetylene. Methyl phenyl selenoxide forms the analogous ylide. Similar reactions have been observed under more vigorous conditions for sulfoxides[13] and phosphine imides.[14]

The evidence presented points out several departures of the behavior of selenoxide syn elimination products from that of sulfoxide. In contrast with the observed behavior of sulfenic acid intermediates, the selenenic acid does not revert to selenoixde but instead is attacked by olefin without activation by external electrophilic agents such as acetic anhydride or protic acid necessary for similar reactions of sulfur compounds. Olefin may attack the selenenic acid directly to give an episelenonium ion. An alternative electrophilic selenium species is the selenenic acid anhydride (or protonated form thereof), a proposed intermediate along the disproportionation pathway of selenenic acids.[15] The anhydride may take either of the forms pictured (the selenolseleninate is precedented by the known thiolsulfinate, an established intermediate along the disproportionation pathway of sulfenic acids[12a,f,18]) as either provides the identical suitable leaving group, the selenenate anion $RSeO^-$, for displacement by olefin. For simplicity, the active electrophile will hereafter be referred to as "ArSeOH".

RSe(=O)SeR or RSeOSeR

Sulfenic acid anhydrides, thiolsulfinates, though they do not undergo direct nucleophilic attack by π systems are attacked at sulfenyl sulfur by alkyl mercaptide ions.[19]

Scheme I is a representation and interpretation of the observed results. Apparently the selenenic acid reacts further more rapidly than it can revert to selenoxide; "ArSeOH" is intramolecularly attacked by olefin to form the episelenonium ion more rapidly than it can continue along the disproportionation pathway to diselenide and seleninic acid.[15] Diethylamine reacts with "ArSeOH" faster than olefin capture. In either case the selenenamide must be in equilibrium with the active species in order to gain access to the episelenonium ion. Water can attack the episelenonium ion at the secondary (to

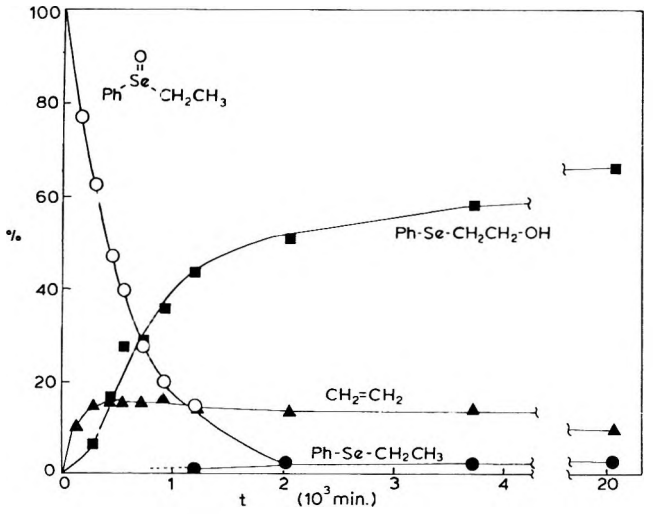


Figure 1. Decomposition of ethyl phenyl selenoxide (0.4 M) in $CDCl_3$ at 38 °C: ○ ethyl phenyl selenoxide; ● ethyl phenyl selenide; ■ β-hydroxyethyl phenyl selenide; ▲ ethylene *in solution* (a large fraction of the ethylene is in the gas phase).

give **2**) or quaternary carbon (**3**). When present, diethylamine competes with water by attack at the less hindered secondary site to give **7**.

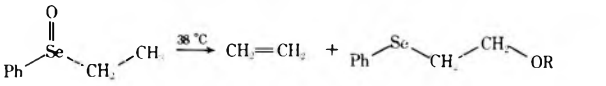
Thermolysis of Alkyl Phenyl Selenoxides. The facile intramolecular selenenic acid olefin addition described above raised the question whether such reactions also occur intermolecularly. When a solution of ethyl phenyl selenoxide in $CDCl_3$ was heated at 38 °C, slow decomposition ($t_{1/2}$ = 360 min) occurred to give ethylene and a second product which was identified as β-hydroxyethyl phenyl selenide (Table I).[20] Depending on reaction conditions, the latter product amounts to 50–85% of the product.[19] Figure 1 shows product composition as a function of time for this reaction. Note that the formation of the β-hydroxy selenide does not proceed to completion even after long reaction times. Other alkyl selenoxides behave in a similar fashion. The formation of β-hydroxyethyl phenyl selenide is completely suppressed by the addition of alkyl amines, but is only slightly affected by pyridine. The intermolecular electrophilic addition is thus more easily prevented than the intramolecular case, since the latter is unaffected by either tertiary or hindered secondary amines.

Additional experiments with 2-phenylpropyl phenyl selenoxide (**9**) led to the results reported in Table II. As observed for the ethyl selenoxide, most or all of the olefin presumably formed by syn elimination reacts with a selenium(II) electrophile to give β-hydroxy selenide **10** *unless base is present.*[22]

Solvent Effects. Protic solvents exert a profound effect on both product composition and rate of the syn elimination. For example, ethyl phenyl selenoxide gives 2-acetoxyethyl phenyl selenide as essentially the only product when as little as 1.5 equiv of acetic acid is added to the $CDCl_3$ solution, and the rate of elimination slows down by approximately a factor of 5! In pure methanol, selenoxide **9** eliminates only one-tenth as rapidly as in $CDCl_3$ solution, and no olefin (**11**) is formed, only the addition product **10** (R = CH_3). In acetic acid the rate is <1% that in $CDCl_3$. The solvent effect on rate is probably a consequence of the powerful hydrogen-bonding properties of selenoxides. Some disruption of the solvation may be necessary to achieve the syn elimination transition state.

Redox Equilibria Involving Selenenic Acids. The selenium species that reacts with olefin is probably selenenic acid or some derivative ("PhSeOH").[15] An important observation was that the normal disproportionation products of benzeneselenenic acid (eq 2)[23] react with olefins to give β-hydroxy selenides (eq 3) at rates comparable to syn elimination rates. The reaction does not go to completion when olefin, $PhSeO_2H$, and Ph_2Se_2 are used in a stoichiometric ratio (3:1:1). A portion of the Ph_2Se_2 remains, suggesting that some process is causing reduction of $PhSeO_2H$.[24,25] This was also observed during syn elimination experiments (Figure 1).

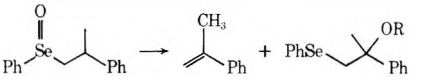
Table I. Product Data for Syn Elimination of Ethyl Phenyl Selenoxide



Solvent	Product ratio[a]
$CDCl_3$	53:47 (R = H)[b]
$CDCl_3$ + 1.5 equiv of pyridine	70:30
$CDCl_3$ + 1.5 equiv of NMe_3 or $HNMe_2$	100:0
$CDCl_3$ + 1.5 equiv of CH_3CO_2H	0:100 (R = CH_3CO_2)

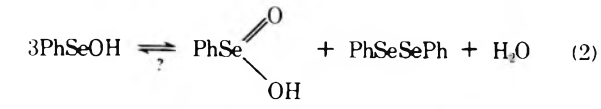
[a] At 80% reaction. [b] Approximately 5% of ethyl phenyl selenide was formed in this run only.

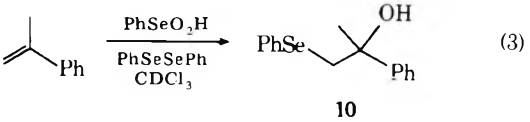
Table II. Rate and Product Data for Syn Elimination of 2-Phenylpropyl Phenyl Selenoxide (9)



Solvent	k_{rel} ($t_{1/2}$, min)	Product ratio (11/10)[a]
$CDCl_3$	1.0[b]	40:60[d]
$CDCl_3$ + 1.5 equiv of $HNMe_2$	1.0[c]	100:0
CD_3OD	0.13[b]	0:100[e]
CD_3OD + 1.5 equiv of $HNMe_2$	0.1	100:0
CD_3CO_2D	<0.01	0:100[f]

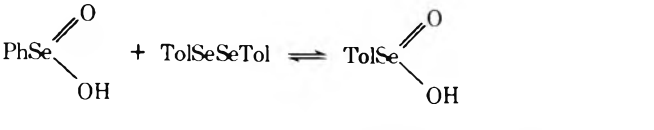
[a] At 80% reaction. [b] The reaction did not follow good first-order kinetics (inhibition by products). [c] First-order rate constant: $k = 4.0 \times 10^{-4}$ s^{-1} at 38 °C. [d] Approximately 5% of selenide was formed. [e] R = CD_3O. [f] R = CD_3CO_2.





10

Since neither $PhSeO_2H$ nor PhSeSePh alone in $CDCl_3$ give β-hydroxy selenides rapidly in the presence of olefins,[28] this observation strongly suggests that the disproportionation of eq 2 is reversible, and that the reverse process provides the active electrophile. The occurrence of such a comproportionation[29] is experimentally supported: diselenide and seleninic acid in $CDCl_3$ exchange oxidation states (eq 4) in an acid-catalyzed process more rapidly than the addition of eq 3. This redox reaction can be most reasonably interpreted as proceeding through PhSeOH or a related symmetric species such as PhSeOSePh.



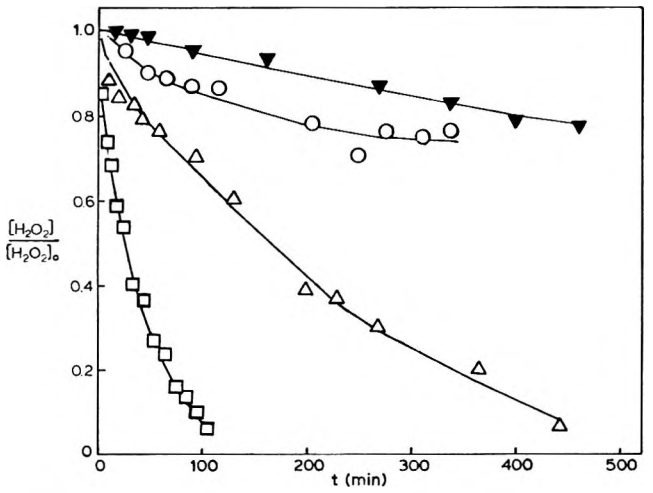
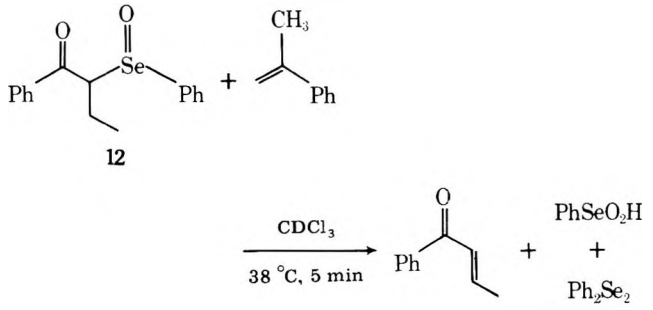


Figure 2. Decomposition of hydrogen peroxide (0.18 M) at 38 °C catalyzed by methyl aryl selenoxides (0.018 M): ▼ phenyl methyl selenoxide in 90% THF/10% H_2O–H_2O_2; ○ methyl 2-nitrophenyl selenoxide in 90% CH_3OH/10% H_2O–H_2O_2; ▽ methyl 3-trifluoromethylphenyl selenoxide in 90% CH_3OH; □ methyl phenyl selenoxide in 90% CH_3OH. Benzeneseleninic acid ($PhSeO_2H$) caused <5% decomposition after 400 min in 90% methanol.

That a comproportionation (eq 2) is the source of most of the selenium electrophile, rather than PhSeOH adding directly to the olefin as it is formed, is demonstrated by the following experiment: syn elimination of selenoxide **12** in $CDCl_3$ (complete in seconds at 38 °C) in the presence of 2-phenylpropene leads to enone, the normal disproportionation products, and only 10% of the hydroxy selenide **10.**

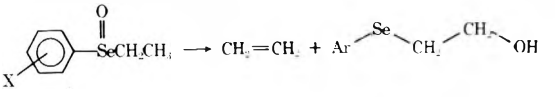


Hori and Sharpless[30] have developed a synthetically viable procedure using the acid-catalyzed comproportionation of $PhSeO_2H/Ph_2Se_2$ for the conversion of olefins to β-hydroxy selenides and hence to allyl alcohols by selenoxide syn elimination. High regioselectivity in favor of the tertiary alcohol is observed when a trisubstituted olefin is used.

Side Reactions during Selenoxide Syn Eliminations. The above observations clearly show that "PhSeOH"–olefin reactions are likely to occur during selenoxide syn eliminations if the olefin formed is not deactivated toward electrophilic addition. We feel that low or erratic yields sometimes observed are a consequence of such reactions, and that high yields can routinely be achieved by thermolysis of the selenoxide in the presence of an amine. Side reactions involving "PhSeOH" have been detected during syn elimination of some α-phenylseleno ketones.[3a] These are also prevented by the presence of an unhindered secondary amine which converts "PhSeOH" to $PhSeNR_2$.

Hydrogen peroxide has frequently been used for the conversion of selenides to selenoxides and hence to olefins by syn elimination.[3-6] Excess H_2O_2 is usually used, resulting in a convenient workup procedure since Ph_2Se_2 is rapidly oxidized to $PhSeO_2H$, which is easily removed. This should also, in principle, prevent the formation of β-hydroxy selenides. We were thus quite surprised to find that treatment of 2-phenylpropyl phenyl selenide under typical synthetic oxidation conditions (10 equiv of H_2O_2) led to the formation of mixtures of products containing a large amount of the β-hydroxy selenide **10.** A control experiment showed that $PhSeO_2H$ in the presence of 2-phenylpropene gave only 8% of **10.** The explanation for these observations is that hydrogen peroxide is catalytically decomposed to oxygen by selenoxides.[31] Figure 2 illustrates that H_2O_2 is rapidly destroyed in aqueous methanol in the presence of a catalytic amount (10%) of methyl phenyl selenoxide ($PhSeO_2H$ does not destroy H_2O_2). The decomposition is much slower in tetrahydrofuran. Primary selenoxides thus may cause destruction of even a large excess of H_2O_2 before syn elimination is complete, and "PhSeOH" readdition can occur. To achieve optimum yields by selenoxide syn elimination it is thus desirable to either ensure the presence of excess oxidant throughout the elimination, or to form selenoxide at low temperature and carry out the elimination with amine present as a separate step. These precautions are less important when selenoxide elimination leads to olefins inductively or conjugatively deactivated toward electrophilic attack by the presence of electron-withdrawing substituent (i.e., α,β-unsaturated carbonyl compounds and nitriles, vinyl halides), or when syn elimination is very rapid. The rate data reported below allow estimation of syn elimination rates for typical selenoxides so that experimental conditions can be properly chosen.

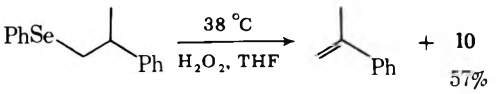
Table III. Products and Rate Data for Selenoxide Syn Elimination of Ethyl Aryl Selenoxides (38 °C in $CDCl_3$)



13

	X	Registry no.	k_{rel} ($t_{1/2}$, min)[a]	Product ratio[b]
13a	H	65275-41-4	1.0 (360)	53:47
b	4-CH_3	65275-42-5	0.33 (550)	
c	3-CF_3	65275-43-6	1.7 (217)	75:25
d	2-NO_2-4-CH_3	65275-44-7	24 (18)	97:3
e	4-NO_2	65275-45-8	4.4 (80)	*c*
f	4-OCH_3	65275-46-9	0.40 (890)	

[a] Rates were measured at 38 °C in $CDCl_3$ in the presence of 1.5 equiv of dimethylamine. [b] At 80% reaction in $CDCl_3$, no amine added, ethylene/β-hydroxyethyl selenide. [c] After 73% of selenoxide had disappeared, 50% of product appeared as ethyl 4-nitrophenyl selenide (reduction).



Effects of Substituents on the Aryl Ring. Improved yields of olefins have been reported by Sharpless and Young for aryl alkyl selenoxides bearing electron-withdrawing substituents on the aromatic ring[6a] and considerable use has been made of this effect by Grieco in several natural products syntheses.[6b,c] In principle this could be a consequence of faster elimination rates, less tendency toward "ArSeOH" addition to olefin products, reduced rates of comproportionation, reduced rates of H_2O_2 destruction, or some combination of these. All of these factors have been briefly studied, and results for several systems are presented in Table III.

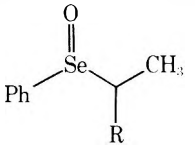
The rate constants in Table III were measured in the presence of a small amount of amine, since otherwise the elimination does not always follow good first-order kinetics because protic materials generated during the reaction ($ArSeO_2H$, β-hydroxy selenide) slow it down. The substituent effects for elimination of ethyl aryl selenoxides ($\rho = 0.8$) are

quite similar to those observed for elimination of propyl aryl sulfoxides (ρ = 0.5 at 180 °C in diphenyl ether).[32]

The o-nitro substitution in the aryl selenide provides a dramatic increase in the elimination rate, as well as a minimum (although not complete absence) of "ArSeOH" addition products. The use of o-nitrophenyl selenides is clearly justified, particularly for difficult systems of the isobutyl type (primary selenide, tertiary hydrogen) where syn elimination is very slow.

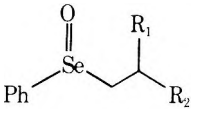
The destruction of hydrogen peroxide by methyl *o*-nitrophenyl selenoxide also appears to be less efficient than in the unsubstituted system (Figure 2).

Selenoxide Syn Elimination Rates. The rates of elimination of a series of alkyl phenyl selenoxides were measured in $CDCl_3$ at 38 °C under conditions such that β-hydroxy selenide formation is suppressed (1.5 equiv of $(CH_3)_2NH$ added). As expected from behavior of sulfoxides,[32b] α-alkyl substituents accelerate elimination, whereas β-alkyl groups retard the rate. Phenyl and chloro substitution causes an acceleration of the elimination, particularly in the α position.



14

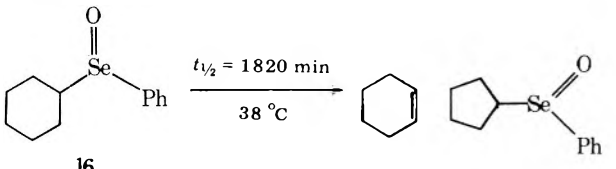
	R	k_{rel} ($t_{1/2}$, min)
13a	H	1.0 (360)
14a	CH_3	9.5 (38)
b	CH_2OCH_3	10 (35)
c	Ph	>360 (<1)
d	Cl	12 (31)



15

	R_1	R_2	k_{rel} ($t_{1/2}$, min)
13a	H	H	1.0 (360)
15a	H	CH_3	0.5 (675)
b	CH_3	CH_3	0.18 (1800)
c	H	Ph	37 (9)
d (9)	CH_3	Ph	4.4 (72)
e	H	Cl	1.4 (280)
f	H	OCH_3	~0.07 (~70 h)

Cyclohexyl (**16**) and cyclopentyl (**17**) phenyl selenoxides are the only cyclic systems we have examined. As expected from the qualitative results in the published literature, the rate of elimination of **16** is unusually slow compared to isopropyl phenyl selenoxide (k_{16}/k_{14a} = 1/48). This means that cyclohexyl eliminations will be very prone to side reactions, an observation already made in connection with the formation of cyclohexenones by oxidation of 2-phenylselenocyclohexanones.[3a] Special care must be taken to use proper reaction conditions for elimination of cyclohexyl selenoxides. The more favorable dihedral angles in the cyclopentyl compound **17** results in an unusually fast syn elimination rate.



16 17, $t_{1/2}$ <5 min

β-Heteroatom substituents are of great interest since the high regioselectivity of elimination for β-hydroxy (as well as β-OCH_3 and β-OAc) selenides to give allyl alcohols rather than enols, first reported by Sharpless and co-workers,[16,33] has resulted in several important applications of selenium reagents.[33,3b,34] β-Methoxyethyl selenoxide (**15f**), as expected, eliminates extremely slowly. When, as in **14b** the selenoxide can eliminate toward or away from an oxygen function, only the allyl ether is formed at a rate similar to the elimination of **14a.** This demonstrates that the directive effect of hydroxy, alkoxy, and acetoxy groups is *not* a consequence of accelerated elimination away from the substituent, but rather a result of retarded elimination toward the substituent. We found also that elimination toward chlorine is slightly accelerated, a result consistent with the observation that a β-chloro selenoxide eliminates to give comparable amounts of vinyl and allyl chlorides.[16]

Conclusions

The following factors should be considered when performing selenoxide syn eliminations.

1. Areneselenenic acids generated during selenoxide syn elimination are in equilibrium with diaryl diselenide and areneseleninic acid. Under neutral or acidic conditions they react with olefins to yield β-hydroxy selenides. This readdition is inhibited in a basic medium.

2. Protic solvents such as water, methanol, and acetic acid should be avoided for the following reasons: they greatly slow down syn elimination rates, and they promote both solvolytic heterolysis of the C–Se bond (particularly when unusually stable carbonium ions can be formed)[35] and "PhSeOH" addition to olefins (Table II).

3. Hydrogen peroxide is destroyed catalytically by selenoxides under some conditions. When used as an oxidant for syn elimination care must be taken to ensure that excess oxidant is present until syn elimination is complete. Otherwise "PhSeOH" readdition may occur.

4. The use of *o*-nitrophenyl alkyl selenoxides results in a faster rate of elimination as well as reduced tendency for ArSeOH addition to olefinic products.

5. When tetra-, tri-, and even some disubstituted olefins are being formed, hydrogen peroxide together with seleninic acids can lead to epoxide formation, presumably via areneperseleninic acid.[29,36] The epoxidation is particularly rapid when the aryl group bears electron-withdrawing substituents.

6. When peracids are used to oxidize selenoxides, the presence of amine during the syn elimination step is obligatory since carboxylic acids greatly retard syn elimination and promote electrophilic olefin addition (Table I).

7. Most of the difficulties mentioned above are not encountered when the following procedure is used: (1) oxidation to selenoxide at low temperature (*m*-CPBA in CH_2Cl_2 or THF, ozone in CH_2Cl_2, or even H_2O_2 for slow to eliminate selenoxides); (2) addition of 2 equiv of amine ($HNiPr_2$, NEt_3, $HNEt_2$, etc.); and (3) thermolysis of the basic selenoxide solution by addition to refluxing hexane or carbon tetrachloride. Under these conditions no selenenic acid additions, epoxidations, or selenoxide reductions occur. The nonpolar medium also suppresses formation of carbonium ions by C–Se bond solvolysis. Even β,β-disubstituted alkyl phenyl selenoxides usually give good yields of olefins under these conditions, and use of the *o*-nitrophenyl selenides (which are more expensive, less easily prepared, and less easily oxidized to selenoxides) is not necessary. It should be emphasized that side reactions do not occur in all systems and simple oxidation procedures frequently give good yields of olefins. When problems are encountered, however, the above procedure will frequently solve them.

Table IV. Rate Constants for Selenoxide Syn Eliminations and NMR Spectral Data for Selenides and Selenoxides

Compd	$k \times 10^4$[a]	Registry no. of selenide	NMR chemical shifts[b] Selenide α-H	Selenide β-H	Selenide Other	Selenoxide α-H	Selenoxide β-H	Selenoxide Other
13a	0.32	17774-38-8	2.93 (q)*	1.39 (t)*		2.89 (m)	1.28 (t)	
b	0.20	37773-43-6	2.88 (q)	1.40 (t)		2.85 (m)	1.25 (t)	
c	0.54	37773-36-7	2.94 (q)*	1.45 (t)*		2.90 (dq), 3.03 (dq)	1.30 (t)	
d	7.7	65275-57-2	2.95 (q)	1.48 (t)		3.00 (m)	1.27 (t)	
e	1.4	65275-58-3	3.00 (q)	1.43 (t)		2.92 (m)	1.27 (t)	
f	0.12	37773-41-4	3.12 (q)	1.36 (t)		2.84 (m)	1.25 (t)	
14a	3.0	22233-89-2	3.45 (sept)	1.43 (d)		3.08 (sept)	1.30 (dd)	
b	3.3	65275-34-5	3.5 (m)	3.5 (m), 1.42 (d)	3.35 (s)	3.0–4.0 (m)	3.0–4.0 (m), 1.14 (dd)	3.44 (s)
c	>150	39192-26-2	4.44 (q)	1.73 (d)			1.75 (d) 1.55 (d)	
d	3.7	63017-68-5	5.48 (q)	1.97 (d)		4.85 (q), 4.66 (q)	1.89 (d), 1.52 (d)	
16[d]	0.062	22233-91-6	3.30 (m)	1.5–2.1 (m)	1.3–1.8 (m)	2.9 (m)	1.3–1.9 (m)	1.3–1.9 (m)
17[d]	~20	65275-35-6	3.60 (m)	1.6–2.2 (m)				
15a	0.17	22351-63-9	2.90 (t)	1.72 (hex)	1.00 (t)	2.84 (t)	1.67 (m)	1.04 (t)
b	0.064	22233-92-7	2.92 (d)	1.87 (m)	1.04 (d)	2.88 (dd)	2.24 (m)	1.10 (dd)
c	~13	65275-36-7	2.95 (m)	2.95 (m)		3.11 (m)	3.11 (m)	
d ($CDCl_3$)	1.3	65275-37-8	3.0 (m)*	3.0 (m)*	1.35 (d)	3.0 (m)	3.49 (m)	1.43 (t)
(CD_3OD)	0.21					3.25 (m)	3.25 (m)	1.43 (dd)
(CD_3CO_2D)[c]	~0.02					3.5 (m)	3.5 (m)	1.43 (d)
e	0.41	50630-24-5	3.10 (AA'BB)*	3.65 (AA'BB')*		3.28 (dt)	3.60 (dt), 4.08 (dt)	
f	~0.03	65275-38-9	3.00 (t)*	3.55 (t)*	3.28 (s)*	3.08 (t)	3.62 (dt), 3.90 (dt)	3.40 (s)

[a] Measured in $CDCl_3$ at 38 °C (unless noted otherwise), 0.2 M selenoxide, 0.3 M Me_2NH. Error limits for the rate constants are ±5 to ±15% unless they are indicated as approximate values, in which case they are ±50%. [b] Measured in $CDCl_3$ in ppm (δ) from Me_4Si except for selenide chemical shifts identified by an asterisk, which were measured in CCl_4. [c] No Me_2NH was added in this run. [d] Registry no.: **16**, 65275-39-0; **17**, 65275-40-3.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a JEOL MH-100 and Varian XL-100 spectrometers and mass spectra were obtained on an AEIMS-902 spectrometer at an ionizing voltage of 70 eV. Ozonizations were carried out using a Welsbach ozonator. Preparative thin layer chromatography was carried out using Merck PF-254 silica gel. Elemental analyses were performed by Spang Microanalytical Laboratories or by Galbraith Laboratories, Inc.

Diphenyl diselenide,[3a] 3,3′-bis(trifluoromethyl)diphenyl diselenide,[3a] benzeneselenenyl chloride,[3a] 4-methyl-2-nitrophenyl selenocyanate,[37] and 4-nitrophenyl selenocyanate[6a] were prepared by literature procedures. Alkyl aryl selenides (except for selenide precursors for **14d** and **15e**) were prepared by reaction of $ArSe^-$ with the appropriate methanesulfonate (for **14b** and **15f**) or halide according to the model procedures below. NMR spectra of selenides and selenoxides are reported in Table IV.

CAUTION. Selenium compounds are toxic and should be handled with due care.

2-Phenylpropyl Phenyl Selenide. To a 250-mL three-neck round-bottom flask fitted with a reflux condenser, addition funnel, and a thermometer were added diphenyl diselenide (8.58 g, 22.5 mmol) in 60 mL of ethanol, sodium formaldehyde sulfoxylate (4.53 g, 24.1 mmol), and sodium hydroxide (3 g, 75 mmol) in 25 mL of water. The system was purged with nitrogen and warmed to 50 °C under N_2 for a 30-min period. 1-Bromo-2-phenylpropane (10.45 g, 7.94 mL, 55 mmol) was added to the reaction mixture. After stirring for 16.5 h, 100 mL of 10% HCl was added and the mixture was extracted with hexane (3 × 60 mL). The combined organic extracts were washed with 40 mL of saturated $NaHCO_3$ and 40 mL of NaCl solution. The crude product was distilled [Kugelrohr, 97 °C (0.032 mm)] to give 14.85 g (98.2%) of the selenide as a clear oil.

Anal. Calcd for $C_{15}H_{16}Se$: C, 65.45; H, 5.86. Found: C, 65.68; H, 5.94.

Ethyl 4-Methyl-2-nitrophenyl Selenide. 4-Methyl-2-nitrophenyl selenocyanate (1.69 g, 7.0 mmol) and 30 mL of absolute EtOH were placed in a flask equipped with a condenser and flushed with nitrogen. $NaBH_4$ (0.348 g, 9.0 mmol) was added slowly through the top of the condenser. The solution became deep red. After an additional 15 min, ethyl bromide (0.530 mL, 7.1 mmol) was added and the solution was stirred at room temperature for 5 h and poured into 30 mL of 1.2 N HCl and 40 mL of 1:1 ether–hexane. The organic layer was washed with dilute HCl, 7% $NaHCO_3$ solution, and saturated NaCl solution and filtered through Na_2SO_4, and the solvent was removed to give a yellow solid. Recrystallization from ether–hexane gave fine gold needles (1.18 g, 69%): mp 49.5–50 °C; MS *m/e* 244.9955 (M^+) (calcd for $C_9H_{11}NO_2Se$: 244.9950).

Anal. Calcd: C, 44.27; H, 4.54. Found: C, 44.05; H, 4.64.

1-Methoxy-2-phenylselenopropane. 1-Methoxy-2-propanol was converted to the mesylate according to the procedure of Crossland and Servis:[38] NMR ($CDCl_3$) δ 1.28 (d, J = 6 Hz, 3 H), 3.08 (s, 3 H), 3.44 (s, 3 H), 3.50 (d, J = 6 Hz, 2 H), 4.85 (m, 1 H).

$NaBH_4$ (~0.6 g) was added slowly to a suspension of 1.35 g (4.33 mmol) of diphenyl diselenide in 20 mL of absolute EtOH under nitrogen until the solution became colorless. After cooling to 25 °C, the mesylate from 0.895 g (9.94 mmol) of 1-methoxy-2-propanol in 5 mL of EtOH was added dropwise. After stirring overnight at 25 °C the suspension was poured into 50 mL of 1.2 N HCl and 50 mL of 1:1 ether–pentane. Workup and distillation gave 1.26 g (63%) of selenide: MS *m/e* 230.0210 (M^+) (calcd for $C_{10}H_{14}OSe$: 230.0217).

Anal. Calcd: C, 52.41; H, 6.16. Found: C, 52.59; H, 6.24.

2-Chloroethyl Phenyl Selenide.[39] Ethylene was passed into 75 mL of CH_2Cl_2 in a flask fitted with a dry ice–EtOH condenser. A solution of 2.03 g of benzeneselenenyl chloride (10.6 mmol) in 60 mL of CH_2Cl_2 was added slowly by cannula with the cannula tip in the ethylene solution. Ethylene was slowly added for 1 h after addition was complete and then the solvent was removed to give an oil (2.31 g) 92% pure by NMR. Distillation [60 °C (0.05 mm)] gave 1.80 g of product: MS *m/e* 219.9558 (M^+) (calcd for C_8H_9ClSe: 219.9555).

1-Chloroethyl Phenyl Selenide. Diphenyl diselenide (3.12 g, 10.0 mmol) was stirred in 40 mL of CH_2Cl_2 and 50 mL of concentrated HCl under N_2. Zn dust (5.1 g, 78 mmol) was added slowly until the solution became colorless. The two layers were separated and the organic layer was washed with 10 mL of concentrated HCl under N_2, after which it was added slowly to distilled acetaldehyde (1.8 mL, 41 mmol) in 40 mL of CH_2Cl_2 and 40 mL of concentrated HCl at 50 °C under N_2. The mixture was stirred for 8 h and the layers were then separated. The CH_2Cl_2 solution was washed twice with 40 mL of 7% $NaHCO_3$ and then saturated NaCl and filtered through anhydrous Na_2SO_4, and the solvent was removed. Distillation [56 °C (0.1 mm)] gave 2.96 g (67%) of product: MS *m/e* 219.9558 (M^+) (calcd for C_8H_9ClSe: 219.9555).

2,3-Dihydro-2,2-dimethylbenzo[*b*]selenophene. The compound was prepared by an extension of the literature procedure for 2-methyldihydrobenzo[*b*]selenophene[40] from methallyl phenyl selenide. Diphenyl diselenide (31.2 g, 0.1 mol) was slurried under N_2 at 55 °C in 300 mL of EtOH with 15.4 g (0.1 mol) of Rongalite ($CH_2OHOSONa \cdot 2H_2O$, sodium formaldehyde sulfoxylate). A solution of 12 g of NaOH in 200 mL of absolute ethanol was added with an addition funnel and the resulting mixture was stirred until the yellow color of diphenyl diselenide had disappeared. Methallyl chloride (19.9 g, 0.22 mol) was added and the mixture was refluxed for 2 h. The reaction was diluted with 200 mL of water and extracted with four portions of 75 mL of pentane. The pentane layer was washed with 150 mL of 7% $NaHCO_3$ and 150 mL of saturated NaCl. After drying over Na_2SO_4 the product was fractionally distilled under vacuum to give 38.57 g (91%) of methallyl phenyl selenide, bp 80 °C (0.5 mm).

The methallyl phenyl selenide (29.0 g) was mixed with 70 g of freshly distilled quinoline and refluxed under an air-cooled condenser for 45 min while N_2 was bubbled through the mixture. (The mixture was purged with N_2 for 15 min prior to heating.) The cooled mixture was poured in 400 mL of ether and washed three times with 500 mL of 0.5 N HCl, 200 mL of 5 N HCl, and finally with water. The organic layer was filtered through a pad of Celite, washed with saturated NaCl, and dried over Na_2SO_4. Fractional distillation under vacuum gave 6.54 g (22.6%) of selenide: bp 64 °C (0.8 mm); NMR ($CDCl_3$) δ 1.67 (s, J_{SeH} = 11 Hz, 3 H), 3.12 (s, 2 H), 7.04 (m, 3 H), 7.24 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 30.6 (q, J_{SeC} = 13.7 Hz), 44.7 (s, J_{SeC} = 44.7 Hz), 54.0 (t, J_{SeC} = 3.1 Hz), 124.4 (d), 125.0 (d, J_{SeC} = 2.9 Hz), 125.9 (d, J_{SeC} = 12.3 Hz), 126.9 (d, J_{SeC} = 3.8 Hz), 142.2 (s), 138.0 (s, J_{SeC} = 100.0 Hz); MS *m/e* 212.0106 (calcd for $C_{10}H_{12}Se$: 212.0104). An analytical sample was prepared by GC with a 2.5-ft SE-30 column at 110 °C.

Anal. Calcd for $C_{10}H_{12}Se$: C, 56.88; H, 5.73. Found: C, 56.84; H, 5.69.

2,3-Dihydro-2,2-dimethylbenzo[*b*]selenophene 1-Oxide (1). Samples of this compound were prepared by ozonization of the selenide in various solvents at −60 to −78 °C. To prepare an IR sample, 211 mg (1 mmol) of selenide in 5 mL of $CHCl_3$ was ozonized at −60 °C to a blue color. Excess ozone was purged with a stream of N_2 and the sample was kept at 0 °C to avoid decomposition until the IR scan could be made: IR ($\nu_{Se=O}$) 810 cm^{-1}. After the sample was stored at room temperature overnight this IR absorption disappeared. NMR samples were prepared similarly using $CDCl_3$ or $CHClF_2$.

Decomposition of 1 in Organic Solvent under Neutral Conditions. Preparation of 2,3-Dihydro-2-(hydroxymethyl)-2-methylbenzo[*b*]selenophene (2) and 3-Hydroxy-3-methylselenochroman (3). When a CH_2Cl_2 solution of 1 (1 mmol in 5 mL) was allowed to completely decompose over several hours at room temperature and the resulting solution was evaporated to dryness and chromatographed by preparative TLC (silica gel, buffered with triethylamine; 50% ether–pentane), 174 mg of an 85:15 mixture (by NMR integration) of **2** and **3** was obtained (77% combined yield). By more careful chromatography (TLC on silica gel, 20% ether–pentane) using multiple elutions and by taking only part of the TLC band, relatively pure samples of **2** were obtained for derivatization (see below). Compound **2**: NMR (C_6D_6) δ 1.44 (s, J_{SeH} = 12.0 Hz, 3 H), 1.64 (br s, 1 H), 2.70, 2.96 (ABq, *J* = 15.2 Hz, 2 H), 3.29, 3.35 (ABq, *J* = 11.0 Hz, 2 H), 6.64 (m, 3 H), 6.83 (m, 1 H); MS *m/e* 228.0048 (calcd for $C_{10}H_{12}OSe$: 228.0053). Compound **3**: NMR (C_6D_6) δ 1.18 (s, 3 H), 1.2 (br, s, 1 H), 2.16, 2.32 (ABq, *J* = 15.5 Hz, 2 H), 2.47, 2.65 (ABq, *J* = 11.0 Hz, 2 H), 6.80 (m, 3 H), 7.15 (m, 1 H); MS *m/e* 228.0050 (calcd for $C_{10}H_{12}OSe$: 228.0053).

Derivatization of 2 *p*-Nitrobenzoate. A 170-mg sample of alcohol **2** was dissolved in 0.6 mL of pyridine and 100 mg of *p*-nitrobenzoyl chloride and the mixture was heated briefly to boiling. Water (2 mL) was added and the aqueous layer was decanted, leaving behind a yellow oil which was dissolved in 10 mL of ether. The ethereal solution was washed with 1 mL of saturated Na_2CO_3 and dried over Na_2SO_4. Evaporation of the solvents gave an oily residue which was recrystallized from 95% ethanol to give 138 mg (50%) of light yellow prisms: mp 80–81 °C; IR 1760 cm^{-1}; NMR ($CDCl_3$) δ 1.83 (s, 3 H), 3.26, 3.42 (ABq, *J* = 16 Hz, 2 H), 4.56 (s, 2 H), 7.1–7.4 (m, 4 H), 8.03, 8.25 (AA'BB', *J* = 8 Hz, 4 H).

Anal. Calcd for $C_{17}H_{15}NO_4Se$: C, 54.27; H, 4.02. Found: C, 54.26; H, 4.05.

Decomposition of 1 in Organic Solvent with Acid or Base Present. Fresh solutions of 0.25 mmol of **1** were prepared as above in 1 mL of chloroform or methylene chloride and acid or base was added to the solutions prior to decomposition. **Acid.** When 0.01 mL of acetic acid was added, a 63% combined yield of alcohols **2** and **3** was obtained in a ratio of 90:10 (NMR integration) on decomposition and isolation by TLC. **Base.** When 0.01 mL of triethylamine was added, an 80:20 ratio of **2** and **3** in 78% combined yield was obtained. Product ratios were determined by NMR integration.

Decomposition of 1 in Deuterium Oxide Solution with Acid or Base Present. Two solvent-free samples of **1** were prepared by ozonization of 0.25 mmol of the selenide in $CHClF_2$ and flash evaporation of the solvent (bp −40 °C) at 0 °C, and 0.01 N DCl or D_2O containing dissolved anhydrous Na_2CO_3 (10 mg in 1 mL) was added to each sample. Initially, colorless homogeneous solutions were obtained; however, on standing over several days light yellow droplets of product formed. After a week of standing the product alcohols were extracted into ether and the alcohols were purified by TLC. Analysis of the two samples for deuterium incorporation (any alcoholic deuterium was washed out in workup) by low electron volt and expanded–intensified mass spectra showed <5% deuterium incorporation for both the acid and base samples.

Formation of *N,N*-Diethyl-2-(2-methyl-2-propenyl)benzeneselenamide (5). A solution of 0.5 mmol of **1** in 0.5 mL of $CDCl_3$ was prepared by ozonization at −65 °C. After the excess ozone was removed in a stream of N_2, excess diethylamine (0.1 mL) was added and the solution was warmed to room temperature for a few hours. The progress of the reaction was monitored by ^1H NMR spectroscopy. When all the selenoxide **1** had decomposed as indicated by the disappearance of the *gem*-dimethyl resonances at δ 1.26 and 1.65 in the ^1H NMR spectrum, the spectrum showed **5** (vinyl resonances) and very little of alcohols **2** and **3** to be present: NMR ($CDCl_3/HNEt_2$, ~6:1) δ 1.13 (t, *J* = 7 Hz, 6 H), 1.69 (s, 3 H), 3.08 (q, *J* = 7 Hz, 4 H), 3.28 (s, 2 H), 4.59 (s, 1 H), 4.80 (s, 1 H), 7.1 (m, 3 H), 7.75 (m, 1 H). A carbon NMR spectrum of **5** was obtained on the same solution at −15 °C: δ 14.6 (q), 22.5 (q), 43.1 (t), 54.1 (t, J_{SeC} = 10 Hz), 112.7 (t), 125.8, 126.6, 128.1, 129.7 (doublets), 137.0, 137.2, 143.6 (singlets). When the excess diethylamine was removed by evacuation of a similarly prepared solution under oil pump vacuum, the vinyl resonances of **5** vanished and only resonances corresponding to alcohols **2** and **3** were observed.

Formation and Isolation of 2,3-Dihydro-2-(*N,N*-diethylaminomethyl)-2-methylbenzo[*b*]selenophene (7). A solution of selenenamide **5** prepared from 0.25 mmol of selenoxide **1** (from ozonization of 52 mg of selenide in $CHClF_2$ at −78 °C) and a fourfold excess of diethylamine was kept at room temperature for 1 day. The solution was chromatographed on silica gel (TLC) with 20% ether–pentane to give 12 mg (17%) of **7**, identified by ^1H NMR spectroscopy, along with 10 mg (18%) of alcohols **2** and **3**: NMR (C_6D_6) δ 0.88 (t, *J* = 7 Hz, 6 H), 1.61 (s, 3 H, J_{SeH} = 12.0 Hz), 2.47 (q, *J* = 7 Hz, 4 H), 2.68, 2.77 (ABq, *J* = 11.0 Hz, 2 H), 2.83, 3.24 (ABq, *J* = 15.5 Hz, 2 H), 7.0 (m, 3 H), 7.2 (m, 1 H). A sample of **7** suitable for mass spectral analysis was obtained by GC on a 20% SE-30 column: MS *m/e* 283.0846 (calcd for $C_{14}H_{21}NSe$: 283.0839).

Preparation of Methyl 2-(2′-Methylpropenyl)phenyl Selenide (6) from Selenenamide 5. Selenenamide **5**, prepared by ozonization of 211 mg (1 mmol) of selenide in 3 mL of ether followed by addition of 4 mL of diethylamine to the solution of 1 and 45 min of standing at room temperature, was added to a slurry of 100 mg of $LiAlH_4$ in 20 mL of ether at 0 °C. The mixture was stirred 10 min and 5 mL of methyl iodide was added. After 30 min the reaction was quenched with saturated NH_4Cl. The ether layer was decanted, washed with water, and dried over Na_2SO_4. Evaporation of the solvent and preparative TLC (silica gel, pentane) gave 135 mg (60%) of the aryl methyl selenide: NMR ($CDCl_3$) δ 1.76 (s, 3 H), 2.28 (s, 3 H, J_{SeH} = 12.0 Hz), 3.44 (s, 3 H), 7.16 (m, 3 H), 7.40 (m, 1 H); MS *m/e* 226.0258 (calcd for $C_{11}H_{14}Se$: 226.0261). An analytical sample was prepared by GC on a 20% SE-30 column.

Anal. Calcd for $C_{11}H_{14}Se$: C, 58.67; H, 6.27. Found: C, 58.68; H, 6.23.

Formation of a Selenonium Ylide from 1 and Dimethyl Acetylenedicarboxylate, Compound 8. To a solution of 1 mmol of **1** in 0.5 mL of $CDCl_3$ at 0 °C was added 0.123 mL (1 mmol) of dimethyl acetylenedicarboxylate. An immediate exothermic reaction ensued. After 15 min a ^1H NMR spectrum of the reaction showed that the selenoxide **1** had completely reacted and a single product had been formed. Preparative TLC (silica gel–methyl acetate or acetone) afforded a gummy yellow product (286 mg, 78%) identified as the selenonium ylide **8** on the basis of its NMR properties and IR data: NMR ($CDCl_3$) δ 1.62 (s, 3 H, J_{SeH} = 12.0 Hz), 1.71 (s, 3 H, J_{SeH} = 24.0 Hz), 3.55 (s, 3 H), 3.66 (s, 3 H), 3.17, 4.04 (ABq, *J* = 15.5 Hz, 2 H), 7.0 (m, 3 H), 7.25 (m, 1 H); IR ($CHCl_3$) 1745, 1680, 1570 cm^{-1}. Attempts to crystallize the product were unsuccessful. An analytical sample was prepared by careful preparative TLC (silica gel–acetone).

Anal. Calcd for $C_{16}H_{18}O_5Se$: C, 52.04; H, 4.91. Found: C, 52.13; H, 4.93.

Preparation of an Analogous Selenonium Ylide from Methyl Phenyl Selenoxide. Methyl phenyl selenoxide was prepared by

ozonization of 171 mg (1 mmol) of methyl phenyl selenide in 5 mL of CH_2Cl_2 at −78 °C. The excess ozone was removed in a stream of N_2. Dimethyl acetylenedicarboxylate (0.125 mL, 1 mmol) was added and the mixture was warmed to room temperature. Some exothermicity was observed as the temperature of the solution neared 0 °C. The solvent was evaporated and the residue was chromatographed, TLC on silica with 10% methanol–ether, to give 180 mg (55%) of the yellow, gummy ylide: NMR ($CDCl_3$) δ 3.21 (s, 3 H, J_{SeH} = 30.0 Hz), 3.68 (s, 3 H), 3.87 (s, 3 H), 7.5 (m, 3 H), 7.7 (m, 2 H); IR ($CHCl_3$) 1735, 1670, 1560 cm^{-1}. An analytical sample was prepared by careful TLC (silica gel–acetone): MS *m/e* 330.0000 (calcd for $C_{13}H_{14}O_5Se$: 330.0006).

Isolation of 2-Hydroxyethyl Phenyl Selenide from the Elimination of Ethyl Phenyl Selenoxide (13a). Ethyl phenyl selenide (0.287 g, 1.55 mmol) was ozonized in 4.5 mL of $CHCl_3$ at −60 °C. The selenoxide was warmed to 38 °C for 70 h in a sealed tube, after which it was poured into 10 mL of 7% $NaHCO_3$ solution and 10 mL of ether. The organic layer was washed with saturated NaCl solution and filtered through anhydrous Na_2SO_4 and the solvent was removed. Preparative TLC (1% NEt_3–10% ether–89% pentane), R_f 0.06, gave 1.57 g (50%) of 2-hydroxyethyl phenyl selenide: NMR (CCl_4) δ 7.4 (m, 2 H), 7.15 (m, 3 H), 3.65 (t, *J* = 7 Hz, 2 H), 3.32 (bs), 2.95 (t, *J* = 7 Hz, 2 H); MS *m/e* 201.9897 (M^+) (calcd for $C_8H_{10}OSe$: 201.9897). The dibromide was prepared by slow addition of bromine in CCl_4 to a solution of the selenide in CCl_4. The solvent was removed from the pale yellow precipitate. Recrystallization in EtOH gave a fine yellow crystalline solid, mp 117–119 °C (lit. mp[44] 113 °C).

2-Phenyl-1-phenylseleno-2-propanol (10). Diphenyl diselenide (0.219 g, 0.702 mmol) was stirred in 9 mL of absolute EtOH under nitrogen. $NaBH_4$ (0.067 g, 1.7 mmol) was added until the solution became colorless, after which α-methylstyrene oxide (0.190 g, 1.42 mmol) was added. The solution was stirred at room temperature for 0.5 h, refluxed for 1.5 h, and poured into 10 mL of 1.2 N HCl and 10 mL of ether. The ether layer was washed with 7% $NaHCO_3$ and saturated NaCl and filtered through anhydrous Na_2SO_4, and the solvent was removed. Preparative TLC (1% NEt_3–10% ether–89% pentane), R_f 0.2, gave 0.313 g (76%) of **10**: NMR ($CDCl_3$) δ 7.5–7.1 (m, 10 H), 3.56 (d, *J* = 12 Hz, 1 H), 3.30 (d, *J* = 12 Hz, 1 H), 2.8 (bs, 1 H), 1.60 (s, 3 H); IR (neat) 3460, 3060, 2980, 1580, 1480, 1440, 1062, 1022, 765, 738, 698 cm^{-1}; MS *m/e* 292.0366 (M^+) (calcd for $C_{15}H_{16}OSe$: 292.0361). The selenide **10** was converted to the corresponding selenoxide (2-phenyl-1-phenylselenino-2-propanol) by ozonization and crystallization from pentane–ethyl acetate. A single diastereomer crystallized: mp 125–125.5 °C; NMR ($CDCl_3$) δ 7.6–7.3 (m, 10 H), 3.55 (d, *J* = 12 Hz, 1 H), 3.35 (d, *J* = 12 Hz, 1 H), 1.65 (s, 3 H).

Anal. calcd for $C_{15}H_{16}O_2Se$: C, 58.64; H, 5.25. Found: C, 58.21; H, 5.48.

Equilibration of Ditolyl Diselenide and Benzeneseleninic Acid. Solutions of benzeneseleninic acid in $CDCl_3$ (0.30 mL, 0.037 M, 0.011 mmol) and ditolyl diselenide in $CDCl_3$ (0.15 mL, 0.073 M, 0.011 mmol) were combined in a NMR tube and immediately inserted in the NMR probe (38 °C). Equilibration as demonstrated by the appearance of a new $ArCH_3$ resonance occurred within 15 min, at which time the methyl peak due to ditolyl diselenide (δ 2.35) and that due to tolueneseleninic acid (δ 2.45) were in a 2:1 ratio. In the presence of 1 drop of pyridine, the equilibration took 1.5–2 h, while the equilibration was complete within 1 min when 1 drop of trifluoroacetic acid was added instead.

Elimination of 12 in the Presence of 2-Phenylpropene. 1-Phenyl-2-phenylseleno-1-butanone (33.9 mg, 0.112 mmol) was ozonized in 0.55 mL of $CHCl_3$ at −60 °C. 2-Phenylpropene (0.012 mL, 0.112 mmol) was added and the solution was warmed to 38 °C for 5 min. Triethylamine (0.03 mL, 0.21 mmol) was then added to inhibit further readdition. The solution was poured into 5 mL of ether and 5 mL of 7% $NaHCO_3$ solution. The ethereal layer was rinsed with a saturated NaCl solution and filtered through anhydrous Na_2SO_4 and the solvent was removed. The product mixture contained 1-phenylpropenone, 2-phenylpropene, $(PhSe)_2$, and **10**. The NMR of the mixture indicated that 12% of the 2-phenylpropene had reacted to form **10**.

Reaction of 2-Phenylpropene with $PhSeO_2H$ and Ph_2Se_2. Diphenyl diselenide (12.8 mg, 0.041 mmol) and benzeneseleninic acid (7.8 mg, 0.041 mmol) were placed in an NMR tube with 0.3 mL of $CDCl_3$ at 0 °C. 2-Phenylpropene (0.016 mL, 0.125 mmol) was added and the tube was warmed to 38 °C. The readdition was followed by NMR. After 4 h, 50% of the 2-phenylpropene was converted to 2-phenyl-1-phenylseleno-2-propanol (**10**). Only 66% conversion occurred after 66 h.

Oxidation of 1-Phenylseleno-2-phenylpropane. To a stirred solution of 1-phenylseleno-2-phenylpropane (0.550 g, 0.413 mL, 2 mmol) in 2.4 mL of THF was added 2.3 mL of 30% H_2O_2 (20 mmol), 1.1 mL initially and the rest 10 min later. After stirring for 5 h at 38 °C, the reaction was cooled and extracted with 3 × 60 mL of CH_2Cl_2. Purification by preparative TLC (10% ether–pentane) gave 0.333 g (57.2%) of hydroxy selenide **10**.

Catalytic Decomposition of H_2O_2 by Methyl Phenyl Selenoxide. A 1.83 M aqueous H_2O_2 solution was prepared by dilution of 4.50 mL of commercial 30% H_2O_2 (found to be 10.15 M by iodometric titration) to 25.00 mL. Methyl phenyl selenide (0.0604 mL, 0.500 mmol) was diluted to 25.00 mL with anhydrous methanol (0.0200 M) and 18.00 mL of selenide solution plus 2.00 mL of the H_2O_2 solution were combined at 38 °C. Aliquots of the solution were titrated iodometrically[42] at intervals. A similar procedure was followed for the other H_2O_2 decomposition runs.

Elimination Rates of Selenoxides. All selenoxides were prepared by ozonization (−60 °C) of solutions of the selenides in $CDCl_3$ or CD_3OD. Phenyltrimethylsilane was added as a standard. The cold solutions were transferred to NMR tubes, 1.3–1.5 equiv of Me_2NH was added, and enough solvent was added to dilute to 0.2 M. The tubes were sealed and warmed to 38 °C. The reactions were followed by NMR integration (probe temperature 38 °C). Between 8 and 15 points were recorded during the first 3 half-lives for each selenoxide. The chemical shifts of the selenides and selenoxides as well as the rate constants are reported in Table IV.

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Registry No.—1, 60096-30-2; **2**, 60430-44-6; **2**,*p*-nitrobenzoate derivative, 65275-30-1; **3**, 60430-45-7; **5**, 60430-46-8; **6**, 60430-47-9; **7**, 60430-48-0; **8**, 60096-31-3; **10** (R = H), 55188-76-4; **14a**, 65275-47-0; **14b**, 65275-48-1; **14c**, 65275-49-2; **14d**, 65275-50-5; **15a**, 65275-51-6; **15b**, 65275-52-7; **15c**, 65275-53-8; **15d**, 65275-54-9; **15e**, 65275-55-0; **15f**, 65275-56-1; diphenyl diselenide, 1666-13-3; 1-bromo-2-phenylpropane, 1459-00-3; 4-methyl-2-nitrophenyl selenocyanate, 65275-29-8; 1-methoxy-2-propanol mesylate, 24590-51-0; benzeneselenyl chloride, 5707-04-0; 2,3-dihydro-2,2-dimethylbenzo[*b*]selenophene, 60096-27-7; methallyl chloride, 563-47-3; methallyl phenyl selenide, 59085-70-0; *p*-nitrobenzoyl chloride, 122-04-3; diethylamine, 109-89-7; dimethyl acetylenedicarboxylate, 762-42-5; methyl phenyl selenoxide, 25862-09-3; methyl phenyl selenide, 4346-64-9; methylphenylselenonium ylide, 65275-31-2; 2-hydroxyethyl phenyl selenide, 65275-32-3; α-methylstyrene oxide, 2085-88-3; 2-phenyl-1-phenylselenino-2-propanol, 65275-33-4; 1-phenyl-2-phenylseleno-1-butanone, 57204-89-4; 2-phenylpropene, 98-83-9; benzeneseleninic acid, 6996-92-5.

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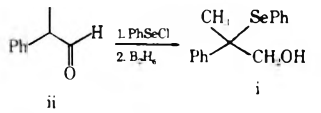

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Secondary Isotope Effects in Intramolecular Catalysis. Mono-*p*-bromophenyl Succinate Hydrolysis[1]

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Kinetic isotope effects have been measured for the intramolecular nucleophilic carboxylate-catalyzed hydrolysis, k_s, of mono-*p*-bromophenyl succinate and mono-*p*-bromophenyl succinate-d_4. The resulting isotope effect, $k_s^{h_4}/k_s^{d_4}$, equals 1.035, a *normal* effect. This is contrary to what is expected for acyl transfer reactions where the transition-state structure resembles a tetrahedral intermediate. However, the direction of the isotope effect is in agreement with a transition-state structure resembling succinic anhydride. Combining this result with previous kinetic and structural studies, a detailed transition-state structure for the hydrolysis reaction is proposed.

Intramolecularly catalyzed reactions have been studied as chemical models for reactions of an enzyme–substrate complex.[3] An additional reason to study this class of reactions is that it represents the simplest reactions in which detailed pictures of transition-state structures can be developed. Transition-state structure elucidation is facilitated in these reactions since the "diffusion complex" is already formed and thus its structure is defined.

To resolve in great detail the transition-state structure for succinate half-ester hydrolysis is an important goal for a variety of biochemical reasons. Succinates are a major tool for the reversible derivitization of bioactive agents for the purpose of improving their chemical and physical properties as drugs (thus for the design of prodrugs[4]). Hydrolytic rate studies of half-esters of succinate and of various succinate derivatives have been essential in developing theories of catalytic power.[3,5]

Half-esters of succinic acid exhibit large rate accelerations in the comparison of their intramolecularly catalyzed hydrolysis to biomolecular carboxylate-catalyzed ester hydrolysis.[6] Additional rate enhancements are observed when alkyl groups are substituted in the succinyl backbone.[7,8] Rate increases brought about by alkyl substitution are well-known phenomena in other intramolecular reactions.[9,10]

A further essential contribution to the study of these rate effects would be to examine the transition state. The kinetic isotope effects method offers a distinct advantage over alkyl substitution in that substitution of one isotope for another

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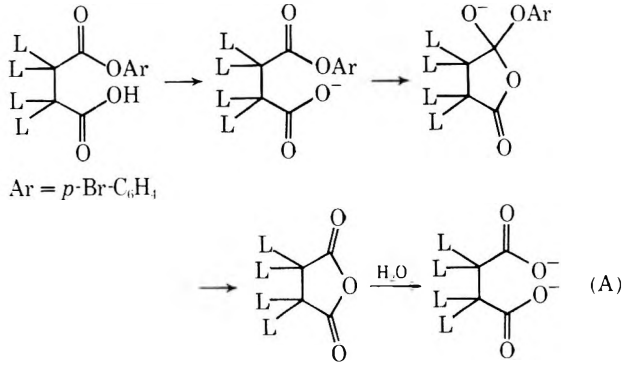
Table I. Observed First-Order Rate Constants for Hydrolysis of 5×10^{-4} M *p*-Bromophenyl Succinate and *p*-Bromophenyl Succinate-d_4 at 25.00 ± 0.02 °C in 50/50 v/v Dioxane/Water, μ = 0.65

pH	$10^6 k_{obsd}$, s^{-1} 1, L = H[b]	$10^6 k_{obsd}$, s^{-1} 1, L = D[c]
4.71	751.3, 764.0, 757.6, 754.1, 756.6, 745.6, 767.4, 760.8, 765.8, 764.1	725.1, 735.5, 724.2, 739.8, 720.9, 724.4, 736.0, 732.1, 728.3, 728.6
Mean	758.7 ± 2.2[a]	730.4 ± 1.9
5.10	1686, 1676, 1714, 1689, 1700, 1717, 1690, 1687	1661, 1668, 1649, 1648, 1662, 1635, 1633, 1669
Mean	1695 ± 5.1	1653 ± 5
5.84	5313, 5331, 5282, 5370, 5333, 5296, 5392	5140, 5196, 5223, 5148, 5189, 5222, 5210
Mean	5331 ± 15	5190 ± 13
6.10	6584, 6687, 6633, 6586, 6691, 6687, 6621	6448, 6411, 6405, 6373, 6381, 6433, 6443
Mean	6641 ± 18	6413 ± 11
6.58	8746, 8735, 8550, 8790, 8626, 8563	8245, 8191, 8278, 8133, 8199, 8196, 8187
Mean	8668 ± 42	8204 ± 17
6.84	9194, 9149, 9166, 9120, 9130, 9135, 9153, 9122	8857, 8878, 8863, 8852, 8874, 8879, 8889, 8880
Mean	9146 ± 9	8872 ± 5
7.05	9475, 9516, 9465, 9523, 9494, 9549, 9492, 9492	9179, 9254, 9247, 9271, 9214, 9182, 9235, 9223
Mean	9501 ± 10	9226 ± 12
7.20	9600, 9564, 9513, 9497, 9481, 9631, 9594, 9595	9234, 9294, 9282, 9262, 9351, 9192, 9226, 9314
Mean	9559 ± 20	9269 ± 18

[a] Standard error of estimate. [b] Registry no. 29493-07-0. [c] Registry no. 65150-65-4.

does not change the electronic character of the reaction.[11] Consequently, isotopes are a powerful tool for probing the structure of a transition state. Development of pictures of the catalytic transition-state structure for these intramolecular reactions should greatly aid in uncovering the reasons for such large accelerations.

Previous kinetic work[7] on hydrolysis of mono-*p*-bromophenyl succinate, 1 (L = H), revealed an intramolecular catalyzed reaction when the carboxyl was ionized (eq A). This



1. Ar = *p*-Br-C_6H_4

(A)

study firmly established a mechanism proceeding via a rate-limiting formation of a cyclic anhydride intermediate.

This paper reports the measurement of a β-secondary kinetic isotope effect resulting from the replacement of protium atoms by deuterium atoms on the succinyl backbone (1, L = H vs. 1, L = D). The results are used along with data from previous work[7,12] to formulate a transition-state structure for this reaction.

β Secondary Isotope Effects. Shiner[13] and his school have demonstrated the utility of β secondary isotope effects in studies of nucleophilic substitution. It has been shown in a number of cases that for S_N1 reactions (the reaction center is being converted from a tetrahedral carbon to a planar carbocation) when the protons adjacent (β) to the reaction center are replaced with deuterium atoms a decrease in the rate constant occurs; i.e., a *normal* kinetic isotope effect is observed. In carbonyl addition, the reverse is occurring (a planar, somewhat positive reaction center is converted into a more electrically neutral or negative tetrahedral structure) and an *inverse* kinetic isotope effect would be expected. A large number of examples of additions to carbonyl centers suport this expectation.[14] Typically, the equilibrium value for K^H/K^D in creating a tetrahedral center at a carbonyl carbon is 0.95 (hemiketal[14b] and ketal[14d] formation in acetone) to 0.91 (hemiketal formation in cyclopentanone[14b] and ketal formation in acetophenone[14d]) *per deuterium atom*. Most kinetic isotope effects[14c] for addition reactions to carbonyls lie between these values and 1.0. Vibrational-analysis calculations[15] on the addition of hydroxide ion to acetaldehyde and acetaldehyde-d_3 suggest a linear dependence of the magnitude of the inverse isotope effect on the bond order of the forming carbonyl carbon–hydroxide oxygen bond. These results suggest that the magnitude of the β secondary kinetic isotope effect in carbonyl addition reactions is a direct measure of the degree of tetrahedrality about the carbonyl carbon in the rate-determining transition state of biomolecular reactions. For intramolecular acyl transfer reactions, as discussed below, other sources may contribute to the isotope effect.

Experimental Section

Materials. Sodium acetate (NaOAc) and acetic acid (HOAc) were purified as described previously.[16] Potassium chloride (KCl, Baker, reagent grade) was dried in an oven at 130 °C for 24 h. Dioxane was distilled from lithium aluminum hydride. Mono-*p*-bromophenyl succinate was prepared from *p*-bromophenol and succinic anhydride by a method developed for monophenyl succinate.[17] Mono-*p*-bromophenyl succinate-d_4 was prepared in a similar manner from *p*-bromophenol and succinic anhydride-d_4.[18] This half-ester contained 93 atom % D as determined by mass spectral analysis.

Buffer solutions were prepared by mixing an appropriate amount of 0.100 M HOAc in 50/50 v/v dioxane/water with 0.650 M KCl solution and an appropriate amount of 0.100 M NaOAc in 50/50 v/v dioxane/water with 0.650 M KCl. The pH was measured with a combination electrode and the value converted to a_H.

Instrumentation. Rate measurements were made spectrophotometrically, employing a Cary 16 UV–visible spectrophotometer interfaced to a Hewlett-Packard 2100A minicomputer. Output of the photomultiplier tube, consisting of a 60-Hz pulse train of alternating sample and reference pulses, was conveyed to an Analogic 5800N analogue-to-digital converter through a synchronizer circuit which identified the pulses. Fifteen measurements of the height of both reference and sample pulses were averaged across each cycle and values of the absorbance were calculated from the logarithm of the ratio of these averages. Run times were divided into 1000 segments and absorbances were then time-averaged across each segment. Run times were typically 5 half-lives of the particular reaction being observed. The 1000 data points were analyzed by a nonlinear least-squares method to give the observed rate constant. The standard error of estimate for an individual rate constant within a single run was normally ±0.08%.

Kinetics Procedure. Experiments were conducted in thermostated cell holders and were initiated after thermal equilibration. A 6×10^{-2} M ester solution (25 μL) in dioxane was injected into a cu-

Table II. Catalytic Constants and Isotope Effects for *p*-Bromophenyl Succinate-d_4 Hydrolyses[a]

	$10^6 k_s$, s^{-1}			$10^6 K_a$, M		
	h_4	d_4	$k_s^{h_4}/k_s^{d_4}$	h_4	d_4	$K_a^{h_4}/K_a^{d_4}$
Eq 1	9982 (±36)	9641 (±47)	1.035 (±0.006)	1.630 (±0.030)	1.628 (±0.040)	1.001 (±0.031)
Eq 2	9999 (±42)	9650 (±63)	1.036 (±0.008)	1.613 (±0.014)	1.621 (±0.022)	0.995 (±0.016)

[a] Standard error of estimate in parentheses.

vette containing 3 mL of buffer. An increase in absorbance was monitored at 280 mm.

Results

First-order rate constants for the hydrolysis of *p*-bromophenyl succinate and *p*-bromophenyl succinate-d_4 are given in Table I. A careful examination of these data reveals that for a given pH value, there is no overlap in ranges of the observed rate constants, k_{obsd}, for succinate and succinate-d_4. This indicates that the reliability of our measurements of k_{obsd} at a given pH value is excellent. The standard error of estimate for the mean value of a given set of rate constants ranged from ±0.06% to ±0.48% with an average of ±0.23%. These results attest to the reality of the isotope effect and the quality of our kinetics procedure.

Equation 1 is the rate law for the hydrolysis of the *p*-bromophenyl succinate esters,[7] where k_s is the rate constant for spontaneous hydrolysis, K_a is the dissociation constant of the carboxyl group, and a_H is the activity of hydrogen ion.

$$k_{obsd} = k_s \frac{K_a}{K_a + a_H} \quad (1)$$

Values of k_s and K_a are determined by a nonlinear least-squares procedure[19] and reported in Table II. Since an analysis of variance among pH levels for an entire data set for each compound reveals that the variation in pH is 99.99% of the variation in k_{obsd}, the small error associated with a mean value of k_{obsd} is highly insignificant in fitting the curve described by eq 1. Thus, the values reported in Table II are determined from a fit of the mean values of k_{obsd} and measured values of a_H. Standard error of estimates for k_s and K_a reveal that most of the error occurs in determining K_a and that the values for k_s are quite accurate (±0.36% and ±0.49%). Estimation of the error in the isotope effects follows from the standard equation for propagation of error in a ratio.[20] The errors associated with the isotope effects on k_s and K_a are ±0.6% and ±3.1%, respectively.

Alternatively, eq 1 can be rearranged to a linear form, eq 2, and solved by linear least-squares analysis.

$$k_{obsd} = k_s - \frac{1}{K_a}(k_{obsd} a_H) \quad (2)$$

The values of k_s and K_a reported in Table II are determined from a fit of the mean values of k_{obsd} and measured values of a_H. The values obtained for k_s and K_a are essentially identical to those produced in the fitting of the data to eq 1. Estimates of error are handled in a similar manner as described above. The errors associated with the isotope effects on k_s and K_a are ±0.8% and ±1.6%, respectively.

Discussion

The mechanism described by eq A suggests the formation of an intermediate tetrahedral compound preceding formation of succinic anhydride. It has previously been suggested[21] that the breakdown of the tetrahedral intermediate to form the cyclic anhydride is the rate-limiting step. This proposal is largely based on the sensitivity of the rate on the nature of the departing aryloxide ion. If this breakdown step is rate limiting, then a significant amount of bond breaking to the aryloxide is expected in the transition state. This thought is well-supported when previous kinetic data for a series of monoaryl succinates[12] are examined. Regression of log k_s on pK_a of the leaving group yields a slope of −1.17, which indicates bond cleavage is well-advanced in the transition state.

Structure–reactivity correlations of this type are normally utilized for the reverse reaction, nucleophilic attack on a carbonyl.[22] Slopes of plots of log (rate constant) vs. pK_a of the attacking nucleophile are defined as β_n. Values of β_n are expected to lie between 0 and 1.7.[22b] For strongly basic nucleophiles attacking carbonyl groups, β_n values of 0.3–0.7 are typical.[21a] This is interpreted as an indication that bond formation has occurred only to a modest extent, i.e., an "early" transition state. Large β_{lg} values, 1.4–1.0, would be expected for the reverse reaction, the departure of a strong basic group to form a carbonyl. β values of this magnitude have only been observed in intramolecular nucleophilic attack of carboxylate on ester groups.[21] It is concluded then that the rate-limiting transition state for the hydrolysis of 1 occurs "late" in the breakdown step.

Isotope Effects. The kinetic isotope effect, $k_s^{h_4}/k_s^{d_4}$, is 1.035 (1.008 per deuterium), a *normal* isotope effect. This is in marked contrast to the expected isotope effect for acyl transfer (vide supra), if the rate-limiting transition-state structure resembles a tetrahedral intermediate. An explanation of this *normal* isotope effect is that in the rate-controlling transition-state structure the backbone hydrogens are in a "looser" vibrational force field than in the reactant. Another explanation would be that the small *normal* isotope effect arises from contributions of the ratio of imaginary frequencies.[23] Possibly, both factors contribute in this case. In any case the effect is inconsistent with a near-tetrahedral structure for the transition state.

But how could one account for a "looser" vibrational force field about the backbone hydrogens? One possible implication is that a relief of steric interactions has taken place in going from reactant state to transition state. Such a relief of ground state strain has been suggested as the driving force behind rate accelerations observed for ring closing reactions when the succinyl backbone is substituted with alkyl groups (L = alkyl), but this steric relief has been theorized as absent for the unsubstituted case (L = H).[3] In fact, some have proposed that there is an *increase* in steric interactions between the backbone hydrogens when the anhydride ring is formed.[24] The conclusion from the observation of a *normal* isotope effect is that this latter proposal is incorrect. An alternative possibility is that an increase in hyperconjugation (leading to a decrease in force constants) arises in an anhydride-like transition state relative to the reactant. Such an effect would have to outweigh any increased steric interaction which again suggests that the steric effect, if adverse, is small.

A relatively "freer" environment of the methylene hydrogens in the anhydride form could be supported by experimental structural data on succinic anhydride[24] and succinate dianion[26] as well as theoretical structural data on succinic anhydride and succinic acid.[27] All the methods reveal that the nearest neighbor contact distances are longer in the anhydride than in an acyclic form. This lengthening of nearest neighbor interactions is a result of the "fanning out" of the pairs of methylene hydrogens in the cyclic form relative to the open chain. Although the hydrogens are eclipsing in the anhydride,

their nearest neighbor interactions are with two other hydrogens and an oxygen, whereas in the open chain structure (assuming a staggered conformation) the nearest neighbors are a hydrogen, a carbon, and an oxygen.

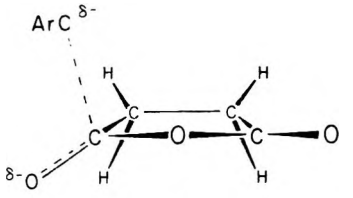
Evaluation of contact distances is only suggestive of the "looser" environment for the backbone hydrogens in the anhydride compared to the acyclic form. A better method would involve a complete vibrational analysis. Vibrational studies[28] on succinic anhydride and succinic-d_4 have been performed as well as similar studies on succinic acid and its deuterated analogues.[29] Unfortunately, missing frequencies preclude a total vibrational analysis.

The isotope effect of *unity* on the acid dissociation constant, K_a, of **1** is unexpected. The isotope effect on K_a for acetic acid and acetic-d_3 acid is 1.035.[30] However, the uncertainty associated with the isotope effect on the K_a of **1** (see Table II) is too great to allow for speculation on the origin of such a result.

Transition-State Structure. A quantitative way of looking at the transition-state structure is to compare the value of β_{lg} to the maximum possible value. This ratio of β_{lg} values yields the fraction of bond cleavage that has occurred in the transition state. The bond order of the breaking bond is equal to $1 - (\beta_{lg}/-1.7)$. For monoaryl succinate hydrolysis the bond order of the breaking bond is 0.31. Substitution of this value in Pauling's bond order equation,[31] eq 3, and utilizing 1.41 (single bond C–O) for D_1 give a breaking C–O bond distance of 1.77 Å.

$$D_n = D_1 - 0.71 \text{ Å} \log n \qquad (3)$$

The isotope effect suggests a planar anhydride-like ring structure, so that the picture of the transition-state structure that emerges is represented by **2**. The planar ring structure



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is further supported by calculations[27] on a reverse reaction, addition of $^-$OH to succinic anhydride, which occurs with no change in the planarity of the ring atoms.

Summary and Conclusion. The β secondary isotope effect probe of transition-state structure in the hydrolysis of **1** suggests that relief of ground state steric interactions is important in driving the ring closure when L = H just as when L = alkyl. Consequently, the dominant factor affecting rate accelerations in reactions described by eq 1 is the equilibrium driving force for ring closure. Isotope effects are consistent with the conclusion from structure–reactivity relations that the transition state is "late", resembling an alkoxide ion and succinic anhydride. Since the isotope effect, which probes force-constant alterations near the carbonyl, and the structure–reactivity probe, which measures charge development in the leaving group, yield similar conclusions, these two processes (force-constant alteration at carbonyl and leaving group charge development) appear to be highly *coupled* along the reaction path.

References and Notes

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$$\left[\frac{(172 + 100.1)/(172 \times 100.1)}{(172 + 104.1)/(172 + 104.1)}\right]^{1/2} = 1.012$$
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Structural Effects in Solvolytic Reactions. 25. Solvolysis of Aryl(2-norbornyl)methylcarbinyl *p*-Nitrobenzoates. Search for a Special Stereoelectronic Effect with the Tool of Increasing Electron Demand

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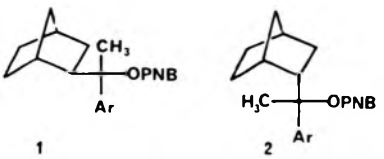
The relative electronic stabilization of a carbonium center by α *exo*- and *endo*-norbornyl groups was studied by synthesizing and solvolyzing representative aryl(2-norbornyl)methylcarbinyl *p*-nitrobenzoates in 80% aqueous acetone. The endo derivatives solvolyze four or five times faster than the exo derivatives, presumably attributable to enhanced steric strain facilitating the ionization of the endo isomer. The exo derivatives yield a value of ρ^+ of −4.44, almost identical with the value of ρ^+ of −4.47 observed for the endo derivatives. It is concluded that the application of the tool of increasing electron demand to these systems fails to reveal any significant electronic factor in the exo isomers facilitating their ionization, an electronic factor not present in the corresponding endo derivatives.

A number of proposals have appeared for the existence of special stereoelectronic factors operating in *exo*-norbornyl derivatives so as to favor their reactions as compared to the endo isomers.[2] The original proposal was that σ bridging favored the solvolysis of *exo*-norbornyl derivatives, but was stereoelectronically inoperative in the corresponding endo isomers.[3] Later, it was suggested that the stereoelectronic contribution need not involve σ bridging. Instead, it was proposed that the *exo*-norbornyl transition state could be stabilized by hyperconjugative interactions involving the 1,6-bonding pair.[4,5] This stereoelectronic interpretation differs from the older nonclassical ion proposal in that major distortion of the structure is not essential for the operation of the electronic contribution facilitating ionization of the exo isomer.[4,5]

More recently it has been suggested that such stereoelectronic contributions from the 2-norbornyl system also operate to stabilize developing electron deficiencies in the position α to the 2-norbornyl structure preferentially from the exo direction.[6-8]

We had earlier applied the tool of increasing electron demand[9] to test for enhanced electronic contributions from the *exo*-norbornyl system to stabilize a developing electron deficiency at the 2 position.[10] It appeared desirable, therefore, to apply the tool of increasing electronic demand to this newer proposal of a preferential stereoelectron contribution in *exo*-norbornyl derivatives which can stabilize a developing electron deficiency in the α position. Accordingly, we undertook to synthesize and to determine the rates of solvolysis of the aryl(2-norbornyl)methylcarbinyl *p*-nitrobenzoates (**1** and **2**).



1 **2**

Results

Synthesis. The preparation of *exo*- and *endo*-2-acetylnorbornane was described earlier.[11] The addition of the appropriate Grignard reagents to the 2-acetylnorbornanes gave the tertiary alcohols. The *p*-nitrobenzoates of the tertiary alcohols were obtained by the *n*-butyllithium method.[12]

Solvolysis. The rates of solvolysis of the *p*-nitrobenzoates were determined in 80% aqueous acetone by the titrimetric procedure.[12] The rate constants for the highly reactive *p*-methoxy derivatives were obtained by multiplying the rate of the benzoate by a factor of 20.8.[13] The pertinent rate data and activation parameters are summarized in Table I.

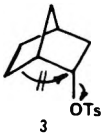
Discussion

The high exo/endo rate ratio exhibited in the acetolysis of the 2-norbornyl tosylates (**3** and **4**) has long intrigued chemists.[2] It was originally proposed that the faster rate of the exo isomer (**4**) was the result of σ participation by the 1,6-bonding pair, leading to a stabilized σ-bridged cation (**5**).[3,15] The endo isomer (**3**) is postulated to be stereoelectronically unfavorable for such participation.[16]

3 **4**

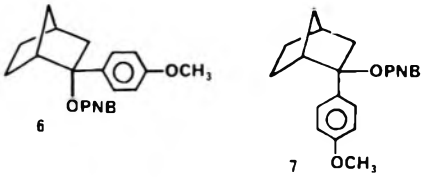
Rel rate (25°C)[14] 1.00 280

4 **5**



3

It is a well-established characteristic of such participation that it requires a cationic center with considerable electron demand—a highly stabilized cationic center should not involve such σ bridges.[2] Yet the solvolysis of the 2-*p*-anisyl-2-norbornyl *p*-nitrobenzoates (**6** and **7**) exhibits equally high exo/endo rate ratios.[17]



6

Rel rate (25°C) 1.00 284

Indeed, 2-*p*-anisyl-2-camphenilyl (**8** and **9**) exhibits a much higher exo/endo rate ratio.[17]

Merely by varying the steric requirements, it has proven possible to realize enormous changes in the exo/endo rate ratios (**10**, **11**, and **12**).[18]

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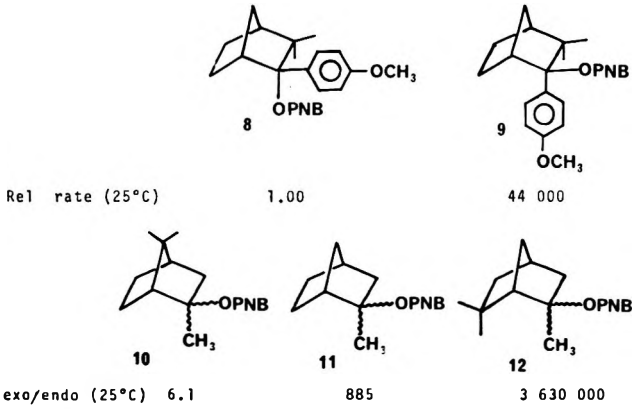
Table I. Rates of Solvolysis of Aryl(2-norbornyl)methylcarbinyl *p*-Nitrobenzoates

System	Substituent in aryl	$k_1 \times 10^{-6}$, s^{-1} T_1, °C	T_2, °C	25 °C	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	Rel rate 25 °C
1 (exo)	*p*-CH_3O			112[a]			0.16
	p-H	359 (100)	28.0 (75)	0.0472[b]	25.8	−5.7	0.33
	p-CF_3	503 (150)	47.0 (125)	6.73×10^{-5} [b]	31.2	−0.6	0.22
	3,5-$(CF_3)_2$	605 (175)	60.1 (150)	1.04×10^{-6} [b]	34.3	2.4	0.19
2 (endo)	*p*-CH_3O			708[a]			1.00
	p-H	776 (100)	66.8 (75)	0.144[b]	25.7	−8.6	1.00
	p-CF_3	102 (125)	8.02 (100)	3.02×10^{-4} [b]	29.4	−3.4	1.00
	3,5-$(CF_3)_2$	82.1 (150)	6.92 (125)	5.52×10^{-6} [b]	32.5	−0.9	1.00

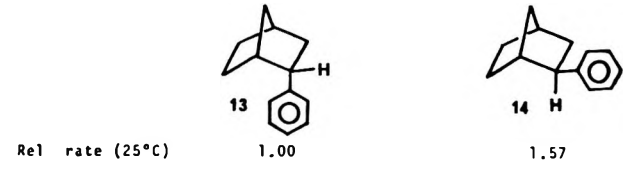
[a] Calculated by multiplying the rate of benzoate by a factor of 20.8.[9] [b] Extrapolated from data at higher temperatures.



These results have led to the alternative proposal that solvolysis is related to other reactions of the norbornyl system, with separation of the group being more favored from the exposed exo face than from the hindered U-shaped endo face.[2]

The newer proposal of a hyperconjugative interaction of the 1,6-bonding pair with the developing electron deficiency at the *exo*-2 position[4,5] appears to suffer from the same difficulty. Such hyperconjugative interactions would also be expected to decrease with decreasing electron demand by the developing cationic center at C-2. Yet such variation in the exo/endo rate ratio with increasing electron demand at C-2 is not observed.[10]

Let us now consider the more recent proposals for a significant stereoelectronic contribution operating preferentially from the exo direction of the norbornyl structure to stabilize a developing electron deficiency in the α position. Jensen and Smart observed that the benzoylation of 2-phenylnorbornanes is somewhat faster for the exo isomer (**14**) than for the endo (**13**).[6]

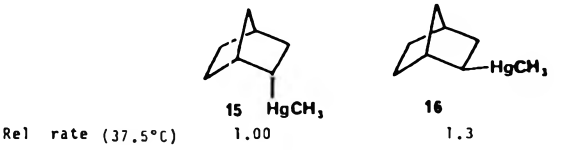


They observed that 1-phenylnorbornane was even more reactive (relative rate (25 °C), 1.72) than *exo*-phenylnorbornane (1.57). They proposed that the strained σ bonds of the norbornane structure could stabilize the developing positive charge in the aromatic ring by enhanced hyperconjugative interactions.

The interpretation is similar to that later advanced by Traylor and co-workers.[5] According to this stereoelectronic interpretation, "vertical stabilization" or conjugation involving strained σ bonds can stabilize the developing cationic center. In **13** and **14** it is considered that the developing positive charge at the position of the phenyl ring where it is attached to the norbornane structure would be stabilized by hyperconjugative interactions with the strained 1,2 and 2,3 σ bonds.

Although Jensen and Smart did not discuss this question in their publication, in private communications to one of the present authors (H.C.B.) they attributed the difference in reactivities of the exo and endo isomers, **14** vs. **13**, to more favorable hyperconjugative contributions in the former.

The acetolyses of *exo*- and *endo*-2-norbornylmethylmercury (**15** and **16**) similarly show a small preference for the exo

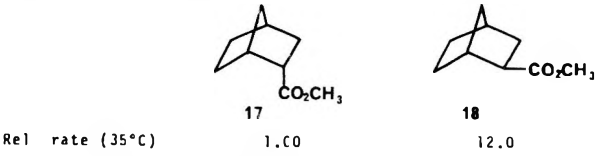


isomer.[7] The reaction involves formation of methane by rupture of the Hg–CH_3 bond.

$$RHgCH_3 + CH_3CO_2H \rightarrow RHgO_2CCH_3 + CH_4$$

It is postulated to proceed through an intermediate or transition state with an electron deficiency on mercury, RHg^+.[19]

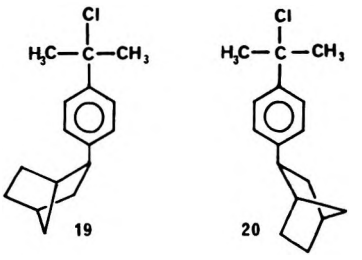
These differences between *exo*- and *endo*-norbornyl derivatives are very small. Experience teaches us the dangers in attempting to interpret such small differences in chemical reactivity. For example, the difference in the rates of alkaline hydrolysis of *endo*- and *exo*-norbornanecarboxylic acid esters is considerably larger[21] (**17** and **18**). Surely we cannot take this



difference as evidence for a significant difference in the electronic supply from the *exo*- and *endo*-norbornyl structures to the reaction center. The relative rates are more plausibly interpreted in terms of the large steric difference between *endo*- and *exo*-norbornyl derivatives.[2,11] A similar steric factor may also contribute to the small differences in the relative reactivities of **13** and **14**, and **15** and **16**.

Our preferred approach to test the relative abilities of various groups to contribute to electron-deficient centers has involved the *tert*-cumyl system.[22] Here also we observe a small difference in rates, 1.15, between *exo*- and *endo*-norbornyl (**19** and **20**).[22a]

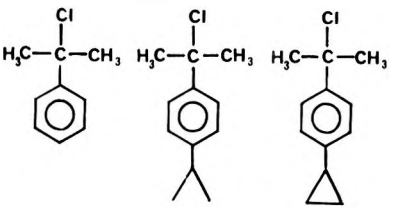
It should be pointed out that comparable variations in reactivity are realized for *p*-cyclobutyl (20.7), *p*-cyclopentyl (23.7), and *p*-cyclohexyl (19.6).[22b] Consequently, we concluded that such small variations could well arise from minor variations in conformations and in hyperconjugative contributions and could not be attributed with any confidence to a significant difference in stereoelectronic contributions of *exo*- and *endo*-norbornyl.[11,23]



	19	20
Rel rate (*p*-H = 1.00) (25°C)	21.8	25.2

These effects are all very small. It has been argued that the amount of positive charge delocalized to the para position of the *tert*-cumyl system is relatively small. Such a small deficiency can make but a small demand on the alkyl group for electronic contributions.

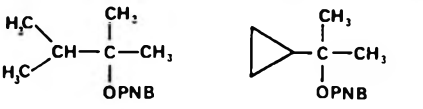
In the case of other groups, the observed effect is significant. Thus the cyclopropyl group in the *tert*-cumyl system (**23**) is



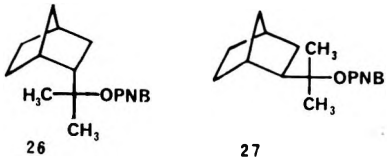
	21	22	23
Rel rate (25°C)	1.00	18.0	154

unambiguously better than a simple alkyl group in providing electronic stabilization.[24]

By placing the developing charge α to the group, the electronic demand and the observed effect should be much larger. For example, cyclopropyldimethylcarbinyl *p*-nitrobenzoate (**25**) solvolyzes enormously faster than the corresponding isopropyl derivative (**24**).[25] We tried to utilize this approach



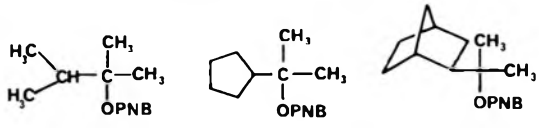
	24	25
Rel rate (25°C)	1.00	170 000



	26	27
Rel rate (25°C)	1.00	0.055

with 2-norbornyl (**26** and **27**).[11] However, it was the endo isomer, not the exo isomer, that exhibited the enhanced rate. Presumably, relief of steric strain in the more hindered endo derivative dominates the situation, swamping out any small differences in the electronic contributions of the *exo*- and *endo*-norbornyl groups.

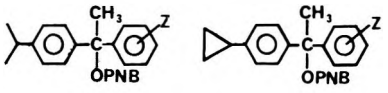
That the electronic contribution of the *exo*-norbornyl group cannot be very large compared to other aliphatic and alicyclic groups is indicated by the following comparison of isopropyl (**24**), cyclopentyl (**28**), and *exo*-norbornyl (**27**) derivatives.[9] Compare these values with **25**/**24**.



	24	28	27
Rel rate (25°C)	1.00	1.54	2.78

The tool of increasing electron demand appeared to offer a more objective means for comparing the electronic contributions of the *exo*- and *endo*-norbornyl groups. Here we vary the electron demand by introducing appropriate substituents in the meta and para positions of the aryl group. Consequently, within each series the steric effects are maintained constant as the electron demand is varied.

We have established that the tool of increasing electron demand is quite sensitive. By introducing a phenyl group between the isopropyl and cyclopropyl groups and the developing electron-deficient center we greatly damped out the effects of these groups. The parent compounds (X = *p*-H) exhibit a relative reactivity of only 2.8 (**29** and **30**).[26] Yet the



	29	30
Rel rate (Z = H) (25°C)	1.00	2.8
ρ^+	-2.91	-2.24

values of ρ^+ clearly establish a greater electron supply from the *p*-cyclopropyl substituent (ρ^+ −2.24) than the *p*-isopropyl substituent (ρ^- −2.91) with $\Delta\rho^+$ −0.67.

Recently Peters has applied the tool of increasing electron demand to the cyclobutyl system.[27] Examination of the solvolysis of the usual substituted arylcyclobutylmethylcarbinyl *p*-nitrobenzoate yielded a value of ρ^+ of −3.94, as compared to a value of −4.65 for the related arylisopropylmethylcarbinyl derivatives. The author concluded that in these cyclobutyl derivatives the strained σ bonds do make a significant contribution to the stability of the developing cationic center.[28] Consequently, it appeared of special interest to establish what the tool of increasing electron demand would reveal about electronic contributions from the two isomeric groups—α-*exo*-norbornyl and α-*endo*-norbornyl.

Solvolysis of the aryl(2-norbornyl)methylcarbinyl *p*-nitrobenzoates revealed that here also the endo isomers exhibit the faster rates, as in the corresponding dimethyl derivative, **26**. However, the exo/endo rate ratios (**1**/**2**), ~4.8, are considerably smaller than the value (18.2) for the corresponding methyl derivatives (**27**/**26**). This suggests that the steric requirements of the phenyl group in **1** and **2** must be somewhat smaller than the steric requirements of the corresponding methyl groups in **26** and **27**.

However, more critical for the main objective of the present study is an examination of the sensitivity of the developing cationic center to electronic contributions from the substituents in the aromatic ring. The larger the electronic contributions from the norbornyl structure, the less demand there should be for electron supply from the aromatic ring, and the smaller should be ρ^+. However, no significant difference in ρ^+ is observed.

	2	1
ρ^+	-4.47	-4.44

We have now tested for differential electronic supply from *exo*-norbornyl, as compared to *endo*-norbornyl, in three ways. First, we placed the groups in the para position of the *tert*-cumyl system.[22] The small difference in relative rates, 1.00 vs. 1.15, comparable to the differences found for *p*-cyclobutyl, *p*-cyclopentyl, and *p*-cyclohexyl, does not support a significant stereoelectronic contribution from *exo*-norbornyl to the stabilization of the developing cation.

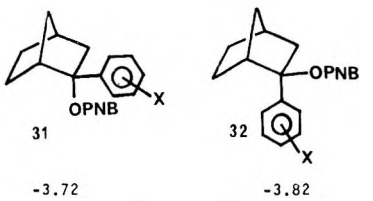
Then we have placed the two groups α to the developing

Table II. Properties of Aryl(2-norbornyl)methylcarbinyl *p*-Nitrobenzoates

System	Substituent in aryl	Yield, %	Mp, °C	Analyses
1 (exo)	*p*-H	68	141–142	C, H, N
	p-CF_3	61	146–147	C, H, N, F
	3,5-$(CF_3)_2$	65	100.5–101	C, H, N, F
2 (endo)	*p*-H	77	115–116 dec	C, H, N
	p-CF_3	81	155.5	C, H, N, F
	3,5-$(CF_3)_2$	71	127.5–128	C, H, N, F

electron-deficient center. The differences in ρ^+, −4.47 vs. −4.44, fail to reveal any evidence for greater electronic supply from the exo center.

Finally, we have placed the developing electron-deficient center on C-2 of the norbornyl structure (**31** and **32**).[10] Again,



ρ^+ fails to detect any significant difference in the stereoelectronic properties of *exo*- and *endo*-norbornyl. (The small difference, −3.72 vs. −3.82, is actually in the opposite order for a preferential stereoelectronic contribution in the exo isomer.)

Conclusion

We conclude from the present solvolytic study that the stabilization of the developing carbonium ion center by α *exo*- and *endo*-norbornyl groups is nearly the same, without significantly greater electron supply from exo as compared to endo. Finally, even when the developing electron deficiency is actually on the ring (C-2), no differential electron supply for the exo isomer, as compared with the endo isomer, is observed.

Experimental Section

Preparation of Tertiary Alcohols. The Grignard reagents prepared from *p*-bromoanisole, bromobenzene, *p*-bromobenzotrifluoride, and 3,5-bis(trifluoromethyl)bromobenzene were added to *exo*- and *endo*-2-acetylnorbornanes to afford the tertiary alcohols.

Preparation of *p*-Nitrobenzoates. These derivatives were synthesized by treating the tertiary alcohols with *n*-butyllithium and *p*-nitrobenzoyl chloride in THF.[12] Properties of the *p*-nitrobenzoates are listed in Table II.

Kinetic Measurements. The rates of solvolysis of the *p*-nitrobenzoates were determined in 80% aqueous acetone following the titrimetric procedure.[12] The rate data and activation parameters are listed in Table I. The rate constants are reproducible to within ±1%.

Registry No.—**1/2** (Ar = *p*-$CH_3OC_6H_4$), 65749-06-6; **1/2** (Ar = *p*-$CH_3OC_6H_4$) free alcohol, 65749-07-7; **1/2** (Ar = C_6H_5), 65749-08-8; **1/2** (Ar = C_6H_5) free alcohol, 65749-09-9; **1/2** (Ar = p-$CF_3C_6H_4$), 65749-10-2; **1/2** (Ar = p-$CF_3C_6H_4$) free alcohol, 65749-11-3; **1/2** (Ar = 3,5-$(CF_3)_2C_6H_4$), 65749-12-4; **1/2** (Ar = 3,5-$(CF_3)_2C_6H_4$) free alcohol, 65749-13-5; *p*-bromoanisole, 104-92-7; bromobenzene, 108-86-1; *p*-bromobenzotrifluoride, 402-43-7; 3,5-bis(trifluoromethyl)bromobenzene, 328-70-1; *exo*-2-acetylnorbornane, 824-59-9; *endo*-2-acetylnorbornane, 824-58-8; *p*-nitrobenzoyl chloride, 122-04-3.

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$$RHgMe \rightarrow RHgMe^+ + e$$

and therefore attribute both the greater ease of ionization and the faster rate of acetolysis of the exo isomer to the relative ease of electron release by *endo*- and *exo*-norbornyl groups to the electron deficiency. Difficulties with their interpretation of the vertical ionization potentials is discussed in a manuscript by W. L. Jorgensen and J. E. Munroe (ref 20) soon to appear. However, on a more pragmatic level, Kochi and his co-workers report that the rate of acetolysis of 2-propylmethylmercury is essentially identical with that for *exo*-norbornylmethylmercury. This is not consistent with the proposed enhanced electronic contribution from the *exo*-norbornyl group.

The authors attribute the slightly greater reactivity of the exo isomer (**16**) over the endo isomer (**15**) loosely to "σ participation." However, they must be referring to σ conjugation or hyperconjugation involving the electron deficiency on mercury and the strained 1,2 and 2,3 carbon–carbon bonds, as in the Jensen–Smart system (**13** and **14**).[6] See ref 2, pp 63–66, for a discussion of the difference between π and σ conjugation and participation.
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Model Studies of Thiamin Catalysis. Comparison of the Effects of Heteroatoms at Annular Positions on Side-Chain Kinetic Acidity

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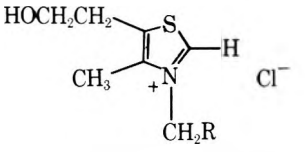
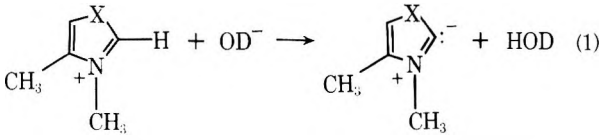
General-base-catalyzed deprotonation of the 2-methyl groups of 2,3-dimethylbenzothiazolium (II), 1,2,3-trimethylbenzimidazolium (III), and 1,2,3,-trimethylimidazolium (IV) ions was studied by means of hydrogen–deuterium isotope exchange. At 75 °C and 1.0 M ionic strength II, III, and IV show the following relative reactivity order toward deuterioxide ion: 3.0×10^5; 3.4×10^2; 1, respectively. Toward pyridine II is 9.5×10^3 times more reactive than III. The Brønsted β value for a series of bases, excluding water and lyate ion, reacting with II is 0.63. A more limited series of bases gives the value 0.8 for III. A comparison is made between the reactivities of sp^2- and sp^3-hybridized carbon centers in deprotonation reactions involving thiazolium ions.

Thiamin (I) or vitamin B-1 when catalyzing carbon–carbon bond forming reactions is converted to an ylide and subsequently to an enamine intermediate, both of which act as nucleophiles toward carbonyl electrophiles.[1–4] Many studies have been carried out to obtain an understanding of the various steps in the multistep catalyzed conversions. For example, the ability of several annular heteroatoms to facilitate ylide formation[5] in deprotonation reactions, eq 1, has been explored.



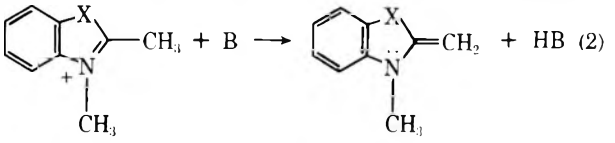
I, R = 2-methyl-4-amino-5-pyrimidinyl



(1)

Results show that reactivity increases in the order X=NCH$_3$, S, and O.[6] By contrast, little is known about the influence of similar heteroatoms on the kinetic acidity of an alkyl side chain which gives an enamine rather than an ylide on proton loss.

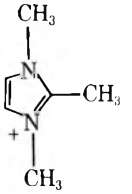
In this article we examine the effects of annular heteroatoms on the kinetic acidities of ions II–V containing an acidic methyl group. Equation 2 shows the enamine which forms



(2)

II, X = S
III, X = NCH$_3$
V, X = O

VI, X = S



IV

when fused-ring heteroaromatic ions II, III, and V undergo deprotonation. The accompanying paper explores the influence of methyl and hydroxy substituents bonded to the 2-methyl group of II on the kinetic acidity of this position.[7]

Results

No evidence exists to indicate that the 4-methyl and 5-β-hydroxyethyl substituents of the thiazolium ion ring of I provide other than expected, small, electronic effects on deprotonation reactions at position 2 under biological conditions. For this reason these substituents were not incorporated into our models. In order to simplify our models a methyl group was added to N-3 in place of the pyrimidinylmethyl substituent. Because of their ready availability and because they contain the essential structural elements, compounds II–V were selected as model substrates. The conjugate base of II, 3-methyl-2-methylenebenzothiazolene (VI), which is formed as an intermediate in our reactions has been isolated.[8]

All of the studies employ NMR to determine rates of carbon deprotonation. Reactions were carried out using D_2O as the reaction medium, leading to replacement of H by D in the side chains. Except where indicated, the reaction temperature is 75.0 °C.

2,3-Dimethylbenzothiazolium Ion (II). Deprotonation of the *C*-methyl group of this substrate was found to take place readily in 0.1 M DCl. Catalysis was also observed with the following buffers, listed in order of increasing basicity: 3-chloropyridine, phthalazine, formic acid, acetic acid, pyridine, and 2,6-lutidine (Table I). Buffer ratios and pD were varied in order to determine whether water, buffer base, and deuterioxide ion contributed to the general-base-catalyzed deprotonation reactions. Pseudo-first-order rate constants were analyzed using eq 3

$$k_\psi = k_{D_2O}[D_2O] + k_B[B]_{tot}\frac{K_a}{[D] + K_a} + k_{OD}\frac{K_w^D}{[D]} \quad (3)$$

where k_{D_2O}, k_B, and k_{OD} are second-order rate constants for water, buffer, and deuterioxide ion bases, respectively, and K_a and K_w^D are the dissociation constants of buffer and the ion product of D_2O, respectively.

Significant catalysis by deuterioxide ion was observed only with the most basic buffer, 2,6-lutidine. Thus, the value of k_{OD} was established using the data derived with this buffer. Application of the term $k_{OD}[OD^-]$ to the data obtained with other buffers indicates that deuterioxide ion measurably influences reactivity only in two other kinetic runs, those at pD 4.09 involving acetic acid and pyridine buffers. The kinetic contribution of this base represents about 13% of the total catalysis in both cases. With these two kinetic runs and also the lutidine studies as exceptions, deprotonation in the other buffered media was catalyzed only by water and by buffer base.

Since the k_{OD} term was obtained with only one buffer, another method was employed as a check. This involved the use of a pH-stat in place of a buffer to adjust the pD of the reaction medium. From runs at pD 5.25 and 5.45 this approach gave

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Table I. Kinetic Results for Hydrogen–Deuterium Exchange at the 2-Methyl Group of 2,3-Dimethylbenzthiazolium Ion (II) in Buffered D_2O at 75.0 °C and 1.0 M Ionic Strength

Buffer	pK_a	pD[a]	Total buffer, M	Obsd $10^5 k_\psi$, s^{-1}	Calcd[b] $10^5 k_\psi$, s^{-1}	k_B, $M^{-1} s^{-1}$
DCl	--	--	0.1	2.65 ± 0.23[c]		(4.90 × 10^{-7} [d])
3-Chloropyridine	3.07	2.49	1.20 × 10^{-1}	13.15	12.3	3.84 × 10^{-3}
		2.65	4.80 × 10^{-2}	8.00	7.80	
		2.73	2.40 × 10^{-2}	5.23	5.61	
Phthalazine[e]	3.79	3.20	1.01 × 10^{-1}	34.9	34.9	1.56 × 10^{-2}
		3.37	2.12 × 10^{-2}	11.45	11.7	
Formic acid	4.03	3.22	4.40 × 10^{-2}	12.1	12.2	1.62 × 10^{-2}
		3.33	3.33 × 10^{-2}	11.5	11.6	
		3.33	1.10 × 10^{-2}	5.17	5.61	
		3.35	2.20 × 10^{-2}	8.48	8.82	
Acetic acid	5.12	3.75	4.20 × 10^{-2}	23.7	20.4	1.00 × 10^{-1}
		4.09	3.33 × 10^{-3}	9.60	11.0	
Pyridine	5.27	3.98	4.20 × 10^{-2}	22.1	21.8	8.90 × 10^{-2}
		4.09	8.44 × 10^{-3}	8.33	8.42	
2,6-Lutidine	6.44	5.10	1.20 × 10^{-1}	99.3	96.5	
		5.20	6.05 × 10^{-2}	60.8	68.8	1.57 × 10^{-1} (B)
		5.43	6.05 × 10^{-3}	38.7	35.8	3.08 × 10^4 (OD^-)
		5.51	2.00 × 10^{-3}	40.6	35.7	
DCl[f,g]	--	--	0.1	0.010	--	(1.81 × 10^{-9} [d])
Acetic acid[f,h]	5.25	4.27	4.54 × 10^{-2}	0.270	0.260[i]	5.81 × 10^{-4} [i]
		4.27	8.48 × 10^{-3}	0.0544	0.0567[i]	

[a] Measured at 75.0 °C. [b] Using equation 3. [c] Average of four determinations. [d] $k_\psi/[D_2O]$. [e] 2,3-Diazanaphthalene. [f] At 25.0 °C and 0.5 M ionic strength. [g] $\Delta H^\ddagger$ = 22.4 kcal/mol; $\Delta S^\ddagger$ = −4.12 eu. [h] $\Delta H^\ddagger$ = 20.7 kcal/mol; $\Delta S^\ddagger$ = −4.12 eu. [i] Neglects any contribution from OD^-.

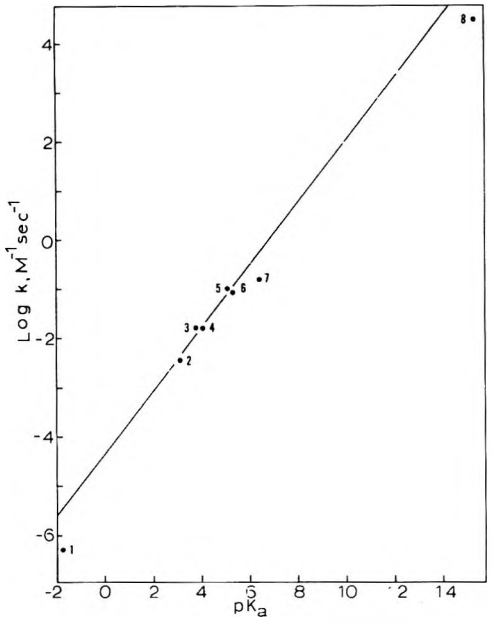


Figure 1. Brønsted plot for hydrogen–deuterium exchange at the 2-methyl group of II in D_2O at 75 °C and 1.0 M ionic strength. Buffers include: 1, water; 2, 3-chloropyridine; 3, phthalazine; 4, formic acid; 5, acetic acid; 6, pyridine; 7, 2,6-lutidine; and 8, deuterioxide ion. No statistical corrections have been applied. The least-squares line does not include points 1, 7, and 8.

a value of 3.80 ± 0.16 × 10^4 $M^{-1} s^{-1}$ which is only 23% larger than that derived from the lutidine studies.

The quality of our results may be assessed by comparing the observed pseudo-first-order rate constants with those calculated with the aid of eq 3 and the second-order constants listed in Table I. In carrying out the computations the buffer-derived value of k_{OD} was employed. The largest differences are found in the results obtained with acetic acid and lutidine buffers where the results with the poorest agreement differ by about 14%. Differences between observed and calculated values are substantially less in all other cases.

The spread in second-order rate constants between the least (D_2O) and most (OD^-) reactive bases is a factor of 6.3 × 10^{10}. The variation in reactivity for buffer bases unrelated to solvent is a factor of 41.

A Brønsted plot may be constructed using the results in Table I. Without making any statistical corrections for the number of basic sites in a buffer a single plot (Figure 1) is obtained, excluding points for water, deuterioxide ion, and 2,6-lutidine. The slope, β, is 0.63 and the intercept is −4.305. The correlation coefficient is satisfactory, being 0.991. On the basis of this plot, 2,6-lutidine is 3.7 times less reactive than expected from a consideration of its pK_a value, no doubt reflecting a modest steric hindrance to general base catalysis.[9] Water and deuterioxide ion deviate; observed reactivity in both cases is about 8 times less than that calculated. Negative deviations for these are not uncommon. The reduced reactivities of the two bases with carbon acids is said to be a consequence of a lack of hydrogen bonding between reactants in the ground state.[10,11]

When rate and equilibrium constants are statistically corrected for the two basic centers found in phthalazine and in the carboxylate anions, two correlation lines now are generated, one for carboxylic acids and one for pyridines. The line for carboxylate ion bases is displaced above that for the pyridines. Phthalazine now deviates from the pyridine correlation line in the sense that its reactivity is about 4 times greater than that predicted by its basicity. Phthalazine is known to show an enhanced reactivity (α effect) toward esters,[12] but it is likely that the present deviation is not significant. Thorough studies of α-effect nucleophiles in carbon deprotonation reactions have failed to uncover enhanced reactivities.[13,14] Although it is customary to make statistical corrections in constructing Brønsted plots,[15] good correlations using uncorrected data are known for carbon deprotonation.[13]

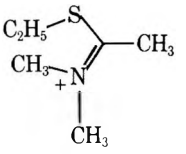
Some kinetic information was also obtained at 25.0 °C so that the reactivity of II could be compared with that of the *C*-methyl group of its acyclic relative VII, *N,N*-dimethyl-

Table II. Kinetic Results for Hydrogen–Deuterium Exchange at the 2-Methyl Groups of 1,2,3-trimethylbenzimidazolium Ion (III) and of 1,2,3-Trimethylimidazolium Ion (IV) in Buffered D_2O at 75.0 °C and 1.0 M Ionic Strength

Compd	Buffer	pK_a	pD[a]	Buffer, M	Obsd k_ψ, s^{-1}	Calcd[b] k_ψ, s^{-1}	k_g[c] M^{-1} s^{-1}
III	DCl	--	--	0.1	$<0.5 \times 10^{-7}$	--	--
	Pyridine	5.27	5.60	0.303	2.30×10^{-6}	2.33×10^{-6}	9.36×10^{-6} (B)
			5.76	0.0303	7.46×10^{-7}	7.94×10^{-7}	31.1 (OD^-)
	Phosphate	7.10	6.61	0.140	2.25×10^{-5}	2.26×10^{-5}	5.40×10^{-4} (B)
			6.98	0.0200	1.64×10^{-5}	1.43×10^{-5}	41.4 (OD^-)
			7.12	0.280	9.46×10^{-5}	9.05×10^{-5}	
			7.50	0.300	1.59×10^{-4}	1.47×10^{-4}	
	Glycine	9.17	7.83	0.0550	1.07×10^{-4}	1.17×10^{-4}	2.02×10^{-2} (B)
			7.87	0.110	1.72×10^{-4}	1.81×10^{-4}	29.2 (OD^-)
			8.17	0.220	5.32×10^{-4}	5.53×10^{-4}	
IV	Carbonate	9.93	10.00	0.120	2.88×10^{-5}	3.01×10^{-5}	
			10.25	0.350	5.35×10^{-5}	5.38×10^{-5}	1.01×10^{-1} (OD^-)
			10.86	0.275	2.26×10^{-4}	2.15×10^{-4}	

[a] At 75.0 °C. [b] Using eq 3, the k_B values listed for each base and the average value for k_{OD} of 33.9 m^{-1} s^{-1}. [c] For buffer base and/or deuterioxide ion.

thioacetimidate, under similar conditions.[16] Rate constants were obtained for water and acetate ion bases (Table I). Our second-order rate constant for acetate ion may be somewhat too large if deuterioxide ion makes a contribution to catalysis. No attempt was made to obtain a k_{OD} term at the lower temperature in order to estimate the magnitude of any contribution by lyate ion. However, a fivefold dilution of buffer failed to change the apparent second-order rate constant for acetate ion catalysis, suggesting that lyate ion catalysis is small.



VII

The enthalpies of activation, $\Delta H^{\ddagger}$, for water and acetate ion reacting with II are 22.4 and 20.7 kcal/mol, respectively, while the entropies, $\Delta S^{\ddagger}$, are −23.6 and −4.1 eu, respectively. Very similar entropy values have been reported for quinolinium ion–cyanine dye deprotonation reactions.[17] The less negative value associated with the ionic base probably reflects the release of solvent molecules in the transition state as the charges on the two reactants are being neutralized. By comparision, when water acts as a base, charge is maintained.

A pK_a value for II may be estimated using the rate constants for water acting as a base and an assumed rate constant for reverse reaction in which conjugate base VI reacts with D_3O^+. If it is assumed that the reverse reaction proceeds with a diffusion-controlled rate constant, about 10^{10} M^{-1} s^{-1}, the pK_a of II is 15 and 17 at 75 and 25 °C, respectively. These are likely to be upper limits because the reverse reaction, as suggested by the Brønsted β value of less than 1, is likely to be slower than estimated.[18]

1,2,3-Trimethylbenzimidazolium Ion (III) and 1,2,3-Trimethylimidazolium Ion (IV). Similar but more limited studies involving base-catalyzed H–D exchange at the *C*-methyl groups of III and IV were carried out. Both of these ions undergo deprotonation much more slowly than II, IV being less reactive than III. Fused ring substrate III undergoes deprotonation by the action of water extremely slowly; our value in Table II is only an estimate of an upper limit based on <5% hydrogen isotope exchange observed over 3 weeks. Convenient rates of deprotonation of III were obtained using pyridine, phosphate ion, and glycine buffers. Under these conditions both buffer base and deuterioxide ion catalyze deprotonation. Rate constants k_B and k_{OD} were obtained for each buffer. The three values obtained for k_{OD} using these buffers are in satisfactory agreement (Table II). The variation in k_B is a factor of 2.2×10^3.

An estimation of the experimental scatter in our results may be obtained by comparing observed and calculated pseudo-first-order rate constants. Calculations were performed using eq 3 and the average value of k_{OD} obtained from the three buffers and the appropriate k_B value (Table II). Calculated values for pyridine base are high by an average of 3.2%; for phosphate buffer they fall within ±6.1% of the observed value and for glycine they are systematically high by 6.1%. The systematic, small deviations found for pyridine and glycine result because the values of k_{OD} determined using these buffers separately are smaller than the average calculated from the data for the three buffers.

A Brønsted plot constructed from these data, excluding k_{OD}, without making any statistical corrections has $\beta = 0.85$, intercept −9.454, and a correlation coefficient of 0.998. The observed value of k_{OD} is 108 times smaller than that calculated using this correlation. Making statistical corrections for the number of acidic and basic sites in a buffer improves the correlation, β now being 0.76, the intercept −9.130, and the correlation coefficient 0.9997. Deuterioxide ion now is found to be only 11 times less reactive than predicted. Both treatments produce remarkably good correlations. Superior correlations generally, but not always,[13] are observed when data for structurally similar bases having the same charge are correlated.[11] Caution should be exercised when attempting to interpret our results in view of the limited number of buffers employed.

The reactivity of compound IV was examined using only a carbonate ion buffer. Apparently, deuterioxide ion and not carbonate ion catalyzes deprotonation of this substrate as evidenced by the good agreement between observed pseudo-first-order rate constants and those calculated solely with the term $k_{OD}[OD^-]$ (Table II). In this study the carbonate ion concentration was varied by a factor of 3.8, deuterioxide ion by 7.1. Note that this conclusion is to be expected in view of the Brønsted plots observed for II and III.

2,3-Dimethyloxazolium Ion (V). No information about the rate of deprotonation of the *C*-methyl group of this ion could be obtained. After just 15 min of heating in 0.1 M DCl at 75 °C there was clear evidence in the NMR spectrum of substrate degradation. This decomposition is to be expected on the basis of studies which show that cleavage of the het-

erocyclic ring is a facile process, having a half-life of 3.1 h at pH 1 and 25 °C.[19]

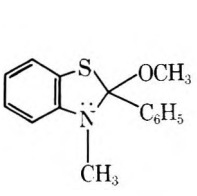
Discussion

Reactivities. Comparison of the reactivities of cations II–IV when undergoing deprotonation at a 2-methyl group by the action of deuterioxide ion shows that II is 9.1×10^2 times more reactive than III and 3.0×10^5 times more reactive than IV.[20] Toward pyridine, II is 9.5×10^3 times more reactive than III. These large values confer a distinct advantage in kinetic carbon acidity on the thiazolium derivative over both diazolium substrates. In addition, comparison of the reactivities of III and IV toward deuterioxide ion reveals that fusing a benzene ring onto the imidazolium ion leads to a 340-fold increase in kinetic acidity.

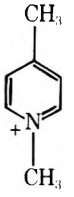
An interesting comparison involves II and its acyclic relative VII. Both cations undergo deprotonation by water and acetate ion bases. At 25 °C II is just 2.2 times more reactive than VII when acetate ion is the base and approximately 14 times less reactive when water is the catalyst.

An understanding of the origin of the coincidentally similar kinetic acidities of II and VII can be found in a consideration of the resonance energy of cyclic acid II and the extent of the change in this stabilization in the transition state for deprotonation.[22] The resonance energy of II is estimated to be about 52 kcal/mol and that for a thiazolium ion not having a fused benzene ring as about 21 kcal/mol.[23] These large values clearly show that a thiazolium ion ring has a substantial delocalization energy. Significantly, the delocalization energy of VIII, a model of VI in which the aromatic thiazolium ion ring no longer is present, is expected to be about the same as that for III. This resonance energy which is well above the value of 36 kcal/mol associated with benzene itself is due to interactions of the two heteroatoms with the aromatic ring.[23]

In view of the expected similar resonance energies of II, VI, and VIII, we suggest that the energy of activation associated with the conversion of II to VI will be largely free of a contribution reflecting a change in resonance energy. This is true in spite of the fact that II with its two aromatic rings is being converted to VI with essentially a single aromatic ring. Substrates II and VII are similar in that the reactivities of both are affected in only a minor way by changes in resonance energies associated with proton loss. Clearly, if the fused-benzene ring were not present in II to provide extensive activation, the resultant single-ring thiazolium ion would be very much less reactive than VII.



VII



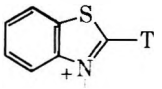
IX

Deprotonation of II then represents a most interesting and unusual example of an aromatic carbon acid which undergoes a small change in resonance energy on deprotonation at an exocyclic α position in spite of extensive proton transfer in the transition state. This conclusion contrasts with that for carbon acid IX, for example, which has a large energy barrier opposing conversion to its nonaromatic conjugate base by removal of a proton from the 4-methyl group.[24] Part of this barrier reflects the fact that the conjugate base of IX has about 19 kcal/mol less resonance energy.[25]

A number of widely varying estimates have been made concerning the resonance energies of III and IV[25] and little is known about the magnitudes of the changes in their delocalization energies when the acids are converted to their conjugate bases. However, it seems likely that the 340-fold greater reactivity of III over IV reflects in large measure both a smaller energy of activation due to a smaller loss of resonance energy on proton transfer and the possibility of more extensive electron delocalization. The aromaticity of the heterocyclic ring in the fused-ring compound is likely to be less than that of the single-ring compound.

Ylide and Enamine Formation. Our results show that the reactivity of II is 908 times greater than that of III toward lyate ion. In other terms, the annular sulfur atom increases kinetic, carbon acidity much more than an annular nitrogen atom. Here proton loss produces an enamine. Similarly, ylide formation, eq 3, is promoted by a factor of 3200 when the annular atom is sulfur rather than nitrogen.[6] These two comparisons show that at both the ylide and also the enamine stages of deprotonation sulfur confers greater reactivity than nitrogen and by similar amounts for the substrates considered. This conclusion reinforces an earlier suggestion based only on data pertaining to ylide formation:[26] nature selected a heterocyclic ring for the enzyme cofactor which contains a sulfur atom rather than a nitrogen or oxygen atom because the thiazolium ion ring has the proper combination of reactivity and stability toward hydrolysis.[27]

Using our results, a comparison can now be made of the rate constants for ylide and enamine formation. Consider, for example, benzothiazolium ion X forming an ylide and II forming an enamine. The second-order rate constant for X reacting



$CH_2C_nH_5$

X

with lyate ion[28] is about 10^4 times greater than that for II under similar conditions.[29] However, deprotonation of II is subject to marked general base catalysis while that for X is not.[28] Therefore, the reactivity difference under other conditions need not be as great as that just indicated. As an illustration, consider a buffer base of pK_a 8 at pH 8 present in 0.1 M concentration; assume its rate constant is that predicted by the Brønsted equation observed for II. Under these conditions deprotonation of II is only about 460 times slower than that of X, not the factor of 10^4 reflecting lyate ion reactivities. Although this comparison involves benzothiazolium ion reactants, similar conclusions are expected to apply to thiamin-like molecules containing thiazolium ion rings.[32]

Now that kinetic data have become available for deprotonation reactions leading to ylide and enamine intermediates, future kinetic studies should focus on reactions involving capture of these intermediates by carbonyl electrophiles. A detailed understanding of the way in which thiamin functions as a catalyst will begin to emerge.

Experimental Section

Reagents. 3-Chloropyridine hydrochloride was prepared by bubbling hydrogen chloride into an etheral solution of 3-chloropyridine (Aldrich); the white precipitate was sublimed and then titrated with standard alkali. Alkylation of 2-methylbenzimidazole (Aldrich) in methanol gave 1,2,3-trimethylbenzimidazolium iodide, mp 265–266 °C (lit.[33] mp 258–259 °C) while 2-methylbenzothiazole (Aldrich) gave 2,3-dimethylbenzothiazolium iodide, mp 221–222 °C (lit.[34] mp 221–222 °C), or perchlorate,[35] mp 122–123 °C, and 2-methylbenzoxazole (Aldrich) gave 2,3-dimethylbenzoxazolium iodide, mp 194–196 °C (lit.[19] mp 196 °C). Pyridine (Mallinckrodt) and 2,6-dimethylpyridine (Eastman) were dried over sodium and distilled from zinc powder. Sodium acetate (Mallinckrodt), sodium formate (Fisher), phthalazine (Aldrich), and reagent grade inorganic chemicals were used as received. Deuterium oxide (99.8%) was obtained from Columbia Organic Chemicals. Buffer solutions were prepared by

mixing DCl (D_2O and concentrated HCl) or KOD (D_2O and KOH) with appropriate materials.

1,2,3-Trimethylimidazolium perchlorate, mp 250–251 °C, was prepared by treating its methosulfate with perchloric acid dissolved in a mixture of ethanol–ethyl acetate. The methosulfate was prepared by the method used for benzimidazoles.[36]

Anal. Calcd for $C_6H_{11}ClN_2O_4$: C, 34.20; H, 5.27; N, 13.30. Found: C, 34.38; H, 5.40; N, 13.16.

Instrumentation. Nuclear magnetic resonance spectra were recorded on a Varian Associates A-60A instrument while pD was determined on a Beckman Model 1019 Research pH meter equipped with either a Corning (476050) or a Sargent (S-300-70-10) semimicro combination electrode. Measurements of pD and kinetic runs were carried out at 75.0 °C using a Lauda/Brinkman Model K-2 constant-temperature bath. Temperature was measured using a National Bureau of Standards certified thermometer. A Radiometer TTTl-c titrator with jacketed reaction vessel was used in pH-stat work. Least-squares calculations were performed on a Texas Instruments SR-51 calculator.

Kinetics of Hydrogen–Deuterium Exchange. Substrate and KCl to maintain constant ionic strength were weighted into a 3-mL volumetric flask. Buffer was added by weight or by syringe when dealing with a stock solution. After diluting to the mark with D_2O, substrate concentration was 0.15–0.20 M and the ionic strength 1.0 M. A sample in a sealed NMR tube was heated in a bath at 75.0 °C and then was removed periodically and quenched in an ice bath. The area of the *C*-methyl peak was integrated several times using the *N*-methyl area as a reference. Reactions using 2,6-lutidine buffer were so fast that 0.6-mL aliquots were removed from a sample and quenched with 1 M DCl prior to analysis. Reactions generally were followed for 2–3 half-lives, except the slowest runs. Rate constants were obtained in the usual way from plots based on the *C*-methyl to *N*-methyl area ratio.[37,38] Plots were nicely linear. Rate constants reflect the removal of a single proton. The NMR signals employed have the following shifts (N-CH_3 listed before C-CH_3): II, τ 5.76 and 6.80; III, 6.01 and 7.09; IV, 6.22 and 7.42.

Following a kinetic run, pD measurements were made at 75.0 °C on the heated mixture as well as the unheated stock solution according to the method of Bates.[39] The electrode was allowed to equilibrate at 75 °C in 4 M KCl for 20 min prior to use. Reproducibility of the measurements was about 0.03 while the difference in pD between heated and unheated samples was about 0.04 or less. When differences exceeded these values, runs were discarded. The pD of a buffer solution was obtained by adding the factor 0.35[38] to the meter reading.[40] The concentration of deuterioxide ion was calculated from the expression $pOD = pK_w^D - pD$ where K_w^D is the dissociation constant for D_2O. The value of pK_w^D, 13.526 at 75.0 °C, was calculated from reported data[41] and is uncorrected for salt effects which are expected to be small.[42]

A pH-stat also was employed to obtain kinetic data on II. A 0.11 M solution of the perchlorate salt of II brought to 1 M ionic strength with NaCl was acidified with DCl and raised to 75.0 °C in a jacketed titration vessel. The pD of the mixture then was increased to the desired value by adding KOD from the titrator. Aliquots of this mixture were removed from the sample and analyzed by NMR. The following results were obtained: at pD 2.5 where only D_2O catalyzes the reaction $k_\psi = 2.54 \times 10^{-5}\ s^{-1}$. This value is 4.1% lower than the average value derived from the 0.1 M DCl runs. At pD 5.25 $k_\psi = 2.19 \times 10^{-4}\ s^{-1}$ and at pD 5.45, $3.59 \times 10^{-4}\ s^{-1}$. After correcting for water catalysis these last two runs give $k_{OD} = 3.80 \pm 0.16 \times 10^4\ M^{-1}\ s^{-1}$. No base was consumed during these runs. The run at pD 5.45 was followed for 3 half-lives, the rate plot being linear.

The pK_a values for buffers were calculated from the known composition of the buffer mixtures employed in the kinetic studies and the measured pD of these mixtures at 1.0 M ionic strength. Hydrolysis corrections of concentrations were made as required.[43] The pK_a of 2,6-lutidine was determined using samples which did not contain substrate. Uncertainties in values reflect the scatter in the pD measurements.

Control Runs to Determine the Stability of Substrates. In order to learn whether substrate might have degraded during kinetic studies and escaped detection by NMR because of conversion to deuterated materials, controls were run using H_2O as the medium. This supplements attempts to detect degradation by comparing the pD of heated and unheated samples. Generally, in performing proteo control runs, conditions were selected which matched the most severe, i.e., the most alkaline solution with the highest concentration of buffer used in kinetic studies.

The stability of 2,3-dimethylbenzthiazolium iodide and perchlorate toward hydrolysis was ascertained using a pH-stat. The method of sample preparation and analysis was the same as that employed in kinetic studies. After 30 min at 75 °C and pD 6.4, NMR spectra failed to provide evidence of hydrolysis; no alkaline titrant was consumed even after 6 h. But at pD 7.5 new signals were evident in NMR spectra after 20 min, indicating decomposition. Since pD values in kinetic runs were much lower than those in the control studies, substrate degradation is likely to be unimportant. Ring cleavage studies support this conclusion.[35]

1,2,3-Trimethylbenzimidazolium iodide was heated at 75 °C in a mixture of 0.105 M glycine–0.005 M glycinate ion in H_2O containing KCl for 20 h, corresponding to a period of >10 half-lives for H–D exchange. The NMR spectrum of this mixture showed no sign of substrate degradation; no pH change was observed.

1,2,3-Trimethylimidazolium perchlorate was heated at 75 °C in 0.25 M sodium carbonate–0.025 M sodium bicarbonate for 8.5 h, a period corresponding to 10 half-lives for isotope exchange. No evidence for decomposition was detected by NMR.

Acknowledgment. This work was kindly supported in part by grant AM-17442 from the National Institutes of Arthritis, Metabolism, and Digestive Diseases. Dr. L. S. Helmick kindly carried out the pH-stat experiments.

Registry No.—I, 59-43-8; II iodide, 2785-06-0; II perchlorate, 706-67-2; III iodide, 3805-38-7; IV perchlorate, 65086-11-5; IV methosulfate, 65086-12-6; 2-methylbenzimidazole, 615-15-6; 2-methylbenzothiazole, 120-75-2.

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activity by about 50.[7] These changes result in an additional decrease in the reactivity of the sp^3 relative to the sp^2 carbon by an approximate factor of $10^{2.7}$.
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Model Studies of Thiamin Catalysis. Steric Inhibition of Deprotonation of a Hydroxyethyl Side Chain

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Rate constants have been obtained for deprotonation of the 2 position of a series of 2-substituted 3-methylbenzothiazolium ions involving formate ion and water as bases in D_2O. Relative rate constants for the two bases are very similar in spite of the reactivity of formate ion being about 3.4×10^4 times greater than that for water. Second-order rate constants for formate ion at 75.0 °C and 1 M ionic strength are: 2-ethyl, 2.28×10^{-2}; 2-hydroxymethyl, 1.10×10^{-2}; 2-isopropyl, 2.28×10^{-4}; and 2-(1-hydroxyethyl), 4.50×10^{-4} M^{-1} s^{-1}. The major influence on reactivity is found in the latter two substances where steric inhibition of resonance is dominant. It is suggested that a similar steric effect will be present in the conjugate base of 2-(1-hydroxyethyl)thiamin and will influence rates and equilibria in nonenzymatic and possibly in enzymatic reactions as well.

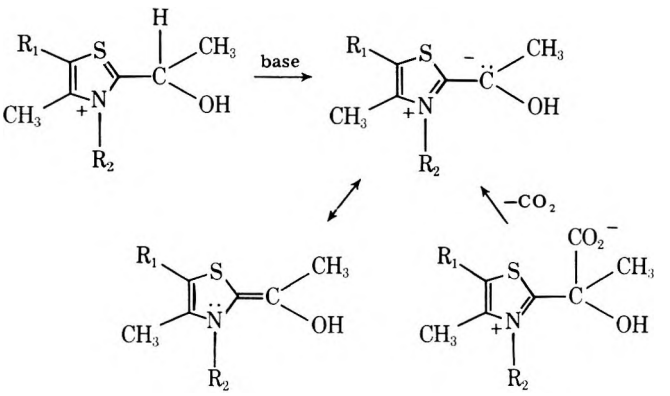
The enzyme cofactor thiamin pyrophosphate participates in a number of significant biological transformations. One very important derivative, an "enamine", is shown in Scheme I where it is formed by deprotonation of the corresponding 2-(1-hydroxyethyl) modification of the cofactor as well as by decarboxylation.[1] Prior to this study information has not been reported above how the methyl and hydroxy groups bonded to the exocyclic carbon atom of the enamine affect its rate of formation.

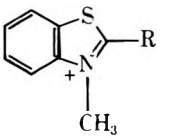
Generally, the effects of methyl and hydroxy or alkoxy substituents on the rates of deprotonation of a carbon atom to which they are bonded are variable and complex. The net effect is likely to be dependent on the hybridization of carbon in the transition state leading to deprotonation. Effects produced when the reactive site is pyrimidal can be different from those when the site is planar. Factors affecting reactivity include inductive and resonance effects, bond strengths as influenced by hybridization,[2] and electron pair repulsion associated both with electrostatic and Pauli exclusion principle effects.[3,4] Examples are known where an alkoxy group hinders[2] as well as facilitates[5] deprotonation of an adjacent sp^3 hybridization carbon.

In addition, the methyl and hydroxy substituents of the thiamin derivative in Scheme I may influence the rate of deprotonation by a steric effect. Interaction of the side chain and R_2 group may prevent the substituents and the ring from adopting a planar configuration, thereby hindering electron delocalization leading to effective charge neutralization. That is, there may be steric inhibition of resonance in the transition state and in the conjugate base.

We have studied a series of 2-substituted 3-methylbenzothiazolium ion model compounds I–V in order to obtain insight into the effects operating in the deprotonation reaction given in Scheme I. Starting with a 2-methyl substituent, the hydrogen atoms have been systematically replaced, first by a methyl and then by a hydroxy group, to yield 2-ethyl (II) and 2-hydroxymethyl (III) substrates. Next, two such substitutions give rise to 2-isopropyl (IV) and 2-(1-hydroxyethyl) (V) model compounds. We believe the effects of these replacements on rates of deprotonation provide considerable insight into the factors affecting reactivity of the enzyme cofactor not only in deprotonation but also in decarboxylation reactions as well.

Scheme I





I, R = CH_3
II, R = CH_2CH_3
III, R = CH_2OH
IV, R = $CH(CH_3)_2$
V, R = $CHOHCH_3$

Results

Hydrogen–deuterium exchange reactions were carried out at 75.0 °C in D_2O solution, generally using a formate buffer.

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Table I. Kinetic Results of Hydrogen–Deuterium Exchange at Position 2 of 2-Substituted 3-Methylbenzthiazolium Ions in Formic Acid Buffers (D_2O) at 75.0 °C and 1.0 M Ionic Strength

Compd	Registry no.	pD[a]	Total buffer, M	Obsd k_ψ, s^{-1}	Calcd[b] k_ψ, s^{-1}	k_B, M^{-1} s^{-1}	k^B_{rel}	$k^{D_2O}_{rel}$
I	40265-71-2	3.22	0.108	2.44×10^{-4}		1.50×10^{-2}		
						(1.62×10^{-2}[c])	1.0	1.0
II	46005-85-0	—	0.1 M DCl	4.18×10^{-5}		(7.73×10^{-6}[d])		
		3.14	0.108	2.56×10^{-4}	3.22×10^{-4}		1.46	1.58
		3.17	0.325	1.02×10^{-3}	9.40×10^{-4}	2.28×10^{-2}		
		3.25	0.0325	1.54×10^{-4}	1.47×10^{-4}			
III	46005-87-2	—	0.1 M DCl	1.34×10^{-5}		(2.48×10^{-7}[d])		
		3.17	0.325	5.09×10^{-4}	4.47×10^{-4}		0.71	0.51
		3.22	0.108	1.49×10^{-4}	1.73×10^{-4}	1.10×10^{-2}		
		3.25	0.0325	6.21×10^{-5}	6.42×10^{-5}			
IV	65102-07-0	—	0.1 M DCl	3.7×10^{-7}		(6.8×10^{-9}[d])		
		3.16	1.20	3.56×10^{-5}	3.30×10^{-5}			
		3.87	0.200	1.99×10^{-5}	1.90×10^{-5}		0.015	0.014
		3.89	0.200	1.56×10^{-5}	1.95×10^{-5}	2.28×10^{-4}		
		3.92	0.600	(3.85×10^{-5})				
V	65102-08-1	—	0.1 M DCl	7.5×10^{-7}		(1.4×10^{-8}[d])		
		3.16	1.20	6.56×10^{-5}	6.51×10^{-5}		0.029	0.028
		3.87	0.200	3.72×10^{-5}	3.76×10^{-5}	4.50×10^{-4}		
		3.92	0.595	(6.92×10^{-5})				

[a] Measured at 25 °C. [b] $[B]_{free} = [buffer]_{tot} \times K_a/([D] + K_a)$ where $pK_a = 4.03$. [c] Reference 6. [d] $k_\psi/[D_2O] = k_{D_2O}$.

Our extensive studies of the 2-methyl substrate have shown that in this buffer both D_2O and formate ion act as catalysts to deprotonate the methyl group; deuterioxide ion does not play an important role kinetically.[6] Therefore, it is assumed that only these two bases are effective with benzothiazolium ions II–V. The pseudo-first-order rate constant for isotope exchange, k_ψ, then is given by eq 1

$$k_\psi = k_{D_2O}[D_2O] + k_B[\text{formate}]_{tot} \times \frac{K_a}{[D] + K_a} \quad (1)$$

where k_{D_2O} and k_B are second-order rate constants for water and formate ions acting as general bases, K_a is the dissociation constant for formic acid ($pK_a = 4.03$), and $[\text{formate}]_{tot}$ is the total buffer concentration.[7]

Because the pK_a of formic acid changes only slightly with temperature[11] the pD of the reaction medium was measured at 25 °C instead of the 75 °C reaction temperature. As a check on this assumption, one kinetic run was carried out on the methyl substrate which we have already investigated extensively.[6] The second-order rate constant was calculated according to eq 1 using the pD measured at 25 °C and the value of k_{D_2O} obtained earlier.[6] The k_B values, Table I, are very similar; the one obtained using pD's determined at 75 °C is only 9.2% smaller than the one derived with pD values measured at 25 °C.

Kinetic data collected on the four other substrates are summarized in Table I. In each case a rate constant was obtained in the absence of any formate buffer; by using 0.1 M DCl the term k_{D_2O} was obtained. The k_B term representing formate ion catalysis then was derived from these results and eq 1. By comparing in Table I the observed and calculated values of k_ψ, the good agreement between these values becomes apparent. The average deviation is about 12% except in the case of V where it is less.

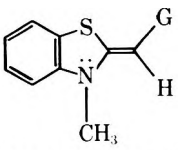
High buffer concentrations were employed with the two less reactive ions IV and V in order to obtain convenient rates. Interestingly, the results obtained for each ion in the presence of the highest free base concentration examined, 0.26 M formate ion, do not agree with those found at lower base concentrations. The first-order rate constants estimated with the aid of data from the other runs at lower formate ion concentrations are about 1.7 times as great as those observed. The deviant results were therefore not used in calculating a k_B value.

Buffer association needs to be considered as a possible reason for the low reactivity at high formate ion concentrations. Formic acid and formate ion from a complex; at 25 °C the association constant for this process is 0.25 M^{-1}.[12] If this value is applied to our data and no consideration is given to temperature differences and the fact that light and heavy water are involved, then it can be calculated that 8% of the formate ion appears as unreactive complex. This value which is likely to overestimate the true amount of complex at the higher temperature employed in our study is too small to provide an explanation of our deviations. Although there are a number of reasons for nonlinear buffer concentration–rate plots,[12] a likely explanation of our deviant data is found in salt effects.

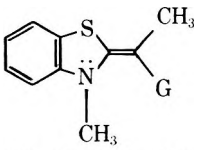
Discussion

Reactivity and Selectivity. The results in Table I in the form of relative rate constants, k_{rel}, using the reactivity of the 2-methyl substrate as a reference show that formate ion and water have very similar selectivities in deprotonating the carbon acids. Therefore in making comparisons an average of the relative reactivities for the pair of bases is considered. On this basis, the spread between the most and least reactive substrate is a factor of 105.

Relative rate constants show that introduction of a single substituent onto the 2-methyl group of the benzothiazolium ion does very little to reactivity. Methyl substitution to give II increases reactivity by about the same extent (50%) that hydroxy substitution to yield III decreases it (70%). The conjugate bases formed from these acids probably have *Z* configuration VI for steric reasons. The exocyclic double bond



VI, G = CH_3, OH



VII, G = CH_3, OH

in these conjugate bases is expected to be well developed. For example, the methylene protons of the base formed on deprotonation of I show nonequivalent NMR signals.[13] This is consistent with the presence of a substantial barrier to rotation.

Precise interpretations of how substituents influence re-

Table II. Elemental Analyses of 2-Substituted 3-Methylbenzothiazolium Perchlorates

Substituent	Mp, °C	% Calcd C	% Calcd H	% Calcd N	% Found C	% Found H	% Found N
C_2H_5	136–138	43.25	4.36	5.04	43.09	4.38	4.98
$(CH_3)_2CH$	141–142	45.28	4.84	4.80	45.14	4.88	4.74
CH_3CHOH	115–116	40.89	4.12	4.77	40.9[illegible]	4.15	4.83

activity in the case of II and III are difficult to make. If the transition state were highly pyramidal, then the hydroxy group would exert a large rate accelerating effect due to the electron withdrawing character of oxygen. A methyl group, however, would exert a marked rate retarding effect. Neither is observed. Therefore, in the transition state the carbon atom must lose p-orbital character in its σ bonds and begin to approach an sp^2 geometry. Electron–electron interactions associated with the carbon and oxygen centers coupled with a decrease in the strength of the carbon–oxygen bond oppose the inductive activation of the oxygen atom. The bond between the methyl substituent and the reactive carbon gets stronger as p-orbital character is removed from it; this beneficial change opposes the unfavorable inductive effect. Thus, it is possible to rationalize the small net result on reactivity of the two substituents in terms of these opposing effects. Of course, as the reactive bond acquires more p character, more negative charge is delocalized into the positively charged ring resulting in a more developed exocyclic double bond. The double bond when highly developed in the product will be stabilized by both the hydroxy and methyl groups.[14]

In contrast to the very small changes in rate constants resulting from introducing a single substituent onto the 2-methyl group, disubstitution produces much larger changes which are reductions in reactivity. Isopropyl and hydroxyethyl substrates are about 70 and 35 times less reactive, respectively, than reference acid I. The origin of this diminished reactivity can only be steric and reflects inhibition of resonance in the transition state.

A reversal in the relative reactivities of hydroxy substrate and its alkyl counterpart occurs at the levels of mono- and disubstitution. Thus, monosubstitution gives rise to a methyl derivative which is 2.6 times more reactive than the corresponding hydroxy cation, II vs. III. But with disubstituted substrates the methyl derivative is 0.51 times less reactive than its hydroxylated counterpart, IV vs. V. These same results may be considered in another way, in terms of the kinetic effects produced by introducing a methyl substituent. The reactivity of a hydroxy compound is decreased by a factor of 21 (III vs. V) while that of an alkyl ion is diminished by 105 (II vs. IV).

Two explanations seem relevant. First, steric compressions which dominate the reactivites of IV and V may be smaller in the hydroxylated material. The transition state leading to conjugate base may adopt a conformation which positions the smaller hydroxy substituent close to the *N*-methyl group, the site of the energetically unfavorable steric interaction. That is, *E* configuration VII is formed on deprotonation. The extent of the steric inhibition is thereby reduced and the resultant reactivity is greater. Second, and in addition to the first conformational factor, transition states for the two disubstituted compounds could be more pyramidal than those for the monosubstituted substrates. The more a transition state retains sp^3 geometry, the smaller will be steric repulsions which are greatest in the conjugate base where the side chain and ring attempt to become coplanar. Moreover, it is possible that in a pyramidal transition state the hydroxy group exerts an activating inductive effect which opposes and is larger than the destabilizing effect of the methyl group. It should be noted that considerable electron delocalization into a ring can take place from a pyramidal center.[15]

Support for our configurational assignment comes from another source. From an examination of molecular models in conjunction with studies on the decarboxylation of 2-(1-carboxy-1-hydroxyethyl)thiazolium ions, the suggestion was advanced that the enamine derivative will exist in a configuration which minimizes steric interactions,[16] i.e., the *E* configuration.

Significant information becomes apparent when the reactivities of formate ion and water are compared. Formate ion is more reactive than water by an almost constant factor of 3.4×10^4. This corresponds to a difference in free energies of activation of 7.2 kcal/mol. Results can be considered in quantitative terms in the form of a linear free energy relationship which compares the logarithms of the second-order rate constants for formate ion with those for water. This excellent relationship has a slope of 0.995 and a correlation coefficient of 0.998. The free energy relationship shows that steric effects are not dependent on the charge and identities of the two catalysts and must primarily be associated with interactions in the substrate and not between substrate and base.

In giving rise to conjugate base with an *E* configuration substrate must assume a particular conformation in the transition state. A hydroxyethyl reactant, for example, has the hydroxy group positioned close to the nitrogen atom of the thiazolium ion and the methyl substituent close to the sulfur atom so as to minimize steric compressions as product forms. However, this may not be the major conformer in the ground state. X-ray data on 2-(1-hydroxyethyl)thiazolium ions reveal that in the solid state the positions of the hydroxy and methyl groups are reversed to those for the transition state; i.e., the hydroxy group is close to the sulfur atom.[17] If this conformation is also the major one in solution, then proton transfer must proceed thorough a rotomer present as a minor component of the mixture of conformers.

Steric inhibition of resonance should also be kinetically important for deprotonation reactions in which other groups such as hydroxybenzyl[9] are bonded to thiazolium ion rings. Again, the configuration of the intermediate is expected to be *E* because the smaller hydroxy rather than the larger phenyl group is positioned close to the N substituent.

An explanation for an unsuccessful reaction in terms of a steric effect becomes apparent for a heretofore puzzling result. The *N*-benzyl derivative of thiamin serves almost equally as well as thiamin in acting as a catalyst for the nonenzymatic conversion of pyruvate ion to acetoin. However, the α-methylbenzyl derivative is inactive.[18] We suggest that the inactivity is associated with steric hindrance to the formation of the intermediate enamine. The α-methyl group prevents the ring and the side chain from becoming coplanar, thereby substantially reducing conjugation between the two portions.

In view of the constant steric effect toward two bases of very different reactivities in the case of the 2-(1-hydroxyethyl)-benzothizolium ion model compound we make this suggestion: steric hindrance of similar magnitude will be observed in the reactions of 2-(1-hydroxyethyl)thiamin. This steric inhibition of deprotonation will be observed in purely chemical systems involving the substituted enzyme cofactor and in enzyme catalyzed reactions as well, unless the enzyme constrains the intermediate to adopt a pyramidal form. Similar steric in-

teractions will also be present when the intermediate enamine is formed by decarboxylation.

Experimental Section

The reagents and instrumentation employed in this study are listed in the accompanying paper.[6]

Preparation of 2-Substituted 3-Methylbenzothiazolium Salts. 2-Substituted benzothiazoles[19] were made by heating *o*-aminobenzenethiol with an equivalent amount of the appropriate carboxylic acid or acid anhydride in a bomb at temperatures ranging from 120 to 165 °C.[20] They were quaternized with methyl iodide.[21] The 2-hydroxymethyl iodide was used as such, mp 227–228 °C (lit.[20] mp 219 °C), but the others were converted to perchlorates. Perchlorate salts were prepared either by dissolving the iodides in a warm saturated solution of magnesium perchlorate in absolute ethanol or by dissolving in a mixture of ethyl acetate, absolute ethanol, and 70% perchloric acid (36:8:5 by volume). Perchlorate salts crystallized on cooling and were recrystallized from ethanol. Melting points and analyses were recorded in Table II. Analyses were made by Atlantic Microlab, Inc. Chemical shifts (τ, D_2O) of *N*-methyl, *C*-methyl, and CH protons observed during kinetic runs are: C_2H_5, 5.74, 8.36, and 6.45; $(CH_3)_2CH$, 5.69, 8.37, and 6.00; CH_2OH, 5.78 and 4.55; CH_3CHOH, 5.69, 8.23, and 4.18, respectively.

Kinetics of Hydrogen–Deuterium Exchange. Details are similar to those in the accompanying article.[6] Stock solutions of formic acid and sodium formate were employed. Ionic strength was maintained at 1 M using KCl (with iodides) or NaCl (with perchlorate salts). Reactions were followed for 2–3 half-lives except for the slowest runs involving 0.1 M DCl where only 1 half-life was observed. In addition to substrates being examined separately, a run was also made on a pair of substrates with similar reactivities in the same mixture.

Following a kinetic run pD measurements were made at 25.0 °C on both heated and unheated reaction mixtures. Differences were of the order 0.03 except in the case of two runs with IV at the lowest buffer concentrations: one of these also contained hydroxyethyl compound. Curiously, in these cases the difference in pD was 0.12; the pD of the unheated sample was recorded. This makes the free base concentration uncertain by about 15%. A pH reading was converted to pD by adding 0.40.[22]

Control Studies to Determine the Stabilities of Substrates. Each compound was heated in formate buffer in H_2O for a period corresponding to 10–20 half-lives for isotope exchange. No decomposition was detected by NMR; pH differences between heated and unheated samples were no greater than 0.03.

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Kinetics and Mechanism of the Deamination of 1-Methyl-5,6-dihydrocytosine

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Kinetic studies of the deamination of 1-methyl-5,6-dihydrocytosine (MDC) have been carried out in acidic and basic aqueous solutions at 37 °C, μ = 1.0 (ionic strength). General-base catalysis was observed under acidic but not basic conditions. The Brønsted relationship for this reaction showed β = 0.19. No dependence on hydroxide ion concentration was demonstrable under alkaline conditions. Activation enthalpies and entropies were measured for this reaction in the absence of general catalysts in acidic and basic media for the range 20–47 °C. Direct hydroxide ion attack on the protonated substrate is a plausible mechanism for the reaction in alkaline media. An alternative mechanism involving participation of water as a proton-transfer agent in the transition state with either formation or reaction of the tetrahedral intermediate as the rate-determining step is also consistent with all of the kinetic data.

The deamination of cytosine to uracil by bisulfite[1,2] has been applied widely, as a synthetic method in nucleoside chemistry and as a tool for the modification of nucleic acids.[3] Mutations are induced in bacteria and viruses upon treating them with high concentrations of bisulfite and acidic pH.[4] The mutagenic specificity observed indicates that the mutations are caused by cytosine deamination within DNA.[4] The possibility exists that environmental bisulfite and sulfur dioxide may constitute a mutagenic hazard[5] to the general public. To evaluate this hazard, it is necessary to be able to extrapolate deamination rates to low bisulfite concentrations at neutral pH.

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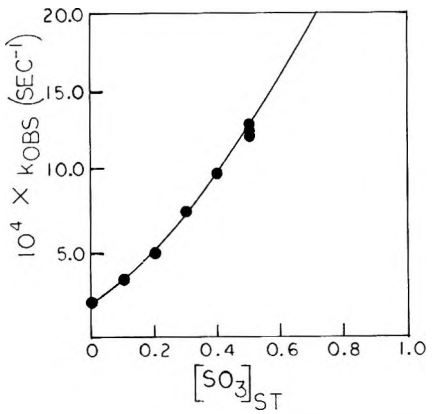
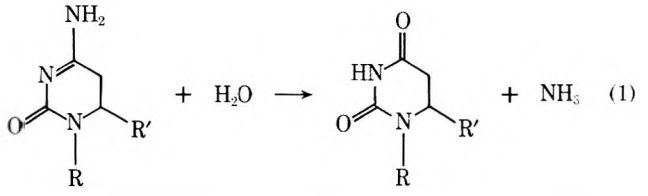


Figure 1. Deamination of MDC, 37 °C, μ = 1.0, pH 4.40. Dependence of observed rate constant on stoichiometric sulfite concentration. Curvature due to varying pyrosulfite ion catalysis.

A number of aspects of the deamination mechanisms have been explored.[6,7] A remaining point of uncertainty has been the nature of the buffer catalysis involved in the deamination of the dihydrocytosine intermediate in the reaction scheme (**1a** → **2a**).



1a, R = β-D-ribofuranosyl; R′ = SO_3^-
b, R = CH_3, R′ = H

2a, R = β-D-ribofuranosyl; R′ = SO_3^-
b, R = CH_3; R′ = H

In order to explore the mechanism of this reaction without the complications arising from the possible loss of bisulfite with **1a** and **2a**, we have conducted a detailed study of the deamination of a model compound, 1-methyl-5,6-dihydrocytosine. Preliminary observations on this system were reported earlier.[7,8]

Results

Kinetics of the Deamination of MDC in Acidic Media. The kinetics of the deamination of 1-methyl-5,6-dihydrocytosine, MDC, to 1-methyl-5,6-dihydrouracil (**1b** → **2b**) at 37 °C, μ = 1.0, were measured in the presence of 0.5 M HCl and appropriate buffers (pH range 4.40–7.52). In this range from 8 to 100% of the substrate (pK_a = 6.40 ± 0.03) is protonated. Excellent first-order kinetic plots were obtained and this reaction was found to be subject to general base catalysis. The catalytic coefficients were measured for a series of nine bases. Corrections were made for the mole fraction of substrate protonated in accordance with eq 4 since the neutral substrate demonstrated no general base catalysis.

$$d[P]/dT = k[HSub^+][B] = k\chi_{HSub^+}[Sub]_{ST}[B] \quad (2)^9$$

$$\frac{1}{[Sub]_{ST}}\frac{d[P]}{dt} = k\chi_{HSub^+}[B] = k_{obsd} \quad (3)$$

$$\frac{k_{obsd}}{[B]\chi_{HSub^+}} = \frac{k'_{obsd}}{\chi_{HSub^+}} = k \quad (4)$$

For sulfate ion, acetate ion, Tris, and imidazole, the catalytic coefficient, $k_{obsd}/[B]$, was obtained directly from the slope of a plot of k_{obsd} against [B]. This procedure was followed for a series of buffered solutions of varying base concentration at constant pH and ionic strength. In the case of the sulfite and phosphate buffers, more than one catalytic species is present,

Table I. Sulfite Catalyzed Deamination of MDC, 37 °C, μ = 1.0 M

pH	χ_{HSub^+}[a]	$10^3 \times k_{obsd}/\chi_{HSub^+}$, M^{-1} s^{-1}	$10^3 \times k_{calcd}$,[c] M^{-1} s^{-1}
4.40	0.990	1.455[b]	1.43
5.00	0.962	1.44[b]	1.48
5.40	0.909	1.46[b]	1.575
6.00	0.715	1.945	1.88
7.30	0.112	3.25	3.52
7.45	0.0814	3.88	3.615

[a] χ indicates mole fraction. [b] k_{obsd} from slope determination based on lowest two concentrations of $(SO_3)_{ST}$ at this pH as explained in the text. [c] k_{calcd} based on $k_{HSO_3^-}$ = 1.41 × 10^{-3} M^{-1} s^{-1}, $k_{SO_3^{2-}}$ = 3.90 × 10^{-3} M^{-1} s^{-1}, and calculated values of χ_{HSub^+}, $\chi_{HSO_3^-}$, $\chi_{SO_3^{2-}}$ at each pH.

and the resulting overall rate effect of any stoichiometric concentration is due to the contribution of several bases. Separation of the total catalytic effect of each "phosphate" solution into the component rates due to monohydrogen phosphate and dihydrogen phosphate ions was achieved according to

$$\frac{k_{obsd}}{[PO_4]\chi_{HSub^+}} = \frac{k'_{obsd}}{\chi_{Sub^+}} = k = k_{HPO_4^{2-}}\chi_{HPO_4^{2-}} + k_{H_2PO_4^-}\chi_{H_2PO_4^-} \quad (5)$$

k is measured at two different pH values and $\chi_{HPO_4^{2-}}$ and $\chi_{H_2PO_4^-}$ are calculated from the known pK_a for $H_2PO_4^-$ for these conditions. The two simultaneous equations are solved for the two unknowns, $k_{HPO_4^{2-}}$ and $k_{H_2PO_4^-}$.

The above treatment proved unsuccessful in the case of sulfite ion. Sulfite ion buffers in the pH region 4.40 to 6.00 contain more than two catalyzing species. Spectrophotometric studies of acidified aqueous solutions of sulfite ion revealed the presence of pyrosulfite ion (λ_{max} 255 nm, ϵ = 1.98 × 10^3 M^{-1}) in accordance with the equilibrium $2HSO_3^- \rightleftarrows S_2O_5^{2-} + H_2O$, $K_{eq} = [S_2O_5^{2-}]/[HSO_3^-]^2$. The value of K_{eq} was measured spectrophotometrically to be (2.16 ± 0.08) × 10^{-1} M^{-1} at 37 °C, μ = 1.0. This compares well with a literature value[10] of 2.20 × 10^{-1} M^{-1}, 25 °C, μ = 0.9. As the concentration of pyrosulfite ion depends on the square of the concentration of bisulfite ion, its mole fraction, and therefore its relative catalytic effect, vary with bisulfite ion concentration, even at constant pH. This perturbing effect of pyrosulfite ion on the kinetics of this reaction gives rise to curvilinear plots when the observed rate constant is plotted against the stoichiometric sulfite ion concentration (Figure 1). The slopes of these plots increase with increasing stoichiometric sulfite concentration as expected.[11]

To simplify the situation, the sulfite rate data were treated in the following manner: The slopes of k_{obsd} against stoichiometric sulfite concentration (as defined by the two points of lowest concentration) were measured and used to estimate the effective rate contribution of bisulfite and sulfite ions alone. When these values of k'_{obsd}/χ_{HSub^+} were then treated in the same manner as the data for phosphate ion, the resulting rate constants for sulfite and bisulfite ions showed excellent agreement with the experimental rate slopes at six different pH values, as shown in Table I.

When the catalytic effects of sulfite and bisulfite ions were subtracted from the overall reaction rate observed at the more concentrated stoichiometric sulfite solutions in the pH 4.40, 5.00, and 5.40 buffers, the enhancement of reaction rate due to pyrosulfite ion was obtained. This rate informaton was combined with the calculated pyrosulfite ion concentration and the mole fraction of protonated substrate for the above conditions to permit calculation of the catalytic coefficient

Table II. Pyrosulfite Ion Catalyzed Deamination of MDC, 37 °C, μ = 1.0 M

pH	χ_{HSub^+}	$10^3 \times k_{obsd}$, s^{-1}	$10^3 \times k^a_{sulfite}$, s^{-1}	$[S_2O_5^{2-}]^b$	$10^3 \times (k_{obsd} - k_{sulfite})/\chi_{HSub^+}[S_2O_5^{2-}]$, $M^{-1} s^{-1}$
4.40[c]	0.990	1.27	0.89	0.050	7.68
5.00[d]	0.962	1.42	0.94	0.050	9.88
5.40[e]	0.909	2.11	1.42	0.040	9.52

[a] $k_{sulfite}$ is the expected catalytic effect of sulfite and bisulfite ions alone for this stoichiometric sulfite concentration. [b] Calculated from $[S_2O_5^{2-}] = 0.216[HSO_3^-]^2$ at this stoichiometric sulfite concentration. [c] $[SO_3]_{ST}$ = 0.50 M. [d] $[SO_3]_{ST}$ = 0.50 M. [e] $[SO_3]_{ST}$ = 0.685.

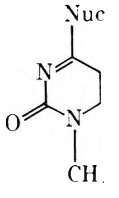
Table III. Base Catalysis of the Deamination of MDC, 37 °C, μ = 1.0 M

Base	pK_a[a]	$[B]_{ST}$, mol	pH	$10^3 \times k'_{obsd}/\chi^b_{HSub^+}$, $M^{-1} s^{-1}$
SO_4^{2-}	1.16	0.1–0.3	4.40	0.183 ± 0.009
HSO_3^-	1.47	0.1–0.7	4.40–7.45	1.41[d]
$H_2PO_4^-$	1.70	0.2–0.75	4.98–5.33	0.423[d]
$S_2O_5^{2-}$	?	0.1–0.7	4.40–5.40	9.0 ± 1.2[d]
$CH_3CO_2^-$	4.60	0.2–1.0	5.05	0.299 ± 0.027
HPO_4^{2-}	6.31	0.2–0.75	4.98–5.33	2.18[d]
SO_3^{2-}	6.55[c]	0.2–0.7	4.40–7.45	3.90[d]
Imidazole	6.92	0.1–0.8	5.40	1.50 ± 0.28
Tris	8.24	0.05–0.3	6.58–7.52	1.76 ± 0.33

[a] pK_a for these conditions as determined from the best values or estimates from 33–39. [b] χ denotes mole fraction. [c] Measured in this work. [d] Correction for χ_{HSub^+} included in calculation of k_{obsd} as explained in the text.

of pyrosulfite ion for MDC deamination (Table II). The resulting value of $k_{S_2O_5^{2-}} = (9.0 \pm 1.2) \times 10^{-3}\ M^{-1} s^{-1}$ indicates the large catalytic effect of pyrosulfite ion. Although pyrosulfite ion is a weaker base than sulfite ion,[12] it is a stronger catalyst in this reaction:[13] $(k/q)_{S_2O_5^{2-}}/(k/q)_{SO_3^{2-}} = 1.4$.

The catalytic coefficients for all nine bases studied are summarized in Table III. Bisulfite ion demonstrates a large positive deviation from the Brønsted relation[13] defined by the other bases (Figure 2)[14] and the best Brønsted relation defined by the other bases gives $\log (k/q) = (0.19 \pm 0.03)(pK_a + \log p/q) - (4.31 \pm 1.9)$. A comparison of the relative rate constants of imidazole and biphosphate ion, $(k/q)_{IM}/(k/q)_{HPO_4^{2-}} = 2.06$, shows clearly that nucleophilic catalysis, which is characterized by large rations of imidazole to biphosphate rate constants[16] (1000:1), is not present in this system; therefore, nu-



cleophilic attack by general bases to form an intermediate, which undergoes subsequent rapid hydrolysis to form the final product, can be excluded from this mechanism.

The Kinetics of the Deamination of MDC in Basic Media. For MDC deamination of studies at 37 °C, μ = 1.0 in the pH range 8.55–8.95, the extent of protonation of the substrate is approximately 0.3–0.9%. When the catalytic coefficients for general bases present and water are taken into account, it becomes apparent that less than 1% of the observed rate (Table IV) is due to the reaction path observed in acid.

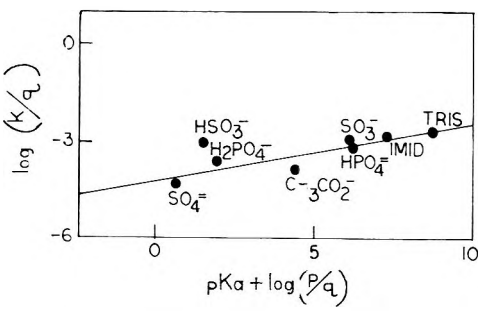


Figure 2. Brønsted relationship for base-catalyzed MDC deamination, 37 °C, μ = 1.0, acidic conditions. Based on Table III.

Table IV. Deamination of MDC in Basic Media, Presence of General Bases, μ = 1.0 M, 37 °C

pH	Base	Concn range, mol	$10^5 \times k_{obsd}$, s^{-1}
8.55	Tris	0.1–0.6	6.39 ± 0.30
	SO_3^{2-} [a]	0.05–0.10	6.40 ± 0.38
8.95	Tris	0.2–0.4	6.59 ± 0.13
	SO_3^{2-} [a]	0.1	6.55
	Imidazole[a]	0.1–0.6	5.88 ± 0.27

[a] In the presence of 0.2 M Tris.

Table V. Rate Constants for the Deamination of MDC in Acidic and Basic Media at Various Temperatures, μ = 1.0 M

Temp, °C	$10^5 \times k_{obsd}$, s^{-1} pH 8.55–8.95[a]	$10^5 \times k_{obsd}$, s^{-1} pH 0.4[b]
20.0	1.10	1.81 ± 0.09
37.0	6.49 ± 0.1	14.1 ± 0.5
47.0	13.7 ± 0.5	36.6 ± 1.5

[a] In the presence of 0.2–0.4 M Tris. [b] In the presence of 0.4 M HCl.

The kinetic results clearly show that (within experimental error) the observed deamination rate is insensitive both to the pH of the medium and the presence and concentration of added bases such as imidazole, Tris, and sulfite ion. The neutral substrate therefore suffers neither specific nor general base catalysis upon deamination in alkaline media. The possibility of a reaction of the protonated substrate with hydroxide ion will be considered subsequently.

Activation Parameters. Measurement of MDC deamination rate constants in acidic and basic media at several temperatures (Table V, Figure 3) allowed the calculation of activation parameters for these reactions. These were found to be: $\Delta H^{\ddagger} = 20.7 \pm 0.8$ kcal/mol, $\Delta S^{\ddagger} = -11.0 \pm 2.6$ eu for the reaction of protonated MDC in acidic media, and $\Delta H^{\ddagger} = 17.0 \pm 1.1$ kcal/mol, $\Delta S^{\ddagger} = -23.2 \pm 3.6$ eu for the neutral substrate in basic media. It appears that the relative speed of the reaction in acidic media is due to the compensation by a favorable activation entropy for an unfavorable enthalpy.

The Reaction with Water. The measured rate constants for the reactions of protonated and neutral substrates with water can be used to calculate the expected reaction rate at zero buffer concentration for a series of rate studies at various pH values according to the formula,

$$k_{obsd}^{intercept} = k_{HSub^+}\chi_{HSub^+} + k_{Sub}\chi_{Sub}$$

where $k_{HSub^+} = 1.41 \times 10^{-4}\ s^{-1}$ and $k_{Sub} = 6.49 \times 10^{-5}\ s^{-1}$ at 37 °C, μ = 1.0. A comparison of the calculated and observed values of these rate constants is presented in Figure 4. The observed reaction rates are well described by this relationship.

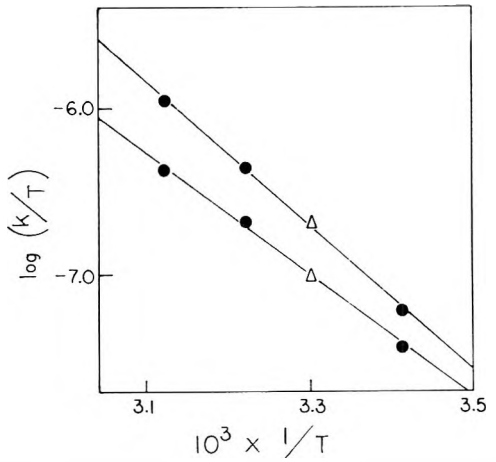


Figure 3. Dependence of background deamination rate constant on temperature for MDC, μ = 1.0, acidic and basic conditions: (●) data from this work; (△) data from ref 7.

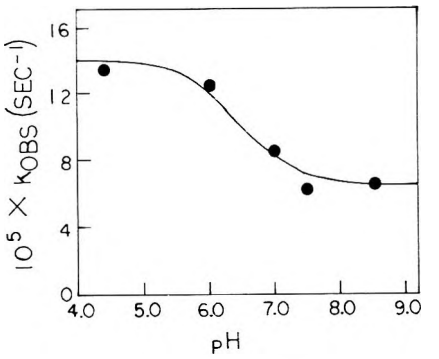
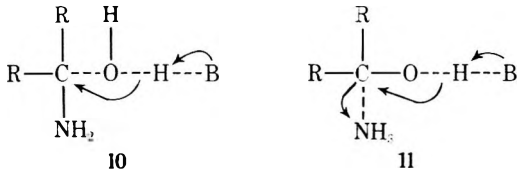


Figure 4. pH dependence of the observed intercepts of general base catalyzed MDC deamination, 37 °C, μ = 1.0. The points represent experimental determinations. The curve was calculated according to the equation, $k_{obsd} = 1.41 \times 10^{-4}$ (s^{-1}) $\chi_{HSub^+} + 6.49 \times 10^{-5}$ (s^{-1})χ_{Sub} as explained in the text.

Discussion

Mechanism of MDC Deamination. Acidic Conditions. The dependence of the MDC deamination rate on the concentration of the protonated substrate, [HSub⁺], the presence of general base catalysis reported here, and the absence of general acid catalysis reported previously[7] are consistent with the mechanism presented in Scheme I: **3** → **4** → **6** → **7** → **8** where either tetrahedral intermediate formation, **4** → **6**, or reaction, **7** → **8**, may be rate determining. The general base would be present in either transition state **10** or **11**.



10 **11**

Mechanism of MDC Deamination. Basic Conditions. The mechanism for MDC deamination in basic conditions must explain the following facts: (1) the reaction rate is pH independent in the range studied, 8.5–9.0; (2) no general base catalysis is observed; (3) the activation entropy is negative and large.

Several reaction mechanisms need to be considered in analyzing the reaction in basic media. Intermediate formation, if rate determining, could occur in two ways. In mechanism A, direct nucleophilic attack of hydroxide ion on the protonated substrate forms the reaction intermediates (Scheme I: **3** → **4** → **6** → **8** where **4** → **6**, OH^- is slow), while in mechanism B, attack by water occurs on the neutral substrate without base assistance (Scheme I: **3** → **6** → **8**, where **3** → **6** is slow). Rate-determining product formation from the intermediate is another possible mechanism that is consistent with the kinetic results (Scheme I: **6** → **8**, slow), as in mechanism C. Since all three mechanisms yield the same rate law, which can be shown by the steady state approximation to be of the form,

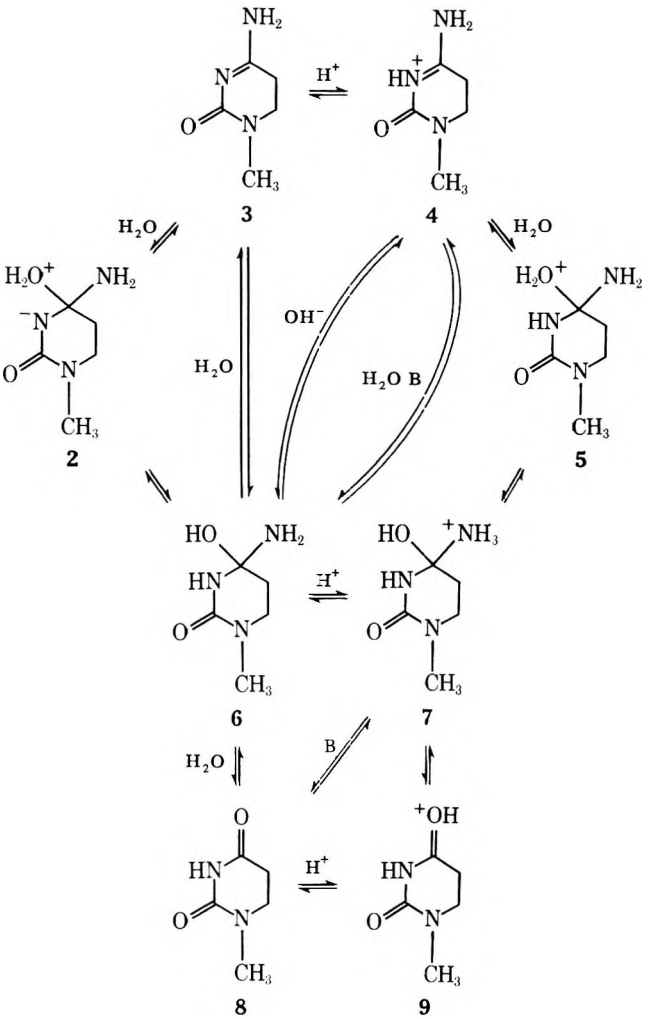
$$k_{obsd} = \frac{1}{[Sub]_{ST}} \frac{d[P]}{dT} = kK\chi_{Sub}$$

they all predict lack of rate dependence on base concentration.

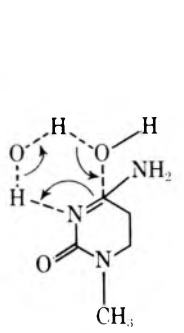
The catalytic properties of this reaction are consistent with all three suggested mechanisms. The change from general base catalysis of the deamination reaction in acidic media to no base dependence in basic media can be understood as arising from a change in mechanism from base-assisted reaction of the protonated substrate with water in acidic media to nucleophilic attack of hydroxide ion on the protonated substrate in basic media. This change is due to the large increase in [OH^-]. The base-catalyzed reaction with water decreases with decreasing χ_{HSub^+} during this change in conditions and becomes kinetically less favorable with respect to mechanism A under basic conditions.

If the transition state of mechanisms B and C involved the participation of a second water molecule functioning as a proton-transfer agent, then the catalytic change from acidic

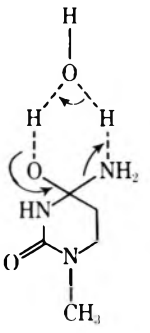
Scheme I. Mechanism of MDC Deamination in Aqueous Solutions



to basic media may be explained in the following manner. If the formation of the intermediate is rate determining as in mechanism B, then the assistance of this second water molecule in the transition state **12** would remove the need for base



12



13

catalysis. A similar explanation can be used for mechanism C, where the reaction of the intermediate is rate determining, as in the transition state of structure **13**. The uncatalyzed reaction of water with the neutral substrate becomes faster than the base-catalyzed water reaction of the protonated substrate as the reaction conditions become basic, since the χ_{HSub^+} decreases markedly during this transition.

The mechanism discussed here must also be examined in connection with the observed reaction activation entropy, −23 eu. This negative and large entropy is consistent with each of the above mechanisms. For mechanism B, a large, negative $\Delta S^{\ddagger}$ is expected, due to the participation of the proton-transfer water molecule in the transition state. Thus, three molecules (Sub + $2H_2O$) go to one moiety in the transition state and there is a loss of translational freedom of motion for two molecules. In addition, there is a generation of scattered partial charges at various polar centers in a highly structured and concerted transition state. These factors are all expected to produce a more negative entropy.[17] The participation of water as a proton-transfer agent in the transition state of mechanism C would also be consistent with the observed $\Delta S^{\ddagger}$.

Bell et al.[18,19] have found in their studies of the hydration of 1,3-dichloroacetone in aqueous acetone mixtures that the activation entropy of the reaction depended on the number of water molecules participating in the transition state. Based on the kinetic order with respect to water, and kinetic isotope effects, it was determined that in addition to the reacting water molecule, extra water molecule(s) are contained in the transition state for the reaction in the absence of general acid catalysts. The transition state for the benzoic acid catalyzed hydration reaction contained one less extra water molecule. This finding was supported by the activation parameters which showed the acid-catalyzed reaction having higher activation enthalpies ($\delta\Delta H^{\ddagger}$ = 3.83 kcal/mol) and entropies ($\delta\Delta S^{\ddagger}$ = 17.6 eu)[20] than the uncatalyzed reaction with water. This compares with MDC deamination where the base catalyzed reaction in acidic media has higher activation parameters ($\delta\Delta H^{\ddagger}$ = 3.7 kcal/mol, $\delta\Delta S^{\ddagger}$ = 12 eu) than the uncatalyzed reaction in basic media. Thus, the results reported here can similarly be explained by the involvement of an additional water molecule in the transition state for the reaction in basic media (**12**, **13**) in place of the general base present in the transition state for MDC deamination in acidic media (**10**, **11**).

On the basis of the experimental $\Delta S^{\ddagger}$, one might be tempted to exclude mechanism A which involves a transition state of much greater charge dispersion than the ground state and, therefore, a predicted activation entropy closer to zero. However, kinetic studies of related systems such as Schiff bases[21a] have demonstrated activation entropies of −30 eu for reactions proceeding through a nucleophilic attack by hydroxide on the protonated substrate (imine) in basic media.

Bisulfite Ion Catalysis in Deamination Reactions. Our results demonstrate that bisulfite ion is not exceptionally stronger than other catalysts in the deamination of 1-methyldihydrocytosine. It is effective as a general base catalyst for deamination of the protonated substrate, but many other buffers also catalyze the reaction. There is no buffer catalysis for the deamination of the unprotonated substrate. If the above mechanisms also hold for the deamination of dihydrocytosine **1a** to **2a**, then bisulfite plays no unique role in that deamination either. The important role for bisulfite in the conversion of cytosine to uracil is the formation of the adduct **1a** from cytosine. If one were extrapolating to low bisulfite concentrations in calculating cytosine deamination rates, and if a constant concentration of another buffer effective in catalyzing the deamination step were present, one would then expect the deamination rate to fall in direct proportion to the bisulfite concentration (rather than to the square of the concentration).

Amidine Hydrolysis. The mechanistic considerations presented here are fully consistent with kinetic studies of related amidines. Deamination rates of MDC, 1,3-dimethyl-5,6-dihydrocytosine (DDC), and 1-cyclohexyl-*N*(4)-dimethyl-5,6-dihydrocytosine (CDDC) were previously measured[8] in acidic and basic media at 20 °C, μ = 0.01, and the pK_a and observed deamination rate constants in acidic and basic media for these compounds respectively were: for MDC 6.62, 2.78×10^{-5} s^{-1}, 8.35×10^{-6} s^{-1}; for DDC 8.05, 2.50×10^{-5} s^{-1}, 9.73×10^{-5} s^{-1}; for CDDC 6.40, 2.78×10^{-5} s^{-1}, 8.35×10^{-6} s^{-1}. Although MDC deaminates at a slower rate in basic than acid media under these conditions, DDC exhibits a rate enhancement by a factor of almost 4 as the pH is raised from 7 to 9, after which the rate remains constant. This compound, which for structural reasons must deaminate by a mechanism not involving the water-bridged transition state, structure **5**, may demonstrate a nucleophilic hydroxide ion attack on protonated substrate, similar to mechanism A, thereby accounting for rate acceleration in basic media. Alternatively, the different pH profiles can be attributed to the variation in pK_a of the substrates.[21b,c]

Deamination studies of the photohydrate of 3′-cytidylic acid, a closely related compound,[22] are also consistent with the results reported here for MDC. The pK_a was measured to be 5.56 at 0 °C, μ = 0.05. Deamination rate constants demonstrated a pH dependence resembling that of Figure 4. There was a decrease in rate constant by a factor of 2.5 on going from pH 4.0 to pH 8.0. The activation parameters which can be derived from the original rate data are $\Delta H^{\ddagger}$ = 16.2 ± 0.1 kcal/mol, $\Delta S^{\ddagger}$ = −19.4 ± 1 eu (pH 4.0) and $\Delta H^{\ddagger}$ = 17.3 ± 0.1 kcal/mol, $\Delta S^{\ddagger}$ = −15.5 ± 1 eu (pH 8.0). No general base catalysis was observed for the deamination reaction under basic conditions.

Diarylformamidine hydrolysis has been studied under acidic and basic conditions in 20% aqueous dioxane mixtures.[23,24] It was found that, in acidic media, the reaction demonstrated general base catalysis (β = 0.29), electron withdrawing groups accelerate the reaction rate (ρ = 3.78 at 40 °C), and the activation entropy was −22 ± 3 eu. The reaction rate in concentrated solutions of strong acids varied directly with hydronium ion concentration and water activity and inversely with h_0. It was suggested that a general base and at least two molecules of water are present in the transition state.

Similar rate results were obtained for diarylacetamidine hydrolysis in 20% aqueous dioxane. Since diarylacetamidines are 1000–2500 times slower in this reaction than diarylformamidines (due to an increase of 4.5 kcal/mol in $\Delta H^{\ddagger}$), it was reasoned that nucleophilic attack of water on the pro-

tonated substrate was most likely to be the rate-determining step.

Extensive hydrolysis studies have been made on the amidines 1,3-diphenyl-2-imidazolinium chloride (DPIC)[25] and $N^{5,10}$-methenyltetrahydrofolic acid (MTF).[24] Brønsted correlations for the reaction pathways first order in base and second order in base were measured at 25 °C, μ = 1.0, in the pH range 7–11. It was argued that the reaction mechanism involved rate-determining reaction of the tetrahedral intermediate. Direct spectral evidence for the existence of the tetrahedral intermediate in this reaction was obtained at pH 12.[26] In the case of MTF at high buffer concentrations, the formation of the tetrahedral intermediate became rate determining.

In conclusion, it can be said that amidine hydrolysis occurs through a sequence of steps closely balanced in individual rate constants so that the identity of the rate-determining step is highly dependent on substituents, pH, and the presence of general bases.

Experimental Section

Materials. 1-Methyl-5,6-dihydrocytosine (MDC) was synthesized by the method of Chang and Lewis.[27] Sigma Trizma base and Trizma HCl were used in the preparation of solutions of Tris(hydroxymethyl)aminomethane, (Tris). Aldrich Reagent grade imidazole was recrystallized three times from benzene before use (mp 88.5–89.0 °C, lit. mp 90–1 °C). All other materials were commercially available reagent grade and were used as supplied. Water used in kinetic and equilibrium measured was double distilled in Pyrex vessels and degassed with nitrogen.

Apparatus. Measurements of pH were made on a Radiometer Model 22 pH meter equipped with a glass electrode. Potentiometric titrations were performed on a Radiometer assembly, including Titrator II, Autoburette ABU 12, pH meter 26, and Titrigraph SBR 2C, having a constant temperature bath jacketing the titration vessel. Ultraviolet absorbance measurements were recorded on a Cary 15 recording spectrophotometer.

Kinetics of the Deamination of 1-Methyl-5,6-dihydrocytosine (MDC). Reaction mixtures were kept in the Cary 15 spectrophotometer thermostated cell compartment, and the variation of ultraviolet absorbance at 245 nm was recorded as a function of time. Reduced path lengths of 0.1 to 0.3 mm were employed when appropriate. Temperatures were measured with a thermometer calibrated by the National Bureau of Standards and were stable to within ±0.1 °C. The slope of the plot of ln (OD − OD_∞) vs. time was analyzed by the method of least squares on a Hewlett Packard 3000 computer. Catalytic coefficients of general bases were obtained by rate measurements in aqueous buffers of varying catalyst concentration and constant pH and ionic strength. When aqueous solutions of bisulfite ion were used, 10^{-3} M hydroquinone was present as a radical inhibitor.

Determination of the pK_a of MDC and Bisulfite Ion. The pK_a values for the dissociation of MDC were determined to be 6.40 ± 0.03 (potentiometric titration) and 6.49 ± 0.02 (spectroscopic method) at 37 °C, μ = 1.0, and the first value was considered to be less subject to errors and used in subsequent calculations. The pK_a for bisulfite ion dissociation was measured potentiometrically to be 6.55 under the same conditions.

Determination of the K_{eq} for Pyrosulfite Ion Formation. The equilibrium constant, K_{eq}, for pyrosulfite ion formation from bisulfite ion in acidic media was measured spectrophotometrically to be (2.16 ± 0.08) × 10^{-1} M^{-1} at 37 °C, μ = 1.0, where $K_{eq} = [S_2O_5^{2-}]/[HSO_3^-]^2$. This was based on a value of $\epsilon = 1.98 \times 10^{-3}$ M^{-1} cm^{-1}, λ_{max} 255 nm.[10] The value reported here compares well with 2.2×10^{-1} M^{-1} at 25 °C μ = 0.9, based on this value of ϵ.[10,23] This constant is known to be very dependent on ionic strength, changing from 0.076 (μ = 0) to 0.34 (μ = 2.0) at 25 °C.[10]

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Registry No.—MDC, 696-10-6.

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(9) d[P]/dT represents the rate of product formation; χ represents the mole fraction of a given species of the overall stoichiometric mixture of related materials, e.g., χ_{HSub^+} represents the mole fraction of protonated substrate; ST denotes stoichiometric; Sub denotes substrate; k_{obsd} is the observed rate constant; and k_{calcd} is the calculated rate constant as described in the text.
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(11) Previously reported data[7] for sulfite ion catalyzed deamination of MDC, 30 °C, μ = 1.0, pH 4.4, 5.0, needs to be corrected for pyrosulfite catalysis under these conditions.
(12) $HS_2O_5^-$ is completely dissociated under conditions where HSO_3^- is only partially ionized.[10]
(13) k is the rate constant and q and p are respectively the statistical correction for the number of basic sites in the catalyst and acidic sites in the conjugate acid. See, for example, W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969.
(14) In a kinetic study of the general base-catalyzed deamination of the related amidine, 1,3-diphenyl-2-imidazolinium chloride,[15] it was found that HPO_4^{2-} had an exalted catalytic effect due to a possible bifunctional acid–base catalytic role. This special effect may explain bisulfite ion's enhanced catalytic properties here as well as those of pyrosulfite ion.
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(20) Since the values reported here indicated a decreasing $\Delta S^{\ddagger}$ with increasing mole fraction of water,[18] a value of $\delta\Delta S^{\ddagger}$ less than 17.6 eu would be expected for one mole fraction of water.
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(28) Calculated values of K_{eq} are subject to uncertainties in ϵ since the pyrosulfite concentration is calculated from the observed absorbance by the expression [pyrosulfite] = ($OD_{pyrosulfite}/\epsilon_{pyrosulfite}$). For example, had an alternative value of $\epsilon = 4 \times 10^3$ been used,[28] the calculated K_{eq} would have been (1.07 ± 0.04) × 10^{-1} M^{-1}. Values of ϵ and K reported earlier[29–32] have been criticized[10] and the best available value was used here.
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An Approach to the Synthesis of *F*-Tertiary Amines

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F-tertiary amines, industrially important fluids and biomedically important potential artificial blood candidates, can be prepared in high yields as sole products by treating >NCO– containing fluorinated precursors with SF_4/HF at moderate temperatures. Thus the amide $C_7F_{15}CON(CF_3)_2$ and cyclic imide $C_6F_5N(COCF_2)_2CF_2$ are completely converted to the amines $C_8F_{17}N(CF_3)_2$ and $C_6F_5N(CF_2CF_2)_2CF_2$ in 78 and 86% isolated yields, respectively, under appropriate reaction conditions. The consequence of structural variation on yield, reaction rate, and products is discussed.

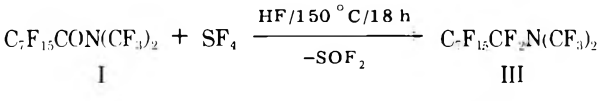
F-Tertiary amines are commercially important[1] as evaporation coolants, hydraulic fluids, and dielectric fluids for transformers. Recent attention has been focused on fluorocarbons in biomedical applications as potential anesthetics,[2] and in particular *F*-tertiary amines as potential fluid oxygen/CO_2 transport agents in artificial blood.[3]

The titled compounds have been isolated from a variety of reactions,[4-7] none of which seem of general synthetic applicability due to low yields and broad product distributions. Their classical preparation[8] involves the electrochemical fluorination of the corresponding hydrocarbon derivative in HF. This method suffers from inconvenience, the inability to prepare unsaturated derivatives, and the difficulty of pure component isolation as well as the disadvantages mentioned above.

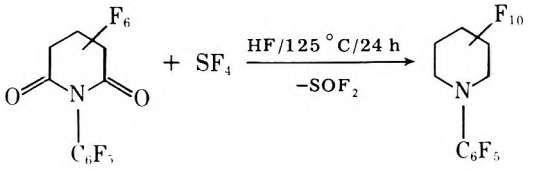
Thus, general routes to *F*-tertiary amines using ordinary laboratory equipment are essentially nonexistent, and as a consequence a structual variety of these compounds is inaccessible to experimentalists. These factors prompt this report which describes the preparation of several titled compounds as sole products from the reaction between substrates containing >NCO– groups with SF_4/HF under moderate conditions.

Results and Discussion

The *F*-amide I and imide II[9] were treated with SF_4 in HF in a stainless steel autoclave to afford the corresponding tertiary amines III and IV in 78 and 86% isolated yields, respectively.



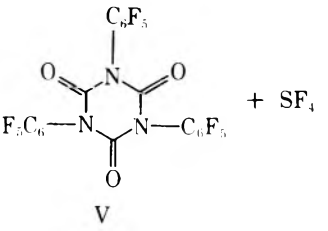
I III



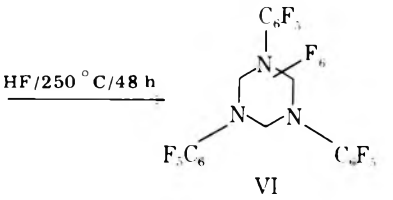
II IV

Crude reaction mixtures were clear, tar-free, and colorless after degassing (–HF, SF_4, SOF_2); VPC showed >98% conversion of the starting materials to the tertiary amines as sole product; i.e., the reactions are essentially quantitative. This is in sharp contrast with similar treatment of hydrocarbon *N,N'*-dialkylamides and related materials which afford low yields[10] of desired products and considerable tarring.[11] Presumably, these yield differences reflect the kinetic stability of the fluorocarbon reactants and products.

Under more forcing conditions the isocyanurate V[9] is partially converted (10%) to VI in a surprisingly clean reaction (>95% yield). In a similar partial conversion experiment of II → IV (85 °C/15 h/40% conversion) only product and reactant

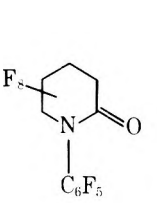


V

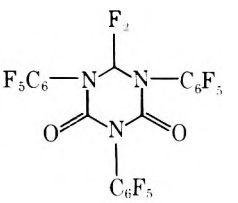


VI

were detected; intermediate lactam VII was not observed. From consideration[12] of the proposed mechanism and the metastable intermediates, i.e., $R_fC(OH)FNR_f'_2$ and $R_fC(OSF_3)FNR_f'_2$, of the reaction, it is reasonable to assume that VII (and similarly VIII) intervenes in their respective schemes. The relative rates of reaction of these substrates must decrease in the order VII > II > V and as a conservative estimate span four orders of magnitude.

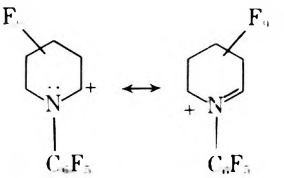


VII

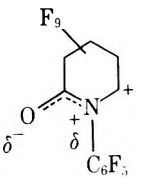


VIII

To digress briefly, hydrocarbon amides (DMF) show a high degree of C–N bond order as evidenced by restricted rotation about the C–N bond; as expected, substitution by an electronegative atom on nitrogen (F for CH_3) decreases[13] the bond order significantly. Even though fluorinated acyclic amide I is freely rotating 25°, rate differences between the cyclic fluorinated derivatives II and VII suggest that –N–C–O interaction cannot be ignored. As positive charge is generated in the rate-determining step, the intermediate and consequently its transition state derived from VII must be of lower energy than those derived from II, i.e.,



is more stable than



Rate differences presumably are not attributable to ground-state energies since bond energy estimates indicate that VII is more stable than II. Thus, it is suspected that the rate differences implicate an additive destabilizing effect of an >NCO– resonance interaction adjacent to a carbocation center in the intermediate forming transition state. For comparative purposes the relative rate of SF_4 reaction between II and one of a series of reported[14] fluorinated esters, $C_7F_{15}CO_2CH_2C_2F_5$, was measured in a competitive experiment and found to be $k(II)/k(ester) = 1.2$ (85 ± 2 °C).

It is notable that treatment of the linear imide IX[9] with SF_4/HF under relatively mild reaction conditions afforded products exclusively resulting from acyl–nitrogen bond fission. The azaolefin product X is extremely moisture sensitive and hydrolyzes to the amide XI in solution or neat.

$(C_3F_7CO)_2NC_6F_5 + SF_4$

IX

$$\xrightarrow[-SOF_2]{HF/85\,^\circ C/15\ h} C_3F_7CF{=}NC_6F_5 + C_3F_7COF$$

X (73%)

$$\xrightarrow{H_2O} C_3F_7CONHC_6F_5$$

XI

Product and reactivity differences between cyclic (II) and linear (IX) imide may be due to a preferred preliminary reaction between IX and HF affording *F*-butyryl fluoride and amide XI which subsequently is converted to X by SF_4 in HF in a relatively facile reaction. Analogous HF induced heterolysis of hydrocarbon[15] or fluorocarbon[16] anhydrides is well documented.

Even though the above reactions have not been subjected to extensive experimental scrutiny, there is no apparent reason why a variety of *F*-tertiary amines derived from *F*-(*N*,*N*-dialkylamides) or *F*-(N-substituted) medium sized cyclic imides could not be prepared by this method.

Experimental Section

General. Vapor phase chromatographic analysis was performed on a Hewlett-Packard Model 700 instrument using an 8 ft × 0.25 in. 15 or 35% PFO-XR on Gas-Chrom R 60–80 mesh column. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer. ^{19}F NMR spectra were recorded on a Varian XL-100 spectrometer at 94.1 MHz. The mass spectra were recorded on Model 14-107 Bendix time of flight spectrometer.

Materials. II, V, and IX were prepared according to published procedures.[9] *F*-Azapropene was prepared by static pyrolysis (250–270 °C) of carboxynitroso rubber (C_2F_4, CF_3NO, $HO_2C(CF_2)_3NO$ terpolymer). HF, SF_4, and *F*-octanoyl chloride were supplied by PCR, Inc., and were used without further purification.

Preparation of I. Bis(bis(trifluoromethyl)amino)mercury was prepared from *F*-azapropene according to a literature procedure.[17] This organomercurical (8.7 g, 0.017 mol) was frozen at −183 °C; then *F*-octanoyl chloride (14.9 g, 0.0344 mol) was rapidly added in an atmosphere of nitrogen. The mixture was allowed to warm to 25 °C and maintained at that temperature with stirring for 18 h. At that time the precipitated mercuric chloride was separated by pressure filtration and washed with Freon-113 (3 × 5 mL). Distillation of the resulting mixture gave the titled compound, bp 52–55 °C (12 mm) (11.6 g, 61% yield). The amide was protected from atmospheric moisture. VPC analysis showed <1% impurities: IR (film) 5.6, 7.4, 8.2, 8.7, 9, 9.5, 11, 11.15, 12.95, 14.1 μm; ^{19}F NMR (CCl_4, CF_3CO_2H external) −22.1 (t, 6), 4.1 (t of t, 3), 38.3 (m, 2), 43.1 (m, 9), 44.7 (m, 4), 48.9 (m, 2) ppm.

Anal. Calcd for $C_{10}F_{21}NO$: C, 21.8; N, 2.6. Found: C, 21.6; N, 2.8.

Preparation of III. A 300-mL stainless steel autoclave equipped with a 3000 psi bursting disk was charged with I (8.7 g, 0.016 mol). The vessel was cooled to −183 °C and HF (anhydrous, 40 g) and SF_4 (23.8 g, 0.220 mol) were introduced by vacuum techniques. The autoclave was heated with rocking at 150 °C for 18 h, cooled to 25 °C, vented to atmospheric pressure slowly in a hood (SF_4 and SOF_2 are toxic), and subjected to aspirator vacuum. The contents of the autoclave were diluted with Freon-113 (50 mL) and transferred to a polyethylene flask containing NaF to scavenge residual HF. After overnight storage the colorless solution was decanted and distilled; the fraction bp 64–65 °C (22 mm) (7.1 g, 78% yield) was the desired amine. VPC analysis of the crude reaction mixture in Freon 113 showed >99% conversion of starting material to the sole product. The isolated amine showed the following spectral properties: IR (neat) 7.5, 8.4, 9.2, 9.4, 10.1, 10.9, 13.75, 14.1 μm; ^{19}F NMR (neat, ext. CF_3CO_2H) −24 (t of t, 6), 5 (t, 3), 13.5 (m, 2), 44.9 (m, 10), 49.5 (m, 2) ppm.

Anal. Calcd for $C_{10}F_{23}N$: C, 21.0; N, 2.5. Found: C, 20.7; N, 2.6.

Preparation of IV. In a manner analogous to the above procedure, II (10.0 g, 0.0266 mol), HF (25 g), and SF_4 (32.6, 0.302 mol) were charged into a 300-mL stainless steel autoclave and heated with rocking at 125 °C (24 h). Typical workup afforded IV, bp 93–95 °C (40 mm) (9.5 g, 86% yield), which was >99% pure by VPC: IR (neat) 6.05, 6.6, 7.3, 7.55, 7.8, 7.95, 8.25, 8.4, 8.8, 8.9, 9.3, 9.52, 10.4, 11.15, 13.6 μm; ^{19}F (neat, ext. CF_3CO_2H), 15.6 (m, 4), 55.8 (m, 4), 56.3 (m, 2), 65.0 (m, 2), 73.0 (t of t, 1), 84.7 (m, 2) ppm; MS (70 eV) *m/e* 431, 412, 231, 167, 131, 100, 69.

Anal. Calcd for $C_{11}F_{15}N$: C, 30.6; N, 3.24. Found: C, 30.8; N, 3.47.

Reaction between V and SF_4. V (1.0 g, 1.6 mmol), HF (10 mL), and SF_4 (20.2 g, 0.188 mol) were charged into a 100-mL stainless steel autoclave and heated with rocking for 48 h at 250 °C. Usual workup afforded 1.0 g of a solid, mp 108–140 °C. VPC analysis showed a 1:9 ratio of a sole product to starting material (as a mixture with V): IR (Nujol) 8.25 μm (CF_2); ^{19}F NMR (aetone, ext. CF_3CO_2H) −27 ppm (CF_2); MS (70 eV)−VPC *m/e* 693, 674, 231, 167, 69.

Reaction between IX and SF_4. IX (9.0 g, 0.015 mol), HF (25 mL), and SF_4 (25.0 g, 0.232 mol) were charged in a 300-mL stainless steel autoclave and heated with rocking at 85 °C/15 h. The vessel was cooled to 25 °C and vented through a 3 × 24 in. steel pipe packed with anhydrous NaF pellets and the volatiles were collected at −183 °C and transferred into a gas cylinder. VPC of the volatiles showed a SF_4/SOF_2 product ratio of 8:1; the product was collected by VPC and showed to be C_3F_7COF by comparison of its IR spectrum and VPC retention time to that of an authentic sample. The material remaining in the autoclave was worked up as usual; distillation afforded the azaolefin, X: bp 85–87 °C (41 mm); IR (neat) 5.7, 6.6, 7.4, 8.1, 8.2, 8.8, 9.35, 10, 10.6, 11, 12.1, 13.35 μm; ^{19}F NMR (CCl_4, ext. CF_3CO_2H) −42.9 (m, 1), 3.1 (t, 3), 39.6 (q of d, J = 9 and 12.5 Hz, 2), 49 (d, 2), 69.2 (m, 2), 78.5 (m, 1), 84.3 (m, 2).

Anal. Calcd for $C_{10}F_{13}N$: C, 31.5; N, 3.67. Found: C, 31.6; N, 3.6.

X (1.0 g) was dissolved in 25 mL of Et_2O and this solution was slurried with 25 mL of H_2O overnight. The Et_2O layer was separated, dried (Na_2SO_4), and concentrated leaving 0.98 g of the amide XI.[9]

Relative Reaction Rate. The ester $C_7F_{15}CO_2CH_2C_2F_5$ (0.7101 g, 1.301 mmol), imide II (0.2378 g, 0.6140 mmol), and Freon-E4 (standard, 0.5104 g) were charged into a 30-mL stainless steel autoclave along with HF (7.0 g) and SF_4 (2.21 g, 20.05 mmol). The vessel was heated with rocking at 85 ± 2 °C for 15 h, then cooled and worked up in the usual manner. VPC indicated that 0.541 mol of ester and 0.206 mmol of imide remained. This corresponds[14] to $k(imide)/k(ester) = 1.24$ (not statistically corrected).

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Registry No.—I, 58955-22-9; II, 58955-21-8; III, 58966-63-5; IV, 58955-19-4; V, 58955-23-0; VI, 58955-20-7; IX, 65465-73-8; X, 654-74-9; bis(bis(trifluoromethyl)amine)mercury, 7276-63-3; *F*-octanoyl chloride, 335-64-8.

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Energies of the Cycloalkyl and 1-Methylcycloalkyl Free Radicals by the Decarbonylation Method

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The relative rates of formation of cycloalkyl and 1-methylcycloalkyl free radicals by decarbonylation of the corresponding acyl radicals have been measured for ring sizes 3–6. The relative rates at 135 °C for cycloalkyl radicals in descending order of ring size from 6 to 3 are 0.268, 0.316, 0.0795, and 0.0121. For the 1-methylcycloalkyl radicals of the same ring sizes they are 14.1, 11.1, 1.18, and 0.542. The relationships of these values to other measures of cycloalkyl radical stabilities are presented and discussed.

The first quantitative measurements of the energies of simple bridgehead radicals were reported by Applequist and Kaplan in 1965.[1] Their method was to measure by analysis of products the competition between decarbonylation of acyl radicals (eq 1) and capture by carbon tetrachloride (eq 2). The

$$R{-}C(=O)\cdot \xrightarrow{k_1} R\cdot + CO \qquad (1)$$

$$R{-}C(=O)\cdot + CCl_4 \xrightarrow{k_2} RCOCl + CCl_3\cdot \qquad (2)$$

rate for eq 2 was assumed constant (independent of R), for which supporting facts and arguments were presented. The acyl radicals were generated from the corresponding aldehydes by reaction with di-*tert*-butyl peroxide. Values of k_1/k_2 were found to correlate with known values of the dissociation enthalpies (D_{R-H}) of simple alkanes to form alkyl radicals, and this correlation was used to propose values of D_{R-H} for the bridgehead position studies of the following radicals: 90.1 kcal for 1-adamantyl, 91.0 kcal for 1-bicyclo[2.2.2]octyl, and 97.7 kcal for 1-norbornyl.

Subsequently, three groups have investigated the same bridgehead series using a better-known method, the rates of decomposition of *tert*-butyl peresters (eq 3).[2–4] In Table I are

$$RCO_2O\text{-}t\text{-}Bu \rightarrow R\cdot + CO_2 + t\text{-}BuO\cdot \qquad (3)$$

shown their results in the form of relative rates, together with the earlier k_1/k_2 values from decarbonylation. Viewed in this form, the results of the two approaches are strikingly similar, which supports the validity of both methods. The adamantyl, *tert*-butyl, and 1-bicyclo[2.2.2]octyl radicals have roughly the same stability, while the 1-norbornyl radical is destabilized. Some authors[2,3] have attempted to extract evidence for geometric destabilization of even the adamantyl and bicyclo[2.2.2]octyl radicals by factoring out the inductive stabilization of the perester transition states leading to these radicals, but the meaning of such geometric destabilization is unclear now that the geometry of the *tert*-butyl radical is known to be pyramidal and probably close to tetrahedral.[5,6] The point remains, however, that the perester transition states are subject to inductive effects and therefore may be polarized to such an extent that the rates may to some degree reflect carbonium ion stability in addition to radical stability. The extent of such influences in the decarbonylation transition states is entirely unknown, but by the aforementioned technique of empirical correlation with known D_{R-H} values any polar contribution may be automatically canceled.[1]

In addition to the tenuous advantage of the decarbonylation method in avoiding polar kinetic effects, the method has a large advantage over perester thermolysis in that the latter changes mechanism to a one-bond (–O–O–) cleavage when the alkyl radical is of high energy, and it seems likely that the 1-norbornyl radical is about at (if not beyond) the limit of the range of radicals that can be studied this way.[4,7] The decarbonylation method has been extended to the less stable 1-triptycyl radical[8] (D_{R-H} = 98.3 kcal) and even further in the present work (vide infra).

Other kinetic approaches to the measurement of bridgehead free-radical energies have also been employed and deserve mention here.

Rüchardt[9–14] has measured the rates of the unimolecular decompositions of symmetrical azo compounds, RN=NR. When the R groups were the bridgehead radicals listed in Table I, the rates at 300 °C in benzene were, relative to each other, much like those in the perester thermolysis: the relative rates of 1-adamantyl/1-bicyclo[2.2.2]octyl/1-norbornyl were (1.00):0.36:0.071.[15] The interpretation is clouded, however, by the fact that even the 1-adamantyl case is slower than the *tert*-butyl case (2,2-azoisobutane) by a factor of 0.02.[15] Rüchardt concluded that the bridgehead cases are slower because the transition state in the endothermic azo decomposition is more advanced so that planarity at the radical center is more closely approached.[9] But to explain the similar relative rates

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Table I. Relative Rates of Reactions Forming Free Radicals at 135 °C[a]

Radical	Decarbonylation[b]	Perester thermolysis
1-Adamantyl	2.48	2.00,[c] 1.66,[d] 4.57[e]
tert-Butyl	(1.00)	(1.00)
1-Bicyclo[2.2.2]octyl	1.24	0.245,[c] 0.225[e]
1-Norbornyl	0.0068	0.0149,[c] 0.0135[e]

[a] The perester rates were all taken at lower temperatures but extrapolated to 135 °C by least-squares fitting to the Eyring equation using all reported rate constants[2-4] with equal weights. [b] Reference 1. [c] Reference 3. [d] Reference 2. [e] Extrapolated rate constants from ref 4 relative to the average rate at 135 °C for *tert*-butyl (0.065 s^{-1}) from ref 2 and 3.

within the bridgehead series for azo compounds and peresters he suggested[11] that most of the strain increase is already present in transition states in which the bridgehead bonds are only slightly broken. This interpretation is difficult to accept even in terms of planar tertiary radicals, but if the radicals are indeed pyramidal then something else must surely be invoked to account for the azo data.[16] The rates of azo decomposition do not appear to have been correlated with known energies of alkyl radicals (but see further discussion below). The method must be regarded as one with some promise but with hazards in interpretation.

Danen[17] determined the relative rates of iodine atom abstraction by a phenyl radical (eq 4). The empirical correlation

$$RI + C_6H_5\cdot \rightarrow R\cdot + C_6H_5I \qquad (4)$$

of these rates with known aliphatic D_{R-H} values gave a line from which the following values for the bridgehead positions were read off: 92.2 kcal for 1-adamantyl, 93.2 kcal for 1-bicyclo[2.2.2]octyl, and 99.4 kcal for 1-norbornyl. These values are 1.7–2.2 kcal larger than the decarbonylation figures[1] (vide supra). The reason for the discrepancy is not evident. The iodine atom abstraction method should be tested further.

The purpose of this publication is to present the results of measurement of the energies of cycloalkyl and 1-methylcycloalkyl radicals by the decarbonylation method. Values of k_1/k_2 and values of D_{R-H} inferred from them by the previous correlation[1] are listed in Table II.

Discussion

All of the radical studies in this work have also been investigated by Rüchardt and co-workers using the perester thermolysis.[19] To facilitate comparison of their rates with the decarbonylation data, all rates have been converted to relative rates with the six-membered rings as the standard (Table III). As in the bridgehead series, the data are very similar. The most obvious differences are that the cyclopentyl and 1-methylcyclopentyl radicals are formed more easily in the decarbonylation method than in the perester thermolysis, by a factor of about 2 in each case, and that the 1-methylcyclopropyl radical is formed much faster by decarbonylation than by perester thermolysis.

Both sets of data are in contrast with the rates of solvolysis of cycloalkyl tosylates[20] and the rates of decomposition of azobiscycloalkane nitriles,[21] in both of which the 5-ring case goes considerably faster than the 6-ring case. These examples were easily understood in terms of transition states approaching planarity where eclipsing would be relieved in the cyclopentanes but increased in the cyclohexanes. In order to interpret the free-radical reactions in a way consistent with planar free radicals, it is necessary to propose early transition states (still tetrahedral) in the perester thermolysis and decarbonylation. If the radicals are actually tetrahedral or insensitive to out-of-plane distortion, then the transition states for their formation could be tetrahedral no matter how far bond breaking had gone. A small degree of polarization in the transition state might produce some transient flattening toward carbonium ion geometry, and such an effect could be contributing to the differences between the two methods. Alternatively, if the transition state for decarbonylation is more advanced than that for perester thermolysis, then eclipsing involving the leaving group in the starting material might be more relieved in the former and produce the relatively faster reaction in the cyclopentyl cases.

The large discrepancy between the decarbonylation rate and perester thermolysis rate for formation of the 1-methylcyclopropyl radical is not fully explainable with the information at hand. If the perester data are for two-bond cleavage transition states, then the cyclopropyl radical is only slightly stabilized, if at all, by an α-methyl group: the rate constants for cyclopropyl and 1-methylcyclopropyl were 4.2×10^{-5} and 7.4×10^{-5} s^{-1}, respectively, at 110 °C.[19] On the other hand, the data in Table II (decarbonylation) show an acceleration factor due to methyl of 45 in the cyclopropyl case, compared with 15, 35, and 53 in the cyclobutyl, cyclopentyl, and cyclohexyl cases, respectively. Perhaps the cyclopropyl and 1-methylcyclopropyl cases in the perester series have gone beyond the expected stability limit where the mechanism shifts to the one-bond cleavage (O–O), which would be insensitive to the α-methyl substituent. This would still leave unexplained the relatively easy formation of 1-methylcyclopropyl from decarbonylation since a competing one-bond mechanism for perester thermolysis should make the rate *larger* than expected from the radical stability.

If conformational and strain effects are of only small importance in determining the values of D_{R-H} or the correlated rate constants, then one must ask what determines the general reaction orders shown in Tables II and III (ring sizes $6 \cong 5 > 4 > 3$). Rüchardt[19] has pointed out that the logarithms of the perester rates give rough linear correlation with values of $J_{^{13}C-H}$ for the corresponding cycloalkanes.[22] The decarbonylation data in Table II for secondary radicals correlate about as well as the perester data (ring sizes 3–6) with $J_{^{13}C-H}$ (correlation coefficients $r = 0.972$ and 0.961, respectively) but not as well for the tertiary radicals ($r = 0.864$ and 0.997 for decarbonylation and perester thermolysis, respectively). Although the hybridization state of carbon as measured by $J_{^{13}C-H}$ is clearly not the sole determinant of radical stability, it may be the principal contributor to the differences within the cycloalkyl or 1-methylcycloalkyl series up through the six-membered ring.

Some of the 1-methylcycloalkyl radicals have also been investigated by the azoalkane decomposition method.[23] The relative rates at 200 °C in benzene for formation of 1-methylcyclohexyl, 1-methylcyclopentyl, and 1-methylcyclobutyl radicals were (1.00):1.66:0.076.[15] These results are not very different from the decarbonylation and perester results (Table III), but they do show still another small enhancement of the 5 ring relative to the other two ring sizes.

The values of D_{R-H} for the secondary cycloalkyl radicals have been determined by gas phase kinetic studies of the reactions of cycloalkanes with various free radicals. The best values as selected by Ferguson and Whittle[18] are shown in Table II. The values are similar to those derived from decarbonylation and show the same relative stabilities, which further supports the validity of the decarbonylation method.

The relative stabilities of cyclopentyl and cyclohexyl radicals (as well as larger ring sizes) have been studied by Bunce and Hadley[24] by measuring the relative reactivities of the cycloalkanes with various hydrogen-abstracting radicals: chlorine and bromine atoms, *tert*-butoxy, phenyl, and trichloromethyl. The relative reactivities per methylene group vary from near unity to about a factor of 4 in favor of the cy-

Table II. Energies of Cycloalkyl Radicals by the Decarbonylation Method

Registry no.	Radical	k_1/k_2 (135 °C)[a]	Runs	D_{R-H} (25 °C)[b]	D_{R-H} (lit.)[c]
3170-58-9	Cyclohexyl	0.268 ± 0.050	5	96.2 ± 0.3	95.5
3889-74-5	Cyclopentyl	0.316 ± 0.039	8	96.0 ± 0.2	94.2
4548-06-5	Cyclobutyl	0.0795 ± 0.0164	3	97.8 ± 0.3	96.5
2417-82-5	Cyclopropyl	0.0121 ± 0.0032	3	100.2 ± 0.4	100.7
16998-65-5	1-Methylcyclohexyl	14.1 ± 2.9	5	91.1 ± 0.3	
33968-73-9	1-Methylcyclopentyl	11.1 ± 3.0	4	91.4 ± 0.4	
53249-17-5	1-Methylcyclobutyl	1.18 ± 0.12	3	94.3 ± 0.2	
65338-31-0	1-Methylcyclopropyl	0.542 ± 0.144	3	95.3 ± 0.4	

[a] Experimental error is the average deviation from the average of all runs. [b] In units of kcal/mol. [c] From gas phase kinetic studies summarized in ref 18.

clopentyl radical. The reactivity ratios were sensitive to solvent as well as the attacking radical. It would be difficult to draw firm conclusions about the relative stabilities of the two cycloalkyls from these complicated data, but the numbers are at least not in obvious conflict with the other data described above.

A modification of the decarbonylation method, apparently not yet applied to the cycloalkyl cases, is the use of an *efficient* acyl radical trap, such as nitrosoisobutane, in order to reduce the risk of variation of k_2 with structure.[25] A problem with this method seems to be the difficulty of maintaining a known concentration of the trap low enough to permit any decarbonylation of acyl radicals which would produce primary alkyl or comparably unstable radicals. The method is thus apparently restricted to approximately the same range of radical types as the perester thermolysis method.

Table III. Comparison of Decarbonylation and Perester Thermolysis Data for Formation of Cycloalkyl Free Radicals

Radical	Rel. k_1/k_2 from decarbonylation at 135 °C	Rel. k from perester thermolysis[a]
Cyclohexyl	(1.00)	(1.00)
Cyclopentyl	1.18	0.468
Cyclobutyl	0.297	0.233
Cyclopropyl	0.045	0.061
1-Methylcyclohexyl	(1.00)	(1.00)
1-Methylcyclopentyl	0.787	0.334
1-Methylcyclobutyl	0.084	0.119
1-Methylcyclopropyl	0.038	0.0017

[a] Data at 110 °C for the secondary radicals and 80 °C for the tertiary radicals.

Experimental Section

All boiling points and melting points are uncorrected. Infrared spectra were obtained on Perkin-Elmer Infracord and Model 237 grating infrared spectrometers and calibrated with the 1603-cm^{-1} band of polystyrene. All NMR spectra were measured with Varian Models A56/60, A60A, and T-60 spectrometers at 60 MHz. Chemical shifts are expressed in parts per million relative to an internal standard of Me_4Si. Preparative vapor phase chromatography was performed on a Varian Aerograph Model A-700 Autoprep instrument. Quantitative vapor phase chromatography was performed on an F and M Model 300 instrument. Elemental analyses were performed by Mr. J. Nemeth and his associates. Mr. Robert Thrift assisted in operation of the NMR spectrometers.

Materials. Carbon tetrachloride (Baker, spectrophotometric grade) was distilled under argon from phosphorus pentoxide through a 1.7 m Podbielniak column and collected at 76.0–76.2 °C (751 mm). Di-*tert*-butyl peroxide (Matheson Coleman and Bell, practical grade) was distilled under argon through a 1.7 m Podbielniak column and collected at 40.0–40.5 °C (60 mm) [lit.[26] bp 37 °C (48 mm)]. *o*-Dichlorobenzene (Eastman, reagent grade) was distilled through a 1.7 m Podbielniak column and collected at 95.8–96.3 °C (55 mm). *p*-Chlorotoluene (Eastman, reagent grade) was distilled through a 1.7 m Podbielniak column and collected at 75.0–75.2 °C (27 mm). 1,2-Dimethoxyethane (Eastman, reagent grade) was distilled though a 30 cm glass helices packed column and collected at 82.0–82.7 °C (748 mm). Ethanol (U.S.I., absolute) was distilled from magnesium ethoxide[27] under argon and collected at 78.2–78.4 °C (753 mm); the product was stored under argon. Methanol (Baker, reagent grade) was distilled from magnesium methoxide[27] under argon and collected at 64.3–64.6 °C (751 mm); the product was stored under argon. Hexachloroethane (Aldrich Chemical Co.) was recrystallized from ether and melted at 187–188 °C (sealed capillary) [lit.[28] mp 189 °C (sealed capillary)]. *tert*-Butyl chloride (Aldrich Chemical Co.) was distilled through a 30 cm spiral wire column and collected at 49.3–49.8 °C. Tetrahydrofuran (Baker, reagent grade) was dried over calcium hydride, distilled from lithium aluminum hydride, and collected at 63.8–64.7 °C (750 mm); the product was stored under argon. Cyclohexyl chloride (Aldrich Chemical Co.) was distilled through a 30 cm glass helices packed column and collected at 140.8–141.3 °C (742 mm) [lit.[29] bp 40.3 °C (21 mm)]. Cyclopentyl chloride (Columbia Organic Chemicals) was distilled through a 30 cm glass helices packed column and collected at 114.2–114.8 °C (750 mm) (lit.[30] bp 114.5–115.0 °C). 1-Methylcyclohexene (Aldrich Chemical Co.) was distilled under argon through a 30 m glass helices packed column and collected at 108.0–108.6 °C (750 mm) (lit.[31] bp 110.2–110.4 °C). Cyclopropanecarboxylic acid (Aldrich Chemical Co.) was distilled through a 15 cm Vigreux column and collected at 96.0–97.0 °C (40 mm) [lit.[32] bp 97–98 °C (40 mm)]. Cyclohexanecarboxylic acid (Aldrich Chemical Co.) was distilled through a 15 cm Vigreux column and collected at 113.1–114.2 °C (10 mm) [lit.[29] bp 110 °C (8 mm)]. Cyclopropane (Matheson, high purity grade) was used without further purification.

Impurities in compounds directly used for the decarbonylation experiments and product determination studies were less than 0.5% as determined by NMR and infrared spectral or vapor phase chromatographic analyses.[33]

Vapor Phase Chromatographic Analyses. The vapor phase chromatographic analyses were performed on an F and M Model 300 instrument with helium as the carrier gas. The separations were carried out on the following 0.25-in diameter columns: (A) 15 ft 10.5% SE-30 on Chromosorb P-AW-DMCS, (B) 15 ft 5.0% SE-30 on Chromosorb P-AW-DMCS, (C) 15 ft 20.0% Carbowax 20M on Anakrom ABS 60–70 mesh, and (D) 12 ft 20.0% Carbowax 20M on Anakrom ABS 100–110 mesh. Collections of products for identification purposes were carried out on the above columns or on the following two preparative columns: (1) 15 ft × 0.375 in 19.5% SE-30 on Chromosorb P-AW-DMCS and (2) 15 ft × 0.375 in 20.0% Carbowax 20M on Chromosorb P-AW-DMCS.

Quantitative analyses were performed using temperature programming. Peak areas were measured for each analysis by a disc chart integrator and a polar planimeter and finally checked by cutting out the peaks and weighing them. Decarbonylation products were usually identified by comparison of retention times and by comparison of infrared spectra of collected materials with those of authentic compounds, the preparations of which are described below.

Relative response data for the quantitative determination of the amounts of decarbonylation products present were obtained from prepared solutions of known composition. The relative amounts of the compounds in the prepared solutions approximated those occurring in the decarbonylation reaction mixtures. The vapor phase chromatographic analysis operational procedure for these determinations was identical with that of the actual decarbonylation analysis operational procedure for each series.

Aldehydes. With the exception of 1-methylcyclopropanecarboxaldehyde, all of the aldehydes used in this work were prepared by the reduction of the corresponding 1-acylaziridines (from the acids via acid chlorides) with lithium aluminum hydride following the general procedure of Brown and Tsukamoto.[34] All of the aldehydes had sat-

isfactory NMR and infrared spectra[33] and all gave 2,4-dinitrophenylhydrazones whose melting points agreed with literature values, except in the case of 1-methylcyclobutanecarboxaldehyde, where no literature melting point was found. The boiling points of the aldehydes and yields from acid chlorides were as follows: cyclohexanecarboxaldehyde, bp 57.5–58.5 °C (10 mm) (lit.[35] bp 159–160 °C), 47%; cyclopentanecarboxaldehyde, bp 42–44 °C (20 mm) [lit.[36] bp 41–43 °C (18 mm)], 49%; cyclobutanecarboxaldehyde, bp 114.0–115.5 °C (753 mm) (lit. bp 116–118[37] and 113–115 °C[38]), 54%; cyclopropanecarboxaldehyde, bp 39–41 °C (12 mm) [lit. bp 98–101[39] and 42–44 °C[40] (14 mm)], 52%; 1-methylcyclohexanecarboxaldehyde, bp 55–56 °C (6 mm) [lit. bp 166.5–167.0[35] and 120 °C[41] (54 mm)], 56%; 1-methylcyclopentanecarboxaldehyde, bp 47.3–48.4 °C (25 mm) [lit. bp 142.0–142.5[35] and 31–33 °C[36] (10 mm)], 43%.

1-Methylcyclobutanecarboxaldehyde was isolated in 56% yield by preparative VPC on Carbowax. The NMR spectrum (CCl_4) showed a singlet at δ 9.52 (1.0 H) assigned to the aldehydic proton, a multiplet in the region δ 1.40–2.65 (6.0 H) assigned to the cyclobutyl methylene protons, and a singlet at δ 1.27 (3.0 H) assigned to the 1-methyl protons. The infrared spectrum (film) showed bands at 3425 (vw), 2967 (m), 2874 (m), 2793 (m), 2710 (m), 1721 (s), 1456 (m), 1439 (m), 1393 (w), 1379 (w), 1312 (w), 1287 (vw), 1255 (w), 1247 (w), 1212 (w), 1195 (w), 1151 (w), 1053 (vw), 982 (vw), 929 (m), 889 (w), 858 (w), and 722 (w) cm^{-1}.

The 2,4-dinitrophenylhydrazone of 1-methylcyclobutanecarboxaldehyde, recrystallized from ethyl acetate–ethanol–water, melted at 176.4–177.3 °C.

Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.80; H, 5.07; N, 20.13. Found: C, 51.90; H, 5.03; N, 20.38.

When they were not commercially available, the carboxylic acids used for the above preparations were prepared by standard literature methods. An exception was 1-methylcyclobutanecarboxylic acid, which was prepared in 72% yield, bp 56.5–59.5 °C (0.3–0.4 mm) [lit.[42] bp 98 °C (13 mm)], by the α-methylation of cyclobutanecarboxylic acid following the technique of Pfeffer and Silbert[43] and Creger.[44]

1-Methylcyclopropanecarboxaldehyde, bp 102.5–104.5 °C (750 mm) (lit.[45] bp 103–104 °C), was prepared in 44% yield by the lithium aluminum hydride reduction of 1-methylcyclopropanecarbonitrile[46] using the procedure of Smith and Rogier[47] as modified by Schuster and Roberts.[45]

Ethyl 1-Methylcyclobutanecarboxylate. To a 50-mL flask containing 3.0 g (0.023 mol) of 1-methylcyclobutanecarbonyl chloride at 0 °C was slowly added 8.0 g (0.173 mol) of ethanol, and the solution was stirred for 36 h. The crude ester was washed with portions of a saturated sodium bicarbonate solution until carbon dioxide evolution ceased. Distillation afforded 2.95 g (92%) of ethyl 1-methylcyclobutanecarboxylate, bp 154.3–155.2 °C (735 mm). The NMR spectrum (CCl_4) showed a quartet centered at δ 4.08 (J = 7.0 Hz, 2.0 H) assigned to the ethyl methylene protons, a multiplet in the region δ 1.62–2.65 (6.0 H) assigned to the ring methylene protons, a triplet centered at δ 1.23 (J = 7.0 Hz) assigned to the methyl protons of the ethyl group, and a singlet at δ 1.36 assigned to the 1-methyl protons. The infrared spectrum (film) showed absorption at 3448 (vw), 2976 (s), 2933 (m), 2907 (m), 2874 (m), 1724 (vs), 1460 (m), 1391 (m sh), 1374 (m), 1348 (w), 1304 (s), 1252 (m), 1220 (m), 1208 (m), 1174 (m), 1126 (vs), 1098 (m), 1044 (m), 1026 (m), 922 (w), and 864 (m) cm^{-1}.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.57; H, 9.89.

Decarbonylation of Aldehydes. The general procedure has been described earlier[1] and has been modified only in minor ways.[33] The reaction products were all identified by comparison with authentic samples, to which literature references are given where appropriate. The products and analytical conditions used were as follows.

Cyclohexanecarboxaldehyde: The products were chlorocyclohexane and ethyl cyclohexanecarboxylate[48] (from ethanolysis of the acid chloride during the analytical procedure[1]). The analysis was done on column A, programmed between 50 and 230 °C. A control showed that a mixture of chlorocyclohexane and cyclohexanecarbonyl chloride did not change composition when included in a decarbonylation run of cyclobutanecarboxaldehyde.

Cyclopentanecarboxaldehyde: The products were chlorocyclopentane and ethyl cyclopentanecarboxylate.[48] The analysis was done on column B, programmed between 50 and 230 °C. A control showed that a mixture of chlorocyclopentane and cyclopentanecarbonyl chloride did not change composition when included in a decarbonylation run of cyclobutanecarboxaldehyde. The cyclopentanecarboxaldehyde case was unique among those studied here in giving also a nonvolatile product in about 25% yield. This material decomposed at 275 °C in the injection port of the gas chromatograph to give 93–95% of the original aldehyde. A polymerization of the aldehyde evidently competes with the reactions of interest but should not substantially affect the determination of k_1/k_2.

Cyclobutanecarboxaldehyde: The products were chlorocyclobutane[29] and ethyl cyclobutanecarboxylate.[49] The analysis was done on column A, programmed between 25 and 230 °C. A careful search for cyclobutane[50] product at the highest instrument sensitivity (column C) revealed none. A control showed that a mixture of chlorocyclobutane and cyclobutanecarbonyl chloride did not change composition when included in a decarbonylation run of cyclohexanecarboxaldehyde.

Cyclopropanecarboxaldehyde: The products were cyclopropyl chloride[51] and ethyl cyclopropanecarboxylate.[52] The cyclopropyl chloride was formed in amounts too small for collection and spectroscopic identification, so it was identified by its retention time on column C at 25 °C in comparison with that of an authentic sample. The analysis of the rest of the mixture was done on column A using the same conditions as for cyclobutanecarboxaldehyde. No cyclopropane or allyl chloride could be detected. A control showed that a mixture of cyclopropyl chloride and cyclopropanecarbonyl chloride did not change composition when included in a decarbonylation run of cyclohexanecarboxaldehyde.

1-Methylcyclohexanecarboxaldehyde: The products were methylenecyclohexane,[53] 1-methylcyclohexene, 1-chloro-1-methylcyclohexane,[54] and ethyl 1-methylcyclohexanecarboxylate.[55] It was shown that the first two were formed from the third in the injection port (205 °C) of the gas chromatograph. The analysis was done on column A, programmed between 50 and 233 °C. A control showed that a mixture of 1-chloro-1-methylcyclohexane and 1-methylcyclohexanecarbonyl chloride did not change composition when included in a decarbonylation run of 1-methylcyclopropanecarboxaldehyde.

1-Methylcyclopentanecarboxaldehyde: The products were methylenecyclopentane,[56] 1-methylcyclopentene,[57] 1-chloro-1-methylcyclopentane,[54] and ethyl 1-methylcyclopentanecarboxylate.[48] The first two products were shown to arise from the third in the injection port of the gas chromatograph. The analysis was done on column A, programmed between 50 and 233 °C. A control showed that a mixture of 1-chloro-1-methylcyclopentane and 1-methylcyclopentanecarbonyl chloride did not change composition when included in a decarbonylation run of 1-methylcyclopropanecarboxaldehyde.

1-Methylcyclobutanecarboxaldehyde: The products were 1-chloro-1-methylcyclobutane[54] and ethyl 1-methylcyclobutanecarboxylate. The analysis was done on column A, programmed between 50 and 233 °C. Analysis on column D at 25 °C demonstrated the absence of methylenecyclobutane, 1-methylcyclobutene, and methylcyclobutane. A control showed that a mixture of 1-chloro-1-methylcyclobutane and 1-methylcyclobutanecarbonyl chloride did not change composition when included in a decarbonylation run of 1-methylcyclopropanecarboxaldehyde.

1-Methylcyclopropanecarboxaldehyde: The products were 1-chloro-1-methylcyclopropane and methyl 1-methylcyclopropanecarboxylate.[58,59] Analyses were done on columns A, C, and D, each programmed between 50 and 230 °C. A control showed that a mixture of 1-chloro-1-methylcyclopropane and 1-methylcyclopropanecarbonyl chloride did not change composition when included in a decarbonylation run of 1-methylcyclobutanecarboxaldehyde.

1-Chloro-1-methylcyclopropane. The procedure of Kirmse, Kapps, and Hager for the addition of diazomethane to allylic chlorides was used here.[60] A 250-mL distillation flask was equipped with a short stem addition funnel, a magnetic stirring bar, and a condenser set downward for distillation. A 500-mL receiving flask was equipped with a reflux condenser with an attached drying tube and a magnetic stirring bar. To the distilling flask was added a solution of 10.6 g (0.189 mol) of potassium hydroxide dissolved in 18 mL of water followed by 62 mL of 2-(2-ethoxyethoxy)ethanol and 35 mL of ether. The stirred solution was heated to 65–70 °C, and as soon as the ether began to distill a solution of 38.1 g (0.178 mol) of N-methyl-N-nitroso-p-toluenesulfonamide in 350 mL of ether was added over a period of 140 min.[61] The ethereal diazomethane distilled into a vigorously stirred solution of 34.9 g (0.456 mol) of 2-chloropropene[62] and 0.6 g of cupric chloride dihydrate at 8–15 °C. After all of the diazomethane had been added, the solution was stirred for an additional 10 h at room temperature. The catalyst was then filtered off, and the ether was removed by fractionation through a 1.7 m modified Podbielniak column with a total reflux head. The reflux to take-off ratio was kept at greater than 5:1. After the major part of the ether had been removed, the residue was flash distilled to afford approximately 4 g of a clear mobile liquid, bp 50–72 °C. Vapor phase chromatographic analysis (column A) of the distillate showed the presence of ether and one minor and two major products.

The crude distillate was separated by preparative vapor phase

chromatography (column 1). One of the two major components proved to be 1-chloro-1-methylcyclopropane, isolated as a clear mobile liquid in 8.4% yield. The NMR spectrum (CCl_4) showed a singlet at δ 1.60 (3.0 H) assigned to the 1-methyl protons and a typical A_2B_2 pattern in the region δ 0.55–1.15 (4.0 H) assigned to the cyclopropyl methylene protons. The infrared spectrum (film) showed absorption at 3086 (m), 3003 (m), 2967 (m), 2924 (m), 2882 (m), 2747 (vw), 1451 (m), 1429 (m), 1408 (m), 1387 (m), 1311 (w), 1198 (m), 1151 (w), 1103 (m), 1053 (w sh), 1026 (m), 1017 (m), 929 (m), 861 (m), and 807 (m) cm^{-1}.

Anal. Calcd for C_4H_7Cl: C, 53.06; H, 7.79; Cl, 39.15. Found: C, 53.25; H, 7.79; Cl, 38.89.

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Registry No.—1-Methylcyclobutanecarboxaldehyde, 65338-30-9; 1-methylcyclobutanecarboxaldehyde 2,4-DNP, 65338-29-6; 1-methylcyclobutanecarbonyl chloride, 21890-82-4; ethanol, 64-17-5; ethyl 1-methylcyclobutanecarboxylate, 65338-28-5; cyclohexanecarboxaldehyde, 2043-61-0; cyclopentanecarboxaldehyde, 872-53-7; cyclobutanecarboxaldehyde, 2987-17-9; cyclopropanecarboxaldehyde, 1489-69-6; 1-methylcyclohexanecarboxaldehyde, 6140-64-3; 1-methylcyclopentanecarboxaldehyde, 6140-63-2; 1-methylcyclopropanecarboxaldehyde, 4515-89-3; 1-chloro-1-methylcyclopropane, 50915-28-1; diazomethane, 334-88-3; 2-chloropropene, 557-98-2.

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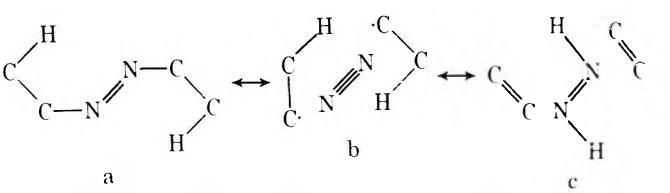
(15) The square roots of the measured rate ratios are shown to correct statistically for the fact that two C–N bonds are being broken simultaneously.
(16) One possibility is that the transition state for azo decomposition is stabilized by a contribution of a hyperconjugative resonance structure (c):



Contribution of c to the bridgehead cases is prohibited by Bredt's rule.
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Radical Reactions in the Coordination Sphere. 4.[1] Addition of Carbon Tetrachloride to *cis*-Cyclooctene Catalyzed by Dichlorotris(triphenylphosphine)ruthenium(II)

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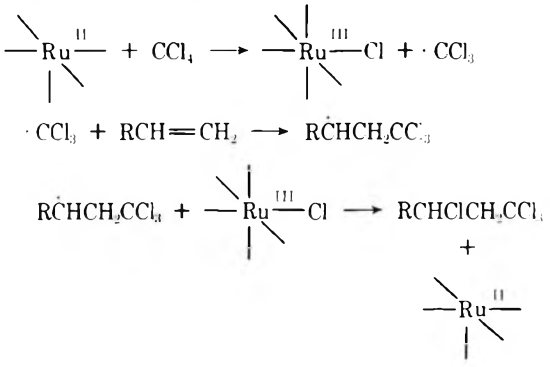
Addition of carbon tetrachloride to *cis*-cyclooctene catalyzed by dichlorotris(triphenylphosphine)ruthenium(II) gave a mixture of 1,2 and 1,4 adducts, in which 1-chloro-4-(trichloromethyl)cyclooctane predominated, in exceedingly high yields. Relative amounts of the two products were found to be linearly correlated with the catalyst concentrations at a stipulated temperature. With a fixed concentration of the catalyst, the product ratios were determined at different temperatures and activation parameters for the 1,2 and 1,4 additions were estimated.

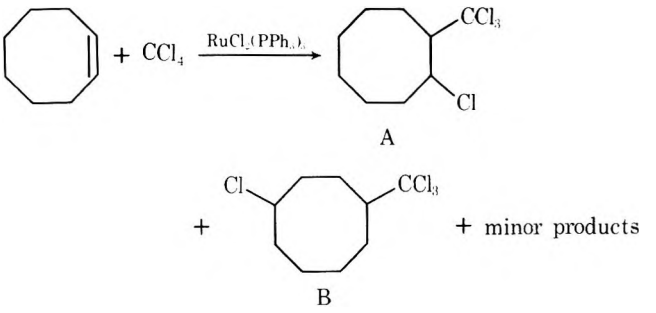
Carbon tetrachloride and other organic polyhalides are known to add olefins in the presence of various catalysts such as peroxides,[2] metal salts,[3] or metal carbonyls.[3] Recently, we have found that these addition reactions can be best effected by a homogeneous ruthenium complex, dichlorotris(triphenylphosphine)ruthenium(II).[1,4] This newly found catalytic reaction has been shown to contain several distinctive features (high yields of 1:1 adducts, unique selectivities, highly efficient catalytic cycles, etc.) and a homolytic mechanism being operative in the coordination sphere was suggested.



In the present investigation, the ruthenium(II) complex catalyzed addition of carbon tetrachloride to *cis*-cyclooctene was examined in some detail in order to shed further light into the mechanistic aspects of the catalytic processes. This choice was made because there are available extensive investigations of Traynham and Couvillon[5] on the free-radical additions of carbon tetrachloride and other polyhalides to *cis*-cyclooctene under various conditions. They showed that photochemically or thermally initiated additions of carbon tetrachloride give mainly stereoisomeric 1-chloro-4-(trichloromethyl)cyclooctanes, products of transannular addition, with minor amounts of the stereoisomeric 1,2-addition products.[5a,b] The ruthenium(II) complex catalyzed reactions are also expected to give similar product mixtures and the present work aims to determine relative amounts of the two sets of the addition products from which activation parameters would be derived for the transannular hydrogen and intermolecular chlorine abstractions by the intermediate 2-(trichloromethyl)cyclooctyl radical. A comparison of these parameters between the reported free radical and the present additions is made, for it seemed to us that such a comparison would provide better understanding about the factors controlling unique selectivities exhibited in the ruthenium(II) catalysis.

Results and Discussion

Product study experiments were conducted in a sealed Pyrex tube at 90 °C. When *cis*-cyclooctene was allowed to react with 4 equiv of carbon tetrachloride in the presence of 0.7 mol % (based on the olefin charged) of dichlorotris(triphenylphosphine)ruthenium(II), a mixture of isomeric $C_9H_{14}Cl_4$ compounds was obtained in 93% yield. Formation of by-products was of little importance and only (trichloromethyl)cyclooctane was detected by GLC in 2% yield. Other very minor products were also found by GLC but their structures were not further examined. The mixture of $C_9H_{14}Cl_4$ compounds was shown by GLC analysis to consist of 25% 1-chloro-2-(trichloromethyl)cyclooctane (A) and 75% 1-chloro-4-(trichloromethyl)cyclooctane (B). These values



were doubly checked by NMR integration of signals for CHCl protons which are diagnostic to differentiate the 1,2 and 1,4 isomers[5a,b] and the sample was found to be a 26:74 mixture of A and B. Structures of these products were confirmed by comparing their IR and NMR spectra with the reported values.[5b]

Interestingly, the relative amounts of the 1:1 adducts were found to depend upon the concentration of the ruthenium(II) complex. As the catalyst concentration increases, the ratio of amount of A to that of B increases. For example, the ratio was 0.09 at a catalyst concentration of 0.12 mol % and 0.74 at 1.5 mol % (see Table I). In a single experiment, however, the ratio was virtually constant throughout the reaction (see Figure 1). Furthermore, in control experiments,[6] isomerization between A and B in the presence of the ruthenium(II) complex was found not to occur to any detectable extent. From these observations, it must be concluded that the dependency of the product ratio on the catalyst concentration is real.

In a simplified interpretation of these phenomena, the intermediacy of $Ru^{III}Cl$ complex from which the (trichloromethyl)cyclooctyl radicals abstract a chlorine atom, as suggested before, can be invoked.[4,5b] If we accept this view, the product determining in addition processes may be envisioned as shown below.[7]

According to the proposed scheme, rate expressions for the formation of the products, A and B, are

$$d[A]/dt = k_2[R^1\cdot][Ru^{III}Cl] \quad (1)$$

$$d[B]/dt = k_3[R^2\cdot][Ru^{III}Cl] \quad (2)$$

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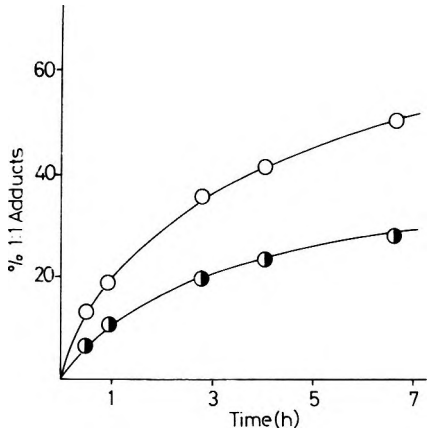
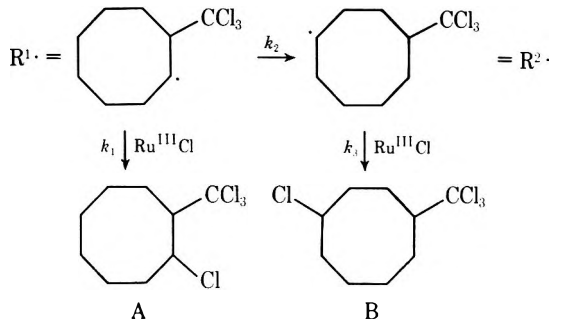


Figure 1. Typical concentration-time profiles for 1,2 adduct, A, and 1,4 adduct, B, in the reaction of *cis*-cyclooctene (10 mmol) with carbon tetrachloride (42 mmol) catalyzed by $RuCl_2(PPh_3)_3$ (0.12 mmol) at 90 °C: (○) A, (◑) B.

Table I. Effect of the Catalyst Concentration on the 1,2 Adduct/1,4 Adduct Ratios[a]

$[RuCl_2(PPh_3)_3]$, mmol	[1,2 adduct]/[1,4 adduct]	$[RuCl_2(PPh_3)_3]$, mmol	[1,2 adduct]/[1,4 adduct]
0.012	0.09	0.088	0.49
0.023	0.13	0.116	0.58
0.059	0.28	0.153	0.74

[a] Reaction conditions; *cis*-C_8H_{14} (10 mmol), CCl_4 (42.2 mmol), C_6H_6 (5 mL) at 90 °C for 0.5–3 h. [b] Determined by GLC. [c] Average in triplicate runs.



Since the steady-state treatment can be applied to the intermediate $R^{2}\cdot$,

$$d[R^{2}\cdot]/dt = k_2[R^{1}\cdot] - k_3[R^{2}\cdot][Ru^{III}Cl] = 0$$

and there results

$$k_3[R^{2}\cdot][Ru^{III}Cl] = k_2[R^{1}\cdot]$$

This substituted into eq 2 yields

$$d[B]/dt = k_2[R^{1}\cdot] \quad (3)$$

The simultaneous eq 1 and 3 are readily solved, giving

$$d[A]/d[B] = (k_1/k_2)[Ru^{III}Cl] \quad (4)$$

The concentration of the reactive intermediate complex, $Ru^{III}Cl$, is considered to be proportional to initial concentration of the added complex, $RuCl_2(PPh_3)_3$, so that we find after integration

$$[A]/[B] = (k_1/k_2)C[RuCl_2(PPh_3)_3] \quad (5)$$

where C is the proportionality constant.[8]

The final result, eq 5, implies that the ratio of the product concentrations, [A]/[B], must be linearly correlated with the initial catalyst concentration. This was found to be the case

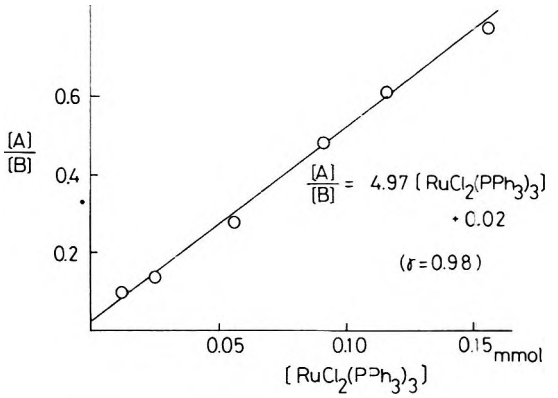


Figure 2. Dependence of relative amounts of the 1,2 and 1,4 adducts on the catalyst concentration.

Table II. Temperature Dependences of [1,2 Adduct (A)]/[1,4 Adduct (B)]

System	A/B
$RuCl_2(PPh_3)_3$ catalysis[a]	1/4.6 (90 °C)[b]; 1/7.8 (155 °C)[b]
Photochemically and thermally induced reactions[c]	1/17 (44 °C); 1/99 (150 °C)

[a] Reactions were carried out using 10.0 mmol of *cis*-C_8H_{14}, 42.2 mmol of CCl_4, 0.43 mmol of $RuCl_2(PPh_3)_3$, and 5 mL of C_6H_6 for 0.3–2 h. [b] Determined by GLC. [c] From ref 5.

Table III. Activation Parameters for Intermolecular Chlorine Abstraction and for Transannular Hydrogen Abstraction[a]

Initiation	$\Delta\Delta H^{\ddagger}$, kcal/mol[b]	$\Delta\Delta S^{\ddagger}$, eu[c]
$RuCl_2(PPh_3)_3$	−3	−4
Photochemical and thermal	−4	−21

[a] Obtained from the data in Table II. [b] $\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}(A) - \Delta H^{\ddagger}(B)$. [c] $\Delta\Delta S^{\ddagger} = \Delta S^{\ddagger}(A) - \Delta S^{\ddagger}(B)$

as is shown in Figure 2, where [A]/[B] is plotted against $[RuCl_2(PPh_3)_3]$ under a certain set of conditions (see Table I).

The relative extents of vicinal and transannular additions were next determined at different temperatures. Results are listed in Table II together with reported [A]:[B] ratios for photochemically and thermally induced additions.[5b] These data lead to calculated differences in enthalpy change [$\Delta\Delta H^{\ddagger} = \Delta H^{\ddagger}(A) - \Delta H^{\ddagger}(B)$] as well as those in entropy change [$\Delta\Delta S^{\ddagger} = \Delta S^{\ddagger}(A) - \Delta S^{\ddagger}(B)$] for the two sets of addition reactions (see Table III). In both cases it appears that the enthalpy of activation favors the bimolecular chlorine abstraction from $Ru^{III}Cl$ complex or from carbon tetrachloride by the 2-(trichloromethyl)cyclooctyl radical over the unimolecular transannular hydrogen abstraction by 3 or 4 kcal/mol, while the entropy of activation favors the latter reaction over the former by 4 or 21 eu, respectively. However, it was felt that, because of possible uncertainties involved in the calculated figures, an exact interpretation of the difference in energy of activation is difficult. Nevertheless, it seemed at least qualitatively true that loss in the entropy of activation for the 1,2 addition compared to the 1,4 addition is very much larger in the typical free-radical reaction than in the ruthenium(II) complex catalyzed reaction. The large difference in entropy change between the two additions (4 vs. 21 eu) might be explained by considering the degree of freedom associated with the intermediate 2-(trichloromethyl)cyclooctyl radical. Under

free-radical conditions, little interaction is expected between the intermediate radicals and other chemical species present. On the other hand, the 2-(trichloromethyl)cyclooctyl radical produced in the ruthenium(II) catalysis is likely to be coordinated to the metal center. This is to say that in the ruthenium(II) complex catalyzed reaction the degree of freedom associated with the intermediate radical abstracting chlorine atom would not be as large as in the typical free-radical reactions. Thus, the smaller loss in entropy of activation for the 1,2 addition found in the present case perhaps will reflect coordination of radicals to the metal center and can be taken as support for the homolytic mechanism which is operative in the coordination sphere.

Experimental Section

Boiling points are uncorrected. NMR spectra were recorded on Varian A-60D and HA-100 spectrometers in 15–20% carbon tetrachloride solution. IR spectra were recorded on a Hitachi EPI-3G spectrophotometer with neat samples. GLC analyses were performed with a Ohkura Model 802T instrument equipped with a thermal conductivity detector. Teflon columns (150–200 × 0.4 cm) packed with 10% DCQF-1, 10% polydiethylene glycol adipate 10% SF-96 on 60–80 mesh Chromosorb W, were utilized for analytical studies. Corrections were made for thermal conductivity of the various components.

Carbon tetrachloride, *cis*-cyclooctene, and benzene were commercially available chemicals of over 99% purity and purified by distillation under nitrogen prior to use. Dichlorotris(triphenylphosphine)ruthenium(II) was prepared according to the literature.[9]

Reaction of *cis*-Cyclooctene with Carbon Tetrachloride in the Presence of Dichlorotris(triphenylphosphine)ruthenium(II). Examples of Product Study. A mixture of *cis*-cyclooctene (8.08 g, 73.3 mmol), carbon tetrachloride (45.1 g, 293 mmol), the ruthenium(II) complex (0.51 g, 0.53 mmol), and benzene (15 mL) in a heavy-walled Pyrex tube was cooled in liquid nitrogen, degassed (one time) at 0.3 mm, sealed, and heated at 90 °C for 21 h with stirring. GLC analysis of the resulting mixture disclosed that the olefin had been completely consumed and that the two principal products and some by-products had been formed. The mixture was then diluted with 60 mL of *n*-pentane to precipitate the catalyst which was removed by filtration. Excess carbon tetrachloride and the solvent were evaporated from the filtrate under reduced pressure and vacuum distillation of the residual oil gave two fractions: (a) 0.65 g, a colorless oil, bp 85–105 °C (1.3 mm); (b) 17.1 g, a colorless viscous oil, bp 105–134 °C (1.3 mm).

Among the by-products, only (trichloromethyl)cyclooctane was isolated in approximately 95% purity from fraction (a) by GLC. The IR and NMR spectra of this compound corresponded to the reported spectra:[5b] IR (neat) 2960, 2850, 1470, 1450, 1360, 1245, 985, 890, 760 (s, C-CCl_3), 705 cm^{-1}; NMR (CCl_4) δ 2.35 (m, 1 H), 2.18 (m, 4 H), 1.63 (m, 10 H). There existed two peaks (27:73) on the GLC chromatogram of fraction (b) and each component was isolated in pure form by GLC separation. The IR and NMR spectra of the first eluted compound agreed with the reported spectra[5b] of a mixture of *cis*- and *trans*-1-chloro-2-(trichloromethyl)cyclooctane: IR (neat) 2950, 2860, 1470, 1445, 1240, 975, 830, 760 (s, $CCCl_3$), 690 cm^{-1} (w, CCl); NMR (CCl_4) δ 4.89 (m, 0.2 H, CHCl (cis isomer)), 4.53 (m, 0.8 H, CHCl (trans isomer)), 2.86 (m, 1 H), 2.25 (m, 4 H), 1.68 (m, 8 H). The IR and NMR spectra of the second peak corresponded to the reported spectra[5b] of 1-chloro-4-(trichloromethyl)cyclooctane: IR (neat) 2950, 2860, 1470, 1445, 1240, 980, 950, 840, 760 (s, $CCCl_3$), 675 (w, CCl), 670 cm^{-1} (w, CCl); NMR (CCl_4) δ 4.17 (m, 1 H), 2.71 (m, 1 H), 2.23 (m, 8 H), 1.65 (m, 4 H).

In order to obtain precise data of the product composition, an addition reaction was carried out at 90 °C for 21 h using 2.21 g (20.1 mmol) of *cis*-cyclooctene, 13.02 g (84.6 mmol) of carbon tetrachloride, 0.138 g (0.14 mmol) of the ruthenium(II) complex, and 6 mL of benzene. GLC analysis of the resulting mixture showed production of a 25:75 (26:74 by NMR analysis) mixture of the 1,2 and 1,4 isomers in 93% yield, along with 2% yield of (trichloromethyl)cyclooctane.

Dependence of the Ratios of the 1,2 and 1,4 Adducts on the Catalyst Concentration. Solutions of *cis*-cyclooctene (1.10 g, 10.0 mmol), carbon tetrachloride (6.49 g, 42.2 mmol), the ruthenium(II) complex (0.0113–0.147 g, 0.012–0.153 mmol), and benzene (5 mL) were heated in sealed Pyrex tubes at 90 °C for 0.5–3.0 h during which time reactions proceeded to 15–40% completion. The relative concentrations of the 1,2 and 1,4 adducts were determined by GLC. All runs and determinations were performed in triplicate and the results are presented in Table I.

Temperature Dependence of the Ratios of the 1,2 and 1,4 Adducts. A solution of *cis*-cyclooctene (1.10 g, 10.0 mmol), carbon tetrachloride (6.49 g, 42.3 mmol), the ruthenium(II) complex (0.041 g, 0.043 mmol), and benzene (5 mL) was heated in a sealed Pyrex tube at 90 °C for 1–2 h and 155 °C for 0.3–0.6 h. The resulting mixture was submitted to GLC analysis. The results are presented in Table II. Values listed were obtained from triplicate runs.

Registry No.—*cis*-Cyclooctene, 931-87-3; CCl_4, 56-23-5; $RuCl_2(PPh_3)_3$, 15529-49-4; (trichloromethyl)cyclooctane, 7540-99-0; *cis*-A, 65311-43-5; *trans*-A, 65311-44-6; B, 16844-39-6.

References and Notes

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(2) For reviews, see (a) C. Walling, "Free Radicals in Solution", Wiley, New York, N.Y., 1957, p 247; (b) C. Walling and E. S. Huyser in "Organic Reactions", Vol. 13, C. Cope Ed., Wiley, New York, N.Y., 1963, p 91; (c) G. Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry", MacMillan, New York, N.Y., 1964, p 19.

(3) For reviews, see (a) Y. Mori and J. Tsuji, *Kagaku No Ryoiki*, **27**, 197 (1973); (b) R. Kh. Freidlina and E. C. Chukovskaya, *Synthesis*, 477 (1974); (c) F. Minisci, *Acc. Chem. Res.*, **8**, 165 (1975).

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(5) (a) J. G. Traynham and T. M. Couvillon, *J. Am. Chem. Soc.*, **87**, 5806 (1965); (b) *ibid.*, **89**, 3205 (1967); (c) J. G. Traynham, T. M. Couvillon, and N. S. Bhacca, *J. Org. Chem.*, **32**, 529 (1967).

(6) A sample of 1.20 g (4.9 mmol) of a 34:66 mixture of 1-chloro-2-(trichloromethyl)cyclooctane and 1-chloro-4-(trichloromethyl)cyclooctane, 0.052 g (0.054 mmol) of the ruthenium(I) complex, 5 mL of carbon tetrachloride, and 3 mL of benzene remained intact when heated in a sealed Pyrex tube at 90 °C for 25 h or 155 °C for 6 h.

(7) Supporting evidence for the homolytic nature of the present reaction comes from the result that the reaction was strongly retarded by adding a small amount of galvinoxyl to the reaction mixture.

(8) To the first approximation, the value of the proportionality constant, C, is likely to be unity, since the $RuCl_2(PPh_3)_3$ catalyst appears to be fully converted to the intermediate complex, $Ru^{III}Cl$, during the reaction. This hypothesis is derived from the facts that the ruthenium(II) catalyst was completely dissolved and also that $[CCl_4] \gg [RuCl_2(PPh_3)_3]$.

(9) T. A. Stephenson and G. Wilkinson, *J. Inorg. Nucl. Chem.*, **28**, 945 (1966).

Flow Nuclear Magnetic Resonance Measurement of Nucleophilic Addition to Pyruvate Anion[1]

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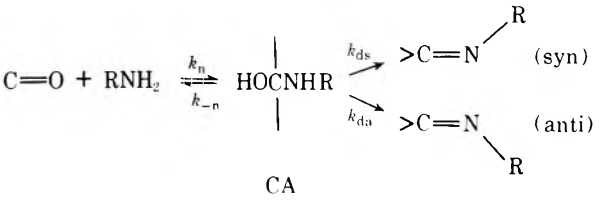
The rate of addition of nucleophiles such as hydroxylamine, methoxyamine, hydrazine, and semicarbazide to the conjugate base of pyruvic acid in water has been determined by line-shape analysis of proton nuclear magnetic resonance signals measured while flowing the reaction mixture. Under these conditions a steady-state concentration of the carbinolamine intermediate is maintained and the signal due to this intermediate is detected either separately or as a coalescence signal. The rate constant for the addition of the nucleophile to form the carbinolamine is found to correlate with K, the equilibrium constant, and not with K_a for the nucleophile. The rate of dehydration of the carbinolamine is found to agree with data found previously. The signals of the syn and anti isomers of the Schiff base products are detected, and the ratios, which may correspond to kinetic control, are reported.

The elaboration of details of the mechanism of the addition of nucleophiles to carbonyl compounds has been of interest to us. The proton nuclear magnetic resonance spectroscopy (NMR) of flowing liquids has been particularly useful in the study of the nucleophilic addition step as well as the dehydration step (and any other subsequent steps). The application of this technique to the study of addition to pyruvic acid (PA) was of interest to us because PA has a somewhat different structure than those studied previously and could, perhaps, provide additional information concerning the preequilibrium addition step. Furthermore, PA plays a key role in many biological pathways, and there may be a possible analogy of our reaction system with some enzyme-catalyzed reactions, e.g., the amino transferase.[2] We wish, therefore, to report the results of a study of the preequilibrium as well as the dehydration step for the reaction of various nucleophiles with PA. This system has been studied previously[3,4] by UV spectroscopy, and the accepted mechanism may be formulated as shown in Scheme I.[5] The detection by our technique of the carbinolamine intermediate CA enabled us to measure the rate constants for the forward and reverse steps k_n and k_{-n} of the equilibrium and those (k_{ds} and k_{da}) for the dehydration of CA to the syn and anti Schiff bases. The values of k_n and k_{-n} are found to be independent of buffer concentration and pH over a limited pH range for all the nucleophiles studied. The values for k_n which ranged from 49 M^{-1} s^{-1} for semicarbazide (SC) to 63 000 M^{-1} s^{-1} for hydroxylamine (HA) correlate with the equilibrium constant K_n for the addition, which was determined using UV spectroscopy with flowing liquids, and not with the pK_a values for the conjugate acids of the nucleophiles. Hydroxylamine, methoxyamine (MA), and hydrazine (HY) have nearly similar values of k_{-n} whereas the value for SC is smaller by at least two orders of magnitudes. The rate for the dehydration step is catalyzed by buffer and hydronium ion. The values in the absence of buffer, obtained by extrapolation, are in reasonable agreement with those reported previously.[3,4]

Scheme I



Experimental Section

The ^1H NMR spectra at 100 MHz were measured at 30.0 ± 0.3 °C under static and flowing conditions without spinning using a suitably modified Varian HA 100-15 spectrometer equipped with a flow system described earlier.[6] All chemicals were obtained from suppliers and the pyruvic acid was distilled before using. Glass distilled water was used for the solutions, which were prepared with an ionic strength of 1.3 (KCl). The pH was measured using a Radiometer PHM 63 digital pH meter equipped with a glass electrode and is reported to ±0.02 unit. The pH of the reaction mixtures was measured as a function of time at 10-s intervals immediately after mixing and was constant to within 0.1 pH unit.

The equilibrium constants for the equilibrium (Scheme I) were measured using UV and flowing liquids in a high-pressure mixing chamber as reported earlier.[6] The discrete rate constants for the forward k_n and reverse k_{-n} steps of the equilibrium were determined by analysis of the NMR line shape for spectra obtained while flowing, as described below. The rate constants for the dehydration step were obtained by stopped flow experiments and an example, obtained by repetitive sweeping of the product oxime CH_3 signals (syn and anti isomers) for the reaction of PA with HA, is illustrated in Figure 1.

The pK_a of each buffer and nucleophile at an ionic strength of 1.3 M KCl was determined potentiometrically at 30 °C and is reported as pK_a'.

Results and Discussion

Figure 2 illustrates the types of 100-MHz proton resonance spectra observed at 30 °C for static solutions (Figures 2A and 2D) and while flowing at 20 mL/min after mixing a solution containing pyruvic acid with one containing a nucleophile. Figure 2A is due to a solution (buffered at 7.5) containing 0.2 M PA prior to mixing; Figure 2B is due to a reaction mixture buffered at pH 7.5 containing 0.1 M PA and 0.2 M SC initially; Figure 2C is due to a reaction mixture buffered at pH 7.5 containing 0.1 M pyruvic acid and 0.2 M hydroxylamine. Figure 2D is obtained for a static solution at the end of the reaction with semicarbazide. The three signals in Figure 2A are assigned to the CH_3 proton resonances of methanol (lowest field), which is used as a reference, the pyruvate anion (middle signal), and the hydrate of pyruvate anion (highest field). According to the relative intensities for these two signals only 10% of the pyruvate anion exists as the hydrate. This value is similar to previously reported results.[7] Upon mixing with SC a new signal at higher field is observed in addition to that due to the pyruvate anion CH_3 group. For several reasons, this signal is assigned to the CH_3 proton resonance of the carbinolamine intermediate arising from the addition of SC. First, it cannot be due to the hydrate of pyruvate anion because its intensity and chemical shift do not coincide with that observed in the absence of semicarbazide. Furthermore the small signal due to the hydrate can also be observed. Second it is a transient signal whose rate of decay is identical to the rate of growth observed for the syn and anti isomers of the semicarbazone whose CH_3 proton resonances are at lower field (Figure 2D). Third, this transient signal has a chemical shift close to

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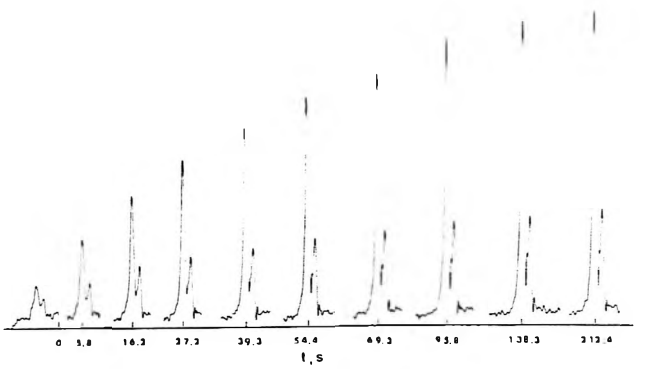


Figure 1. Time dependence for the CH_3-proton resonances of the syn and anti oximes obtained by repetitive scanning of these resonances after the flow had been stopped for a solution at pH 7.5 containing 0.1 M pyruvate anion and 0.2 M NH_2OH initially.

the hydrate signal and, therefore, is probably due to a CH_3 group bound to a tetrahedral carbon atom. Fourth, the intensity ratio, transient/pyruvate anion, depends upon the concentration of semicarbazide and corresponds to an equilibrium constant of 11 M^{-1}, which is very close to 12 M^{-1} measured using flow UV and 10 M^{-1} measured previously.[3] Based on extrapolation of the UV absorbance to infinite nucleophile concentration, Jencks[3] concluded that the intermediates arising from addition of SC, HA, and MA have very small absorbances, i.e., less than 10% of the original absorbance. As illustrated in Figure 2C, the spectrum observed for the NH_2OH reaction mixtures differs markedly from the semicarbazide case in that only one broad signal is observed. The line width and chemical shift of this signal are dependent upon the NH_2OH initial concentration. When the initial concentration of pyruvate ion is held constant, the line width of this signal increases and it moves upfield as the initial concentration of NH_2OH is increased, indicating that this signal is a coalescence of two signals and, therefore, that CH_3 proton exchange between two sites is occurring.[8] In view of the semicarbazide result, this exchange probably is due to the rapid equilibrium between pyruvate anion and its carbinolamine resulting from addition of NH_2OH. Additional support for this exchange process is that the chemical shift for the CH_3 proton resonance of this carbinolamine (δ 1.58) is close to that observed for the one formed by addition of semicarbazide (δ 1.61). This chemical shift was calculated from the NH_2OH concentration dependence of the chemical shift of the broad line using the nucleophilic addition equilibrium constant K_n determined by flow UV. The other two nucleophiles, hydrazine and *O*-methyhydroxylamine, that have been studied give flow NMR spectra similar to that observed for NH_2OH.

Upon stopping the flow after mixing, the resultant spectra are time dependent in the case of each nucleophile; the pyruvate CH_3 resonance or the coalescence signal decays and the signals due to the Schiff base grow. An example of the time dependence of the growth of the syn and anti oximes is illustrated in Figure 1, which was obtained by repetitive scanning of these two signals immediately after stopping the flow. Data of this type and the line width data discussed above were used to obtain information about the rate constants for various steps in Scheme I. The line width data provide values for k_n and k_{-n}, the rate constants for the forward and reverse steps of the rapid preequilibrium, and the time dependence of the various signals provides values for k_{ds} and k_{da}, the rate constants for the dehydration of the carbinolamine CA to form the syn and anti oximes, respectively. The interconversion of syn and anti isomers was not studied since the intensity of the signals due to these compounds is time independent over the

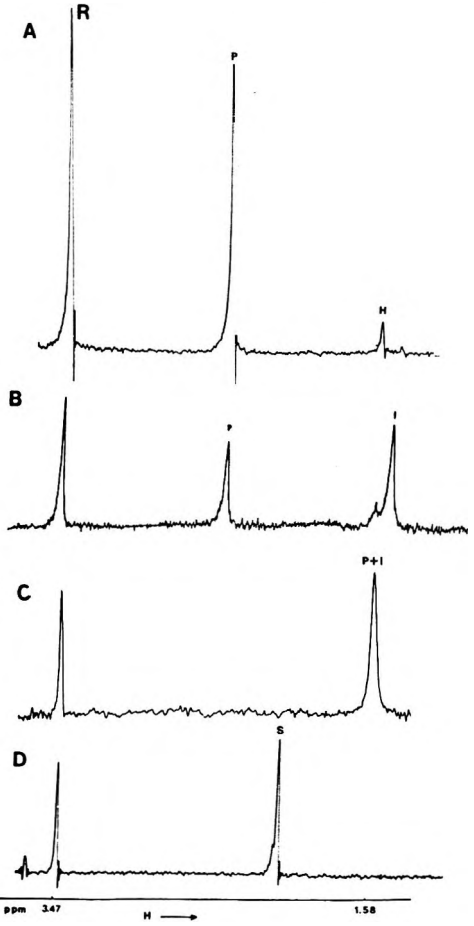


Figure 2. Partial NMR spectra (of CH_3 region only) obtained under static and flowing (20 mL/min) conditions obtained at 30 °C and 100 MHz without spinning. (A) Solution at pH 7.5 containing 0.2 M PA and methanol (labeled R), which acts as intensity and line width reference. The assignment is: P, CH_3 of PA anion; H, CH_3 of PA anion hydrate. (B) Solution at pH 7.5 containing methanol, 0.1 M PA, and 0.2 M semicarbazide initially after mixing; spectrum obtained while flowing. The line labeled I is assigned to the CH_3 resonance of the carbinolamine intermediate. (C) Spectrum obtained while flowing a solution buffered at pH 7.5 containing 0.1 M PA and 0.2 M NH_2OH. Signal labeled P + I is a coalescence of the signals due to the CH_3 protons of PA anion and the carbinolamine intermediate. (D) Static spectrum obtained after the CH_3 signals due to P and I had disappeared for the solution similar to that described in B. Signals labeled S are due to the CH_3 resonances of the syn and anti isomers of the semicarbazone. The resonance due to the anti isomer is a small shoulder to the left of the dominant signal.

time range that they have been monitored (about 2 hours), indicating several possibilities: (a) that these isomers are formed under thermodynamic control, (b) that they are formed under kinetic control and equilibration is fast, (c) that they are formed under kinetic control and equilibration is very slow. The present results give no indication about which of these possibilities obtains; however, in the case of acetaldehyde,[9] the isomers appear to form according to (c). Before presenting and discussing the data from the study of the time dependence, the line width data will be considered.

Methyl-Proton Exchange. Because the flow rate of the liquid is fast relative to the rate of dehydration of CA and is slow relative to the forward and reverse rates of the preequilibrium, a steady-state concentration of CA is maintained while the solution is flowing, and CA is in equilibrium with the pyruvate anion and the nucleophile. For the nucleophiles, semicarbazide and *O*-methylhydroxylamine, the reaction was studied at pH values that are at least 1 pH unit larger than the pK_a of their conjugate acids, and therefore, the concentration for CA could be calculated using the initial concentrations of

Table I. Kinetic Data for the Addition of Semicarbazide to Pyruvate at 30 °C and μ = 1.3 (KCl)

pH	[Buffer],[a] (total), M	SC[b] (total), M	k_n, M^{-1} s^{-1}	k_{-n}, s^{-1}	k_d(anti)[c] × 10^3, s^{-1}	k_d(syn)[c] × 10^3, s^{-1}	k_d(int)[c] × 10^3, s^{-1}	k_{da}/k_{ds}[d]
7.50	Phos							
	0.30	0.20	49.5 ± 0.3		13.7 ± 1.8	15.3 ± 3.5	16.2 ± 0.1	2.9
		0.40	48.6 ± 0.4	4.0 ± 0.1	9.1 ± 0.8	8.1 ± 0.8	8.4 ± 0.5	
		0.80	48.9 ± 0.9	4.1 ± 0.1	10.9 ± 0.6	11.0 ± 0.4	10.3 ± 0.4	3.0
	0.10	0.20	47.5 ± 1.2		6.7 ± 0.1	7.2 ± 0.3	6.9 ± 0.5	
	0.20		49.2 ± 0.8		15.8 ± 3.8		9.3 ± 0.7	
	0.30		48.7 ± 1.1		12.4 ± 0.7	13.7 ± 0.7	11.6 ± 0.4	3.1
7.00	0.30	0.20	47.3 ± 0.8					
		0.40	48.5 ± 0.4	4.0 ± 0.1	33.8 ± 1.9		28.6 ± 1.4	
		0.80	49.3 ± 0.6	4.1 ± 0.7	29.2 ± 0.8		28.8 ± 0.9	
	0.10	0.20	49.0 ± 0.1		18.9 ± 1.3	19.6 ± 1.8	21.24 ± 0.5	
	0.20		46.9 ± 1.3		25.4 ± 2.0	27.0 ± 0.8		
	0.30		48.7 ± 1.1	3.7 ± 0.6	29.4 ± 0.9		31.3 ± 1.6	3.2

[a] Approximate total concentration after mixing (includes all degrees of protonation). The exact values deviated by no more than ±10% from those indicated in the table. [b] Approximate total initial concentration after mixing (includes all degrees of protonation). The exact values, which were used in all calculations, deviated by no more than ±10% from those indicated in the table. The initial concentration of pyruvate anion after mixing was approximately 0.1 M in all runs. [c] Calculated from the decay of the coalescence signal (int) and growth of the syn and anti oxime signals. $k_d = k_{ds} + k_{da}$, first order rate constant calculated as described in text. [d] Obtained from the ratio of the anti to syn oxime signals after completion of the dehydration step.

the starting materials and K_n, the equilibrium constant for addition determined by flow UV. For NH_2OH and NH_2NH_2, the pH of some of the solutions was close to the pK_a of their conjugate acids, and therefore, the pK_a of CA as well as the nucleophile had to be included in the calculation of the equilibrium concentration of CA and CAH^+, the conjugate acid of CA, as will be described in another paper.[10] For this purpose, pK_a values of CAH^+ derived from hydroxylamine and hydrazine were estimated to be 5.29 and 7.20, respectively, using pK_a values for the cations of *N*-methylhydroxylamine[11a] and *N*-methylhydrazine[11b] and adjusting for the substituent effects of the hydroxyl and carboxylate groups by using[12] σ_I = 0.25 and −0.17, respectively, and ρ_I = −3.4. From this equilibrium concentration of CA (plus CAH^+ when appropriate), the proton fraction of the intermediate P_I and pyruvate anion P_P can be calculated, and the average lifetime τ for proton exchange is calculated according to either the equation for slow exchange or the one for fast exchange between two sites.[8]

Slow Exchange: Semicarbazide. Because the CH_3 signals due to pyruvate anion and CA are resolved and do not shift as the concentration of semicarbazide is increased, the exchange rate resulting from the equilibrium is slow relative to $1/\delta$, the reciprocal of the chemical shift between the two signals,[8] and therefore, $1/\tau_P = \Delta_P$ and $1/\tau_{CA} = \Delta_{CA}$ in which $\Delta = \pi(\Delta\nu_e - \Delta\nu_0)$, $\Delta\nu$ is the width at half-height of the appropriate signal, and the subscripts e and 0 denote exchange and no exchange, respectively. For pyruvate, $\Delta\nu_0$ is obtained when semicarbazide is absent. The intermediate CA is assumed to have the same value. The rate constants, which are listed in Table I, are related to exchange lifetimes by the following equations: $1/\tau_{CA} = k_{-n}$ and $1/\tau_P = k_n[N]$ in which [N] is the equilibrium concentration of the semicarbazide free base. Each number listed is an average of at least three measurements. Although the precision of the values appears very satisfactory, it may be somewhat fortuitous since Δ does not always make the major contribution to the total line width, i.e., $\Delta\nu_0$ is about 2.3 Hz and $\Delta\nu_e$ varies from 3 to 6 Hz as the concentration of semicarbazide increases. At any rate since $\Delta\nu$ can be measured to within 0.3 Hz, the rate constants are probably accurate to within about 40% at the low concentrations, and the accuracy improves as the concentration of semicarbazide increases. The fact that the ratio k_n/k_{-n} is about 12 M^{-1}, the same value as obtained for the equilibrium constant K_n determined by flow UV, for all the data in the table indicates that the accuracy is probably no worse than the above mentioned since k_n and k_{-n} are obtained independently. As indicated in the table, k_n is independent of phosphate buffer concentration of semicarbazide. In addition, it remains constant as the pH is increased from 7.00 to 7.50. This absence of any acid or base catalysis is also observed for the other nucleophiles, and the mechanistic implications will be discussed below.

Fast Exchange: NH_2OH, CH_3ONH_2, NH_2NH_2. As mentioned above, when the nucleophile is NH_2OH, CH_3ONH_2, or NH_2NH_2 the preequilibrium of Scheme I is sufficiently fast to make the methyl-proton exchange rate fast relative to $1/\delta$. Consequently, the exchange lifetime is calculated using the equation $\Delta = P_P P_I \delta^2 \tau$, which was derived for exchange between two sites.[8] In this equation, $\Delta = \pi(\Delta\nu_e - (\Delta\nu_0)_P P_P - (\Delta\nu_0)_I P_I)$ and $1/\tau = k_n[N] + k_{-n}$, in which [N] is the equilibrium concentration of nucleophile free base. Thus, using the value for τ and K_n, k_n can be obtained. At pH values for which the concentration of CAH^+ is not negligible, its proton fraction was included, i.e., $P_I = P_{CA} + P_{CAH^+}$. In other words, the exchange is considered to occur between the methyl protons of pyruvate anion and those of CA and CAH^+. This description seems reasonable since the equilibration between CA and CAH^+, which involves only a proton transfer, is expected to be faster than the nucleophile addition, as suggested in another paper.[10] For the three nucleophiles studied under these conditions, Δ makes a major contribution to the line width of the coalescence signal, and the values for k_n listed in Tables II, III, and IV for NH_2OH, CH_3ONH_2, and NH_2NH_2, respectively, are probably more accurate than the semicarbazide results. The values for k_{-n} are also listed in the tables; however, they are not determined independently as they are calculated using k_n and K_n. As in the case of semicarbazide, k_n for the addition of these nucleophiles to the pyruvate anion is independent of pH and the concentration of buffers employed. This absence of catalysis in this pH range has been observed previously,[6a] and the suggested description is illustrated in Scheme II, which is similar to one discussed by Jencks.[5] In this scheme N, >C=O, and >C=N represent nucleophile free base, pyruvate anion, and Schiff base, respectively, and $CA^{\pm}$, CAH^+, and CA represent three possible

Table II. Rate Constants for Addition k_n and Dehydration k_d Steps at 30 °C and μ = 1.3 (KCl) for Hydroxylamine

pH	[Buffer][a]	[NH_2OH][b] (total), M	$k_n \times 10^{-4}$, $M^{-1}\ s^{-1}$	k_d[c](anti) $\times 10^3$, s^{-1}	k_d[c](syn) $\times 10^3$, s^{-1}	k_d[c](int) $\times 10^3$, s^{-1}	k_{da}/k_{ds}[d]
7.50	Phos						
	0.10	0.20	6.3 ± 0.2	10.7 ± 0.1	9.8 ± 0.1		3.2
		0.40	6.2 ± 0.9	9.7 ± 0.4	9.2 ± 0.5	10.5 ± 0.7	3.3
		0.50	6.5 ± 0.9	8.6 ± 0.4	8.6 ± 0.3	8.9 ± 0.4	3.1
	0.10	0.40	6.4 ± 0.7	8.6 ± 0.3	8.5 ± 0.2	8.8 ± 0.3	3.1
	0.30		6.4 ± 0.3	11.0 ± 0.6	11.1 ± 0.7	10.9 ± 0.5	3.3
7.00	Phos						
	0.10	0.40	6.5 ± 0.1	23.1 ± 0.8			
		0.50	6.1 ± 0.9	21.9 ± 0.5			
	0.10	0.40	6.5 ± 0.1	23.3 ± 0.2			
	0.20		6.4 ± 0.1	26.2 ± 0.4	27.9 ± 0.4		
	0.30		6.2 ± 0.2	29.8 ± 0.1	28.1 ± 0.2	28.5 ± 0.8	3.3
6.50	Phos						
	0.30	0.40	5.9 ± 0.4	42.5 ± 0.6	44.5 ± 0.4	43.8 ± 0.8	3.1

[a] Approximate total concentration after mixing (includes all degrees of protonation). The exact values deviated by no more than ±10% from those indicated in the table. [b] Approximate total initial concentration after mixing (includes all degrees of protonation). The exact values, which were used in all calculations, deviated by no more than ±10% from those indicated in the table. The initial concentration of pyruvate anion after mixing was approximately 0.1 M in all runs. [c] Calculated from the decay of the coalescence signal (int) and growth of the syn and anti oxime signals. $k_d = k_{ds} + k_{da}$; first order rate constant calculated as described in text. [d] Obtained from the ratio of the anti to syn oxime signals after completion of the dehydration step.

Table III. Kinetic Data for the Addition of CH_3ONH_2 to Pyruvate at 30 °C and an Ionic Strength of 1.3 (KCl)

pH	[Buffer][a] (total), M	[CH_3ONH_2][a] (total), M	$k_n \times 10^{-4}$, $M^{-1}\ s^{-1}$	$k_{-n} \times 10^{-3}$, s^{-1}	k_d(prod)[b] $\times 10^3$, s^{-1}	k_d[b](int) $\times 10^3$, s^{-1}
6.50	Phos					
	0.10	0.05	3.8 ± 0.1	1.0 ± 0.1	20.3 ± 0.1	18.8 ± 1.8
		0.20			19.5 ± 0.1	20.0 ± 0.4
		0.40	3.7 ± 0.1	1.0 ± 0.1	15.1 ± 3.0	13.1 ± 0.9
	0.20	0.10	4.1 ± 0.2	1.1 ± 0.1	17.7 ± 2.9	17.3 ± 2.1
		0.20	3.9 ± 0.4	1.0 ± 0.1	13.2 ± 3.9	12.3 ± 0.2
	0.30	0.05	4.1 ± 0.3	1.1 ± 0.1	20.3 ± 0.7	18.8 ± 1.8
		0.15	3.8 ± 0.2	1.0 ± 0.1	17.7 ± 1.2	17.9 ± 2.6
		0.20	3.8 ± 0.1	1.0 ± 0.1	20.7 ± 0.9	27.5 ± 4.8
7.00	0.10	0.20	3.8 ± 0.2	1.0 ± 0.1	4.7 ± 0.1	4.6 ± 0.2
	0.30		3.7 ± 0.2	1.0 ± 0.1	4.8 ± 0.2	4.8 ± 0.3
	0.20	0.20	3.7 ± 0.1	1.0 ± 0.1	4.6 ± 0.1	4.9 ± 0.2
		0.40	3.9 ± 0.2	1.1 ± 0.1	4.8 ± 0.1	4.8 ± 0.6

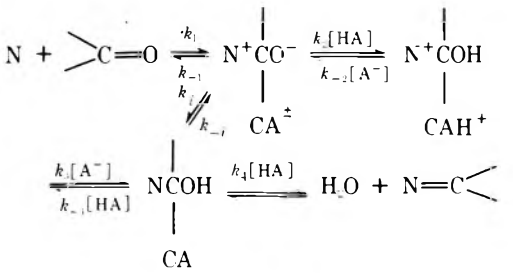
[a] Concentrations after mixing as described in Table I. [b] Obtained from growth of the product signal and decay of the coalescence signal (int). Syn and anti signals are not resolved.

Table IV. Rate Constants for Addition k_n and Dehydration k_d Steps at 30 °C and μ = 1.3 (KCl) for Hydrazine

pH	[Buffer][a] (total), M	[NH_2NH_2][a] (total), M	$k_n \times 10^{-3}$, $M^{-1}\ s^{-1}$	$k_{-n} \times 10^{-2}$, s^{-1}	k_d(prod)[b] $\times 10^2$, s^{-1}	k_d(int)[b] $\times 10^2$, s^{-1}	k_{ds}/k_{da}
8.5	Dabco						
	0.10	0.40	14.3 ± 0.9	6.2 ± 0.1	4.3 ± 0.3	4.6 ± 0.4	
	0.30		14.0 ± 1.1	6.0 ± 0.1	6.5 ± 0.3		
	0.60		13.9 ± 1.7	5.9 ± 0.7	9.2 ± 0.3		
	0.30	0.10	14.8 ± 1.3	6.4 ± 0.1	6.1 ± 0.4		
		0.20	14.5 ± 0.8	6.3 ± 0.1	6.4 ± 0.3		3.0
9.0	0.10	0.40	15.3 ± 1.2	6.4 ± 0.1	5.6 ± 0.1	3.8 ± 0.2	3.4
	0.30		15.8 ± 1.4	6.6 ± 0.1	5.5 ± 0.3	5.8 ± 0.4	
	0.60		14.9 ± 0.9	6.2 ± 0.1	9.5 ± 0.8		
	0.30	0.10	15.2 ± 1.4	6.3 ± 0.1	5.2 ± 0.2		
		0.20	15.7 ± 1.9	6.5 ± 0.8	6.2 ± 0.7		

[a] Concentration after mixing, as described in Table I. [b] Obtained from product signal growth and decay of the coalescence signal (int).

Scheme II



intermediates of which CA (and CAH^+ at lower pH) is believed to exist in appreciable quantity. According to this scheme, the addition reaction involves three distinct steps: nucleophilic addition to form $CA^{\pm}$, protonation of $CA^{\pm}$ to form CAH^+, and deprotonation of CAH^+ to form CA. As can be seen, two steps in this scheme that are independent of acid and base catalysis are the addition step to form $CA^{\pm}$ and direct conversion of $CA^{\pm}$ to CA. Consequently our results for all four nucleophiles are consistent with this path in the pH range studied. This conclusion is consistent with rates of proton exchange found previously for acid–base reactions. Rate constants for proton transfer between nitrogen acids and bases are commonly between 10^7 and 10^9 M^{-1} s^{-1}.[14a] The analogous reaction for phenol-phenoxide ion is equally fast.[14b] Since the concentration of buffer is at least 0.1 M and that for the nucleophile is usually 0.1 M or larger, the overall rate constant for methoxyamine addition via the intermolecular proton transfer steps is estimated to have an upper limit of 2×10^3 M^{-1} s^{-1}, which is one order of magnitude lower than the observed value.[15,16]

Our results provide some information concerning the nature of the proton switch step. A proton switch mechanism involving the OH proton has been suggested as a possibility for the conversion of $CA^{\pm}$ directly to CA in the case of addition of NH_2OH to *p*-chlorobenzaldehyde under conditions in which no buffer is present.[17] Although this mechanism requires no acid–base catalysis and could apparently apply to the present reaction for NH_2OH (and also perhaps for NH_2NH_2 and semicarbazide since the adjacent nitrogens have available protons), this mechanism cannot apply when CH_3ONH_2 is the nucleophile since the oxygen contains no transferable protons. Consequently, we see no need to invoke this type of switch mechanism for the present system since there is no reason to suspect CH_3ONH_2 acts in a different manner than do the other nucleophiles, i.e., its rate of addition is comparable to that for NH_2OH and NH_2NH_2. The absence of buffer effect also precludes a preassociation mechanism.[18]

Apparently, the only data available for comparison purposes concern the addition of semicarbazide[4] in the pH range 3.5 to 5.5. In this pH range, it was suggested that a transition from rate-determining dehydration to rate-determining addition occurs and that this transition is complete at pH 4.0. This conclusion is based on the fact that a plot of the observed rate constant vs. pH exhibits a break, which is commonly considered diagnostic of a transition from one type of rate-determining step to another.[5] Two addition rate constants (one uncatalyzed, the other hydronium ion catalyzed) were obtained by a fit of this pH dependence (in absence of buffer) according to a mechanism similar to Scheme I using the steady-state approximation for CA. Since our results do not indicate a hydronium ion dependence for k_n, the mechanism for addition at lower pH is apparently different than the one proposed for pH range of the present study.

Table V lists the average values of k_n for each nucleophile as well as their pK_a values and K_n. For all of the nucleophiles,

Table V. Values for pK_a', K_n, and the Addition Rate Constant k_n for each Nucleophile

Nucleophile	pK_a'	K_n,[a] M^{-1}	k_n, M^{-1} s^{-1}	k_{-n}, s^{-1}
Semicarbazide	3.76	12.0	49	4.1
Methoxyamine	4.65	36.5	38000	1040
Hydroxylamine	6.08	54.3	63000	1160
Hydrazine	8.24	24	14500	604

[a] Determined by flow UV spectroscopy.

k_n does not correlate with K_a. On the other hand, k_n correlates well with K_n for all nucleophiles except semicarbazide, i.e., a plot of log k_n against log K_n is linear with only the point for semicarbazide deviating from the line. The reason for this deviation is unclear; to correlate, k_n for semicarbazide would have to be two powers of ten larger. Also listed in Table V are the average values for k_{-n}, which is equal to the reciprocal of τ_{-n}, the average lifetime for the break down of the carbinolamine intermediate into starting materials. Thus, the lifetime for this intermediate is about the same for all the nucleophiles except semicarbazide. The factors affecting the lifetime of the intermediate are not clear at this time and will have to await the accumulation of more data on other systems.

Dehydration of Carbinolamine. Because of the values of K_n, the concentration of each nucleophile is such that the equilibrium concentrations of pyruvate anion and carbinolamine intermediate are appreciable. Consequently, while the decay of the pyruvate anion and CA is pseudo-first-order, the rate constant obtained from such a treatment is not the dehydration rate constant k_d. However, k_d may be obtained from the time dependence of the coalescence signal and Schiff base signals in the following manner. Since the intermediate is detected, the rate-determining step is dehydration, and rate $= k_d[CA]$ may be converted to rate $= k_d[PA]_t K_n[N]/(K_n[N] + 1)$ in which $[PA]_t$ is the total concentration of pyruvate anion and [N] is the equilibrium concentration of nucleophile free base.[19,20] If [N] is constant this rate expression may be integrated to give $\ln [PA]_t = k_d\beta t + C$ in which $\beta = K_n[N]/(K_n[N] + 1)$. However, under the present conditions [N] is not constant. Nevertheless this type of expression was used to describe the time dependence of the above-mentioned signals by allowing β to be a variable also. Thus, at each t, [N] was calculated using the appropriate equilibrium constants and taking into account the amount of PA and nucleophile that had been converted to product, and k_d was evaluated as the slope of a least-squares fit of $\ln [PA]_t$ vs. βt. To determine the accuracy of this technique, the time dependence of the concentration of PA was simulated by an incremental method using the above-mentioned rate expression with a specific rate constant similar to those found in our study. Using this simulated time dependence, the rate constant was then calculated according to the least-squares approach mentioned above and compared with the "real" value that had been specified. The deviation of the least-squares value was found to be largest when the concentration of nucleophile is equal to that of PA. Thus, for an initial concentration of 0.1 M PA, the least-squares value was larger than the real value by 25, 10, and 6% for initial concentrations of 0.1, 0.2, and 0.3 M nucleophile, respectively. PA and nucleophile have identical concentrations for only two solutions, and most of the data are for initial nucleophile concentrations of 0.2 M or greater. Therefore, the rate constants listed in Tables I, II, III, and IV are not corrected since the correction is 10% or less. Values labeled "int" were calculated from the time dependence of the coalescence signal; others are calculated from syn or anti Schiff base signals as specified. As indicated, values of k_d calculated from the time dependence of the various signals for a given solution

Table VI. Kinetic Parameters for Buffer Catalysis of the Dehydration Step in the Reaction of NH_2OH, Semicarbazide, and Hydrazine with Pyruvate Anion

Nucleophile	Catalyst	pK_a	pH	Concn range (total), M	Fraction acid[a]	Slope[b] × 10^2 M^{-1} s^{-1}	$k_4^0 \times 10^3$, s^{-1}	k_4^{GA}, M^{-1} s^{-1}	k_4^{GB}, M^{-1} s^{-1}
NH_2OH	Phosphate	6.37	7.5	0.10–0.30	0.069	2.40	7.0	0.10[c]	0.02[c]
			7.0	0.10–0.30	0.190	3.38	20.0		
			6.5	0.30	0.430	5.21	28[d]		
Semicarbazide	Phosphate	6.37	7.5	0.10–0.30	0.069	3.53	5.0	0.10[c]	0.03[c]
			7.0	0.10–0.30	0.190	4.40	16.8		
NH_2NH_2	Dabco	9.24	9.0	0.1–0.60	0.63	12.54	24.0	0.058[c]	0.24[c]
			8.5	0.1–0.60	0.85	8.52	28.0		

[a] Fraction of buffer in the acid form. [b] Obtained by least-squares fit of k_d vs. the total concentration of catalyst. [c] Obtained from a plot of slope vs. fraction acid. [d] Assuming k_4^{GA} and k_4^{GB} have the indicated values.

are within experimental error. In addition, k_d appears to be independent of nucleophile concentration but dependent on buffer concentration except for the nucleophile CH_3ONH_2 as discussed below. For NH_2NH_2, NH_2OH, and semicarbazide, the CH_3 proton resonances to the syn and anti isomers can be resolved. The ratio of these resonances for each nucleophile is independent of time over the time period studied. Consequently this ratio is assumed to be k_{da}/k_{ds}, the ratio of the first-order rate constants for the formation of these isomers from CA,[21,22] and this ratio, which is listed in Tables I, II, and IV, appears to be independent of the nature and concentration of the nucleophile as well as the pH in the range studied. Whether this ratio represents kinetic or thermodynamic control of product formation cannot be decided from our results.

As mentioned above the rate of dehydration of CA depends on the concentration of buffer for all nucleophiles except methoxyamine. The plots of k_d vs. buffer concentration are linear, and the slope which was calculated by least-squares fit is listed in Table VI, along with the buffer concentration range. The general acid k_4^{GA} and general base k_4^{GB} (Scheme II) catalytic rate constants that are listed in this table are calculated in the manner described previously,[6a] assuming a linear relationship between the slope and the fraction of buffer existing in its acid form. According to the results, the phosphate buffer has the same general acid catalytic effect as well as the same general base catalytic effect on the dehydration step of CA when NH_2OH and semicarbazide are the nucleophiles. In addition, Dabco appears to be more effective as a general base catalyst than as a general acid for dehydration of CA when NH_2NH_2 is the nucleophile.

The intercept of the least-squares plot k_4^0, which is also listed in Table VI, appears to be linearly related to the hydronium ion concentration for the nucleophiles, NH_2OH and semicarbazide, although the data are quite limited. The value for pH 6.5, calculated using k_4^{GA} and k_4^{GB}, is based on only one buffer concentration and, therefore, should be considered approximate. For NH_2NH_2, k_4^0 is not linear in hydronium ion concentration, indicating, perhaps, that hydroxide ion may be acting as a catalyst or, perhaps, that an uncatalyzed dehydration process is occurring in this case. Although the data from previous studies were obtained under somewhat different conditions than the present study,[3,4] they appear to be in reasonable agreement with the present results. For semicarbazide, $K_n k_4^0$, which has a value of 0.12 M^{-1} s^{-1} from a previous study,[4] agrees fairly well with the present value of 0.2 M^{-1} s^{-1}. From an earlier work by Jencks,[3] k_4^0 has the following values at 25 °C and an ionic strength of 0.3: 0.007, 0.004, 0.01, 0.08 s^{-1} for NH_2OH (pH 7.0), CH_3ONH_2 (pH 6.5), NH_2NH_2 (pH 8.5), and semicarbazide (pH 7.0), respectively. The difference between these and the values in Tables III and VI could be due to the difference in ionic strength and temperature.

We thank the referee for suggesting the method for estimating $K_\pm$, K_z, and pK_a values for the carbinolamine cations.

Registry No.—Semicarbazide, 57-56-1; pyruvate, 57-60-3; hydroxylamine, 7803-49-8; CH_3ONH_2, 67-62-9; hydrazine, 302-01-2.

References and Notes

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(20) When the concentration of CAH^+ is significant, this expression must be modified. Thus, if CAH^+ is also considered to dehydrate, rate = $(B/Q)\cdot[PA]_t K_n[N]/(1 + K_n[N])$ in which $B = k_d + k_d^+[H^+]/K_a$ and $Q = 1 + [H^+]/K_a$ in which K_a is the acid dissociation constant for CAH^+ and k_d and k_d^+ are dehydration rate constants for CA and CAH^+, respectively.
(21) This assumption is based on the observation that equilibration of syn and anti oximes is slow in this pH range for acetaldehyde (see ref 9) and for diethylacetonyl phosphonate (unpublished results). The assignment of the signals is based on the results of Karabatsos; see ref 22.
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The Search for Stable Nitrenium Ions: Protonation of Benzoquinone Monooximes in Superacids and the Study of Their Structure by Proton and Carbon-13 Nuclear Magnetic Resonance Spectroscopy[1]

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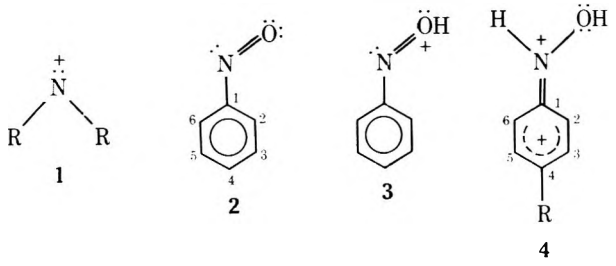
A series of substituted benzoquinone monooximes were protonated with HSO_3F–SbF_5 in SO_2 solution. ^1H NMR spectroscopy has shown that these precursors form diprotonated heteroatom species. Using ^{13}C NMR spectroscopy, the nature of the diprotonated cations was determined by a comparison of the chemical shift data with those of related model compounds. It was demonstrated that the dications are of onium–benzenium ion nature, with the nitrenium ion form not contributing significantly to the overall structure. The γ-substituent effects observed for the dicationic species were studied in relation to the geometry of the substituent to the syn and anti ring carbons. A secondary γ-substituent effect was also observed in the dications. Both effects were empirically measured and shown to be constant and additive.

Gassman and co-workers suggested that nitrenium ions (**1**) are involved as intermediates in the reactions of *N*-hydroxy- and *N*-chloroaniline derivatives under neutral conditions.[2-5] Kinetic data and product analysis support the intermediacy of the nitrenium ions. However, in the recent papers of Okamoto and co-workers[6-8] on the strong acid-catalyzed reactions of nitrobenzene, *N*-hydroxyanilines, and dialkylaniline oxides with benzene, it was proposed that the intermediates are iminiumbenzenium dications (**4**) rather than nitrenium ions (**3**).



1 **2** **3** **4**

In the anodic oxidation of substituted diphenylamines by Serve,[9] it was possible to identify substituted diarylnitrenium ions under basic conditions and the doubly charged substituted N-protonated *N*-phenylanilenium ion under acidic conditions. The lifetime of these intermediates, however, was too short under the conditions employed, and it was thus not possible to examine the nature and structure of these nitrenium and protonated nitrenium ions.

In order to study the possibility of long-lived arylnitrenium ions, we have extended our continued study of cationic organic intermediates to the protonation of nitrosobenzenes (**2**) with "magic acid" in sulfur dioxide solution. ^1H NMR spectroscopy shows that diprotonated derivatives of **2** are observed as stable species (**4**). The nature of these species was determined by ^{13}C NMR spectroscopy. Geometrical isomers of the para-substituted derivatives of **4** were also identified from the ^{13}C NMR spectra. By using methyl groups to control the geometry, unequivocal peak assignments were possible for the isomers.

The latter part of our studies deals with the question of γ-substituent effects in these systems. A comparative study with selected model compounds allowed some qualitative conclusions to be made concerning the effects of γ substituents in the eclipsed conformations.

Results

A series of para-substituted nitrosobenzenes were prepared and protonated with magic acid (1:1, HSO_3F–SbF_5) in SO_2 solution. The ^1H NMR chemical shift data, which are summarized in Table I, were assigned based on comparison between **5** and **6**. The absence of the highly deshielded absorption at δ 14.3 in **6** proved that this absorption in **5** is due to the protonated ketone function (4-OH) since protonated ketones absorb near $\delta_{^1H}$ ~14. The broadened absorption around $\delta_{^1H}$ 13 indicates a proton bonded to nitrogen. The remaining peak around $\delta_{^1H}$ 12 was assigned to that of the proton on the nitroso oxygen atom. In the ^1H NMR spectra, the chemical shifts of the ring protons of the protonated benzoquinone monooximes were usually complex and overlapped, so that specific assignments were generally not possible. In the substituted derivatives **10B**, **11**, and **12A**, however, the methyl group simplified the spectra and assignments could be made unequivocally. All of the ^1H NMR spectral parameters of the benzoquinone monooximes in magic acid solution show them to be diprotonated species.

In order to obtain more information about the structure and nature of the diprotonated benzoquinone monooximes, their ^{13}C NMR spectra were also measured in the cases of **5A–16** (Table II). The assignments of the ^{13}C NMR chemical shifts given in Table II are based on the usual combination of proton-decoupled and -coupled NMR techniques and a comparison of methyl-substituted derivatives of **5** with related model compounds.

From the proton-decoupled and partially coupled ^{13}C NMR spectra, assignments for C_1 and C_4 were determined. A comparison between **16**, where C_1 is equivalent to C_4, and the other dications allowed C_1 and C_4 to be assigned unequivocally from $\delta_{^{13}C}$ 145.3–148.2 and 192.1–197.9, respectively. The assignments for C_1 and C_4 of **13A** and **14** are based on the additivity relationships generally observed for monosubstituted benzenes.

The complexity of spectral parameters for C_2, C_3, C_5, and C_6 made their ^{13}C chemical shift assignments difficult. For example, when a benzoquinone monooxime was protonated in magic acid, ten peaks were observed in the ^{13}C NMR spectrum. The chemical shifts for C_1 and C_4 were, however, readily assigned, as discussed above. The eight remaining chemical shifts can be explained in terms of two structural isomers of **5**, designated as **5A** and **5B**.

A careful analysis of this system shows eight absorptions for C_2, C_3, C_5, and C_6 where the protonated ketone function affects C_3 and C_2 and/or C_5 and C_6. If the hydroxylamine group would have only affected C_2 and C_6 and the protonated

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Table I. The ^{1}H NMR Chemical Shifts (δ) of Diprotonated Benzoquinone Monooximes[a]

Structure	R	Substituent[c,d]	Registry no.	OH	NOH	NH	C_2	C_3	C_5	C_6	Other
5	4-OH		65355-17-1	14.3 (s)	12.1 (d)	13.5 (br)			8.1 (mult)		
6	4-OCH_3		65355-18-2		12.2 (d)[b]	13.8 (br)			8.4 (mult)		5.4 (s, OCH_3)
7	4-OH	6-CH_3	65355-19-3	13.8 (s)	12.0 (d)	13.1 (br)		8.6 (d)	8.0 (br)	7.8 (m)	2.8 (s, 6-CH_3)
8	4-OH	2,6-di-CH_3	65355-20-6	13.4 (s)	12.2 (d)	13.2 (br d)		7.5 (s)	7.5 (s)		2.7 (s, 2-CH_3), 2.9 (s, 6-CH_3)
9	4-OH	3- and 5-CH_3	64355-21-7	14.6 (s)	12.0 (d)	13.5 (br)		8.6 (mult)			2.7 (s, 3- and 5-CH_3)
10B	4-OH	5,6-di-CH_3	65355-22-8	14.1 (s)	12.0 (d)	13.2 (br d)	8.6 (d)	7.8 (d)			2.5 (s, 5-CH_3), 2.8 (s, 6-CH_3)
11	4-OH	3,5-di-CH_3	65355-23-9	13.7 (s)	11.5 (d)	12.9 (br)	8.3 (br s)		7.8 (br s)		2.4 (br s, 3- and 5-CH_3)
12A	4-OH	3,6-di-CH_3	65355-24-0	14.1 (s)	12.1 (d)	13.2 (br)	8.4 (br s)		7.5 (br s)		2.5 (s, 3-CH_3), 2.8 (s, 6-CH_3)

[a] The chemical shifts are referenced from external Me_4Si. [b] There are two peaks with a chemical shift difference of less than δ 0.1. [c] All of the spectra were measured at −60 °C. [d] All of the structures are derivatives of **2**.

5A

5B

ketone group C_3 and C_5, then the chemical shifts of the four carbons C_2, C_3, C_5, and C_6 of **5A** would also be similar to the corresponding ones of **5B**, and only four carbon absorptions would be observed. Thus, the two isomers **5A** and **5B** have different chemical shifts due to their geometry and the substituent effect of the hydroxylamine and protonated ketone groups.

The first approach used to assign the eight remaining carbon chemical shifts of **5** involved substituting methyl groups at the ring positions. Thus, the geometry of the isomers could be limited to specific structures still closely related to the complex spectra of the parent systems. For example, the substitution of methyl groups at the C_3 and C_6 positions of **12** resulted in the observation of six ^{13}C chemical shifts. Of the four possible isomers it can be assumed that **12A** is thermo-

12A

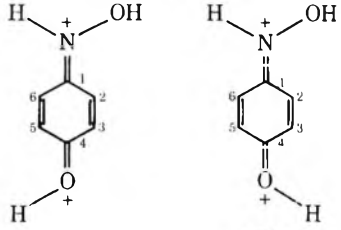
10B

dynamically more stable than the others for static reasons. The same argument holds in the case of diprotonated 5,6-dimethylbenzoquinone monooxime **10**, where structure **10B** should be the most stable.

The assignments of **7A, 7B, 9A,** and **9B** could be made using the chemical shift assignments of **10B** and **12A** as a comparison (Table II). Again applying the chemical shifts of **7A, 7B, 9A,** and **9B,** the peaks for **5A, 5B, 8A, 8B, 11A,** and **11B** were assigned. A majority of the ^{13}C NMR chemical shifts for **5A, 5B, 7A, 7B, 8A, 8B, 9A, 9B, 10B, 11A, 11B,** and **12A** were designated using this comparative method. However, the assignments of a number of the absorptions are interchangeable (**5A, 5B, 7A, 7B, 8B,** and **11B**), as indicated by asterisks and double asterisks, respectively, in Table II. The chemical shift differences are too small to assign these absorptions unequivocally by comparison, and a more specific approach such as substitution or selective labeling experiments would be necessary.

It has been consistently observed in our study that the hydroxylamino group shields C_2 relative to C_6. Thus, the hydroxylamino group should shield the carbon eclipsed by the hydroxyl relative to the carbon anti to it (**5**). This effect can be called the γ-substituent effect. A similar observation can be seen for the protonated ketone group. The C_5 position of **5A** and C_3 of **5B** are shielded relative to C_3 of **5A** and C_5 of **5B,** respectively. Again the protonated ketone group shields the carbons eclipsed with the proton relative to the anti carbon (**5**). These effects can be simply summarized by designating the carbons that are shielded relative to the deshielded ones as S and D, respectively. (It should be noted that S and D are presently only relative terms used to characterize the ^{13}C NMR patterns.) As mentioned before, if these are the only effects, in view of the experimental data, a total of six carbon

Table II. The ^{13}C NMR Chemical Shifts (δ) of Some Parent and Diprotonated Para-Substituted Nitrosobenzenes [a]



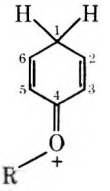
5A

5B

Structure	R	Substituent	Registry no.	C_1	C_2	C_3	C_4	C_5	C_6	Other
5A [b]	4-OH			145.3 (s) [c]	136.8 (d)**	136.1 (d)	196.8 (s)	131.6 (d)	141.5 (d)**	
5B	4-OH			145.3 (s)	136.9 (d)**	133.9 (d)*	196.8 (s)	133.8 (d)*	141.2 (d)**	
6A	4-OCH_3			145.7 (s)	133.6 (d)	136.9 (d)	196.6 (s)	127.3 (d)	141.9 (d)	70.1 (q, OCH_3)
6B	4-OCH_3			145.7 (s)	137.4 (d)*	129.2 (d)	196.6 (s)	134.6 (d)	137.7 (d)*	70.1 (q, OCH_3)
7A	4-OH	6-CH_3		146.3 (s)	136.4 (d)**	135.8 (d)	195.3 (s)	129.9 (d)	157.2 (s)	17.8 and 17.6 (q, 6-CH_3)
7B	4-OH	6-CH_3		146.3 (s)	136.6 (d)**	133.4 (d)	195.3 (s)	132.0 (d)	156.4 (s)	
8A	4-OH	2,6-di-CH_3		146.0 (s)	155.5 (s)	133.8 (d)	192.1 (s)	129.2 (d)	158.5 (s)	17.9 (q, 6-CH) 25.7 and 25.6 (q, 2-CH_3)
8B	4-OH	2,6-di-CH_3		146.0 (s)	156.4 (s)	131.6 (d)*	192.1 (s)	131.3 (d)*	157.4 (s)	17.9 (q, 6-CH_3)
9A	4-OH	3-CH_3		145.4 (s)	132.4 (d)	149.4 (s)	197.2 (s)	131.6 (d)	141.3 (s)	16.4 and 15.8 (q, 3- and 5-CH_3)
9B	4-OH	5-CH_3		145.7 (s)	136.5 (d)	133.7 (d)	197.2 (s)	146.5 (s)	136.5 (d)	
10B	4-OH	5,6-di-CH_3		146.5 (d)	135.9 (d)	133.9 (d)	195.3 (s)	142.9 (s)	150.4 (s)	14.3 (q, 6-CH_3), 12.1 (q, 5-CH_3)
11A	4-OH	3,5-di-CH_3		145.4 (s)	132.1 (d)	140.4 (s)	197.9 (s)	143.0 (s)	137.7 (d)	16.7, 16.1, 16.1, 15.5 (q, 3- and 5-CH_3)
11B	4-OH	3,5-di-CH_3		145.4 (s)	133.2 (d)	146.5 (s)*	197.9 (s)	145.6 (s)*	136.5 (d)	
12A	4-OH	3,6-di-CH_3		146.2 (s)	131.9 (d)	148.8 (s)	195.6 (s)	129.8 (d)	157.0 (s)	7.5 (q, 6-CH_3), 16.1 (q, 3-CH_3)
13	2-OCH_3		65355-25-1	163.8 (s)	107.5 (d)	115.0 (d)	165.8 (s)	113.1 (d)	141.4 (d)	55.8 (q, OCH_3)
14	2-N-$(CH_3)_2$		65355-26-2	163.8 (s)	107.5 (d)	111.6 (d)	156.1 (s)	111.6 (d)	142.8 (d)	41.9 (q, $N(CH_3)_2$)
15a	4-N-$(CH_3)_2$		65355-27-3	145.4 (s)	126.8 (d)	129.8 (d)	160.3 (s)	129.8 (d)	132.2 (d)	47.2 (q, $N(CH_3)_2$)
16, 17	4-NOH(H)		65528-83-8 65528-84-9	148.2 (s)	126.8 (d)	129.8 (d)	148.2 (s)	126.8 (d)	129.8 (d)	

[a] The chemical shifts are referenced from external Me_4Si. Absorption values indicated by asterisks and double asterisks are interchangeable. [b] A and B refer to the geometry of the species. [c] Coupling determined by an off-resonance proton-decoupling experiment.

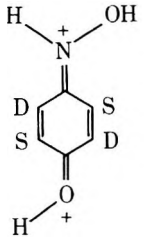
Table III. The ^{13}C NMR Chemical Shifts (δ) of Para-Protonated Phenol and Ortho-Substituted Anisoles[a]



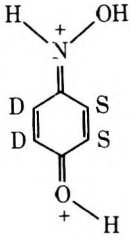
Structure	R	Substituent	Registry no.	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8
18	H[c]		65355-28-4	40.3 (t)[e,f]	173.8 (d)	125.2 (d)	190.8 (s)	125.2 (d)	173.8 (d)		
19	CH_3[b]		37396-37-5	39.9 (t)	168.4 (d)	126.7 (d)	191.9 (s)	120.7 (d)	175.1 (d)	62.2 (q)	
	J_{C-H} (Hz)			126.0	169.3	174.6		173.4	170.5	152.3	
20	CH_3[c]	3-F	65354-79-2	39.6 (t)	144.4 (d)	153.6 (s)	184.3 (s)	121.5 (d)	175.8 (d)	63.6 (q)	
	J_{CF} (Hz)					261.9					
	J_{CCF}				12.8			12.9			
	J_{CCCF}			5.1							
21	CH_3[c]	3-Cl	65354-78-1	41.2 (t)	164.7 (d)	131.1 (s)	187.9 (s)	120.7 (d)	175.1 (d)	63.7 (q)	
	J_{CH} (Hz)			125.3	174.8			174.4	172.7	153.5	
22	CH_3[d]	3-CH_3 (C_8)	37145-56-5	39.4 (t)	164.9 (d)	135.6 (s)	191.0 (s)	120.1 (d)	173.5 (d)	62.0 (q)	15.1 (q)
	J_{C-H} (Hz)			127.6	173.3			172.4	167.2	152.4	130.6

[a] All chemical shifts are measured from external Me_4Si. [b] Measurements were obtained from ref 11. [c] These benzenium ions were made in $HF-SbF_5$ (1:1) in SO_2ClF at −60 °C. [d] This cation was made in HSO_3F-SO_2 at −60 °C. [e] Singlet (s), doublet (d), triplet (t), quartet (q). [f] The off-resonance assignments of s, d, t, or q only represent the C–H coupling and not long-range coupling. These were obtained from off-resonance or fully coupled experiments.

peaks would be observed, but secondary effects are also significant.

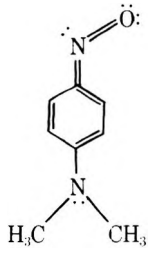


5A

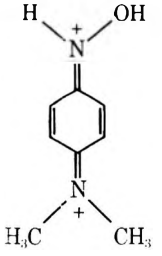


5B

These secondary effects, which result in different ^{13}C NMR chemical shifts, are sometimes small and difficult to assign unequivocally. For example, the effect of a protonated carbonyl group on C_2 and C_3 of **5A** and **5B**, respectively, is too small to be designated. Protonated phenol shows no difference between C_2 and C_6 or C_3 and C_5, and protonated nitrosobenzene itself is unstable. Even diprotonated *p*-dimethylaminonitrosobenzene (**15**) showed no observable differences in the ^{13}C chemical shifts of C_3 and C_5.



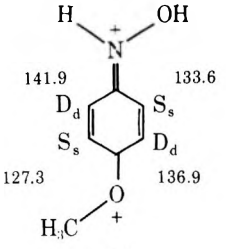
15



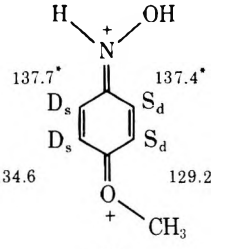
15a

It is known that the ^{13}C NMR chemical shifts of C_2 and C_6 and C_3 and C_5 are nonequivalent in para ring protonated anisole (**19**, Table III).[10,11] The ^{13}C NMR chemical shifts of **19** have not yet been assigned unequivocally. Therefore, a series of ortho-substituted anisoles were protonated and their ^{13}C NMR spectra measured (Table III). The substitution at the ortho position resulted in only one isomer in all cases. A comparison of the ^{13}C NMR chemical shifts and use of the fully coupled spectra for **19–22** resulted in the assignments given in Table III. The same chemical shifts for **19** were deduced and tentatively assigned based on previous work on the rearrangements of benzenium ions.[11]

The ^{13}C chemical shifts show that C_5 is shielded relative to C_3 of **19**. The same primary shielding effect is observed for the methyl carbon of the methoxy group eclipsed with the C_5 relative to the anti C_2. The secondary effect shows that C_2 is shielded relative to C_6. The secondary effects for simplicity will be designated as subscripts d and s. Application of this observation to **6** resulted in the assignments of the ^{13}C NMR chemical shifts shown for **6A** and **6B** in Table II. Similar



6A



6B

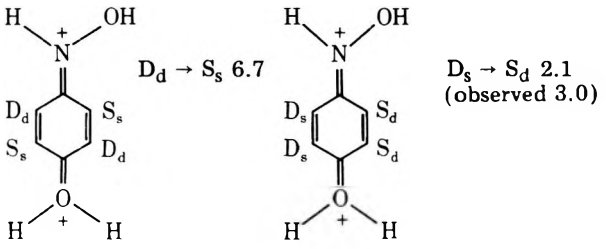
	$C_{2,6}$	$C_{3,5}$
$D_d \rightarrow D_s$	3.8	1.9
$S_s \rightarrow S_d$	−4.2	−2.3
$D_d \rightarrow S_d$	−4.5	−7.7
$S_s \rightarrow D_s$	4.1	7.3

considerations were also applied subsequently to **7A–12A** and **15**. In every case a good correlation was observed with the chemical shifts assigned on the basis of the comparison technique. Additionally, the ^{13}C chemical shifts for the carbons noted in Table II by double asterisks were also designated using this method. For example, whereas **6A** and **6B** were assigned tentatively in a qualitative manner, the present empirical method, however, can be used quantitatively.

Using **6A** and **6B**, the primary and secondary substituent effects can be calculated from the ^{13}C NMR chemical shifts of carbons C_2 and C_6, as well as C_3 and C_5, and are listed accordingly. For example, the secondary effect of the methoxy group can be estimated by the difference of chemical shifts of C_6 of **6A** and C_3 of **6B**, designated as $D_d \rightarrow D_s$, and of C_2 of **6A** and C_2 of **6B**, designated as $S_s \rightarrow S_d$, respectively. If the

effects are additive, the $D_d \rightarrow D_s$ difference should be equal in size but opposite in direction to the $S_s \rightarrow S_d$ difference. In this manner the remaining interchangeable ^{13}C chemical shifts of Table II were assigned (except for C_2 and C_6 of **6B**). The presently assigned ^{13}C chemical shifts showed the smallest overall deviations.

When benzoquinone dioxime was protonated and its ^{13}C spectrum was measured, only three carbon absorptions were observed, indicating that only one isomer was formed. Using the above discussed quantitative method of assignment and the proper $D_s \rightarrow S_s$ and $S_d \rightarrow S_s$ values, it was found that structure **17** best fits the data.

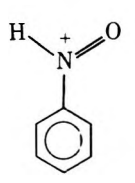


16 **17**

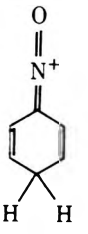
Structures **13A** and **14** were assigned only by the qualitative method. The C_2 and C_6 chemical shift assignments of **14** seem to be reversed from those reported by Grishin, Sergeev, Subbotin, and Ustynyuk.[12]

Discussion

Nitrenium, Onium, and Benzenium Ions. In the protonation of nitrosobenzene, there are three possible sites of protonation: O-protonation (**3**), N-protonation (**27**), and C-protonation (**28**). A resonance structure of **3** can be drawn where the formal charge is placed on the nitrogen (**3B**), thus



27



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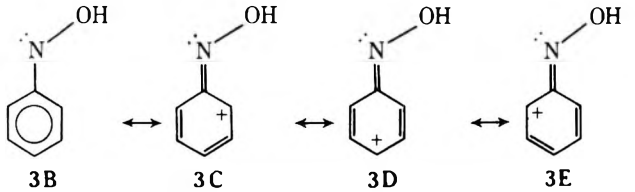


3B **3C** **3D** **3E**

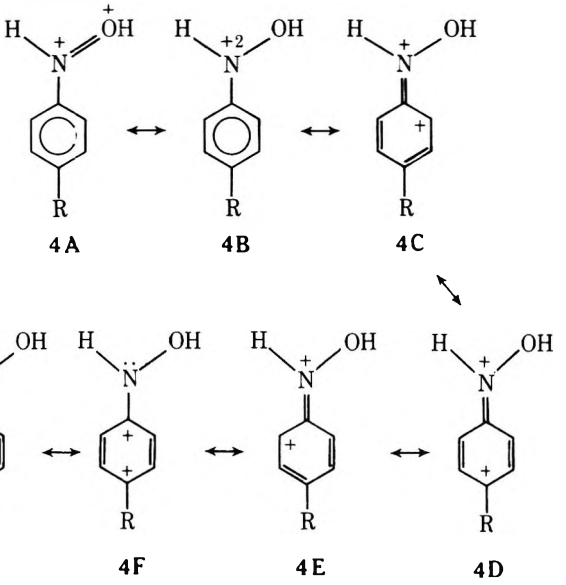
formally giving a nitrenium ion. Additionally, the phenyl ring would stabilize the positive charge by delocalization through structures **3C–E**. Thus, the overall structure of **3** combines the properties of an O-protonated nitroso compound, a nitrenium ion, and a benzenium ion.

Protonation on nitrogen would result in structure **27**, which can be considered similar to an ammonium compound. This compound would be primarily stabilized by the inductive effect due to the electronegativity of nitrogen. Stabilization by resonance contributors would not be expected.

Protonation on the aromatic ring, as in **28**, would result in a benzenium ion whose primary stabilization is through the nitroso group. However, as the para position is substituted with a heteroatom, protonation can be excluded at this position.

When substituted nitrosobenzenes were protonated with magic acid in SO_2 solution, protons added formally at both the nitrogen and oxygen atoms of the nitroso group (Tables I and II), forming the diprotonated cations **4**. The diprotonation of the species was concluded from ^1H and ^{13}C NMR analysis of solutions. These dication species are similar to those proposed by Okamato and co-workers as intermediates in the strong acid-catalyzed reactions of nitrosobenzene.

The protonated dications **4** are stabilized by the combination of structures **3C–E** and **18**, and resonance structures **4A–E** can be written. Structure **4B** would be expected to contribute very little to the overall stabilization because of the two formal charges on nitrogen. Besides the above structures **4A** and **4C–E**, resonance structures **4F**, formally a 4 π system, and **4G**, stabilized by the heteroatoms, will contribute to the overall structure and stabilization of **4**.



4A **4B** **4C**

4G **4F** **4E** **4D**

From the ^{13}C NMR spectroscopic studies it is possible to clarify the structure of the diprotonated species. The ^{13}C NMR chemical shifts of C_1 in Table II are similar to those of the protonated aliphatic oximes[13] and those of C_4 to the para ring protonated phenol and anisole (Table III) and protonated aliphatic imines.[14] Additionally, a comparison of the ^{13}C chemical shifts of C_2, C_3, C_5, and C_6 of **6** and **7** with those of **18** and **19** showed a relative shielding for C_2 and C_6 and a deshielding of C_3 and C_5 for the dications (**6** and **7**) relative to the benzenium ions (**18** and **19**). For a dication one might have expected a much larger deshielding of these ring positions. The absence of significant charge in the ring indicates that the heteroatoms are stabilizing the dications by electron donation.[15] Thus, structure **4A** and **4G** contribute significantly to the overall structure. Some stabilization is provided by delocalization into the ring (**4C–F**) since diprotonated oximes and hydroxylamines similar to **4A** are exchanging under the same conditions.[13]

From previous studies on the structures of carbocations, particularly the styryl and α-methylstyryl cations, substitution at the para phenyl ring position resulted in an overall stabilization of the carbocation through electron delocalization. For example, if the parent styryl cation is compared to substituted *p*-methoxystyryl cations, the carbenium center is shielded and the ortho and para carbons are deshielded relative to those of the parent.[11]

From the substituted cations **5–12** (Table II) the general nature of the parent dictation **4** (R = H) can be inferred by using suitable comparisons. From the ^{13}C NMR data it was shown that structures **4A** and **4G** are the major contributors to the overall stabilization. Replacement of the hydroxyl, methoxy, and dimethylamino groups in the para position by hydrogen should increase the importance of **4A** relative to **4G**. The contributions of **4B–F** will remain about the same in the substituted and unsubstituted cases.

From our study it can thus be concluded that **4** (R = H) is stabilized primarily by **4A** with lesser contributions from **4C–E.** These onium–benzenium-type dications were used by Okamoto and co-workers to explain their products. The increased reactivity was justified by the strong benzenium ion character of **4.** Our work shows that these dications are primarily both a contribution of onium and benzenium ion nature, which results in stabilization of the overall structure and accounts for the increased reactivity observed in reported reactions. However, in sulfuric acid these dications (**4,** R = H) are probably in equilibrium with **27.** The nitrenium ion form **4B** contributes very little, if any, to the overall structure.

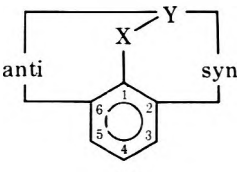
The ^{13}C NMR γ-Substituent Effect. The ^{13}C γ-substituent shielding effect in the gauche or syn configurations has been found for a variety of organic compounds such as alkanes, cycloalkanes, alcohols, amines, aldehydes, oximes, alkenes, alkylbenzenes, alkyl and aryl carbenium ions, and onium ions.[16] These observations make the γ-substituent effect a useful qualitative tool in the assignment of ^{13}C NMR spectra of stereochemically complex molecules.[17]

The basis of the γ-substituent effect was proposed by Grant and Cheney,[16c] who suggested that the interactions of the hydrogens bonded to the α and δ carbons (H–CCCC–H) were sterically perturbating the carbons, causing the shielding effect. Their model was based on nonbonded interactions, which depend on the bond angles and distances. Their theoretical model, developed from the work of Cignette and Allen, was then fitted to their experimental data, forming an empirical equation.

By definition, this model is not generally applicable to systems where nonbonded interactions are not possible, as in the cases of heteroatoms without directly attached hydrogens. In addition, it is generally assumed in hydrocarbons that the γ-shielding effect arises primarily from 1,4-gauche interactions. In contrast, from a variety of examples involving heteroatoms it was shown that the γ-shielding effect in the anti position is larger than that in the gauche position. Additionally, the results of some recent studies[16d,18,19] showed that a hydrogen–hydrogen nonbonded interaction does contribute to the shielding effect where it is applicable. However, it was concluded that other mechanisms play a role, i.e., such as bond angle distortions[19] and conformational effects,[20] in the γ-shielding effect in ^{13}C NMR spectroscopy. Despite the numerous examples of the γ-substituent effects, there is no quantitative method that can predict the relative magnitude for the different cases.

The ^{13}C NMR results of the two structural isomers of diprotonated benzoquinones, such as **5A** and **5B,** showed the nonequivalency of the C_2 and C_6 carbons as well as the C_3 and C_5 carbons. The ^{13}C NMR chemical shifts of these isomers were assigned by comparison with model compounds in Tables II and III, as well as through the use of empirical calculations from substituent effects. The origin for the nonequivalency of C_2 and C_6 and C_3 and C_5 and the basis of their assignments are called under the general term, the γ-substituent effect.

In all of the benzoid systems to be discussed it can be assumed that all of the atoms are in the same plane. Therefore, the γ-substituent effects observed from the ^{13}C NMR spectra result from the syn or anti configuration of a γ group relative to the group on the C_2 and C_5 carbons (**23**), respectively. In

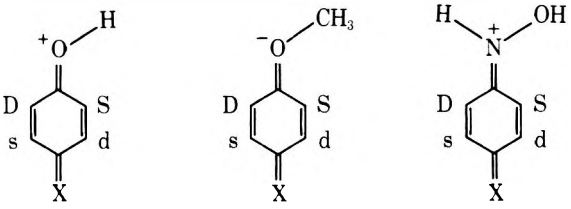


23

such aromatic systems where restricted rotation is slow the C_2 and C_6 carbons, and sometimes C_3 and C_5, of **23** are nonequivalent in the ^{13}C NMR spectra. The sources of the latter's nonequivalence (π polarization, induced dipole, or field effect) are not immediately obvious. It was therefore necessary to ascertain the assignment of these ^{13}C NMR chemical shifts as well as those for the C_2 and C_6 carbons.

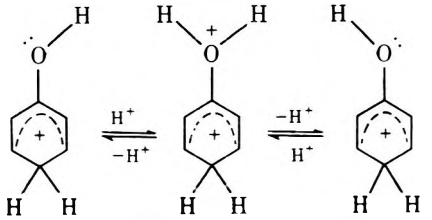
In the case of para ring protonated anisole and benzoquinone monooximes, the C_3 and C_6 carbons, respectively, were sterically blocked by the γ substituent (methyl group, fluorine or chlorine group). Thus, the C_2 carbon is always situated syn to the γ substituent. The absorption, therefore, could be unequivocally assigned by a comparison of the ^{13}C chemical shifts in Tables II and III.

From the assignments of the ^{13}C NMR spectra of the corresponding hydroxyl, methoxy, and hydroxylamino derivatives, the general pattern of relative shielding was determined and is shown in **24–26.** The letters S and s designate that these



24 **25** **26**

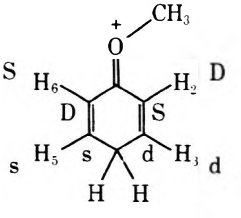
carbons are shielded relative to those labeled D and d, respectively. It is interesting to note, however, that the ring protonated phenol itself does not show any nonequivalence of C_2 and C_6 or C_3 and C_5. This apparent discrepancy is probably due to some exchange of the hydroxyl hydrogen with the strong protic acid since this hydroxyl proton was not observed in the ^1H NMR spectrum.



However, the effect of the hydrogen of the protonated ketone group in the diprotonated benzoquinone monooximes does show a relative γ-shielding effect of approximately 2 ppm in every case. It had been usually assumed previously that there was no γ-substituent effect for a hydrogen atom itself. The secondary effects (d, s) of the γ-substituent effects in the diprotonated benzoquinones were now also observed for the hydrogen atom. These effects were usually less than 1 ppm, which is much smaller than that observed in the case of protonated anisole (i.e., 6.7 ppm).

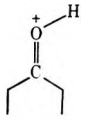
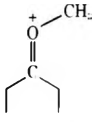
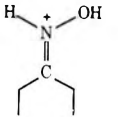
The average γ-substituent effects as well as the secondary effects of **24–26** are summarized in Table IV. Generally, the values show that the γ shielding and the secondary effects for a specific γ substituent produce the same values, indicating that the γ-substituent effect is additive. However, the different values of γ-substituent effect for the different γ substituents suggest that a different interaction mechanism(s) results in a different contribution to the overall effect.

The secondary effect had been previously observed in the ^{13}C NMR spectrum of **19.** Secondary effects have also been



19

Table IV. Relative γ-Substituent Effects for Benzoid Cations

Function	γ effect (C_2 and C_6), ppm	Exp[b]	Secondary effect (C_3 and C_5), ppm	Exp[b]
 24	−2.3 ± 0.1	3	−0.2 ± 0.1	3
 25	−7.0 ± 1.0	3	−4.9 ± 1.9	3
 26	−4.6 ± 0.9	6	−1.8 ± 0.5 −2.2 ± 0.3[a]	6 5

[a] The 0.0-ppm value obtained from 15 was excluded from the average. [b] Number of experimental measurements.

noted in various other ring systems where restricted rotation produces an observable nonequivalency of ring carbons and hydrogens. However, they have not been attributed to the γ substituent.

Unlike the γ-substituent effects in saturated systems, the γ-substituent effects of these benzoid ring systems are observed in the ^1H NMR spectra. For example, the effect was observed in the ^1H NMR spectrum of the para ring protonated anisole. By substituting the C_3 of **19** with a blocking group, the methoxyl methyl group always positions itself syn to the C_2 carbon. Thus, it should be possible to assign the ^1H NMR chemical shifts in a manner similar to the ^{13}C NMR shifts. However, the differences found are approximately intermediary, and thus only a tentative assignment can be made with H_2 and H_3 being shielded relative to H_6 and H_5, respectively. This suggests that the secondary effects result from π polarization of the double bonds of the quinoidal structure **19** rather than an induced dipole or a field effect being operative. These results are, however, only tentative, and more unequivocal assignments of the ^1H and ^{13}C NMR spectra as well as a functional theoretical basis will be necessary before a generalized approach can be presented.

There are two anomalies which cannot be explained by the overall concept, i.e., the diprotonation of **13** and **14**. Since both compounds show the same discrepancy, only **14** will be discussed for simplicity. The ^{13}C NMR assignments of **13** and **14** are based on the assumption that the oxygen atom of the nitroso function shields C_2 relative to C_6. However, upon protonation it is expected that all of the ring carbons will be deshielded due to charge stabilization. In fact, the C_2, C_3, and C_5 carbons are deshielded; however, the C_6 carbon becomes shielded by 10.6 ppm. It was shown that the hydroxyl proton of a protonated ketone **23** relatively shields the syn ring carbon by 2.0 ppm. Thus, the hydroxyl proton of hydroxylamine cannot be the cause of the larger shieldings. The effect probably results from the fact that the mechanism of the γ-substituent effect of the nitroso function changes on protonation. Thus, the γ-substituent effect of the hydroxylamino group cannot be compared with that of the nitroso function since they are significantly different groups.

Planar systems, as studied above, offer a convenient way to investigate the γ-substituent effects in the syn and anti configurations. With unequivocal assignments of the ^1H and ^{13}C NMR spectra it will be possible to make more conclusive statements about the γ-substituent effect and its mechanism, including the observed secondary effects.

Conclusions

The NMR study of diprotonated benzoquinone monooximes (or *p*-nitrosophenols) showed that they are heteroatom protonated dications. Although protonation formally occurred on the adjacent nitrogen and oxygen atoms of the nitroso function, the dications are very stable since the charge is primarily delocalized between the distant hydroxylamine and hydroxyl groups. Thus the diprotonated benzoquinone monooximes are best described as containing a protonated oxime and a protonated ketone group. The contribution by any nitrenium ion form is minimal, if any, for the diprotonated benzoquinone monooximes.

The nature of N,O-diprotonated nitrosobenzene can be inferred to from that of the diprotonated benzoquinone monooxime. From a comparison of related substituted onium ions, the only expected difference is a change in charge delocalization. However, the absence of a charge stabilizing group results in a significant change in the electron density distribution as well as overall stabilization as reflected by the NMR shifts. Based on these considerations, N,O-diprotonated nitrosobenzene is an iminiumbenzenium dication, as proposed by Okamoto and co-workers.[6-8]

The planar diprotonated benzoquinone monooximes offer suitable models to study the γ-substituent effect of the syn and anti configurations. From these studies it was possible to show that even a hydrogen atom produces a γ-substituent effect. The hydrogen and methyl γ-substituent effects of a protonated or methylated carbonyl group or a protonated oxime group, respectively, were relatively measured by ^{13}C NMR spectroscopy and found to be constant and additive. Additionally, secondary effects of the nonequivalent C_3 and C_5 carbons related to the γ substituent were also observed and found to be consistent for each functionality. The ^{13}C NMR γ-substituent and secondary effects show a qualitatively predictable pattern. Thus, these systems provide a means of studying the γ-substituent effect. However, more work is necessary before these results can be placed on a more solid quantitative basis.

Experimental Section

Starting Materials. The precursor benzoquinone monooximes, benzoquinone dioxime, *p*-nitrosoanisole, and *p*-nitroso-*N,N*-dimethyaniline were prepared by known methods. The preparation of the benzoquinone monooximes was carried out by nitrosation of the appropriate phenol derivatives used in the work of Sternhell and Norris.[20] Benzoquinone dioxime was made from the condensation reaction of hydroxylamine and benzoquinone.[21] *p*-Nitroso-*N,N*-dimethylaniline was prepared by the nitrosation of *N,N*-dimethylaniline.[22] The esterification of *p*-nitrosophenol was carried out with methanol and sulfuric acid.[23]

Anisole and its ortho-substituted derivatives, used in the formation of the corresponding benzenium ions shown in Table IV, were commercially available (Aldrich Chemical Co.) and were used without further purification.

Preparation of Solutions of the Ions. Solutions of the dications (**5A–12A, 15,** and **16**) were prepared at −78 °C in a dry ice–acetone bath. The precursors (0.1–0.3 g) were dissolved in SO_2 (1 mL), and these solutions were carefully added to a well-stirred solution of HSO_3F–SbF_5 (1:1 molar, 2.0–3.0 g) dissolved in SO_2 (1 mL).

The benzenium ions shown in Table IV were prepared by the same method. However, the specific acids used in each case are different and are listed in Table IV.

Nuclear Magnetic Resonance Spectroscopic Studies. The ^1H NMR spectra were recorded on a Varian Associates Model A56-60 NMR spectrometer equipped with a variable temperature unit. All ^1H NMR chemical shifts were measured from external Me_4Si.

The ^{13}C NMR spectra were recorded on a Varian XL-100-15 NMR spectrometer equipped for proton decoupling, with a variable temperature unit and a 620/L computer with 16K data points. The instrument was run in the Fourier transform pulse mode with proton

decoupling of the fully coupled measurement obtained from a pulse routine that produces some nuclear Overhauser enhancement. The pulse width (H_1 field) in typical experiments was 2–25 σ, where a 42-μs pulse is equivalent to a 90° pulse. Acquisition times were between 0.3–0.8 s with pulse delays of 0–9 s depending on the experiment. The total number of transients for a suitable signal to noise ratio for each absorption varied from 100 to 7000 passes. The radio frequency was 25.16 MHz with the absorption referenced from 5% enriched external Me_4Si.

Acknowledgment. The National Institutes of Health are gratefully acknowledged for their support of this work.

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Studies on Terpenes. 5. Synthesis of (+)-Hinesol and (+)-10-Epihinesol

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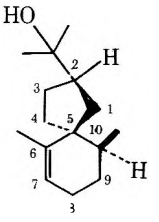
(−)-β-Pinene was converted into 9-methyl-6-carboethoxymethyl-7-oxatricyclo[4.3.0.$0^{3,9}$]nonane (**12**, R = H) which was homologated to the ester **15**. The ester **15** was rearranged to the diacetate **16** which on further elaboration gave **31**. Fragmentation of **31** as outlined (**9** → **10**) gave the spiro[4.5]decane **32**, which was readily transformed into a mixture of (+)-hinesol and 10-epihinesol. The synthesis correlates (−)-β-pinene with (+)-hinesol.

Since the revision of the structures of the vetivane sesquiterpenes[3] from hydroazulenes to spiro[4.5]decane skeletal types,[4] many syntheses of this unusual class of terpenes have been reported.[5] Only one synthesis of optically active spiro[4.5]decanes has been described.[6] Here we report the synthesis of (+)-hinesol (**1**)[23] from (−)-β-pinene as part of our



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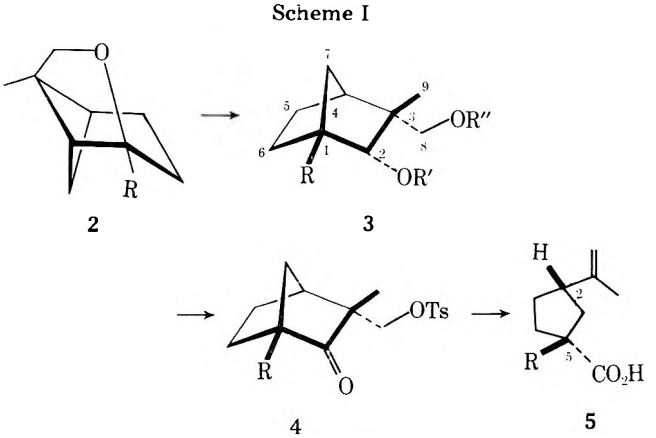
general program that led to the conversion of (−)-β-pinene into grandisol.[7]

The overall strategy of our approach was established by the observation that certain 7-oxatricyclo[4.3.0.$0^{3,9}$]nonane derivatives **2** can be rearranged to 8-substituted 1,3,3-trimethylnorbornane derivatives **3**. Subsequent fragmentation of the compound **4** to a cyclopentane derivative **5** provides a simple, yet effective way of establishing the correct absolute configuration at C-2 and C-5 in hinesol.[7,8] Scheme I summarizes this strategy. To provide a synthesis of (+)-hinesol (**1**) the substituent R in **2** must be capable of being elaborated to eventually become part of the cyclohexene ring of **1**.

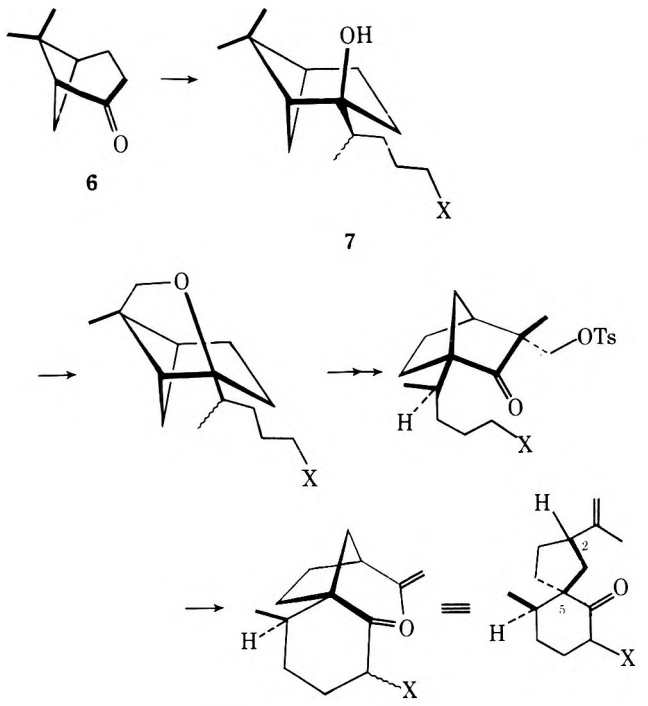
The standard method of preparing 7-oxatricyclo[4.3.0.$0^{3,9}$]nonane derivatives[8,9] **2** involves the addition of Grignard reagents or organolithiums to (+)-nopinone (**6**) and subsequent intramolecular oxidation of the resulting products **7** to the ethers **2**. All attempts to introduce a suitable R group that contained all the requisite carbon atoms, namely a C_5 unit, were unsuccessful.[10] Extension of Scheme I to the spe-

Scheme I



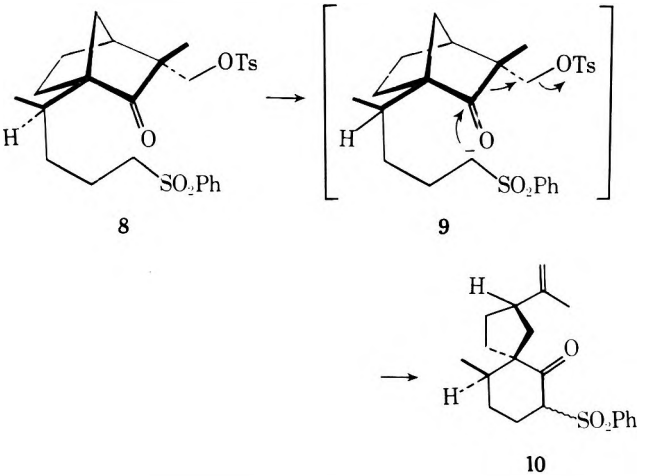
2 **3** **4** **5**

Scheme II

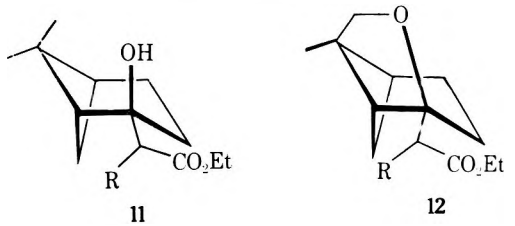


cific case where R is a group that can eventually provide (+)-hinesol is outlined in Scheme II.

The group X must be capable of supporting an adjacent negative charge, and for this purpose we chose the phenylsulfonyl group (X = SO_2Ph) for the following reasons: it is stable to oxidation; and it.can be removed under mild conditions that do not reduce carbonyl groups. The overall strategy outlined in Scheme II can be extended to the specific objective of synthesizing 8 and examining its conversion via the anion 9 into 10. Since we had to build the five-carbon side chain

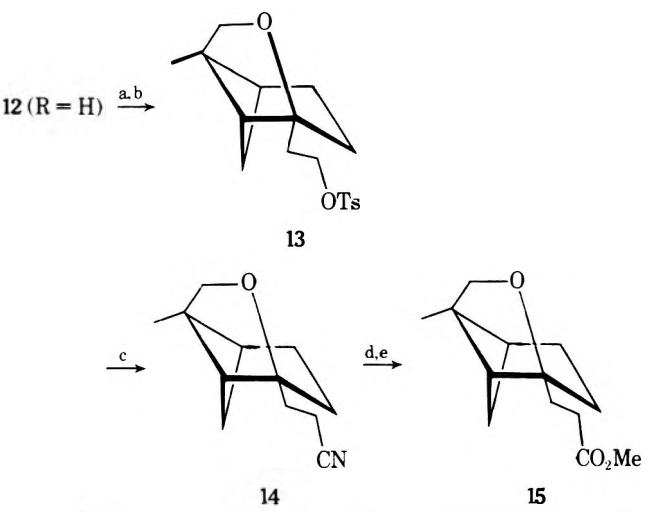


stepwise, a suitable starting material is 11 (R = H), which is conveniently prepared by a Reformatsky reaction on (+)-nopinone using ethyl bromoacetate.[11] Intramolecular oxidation (I_2/HgO/$h\nu$) of 11 (R = H) gave the required ether 12 (R



= H)[9] in excellent yields. Efforts to introduce the *sec*-methyl group at the eventual C-10 by the Reformatsky reaction between (+)-nopinone (6) and ethyl α-bromopropionate gave the β-hydroxy ester 11 (R = Me), but treatment of 11 (R = Me) with I_2/HgO/$h\nu$ gave mainly radical fragmentation to (+)-nopinone with only small amounts of the ether 12 (R = Me) being present.

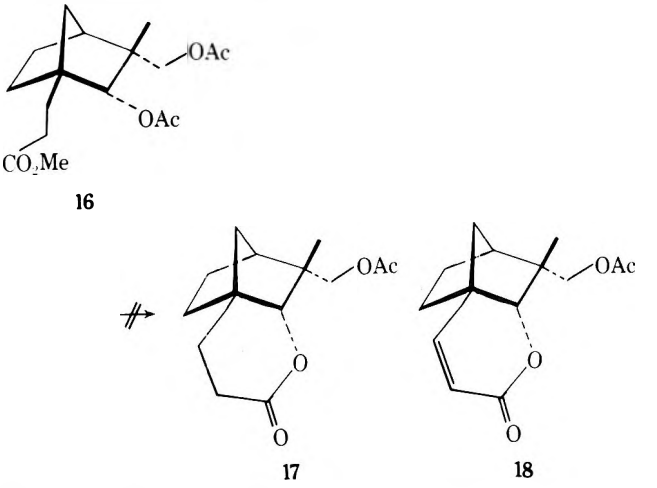
Scheme III



(a) $LiAlH_4$/THF (68–82%); (b) TsCl/pyridine (74–98%); (c) NaCN/Me_2SO (78–91%);[12] (d) NaOH/H_2O/EtOH (73–98%);[13] (e) MeOH/resin IR-120(H) (80–91%).

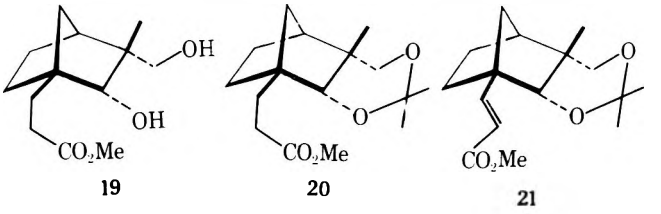
The ether 12 (R = H) was converted into the homologous ester via standard procedures (Scheme III). The cited yields represent the low end and high end of a number of preparations, both on a small and large scale.

When the ester 15 was exposed to BF_3·OEt_2 at 0 °C in acetic anhydride the rearranged ester diacetate 16 was formed in excellent yield (90–100%).[8] All efforts to convert 16 into the lactone 17 were unsuccessful. The lactone 17 might have provided a stereospecific method of introducing the methyl

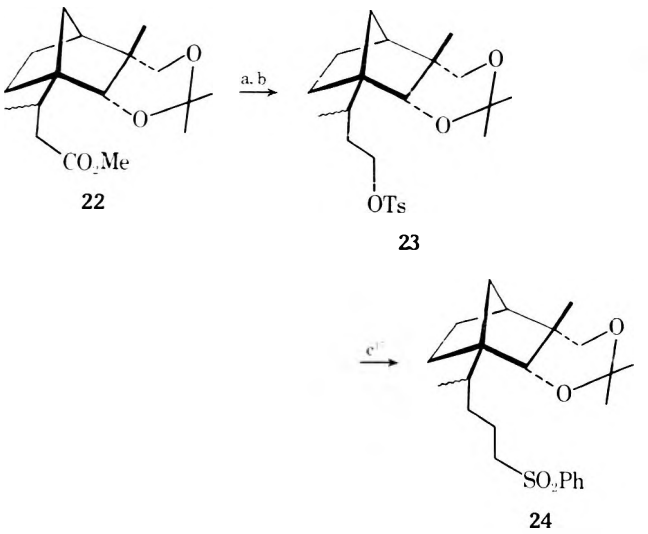


group at C-10 via conjugate addition (Me_2CuLi) to the dehydro lactone 18 (exo approach).

Hydrolysis of the diacetate 16 using sodium methoxide in methanol gave the ester diol 19 in mediocre yield (49%), whereas treatment of the diacetate 16 with methanolic sulfuric acid gave 19 in 96% yield. The 1,3-dihydroxy system in 19 was protected as the acetonide derivative 20,[14] which was con-

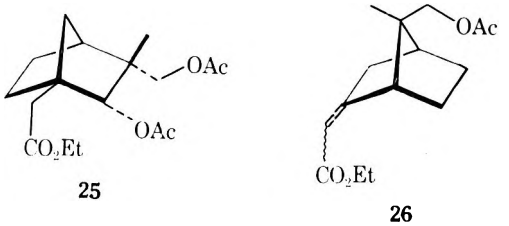


Scheme IV



(a) $LiAlH_4$/THF (94–100%); (b) TsCl/pyridine (95–100%); (c) $PhSO_2Me/NaH/Me_2SO$ (68–69%).

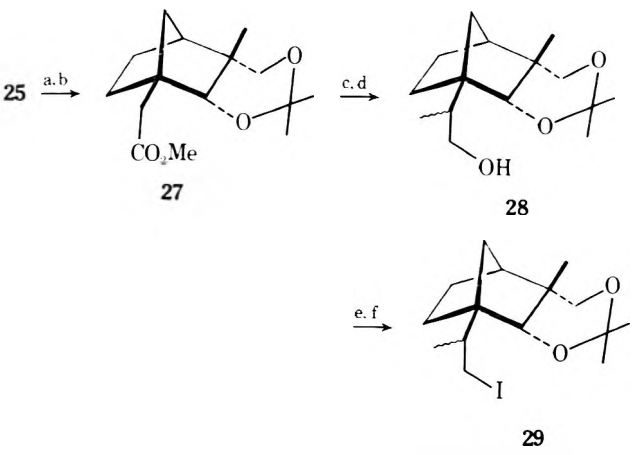
verted into the α,β-unsaturated ester **21** using LDA/$(PhSe)_2/NaIO_4$.[15] The only product formed in this dehydrogenation sequence was the trans isomer (96%). The α,β-unsaturated ester **21**, on treatment with dimethylcopperlithium[16] in ether, gave **22** as a 1:1 mixture of epimers at C-10 as judged from the relative intensities of the NMR signals for the methyl group (C-10) at τ 9.1 and 9.05 (J = 6 Hz). All attempts to separate the epimers were unsuccessful. The ester **22** was converted into the sulfone **24** by the sequence of reactions outlined in Scheme IV. While the above described route to **24** is efficient in terms of yield for each individual step, resulting in an overall yield from **11** (R = H) to **24** of 26.5%, the number of stages is large, namely 14. Consequently we sought a shorter route from **11** (R = H) to **24**. The cyclic ether **12** (R = H) was reacted with acetic anhydride/boron trifluoride etherate at 0 °C for 15 min to give the rearranged product **25**.



Longer reaction times led to further rearrangement resulting in **26**. The diacetate **25** was converted through the sequence of reactions in Scheme V into **29**. The iodide **29** was treated with lithium wire in pentane at reflux followed by 1-pentynylcopper/2HMPT,[18] and the resulting complex was treated with phenyl vinyl sulfone[19] to give **24**, albeit in low yield (5–10%). This low yield could not be increased despite many efforts and modifications. Consequently, while the number of stages through the sequence from **11** (R = H) to **24** is only eight, the overall yield is 2.5%, largely because of the last step.

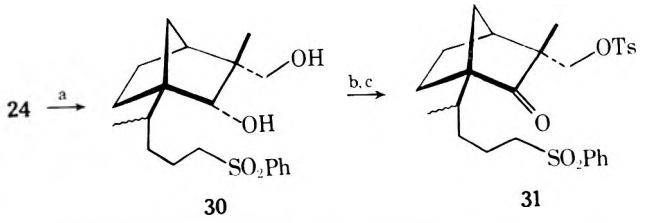
The acetonide **24** was hydrolyzed to the diol **30** and converted into the keto tosylate **31** (Scheme VI). The keto tosylate **31** was treated with sodium hydride in Me_2SO at room temperature to give the β-keto sulfone **32** (65%) and a product **33** formed in approximately 5% yield. If the above fragmentation reaction was carried out at higher temperatures (~50 °C), the yield of the product **33** increased to at least 20%. It is essential in this reaction that all traces of water are scrupulously removed, otherwise the carboxylic acid **34** is formed. Other combinations of base systems, such as LDA/THF, t-BuOK/

Scheme V



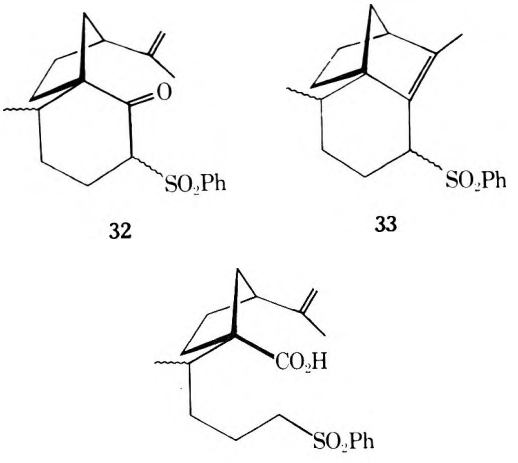
(a) $MeOH/H_2SO_4$ (95%); (b) acetone/$CuSO_4/H_2SO_4$ (77%); (c) LDA/THF/MeI (82%); (d) $LiAlH_4$/THF, −70 °C (67%); (e) $MeSO_2Cl$/pyridine (92%); (f) NaI/MEK (91%).

Scheme VI



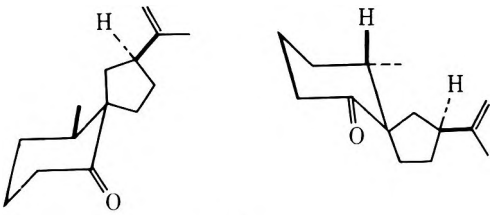
(a) 6 N $HCl/CHCl_3$/dioxane (4:1) (55–79%); (b) TsCl/pyridine (94–100%); (c) CrO_3/2 pyridine/CH_2Cl_2 (75–98%).

THF, and t-BuOK/t-BuOH, reacted with the keto tosylate **31** to give a complex mixture which contained very little of the β-keto sulfone **32**. The NMR spectrum of **32** displays two



distinct doublets for the epimeric methyl groups (τ 9.22 and 9.03, J = 6 Hz) and two well-separated singlets (τ 8.32 and 8.43) for the isopropenylmethyl group. All attempts to separate the epimers of **32** were unsuccessful. The β-keto sulfone **32** was treated with aluminum amalgam[20] in aqueous THF to give the ketone **35** (70–90%). The NMR spectrum of **35** shows a singlet at τ 5.28 corresponding to the vinylic protons, and a pair of overlapping doublets (J = 6 Hz) at about τ 9, corresponding to the epimeric methyl groups at C-10. In the presence of tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium (III), the NMR spectrum shows two well separated singlets of equal intensity, corresponding to the vinylic protons. The two overlapping doublets, also of equal intensity, are shifted downfield (τ 8.7).

The mixture of ketones **35** was reacted with methylmagnesium iodide to give the tertiary alcohol **36** (74–97%), which



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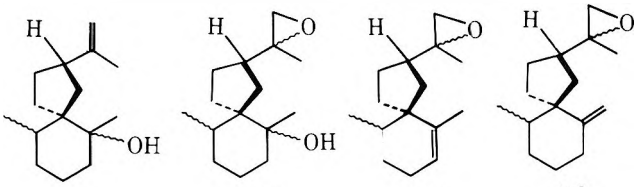
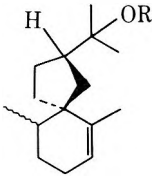
was converted into the epoxide **37** (88%) using *m*-chloroperbenzoic acid. The epoxidation was carried out in the presence of sodium bicarbonate to prevent possible acid-catalyzed formation of byproducts because of the proximity of the hydroxyl group and epoxide group.[21] Indeed, in the absence of sodium bicarbonate a large number of products were formed, whereas in the presence of this base the transformation to the epoxide **37** took place cleanly. Dehydration of **37** using the Burgess reagent[22] gave a mixture and endo- (**38a**) and exocyclic (**38b**) olefin isomers in an average ratio at 1.6:1. The



36 **37** **38a** **38b**

exocyclic isomer **38b** can be converted into the endocyclic isomer by treatment with *p*-toluenesulfonic acid in benzene, resulting in an overall yield of 44%. Reduction of **38a** with lithium aluminum hydride gave an alcohol whose spectral properties are compatible with the structure **39** (R = H), namely (+)-hinesol and its C-10 epimer.[25] (The specific rotation of **39** as 1:1 epimers is +35.4°, confirming the dex-



39

trorotatory form of the product. The literature values[3,4,5] are −40.2 and −47.8°.) Since the acetates of **39** (R = H) and its 10-epimer are known[5] and separable (VPC), this constitutes a synthesis of optically active (+)-hinesol and 10-epihinesol.

This synthesis correlates (+)-hinesol (**39**, R = H) with (−)-β-pinene, and utilizes two novel key rearrangements, **15** → **16** and **31** → **32**, to achieve this synthesis.

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded for Nujol mulls or liquid films on Pye Unicam SP200 and Perkin-Elmer 257 instruments. Ultraviolet spectra were measured on a Pye Unicam SP800 spectrometer, and NMR spectra were recorded with a Varian T-60 spectrometer for solutions in [^{2}H]chloroform using Me_4Si as an internal standard unless otherwise indicated. Mass spectra were run on an AEI MS-9 high-resolution instrument. Optical rotations were measured as solutions in given solvents on a Perkin-Elmer 141 polarimeter. Analytical preparative GLC was performed by a Perkin-Elmer F11 and a Pye 105 instrument, respectively. Solvents were purified and dried by standard techniques. Light petroleum refers to the fraction, bp 40–60 °C.

9-Methyl-6-carboethoxymethyl-7-oxatricyclo[4.3.0.0^{3,9}]nonane (12, R = H). Ethyl nopinolacetate **11** (R = H) (1.0 g) in dry carbon tetrachloride (30 mL) at −10 °C was treated with yellow mercuric oxide (3 g dried under vacuum at 80 °C), followed by iodine (1.3 g). The mixture was irradiated (tungsten lamp, 750 W) under a stream of N_2 and slowly warmed to room temperature. After 48 h the above mixture was filtered and the filtrate was washed with saturated aqueous sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. The crude product was purified by passing through alumina (G3, 15 g) and eluting with light petroleum/ethyl acetate (9:1) to give the pure ether **12** (R = H) (0.7 g; 70%):[9] IR 1740, 1205, 1175, and 1055 cm^{-1}; NMR τ 8.76 (3 H, t, *J* = 7 Hz), 8.73 (3 H, s), 7.43 (2 H, s), 6.18, 6.64 (2 H, ABq, *J* = 9 Hz), and 5.87 (2 H, q, *J* = 7 Hz). For this and subsequent NMR data only diagnostic signals are reported.

In subsequent runs on a 25-g scale the ether **12** (R = H) was obtained in 100% crude yield, sufficiently pure for the next stage.

9-Methyl-6-(2′-toluene-*p*-sulfonyloxyethyl)-7-oxatricyclo-[4.3.0.0^{3,9}]nonane (13). The ether **12** (R = H) was reduced with lithium aluminum hydride to give (1*R*,3*S*,6*S*,9*S*)-9-methyl-6-(2′-hydroxyethyl)-7-oxatricyclo[4.3.0.0^{3,9}]nonane; bp 100 °C (5 × 10^{-4} mm); $[\alpha]^{21}_D$ +9.9° (*c* 2.8 in $CHCl_3$); IR 3445 and 1045 cm^{-1}; NMR τ 8.72 (3 H, s), 6.25, 6.62 (2 H, ABq, *J* = 9 Hz), and 6.1–6.45 (3 H, m). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.05; H, 9.85.

The above alcohol (16.3 g, 0.089 mol) in dry pyridine (240 mL) at 0 °C was treated with *p*-toluenesulfonyl chloride (46 g, 2.7 equiv). The mixture was stirred at 0 °C for 18 h and poured into ice–water. Workup in the conventional manner gave the tosylate **13** (29.4 g; 98%); mp 66–69 °C (from light petroleum–ether); $[\alpha]^{20.5}_D$ +4.2° (*c* 2.2 in $CHCl_3$); IR 1600, 1370, 1185, 1045, 985, 860, and 680 cm^{-1}; NMR τ 8.77 (3 H, s), 7.54 (3 H, s), 6.18, 6.68 (2 H, ABq, *J* = 9 Hz), 5.84 (2 H, t, *J* = 7 Hz), and 2.17, 2.62 (4 H, AA′BB′, *J* = 8 Hz). Anal. Calcd for $C_{18}H_{24}O_4S$: C, 64.26; H, 7.19; S, 9.53. Found: C, 64.32; H, 7.32; S, 9.53.

9-Methyl-6-(2′-cyanoethyl)-7-oxatricyclo[4.3.0.0^{3,9}]nonane (14). The tosylate **13** (3 g, 8.9 mmol) in dry dimethyl sulfoxide (30 mL) was treated with sodium cyanide (0.66 g, 1.5 equiv) and the mixture was stirred for 15 h at 60 °C under N_2. Workup in the usual way gave the cyanide **14** (1.55 g; 91%); bp 100 °C (5 × 10^{-4} mm); $[\alpha]^{20.5}_D$ +16.0° (*c* 2.3 in $CHCl_3$); IR 2265 and 1045 cm^{-1}; NMR τ 8.75 (3 H, s), 7.57 (2 H, t, *J* = 6 Hz), and 6.18, 6.62 (2 H, ABq, *J* = 9 Hz). Anal. Calcd for $C_{12}H_{17}ON$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.12; H, 8.80; N, 7.14.

9-Methyl-6-(2′-carbomethoxyethyl)-7-oxatricyclo[4.3.0.0^{3,9}]-nonane (15). The nitrile **14** (12 g, 0.063 mol) in ethanol (170 mL) and 10 N aqueous sodium hydroxide (170 mL) was stirred under reflux for 20 h. Workup gave the corresponding acid (12.9 g; 98%): bp 140 °C (5 × 10^{-4} mm); $[\alpha]^{20}_D$ +2.0° (*c* 2.7 in $CHCl_3$); IR 3040, 2700, 1735, and 1030 cm^{-1}; NMR τ 8.72 (3 H, s), 7.54 (2 H, t, *J* = 6 Hz), 6.12, 6.60 (2 H, ABq, *J* = 8 Hz), and −0.37 (1 H, s). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.42; H, 8.43. The crude acid (13.6 g, 0.065 mol) in dry methanol (320 mL) was treated with 'Amberlite' resin IR-120(H) (41 g) under reflux for 5 h. The mixture was filtered and the filtrate was evaporated to give the ester **15** (14.3 g) which was passed through a column of neutral alumina (G3, 100 g) and washed with light petroleum/ethyl acetate (5:2) to afford the pure ester **15** (13.15 g; 91%); bp 90 °C (5 × 10^{-4} mm); $[\alpha]^{22}_D$ +3.9° (*c* 2.7 in $CHCl_3$); IR 1740 and 1030 cm^{-1}; NMR τ 8.74 (3 H, s), 7.57 (2 H, t, *J* = 7 Hz), 6.14, 6.62 (2 H, ABq, *J* = 9 Hz), and 6.31 (3 H, s). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.45; H, 8.91.

1-(2′-Carbomethoxyethyl)-2α-acetoxy-3β-methyl-3α-acetoxymethylnorbornane (16). The ester **15** (12 g, 0.053 mol) in acetic anhydride (128 mL) at 0 °C was treated with BF_3·OEt_2 (22.9 mL). The mixture was stirred for 19 h at 0 °C. Workup by pouring the above mixture into water (400 mL), extraction with chloroform (3 × 100 mL), washing with saturated aqueous sodium hydrogen carbonate, drying (Na_2SO_4), and evaporation gave the diacetate **16** (17.5 g, 100%): bp 140 °C (5 × 10^{-4} mm); $[\alpha]^{24.5}_D$ +33.6° (*c* 3.8 in $CHCl_3$); IR 1750, 1730, 1430, 1370, 1240, and 1045 cm^{-1}; NMR τ 8.85 (3 H, s), 7.97 (3 H, s), 7.95 (3 H, s), 6.32 (3 H, s), 5.88, 6.16 (2 H, ABq, *J* = 11 Hz), and 5.33 (1 H, s). Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.60; H, 7.97.

1-(2′-Carbomethoxyethyl)-2α-hydroxy-3β-methyl-3α-hydroxymethylnorbornane (19). The diacetate **16** (18.6 g) in dry methanol (190 mL) was treated with concentrated sulfuric acid (3.2 mL) and the mixture was heated at reflux for 4 h. Workup in the conventional manner gave the diol **19** (13.3 g, 96%); bp 140–150 °C (5 × 10^{-4} mm); $[\alpha]^{24}_D$ −19.0° (*c* 2.4 in $CHCl_3$); IR 3470, 1730, 1065, and 1020 cm^{-1}; NMR τ 8.9 (3 H, s), 7.59 (2 H, t, *J* = 7 Hz), 6.8 (2 H, br s), 6.51 (1 H, s), 6.02, 6.62 (2 H, ABq, *J* = 11 Hz), and 6.3 (3 H, s). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.54; H, 8.91.

1-(2′-Carbomethoxyethyl)-2α-hydroxy-3β-methyl-3α-hydroxymethylnorbornane Isopropylidene Acetal (20). The crude diol **19** (13.2 g) in dry acetone (200 mL) was treated with anhydrous

cupric sulfate (6.6 g) and concentrated sulfuric acid (0.25 mL). The mixture was stirred at room temperature for 1 h, filtered, and diluted with water. Extraction with dichloromethane, drying (Na_2SO_4), and evaporation gave an oil which was purified by chromatography over alumina (G3), eluting with light petroleum/ethyl acetate (13:1), to give the acetonide **20** (11.6 g; 75%); bp 90–98 °C (5×10^{-4} mm); $[\alpha]^{22.5}_D$ +23.4° (c 3.3 in $CHCl_3$); IR 1740, 1225, 1065, and 1030 cm^{-1}; NMR τ 8.85 (3 H, s), 8.68 (6 H, s), 6.71 (1 H, s), 6.20, 6.90 (2 H, ABq, J = 11 Hz), and 6.30 (3 H, s). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 68.02; H, 9.28.

1-(2′-Carbomethoxy-(*E*)-ethenyl)-2α-hydroxy-3β-methyl-3α-hydroxymethylnorbornane Isopropylidene Acetal (21). Diisopropylamine (0.36 g) in dry tetrahydrofuran (3 mL) under N_2 at −78 °C was treated with 2.1 M *n*-butyllithium in hexane (1.7 mL) followed by a solution of the acetonide **20** (0.5 g) in dry tetrahydrofuran (3 mL). The mixture was stirred at −78 °C for 20 min and a solution of diphenyl diselenide (0.66 g) in dry tetrahydrofuran (3 mL) was added. The solution was stirred at −78 °C for 30 min and allowed to warm to 20 °C over a period of 2 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride and extracted twice with ethyl acetate. The ethyl acetate extracts were washed successively with 1 N hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated. The residue was dissolved in tetrahydrofuran and treated dropwise at 20 °C with sodium periodate (0.76 g) in methanol–water (50 mL, 7:3). After 0.5 h the mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted with ether. The ether extracts were washed with water and 1 N hydrochloric acid, dried (Na_2SO_4), and evaporated. The residual yellow oil was purified by chromatography over silica gel, eluting with light petroleum/ethyl acetate (13:1), to give the unsaturated ester **21** (0.35 g; 71%): $[\alpha]^{23}_D$ +49.4° (c 2.4 in $CHCl_3$); IR 1725, 1650, 1220, 1090, 1030, 985, and 855 cm^{-1}; NMR τ 8.82 (3 H, s), 8.65 (6 H, s), 6.52 (1 H, s), 6.88, 6.20 (2 H, ABq, J = 11 Hz), 6.25 (3 H, s), 4.18, 2.84 (2 H, ABq, J = 16 Hz). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.27; H, 8.44. Scaling the reaction up to 4 g gave a 96% yield of the unsaturated ester **21**, but beyond this scale the yield dropped.

1-(1′-Methyl-2′-carbomethoxyethyl)-2α-hydroxy-3β-methyl-3α-hydroxymethylnorbornane Isopropylidene Acetal (22). Ethereal methyllithium (36.3 mL, 1.9 M) was added to a slurry of cuprous iodide (7.0 g) in dry ether (60 mL) under argon at 0 °C. After stirring the mixture at 0 °C for 30 min, the unsaturated ester **21** (1.0 g) in dry ether (20 mL) was added and the mixture was stirred at 0 °C for a further 3 h. Workup in the usual way followed by chromatography over silica gel, eluting with light petroleum/ethyl acetate, gave 95% yield of ester **22**: $[\alpha]^{18}_D$ +27.6° (c 2.0 in $CHCl_3$); IR 1735, 1220, and 1080 cm^{-1}; NMR τ 9.1 and 9.05 (3 H, 2 d, J = 6 Hz), 8.91 (3 H, s), 8.74 (3 H, s), 8.73 (3 H, s), 6.71 and 6.66 (1 H, 2 s), 6.14, 6.84 (2 H, ABq, J = 11 Hz), and 6.4 (3 H, s). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 69.22; H, 9.49.

1-(1′-Methyl-3′-toluene-*p*-sulfonyloxypropyl)-2α-hydroxy-3β-methyl-3α-hydroxymethylnorbornane Isopropylidene Acetal (23). The ester **22** (4.05 g) in dry tetrahydrofuran (40 mL) was treated with lithium aluminum hydride (2.4 g) in the usual way. Workup gave the alcohol (3.55 g; 97%): $[\alpha]^{23}_D$ +26.2° (c 2.0 in $CHCl_3$); IR 3350, 1220, and 1080 cm^{-1}; NMR τ 9.06 (3 H, d, J = 6 Hz), 8.87 (3 H, s), 8.68 (6 H, s), 6.61 (1 H, s), 6.15, 6.91 (2 H, J = 11 Hz), and 6.28–6.51 (3 H, m). Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.51. Found: C, 71.38; H, 10.64. The crude alcohol was converted into the tosylate **23** (95%) in the usual way. It has: $[\alpha]^{24}_D$ + 16.7° (c 2.2 in $CHCl_3$); IR 1590, 1360, 1220, 1170, 1080, and 935 cm^{-1}; NMR τ 9.15 (3 H, d, J = 6 Hz), 8.90 (3 H, s), 8.72 (6 H, s), 7.53 (3 H, s), 6.75 and 6.67 (1 H, 2 s), 6.00, 6.98 (2 H, ABq, J = 11 Hz), 5.91 (2 H, t, J = 6 Hz), and 2.42 (4 H, ABq, J = 8 Hz). Anal. Calcd for $C_{23}H_{34}O_5S$: C, 65.37; H, 8.11. Found: C, 65.66; H, 7.96.

1-(1′-Methyl-4′-phenylsulfonylbutyl)-2α-hydroxy-3β-methyl-3α-hydroxymethylnorbornane Isopropylidene Acetal (24). To a slurry of sodium hydride (10.5 equiv from 2.2 g of 60% dispersion in mineral oil) in dimethyl sulfoxide (26 mL) under argon was added methyl phenyl sulfone (1.3 g) in dimethyl sulfoxide (26 mL). The above mixture was stirred at room temperature for 10 min and the tosylate **23** (2.2 g) in dimethyl sulfoxide (44 mL) was added. After stirring at room temperature for 15 h the mixture was poured into dilute hydrochloric acid (100 mL, 6 N) and extracted with chloroform. The extract was washed with saturated aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated to give the crude product. Chromatography over silica gel, eluting with light petroleum/ethyl acetate (13:1), gave the pure sulfone **24** (1.45 g; 69%): $[\alpha]^{23}_D$ +18.0° (c 2.1 in $CHCl_3$); IR 1300, 1220, 1140, and 1080 cm^{-1}; NMR τ 9.15 (3 H, d, J = 6 Hz), 8.90 (3 H, s), 8.72 (6 H, s), 6.95 (2 H, t, J = 7 Hz), 6.70 (1 H, s), 6.20, 6.86 (2 H, ABq, J = 11 Hz), and 1.9–2.5 (5 H, m). Anal. Calcd for $C_{23}H_{34}O_4S$: C, 67.94; H, 8.43; S, 7.89. Found: C, 68.22; H, 8.19; S, 7.30.

1-Carboethoxymethyl-2α-acetoxy-3β-methyl-3α-acetoxymethylnorbornane (25). The ether **12** (R = H) (0.5 g) was treated with acetic anhydride (10 mL) at 0 °C, followed by boron trifluoride etherate (0.5 mL). After 15 min at 0 °C, water (30 mL) was added to the above mixture. Extraction with ether, washing with saturated aqueous sodium hydrogen carbonate, drying (Na_2SO_4), and evaporation gave the diacetate **25** (76%): IR 1730, 1370, 1240, and 1040 cm^{-1}; NMR τ 8.86 (3 H, s), 8.76 (3 H, t, J = 8 Hz), 8.04 (3 H, s), 8.02 (3 H, s), 7.65 (2 H, s), 6.00 (4 H, q), 5.35 (1 H, b s); MS 326.39 for $C_{17}H_{26}O_6$.

If the above reaction is run for longer times (~1 h) the product **26** is formed: IR 1740, 1710, 1650, 1240, 1200, and 1040 cm^{-1}; NMR τ 8.98 (3 H, s), 8.73 (3 H, t, J = 8 Hz), 7.94 (3 H, s), 6.13 (2 H, s), 5.86 (2 H, q, J = 8 Hz), 4.32 (1 H, b s).

1-Carbomethoxymethyl-2α-hydroxy-3β-methyl-3α-hydroxymethylnorbornane Isopropylidene Acetal (27). The diacetate **25** (0.30 g) in methanol (4 mL) was treated with concentrated sulfuric acid (3 drops). The mixture was heated at reflux for 3 h and worked up in the usual way to give the diol (100%): IR 3420, 1710, 1435, 1355, 1200, 1070, and 1020 cm^{-1}; NMR τ 8.86 (3 H, s), 8.25 (2 H, b s), 7.92 (2 H, s), 6.36 (1 H, s), 6.30 (3 H, s), 6.75, 6.18 (2 H, q, J = 11 Hz).

The diol (3.5 g) in acetone (60 mL) was treated with anhydrous cupric sulfate (2.0 g) and concentrated sulfurate acid (3 drops). After stirring the above mixture at room temperature for 1.5 h, workup gave the acetonide **27** (77%): IR 1730, 1370, 1220, 1080, and 1025 cm^{-1}; NMR τ 8.88 (3 H, s), 8.75 (6 H, s), 7.55 (2 H, s), 6.98, 6.27 (2 H, q, J = 11 Hz), 6.45 (1 H, s), 6.35 (3 H, s); MS 268.34 for $C_{15}H_{24}O_4$.

1-(2′-Methyl-2′-hydroxyethyl)-2α-hydroxy-3β-methyl-3α-hydroxymethylnorbornane Isopropylidene Acetal (28). The ester **27** (0.30 g) was added to a solution of lithium diisopropylamide (prepared from diisopropylamine (0.31 mL) and *n*-butyllithium (1 mL) in dry tetrahydrofuran (5 mL) under N_2 at −78 °C). The solution was stirred for 20 min at −78 °C and methyl iodide (0.1 mL) was added. The reaction was quenched and worked up in the usual way to give the methylated product (82%): IR 1730, 1460, 1370, 1220, and 1080 cm^{-1}; NMR τ 8.85 (3 H, s), 8.79 (3 H, s), 8.70 (6 H, s), 8.45 (1 H, q, J = 5.5 Hz), 6.35 (3 H, s), 6.88, 6.15 (2 H, ABq, J = 11 Hz); MS 282.35 for $C_{16}H_{26}O_4$. The methylated ester (0.245 g) in dry tetrahydrofuran (2 mL) was added dropwise to a slurry of lithium aluminum hydride (0.158 g) in dry tetrahydrofuran (5.2 mL) at −78 °C. The mixture was allowed to warm to room temperature over 2 h and worked up the usual way to give the alcohol **28** (67%): IR 3550–3100, 1220, 1075, and 875 cm^{-1}; NMR τ 9.12 (3 H, d, J = 8 Hz), 8.94 (3 H, d, J = 8 Hz), 8.80 (3 H, s), 8.62 (6 H, s), 7.95 (1 H, s, exchange by D_2O), 6.15, 6.80 (2 H, ABq, J = 11 Hz), 6.53 (2 H, d, J = 8 Hz). The alcohol **28** was converted into the iodide **29** without purification.

1-(1′-Methyl-2′-iodoethyl)-2α-hydroxy-3β-methyl-3α-hydroxymethylnorbornane Isopropylidene Acetal (29) and Its Conversion into 24. The alcohol **28** (0.139 g) in dry pyridine (1 mL) was treated with methanesulfonyl chloride (0.03 mL) at 0 °C. The reaction was quenched with ice water and worked up in the usual way to give the mesylate (92%): IR 1465, 1355, 1220, 1175, and 950 cm^{-1}; MS 342.43 for $C_{16}H_{28}O_5S$.

The mesylate (0.062 g) in methyl ethyl ketone (3 mL) and sodium iodide (0.1423 g) was heated at reflux for 4 h, quenched with water, and worked up in the usual way to give the iodide **29** (91%): IR 1460–1450, 1370, 1265, 1220, 1070, 1025, and 875 cm^{-1}; NMR τ 8.9 (3 H, d), 8.80 (3 H, s), 8.68 (6 H, s), 7.08 (2 H, d), 5.7 (3 H, m). MS 364.24 for $C_{15}H_{25}O_2I$, 237.34 for ($M^{+\cdot}$ − I).

The iodide **29** (0.20 g) in dry pentane (10 mL) containing lithium wire (2 equiv) under argon was heated at reflux for 5 h. Dry ether (5 mL) was added and the mixture was stirred at room temperature overnight. Addition at −78 °C of 1-pentynylcopper[18] (0.078 g) and hexamethylphosphoric triamide (0.2 mL) gave a homogeneous solution which was treated with phenyl vinyl sulfone[19] (0.103 g). After stirring at −78 °C for 1 h and warming to room temperature the reaction was worked up by quenching in saturated aqueous ammonium chloride, extraction with ether, drying (Na_2SO_4), and evaporation. The resulting dark oil was chromatographed over alumina, eluting with ethyl acetate/light petroleum (1:9), to give the sulfone **24** (8%): IR, NMR, MS, and TLC identical with an authentic sample.

1-(1′-Methyl-4′-phenylsulfonylbutyl)-2α-hydroxy-3β-methyl-3α-hydroxymethylnorbornane (30). The sulfone **24** (210 mg) in chloroform (4 mL) and dioxane (1 mL) was stirred vigorously with 6 N hydrochloric acid (10 mL) for 4 h at room temperature. The organic layer was then separated and the aqueous layer was diluted with water and extracted with chloroform. The combined chloroform ex-

tracts were washed with water, dried (Na_2SO_4), and evaporated to give a viscous oil. Passing this through a silica gel column and washing with petrol/ethyl acetate (4:3) gave the diol **30** (150 mg; 79%): $[\alpha]^{19}_D$ −3.0° (*c* 1.0 in chloroform); IR 3490, 1300, and 1140 cm^{-1}; NMR τ 9.11 (3 H, d, J = 6 Hz), 8.94 (3 H, s), 7.3–7.9 (2 H, br), 6.92 (2 H, t, J = 7 Hz), 6.37 (1 H, s), 6.68, 6.06 (2 H, ABq, J = 10 Hz), and 1.9–2.5 (5 H, m). Anal. Calcd for $C_{20}H_{30}O_4S$: C, 65.54; H, 8.25. Found: C, 66.87; H, 7.97.

The diol **30** was also obtained in a large-scale preparation directly from tosylate **23** in 68% yield when the latter was subjected to the alkylation described earlier.

1-(1′-Methyl-4′-phenylsulfonylbutyl)-2-oxo-3β-methyl-3α-toluene-*p*-sulfonyloxymethylnorbornane (31). A mixture of the diol **30** (5.1 g) in dry pyridine (100 mL) and *p*-toluenesulfonyl chloride (5.4 g) was stirred overnight at 0 °C, then poured into ice and extracted with chloroform. The chloroform extracts were washed with 6 N hydrochloric acid and water and dried (Na_2SO_4). Evaporation of chloroform gave the tosylate (6.8 g; 94%): $[\alpha]^{22.5}_D$ +9.5° (*c* 2.2 in chloroform); IR 3540, 1590, 1350, 1300, 1170, 1140, and 950 cm^{-1}; NMR τ 9.15 (3 H, d, J = 6 Hz), 9.02 (3 H, s), 7.55 (3 H, s), 7.3 (1 H, br), 6.94 (2 H, t, J = 7 Hz), 6.40 (1 H, s), 6.0 (2 H, s), 2.10. 2.68 (4 H, AA′BB′, J = 8 Hz), and 1.9–2.5 (5 H, m). The product was used without any purification.

To chromium trioxide (0.24 g, 6 equiv, dried in vacuum at room temperature) in dichloromethane (6 mL) was added pyridine (0.37 mL, 12 equiv). After stirring for 15 min at room temperature the mixture was treated with the above tosylate (0.2 g) in dichloromethane (3 mL). After stirring for 20 min further the mixture was decanted and the residue was washed with more solvent. The combined dichloromethane solutions were washed successively with 3 N sodium hydroxide, 2 N hydrochloric acid, saturated sodium hydrogen carbonate, and saturated sodium chloride, then dried (Na_2SO_4) and evaporated to give a thick oil. Filtration of this oil through a silica gel column using petrol/ethyl acetate (5:2, 1:1) as eluent gave the keto tosylate **31** (165 mg; 83%): $[\alpha]^{20}_D$ −26.1° (*c* 0.9 in chloroform); IR 1730, 1590, 1360, 1300, 1170, and 1140 cm^{-1}; NMR τ 9.15 (3 H, d, J = 6 Hz), 8.99 (3 H, s), 7.55 (3 H, s), 6.94 (2 H, t, J = 7 Hz), 6.13 (2 H, s), 2.10, 2.66 (4 H, AA′BB′, J = 8 Hz), and 1.98–2.53 (5 H, m). Anal. Calcd for $C_{27}H_{34}O_5S_2$: C, 62.52; H, 6.61. Found: C, 62.69; H, 6.89.

Large-scale preparations of **31** afforded in 75–98% yields the crude material, which required no further treatment.

(2*S*,5*R*)-2-Isopropenyl-6-oxo-7-phenylsulfonyl-10-methylspiro[4.5]decane (32). The keto tosylate **31** (0.95 g) in dimethyl sulfoxide (30 mL) was added dropwise to a slurry of sodium hydride (10 equiv, from 0.76 g of 60% dispersion in oil) in dimethyl sulfoxide (20 mL) under argon at 40 °C. The mixture was stirred at 40–50 °C for 1 h. Excess sodium hydride was destroyed by adding water and the resulting mixture was acidified with 6 N hydrochloric acid and extracted with chloroform. The chloroform extracts were washed with water, dried (Na_2SO_4), and evaporated. The resulting residue was chromatographed (silica gel column) into three fractions. Fraction 1 (eluted with petrol/ethyl acetate, 6:1) consisted of a crystalline byproduct **33** (26 mg); mp 89 °C; IR 1600, 1300, 1280, 1140, 1080, and 730 cm^{-1}; NMR τ 9.11 (3 H, d, J = 7 Hz), 8.87 (3 H, s), 5.75–6.1 (1 H, m), and 2.0–2.6 (5 H, m); M^+· *m/e* 316, 219, 218, 286, 256, 175 (M^+· − SO_2Ph; calcd for $C_{13}H_{19}^+$), 147, 145, 105, 91, 77, 55, 41, 32. Fraction 2 (eluted with petrol/ethyl acetate, 5:2) gave the major product **32** (253 mg of viscous oil, 40%); $[\alpha]^{22.5}_D$ −26.1° (*c* 0.16 in chloroform); IR 1710, 1635, 1300, 1140, and 880 cm^{-1}; NMR τ 9.22 and 9.03 (3 H, 2 d, J = 6 Hz), 8.43 and 8.32 (3 H, 2 s), 5.55–6.1 (1 H, m), 5.37 (2 H, s), and 1.8–2.6 (5 H, m); M^+ *m/e* 346 (M^+ − SO_2Ph), 205, 187, 107. Anal. Calcd for $C_{20}H_{26}O_3S$: C, 69.33; H, 7.56. Found: C, 69.37; H, 7.55. Fraction 3 (eluted with petrol/ethyl acetate, 5:2) consisted of the byproduct **34** (63 mg of oil): IR 3250, 3070, 1720, 1640, 1300, 1145, and 890 cm^{-1}; NMR (CCl_4) 9.11 (3 H, d, J = 6 Hz), 8.32 (3 H, s), 7.03 (2 H, t, J = 7 Hz), 5.32 (2 H, s), 2.0–2.6 (5 H, m), and −0.57 (1 H, s). The compound **32** may be obtained in 65% yield on a larger scale.

(2*S*,5*R*)-2-Isopropenyl-6-oxo-10-methylspiro[4.5]decane (35). The sulfone **32** (1.035 g) in tetrahydrofuran (40 mL) was treated with aluminum amalgam[20] and the mixture was heated at reflux for 3 h then filtered. The filtrate containing some added ether was washed with water and saturated sodium chloride and concentrated. The crude residual mixture was chromatographed on a column of silica gel; elution with petrol/ethyl acetate (6.5:0.5) gave the ketone **35** (480 mg; 90% based on reacted starting material): $[\alpha]^{21.5}_D$ −4.8° (*c* 0.25 in chloroform); IR 1705, 1640, and 890 cm^{-1}; NMR τ 9.09 and 9.04 (3 H, 2 d, J = 3 Hz), 8.27 (3 H, s), 7.58 (2 H, br t, J = 7 Hz), and 5.28 (2 H, s); M^+· *m/e* 206, 191 (M^+· − CH_3), 163, 135, 125, 107, 93, 82, 57. Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; 10.75. Found: C, 81.41; H, 10.81.

GLC analysis at 150 °C showed a single peak, retention time 4.5 min. Multiple TLC using petrol/ethyl acetate solvent gave a single spot of **35.**

The NMR spectrum in the presence of tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium(III) (1.2 equiv) shows signals at τ 5.16 and 5.3 (2 H, s), 8.67 and 8.69 (3 H, 2 d, 2-Hz separation, J = 6 Hz). With 0.08 equiv of shift reagent, 4.5-Hz separation between the two doublets is observed; the separation decreases (more overlapping) with increasing concentration of the shift reagent.

(2*S*,5*R*)-2-Isopropenyl-6-hydroxy-6,10-dimethylspiro-[4.5]decane (36). The ketone **35** (245 mg) in dry ether (25 mL) was added dropwise to a freshly prepared ether solution of methylmagnesium iodide (3.5 equiv). After 15–20 min of stirring at room temperature, the mixture was worked up in the usual way to give the crude product. Chromatography over neutral alumina (grade 1), eluting light with petroleum/ethyl acetate (13:1), gave the pure alcohol **36** (viscous oil, 195 mg; 74%): $[\alpha]^{19}_D$ −10.5° (c 0.2 in chloroform); IR 3450, 1640, and 890 cm^{-1}; NMR τ 9.12 (3 H, d, J = 6 Hz), 8.77 and 8.82 (3 H, 2 s), 8.25 (3 H, s), 7.7 (1 H, br), and 5.31 (2 H, s). Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.78. Found: C, 80.94; H, 11.66. Multiple TLC developed with petrol–ethyl acetate solvent system gave a single spot of **36.**

(2*S*,5*R*)-2-(1′,2′-Epoxy-1′-methylethyl)-6-hydroxy-6,10-dimethylspiro[4.5]decane (37). The olefin **36** (55 mg) in dichloromethane was treated with 85% *m*-chloroperbenzoic acid (55 mg, 1.1 equiv of peracid) in dichloromethane. After 0.5 h at room temperature, the excess peracid was then destroyed by addition of 10% aqueous sodium sulfite. The resulting mixture was washed successively with saturated sodium hydrogen carbonate, water, and saturated aqueous sodium chloride and then dried (Na_2SO_4) and the solvent was evaporated. The residue was passed through a column of silica gel and eluted with petrol/ethyl acetate (6:1, 5.5:1.5) to yield a colorless viscous liquid **37** (52 mg, 88%): $[\alpha]^{24}_D$ −0.8° (*c* 0.25 in chloroform); IR 3450, 1460, 1370, 1045, 975, and 915 cm^{-1}; NMR τ 9.15 (3 H, d, J = 6 Hz), 8.85 and 8.8 (3 H, 2 s), 8.7 and 8.63 (3 H, 2 s) and 6–7.6 (2 H, m). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.66; H, 11.06.

For subsequent preparation of epoxide **37,** the following condition was used. Olefin **36** (220 mg) in tetrahydrofuran (13 mL) was stirred at room temperature and added with sodium bicarbonate (129 mg), followed by 85% *m*-chloroperbenzoic acid (583 mg, 2.9 equiv of peracid) in tetrahydrofuran (6 mL) dropwise. After addition the mixture was stirred for 3 h, then poured into 2 N sodium hydroxide (20 mL) and ether (10 mL). The aqueous layer was separated and the organic layer was washed with another 20 mL of 2 N sodium hydroxide, then water and saturated brine. Drying (Na_2SO_4) and removal of solvent from the organic solution gave the epoxide **37** as a viscous colorless oil (236 mg; 100%).

(2*S*,5*R*)-2-(1′,2′-Epoxy-1′-methylethyl)-6,10-dimethylspiro[4.5]dec-6-ene (38a). (Carboxysulfamoyl)triethylammonium hydroxide inner salt methyl ester[22] (1.3 g, 5 equiv) was added to a stirred solution of alcohol **36** (236 mg) in benzene (33 mL) and the mixture was stirred at room temperature for 3 h. Workup by washing repeatedly with water, drying (Na_2SO_4), and evaporation gave the residue (~0.5 g), still containing some of the inner salt. Chromatography over silica gel (23 g), eluting with light petroleum, gave 40 mg (18%) of the exocyclic olefin isomer **38b:** IR 1635, 1450, 1370, and 885 cm^{-1}; NMR τ 9.17 (3 H, d, J = 6 Hz), 8.74 (3 H, s), 7.15–7.92 (2 H, m), and 4.25–5.5 (2 H, m). Elution with light petroleum/ethyl acetate (95:5) gave 57 mg (26%) of the endocyclic olefin isomer **38a:** IR 1640, 1450, 1370, and 890 cm^{-1}; NMR τ 9.13 (3 H, d, J = 6 Hz), 8.73 (3 H, s), 8.35 (3 H, br s), 7.7 (2 H, m), and 4.67 (1 H, m). Treatment of **38b** in benzene with a catalytic amount of *p*-toluenesulfonic acid at room temperature gave **38a** in quantitative yield.

Hinesol (39, R = H). The epoxide **38a** (36 mg) in dry ether (2 mL) was added dropwise to an ice-cooled slurry of lithium aluminum hydride (90 mg) in dry ether (2 mL). The mixture was stirred for 6 h, then worked up with saturated ammonium chloride. Ether extraction gave 25 mg of the crude product which was purified by a chromatography over neutral alumina (grade 1). Elution with petrol/ethyl acetate (6:1, 5.5:1.5) gave 11 mg (30%) of the alcohol **39** (R = H) as a liquid which failed to crystallize upon prolonged cooling: $[\alpha]^{25}_D$ +35.4° (*c* 0.5 in chloroform); IR 3345, 1630, 1445, 1365, 1230, 1130, 1025, 885, and 795 cm^{-1}; NMR τ 9.05 (3 H, d, J = 6 Hz), 8.75 (6 H, s), 8.36 (3 H, br s), 6.45 (1 H, br s), and 4.70 (1 H, m); *m/e* 222 (M^+·), 207 (M^+· − CH_3), 204 (M^+· − H_2O), 189, 163, 121, 107, 95, 93, 81, 55. TLC of this alcohol **39** (R = H) on a silica gel plate impregnated with 20% silver nitrate and developed with 0.5% glacial acetic acid in chloroform did not give a satisfactory separation of the epimeric mixture (a slightly elongated spot was obtained).

Hinesol Acetate (39, R = Ac). The alcohol **39** (R = H) (~10 mg) and sodium acetate (40 mg) were dissolved in acetic anhydride (0.5 mL) and the mixture was heated at reflux for 3 h. The cooled mixture

was stirred at room temperature for 1 h with saturated sodium bicarbonate (4 mL) and ether (3 mL). The crude acetate **39** (R = Ac) (15 mg) was isolated by ether extraction as a light yellow oil: IR 1735, 1655, 1445, 1365, 1230, 1030, 880, and 800 cm^{-1}; NMR τ 9.15 (3 H, d, J = 6 Hz), 8.66 (6 H, s), 8.16 (3 H, br s), 7.96 (3 H, s), and 4.74 (1 H, m). TLC of the acetate **39** (R = Ac) on a silica gel plate impregnated with 20% silver nitrate, developed with petrol/ethyl acetate (13:1) or 0.5% glacial acetic acid in chloroform, gave a slight elongation of the spot. Analytical GLC using the usual columns was unsatisfactory. The above acetate **39** (R = Ac) had IR and NMR spectra in agreement with literature values.

Acknowledgment. We thank Professor J. A. Marshall for supplying spectra of authentic (±)-hinesol

Registry No.—**11,** 65354-38-3; **12,** 23971-53-1; **13,** 65338-83-2; **13** alcohol, 65338-84-3; **14,** 65338-85-4; **15,** 58698-24-1; **15** acid, 65338-86-5; **16,** 58698-25-2; **19,** 58698-26-3; **20,** 58700-62-2; **21,** 58700-63-3; **22** isomer 1, 65378-09-8; **22** isomer 2, 65378-10-1; **23,** 65338-87-6; **23** alcohol, 65338-88-7; **24,** 58698-28-5; **25,** 65338-89-8; **25** diol, 65338-90-1; **26,** 65338-91-2; **27,** 65338-92-3; **28,** 65338-75-2; **28** mesylate, 65338-76-3; **29,** 65338-77-4; **30,** 65338-78-5; **30** 3-tosylate, 65366-44-1; **31,** 58698-29-6; **32,** 58698-30-9; **33,** 65338-79-6; **34,** 65338-80-9; (10*R*)-**35,** 65378-05-4; (10*S*)-**35,** 65378-06-5; **36,** 65338-81-0; **37,** 58700-60-0; **38a,** 58700-61-1; **387,** 65338-82-1; (+)-hinesol, 59331-07-6; 10-epihinesol, 59331-08-7; (+)-hinesol acetate, 65378-07-6; (+)-10-epihinesol acetate, 65378-08-7; *p*-toluenesulfonyl chloride, 98-59-9; acetic anhydride, 108-24-7; acetone, 67-64-1; methyllithium, 917-54-4; methyl phenyl sulfone, 3112-85-4; methyl iodide, 74-88-4.

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(2) Inquiries should be sent to the Evans Laboratory, Department of Chemistry, The Ohio State University, Columbus, Ohio 43210.
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(23) (+)-Hinesol is the mirror image of the natural isomer; see ref 8 for a discussion of the relevant stereochemical relationships.

Photochemical Transformations. 21. Photochemical and Thermal Methanolyses of Two Epimeric Bridged Polycyclic Bromides[1]

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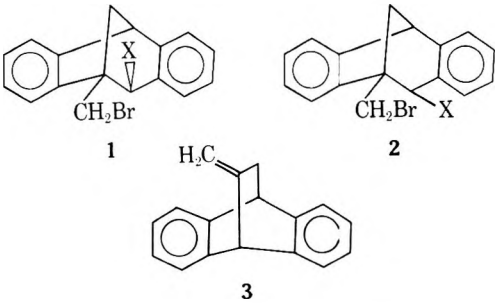
Addition of bromine to 7-methylenedibenzobicyclo[2.2.2]octadiene (3) gave a mixture of the epimeric 5-bromomethyl-4-bromodibenzobicyclo[3.2.1]octadienes (1-Br and 2-Br). The dibromides suffer methanolysis in THF–methanol solutions in the dark at 60 °C and upon direct irradiation at room temperature to form the corresponding 4-methyl ethers (1-OCH_3 and 2-OCH_3). The solvolyses are neither stereoselective nor stereoconvergent, although in all cases the exo ether (1-OCH_3) is the principal solvolysis product. Plausible rationalizations of the product differences are discussed.

Photoinduced solvolyses of a number of benzyl derivatives have been reported;[2] these have been shown to proceed through benzylic cation intermediates. It seemed to us that an interesting question is whether cationic intermediates, otherwise identical, but produced on the one hand from an electronically excited species and on the other hand from a ground-state species, would be different enough to note experimentally. Obviously, any differences could be noted only if bimolecular capture occurred more rapidly than unimolecular relaxation processes.

As one test, we decided to investigate the epimeric 5-bromomethyl-4-bromo-2,3;6,7-dibenzobicyclo[3.2.1]octadienes (1-Br and 2-Br). These offered the additional possibility that the two epimers might show differences among themselves, and in addition, we needed to have a system whose



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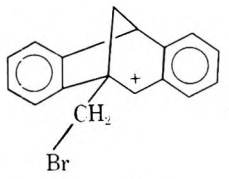
thermal solvolysis was not so fast as to overwhelm photosolvolysis. The 5-bromomethyl group was expected to provide enough electron attraction to accomplish the latter.

A mixture of exo dibromide (1-Br) and endo dibromide (2-Br) was produced in an almost equimolar ratio, when bromine was added in ethyl acetate to 7-methylenedibenzobicyclo[2.2.2]octadiene (3). No unrearranged (1,2) addition products were noted. The formation of both epimers suggests the intervention of benzylic ion 4 (as part of its several ion pairs with bromide ion), rather than of the phenonium ion 5 as the principal product precursor in the addition reaction. Obviously 5 intervenes in the rearrangement to 4, but it must



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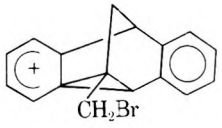

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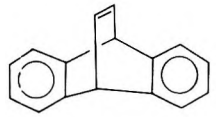

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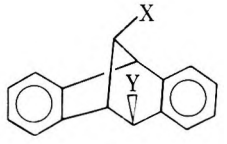

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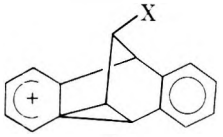
be transformed rapidly to 4. This is in marked contrast to additions to 6, where the formation of syn-exo products 7,[3] as well as other data,[4] suggests that phenonium ions 8, rather than benzylic ions, are principal product precursors in addition reactions. At equilibrium the *exo*-1-Br to *endo*-2-Br ratio is approximately 1:3.

The epimeric dibromides were separated by fractional crystallization. Reduction of 1-Br and 2-Br with tri-*n*-butyltin hydride gave 9, which has been previously described,[5] thus



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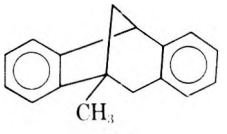

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confirming the carbon skeleton. The configurations of the two epimers were assigned on the basis of their ^{1}H NMR spectra, in particular the chemical shifts of the 4-proton (exo protons farther downfield than endo in dibenzobicyclo[3.2.1]octadiene systems,[6] as well as in others.[7])

Neither 1-Br nor 2-Br reacted measurably when allowed to stand in 50:50 methanol/tetrahydrofuran solution[8] at room temperature for 24 h. Reaction occurred slowly at 60 °C with each isomer to give a mixture of methyl ethers 1-OCH_3 and 2-OCH_3. The exo bromide was slightly more reactive than the endo (half-life ~3 h vs. ~18 h). Neither isomer reacted stereospecifically. The exo bromide (1-Br) gave *exo*-1-OCH_3 and *endo*-2-OCH_3 in a ratio of about 7 to 1, while the endo bromide (2-Br) gave these in a ratio of about 2.5 to 1.

Photosolvolysis of both bromides proceeded rapidly in a methanol–THF solution at room temperature upon direct irradiation with 254- and 300-nm light. Just as in the ground-state reaction, the principal product was the exo ether 1-OCH_3 With the exo bromide, (1-OCH_3) was produced in a ratio of approximately 9:1 over 2-OCH_3; the endo bromide gave a ratio of about 4:1. The photosolvolyses both proceed without apparent epimerization either of the bromides or of the ether products. Attempts to photosensitize the solvolyses with acetone, acetophenone, and benzophenone were unsuccessful, and the photosolvolyses were not quenched significantly by piperylene at concentrations at or below 0.5 M.

Discussion of Results

The results described above raise certain points for discussion. Among these are differences between product formation from the two epimers, differences between ground-state and excited-state reactions, questions of possible ion-pair return, and excited-state multiplicities.

As noted above, neither epimer gives stereospecific displacement, but the exo bromide 1-Br gives substantially more exo ether than does the endo bromide, in both ground-state and photochemical solvolyses. These solvolyses certainly involve cationic intermediates, and a plausible rationalization suggests the intervention of the phenonium ion 5 in the 1-Br reaction in competition with reaction via the benzylic ion 4. 5 cannot be formed directly in an inversion process from the endo epimer 2-Br. Our enthusiasm for this explanation is cooled markedly by the lack of stereospecificity in the 1-Br reaction and by the failure of 5 to intervene substantially as a product-determining intermediate in the addition of bromine to 3. We therefore propose an alternative explanation based upon consideration of possible conformations of the bromomethyl group at C-5.

Models of 1-Br and of 2-Br suggest that the bromomethyl groups have considerably different conformations. Due to steric and electrostatic repulsions by the exo bromine atom in 1-Br, it seems likely that the bromine atom of the bromomethyl group is projected toward the adjacent aromatic ring. Evidence for this conformation is seen in the ^{1}H NMR spectrum, where the diastereotopic geminal protons have no chemical shift difference (both absorb at δ 4.11). On the other hand, the endo bromine in 2-Br does not interfere with the bromomethyl group, and a conformation with the bromine atom projected away from the adjacent aromatic ring is apparently favored. The ^{1}H NMR spectrum is consistent with this interpretation; the diastereotopic geminal protons are no longer in similar environments. One is over the shielding cone of the ring and is moved upfield to δ 3.73 and the other is in the deshielding plane and absorbs at δ 4.37. The coupling constant between the two protons is 10.5 Hz.

If we assume that these conformations are maintained in the heterolyses, the ion or ion pair from 1-Br will have a less internally crowded exo face than that from 2-Br. As a result the intermediate from 1-Br may be anticipated to coordinate with methanol from the exo face somewhat more readily than that from 2-Br. This explanation requires that coordination with solvent proceeds at a faster rate than relaxation of the intermediate by bond rotation. There are, by now, a number of cases[9] where otherwise identical ions from different sources behave differently, and conformational explanations have been given, with similar assumptions required.

The photomethanolyses of 1-Br and 2-Br follow the same trend as the ground-state reactions, although somewhat more *exo*-methyl ether (1-OCH_3) is produced in each case photochemically. The differences are not dramatic and may be caused, in part at least, by the higher temperature of the ground-state reaction. It would therefore appear that, in this work, the intermediates produced by normal heterolysis and by photoheterolysis do not differ markedly, at least at the time of coordination with nucleophile.

In neither the photomethanolysis nor the ground-state reaction was there any evidence for epimerization (1-Br $\rightleftarrows$ 2-Br) during the reaction. Thus this test for ion-pair return[2f] was negative. Perhaps use of a less nucleophilic solvent or of a more stable ion would provide positive evidence. We are presently looking for such examples.

The question of multiplicity in bond heterolysis of benzyl systems remains enigmatic. Upon direct irradiation in THF–methanol, both 1-Br and 2-Br solvolyze readily with a quantum yield near 0.01, and the reaction was not quenched

Table I. Photomethanolysis of 2-Br in 1:1 Tetrahydrofuran/Methanol

Irradiation wavelength, nm	Time of irradiation, min	Recovered bromide % 1-Br	Recovered bromide % 2-Br	Solvolysis products % 1-OCH_3	Solvolysis products % 2-OCH_3	*exo*-(1-OCH_3)/*endo*-(2-OCH_3)
254	0	0	100	0	0	
254	15	0	87	10.5	2.5	4.2
254	30	0	62	31	7	4.4
254	60	0	36	47	12	3.9
254	120	0	13	74	13	5.7
						Av 4.5
300	0	0	100	0	0	
300	140	0	65	30	5	6
300	235	0	43	46	11	4.2
300	360	0	32	52	16	3.3
						Av 4.5

Table II. Photomethanolysis of 1-Br in 1:1 Tetrahydrofuran/Methanol at 254 nm

Irradiation time, min	Recovered bromide % 1-Br	Recovered bromide % 2-Br	Solvolysis products % 1-OCH_3	Solvolysis products % 2-OCH_3	*exo*-(1-OCH_3)/*endo*-(2-OCH_3)
0	90	10			
15	47	10	38	5	7.6
30	32	9	54	5	10.8
60	10	10	72	8	9.0
90	0	5	85	10	8.5
120	0	0	80	10	8.0
					Av 8.8

Table III. Methanolysis of 1-Br and 2-Br in 1:1 Tetrahydrofuran/Methanol at 60 °C

Run no.	Time, h	Composition of mixture % 1-Br	Composition of mixture % 2-Br	Composition of mixture % 1-OCH_3	Composition of mixture % 2-OCH_3	1-OCH_3/2-OCH_3
1	0.0	100	0			
	5.8	21	0	69.1	9.3	7.5
	18.0	0	0	88.6	11.4	7.7
						Av 7.6
2	0.0	0	100			
	5.8	0	83	11.7	5.3	2.2
	18.0	0	46	39.4	14.6	2.7
	26.3	0	31	48.1	20.8	2.3
	42.0	0	12	63.5	24.5	2.6
	91.0	0	0	75.6	24.4	3.1
						Av 2.6

with piperylene at concentrations up to 0.5 M. Chemical yields were 70–75%. Homolysis products were not observed.

When the endo bromide (2-Br) was photosensitized with acetophenone in THF–methanol, the 2-Br disappeared with a yield of about 10–20% of ethers and 80% of unidentified material, the latter possibly the result of carbon–bromine bond homolysis. This is just opposite to results obtained with benzyl chloride,[2i,j] where the triplet sensitized reaction gives principally solvolysis and direct irradiation gives principally homolysis, but is similar to that of benzyltrimethylammonium ion.[2g,h] Experiments in our laboratory indicate that structural and leaving group modifications affect this dichotomy, but we still lack understanding of this phenomenon.[2i]

Experimental Section

^1H NMR data were obtained with a Varian Associates model A-60-A spectrometer, using $CDCl_3$ as solvent with tetramethylsilane as an internal standard. Irradiations with 300- and 350-nm light were performed in a Rayonet photoreactor equipped with a merry-go-round while those at 254 nm were carried out with a Photochemical Quartz Product lamp. Melting points were determined on a Thomas-Hoover Unimelt apparatus. Elemental analyses were performed by Galbraith Laboratories. Mass spectra were recorded with a Varian MAT Model CH-5 single-beam mass spectrometer.

Methanol used in all cases was spectral grade. Tetrahydrofuran was freshly distilled from lithium aluminum hydride and stored over molecular sieves. 1,3-Pentadiene was redistilled and stored in a refrigerator until used.

***exo*- and *endo*-5-Bromomethyl-4-bromodibenzobicyclo[3.2.1]octadiene (1-Br and 2-Br).** A solution of 5 g (22 mmol) of 7-methylenedibenzobicyclo[2.2.2]octadiene (3)[5] in 25 mL of reagent-grade ethyl acetate was cooled in an ice bath. Bromine was added until the solution maintained an orange color for several minutes. The solvent was removed on a rotovac to give 8 g (97%) of an orange oil. ^1H NMR analysis of the oil indicated a mixture of 45% of 1-Br and 55% of 2-Br. The endo epimer (2-Br) was crystallized by pouring 100 mL of reagent-grade hexane on the oil. After 2 days the crystals were filtered off: mp 143–145.5 °C; UV (hexane) 300 (ϵ 180), 254 (ϵ 3170), max 221 nm (ϵ 26 000); ^1H NMR δ 7.67–7.0 (m, 8, aromatic), 6.11 (s, 1, H-4), 4.37 (d, 1, J = 10.5 Hz, CH_2Br), 3.95 (m, 1, H-1), 3.73 (d, 1, J = 10.5 Hz, CH_2Br). and 2.50 (m, 2, H-8). Anal. Calcd for $C_{17}H_{14}Br_2$: C, 54.00; H, 3.79; Br, 42.27. Found: C, 53.90; H, 3.69; Br, 42.01.

Successive fractional crystallizations from hexane gave pure needlelike crystals of 1-Br: mp 89–91 °C; UV (hexane) 300 (ϵ 200), 254 (ϵ 1420), max 210 nm (ϵ 23 400); ^1H NMR δ 7.83–7.08 (m, 8, aromatic), 5.56 (s, 1, H-4), 4.11 (s, 2, CH_2Br), 3.99 (m, 1, H-1), and 2.61 (m, 2, H-8). Anal. Calcd for $C_{17}H_{14}Br_2$: C, 54.00; H, 3.79; Br, 42.27. Found: C, 53.86; H, 3.72; Br, 42.26.

***exo*- and *endo*-5-Bromomethyl-4-methoxydibenzobicyclo[3.2.1]octadiene (1-OCH_3 and 2-OCH_3).** A solution of 3 g (8

mmols) of endo dibromide 2-Br in 30 mL of methanol was heated at reflux for 24 h and the solvent was removed in a rotovac. Thirty milliliters of reagent grade hexane was added to the colorless oil. After 24 h at room temperature colorless crystals began to form. The isolated crystals proved to be largely *exo*-methyl ether 1-OCH_3. These were recrystallized from hexane to give 567 mg (23%) of 1-OCH_3: mp 102.5–104.5 °C; ^{1}H NMR δ 7.07–7.76 (m, 8, aromatic), 4.31 (s, 1, H-4), 4.24 (d, 1, J = 10.5 Hz, CH_2Br), 4.00 (d, 1, J = 10.5 Hz, CH_2Br), 3.99 (m, 1, H-1), 3.68 (s, 3, OCH_3), and 2.49 (m, 2, H-8). Anal. Calcd for $C_{18}H_{17}OBr$: C, 65.67; H, 5.21. Found: C, 65.41; H, 5.12.

The mother liquors from the first crystallization were stripped on a rotovac to yield a colorless oil. Enough hexane was added to dissolve the oil. The pure *endo*-methyl ether (2-OCH_3) was isolated as an oil by HPLC collection from a silica gel column, eluting with 10% ether in hexane. ^{1}H NMR δ 7.01–7.20 (m, aromatic, 8), 4.97 (s, 1, H-4), 4.34 (d, 1, J = 10.5 Hz, CH_2Br), 3.90 (m, 1, H-1), 3.79 (s, 3, OCH_3), 3.78 (d, 1, CH_2Br, J = 10.5 Hz), and 2.46 (m, 2).

General Procedure for Photosolvolysis. All tubes used for photosolvolyses were 1.2 by 25 cm. Five milliliters of solution was added to each tube. The tubes were sealed with rubber septa and cooled to −30 °C. Dry nitrogen was bubbled through the solution for 30–40 min. After being warmed to room temperature, each tube was taped above the solution line to remove the possibility of gas-phase reaction. Usually one tube was completely taped for a dark reaction. Analysis was by ^{1}H NMR, using the geminal proton peaks.

Direct Irradiation of the Endo Dibromide 2-Br. A 0.043 M solution of 2-Br in 1:1 tetrahydrofuran/methanol was placed in six quartz tubes, prepared in the usual fashion. Each tube was irradiated with 254-nm or 300-nm light. Tubes were withdrawn from time to time, and immediately following irradiation, solvent was removed on a rotovac at room temperature. Methanolysis to 1-OCH_3 and 2-OCH_3 was monitored. Data are reported in Table I. No reaction occurred in the dark (taped) tubes.

Sensitized Irradiation of 2-Br Using 350-nm Light. A solution 0.042 M in 2-Br and 0.05 M in acetophenone was prepared in 1:1 tetrahydrofuran/methanol as solvent. Under these conditions the acetophenone absorbs 99.5% of the light. Five uranium glass tubes were prepared in the usual fashion and deaerated with nitrogen. A control tube was irradiated in the absence of sensitizer for 24 h. The tubes were irradiated for periods from 45 min to 24 h. Solvents were removed in a rotovac and analysis was by ^{1}H NMR. Approximately 10% solvolysis and 90% loss of starting material was observed after 24 h of irradiation in the sensitized tubes. The control tubes demonstrated a 5% loss of 2-Br to solvolysis products.

Direct Irradiation of 1-Br. A 0.041 M solution of a mixture of 9:1 1-Br/2-Br in 1:1 tetrahydrofuran/methanol was placed in six quartz tubes and treated as described for the endo isomer. Solvolysis to the methyl ethers 1-OCH_3 and 2-OCH_3 was monitored. Results are given in Table II.

Control Reactions Using Sodium Bicarbonate. When similar irradiations of dibromide epimers were performed in the presence of 0.1 g of solid sodium bicarbonate, similar results were obtained.

Direct Irradiation of the Methyl Ether in Methanol Using 254-nm Light. An approximately 0.04 M solution of the methyl ether 1-OCH_3 in 1:1 tetrahydrofuran/methanol showed no reaction or epimerization after 6 h of irradiation. The quartz tubes were prepared in the usual fashion and each contained a trace of acid.

Quenching Study of the Methyl Ether Formation by 1,3-Pentadiene. A standard solution of 2-Br in 1:1 tetrahydrofuran/methanol was prepared. Five quartz tubes were prepared by the standard method with an additional 25, 50, 250, and 1000 μL of 1,3-pentadiene injected into four tubes, respectively, before irradiation. The fifth tube was the control. After irradiation with 254-nm light for 1 h, the tubes were stripped of solvent and analyzed. There was 20% methanolysis in the control tube and similar reaction in the first three tubes with quencher concentrations at 0.05, 0.1, and 0.5 M. The fourth tube with a 2 M quencher concentration showed between 30 and 40% reduction in solvolysis.

Ground-State Methanolysis of 1-Br. A solution containing 511 mg (1.4 mmol) of 1-Br in 50 mL of 1:1 tetrahydrofuran/MeOH was divided equally into six preconstricted thick-walled Pyrex tubes. The tubes were cooled in a dry ice–acetone bath and sealed. After being warmed to room temperature, the tubes were heated at 60 °C. At various intervals tubes were cooled and opened and the contents were examined by ^{1}H NMR (see Table III).

Ground-State Methanolysis of 2-Br. A similar experiment was carried out with 520 mg (1.4 mmol) of 2-Br. Results are given in Table III.

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Registry No.—1-Br, 64771-42-2; 1-OMe, 64771-43-3; 2-Br, 64812-29-9; 2-OMe, 64812-30-2; 3, 19978-14-4.

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Rates and Scope of the Oxidative Carbon–Carbon Cleavage of Epoxides by Alkaline Hydrogen Peroxide[1]

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The scope and mechanism for the oxidative C–C cleavage of simple epoxides c-$R_1R_2COCR_3R_4$ with alkaline hydrogen peroxide has been studied. The cleavage occurs with most terminal epoxides ($R_3 = R_4 = H$), but was unsuccessful when R_1 = alkyl and $R_2 = H$, in this case affording the corresponding glycol. The cleavage proceeds via the β-hydroperoxy alcohol, which can be isolated in some cases. Base-catalyzed decomposition of β-hydroperoxy alcohols was studied kinetically. The substituent effect for the concerted fragmentation is explained by (i) an acceleration by the phenyl group via resonance with developing carbonyl, (ii) a possible steric acceleration, and (iii) the effect of acidities of the HOO and HO groups.

Ring-opening reactions of epoxides with nucleophiles have been extensively studied,[2] but reports on peroxides as nucleophiles are relatively limited. The acid-[3] and base-catalyzed[4] additions of hydroperoxides to epoxides have been shown to give β-hydroxy peroxides. Alkaline H_2O_2 cleavage of epoxides from α,β-unsaturated ketones was reported to proceed via a retro-Darzens condensation,[5] but α-methylstyrene oxide is the only simple epoxide reported to give C–C cleavage.[6] Here we wish to report our study on the scope and kinetics of the oxidative cleavage of some other simple epoxides.

Results and Discussion

Reaction of Epoxides with Alkaline Hydrogen Peroxide. The reaction of epoxides **1a–h** (Table I) with excess H_2O_2 was conducted in 70% MeOH containing 0.36 M KOH at 25 °C. The oxidative C–C cleavage occurred with epoxides **1a–d** to afford ketones. When $R_2 = H$, produced aldehyde R_1CHO was oxidized to acid R_1CO_2H (see Table I). No reaction took place for the case of **1e** and **1f**, which indicates no occurrence of S_N2 attack of HOO^- because of the steric retardation by methyl group.

$$R_1R_2C(O)CR_3R_4 \xrightarrow[70\%\ MeOH]{H_2O_2\text{–}KOH} R_1R_2C{=}O \qquad (1)$$

1

The reaction of **1g** and **1h** affords β-hydroperoxy alcohols, **2g** ($R_1 = n$-Pr; R_2 = Me; $R_3 = R_4 = H$) and **2h** ($R_1 = n$-C_7H_{15}; $R_2 = R_3 = R_4 = H$), respectively, together with other products. Interestingly, in spite of the occurrence of C–C cleavage with **2g**, peroxide **2h** is only converted slowly to 1,2-glycol. Likewise, cyclohexene oxide gave only cyclohexane 1,2-glycol after prolonged reaction.

$$R_1R_2C(O)CR_3R_4 \xrightarrow[S_N2]{H_2O_2\text{–}KOH} R\,R_2C(HO)CR_3R_4(OOH) \qquad (2)$$

1 2

The rates of disappearance of **1** were followed by NMR and/or GLC analysis. The relative rates are in the order **1h** > **1b** > **1a** > **1d** ≫ **1e, 1f**, which reflects the steric retardation by α substituents (R_3 and R_4) and also by β substituents (R_1 and R_2) in the S_N2 attack of HOO^- on the right side carbon of epoxide.

These results suggest that this kind of cleavage of epoxides is not always general but seems to be effective for terminal epoxides ($R_3 = R_4 = H$) except when R_1 = alkyl and $R_2 = H$ (e.g., **1h**).

Base-Catalyzed Reaction of β-Hydroperoxy Alcohols. In order to study the base-catalyzed decomposition of **2**, some other β-hydroperoxy alcohols were synthesized by the trifluoroacetic acid-catalyzed addition of H_2O_2 to epoxides. Here, the course of addition was normal and gave the adduct **3** as the

$$R_1R_2C(O)CH_2 + H_2O_2 \xrightarrow[Et_2O,\ reflux]{CF_3CO_2H} R_1R_2C(OOH)CH_2OH \qquad (3)$$

1 3

only product. These structures were identified by NMR and by comparison with authentic glycols after reduction with KI.

The rates and products from the base-catalyzed decomposition of **2** and **3** are listed in Table II. In most cases the fission of C–C and O–O bonds occurred to give high yields of ketones; **3b** gave benzaldehyde instead of benzoic acid in contrast to the cleavage of epoxide **1b** with excess H_2O_2 (see Table I). But the peroxy alcohols **2h** and **3h** were only converted to the same glycol without any C–C fission. This slow conversion to glycol is the homolytic decomposition of the hydroperoxide. The homolysis is assumed, since H_2O_2 itself decomposes also gradually evolving O_2 under the same condition, which is significantly reduced by addition of EDTA.

The rate for **3a** increases with increasing [KOH] and approaches a constant value (Figure 1). For comparison, the decomposition of the corresponding β-*tert*-butylperoxy alcohol PhMeC(OO-*t*-Bu)CH_2OH (**4a**) was also studied; a linear increase of the rate with increasing [KOH] was observed in this case. Similar results were also reported for Me_2C(OO-*t*-Bu)CH_2OH (**4b**).[7] The reaction of **3a** with lower concentrations of base (i.e., [KOH] ≲ 0.1 M) is about two times faster than that of **4a** but becomes slower when [KOH] is above ca. 0.36 M (Figure 1). The linear relationship between the rate and [KOH] is explained by Scheme I.[7] The nonlinear relationship for the case of **3a** suggests that the dissociation of β-hydroperoxy group inhibits the fragmentation (Scheme II).

Hydroperoxides are much stronger acids than alcohols[8] and the K_7 value of **3a** can be estimated to be 4.0 M^{-1} in 70% MeOH according to the reported method.[9,10] The curvature

Scheme I

$$R_1R_2C(OO\text{-}t\text{-}Bu)CH_2OH + MeO^- \overset{K}{\rightleftharpoons} R_1R_2C(OO\text{-}t\text{-}Bu)CH_2O^- + MeOH \qquad (4)$$

4

$$R_1R_2C(OO\text{-}t\text{-}Bu)CH_2O^- \xrightarrow{k_2} R_1R_2C{=}O + CH_2O + t\text{-}BuO^- \qquad (5)$$

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Table I. Rates and Products for the Reaction of Epoxides with Alkaline Hydrogen Peroxide in 70% MeOH at 25.0 °C[a]

	Registry no.	$R_1R_2C(O)CR_3R_4$ R_1, R_2, R_3, R_4	$10^5 k_{obsd}$,[b] M^{-1} s^{-1}	Products (%)[c]
1a	2085-88-3	Ph, Me, H, H	3.69	PhCOMe (71)
1b	96-09-3	Ph, H, H, H	5.33	$PhCO_2H$ (85)
1c[d]	17619-97-5	Ph, H, H, Ph	*e*	$PhCO_2H$
1d	882-59-7	Ph, Ph, H, H	1.22	PhCOPh (88)
1e	4741-91-7	Ph, Ph, H, Me	Too slow	none
1f	60227-39-6	Ph, Ph, Me, Me	Too slow	none
1g	3657-41-8	*n*-Pr, Me, H, H	ca. 3	**2g**[f] (38), *n*-PrCOMe (~45)
1h	28114-20-7	*n*-C_7H_{15}, H, H, H	10	**2h**[f] (60–80), glycol (10–30)

[a] Reaction with 0.1 M **1**, 1–3 M H_2O_2, and 0.36 M KOH in 70 vol % MeOH at 25.0 °C. [b] Second-order rate constants were calculated according to $v = k_{obsd}[1][HOO^-]$. $[HOO^-]$ was estimated from the corresponding K_7 value of 15 M^{-1} for H_2O_2. [c] Products were determined after 48 h's reaction by GLC, NMR, and/or UV analyses. Other minor products are the corresponding 1,2-glycols and/or α-methoxy alcohols (i.e., the addition products of MeO^-). [d] Reaction in 95% MeOH. [e] Not determined. [f] See Table II for structures. Prolonged reaction afforded the corresponding ketone and the glycol, respectively.

Table II. Rates and Products from the Base-Catalyzed Decomposition of α-Hydroperoxy Alcohols[a]

	$R_1R_2C(OOH)CH_2OH$ R_1	R_2	$10^3 k_{obsd}$,[b] s^{-1}	Products (%)[a]
3a	Ph	Me	4.20	PhCOMe (94)[c]
3b	Ph	H	0.32	PhCHO (89)
3d	Ph	Ph	2.19	PhCOPh (98)[c]
3g	*n*-Pr	Me	0.083	*n*-PrCOMe (81)[c]
3h	*n*-C_7H_{15}	H	0.022	*n*-$C_7H_{15}CH(OH)CH_2OH$ (100)
2g	*n*-PrMeC(C(OH)CH_2OOH		0.0019	*n*-PrCOMe (~65)[c]
2h	*n*-$C_7H_{15}CH(OH)CH_2OOH$		<0.001[d]	*n*-$C_7H_{15}CH(OH)CH_2OH$ (100)

[a] Reaction with 0.1 M **2** or **3** and 0.36 M KOH in 70 vol % MeOH at 25.0 °C. Products were determined by GLC and/or NMR analyses. [b] First-order rate constants were determined iodometrically from the rate equation $v = k_{obsd}$[**2** or **3**]. [c] Glycols or other products were not detected by GLC or NMR. [d] Reproducibility of the reaction rate was poor.

Scheme II

$$R_1R_2C(OOH)CH_2OH + MeO^- \underset{}{\overset{K_6}{\rightleftharpoons}} R_1R_2C(OOH)CH_2O^- + MeOH \quad (6)$$

3 **5**

$$3 + MeO^- \overset{K_7}{\rightleftharpoons} R_1R_2C(OO^-)CH_2OH + MeOH \quad (7)$$

6

$$5 \xrightarrow{k_8} R_1R_2C{=}O + CH_2O + HO^- \quad (8)$$

in Figure 1 can be reproduced by assuming $K_7 = 4.0$ M^{-1} for **3a**. Similar curves were obtained for the other peroxy alcohols, **3b** and **3g**, and the estimated K_7 values are 4.5 and 2.7 M^{-1}, respectively. These facts suggest that peroxy anion **6** is stable and the fragmentation proceeds via alkoxide ion **5**.

Since the same magnitude of the pK_a value may be assumed for primary alcohols,[7] $K_4 \simeq K_5 \simeq 1$, which means that only 1/300 of **3** is dissociated into **5** (molar ratio of MeOH:**3** is 300:1). Thus, a rough estimate of k_5 and k_8 values is possible: k_5 for **4a** is 3.5 s^{-1} and k_8 for **3a** is 8.3 s^{-1} in 70% MeOH at 25 °C.[12] That is, k_8 for **3a** is 2.4 times larger than k_5 for **4a**; the order is reasonable, since the HO group is a better leaving group than *t*-BuO.

Substituent Effects. The rate data for the base-catalyzed fragmentation of β-hydroperoxy alcohols in Table II can be summarized as follows:

(i) The peroxy alcohol **3a** (R_1 = Ph) is decomposed 50 times faster than **3g** (R_1 = *n*-Pr). The k_{obsd} value of 6.33×10^{-3} s^{-1} for **4a** (R_1 = Ph) with 0.08 M KOH in 40% MeOH at 30 °C is 18 times larger than the corresponding value of 0.372×10^{-3} s^{-1} for **4b** (R_1 = Me).[7] This indicates that resonance stabilization of the developing carbonyl by the phenyl group is important in the transition state for fragmentation (**7**).

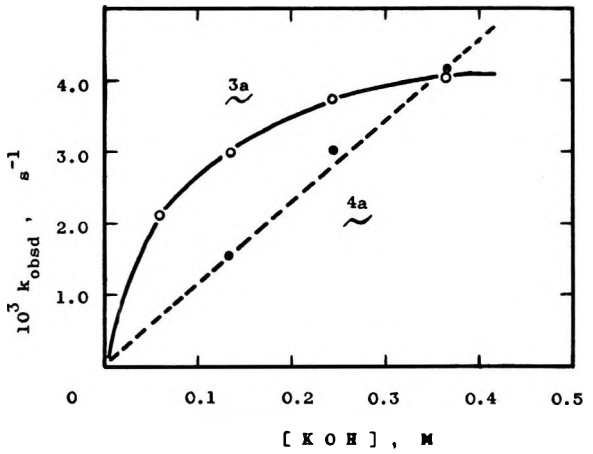
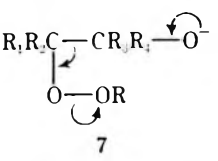


Figure 1. Effect of [KOH] on the decomposition of peroxy alcohols, **3a** and **4a**, in 70% MeOH at 25.0 °C.



7

Similar acceleration by the phenyl group has been reported for related peroxide reactions, e.g., the base-catalyzed reaction of α-hydroperoxy ketones[13] and α-ketols with H_2O_2.[14]

(ii) The rate for **3a** is much faster than **3b**; the fragmentation of **2g** and **3g** occurs, but that of **2h** and **3h** does not. These facts probably reflect a steric acceleration in the C–C fission as a second driving force for the fragmentation. Molecular models for **2** and **3** show their crowded structures. It is natural that the transition state **7** for the fragmentation is sterically assisted by releasing the steric strain.

Table III. NMR Data for β-Peroxy Alcohols (2, 3, and 4) and 1,2-Glycols[a]

β-Peroxy	Registry no.	Alcohols (R_1, R_2)	Corresponding 1,2-glycols
3a (Ph, Me)	33334-31-5	1.55 (s, CH_3), 3.87 and 3.90 (asym CH_2), 7.28 (s, ArH)	1.52 (s, CH_3), 3.63 and 3.68 (asym CH_2), 7.24 (s, ArH)
3b (Ph, H)	61040-96-8	3.70, 3.79, and 3.82 (asym CH_2), 5.03 (q, J = 5 and 7 Hz, CH), 7.24 (s, ArH)	3.53, 3.57, and 3.66 (asym CH_2), 4.74 (q, J = 5 and 7 Hz, CH), 7.25 (s, ArH)
3d (Ph, Ph)	33334-32-6	4.46 (s, $-CH_2O-$), 7.27 (s, ArH)	4.10 (s, $-CH_2O-$), 7.26 (s, ArH)
2g (*n*-Pr, Me)	65311-38-8	0.94 (m, CH_3), 1.10 (s, CH_3), 1.45 (m, $(CH_2)_2$), 3.83 (s, CH_2OO)	0.88 (m, CH_3), 1.08 (s, CH_3), 1.44 (m, $(CH_2)_2$), 3.30 (s, $-CH_2O-$)
3g (*n*-Pr, Me)	65311-39-9	0.89 (m, CH_3), 1.10 (s, CH_3), 1.45 (m, $(CH_2)_2$), 3.45 (s, $-CH_2O-$)	
2h (C_7H_{15},H)	65311-40-2	0.89 (m, CH_3), 1.33 (m, $(CH_2)_6$), 3.85 (m, $-CH_2O-$), 3.85 (m, CH)	0.88 (m, CH_2), 1.34 (m, $(CH_2)_6$), 3.40 (m, $-CH_2O-$), 3.55 (m, CH)
3h (C_7H_{15}, H)	65311-41-3	0.89 (m, CH_3), 1.32 (m, $(CH_2)_6$), 3.70 (m, CH_2), 3.83 (m, CH)	
4a (Ph, Me)	65311-42-4	1.27 (s, $C(CH_3)_3$), 1.50 (s, CH_3), 3.86 and 3.89 (asym CH_2), 7.26 (s, ArH)	

[a] Chemical shifts (δ vs. Me_4Si) in $CDCl_3$ for **3a, 3b, 3d,** and the corresponding glycols or in CCl_4 for **2g, 3g, 2h, 3h, 4a,** and the corresponding glycols. Ratios of peak areas are in accord with each structure. Peaks of OOH and OH protons were broad and their chemical shift changed by each determination.

(iii) The effect of the acidity of the peroxy alcohols is also important. That is, the fragmentation occurs for most of the primary alcohols, i.e., **3a,b,d,g,** while the secondary alcohol **2g** is cleaved more slowly. This sharp difference is explicable by reaction via **5,** since the acidities of secondary alcohols are less than one-tenth of primary alcohols.[15]

Considering the above arguments, the nature of the oxidative cleavage of epoxides may be summarized as follows. The successful C–C cleavage of epoxides may be due to any of three factors, i.e., the stabilization of developing carbonyl by the phenyl group, steric acceleration, or the acidity of the intermediary alcohols. On the other hand, the unsuccessful cleavage of **1h** and cyclohexene oxide may be due to the intermediary formation of less reactive peroxy alcohols.

Of course, a very important driving force for fragmentation is the strong electron-releasing effect of α-oxy anion. A similar effect of the α-oxy anion is well known for other peroxides fragmentations, e.g., the base-catalyzed reactions of β-peroxy alcohols,[7] carboxylic acids,[16] α-hydroperoxy ketones,[13] esters,[17] and α-ketols with H_2O_2.[14]

Experimental Section

Melting points were measured by a Yanagimoto micro melting point apparatus and are corrected. Boiling points are uncorrected. IR spectra were recorded with a Perkin-Elmer 337 grating spectrophotometer, UV spectra with a Hitachi 124 spectrophotometer, and ^1H NMR spectra with a Hitachi R-24B spectrometer. GLC analyses were performed with a Yanagimoto G 180 gas chromatograph with a flame ionization detector using diphenyl as an internal standard and two different columns: PEG 20M, 20% on Chamelite CK; Silicon OV17, 5% on Shimalite W.

Substituted Epoxides. α-Methylstyrene oxide (**1a**), styrene oxide (**1b**), 2-methyl-1-pentene oxide (**1g**), and 1-nonene oxide (**1h**) were prepared by treating the corresponding olefins with acetonitrile and alkaline H_2O_2.[18] Stilbene oxide (**1c**), 1,1-diphenylpropylene oxide (**1e**), and 1,1-diphenyl-2-methylpropylene oxide (**1f**) were prepared by treating the corresponding olefins with peracetic acid.[19] 1,1-Diphenylethylene oxide (**1d**) was prepared by Zaugg's method.[20] The compounds were purified by distillation and/or recrystallization; **1a,** bp 107–112 °C (47 mm) (lit.[21] bp 75–76 °C (12 mm)); **1b,** bp 95–98 °C (30 mm) (lit.[18] bp 86–87 °C (27 mm)); **1c,** mp 68–69 °C (lit.[19] mp 68–69 °C); **1d,** mp 52 °C (lit.[20] mp 56–57 °C); **1e,** bp 150–155 °C (7 mm) (lit.[22] bp 178–180 °C (21 mm)); **1f,** bp 140–142 °C (6 mm) (lit.[23] bp 162–163 °C (15 mm)), mp 61 °C (lit.[23] mp 61–62 °C); **1g,** bp 108–110 °C; **1h,** bp 92–94 °C (30–31 mm).

The structures of these epoxides were ascertained by their IR and NMR spectra. NMR data for epoxides are as follows (δ vs. Me_4Si in CCl_4): Ratios of peak areas are in accord with each structure. Data for **1a:** 1.63 (s, CH_3), 2.58 and 2.77 (two d, J = 6 Hz, CH_2), 7.27 (s, ArH). Data for **1b:** 2.62 and 2.94 (two q, J = 6 and 3.5 Hz and J = 6 and 4.5 Hz, CH_2), 3.65 (q, J = 4.5 and 3.5 Hz, CH), and 7.12 (s, ArH). Data for **1c:** 3.66 (s, CH), 7.19 (s, ArH). Data for **1d:** 3.08 (s, CH_2), 7.20 (s, ArH). Data for **1e:** 1.12 (d, J = 6 Hz, CH_3), 3.26 (q, J = 6 Hz, CH), 7.10 and 7.20 (s, ArH). Data for **1f:** 1.13 (s, CH_3), 7.18 (m, ArH). Data for **1g:** 0.95 (m, CH_3), 1.22 (s, CH_3), 1.45 (m, CH_2CH_2), 2.38 (s, $-CH_2O-$). Data for **1h:** 0.89 (m, CH_3), 1.32 (m, $(CH_2)_6$), 2.28 and 2.51 (two q, J = 5.5 and 3 Hz and J = 5.5 and 5 Hz, CH_2), 2.67 (m, CH).

β-Hydroperoxy Alcohols. α-Methylstyrene oxide (2 g, 0.015 mol) and CF_3CO_2H (0.05 mL) were added with stirring to a Na_2SO_4-dehydrated ether solution of 90% H_2O_2 (10 mL of 90% H_2O_2 in 100 mL of Et_2O). After refluxing for 4 h, the reaction mixture was washed twice with a small amount of aqueous NaCl[24] and then with aqueous $NaHCO_3$ and dried over Na_2SO_4. The removal of the solvent under slightly reduced pressure gave crude 2-hydroperoxy-2-phenyl-1-propanol (**3a**) (0.53 g, 21% yield), which was purified by recrystallization from ether–*n*-hexane to give 0.18 g (7% yield) of pure **3a,** mp 60–61 °C (lit.[3b] mp 65–67 °C), 94% pure by iodometry.

The other β-hydroperoxy alcohols, **3b, 3d, 3g,** and **3h,** were prepared similarly from the corresponding epoxides. Peroxy alcohols, **3b** and **3d,** were purified by recrystallization, mp being 71–73 °C (97.3% pure) and 124–125 °C (96.4% pure) (lit.[3b] mp 123–124 °C). The peroxy alcohols, **3g** and **3h,** could not be crystallized but were pure enough for our use, i.e., over 80% pure by NMR. These β-hydroperoxy alcohols were identified by their IR and NMR spectra and by the KI reduction to the corresponding 1,2-glycol.[25] The IR spectra of **3a–h** are practically the same as those of the corresponding 1,2-glycols, but the NMR spectra differ from each other characteristically (see Table III).

β-*tert*-Butylperoxy Alcohol. α-Methylstyrene oxide (2 g, 0.015 mol) and then CF_3CO_2H (0.05 mL) were added with stirring to a ethereal 10% solution of *t*-BuOOH (100 mL). After refluxing for 4 h, the mixture was washed twice with aqueous NaCl and then with aqueous $NaHCO_3$. Drying over Na_2SO_4 and evaporation of the solvent gave 2-*tert*-butylperoxy-2-phenyl-1-propanol (**4a**) of over 90% purity.

The Reaction of Epoxides with Alkaline Hydrogen Peroxide. The reaction of **1** (ca. 0.1 M) with 1–3 M H_2O_2 was carried out in 70% aqueous methanol containing 0.36 M KOH at 25.0 °C for 48 h. The reaction mixture was poured into water and extracted with CH_2Cl_2 and/or ether. 1,2-Glycols and the peroxy alcohol **2** are soluble only in ether. Products were identified by means of IR, NMR, and GLC analyses. The yields of products were determined mostly by GLC.

The formation of product (a carbonyl compound) was followed spectrophotometrically in the UV for **1a, 1b,** and **1d.** For the case of **1g** and **1h,** the consumption of epoxide was followed by GLC and/or NMR.

Base-Catalyzed Reaction of β-Hydroperoxy Alcohols. The base-catalyzed reaction of peroxy alcohols **2** or **3** (0.1 M) with KOH (mostly 0.36 M) was carried out in 70% aqueous MeOH at 25.0 °C. The consumption of β-hydroperoxy alcohol was followed by iodometry.[13] Products were determined as described above.

The base-catalyzed reaction of β-*tert*-butylperoxy alcohol **4a** was performed similarly. The rate was followed by determining acetophenone produced by means of UV spectrophotometry.

References and Notes

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(12) This was estimated from $k_{obsd} = 4.1 \times 10^{-3}$ s^{-1} for **3a** with 0.36 M KOH in 70% MeOH. That is, $k_8 = 4.1 \times 10^{-3}/(0.36 \times 0.41 \times (1/300)) = 8.3$, where 0.41 is a factor of undissociated **3a** (cf. $K_7 = 4$ M^{-1}) and 1/300 is the molar ratio of **5:3.**
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(24) Washing with a large amount of aqueous NaCl lowered the yield significantly.
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Application of the Hammett Equation to Equilibrium Acidities of Meta- and Para-Substituted Acetophenones

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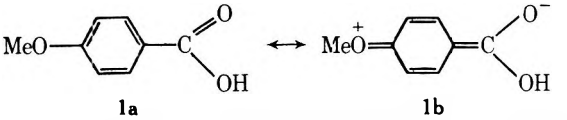
Equilibrium acidities in dimethyl sulfoxide solution are reported for 23 meta- and para-substituted acetophenones. A plot of the pK values for 14 of these vs. Hammett σ constants gave a linear correlation with $\rho = 3.55 \pm 0.05$ and $r = 0.9990$. The fit of these points to the line appears to be within the experimental error of the measurements. The slightly greater deviations for the remaining nine points can be rationalized. The excellent correlation argues against direct ("through") conjugative effects for *p*-Me$_2$N, *p*-MeO, and like groups in benzoic acids and acetophenones. Also, for at least 14 substituents solvation effects must be proportional in water and in dimethyl sulfoxide solutions. The absence of direct conjugative effects and solvent effects for most substituents accounts for the general success of the Hammett equation. The close similarity in geometry between the benzoic acids and their carbon analogues, the acetophenones, accounts for the good correlation observed in this particular instance.

The Hammett equation has proved to be of great utility in physical-organic chemistry[1] and has found application in various other areas of chemistry as well.[1d] Both kinetic and equilibrium data have been correlated by the equation in many types of benzenoid and heterocyclic systems in all types of media, including the gas phase. Its influence may be judged by the fact that a review of the subject by Jaffe,[1b] published in 1953, 13 years after the appearance of the first edition of Hammett's classical text,[1a] has become one of the most cited papers in all of chemistry. The literature in this area has continued to grow at a rapid pace in the ensuing years.[1] Despite its remarkable success, there are a number of problems with the Hammett treatment. In particular, the Hammett σ constants are empirical in nature and do not appear to be "constants" at all in the true sense of the word, since they contain resonance components which vary with the nature of the reactive site. For example, the σ_p constants for substituents having one or more electron pairs on the atom attached to the benzene ring (Me$_2$N, H$_2$N, MeO, HO, F, Cl, Br, I, and the like) are believed to be composed of two component parts, an electron-withdrawing polar (inductive) component and an electron-releasing resonance (mesomeric) component. When Me$_2$N, H$_2$N, MeO, or HO is substituted into the para position of benzoic acid, the resonance component is dominant, and these substituents are acid weakening. This was accounted for as a direct resonance effect by Ingold in 1933,[2] as depicted by resonance contributor **1b**, and this interpretation has gained general acceptance.[1]



1a **1b**

In benzenoid systems where CO$_2$H has been replaced by some other reactive site, the size of the resonance component varies with the degree of interaction between the two para substituents. When a saturated center intervenes between the benzenoid ring and the reactive site, such as in the arylacetic acids, direct conjugative interactions of type **1b** and **3b** are not possible and the use of σ^n and σ^0 constants has been proposed.[1] When the reactive site is an ion or radical directly attached to the aryl ring, conjugative interactions reach extremes. For cationic sites the use of Brown's σ_p^+ constants (based on rates of formation of cumyl "cations", i.e., ion pairs, in 90% aqueous acetone) is common, whereas for anionic sites σ_p^- constants (based on equilibrium acidities of phenols or anilinium ions in water) are generally used. The degree of direct conjugation of this type is believed to vary with the systems under scrutiny.

The σ_p constants for substituents in which the atom attached to the benzene ring is part of a multiple bond (NO$_2$, CN, COCH$_3$, SO$_2$CH$_3$, etc.) also have polar and resonance components. In this instance both components exert electron-withdrawing effects. Direct resonance interaction between these substituents and the carboxyl group in benzoic acid is not possible, but the presence of the resonance component is indicated by the fact that the effects are larger from

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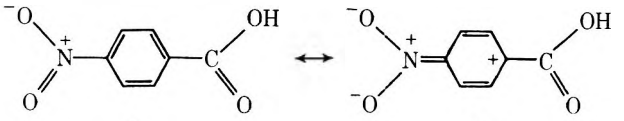
the para position than from the meta position. This is usually accounted for by resonance interaction with the benzene ring resulting in a buildup of positive charge in the para position, which exerts a polar effect on the carboxyl group (and/or the carboxylate ion), as illustrated in valence-bond symbolism by resonance contributor **2b.**[3]



2a **2b**

Aside from the problem of the dual electronic nature of Hammett σ constants, there is also the problem of solvent effects. The primary σ constants are derived from the equilibrium constants for the substituted benzoic acids in water, but in some instances aqueous ethanol has been used for solubility reasons.[1] There is evidence for solvent dependence of σ for charged substituents[4] and also for a few neutral substituents.[1,5] Analysis of the thermodynamic data available for meta- and para-substituted benzoic acids shows that the variations in $\Delta G°$ are caused as much by variations in $\Delta S°$ as by variations in $\Delta H°$.[6] Indeed, the success of the equation appears to depend essentially on compensation of ΔH_{ext} and ΔS_{ext} parameters, allowing $\Delta G°$ to vary linearly with ΔH_{int}.[6]

The development of a method for accurate measurement of equilibrium acidities of very weak acids in dimethyl sulfoxide (Me_2SO) solution has provided us with an alternative method for derivation of Hammett σ constants and allows, therefore, a reexamination of the Hammett relationship. It now becomes possible to derive σ constants in a single medium from equilibrium acidities of meta- and para-substituted acetophenones, the carbon acid analogues of the benzoic acids, or from meta- and para-substituted benzamides, the nitrogen acid analogues of the benzoic acids. We anticipated finding substantial deviations from the Hammett relationship for acetophenones caused by the change from the strongly hydrogen-bonding hydroxylic solvent (H_2O) to the non-hydrogen-bonding dipolar "aprotic" solvent (Me_2SO) and by the change from the carboxyl function, with its high degree of internal resonance energy (RE), to the aceto function wherein resonance is confined to the carbonyl group (compare formulas **3** and **4**).

Most substituents have one or more unshared electron pairs which can interact to varying degrees with the water by hydrogen bonding. Such hydrogen bonding effects are absent in Me_2SO, where solvation is principally by dipole–dipole interactions.

Experimental Results

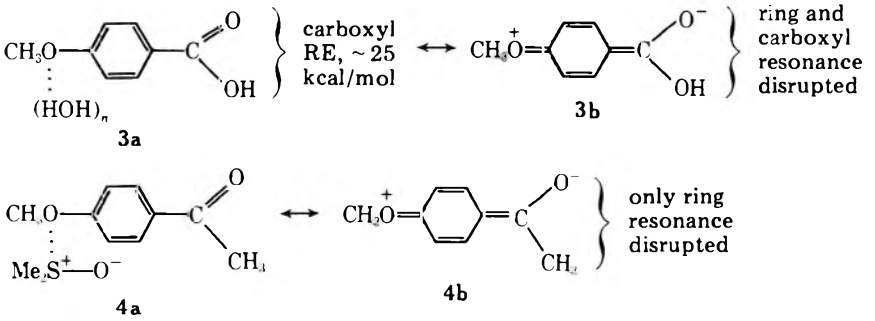
The equilibrium acidities for 23 meta- and para-substituted acetophenones were determined in dimethyl sulfoxide solution by the indicator method described earlier.[7] The pK values and appropriate σ constants are listed in Table I. Of the 23 compounds listed in Table I, 13 compounds with m- and p-CH_3, m-$N(CH_3)_2$, m- and p-OCH_3, p-Ph, H, m-SPh, m- and p-SOPh, m- and p-CF_3, and m-SO_2Ph substituents were measured several times against two or more indicators. For these compounds the values listed in Table I were determined by averaging the results for each indicator separately and then averaging the averages against the several indicators. Substituted acetophenones of acidity equal to or greater than p-bromoacetophenone showed a tendency toward lower pK values in successive points of a multiple point run. This suggests interference from a slow reaction of the enolate ions of some kind. The nature of this reaction was not investigated. This tendency appeared to increase with the electron-withdrawing ability of the substituents. For the m- and p-CF_3 and p-CN substituted acetophenones, the pK was determined by extrapolating the absorbance back to the time of mixing. (The correction was small.)

Table I. Equilibrium Acidity Constants for Meta- and Para-Substituted Acetophenones in Dimethyl Sulfoxide Solution

Substituent	Registry no.	pK_{obsd}[a]	σ[b]	pK_{calcd}[g]	ΔpK[h]
p-$N(CH_3)_2$	2124-31-4	27.48	−0.83	27.56	−0.08
p-OCH_3	100-06-1	25.70	−0.27	25.56	0.14
m-$N(CH_3)_2$	18992-80-8	25.32	−0.21	25.35	−0.03
p-CH_3	122-00-9	25.19	−0.17	25.21	−0.2
m-CH_3	585-74-0	24.95	−0.07	24.85	0.10
p-Ph	92-91-1	24.51	−0.01	24.64	−0.13
H	98-86-2	24.70	0.0	24.60	0.10
p-F	403-42-9	24.45	0.06	24.39	0.06
p-SPh	10169-55-8	24.11	0.075[d]	24.33	−0.22
m-OCH_3	586-37-8	24.52	0.12	24.17	0.35
m-SPh	26388-18-1	23.65	0.18[e]	23.96	−0.31
p-Br	99-90-1	23.81	0.23	23.78	0.03
p-Cl	99-91-2	23.78	0.23	23.78	0.00
m-F	455-36-7	23.45	0.34	23.39	0.06
m-Cl	99-02-5	23.18	0.37	23.28	−0.10
m-Br	2142-63-4	23.19	0.39	23.21	−0.02
m-CF_3	349-76-8	22.76	0.43	23.06	−0.30
p-SOPh	65085-80-5	23.18[c]	0.47[d]	22.92	0.26
m-SOPh	65085-81-6	22.97	0.52[e]	22.74	0.23
p-CF_3	709-63-7	22.69	0.54	22.67	0.02
m-SO_2Ph	65085-82-7	22.32	0.62[f]	22.39	−0.07
p-CN	1443-80-7	22.04	0.66	22.24	−0.20
p-SO_2Ph	65085-83-8	22.12	0.71[f]	22.07	0.05

[a] ±0.05 unit, not statistically corrected. [b] Values from data in water or 50% ethanol–water were compiled by D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958), unless otherwise noted. [c] ±0.11 unit. [d] L. Litvenenko, *Izv. Akad. Nauk*, 1653 (1962). [e] H. Szmant and G. Suld. *J. Am. Chem. Soc.*, **78**, 3400 (1956). [f] O. Exner, *Collect. Czech. Chem. Commun.*, **31**, 65 (1966). [g] Calculated from pK = -3.57σ + 24.60. [h] pK_{obsd} − pK_{calcd}.

For the other ten compounds whose pK values are listed in Table I, p-$N(CH_3)_2$, m- and p-F, m- and p-Cl, m- and p-Br, p-SPh, p-SO_2Ph, and p-CN, the values in Table I are averages of at least three runs against only one indicator. In each case the compound or its anion had a significant absorbance in the useful range of the alternative available indicator or under-



3a **3b** **4a** **4b**

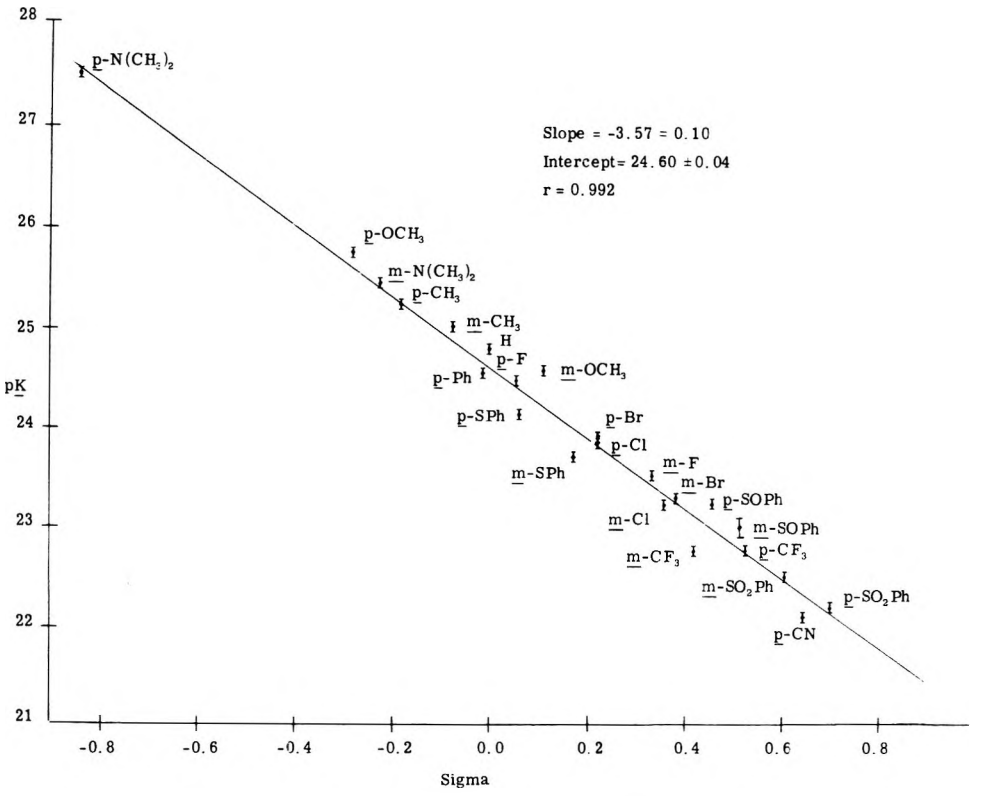


Figure 1. Plot of pK values for meta- and para-substituted acetophenones in dimethyl sulfoxide solution vs. Hammett σ constants.

went an apparent reaction with the indicator. The anions of p-$N(CH_3)_2$, p-Ph, m- and p-SOPh, m- and p-SO_2Ph, m- and p-CF_3 and p-CN substituted acetophenones were all visibly yellowish in color. The absorbance of the anions of p-Ph, m- and p-SOPh, and m- and p-CF_3 was, however, negligible at the concentrations used for pK determination (ca. 10^{-2}–10^{-3} M) at the wavelength of the appropriate indicators. The anion of the p-$N(CH_3)_2$ substituted acetophenone had an absorbance of slightly over 0.1 unit at the concentrations used for pK determination in the useful range (ca. 622 nm) of 9-phenylxanthene. The absorbance of the anions of m- and p-SO_2Ph and p-CN tailed out too far to measure against fluorene at ca. 525 nm, and p-SO_2Ph and p-CN could not even be measured against 3-methylfluorene at ca. 540 nm. The absorbance of these anions was, however, low enough (<0.1 unit) to be compensated for at 572 nm in measurement against 9-methylfluorene. In addition p-N,N-dimethylaminoacetophenone could not be measured against 9-phenylxanthene, and m- and p-SPh substituted acetophenones could not be measured against 1,3,3-triphenylpropene because of apparent reactions with the indicator. The apparent reactions resulted in unsteady, rapidly falling then rising, or immediately rising absorbances. The m- and p-SOPh substituted acetophenones when measured against fluorene showed absorbances which fell rapidly, leveled off, and then rose slowly. The absorbance as it leveled off was used to calculate the pK values. The halo-substituted acetophenones also showed an apparent reaction with fluorene in which the absorbance fell, leveled off, and then rose. In all cases except p-fluoroacetophenone the rise in absorbance was slow enough that the pK could be based on the level absorbance value.

The color of the halo-substituted acetophenone pK solutions all appeared to change from the yellow of the fluorenyl anion to a very intense dark reddish purple in a period of ca. 0.5 h to several hours. To investigate this change a sample of p-bromoacetophenone was treated with 1 equiv of fluorene in Me_2SO containing 1 equiv of $CH_3SOCH_2^-K^+$ for several days under an inert atmosphere. After quenching and concentration of the ether extracts, the residue consisted of ~70% unchanged acetophenone and fluorene and 25% p-(9-fluorenyl)acetophenone by NMR analysis.

For each of these ten compounds a single acceptable indicator was available and at least three separate experiments exhibited reproducible results with an average deviation from the mean of less than 0.04 unit.

For all of the compounds in Table I measured against two or more indicators, the averages against each indicator deviated from the final average by 0.05 unit or less with the exception of p-benzenesulfinylacetophenone, which had a mean deviation of 0.11 unit for three indicators. As stated above the pK values of those compounds measured against one indicator showed deviations 0.04 unit or less from their average values. The uncertainty in the pK values listed in Table I is therefore taken as 0.05 unit for all compounds except p-benzenesulfinylacetophenone, which is taken as 0.11 unit.

The acetophenone pK values were plotted against the best available Hammett σ constants. For the most part these are "primary" values derived from the acidities of benzoic acids in water. The slope of the line, as determined by least-squares regression analysis, is -3.57 ± 0.10 with an intercept of 24.60 $\pm$ 0.04. The correlation coefficient is 0.992 (see Figure 1).

Since ketones sometimes undergo reactions in basic media, an experiment was performed to determine if the acetophenone could be recovered unchanged after equilibration under pK conditions. Acetophenone, 106 mg, was mixed with a small molar excess of 1,3,3-triphenylpropene and its anion for 5 min under pK measurement conditions. The mixture took on the expected deep red color of the triphenylpropenyl anion. The mixture was then quenched with water and extracted with ether. Evaporation of the ether left a mixture of acetophenone and the 1,3,3 and 1,1,3 isomers of triphenylpropene in a 20:80 ratio, as shown by NMR. The mixture was separated by chromatography and analyzed by TLC and NMR. In this way 95 mg of acetophenone was recovered, representing a 90% recovery of the original amount as compared to a 93% recovery in an identical blank experiment omitting only the base.

Discussion

Correlation of Acetophenone Acidities with Hammett σ Constants. The correlation of the acetophenone acidities in Me_2SO with those of the benzoic acids in water (as represented by Hammett σ values) was found to be much better than we anticipated. The standard deviation from the line of ±0.1 pK unit (see Experimental Results section) is, however, outside the error in the measurements (±0.05 pK unit). The deviations of the various observed pK values from the calculated pK values are shown as ΔpK in Table I. The ΔpK values for 14 of the 23 compounds are ±0.10 unit or less. Of the remaining nine compounds, the points for p-OMe and p-Ph deviate by +0.14 and −0.13 unit, respectively, while those for m-OMe, m- and p-SPh, m-CF_3, m- and p-SOPh, and p-CN show deviations of ±0.20 to ±0.35 unit. The uncertainty in the calculated pK can be determined from the partial differential of the Hammett equation and the uncertainties in the slope and intercept. For the nine points with ΔpK of 0.13 unit or more, the sum of the uncertainty in the observed pK and the calculated pK is less than the ΔpK and in most cases less than half of ΔpK. If these nine points are omitted, and the remaining 14 points fitted by least-squares regression, the slope is −3.55 ± 0.05 with an intercept of 24.60 ± 0.02 and a correlation coefficient, r, of 0.9990. While the slope and intercept are unchanged, this new line represents a 50% reduction in the uncertainty of both slope and intercept and a 100% improvement in the correlation coefficient.

A new set of σ constants (σ_D) may be calculated using this new line and the pK values for the nine deviant points. The σ_D values for these points differ from the literature σ values by 0.04 to 0.10 unit (Table II). The excellent correlation observed for acidities of benzoic acids in water vs. acetophenones in Me_2SO for 14 of 23 substituents makes it seem likely that the differences in (calculated) σ_D values and literature σ values may be due to specific solvation effects or experimental error in the literature or observed values. The σ_D value of 0.27 for m-SPh derived herein for σ is in much better accord with Hammett correlations that we have obtained for acidities in Me_2SO in the $ArCH_2CN$ and $ArCH_2SO_2Ph$ carbon acid series[8] than is the lower literature value (0.18). We believe, therefore, that the literature value is suspect. On the other hand, the data from the $ArCH_2CN$ and $ArCH_2SO_2Ph$ series, and also for the aniline series,[9] are in better agreement with the original σ value for m-CF_3 than the one derived herein. We conclude, therefore, that the m-$F_3CC_6H_4COCH_3$ pK value is suspect. There are, indeed, experimental reasons to question the accuracy of this value, as well as that for p-$CNC_6H_4COCH_3$ (see the Experimental Results section). The rather strong deviation observed for the m-OMe point has been observed also for acidities of $ArCH_2CN$, $ArCH_2SO_2Ph$, and $ArNH_2$ in Me_2SO.[8,9] In each of these series, as well as in the fluorene series,[10] use of the σ_D of 0.02 for m-OMe derived herein will bring the point much closer to the Hammett line than will the normal σ of 0.12 or even the value of 0.06 suggested by Taft[5a] for use in organic solvents. Here it seems likely that a solvent effect may be responsible. Hydrogen bonding to oxygen in the aqueous medium may enhance the electron-withdrawing properties of the methoxyl group and thereby increase its apparent σ constant. A similar effect would be expected for other functions capable of strong H bonding. An effect of this kind would account for the appreciably larger σ constants derived for m- and p-PhSO substituents in water than in Me_2SO (0.06 and 0.07 unit larger, respectively). The smaller value for m-PhSO in Me_2SO gives a better fit for this point in the 2-substituted fluorene series.[10]

We conclude that the Hammett σ constants derived from benzoic acids in water are applicable with remarkable precision for most acetophenones in Me_2SO. The exceptions noted are m- and p-OCH_3, m- and p-SOPh, and m- and p-SPh. These σ_D values may be useful in other aprotic media also.

Table II. Differences in σ Values Derived in Water for Benzoic Acids and in Dimethyl Sulfoxide for Acetophenones

Substituent	σ^a	$\sigma_D{}^b$	$\sigma - \sigma_D$
p-OMe	−0.27	−0.31	0.04
p-Ph	−0.01	0.03	−0.04
p-SPh	0.075	0.14	−0.065
m-OMe	0.12	0.02	0.10
m-SPh	0.18	0.27	−0.09
m-CF_3	0.43	0.52	−0.09
p-SOPh	0.47	0.40	0.07
m-SOPh	0.52	0.46	0.06
p-CN	0.66	0.72	−0.06

[a] Derived from benzoic acids in water. [b] Derived from acetophenones in dimethyl sulfoxide.

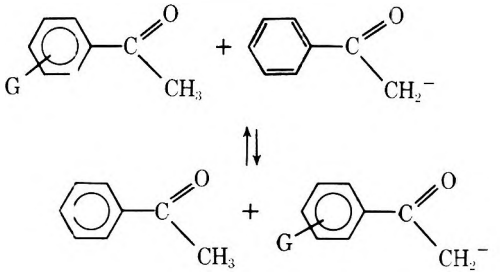
Comparison with Acidity Data in Other Solvents. No direct comparison can be made between the absolute pK of acetophenone in Me_2SO with the values of 19 in benzene solvent[11] or 19.1 in polyether solvent,[12] since the latter "pKs" are "ion pair pKs", and are based on an arbitrary reference standard.[13] It is of interest to note, however, that in benzene acetophenone appears to be a *stronger* acid than fluorene by about six powers of 10, whereas in Me_2SO it is a *weaker* acid than fluorene by about two powers of 10.

A pK for acetophenone in aqueous medium of 19.2 was estimated by Bell from kinetic data.[14] Another kinetic approach places the pK several units lower (~16).[15] The latter value indicates that the acidity of acetophenone in water is about 7–8 units higher than that in Me_2SO, which is comparable to the difference in acidity for nitroalkanes in H_2O vs. Me_2SO (6–9 pK units[16]).

In H_2O–Me_2SO mixtures containing about 60% Me_2SO, the apparent pK of acetophenone is 21.5, i.e., about 4.5 pK units above that in water and about 3.2 pK units below that in 100% Me_2SO.[17,18] For 9-substituted fluorenes apparent relative acidities as determined by the H_- method were found to be contracted compared to those in Me_2SO. This is probably due to high apparent pK values in the more aqueous medium arising from the fact that fluorenes have lower acidities in water than in Me_2SO.[7] On the other hand, acetophenones have higher acidities in the more aqueous medium, and the apparent pK values in this region will be low, which would be expected to lead to an expanded scale in the H_2O–Me_2SO medium. This is what is observed.[17] For example, the ΔpK for p-cyanoacetophenone and acetophenone is 3.1 units in the H_2O–Me_2SO medium, as compared to 2.7 units in Me_2SO. For a series of para-substituted acetophenones (CN, Br, Cl, H, and Me), a roughly linear Hammett correlation was observed in the mixed H_2O–Me_2SO medium with $\rho = 4.6$,[17] as compared to our value of 3.55. The p-OMe and p-NMe_2 points deviated badly from this line, the compounds being much more acidic than predicted. As a consequence, ΔpK between p-NMe_2 and p-CN substituted acetophenones is considerably smaller in the H_2O–Me_2SO medium (4.2 units) than in Me_2SO (5.5 units).[19]

Solvation, Conjugative, and Geometric Effects. In the introduction we showed that because of appreciable differences in solvation in H_2O vs. Me_2SO, and because of appreciable differences in the conjugative abilities of the aceto and carboxyl functions, that a poor fit with the Hammett equation when applied to acetophenones in Me_2SO would not be surprising. Instead, the correlation between the acidities of meta- and para-substituted benzoic acids in water and the acidities of corresponding acetophenones in Me_2SO appears to be as good or better than is usually achieved with as many as 14

substituents. Furthermore, the deviations observed for most of the remaining nine substituents studied are not far outside of experimental error. This remarkable correlation indicates that the large differences in solvation effects of H_2O vs. Me_2SO on acetophenone and benzoic acid, as revealed by the large differences in acidities of these parent acids in the two media,[7] are unimportant. Either the solvation effects remain constant as meta and para substituents are introduced or the solvation effects vary in a proportional manner with substitution in the two media. The substantial changes in $\Delta S°$ of ionization with substitution for the benzoic acids in water indicate that solvation is changing in this medium. Presumably, the changes in $\Delta S°$ are complemented by changes in ΔH_{int}.[6] In Me_2SO a roughly linear correlation between enthalpies of deprotonation of a variety of weak acids by $CH_3SOCH_2^-K^+$ and equilibrium acidities has been observed to hold over a range of about 20 powers of 10.[20] The slope of this line indicates that $\Delta S°$ is often zero in Me_2SO.[20] Pitzer has pointed out that ΔS_{int} for a reaction of the type shown in eq 1 is nearly zero.[21] If $\Delta S°$ for

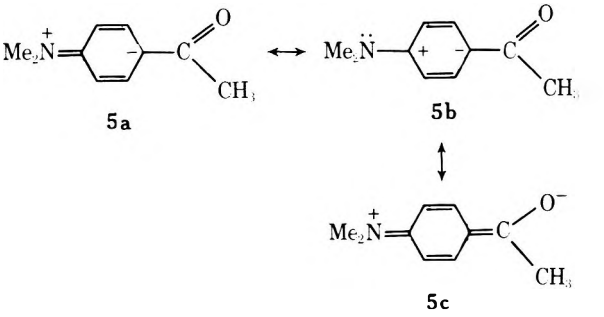


(1)

this reaction is close to zero, as the $\Delta H°$ vs. $\Delta G°$ correlation suggests, this would mean that in Me_2SO ΔS_{ext}, as well as ΔS_{int}, remains essentially constant with meta and para substitution. In this instance the change in substituent effects must correspond to a change in ΔH_{int}. Since Kolthoff and Chantooni have observed that ρ for phenols remains essentially constant in Me_2SO, CH_3CN, and $HCONMe_2$ solvents, despite a change of over 10 pK units in acidities in these solvents,[22] this is no doubt true also in other dipolar aprotic solvents. From these results it would appear that, in protic solvents and dipolar aprotic solvents, solvation effects vary in a proportional manner with meta and para substitution and that this accounts for the ability of the Hammett equation to accommodate data in all types of media. Another reason for the success of the Hammett equation apparently lies in the relative unimportance of direct ("through") conjugative effects.

The close correspondence in effects for p-F, p-Ph, p-Me, p-MeO, and p-NMe_2 substituents on benzoic acids in water and acetophenones in Me_2SO argues against major contributions from direct conjugative interactions such as those depicted by formulas **1b, 3b, 4b,** and **5c.** "Through conjugation" of this type would be expected to be much more important for acetophenones than for benzoic acids, and this is not observed.[23] These functions are obviously engaged in an electron-releasing resonance interaction involving the benzene ring, but evidently this does not include the carboxyl or carbonyl function to any appreciable degree. Instead, the negative charge generated next to the CO_2H or $COCH_3$ function by this interaction must operate primarily by an electrostatic effect. This can be depicted in valence-bond symbolism by resonance contributors such as **5a** and **5b.** [Resonance contributor **5c** is of minor importance because (a) a high degree of charge separation is required and (b) the aromaticity of the benzene ring is lost.] Resonance of this type will stabilize the undissociated acid and will destabilize the corresponding anion. Both effects are acid weakening.

Direct conjugation of the type depicted by **3b** (or **5c**) is no longer possible when a methylene group is interposed between



the benzene ring and the acidic site, as in the arylacetic acids. Nevertheless, Dippy showed many years ago that a p-MeO substituent is acid weakening, not only in the benzoic acid series but also in the phenylacetic, β-phenylpropionic, and cinnamic acid series.[24] This is true also in carbon acids of the type $ArCH_2G$, where G is an electron-withdrawing group.[8] This acid weakening effect is clearly a property of a methoxy group attached to a benzene ring, irrespective of the type of acidic site attached in the para position. It can be properly represented as in **5a** or **5b;** contributors of type 5c can be ignored. It follows that attempts to derive precise σ constants lacking a resonance component (σ^0 or σ^n) from data taken from p-$MeOC_6H_4CH_2CO_2H$ and like systems are doomed to failure. The relative importance of contributors **5a** and **5b** is uncertain. The similar size of the orbitals on first-row elements permits better overlap between carbon and first than second row elements, allowing representation **5a** to be used to account for the larger electron-releasing effects from first-row elements (e.g., $CH_3O > CH_3S$).[1f] On the other hand, **5b** requires less separation of charge, as compared to **5a,** and **5b** allows maintainence of the aromaticity of the benzene ring (6π electrons), whereas **5a** does not. Furthermore, there is reason to believe that the surprisingly large electron-releasing effect of fluorine, as compared to other halogens, is dictated primarily by a high internal energy caused by the high concentration of unshared electrons on this small (first-row) element.[25] Similar effects may be operative to a greater or lesser extent for OMe and NMe_2 functions. Polarization of the benzene ring, as in **5b,** provides a means of lowering this energy, at the same time stabilizing the carbonyl function (C=O ↔ C^+—O^-).

Another factor contributing to the excellent Hammett correlation observed between the acidities of the acetophenones and benzoic acids is the close correspondence in geometry between the two systems (compare 3 and 4). Part of the transmission of the electronic effects of substituents to the acidic site must be relayed through the molecular cavity, including the solvent. (In aliphatic systems there is evidence that this is the *major* mode of transmission, σ bonds, and even isolated π bonds, playing minor roles.[26]) The degree of transmission will depend on the medium, as well as the nature and geometry of the substrate. For example, ρ increases from 1.0 to ~2.5 to ~10 for benzoic acids as the medium is changed from water to Me_2SO to the gas phase, and ρ increases from ~2.5 to 3.5 as the substrate is changed from benzoic acids in Me_2SO to acetophenones in Me_2SO. One of the major causes of the latter increase is probably the concentration of charge on the single oxygen atom in the enolate ions derived from the acetophenones, as compared to a distribution of charge equally over two oxygen atoms in the benzoate ions. In substrates such as $ArCH_2CO_2H$, $ArCH{=}CHCO_2H$, ArOH, $ArCH_2CN$, etc., the geometric relationship between the individual meta and para substituents and the acidic site has changed, and we cannot expect Hammett σ constants derived for benzoic acids to fit precisely. When one atom intervenes between the benzene ring and the acidic site, as in the acetophenones (and benzoic acids), the present study shows that

solvent and direct conjugative effects can be ignored, leaving differences in the nature and geometry of the substrate as the principal variables. If the acidic site is moved closer to the ring, as in phenols, enhanced interactions are encountered. These will be discussed in the next paper in this series.

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Substituent Effects and Additivity in the Carbon-13 Nuclear Magnetic Resonance Spectra of Chlorinated Naphthalenes and Their Chlorinated Naphthol Metabolites

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Carbon-13 and proton nuclear magnetic resonance spectra were obtained for 12 chlorinated naphthalenes and six chlorinated naphthols, some of which are metabolites of the naphthalenes. The validity of the use of additivity of chlorine and hydroxyl substituent effects to predict ^{13}C chemical shifts in these compounds was examined. Deviations from the additivity predictions resulted from peri and ortho substituent interactions, both steric and hydrogen bonding. Despite these deviations, additive substituent parameters could be used to assign ^{13}C spectra correctly and to distinguish uniquely between similar isomers.

Polychlorinated naphthalenes are widely used industrially as complex mixtures of chlorinated naphthalene isomers. Because of the large volume and wide distribution of their use, the potential human exposure to these compounds is great. Characterization of the metabolites and elucidation of the metabolic pathways for chlorinated naphthalenes have been the focus of several investigations in the past few years. Recent work has shown that some individual chlorinated naphthalene isomers are metabolized to chlorinated naphthols.[1,2]

Our interest centered on the identification and characterization of the individual chlorinated naphthalenes and their known and potential metabolites. We were particularly interested in those characteristics which might influence the metabolism or toxicity of these compounds. For example, their steric properties may influence the rate at which hydroxylation takes place. Intramolecular hydrogen bonding in the metabolites may affect the relative rates of excretion and hence the relative toxicities.

Several studies of substituent effects on the ^{13}C shieldings of aromatic compounds have appeared in the literature. Substituent effects in monosubstituted benzenes[3] and halobenzenes[4,5] have been examined. Carbon-13 NMR substituent effects in 4-substituted biphenyls,[6] 4,4′-disubstituted biphenyls,[7] and polychlorinated biphenyls[7,8] have also been studied. Substituent effects on the ^{13}C shieldings of methylnaphthalenes,[9,10] halonaphthalenes,[11,12] and some other naphthalenes[13,14] have been reported. Kitching et al.[15] have analyzed ^{13}C chemical shift data for a large number of 1- and

2-substituted naphthalenes, in terms of the Taft dual substituent parameter equation, to probe the nature of the transmission of substituent effects in these systems.

Additivity of substituent effects for a single type of substituent, for example, methyl or chlorine, has been used successfully to predict the ^{13}C chemical shifts of the compounds in some of these studies. The exceptions appear to be for compounds in which significant steric interference between the substituents may occur, as in ortho,ortho'-disubstituted biphenyls[8] and 1,8-disubstituted naphthalenes.[10,12] For example, in the halonaphthalenes[12] good agreement with additivity predictions was observed for 1,5- and 2,7-X_2-naphthalenes (X = F, Cl, or Br), but large deviations from the predicted chemical shift values were observed for 1,8-X_2-naphthalenes.

Our objectives in this study were fourfold: first, to obtain ^{13}C NMR parameters for individual chlorinated naphthalenes and their hydroxylated metabolites;[16] second, to test the validity of the assumption that substituent effects on ^{13}C shieldings are additive for naphthalenes with multiple chlorine and hydroxyl substitution; third, to examine the effects of intramolecular steric and hydrogen bonding interactions on the ^{13}C shieldings; and fourth, to determine how well additivity predictions work in uniquely identifying particular isomers without resorting to complete and unequivocal assignment of the ^{13}C spectra.

Experimental Section

Materials. Reagent quality samples of 1-chloro-, 2-chloro-, 2,7-dichloro-, 1,2,5,4-tetrachloro-, and 1,2,3,4,5,6,7,8-octachloronaphthalene, and 1-chloro-4-hydroxynaphthalene were obtained commercially. The dichloronaphthol metabolite of 2,6-dichloronaphthalene was provided by Dr. Ih Chu.[2] The remaining naphthalenes were synthesized in these laboratories by the following methods. The purity and identity of all the naphthalenes synthesized were confirmed by gas chromatography-mass spectrometry, infrared spectroscopy, and melting point measurements.

1,2-Dichloronaphthalene. 1,2-Dichloronaphthalene was prepared from 2-amino-1-nitronaphthalene (Aldrich) by the method of Clemo et al.[17] and purified by column chromatography on silica gel to give mp 34 °C (lit. mp 35 °C).

1,5-Dichloronaphthalene. 1-Amino-5-nitronaphthalene (Aldrich; 2.0 g, 10.6 mmol) was reduced by heating for 6.5 h on a steam bath with iron powder (Alfa Products; 325 mesh; 6.62 g, 0.118 g-atom), water, and a few drops of concentrated hydrochloric acid.[18] The mixture was cooled and extracted with ethanol. The extract was filtered and evaporated to dryness with a rotary evaporator. The resulting diamine was dissolved in 10 mL of 50% concentrated hydrochloric acid, cooled in an ice bath, and tetrazotized with sodium nitrite (1.538 g, 22.3 mmol) in 5 mL of water. The diazonium salt was decomposed by stirring it with a boiling solution of copper(I) chloride (2.62 g) in concentrated hydrochloric acid for 2.5 h. Water was added and the mixture was extracted with benzene. The organic layer was washed with 10% potassium hydroxide solution, water, and saturated sodium chloride and dried over anhydrous sodium sulfate. The solution was filtered and evaporated to dryness on a rotary evaporator, and the residue was purified by column chromatography on silica gel to yield 328 mg (15.7%) of 1,5-dichloronaphthalene, mp 105.5–106 °C (lit.[19] mp 105–107 °C).

1,4-Dichloronaphthalene. 1,4-Dichloronaphthalene was prepared by diazotization of 1-amino-4-chloronaphthalene (Aldrich) followed by decomposition of the diazonium salt in copper(I) chloride in hydrochloric acid. The crude product was purified by column chromatography on silica gel (Woelm, activity grade 1), eluting with hexane. Gas chromatographic analysis indicated a purity of greater than 99%. The compound had mp 66.5–67.5 °C (lit.[20] mp 67–68 °C).

1,8-Dichloronaphthalene. 1-Chloro-8-nitronaphthalene (Aldrich) was reduced with iron powder by the procedure described previously for 1-amino-5-nitronaphthalene. The resulting amine was diazotized, followed by decomposition of the diazonium salt with copper(I) chloride in hydrochloric acid. The product was extracted and purified as in the preceding procedures to yield 123 mg (17.1%) of 1,8-dichloronaphthalene with a purity of 98% by gas chromatography and mp 85–86.5 °C (lit. mp 83[21] and 88 °C[22]).

2,6-Dichloronaphthalene. 2,6-Dichloronaphthalene was prepared from the disodium salt of 2,6-naphthalenedisulfonic acid (Aldrich) and phosphorus pentachloride according to the method of Beattie and Whitmore,[23] mp 134.5–136.5 °C (lit. mp 136 °C). Purity by gas chromatography was better than 99%.

1,2,3-Trichloronaphthalene. 1,2-Dichloro-3-nitronaphthalene (Aldrich) was reduced with iron powder as described previously. The resulting amine was diazotized, followed by decomposition of the diazonium salt with copper(I) chloride in hydrochloric acid. After purification, a white solid, mp 75–77 °C (lit.[24] mp 81 °C), was obtained. The purity of the 1,2,3-trichloronaphthalene was greater than 91% by gas chromatography. Combined GC–MS confirmed the major component as the trichloronaphthalene; the minor component was a dichloronaphthalene.

2-Chloro-1-naphthol and 1-Chloro-2-naphthol. 2-Chloro-1-naphthol and 1-chloro-2-naphthol were prepared from 1-naphthol and 2-naphthol, respectively, by reaction with *tert*-butyl hypochlorite as described by Ginsberg:[25] 2-chloro-1-naphthol, mp 62–63.5 °C (lit. mp 64–65 °C); 1-chloro-2-naphthol, mp 68–70 °C (lit. mp 71 °C).

1-Chloro-8-naphthol. The procedure of Woroshtzow and Koslow[26] was attempted without success. Likewise, diazotization of 1-amino-8-chloronapthalene[18] followed by addition of the diazonium salt to boiling sulfuric acid was unsuccessful as a synthesis for 1-chloro-8-naphthol. The procedure used to synthesize this compound successfully is as follows.

1-Amino-8-chloronaphthalene (400 mg) and 6 mL of 6 M sulfuric acid were sealed in a thick-walled glass tube and kept at 200 °C for 16 h. The tube was broken open and the contents were extracted with benzene. The organic layer was washed with 5% aqueous sodium hydroxide. The aqueous layer was then acidified and extracted with benzene. The extract was washed with water and a saturated sodium chloride solution, dried over anhydrous sodium sulfate, and concentrated to yield 226 mg of crude chloronaphthol. This residue was chromatographed on silica gel to yield 200 mg of pure (99.6% by gas chromatography) 1-chloro-8-naphthol, mp 65–66 °C (lit.[26] mp 65–66 °C).

Anal. Calcd for $C_{10}H_7ClO$: C, 67.24; H, 3.95; Cl, 19.85. Found: C, 67.09; H, 3.93; Cl, 19.99.

Spectral Analyses. Samples. Samples for NMR analysis were 10% w/v solutions in chloroform-*d* (Merck Isotopes) with approximately 0.5% added tetramethylsilane (Me_4Si). The samples were contained in 5 mm NMR tubes.

Spectra. Both ^1H and ^{13}C NMR spectra were recorded on a Varian XL-100 spectrometer with a Nicolet TT-100 Fourier transform system. Proton spectra at 270 MHz were obtained on the Bruker HX-270 superconducting NMR system at Florida State University. Natural abundance ^{13}C NMR spectra were obtained with 5 kHz spectral widths and 16K Fourier transforms at approximately 40 °C. The ^1H noise-decoupled ^{13}C spectra were obtained with a decoupler power of 10 W (reflected power less than 0.5 W) and a noise band width of 1.8 kHz. For selectively decoupled ^{13}C spectra the ^1H decoupler power was low, ca. 100–105 dB on the XL-100 spectrometer, and was set at the proper single frequencies for each individual proton resonance in turn. These frequencies were determined by analyses of the ^1H spectra. Mass spectra were obtained by gas–liquid chromatography and 70 eV electron impact mass spectrometry on a Hewlett-Packard 5930 mass spectrometer with a Hewlett-Packard 5700 gas chromatograph. Infrared spectra were obtained on a Perkin-Elmer 257 grating infrared spectrophotometer.

Proton Spectra. Proton spectra of 1,4-, 1,5-, 1,8-, 2,6-, and 2,7-dichloronaphthalene, and 1,2,3,4-tetrachloronaphthalene were analyzed with the aid of the iterative spectral fitting program LAOCOON III.[27] For 1- and 2-chloronaphthalene the partial assignments of Ernst[12] were used. The remaining ^1H spectra were partly assigned by standard techniques.

Carbon Spectra. Carbon-13 spectra were first obtained with proton noise decoupling to measure the individual ^{13}C chemical shifts. Definitive assignments of most of the hydrogen-bearing carbon resonances were made by selective decoupling. For naphthalenes whose ^1H spectra were only partially assigned, for example, 1- and 2-chloronaphthalene, the ^{13}C spectra of their symmetrically disubstituted counterparts, e.g. 2,7-dichloronaphthalene, and the data of Ernst[12] were used as guides. Additional information was obtained from the proton-coupled ^{13}C spectra. These spectra allowed recognition of the number of vicinal protons and their relationship to a given ^{13}C nucleus.

Quaternary carbon resonances were additionally challenging. Those carbons directly bonded to chlorine or hydroxyl groups have characteristic chemical shifts. Resonances of the hydroxyl-substituted carbons and carbons ortho to them were broadened and shifted slightly in the presence of tris(acetylacetonato)chromium(III).

Table I. Proton NMR Parameters for Some Chlorinated Naphthalenes and Napthols

Naphthalene substitution	Chemical shifts, δ								
	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	OH
2-Cl[a]	7.8–7.9		7.42	7.8–7.9	7.8–7.9	←7.48–7.55→		7.8–7.9	
1,2-Cl_2			←7.38–7.81→					8.22	
1,4-Cl_2		7.428	7.428		8.207	7.571	7.571	8.207	
1,5-Cl_2		7.590	7.439	8.181		7.590	7.439	8.181	
1,8-Cl_2		7.601	7.333	7.727	7.727	7.333	7.601		
2,6-Cl_2	7.757		7.411	7.642	7.757		7.411	7.642	
2,7-Cl_2	7.630		7.346	7.655	7.655	7.346		7.630	
1,2,3,4-Cl_4					8.286	7.649	7.649	8.286	
1-Cl,2-OH			7.21	←7.30–7.74→				8.00	5.89
1-Cl,4-OH		7.364	6.708		8.15–8.25	←7.41–7.74→		8.15–8.25	4.98
1-Cl,8-OH		7.380	7.277	7.718	7.39	7.39	7.034		8.10
2-Cl,1-OH			←7.45–7.56→		8.23	7.75	7.75	8.23	6.00
1,6-Cl_2,2-OH[b]			7.44	7.84	7.98		7.62	8.16	
2,4-Cl_2,1-OH			7.497		8.17–8.22	←7.54–7.65→		8.17–8.22	5.95

Naphthalene substitution	Coupling constants, Hz									
	$J_{1,3}$	$J_{1,4}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{5,6}$	$J_{5,7}$	$J_{5,8}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$
1,4-Cl_2						8.6	1.3	0.6	6.9	1.3	8.6
1,5-Cl_2			7.6	0.6	8.4				7.6	0.6	8.4
1,8-Cl_2			7.6	1.2	8.1	8.1	1.2		7.6		
2,6-Cl_2	2.0	0.1			8.8		2.0	0.1			8.8
2,7-Cl_2	1.9	0.0			8.5	8.5		0.0		1.9	
1,2,3,4-Cl_4						8.6	1.1	0.1	6.5	1.1	8.6
1-Cl,4-OH			8.1								
1-Cl,8-OH			7.9	1.2	8.3						
1,6-Cl_2,2-OH[b]					9.5		2.5				9.0

[a] From ref 12. [b] From ref 2.

Table II. ^{13}C Chemical Shifts (δ) of Chlorinated Naphthalenes and Naphthols[a]

Substitution	Registry no.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1-Cl	90-13-1	131.92	126.09	125.67	(127.12)	128.16	(126.96)	(126.65)	124.41	130.81	134.58
2-Cl	91-58-7	126.57	131.55	126.72	129.47	127.77	126.09	127.04	126.88	134.03	131.63
1,2-Cl_2	2050-69-3	129.38	(131.72)	126.63	128.14	(127.86)	(127.19)	(127.71)	124.57	(130.33)	132.60
1,4-Cl_2	1825-31-6	130.92	125.87	125.87	130.92	124.96	127.74	127.74	124.96	131.63	131.63
1,5-Cl_2	1825-30-5	131.91	127.02	126.66	123.70	131.91	127.02	126.66	123.70	132.27	132.27
1,8-Cl_2	2050-74-0	130.43	130.78	126.05	128.48	128.48	126.05	130.78	130.43	127.46	137.18
2,3-Cl_2	2050-75-1	127.02	(130.11)	(130.11)	127.02	126.85	128.78	128.78	126.85	(132.28)	(132.28)
2,6-Cl_2	2065-70-5	126.54	(131.97)	127.89	128.58	126.54	(131.97)	127.89	128.58	(132.21)	(132.21)
2,7-Cl_2	2198-77-8	125.67	132.81	127.01	129.24	129.24	127.01	132.81	125.67	134.50	129.77
1,2,3-Cl_3	50402-52-3	129.35	130.38	131.41	127.27	127.27	(127.91)	(127.67)	124.81	130.05	132.04
1,2,3,4-Cl_4	20020-02-4	130.12	130.33	130.33	130.12	125.39	128.73	128.73	125.39	129.96	129.96
1,2,3,4,5,6,7,8-Cl_8	2234-13-1	128.74	135.01	135.01	128.74	128.74	135.01	135.01	128.74	129.42	129.42
1-Cl,2-OH	633-99-8	113.37	149.40	117.24	128.19	128.40	124.10	127.54	122.75	131.11	129.52
1-Cl,4-OH	604-44-4	123.57	125.74	108.65	150.57	122.10	126.02	127.58	124.49	131.63	125.50
1-Cl,8-OH	65253-31-8	127.18	127.45	125.40	128.61	120.90	127.63	113.14	152.81	119.84	137.03
2-Cl,1-OH	606-40-6	147.12	113.58	(126.07)	122.16	127.60	(126.66)	125.85	120.93	124.55	133.33
1,6-Cl_2,2-OH	65253-32-9	113.52	149.67	118.51	124.59	127.54	130.12	128.39	126.90	129.54	130.06
2,4-Cl_2,1-OH	2050-76-2	146.37	112.66	125.44	(124.93)	124.44	127.66	126.85	122.51	(123.41)	130.25

[a] Similar values in parentheses may be interchanged.

The relative intensities of the quaternary carbon resonances are influenced by the degree of carbon–hydrogen dipole–dipole relaxation. The efficiency of this relaxation depends on the C–H internuclear distance, r, as $1/r^6$. Carbons with no nearby protons tend to have longer spin lattice relaxation times and smaller nuclear Overhauser enhancements (NOEs) under conditions of proton noise decoupling than do carbons with nearby protons. Hence, the carbons without nearby protons tend to have less intense resonances.

With selective proton decoupling, selective intensity increases of the resonances of nearby quaternary carbons can be observed. These intensity increases may be due entirely to NOEs. They may also be due to removal of small long-range couplings to the proton being irradiated. For example, in 1,5-dichloronaphthalene a selective intensity increase in the C-9,10 resonance was observed when the protons nearest C-9 and C-10, H-4 and H-8, were irradiated. The C-9,10 resonance increased in intensity by 50% relative to the intensity of the C-1,5 resonance.

After application of the assignment techniques above, those few carbon resonances remaining without explicit assignments were assigned to give mutual consistency in the ^{13}C chemical shifts for the entire series of chlorinated naphthalenes and naphthols.

Results and Discussion

Chlorinated Naphthalenes. NMR Parameters. Proton chemical shifts and coupling constants for the compounds studied are given in Table I. Carbon-13 chemical shifts are given in Table II.

Substituent Effects. To derive parameters describing the effects of a 1-chlorine or a 2-chlorine substituent on the ^{13}C chemical shifts of naphthalene, ^{13}C chemical shifts for six chlorinated naphthalenes were used. These naphthalenes all lack significant chlorine–chlorine steric interactions; that is,

Table III. Chlorine and Hydroxyl Substituent Effects (ppm) on the ^{13}C Chemical Shifts of Naphthalene

Substituent	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1-Cl	3.99	0.30	0.04	−0.85	0.23	1.12	1.03	−3.08	−2.58	1.19
2-Cl	−1.23	5.92	0.95	1.77	0.07	0.46	1.34	−0.89	0.66	−1.75
1-OH[a]	23.36	−16.99	0.06	−7.08	−0.16	0.67	−0.47	−6.38	−9.12	1.26
2-OH[a]	−18.26	27.57	−8.00	2.04	−0.05	−2.08	0.80	−1.44	1.15	−4.45

[a] From ref 13a.

Table IV. Differences between Predicted and Observed ^{13}C Chemical Shifts[a] in Some Substituted Naphthalenes

Substitution	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
1,2-Cl_2	−1.08	−0.1	0.04	−0.48	−0.14	0.01	−0.26	0.84	−1.05	−0.14
1,8-Cl_2	1.82	3.85	−0.71	1.40	1.40	−0.71	3.85	1.82	−0.68	1.50
2,3-Cl_2	−1.22	−2.36	−2.36	−1.22	0.03	1.38	1.38	0.03	1.07	1.07
1,2,3-Cl_3	−2.88	−2.39	−1.10	−0.12	0.16	−0.61	−0.76	1.01	0.42	−1.36
1,2,3,4-Cl_4	−1.26	−2.48	−2.48	−1.26	1.36	−0.82	−0.82	1.36	−0.86	−0.86
1,2,3,4,5,6,7,8-Cl_8	2.29	0.73	0.73	2.29	2.29	0.73	0.73	2.29	1.94	1.94
1,2-Me_2[b]	−2.1	−3.2	1.2	0.1	0.2	−0.2	−0.0	−0.1	0.0	0.5
1,8-Me_2[b]	5.1	3.0	−0.2	1.0	1.0	−0.2	3.0	5.1	1.2	1.7
2,3-Me_2[b]	1.2	−2.3	−2.3	1.2	−0.5	−0.1	−0.1	−0.5	0.6	0.6
1-Cl,2-OH	−0.06	−4.07	−0.40	−0.70	0.52	−0.54	0.11	−0.43	−0.76	−0.52
1-Cl,4-OH	−1.04	−0.22	0.00	0.36	0.55	−0.23	0.28	0.08	−0.35	0.13
2-Cl,1-OH	−2.71	−0.95	−0.54	−1.46	−0.01	−0.07	−0.62	1.73	−0.29	0.52
2,4-Cl_2,1-OH	−2.61	−1.91	−1.47	−1.45	−0.09	−0.10	−0.74	1.85	−2.62	0.02
1-Cl,8-OH	1.87	1.83	−0.94	1.65	−0.18	0.61	3.48	4.83	−1.76	1.28

[a] Observed − predicted values are given in ppm. [b] From ref 10.

they lack ortho or peri disubstitution. Additivity of chlorine substituent effects was assumed. A set of parameters which describes the effects of a 1- or 2-chlorine substituent was derived. The resulting "best fit" parameters give the smallest average deviation between the observed and the predicted ^{13}C chemical shifts assuming additivity. These parameters are given in Table III. They are in good agreement with those reported by Ernst[12] for a smaller set of compounds in a different solvent.

As an example of the use of these parameters, to predict the ^{13}C chemical shift of C-8 in 1,4-dichloronaphthalene the chemical shift of this carbon in naphthalene itself is used, δ 127.74. Add to this −3.08 ppm for the effect of the 1-chlorine at the 8 position. Then add 0.23 ppm for the effect of the 4-chlorine to get a predicted chemical shift for C-8 of δ 124.89. The observed value is δ 124.96, only 0.07 ppm greater than the predicted value.

For the six nonhindered chlorinated naphthalenes, the average deviation for 41 independent positions was only 0.09 ppm.

It is interesting that the effects of a chlorine substituent are substantial, even in the unsubstituted ring. This phenomenon has been observed previously in other systems, for example, in chlorinated biphenyls[7] where a significant substituent effect is transmitted through as many as eight covalent bonds.

In chlorinated naphthalenes where there is steric crowding of the chlorine substituents there are deviations from the ^{13}C chemical shifts predicted by additivity. The deviations observed for several chlorinated naphthalenes are given in Table IV.

Where the chlorines are ortho, as in 1,2- and 2,3-dichloro-, 1,2,3-trichloro-, and 1,2,3,4-tetrachloronaphthalene, steric crowding leads to increased shielding of the carbons in the substituted ring. Increased shielding of closely lying carbons separated by three bonds and the other carbons associated with the crowded part of the molecule has been observed in many systems.[10,28,29] Steric crowding of other substituents separated by three bonds appears to have a similar effect on the associated carbons.

Chlorine has been shown to shield a γ-gauche carbon to approximately the same extent as a methyl group in some monochlorocyclohexanes.[30] Likewise, the increased shielding of the β-carbon, resulting from the γ-gauche interaction, is approximately the same for a chlorine (−3.73 ppm) as for a methyl (−3.62 ppm) substituent on cyclohexane. Comparison of the deviations from additivity for C-2 and C-3 in 2,3-dimethyl- and 2,3-dichloronaphthalene, −2.3 and −2.36 ppm, respectively, suggests that a similar situation exists in aromatic systems. The results for dichloro steric interactions in aromatic systems suggest the need to reinterpret these steric effects without employing a model dependent on nonbonded hydrogen–hydrogen interactions. Recently, Beierbeck and Saunders[31] have suggested the need for such reinterpretation in alicyclic compounds.

Carbons in the unsubstituted ring of the ortho-chlorine-substituted naphthalenes are deshielded at the α positions (C-5 and C-8) but are shielded at the β positions (C-6 and C-7) relative to the predicted values. Octachloronaphthalene is the only exception; all of its carbons are less shielded than predicted.

The magnitudes of the deviations from additivity for the carbons in the crowded part of the molecule appear to be about the same for ortho chlorine and methyl substituents. However, in the unsubstituted ring the effects of ortho methyl interactions are not as large as those of chlorine interactions. Although methyl and chlorine substituents are often considered to have the same steric requirements, the greater ease of distortion of methyl groups may result in less distortion of the overall ring geometry by methyl than by chlorine interactions.

As with ortho disubstitution, the effects of peri disubstitution are large at all positions. Unlike the ortho case, however, the substituted carbons in 1,8-dichloronaphthalene are *de*shielded, as they are in 1,8-dimethylnapthalene. The effect at C-9 of the peri interactions is opposite for the chloro and the methyl compounds. This may reflect greater distortion of the substituted part of the molecule with greater opening of the Cl–C-1–C-9 angle in the chloro compound.[12]

Chlorinated Naphthols. When individual chlorinated naphthalene isomers are administered to pigs or to rats they

Table V. Observed and Predicted ^{13}C Chemical Shifts[a] for a Chloronaphthol

	δ_C observed	δ_C predicted for 1-Cl,2-OH	Observed − predicted	δ_C predicted for 2-Cl,1-OH	Observed − predicted
Quaternary carbons	147.12	*153.47*	−6.35	*149.83*	−2.71
	133.33	131.87	1.46	132.84	0.49
	124.55	*130.04*	−5.49	*124.84*	−0.29
	113.58	113.43	0.15	114.53	−0.95
CH carbons	127.60	128.89	−1.29	127.61	−0.01
	126.66	127.88	−1.22	126.73	−0.07
	126.07	127.43	−1.36	126.61	−0.54
	125.85	124.64	1.21	126.47	−0.62
	122.16	123.18	−1.02	122.39	−0.23
	120.93	*117.64*	3.29	*120.43*	−0.50

[a] Observed − predicted values are given in ppm.

are converted to chlorinated naphthols. Generally, the major metabolites are hydroxylated at the α positions (1,4,5, or 8). There are a few exceptions; for example, 2-chloronaphthalene is metabolized to 2-chloro-3-hydroxynaphthalene.[1] Since the α position is usually preferred, however, most of the chlorinated naphthols which we examined are α-naphthols.

Substituent Effects. To predict the effects of hydroxyl substituents on the ^{13}C shieldings of chlorinated naphthalenes we used the changes in the ^{13}C chemical shifts of naphthalene produced by a 1- or 2-hydroxyl substituent. Since our measured values of these changes agreed with those of Ernst,[13a] we have used his values. These values are given in Table III.

The effects of a hydroxyl substituent are very large, particularly the deshielding of the hydroxyl-substituted carbon and the increased shielding of the carbons ortho and para to it. Because these effects are so large they nearly dominate the ^{13}C shieldings of the chlorinated naphthols.

To predict the ^{13}C chemical shifts of the chlorinated naphthols the additivity of chlorine and hydroxyl substituent effects was assumed. The deviations of the observed from the predicted chemical shifts are given in Table IV.

In 1-chloro-4-hydroxynaphthalene no steric interaction occurs between the substituents. The observed ^{13}C chemical shifts for this compound are reasonably close to the predicted values, except at C-1 and C-5. At C-1 the deviation from additivity of −1.04 ppm may result from hydrogen bonding of the para hydroxyl group, which would markedly change the electron density at C-1. The deviation of 0.55 ppm at C-5 results from a peri interaction with the 4-OH group.

For all the chlorinated naphthols an OH substituent results in increased shielding of the carbon para to the OH. The increase over that predicted by additivity has a mean value of −1.12 ppm with a smaller increase for a β than for an α hydroxyl.

The second chlorinated naphthol, 1-chloro-2-hydroxynaphthalene, has a marked increase in shielding, −4.07 ppm, over the additivity prediction at the OH-substituted carbon. There are smaller shielding increases at positions meta, −0.76 and −0.70 ppm, and para, −0.52 ppm, to the hydroxyl. It is likely that intramolecular hydrogen bonding to the ortho chlorine accounts for most of the deviations from additivity in this compound.

In 1-hydroxy-2-chloro- and 1-hydroxy-2,4-dichloronaphthalene there are large deviations from additivity at all carbons in the substituted ring and at C-8. All deviations except that for C-8 reflect increased shielding. Since the unsubstituted ring shows only small deviations from additivity, except for C-8, significant geometric distortion of the molecule is probably not responsible for the differences from the predicted chemical shifts. Either a 2-chlorine or a 1-hydroxyl substituent by itself leads to increased shielding of C-8. With intramolecular hydrogen bonding and steric interactions between the two substituents, the shielding of C-8 is decreased by almost 2 ppm.

The peri-substituted chloronaphthol in this study, 1-chloro-8-hydroxynaphthalene, exhibits deviations from the additivity predictions which are quite different from those of the other chloronaphthols. As in 1,8-dichloro- and 1,8-dimethylnaphthalene, the peri substitution leads to deshielding of C-1 and C-8. The chlorine-substituted carbon is deshielded to the same extent in both 1,8-dichloronapthalene and 1-chloro-8-hydroxynaphthalene, 1.82 and 1.87 ppm, respectively. The hydroxyl carbon in 1-chloro-8-hydroxynaphthalene is deshielded by 4.83 ppm, in marked contrast to the increased shielding, −2.71 and −2.61 ppm, of this carbon in 2-chloro-1-hydroxy- and 2,4-dichloro-1-hydroxynaphthalene. Perhaps the greater separation of the substituents in the peri compounds, relative to the ortho compounds, leads to reduced intramolecular hydrogen bonding. The reduced shielding seems more characteristic of a peri steric interaction than intramolecular hydrogen bond formation.

Use of Additivity Predictions. To assign all the resonances in a ^{13}C spectrum unequivocally often requires many lengthy separate experiments, such as selective deuteration and selective proton decoupling. Unfortunately, the amount of material available, particularly in metabolism studies, is usually small, 1 mg or less. This increases the required experimental time beyond that available to most researchers. To surmount this problem can we rely on additivity predictions to interpret the ^{13}C spectra of similar isomers which are indistinguishable by other nondestructive means?

As a test of the utility of additivity predictions in distinguishing closely similar isomers, a comparison was made between these predictions for 1-chloro-2-hydroxy- and 2-chloro-1-hydroxynaphthalene, whose gas chromatographic data and infrared, ^1H NMR, and mass spectral characteristics are insufficient to characterize the two isomers uniquely. The ^{13}C chemical shifts were divided into two groups, those for quaternary and those for protonated carbons, which are readily ascertained from the ^1H noise-decoupled ^{13}C spectrum. The chemical shifts predicted using the hydroxyl and chlorine substituent parameters in Table III were then listed in order of decreasing frequency for each group. These were compared with a similar list obtained from the experimental ^{13}C spectrum (for 2-chloro-1-hydroxynaphthalene). The results of comparisons of these lists are given in Table V. The mean deviation between the observed and the predicted chemical shifts is 2.28 ppm for a 1-Cl,2-OH structure, but only 0.64 ppm for a 2-Cl,1-OH structure. If a reasonable agreement of ±1 ppm is required, all shifts except one predicted for a 2-Cl,1-OH structure agree with those observed, whereas only two shifts predicted for the 1-Cl,2-OH structure agree with those observed. Three chemical shifts are definitive in es-

Table VI. Observed and Predicted ^{13}C Chemical Shifts for a Dichloronaphthol Metabolite of 2,6-Dichloronaphthalene

	δ_C observed	δ_C predicted for 2,6-Cl_2,1-OH	δ_C predicted for 1,6-Cl_2,2-OH	Deviations from mean predicted values, ppm: 2,6-Cl_2,1-OH	Deviations from mean predicted values, ppm: 1,6-Cl_2,2-OH
Quaternary carbons	149.67	147.19–149.90	148.96–154.12	0.42	−2.67
	130.12	*131.58–133.55*	*130.12–131.77*	−2.90	−0.58
	130.06	*132.58–132.68*	*130.02–130.80*	−2.58	−0.40
	129.54	*123.09–125.21*	*127.77–130.79*	5.90	−0.21
	113.52	114.04–115.02	113.44–113.73	−1.24	−0.04
CH carbons	128.39	127.41–128.12	128.38–128.49	0.53	−0.03
	127.54	126.80–127.52	127.30–128.27	0.25	−0.32
	126.90	126.37–126.38	126.65–127.17	0.52	0.00
	124.59	*122.20–122.70*	*124.52–124.95*	2.25	−0.15
	118.51	*121.27–121.50*	*118.56–119.01*	−2.93	−0.34

tablishing the structure: those for the first and third quaternary carbons and that for the last (lowest frequency) protonated carbon.

Thus, without specific assignments of ^{13}C resonances, and despite the complications of steric and hydrogen bonding effects, the use of additive substituent parameters is effective in isomer identification.

The same technique was used to identify a metabolite of 2,6-dichloronaphthalene. The mass spectrum and the ^1H NMR spectrum showed the metabolite to be a dichloronaphthol but could not unambiguously indicate whether it was 2,6-dichloro-1-hydroxynaphthalene or 1,6-dichloro-2-hydroxynaphthalene.[2] A range for the ^{13}C chemical shift of each carbon in each of the two isomers was predicted. For the 1-hydroxyl isomer the predictions were based on the following: (a) naphthalene chemical shifts plus parameters from Table III; (b) 2,6-dichloronaphthalene chemical shifts plus 1-OH parameters from Table III; (c) 2-chloro-1-hydroxynaphthalene chemical shifts plus 6-Cl parameters from Table III; and (d) 2-chloronaphthalene chemical shifts plus 1-OH and 6-Cl parameters from Table III. For the 2-hydroxyl isomer predictions were made similarly using the chemical shifts of (e) naphthalene, (f) 1-chloro-2-hydroxynaphthalene, and (g) 1-chloronaphthalene, plus the appropriate substituent parameters from Table III.

The observed ^{13}C chemical shifts for the metabolite are compared with the additivity predictions in Table VI. The average deviation from the mean predicted chemical shift for each carbon is only 0.47 ppm for the 2-naphthol but 1.95 ppm for the 1-naphthol. All observed values lie in the predicted range for the 2-naphthol, whereas only two observed values lie therein for the 1-naphthol. If reasonable agreement between experimental and predicted chemical shifts is defined as the predicted range ±1 ppm, all shifts for the 2-naphthol are still in agreement with those predicted, but only five are so for the 1-naphthol. Five chemical shifts are definitive: the second, third, and fourth for the quaternary carbons and the last two for the protonated carbons. Clearly, the metabolite is 1,6-dichloro-2-hydroxynaphthalene.

Naturally, one would expect that the more closely related the chosen model compound is to the compound of interest the better the agreement would be between the predicted and observed ^{13}C chemical shifts. This is indeed the case. The best agreement, with an average deviation of 0.50 ppm, is for (f), which includes the ortho chlorine hydroxyl interactions in the chemical shifts of the parent compound. But (e) works nearly as well, with an average deviation of 0.75 ppm; yet only the shifts of naphthalene itself, plus the appropriate substituent parameters, were used.

We have recently[32] used this method to identify a metabolite of 4,4′-dichlorobiphenyl as 3,4′-dichloro-4-hydroxybiphenyl rather than the expected isomer 4,4′-dichloro-3-hydroxybiphenyl. This identification was confirmed by comparison with a synthetic standard.

Thus, additivity works well and, in fact, far better than expected in systems where steric and hydrogen bonding interactions cause deviations from predicted ^{13}C chemical shifts. Despite these deviations, unambiguous characterization of similar isomers can be accomplished.

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Registry No.—1-Amino-8-chloronaphthalene, 59107-51-6; 2,6-dichloronaphthalen-1-ol, 62857-75-4.

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Synthetic Approaches to α-Methylene γ-Lactones via Cycloadditions of Ketenes[1]

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Methylchloroketene was cycloadded to several cycloalkenes and cycloalkadienes to produce fused substituted cyclobutanones which can be transformed by Baeyer–Villiger oxidation into lactones. Exocyclic elimination of HCl from the latter produces ring-fused α-methylene γ-lactones **4**. This route, adaptable to a larger scale, serves as a three-step fair-yield synthesis of **4** from cyclic olefins.

The α-methylene γ-butyrolactone unit is found in a number of biologically active, naturally occurring compounds.[2] Many of these natural products are antitumor agents,[3] and this has stimulated much of the recent research devoted to the development of new synthetic routes to α-methylene lactones. Consequently, there have been developed a variety of methods for the synthesis of this moiety.[4]

Most of these procedures involve the introduction of the α-methylene group into a preformed lactone. For example, Grieco and co-workers[5] have devised a route involving bromination, formation of the phosphonium salt and then ylide, and finally a Wittig reaction. Other methods using γ-lactones were recently described.[6]

In previous studies[7] we showed that cycloalkenes react readily and regioselectively with dichloroketene to produce fused cyclobutanones which can be oxidized to lactones.

Results

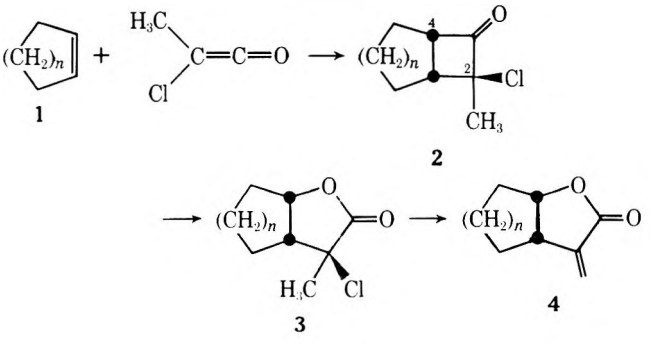
We report here a method for the facile transformation of cyclic olefins into cis-fused α-methylene γ-butyrolactones in three steps (Scheme I).[8] The overall results are summarized in Table I.

The cycloaddition step proceeded well with a variety of cyclic olefins by in situ generation[9] of a methylchloroketene from α-chloropropionyl chloride and triethylamine. The ketene cycloaddition appears to be highly stereoselective since only one chloro ketone isomer is isolated in each case. This is indicated by a methyl singlet in the NMR spectra of the adducts. Baeyer–Villiger oxidation of the cyclobutanones **2** led to lactones **3**. Among the different peroxidizing agents tried (*m*-chloroperbenzoic acid, acidic and basic hydrogen peroxide), the best results were obtained with hydrogen peroxide in acetic acid, producing lactones **3** in 65–90% yields. The α-methylene lactones are obtained in good yields after base-catalyzed dehydrochlorination (Table I). No extensive search for optimum yields has been carried out, but the best conditions of those examined for this step are the use of 1,4-diazabicyclo[2.2.2]octane (Dabco) and sodium iodide at 80 °C in dimethyl sulfoxide (Me_2SO). As a specific example, cyclooctene (**1d**, Table I) gives an 83% isolated yield of the ketene adduct **2d**, which is oxidized to the lactone **3d** in 87% yield. Elimination of the elements of HCl provides a 78% yield (40% after distillation) of the α-methylene lactone **4d**.

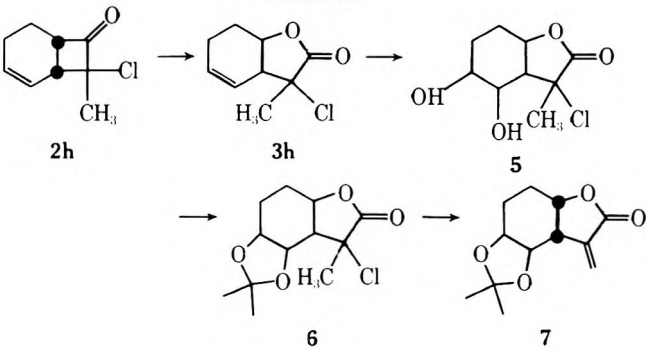
This method is not limited to small scale reactions (0.01 mol or less). For example, 0.08 mol of cyclooctene (**1d**) has been converted to the α-methylene lactone **4d** with percent yields in each step comparing favorably with small scale values (see Table I). It should be noted that distillation of α-methylene lactones often results in polymerization; about one-third of the crude product (pure by NMR) remained as a thick residue after distillation.

As a synthetic route to polyfunctional α-methylene lactones related to sesquiterpenes of plant origin, we examined the

Scheme I



Scheme II



reactions of the unsaturated chloro ketone **2h**. Baeyer–Villiger oxidation to **3h** was followed by OsO_4 oxidation of the residual double bond to the diol **5**. This was protected as the ketal **6** and converted to the α-methylene lactone **7** in good yields (see Scheme II).

Discussion

The success of Scheme I depends largely on two factors: the preferential migration of C-4 over C-2 in the Baeyer–Villiger oxidation (**2** → **3**) and the preferential exocyclic vs. endocyclic elimination of HCl from **3**. The latter event is based on the stereochemical outcome of the cycloaddition step.

The first step in the scheme, the ketene cycloaddition, is presumably concerted and is known to be highly stereoselective.[9] Although two adducts have often been isolated, the major product has been shown to be the *exo*-chloro isomer.[9,10] This is precisely the stereochemistry necessary for placing the chlorine substituent cis to the ring junction proton, rendering endocyclic elimination of HCl energetically somewhat unfavorable.[11] The results of the base-catalyzed HCl elimination (exocyclic) suggest that the original adducts **2** indeed possess an *exo*-chlorine.

The high degree of regioselectivity observed,[12] i.e., exclusive isolation of **2h** and **8**, and the lack of rearrangement in the

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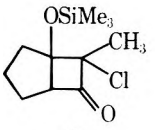
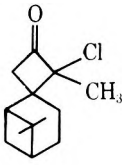


8



2f

β-pinene adduct **2f** also point toward the concertedness of these cycloadditions.

In Baeyer–Villiger oxidations, the more substituted carbon (C-2 in ketone **2**) is usually found to migrate.[13a] However, we expected the presence of the electron-withdrawing chlorine substituent[13b] at C-2 to influence the migratory aptitudes and thus favor migration of the more electron-rich C-4. Indeed this led to the isolation of lactones **3**.

Finally, the synthesis of **7** indicates the usefulness of the overall reaction sequence as a route from readily available cycloalkenes to functionalized, fused α-methylene lactones.

Experimental Section[14]

Methylchloroketene Adducts 2 from Olefins.[15] General Procedure. Cyclopentene Adduct 2a. Cyclopentene (11.0 mL, 0.125 mol) and triethylamine (8.4 mL, 0.06 mol) in 60 mL of hexane were refluxed under nitrogen. α-Chloropropionyl chloride (4.8 mL, 0.05 mol) in 15 mL of hexane was added dropwise over 60 min. This was refluxed another 3.5 h and stirred at room temperature for 19 h. The reaction mixture was filtered, and the filtrate was washed with cold $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and concentrated to give 7.6 g of an oil which on distillation provided 6.1 g (77%) of adduct **2a**: bp 43–46 °C (0.7 mm) [lit.[9d] 48–58 °C (1.0 mm)]; NMR (CCl_4) δ 1.47 (s, 3, CH_3), 3.05 (m, 1, CH), 4.05 (m, 1, CH).

Cyclohexene Adduct 2b. Similarly, from 0.05 mL of acid chloride was obtained 1.9 g (22%) of colorless liquid: bp 75–80 °C (1.8 mm) [lit.[9c] 55–67 °C (1.0 mm)]; NMR (CCl_4) δ 1.53 (s, 3, CH_3), 2.68 (m, 1, CH), 4.0 (m, 1, CH); IR (neat) 1785 (C=O) cm^{-1}.

Cycloheptene Adduct 2c. From 0.01 mol of acid chloride was obtained 1.23 g (66%) of colorless liquid: bp 65–70 °C (0.4 mm); NMR (CCl_4) δ 1.5 (s, 3, CH_3), 2.8 (m, 1, CH), 3.95 (m, 1, CH).

Cyclooctene Adduct 2d. From 0.01 mol of cyclooctene was obtained 1.65 g (83%) of colorless liquid: bp 95–100 °C (0.1 mm) [lit.[9c] 122–129 °C (0.5 mm)]; NMR (CCl_4) δ 1.47 (s, 3, CH_3), 2.64 (m, 1, CH), 3.57 (m, 1, CH). In an eightfold scale the yield of **2d** was 11.3 g (71%).

Methylenecyclohexane Adduct 2e. From 0.01 mol of acid chloride was obtained 0.93 g (50%) of colorless liquid: bp 69–74 °C (0.5 mm) [lit.[12c] 67–70 °C (0.6 mm)]; NMR (CCl_4) δ 1.6 (s, 3, CH_3), 2.85 (s, 2, CH_2).

β-Pinene Adduct 2f. From 0.01 mol of acid chloride was obtained 1.65 g (73%) of colorless liquid: bp 95–101 °C (0.4 mm) [lit.[12f] 95–98 °C (0.25 mm)]; NMR (CCl_4) δ 1.6 (s, 3, CH_3), 2.95 (s, 2, CH_2).

1,5-Cyclooctadiene Adduct 2i. From 0.01 mol of olefin was obtained 1.0 g (50%) of colorless liquid: bp 94–97 °C (0.4 mm); NMR (CCl_4) δ 1.55 (s, 3, CH_3), 2.8 (m, 1, CH), 3.75 (m, 1, CH); IR (neat) 1785 (C=O), 1650 (C=C) cm^{-1}.

Cyclopentadiene Adduct 2g. From 0.03 mol of acid chloride at room temperature was obtained 4.0 g (85%) of colorless liquid: bp 36–42 °C (0.04 mm) [lit.[12f] 70–72 °C (5.0 mm)]; NMR (CCl_4) δ 1.45 (s, 3, CH_3), 2.65 (m, 2, CH_2), 3.7 (m, 1, CH), 4.3 (m, 1, CH), 5.9 (m, 2, CH=CH).

1,3-Cyclohexadiene Adduct 2h. From 0.01 mol of acid chloride at room temperature was obtained 1.1 g (65%) of colorless liquid: bp 65–70 °C (0.4 mm); IR 1800 (C=O) cm^{-1}; NMR (CCl_4) δ 1.5 (s, 3, CH_3), 3.15 (m, 1, CH), 4.2 (m, 1, CH), 5.95 (m, 2, CH=CH). Its identity was proven by comparison with published spectra.[9c]

Trimethylsiloxycyclopentene Adduct 2j. From 0.01 mol of the silyl enol ether at room temperature was obtained 1.9 g (71%) of colorless liquid: bp 70–80 °C (0.06 mm); NMR (CCl_4) δ 0.2 (s, 9, $SiMe_3$), 1.47 (s, 3, CH_3), 3.4 (m, 1, CH); IR (neat) 1780 (C=O) cm^{-1}.

Trimethylsiloxycyclohexene Adduct 2k. From 0.01 mol of the silyl enol ether at room temperature was obtained 0.51 g (20%) of colorless liquid: bp 125–135 °C (0.4 mm); NMR (CCl_4) δ 0.2 (s, 9, $SiMe_3$), 1.7 (s, 3, CH_3), 3.35 (m, 1, CH); IR (neat) 1788 (C=O) cm^{-1}.

Lactones 3 from Cyclobutanones 2.[6] Cyclopentane Lactone 3a. The cyclobutanone from cyclopentene (0.79 g, 5.0 mmol) was dissolved in 5 mL of 90% HOAc and cooled to 0 °C. A solution of 2.5 g of 30% H_2O_2 in 3 mL of 90% HOAc was added. This was maintained at 0 °C for 24 h, poured into H_2O, and extracted with Skellysolve F. The organic extract was washed with $NaHSO_3$ solution and H_2O, dried ($MgSO_4$), and concentrated to give 0.57 g (65%) of colorless liquid: NMR (CCl_4) δ 1.75 (s, 3, CH_3), 3.0 (m, 1, CH), 5.1 (m, 1, CH).

Table I. Conversion of Olefins into α-Methylene Lactones

Registry no.	Olefin 1	Cyclobutanone 2[a]	Lactone 3[b]	α-Methylene lactone 4
142-29-0	Cyclopentene (**a**)	77	65	73,[b] 40[a]
110-83-8	Cyclohexene (**b**)	22	90	
628-92-2	Cycloheptene (**c**)	66	77	50[a]
931-88-4	Cyclooctene (**d**)	83	87	78,[b] 40[a]
		71[c]	80[c]	63,[b,c] 44[a,c]
1192-37-6	Methylenecyclohexane (**e**)	50		
127-91-3	β-Pinene (**f**)	73		
542-92-7	Cyclopentadiene (**g**)	85	27	
592-57-4	1,3-Cyclohexadiene (**h**)	65	67	
111-78-4	1,5-Cyclooctadiene (**i**)	50		
19980-43-9	1-Cyclopentenyl trimethylsilyl ether (**j**)	71		
6651-36-1	1-Cyclohexenyl trimethylsilyl ether (**k**)	20		

[a] Yield in percent of distilled product. [b] Yield in percent of crude product. [c] Large scale.

Cyclohexane Lactone 3b. From 0.17 g (1.0 mmol) of ketene adduct was obtained 0.17 g (90%) of pale yellow liquid: NMR (CCl_4) δ 1.7 (s, 3, CH_3), 4.9 (m, 1, CH); IR (neat) 1780 (C=O) cm^{-1}.

Cycloheptane Lactone 3c. From 0.93 g (5.0 mmol) of ketene adduct was obtained 0.78 g (77%) of colorless liquid: NMR (CCl_4) δ 1.7 (s, 3, CH_3), 2.7 (m, 1, CH), 4.95 (m, 1, CH).

Cyclooctane Lactone 3d. From 0.80 g (4.0 mmol) of ketene adduct was obtained 0.76 g (87%) of pale yellow liquid: NMR (CCl_4) δ 1.7 (s, 3, CH_3), 2.7 (m, 1, CH), 4.8 (m, 1, CH).

Cyclopentadiene Lactone 3g. From 3.6 g (23 mmol) of ketene adduct was obtained 1.07 g (27%) of pale yellow liquid: NMR (CCl_4) δ 1.75 (s, 3, CH_3), 2.7 (m, 2, CH_2), 3.7 (m, 1, CH), 5.2 (m, 1, CH), 5.7 (m, 1, CH=C), 5.9 (m, 1, CH=C).

2-(*cis*-2-Hydroxy-5-cyclohexenyl)-2-chloropropanoic Acid Lactone (3h). From 8.5 g (50 mmol) of ketene adduct **2h** was obtained 5.46 g (59%) of white crystalline solid: mp 45–47 °C; IR 1795 (C=O) cm^{-1}; NMR (CCl_4) δ 1.5 (s, 3), 1.6–2.3 (m, 4), 2.95 (m, 1), 4.8 (m, 1), 5.25 (m, 1), 5.8 (m, 1); MS 187 (M^+).[18]

2-(*cis*-2,5,6-Trihydroxycyclohexyl)-2-chloropropanoic Acid 2-Lactone (5).[16] To 12.2 g (65.5 mmol) of lactone **3h** in 220 mL of THF and 150 mL of H_2O were added 3.84 g (36 mmol) $NaClO_3$ and 80 mg of OsO_4. This was stirred at room temperature for 80 h and then poured into 150 mL of saturated NaCl. The aqueous phase was extracted with ether (2 × 100 mL). The organic phase was dried and, after the solvent was removed, placed under vacuum (0.5 mm) for 2 h. The resultant oil was crystallized by adding a minimal amount of petroleum ether and allowing the mixture to stand overnight. The crystals were filtered and washed with cold petroleum ether, yielding 4.4 g (30.6%) of crystals: mp 138–140 °C; IR (Nujol) 3500, 3450–3220 (OH free and bonded), 1785 (C=O) cm^{-1}; NMR (acetone-d_6) δ 1.85 (s, 3), 1.9 (m, 4), 2.5 (dd, 1), 3.35 (m, 1), 3.95 [m, 3 (20)], 4.9 (m, 1); MS 221 (M^+).

Anal. Calcd for $C_9H_{13}O_4Cl$: C, 49.0; H, 5.90; Cl, 16.04. Found: C, 48.89; H, 5.93; Cl, 15.99.

2-(*cis*-2-Hydroxy-5,6-isopropylidenedioxycyclohexyl)-2-chloropropanoic Acid Lactone (6). A solution of 4.0 g (18.4 mmol) of glycol **5**, 2.85 g (27.2 mmol) of 2,2-dimethoxypropane, 75 mL of dry benzene, and a trace of *p*-toluenesulfonic acid was refluxed overnight. The cooled solution was neutralized with ~1 mL of Et_3N and washed three times with 30 mL of saturated $NaHCO_3$, and the resultant

washes were extracted with 30 mL of Et_2O. The organic phase was dried and the solvent stripped. Placing the resultant product under vacuum (0.5 mm) gave 4.29 g (90%) of a white crystalline solid: mp 99–100 °C; IR (Nujol) 1775 (C=O) cm^{-1}; NMR (CCl_4) δ 1.15 (s, 3), 1.35 (s, 3), 1.75 (s, 3), 1.8 (m, 4), 2.35 (m, 1), 3.7 (m, 1), 4.2 (m, 1), 4.8 (m, 1); MS 261 (M^+).

Anal. Calcd for $C_{12}H_{17}O_4Cl$: C, 55.3; H, 6.53; Cl, 13.59. Found: C, 55.15; H, 6.53; Cl, 13.51.

α-Methylene Lactones 4. General Procedure. (THF is added for homogeneity if necessary). **Cyclopentane α-Methylene Lactone 4a.** The α-chloro-α-methyl lactone from cyclopentene (0.08 g, 0.5 mmol) was mixed with Dabco (0.22 g, 2.0 mmol), NaI (0.30 g, 2.0 mmol), and 1 mL of Me_2SO at 80 °C for 24–70 h. The cooled reaction mixture was poured into Skellysolve F/dilute HCl and extracted. The organic extract was washed with H_2O, dried ($MgSO_4$), and concentrated to give 0.05 g (73%) of yellow liquid.

Similarly, from 0.44 g (2.5 mmol) of lactone was obtained 0.14 g (40%) of colorless liquid: bp 85–90 °C (0.24 mm); NMR (CCl_4) δ 4.9 (m, 1, CH), 5.55 (d, 1, CH=C), 6.1 (d, 1, CH=C); IR (neat) 1755 (C=O), 1660 (C=C) cm^{-1}.

Cycloheptane α-Methylene Lactone 4c. From the cycloheptane lactone (0.78 g, 3.8 mmol) was obtained 0.32 g (50%) of colorless liquid: bp 110–115 °C (0.07 mm); NMR (CCl_4) δ 4.7 (m, 1, CH), 5.5 (d, 1, CH=C), 6.15 (d, 1, CH=C); IR (neat) 1755 (C=O), 1665 (C=C) cm^{-1}. Its identity was proved by comparison with published spectra.[17]

Cyclooctane α-Methylene Lactone 4d. From 0.11 g (0.5 mmol) of lactone was obtained 0.07 g (78%) of yellow oil.

Similarly, from 0.65 g (3.0 mmol) of lactone was obtained 0.21 g (40%) of colorless liquid: bp 120–130 °C (0.2 mm); NMR (CCl_4) δ 4.65 (m, 1, CH), 5.5 (d, 1, CH=C), 6.15 (d, 1, CH=C); IR (neat) 1755 (C=O), 1660 (C=C) cm^{-1}.

Cyclooctane α-Methylene Lactone 4d. From 9.05 g (41.8 mmol) of lactone was obtained 4.73 g (63%) of orange liquid, which was distilled to give 3.32 g (44%) of colorless liquid, bp 108–112 °C (0.4 mm).

2-(*cis*-2-Hydroxy-5,6-isopropylidenedioxycyclohexyl)-2-propenoic Acid Lactone (7). A solution of 0.7 g (2.72 mmol) of acetal lactone **6**, 1.21 g (10.8 mmol) of diazabicyclo[2.2.2]octane, 1.64 g (10.8 mmol) of sodium iodide, and 30 mL of Me_2SO was warmed to 80 °C for 4 days. The cooled solution was then extracted with petroleum ether (4 × 50 mL) followed by extraction with 1:1 petroleum ether/ether (2 × 50 mL). The combined extracts were washed with cold 0.1 N HCl (2 × 50 mL), saturated $NaHCO_3$ (1 × 25 mL), and H_2O (1 × 25 mL). The organic layer was dried and the solvent stripped to yield 263 mg (51.8%) of white crystalline solid: mp 89–91 °C; IR (CCl_4) 1770 (C=O) cm^{-1}; NMR δ 1.3–1.85 [m, 10: 1.30 (s), 1.43 (s)], 3.45 (m, 1), 4.32 (m, 2), 4.76 (m, 1), 5.6 (d, 1), 6.2 (d, 1); MS 225 (M^+).

Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.28; H, 7.14. Found: C, 64.06; H, 7.17.

Acknowledgment. Support of this research by Grant CA 19203 from the National Cancer Institute of the National Institutes of Health is gratefully acknowledged.

Registry No.—**2a**, 25370-65-4; **2b**, 65337-65-7; **2c**, 65277-03-4; **2d**, 65277-04-5; **2e**, 42200-05-5; **2f**, 42077-49-6; **2g**, 13363-87-6; **2h**, 56084-87-8; **2i**, 65277-05-6; **2j**, 65277-06-7; **2k**, 65277-07-8; **3a**, 61769-60-6; **3b**, 65277-08-9; **3c**, 65277-09-0; **3d**, 65277-10-3; **3g**, 61769-65-1; **3h**, 65277-11-4; **4a**, 61747-55-5; **4c**, 3725-04-0; **4d**, 65277-12-5; **5**, 65277-13-6; **6**, 65277-14-7; **7**, 65277-15-8; α-chloropropionyl chloride, 13363-86-5; 2,2-dimethoxypropane, 77-76-9.

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(14) NMR spectra were obtained using a Varian EM-360 spectrometer with Me_4Si as an internal standard and were consistent with the proposed structures or with spectra previously reported (ref 9). IR spectra were run on either a Perkin-Elmer 337 or 451 spectrometer. Mass spectral data (run on a CH5 spectrometer) were obtained for most compounds and were consistent with the proposed structures.
(15) For valuable or nonvolatile olefins, an excess of α-chloropropionyl chloride (10–15%) is used. Otherwise, the olefin is in excess (10–100%).
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(18) The mass spectra of these compounds exhibit a M + 1 peak rather than the expected M^+ peak; however, the fragment ions are consistent with their structures.

Addition of Carbenes to 1,1-Dimethylallene. Formation and Rearrangement of Substituted Methylenecyclopropanes

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Addition of photolytically generated carboethyxoycarbene as well as the copper carbenoid species to 1,1-dimethylallene (1) gives cyclopropanation of both of the allenyl double bonds of 1. Also produced are small amounts of 1-carboethoxymethylene-2,2-dimethylcyclopropanes 4 and 5 as well as C–H insertion products 6 and 7 in the case of the photolytically generated carbene. The photosensitized triplet carbene addition gives similar products in a differing ratio. The intervention of perpendicular trimethylenemethane intermediates is discussed, and a rationale is offered to account for these products. Phenylcarboethoxycarbene, methylcarboethoxycarbene, and substituted phenylcarbenes have also been added to 1. Thermal rearrangements of the methylenecyclopropane products have been observed. The effect of substituents on rate has been determined and is quite small. The substituent effect has been interpreted in terms of an early transition state in the formation of the intermediate perpendicular trimethylenemethane or a concerted process with only partial radical character in the transition state.

The addition of carbenes to olefins forming cyclopropanes has been thoroughly investigated and is of great synthetic utility. Additions to allenes to form methylenecyclopropanes have also been observed. Previous examples include dihalocarbene additions,[2a-e] the copper-catalyzed addition of ethyl diazoacetate,[2d] and the addition of methylene.[2d,e] Additions of dimethylvinylidenecarbene,[2e,g] isopropylidenecarbene,[2f] biscarbomethoxycarbene,[4b] carbomethoxycarbene,[4b] and diphenylcarbene[12] to allene and substituted allenes have also been reported. Our interest in cyclopropanation reactions and trimethylenemethanes has led us to investigate the feasibility of further extending the scope of the reaction of carbenes with allenes to produce a variety of substituted methylenecyclopropanes. The rearrangement of these substrates is also of interest mechanistically. Reported here are the results of a study of the reaction of 1,1-dimethylallene (1) with carboethoxy-, methylcarboethoxy-, phenylcarboethoxy-, and arylcarbenes from a preparative and a mechanistic standpoint. Also presented are data on the thermal rearrangement of the resultant methylenecyclopropanes and the implications concerning reaction mechanism.

Results and Discussion

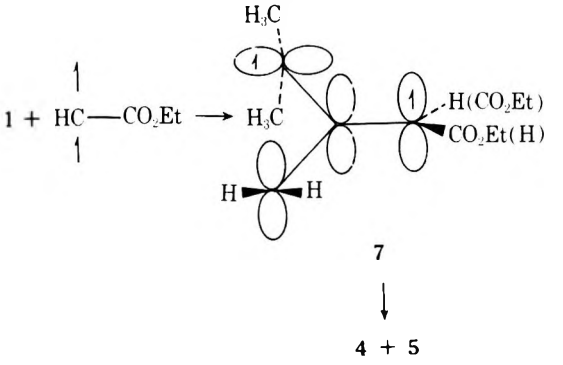
Carboethoxycarbene. The copper-catalyzed reaction of ethyl diazoacetate with 1,1-dimethylallene (1) has previously been carried out and reported to give methylenecyclopropanes 2 and 3 in a 96:4 ratio (Table I).[2d] Carboethoxycarbene (as the carbenoid) generated from the diazoester and copper is relatively nondiscriminating in additions to substituted ethylenes.[3] The reported high selectivity in preference for the more substituted bond in 1,1-dimethylallene (1) was therefore quite surprising. The copper-catalyzed carboethoxycarbene addition to 1 was therefore repeated and results are given in Table I. We have found that the copper carbenoid is indeed quite nonselective, giving similar amounts of methylenecyclopropanes 2 and 3 which arise via addition into both olefinic bonds of the allene. Also produced were small amounts of the two methylenecyclopropanes 4 and 5, which cannot be derived by direct addition of the carbene into the olefinic bonds of the allene. The origin of the discrepancy between the present results and those previously reported is unclear.

The structures of methylenecyclopropanes 4 and 5 and the stereochemistries of the carboethoxy groups were inferred from their NMR spectra. Molecular models indicate that the methylene protons of 5 are in the deshielding region of the carbonyl group. Therefore, the product with the methylene doublet (J = 2.5 Hz) at δ 1.33 is assigned structure 5 while the product with the doublet (J = 1.8 Hz) at δ 1.11 is assigned to 4. The magnitudes of the coupling constants are also of the same order as in the anti and syn rearrangement products of Feists ester.[11g] Additionally, the methyl groups of 4 are deshielded (δ 1.25) relative to the methyl groups of 5 (δ 1.22).

A study of the reaction of photolytically generated carboethoxycarbene with 1,1-dimethylallene (1) was next undertaken. Direct irradiation of ethyl diazoacetate in the allene as solvent gave the expected addition into both olefinic bonds of the allene in a ratio similar to the copper-catalyzed reaction. The two methylenecyclopropanes 4 and 5 produced in small amounts in the copper-catalyzed reaction are also produced in the direct irradiation. Also formed are the two products 6 and 7, which are formally derived from insertion into the C–H bonds of the methyl group and the allenic C–H bonds.

The benzophenone-sensitized reaction of ethyl diazoacetate with 1,1-dimethylallene (1) gave products of the same structures as the photolytically generated carbene. Product ratios were quite different with the sensitized reaction giving much larger amounts of methylenecyclopropane 3 and only one of the C–H insertion products. In general, these reaction products contrast significantly with those produced in carbomethoxycarbene additions to 1,2-propadiene.[4b]

The origin of methylenecyclopropanes 4 and 5 in these reactions is of interest mechanistically. The sensitized reaction can be interpreted in terms of addition of a triplet carboethoxycarbene[4] to the allene, forming a diradical species such as 7. Closure of 7 after spin inversion at the methylene end of the "allylic radical" could produce 4 and 5.



The formation of 4 and 5 in the copper-catalyzed and unsensitized reactions is more difficult to rationalize. Control experiments show that they are primary products and not derived from subsequent isomerization of 2 and 3 under the reaction conditions. Products 2 and 3 are photostable both in the absence and presence of benzophenone. Photolysis of pyrazoline intermediates derived from cycloaddition of ethyl

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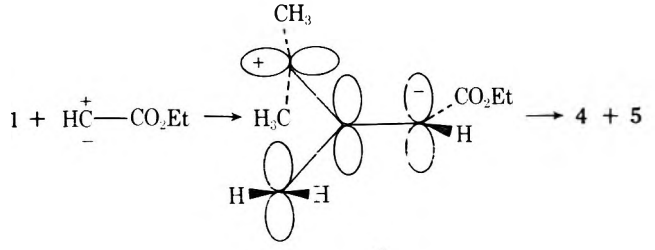
Table I. Reaction of Ethyl Diazoacetate with 1,1-Dimethylallene

Conditions	Total yield, %	Product ratios: 2	3	4	5	6	7
Cu[a]	25	1.0	0.83	0.07	0.04		
$h\nu$[b]	51	1.0	1.1	0.15	Trace	0.24	Trace
$h\nu$/Ph_2CO[b]	40	1.0	3.4	0.8	1.1	0.37	

[a] Di-*n*-butyl ether as cosolvent. [b] 1,1-Dimethylallene as solvent.

diazoacetate and **1** has also been ruled out as pyrazoline formation is not observable under nonphotolytic conditions. Photoinitiated pyrazoline formation, however, can not be ruled out. Neither can rearrangement from a thermally excited state of **2** or **3**. A further possibility to be considered for the formation of **4** and **5** is singlet–triplet interconversion under the conditions of the direct irradiation[5] followed by addition of the triplet carbene to the allene. However, the ratio of **4**/**5** produced in the sensitized photolysis is 0.7, while the direct irradiation gave a much larger ratio. This argues against a singlet–triplet interconversion mechanism. Such a mechanism is also highly improbable in the copper-catalyzed reaction which is believed to involve a copper-complexed carbene.[6]

A process that should be considered is a stepwise mechanism involving addition of the singlet carbene (or carbenoid) to the allene, giving a zwitterionic intermediate such as **8**. Such



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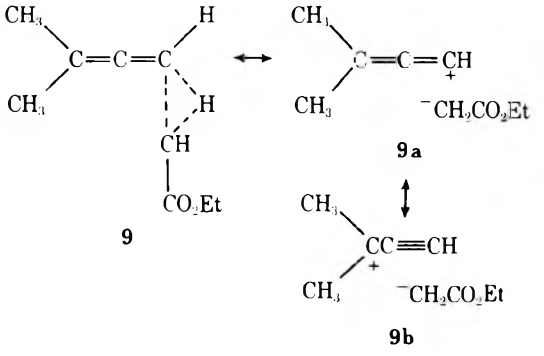
stepwise singlet carbene processes are rare, but precedents are the addition of iodocarbene to 1,2-dimethylcyclobutene[7a] and the stepwise addition–rearrangements in the reaction of methylene and dihalocarbenes to bicyclobutanes.[7b,c] A favorable electrostatic interaction in **8** might account for the predominance of **4** over **5** in which the carboethoxy group is in closer proximity to the dimethyl grouping.

The presence of insertion products **6** and **7** in the direct irradiation also deserves comment. These products imply that the same species is not involved in both the photolytic and the copper-catalyzed reaction. The intermediate "photolytic" carbene is even capable of insertion into the allenic C–H bond. Stabilization of the transition state (**9**) for this type of insertion as indicated by **9a** and **9b** may account for the unusual insertion into a formally olefinic C–H bond.



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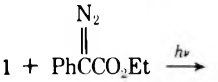
9a

9b

Phenylcarboethoxycarbene and Methylcarboethoxycarbene. Direct irradiation of ethyl diazophenylacetate (**10**)



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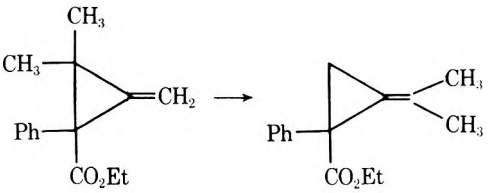
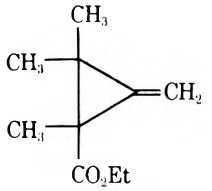


11 **12**

in 1,1-dimethylallene (**1**) gave methylenecyclopropane **12** as the sole product in 92% yield. This product of formal addition to the *least*-substituted allenic bond was initially quite surprising. Singlet–triplet interconversion of the intermediate carbene was ruled out to account for **12** since it has been found that photochemical addition of **10** to both *cis*- and *trans*-2-butene was stereospecific according to the Skell hypothesis.[8] The possibility that **12** was not a primary product was next investigated. Indeed, when the photolysis was carried out at 0 °C, the methylenecyclopropane **11** was the major photoadduct along with only small amounts of **12**. The initial product **11** rearranged thermally to give **12** and accounts for the initial difficulty in detecting this primary product. Rate data will be subsequently presented.

The benzophenone-sensitized irradiation of ethyl diazopropionate (**13**) in **1** also gave exclusively the product of formal addition into the least-substituted olefinic bond.[9] None of the product from addition to the most-substituted bond of **1**, ester **15**, was detected. The sole product **14** is in contrast to the



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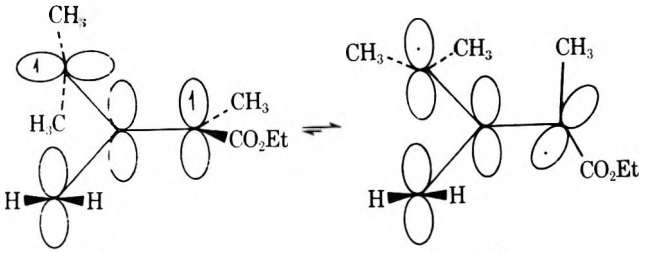
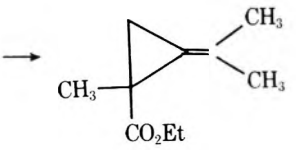
photosensitized reaction of ethyl diazoacetate in **1** (Table I) and may reflect the increased ability of an initially formed perpendicular triplet trimethylenemethane **16** to interconvert to forms such as **17**.

The direct irradiation of ethyl diazopropionate (**13**) in **1** gave an extremely complex product mixture from which the product of addition into the more-substituted bond (**15**), as well as **14**, could be isolated.



16 17



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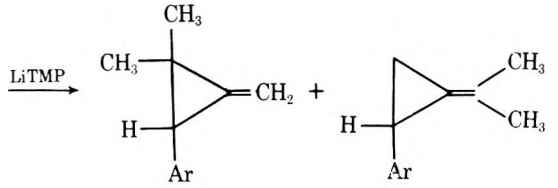
Arylcarbenes. The behavior of arylcarbenes with 1,1-dimethylallene (1) contrasts with that of the carboethoxy-substituted carbenes. Table II summarizes the reaction of arylcarbenoids generated from benzyl halides and lithium tetramethylpiperidide (LiTMP). As implied by our previous work,[10] there is a distinct preference for addition into the more-substituted bond in contrast to carboethoxycarbene. The products **19** are primary products and do not result from rearrangement of **18** under the reaction conditions. Yields

1 + $ArCH_2Cl$



18 19

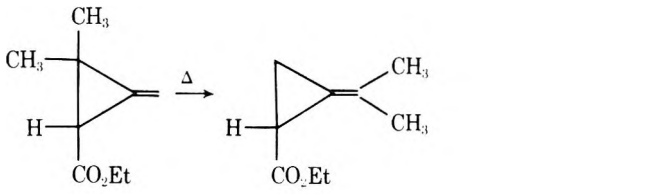
were fair with electron-donating groups on the benzyl halide, but they were poor with carbenoids generated from benzyl halides bearing electron-withdrawing substituents. In fact, *p*-nitrobenzyl chloride and *p*-trifluoromethylbenzyl chloride gave no cyclopropanation products. The benzophenone-sensitized reaction of phenyldiazomethane and 1 also gave a predominance of addition into the more-substituted bond of the allene. However, the product ratio is reduced to 1.8. Of interest is the fact that there is no crossover into the benzylidinecyclopropane series of products and no significant amounts of C–H insertion products.

Thermal Rearrangements of Substituted Methylenecyclopropanes. The availability of a variety of substituted methylenecyclopropanes by reaction of 1,1-dimethylallene with carbenes has led us to examine rearrangement rates to isomeric methylenecyclopropanes as a function of substitution. This type of rearrangement has been a subject of continuing interest with respect to mechanism[11] since the observation of the thermal rearrangement of Feists ester.[11a] Recently the effect of alkoxy substituents on the course of the rearrangement has been reported.[11i] The effect of aryl and carboethoxy substituents is now reported. Table III gives rearrangement rates of a series of substituted methylenecyclopropanes as determined by NMR spectroscopy. Rearrangement of **2** gave methylenecyclopropanes **3** and **5**. Unlike the carbene addition reaction, little if any of the isomeric **4** is produced. The aryl-substituted methylenecyclopropanes **18** gave the exocyclic isopropylidenecyclopropanes **19** as the sole thermal rearrangement products at 100 °C. At 200 °C further rearrangement of **19** (Ar = Ph) occurred to produce an equilibrium mixture of **19** (55%) and two benzylidenecyclopropanes **20a** and **20b** (45%). No indenes were produced as in the

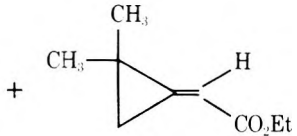
Table II. Reaction of Benzyl Halides and LiTMP with 1,1-Dimethylallene

Benzyl halide	Registry no.	Yield[a] of 18 and 19, %	Ratio[b] 18/19
$PhCH_2Cl$	100-44-7	35[c]	4.1
p-CH_3PhCH_2Cl	104-82-5	33[c]	3.9
p-CH_3OPhCH_2Cl	824-94-2	31[c]	Large
p-$ClPhCH_2Cl$	104-83-6	21	5.1
1-Naphthyl-CH_2Cl	86-52-2	20	3.0
m-$ClPhCH_2Cl$	620-20-2	7	~4[d]
m-CH_3OPhCH_2Cl	824-98-6	33	3.9
m-$FPhCH_2Cl$	456-42-8	13	4.1
$PhCH(=N_2)$[e]	766-91-6	54	1.8

[a] After chromatography and/or distillation. [b] Determined by NMR spectroscopy. [c] See ref 9 for a discussion of the formation of an acetylenic side product. [d] Impurity prevents precise determination. [e] Benzophenone-sensitized reaction.



2 3



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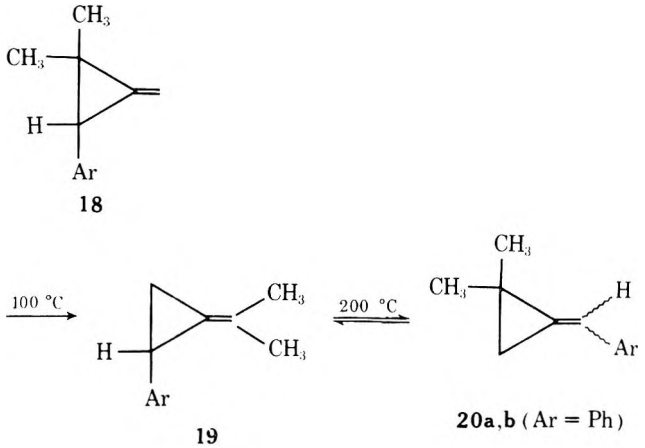
thermal rearrangement of 2,2-diphenylmethylenecyclopropane.[11h,12]



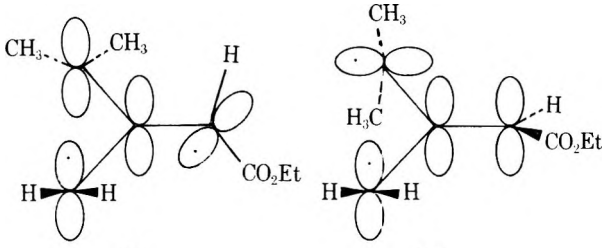
18 19 20a,b (Ar = Ph)

Diradical mechanisms have been suggested for the methylenecyclopropane rearrangement.[11d-i] In terms of such diradical mechanisms, the formation of **3** and **5** in the rearrangement of **2** would be consistent with the involvement of **21** and **22**, respectively. The fact that **5** (and not **4**) is produced suggests that the opening of **3** occurs to give the carboethoxy group anti to the dimethyl grouping, as in **22**. Rearrangement of **18** at 100 °C gives only **19**, which implies only one type of diradical (**23**) is involved. Diradical **23** should be more stable than **24** due to the low demand for further conjugation at the stabilized "aryl radical center." The demand for further conjugation at the "dimethyl-substituted radical center" is not satisfied in **24**. This precludes formation of **24** at lower temperatures, which acccounts for the absence of benzylidenecyclopropanes **20** despite thermodynamic stability

Table III. Rearrangement Rates of Substituted Methylenecyclopropanes in Isooctane

Compd	Registry no.	Temp, °C	10^5k, s^{-1}	$k_{rel}^{100\ °C}$	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, eu
18 (*p*-H)	65108-25-0	200.0	1.56×10^{5a}			
		100.0	35.5	1.0	28.6	2
		80.0	3.77			
18 (*p*-CH_3)	65108-26-1	100.0	46.5	1.3	27.1	−2
		80.0	5.55			
18 (*p*-Cl)	65354-61-2	100.0	47.5	1.3	29.5	5
		80.0	4.72			
18 (*p*-OCH_3)	65108-27-2	100.0	61.6	1.7	26.6	−2
		80.0	7.63			
18 (1-naphthyl)	65354-62-3	100.0	56.5	1.6	27.7	0
		80.0	4.64			
18 (*m*-Cl)	65354-63-4	100.0	33.0	0.9	29.9	4
		80.0	3.47			
18 (*m*-OCH_3)	65354-64-5	100.0	34.0	1.0	27.4	−1
		80.0	3.97			
18 (*m*-F)	65354-65-6	100.0	31.7	0.9	28.8	2
		80.0	3.33			
18 (*p*-Br)	65354-66-7	100.0	48.8	1.4	27.4	−1
		80.0	5.72			
2		150.0	19.7		33.4	3
		130.0	2.63			
		100.0	0.0849^a	2.4×10^{-3}		
11	65354-67-8	38.0	19.1			
		49.9	80.5	1.0×10^{3b}	23.4	0
25	4372-94-5	200.0	5.33^c	3.4×10^{-5d}		

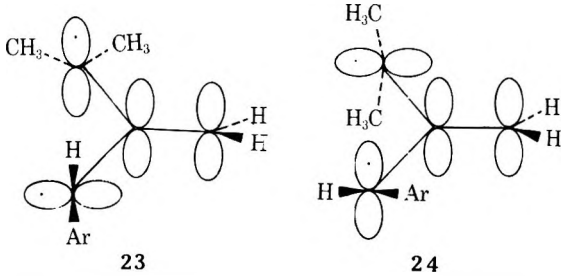
[a] Extrapolated value. [b] Comparison made at 499 °C. [c] The solvent was *n*-dodecane. [d] Comparison made at 200 °C.



21 22

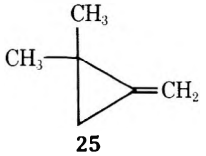
3 5

comparable to that of **19**. Further rearrangement of **19** (Ar = Ph) to **20** at 200 °C would involve the intervention of **24** at the elevated temperatures.



23 24

The kinetic data is of interest when one considers the perpendicular trimethylenemethane diradical intermediate suggested for the methylenecyclopropane rearrangement. Initially apparent are the rate enhancements relative to dimethylmethylenecyclopropane **25**. The rate enhancing effect

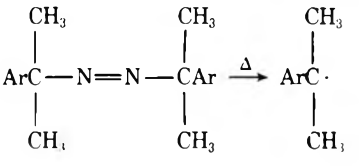


25

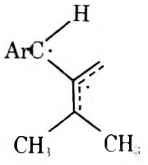
of the aryl group is larger than the carboethoxy group. However, the rate enhancement is only 2.7×10^2 for the carboethoxy group and 2.9×10^4 for the phenyl group. These rate enhancements must be considered quite small in light of the resonance stabilization energy of a benzyl radical (13.5 kcal/mol).[13] If aryl stabilization in **23** is comparable to that of a benzyl radical, then the rate enhancement of **18** vs. **25** should be *greater than*[14] 2.9×10^4.

The effect of substituents on the aryl group is also minimal. The entire spread in rate in **18** is only a factor of two between the slowest and fastest. Differences in enthalpies and entropies of activation were also found to be small. This data raises the question of the actual intermediacy of discrete radical intermediates such as **23**. If an intermediate with "full radical character" is involved, what is the expected substituent effect? It is known that, in general, substituent effects on rate of formation of free radicals are small. Data have been presented showing that polar factors can contribute to radical reactions.[15] However, polar effects should be minimal in the methylenecyclopropane rearrangement, and there is no reason to expect correlation of rate with σ or σ^+ substituent constants.

Kovacic, Shelton, and Liang have examined substituent effects in the pyrolysis of para-substituted azocumenes **26** and



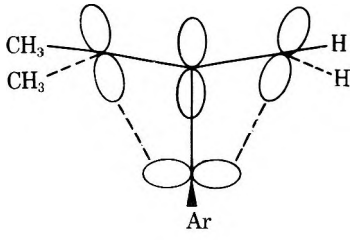
26 **27**



23

have found a small rate effect.[16] These effects were attributed to resonance effects in the intermediate radical **27**. These azocumene pyrolyses should be relatively devoid of the polar

effects seen in many radical reactions. The rate effects in these azocumene pyrolyses are somewhat larger than in the pyrolysis of **18** *despite the fact that a tertiary radical is involved*. The cumyl radical **27** should require *less* of a substituent stabilizing effect than benzylic radical **23**. If **23** is involved in the pyrolysis of **18**, then the transition state has less radical character at the benzylic position than in the pyrolysis of azocumene **26**. The origin of the reduced radical character in the transition state could be an early transition state in the methylenecyclopropane rearrangement. Alternately, the minimal substituent effect is not inconsistent with a concerted process having a transition state resembling **27**, in which there



27

is only partial radical character at the benzylic position. Without further data on the effect of substituents on radical reactions devoid of polar character, a choice between these two suggestions cannot be made.

Experimental Section

NMR spectra were recorded on a Varian A-60A spectrometer or a Varian XL-100 spectrometer using the Fourier transform mode. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer.

Copper-Catalzyed Reaction of Ethyl Diazoacetate with 1,1-Dimethylallene. A solution of 5.00 g of ethyl diazoacetate in 5 mL of dry di-*n*-propyl ether was added dropwise over 6 h to a mixture of 7 g of 1,1-dimethylallene[17] and 8 mL of di-*n*-propyl ether containing 70 mg of copper acetylacetonate. The mixture was heated in an oil bath at 60–70 °C during the addition. Initially no nitrogen evolution was observed. After 1 h, 300 mg of copper bronze was added. Shortly thereafter nitrogen evolution began and was spontaneous with the addition of the diazoester. Upon completion of the addition, heating was continued for an additional hour. The solvents were removed under reduced pressure, and the residue was distilled at 0.5 mm with the bath temperature below 90 °C. The distillate (2.73 g) was analyzed by gas chromatography on a 5 ft, 5% SE-30 on Chromosorb G column at 75 °C. Samples of each product, esters **2–5**, ethyl fumarate, and ethyl maleate, were isolated by preparative gas chromatography with the injector and detector temperatures below 140 °C. The yields of esters **2**, **3**, **4**, and **5** are given in Table I along with the ratios as determined by gas chromatography. The distillate also contained 37% of ethyl fumarate and ethyl maleate as determined by NMR spectroscopy. The NMR spectrum of **2**[2d] (CCl_4) showed δ 5.35 (2 H, t, J = 2 Hz), 4.07 (2 H, q, J = 7 Hz), 1.94 (1 H, t, J = 2 Hz), 1.29 (6 H, s), and 1.24 (3 H, t, J = 7 Hz); NMR of **3** (CCl_4) δ 4.08 (2 H, q, J = 7 Hz), 2.05 (1 H, m), 1.80 (6 H, m), 1.58 (2 H, m), 1.23 (3 H, t, J = 7 Hz); NMR of **4** ($CDCl_3$) δ 6.08 (1 H, t, J = 1.8 Hz), 4.21 (2 H, q, J = 7 Hz), 1.32 (3 H, t, J = 7 Hz), 1.25 (6 H, s), 1.11 (2 H, d, J = 1.8 Hz); NMR of **5** ($CDCl_3$) δ 6.20 (1 H, t, J = 2.5 Hz), 4.22 (2 H, q, J = 7.2 Hz), 1.30 (3 H, t, J = 7.2 Hz), 1.33 (2 H, d, J = 2.5 Hz). 1.22 (6 H, s).

The reaction of ethyl diazoacetate with **1** in di-*n*-butyl ether using copper bronze powder under conditions similar to those described above gave a similar product ratio to the reaction in di-*n*-propyl ether.

Photolysis of Ethyl Diazoacetate in 1,1-Dimethylallene. A solution of 120 mg of ethyl diazoacetate (Aldrich Chemical Co.) in 5.5 mL of 1,1-dimethylallene under nitrogen was degassed at 0.1 mm and sealed in a Pyrex tube under vacuum. The mixture was irradiated at room temperature for 3 h using a 450-W Hanovia medium-pressure lamp with a Pyrex filter. Upon completion of the irradiation the yellow color had faded substantially. The solvent was removed under vacuum, and the residue was distilled at 0.08 mm to give 83 mg (51%) of a mixture of esters **2–7**. Samples of each product were isolated by preparative gas chromatography on a 6 ft, 10% XE-60 on Chromosorb P column at 105 °C with the injector and detector temperatures below 140 °C. Ester **5** was separated on an SE-30 column since the retention time on the XE-60 column was identical to **2**. Ester **6** showed the following: NMR ($CDCl_3$) δ 4.64 (2 H, sextet, J = 3.2 Hz), 4.13 (2 H, q, J = 7 Hz), 2.43 (2 H, m), 2.23 (2 H, m), 1.71 (3 H, t, J = 3.2 Hz), 1.25 (3 H, t, J = 7 Hz); IR 5.09 μm. Ester **7** showed the following: NMR ($CDCl_3$) δ 5.08 (1 H, m), 4.16 (2 H, q, J = 7 Hz), 2.98 (2 H, d, J = 7 Hz), 1.69 (6 H, d, J = 3 Hz), 1.27 (3 H, t, J = 7 Hz). The product ratios in Table I were also determined by gas chromatography.

Benzophenone-Sensitized Photolysis of Ethyl Diazoacetate in 1,1-Dimethylallene. A degassed solution of 150 mg of ethyl diazoacetate and 0.5 g of benzophenone in 6 mL of 1,1-dimethylallene was sealed in a Pyrex tube under vacuum and irradiated for 3 h with Pyrex-filtered light from a 450-W Hanovia medium-pressure source. After completion of the irradiation, the ester products **2–6** were isolated by distillation as previously described, giving 81 mg (40%) of products. Product separation was carried out by gas chromatography using an XE-60 or SE-30 column. The product ratios were also determined by gas chromatography. In a second run, the ratio of benzophenone to ethyl diazoacetate was doubled, but the product ratio was the same as before.

Sensitized and Direct Irradiation of 2 and 3. Control Experiments. A 16.4-mg sample of **2** was dissolved in 3 mL of 1,1-dimethylallene containing 250 mg of benzophenone, degassed, and sealed under vacuum. The mixture was irradiated with Pyrex-filtered light from a Hanovia 450-W medium-pressure source and a General Electric sunlamp for 2 h and 15 min. Gas chromatographic analysis of the mixture after irradiation showed only ester **2**.

Similar irradiation of 13.2 mg of ester **3** in 3 mL of 1,1-dimethylallene containing 250 mg of benzophenone gave only unchanged **3**. Direct irradiation of degassed solutions of **2** and **3** for 3 h with a Hanovia 450-W medium-pressure source also gave no observable change.

Photolysis of Ethyl Diazophenylacetate in 1,1-Dimethylallene. A degassed solution of 140 mg of ethyl diazophenylacetate[18] in 5 mL of 1,1-dimethylallene was sealed under vacuum and irradiated for 3 h with Pyrex-filtered light from a 450-W Hanovia high-pressure source. During the irradiation, the temperature was approximately 35 °C. After completion of the irradiation, the solvent was removed under vacuum. The NMR spectrum of the crude residue showed only ester **12**. Distillation of the residue gave 156 mg (92%) of ester **12**: bp 86–87 °C (0.1 mm); NMR ($CDCl_3$) δ 7.10 (5 H, s), 3.95 (2 H, q, J = 7 Hz), 2.14 (1 H, m) 1.73 (6 H, m), 1.36 (1 H, m), 1.00 (3 H, t, J = 7 Hz); mass spectrum, m/e 230.1320 (calcd for $C_{15}H_{18}O_2$, 230.1307).

Photolysis of Ethyl Diazophenylacetate in 1,1-Dimethylallene at 0 °C. A degassed solution of 100 mg of ethyl diazaophenylacetate in 4 mL of 1,1-dimethylallene was sealed under vacuum and immersed in an ice-water mixture in a Pyrex crystallizing dish. The mixture was irradiated at 0 °C for 2.5 h. The solvent was then removed under vacuum, and the temperature was not allowed to exceed 0 °C. The NMR spectrum of the crude residue showed methylenecyclopropanes **11** and **12** in an approximate ratio of 4:1. Compound **11**: NMR ($CDCl_3$) δ 7.7–7.2 (5 H, m) 5.83 (1 H, s), 5.63 (1 H, s), 4.12 (2 H, q, J = 7 Hz), 1.38 (3 H, s), 1.20 (3 H, t, J = 7 Hz), 0.85 (3 H, s).

Rearrangement of **11** to **12** occurs in the probe of the NMR instrument with a half-life of approximately 50 min. Rate data in isooctane is given in Table III.

Benzophenone-Sensitized Photolysis of Ethyl Diazopropionate in 1,1-Dimethylallene. A mixture of 140 mg of ethyl diazopropionate[19] in 7 mL of 1,1-dimethylallene and 500 mg of benzophenone in a Pyrex tube was sealed under nitrogen. The mixture was irradiated for 3 h with the usual Pyrex-filtered light. After removal of the solvent under vacuum, the residue was distilled with the pot temperature below 90 °C to give 69 mg (38%) of ester **14**: bp 48 °C (1.6 mm); NMR (CCl_4) δ 4.07 (2 H, q, J = 7 Hz), 2.1–1.7 (7 H, m), 1.5–1.2 (4 H, m, with a 3-H s at δ 1.33), 1.20 (3 H, t, J = 7 Hz). Ester **14** has been previously reported,[9] but no spectral data were given.

Photolysis of Ethyl Diazopropionate in 1,1-Dimethylallene. A solution of 180 mg of ethyl diazopropionate in 6 mL of 1,1-dimethylallene was degassed and sealed in a Pyrex tube under vacuum. After a 3-h irradiation and removal of the solvent under reduced pressure, 57 mg of volatile products was isolated by distillation at 0.1 mm. Gas chromatographic analysis of the mixture on 5 ft, SE-30 column showed a complex, poorly resolved mixture of at least six components. Isolation of two of the major components was accomplished by preparative gas chromatography with the injector and detector temperatures below 140 °C. The product of longer retention time was shown to be ester **14** by spectral comparison with a sample produced as described above.

The product of shorter retention time, ester **15**, showed the following: NMR ($CDCl_3$) δ 5.37 (1 H, s), 5.33 (1 H, s), 4.14 (2 H, q, J = 7 Hz), 1.37 (3 H, s), 1.24 (3 H, t, J = 7 Hz), 1.22 (6 H, s). Ester **15** has

Table IV. NMR Spectra (δ) of 18 in CCl_4 and 19 in $CDCl_3$

Compd	Registry no.	Ar	CH_2	HCAr	OCH_3	CH_3
18 (*p*-Cl		7.1	5.54	2.40		1.33, 0.83
18 (1-naphthyl)		8.2–7.2	5.68	2.78		1.53, 0.73
18 (*m*-Cl)		7.1	5.55	2.38		1.34, 0.86
18 (*m*-OCH_3)		6.7	5.53	2.39	3.73	1.33, 0.86
18 (*m*-F)		7.4–6.6	5.56	2.42		1.35, 0.87
18 (*p*-Br)[a]		7.6–7.0	5.58	2.42		1.33, 0.83
19 (*p*-Cl)	57765-59-0	7.4–6.8	1.70, 1.07	2.52		1.91, 1.77
19 (1-naphthyl)	65354-68-9	8.5–7.0	1.78, 0.90	3.06		1.97
19 (*m*-Cl)	65354-69-0	7.4–6.9	1.70, 1.10	2.52		1.91, 1.78
19 (*m*-OCH_3)	65354-70-3	7.4–6.6	1.70, 1.10	2.55	3.78	1.91, 1.79
19 (*m*-F)	65354-71-4	7.4–6.6	1.70, 1.10	2.54		1.91, 1.77
19 (*m*-Br)[b]	65354-72-5	7.5–6.8	1.70, 1.10	2.48		1.91, 1.77

[a] In $CDCl_3$. [b] In CCl_4.

been previously reported,[9] but no spectral data were given.

Reaction of Benzyl Chlorides with Lithium Tetramethylpiperidide in 1,1-Dimethylallene. General Procedure. A mixture of 6 mmol of the appropriately substituted benzyl chloride, 3.5 g of 1,1-dimethylallene, and 3 mL of ether was placed in a water bath at room temperature under nitrogen. A solution of 77 mmol of lithium tetramethylpiperidide prepared from tetramethylpiperidine and methyllithium in ether was added dropwise over a 2-h period. After stirring for an additional hour an aqueous workup followed. Tetramethylpiperidine was removed by extraction with dilute hydrochloric acid, and the products were isolated by distillation and/or chromatography on neutral alumina with pentane elution. Products 18 (*p*-Cl, 1-naphthyl, *m*-Cl, *m*-OCH_3, and *m*-F) were all chromatographed before distillation. Product 18 (1-naphthyl) was not distilled. The ratio of 18/19 was determined by NMR integration of the olefinic protons of 18 vs. the methyl protons of 19. Pure samples of 19 were isolated by preparative gas chromatography on the thermolysis products of 18. NMR spectral data are given in Table IV. Data on 18 and 19 (*p*-H, *p*-CH_3, and *p*-OCH_3) have been reported.[10]

Thermal Rearrangement of Substituted Methylenecyclopropanes. Kinetics Procedure. Approximately 80 mg of 18 and an internal standard (dimethyl phthalate) were dissolved in isooctane in an NMR tube and sealed under nitrogen. The tube was heated in a constant temperature bath at the appropriate temperature for a given amount of time. Periodically the tube was analyzed for remaining 18 by integration of the signal at δ 5.5–5.7. Integrals were corrected for detector response, and rate constants were calculated by the least-squares method. Correlation coefficients were in all cases better than 0.999. For product analyses the sample was heated for a minimum of ten half-lives and the tube contents were analyzed by gas chromatography. Samples of each product 19 were also isolated by preparative gas chromatography or by distillation of the thermolysis product of neat 18. 19 (1-naphthyl) was not stable to gas chromatographic conditions.

The rearrangement of ester 2 was monitored by gas chromatography with the injection port temperature below 140 °C. A sample of approximately 10 mg of 2 and 5 mg of mesitylene (internal standard) was diluted to 1 mL with isooctane, and portions were sealed in tubes under nitrogen. The tubes were immersed in a constant temperature bath, and at appropriate time intervals the contents of the various tubes were analyzed by gas chromatography on an SE-30 column at 72 °C for remaining 2. Rate constants were calculated in the usual manner. Samples of products 3 and 5 were also isolated for identification purposes by preparative gas chromatography.

Rearrangement of 19 (Ar = Ph) at 200 °C. A 30-mg sample of 19 (Ar = Ph) was sealed under nitrogen and heated at 200 °C for 1 h. Gas chromatographic analysis on a 6 ft, 10% XE-60 on Chromosorb P column at 110 °C showed unchanged 19 (Ar = Ph) (approximately 55%) along with *syn*-2,2-dimethylbenzylidenecyclopropane (**20a**; 20%) and *anti*-2,2-dimethylbenzylidenecyclopropane (**20b**; 25%). Further heating for 1.5 h at 220 °C did not change the ratio. Samples of each product were isolated by preparative gas chromatography, and structures of **20a** and **20b** were assigned by NMR spectroscopy. *syn*-2,2-Dimethylbenzylidenecyclopropane (**20a**) showed the following: NMR ($CDCl_3$) δ 7.42–7.10 (5 H, m), 6.66 (1 H, t, J = 1.8 Hz), 1.32 (6 H, s), 1.05 (2 H, d, J = 1.8 Hz). *anti*-2,2-Dimethylbenzylidenecyclopropane (**20b**) showed the following: NMR ($CDCl_3$) δ 7.60–7.20 (5 H, m), 6.75 (1 H, t, J = 2.5 Hz), 1.27 (2 H, d, J = 2.5 Hz), 1.24 (6 H, s).

The same mixture of 19 (Ar = Ph), **20a**, and **20b** could be produced by heating **20b** at 205 °C for 1 h.

Preparation of 1,1-Dimethyl-2-methylenecyclopropane (25).[2a] Potassium *tert*-butoxide (120 mg) was dissolved in 3 mL of dry dimethyl sulfoxide, and 260 mg of 1,3,3-trimethylcyclopropene[20] was added. A mildly exothermic reaction followed. After 15 min, NMR analysis showed no remaining cyclopropene. *n*-Dodecane (3 mL) was added followed by 8 mL of water. The dodecane extract was dried over sodium sulfate and used directly for the kinetics experiments. The NMR spectrum of **25** in the dodecane extract showed the characteristic olefinic multiplet at δ 5.3.[2a]

Thermal Rearrangement of 1,1-Dimethyl-2-methylenecyclopropane (25). A solution of **25** in dodecane prepared as described above and 16 mg of dimethyl phthalate (internal standard) were sealed in an NMR tube. The tube was heated in refluxing methyl benzoate (200.0 °C) for an appropriate amount of time and analyzed for remaining **25** by integration of the olefinic signal. The isomerization gives an equilibrium mixture[21] of isopropylidenecyclopropane and **25** in a ratio of 4.4:1 as determined by NMR integration of the remaining **25** after 20 half-lives. Rate constants were calculated from data acquired during the first half-life only.

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Registry No.—**2**, 30762-78-8; **3**, 65354-58-7; **4**, 65354-59-8; **5**, 65354-60-1; **6**, 20387-99-9; **7**, 30333-01-8; **10**, 22065-57-2; **12**, 65354-73-6; **13**, 6111-99-5; **14**, 65354-74-7; **15**, 65354-75-8; **19** (Ar = Ph), 56701-47-4; **20a**, 65454-76-9; **20b**, 65354-77-0; ethyl diazoacetate, 623-73-4; 1,1-dimethylallene, 598-25-4; 1,3,3-trimethylcyclopropene, 3664-56-0; isopropylidenecyclopropane, 4741-86-0.

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Hydrogenation of 2,5-Diacetoxy-2,5-dimethyl-3-hexyne over Palladium[1a]

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The hydrogenation of **1** over 10% palladium on charcoal proceeds to give seven products (**2**–**8**). Alkene **2** is the precursor of the other products. A concerted process including hydrogenation, hydrogenolysis, and isomerization is postulated to account for the direct formation of **5** from **2**. The effect of added nitrogen bases on the product distribution is presented, and several mechanistic alternatives are discussed.

One of the most useful reactions for the preparation of pure cis olefins has been the catalytic hydrogenation of acetylenes over deactivated catalysts at room temperature and atmospheric pressure.[2] The classic catalyst for this reaction is Lindlar's catalyst, lead-poisoned palladium on calcium carbonate.[3] The partial hydrogenation of acetylenic carbinols has been studied by many workers. These are useful synthetic intermediates due both to their ease of synthesis and to the possibility of transforming them into molecules containing different functionality.[4] Thus, much of the work on acetylenic carbinols has been directed toward their selective hydrogenation to the olefinic stage without any further reduction to the alkane system.

Moderation of palladium catalysts with added pyridine has been employed to hydrogenate acetylenic carbinols to allylic alcohols.[5] The pyridine apparently functions to poison the catalyst by being absorbed more strongly on the catalyst surface than the alkene but less strongly adsorbed than the acetylene. This could result in selective hydrogenation,[6] although recently it has been suggested that selectivity in alkyne hydrogenation is not due to different strenghts of adsorption of alkenes and alkynes but rather to different kinds of surface adsorption sites.[7] The self-poisoning effect of pyridine on its own hydrogenation has been reviewed.[8] The reduction of pyridine to piperidine results in even stronger catalyst poisoning by the piperidine. The unshared electron pair on the nitrogen atom apparently causes the effect since pyridinium salts are readily hydrogenated without any self-poisoning of the catalyst.

Many other catalyst inhibitors have been employed for partial hydrogenation of acetylenes over palladium. These include, for example, morpholine,[9] barium carbonate,[10] calcium carbonate,[11] combinations of lead acetate and quinoline with calcium carbonate,[12] barium sulfate,[11] potassium hydroxide,[13] etc.

Although palladium is one of the most commonly used hydrogenation catalysts, isomerization[14] or hydrogenolysis[15] can be serious problems with this catalyst. In some cases catalyst modifiers can be employed to prevent these reactions. For example, potassium hydroxide prevents the hydrogenolysis of the hydroxyl groups of propargyl alcohols.[16]

We have undertaken a study of the hydrogenation of 2,5-diacetoxy-2,5-dimethyl-3-hexyne (**1**) over 10% palladium on charcoal in the presence of pyridine and piperidine as catalyst modifiers. We had inadvertently observed that upon hydrogenation of **1**, varying quantities of 2-acetoxy-2,5-dimethyl-4-hexene (**5**) were produced.[1a] The production of this novel reaction product involves hydrogenation, isomerization, and hydrogenolysis. The hydrogenation of **1** has been previously reported, but the only isolated product was the alkene **2**.[17]

Results and Discussion

Hydrogenation of **1** over 10% palladium on charcoal at atmospheric pressure in absolute ethanol results in the formation of seven different compounds (**2**–**8**, Scheme I) along with acetic acid from hydrogenolysis of some of the acetate groups. The composition of the reaction mixture was followed as a function of equivalents of hydrogen absorbed by the system. This plot is shown in Figure 1. Examination of the figure shows that the concentrations of **2** and **5** steadily increase to a maximum and then decrease as they are further transformed. Figure 2 shows the data for hydrogenation of **2** under similar conditions. It is clear that **2** is the precursor to the other reaction products, while **4**, **7**, and **8** are end products which are not further transformed. Scheme I shows a plausible sequence to account for each of the products observed.

The initial hydrogenation of **1** proceeds to give predominantly the cis alkene (**2**) along with a small quantity of the trans alkene (**3**). The trans alkene could have been formed directly from the acetylene[18] or as a result of isomerization of the cis alkene over the palladium catalyst.[19] The former is preferred since **3** is not formed during hydrogenation of **2** nor is **2** formed during hydrogenation of **3**. Presumably, in either case, formation of **3** would be due to a stepwise addition of hydrogen atoms, with the first addition step being reversible.[20]

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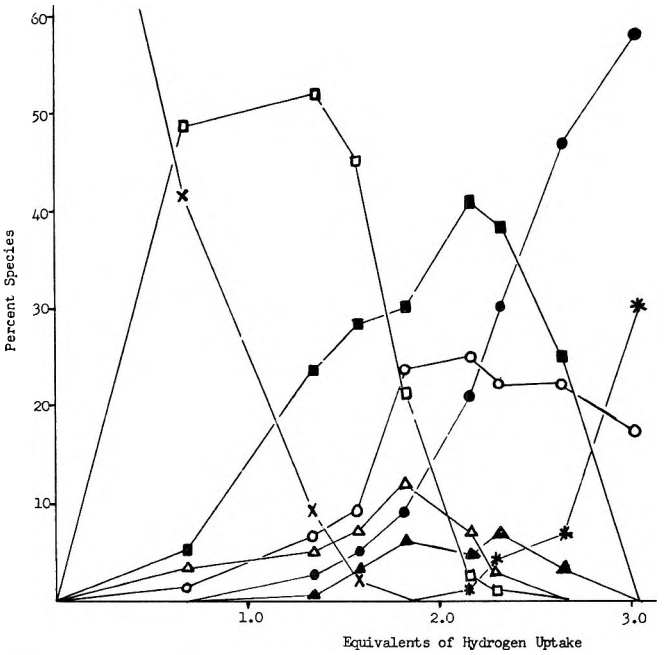


Figure 1. Plot of product composition vs. equivalents of hydrogen uptake during hydrogenation of **1**: 1 (x), 2 (□), 3 (△), 4 (○), 5 (■), 6 (▲), 7 (●), 8 (*).

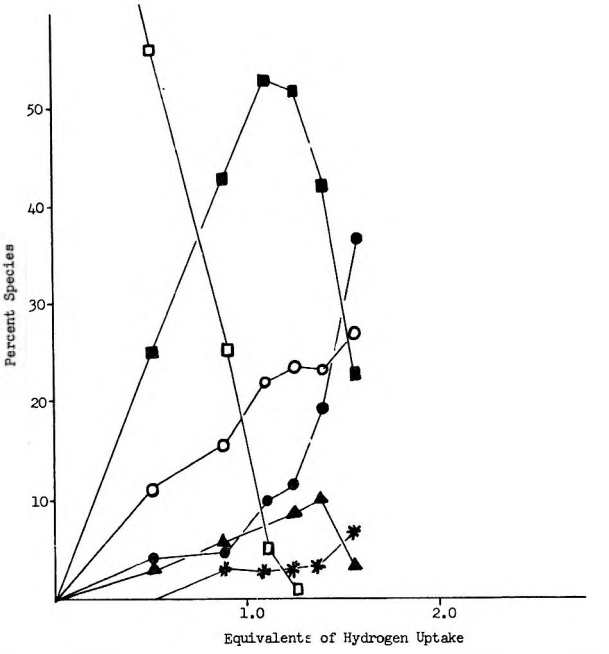
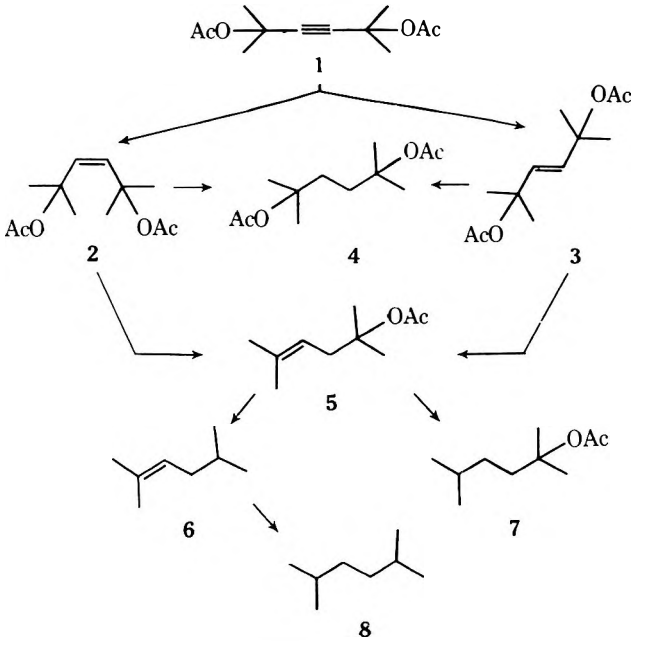


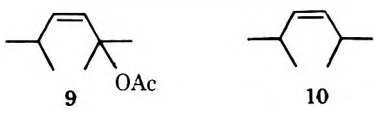
Figure 2. Plot of product composition vs. equivalents of hydrogen uptake during hydrogenation of **2**: 2 (□), 3 (△), 4 (○), 5 (■), 6 (▲), 7 (●), 8 (*).

Scheme I

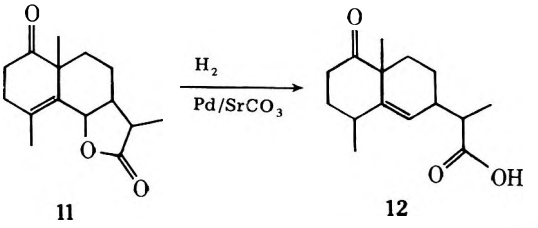


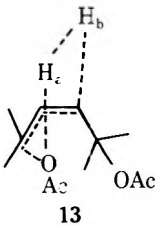
The fully saturated diester **4** is formed in a straightforward hydrogenation from either **2** or **3**.

The origin of acetate **5** is very intriguing since its direct formation from either **2** or **3** would require concomitant hydrogenolysis and double-bond isomerization. If hydrogenolysis occurs in allylic systems via initial C–O cleavage followed by hydrogen addition, as has been suggested,[21] it is not surprising that we observe addition of the hydrogen at a position allylic to the original acetate group. This results in the formation of the most substituted alkene isomer. Alternatively, hydrogenolysis without rearrangement would give **9**, which could then isomerize to **5**. The isomerization of **10** to **6** has been observed during hydrogenation of **10** (and its trans isomer) over palladium.[22]



A reaction very similar to that reported here occurs during the hydrogenation of deoxypseudosantonin (**11**) over 5% Pd/$SrCO_3$.[23] In this case the double bond has migrated to the less substituted position, while in our case the more substituted alkene is formed. In both cases, none of the other isomer was formed. These observations lead us to favor a third mechanism for the formation of **5**. A concerted (or nearly concerted) addition of hydrogen via the six-centered transition state **13** would give exclusive formation of **5**. Furthermore, a similar mechanism for the hydrogenation of **11** would also lead to the formation of **12**. Models indicate that the two atoms to which hydrogen is being added can approach to within 2.6 Å of one another. The planarity of the C=C—C—O system would be insured by binding of both the π system and the oxygen atom to the catalyst surface.





A related system is the hydrogenolysis of benzylic esters which has been studied in great detail. They are thought to hydrogenolyze by hydride attack of the protonated ester in an S_N2-like reaction.[24] If transition state **13** were polarized with $H_a^{\delta+}$–$H_b^{\delta-}$, this would be similar to an S_N2' reaction and consistent with our results.

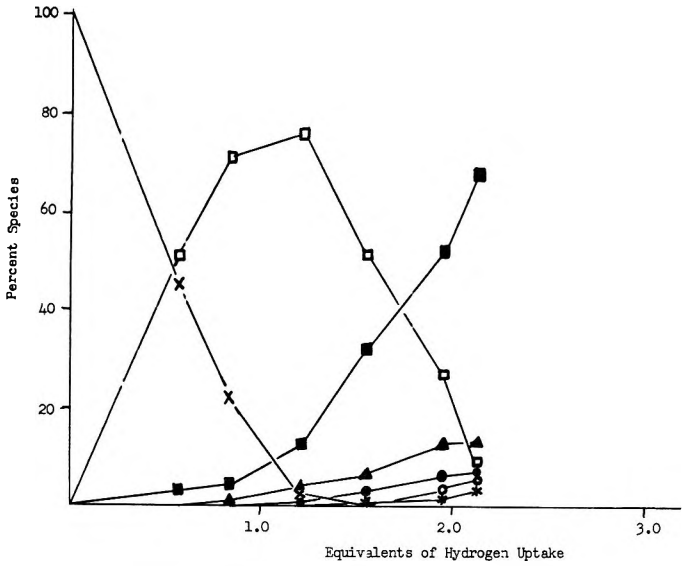


Figure 3. Plot of product composition vs. equivalents of hydrogen uptake during hydrogenation of 1 in the presence of pyridine: 1 (x), 2 (□), 4 (○), 5 (■), 6 (▲), 7 (●), 8 (*).

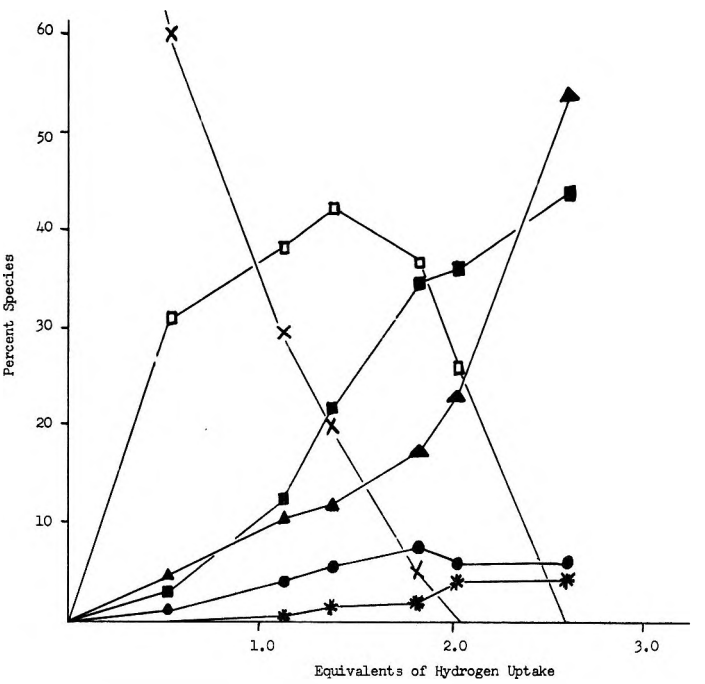


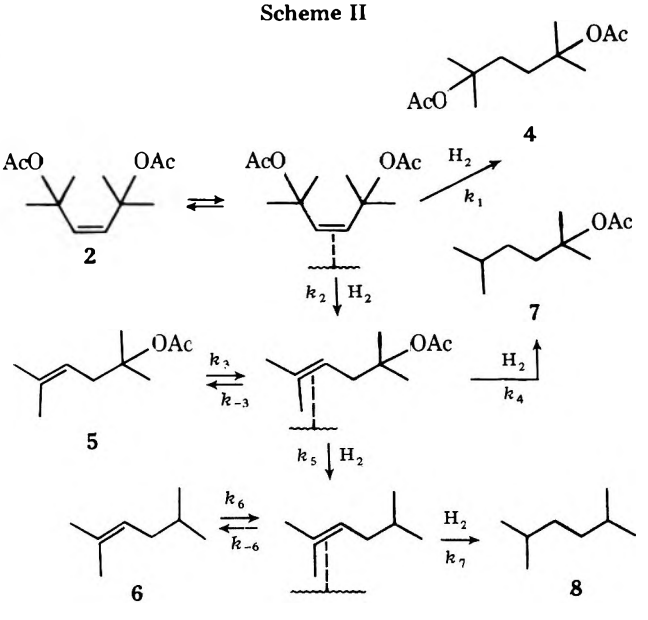
Figure 4. Plot of product composition vs. equivalents of hydrogen uptake during the hydrogen of 1 in the presence of piperidine: 1 (x), 2 (□), 5 (■), 6 (▲),7 (●), 8 (*).

Several other pathways in Scheme I have been verified by separate hydrogenation. Hydrogenation of **3** gives very similar results to those obtained with **2**. Acetate **7** is cleanly produced by hydrogenation of pure **5**, while **8** is produced quantitatively by hydrogenation of **6**. The formation of **6** by hydrogenolysis of **5** will be discussed later. Hydrogenation of **4** and **7** both failed to give any reaction under a variety of conditions, thus ruling out **4** → **7** and **7** → **8**.

The hydrogenation products from **1** and **2** as well as the rate of hydrogen uptake are significantly altered by the addition of small quantities of nitrogen bases. The product ratio plotted vs. equivalents of hydrogen absorbed for both pyridine and piperidine is shown in Figures 3 and 4, respectively. Hydrogenation of **2** in the presence of pyridine or piperidine again showed **2** to be the precursor of the other products. The presence of the catalyst modifier supresses the formation **4**, **7**, and **8**. Thus, simple alkene hydrogenation is inhibited by these nitrogen bases. This is reasonable in view of the known poisoning of palladium catalysts by nucleophiles.[5,9,11,25]

Piperidine has the further effect of enhancing the hydrogenolysis of **5** to produce **6**, which becomes the major product. However, prolonged hydrogenation of **1** does not change the 54:44 ratio of **6**/**5**. Furthermore, when pure **5** is hydrogenated in the presence of piperidine, no reaction occurs. In the absence of piperidine, **5** is smoothly converted to **7** without any formation of **6**. This anomolous behavior can be explained by the mechanism shown in Scheme II. In the presence of either pyridine or piperidine, k_1, k_4, and k_7 are dramatically decreased. Pyridine has no effect on k_5, whereas piperidine increases k_5 to the extent that **6** becomes the major product. We propose that piperidine is simultaneously inhibiting k_4 and enhancing k_5, while assuring that **5** can not be readsorbed on the catalyst surface ($k_3 \sim 0$). Thus, the ratio of **5**/**6** is determined by the relative rates of hydrogenolysis (k_5) and desorption from the catalyst surface (k_{-3}). Since piperidine prevents the adsorption of **5** onto the catalyst surface, **6** can only be formed when **5** is produced from **2** directly on the catalyst surface. Piperidine also prevents **6** from being readsorbed ($k_6 = 0$). Thus, prolonged hydrogenation does not change the **5**/**6** ratio. In the absence of piperidine, k_4 is much larger than k_5 so that **6** is a minor product. Alternate explanations are possible. For example, piperidine could be decreasing, but to different extents, the concentration of **5** adsorbed at the specific catalyst sites responsible for hydrogenation and hydrogenolysis.

Scheme II



These nitrogen bases also have a marked effect on the rate of hydrogen uptake. In all cases, the slope from a plot of equivalents of hydrogen uptake vs. time remained constant for at least 0.5 equiv of hydrogen uptake. These initial slopes are given in Table I for varying concentrations of pyridine and piperidine. Pyridine retards the rate for all concentrations, and piperidine enhances the rate at low concentration while retarding the rate at high concentration. It is not clear what interpretation should be given this result.

Several reaction variables have been studied. The substrate/catalyst ratio was varied from 5:1 (by weight) to 30:1 without any significant change in the product ratio (Table II). The inhibitor/catalyst ratio was varied over a small range, again without any significant change in product ratios. The product curves were essentially superimposable on the curves of Figures 3 and 4 when 200 μL of inhibitor was used rather than 50 μL.

Table I. Initial Rate of Hydrogen Uptake[a]

Nitrogen base	Amount	Initial rate[b]
Pyridine	50 μL	1.0
	200 μL	0.7
	500 μL	0.6
	5 mL	0.3
	15 mL	0.1
Piperidine	50 μL	1.9
	200 μL	1.8
	500 μL	1.6
	5 mL	0.9
	15 mL	0.7
None		1.5

[a] Each run contained a total volume of 30 mL of solvent (absolute ethanol plus nitrogen base), 5 mg of 10% Pd/C, and 75 mg of **1**. They were carried out at 25 °C and 1 atm of hydrogen pressure. [b] Slope of equivalents of H_2 uptake vs. time through the first 0.5 equiv of hydrogen uptake.

Experimental Section

General. Analytical gas chromatography (GC) was performed on a Perkin-Elmer Model 810 (hydrogen flame detector) chromatograph using temperature programming. Preparative GC was performed on a Varian Aerograph A-90-P (thermal conductivity detector) chromatograph. The analytical column was 10 ft × ⅛ in 15% FFAP on 60–80 mesh Chromosorb W; preparative columns were 10 ft × ¼ in 15% FFAP or 15% Carbowax 20 M on 60–80 mesh Chromosorb W. Percent composition data were estimated by peak areas (uncorrected). Anhydrous magnesium sulfate was used for all drying operations. Nuclear magnetic resonance (NMR) spectra were determined on a Varian Associates A-60 spectrometer. Infrared (IR) spectra were determined on a Perkin-Elmer Model 137 spectrophotometer. Melting points were measured with a Thomas-Hoover capillary melting point apparatus and are uncorrected.

All products were identified by independent synthesis as described below, with the exception of **8**, which was identified by direct comparison with a sample obtained from the Aldrich Chemical Co. All chemicals used were reagent grade. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

Analytical Hydrogenation Procedure. A semimicro atmospheric pressure apparatus was employed.[26] A 50-mL Erlenmeyer flask equipped with a magnetic stirrer and side-arm addition tube was charged with 5 mg of palladium on charcoal (Engelhard Industries) followed by the addition of 10 mL of absolute ethanol along with any catalyst modifier (50 μL of pyridine or piperidine). The flask was evacuated and filled with hydrogen three times to eliminate air. The catalyst was then reduced by stirring at atmospheric pressure for 15 min. A solution of 75 mg of substrate in 10 mL of absolute ethanol was added via the side arm followed by an additional 10 mL of absolute ethanol. The mixture was hydrogenated at atmospheric pressure.

After an appropriate uptake of hydrogen, the flask was evacuated. The solution was filtered to remove the catalyst, 150 mL of water was added, and the resulting mixture was extracted with two 25-mL portions of ether. The combined ether extracts were washed first with 25 mL of 5% hydrochloric acid (if pyridine or piperidine was used) and then with 50 mL of saturated sodium bicarbonate. The solution was *not* dried since it was found that drying agents adsorbed a significant amount of product. The ether solution was then analyzed directly by analytical GC. The equivalents of hydrogen uptake agreed to within 5% of that calculated from the GC analyses.

2,5-Diacetoxy-2,5-dimethyl-3-hexyne (1). A mixture of 360 mL of pyridine, 100 g (0.7 mol) of 2,5-dimethylhex-3-yne-2,5-diol, and 214 g (2.1 mol) of acetic anhydride was heated at 85 °C with stirring for 50 h. The mixture was cooled, poured onto 1500 mL of cold water, and extracted with three 200-mL portions of 30–60 °C petroleum ether. The combined petroleum ether extracts were washed with three 100-mL portions of 5% HCl, 200 mL of 5% sodium carbonate, and three 200-mL portions of water and dried. Removal of the petroleum ether by rotary evaporation followed by fractional distillation gave 155 g (96%) of **1**: bp 63–65 °C (1 mm) [lit.[27] bp 106–107 °C (18 mm)]; IR (neat) 5.75, 6.82, 6.95, 7.35, 7.79, 8.03, 8.37, 8.80, 9.83, 10.40, 10.51, 11.52, 12.00, 12.59 μm; NMR (CCl_4) δ 3.18 (12 H, s), 3.90 (6 H, s).

***cis*-2,5-Diacetoxy-2,5-dimethyl-3-hexene (2).** A solution of 60 g (0.27 mol) of **1**, 0.25 mL of synthetic quinoline, 0.52 g of 5% palladium on barium sulfate, and 250 mL of methanol was hydrogenated at room temperature for 3 h using a Paar hydrogenation apparatus. The hydrogen pressure was maintained at 30 psig. The catalyst was removed by filtration, the filtrate was added to 800 mL of cold water, and the resulting mixture was extracted with three 150-mL portions of 30–60 °C petroleum ether. The combined extracts were washed with 50 mL of 5% hydrochloric acid and 50 mL of water and then dried. Removal of the solvent by rotary evaporation followed by fractional distillation gave 51.4 g (85%) of **2**: bp 110–112 °C (13 mm) [lit.[25] bp 112 °C (14 mm)]; IR (neat) 5.75, 6.04, 6.78, 6.85, 6.95, 7.30, 7.95, 8.12, 8.40, 8.75, 9.75, 10.52 μm; NMR (CCl_4) δ 1.58 (12 H, s), 1.94 (6 H, s), 5.29 (2 H, s).

***trans*-2,5-Diacetoxy-2,5-dimethyl-3-hexene (3).** Using a literature procedure,[17] 20.5 g (0.14 mol) of 2,5-dimethylhex-3-yne-2,5-diol was reduced by lithium aluminum hydride to 14.1 g of crude product, which was shown by NMR analysis to be 63% *trans*-2,5-dimethyl-3-hexene-2,5-diol[28] and 37% reactant. The crude sample was acetylated by the same procedure used in the preparation of **1**. This crude product was separated by preparative GC to give a pure sample of **3**: mp 73–74 °C; IR (CCl_4) 5.75, 7.30, 8.00, 8.84, 9.75 μm; NMR (CCl_4) δ 1.48 (12 H, s), 1.92 (6 H, s), 5.84 (2 H, s).

Anal. Calcd: C, 63.14; H, 8.83. Found: C, 62.90; H, 8.75.

2,5-Dimethyl-2,5-diacetoxyhexane (4). Using the procedure described for the synthesis of **1**, 25 g (0.17 mol) of 2,5-dimethylhexane-2,5-diol, 150 mL of pyridine, and 38.4 g (0.38 mol) of acetic anhydride gave 34 g (87%) of **4**: bp 120–121 °C (20 mm) [lit.[29] bp 117–118 °C (19 mm)]; IR (neat) 5.75, 6.55, 6.85, 7.28, 7.90, 8.15, 8.96, 9.70 μm; NMR (CCl_4) δ 1.40 (12 H, s), 1.78 (4 H, s), 1.92 (6 H, s).

2,5-Dimethyl-2-hexene (6). To 0.5 g (0.0038 mol) of 2,5-dimethyl-2-hexanol was added 10 g of pyridine and 0.8 g of phosphorous oxychloride. The mixture was stirred at 25 °C for 12 h and then at 100 °C for 1.5 h, cooled, and poured into 4 g of ice. To the resulting mixture was added 100 mL of water, and the solution was extracted with three 20-mL portions of pentane. The combined pentane extracts were washed with two 25-mL portions of 5% hydrochloric acid and two 20-mL portions of saturated sodium bicarbonate and dried. The solvent was removed by rotary evaporation to give 0.2 g of crude product. NMR analysis indicated that the sample was 60% 2,5-dimethyl-1-hexene and 40% **6**.[30]

2,5-Dimethyl-2-acetoxy-4-hexene (5). The sample isolated from the hydrogenation of **1** gave NMR and IR data identical to that published by Bly.[31] The sample was further identified by its reduction to 2,5-dimethyl-4-hexen-2-ol.

2,5-Dimethyl-4-hexen-2-ol. A 2.34-g (0.0138 mol) sample of **5** was dissolved in 50 mL of anhydrous ether and slowly added to a stirred slurry of 1.60 g of lithium aluminum hydride in 50 mL of anhydrous ether. After the addition was complete, the mixture was refluxed for

Table II. Effect of Substrate/Catalyst Ratio[a]

1, mg	Catalyst, mg	Equiv of H_2	1/catalyst	Products, % 1	2	3	4	5	6	7	8
152.9	5.5	1.19	27.8	9.3	60.3	6.9	5.4	14.3	1.4	2.3	0
103.5	5.3	1.24	19.5	4.2	61.8	7.3	6.4	16.7	0.8	2.8	0
80.1	5.0	1.29	16.0	8.0	56.5	3.6	8.7	18.4	2.4	2.4	0
71.8	5.8	1.61	12.5	0.6	32.8	13.5	11.5	33.3	3.8	4.0	0
79.9	10.1	1.67	7.9	0	36.0	8.0	14.6	30.8	5.0	5.6	0
72.7	5.1	2.04	14.3	0	9.5	7.4	14.5	48.6	7.9	11.1	1.0
51.1	5.0	1.96	10.2	1.5	18.5	3.9	15.5	40.4	9.3	10.1	0.8
53.3	10.2	2.06	5.2	0	12.7	8.1	14.9	45.6	9.5	8.4	0.8

[a] All runs contained 30 mL of absolute ethanol as solvent and were run at 25 °C and 1 atm of hydrogen pressure.

30 min. To the cooled mixture was added dropwise enough 5% sodium hydroxide to discharge the gray color. The mixture was filtered and dried, and the ether was removed by rotary evaporation to give 1.31 g (74%) of 2,5-dimethyl-4-hexen-2-ol. The spectral data was identical with that reported by Crandall.[32]

2,5-Dimethyl-2-acetoxyhexane (7). Using the procedure described for the synthesis of **1**, 1.0 g (0.0077 mol) of 2,5-dimethyl-2-hexanol, 0.87 g (0.0085 mol) of acetic anhydride, and 30 mL of pyridine gave 1.2 g (89%) of **7**: IR (neat) 1735, 1462, 1381, 1255, 1220, 1160, 1140, 1118, 1085, 1020, 945 cm^{-1}; NMR (CCl_4) δ 0.90 (6 H, d, J = 6 Hz), 1.1–1.8 (5 H, m), 1.40 (6 H, s), 1.91 (3 H, s).

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Registry No.—**1**, 34106-07-5; **2**, 65149-96-4; **3**, 65149-97-5; **4**, 56323-20-7; **7**, 65149-98-6; 2,5-dimethylhex-3-yne-2,5-diol, 142-30-3; *trans*-2,5-dimethyl-3-hexene-2,5-diol, 927-81-1; 2,5-dimethylhexane-2,5-diol, 110-03-2; 2,5-dimethyl-2-hexanol, 3730-60-7.

References and Notes

(1) (a) Portions of this work were presented at the 10th Western Regional Meeting of the American Chemical Society, San Francisco, Calif., Oct 16–18, 1974. (b) National Science Foundation Undergraduate Research Participant. Summer 1975. (c) MBS Trainee.
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Asymmetric and Regioselective Hydrogenation of Piperitenone by Homogeneous Rhodium Complexes

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Piperitenone (**1**) has been hydrogenated with homogeneous rhodium catalysts containing chiral phosphine ligands. The major product, pulegone (**2**), has been obtained in up to 38% optical purity. Piperitone (**3**), menthone (**5**), and isomenthone (**6**) were the predominant minor products.

Following the initial report of Knowles and Sabacky,[1a] the use of homogeneous transition metal catalysts for asymmetric synthesis has grown tremendously.[1] In addition, the ability of homogeneous transition metal catalysts to effect selective transformation of functional groups[2] has led to a recognition of the potential for such catalysts to operate on organic molecules in a highly specific manner.

Piperitenone (**1**) offers a unique challenge in selective hydrogenation due to the presence of two different olefinic bonds and one ketonic bond. Hydrogenation of either one or more of these unsaturated sites leads to the structures **2–10**, whereas complete reduction leads to the four diasteromeric alcohols of the menthol series **11–14**.

In addition, piperitenone is prochiral and thus offers the possibility for asymmetric synthesis of pulegone (**2**) and piperitone (**3**). Achievement of chirality at C_1 of **2** is particularly advantageous because the hydrogen atom at C_1 is not labile. Thus, whatever degree of chirality is attained in conducting an asymmetric hydrogenation of **1** to **2** is locked in on further reduction. Pulegone of high optical purity is thus the cornerstone of a direct synthesis of optically active menthol (**11**) since the configuration and enantiomeric excess obtained at

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Table I. Hydrogenation of Piperitenone

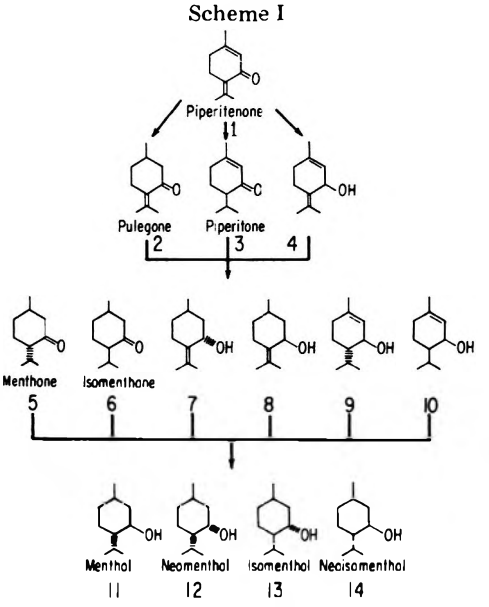
Run No.	Ligand[a]	Solvent	Temp, °C	Press, psig	Conversion, %	Time, h	Product selectivity[b] Pulegone, %	Piperitone, %	Menthones,[c] %	Minor peaks, %	Pulegone, % ee.
1	(+)-15	DMF[d]	30	180	96	18	74	4	22	<3	(−) 33
2	(+)-15	DMF	30	180	94	22	88	3	9	<3	(−) 33
3	(+)-15	DMF	40	180	74	20	92	3	5	<3	(−) 28
4	(+)-15	DMF	30	120	82	6	85	8	7	<3	(−) 27
5	(+)-15	DMF	30	120	88	19	89	4	7	<3	(−) 31
6	(+)-15	DMF	30	325	53	20	76	10	10	4 % menthols	(−) 20
7	(+)-15	DMA[d]	30	180	62	21	51	18	26	5	(−) 15
8	(+)-15	MeOH	30	180	86	2.5	59	26	15	<3	(−) 25
9	(+)-15	MeOH	30	180	84	3.0	68	21	11	<3	(−) 26
10	(+)-15	MeOH	40	180	50	4.0	78	16	6	<3	(−) 12
11	(+)-15	MeOH	30	120	72	3.0	61	30	9	<3	(−) 38
12	(+)-15	MeOH	30	120	48	4.0	71	23	6	<3	(−) 23
13	(+)-15	MeOH	40	120	37	6.5	74	21	5	<3	(−) 6
14	(+)-15	MeOH	30	60	NA[e]		64	25	11	<3	(−) 26
15	(+)-15	MeOH	30	60	62	6.0	68	24	8	<3	(−) 24
16	(−)-16	DMF	30	180	45	22	73	10	17	<3	(+) 2
17	(−)-21	DMF	100	180	32	20	47	25	6	22	(−) 2
18	(−)-21	DMF	30	180	44	20	62	25	13	<3	(−) 6
19	(+)-17	DMF	30	180	55	22	75	10	15	<3	(−) 28
20	(+)-17	DMF	30	120	42	21	67	14	9	10	(−) 31
21	(+)-18	DMF	30	180	18	22	51	25	12	12	(−) 11
22	19[g]	DMF	60	180	8	22	48	38	9	5	Too little
23	20[g]	DMF	60	180	28	20	77	10	10	3	(−) 19
24	(−)-21	MeOH	30	180	76	18	19	47	19	15[f]	(−) 7
25	(+)-22	MeOH	40	180	—	6.5	Very little reaction				Too little
26	(+)-23	MeOH	30	120	52	3.0	25	40	32	3	(−) 2

[a] See list of ligands. All added as $[Rh(diolefin)L_2]BF_4$ complex except run 23 in which we added 2L/Rh as $[Rh(NBD)Cl]_2$. [b] All based on area percent by GC on Carbowax 20 M or Carbowax 400. In cases where the minor impurities constituted <3% of the peak area, the major peaks were normalized to 100%. [c] Total menthone and isomenthone. [d] DMF = dimethylformamide; DMA = dimethylacetamide. [e] NA = not available. [f] 7% menthols, 8% others. [g] Sign of rotation not identified.

the pulegone stage is fully retained on further reduction.[3]

The established ability of homogeneous rhodium catalysts to effect selective hydrogenations as well as asymmetric hydrogenations provided the basis for our decision to investigate the utility of these catalysts first. It had been previously established by Schrock and Osborn[2c] that rhodium catalysts need approximately 1% water in the system to reduce ketones whereas olefin reduction can be conducted in the absence of water, so that we expected the ketonic portion of 1 to survive hydrogenation in anhydrous solvents. Also, it is well known that a variety of rhodium-catalyzed reactions proceed more rapidly on unsubstituted olefins than on highly substituted olefins.[2b,d] Thus, we had good grounds for expecting to achieve our objective of the formation of a predominance of **2** over **3**.

Scheme I



Results

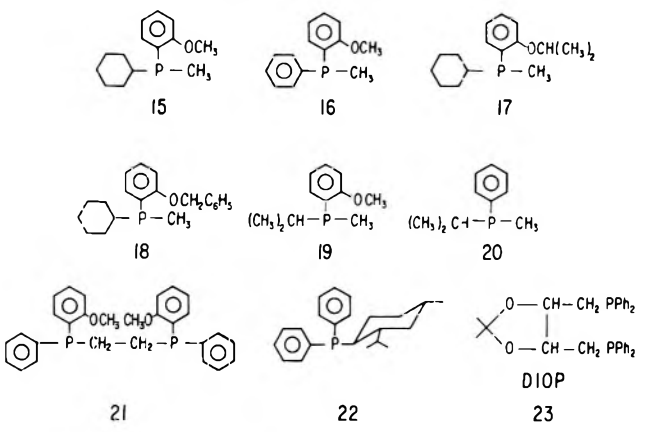
Our expections concerning the stability of the ketone bond were generally met as the amount of diastereomeric menthols or unidentified by-products was usually less than 3%.[4] The selectivity toward **2** vs. **3** normally resulted in an excess of **2** as expected (see Table I), but the ratio of **2** to **3** was quite dependent on reaction conditions. However, in methanol, the use of bidentate ligands **21** and **23** resulted in a predominance of product **3** (runs 24 and 26).

The majority of our runs were performed with the chiral ligand **15**, cyclohexylanisylmethylphosphine. In DMF, fairly long times (18–22 h) were usually required to achieve 70–96% conversion. High selectivity to pulegone (85–92%) could be obtained easily (runs 2–4) and the optical purity of the pulegone often reached 27–33% (runs 1–5). The use of DMA as solvent produced a drastic increase in piperitone content accompanied by a loss of pulegone optical purity (run 7 vs. run 2).

In methanol, the hydrogenations proceeded much more rapidly but the amount of piperitone produced increased five- to tenfold. The pulegone optical purity did not vary over a great range when the hydrogenations were run in DMF but did so to a greater extent in methanol. The highest optical purity, 38%, was obtained in methanol when the hydrogenation was run at 80 °C and 120 psi H_2 (run 11).

The use of a variety of other ligands was explored in DMF (ligands 16–21, runs 16–23) and in methanol (ligands 21–23, runs 24–26). In general, these offered pulegone of much lower

optical purity and with less selectivity than ligand **15**. Ligand **17**, the isopropyl ether analogue of ligand **15**, gave pulegone of optical purity comparable to that with **15** but the selectivity to pulegone was significantly reduced (runs 2 and 5 vs. runs 19 and 20). Of great interest was the result with the bidentate ligands **21**[5] and **23** in that piperitone was the predominant product with these ligands in methanol whereas pulegone had predominated in DMF. This may be one of the rare instances in homogeneous catalysis in which hydrogenation of a more-substituted double bond takes precedence over hydrogenation of a less-substituted double bond.



One interesting sidelight to this work concerned the composition of the menthones in regards to the ratio of menthone to isomenthone. The equilibrium ratio is well known to be ca. 70:30 in favor of menthone[6] and relatively pure menthone can be produced by oxidation of menthol[7] or equilibrative distillation of a menthone–isomenthone mixture.[8] We found that reduction of piperitenone in our catalyst system afforded a predominance of isomenthone except for run 17 at 100 °C and run 23 which contained chloride. In some cases, this predominance was only very slight but in methanol it often approached 80% of the mixture with ligand **15**. Run 9 afforded 82% isomenthone.

Experimental Section

All hydrogenations were carried out in glass Fisher-Porter aerosol compatibility tubes attached to a regulated gas manifold. Hydrogen was supplied from a small high-pressure reservoir through a regulator to maintain constant reactor pressure. Solvents were commercially available, nominally dry materials used without further purification. Piperitenone was initially prepared by the procedure of Beereboom[9] and later by that of ourselves.[10] Ligands chiral at phosphorus were supplied by W. S. Knowles,[11] generally in the form of the anionic complex.[12] Ligands **22** and **23** were purchased from Strem Chemicals. Product analyses were performed by GC on either Carbowax 20 M or Carbowax 400 columns. GC peak comparison followed by preparative GC and NMR was used for the determination of the pulegone, piperitone, and menthones peaks. Pulegone for determination of optical purity was obtained by preparative GC on a large FFAP column.

Run 11. Into a F-P tube containing a magnetic stirring bar were placed Rh(COD)(cyclohexylanisylmethylphosphine)$_2$BF$_4$ (44.8 mg, 0.06 mmol), methanol (20 mL), and piperitenone (4.5 g, 30 mmol). The mixture was bubbled with N_2 and the tube was attached to the gas manifold. Stirring was commenced and the whole apparatus was flushed four times with 120 psig H_2. The mixture was then pressurized to 120 psig H_2 and an 80 °C oil bath was brought up to surround the reaction tube. Gas uptake proceeded for 3 h at which time the rate of uptake had slowed to $\frac{1}{10}$ its original value. The oil bath was removed and the cooled system was vented. The mixture was concentrated on a rotary evaporatory to afford reaction concentrate for GC analysis.

Registry No.—**1**, 491-09-8; **2**, 89-82-7; **3**, 89-81-6; (+)-**15**, 35144-03-7; (−)-**16**, 65337-14-6; (+)-**17**, 65253-51-2; (+)-**18**, 65253-52-3; **19**, 65253-53-4; **20**, 36050-92-7; (−)-**21**, 55739-58-7; (+)-**22**, 65392-08-7; (+)-**23**, 37002-48-5; [Rh(NBD)Cl]$_2$, 12257-42-0; Rh, 7440-16-6; Rh(COD)(cyclohexylanisylmethylphosphine)$_2$BF$_4$, 65375-70-4.

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(10) The condersation of mesityl oxide with 4-hydroxy-2-butanone, originally developed by Friederang and Pasedach,[13] has several advantages over Beereboom's reaction of mesityl oxide with methyl vinyl ketone.[9] Neither reaction, however, affords clean piperitone without employing Naves' bisulfite extraction procedure. We have now found that pure piperitenone, free of codistilling by-products, can be synthesized directly in 57–62% yield by reacting mesityl oxide with 4-hydroxy-2-butanone under a variation of Friederang and Pasedach's conditions. Maximum purity is obtained by running the reaction at 95 °C and keeping the 4-hydroxy-2-butanone concentration as low as possible, preferably by adding it through a syringe drive set for 2.5 h total delivery time.
(11) We thank Dr. Knowles and his colleagues for a generous supply of the cationic complexes of these ligands.
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Alkylmetal Asymmetric Reduction. 9.[1] Asymmetric Reduction of Alkyl Phenyl Ketones by Sterically Hindered Chiral Organoaluminum Compounds

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Optically active aliphatic organoaluminum compounds, containing groups of different steric requirements on the β-chiral carbon atom, have been prepared via an alkyl exchange reaction from the corresponding trialkylboranes. The organoaluminum compounds were allowed to react with alkyl phenyl ketones to yield optically active alkylphenylcarbinols. The extent of asymmetric reduction and the absolute configuration of the predominant enantiomeric carbinol were found to depend both on the structure of the alkyl substituent on the aluminum atom and on the experimental conditions adopted. The stereoselectivity of the reduction process is discussed and rationalized in terms of the previously suggested stereochemical approach.

Recently we have investigated the reduction of alkyl phenyl ketones by optically active aliphatic Grignard reagents containing an isopropyl or a *tert*-butyl group on the chiral carbon atom.[2] The data obtained have shown an anomalous trend in the asymmetric reduction of ketones by these sterically hindered Grignard reagents.[2] In fact, simple considerations of conformational analysis do not correctly predict the absolute configuration of the predominant enantiomeric carbinol in all the cases investigated, although the general trend may be rationalized in terms of the effective sizes of the groups being compressed in the transition states.

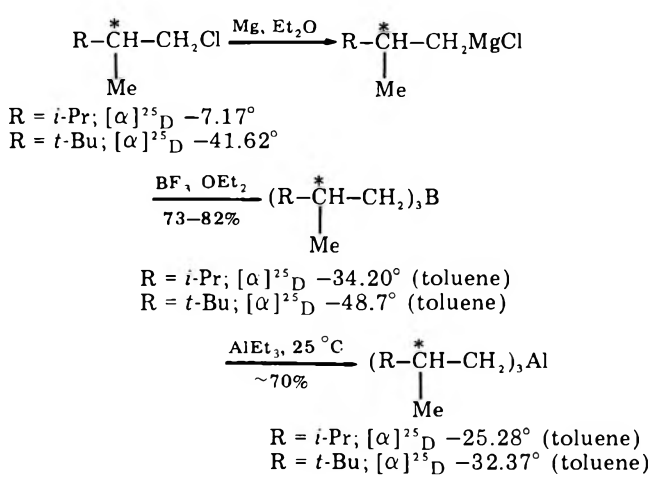
Therefore, taking into account the ability of chiral organoaluminum compounds to reduce carbonyl compounds asymmetrically,[3,4] we have undertaken this research to further check the stereochemical picture previously proposed[3-5] by using tris[(*R*)-2,3-dimethylbutyl]aluminum [(*R*)Al2,3DMB] and tris[(*R*)-2,3,3-trimethylbutyl]aluminum [(*R*)-Al2,3,3TMB].

Results and Discussion

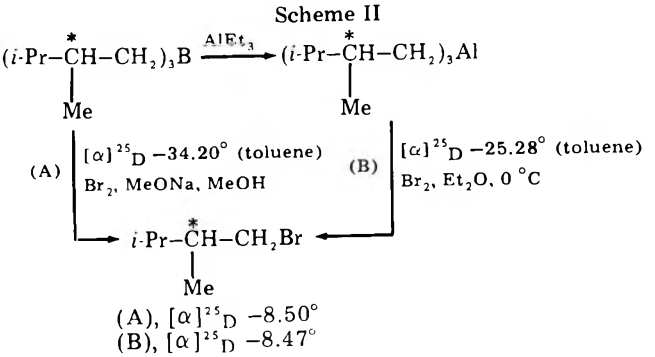
Synthesis of the Organometallic Compounds. The preparation of the optically active trialkylaluminum compounds was carried out via the corresponding trialkylboranes (Scheme I). Tris[(*S*)-2,3-dimethylbutyl]boron [(*S*)B2,3DMB] and tris[(*S*)-2,3,3-trimethylbutyl]boron [(*S*)B2,3,3TMB] were obtained by the reaction of (*R*)-2,3-dimethylbutyl- and (*R*)-2,3,3-trimethylbutylmagnesium chloride, respectively, with a slight excess of boron trifluoride diethyl etherate.[6] The boron compounds were isolated in a good yield by simple distillation at reduced pressure and characterized through quantitative determination of the boron.[6]

The trialkylboranes were then converted into the corresponding trialkylaluminum compounds by an alkyl exchange reaction with $AlEt_3$ (Scheme I), according to a known procedure.[7] Purification of the aluminum compounds was achieved by molecular distillation at 10^{-5} mmHg since the usual distillative procedure at 0.05 mmHg causes the formation of dialkylaluminum monohydride and olefin. The trialkylalanes were characterized through quantitative determination of the aluminum[8] and through cryoscopic molecular weight determinations.

Scheme I



Scheme II



The minimum optical purity of the organometallic compounds was evaluated by their stereospecific conversion into optically active organic products. So (*S*)B2,3DMB and (*R*)-Al2,3DMB were related to (*R*)-1-bromo-2,3-dimethylbutane[9] by reaction with bromine and sodium methoxide in methanol solution[10] and with bromine in diethyl ether at 0 °C,[11] respectively (Scheme II). Based on the maximum rotatory power of the alkyl bromide,[9b-d,12] both (*S*)B2,3DMB and (*R*)-Al2,3DMB were assigned the same optical purity as that of the starting alkyl chloride (Scheme I). Accordingly, a sample of (*R*)Al2,3,3TMB yielded (*R*)-1-bromo-2,3,3-trimethylbutane (Scheme III). In order to determine the minimum optical purity of this product, a sample of (*R*)-1-bromo-2,3,3-trimethylbutane, $[\alpha]^{25}_D$ −31.83° [from (*R*)-2,3,3-trimethyl-1-butanol, $[\alpha]^{25}_D$ −26.22° (ethanol)[13]], was converted into (*S*)-3,4,4-trimethylpentanoic acid, $[\alpha]^{25}_D$ −13.58° (ethanol), optical purity 65.9%,[2] through the corresponding Grignard reagent and successive treatment with carbon dioxide. Un-

Scheme III

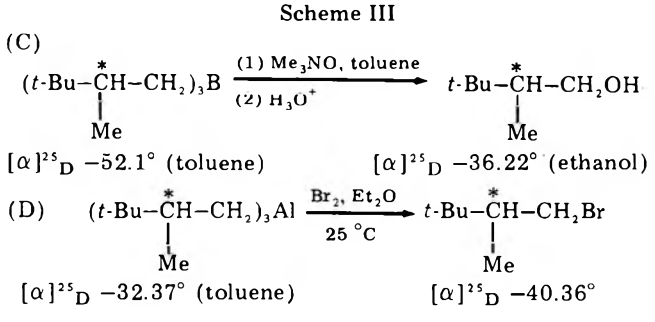


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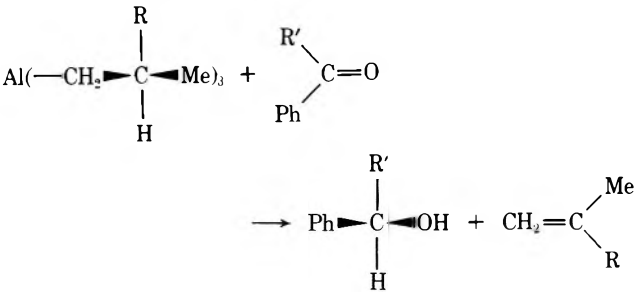
Table I. Asymmetric Reduction of Phenyl Alkyl Ketones by Optically Active Organoaluminum Compounds



R	R′	Temp, °C	Asymmetric reduction, %	$\Delta\Delta G^{\ddagger}$,[a] cal/mol
Et[b]	Et	0	13.2	−144
	i-Pr	0	44.3	−515
	t-Bu	0	29.9	−335
i-Pr	Et	0	22.2	−245
	i-Pr	0	56.1	−688
	t-Bu	0	25.8	−286
t-Bu	Et	0	23.0	−254
		68.7	32.2	−453
	i-Pr	0	19.9	−219
		36	57.4	−802
		68.7	53.1	−803
		98.4	44.4	−703
	t-Bu	0	[12.8][c]	+139
		36	0.0	
		68.7	13.7	−187

[a] Calculated from $\Delta\Delta G^{\ddagger} = -RT \ln (k_R/k_S) = -RT \ln([R]/[S]) = -RT \ln [(1 + a)/(1 - a)]$, where a = asymmetric reduction. [b] See ref 5. [c] Brackets indicate opposite configuration.

fortunately the bromination of (*S*)B2,3,3TMB, according to the above procedure,[10] gives rise, in low yield, to the corresponding alkyl bromide together with considerable amounts of byproducts. Therefore, (*S*)B2,3,3TMB was converted into (*R*)-2,3,3-trimethyl-1-butanol[13] by reaction with trimethylamine oxide in boiling toluene[14] (Scheme III). Also in these cases the optical purity of the products of conversion of the organometallic compounds was the same as that of the starting alkyl chloride. The overall results therefore confirm the stereospecificity of the schemes of sequences adopted, and in particular, that of the alkyl exchange reaction.[7]

Asymmetric Reduction of Alkyl Phenyl Ketones. The asymmetric reductions have been carried out in hydrocarbon solvents, following previously published procedures;[3-5] the results are summarized in Table I. Analogous to what has been observed for the reduction of ketones by tris[(*S*)-2-methylbutyl]aluminum [(*S*)Al2MB],[3] (*R*)Al2,3DMB and (*R*)-Al2,3,3TMB react with alkyl phenyl ketones to give essentially the corresponding carbinol. The reactions are very fast in the case of Al2,3DMB, the reduction being practically complete within 30 min, but the reduction rate drops using Al2,3,3TMB, and the reaction requires more than 1 h at 0 °C. In all the cases investigated, the recovered carbinols were optically active and had the absolute *R* configuration, with the exception of the reduction product from phenyl *tert*-butyl ketone by (*R*)-Al2,3,3TMB at 0 °C (Table I).

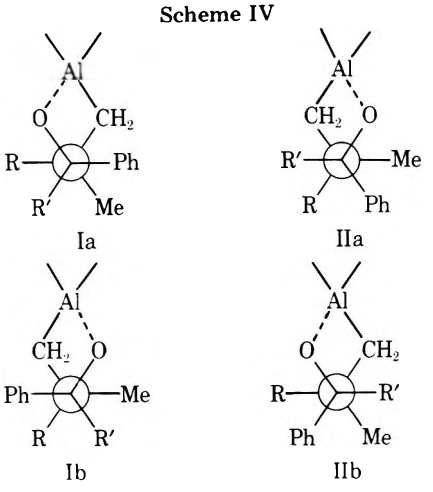
By comparing these results with those previously reported,[3,5] we can observe that the stereoselectivity of reduction depends upon the structure of the alkyl phenyl ketone employed and on that of the alkyl substituent on the chiral carbon atom in the position β to the aluminum atom. In particular, at 0 °C, on increasing the bulkiness of the *R* alkyl group of the aluminum compound in the order Et < *i*-Pr < *t*-Bu, the extent of asymmetric reduction of ethyl phenyl ketone increases while that of *tert*-butyl phenyl ketone decreases. Regarding the reduction of isopropyl phenyl ketone at 0 °C, the highest value of stereoselectivity is encountered when the reducing agent is (*R*)Al2,3DMB (Table I). The trend of asymmetric reduction of phenyl alkyl ketones by (*R*)-Al2,3DMB is, however, similar to that observed in the reduction of the same series of ketones by (*S*)Al2MB,[3] while the stereoselectivity of the reduction at 0 °C by (*R*)Al2,3,3TMB decreases in the order of Et > *i*-Pr > *t*-Bu. Contrary to what has been observed for the reduction of alkyl phenyl ketones by (*S*)Al2MB,[5] in the case of (*R*)Al2,3,3TMB an increase of reaction temperature generally results in an increase of stereoselectivity of the reduction. It is noteworthy that the reduction of *tert*-butyl phenyl ketone by (*R*)Al2,3,3TMB at 69 °C occurs with a reversal of the stereochemistry at 0 °C (Table I).

On the basis of our previous considerations,[3-5] the reduction of ketones by chiral organoaluminum compounds is assumed to proceed via diastereomeric cyclic transition states, not essentially planar but able to minimize their mutual steric and electronic interactions by assuming more of a chair-like conformation.[15] Thus, we can now consider four transition-state conformations, viewed as Newman-type projections along the C - - - H - - - C axis (Scheme IV). Under the assumption that electronic interactions play the main role in stabilizing the transition states, the conformations IIa and IIb must have the highest energies. Therefore the extent of stereoselectivity should depend on the balance between the conformations Ia and Ib in relation to the different ability of the groups to minimize their steric compression. Since the conformation Ia is more favored than Ib for steric requirements, the carbinol from asymmetric induction must have the absolute *R* configuration. According to this picture, when R or R′ increase in bulk, a buttressing effect will operate in both the conformations to separate R and R′. So the conformation Ib is further destabilized, as the phenyl and R groups are pushed together. Consequently, the extent of stereoselectivity might rise with increasing bulk of the alkyl groups both in the reagent and in the substrate.

However, this stereochemical approach does not fit all the results obtained. In fact, when a *tert*-butyl group is present either in the reagent or in the substrate, the stereoselectivity of the reduction drops, and when the *tert*-butyl phenyl ketone is reduced at 0 °C by (*R*)Al2,3,3TMB, the carbinol recovered has the absolute configuration opposite to the predicted one (Table I).

In this respect a helpful suggestion is to consider that as the alkyl groups both in the organoaluminum compound and in the ketone increase in bulk, the conformational mobility of the phenyl group decreases, its size changing formally.[3,5] On this basis the anomalous results (Table I), and in particular those relating to the reduction by (*R*)Al2,3,3TMB, may be due

Scheme IV



to a combined effect of noncoplanarity and consequent change in steric and electronic interactions of the phenyl group. If the electronic interactions cannot contribute any more to stabilize the transition-state conformations, it is evident that conformation IIb, leading to (*S*)-carbinol, may become the most stable one for steric reasons, and its contribution to the stereoselectivity of the reduction will become more important the more conformationally rigid the transition state becomes. In this manner we can rationalize both the decrease in stereoselectivity observed in the reduction of *tert*-butyl phenyl ketone as well as the formation of the wrong enantiomer when the same ketone is reduced by (*R*)Al2,3,3TMB at 0 °C.

An increase of the reaction temperature will tend to reduce the conformational rigidity of the groups and thus permit the electronic interactions to again stabilize the conformation Ia, leading to the (*R*)-carbinol. So one can predict that increasing the reaction temperature will result in an increase of the extent of asymmetric reduction. Indeed the results obtained at different temperatures (Table I) are consistent with this last hypothesis,[16] confirming the stereochemical approach previously proposed.[3-5] In this context, it is interesting to note that the reduction of *tert*-butyl phenyl ketone by (*R*)-Al2,3,3TMB at 69 °C leads to the formation of the predicted *R* enantiomer.

However, it is noteworthy that the free-energy differences, $\Delta\Delta G^{\ddagger}$, involved are generally relatively small, indicating subtle differences of the group interactions in the transition states, so that even minor changes in the experimental conditions may result in different stereochemical courses. Therefore, it appears that only a more accurate knowledge of other variables, e.g., reaction rate, solvent effect, etc., will clarify the actual nature of the transition-state models for asymmetric hydride transfer.

Experimental Section

Boiling points are uncorrected. GLC analyses (200 × 0.29 cm column packed with 8% Carbowax + 2% KOH on 80–100 mesh Chromosorb W) were performed on a Perkin–Elmer F 30A instrument with flame ionization detectors and nitrogen as a carrier gas, while preparative GLC was carried out on a Perkin-Elmer F 21 chromatograph. Optical rotations were measured with a Perkin-Elmer 142 photopolarimeter and refer to pure liquids unless otherwise stated.

The solvents and commercial reagents were distilled and dried by conventional methods before use. The ketones employed were obtained by purification of commercial products; *tert*-butyl phenyl ketone was prepared according to the procedure already mentioned.[3] (*R*)-1-Chloro-2,3-dimethyl- and (*R*)-1-chloro-2,3,3-trimethylbutane were synthesized from the corresponding optically active 1-butanols by treatment with thionyl chloride in pyridine.[2] All the organoaluminum compounds were stored under nitrogen in sealed glass vials in weighed amounts, and all the reactions were carried out in a dry purified nitrogen atmosphere.

Tris[(*S*)-2,3-dimethylbutyl]boron [(*S*)B2,3DMB]. Freshly distilled boron trifluoride etherate (40.8 g, 0.290 mol) was added dropwise at room temperature to an ethereal solution of the Grignard reagent from (*R*)-1-chloro-2,3-dimethylbutane (104 g, 0.86 mol), $[\alpha]^{25}_{D}$ −7.17°. The reaction mixture was refluxed (4 h), cautiously hydrolyzed with dilute sulfuric acid, and extracted with ether. The solvent was evaporated under reduced pressure, and the crude product was twice distilled (53.6 g, 73% yield): bp 65.5 °C (0.1 mmHg); $[\alpha]^{25}_{D}$ −34.20° (*c* 2.99, toluene).

Anal.[6] Calcd for $C_{18}H_{39}B$: B, 4.05. Found: B, 4.19.

Tris[(*S*)-2,3,3-trimethylbutyl]boron [(*S*)B2,3,3TMB]. By the same general procedure, (*R*)-1-chloro-2,3,3-trimethylbutane, $[\alpha]^{25}_{D}$ −41.62°, was converted (73% yield) into (*S*)B2,3,3TMB: bp 80 °C (0.005 mmHg); $[\alpha]^{25}_{D}$ −48.7° (*c* 9.32, toluene).[17]

Anal.[6] Calcd for $C_{21}H_{45}B$: B, 3.50. Found: B, 3.52.

Tris[(*R*)-2,3-dimethylbutyl]aluminum [(*R*)Al2,3DMB]. To (*S*)B2,3DMB (53.6 g, 0.201 mol), $[\alpha]^{25}_{D}$ −34.20° (toluene), was added triethylaluminum (22.9 g, 0.201 mol) at room temperature. After 2 h, all of the volatile products were removed from the mixture by prolonged evacuation (48 h, 0.5 mmHg) with stirring at 25 °C and the residue was transferred under nitrogen into a molecular distillation apparatus. Pure (*R*)Al2,3DMB was recovered at 4 × 10^{-5} mmHg (oil bath temperature, 70°C; 66% yield), $[\alpha]^{25}_{D}$ −25.28° (*c* 4.03, toluene).

Anal.[8] Calcd for $C_{18}H_{39}Al$: Al, 9.50; mol wt, 282.4. Found: Al, 9.52; mol wt (cryoscopic determination in benzene), 282.

Tris[(*R*)-2,3,3-trimethylbutyl]aluminum [(*R*)Al2,3,3TMB]. By an analogous procedure, (*S*)B2,3,3TMB, $[\alpha]^{25}_{D}$ −48.7° (toluene), yielded (75%) (*R*)Al2,3,3TMB, $[\alpha]^{25}_{D}$ −32.37° (*c* 5.94, toluene), after molecular distillation (5 × 10^{-5} mmHg; oil bath temperature, 75 °C).

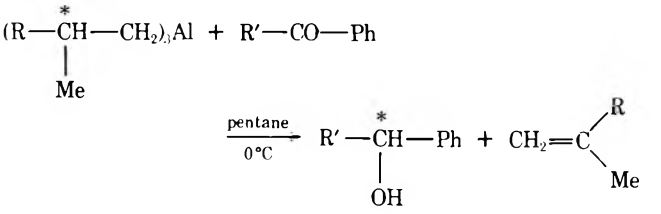
Anal.[8] Calcd for $C_{21}H_{45}Al$: Al, 8.31; mol wt, 324.5. Found: Al, 8.33; mol wt (cryoscopic determination in benzene), 327.

(*R*)-1-Bromo-2,3-dimethylbutane. A. From (*S*)B2,3DMB. An ice-cooled solution of (*S*)B2,3DMB (5.97 g, 22.4 mmol), $[\alpha]^{25}_{D}$ −34.20° (toluene), in 30 mL of dry THF was treated with bromine (14.3 g, 89.6 mmol), followed by a dropwise addition of a 4.16-M solution (32 mL) of sodium methoxide in anhydrous methanol at such a rate that the temperature of the reaction mixture never rose above 5 °C. The mixture was allowed to warm to room temperature and was worked up as previously described.[10] Distillation gave (*R*)-1-bromo-2,3-dimethylbutane (pure by GLC analysis) (7.7 g, 69.6% yield): bp 97 °C (165 mmHg); n^{25}_{D} 1.4486; $[\alpha]^{25}_{D}$ −8.50° (lit.[9b] bp 140 °C; d^{25}_{4} 1.187).

B. From (*R*)Al2,3DMB. Bromine (6.14 g, 38.4 mmol) was added dropwise at −25 °C to a solution of (*R*)Al2,3DMB (3.62 g, 12.8 mmol), $[\alpha]^{25}_{D}$ −25.28° (toluene), in ether (40 mL). The reaction mixture was kept at 25 °C (1 h), hydrolyzed with dilute sulfuric acid, and extracted with ether. Careful distillation gave pure (*R*)-1-bromo-2,3-dimethylbutane (3.6 g, 57% yield): n^{25}_{D} 1.4486; $[\alpha]^{25}_{D}$ −8.47°.

(*R*)-1-Bromo-2,3,3-trimethylbutane. A. From (*R*)-2,3,3-Trimethyl-1-butanol. A sample of (*R*)-2,3,3-trimethyl-1-butanol (30 g, 0.26 mol), $[\alpha]^{25}_{D}$ −26.22° (*c* 2.41, ethanol),[13] in pyridine (7.3 mL) was treated at 0 °C with phosphorus tribromide (28 g, 0.10 mol), and the reaction mixture was kept at 0 °C for 3 h. The crude bromide was distilled at reduced pressure (20 mmHg), diluted with hexane, and treated with concentrated sulfuric acid. The organic layer was washed with water and dried (Na_2SO_4). Distillation gave (*R*)-1-bromo-

Table II. Experimental Reduction Data



Run	R	R′	Carbinol: Conversion,[a] %	Carbinol: $[\alpha]^{25}_{D}$ (*c*, ether),[b] deg
1[c]	*i*-Pr	Et	87	+4.56 (neat)
2[c]			89	+8.36 (6.64)
3[c]		*i*-Pr	96	+19.52 (8.29)
4[c]			89	+19.24 (4.77)
5[c]		*t*-Bu	98	+6.67 (8.79)
6[c]			99	+6.87 (7.10)
7[d]	*t*-Bu	Et	63	+5.26 (neat)
8[d]			75	+5.46 (neat)
9[e]		*i*-Pr	90	+5.85 (6.90)
10[d]			70	+7.98 (9.06)
11[d]		*t*-Bu	99	−3.74 (7.91)
12[d]			95	−3.76 (8.05)
13[f,g]		*i*-Pr	97	+22.41 (8.08)
14[d,g]		*t*-Bu	99	+0.94 (8.74)
15[d,g]			99	−1.21 (8.52)
16[f,h]		Et	92	+7.59 (neat)
17[f,h]		*i*-Pr	96	+20.35 (10.27)
18[d,h]		*t*-Bu	95	+4.10 (8.22)
19[d,h]			95	+4.06 (7.85)
20[f,i]		*i*-Pr	93	+17.36 (9.45)

[a] Based on GLC analyses of the crude products. [b] See ref 2. [c] (*R*)Al2,3DMB, $[\alpha]^{25}_{D}$ −25.28° (toluene). [d] (*R*)Al2,3,3TMB, $[\alpha]^{25}_{D}$ −32.37° (toluene). [e] (*R*)Al2,3,3TMB, $[\alpha]^{25}_{D}$ −24.48° (toluene). [f] (*R*)Al2,3,3TMB, $[\alpha]^{25}_{D}$ −32.66° (toluene). [g] In pentane at 36 °C. [h] In hexane at 68.7 °c. [i] In heptane at 98.4 °C.

2,3,3-trimethylbutane (46% yield), which was further purified by preparative GLC (20% Carbowax 20M, 100 °C): bp 82 °C (60 mmHg); n^{25}_D 1.4545; d^{25}_4 1.1545; $[\alpha]^{25}_D$ −31.83°.

In order to determine its optical purity, (*R*)-1-bromo-2,3,3-trimethylbutane (8.7 g, 48.3 mmol) was converted into the corresponding Grignard reagent, which was then carboxylated to yield 42% of (*S*)-3,4,4-trimethylpentanoic acid: bp 126 °C (18 mmHg); n^{25}_D 1.4312; $[\alpha]^{25}_D$ −13.58° (*c* 3.84, ethanol).[2]

B. From (*R*)Al2,3,3TMB. An ethereal solution of (*R*)Al2,3,3TMB (2.0 g, 61.6 mmol), $[\alpha]^{25}_D$ −32.37° (toluene), was treated at room temperature with bromine (3.28 g, 20.5 mmol), and the reaction mixture was worked up as described above. After preparative GLC (20% Carbowax 20M, 100 °C), a sample of (*R*)-1-bromo-2,3,3-trimethylbutane, n^{25}_D 1.4545, $[\alpha]^{25}_D$ −40.36°, was recovered.

(*R*)-2,3,3-Trimethyl-1-butanol from (*S*)B2,3,3TMB. A solution of (*S*)B2,3,3TMB (3.5 g, 11.3 mmol), $[\alpha]^{25}_D$ −52.1° (c 6.08, toluene), in toluene (40 mL) was dropped into a boiling suspension of trimethylamine oxide (2.6 g, 34.4 mmol) in toluene (13 mL), and the reaction mixture was refluxed for 1 h. After removal of the solvent, the residue was treated with dilute sulfuric acid and extracted with ether. Distillation gave (*R*)-2,3,3-trimethyl-1-butanol (1.9 g, 50% yield), which was purified by preparative GLC (20% Carbowax 20M, 100 °C), $[\alpha]^{25}_D$ −33.22° (*c* 3.54, ethanol).[13]

Asymmetric Reductions of Alkyl Phenyl Ketones. A. By (*R*)Al2,3DMB in Pentane at 0 °C (runs 1–6). The following procedure (run 3, Table II) is representative of all the experiments. Isopropyl phenyl ketone (1.57 g, 10.6 mmol) in anhydrous pentane (10 mL) was added rapidly at 0 °C to a pentane solution (20 mL) of (*R*)-Al2,3DMB (3.15 g, 11.2 mmol), $[\alpha]^{25}_D$ −25.28° (toluene), in a flame-dried two-neck 100-mL flask fitted with a reflux condenser, a dropping funnel, and a magnetic stirrer. A yellow–orange coloration developed immediately and faded slowly. After 2 h the resulting mixture was cautiously hydrolyzed with dilute sulfuric acid and the organic products were extracted with purified ether. GLC analysis of the ether layer showed the presence of unreacted ketone (4%). Preparative GLC purification (8% Carbowax 20M + 2% KOH, 160 °C) afforded isopropyl phenyl carbinol: bp 104 °C (18 mmHg); n^{25}_D 1.5114; $[\alpha]^{25}_D$ +19.52° (c 8.29, ether).

B. By (*R*)Al2,3,3TMB in Pentane at 0 °C (runs 7–12). In a typical run, to an ice-cooled solution of (*R*)Al2,3,3TMB (2.83 g, 8.7 mmol), $[\alpha]^{25}_D$ −32.37° (toluene), in pentane (20 mL) was added rapidly *tert*-butyl phenyl ketone (1.34 g, 8.3 mmol) in pentane (10 mL). After 2 h at 0 °C the resulting mixture was allowed to warm to room temperature (10 min) and then hydrolyzed and worked up as above. By preparative GLC, *tert*-butylphenylcarbinol, bp 115 °C (21 mmHg), $[\alpha]^{25}_D$ −3.74° (c 7.91, ether), was recovered.

C. By (*R*)Al2,3,3TMB in Pentane at 36 °C (runs 13–15). In a representative run, a solution of *tert*-butyl phenyl ketone (1.91 g, 11.8 mmol) in pentane (10 mL) was placed in an addition funnel and (*R*)Al2,3,3TMB (4.04 g, 12.5 mmol), $[\alpha]^{25}_D$ −32.37° (toluene), was placed in a second addition funnel. The ketone and trialkylaluminum were added simultaneously to boiling pentane (20 mL) at a rate such that reflux was always maintained. After 1 h, the reaction mixture was hydrolyzed and worked up as previously described. By preparative GLC, *tert*-butylphenylcarbinol, $[\alpha]^{25}_D$ −1.21° (*c* 8.52, ether), was obtained.

Runs 16–19 and 20 (Table II) were carried out using the same procedure at 68.7 and 98.4 °C in boiling hexane and heptane, respectively.

Registry No.—(*S*)Al2MB, 4023-25-0; (*R*)Al2,3DMB, 65337-63-5; (*R*)Al2,3,3TMB, 65337-64-6; 1-phenyl-1-propanone, 93-55-0; 2-methyl-1-phenyl-1-propanone, 611-70-1; 2,2-dimethyl-1-phenyl-1-propanone, 938-16-9; (*R*)-α-ethylbenzenemethanol, 1565-74-8; (*R*)-α-(1-methylethyl)benzenemethanol, 14898-86-3; (*R*)-α(1,1-dimethylethyl)benzenemethanol, 23439-91-0; (*S*)-α(1,1-dimethylethyl)benzenemethanol, 24867-90-1; (*S*)B2,3DMB, 65337-61-3; boron trifluoride etherate, 353-42-4; (*R*)-1-chloro-2,3-dimethylbutane, 20205-13-4; (*S*)B2,3,3TMB, 65337-62-4; (*R*)-1-chloro-2,3,3-trimethylbutane, 16726-89-9; triethylaluminum, 97-93-8; (*R*)-1-bromo-2,3-dimethylbutane, 15019-28-0; (*R*)-1-bromo-2,3,3-trimethylbutane, 64001-89-4; (*S*)-3,4,4-trimethylpentanoic acid, 64043-89-6; (*R*)-2,3,3-trimethyl-1-butanol, 13332-16-6.

References and Notes

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(10) H. C. Brown and C. F. Lane, *J. Am. Chem. Soc.*, **92**, 6660 (1970).
(11) The stereospecificity of the procedure[10] was previously checked by converting a sample of tris[(*R*)-2-methylbutyl]boron, optical purity 96%,[6] into (*S*)-1-bromo-2-methylbutane (90% yield), optical purity 96%: P. Salvadori, L. Lardicci, and M. Stagi, *Gazz. Chim. Ital.*, **98**, 1400 (1968). Analogously, tris[(*S*)-2-methylbutyl]aluminum, optical purity 95.8%,[3] by bromination at 0 °C yielded (*R*)-1-bromo-2-methylbutane (64%), optical purity 95.6%.
(12) The maximum rotatory power reported, $[\alpha]^{25}_D$ 18.5°,[9a] is to be considered erroneous; in fact, a sample of the bromide, $[\alpha]^{25}_D$ −7.00°, through carboxylation of the corresponding Grignard reagent yielded (*R*)-3,4-dimethylpentanoic acid, $[\alpha]^{25}_D$ −7.38°, optical purity 59.8%: L. Lardicci, R. Rossi, S. Pucci, M. Aglietto, C. Botteghi, and P. Pino, *Chim. Ind. (Milan)*, **50**, 227 (1968). This result is in a good agreement with those of the sequences reported by other authors.[9b-d]
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(16) The decrease of stereoselectivity of the reduction of isopropyl phenyl ketone by (*R*)Al2,3,3TMB from 36 to 98 °C is not easily rationalized. In our opinion, taking into account that the reduction process is not reversible and not time dependent,[3,5] this trend might be due to the competitive thermal racemization of the organoaluminum compound in the reaction mixture, even if we can not exclude the eventual racemization of the aluminum alkoxide formed: G. Giacomelli, L. Lardicci, and R. Santi, *J. Org. Chem.*, **39**, 2736 (1974).
(17) Samples of (*S*)B2,3,3TMB from repeated preparations, whose optical purity (determined by an oxidation procedure) agreed well with that of the starting alkyl chloride, showed different optical rotations (within 10%). This discrepancy may be due to traces of optically active byproducts in the trialkylborane.

Alumina-Catalyzed Ipso Attack in Electrophilic Aromatic Substitution: Methylation of 2,6-Xylenol to 2,3,6-Trimethylphenol

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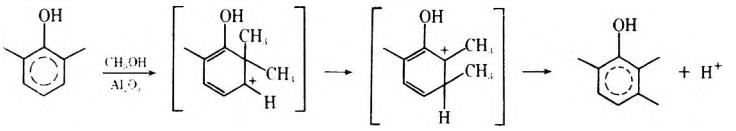
We have observed a highly unexpected meta-methylation in the reaction of 2,6-xylenol with methanol over an alumina catalyst to yield 2,3,6-trimethylphenol (2,3,6-TMP) rather than the expected 2,4,6-TMP. An ipso (Latin:



itself) mechanism is proposed to explain the high selectivity to 2,3,6-TMP. In a continuous reactor isomerization and disproportionation do not occur at 350 °C, 450 psig, due to the water formed in the reaction. Selectivity to 2,3,6-TMP is highest at low temperatures. Substantial evidence for the ipso mechanism was obtained by the reaction of 2,6-xylenol with CD_3OD to give a product with nearly equal amounts of CD_3 in the meta and ortho positions, in agreement with a proposed ipso transition state. The high-purity γ-alumina is strongly ortho-directing and lowers the activation energy for the ipso reaction pathway.

Methylation of 2,6-xylenol to produce 2,3,6-trimethylphenol (2,3,6-TMP) in high selectivity under mild conditions has been reported.[1] The unexpected meta-methylation suggested experiments to determine a mechanism which would explain why 2,3,6-TMP rather than 2,4,6-TMP is the major product. Evidence for an ipso electrophilic aromatic substitution mechanism[2] is presented.

Results and Discussion

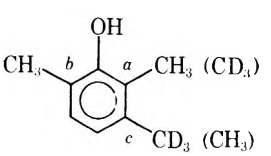
Methylation of gaseous 2,6-xylenol over alumina catalyst yields 2,3,6-TMP in low selectivity with the formation of 2,4,6-TMP as a major component (Table I). A change from vapor phase feed to trickle bed reaction conditions,[3] where most of the 2,6-xylenol and methanol enter the reactor as a liquid, results in a much higher selectivity to 2,3,6-TMP. Uniform reaction temperatures at pressures in the range 400–700 psig, where most of the phenols are in the liquid phase, allowed the determination that the selectivity to 2,3,6-TMP increases at higher pressures (Table II) and lower reactor temperatures (Table III).

In the trickle bed reactor a liquid phase and a gas phase flow concurrently downward through a fixed bed of catalyst while the reaction takes place. The catalyst particles are bathed in liquid which slowly trickles down the reactor. The reactor is in the subcritical region under normal operation. The vapor pressure of the reaction mixture at 360 °C using 0.5 mol of methanol per mole of 2,6-xylenol is about 650 psia. Since the reactor pressure is 490 psia, both gas and liquid phases will be present throughout the reactor. The predicted vapor pressure in the reactor from Raoult's or Henry's Law is much greater than that observed. Therefore, some chemical interaction is occurring in the liquid phase which complexes the light components methanol and dimethyl ether, preventing high vapor pressures. Similar vapor pressure curves were observed for water as for methanol. A complex between 2 molecules of 2,6-xylenol and a molecule of water, methanol, or dimethyl ether was hypothesized to explain the low vapor pressure observed.[4]

Isomerization and disproportionation, which would lead to meta substitution, albeit unselectively, are higher-temperature reactions which do not occur in a continuous reactor at 350 °C, 450 psig, and a contact time of 10 min due to the water formed in the reaction. This is important because the high ratios of 2,3,6-TMP/2,4,6-TMP in the reaction product (Table III) would not be predicted from the effects of the groups in 2,6-xylenol on electrophilic aromatic substitution, and thus meta-alkylation has been previously postulated to involve isomerization or disproportionation.

These reactions do occur with gaseous[5] feed to the reactor and at higher temperatures when the reactor is under pressure. However, at the lower temperatures where the 2,3,6-TMP/2,4,6-TMP ratio is largest, the 2,5-xylenol intermediate expected from isomerization is absent. High selectivity for *m*-alkylphenols is usually realized when the reaction is carried out at high temperatures and/or on catalysts having high acid strength.[6] Application of these principles to 2,6-xylenol methylation results in decreased selectivity to 2,3,6-TMP such that 2,4,6-TMP becomes the major product at higher temperatures and with silica–alumina catalyst. Indeed the highest selectivity to 2,3,6-TMP is observed under mild reaction conditions where 2,6-dimethylanisole[7] is found in increasing quantities.

Substantial evidence for the ipso mechanism was obtained from the reaction of 0.3 mol of CD_3OD per mole of 2,6-xylenol at 350 °C and 475 psig. A sample of the 2,3,6-TMP product was collected after separation on a GLC column and analyzed by Fourier transform NMR spectroscopy. The three methyl groups in 2,3,6-TMP can be distinguished,[8] and the integration of protons due to the methyl groups is reduced by the presence of the CD_3 group in one position. The aromatic protons serve as a standard in the integration and a check on the substitution pattern. No exchange of CD_3 for CH_3 groups occurred in 2,6-xylenol in the reactor. The intensity of the mass 125 peak was <0.1% that of the mass 122 parent peak in the mass spectrum of the 2,6-xylenol fraction. The relative amount of CD_3 at the ortho and meta positions can be determined by assigning the largest integration value to the one unchanged methyl group. If a high percentage of CD_3 was in the meta position, direct attack at that position or the undistinguishable rearrangement of the 2,6-dimethylanisole[9,10] would be implied. An ipso transition state would result in nearly equal migration of CH_3 and CD_3, and experimentally one should see the following.



a = 1.5, *b* = 3, and *c* = 1.5 protons by integration

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Table I. Comparison of Liquid and Vapor Phase 2,6-Xylenol Methylation[a,b]

Product	Feed,[c] % wt	Product composition, % wt			
		Product period, 0–4 h		Product period, 4–8 h	
		Liquid phase	Vapor phase	Liquid phase	Vapor phase
Anisole–MeOH		1.3	0.7	1.1	0.5
o-Methylanisole					
o-Cresol	0.5	1.2	5.0	1.3	3.6
m,p-Cresol	9.9	3.7	0.9	3.7	0.7
2,6-Dimethylanisole					
2,6-Xylenol	89.6	67.9	55.8	68.4	63.3
2,4/2,5-Xylenol		2.2	5.3	2.2	3.3
2,3/3,5-Xylenol		0.3	1.2	0.3	0.5
2,4,6-Trimethylphenol		3.0	8.0	2.9	7.2
2,3,6-Trimethylphenol		12.2	9.1	12.3	9.2
2,3,5/2,4,5-Trimethylphenol		0.6	3.5	0.4	1.9
Pentamethylbenzene		0.6	0.6	0.6	0.4
3,4,5/2,3,4-Trimethylphenol		0.4	0.3	0.3	0.2
2,3,5,6/2,3,4,6-Tetramethylphenol		3.8	6.0	3.8	4.8
2,3,4,5-Tetramethylphenol		0.1	1.1	0.1	1.0
Hexamethylbenzene		Trace	0.2	0.1	0.2
Pentamethylphenol		1.7	1.9	1.8	2.8

[a] Vapor phase refers to vaporized feed entering the reactor. Liquid phase refers to predominantly liquid feed entering the reactor. [b] Liquid hourly space velocity (LHSV) = 4.7 (volume of feed/volume of catalyst per hour); CATAPAL SB alumina $^1/_{16}$-in extrudate, 15 cm^3 of catalyst; reactor temperature set at 355 °C, which defines the operating temperature in the liquid phase, but hot spots occur in the vapor phase which change with time. Maximum temperature in vapor phase during 0–4 h is ~420 °C; 4–8 h, 400 °C. Pressure for liquid phase is 450 psig; vapor phase, 1 atm. [c] Note: the feed contains *m,p*-cresol which adversely affects the selectivity to 2,3,6-TMP.

The spectrum observed is shown in Figure 1, and the integration values are $a \cong 1.5$, $b \cong 3.0$, and $c \cong 1.5$, consistent with the ipso mechanism. Rapid exchange occurs between methyl groups on the alumina surface and the ether methyl in 2,6-dimethylanisole. Direct methyl attack at the occupied ortho position and anisole rearrangement to the same transition state can not be kinetically distinguished.

Benzylation of 2,6-xylenol in the liquid phase at 190 °C with alumina catalyst produced 84% of 3-benzyl-2,6-dimethylphenol and 16% of 4-benzyl-2,6-dimethylphenol, in agreement with the greater migrating tendency of the benzyl group. 2,6-Dibenzylphenol at 220–250 °C formed the benzyl ether but did not yield a tribenzylphenol. Steric hindrance of the two benzyl groups at the ortho positions may have prevented formation of the ipso transition state.

The relative rates of methylation of 2,3- and 2,5-xylenol where the ortho substituent is hydrogen, k_H, can be compared to 2,6-xylenol where the ortho substituent is methyl, k_{CH_3}. The values of k_H/k_{CH_3}, the reactivity ratio of the xylenols, were found to be 6.5 and 3.5 for 2,3- and 2,5-xylenol, respectively, by a competitive reaction with 2,6-xylenol for methanol at 360 °C, 475 psig, and LHSV = 6 (liquid hourly space velocity). If entropy changes are unimportant, the $\Delta H^{\ddagger}$ difference, $\delta(\Delta H^{\ddagger})$, between methyl attack at an ortho position occupied by a methyl group would be 1.6–2.4 kcal/mol greater than attack at the same position occupied by hydrogen. A similar value of k_H/k_{CH_3} of 3.7 was found in the bromination of 2,6-di-*tert*-butylphenols, where the bromination occurred at the para position.[11]

The data in Table III indicate a relatively small $\delta(\Delta H^{\ddagger})$ value for competing exothermic reactions, which requires close temperature control in the reactor to observe the selective rearrangement of the ipso intermediate to 2,3,6-TMP.

The alumina catalyst plays a critical role in the methylation of 2,6-xylenol. Phenol on alumina forms a phenoxide which is located perpendicular to the surface of the catalyst.[12] The ortho positions are closer to the catalyst surface than the meta and para positions, and this argument has been used to explain the ortho-directing effect of alumina.[6]

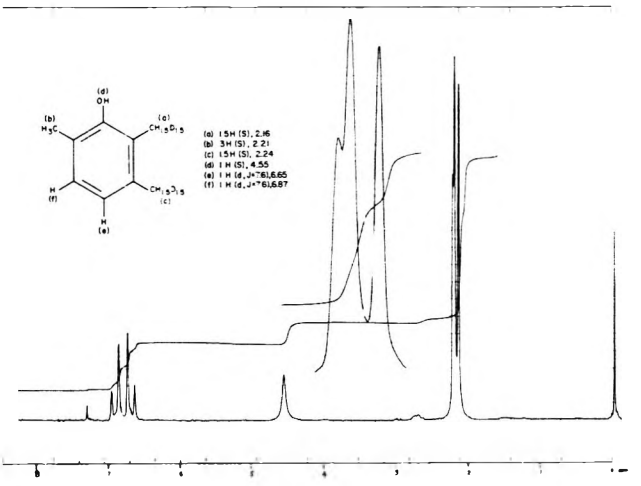

Figure 1. NMR spectrum of 2,3,6-trimethylphenol obtained by the reaction of methanol-d_4 with 2,6-xylenol.

In the past few years, ipso attack has been demonstrated to be significant in some electrophilic nitrations of disubstituted benzenes[13,14] and in photobromination of dihalobenzenes.[15] Ipso mechanisms may operate to a greater extent in electrophilic aromatic substitution reactions than has been realized and may contribute significantly to the reaction products.[16-18]

Wheland intermediates can be written for ortho, meta, and para attachment of methyl to the ring, and repetitive 1,2 shifts can lead to isomerized products. The transition state leading to a Wheland intermediate could be a π complex.[19] Stabilization of the charged Wheland intermediate and π complex in the 2,6-xylenol methylation would be predicted because of the interaction of reactant with alumina catalyst, the liquid vs. vapor phase reactions conditions, and the presence of a $-I$ methyl group in the ortho position.[20] This should particularly stabilize the Wheland intermediate, leading to 2,3,6-TMP as the final product.

Table II. Pressure Effects in the Methylation of Pure 2,6-Xylenol[a]

	Pressure, psig				
	400	450	500	600	700
Product composition, % wt					
2,6 Dimethylanisole	1.22	1.94	3.14	4.95	6.16
2,6-Xylenol	64.55	67.95	70.68	71.04	73.82
2,4/2,5-Xylenol	0.13	0.00	0.00	0.00	0.00
2,3-Xylenol	0.16	0.00	0.04	0.03	0.03
2,4,6-Trimethylphenol	4.24	2.57	1.89	1.77	1.63
2,3,6-Trimethylphenol	16.30	16.19	14.85	14.02	12.40
2,3,5/2,4,5-Trimethylphenol	0.13	0.14	0.18	0.22	0.17
2,3,4/3,4,5-Trimethylphenol	0.79	0.56	0.40	0.22	0.17
2,3,4,6/2,3,5,6-Tetramethylphenol	7.34	6.16	5.01	4.50	3.38
2,3,4,5-Tetramethylphenol	0.41	0.15	0.25	0.21	0.29
Pentamethylphenol	4.72	4.33	3.55	3.04	1.96
Product distribution, % wt					
Methanol	1.37	2.07	4.10	5.25	6.85
Water	6.88	6.49	5.34	4.70	3.80
Total phenols, % wt	91.75	91.45	90.55	90.05	89.36

[a] Reaction conditions: continuous reactor; CATAPAL SB alumina catalyst, 15 cm^3 ($1/16$-in extrudate); LHSV (liquid hourly space velocity, i.e., volume of feed/volume of catalyst per hour) = 4.7; 0.60 mol of methanol per mole of 2,6-xylenol; 355 °C set point on reactor. This defines the temperature under >400 psig pressure, but hot spots are inherent in the vapor phase flow into reactor. The 400-psig run represents a transition between the two regimes.

Table III. Effect of Increasing Reaction Temperature on Liquid Phase Methylation of Pure 2,6-Xylenol

	345 °C	350 °C	355 °C	360 °C	378 °C
Product distribution, % wt					
Methanol–dimethyl ether	3.5	3.2	2.6	1.4	0.6
Product composition, % wt					
o-Methylanisole	0.94	0.03	0.02	0.00	0.02
m,p-Cresol	0.00	0.00	0.00	0.00	0.77
2,6-Dimethylanisole	4.13	4.28	3.49	2.18	0.44
2,6-Xylenol	76.92	77.37	75.90	71.02	66.35
2,4/2,5-Xylenol	0.00	0.00	0.00	0.00	0.56
2,3/3,5-Xylenol	0.43	0.46	0.37	0.13	0.29
2,4,6-Trimethylphenol	0.71	0.71	0.91	2.00	6.53
2,3,6-Trimethylphenol	12.22	12.33	13.29	15.55	14.05
2,3,5/2,4,5-Trimethylphenol	0.06	0.06	0.12	0.43	0.38
2,3,4/3,4,5-Trimethylphenol	0.09	0.11	0.11	0.14	0.39
2,3,4,6/2,3,5,6-Tetramethylphenol	2.94	3.05	3.60	5.17	6.45
2,3,4,5-Tetramethylphenol	0.00	0.00	0.00	0.00	0.21
Hexamethylbenzene	0.05	0.06	0.10	0.30	0.34
Pentamethylphenol	1.51	1.53	2.07	3.07	2.88
High boilers	0.00	Trace	Trace	Trace	0.35
2,3,6-/2,4,6-Trimethylphenol ratio	17.2	17.4	14.6	7.8	2.2

[a] Reaction conditions: continuous reactor; 450 psig; LHSV = 5.0; 0.5 mol of methanol per mole of 2,6-xylenol; 15 cm^3 of CATAPAL SB alumina $1/16$-in extrudate catalyst.

Only highly active γ-alumina of high purity reduces the activation energy for attack at the ortho position sufficiently to bring the ipso pathway involving attack of a methyl group at an ortho position occupied by a methyl group to a lower activation energy than the expected attack at the para position which would yield 2,4,6-TMP. Less active catalysts result in lower selectivity to 2,3,6-TMP at similar conversion levels. In the case of 2,6-xylenol, where ortho hydrogens are replaced by the −I methyl groups, the ipso reaction pathway appears to predominate under mild reaction conditions.

Experimental Section

Reactor. The data were generated using an electrically heated 0.5 × 14 in stainless steel (SS) tube filled with catalyst as the reactor. A $1/8$ in thin-wall SS tube welded at one end served as the thermowell. Temperatures were measured in the center of the reactor with an adjustable thermocouple. The skin temperature of the reactor was controlled to ±1 °C by a Thermo Electric 400 Model 32422 proportional temperature controller. The reactor was well insulated, but heat loss from the large fittings on the ends was unavoidable. The extremities of the reactor were packed with inert glass beads, and the catalyst was confined to the central portion of the reactor (15 cm^3).

The xylenol and methanol were premixed and pumped with a Milton Roy Mini-Pump at a constant rate through a Nupro check valve into a preheater segment of stainless steel tubing to the top of the reactor where the feed enters at 320 °C in a typical run. The reaction products exit at the bottom of the reactor through a water-cooled condensor and a pressure control valve which maintains a set pressure between the check valve and the diaphragm in the control valve. The product was collected for GLC analysis after the reactor ran for 1 h at constant conditions.

Catalyst. The catalyst was a $1/16$-in extrudate of γ-alumina. Typical surface area and pore volume values were 200 m^2/g and 0.45 cm^3/g, respectively. The extrudate was formed from CATAPAL SB alumina which is derived from hydrolysis of aluminum alkoxides. It was calcined for 2 h at 538 °C prior to use.

GLC Analysis. Toluene was added to the reactor product as an internal standard, and actual percentages were calculated by a com-

puterized program which measured the area under the GLC curves. A 10 ft, 10% SE-30 column, 70–300 °C, with a program rate of 6 °C/min using a thermal conductivity detector was used to analyze the phenols. A flame detector was used to determine methanol, dimethyl ether, and the anisoles with a 11 ft, 20% UCON 50 HB 5100 on 80–100 mesh HMDS-treated Chromosorb P column at 70 °C.

Reagents. The phenols were obtained from CONOCO Chemicals and were analyzed by GLC. Methanol and benzenemethanol were of analytical grade. CD_3OD was 99.5% isotopically pure. The $CDCl_3$ used as a solvent for NMR analysis was 99.96% isotopically pure.

3-Benzyl-2,6-dimethylphenol. Benzenemethanol was added dropwise to a stirred flask containing 2,6-xylenol at 190 °C. The water formed in the reaction was removed in a Dean-Stark trap. Analysis by NMR spectroscopy of the product indicated 84% of 3-benzyl-2,6-dimethylphenol and 16% of 4-benzyl-2,6-dimethylphenol.

Methanol-d_4 Experiment. CD_3OD (10 g) was added to 127 g of 2,6-xylenol, and the feed was pumped through the reactor at 350 °C, LHSV = 3, and 475 psig pressure. The product was collected after a 1-h run time and distilled to give a 2,6-xylenol cut and an enriched 2,3,6-TMP cut. A 2,6-xylenol sample was introduced via the direct inlet probe of a Consolidated Electrodynamics Corp. Model 21-110B mass spectrometer. A parent peak at mass 122 was observed at 100 °C, and the intensity of the mass 125 peak (CD_3 incorporation in 2,6-xylenol or ^{13}C contribution) was <0.1% that of the 122 mass parent peak intensity for $C_8H_{10}O$ (2,6-xylenol).

A 10 μL sample of the crude 2,3,6-TMP cut was injected onto the GLC column used to analyze the phenols. The component corresponding to 2,3,6-TMP was collected in a 2.0 × 125 mm tube at the exit port, and the capillary tube was sealed at one end and used as the NMR sample tube. $CDCl_3$ was added, and the NMR spectrum was obtained on a Bruker WP-80 Fourier transform NMR spectrometer with $CDCl_3$ as the lock solvent and Me_4Si as an internal standard. A total of 347 scans were used to generate the spectrum in Figure 1.

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Registry No.—2,6-Xylenol, 576-26-1; 2,3,6-TMP, 2416-94-6; 2,4,6-TMP, 527-60-6.

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Chemistry of the Sulfur–Nitrogen Bond. 13. A New Synthesis of *N*-Alkylidenearenesulfenamides (Sulfenimines): Alkylation of Sulfenamide Enolate Equivalents

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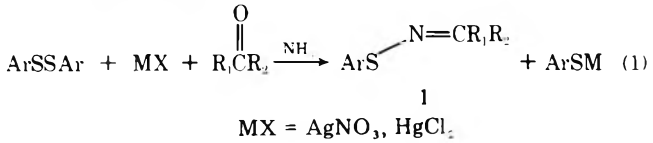
The alkylation of sulfenamide enolate equivalents (**2**), derived by treatment of **1** with LDA, represents a new and important source of sulfenimine derivatives. Not only does this procedure afford **1**, not available by other methods, but it avoids the limitation of the metal-assisted sulfenamide synthesis. These enolate equivalents are formed in excellent yield, with high stability and good regioselectivity. They are, however, highly reactive toward electrophiles such as halides, carbonyl compounds, and aryl disulfides without detectable polyalkylation or self-condensation. Elimination to form phenylthiolate ion and nitrile occurs on treatment of **1**, derived from aldehydes, with LDA.

N-Alkylidenearenesulfenamides (sulfenimines) (**1**) are an important class of reactive sulfur–nitrogen compounds[2] which have recently been shown to be useful intermediates in organic synthesis. These compounds are precursors of 2-arenesulfonyl-3-phenyloxaziridines,[3] a new class of stable oxaziridine derivative. The synthetic utility of **1** as "masked" imine derivatives of ammonia has recently been demonstrated in a convenient, one-step synthesis of secondary and tertiary carbinamines.[4]

Although **1** can generally be prepared in good yield from the corresponding aldehyde or ketone, disulfide, and ammonia using the metal-assisted procedure (eq 1),[1,5] this method has certain limitations.



$$\mathrm{ArSSAr} + \mathrm{MX} + \mathrm{R_1CR_2}\overset{\mathrm{NH}}{\longrightarrow} \underset{\mathbf{1}}{\mathrm{ArS}\!-\!\mathrm{N{=}CR_1R_2}} + \mathrm{ArSM} \quad (1)$$

$\mathrm{MX} = \mathrm{AgNO_3}, \mathrm{HgCl_2}$

First is the inability to prepare **1** from aldehydes or ketones containing bulky and/or reactive functional groups.[1,5] Second, the excess of ammonia required by this method necessitates a correspondingly large excess of the carbonyl compound. From a synthetic point of view this becomes undesirable if the aldehyde or ketone is difficult to prepare.

Enolate equivalents of imines have received relatively little study and have generally not been used to prepare new imine derivatives.[6] They are primarily used as protecting functionalities to avoid self-condensation and polyalkylation reactions observed for the corresponding carbonyl enolates.[7] Corey and Enders have recently reported high regioselectivity for the alkylation of enolate equivalents derived from *N,N*-dimethylhydrazones.[8]

Alkylation of sulfenamide enolate equivalents, **2**, would provide an alternative source of sulfenimine derivatives (eq 2) which would avoid the limitations of the metal-assisted synthesis.[1,5] These enolate equivalents, **2**, are conveniently

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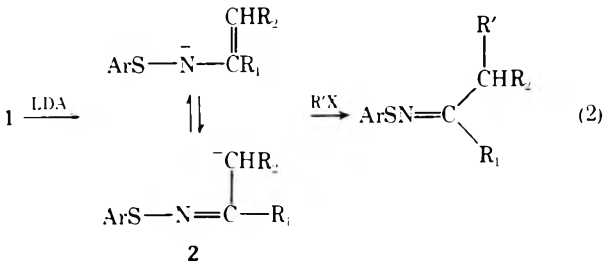
Table I. Synthesis of *N*-Alkylidenearenesulfenamides from Sulfenamide Enolate Equivalents

Entry	Sulfenamide	Registry no.	R–X	Registry no.	Product (% yield)[a]	Registry no.
1	$PhSN{=}CMe_2$	38206-14-3	MeI	74-88-4	$PhSN{=}C(Me)Et$ (95)	50314-94-8
2			$PhCH_2Br$	100-39-0	$PhSN{=}C(Me)CH_2CH_2Ph$ (92)	65276-64-4
3			Ph_2CO	119-61-9	$PhSN{=}C(Me)CH_2C(OH)Ph_2$ (92)	65276-65-5
4			4-ClC_6H_4CHO	104-88-1	$PhSN{=}C(Me)CH_2C(OH)HC_6H_4$-4-Cl (78)	65276-66-6
5			PhS–SPh	882-33-7	$PhSN{=}C(Me)CH_2SPh$ (44)	65276-67-7
6			(4-$ClC_6H_4S)_2$	1142-19-4	$PhSN{=}C(Me)CH_2SC_6H_4$-4-Cl (66)	65276-68-8
7	$PhSN{=}CEt_2$	65276-63-3	Ph_2CO		$PhSN{=}C(CH_2CH_3)CH(Me)C(OH)Ph_2$ (81)	65276-69-9
8	PhSN=CHMe	61501-00-6	MeI[b]		PhSMe (60), Ph_2S_2 (14), PhSN=CHEt (4)	100-68-5, 65276-70-2
9	PhSN=CHPh	52777-99-8	MeI[b]		PhSMe (87), PhCN (79)	100-47-0

[a] Isolated yields unless otherwise noted. [b] Determined by GLC.



2

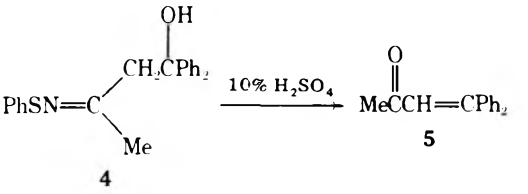
prepared by α-metallation of **1** with 1 equiv (0.5 M) of lithium diisopropylamide (LDA) in dry ether at 0 °C. Alkylation of **2** with halides, carbonyl compounds, and aryl disulfides affords new sulfenamide derivatives in good to excellent yields and in high isolated purity (as judged by TLC, GLC, and NMR). These results are summarized in Table I.

Lower temperatures and/or THF as the solvent resulted in lower yields. With iodomethane, product yields were maximized when 3 equiv were used. Even with a large excess of iodomethane, i.e. >5 equiv, no evidence for polyalkylation was observed. *N*-2(Butylidene)benzenesulfenamide (**3**), the only sulfenimine that could be prepared by both alkylation of **2** (Table I, entry 1) and the metal-assisted procedure, gave only a 50% yield of this compound via the latter method.[4]

Starting material was recovered when **2** was treated with dimethyl disulfide. Enolates derived from *N,N*-dimethylhydrazones[9] and carbonyl compounds[10] react with dimethyl disulfide to afford good yields of the corresponding methyl sulfides. The greater stability and hence lower reactivity of sulfenamide enolates, **2**, is consistent with the known ability of sulfur to stabilize carbanions.[11]

New sulfenimines prepared by alkylation of sulfenamide enolate equivalents (Table I) had IR, NMR, and elemental analysis consistent with the proposed structures. With the exception of **3** (Table I, entry 1) which was isolated as a 26:74 mixture of *Z* and *E* isomers all other sulfenamides were isolated as a single isomer, presumably *E*.[5] Additional evidence for the proposed structures is the acid hydrolysis of **4** to **5**[12] in 75% yield.

Attempts to prepare enolate equivalents of **1** derived from aldehydes (ArSN=CHR) failed. Treatment of *N*-ethylidenebenzenesulfenamide (**6a**)[4] with LDA followed by alkylation with iodomethane gave thioanisole as the major product with only a trace of the desired alkylated sulfenimine (Table I, entry 8).



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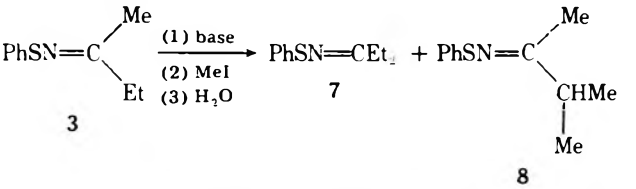
$$\text{Ph-S-N=CHR} \xrightarrow[\text{(2) MeI}]{\text{(1) LDA}} \text{Ph-S-Me + R-CN}$$

6a, R = Me
b, R = Ph

Apparently elimination, giving the phenylthiolate ion and acetonitrile, is favored over formation of **2**. Consistent with these results is the isolation of thioanisole and benzonitrile in 87 and 79% yield, respectively, on treatment of **6b** with LDA–iodomethane (Table I, entry 9).

One of the main problems which limits the use of enolates derived from ketones is their regioselective formation since mixtures of alkylated products result.[13] Base, temperature, reaction medium, and geometry of the carbonyl derivative all have an influence on the regioselectivity.[7-9,13,14]

Treatment of the sulfenimine derived from 2-butanone, **3**,[4] with base followed by alkylation of the enolate equivalents with iodomethane affords **7** and **8**. The influence of reaction



3 7 8

conditions on the yields of these products is summarized in Table II. As observed for other enolate equivalents[7-9,13,14] there is a similar preference for alkylation of the primary

Table II. Regioselectivity of Sulfenamide Enolate Equivalents; Alkylation with Iodomethane of the Enolate Equivalents Derived from Sulfenimine 3

Entry	Base concn, M (equiv)	Temp, C°	Solvent	Time,[a] h	Products[b] (% yield)
1	LDA 1.0 (1)	0	Ether	1.0	7 (73), 8 (9)
2	LDA 0.65 (1)	0	Ether	1.0	7 (73), 8 (9)
3	LDA 0.65 (2)	0	Ether	1.0	7 (78),[c] 8 (5)
4	LDA 0.65 (3)	0	Ether	1.0	7 (75),[c] 8 (8)
5	LDA 0.85 (1)	−78	Ether	2.5	3 (95)
6	LDA 0.65 (1)	0	THF	1.0	3 (37), 7 (40), 8 (4)
7	LDA 0.5 (1)	0	THF	2.0	3 (30), 7 (55), 8 (5)
8	LDA 0.5 (1)	0	THF	3.0	3 (15), 7 (45), 8 (3)
9	LDA 0.5 (3)	0	THF	1.0	7 (45), 8 (5)
10	LiTMP 0.5 (1)	0	Ether	1.0	7 (67), 8 (16)
11	LiTMP 0.65 (1)	0	Ether	1.0	7 (71), 8 (16)
12	LiTMP 1.0 (1)	0	Ether	1.0	7 (67), 8 (14)

[a] Time at which iodomethane was added. [b] Analyzed by GLC. [c] Polyalkylation occurring.

carbanion, leading to **7**. The highest regioselectivity observed for the enolates derived from **3** was with 1–2 equiv of LDA in ether (Table II). However, as the concentration of base increased polyalkylation became a serious problem (Table II, entries 3 and 4). Although the polyalkylated product could not be successfully separated from the reaction mixture it appears to be **9** ($PhSN{=}C(Et)CHMe_2$) as judged by NMR. The use of lithium 2,2,6,6-tetramethylpiperidine (LiTMP), lower temperatures, or THF as the solvent resulted in reduced yields and lower regioselectivity (Table II).

The lower regioselectivity observed for sulfenamide enolate equivalents as compared with *N,N*-dimethylhydrazones may be a result of the geometry of **3**. The barriers to syn-anti isomerization in sulfenimines, **1**, are on the order of 20 kcal/mol[15] and **3** exists as a 26:74 mixture of the *Z* and *E* forms. Jung and Shaw have reported a preference for anti deprotonation in symmetrically substituted hydrazones.[15] Anti deprotonation in **3**, as a result of the bulky S-phenyl group, may therefore lead to the enolate equivalent favoring **8**.

The alkylation of sulfenamide enolate equivalents, derived from readily available **1**,[1,5] represents a new and important source of sulfenimine derivatives. Not only does this procedure afford **1**, not available by other methods, but it avoids the limitations of the metal-assisted sulfenamide synthesis. Sulfenamide enolate equivalents are formed in excellent yield, with high stability and good regioselectivity. These enolate equivalents are, however, highly reactive toward electrophiles such as halides, carbonyl compounds, and aryl disulfides without detectable polyalkylation or self-condensation.

Experimental Section

Melting points were obtained on a Mel-Temp apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 457 spectrometer and NMR spectra on a Varian A60 A spectrometer. Chemical shifts are expressed in ppm downfield from Me_4Si. Solvents were purified by standard procedures. Gas chromatography was performed on a Perkin-Elmer 900 gas chromatograph, FID, using a 6 ft. 6% OV-17 on 60/80 mesh Chromosorb W (regular) column by comparison of peak areas with standard solutions of reaction products. Analyses were performed at least twice and the results averaged.

General Procedure for Alkylation of Sulfenamide Enolate Equivalents. In a 100-mL three-necked flask equipped with magnetic stirrer, condenser, dropping funnel, nitrogen, and syringe inlets was placed 2.2 mmol of a 0.5 M solution of freshly prepared lithium diisopropylamide (LDA) in 4.4 mL of dry ether in an atmosphere of nitrogen. The reaction mixture was cooled to 0 °C and 2 mmol of the appropriate sulfenimine, **1**, in 2 mL of ether was added dropwise over 0.5 h. After being stirred for an additional 0.5 h at 0 °C, the reaction mixture was refluxed for 0.5 h and cooled to 0 °C and 6.0 mmol of iodomethane or 2.0 mmol of the other alkylating agents in 2 mL of ether was added dropwise. After stirring for 2 h in the case of iodomethane and benzyl bromide and 15 h for the carbonyl compounds and disulfides the reaction was quenched with 30 mL of water and the ether solution was dried over anhydrous $MgSO_4$. New sulfenimines were purified by crystallization from ether–pentane or preparative TLC on silica gel.

***N*-2(4-Phenylbutylidene)benzenesulfenamide:** mp 57–58 °C; NMR ($CDCl_3$) δ 2.1 (s, 3 H, Me), 2.6–3.2 (m, 4 H, CH_2CH_2), 7.0–7.5 (m, 5 H). Anal. Calcd for $C_{16}H_{17}NS$: C, 75.39; H, 6.67. Found: C, 75.30; H, 6.80.

***N*-2(4,4-Diphenyl-4-hydroxybutylidene)benzenesulfenamide (4):** mp 98–98 °C; IR (KBr) 3390 cm^{-1} (s, OH); NMR ($CDCl_3$) δ 2.0 (s, 3 H, Me). 3.3 (s, 2 H, CH_2). 5.5 (s, 1 H, OH, exchange D_2O), 7.0–7.4 (m, 15 H). Anal. Calcd for $C_{22}H_{21}NOS$: C, 76.05; H, 6.09. Found: C, 76.28, H, 6.11.

***N*-2(4-(4-Chlorophenyl)-4-hydroxybutylidene)benzenesulfenamide:** mp 65–7 °C; IR (KBr) 3490 cm^{-1} (s, OH); NMR ($CDCl_3$) δ 2.0 (s, 3 H, Me), 2.6 (d, 2 H, CH_2), 4.1 (bs, 1 H, OH), 5.1 (t, 2 H), and 7.0–7.5 (m, 9 H).

Anal. Calcd for $C_{16}H_{16}ClNOS$: C, 62.84; H, 5.27. Found: C, 62.69; H, 5.32.

***N*-2(3-Phenylthiopropylidene)benzenesulfenamide:** oil; NMR ($CDCl_3$) δ 2.15 (s, 3 H, Me), 3.75 (s, 3 H, CH_2), 7.1–7.6 (m, 10 H). A satisfactory elemental analysis could not be obtained.

***N*-2(3-(4-Chlorophenylthio)propylidene)benzenesulfenamide:** mp 33 °C; NMR ($CDCl_3$) δ 2.15 (s, 3 H, Me), 3.7 (s, 2 H, SCH_2), 7.3 (m, 9 H). Anal. Calcd for $C_{15}H_{14}ClNS_2$: C, 58.52; H, 4.58. Found: C, 58.56; H, 4.56.

***N*-3-(5,5-Diphenyl-5-hydroxy-4-methylpentylidene)benzenesulfenamide:** mp 71–3 °C; IR (KBr) 3400 cm^{-1} (s, OH); NMR ($CDCl_3$) δ 1.2 (d-t, 6 H, Me), 2.3 (q, 2 H), 3.7 (q, 1 H), 5.9 (s, 1 H, OH, exchange D_2O), 7.0–7.6 (m, 15 H). Anal. Calcd for $C_{24}H_{25}NOS$: C, 76.76; H, 6.71. Found: C, 76.93; H, 6.76.

Hydrolysis of 4. In a 50-mL single-necked flask was placed 0.1 g (0.37 mmol) of **4** in 10 mL of 2 N H_2SO_4. After refluxing for 2 h the solution was cooled and extracted with ether, 3 × 20 mL portions, and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave an oil which was purified by preparative TLC on silica gel to give 0.045 g (75%) of a low-melting solid mp ~38 °C (lit.[13] mp 34–36 °C) identified as **5**.

Treatment of 6a and 6b with LDA–Iodomethane. Sulfenimines **6a** and **6b** were treated as described above for the alkylation of sulfenamide enolate equivalents. Thioanisole and benzonitrile were analyzed by gas chromatography.

Synthesis of *N*-3(Pentylidene)benzensulfenamide (7) and *N*-2(3-Methylbutylidene)benzenesulfenamide (8). Sulfenimines **7** and **8** were prepared from 10.0 g (0.64 mol) of phenyl disulfide and a fivefold excess of the corresponding ketone using the metal-assisted sulfenamide synthesis previously described.[1,5] Compound **7** was obtained in 53% yield: bp 75–78 °C (0.25 mm); NMR ($CDCl_3$) δ 1.1 (d-t, 6 H, Me), 2.3 (d-q, 4 H, CH_2), and 7.0–7.6 (m, 5 H). Anal. Calcd for $C_{11}H_{15}NS$: C, 68.34: H, 7.82. Found: C, 68.37; H, 7.75.

Compound **8** was obtained in 40% yield: bp 84–6 °C (0.35 mm); NMR ($CDCl_3$) δ 1.1 (d, 6 H, Me, J = 7 Hz), 1.95 (s, 3 H, Me), 2.5 (m, 1 H), and 7.0–7.6 (m, 5 H). Anal. Calcd for $C_{11}H_{15}NS$: C, 68.34; H, 7.82. Found: C, 68.41; H, 7.64.

Regioselectivity of Sulfenamide Enolate Equivalents. In a 100-mL three-necked flask equipped with magnetic stirrer, dropping funnel, nitrogen, and syringe inlets was placed a freshly prepared solution of the appropriate base in ether or THF (Table II) under an atmosphere of nitrogen. The reaction mixture was cooled to the pre-

scribed temperature and 2.0 mmol of *N*-(2-butylidene)benzenesulfenamide (3)[4] in 2.0 mL of the appropriate solvent was added dropwise over 0.5 h. After stirring for the required time, 6.0 mmol of iodomethane was added dropwise and the stirring was continued for an additional 2 h. The reaction was quenched with 30 mL of water and the ether solution was dried over anhydrous $MgSO_4$. Sulfenimines 7 and 8 were analyzed by gas chromatography.

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Registry No.—8, 65276-71-3.

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On the Mechanism of the Thermal Isomerization of 1,2-Diolates. Is the Pinacol Coupling Reaction Reversible?

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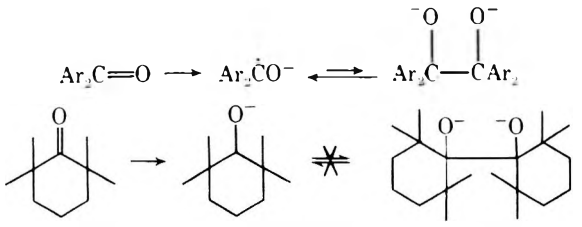
1,2-Diols containing at least one α proton will isomerize when heated to 155 °C as their dilithium salts. The mechanism of the isomerization is shown to be an oxidation–reduction rather than a reverse pinacol coupling as had been suggested by earlier workers. Evidence in support of the proposed mechanism is presented.

The pinacol coupling reaction is a potentially powerful method of carbon–carbon bond formation which has received little attention from synthesis chemists.[1] We have been interested for some time in the synthetic uses of the pinacol reaction,[2,3] and one of the questions which we wished to answer involved the reversibility (or lack thereof) of the reaction. Such information could be valuable if, for example, one wished to plan the stereospecific synthesis of a cyclic 1,2-diol by internal pinacol cyclization.[4]

It has long been known that *certain* pinacol couplings are readily reversible when, for some reason, the central carbon–carbon bond is unusually weak. Such, for example, is the case when diaryl ketones are reductively coupled to tetraarylethanediols.[5] Similarly, although for steric rather than electronic reasons, 2,2,6,6-tetramethylcyclohexanone cannot be reductively coupled to a pinacol because its ketyl will not dimerize.[6]



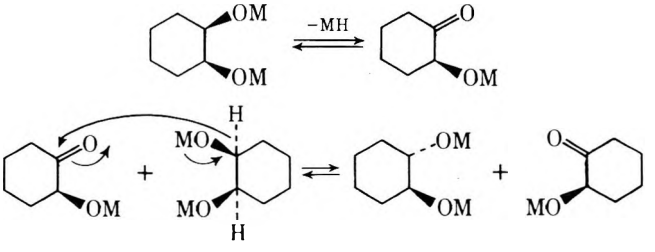
The situation for saturated, sterically uncrowded 1,2-diols is less clear, however. Schlosser, in a 1970 communication, reported the thermal isomerization of a series of dilithium 1,2-diolates and proposed a bond homolysis mechanism (reverse pinacol coupling) to account for his results.[7] *cis*-1,2-Dihydroxycyclohexane, for example, isomerized nearly completely (97%) to its trans isomer when heated as its dilithium salt for 17 h at 155 °C.

Yet a further example was reported sometime later by Sharpless.[8]

In considering the Schlosser report, we were struck by the fact that all of the cases examined were disecondary 1,2-diols and that an alternative oxidation–reduction mechanism, perhaps initiated by a trace amount of ketone, could also account for the observed results. We therefore investigated the isomerization of a selected 1,2-diol, *cis*-1,2-dihydroxycyclohexane (1), in more detail. Our results are summarized in Table I.

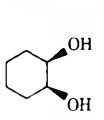
Runs 1–3 were carried out to establish the minimum condition necessary to achieve diol equilibration, and we verified the Schlosser report in this respect. In order to establish whether or not the observed equilibration was due to a catalytic amount of O_2 initiating a redox process, we next (runs 4 and 5) attempted equilibration using scrupulously oxygen-free conditions (freeze–thaw deoxygenation of solvents; sealed tube) under both nitrogen and argon atmospheres. Although the equilibration seemed qualitatively somewhat slower, and although higher yields of recovered products were obtained, it was nevertheless clear that diol equilibration still occurred readily in the absence of oxygen.

An alternative means of generating a trace amount of oxidized material necessary to start the catalytic redox cycle



0022-3263/78/1943-1800$01.00/0

Table I. Isomerization of Some Diols by Thermal Equilibration of Dimetallo Salts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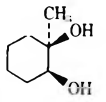
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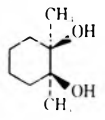

3

Run	Diol	Base	Conditions	Products, %	Yield, %
1	1[a]	*n*-BuLi	Diglyme; N_2; rt; 20 h	100 cis 0 trans	75
2		*n*-Buli	Diglyme; N_2; 155 °C; 1.5 h	17 cis 83 trans	40
3		*n*-BuLi	Diglyme; N_2; 155 °C; 3 h	0 cis 100 trans	40
4		*n*-BuLi	Freeze–thaw degassed diglyme; N_2; 155 °C; 42 h	4 cis 96 trans	60
5		*n*-BuLi	Freeze–thaw degassed diglyme; Ar; 155 °C; 40 h	4 cis 96 trans	90
6		NaH	Diglyme; N_2; 155 °C; 2 h	10 cis 90 trans	33
7		LDA	Diglyme; N_2; 155 °C; 2 h	15 cis 85 trans	35
8		KH	Diglyme; N_2; 155 °C; 3.5 h	97 cis 3 trans	45
9		*n*-BuLi	Freeze–thaw degassed diglyme; Ar; 155 °C; 45 h; 10 mol % $NaBH_4$ present	81 cis 19 trans	52
10	2[b]	*n*-BuLi	Diglyme; N_2; 155 °C; 6 h	43 cis 57 trans	69
11	3[c]	*n*-BuLi	Diglyme; N_2; 205 °C; 2 h	100 cis	70
12		LDA	Diglyme; N_2; 155 °C; 2 h	100 cis	92
13		NaH	Diglyme; N_2; 155 °C; 2 h	100 cis	88
14		*n*-BuLi	Diglyme; N_2; 305 °C (sealed tube); 24 h		0

[a] Registry no. 1792-81-0. [b] Registry no. 52718-65-7. [c] Registry no. 33046-21-8.

would be to assume that a small amount of diolate undergoes loss of metal hydride.[9]

The ketone product then acts as a hydride acceptor for a second diolate, and the catalytic cycle commences. One would expect the feasibility of the initial loss of metal hydride to be dependent on the nature of the counterion, and runs 6 and 8 indicate that this is so. Although sodium hydride as base is nearly as effective as *n*-BuLi and lithium diisopropylamide, potassium hydride is ineffective even under forcing conditions. If the diolate equilibration were occurring by a bond homolysis (reverse pinacol) mechanism, one might expect a dipotassium diolate to be more reactive than disodium or dilithium.[10] If, however, loss of metal hydride occurs to initiate a redox cycle, then loss of the more covalent lithium hydride might be expected to be easier than loss of potassium hydride since bond energies of the alkali hydrides occur in the order LiH (56.9 kcal/mol) > NaH (48 kcal/mol) > KH (43.8 kcal/mol).[11]

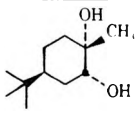
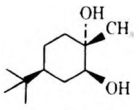
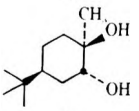
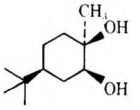
If a trace amount of carbonyl is involved in catalyzing the equilibration, we reasoned that we ought to be able to quench the reaction by adding a carbonyl scavenger to the reaction. Run 9 was therefore carried out under oxygen-free conditions in the presence of 10 mol % $NaBH_4$. Equilibration was, in fact, greatly diminished under these conditions but nevertheless still occurred to a modest degree. Although this result is not clear cut, it would seem to argue for a redox mechanism of equilibration, especially in light of the recent report that borohydride reduction may be reversible under some conditions.[12]

The evidence thus far is inconclusive, and we felt that more definitive results might be found if attempts were made to equilibrate more substituted diols. *cis*-1,2-Dihydroxy-1-methylcyclohexane should be capable of equilibrating by either mechanism, and indeed, we found that its dilithium salt equilibrates readily (run 10). A ditertiary 1,2-diol, however, should be able to equilibrate only by a reverse pinacol mechanism and not by a redox cycle since no α hydrogens are present. Runs 11–14 indicate that under no conditions found does *cis*-1,2-dihydroxy-1,2-dimethylcyclohexane equilibrate with its trans isomer even when the reaction temperature is raised to the point of solvent decomposition. A priori, one might have predicted a ditertiary diol to react faster than a disecondary diol due to steric effects if the reverse pinacol mechanism were operative (see, for example, our earlier comments about the 2,2,6,6-tetramethylcyclohexanone pinacol). The fact that we see no equilibration is good evidence against such a mechanism.

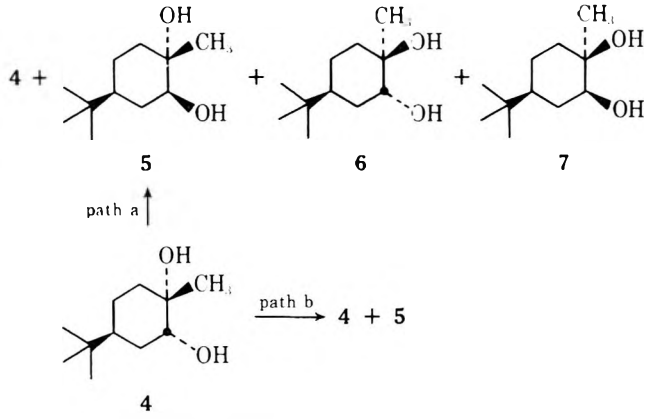
Negative evidence, while strongly indicative, is never as compelling as positive evidence, and we therefore considered experiments which would lead to unambiguous positive results. One such experiment is the attempted equilibration of a secondary–tertiary diol such as **4** in which isomerization relative to another internal chiral center can be followed. We have already established that a secondary–tertiary diol such as **2** undergoes isomerization. If isomerization of **4** occurs by a reverse pinacol mechanism, both hydroxyl containing centers should be epimerized leading to a mixture of four possible products (path a). If isomerization occurs by a redox mechanism, only the secondary hydroxyl should be epimerized and two products result (Scheme I, path b). Our results are summarized in Table II.

All four of the known isomeric diols **4**–**7** were synthesized and submitted to isomerization conditions. The results are compatible only with isomerization through a redox mechanism. As predicted, compounds **4** and **5** were readily interconverted by epimerization at the secondary center. Only in the case of diol **4** does a small amount of isomerization at the tertiary hydroxyl occur, and we thus cannot completely rule out a reverse pinacol mechanism competing to a slight extent with a redox mechanism. We find it surprising that trans diols **6** and **7** evidence no isomerization, but this does not seem to have bearing on the reverse pinacol vs. redox question since neither is occurring.

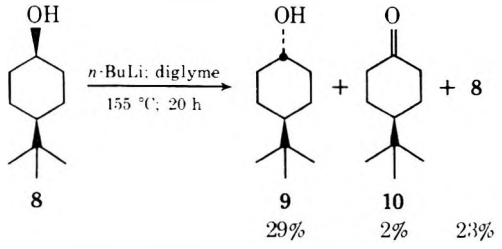
Table II. Isomerization of 1,2-Dihydroxy-4-*tert*-butyl-1-methylcyclohexanes

Starting diol	Registry no.	Products (%)	Yield, %
 4	33817-491	4 (24.4) 5 (67.5) 6 (0) 7 (8.1)	38
 5	43089-39-0	4 (27.5) 5 (72.3) 6 (0) 7 (tr)	75
 6	43089-35-6	4 (0) 5 (2.3) 7 (2.4) 6 (95.3)	33
 7	5951-25-7	4 (0) 5 (0) 6 (0) 7 (100)	57

Scheme I

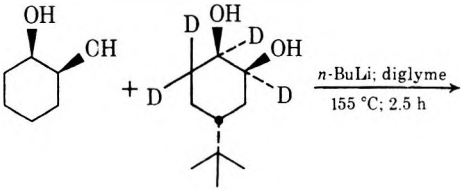


Final proof of the redox mechanism for isomerization of 1,2-diols was gathered by two additional experiments. In the first of these, we hypothesized that a mono alkoxide should be able to undergo a redox isomerization as well as a dialkoxide (though obviously not a reverse pinacol isomerization). We therefore synthesized *cis*-4-*tert*-butylcyclohexanol (8) and submitted its lithium salt to standard conditions. Heating the lithium salt of 8 under N_2 atmosphere to 155 °C for 20 h in diglyme yielded a 44:56 mixture of cis and trans isomers in 52% yield, along with about 2% 4-*tert*-butylcyclohexanone—clear evidence of redox processes occurring:



The final and concluding experiment involved coisomerization of a mixture of *cis*-1,2-dihydroxycyclohexane (1) and *cis*-1,2,6,6-tetradeuterio-1,2-dihydroxy-4-*tert*-butylcyclohexane (14). Both diols should isomerize but if a reverse pinacol mechanism were operative (intramolecular), no deuterium should be exchanged between the two compounds. If a redox mechanism were operative (intermolecular) deuterium should be scrambled between the diols. The synthesis of deuterated diol 14 is given in Scheme II, and the results of the coisomerization experiment are given in Table III.

Table III. Coisomerization (%) of a Deuterated and a Nondeuterated 1,2-Diol



OH	D^0	D^1	D^2	D^3	D^4
1					
Before reaction	100	0	0	0	0
After reaction	34	30	23	10	3
14					
Before reaction	2	5	14	35	43
After reaction	17	28	25	18	10

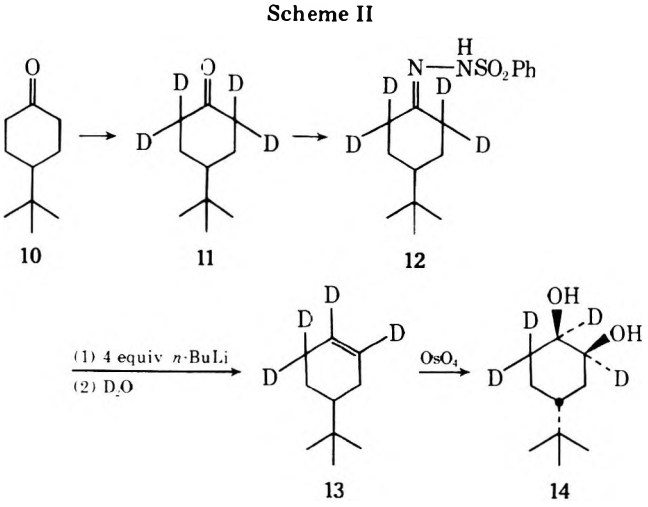
Although separation of products into individual stereoisomers was not carried out, the results clearly indicate a large amount of intermolecular deuterium scrambling consistent only with a redox mechanism.

In conclusion, we feel that our evidence for the mechanism of 1,2-diolate isomerization is compatible only with a redox pathway and not with the reverse pinacol coupling pathway originally proposed by Schlosser. From a synthesis point of view, our results clearly indicate that isomerization can be achieved only at secondary centers and not at tertiary centers; synthetic schemes incorporating a pinacol coupling reaction will therefore have to be constructed with this fact in mind.

Experimental Section

General. Melting points (uncorrected) were obtained on a Thomas-Hoover Unimelt apparatus. ^1H NMR spectra were determined on a Varian A56/60A (60 MHz) or a Jeolco Minimar (60 MHz) instrument. ^{13}C NMR spectra were determined on a Jeolco PFT-100 instrument operating at 25.1 MHz. Chemical shifts were reported in δ downfield from Me_4Si (δ 0). IR spectra were recorded on Perkin-Elmer 237 B or Perkin-Elmer 337 grating spectrophotometers. Analytical vapor phase chromatography (VPC) was performed on a Varian A-200 (FID) instrument using 10% carbowax 20 M on Chromosorb W 60/80 columns (10 ft. × 1/8 in.). Preparative VPC was performed on an Aerograph 90-P instrument employing 20% SE-30 on Chromosorb W 80/100 column (6 ft. × 1/4 in.). Isotopic compositions were determined by gas chromatography/mass spectroscopy on a Finnegan Model 4000 instrument operating with ionization potential at 70 eV and utilizing a 3% OV-1 Chromosorb W glass column (4 ft. × 1/8 in.). High-pressure liquid chromatography (HPLC) was performed on a Water Associates Model ALC 201 instrument employing Porasil-A

Scheme II



packed columns (6 ft. × ¼ in.) and utilizing ethyl acetate/petroleum ether (bp 30–60 °C) solvent system (2/3).

n-BuLi (Alfa) was titrated by the method of Watson.[13] L-Selectride (Aldrich) was used as purchased. *N,N,N',N'*-Tetramethyl-1,2-ethylenediamine (TMEDA, Aldrich) was distilled from CaH_2. Diglyme (Matteson Coleman Bell) was predried by standing over anhydrous $CaCl_2$ and then distilled from CaH_2. Diglyme was dried by stirring over molten potassium metal for an overnight period and then distilled in vacuo. D_2O (99.8%) was purchased from Bio-Rad.

Known cis diols **1**,[14] **2**,[15] and **3**[16] and their trans isomers were prepared according to the literature procedures. Diols **4, 5, 6,** and **7** were prepared according to Barili, Bellucci, Macchia, and Parmigiani[17] and were then purified on HPLC. ^{13}C NMR spectra ($CDCl_3$) of **4, 5, 6,** and **7** were consistent with their structures.[18] Alcohol **8** (96% isomeric purity) was obtained according to the procedure of Brown.[19]

Organic phases from extraction were dried over anhydrous Na_2SO_4. All reactions were performed in oven-dried glassware assembled hot under an N_2 atmosphere except where indicated.

2,2,6,6-Tetradeuterio-4-*tert*-butylcyclohexanone (11). Deuterated cyclohexanone-*2,2,6,6-d*$_4$ was prepared by the deuterium exchange procedure of Eliel;[20] mp 49–50 °C. Isotopic composition: 0% d_0, 0.4% d_1, 3.3% d_2, 24.6% d_3, and 71.8% d_4.

2,2,6,6-Tetradeuterio-4-*tert*-butylcyclohexanone Phenylsulfonylhydrazone (12). Ketone **11** (1.58 g, 10 mmol) was added to a magnetically stirred hot saturated methanolic solution (10 mL) of phenylsulfonylhydrazide (1.72 g, 10 mmol). After being allowed to cool and being stirred at 20 °C for 1 h, no carbonyl was detected by infrared spectroscopy. The solution was refrigerated to induce crystallization, and the white solid was filtered, washed with four portions of H_2O, and dried in vacuo to yield 2.22 g (71%) of product, mp 129–131 °C (lit.[21] mp for undeuterated product 128–130 °C).

1,2,6,6-Tetradeuterio-4-*tert*-butylcyclohexene (13).[22] Into a 100-mL flask fitted with a rubber stopple, a magnetic stirring bar, and an inserted thermometer was placed dry TMEDA (60 mL) and hydrazone **12** (1.87g, 6 mmol). The solution was cooled to −45 °C (internal temperature) and, via syringe, *n*-BuLi (10 mL, 24 mmol) was added at such a rate that internal temperature never exceeded −35 °C. External cooling was removed and the deep red solution was allowed to warm to 20 °C. After stirring for 1.5 h, N_2 evolution had ceased and D_2O (6 mL) was added dropwise to the orange solution cooled by an external H_2O bath. The suspension was poured into H_2O (50 mL). After being saturated with NaCl, the aqueous mixture was extracted with pentane (4 × 30 mL). The combined pentane extracts were washed with saturated NH_4Cl solution (2 × 40 mL), dried, filtered, and concentrated on a rotary evaporator. Preparative VPC of the liquid residue yielded 354 mg (41%) of **13**. Integration of the vinyl proton at δ 5.65 indicated ~90% deuteration.

1,2,6,6-Tetradeuterio-4β-*tert*-butyl-1α,2α-dihydroxycyclohexane (14). Diol **14** was prepared according to the literature procedure[23] for the protio analogue. Isotopic content is given in Table III, mp (hexane) 113–5 °C (lit.[23] mp for undeuterated **9** 117–9 °C).

General Procedure for Isomerization of Diols. The appropriate diol (1.0 mmol) was dissolved in 10 mL of diglyme and a slight excess (2.2 mmol) of base was added. The reaction was then placed under inert atmosphere by successive evacuations and fillings with nitrogen. The reaction mixture was stirred at room temperature for 0.5 h, heated to 155 °C for the proper length of time, cooled, and diluted with water. The aqueous solutions were extracted three times with ethyl acetate, and the extracts were combined, washed with saturated brine, dried (Na_2SO_4), and concentrated at the rotary evaporation. Analysis was carried out by GLC as detailed above. The specific runs are indicated in Tables I–III.

All freeze–thaw reactions (runs 4, 5, 9; Table I) were carried out in thick-walled Pyrex tubing. The proper reaction mixtures were placed in the tubes, frozen in liquid N_2 under high vacuum, and allowed to thaw. After five freeze–thaw cycles, the tubes were sealed under high vacuum. After heating for the appropriate time, the tubes were opened, and the contents were analyzed as above.

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Registry No.—**11**, 15649-46-4; **12**, 65253-49-8; **14**, 65253-50-1.

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Novel Dimeric Products from 10-Methyleneanthrone

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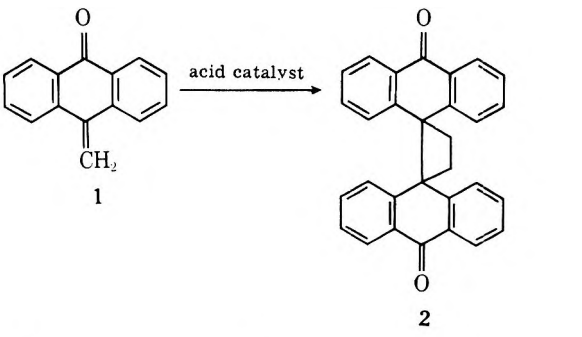
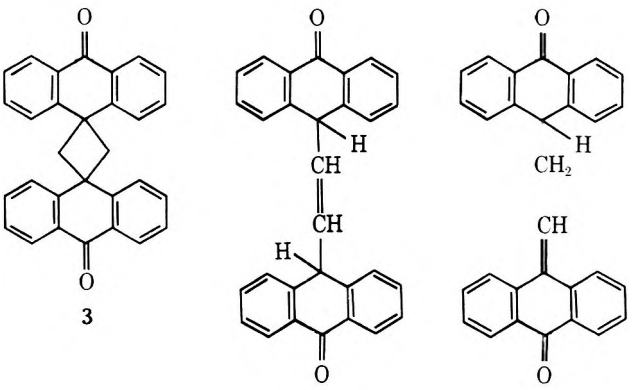
The reaction of 10-methyleneanthrone (**1**) with acid catalysts in alcohols, benzene, or acetic acid gives anthrone-10-spiro-1′-cyclobutane-2′-spiro-10″-anthrone (**2**). Acetylation of **2** yields 7-acetoxy-1,2-dihydro-3*H*-benz[*de*]anthracene-3-spiro-10′-anthrone (**8**). 7-Alkoxy-1,2-dihydro-3*H*-benz[*de*]anthracene-3-spiro-10′-anthrones (**10**) are formed by the reaction of **1** with dialkyl sulfates. Mechanistic studies suggest that **2** is formed via a path involving 1,2-cycloaddition (head-to-head linkage) of **1** and that **2** rearranges with ring expansion to 1,2,3,11b-tetrahydrobenz[*de*]anthrone-3-spiro-10′-anthrone (**11**). The thermal reaction of **2** in usual organic solvents leads to **11**, 2,3-dihydrobenz[*de*]anthrone-3-spiro-10′-anthrone (**12**), and hydroperoxide **13**. Acetylation of **12** involves enolization, yielding 7-acetoxy-3*H*-benz[*de*]anthracene-3-spiro-10′-anthrone (**15**). 7-Alkoxy-3*H*-benz[*de*]anthracene-3-spiro-10′-anthrones (**17**) are formed from the reaction of **12** with an excess of alkyl iodides in alcoholic sodium alkoxide. Oxidations of **2**, **8**, **10**, and **12** by chromium trioxide give 10-(1-anthraquinonyl)-10-carboxymethylanthrone (**18**).

The reaction of 10-methyleneanthrone (**1**) with acid catalysts, such as alcoholic hydrochloric acid, alcoholic sulfuric acid, or formic acid, is known to give a dimeric product. Its structure has been considered to be either **4** or **5**.[1] However, in our reinvestigation of the product, it has been identified as a dimeric product whose structure is of dispiro compound. This dimeric product is expected to be highly reactive because of its high degree of strain. Quinone methides belong to an exceedingly reactive group of substances. Although the dimeric and trimeric forms of the quinone methides have been isolated, the unsubstituted monomeric materials could not be obtained due to their extreme reactivity. Several highly substituted quinone methides are, however, stable and can be isolated. Methyleneanthrone is the sole example of a stable quinone methide having an unsubstituted methylene group.[2] In the literature it has been stated that the phosphite-catalyzed, autoxidative, and reductive dimerizations of **1** give a Diels–Alder dimeric product, a dimeric peroxide, and a reductive dimeric product, respectively.[3] The present paper is concerned with the identification and mechanism of formation of the dimeric product derived from **1** and with its rearrangement.



1 **2**

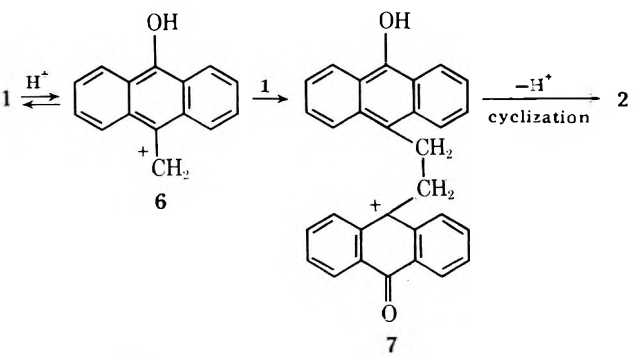


3 **4** **5**

Results and Discussion

The dimerization reaction of 10-methyleneanthrone (**1**) in alcohols, benzene, or acetic acid was carried out by refluxing the solution in the presence of various acid catalysts, such as hydrochloric acid, sulfuric acid, aluminum chloride, ferric chloride, boron trifluoride etherate, *p*-toluene sulfonic acid, or polyphosphoric acid. In all these cases, the major product was anthrone-10-spiro-1′-cyclobutane-2′-spiro-10″-anthrone (**2**), which was a 1,2-cycloaddition product (head-to-head linkage) of **1**. The results are summarized in Table I. The reaction of **1** with weak acids, such as phosphoric acid or zinc chloride as an acid catalyst, was carried out in alcohols. In this case, however, **2** was not formed. Moreover, **1** was not converted to **2** by the reflux with an amount of catalyst less than that shown in Table I. The yield of **2** was independent of the reaction temperature (>ca. 50 °C), reaction time (>ca. 15 min), and amount of catalyst (>that shown in Table I). Therefore, it appears that the yield is dependent upon the nature of catalyst and the solubility of **2** in the solvent. Although no experimental test was made, **2** may be formed by the reaction of **1** with strong acids in any organic solvents other than basic ones. The pure spiroanthrone **2** melts at 248–250 °C and is slightly soluble in usual organic solvents. In the solid state, **2** is stable to air and prolonged heating but decomposes rapidly in solution. Although another structural isomer (**3**, head-to-tail linkage) would be possible as 1,2-cycloaddition product from these reactions, **3** was not isolated in each case. These reactions would also be expected to yield a Diels–Alder dimeric product (**11**), but **11** was not obtained. The only other product identified under these conditions was 2,3-dihydrobenz[*de*]anthrone-3-spiro-10′-anthrone (**12**) (for reasons that will become apparent shortly).

A plausible mechanism for the formation of **2** is shown



below. It might be supposed that the reaction is actually catalyzed by acid in a process involving three steps: protonation of the carbonyl group in the quinone methide, addition of the

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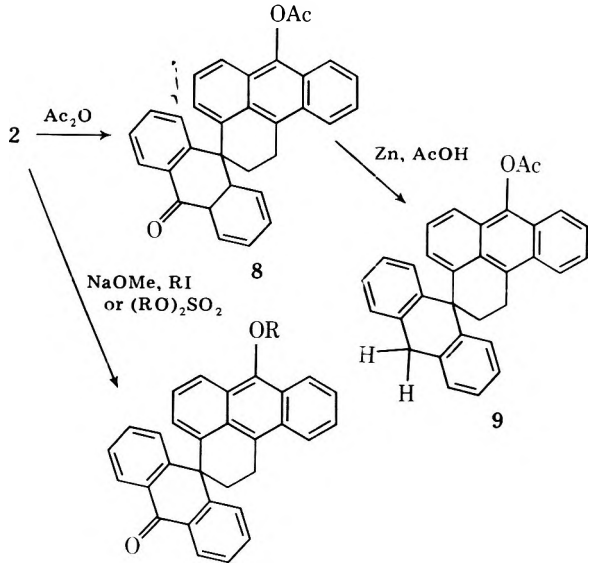
carbocation moiety of **6** to the methylene group of a second quinone methide molecule, and internal cyclization of **7** to form **2** and regenerate the proton. Methyleneanthrone is known to form solid colored complexes with metal halides such as chlorides and bromides of boron and aluminum, in which the carbonyl group of **1** coordinates with metal halides.[4] Many quinones also form hydroxy carbocations in strong acids while undergoing protonation of the carbonyl group in the quinones. These facts support the mechanism for the formation of **2** in the reactions of **1** with acid catalysts as discussed above. The reaction of quinone methides has not been known to form cyclobutane derivatives.

In acetic anhydride, **2** rearranged with simultaneous ring expansion to yield acetylated product 7-acetoxy-1,2-dihydro-3*H*-benz[*de*]anthracene-3-spiro-10′-anthrone (**8**, 64%). The structure of **8** was evident from the fact that it formed 10-(1-anthraquinonyl)-10-carboxymethylanthrone (**19**) on oxidation with chromium trioxide. Reduction of **8** with zinc powder in acetic acid gave 7-acetoxy-1,2-dihydro-3*H*-benz[*de*]anthracene-3-spiro-10′-(9′,10′-dihydroanthracene) (**9**), carbonyl group being reduced. The product **9** could also



10a, R = Et
b, R = Me

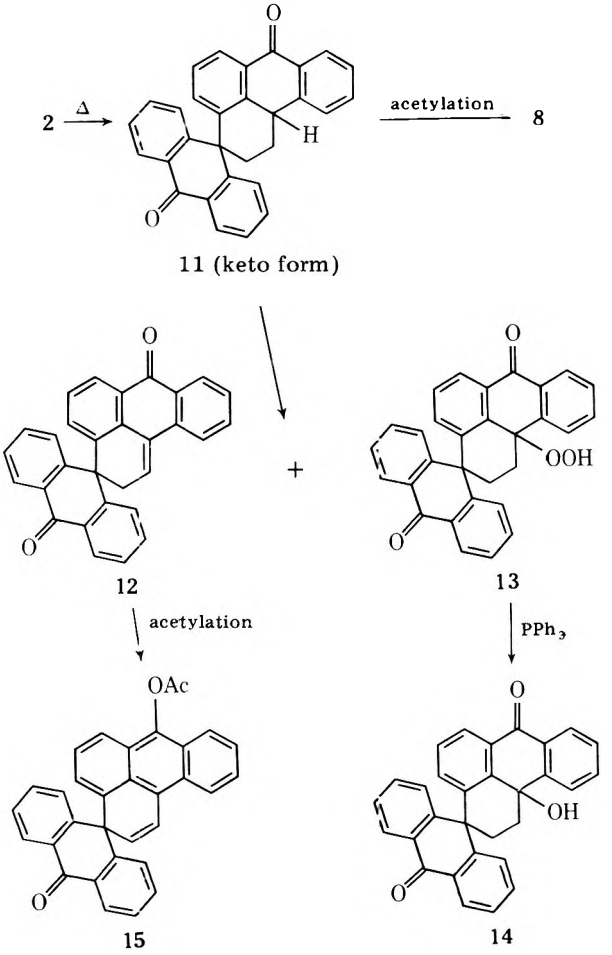
be formed from **2** with zinc powder and acetic anhydride. The reaction of **2** with ethyl iodide and methyl iodide in boiling methanolic sodium methoxide gave 7-ethoxy-1,2-dihydro-3*H*-benz[*de*]anthracene-3-spiro-10′-anthrone (**10a**, 45%) and 7-methoxy compound (**10b**, 42%), respectively, as the major products. Spiroanthrones **10a** and **10b** could also be prepared in ca. 90% yields by the reaction of **2** with diethyl sulfate or dimethyl sulfate in hot ethanolic potassium hydroxide. The structures of these compounds were confirmed by direct comparisons with the authentic samples prepared independently.[2c,3b]

Spiroanthrone **2** readily rearranged in refluxing solvents with ring expansion followed by autoxidation or dehydrogenation to benzanthrone derivatives. Under the atmosphere, the thermal reaction of **2** in benzene led to 1,2,3,11b-tetrahydrobenz[*de*]anthrone-3-spiro-10′-anthrone (**11**), 2,3-dihydrobenz[*de*]anthrone-3-spiro-10′-anthrone (**12**, 15%), and 1,2,3,11b-tetrahydro-11b-hydroperoxybenz[*de*]anthrone-3-spiro-10′-anthrone (**13**). The thermal reaction of **2** using other organic solvents also gave similar results. In this reaction, the formation of hydroperoxide was suggested by a positive peroxide test, the presence of a strong parent peak for **13** at *m/e* 444 in the mass spectrogram, and its infrared absorption for hydroxy group at 3350 cm^{-1}. The structure of **13** was confirmed by the fact that it formed 1,2,3,11b-tetrahydro-11b-hydroxybenz[*de*]anthrone-3-spiro-10′-anthrone (**14**) on reduction with triphenylphosphine. The formation

Table I. Reaction of 10-Methyleneanthrone with Acid Catalysts[a]

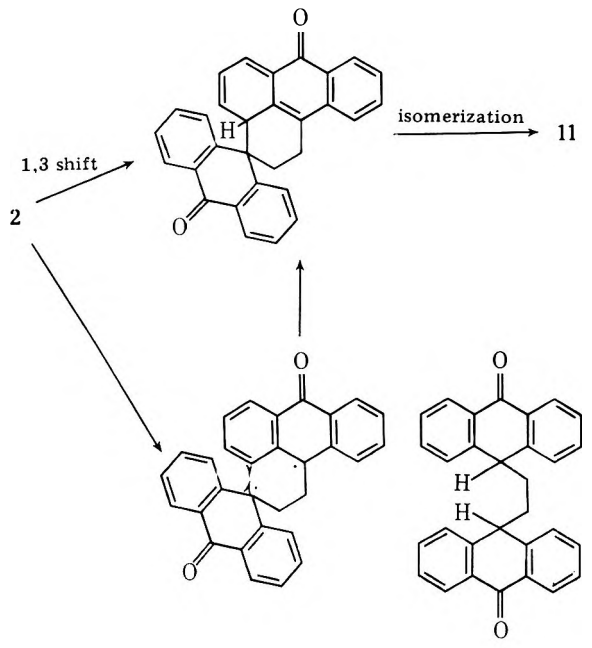
Catalyst (mmol)[b]	Solvent (mL)[c]	Yield, %[d]
HCl (20)	CH_3OH (500)	82
HCl (20)	C_2H_5OH (500)	65
HCl (20)	n-C_3H_7OH (200)	52
HCl (20)	n-C_4H_9OH (50)	97
HCl (20)	CH_3COOH (150)	41
H_2SO_4 (20)	CH_3OH (500)	74
$AlCl_3$ (15)	CH_3OH (500)	82
$FeCl_3$ (60)	CH_3OH (500)	76
$BF_3 \cdot O(C_2H_5)_2$ (15)	C_6H_6 (100)	54
p-$CH_3C_6H_4SO_3H$ (20)	CH_3OH (500)	51
$H_6P_4O_{13}$ (20)	CH_3OH (500)	50

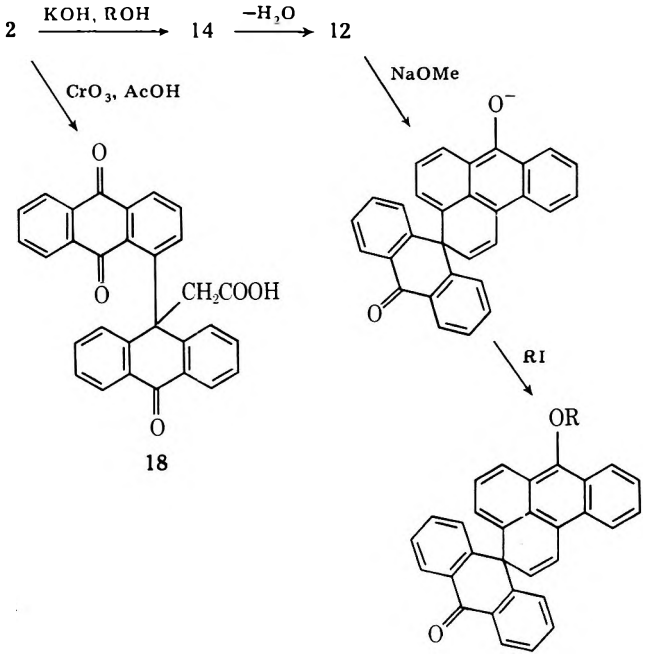
[a] Reaction of **1** (10.3 g, 50 mmol) was carried out at the temperature of the refluxing solvent. [b] The minimum amount of acid catalysts required to react. [c] The minimum volume of solvents required to dissolve **1**. [d] Isolated yields of pure dimeric product; not corrected for the recovered starting material and by-products.



of **11** was suggested by the fact that the acetylated product of the thermal reaction mixture contained **8**. Under the atmosphere spiroanthrone **11** could not be isolated due to its extreme reactivity, and attempts to isolate it led to **12** and/or **13**. The thermal reaction of **2** in solvents under a nitrogen atmosphere mainly yielded **11**. In this case, the analysis of the acetylated products of the reaction sample in benzene by NMR showed that these contained **8** and **15**. Quantitative calculations based on the NMR spectrum showed that the composition of the acetylated products was **8** (95%) and **15**

Scheme I





(5%). The bulk thermal reaction of **2** at its melting point gave **12** (68%).

Two pathways (the biradical and 1,3-sigmatropic pathways) for the rearrangement of **2** are conceivable. If the biradical pathway is operative, **2** would be expected to give 1,2-dianthronylethane (**16**)[5] from the reaction of biradical which abstracts a proton from solvent. However, **16** was not detected in any of the thermal reaction products from **2** even in solvents, such as alcohols, diphenylmethane, or decalin. The presence of the biradical was not confirmed by the ESR measurements of the thermal reactions of **2**. For this rearrangement the sigmatropic pathway rather than the biradical one in Scheme I is seemingly demanded by these facts. However, it does not seem likely that the rearrangement proceeds by the sigmatropic pathway, since thermal 1,3-antarafacial shift with retention is rendered inaccessible by the steric situation at the migrating center. It is probable that the intramolecular cyclization is favorable over the intermolecular reaction, so that **16** is not produced, and also that the cyclization proceeds too fast to detect the ESR signal of the biradical. Therefore, it seems likely that the rearrangement proceeds by the biradical pathway, being followed by isomerization. Analogous reactions have been reported in conversion of vinylcycloalkanes to cycloalkenes[6] and of dibenz[2,4]spirenes to pentalene derivatives.[7]

The reaction of **2** with potassium hydroxide in methanol gave **14** (44%), which was dehydrated to **12** (93%) by refluxing in acetic acid. Although the mechanism of this reaction has not been established, spiroanthrone **14** appears to be obtained by oxidation of **11** which is produced as an intermediate in the rearrangement of **2**. Spiroanthrones **12** and **14** were acetylated in acetic anhydride, yielding acetylated product **15** (67–69%). Alkylation of **12** by the way described for **2** gave 7-ethoxy-3*H*-benz[*de*]anthracene-3-spiro-10′-anthrone (**17a**) and 7-methoxy compound (**17b**). Acetylation and alkylation of **12** involve enolization by a transfer of hydrogen from C-2.[8] Oxidation of **2** by chromium trioxide in acetic acid gave **18** as the main product (47%) along with a small quantity (<2%) of anthraquinone. Under the same conditions, oxidation of **8**, **10**, and **12** gave similar results. The oxidation product **18** reacted with alcohols in the presence of a small amount of hydrogen chloride to yield esters (**19**).

It now appears that 10-methyleneanthrone (**1**) is dimerized by acid catalyst to give spiroanthrone **2** which rearranges readily into the benzanthrone derivatives. It seems reasonable that the reactivity in the rearrangement of **2** depends primarily on strains in the cyclobutane ring. In this case it is almost certain that steric repulsion by the large anthronyl groups may increase these strains. Similar rearrangement of various 2′,2′-disubstituted spirocyclopropaneanthrones will be described in subsequent publications.

Experimental Section

Melting points were determined with a Meihoh thermoanalyzer MP-2. Elemental analyses were performed on a Coleman Model 33 carbon hydrogen analyzer. Infrared, 60-MHz NMR, and mass spectra were obtained with JASCO Model IRA-1, JEOL JNM-3H-60, and JEOL JMS-01SG-2, respectively. The NMR measurements were made at ambient temperature on dilute solutions containing Me_4Si as internal standard. The column chromatography was carried out on silica gel M and the TLC used on 0.25 mm thick silica gel G layers. Substances were visualized on these plates either by exposure to iodine vapor or by spraying an alkaline sodium dithionite solution.

Materials. The chemicals used were either highly purified articles of commerce or materials prepared by standard literature, as indicated below. Purities were verified by spectral measurements, TLC, VPC analyses, and the determination of appropriate physical constants.

Reaction of 10-Methyleneanthrone (1) with Acid Catalysts. Fine powder of **1**[3b] was completely dissolved in solvent with stirring and refluxing. Acid catalyst was then introduced dropwise into the mixture during 5 min, while stirring and refluxing were continued. Almost immediately the color of the mixture changed to light brown and the product precipitated slowly. After an additional 20 min of stirring and heating, the hot mixture was filtered, and the recovered solid was washed several times with methanol; the product was pure anthrone-10-spiro-1′-cyclobutane-2′-spiro-10″-anthrone (**2**) as light yellow microcrystals: mp 248–250 °C (lit.[1] 254 °C); IR (KBr) 1670 cm^{-1} (ArCOAr C=O), no OH; mass spectrum (75 eV) *m/e* 412 (M^+), 410, 394, 383, 326, 206, 193, and 178. Anal. Calcd for $C_{30}H_{20}O_2$: C, 87.36; H, 4.89. Found: C, 87.40; H, 4.96. The results are summarized in Table I.

Acetylation of 2. A solution of concentrated sulfuric acid (1 mL) in acetic anhydride (5 mL) was added to a suspension of **2** (5.16 g, 12.5 mmol) in acetic anhydride (200 mL). The mixture was stirred and heated under reflux for 1 h. The color of the mixture gradually changed from yellow to greenish yellow. The hot mixture was filtered, and water (500 mL) was added. The mixture was shaken until acetic anhydride was completely hydrolyzed. The yellow solid was collected by filtration and washed with water; the solid then weighed 5.07 g and melted at 273–275 °C. Two recrystallizations of the product from

acetic acid gave 3.64 g (64%) of 7-acetoxy-1,2-dihydro-3*H*-benz[*de*]-anthracene-3-spiro-10′-anthrone (**8**) as microcrystals: mp 283 °C; IR (KBr) 1754 (ester C=O), 1665 cm^{-1} (ArCOAr C=O); NMR ($CDCl_3$) δ 2.35 (t, 2, J = 6.2 Hz, CH_2CH_2Ar), 2.67 (s, 3, CH_3), 3.48 (t, 2, J = 6.2 Hz, CH_2Ar), and 6.5–8.5 (m, 15, aromatic **H**); mass spectrum (75 eV) m/e 454 (M^+), 412, 383, and 193. Anal. Calcd for $C_{32}H_{22}O_3$: C, 84.56; H, 4.88. Found: C, 84.58; H, 4.94.

Reduction of 8. A solution of **8** (4.54 g, 10.0 mmol) in acetic acid (150 mL) was stirred and heated under reflux with zinc powder (20 g) for 15 h. The color of the mixture gradually changed to yellow with a blue fluorescence. The hot mixture was filtered, and water (500 mL) was added to the filtrate. The light yellow solid was recovered by filtration and washed with water; the solid then weighed 4.50 g. The product was purified by column chromatography using benzene as developer. Evaporation of appropriate fractions yielded 2.55 g (58%) of 7-acetoxy-1,2-dihydro-3*H*-benz[*de*]anthracene-3-spiro-10′-(9′,-10′-dihydroanthracene) (**9**) as light yellow microcrystals (single spot on TLC): mp 258–259 °C; IR (KBr) 1760 cm^{-1} (ester C=O); NMR ($CDCl_3$) δ 2.28 (t, 2, J = 6.2 Hz, CH_2CH_2Ar), 2.67 (s, 3, CH_3), 3.36 (t, 2, J = 6.2 Hz, CH_2Ar), 4.25 (center of AB quartet, 2, J = 21.0 Hz, $\delta_A - \delta_B$ = 13.5 Hz, 9′-**H**), and 6.7–8.3 (m, 15, aromatic **H**); mass spectrum (75 eV) m/e 440 (M^+), 398, 319, 289, and 207. Anal. Calcd for $C_{32}H_{24}O_2$: C, 87.25; H, 5.49. Found: C, 87.40, H, 5.39.

Reaction of 2 with Alkyl Iodides and Sodium Methoxide in Methanol. Sodium methoxide (1.60 g, 29.6 mmol) was added with stirring to a gently refluxing mixture of **2** (2.00 g, 4,85 mmol) in methanol (100 mL). Ethyl iodide (58.5 g, 0.375 mol) was then introduced dropwise into the dark red-brown mixture during 20 min while stirring and heating were continued. After an additional 35 min of heating, the mixture (now a pale yellow solution) was concentrated at the boiling point until precipitation occurred, cooled to room temperature, and filtered. The recovered solid was washed with several small portions of cold methanol; the solid then weighed 1.08 g. The product was purified by the column chromatography using benzene as developer. A recrystallization of the appropriate fraction from methanol–benzene gave 0.96 g (45%) of pure 1,2-dihydro-7-ethoxy-3*H*-benz[*de*]anthracene-3-spiro-10′-anthrone (**10a**) as bright yellow microcrystals, mp 238–239 °C (lit.[2c,3a] mp 236–237.5 °C), which were shown to be identical with an authentic sample of **10a** by NMR and IR spectral comparisons and mixture melting point test.

Similar reaction of **2** with methyl iodide gave 1,2-dihydro-7-methoxy-3*H*-benz[*de*]anthracene-3-spiro-10′-anthrone (**10b**, 42%) as bright yellow microcrystals, mp 240 °C (lit.[2c,3a] mp 237–239 °C), which were shown to be identical with an authentic sample of **10b**.

Reaction of 2 with Dialkyl Sulfates. A solution of potassium hydroxide (0.56 g, 10 mmol) in absolute ethanol (10 mL) was added to 2.06 g (5.00 mmol) of **2** dispersed in absolute ethanol (50 mL) and the mixture was heated to 50 °C during 2 min with stirring. Diethyl sulfate (2 mL) was added, and stirring was continued at 50 °C until the color of the mixture changed to pale yellow (5–10 min required). Increments of potassium hydroxide and diethyl sulfate were added alternately in a similar manner until a solution of base (5.6 g, 0.10 mol) in absolute ethanol (100 mL) and 20 mL (23 g, 0.10 mol) of the sulfate had been introduced. After cooling to room temperature, the mixture was filtered, and the recovered solid (largely inorganic) was washed several times with fresh portions of ethanol. The filtrate and washing were combined, concentrated by distillation, and diluted with water until the boiling solution exhibited a slight turbidity. Cooling yielded a precipitate, which was collected in the usual way. This product weighed 2.06 g and melted at 234–235 °C. The product was recrystallized from methanol–benzene to give 1.09 g (86%) of pure **10a**. Analogous reaction of **2** with dimethyl sulfate gave **10b** (93%).

Thermal Reaction of 2. A. In Solvents. A suspension of **2** (2.06 g, 5.00 mmol) in dry benzene (300 mL) was heated under reflux for 5 h. The color of the mixture gradually changed from initial light yellow to colorless at the end. TLC (benzene) of the initial mixture showed a major spot having R_f 0.30 corresponding to **2** and two minor spots having R_f 0.35 and 0.12 corresponding to 2,3-dihydrobenz[*de*]-anthrone-3-spiro-10′-anthrone (**12**) and hydroperoxide (**13**), respectively. At the end of the reaction TLC showed a minor spot having R_f 0.30 and two major spots having R_f 0.35 and 0.12. The final mixture contained a white solid, which was recovered by filtration and washed several times with fresh benzene. This solid (fraction A) weighed 1.06 g and gave a positive test for peroxide(s) with potassium iodide in acetic acid. Evaporation of the combined filtrate and washings yielded 0.34 g of pale yellow powder (fraction B). Two recrystallizations of fraction B from benzene gave 0.30 g (15%) of pure **12** as light yellow microcrystals: mp 298–300 °C; IR (KBr) 1665 cm^{-1} (ArCOAr C=O); NMR ($CDCl_3$) δ 3.66 (d, 2, CH_2Ar), and 6.9–8.6 (m, 16, aromatic H and C**H**=Ar); mass spectrum (75 eV) m/e 410 (M^+), 382, 354, 326, and 324. Anal. Calcd for $C_{30}H_{18}O_2$: C, 87.78; H, 4.42. Found: C, 87.50; H, 4.60.

Fraction A was slightly soluble in usual organic solvents, and the TLC (benzene) showed a spot having R_f 0.12. The mass and infrared spectra of fraction A indicated a strong parent peak for hydroperoxide (**13**) at m/e 444 and absorption for hydroxy group at 3350 cm^{-1}, respectively. Attempts to isolate **13** from fraction A were unsuccessful. A suspension of fraction A (0.44 g) in benzene (50 mL) was stirred and heated under reflux with triphenylphosphine (0.325 g, 1.2 mmol) for 3 h. The mixture was concentrated at the boiling point until precipitation occurred, cooled to room temperature, and filtered. The solid was recrystallized from chlorobenzene to yield 0.21 g of 1,2,3,11b-tetrahydro-11b-hydroxybenz[*de*]anthrone-3-spiro-10′-anthrone (**14**) as colorless microcrystals: mp 299–300 °C; IR (KBr) 3390 (OH), 1663 cm^{-1} (ArCOAr C=O); mass spectrum (75 eV) m/e 428 (M^+), 410, 400, 383, and 193. Anal. Calcd for $C_{30}H_{20}O_3$: C, 84.09; H, 4.70. Found C, 84.10; H, 4.80.

A solution of fraction A (0.5 g) in benzene (300 mL) was heated for 5 h. TLC (benzene) of a portion from the reaction mixture showed two spots having R_f 0.35 and 0.12 corresponding to **12** and **13**, respectively. Fraction A was acetylated with acetic anhydride in the manner described for **2**. Analysis of the acetylated products by NMR showed that it contained **8** and 7-acetoxy-3*H*-benz[*de*]anthracene-3-spiro-10-anthrone (**15**). These identifications were confirmed by NMR peak enhancements resulting from addition of the pure substance. Quantitative calculations based on the NMR spectrum showed that the composition of the acetylated products was **8** (29%) and **15** (71%). Acetylation of fraction A indicated that its fraction contained 1,2,3,11b-tetrahydrobenz[*de*]anthrone-3-spiro-10′-anthrone (**11**). The thermal reaction of **2** using toluene, chlorobenzene, carbon tetrachloride, alcohols, chloroform, diphenylmethane, decalin, acetic acid, and dimethyl sulfoxide as solvent gave similar results.

When a suspension of **2** in benzene under a nitrogen atmosphere was refluxed for 10 h, TLC (benzene) of the final mixture showed a minor spot having R_f 0.35 and a major spot having R_f 0.12 corresponding to **12** and **11**, respectively. The composition of the acetylated products of the final mixture was estimated by NMR as **8** (95%) and **15** (5%).

A mixture of **2** (1.03 g, 2.50 mmol) and dimethyl sulfoxide (50 mL) was degassed with nitrogen and allowed to stand at 100 °C for 1 h under a nitrogen atmosphere. After cooling to room temperature, water (300 mL) was added. The yellow solid (**11**) was then collected by filtration and washed with water. Crude **11** weighed 1.01 g (98%) and TLC (benzene) of **11** showed a spot having R_f 0.12. Owing to its instability it was examined without further treatment: mp 180–185 °C dec; IR (KBr) 1662 cm^{-1} (ArCOAr C=O); NMR (DMSO-d_6) δ 2.05–2.50 (m, 2, CH_2CH_2Ar), 3.20–3.65 (m, 2, CH_2Ar), 3.38–3.65 (m, 1, 11b-**H**), and 6.8–8.9 (m, 15, aromatic **H**); mass spectrum (75 eV) m/e 412 (M^+), 410, 394, 393, 383, 326, 276, 206, 193, and 178. Anal. Calcd for $C_{30}H_{20}O_2$: C, 87.36; H, 4.89. Found: C, 87.34; H, 4.96.

B. Bulk Thermal Reaction. Spiroanthrone **2** (2.06 g, 5.00 mmol) was heated without solvent at its melting point for 10 min. The product was purified by column chromatography using chloroform as developer. Evaporation of appropriate fractions yielded 1.39 g (68%) of pure **12**. The presence of the biradical was not confirmed by the ESR measurements (JEOL JES-ME spectrometer) of the thermal reaction sample.

Reaction of 2 with Alcoholic Potassium Hydroxide. A solution of **2** (4.12 g, 10.0 mmol) in methanol (50 mL) containing potassium hydroxide (28 g) was heated with stirring for 24 h under reflux. After cooling to room temperature, water (300 mL) was added. The solid was recovered by filtration and washed well with water; the solid then weighed 4.02 g. Two recrystallizations of the product from chlorobenzene gave 1.09 g (44%) of **14**.

A solution of **14** (1.07 g, 2.50 mmol) in acetic acid (50 mL) was refluxed with stirring for 5 h. The volume of the mixture was reduced to 10 mL by distillation. After cooling, the mixture was filtered, and the collected solid was washed with water; the solid then weighed 1.01 g. The product was recrystallized from chloroform to yield 0.95 g (93%) of pure **12**. On the dehydration of **14**, chloroform and sulfuric acid served as a substitute for acetic acid.

Acetylation of 12 and 14. The procedure employed was similar to that for acetylation of **2**. Spiroanthrone **12** (4.10 g, 10.0 mmol) was acetylated in acetic anhydride (100 mL) in the presence of sulfuric acid (1 mL). Two recrystallizations of the product from acetic acid gave 3.10 g (67%) of pure 7-acetoxy-3*H*-benz[*de*]anthracene-3-spiro-10′-anthrone (**15**) as yellow microcrystals: mp 307–309 °C; IR (KBr) 1754 (ester C=O), 1665 cm^{-1} (ArCOAr C=O); NMR ($CDCl_3$), δ 2.62 (s, 3, CH_3), 6.15 (d, 1, J = 10 Hz, C**H**=CHAr), 7.82 (d, 1, J = 10 Hz, CHAr), and 7.8–8.5 (m, 15, aromatic **H**); mass spectrum (75

eV) *m/e* 452 (M^+), 410, 381, 363, and 350. Anal. Calcd for $C_{32}H_{20}O_3$: C, 84.94; H, 4.45. Found: C, 84.94; H, 4.30.

The acetylated product **15** was also obtained analogously from **14** in a 69% yield.

Alkylation of 12 with Alkyl Iodide and Sodium Methoxide in Methanol. The procedure employed for alkylation was similar to that of **10a**. 7-Ethoxy-3*H*-benz[*de*]anthracene-3-spiro-10′-anthrone (**17a**) was obtained as yellow microcrystals in a 35% yield: mp 300–301 °C; IR (KBr) 1672 cm^{-1} (ArCOAr C=O); NMR ($CDCl_3$) δ 1.65 (t, 3, J = 7.5 Hz, CH_3), 4.30 (q, 2, J = 7.5 Hz, CH_2), 6.08 (d, 1, J = 10 Hz, CH=CHAr), 7.80 (d, 1, J = 10 Hz, CHAr), and 6.7–8.2 (m, 15, aromatic **H**); mass spectrum (76 eV) *m/e* 438 (M^+), 410, 409, 350, 276, and 274. Anal. Calcd for $C_{32}H_{22}O_2$: C, 87.65; H, 5.06. Found: C, 87.44; H, 5.00.

Methylation of **12** gave 7-methoxy-3*H*-benz[*de*]anthracene-3-spiro-10′-anthrone (**17b**, 80%) as yellow microcrystals: mp 305 °C; IR (KBr) 1670 cm^{-1} (ArCOAr C=O); NMR ($CDCl_3$) δ 4.18 (s, 3, CH_3), 6.10 (d, 1, J = 10 Hz, CH=CHAr) 7.82 (d, 1, J = 10 Hz, CHAr), and 6.7–8.2 (m, 15, aromatic **H**); mass spectrum (75 eV) *m/e* 424 (M^+) and 409. Anal. Calcd for $C_{31}H_{20}O_2$: C, 87.71; H, 4.75. Found: C, 87.54; H, 4.87.

Oxidation of 2 with Chromium Trioxide. A solution of chromium trioxide (10.0 g, 0.100 mol) in water (30 mL) was added to 4.12 g (10.0 mmol) of **2** suspended in 160 mL of acetic acid, and the resulting dark red-brown mixture was stirred and heated under reflux for 2 h. The hot mixture was filtered, the filtrate was diluted with water (1.5 L), and the solid that separated was recovered by filtration. The solid then weighed 2.51 g and melted at 290–294 °C. Two recrystallizations of the product from acetic acid gave 2.14 g (46.7%) of 10-(1-anthraquinonyl)-10-carboxymethylanthrone (**18**) as yellow microcrystals: mp 295–296 °C; IR (KBr) 1730 (acid C=O), 1668, 1640 cm^{-1} (ArCOAr and quinone C=O, respectively); NMR ($DMSO$-d_6) δ 3.50 (s, 2, CH_2), and 6.8–8.8 (m, 16, aromatic **H**, COO**H**); mass spectrum (75 eV) *m/e* 458 (M^+), 399, 313, and 206. Anal. Calcd for $C_{30}H_{18}O_5$: C, 78.59; H, 3.96. Found: C, 78.38 H, 3.99.

The oxidation product **18** was obtained in ca. 45–50% yields on similar oxidations of **8**, **10**, **11**, and **12**, respectively.

Esterification of 18. Methyl Ester (19a). A solution of 1.00 g (2.18 mmol) of **18** in methanol (60 mL) containing 5 g of hydrogen chloride was refluxed for 2 h; removal of excess reagents in vacuo and a recrystallization of the product from methanol gave 0.78 g (76%) of the methyl ester of **18** as yellow microcrystals: mp 251 °C; IR (KBr) 1745 (ester C=O), 1680, 1675, 1660 cm^{-1} (ArCOAr and quinone C=O); NMR ($CDCl_3$) δ 3.17 (s, 3, CH_3), 3.35 (s, 2, CH_2), and 6.6–8.7 (m, 15, aromatic **H**); mass spectrum (75 eV) *m/e* 472 (M^+), 399, 313, and 256. Anal. Calcd for $C_{31}H_{20}O_5$: C, 78.80; H, 4.27. Found: C, 78.87; H, 4.47.

Ethyl Ester (19b). The oxidation product **18** was esterified with ethanol in the manner described above for methyl ester. A recrystallization of the product from ethanol gave the ethyl ester of **18** as yellow microcrystals in a 80% yield: mp 253 °C; IR (KBr) 1740 (ester C=O), 1674, 1658 cm^{-1} (ArCOAr and quinone C=O, respectively); NMR ($CDCl_3$) δ 0.81 (t, 3, J = 7.5 Hz, CH_3), 3.36 (s, 2, CH_2), 3.63 (q, 2, J = 7.5 Hz, CH_2CH_3), and 6.7–8.8 (m, 15, aromatic **H**); mass spectrum (75 eV) *m/e* 486 (M^+), 399, 312, and 279. Anal. Calcd for $C_{32}H_{22}O_5$: C, 79.00; H, 4.56. Found: C, 78.90; H, 4.6.

Registry No.—**1**, 4159-04-0; **2**, 65252-91-7; **8**, 65252-92-8; **9**, 65252-93-9; **10a**, 24165-82-0; **10b**, 24215-76-7; **11**, 65252-94-0; **12**, 65252-95-1; **13**, 65252-96-2; **14**, 65252-97-3; **15**, 65252-98-4; **16**, 58382-11-9; **17a**, 65252-99-5; **17b**, 65253-00-1; **18**, 65253-01-2; **19a**, 65253-02-3; **19b**, 65253-03-4; ethyl iodide, 75-03-6; methyl iodide, 74-88-4; diethyl sulfate, 64-67-5; dimethyl sulfate, 77-78-1; 1,2-bis(9-acetoxy-10-anthryl)ethane, 58382-04-0.

References and Notes

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(5) (a) In ref 3d, it was reported that reductive dimerization of **1** by ketyl radicals gave **16**. (b) The compound **16** was prepared independently in a 96% yield by the hydrolysis of 1,2-bis(9-acetoxy-10-anthryl)ethane formed on reductive acetylation of **1** with zinc and acetic anhydride: mp 232 °C (lit.[3d] 245 °C); IR (KBr) 1665 cm^{-1} (ArCOAr C=O); NMR ($CDCl_3$) δ 1.48 (t, 4, CH_2), 4.10 (m, 2, 10-, and 10-**H**) and 7.0–8.3 ppm (m, 16, aromatic **H**); mass spectrum 414 (M^+).
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Octopus Molecules in the Cyclotriveratrylene Series

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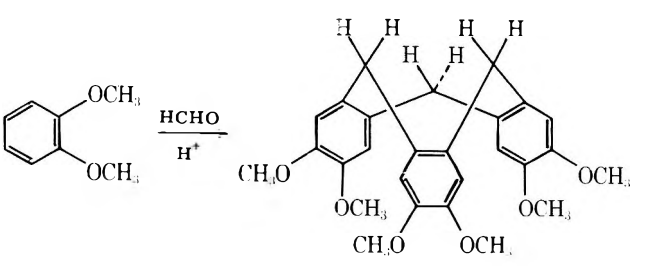
Cyclotriveratrylene (**1**) was converted into a series of oligo(ethylene glycol) ether derivatives (**3a–f**). These many-armed polyethers (octopus molecules) are capable of adopting cavity-containing conformations and possess complexing properties typical of crown ethers. Analogous derivatives of macrocycle **9** do not show crown ether behavior; this is attributed to their lack of conformational rigidity. The length of polyether arms is of less importance than the stereochemistry and conformational rigidity of the framework to which they are attached.

The condensation product of veratrole and formaldehyde, originally described by Robinson[1] and formulated as a dimer, has been shown by Lindsey[2] and by Erdtman and co-workers[3] to possess the conformationally stable[4,5] cyclotriveratrylene structure **1**. Despite the novel crown structure and known clathrate-forming ability of **1**,[3] relatively little chemistry in the series has been reported.[7–9]

Recently, Vögtle and Weber[10] demonstrated that acyclic, many-armed polyether benzene derivatives of the structural type **2** (octopus molecules) act as complex-forming ligands capable of solubilizing alkali-earth salts in aprotic organic solvents. Since such behavior is of considerable utility,[11] we undertook the synthesis and study of analogous compounds in the cyclotriveratrylene series. We anticipated that the fixed



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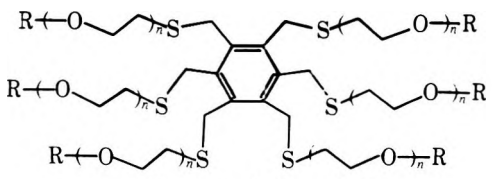
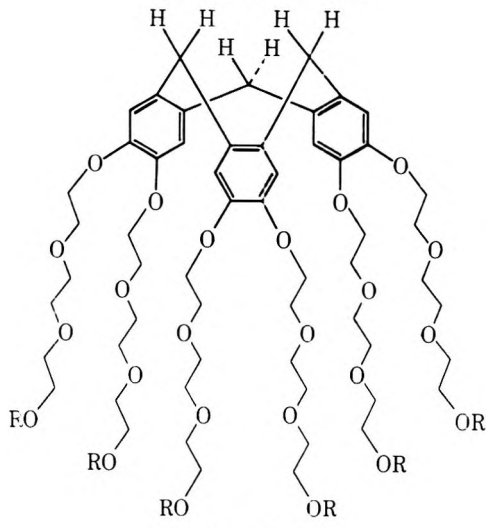


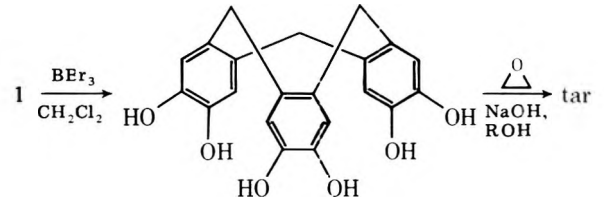
2, n = 1–4; R = alkyl



3e, R = ethyl

crown conformation of **1** would lend increased complex-forming ability to derivatives such as **3**.

Synthesis. Following Lindsey,[9] **1** was demethylated with boron tribromide to afford the air-sensitive hexahydroxy compound **4** in 73% yield. Initial attempts to react **4** with ethylene oxide in the presence of base afforded only intractable material; oxidation of **4** under these conditions occurs



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rapidly enough to preclude clean reaction. Attention was then turned to attaching preformed oligo(ethylene oxy) ether chains to **4**. Commercially available mono-, di-, tri-, and tetraethylene glycol monoethers (**5a–f**) were converted to their respective tosylates (**6a–f**) using *p*-toluenesulfonyl chloride in pyridine. Slow addition of tosylates **6a–f** to a mixture of **4** and excess sodium hydride in dry dimethylformamide (DMF) under oxygen-free conditions, followed by a brief reflux and chromatographic workup, afforded octopus molecules **3a–f** in the indicated yields (Scheme I).

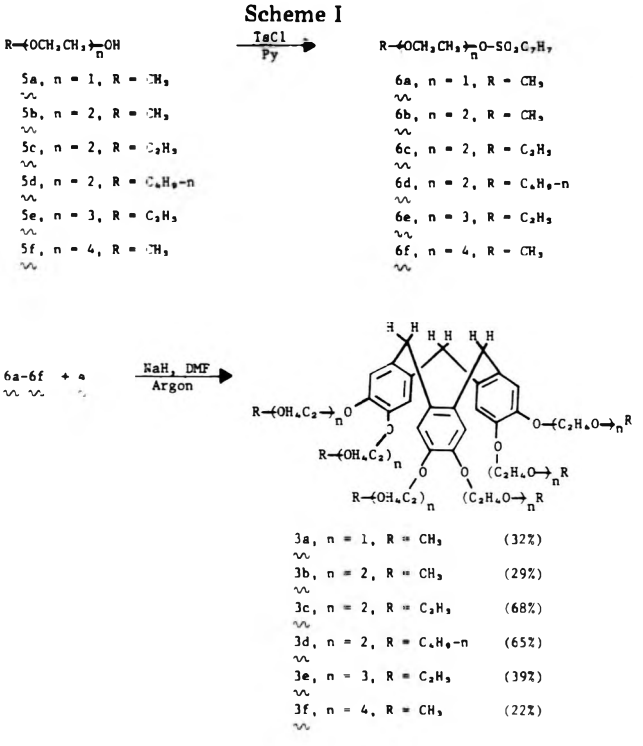
With the exception of **3a** (a crystalline solid), compounds **3** were viscous syrups which occluded solvents strongly and refused to give acceptable combustion analyses. However, high-pressure liquid chromatography showed **3a–f** to be at least 90% pure, and IR, ^{1}H NMR, and ^{13}C NMR spectra were in accord with the structures proposed. Furthermore, **3a** and **3b** were independently synthesized by the routes shown in Scheme II.

The rather circuitous route to **7a** was followed because ethylene glycol monobenzoate was much more easily isolated than either the monotosylate or monotetrahydropyranyl derivative. Compounds **3a** and **3b** produced via this sequence were identical to those prepared from **6a** and **6b**.

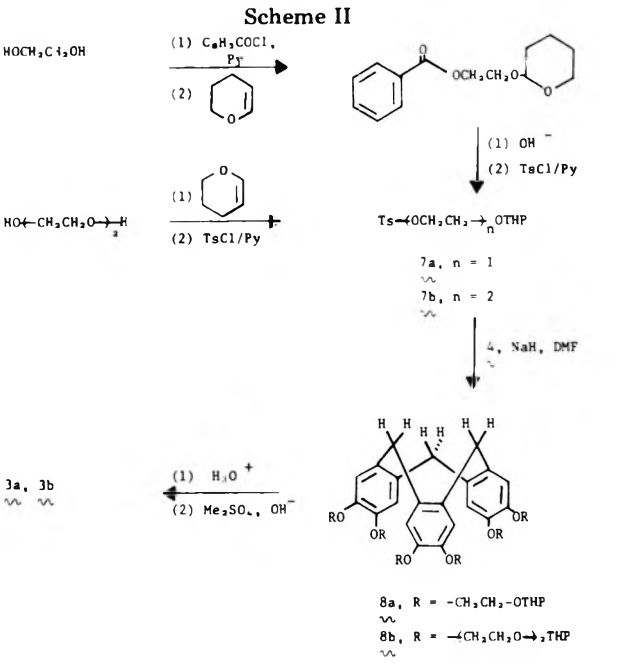
Results and Discussion

Compounds **3a–f** were examined for their ability to solvate

Scheme I



Scheme II



alkali metal salts in organic solvents; the methanol–toluene procedure of Hatay and Meth-Cohn[2] was followed. The results are shown in Table I. It will be noted that the short-armed octopus **3a** is inactive but that the solubilizing power of the longer-armed compounds **3b–f** is generally uniform and comparable to that of 18-crown-6. This contrasts with the octopus molecules **2** prepared by Vötle and Weber,[10] wherein the nature of the alkyl group R strongly influenced complexation behavior.

The importance of a framework of fixed conformation in the complexing ability of octopus molecules was also investigated. Macrocycle **9**, prepared from resorcinol and acetaldehyde,[3,13] is a mobile system which does not readily adopt a crown or bowl-shaped conformation.[14] Elaboration of **9** into octopus molecules **11a** and **11b** was carried out as shown in Scheme III.

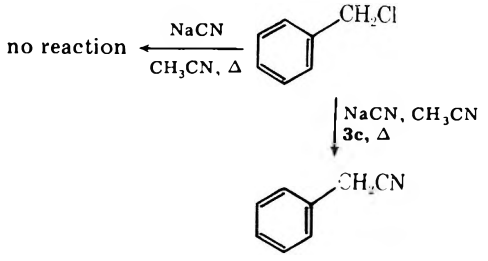
Table I. Complexation Behavior of Octopus Molecules[a,b]

Comp	NaBr	KBr	NH_4I	CsBr	BaI_2	$MgCl_2$
3a	−	−	−	−	−	−
3b	+	+	+	+	±	±
3c	+	+	+	+	±	±
3d	+	+	+	+	±	±
3e	+	+	+	+	±	±
3f	+	+	±	±	−	−
11a	−	±	±	−	−	−
11b	±	±	−	−	−	−
18-Crown-6	+	+	+	+	±	±

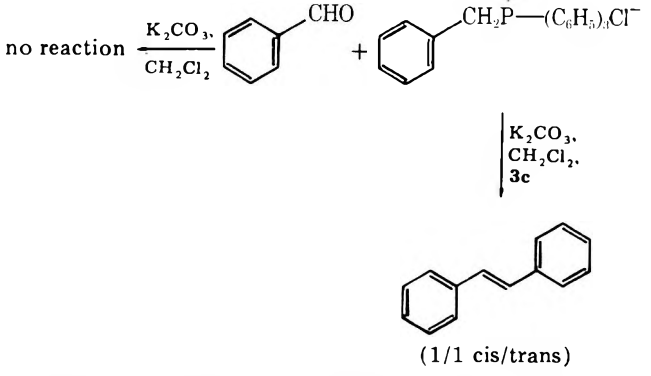
[a] Procedure of ref 12. [b] + indicates strong, rapid complexation. ± indicates weak, slow complexation. − indicates no observed complexation.

As delineated in Table I, compounds **11a** and **11b** have very little complexing or solubilizing ability. Examination of models of **11a** and **11b** demonstrates that a cavity-containing, octopus conformation of the type imposed by the rigid framework in **3a–f** cannot readily be attained in **11a** and **11b.** Therefore, conformational stability and ease of cavity formation, rather than arm length, are crucial factors for complex formation in these octopus molecules.

Although ion-selective complexation was not observed in the series **3a–f,** the utility of such compounds as catalysts was confirmed. Thus, **3c** was capable of transporting such reagents as NaCN and K_2CO_3 into polar, aprotic solvents. Benzyl chloride failed to react with NaCN in CH_3CN at reflux until 5 to 10 mol % **3c** was added; quantitative conversion to phenylacetonitrile then occurred rapidly.



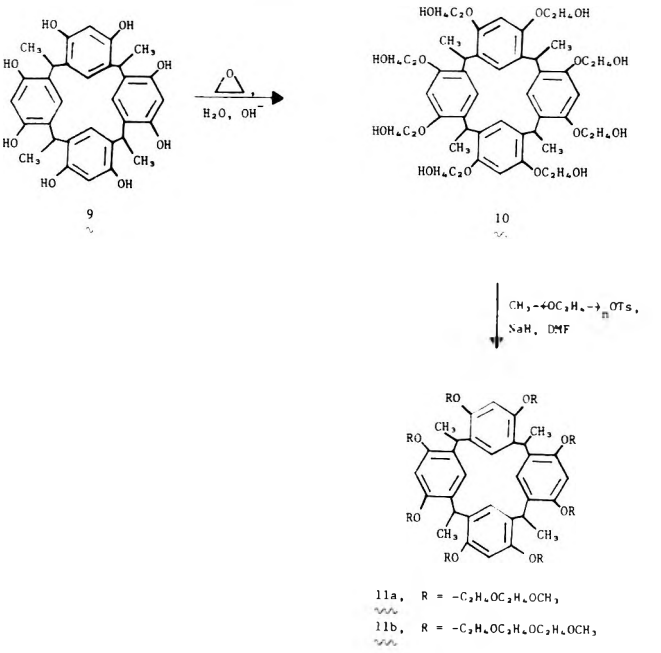
Similarly, benzaldehyde and benzyltriphenylphosphonium chloride failed to react with K_2CO_3 in dichloromethane until 10 mol % of **3c** was added; rapid conversion to 1/1 *cis-/trans*-stilbene then occurred.



(1/1 cis/trans)

Polyether derivatives of cyclotriveratrylene have been prepared and shown to be complexing agents effective in transporting alkali metal salts into polar, aprotic, organic solution. Evidence was obtained which indicates that the length of the polyether arms is of less importance than the shape and conformational stability of the framework to which they are attached. The utility of cyclotriveratrylene octopus molecules as catalysts in organic synthesis was demonstrated.[15]

Scheme III



Experimental Section[16]

Hexaol 4. A solution of 50 g of cyclotriveratrylene (**1**)[17] in 1500 mL of dry, distilled dichloromethane was stirred under argon during the addition (1.5 h, external cooling) of 200 g of boron tribromide. The reaction mixture was stirred at reflux overnight, cooled, and quenched by slow addition of 500 mL of water (external cooling). The resulting emulsion was filtered under argon (24-cm Buchner funnel) and the crude, wet solid was recrystallized from aqueous EtOH (Norit). Yield, 29.8 g (73.2%) of **4,** whose properties were as previously reported.[9]

Tosylates 6a–f. Tosylates were prepared by reaction of the corresponding alcohols **5a–f** with 1.1 equiv of *p*-TsCl in dry pyridine at 20 °C for 8 h, drowning in ice water, Et_2O extraction, and removal of solvent under vacuum. Compounds **6a–f** were all tan syrups which were used without further purification; purity was judged >95% by NMR in each case.

Octopus Molecules 3a–f. The preparation of **3e** is typical of all members of the series. A solution of 7.32 g (0.02 mol) of hexaol **4** in 100 mL of dry dimethylformamide was treated with 53.3 g (0.16 mol) of triethylene glycol monoethyl ether *p*-toluenesulfonate **6e** and stirred during argon purging for 4 h. Sodium hydride, 3.36 g (0.14 mol), was added to the reaction mixture over 1 h, and the mixture was stirred at 90 °C for 4 h. The mixture was let stand overnight, the dimethylformamide was distilled off in vacuo, the semisolid residue was diluted with 100 mL of methylene chloride and filtered, and the filtrate was stripped of methylene chloride in vacuo. The residual crude product was purified by chromatography on silica gel to afford 11.0 g of **3e** as a light yellow syrup (39% yield): IR (neat) 3.52, 6.62, 7.94, 9.0 (br), 10.5, 13.30 μm; NMR ($CDCl_3$) δ 6.91 (s, 6 H), 4.78 (d, J = 16, 3 H), 4.4–3.5 (m, 87 H), 1.20 (t, J = 7, 18 H).

Ethylene Glycol Monotetrahydropyranyl Ether Tosylate (7a). A solution of 62 g (1.0 mol) of ethylene glycol in 400 mL of pyridine was stirred at 10 °C and 1.0 mol of benzoyl chloride was added dropwise. After 3.0 h at 25 °C, the mixture was poured into 1 L of H_2O, the solid (80 g of dibenzoate) was filtered, and the filtrate was extracted with $CHCl_3$. The organic phase was dried, stripped, and distilled to give 40.2 g of ethylene glycol monobenzoate, bp 105 °C (0.5 mm). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.03; H, 6.14.

Monobenzoate (100 g) as prepared previously was treated with 0.25 g of *p*-toluenesulfonic acid and 51.0 g (1.0 equiv) of dihydropyran was added with stirring over 0.5 h. After the initial exotherm subsided, infrared analysis disclosed absence of all OH absorption. The total crude product (150 g, 0.6 mol) was added to a solution of 26 g (0.65 mol) of NaOH in 350 mL of H_2O, and the mixture was stirred at reflux for 1.0 h. The resulting homogenous solution was cooled, extracted with $CHCl_3$, dried, and stripped to afford 64.7 g (76%) ethylene glycol monotetrahydropyranyl ether as a light yellow oil. This crude product was immediately tosylated in pyridine as described for **6a–f** to give **7a** in 72% yield as a light yellow syrup that was used immediately in the preparation of **8a**.

Cyclotriveratrylene Derivative 8a. A solution of 7.32 g (0.02 mol) of **4** in 100 mL of dry dimethylformamide was purged with argon for

4 h, treated with 6.72 g (0.14 mol) of 50% NaH–oil dispersion, and stirred 1 h further under argon. An argon-purged solution of 48 g (0.16 mol) of **7a** in 25 mL of dimethylformamide was added dropwise over 1 h; the mix was heated at 80 to 100 °C for 2 h (foams), cooled, and worked up as was **3e** to give 19.4 g (85%) of **8a** as a yellow syrup. The cyclotriveratrylene derivative was used for deblocking and methylation to afford **3a** without further characterization.

Deblocking of 8a and Preparation of 3a. A solution of 17.5 g of **8a** in 150 mL of MeOH was treated (with stirring at 25 °C) with 15 mL of 10% aqueous HCl. Solid product began to crystallize after 20 min; after 8 h, the mix was cooled and filtered to give 5.96 g (61.3%) of **8a** (R = CH_2CH_2OH), mp 233 to 236 °C. An analytical sample was recrystallized from CH_3OH, and had mp 237 to 239 °C: IR (KBr) 2.95, 6.21, 6.62, 7.95, 8.77, 9.25 (br), 10.47, 11.05, and 13.41 μm; NMR (Me_2SO-d_6) δ 7.18 (s, 6 H), 4.72 (m, 12 H), 4.1–3.5 (m, 24 H); ^{13}C NMR (Me_2SO-d_6) 147.06, 132.56, 116.28, 72.89, 59.63, 35.08. Anal. Calcd for **8a** (R = CH_2CH_2OH)·CH_3OH: C, 61.62; H, 6.99. Found: C, 61.86; H, 6.79.

A sample of the crystalline alcohol thus obtained was methylated with excess dimethyl sulfate in DMF; chromatographic workup afforded **3a** as a white solid: mp 86 to 88 °C; IR (KBr) 6.21, 6.61, 7.92, 8.90, 9.15, 9.68, and 13.38 μm; NMR ($CDCl_3$) δ 6.84 (s, 6 H), 4.65 (d, J = 16, 3 H), 4.12 (m, 12 H), 3.70 (m, 12 H), 3.61 (d, J = 16, 3 H), 3.42, (s, 18 H). Anal. Calcd for $C_{39}H_{54}O_{12}$: C, 65.5; H, 7.62. Found: C, 65.6; H, 7.43.

Compound **3a** prepared from **4** and **6a** was identical in all respects to material prepared as described here. Compounds **7b**, **8b**, and **3b** were also prepared by a sequence analogous to the above.

Macrocycle 9. The macrocycle was prepared according to Niederl and Vogel.[13] It was noted that the yield of **9** was reduced and gummy by-products were formed if the rate or mode of acetaldehyde addition was changed from that reported.[13]

Octahydroxy Compound 10. A solution of 20 g of compound **9** and 5 g of NaOH in 800 mL of H_2O was heated with 25 g of ethylene oxide in an autoclave at 100 °C for 8 h. The cooled reaction mix was filtered and the crude product was recrystallized from EtOH–hexane to give 7.5 g of **10**, mp 310 to 320 °C dec. Compound **10** was characterized as the octaacetate: mp 40 to 49 °C (Et_2O–hexane); IR (KBr) 5.73, 6.65, 7.27, 8.01 (br), 8.37, 9.48 μm; NMR ($CDCl_3$) δ 7.6–6.3 (br m, 8 H), 4.7 (q, J = 7, 4 H), 4.30 (br s, 32 H), 2.16 (s, 24 H), 1.42 (d, J = 7, 12 H). Anal. Calcd for $C_{64}H_{80}O_{24}$: C, 62.32; H, 6.53. Found: C, 61.89; H, 6.68.

Octopus Molecules 11a and 11b. The preparation of **11a** is illustrative: A solution of 0.89 g (1×10^{-3} mol) of ethylene oxide adduct **10** in 5 mL of dry DMF was stirred at 25 °C under argon and treated with 0.3 g (ca. 12 equiv) of sodium hydride. A solution of 2.3 g (10 equiv) of 2-methoxyethyl tosylate in 5 mL of DMF was added over 10 min, and the mix was stirred for 2.0 h. An additional 0.10 g of NaH was added, and after 2.0 h of further stirring, the reaction mixture was poured into 250 mL of water and extracted with ether (2 × 75 mL). The dried (Na_2SO_4) extract was evaporated to leave a yellow syrup containing **11a** and excess tosylate. The mixture was separated by preparative thin-layer chromatography (TLC) and the product band was isolated to afford 1.10 g of **11a** as a clear syrup: IR (neat) 6.21, 6.33, 6.71, 7.77, 8.40, 9.10 (br), 11.8 μm; NMR ($CDCl_3$) δ 6.58 (br, 8 H), 3.5–4.8 (br m, 68 H), 3.58 (s, 24 H), 1.47 (d, J = 7, 12 H). Compound **11a** retained solvent, and combustion analysis was not obtained.

Preparation of Phenylacetonitrile from Benzyl Chloride Using 3c as Catalyst. A mixture of 0.635 g (0.005 mol) of benzyl chloride, 0.50 g of sodium cyanide (0.010 mol), 0.53 g (0.0005 mol) of **3c**, and 15 mL of acetonitrile was stirred at reflux for 3.0 h, at which time vapor-phase chromatographic analysis of the reaction mixture showed complete consumption of benzyl chloride and formation of phenylacetonitrile as the sole product. The reaction mixture was poured into water and extracted with petroleum ether to afford phenylacetonitrile and recovered catalyst **3c** (82% yield).

A control experiment in which the complexing agent **3c** was omitted gave less than 5% conversion to phenylacetonitrile in 3.0 h.

Use of Compound 3c to Catalyze a Wittig Reaction. A reaction mixture composed of 0.26 g (0.0003 mol) of compound **3c**, 0.40 g (0.003 mol) benzyltriphenylphosphonium chloride, 1.2 g (0.003 mol) of benzaldehyde, 0.33 g (0.003 mol) of potassium carbonate, and 15 mL of dichloromethane was stirred at reflux for 2 h. Analysis of the mixture at this point disclosed consumption of the benzaldehyde and benzyltriphenylphosphonium chloride and formation of 1,2-diphenylethylene (1/1 mixture of cis and trans) in about 90% yield.

Registry No.—**1**, 1180-60-5; **3a**, 65338-93-4; **3b**, 63239-73-6; **3c**, 63283-49-8; **3d**, 65338-94-5; **3e**, 63239-74-7; **4**, 1506-76-9; **5a**, 109-86-4; **5b**, 111-77-3; **5c**, 111-90-0; **5d**, 112-34-5; **5e**, 112-50-5; **5f**, 23783-42-8; **6a**, 17178-10-8; **6b**, 50586-80-6; **6c**, 54176-27-1; **6d**, 50964-16-4; **6e**, 62921-75-9; **6f**, 62921-76-0; **7a**, 65338-95-6; **8a** (R = CH_2CH_2OTHP), 65338-96-7; **8a** free hexaol, 65338-97-8; **9**, 65338-98-9; **10**, 65378-51-0; **10** octaacetate, 65338-99-0; **11a**, 65339-00-6; **11b**, 65339-01-7; ethylene glycol monobenzoate, 94-33-7; ethylene glycol monotetrahydropyranyl ether, 2162-31-4; dimethyl sulfate, 77-78-1; 2-methoxyethyl tosylate, 17178-10-8; 18-crown-6, 17455-13-9.

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(15) Portions of the work described here have been disclosed in U.S. Patent 4 018 832 (April 19, 1977, to Eastman Kodak Co.).
(16) Melting points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Model 137 instrument; ^1H NMR spectra were obtained with Varian EM-360 and JEOLCO MH-100 spectrometers, using Me_4Si internal standard. ^{13}C NMR spectra were obtained on a Brüker 90 instrument using Me_2SO-d_6 as internal standard. High pressure liquid chromatography utilized Corasil II columns on Waters equipment.
(17) Parrish Chemical Co.

Notes

A Novel Method for Direct Measurement of the pK_a's of Weakly Acidic Hydrocarbons

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In the construction of thermodynamic acidity scales for hydrocarbons, several important approaches have been used.[1-5] One of these approaches involves using kinetic acidities, a thermodynamic pK_a of a standard compound, and the Brønsted relationship.[1,3] These pK_a's are often measured in different solvents at different temperatures or under conditions where the ionic strengths or types of bases are vastly different. The importance of these differences is emphasized by comparing the ΔpK_a of picric acid vs. benzoic acid as a function of solvent. In water the pK_a difference is 3.5; in methanol, 5.3; in DMF, 9.0; and in Me_2SO, 11.9. Extreme or even subtle changes in solution conditions can greatly affect the pK_a's calculated for weakly acidic hydrocarbons (pK_a ~ 18–30). Other methods for the determination of carbon acidities have been reported recently by Jones,[6] Breslow,[7] and Bordwell.[8]

We wish to report here a relatively easy method for determining thermodynamic pK_a's of weakly acidic hydrocarbons. Our method involves the establishment of equilibrium 1.

$$RH + MeO^- \rightleftarrows R^- + MeOH \quad (1)$$

After equilibrium is attained, the anions (MeO^- and R^-) are converted to their conjugate acids (MeOH and RH) by addition of a known volume of the equilibrated solution to a quench solution with a relative high total concentration of protons and tritons of known isotopic ratio.[9,10]

$$R^- + MeO^- + \text{excess } H^+/T^+ \rightarrow RH(T) + MeOH(T) \quad (2)$$

After mixing, the hydrocarbon is quantitatively removed by extraction with toluene and washed with water to remove any remaining radioactive impurities. The hydrocarbon is then analyzed for tritium concentration by scintillation counting. This permits calculation of the concentration of RT. By knowing the initial and final isotopic ratios of H/T and the concentration of RT, the concentration of the conjugate base of RH(R^-) at equilibrium can be accurately calculated.

The isotope effect, $(K_H/K_T)^{RH(t)}$, for the hydrocarbon–methoxide reaction was calculated from K_H/K_D using the Streitweiser modification[11] of the Swain–Schaad equation.[12] The values of K_H/K_D for phenylacetylene in methanol were calculated by the method of Margolin and Long.[13] Next, the total isotope effect ratio (IER) for all of the exchangeable hydrogens was determined by permitting a mixture of phenylacetylene, methoxide, and tritiated methanol to come to dynamic equilibrium.[14] This was quenched with acidic methanol. By knowing the concentration of all species present including the ratio of protons to tritons in the solvent system, a ratio of the expected statistical incorporation to be experimentally determined quantity of tritium can be found, i.e., IER.

$$IER = \frac{[RT]\ (\text{theor eq})}{[RT]\ (\text{exptl eq})} \frac{(K_H/K_T)^{MeOH(t)}}{(K_H/K_T)^{RH(t)}} = \frac{\text{Methanol–carbanion isotope effect}}{\text{hydrocarbon–methoxide isotope effect}}$$

By this method, the solvent isotope effect for this system was determined. The data are given in Table I.

Since the concentration of R^- is known and since the concentrations of the other species of eq 1 are known or can be calculated, the equilibrium constant can be determined for the reaction by the equation

$$K_{eq}^{I} = \frac{[R^-][MeOH]}{[RH][MeO^-]} \quad (3)$$

After K_{eq}^{I} is calculated and since the K_a of methanol (in pure methanol) is known, the K_a of RH can be determined from the equation

$$K_{eq}^{I} = \frac{K_a^{(RH)}}{K_a^{(MeOH)}} \quad (4)$$

$$PhC{\equiv}CH + MeO^- \rightleftarrows PhC{\equiv}C^- + MeOH$$

The data for the determination of the pK_a of phenylacetylene at 0, 10, and 25 °C are given in Table II. These compare with a value of 23.2 in cyclohexylamine[17,18] and 28.8 in Me_2SO.[8]

Even though sodium methoxide is known to form ion pairs,[19] the activity of methoxide in the concentration used has been shown to be unity.[20] This is supported by the observation that the pK_a of phenylacetylene obtained did not vary as a function of the concentration of NaOMe used. Ion pairing for sodium phenylacetylide does not appear to be important since quenching of the ion pair vs. the free acetylide ion would give the same results.

To test this method further, we have determined the pK_a of several substituted phenylacetylenes. By this method, the pK_a of the *p*-methylphenylacetylene was determined to be 18.24 and the *p*-bromophenylacetylene to be 17.74 at 25 °C. This reflects the electron-withdrawing effects of the *p*-bromo substituent and the electron donating effects of the *p*-methyl

Table I. Rate and Equilibrium Data for Phenylacetylene in Methanol

Compound	Registry no.	Temp, °C	Slope[a]	K_H/K_D	$(K_H/K_T)^{RH(t)}$	IER	$(K_H/K_T)^{MeOH(t)}$
PhC≡CH (RH)	536-74-3	−20	687 ± 10	0.81 ± 0.02	0.74 ± 0.03	2.56	1.89
PhC≡CD (RD)	3240-11-7	−20	844 ± 9				
RH		0	9 670 ± 260	0.92 ± 0.04	0.89 ± 0.06	2.38	2.12
RD		0	10 500 ± 270				
RH		10					2.20[b]
RH		25					2.31[b]

[a] An average of 5–7 points per run. [b] Calculated by extrapolation of the K_H/K_T vs. $1/T$ plot.

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Table II. Phenylacetylene Quench Equilibrium Data[a]

Run	Temp, °C	10^2[RH], M	10^2[OMe^-], M	10^5[R^-], M	$10^{18}K_i$(MeOH), M[b]	pK_a (PhC≡CH)
50	0.0	5.30	7.63	42.0	3.09	18.50
56	0.0	3.78	7.63	29.2	3.09	18.51
102	10.0	3.91	10.2	25.3	6.76	18.37
103	10.0	5.21	10.2	35.4	6.76	18.35
91	25.0	3.67	5.09	7.43	18.7	18.13
92	25.0	3.81	10.2	14.8	18.7	18.15

[a] Average of 5–7 points per run. [b] Reference 16.

substituent as they affect the stability of the resulting anion. The pK_a values of other substituted phenylacetylenes are being determined by this procedure.

This method for the determination of pK_a's of compounds is not limited to systems that have different spectral properties for compounds and their conjugate bases. It can be used for any compound whose pK_a in methanol is between 17 and 21. The limiting factors appear to be the concentration of the anion and the activity of the quench media so that one can obtain sufficient activity above background to give meaningful data.

Experimental Section

Phenylacetylene. This was obtained from Eastman Kodak Co. The IR and NMR spectra were consistent with published Sadtler spectra. The GC analysis showed only a one-component system. High resolution mass spectrographic analysis on a JEOL JMS D100 GC-MS gave a molecular weight of 102.02.

Phenylacetylene-*d*. A procedure used by Johnson[15] was modified for the preparation of this compound. The preparation of phenylacetylene-*d* was initiated by first preparing the ethylmagnesium bromide in ether. The phenylacetylene Grignard was obtained by change of the ethyl Grignard with phenylacetylene in ether. The resulting phenylacetylene Grignard was hydrolyzed by dropping into its ether solution deuterated water (99.82% D). The newly prepared phenylacetylene-*d* was extracted with pentane and purified by distilling twice under aspirator vacuum at a temperature of 48–49 °C. The IR spectrum of phenylacetylene-*d* was similar to that of phenylacetylene except for the difference in the C–H vs. C–D bonds. The NMR showed aromatic protons at δ 7.45 ppm with no noticeable acetylenic protons at δ 3.08 ppm. High resolution mass spectrographic analysis gave a molecular weight of 103.07.

Kinetic Runs. The kinetic rate data were obtained as described previously.[a,13]

Equilibrium Quench Runs. The phenylacetylene solution was prepared by weighing, to 0.00001 g, phenylacetylene, sodium methoxide, and methanol in a 25-mL volumetric flask. The tritiated benzenesulfonic acid was prepared by the same procedure.

The equilibrium quench runs were made by mixing phenylacetylene and base and allowing the equilibrium to establish in methanol at the desired temperature. Once this equilibrium had been established, it was quenched by dropping the solution into tritiated benzenesulfonic acid in methanol. Since the proton to tritium ratio in the BSA solution is known, the concentration of the phenylacetylene anion at equilibrium can be calculated by scintillation counting.

A pro-pipet bulb equipped with a screw clamp was affixed to a graduated 10-mL pipet. The screw clamp was used on the pipet bulb so that the flow rate from the pipet could be controlled. The pipet was jacketed so that bath water (at the desired temperature) could be circulated around the pipet. Once the bath water was circulating through the jacket, the equilibrated phenylacetylene–base solution was drawn into the pipet.

Weighing vials containing the tritiated acid were placed in a bath to bring them to the same temperature as the phenylacetylene solution. After equilibration, they were placed on a magnetic stirrer and by adjustment of the flow rate with the screw clamp, the phenylacetylene solution was slowly dropped into the weighing vials, drop-by-drop, until approximately 1 mL of solution had been transferred into the vials. After the quench, the vials and their contents were weighed. The samples were then transferred to the separatory funnels, washed, and dried. A 2-mL sample of the dried toluene solution was placed in a glass scintillation vial and counted in the liquid scintillation counter.

Blanks for the quench runs were obtained, so that any radioactivity which might be due to exchange occurring after quench could be subtracted from the dpm's for each quench point. These were always very small.

Isotope Effect Ratio. In order to experimentally determine the values which a kinetic point would obtain at infinity time, selected kinetic point solutions[1a] were allowed to run for at least 20 half-lives. Some points were prepared by adding 50 μL of base and 1 mol of stock solution to a 5-mL ampule. The ampules were sealed and placed in a small jar which was submerged in the desired bath. After several days, the ampules were broken open, quenched, washed, and worked up as before.

Tritium Analysis Procedure. Scintillation vials containing 15 mL of scintillation solution (PPO and POPOP in toluene) were prepared and monitored in a nuclear Chicago Model 2 liquid scintillation spectrometer.[1a] Aliquots of samples to be counted were transferred to these vials. Tritium quench standards were used with each analysis with the appropriate standard quench correction curve being used to determine the counting efficiency. The absolute disintegration rate and thus the actual number of tritium atoms could be determined. The other calculations followed the usual analytical procedures.

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(10) (a) A comment from a reviewer suggested the possibility of an error in this measurement. When the phenylacetylene–phenylacetylide mixture is quenched with a mixture of H_2O–T_2O, it is assumed that the phenylacetylide ion will give RH/RT in the same ratio as H/T of the quench solution. This assumes little or no kinetic isotope effect on this step. It was suggested that experiments be done using a high enough concentration of base to convert all of the phenylacetylene to the acetylide ion and then quenching this. The observed H/T ratio would then give the isotope effect for that one step of the process. Several attempts to obtain these data failed due to the large heat of reaction involved with the reaction of the strong base with the strong acid. The isotope effect may be small[10b] or large[10c] which may change the pK_a values by as much as one unit, but in any case, the relative values are still correct. (b) Y. Pocker and J. H. Exner, *J. Am. Chem. Soc.*, **90**, 6764 (1968); (c) S. K. Hsu, C. K. Ingold, and C. L. Wilson, *J. Chem. Soc.*, 78 (1938).
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Use of the Tool of Increasing Electron Demand in Determination of the Status of the Yukawa–Tsuno (YT) Equation

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The YT eq 1[2] has been widely used in correlation of reactions in which a positive charge is generated in conjugation with the site of aryl substitution.

$$\log k/k_0 \text{ or } \log K/K_0 = \rho\{\sigma + r(\sigma^+ - \sigma)\} \quad (1)$$

Deviations of the parameter r from unity arise from three possible effects. (1) The substituted aryl ring is twisted out of full conjugation with the reaction site by steric interaction: a convincing example of this is afforded by the $pK_R^+ - \sigma^+$ correlation for triphenylcarbinols.[3] (2) The overall reaction correlated is of two steps, a preequilibrium and a rate-limiting step, one of which correlates with σ and the other with σ^+. The initial reaction used to elucidate eq 1, the acid-catalyzed decomposition of diazoacetophenones,[4] can be shown[5] to fall into this category. Effects 1 and 2 thus lend themselves in general to clear and unequivocal experimental elucidation. (3) The electronic demand of the reaction site differs from the defining reaction, the S_N1 hydrolysis of substituted phenyldimethylcarbinyl chlorides,[6] a factor which should be reflected in both the ρ and r values of eq 1. This last effect is the one envisaged by Yukawa and Tsuno[2] as responsible for the operation of the YT eq 1 in the cases they considered, and this has received wide support.[7,8]

On the other hand, use of the extended selectivity principle (ESP),[6] in which $\log k_X/k_H$ is plotted against ρ,

$$\log k_X/k_H = \rho\sigma^+ \quad (2)$$

where X is a strong resonance donor, generally affords reasonable straight lines indicative of an essentially constant σ^+ value. Nevertheless, occasional random deviations from precise agreement with the ESP do occur and therefore, because of the wide range of reaction types and conditions encompassed in the definition of the ρ values, there must be some doubt whether these are due to experimental errors or mechanistic ambiguities, or represent realistic manifestations of the operation of eq 1 due to effects 1, 2, or 3.

A critical, sensitive and unequivocal test of the ESP/YT treatments is therefore urgently required, and this is now amply provided by the tool of increasing electron demand initiated by Gassman and Fentiman[10] and extensively exploited by Brown and co-workers.[11] This is particularly appropriate for the following reasons. First, a standard reaction, the S_N1 hydrolysis of tertiary carbinyl systems, has been studied; the procedure is specifically designed to provide different degrees of stabilization of a carbonium ion attached to an aromatic ring, and thus differing extents of charge formation in the transition state of an S_N1 process as measured by the widely variable and often very large ρ values, *precisely the situation the YT equation was set up to elucidate* and designated here as effect 3. Second, the leaving group, *p*-nitrobenzoate (OPNB), is kept constant, as are the conditions for solvolysis (80% aqueous acetone at 25 °C). Third, sensitive tests[12,13] exist for detection of steric interactions in the molecules considered, which could lead to deviations from the ESP and values of r in the YT equation differing from unity because of ring twisting (effect 1, although these tests also give indications of steric interactions other than twisting—see below.). Fourth, and obviously most important, the substit-

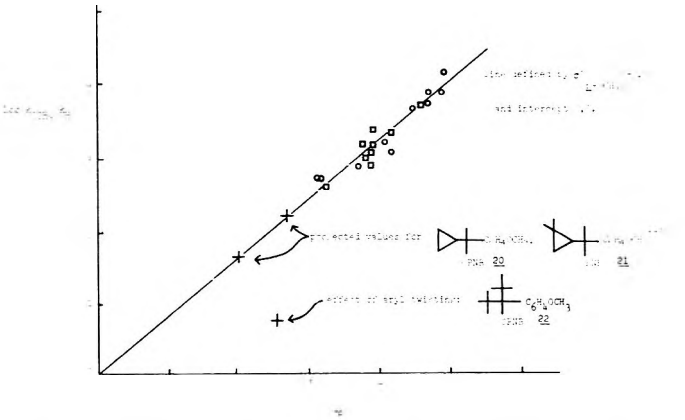
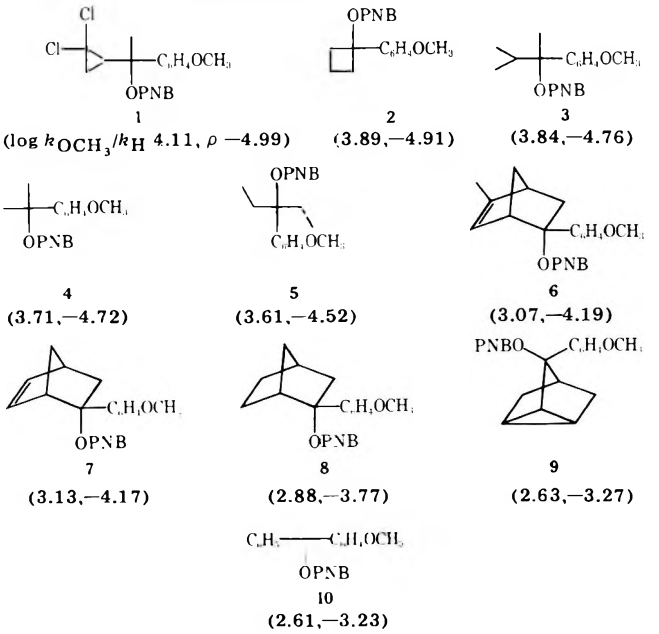
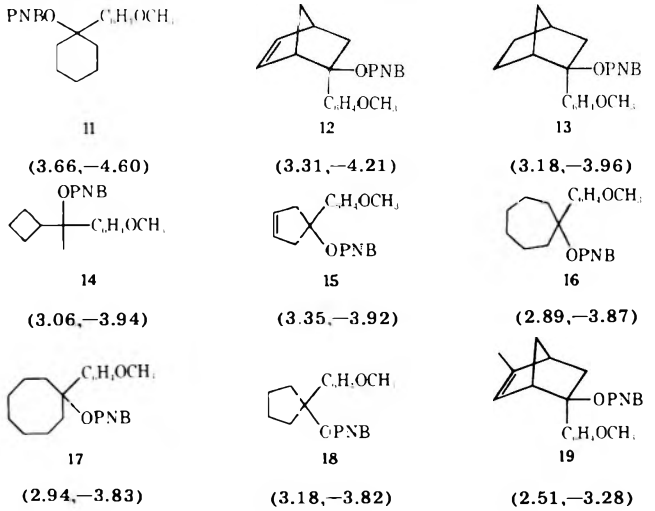


Figure 1. ESP plot: $\log k_{OCH_3}/k_H$ vs. ρ for S_N1 hydrolysis of tertiary carbinyl systems.[11] Full line is drawn with slope −0.78 (σ^+ value for *p*-OCH_3[6]) and intercept 0,0. ⊙ Substrates for which the *p*-methoxy compound was measured directly (1–10).



⊡ Substrates for which the *p*-methoxy compound was measured as the benzoate and multiplied by 20.8[14] (11–19).



Points	Slope	Intercept	Corr coeff
1–10	−0.828 (±0.065)	−0.174	0.976
1–10 and 0,0	−0.795 (±0.027)	−0.030	0.994
1–19 and 0,0	−0.805 (±0.029)	−0.050	0.988

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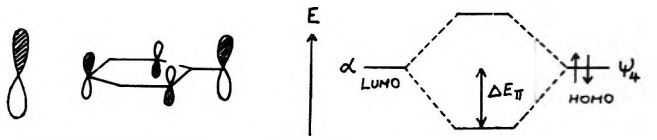

Figure 2. NBMO interaction between vacant carbon p orbital and benzyl anion.

uents measured include p-OCH_3, whose σ^+ value (−0.78) differs widely from its σ value (−0.27).

Figure 1 shows the resultant ESP plot of the log k_{OCH_3}/k_H values vs. ρ.[11] The correlation of the experimental values with the line defined by the coordinates (0,0) and the slope −0.78 is excellent. The graph also shows data for systems **11**–**19** obtained by extrapolation from benzoate hydrolysis, which also closely fit the correlation. This result clearly indicates that effect 3 is not a significant contributor to deviations from the ESP for para-substituted resonance donors. Any such deviations must be sought in the operation of effects 1 or 2, experimental errors or mechanistic complexities, of which effect 2 forms an example. **6**, **7**, and **16** have been found previously to have a degree of steric acceleration associated with them;[13] however, this steric effect does not prevent the aryl group from exerting its maximum effect on stabilizing the carbonium ion. Thus, deviations from the line in Figure 1 are indicative *specifically* of resonance loss due to twisting (effect 1). For example, various data[12,13,15,16,17] for solvolysis of aryldi-*tert*-butylcarbinyl p-nitrobenzoate reveal severe restriction of resonance due to aryl twisting (effect 1); the relevant point[15] on Figure 1 is well off the line.

Why should the methoxy substituent, and apparently other resonance donors, yield an invariant σ^+ value rather than the spectrum of values predicted? The qualitative answer may be that the energy levels defining the through conjugation responsible for adherence to σ^+ are either present or absent; the quantum theory does not permit infinite gradation. The interaction of such substituents with the carbonium ion type transition state can be pictured as a LUMO(carbonium ion)–HOMO(substituent) interaction. This leads to an interaction energy $\Delta E\pi$ of the form

$$\Delta E\pi = (C_H C_L \beta)^2/(E_L - E_H) \quad (3)$$

where $\Delta E\pi$ is the stabilization energy resulting from interaction of the substituent with the positive center, C_H and C_L are the coefficients of the HOMO and LUMO, respectively, at the point of union, and E_H and E_L are their energies. This treatment has, however, been used to argue both for variable[18] *and* constant[19] σ^+ values. In its simplest (but possibly still relevant) form the interaction may be likened to the union of a vacant carbon p orbital and the HOMO of the benzyl anion, both NBMOs (Figure 2). In this case

$$\Delta E\pi = 2\alpha\beta \quad (4)$$

where α and β are the NBMO coefficient and resonance integral, respectively.[20] α will thus measure the influence of the substituent; variations in degree of interaction between HOMO and LUMO, i.e., extent of charge development in the transition state, will be given by the β term, which has been shown to reflect variations in ρ.[20-22] It is likely that this partitioning effect may be retained in more sophisticated theoretical treatments.

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Registry No.—**1**, 61971-63-9; **2**, 64822-39-5; **3**, 41327-33-7; **4**, 23852-76-8; **5**, 64822-35-1; **6**, 54265-32-6; **7**, 37776-01-5; **8**, 20547-61-9; **9**, 55408-73-6; **10**, 60921-49-5; **11**, 60174-87-0; **12**, 37776-03-7; **13**, 20550-37-2; **14**, 62861-28-3; **15**, 57955-44-9; **16**, 64822-42-0; **17**, 64822-46-4; **18**, 57955-42-7; **19**, 54265-31-5; **20**, 41327-36-0; **21**, 61971-59-3; **22**, 65275-59-4.

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Hydrophobic Forces in Selective Hydrolyses of Nonionic *p*-Nitrophenyl Ester and Anionic 3-Nitro-4-acyloxybenzoic Acid Substrates by Hydroxamic Acids

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The elucidation of binding-step mechanism in enzyme reactions is one of the goals in biochemical researches.[1] Recently, hydrophobic (apolar) forces have received considerable attention in the biochemical studies on the hydrolysis of ester substrates by such synthetic enzyme models as poly[4-vinylimidazole],[2] a copolymer of *N*-methylacrylohydroxamic acid

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Table I. $k_{a,obsd}$ ($M^{-1}s^{-1}$) Values for the Hydrolyses of S_n and S_n^- by C_m

S_n or S_n^-	Registry no.	C_4[b]	C_4 + CTAB	r[a]	C_6[c]	C_6 + CTAB	r	C_8[d]	C_8 + CTAB	r	C_{10}[e]	C_{10} + CTAB	r
S_2	830-03-5	26.1	44.4	1.7	27.9	121.4	4.4	28.5	535.2	18.6	40.1	1032.6	25.8
S_4	2635-84-9	12.0	25.6	2.1	12.1	110.9	9.2	13.2	496.4	37.6	20.2	1296.3	64.2
S_6	956-75-2	10.8	33.7	3.1	12.4	150.6	12.2	13.2	628.8	47.6	20.0	1554.4	77.7
S_{10}	1956-09-8	0.56	33.0	58.9	0.63	152.8	242.5	1.4	759.3	542.4	5.8	2292.3	395.2
S_{12}	1956-11-2	0.15	30.6	204.0	0.35	141.3	403.7	0.77	469.5	609.7	4.7	1382.7	294.2
S_{16}	1492-30-4	0.074	4.9	66.2	0.14	19.7	140.7	0.54	168.4	311.9	4.4	450.8	102.5
S_2^-	1210-97-5	26.8	31.7	1.18	25.3	96.7	3.82	27.2	325.0	11.9	31.3	413.1	13.2
S_4^-	56003-42-0	8.3	8.7	1.05	8.6	45.9	5.34	8.8	134.9	21.0	12.2	480.0	39.3
S_6^-	65293-27-8	8.3	7.5	0.90	8.6	33.8	3.93	9.9	190.3	19.2	13.8	497.4	36.0
S_{10}^-	65293-28-9	7.3	6.2	0.85	8.7	30.9	3.55	8.7	143.6	16.5	20.3	298.4	14.7
S_{12}^-	23967-09-1	7.0	5.3	0.76	7.7	28.5	3.70	8.5	145.7	17.1	14.9	346.1	23.2
S_{16}^-	65354-57-6	0.2	5.0	25.0	0.4	25.7	64.3	1.6	156.8	98.0	9.7	312.9	32.3

[a] r = ratio of $k_{a,obsd}$ value in the presence of CTAB to that in its absence. [b] Registry no. 4312-91-8. [c] Registry no. 4312-93-0. [d] Registry no. 7377-03-9. [e] Registry no. 2259-85-0.

and 4-vinylimidazole,[3] polyelectrolytes,[4,5] *N*-alkylamines,[6] and surfactants[7-9] including L-histidine[10,11] and imidazole[12] derivatives.

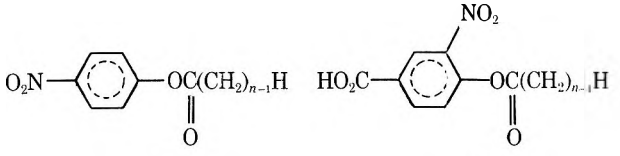
However, the magnitude of the hydrophobic interaction between substrates and catalysts is directly dependent on their apolar alkyl chain lengths and on the micellar effects of surfactants. In this regard, the previous studies on the catalytic hydrolysis of ester substrates[5,6,13] have demonstrated the importance of the hydrophobic interaction between long alkyl chains in substrates and catalysts (and/or surfactants) for the acceleration of the reaction, but there are few documents dealing systematically with the contributions of apolar chains in substrates, catalysts, and/or surfactants to the hydrophobic forces.

The present authors report, here, the selective hydrolysis of ester substrates by nucleophilic agents through the hydrophobic forces in the hydrolysis of nonionic substrates of *p*-nitrophenyl esters (S_n) or anionic substrates of 3-nitro-

$H(CH_2)_{m-1}CONHOH$

C_m

(m = 4, 6, 8, and 10)



S_n S_n^-

(n = 2, 4, 6, 10, 12, and 16)

4-acyloxybenzoic acids (S_n^-) by the nucleophilic agents of hydroxamic acids (C_m) in the absence or presence of cetyltrimethylammonium bromide (CTAB). The present hydrolysis of 5×10^{-5} M S_n and S_n^- substrates by 5×10^{-4} M C_m agents at 31.0 °C, pH 9.06 in 0.083 M Tris–KCl buffer in 10% (v/v) CH_3CN–H_2O, obeys a pseudo-first-order rate law, and the second-order rate constant $k_{a,obsd}$, which is independent of the initial concentrations of the substrates and the nucleophilic agents, was evaluated as:

$$k_{a,obsd} = (k_{total} - k_{spont})/[C_m]_0$$

where k_{total} or k_{spont} denotes respectively the first-order rate constant for the hydrolysis of S_n and S_n^- with or without C_m, and the subscript zero means the initial state of the reaction. Through the present reaction, not only the nucleophilic hydrolysis of the substrates by the C_m agent (hydroxamates at pH 9.06[14]) but also spontaneous hydrolysis of the substrates by the buffer components were recognized. However, the k_{spont} values were always less than 10% of the k_{total} ones in the absence of CTAB or less than 1% of the k_{total} ones in the presence of CTAB. Then, the effect of the apolar chain length in the S_n (or S_n^-) substrates and the nucleophilic C_m agents on the hydrolysis rate will be discussed on the basis of the $k_{a,obsd}$ values. The $k_{a,obsd}$ values obtained in a series of experiments are shown in Table I.

In the absence of CTAB, any substantial contribution of the hydrophobic forces to the hydrolysis acceleration was not recognized in the reactions between the nonionic S_n (n = 2–16) or anionic S_n^- (n = 2–16) substrates and the C_m (m = 4 and 6) agents. The C_m (m = 4 and 6) species possessing no critical micelle concentrations (cmc)[15] decrease the $k_{a,obsd}$ value monotonically with increasing the acyl chain length in the S_n and S_n^- substrates, probably due to the steric hindrance of the long acyl chains in the substrates against the interaction between the substrates and the nucleophilic C_m (m = 4 and 6) species.[5,7,12] However, the C_m (m = 8 and 10) species showing respective cmc around 1×10^{-4} and 5×10^{-5} M appreciably accelerate the hydrolyses of all the S_n and S_n^- substrates in comparison with the C_m (m = 4 and 6) ones, and, interestingly, they exhibit a selective enhancement of the hydrolysis rate of the anionic S_6^- and S_{10}^- substrates, respectively. This selective hydrolysis acceleration might be expected through the selective incorporation of the anionic S_n^- (n = 6 and 10) by the micellar C_m (m = 8 and 10) having the alkyl chain length similar to that in the said substrates through the appropriate hydrophobic interaction between them. In the case of the hydrolysis of the nonionic S_n substrates, such a selective acceleration of the reaction was not recognized. The micellar C_m (m = 8 and 10), as well as the C_m (m = 4 and 6) species, remarkably decreased the hydrolysis rates of the S_n (n = 10–16) substrates possessing long acyl chains, as compared with those of the S_n (n = 2–6) by the micellar C_m (m = 8 and 10). The sharp drop of the hydrolysis rates by the change in the acyl chain length (from n = 6 to 10) in the nonionic S_n substrates, which was also observed in their spontaneous reactions, might be due to a direct shielding of the susceptible carbonyl group in the substrates by the coiling-up of the long acyl chains.[13] Presumably, the coiling-up of the acyl chain is retarded in the anionic S_n^- substrates by the nitro and carbonyl groups on the benzene ring in S_n^-, and, consequently, the relatively high reaction rates were observed in the hydrolysis of the anionic S_n^- (n = 10–16) rather than in the hydrolysis of the nonionic S_n (n = 10–16) ones. It is noteworthy, here, that the hydrolysis of the anionic S_{16}^- substrate having cmc around 1×10^{-5} M was more markedly accelerated (as the C_m varied from m = 4 to 10) than that of the other anionic S_n^- (n = 2–12) ones which have no cmc.

Probably this is not only due to the increase in the hydrophobic interaction between S_{16}^- and C_m with increasing alkyl chain length in the latter but also due to the comicellar effect of the S_{16}^- and C_m (m = 8 or 10) micelles on the hydrolysis acceleration.

In the presence of 5×10^{-3} M CTAB surfactant (cmc = ca. 1×10^{-3} M), the micellar effect of the surfactant was substantially recognized in the present hydrolysis reactions. Such a micellar effect of surfactants on the rate enhancement of the ester hydrolyses has also been observed in the previous works.[16,17] However, the magnitude of the micellar influence of CTAB on the hydrolysis acceleration, which can be measured by the ratio of the $k_{a,obsd}$ value in the presence of CTAB to that in its absence, is fairly different between the hydrolyses of the nonionic and anionic substrates. The C_m (m = 4–10) and CTAB system increases the hydrolysis rates of both kinds of substrates, as the C_m species varies from m = 4 to 10. But, the acceleration of the hydrolysis of the nonionic S_n (n = 10–16) substrates by the C_m (m = 4–10) and CTAB system (especially by the micellar C_m (m = 8–10) and CTAB one) is remarkable in comparison with that of the hydrolysis of S_n^- (n = 10–16) by the same system, even though the hydrolyses of S_n (n = 10–16) by the C_m (m = 4–10) species are very slow in the absence of the CTAB surfactant. This is probably owing to the retardation of the coiling-up of the long acyl chain in the S_n (n = 10–16) substrates by the effective hydrophobic interaction between the S_n (n = 10–16) substrates and the CTAB micelles or between the S_n (n = 10–16) substrates and the C_m (m = 8 or 10)–CTAB comicelles; The comicelle formation of C_m (m = 8 or 10) and CTAB is attained not only through the hydrophobic interaction between them but also through the electrostatic charge attraction between the anionic C_m and the cationic CTAB.

In regard to the selective hydrolysis of the substrates in the presence of the CTAB surfactant, the comicellar system of C_8–CTAB selectively incorporated the nonionic S_{10} and the anionic S_6^-, and that of C_{10}–CTAB selected S_{10} and S_6^- (and/or S_{12}^-). The difference in the selective incorporation of the nonionic and anionic substrates by the C_m (m = 8 or 10)–CTAB comicelles is probably due to the difference in the frameworks of the above substrates. Namely, the anionic substrate (S_6^-) involves more bulky substituents in its benzene ring than the nonionic one (S_{10}). At any rate, the comicellar influence of the C_m (m = 8 or 10)–CTAB system on the S_n and S_n^- substrates was characterized by the selective incorporation of both kinds of substrates (S_{10}, S_6^- and/or S_{12}^-) through the hydrophobic approximation effect[18] of the micelles.

Experimental Section

Materials. The nucleophilic C_m (m = 4–10) agents were prepared by the reaction of $H(CH_2)_{m-1}CO_2C_2H_5$ (m = 4–10) and hydroxylamine, and satisfactory elementary analyses were obtained as below. C_4: Anal. Calcd for $C_4H_9NO_2$: C, 46.59; H, 8.80; N, 12.58. Found: C, 46.72; H, 8.34; N, 12.69. C_6: mp 45–47 °C. Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 55.55; H, 9.78; N, 10.40. C_8: mp 75.6–77.2 °C. Anal. Calcd for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.55; H, 10.52; N, 8.58. C_{10}: mp 85.9–86.7 °C. Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48. Found: C, 64.96; H, 11.10; N, 7.41.

3-Nitro-4-acyloxybenzoic acids (S_2^-–S_{16}^-) were prepared according to Overberger et al.[2] Satisfactory elementary analyses were also given for S_n^- (n = 2–16), and those for new compounds are shown below. S_4^-: mp 113–114 °C. Anal. Calcd for $C_{11}H_{11}NO_6$: C, 52.17; H, 4.35; N, 5.53. Found: C, 52.47; H, 4.25; N, 5.64. S_6^-: mp 75.0–76.0 °C. Anal. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98. Found: C, 54.86; H, 5.29; N, 4.94. S_{10}^-: mp 70.1–72.0 °C. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.29; H, 6.79; N, 4.10. S_{16}^-: mp 87.1–89.0 °C. Anal. Calcd for $C_{23}H_{35}NO_5$: C, 65.53; H, 8.37; N, 3.32. Found: C, 65.24; H, 8.21; N, 3.66.

Commercially available p-nitrophenyl esters (S_2–S_{16}) were used as nonionic substrates without further purification, because elementary analyses of S_n (n = 2–16) gave satisfactory results.

Hydrolysis. The hydrolyses of S_n and S_n^- (5×10^{-5} M) by C_m (5×10^{-4} M) were carried out at 31.0 °C, pH 9.06 in 0.083 M tris(hydroxymethyl)aminomethane buffer involving 0.083 M KCl (μ = 0.083) in H_2O including 10 vol % CH_3CN, and the reactions were followed spectrophotometically by taking notice of phenolate anion formation.

Registry No.—$H(CH_2)_3CO_2C_2H_5$, 105-54-4; $H(CH_2)_5CO_2C_2H_5$, 123-66-0; $H(CH_2)_7CO_2C_2H_5$, 106-32-1; $H(CH_2)_9CO_2C_2H_5$, 110-38-3; hydroxylamine, 7803-49-8.

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A Method for β-C-Acylation and β-Alkylation of α,β-Unsaturated Ketones

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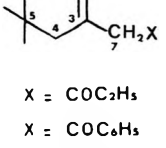
In connection with our interest in the chemistry of 3-substituted 2-cyclohexen-1-ones,[1-3] we required facile synthesis of the β-C-acyl and β-alkyl cyclenones **1**.



1a X = COC_2H_5
1b X = COC_6H_5
1c X = $CO(CH_2)_2CH(CH_3)_2$
1d X = CN
1e X = $CO_2C_2H_5$

Until now, there has been no easy method described to obtain this type of cyclenones with consistent yields.[4-6] So, taking into account the hydrolyzability of an enol ether function we synthesized **1d** and **1e**. Using this advantage and the possibility of transforming a cyano group into a carbonyl

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Table I. 3-Substituted 2-Cyclohexen-1-ones (1)

No.	Registry no.	Yields, %	IR (neat), cm^{-1}	^1H NMR δ	Bp, °C	Mass spectra *m/e* Parent	Base	Formula	Anal. Calcd C	Calcd H	Found C	Found H	Found N
1a	65253-22-7	59	1630, 1670, 1718, 3025	5.76 (s, 1, 2-H), 3.30 (s, 2, 3-CH_2), 2.50 (q, 2, CH_2 of C_2H_5), 2.18 (s, 2, 4-CH_2), 2.11 (s, 2, 6-CH_2), 1.17 (t, 3, CH_3 of C_2H_5), 1.03 (s, 6, 5-$(CH_3)_2$)	103–105 (0.4 Torr)	194 (24)	138 (100)	$C_{12}H_{18}O_2$	74.23	9.28	74.30	9.20	
1b	65253-23-8	70	1584, 1600, 1673.5, 1687.5, 3035, 3065, 3090	8.1–7.2 (m, 5, C_6H_5), 5.87 (t, 1, 2-H), 3.78 (s, 2, 3-CH_2), 2.22 (m, 2, 4-CH_2), 2.13 (s, 2, 6-CH_2), 1.03 (s, 6, 5 $(CH_3)_2$)	*a*	242 (7)	105 (100)	$C_{16}H_{18}O_2$	79.34	7.44	79.40	7.31	
1c	65253-24-9	83	1632, 1670, 1720, 3028	5.80 (s, 1, 2-H), 3.23 (s, 2, 3-CH_2), 2.41 (t, 2, CH_2 of $COCH_2$), 2.16 (s, 2, 4-CH_2), 2.13 (s, 2, 6-CH_2), 1.47 (m, 2, CH_2 of CH_2-*i*Pr), 1.27 (m, 1, CH of *i*Pr), 1.03 (s, 6, *s*-$(CH_3)_2$), 0.88 (d, 6, $(CH_3)_2$ of *i*Pr)	*a*	236 (3)	138 (100)	$C_{15}H_{24}O_2$	76.27	10.17	76.19	10.42	
1d	65253-25-0	68	1620, 1675, 2250, 3030	6.00 (t, 1, 2-H), 3.07 (s, 2, 3-CH_2), 2.23 (d, 2, 4-CH_2), 2.18 (s, 2, 6-CH_2), 1.08 (s, 6, 5-$(CH_3)_2$)	90–95 (0.4 Torr)	163 (17)	107 (100)	$C_{10}H_{13}ON$	73.62	7.98	73.82	7.99	8.10
1e	65253-26-1	53	1245, 1633, 1672, 1737, 3030	5.75 (t, 1, 2-H), 4.06 (q, 2, CH_2 of C_2H_5), 3.08 (s, 2, 3-CH_2), 2.20 (d, 2, 4-CH_2), 2.10 (s, 2, 6-CH_2), 1.25 (t, 3, CH_3 of C_2H_5), 1.05 (s, 6, 5-$(CH_3)_2$)	102–103 (0.3 Torr)	210 (11)	121 (100)	$C_{12}H_{18}O_3$	68.57	8.57	68.20	8.81	

[a] These ketones were purified on silica gel "dry column" chromatography (eluent:benzene).

Scheme I

function by catalyzed addition of a Grignard reagent,[7] we prepared **1a–c**.

The Horner–Emmons modification of the Wittig reaction[8] of the readily available ketone **2**[9] with the anions of diethylphosphonoacetonitrile (X = CN) or triethyl phosphonoacetate (X = CO_2Et) furnishes the dienes **3**, *Z* and *E*, in excellent yields (see Experimental Section).

Condensation of **3a** (*Z* and *E*) with a complex 1:1.5 of lithium perchlorate and various Grignard reagents,[7] RMgBr (R = alkyl or aryl) in ether, results in the formation of iminates **4**, which are hydrolyzed (hydrochloric acid 20%) to δ-diketones **1a–c** in good yields.

While the aqueous acid hydrolysis of **3a** and **3b** furnishes first 3-oxo-5,5-dimethyl-1-cyclohexen-1-ylacetic acid and then isophorone after decarboxylation, their hydrolysis in dioxane with acetic or formic acids leads to the expected compounds **1d** and **1e** with satisfactory yields.

These procedures have been applied only on the 5,5-dimethyl-3-ethoxy-2-cyclohexen-1-one (**2**) and they may represent new general routes for the production of 3-substituted 2-cyclohexen-1-ones from the monoenol ethers of cyclohexan-1,3-diones[9] and various Wittig reagents.

Experimental Section[10]

General Procedure for the Horner–Emmons Reaction. A solution of 0.2 mol of diethylcyanomethyl phosphonate or triethyl phosphonacetate in 100 mL of THF (purified by distillation from lithium aluminum hydride) was added dropwise, with stirring under nitrogen, to 4.8 g (0.2 mol) of sodium hydride in 100 mL of THF. The grey solution was stirred for 3 h with constant nitrogen flushing. To this solution was added 16.8 g (0.1 mol) of the dry ketone **2** in 50 mL of THF. After the addition was complete the solution was heated under reflux and stirred for 24 h (X = CN) or 48 h (X = CO_2Et). The course of the reaction was followed on VPC (Carbowax 20M 5% 170 °C). Water was added to the cold resulting solution and the mixture was extracted with ether after saturation with NaCl. The ethereal phase was washed first with HCl 20% and then with saturated $NaHCO_3$ solution. After drying over magnesium sulfate, the solvent was removed under reduced pressure giving the crude product which was purified by distillation: bp 100–106 °C (1 mm) for **3a** (yield of 92%); bp 117–120 °C (0.9 mm) for **3b** (yield of 79%). The analytical samples of the *Z* and *E* isomers of **3a** and **3b** were separated by VPC[10] ((*Z*)-**3a**:(*E*)-**3a** = 62:38; (*Z*)-**3b**:(*E*)-**3b** = 66:34).

The following spectral data were obtained: NMR (CCl_4) (*Z*)-**3a** δ 1.00 (s, 6 H), 1.37 (t, 3 H), 2.08 (s, 2 H), 2.13 (d, 2 H), 3.98 (q, 2 H), 4.63 (broad, 1 H), and 5.78 ppm (broad, 1 H); IR (neat) (*Z*)-**3a** 3055, 3040, 2200, 1612, 1585, and 1230 cm^{-1}; NMR (CCl_4) (*E*)-**3a** δ 1.03 (s, 6 H), 1.33 (t, 3 H), 2.08 (s, 2 H), 2.35 (d, 2 H), 3.95 (q, 2 H), 4.80 (broad, 1 H), and 5.36 ppm (broad, 1 H); IR (neat) (*E*)-**3a** 3045, 2200, 1612, 1585, and 1195 cm^{-1}; mass spectrum (**3a**) (70 eV) *m/e* 191 (66), 163 (base); NMR (CCl_4) (*Z*)-**3b** δ 0.96 (s, 6 H), 1.23 (t, 3 H), 1.35 (t, 3 H), 2.05 (s, 4 H), 4.03 (q, 4 H), 5.16 (s, 1 H), and 6.89 ppm (s, 1 H); IR (neat) (*Z*)-**3b** 3090, 1700, 1612, 1240, and 1150 cm^{-1}; NMR (CCl_4) (*E*)-**3b** δ 1.00 (s, 6 H), 1.23 (t, 3 H), 1.30 (t, 3 H), 2.08 (s, 2 H), 2.71 (d, 2 H), 3.81

(q, 2 H). 3.91 (q, 2 H), 5.21 (broad, 1 H), and 5.33 ppm (broad, 1 H); IR (neat) (*E*)-**3b** 3090, 1700, 1612, 1215, and 1150 cm^{-1}; mass spectrum (**3b**) (70 eV) *m/e* 238 (55), 121 (base). Anal. Calcd for $C_{12}H_{17}NO$ (**3a**): C, 75.39; H, 8.90; N, 7.33. Found: C, 75.26; H, 8.86; N, 7.46. Calcd for $C_{14}H_{22}O_3$ (**3b**): C, 70.59; H, 9.24. Found: C, 70.44; H, 9.40.

General Procedure for the Grignard Additions. To 0.05 mol of anhydrous lithium perchlorate in 40 mL of anhydrous ethyl ether under nitrogen atmosphere was added 30 mL (0.075 mol) of a solution of 2.5 M RMgBr in ether. To the homogeneous mixture was added dropwise 0.05 mol of nitriles **3** in 30 mL of ether and refluxing (the final solution must be 0.5 mol/L for nitriles). The reaction was followed by VPC (Carbowax 20M 5%, 170 °C). When it was ended (16–24 h), 100 mL of water was added slowly to the cold greenish solution, then, 200 mL of 30% HCl was added and the mixture was stirred at room temperature for 24 h. The product was extracted with several portions of ether. The combined extracts were washed with dilute sodium bicarbonate and dried over anhydrous magnesium sulfate and the ether was evaporated to give essentially the diketones (**1a–c**). The product was purified by distillation when possible or by VPC (Carbowax 20M 5%, 170 °C). (See Table I.)

General Procedure for Acid Hydrolysis of Dienes 3. A solution of 0.05 mol of diene **3** in 50 mL of dioxane, 5 mL of dry acetic acid, or 5 mL of formic acid (98–100%) was refluxed and stirred until the disappearance of diene **3** (Carbowax 20M 5%, 170 °C). The solution was concentrated under reduced pressure and the residue was diluted in ether and washed with dilute sodium bicarbonate. After drying over magnesium sulfate, the solvent was removed giving the crude product which was purified by distillation. (See Table I.)

Acknowledgment. The authors thank Philippe Abbe of I.U.T. of Marseille for his assistance.

Registry No.—**2**, 6267-39-6; (*E*)-**3a**, 65253-27-2; (*Z*)-**3a**, 65253-28-3; (*E*)-**3b**, 65253-29-4; (*Z*)-**3b**, 65253-30-7; diethylcyanomethyl phosphonate, 2537-48-6; triethyl phosphonoacetate, 867-13-0.

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(10) Boiling points are uncorrected. Infrared spectra were measured on a Perkin-Elmer 457 spectrophotometer. NMR spectra were obtained from a Varian Associates A-60-A using tetramethylsilane as an internal standard in CCl_4. Mass spectra were obtained from a MS 30 AEI spectrometer via direct insertion. GLC analyses and isolations were performed with Varian Aerograph (Model 90P) gas chromatograph equipped with thermal conductivity detector and using a 10 ft × 0.375 in. column of 5% Carbowax 20M on 80–100 mesh Chromosorb W at 170 °C (H_2 100 cm^3/min). Microanalyses were performed by CNRS.

Concerning the Reductive Alkylation of Epoxy Ketones

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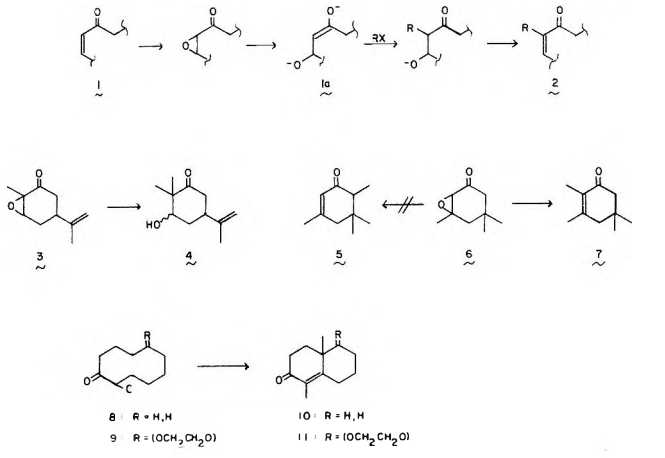
Although the direct functionalization of α,β-unsaturated ketones at the α position may be achieved via generation of the thermodynamic enolate followed by addition of an electrophile, such a sequence inevitably forms the nonconjugated enone along with varying amounts of α', γ, and polyalkylated materials.[2] This transformation is not readily accomplished in cases where electron density at the γ position proves undesirable, due to the presence of eliminatable groups, or impossible, due to the lack of an appropriate acidic hydrogen. Procedures which minimize polyalkylation have appeared but these also require the availability of an acidic γ-hydrogen.[3] A conceptually inverse sequence which achieves the same functionalization has been described.[4] This latter sequence, which relies on the regiospecific attack of an organometallic on an epoxide α,β to a hydrazone, followed by hydrolytic cleavage of the hydrazone, suffers in that it is restricted to substrates which are not otherwise reactive toward alkyl anions or the vigorous hydrolysis conditions required.

Previous work[5,6] suggested that an intermediate in the Me_2CuLi reduction of epoxy ketones, themselves readily accessible from the corresponding enones,[7] is an alkoxy enolate. Alkylation of such an intermediate[8] followed by dehydration would be expected to lead directly to an α-functionalized enone, thus effecting the transformation **1** → **2**. Such a reduction, alkylation sequence has been applied to epoxy ketones using Li/NH_3 as the reducing agent[9] and to α-bromo ketones using Me_2CuLi as the reducing agent.[10]

It was expected that if a cuprate reagent were in fact useable to form an alkoxy enolate that it would prove advantageous since cuprates (a) are known to be a milder, more selective reducing agent than metal in ammonia, thus in principle permitting the presence of unprotected ketones, esters, etc.,[11] (b) would directly form enolates in organic solvents rather than in ammonia, the former often being more amenable to further transformations,[12] and (c) are, on a small scale, more conveniently used in stoichiometric amounts than alkali metals. With these considerations in mind, we proceeded to examine the scope of such a procedure.

Results and Discussion

The dropwise addition of carvone oxide (**3**)[7] in ether to 2.1 equiv of Me_2CuLi in ether (−22 °C) followed by addition of MeI and sufficient HMPA to give a solvent composition ~15% HMPA in ether yielded, after acidic quench, 92% of alkylated hydroxy ketone **4** identical spectrally (NMR, IR) and by GC



to the material obtainable from **3** by following the Li/NH_3, MeI sequence (80% reported).[9] Ommission of MeI gave, after dehydration,[13] only carvone. Similarly, isophorone oxide (**6**),[7] undergoing dehydration on workup, yielded **7** (88%).[14] None of the isomeric **5**[15] which was independently prepared by alkylation (MeI),[16] reduction,[5a] and dehydration[13] of isophorone oxide was observed. Again, ommission of MeI returned only isophorone in nearly quantitative yield. Likewise, the epoxy octalones **8** and **9**[6] were reductively alkylated and dehydrated to give **10** (85%)[3] and **11** (70%),[17] respectively; both compounds were identical (NMR, IR, GC) to authentic samples.[18] In neither case was any starting epoxide or unalkylated enone observed in the reaction product. Under our conditions, collapse to enone followed by conjugate addition does not appear

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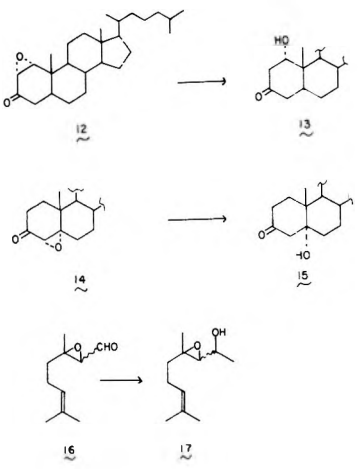
to be a competing process, contrary to the experience of Bull et al.[5a] who performed similar reductions but at higher temperatures.

We note several limitations to the procedure: (a) attempts to use such alkylating agents as BuI resulted in the formation of complex mixtures of products, presumably arising because alkylation with BuI is kinetically slower than proton transfer between alkoxy enolate and alkylated alkoxy ketone; (b) in several cases, reduction of epoxy ketones with Me_2CuLi, treatment with MeI, and finally acidic workup led at low temperatures (−22 °C or lower) to unalkylated hydroxy ketones **12** → **13** and **14** → **15**, as shown by dehydration[13] to



enones containing α-hydrogens (NMR), or at higher temperatures (>−22 °C) to complex mixtures of products (we believe this is again a result of proton transfer from alkylated alkoxy ketones to alkoxy enolates being kinetically faster than alkylation even with MeI when the alkoxy enolate salts are sufficiently hindered); (c) these alkoxy enolate salts are extremely unstable toward proton donors (it is imperative that all solvents and reagents be purified and dried immediately prior to use). Treatment of an epoxy aldehyde (**16**) with Me_2CuLi under these conditions gave an epoxy alcohol believed to be **17** (NMR, IR, MS) in accord with the work of Posner.[19]

That the species generated in these reductions (**1** → **1a**) is a dilithium salt is shown by two experiments: reduction of carvone oxide (**3**) in ether with 2 equiv of Me_2CuLi generates a yellow precipitate which may be collected by filtration in a Schlenk tube; acid hydrolysis of the ether soluble material returns 1 equiv of carvone while hydrolysis of the yellow solid proceeds with the evolution of gas and the generation of 2 equiv of base (by titration). In a separate experiment, the yellow solid was collected and treated with 2 equiv of MeLi in ether to generate an ether soluble species which transfers Me– in a 1,4 sense to enones; the yellow precipitate thus appears to be 2 equiv of MeCu.

Finally, we note that these results contrast with the finding by C. Johnson[20] that Me_2CuLi directly α-methylates α,β-epoxy esters to form α-methyl β-hydroxy esters. This difference in reactivity possibly arises as a result of an ester enolate being thermodynamically less favorable than an otherwise equivalent ketone enolate, as is reflected by the difference in their pK_a's.[2a] We suggest that comparison of the reduction potentials of epoxy ketones and epoxy esters will provide an indirect measure of the energetics governing the partition in the mode of decomposition of cuprates by either electron transfer (to form in this case a β-alkoxy enolate) or alkyl group transfer (to form an α-methyl β-alkoxy ester).[21]

Experimental Section

Unless otherwise noted, nuclear magnetic resonance spectra were obtained on Varian T60 or A-60A spectrometers and are reported in parts per million (δ) downfield of internal Me_4Si, all integrations are ±10%, IR spectra were obtained on a Perkin-Elmer 137 or 727B, and mass spectra were obtained on a JEOL Model 07 spectrometer. GC conditions are described as needed. All solvents and materials were purified and dried immediately prior to use.[22] A typical reductive alkylation procedure is described below.

3-Hydroxy-5-isopropenyl-2,2-dimethylcyclohexanone (4). To a suspension of 404 mg of CuI in 10 mL of ether at −22 °C under argon was added 2 mL of 1.9 M MeLi in ether (just enough to redissolve the yellow MeCu precipitate as Me_2CuLi). To this was dropwise added 168 mg of **3** in 2 mL of ether. A yellow precipitate forms as the addition proceeds. After 5 min, 2 mL of HMPA and 1 mL of MeI were added; the homogeneous mixture was stirred at −22 °C for 30 min, and then allowed to warm to room temperature. The mixture was added to an aqueous NH_4Cl/ether (1:1) mixture, washed with 5% HCl aqueous, saturated $NaHCO_3$, and brine, dried, and evaporated to give 170 mg of oil: ν (film) 3450, 1707, 1654, 890; δ (CCl_4) 4.72 (m, 2), 3.6–3.4 (m, 1), 2.9–2.0 (m, 6), 1.81 (s, 3), 1.2 (br s, 6); GC (10 ft × 0.25 in., 5% SE-30 on Chromosorb G, 195 °C) 3.3 min (<1%, carvone), 3.9 min (<1%, **3**), 6.4 min (2%, 3-hydroxy-5-isopropenyl-2-methylcyclohexanone),[23] 8.3 min (95%, **4**); GCMS of **4**, *m/e* 182 (M^+, 36%), 164 (76%), 139 (100%), 123 (39%), 121 (51%), 97 (90%), 81 (94%).

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Registry No.—**3**, 33204-74-9; **4**, 58008-71-2; **6**, 10276-21-8; **7**, 60417-86-9; **8**, 6432-29-7; **9**, 32137-01-2; **10**, 878-55-7; **11**, 33760-61-1; carvone, 99-49-0; 3-hydroxy-5-isopropenyl-2-methylcyclohexanone, 65378-69-0.

References and Notes

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Selective Hydrolysis of α,β- and β,γ-Unsaturated Ketals: a Method for Deconjugation of β,β-Disubstituted α,β-Unsaturated Ketones

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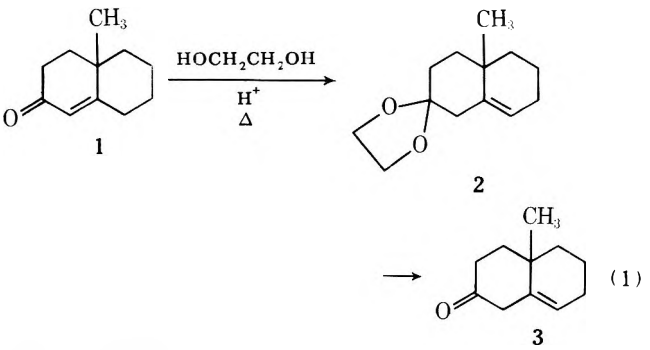
As a starting material for a synthesis project we required substantial quantities of β,γ-unsaturated ketone **3**. Although the latter can be prepared in respectable yield by deconjugation of the readily accessible[1] octalone **1** using the method[2] developed by Ringold and Malhotra, this approach had its disadvantages. It not only required the use of a large excess of strong base (10 equiv of potassium *tert*-butoxide), but the desired β,γ-unsaturated ketone was reported by these same workers[2] to be contaminated with 20% of the conjugated enone (**1**). Although other investigators[3] have studied methods for the deconjugation of α,β-unsaturated ketones, such routes invariably involve deprotonation of the starting material with strong bases, followed by acid treatment of the enolate anions formed, and lead to mixtures of both enones.

Since the ethylene ketal of 10-methyl-1(9)-octal-2-one (**1**) had been previously prepared[4] and assigned structure **2**, we decided to investigate mild conditions for its hydrolysis to the desired β,γ-enone **3** (eq 1). Use of oxalic acid dihydrate (0.5 M solution) in 95% methanol at room temperature proved unsatisfactory, since under these conditions isomerization[5] of enone **3** to conjugated octalone **1** appeared to occur faster

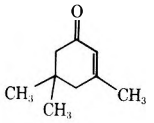
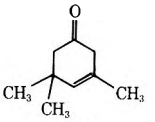
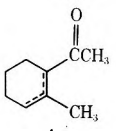
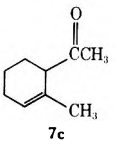


than the hydrolysis of ketal **2**. Use of 80% acetic acid at room temperature required 4 h to effect the hydrolysis of **2**, and the product was a 1:1 mixture of ketones **1** and **3** due to the apparent ease with which the latter compound isomerizes to the more stable enone **1**. However, only 5 min was required to effect the hydrolysis of ketal **2** in 80% acetic acid at 65 °C, and enone **3** could be isolated in 85% yield contaminated with a minor amount (12–15%) of the α,β isomer (**1**).

Since Santelli had reported[6] that preparation of ethylene ketals of α,β-unsaturated ketones of general formula **4** in refluxing toluene using *p*-toluenesulfonic acid as the catalyst afforded the isomeric β,γ-unsaturated ketals (**5**) in yields as high as 90%, accompanied by the anticipated product (**6**), we decided to examine conditions for the hydrolysis of these ketals (**5**) as a possible route to the deconjugated enone **7** (eq 2).

As outlined in Table I, the ethylene ketals of mesityl oxide (**4a**),[7] isophorone (**4b**),[7] and 1-acetyl-2-methylcyclohexene

Table I. Preparation[a] and Hydrolysis of Unsaturated Ketals

			Hydrolysis[c] using oxalic acid dihydrate				
			Reaction	% loss[d] of β,γ-	% yield[e] of β,γ-	Hydrolysis[f] of **5**	
Registry no.	Ketone	% yield[b] of ketals **5** and **6**	time, min	unsaturated ketal **5**	unsaturated ketal **5**	β,γ-enone **7**[g]	% yield[h] of **7**
141-79-7	$(CH_3)_2C{=}CHC(O)CH_3$ **4a**	50[i]	20	<2	57	$CH_2{=}C(CH_3)\text{-}CH_2C(O)CH_3$ **7a**	84
78-59-1	 **4b**	65[j]	10	<5	64	 **7b**	98[k]
	 **4c**	90	10	5–10	58	 **7c**	96

[a] All reactions were run using the general procedure for ketal preparation listed in the Experimental Section. [b] The ratio of β,γ-unsaturated ketal **5** to the α,β isomer **6** was 75:25 for all three systems, as determined by NMR analysis. [c] All reactions were run at room temperature in 95% methanol, the solution being 0.17 M with respect to the ketal and 0.5 M with respect to oxalic acid. [d] Determined by NMR analysis. [e] This yield is based on the starting ketal mixture (**5** and **6**). Since the latter was a 3:1 mixture of **5**:**6**, the maximum yield of β,γ-unsaturated ketal **5** would be 75%. Ketal **5** was isolated from the crude hydrolysis product by chromatography on Florisil (elution with hexane–1% ether). The rest of the material, based on NMR analysis of the crude hydrolysis product, was mainly α,β-unsaturated ketone **4**, obtained from the α,β-unsaturated ketal (**6**) present in the starting ketal mixture. [f] The hydrolysis was effected using 4:1 (v/v) acetic acid:water at room temperature for 4 h. [g] β,γ-enone **7a** has previously been prepared; see ref 5. Ketone **7b** has been reported in several papers (ref 11 and 12), while deconjugated enone **7c** was reported by Dufort and LaFontaine (ref 8). [h] Based on starting β,γ-unsaturated ketal (**5**). NMR analysis indicated the product (**7**) to be >95% pure. No starting ketal (**5**) could be detected in the isolated product. Only in the case of enone **7b** could a minor amount (2–5%) of α,β isomer (**4b**) be detected by NMR analysis. [i] The moderate yield obtained can be ascribed to the difficulty in separating the volatile product mixture [bp 59–61 °C (60 mm)] from toluene. [j] The rest of the product consisted of starting material. The ketal mixture was purified via chromatography on Florisil (50 mL/g of product; elution with hexane–1% ether). [k] After a reaction time of 2.5 h, hydrolysis of ketal **5b** was approximately 95% complete, and no isophorone (**4b**) could be detected. After 4 h, no ketal (**5b**) was left, but the reaction product contained a minor (<5%) amount of isophorone (**4b**). [l] Prepared in 52% yield by Friedel-Crafts acylation of 1-methylcyclohexene with acetyl chloride using stannic chloride as the catalyst, followed by treatment of the crude adduct with *N*,*N*-dimethylaniline under reflux. VPC analysis (6 ft × ⅛ in. SE-30 column, 150 °C) indicated the product [bp 60–70 °C (2.5 mm)] to be a 2:1 mixture of α,β- and β,γ-unsaturated ketones (retention times: 5.2 and 4.2 min, respectively). See ref 8 for further details.

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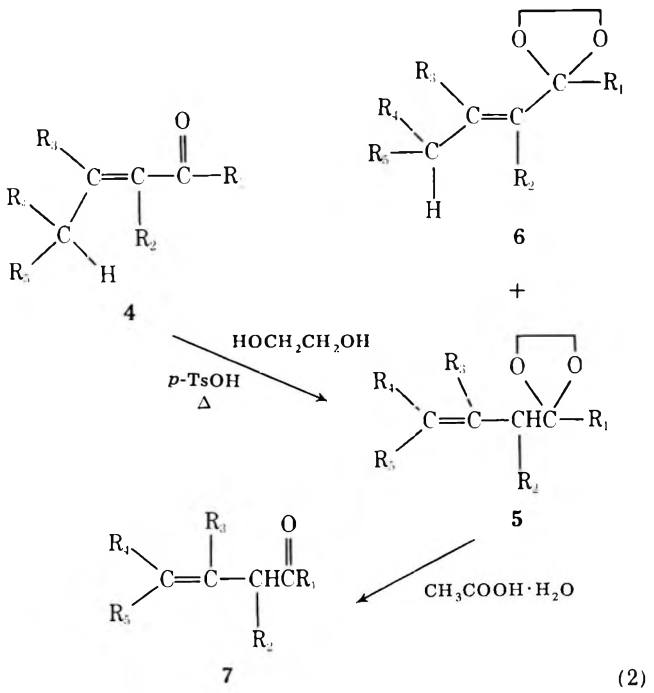

(2)

(4c)[8] were prepared and determined by NMR analysis to consist of approximately 75% of the isomerized[9] ketals (5). Treatment of the mixture of isomeric ketals with oxalic acid dihydrate in 95% methanol at room temperature for a short time, as indicated by the data in this table, led to selective hydrolysis of the α,β-unsaturated ketal (6) with minimum loss (0–10%) of the isomeric ketal (5). After purification by chromatography[10] the β,γ-unsaturated ketal (5) was able to be hydrolyzed to the corresponding deconjugated enone (7), without any concomitant isomerization,[5] by the use of 80% acetic acid at room temperature. Perhaps most remarkable about the latter transformation (5 → 7) was its successful application to the preparation of β,γ-enone **7b**[11] despite the report[12] that the latter converts slowly back to isophorone (**4b**) at room temperature and that this isomerization is accelerated slightly by a trace of acetic acid.

Our results demonstrate that preparation of ethylene ketals and their subsequent hydrolysis under the proper conditions offers an attractive method for deconjugation of α,β-unsaturated ketones of general structure **4**. Since it avoids strongly basic reaction conditions, it complements the method of deconjugation[2] developed by Ringold and Malhotra. Furthermore, it offers the additional advantage of allowing the preparation of the *pure* β,γ-enone (7), uncontaminated by the isomeric compound (4) in most cases. If the α,β-unsaturated ketone (4) obtained by the selective hydrolysis of ketal **6** is recovered[13] and converted back to the mixture of ketals (5 and 6), the overall process is quite efficient in terms of yield.

Experimental Section

General. The isolation of reaction products was accomplished by extracting thoroughly with the specified solvent. The combined extracts were washed with saturated aqueous sodium bicarbonate and saturated brine and were dried over anhydrous magnesium sulfate. The solvent was removed[14] from the dried extracts by using a rotary evaporator under reduced pressure. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The NMR spectra were recorded with a Varian A-60 NMR spectrometer and infrared spectra were obtained using a Beckman Acculab 1 spectrophotometer. The microanalysis was performed by Micro-Tech Laboratories, Inc., Skokie, Ill. 60076.

General Method for Ketal Preparation. A mixture containing 40 mmol of α,β-unsaturated ketone, 7.00 mL (125.5 mmol) of ethylene glycol, and 250 mg of *p*-toluenesulfonic acid monohydrate in 100 mL of toluene was heated at reflux for 16 h with continuous azeotropic removal of water and excess ethylene glycol by means of a Dean-Stark trap.[15] The cooled mixture was washed with saturated aqueous sodium bicarbonate and saturated brine and was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure,[14] followed by either distillation or (if contaminated by starting ketone) chromatography on Florisil (50 mL/g of the product; elution with hexane–1% ether), afforded the ketals in 50–90% yields.

Table II. ^{1}H NMR Spectral Data (CCl_4 vs. Me_4Si, δ in ppm)

Compd	Registry no.	^{1}H Chemical Shifts
5a[a]	4362-28-1	1.24 (s, CH_3), 1.80 (broad s, vinyl CH_3), 2.29 (s, CH_2), 3.85 (s, $-OCH_2CH_2O-$), 4.82 (m, $C=CH_2$)
6a	4362-31-6	1.39 (s, CH_3), 1.70 (broad s, vinyl CH_3), 1.80 (broad s, vinyl CH_3), 3.79 (s, $-OCH_2CH_2O-$), 5.23 (m, $C=CH$)
5b	65339-06-2	1.00 (s, $2CH_3$'s), 1.52 (s, CH_2), 1.65 (broad s, vinyl CH_3), 2.05 (broad s, allylic CH_2), 3.87 (s, $-OCH_2-CH_2O-$), 5.12 (m, vinyl H)
6b	65339-07-3	0.96 (s, $2CH_3$'s), 3.83 (s, $-OCH_2-CH_2O-$), 5.23 (m, vinyl H)
5c[b]	17931-72-5	1.15 (s, CH_3), 3.83 (s, $-OCH_2-CH_2O-$), 5.51 (m, vinyl H)
6c	65339-08-1	1.33 (s, CH_3)
7a	3744-02-3	1.76 (vinyl CH_3), 2.07 (s, CH_3), 3.04 (s, CH_2), 4.85 (broad d, J = 5 Hz, $CH_2=C$)
7b	471-01-2	1.03 (s, $2CH_3$'s), 1.72 (broad s, vinyl CH_3), 2.23 (s, CH_2), 2.65 (broad s, allylic CH_2), 5.43 (m, vinyl H)
7c	15564-32-6	2.05 (s, $C(O)CH_3$), 2.92 (m, $CHC=O$), 5.55 (m, vinyl H)

[a] This compound has been reported previously in the literature. See ref 6. [b] See ref 8 for a previous synthesis of ketal **5c**.

Selective Hydrolysis of the Ethylene Ketal Mixture (5b and 6b) Derived from Isophorone (4b). A solution of 1.820 g (10 mmol) of ketal mixture **5b** and **6b** and 4.34 g (34.4 mmol) of oxalic acid dihydrate in 70 mL of 95% methanol was stirred at room temperature for 10 min. The reaction was then quenched by pouring the mixture into 200 mL of cold saturated aqueous sodium bicarbonate. Dilution of this mixture with 200 mL of saturated brine, followed by extraction with ether, afforded 1.545 g of ketal **5b** contaminated by isophorone (**4b**). Chromatography[10] on Florisil (80 mL; elution with hexane–1% ether), followed by evaporative distillation, afforded 1.16 g (64%) of pure ketal **5b**: bp 40–50 °C (bath temperature, 0.10 mm); ν_{max} (film) 1675 (C=C), 1375, 1350, 1310, 1280, 1255, 1220, 1180, 1145, 1090, 1040, 985, 945, 885, 870, 795 cm^{-1}; δ_{Me_4Si} (CCl_4) see Table II. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.65; H, 9.92.

2,2-Ethylenedioxy-10-methyl-8-octalin (2). In order to ensure the absence of any α,β-unsaturated ketal, the ethylene ketal (1.074 g, 5.17 mmol) prepared from 864 mg of octalone **1**[1] using the general procedure cited above was added to 60 mL of 95% methanol containing 3.829 g (30.4 mmol) of oxalic acid dihydrate. After stirring this mixture for 10 min at room temperature, the product (975 mg) was isolated in the same manner as described for ketal **5b**. Chromatography of this material on 50 mL of Florisil (elution with hexane–1% ether) yielded 660 mg (61%) of pure ketal **2**, the spectral properties of which were identical to those previously reported[4] for this same compound.

General Procedure for the Hydrolysis of β,γ-Unsaturated Ketals (5). A solution of 1 mmol of ketal **5** in 4.0 mL of acetic acid and 1.0 mL of water was stirred at room temperature for 4 h. The mixture was then poured cautiously into 75 mL of cold aqueous sodium bicarbonate. After dilution of the mixture with 50 mL of saturated brine, the product was isolated by extraction with ether.

10-Methyl-Δ^5-octalin-3-one (3). Ketal **2** (218 mg, 1.05 mmol) was added to a mixture of 4.0 mL of glacial acetic acid and 1.0 mL of water in a flask maintained at 65 °C (bath temperature). After stirring this solution at 65 °C for 5 min, the reaction was quenched by pouring the mixture into 75 mL of ice-cold saturated aqueous sodium bicarbonate. Extraction with ether in the usual manner afforded 163 mg (95%) of

enone 3 contaminated by approximately 12–15% of the α,β-isomeric ketone (1) as determined by NMR analysis. Octalone 1 was characterized by an absorption band at δ 5.65 (vinyl H), whereas the corresponding signal for the β,γ-enone 3 occurred at δ 5.41 (m, 1 vinyl H).

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Registry No.—1, 826-56-2; 2, 3287-60-3; 3, 22789-80-6; α,β-unsaturated 4c, 2047-97-4; 1-methylcyclohexene, 591-49-1; acetyl chloride, 75-36-5.

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(7) Available from Aldrich Chemical Co., Inc., Milwaukee, Wis. 53233.
(8) Preparation of ketone **4c** has been reported several times in the Chemical literature. See N. Dufort and J. LaFontaine, *Can. J. Chem.*, **46**, 1065 (1968), and references therein.
(9) Isomerization of the double bond occurs subsequent to ethylene ketal formation. This was demonstrated by isolation of the reaction products (**5a** and **6a**) obtained from mesityl oxide (**4a**) after 3.5 h and discovering it to be a 40:60 mixture of α,β-unsaturated ketal (**6a**) and the isomeric ketal (**5a**).
(10) On a large scale, fractional distillation would be more convenient to separate β,γ-unsaturated ketal **5** from enone **4**.
(11) For previous syntheses of enone **7b**, see J. Meinwald and L. Hendry, *J. Org. Chem.*, **36**, 1446 (1971), and references therein.
(12) M. S. Kharasch and P. O. Tawney, *J. Am. Chem. Soc.*, **63**, 2308 (1941).
(13) No attempt was made to recover α,β-unsaturated ketone **4** after selective hydrolysis of ketal **6** in the presence of β,γ-unsaturated ketal **5**. However, NMR analysis of the crude hydrolysis product, prior to chromatography on Florisil, indicated the expected mixture of ketal **5** and enone **4**, accompanied by minor (1–9%) amounts of the corresponding β,γ-enone **7**.
(14) Due to their volatility, ketals **5a** and **6a**, as well as enone **7a**, were recovered from the extracts by fractional distillation of the solvent at atmospheric pressure.
(15) The apparatus described by W. S. Johnson and W. P. Schneider [*Org. Synth.*, **30**, 18 (1950)] was used to maintain a nitrogen atmosphere.

Photolysis of *o*-Phenylene Oxalate. A High-Yield Photodecarbonylation Reaction

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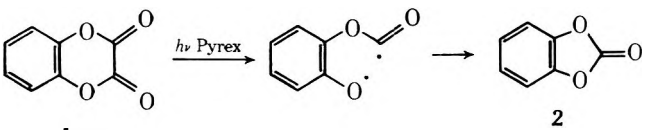
The photolysis of aryl esters in solution generally results in their rearrangement to isomeric phenolic ketones via the photo-Fries pathway.[2] Acyclic aryl oxalates, in particular, have been observed to undergo the photo-Fries rearrangement, with the simultaneous formation of phenols.[3,4] The photochemistry of cyclic oxalate esters, however, has not been studied thoroughly. We therefore have investigated the photolysis of o-phenylene oxalate (1).

In contrast to the photolysis of aryl esters in general and acyclic oxalate esters in particular, the photolysis of 1 induced the formation of no photo-Fries products. Instead, nearly quantitative decarbonylation resulted. Irradiation of deaerated hexane solutions of 1 afforded o-phenylene oxalate (2)

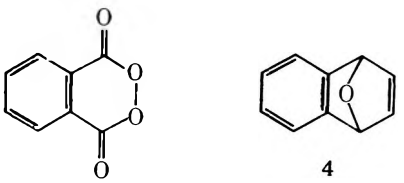


1 2

as the exclusive observed product (by NMR, VPC), identified by comparison of physical and spectral properties with an authentic sample.[5] The chemical yield of 2 was 94% (by VPC) and was found to be independent of the presence of either oxygen or acrylonitrile.

The primary photochemical reaction is evidently an α cleavage of either the acyl–oxygen bond, as is postulated for other aryl esters,[2] or the acyl–acyl bond, as is common in α-dicarbonyl compounds.[6] In any event, decarbonylation of the biradical intermediate, followed by reclosure, results in the observed carbonate 2. The formation of the typical photo-Fries product is probably precluded due to geometrical constraints.

Interestingly, o-phenylene oxalate, unlike its structural isomer phthaloyl peroxide (3), does not photodecarboxylate to benzyne.[7] Thus, photolysis of 1 in the presence of furan did not lead to a detectable amount of the known benzyne adduct 4.



3 4

As is often the case, the mass spectrum of 1, which has been reported previously,[8] parallels the photochemical results. Thus, expulsion of CO is the important initial process for 1 as well as other cyclic oxalates, while no loss of CO_2 from the molecular ion was observed.

In summary, our findings demonstrate that the photolysis of o-phenylene oxalate is qualitatively different from that of other aryl esters, in that α cleavage, followed by decarbonylation, is the exclusive reactive pathway.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 237-B instrument. NMR spectra were obtained with a Varian EM-390 spectrometer. Gas chromatography analyses were performed using a Varian Aerograph Series 2700 flame ionization instrument. Mallinckrodt spectrograde hexane was used as received.

o-Phenylene Oxalate (1). In a modification of the procedure of Gosh,[9] this compound was prepared by the dropwise addition of oxalyl chloride (1.7 mL, 20 mmol) in 5 mL of dry ether to 2.0 g (18 mmol) of catechol and 5.1 mL (36 mmol) of triethylamine in 40 mL of ether. After being stirred vigorously for 3 h, the mixture was filtered and the residue was thoroughly ether extracted. Concentration in vacuo of the combined organic materials afforded crude product, which was sublimed (90–95 °C (0.5 mm)) to give o-phenylene oxalate (2.4 g 79%), mp 185.5–186.5 °C (lit.[8] mp 185 °C), after recrystalization from benzene under nitrogen. The previously unreported spectral data were: IR ($CHCl_3$) 3010, 1805, 1790, 1495, 1740, and 1285 cm^{-1}; NMR (acetone-d_6) δ 7.28 (pseudo-s); UV (hexane) λ_{max} (ϵ) 277 broad (3060), 320 tail (990).

Photolysis of o-Phenylene Oxalate (1). Preparative runs were performed using an immersion well apparatus with a 450 W medium pressure Hg arc and a Pyrex filter sleeve. The solution was purged with dry nitrogen for 1 h prior to and then throughout the photolysis. In a typical run, 1 (90 mg, 0.54 mmol in 400 mL of hexane) was irradiated for 4 h. The course of the reaction was monitored conveniently by UV spectroscopy. Removal of solvent afforded 54 mg of o-phenylene carbonate (2).[4]

Chemical yield and quenching runs were performed using a merry-go-round apparatus with irradiation of ca. 5-mL samples in capped test tubes. Solutions were purged with nitrogen, if appropriate,

0022-3263/78/1943-1823$01.00/0

for 20 min prior to photolysis. The photolysate was analyzed directly by VPC (6 ft column of 3% SE-30 on Chromosorb G, operating between 90 and 120 °C), using dodecane as internal standard. Relative response ratios were obtained from pure authentic samples.

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Registry No.—**1**, 16536-36-0; **2**, 2171-74-6; oxalyl, 79-37-8; catechal, 120-80-9.

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Synthesis and Thermal Decomposition of 1-Methyl-1*H*,3*H*-1,2-benzisothiazole 1-Oxide Hydrochloride[1]

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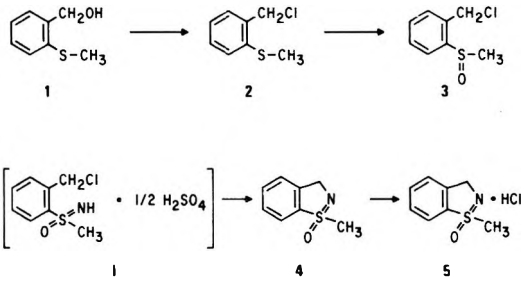
Recently there has been much interest in the sulfoximine function as a synthon and in sulfoximines which possess biological activity.[2] We wish to report the synthesis of a new heterocyclic ring system which contains the sulfoximine function, 1-methyl-1*H*,3*H*-1,2-benzisothiazole 1-oxide hydrochloride, and its thermal decomposition to afford 1,2-benzisothiazole. Experiments pertaining to the mechanism of this thermal decomposition are discussed.

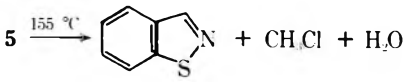
Results and Discussion

The synthesis of 1-methyl-1*H*,3*H*-1,2-benzisothiazole 1-oxide (**4**) and its corresponding hydrochloride (**5**) were accomplished by the sequence of reactions shown in Scheme I. Treatment of *o*-(methylthio)benzyl alcohol (**1**)[3] with thionyl chloride in benzene, according to the procedure of Grice and Owen,[4] afforded *α*-chloro-*o*-tolyl methyl sulfide (**2**) in 73% yield. Oxidation of **2** with *m*-chloroperoxybenzoic acid afforded the corresponding sulfoxide **3** in 54% yield. The conversion of sulfoxide **3** to the sulfoximine proved initially baffling. Treatment of **3** with sodium azide in sulfuric acid and chloroform[5] followed by a basic workup afforded a mixture of the cyclized sulfoximine free base (**4**) and its corresponding hydrochloride (**5**). Isolation of the hydrochloride from a basic workup was confusing. We were subsequently able to isolate the open ring sulfoximine intermediate as the hemi sulfuric acid salt I. Rapid basic treatment of I afforded the hydrochloride **5** in good yield; however, a more prolonged, 20 to 30 min, treatment with base afforded only the free base **4**. This results from the fact that the ring closure of the free base of I in basic medium requires 20 to 30 min for completion. If it is quickly removed from the basic medium, spontaneous ring closure occurs to afford the hydrochloride **5**. The best procedure for the preparation of **4** involves the isolation of I which is subsequently dissolved in water, made basic (pH 12), and stirred at ambient temperature for 0.5 h. Treatment of **4** with ethereal hydrogen chloride afforded the hydrochloride **5**. The structures of **4** and **5** were confirmed by elemental analyses, IR, NMR, and mass spectra (Experimental Section).

Scheme I



When the melting point of **5** was taken, it underwent a smooth gaseous decomposition at ca. 140 °C leaving a clear oil which solidified upon cooling. As a result, this decomposition was carried out on a preparative scale. Compound **5** was heated at 155 °C for 20 min in a small flask to afford a 94% yield of 1,2-benzisothiazole (**6**). 1,2-Benzisothiazole was



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identified by elemental analyses, IR, NMR, and mass spectra (Experimental Section). The organic component of the evolved gas was identified as methyl chloride by infrared and the other component was identified as water by NMR. It was found that this reaction also occurred when **5** was heated at reflux in acetonitrile and in Me_2SO at 110 °C.

The demethylation of *S*-methyl sulfoximines represents a unique reaction of the sulfoximine function. Cram and coworkers[6] observed a similar demethylation when (−)-(*R*)-methyl *p*-tolyl *N*-methylsulfoximide was treated with tosyl chloride in pyridine to afford (−)-(*R*)-*N*-methyl-*N*-tosyl-*p*-toluenesulfinamide.

Johnson and co-workers[7] reported that the reaction of *N,N*-dimethylaminomethylphenyloxosulfonium fluoroborate with sodium methoxide in refluxing methanol afforded *N,N*-dimethylphenylsulfinamide, presumably by attack of the methoxide on the *S*-methyl or by decomposition of the methylide intermediate. The thermolysis of **5** affords a new and simpler method for the preparation of 1,2-benzisothiazole.[8,9]

In an attempt to elucidate the mechanism of the thermal decomposition of **5**, the following experiments were performed. When the decomposition was terminated at about one-half completion and the reaction mixture was analyzed, only starting material and 1,2-benzisothiazole were present. The reaction was also carried out in Me_2SO-d_6 at 110 °C in an effort to detect any transient intermediate by NMR and TLC; however, none was observed. The thermal decomposition of the deuteriochloride salt of **4** afforded 1,2-benzisothiazole which had incorporated **4** to 5% deuterium at the 3 position (mass spectrum analysis). A kinetic study comparing the relative rates of 1,2-benzisothiazole formation from **5** and the corresponding hydrobromide salt (**5a**) in dimethyl sulfoxide at 110 ± 3 °C showed that the hydrobromide reacted approximately four times more rapidly than did the hydrochloride. These observations are consistent with a mechanism in which the halide ion attacks the methyl group of **4**. The rate-determining step involves the attack of the halide ion on the methyl group of **4**.

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Experimental Section

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer Model 421 recording spectrometer in Nujol mulls, the NMR spectra were recorded on a Varian A-60D spectrometer, and the mass spectra were determined on an Atlas CH-4 spectrometer.

α-Chloro-o-tolyl Methyl Sulfoxide (3). *m*-Chloroperoxybenzoic acid (85% pure, 40.1 g; 0.186 mol) in chloroform (400 mL) was added dropwise over a 0.5-h period to a stirred solution of 2[3] (32 g; 0.186 mol) in chloroform (180 mL) maintained at −20 to −10 °C. Stirring was continued for 1.5 h at −20 to −10 °C and the reaction mixture was allowed to stand at 4 °C for 16 h. The precipitate was removed by filtration and the filtrate was extracted with saturated sodium hydrogen carbonate solution containing sodium sulfite (3 × 200 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was recrystallized from hexane to afford 18.96 g (54%) of **3**: mp 65–7 °C; IR 665, 690, 745, 780 (aromatic CH/other), 965, 1020, 1060 (S=O), 1645, and 1670 cm^{-1} (C=C); NMR ($CDCl_3$) δ 2.83 (s, 3 H, $SOCH_3$), 4.73 (d of d, 2 H, J = 11 Hz, CH_2Cl), 7.30–7.77 (m, 3 H, aromatic), 7.95–8.17 (m, 1 H, aromatic); mass spectrum m/e 188 and 190 (M^+). Anal. Calcd for C_8H_9ClOS: C, 50.93; H, 4.77; Cl, 18.83; S, 16.98. Found: C, 51.05; H, 4.88; Cl, 18.88; S, 17.08.

1-Methyl-1*H*,3*H*-1,2-benzisothiazole 1-Oxide (4) and Its Hydrochloride (5). A mixture of **3** (7.52 g; 0.041 mol), concentrated sulfuric acid (25 mL), and chloroform (170 mL) was heated to 45 °C and sodium azide (13.9 g; 0.212 mol) was added portionwise over a 2-h period with stirring. The mixture was stirred at 45 °C for an additional 16 h and cooled. The precipitate (I) was removed by filtration, dissolved in water (800 mL), and made basic (pH 12) with 6 N sodium hydroxide. The basic solution was stirred at ambient temperature for 0.5 h and extracted with dichloromethane (3 × 500 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed in vacuo and the residue was recrystallized from ether to afford 4.44 g (65%) of **4**: mp 81–4 °C; IR 790, 785, 765, 760, 750 (ortho CH), 1255, 1225, 1215, 1185, 1170, 1080, 975, 965, 865 (N=S=O/CH), 1595, 1580 (C=C), 3080, 3060 cm^{-1} (=CH); NMR ($CDCl_3$) δ 3.37 (s, 3 H, CH_3), 4.76 (d of d, 2 H, J = 17 Hz, CH_2), 7.30–8.00 (m, 4 H, aromatic); mass spectrum m/e 166 and 167 ($M^+ - 1$) and (M^+). Anal. Calcd for C_8H_9NOS: C, 57.48; H, 5.39; N, 8.38; S, 19.16. Found: C, 57.55; H, 5.70; N, 8.44; S, 18.82.

Compound 4 (3.95 g; 0.0235 mol) was dissolved in ether and treated with ethereal hydrogen chloride. The precipitate was recrystallized from ethanol–ether to afford 4.08 g (85%) of **5**: mp 138–141 °C dec; IR 760 (ortho CH), 990, 1050, 1250 (N=S=O), 1580, 1600 cm^{-1} (C=C); NMR (Me_2SO-d_6) δ 4.32 (s, 3 H, CH_3), 4.95 (s, 2 H, CH_2), 7.76–8.17 (m, 3 H, aromatic), 8.38–8.63 (m, 1 H, aromatic); mass spectrum m/e 166 and 167 ($M^+ - 1$) and (M^+) for free base; high resolution mass spectrum m/e 167.0409, Calcd for C_8H_9NOS m/e 167.0405. Anal. Calcd for $C_8H_{10}ClNOS$: C, 47.17; H, 4.91; Cl, 17.44; N, 6.88; S, 15.72. Found: C, 47.13; H, 5.20; Cl, 17.59; N, 7.04; S, 15.86.

Thermolysis of 5. Compound **5** (1 g; 4.9 mmol) was heated at 155 °C for a period of 20 min to afford 0.62 g (94%) of 1,2-benzisothiazole (**6**). The analytical sample was recrystallized from pentane to afford colorless crystals: mp 34.5–35.5 °C (lit.[9] mp 37 °C); NMR ($CDCl_3$) δ 7.27–7.72 (m, 2 H), 7.87–8.23 (m, 2 H), 8.94 (s, 1 H); mass spectrum m/e 135 (M^+);[10] high resolution mass spectrum m/e 135.0136, Calcd for C_7H_5NS m/e 135.0143. Anal. Calcd for C_7H_5NS: C, 62.22; H, 3.70; N, 10.37; S, 23.70. Found: C, 62.09; H, 3.78; N, 10.52; S, 23.33.

Compound **5** was heated at ca. 150 °C and the gaseous material was analyzed by IR. The IR spectrum consisted of absorptions characteristic of methyl chloride; however, technical difficulties precluded the positive identification of water. Water was identified as a product when **5** was heated at 150 °C in a small flask equipped with a condenser. The liquid which collected in the condenser was identified as water by NMR (neat).

Kinetic Study for Conversion of 5 and 5a to 6. Compounds **5** (1.30 g; 6.40 mmol) and the corresponding hydrobromide (**5a**) (1.59 g; 6.40 mmol) were separately dissolved in Me_2SO (28 mL) and heated at 110 ± 3 °C. At timed intervals aliquots (2.00 mL) were removed and added to water (10 mL) and extracted with dichloromethane (2 × 5 mL). The combined extracts were washed with water (15 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the residues were dissolved in acetone (0.25 mL). GC analyses of 2.0-μL aliquots were performed on a Hewlett Packard Model 5700A gas chromatograph with a Supelco 3 ft 3% OV-225 on 80/100 Supelcoport column. The instrument was previously calibrated with known amounts of 1,2-benzisothiazole. Least-squares analyses of the data showed that **5a** decomposed ca. 4 times more rapidly than did **5**.

Acknowledgment. We are grateful to the Physical and Analytical Department of The Upjohn Company for determining the elemental analyses, infrared spectra, and mass spectra.

Registry No.—**1**, 33384-77-9; **2**, 26190-68-1; **3**, 65442-16-2; **4**, 65442-17-3; **5**, 65442-18-4; **5a**, 65442-19-5; **6**, 272-16-2; **I**, 65442-21-9.

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(10) The fragmentation is similar to that reported for 1,2-benzisothiazole by A. Selva and E. Gaetani, *Org. Mass Spectrom.*, **7**, 327 (1973).

Base-Catalyzed Cis–Trans Isomerization of Bis(4-benzylideneaminocyclohexyl)methane

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Exhaustive hydrogenation of bis(4-aminophenyl)methane (**1**) to bis(4-aminocyclohexyl)methane (**2**) in the presence of noble metal catalysts under mild conditions produces predominately the kinetically favored cis,cis isomer **2a**.[1] This is in contrast to the hydrogenation run using cobalt or nickel (or its compounds) as catalyst at high temperature (above 200 °C) and high pressures (above 130 atm) of hydrogen which yields an amine mixture containing larger amounts of the thermodynamically favored cis,trans and trans,trans isomers **2b** and **2c**, respectively.[2,3]

Since an isomer mixture enriched in *trans,trans*-**2c** is a major component of several novel polyamide fibers, attempts have been made to convert cis,cis- and cis,trans-rich isomer mixtures into **2c**. Most processes involve heating of cis-rich products with metal (predominately from group 8) catalysts in the presence of hydrogen but the degree of isomerization to **2c** seldom exceeds 50%.[4] Consequently, hydrogenating **1** in the presence of ruthenium catalysts at high temperature and pressure leads directly to trans-rich mixtures of **2**.[5] In addition, several patented processes deal with the separation of the trans,trans isomer from crude hydrogenation mixtures.[6]

We have found a method to isomerize the bis(benzaldimines) **3a** and **3b** of **2a** and **2b** into *trans,trans*-**3c** on treatment with base under very mild conditions. Deprotonation on C-4 and C-4′ of the cyclohexane rings adjacent to the CN double bonds (giving **4a**) will lead to a partial charge distribution over the C–N–C unit with formation of an isomeric azaallylic carbanion **5** and eventually will result in an enrichment of the thermodynamically favored trans,trans-imine **3c** via **4b**.[7] (See Scheme II.)

Thus greater than 90% yield of **3c** is realized on stirring a suspension of **3a** in 1,2-dimethoxyethane (DME) in the presence of 20 wt % of potassium *tert*-butoxide at room temperature for 60–70 h. No significant amounts of by-products

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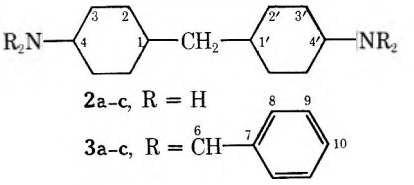
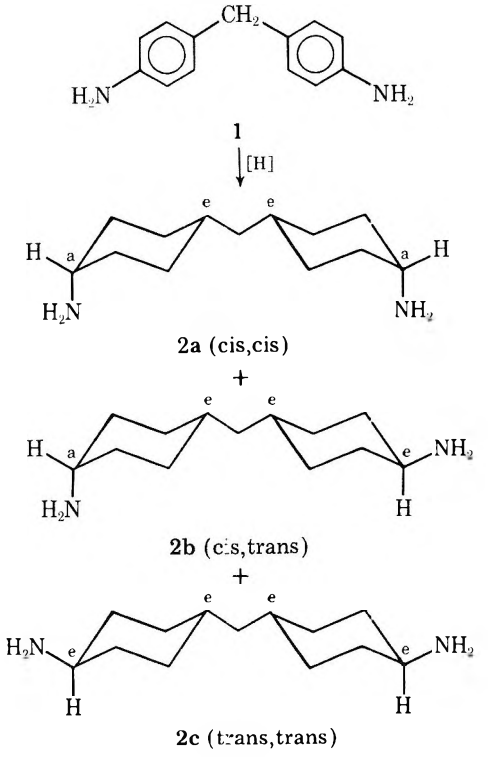
Table I. ^{13}C Chemical Shifts of 2 and 3 (ppm from Me_4Si)[a]



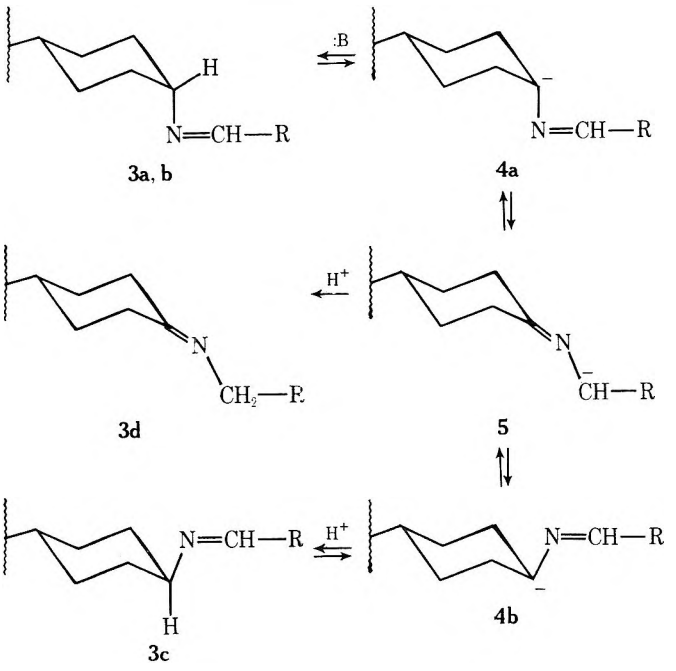
Compd	Registry no.	Cl(Cl′)	C2(C2′) or C3(C3′)	C3(C3′) or C2(C2′)	C4(C4′)	C5	C6(C6′)	C7(C7′)	C8 or C9	C9 or C8	C10
2a	6693-31-8	47.7	32.6	27.9	32.5	40.0					
2b	6693-30-7	50.8 (47.6)	32.3	36.6 (27.8)	33.9	42.2					
2c	6693-29-4	50.8	32.4	36.7	33.9	44.5					
3a	63418-35-9	67.4	31.7	28.5	32.5	39.7	158.0	137.0	128.5	128.1	130.2
3b	63492-46-6	67.4 (70.4)	31.8 (34.3)	32.0 (28.5)	32.4 (34.1)	42.4	158.1 (158.6)	137.0 (136.8)	128.5	128.1	130.2
3c	63492-47-7	70.4	34.2	32.0	33.9	45.0	158.7	136.8	128.5	128.1	130.3

[a] The resonance assignments were made on the basis of the absolute intensities of the resonances, off-resonance coupling experiments, and the chemical shifts of **2** and **3**.

Scheme I



Scheme II

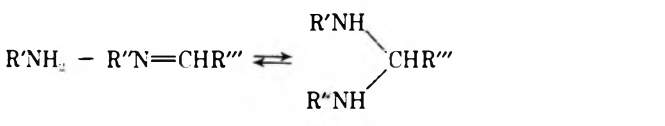


are formed and **3c** can be isolated on diluting the reaction mixture with water. Isomerization conducted with 20 wt % of potassium hydroxide and 2–5 wt % of 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) or 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (Kryptofix 222) give virtually the same results. In addition we found that the solvent/substrate ratio influences the degree of isomerization: High concentrations of imine tended to give more than 90% yield of **3c** while lower concentrations left some **3a** and **3b** unchanged. Precipitation of **3c** during the reaction seems to push the equilibrium toward the right. Too small amounts of solvent, however, resulted in insufficient mixing of the reagents and hence incomplete isomerization. Many other attempts to conduct the isomerization of cis-rich mixtures of **3** with other bases or base/phase transfer agent combinations ($NaOCH_3$, $NaOC_2H_5$, NaH, $KOCH_3$, KOC_2H_5, LiOH, or KOH/*N,N,N′,N′*-tetramethylethylenediamine or benzyltrimethylammonium hydroxide) or with Schiff bases derived from **2** and carbonyl compounds other than benzaldehyde (salicylaldehyde, *p*-nitrobenzaldehyde, pyridine-2-aldehyde, acetone, isatin) gave less favorable results.

The possibility of forming bis(4-iminocyclohexane)methane derivatives of type **3d** via the anion **5** during base treatment is remote: Isomerization studies on ketimines derived from cyclohexanones and benzylamine in the presence of base showed the almost exclusive formation of mixtures of the isomeric benzylidene cyclohexylamines.[8]

Liberation of the *trans,trans*-**2c** from **3c** is accomplished best by treatment with dilute hydrochloric acid at 50–60 °C; the by-product benzaldehyde can also be recovered quantitatively. Another method of enriching *trans,trans*-**2c** involving no hydrolytic process is based on the ability of imines to add amines to its CN double bond giving aminals in a reversible equilibrium. Dissolving *trans,trans*-**3c** and an isomer mixture of **2** high in cis contents (Σcis:Σtrans ≃ 72:28; sample obtained from low temperature–low pressure hydrogenation of **1** with Ru catalyst) in an inert solvent leads to an exchange

between **2** and **3** via aminals as shown below in eq 1. After standing for about 24 h at room temperature, the trans isomer content of **2** increased to ~65%. Separation of the resulting **2** and **3** was not attempted but should be possible by distillation or fractional crystallization. Repeated equilibration with trans-enriched samples of **2** and **3c** would even further increase the trans content of **2**.



$$R'NH_2 - R''N{=}CHR''' \rightleftarrows \begin{matrix} R'NH \\ \diagdown \\ \quad CHR''' \\ \diagup \\ R''NH \end{matrix} \rightleftarrows R''NH_2 + R'N{=}CHR''' \quad (1)$$

R′ = cis-R; R″ = trans-R; R‴ = C_6H_5

The isomer distribution in all samples of amine **2** and imine **3** can be measured from the ^{13}C-NMR spectra of the samples. Use of ^{13}C rather than H NMR for the analysis is desirable as shift reagents are needed to separate coincident peaks in the proton spectra of the isomer mixtures.[9] Table I lists the ^{13}C chemical shifts of the compounds studied. The chemical shifts of several carbon positions, especially C-5, differ sufficiently to determine the isomer distribution by integration of peak areas.

Experimental Section[10]

Starting Materials. The required isomeric bis(4-benzylideneaminocyclohexyl)methanes **3a, 3b,** and **3c** were prepared by heating benzene (or toluene) solutions of the corresponding amine **2a, 2b,** or **2c** with 2 mol of benzaldehyde. The reaction flask is connected to a water separator and heating is continued until water separation is completed. Evaporation of solvent yields the imines in colorless crystals. Samples are recrystalized for analysis from chloroform–methanol (**3a** and **3c**) or methanol–water (**3b**); ^{13}C-NMR data are listed in Table I. **3a:** mp 132–133 °C; colorless plates; IR ($CHCl_3$) 1635 cm^{-1} (C=N). Anal. Calcd for $C_{27}H_{34}N_2$: C, 83.89; H, 8.87; N, 7.25. Found: C, 83.69; H, 9.02; N, 7.07. **3b:** mp 98–99 °C; colorless crystals; IR ($CHCl_3$) 1635 cm^{-1} (C=N). Anal. Calcd for $C_{27}H_{34}N_2$: C, 83.89; H, 8.87; N, 7.25. Found: C, 83.94; H, 8.83; N, 71.4. **3c:** mp 153–154 °C; colorless needles; IR ($CHCl_3$) 1635 cm^{-1} (C=N). Anal. Calcd for $C_{27}H_{34}N_2$: C, 83.89; H, 8.87; N, 7.25. Found: C, 84.00; H, 8.71; N, 7.19.

Cis–Trans Isomerization of 3a to 3c. (a) With Potassium *tert*-Butoxide. A 3.0-g sample of **3a** is suspended in 6 mL of 1,2-dimethoxyethene (DME). After adding 0.6 g of potassium *tert*-butoxide the mixture is stirred for 64 h under a blanket of nitrogen at room temperature, after which the thick suspension is diluted with water (ca. 40–50 mL). Colorless or nearly colorless crystals are left undissolved which are filtered off and after being washed with water are dried at 70 °C; yield 3.0 g, ^{13}C-NMR analysis gives an overall cis–trans ratio of 7:93. Stirring of the crude product with methanol and filtration leaves essentially pure **3c.**

(b) With Potassium Hydroxide–18-Crown-6. A mixture of 5.0 g of isomeric imines **3** with a cis–trans ratio of 72:28, 1.0 g of powdered potassium hydroxide, and 0.2 g of 18-crown-6 is suspended in 10 mL of DME and stirred for 95 h at room temperature in a nitrogen atmosphere. The resulting suspension is diluted with 50–60 mL of water, filtered, and dried at 70 °C, 5.0-g yield. ^{13}C NMR shows the crude material to contain more than 95% trans imine. Similar experiments with about 2–4 wt % Kryptofix 222 instead of 18-crown-6 give comparable results.

Hydrolysis of 3c. A solution of 10.0 g of **3c** in 100 mL of 2 N hydrochloric acid is kept at 50 °C for ca. 60 min. Hydrolysis is indicated by separation of droplets of benzaldehyde. The resulting mixture is extracted with methylene chloride (4 × 10 mL) after cooling. Drying the extracts with sodium sulfate and evaporation of solvent lead to quantitative recovery of benzaldehyde.

On adjusting the pH of the aqueous phase to 9–10 by adding 30% sodium hydroxide solution the *trans,trans*-amine **2c** is separated in fine droplets, which crystalize on scratching. Extraction with methylene chloride (4 × 10 mL) gives 5.5 g (quantitative) of crude **2c** after evaporation of solvent, mp (hexane) 63 °C (Lit.[11] 64–64.4 °C), identical in IR comparison with authentic **2c.**

Equilibration between 3c and an Isomer Mixture of 2. A mixture of isomers of **2** (1.05 g, 0.005 mol), having an overall cis–trans ratio of 71:29, is dissolved in 6 mL of methylene chloride together with 1.93 g (0.005 mol) of **3c.** ^{13}C-NMR analysis of the mixture after 24 h reveals a change of the cis–trans ratio of the amine **2** to 33:66 and of the imine **3** to 35:65.

Registry No.—**1,** 101-77-9; benzaldehyde, 100-52-7.

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(2) The two cyclohexene rings are linked equatorially to the bridging methylene group at C-1 and C-1′. With amino groups on C-4 and C-4′ the cis,cis isomer **2a** has therefore a,e–e′,a′, the cis,trans isomer **2b** a,e–e′,e′, and the trans,trans isomer **2c** e,e–e′,e′ conformation.

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Intramolecular Aldol Condensation of 2,2′-Dimethylbenzil

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During the base-catalyzed condensation of 2,2′-dimethylbenzil (**1**) with 1,3-diphenyl-2-propanone to prepare the reddish-black 2,5-diphenyl-3,4-bis(*o*-tolyl)cyclopentadienone,[1] a crystalline, colorless side product (**2**) was isolated in 9% yield. mp 155–157 °C. Ultimate analysis agreed with the formula $C_{15}H_{14}O_2$, identical with that of the starting material, 2,2′-dimethylbenzil. **2** was insoluble in aqueous alkali. Treatment of **2** with alkali in alcohol restored a yellow color. The infrared spectrum showed the following peaks: 3400 (s, tertiary OH), 1700 cm^{-1} (s, C=O), 1602 (m, Ar), 1210 (s, C—O, C=O), 1055 (s, CO), 960 (w, Ar), and 745, 730, and 715 cm^{-1} (ortho-disubstituted Ar). The 300-MHz NMR spectrum ($CDCl_3$) revealed peaks at δ 2.348 (3 H, s, $ArCH_3$), 2.86 (1 H, s, OH), 3.53 (2 H, s, $ArCH_2$), 7.16 (1 H, m, tolyl H_3), 7.24 (2 H,

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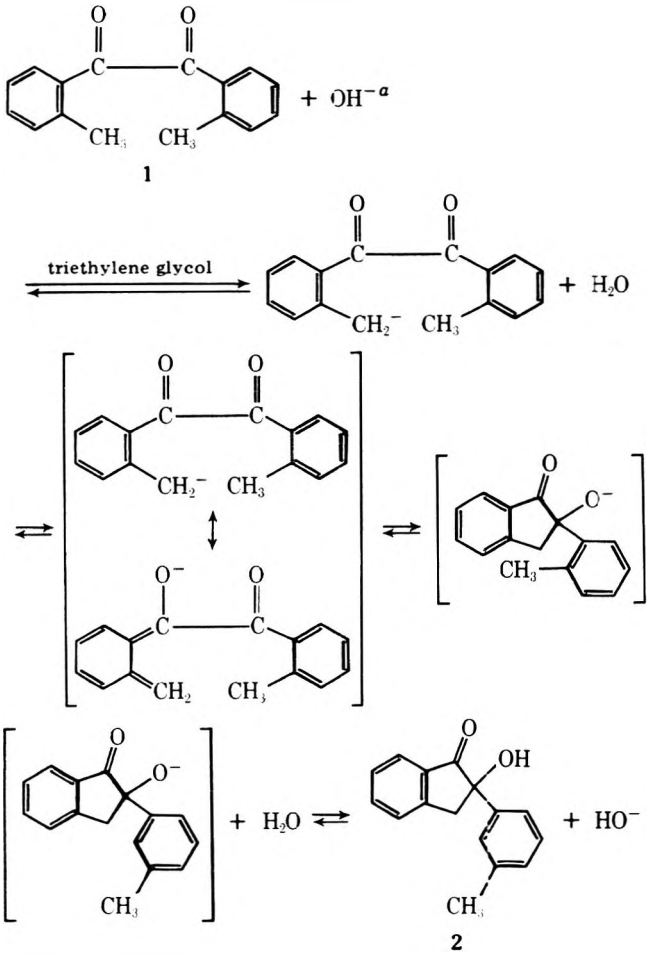
Scheme I



1 2

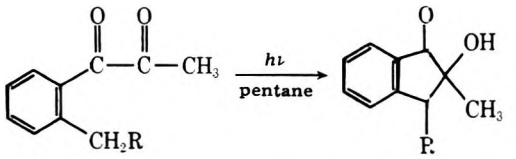
ᵃ From Triton B: $PhCH_2N^+(CH_3)_3OH^-$.

m, tolyl H_4, H_5), 7.37 (1 H, d, J = 8.0 Hz, tolyl H_6), 7.47 (1 H, d, J = 7.5 Hz, indanone H_4), 7.48 (1 H, t, J = 7.5 Hz, indanone H_6), 7.70 (1 H, d, t, J = 1.3, 7.5 Hz, indanone H_5), and 7.94 (1 H, d, J = 7.5 Hz, indanone H_7). Mass spectral analysis exhibited peaks at 238, 220, 119, and 91. These data are in agreement with 2-hydroxy-2-(o-tolyl)-1-indanone as the structure of **2**.

2 may be envisaged as forming from **1** via an intramolecular aldol condensation (Scheme I). The reversible arrows, characteristic of the aldol condensation, rationalize the formation of a yellow color [1?] when **2** is treated with alcoholic alkali.

The peaks in the mass spectrum may be rationalized by decomposition as shown in Scheme II. The peak at 220 might be accounted for by dehydration of **2** to the corresponding indenone in a parallel reaction. Cleavage of benzil to benzoyl in the mass spectrometer has been previously reported.[2]

To the authors' knowledge this kind of rearrangement of a methylated benzil under basic conditions has not been reported. However, a photochemical reaction producing an analogous indanone has been observed[3,4] (eq 1). Therefore **1**

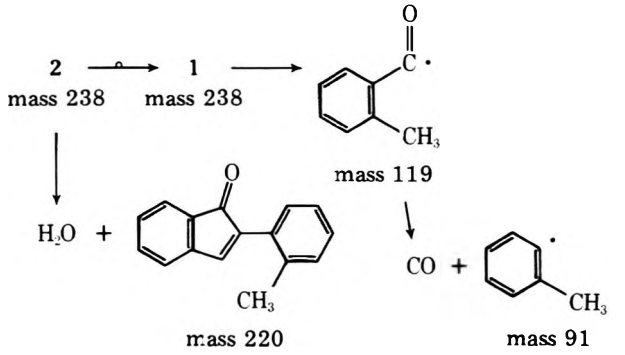


(1)

R = H, CH_3

was subjected to photochemical conditions. In the presence of ultraviolet light in carbon disulfide, **1** afforded **2** in 60% yield. It thus became necessary to ascertain whether light was important in the base-catalyzed reaction. In the dark the base-catalyzed reaction was shown to produce **2**, thus suggesting that the base-catalyzed reaction and photochemical reaction are distinctly different reactions.

Scheme II



Experimental Section

2-Hydroxy-2-(o-tolyl)-1-indanone and 2,5-Diphenyl-3,4-bis(o-tolyl)cyclopentadienone. A solution of 0.224 g (0.94 mmol) of 2,2′-dimethylbenzil and 0.237 g (1.13 mmol) of 1,3-diphenyl-2-propanone in 1.0 mL of triethylene glycol was heated to 95 °C. Triton B (0.4 mL) was added and the solution was kept at 95–100 °C for 20 min. The solution turned dark purple upon addition of the catalyst. After cooling to room temperature, about 10 mL each of benzene and water were added. Separation of the benzene layer and distillation of the benzene at about 100 mm left a thick, purple oil, which was stored in a vacuum desiccator. After 1 h of standing, crystals formed, which were washed with about 3 mL of cyclohexane–benzene (95:5) and filtered quickly. Washing the crystals with a few drops of cold methanol afforded 0.020 g (9.0%) of **2**, mp 155–157 °C. Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.54; H, 6.21.

The purple liquid remaining after filtration of **2** was evaporated to dryness in vacuo, dissolved in a small amount of cyclohexane–benzene (95:5), and chromatographed on a column of neutral alumina (14 × 2.5 cm) using the same solvent as eluant. A yellow and a purple band separated. The column was cut and the alumina containing the purple band was extracted in a Soxhlet apparatus with 125 mL of benzene until the alumina was colorless. Distillation of the benzene left 0.027 g of purple crystals, which were recrystallized from 3 mL of methanol to give 0.015 g (3.9%) of purple-black product, mp 205–207.5 °C (lit.[5] mp 203–204 °C).

2-Hydroxy-2-(o-tolyl)-1-indanone. A. Base Catalyzed. A solution of 0.0687 g (0.288 mmol) of 2,2′-dimethylbenzil in 1.0 mL of triethylene glycol was heated in an oil bath to 100–105 °C. Addition of 0.4 mL of Triton B turned the solution red. After 20 min the solution was green and it was heated 5 min more. Benzene (15 mL) was added and the solution was washed with three 5-mL portions of water at which stage the solution was amber. The benzene layer was distilled slowly leaving brown crystals which turned colorless upon washing with cyclohexane–benzene (19:1): 7.2 mg (0.0302 mmol, 10.6%); mp 155–157 °C.

B. Photochemical. A solution of 0.050 g (0.210 mmol) of 2,2′-dimethylbenzil in 17 mL of carbon disulfide was irradiated at room temperature for 5 h using a Curtis Lighting light fixture holding a GE Bulb UA-3GE360W attached to a G. W. Gates & Co. Power Supply, Model 420-U1. Concentration of the solution and cooling afforded 0.030 g (0.126 mmol, 60%) of colorless **2**, mp 154–156 °C.

Acknowledgments. We wish to thank Merck and Co. for the use of the NMR and MS facilities. We also wish to thank Mr. Jack Smith for the determination and interpretation of the mass spectrum.

Registry No.—**1**, 2048-07-9; **2**, 65311-24-2; 2,5-diphenyl-3,4-bis(o-tolyl)cyclopentadienone, 65375-82-8; 1,3-diphenyl-2-propanone, 102-04-5.

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Hydroboration of Carbonyl Compounds with Borane–Methyl Sulfide

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Borane–methyl sulfide (BMS) is a new hydroborating complex which exists as a stable liquid.[1] We have investigated this complex as a selective reducing agent to be utilized in the presence of an olefinic bond.

In particular, we have examined the effectiveness of BMS toward a range of unsaturated carbonyl compounds. While it is known from the literature that the complex BH_3–THF hydroborates the α,β-unsaturated carbonyl compounds with a formation of saturated carbinol,[2] we have found that with using BMS selective reduction of the C=O group occurs in all α,β-unsaturated ketones examined, with the formation of the corresponding allylic alcohols in good yields (compounds I–V) (Table I). With unconjugated compounds VI and VII, we have observed selective reduction of the carbonyl group in VII, while in VI selective hydroboration of the olefinic double bond occurred, the more difficult being the reduction of a C=O group in a five-membered ring.[4]

Subsequently, a range of reducible functions such as acyl, anhydride, lactone, and ester was tested with BMS in an attempt to isolate the intermediate products of partial hydroboration.

However, we have observed complete reduction, under all conditions, in all cases except for *p*-nitrobenzoyl chloride, which produced the corresponding aldehyde in good yields (60%).

Finally, we have examined the reductive capacity of BMS toward some aromatic electron-rich carbonyl compounds. It is reported that these compounds suffer hydrogenolysis to hydrocarbon when reduced by diborane.[5] The reactions are reported to be catalyzed by the BF_3 present as an impurity.

We have thought it better to reduce these compounds with BMS, which we have found to be practically free from BF_3,[6] for a better understanding of the reaction. It is reported[7] that with anthraquinone at room temperature a very slow reaction occurs with BH_3–THF (1 mmol of compounds consumes 1 mmol of hydride in 7 days), whereas a fast reduction with hydrogenolysis to anthracene occurs after the addition of BF_3. However, using BMS we observed a fast hydrogenolysis with good yields in the formation of anthracene (70%) by raising the temperature to 30–40 °C. This result was confirmed by the fact that, when submitting anthraquinone to hydroboration with diborane developed from $NaBH_4$ and iodine, i.e., free from BF_3, fast hydrogenolysis at 50 °C with formation of anthracene in good yields (60%) occurred. Therefore, we deduced that hydrogenolysis can occur even in the absence of BF_3 by increasing the reaction temperature.

Likewise, we examined the behavior of *p*-dimethylaminobenzaldehyde (VIII) and of veratric aldehyde (IX) with BMS. Conflicting results have been reported for the hydroboration of these compounds with BH_3–THF. In particular, some authors reported the presence of BF_3 as determining the hydrogenolysis reaction and others pointed out that this reaction stopped at the alcohol stage or gave other products despite the presence of BF_3.[8,9]

In the experiments with BMS, we have observed that hydroboration of VIII yielded first the corresponding alcohol (70% after 1 h) and then, after prolonged stirring of the reaction mixture (6 h), the hydrogenolysis product in good yield (90%). Likewise, with IX we have obtained only the corresponding alcohol after 1 h; however, we have observed the formation of some hydrocarbon (30%) by keeping the reaction mixture at 40 °C for 1 day.

Experimental Section

General. Tetrahydrofuran was dried with excess of lithium aluminum hydride and distilled under nitrogen. BMS was used directly as obtained from Aldrich Chemical Co. and was transferred into the reaction vessel by a hypodermic syringe. The carbonyl compounds used were commercial products of the highest purity. All reduction experiments were carried out under a dry nitrogen atmosphere. Melting points were determined with a Kofler apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer 257 Infracord and NMR spectra with a Perkin-Elmer apparatus (90 MHz) in $CDCl_3$. For TLC, Kieselgel G from Merck was used. GLC analyses were carried out with a "Carlo Erba" Fractovap G-1 using a 60-m capillary column with 5% Carbowax as the stationary phase.

Reduction of α,β-Unsaturated Carbonyl Compounds. The following preparative procedure for the reduction of cinnamaldehyde to cinnamyl alcohol is representative. In a 10-mL flask equipped with a magnetic stirring bar and a reflux condenser, tetrahydrofuran (3 mL) was injected. In this solvent the compound was dissolved (297 mg, 2.25 mmol) and to this well-stirred solution under dry nitrogen atmosphere BMS (0.075 ml, 0.75 mmol) was added. After 1 h and 15 min at room temperature, water (0.5 mL) was added to destroy the excess hydride and the solution reaction was extracted by 6 × 10 mL of benzene. Organic extracts were dried (Na_2SO_4) and after evaporation of the solvent an organic residue was obtained, which was chromatographed on a silica gel column (10 g of silica gel from Merck). By elution with hexane–ethyl ether (80:20), cinnamyl alcohol (240 mg,

Table I. Results of the Reaction of BMS with Unsaturated Carbonyl Compounds

Compd[a]	Registry no.	Reaction temp, °C	Reaction time	Molar[b] ratio of reactive compds	Reaction products	Yields,[c] %	Registry no.
Cyclohexenone (I)	930-68-7	0	2 min	0,3	Cyclohexenol	94	822-67-3
Cinnamaldehyde (II)	104-55-2	20	1 h 15 min	0,3	Cynnamyl alcohol	82	104-54-1
10-Methyl-$\Delta^{1(9)}$-octalin-2-one (III)	826-56-2	20	45 min	0,3	10-Methyl-$\Delta^{1(9)}$-octalin-2-ol	65	26675-10-5
17β-Hydroxyandrost-4-en-3-one (IV)	58-22-0	0	1 h 45 min	1	Androst-4-ene-3β,17β-diol	79	1156-92-9
17β-Hydroxyestr-4-en-3-one (V)	434-22-0	0	10 min	0,6	Estr-4-ene-3β,17β-diol	60	19793-20-5
3β-Hydroxyandrost-5-en-17-one (VI)	53-43-0	0	20 min	0,6	3β,6α-Dihydroxy-5α-androstan-17-one	76	14895-71-7
					3β,6β-Dihydroxy-5β-androstan-17-one	18	65375-66-8
Pregn-5-en-3β-ol-20-one (VII)	145-13-1	0	12 min	0,6	Pregn-5-ene-3β,20α-diol	92	59042-34-1

[a] Tetrahydrofuran was used as solvent in all the experiments. [b] Millimole of BMS used per millimole of organic compound. [c] Yields by chromatography on silica gel column, except for cyclohexenol by GLC examination.

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82% yield, characterized by NMR spectroscopy and melting point), cinnamaldehyde (26 mg, 10% yield), and a third unidentified product (16 mg, 5% yield) were obtained. The absence of a possible reaction product, 3-phenylpropanol,[2] was confirmed by a chromatographic comparison of an authentic sample with the reaction mixture (silica gel–$AgNO_3$ plate, elution with hexane–ethyl ether, 80:20).

Reduction of Acyl, Ester, Lactone, and Anhydride Functions. The general technique was the same as described for the reduction of unsaturated ketones. *p*-Nitrobenzoyl chloride (185 mg, 1 mmol) was dissolved in 2 mL of tetrahydrofuran and treated (−18 °C) with 0.33 mmol of BMS under stirring. After 2.5 h, the reaction was stopped and the reaction mixture worked up. By chromatography of the crude mixture on Al_2O_3 (B III, neutral) (6 g) and by elution with hexane–ethyl acetate (95:5), *p*-nitrobenzaldehyde (110 mg, 60% yield) and *p*-nitrobenzyl alcohol (50 mg) were obtained. In other experiments, an increase in temperature (0 °C) led to an increase in yield of the alcohol. Benzyl chloride was unreactive at −18 °C. By raising the temperature to 0 °C, an effective reduction took place, yielding the corresponding alcohol (95%). Likewise, by the same procedure, phenyl methyl ester did not react at −18 °C; by raising the temperature to 15 °C a slow reduction to benzyl alcohol was observed. The phthalic anhydride did not react, even at room temperature. The undecalactone reacted very slowly at room temperature, giving the corresponding diol.

Hydrogenolysis of Electron-Rich Carbonyl Compounds. The following preparative procedures for hydrogenolysis of anthraquinone to anthracene are representative.

Method a (with BMS). This reduction was accomplished, with the general hydroboration procedures previously reported, by dissolving the compound (124 mg, 0.6 mmol) in tetrahydrofuran–benzene (1:1, 6 mL) and by adding, with stirring, BMS (0.68 mmol). The solution was stirred at 30–40 °C for 5 h. At the end of stirring, methanol (0.3 mL) was added and the solvent evaporated in vacuo. The residue was chromatographed on a silica gel column (6 g). By elution with hexane–ethyl ether (80:20), anthracene (72 mg, 70% yield), identical to an authentic sample (R_f value, melting point), and anthraquinone (24 mg, 25% yield) were obtained.

Method b (with Diborane Developed from Sodium Borohydride and Iodine). The compound (124 mg, 0.6 mmol) was dissolved in tetrahydrofuran–benzene (2:1, 12 mL), and the gaseous diborane [generated externally as described[7] using sodium borohydride (840 mg) and iodine (2.8 g)] was bubbled for 1 h in the reaction vessel at 50 °C with stirring. After 2.5 h of additional stirring, the reaction was stopped and the mixture worked up. By chromatography of the crude mixture on a silica gel column (6 g) eluting with hexane–ethyl ether (80:20), anthracene (68 mg, 66% yield) and anthraquinone (31 mg, 30% yield) were obtained. The reduction of aldehydes VIII and IX was accomplished with BMS according to method a using tetrahydrofuran as the only solvent. The crude reaction mixture was chromatographed on a silica gel column eluting with benzene–ethyl ether (90:10), and the reaction products were recognized by NMR spectroscopy and TLC comparison with authentic samples.

Registry No.—VIII, 100-10-7; **IX,** 120-14-9; BMS, 13292-87-0; *p*-nitrobenzoyl chloride, 122-04-3; benzyl chloride, 100-44-7; anthraquinone, 84-65-1; diborane, 19287-45-7.

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(6) We presume, reasonably, that the BMS used would be practically free from BF_3, since we observed a very slow reaction of this reactive with epoxides and lactones, which are both very sensitive to the presence of BF_3,[1a] whereas an effective and fast react on took place after the addition of a catalytic drop of BF_3.

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Correlation of σ^+ and σ^- Substituent Constants with Carbon-13 Shieldings of β Carbons of Para-Substituted β,β-Dichlorostyrenes

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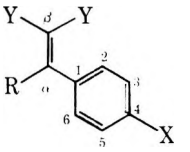
Carbon-13-NMR spectroscopy is an especially valuable tool for studying the electronic properties of aromatic systems.[1] Of particular interest are four recent reports in which the ^{13}C-NMR spectra for various para-substituted styrene derivatives (**1–5**) were presented.[2–4] For the substituted β,β-dicyanostyrenes (**4a–f**) an excellent linear correlation was found for the chemical shifts of the β carbons and σ^+ substituent constants[5] ($\rho = 5.97$; $r = 0.995$).[3] Likewise a correlation of δ ($^{13}C_\beta$) and the Brown–Okamoto σ^+ values[5] proved to be very successful ($\rho = 3.37$; r = 0.998) for the β-nitrostyrenes **5a–f**.[4] During the course of another study,[6] a number of para-substituted β,β-dichlorostyrenes (**6a–f**) were synthesized and analyzed by ^{13}C-NMR spectroscopy, the interesting results of which are discussed in this report.

Results and Discussion

Table I collects the ^{13}C-NMR chemical shifts for compounds **6a–f**; shielding assignments were made on the basis of relative signal intensities and general substituent effects established for substituted benzenes.[7] When the β ^{13}C chemical shifts for the β,β-dichlorostyrenes (**6a–f**) are plotted

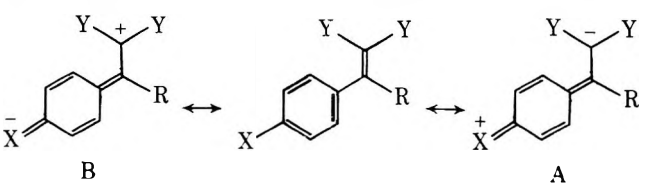


1, Y = R = H
2, Y = H; R = CH_3
3, Y = H; R = $C(CH_3)_3$
4, Y = CN; R = H
5, Y = NO_2, H; R = H
6, Y = Cl; R = H

a, X = H; b, X = CH_3; c, X = OCH_3; d, X = Cl; e, X = CN; f, X = NO_2

as a function of σ^+ substituent constants, a straight line is obtained ($r = 0.989$) with a ρ of 4.35. When the data for the styrenes (**1a–f**)[2a] or the α-methylstyrenes (**2a–d,f**)[2b] are subjected to a similar treatment, results ($\rho = 4.55$, $r = 0.983$ and $\rho = 3.47$, $r = 0.974$, respectively) analogous to those found for **6a–f** are obtained. The low correlation coefficients found for **1, 2,** and **6** are in marked contrast to the results found for **4** and **5.** Examination of the plots reveals that the poor correlations observed for **1, 2,** and **6** are attributable to the points for the 4-cyano and 4-nitro substrates.

In order to rationalize the above observations, it is necessary to consider that a para substituent on the aromatic ring of a styrene system can direct via resonance the distribution of the π electrons in either of two ways: (1) the substituent can *donate* the electrons to the ethylenic bond such that the β carbon acquires enhanced electron density (as in A), or (2) the substituent can *accept* electrons from the ethylenic bond with the



B A

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Table I. Carbon-13 NMR Chemical Shifts for Para-Substituted β,β-Dichlorostyrenes **6**

Compd	X	Registry no.	C-1	C-2	C-3	C-4	C-5	C-6	C_α	C_β	C_X
6a	H	698-88-4	133.3	128.6	128.4	128.4	128.4	128.6	128.4	120.9	
6b	CH_3	4714-37-8	130.5	128.5	129.1	138.4	129.1	128.5	128.5	119.9	21.2
6c	OCH_3	41448-64-0	125.8	130.1	113.9	159.6	113.9	130.1	128.2	118.5	55.1
6d	Cl	5263-17-2	134.2	129.8	128.6	131.6	128.6	129.8	127.3	121.6	
6e	CN	65085-94-1	137.5	129.1	132.2	111.8	132.2	129.1	127.1	124.4	118.4
6f	NO_2	5281-22-1	139.6	129.4	123.7	147.1	123.7	129.4	126.8	125.2	

Table II. Dual Substituent Parameter Treatment for β Carbons of Para-Substituted β,β-Dichlorostyrenes

σ_R type	$\rho_I{}^p$	$\rho_R{}^p$	SD	f^a
σ_R(BA)	5.0	6.3	0.13	0.05
$\sigma_R{}^0$	4.8	7.8	0.20	0.08
$\sigma_R{}^+$	5.4	3.9	0.24	0.10
$\sigma_R{}^-$(A)	2.9	5.8	0.49	0.19

[a] For a comparison of f with standard correlation coefficients (r), see P. R. Wells, S. Ehrenson, and R. W. Taft, "Progress in Physical Organic Chemistry", A. S. Streitwieser, Jr., and R. W. Taft, Ed., Wiley, New York, N.Y., 1968, p 147. For the β,β-dichlorostyrenes **6**, the plot employing both σ^+ and σ^- values gives f = 0.07, whereas when the standard σ constants are utilized, f = 0.13.[14]

effect that the β carbon assumes partial positive character (as in B). In addition, the electronic properties of the β substituents Y should greatly influence the distribution of the π electrons for styrene derivatives.

For the β,β-dicyanostyrenes **4** the contribution of the resonance hybrid B is very minor since the strongly electronegative cyano groups severely destabilize the adjacent electropositive β carbon; thus only hybrid A is important and hence the excellent correlation for the β ^{13}C-NMR shieldings and σ^+ substituent constants.[3] The same argument holds for the β-nitrostyrenes **5**. For the β,β-dichlorostyrenes **6** the situation should not be so restrictive; the geminal electronegative chlorines attached to the β carbon can stabilize the adjacent carbanionic nature of A via induction, but the chlorines should also be able to stabilize the adjacent carbocationic nature of B via resonance.[8] The latter consideration suggests that σ^- constants be utilized in the Hammett treatment for those substrates bearing substituents capable of accepting electrons via resonance (e.g., cyano and nitro). Indeed, when the β ^{13}C-NMR chemical shifts for **6a–f** are plotted against σ^+ or σ^- (Figure 1) a straight line is obtained (r = 0.998) with a ρ of 3.43.[9] A similar analysis for **1a–f** and **2a–d,f** yields correlation coefficients of 0.995 and 0.996 and ρ values of 3.61 and 2.74, respectively.

Clearly, the combined use of σ^+ and σ^- constants provides a considerable improvement to the use of σ^+ constants alone for evaluating the electronic properties of styrenes **1, 2,** and **6** by ^{13}C-NMR spectroscopy.[10] The utilization of σ^+ and σ^- constants on the same abscissa is justifiable since σ^- constants are reasonable extensions of σ^+ constants for electron-withdrawing substituents in which the inductive effects are augmented by resonance.[11] Thus, both resonance hybrids A and B are important contributors to the electronic structures of styrenes **1, 2,** and **6**. Furthermore, the fact that for both the parent styrene system **1** (Y = H) and the β,β-dichlorostyrene system **5** (Y = Cl) the ^{13}C chemical shifts of the β carbons can be satisfactorily correlated jointly with σ^+ and σ^- substituent constants indicates that both hydrogen and chlorine are capable of stabilizing the charge localization of either polarity (negative for A or positive for B) at the β carbons.

In the addition to the combined σ^+, σ^- approach presented above, a dual substituent parameter (DSP) treatment was carried out in order to determine the correlation between the chemical shifts of the β carbons and the combined inductive (I) and resonance (R) effect expression (eq 1):[12]

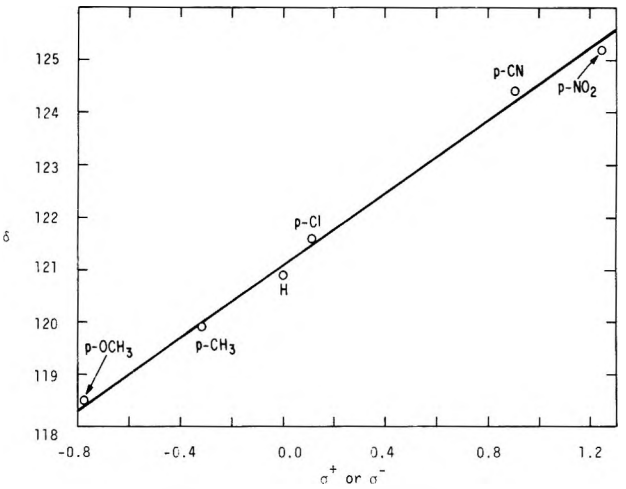

Figure 1. Hammett plot for β carbons of β,β-dichlorostyrenes.

$$P^i = I^i + R^i = \sigma_I \rho_I{}^i + \sigma_R \rho_R{}^i \quad (1)$$

For eq 1, P is a substituent property (in the present situation, the portion of the chemical shift of the β carbon due to the substituent); i is the index of the position of the substituent (in the present case the substituents are located para to the β,β-dichloroethylene moiety); $\rho_I{}^i$ and $\rho_R{}^i$ are the susceptibility or mixing coefficients and depend on the position of the substituent, the nature of the measurement at the detector center (i.e., the β carbon), and the conditions of solvent and temperature; σ_I and σ_R are the substituent constants. There are four types of σ_R values: σ_R(BA), $\sigma_R{}^0$, $\sigma_R{}^+$, and $\sigma_R{}^-$(A).[12] The substituted benzoic acid based constants, σ_R(BA), gave the best correlation (f ≡ SD/rms = 0.05) with the chemical shifts of the β carbons.[13,14] However, the $\sigma_R{}^0$ and $\sigma_R{}^+$ constants also gave satisfactory correlations (f = 0.08 and 0.10, respectively).[14,15] Complete results of the DSP treatment are summarized in Table II.

The excellent correlation of the ^{13}C chemical shifts with eq 1 using σ_R(BA) suggests that standard σ constants might also give a satisfactory fit for **6a–f**. Such an analysis gives a ρ value of 5.91 with a correlation coefficient of 0.991 which is substantially poorer than that achieved when both σ^+ and σ^- constants are employed.[16]

Experimental Section

The β,β-dichlorostyrenes utilized in the present study were prepared by the decarboxylation of the corresponding β lactones which were synthesized by the cycloaddition of the dichloroketene with the appropriate monosubstituted benzaldehyde.[6] Compounds **6a–d,f** were previously known,[17] while **6e** was recently characterized.[6]

Carbon-13 NMR spectra were measured with a Varian CFT-20 spectrometer utilizing ^{1}H decoupling at 80 MHz and simultaneous ^{13}C observation at 20 MHz; the concentrations were approximately 1 g of substrate per 2 mL of $CDCl_3$ with internal Me_4Si as the reference.

Acknowledgment. The author thanks Dr. E. A. Williams, Mr. J. D. Cargioli, and Mrs. C. W. Joynson for obtaining the ^{13}C-NMR spectra and Professor R. W. Taft and Dr. J. Bromilow for carrying out the DSP analyses.

References and Notes

(1) G. L. Nelson and E. A. Williams, "Progress in Physical Organic Chemistry", Vol. 12, R. W. Taft, Ed., Wiley, New York, N.Y., 1976, pp 234–282.
(2) (a) G. K. Hamer, I. R. Peat, and W. F. Reynold, *Can. J. Chem.*, **51**, 897 (1973); (b) G. H. Hamer, I. R. Peat, and W. F. Reynolds, *ibid.*, **51**, 915 (1973); see also N. Inamoto, S. Masuda, W. Nakanishi, and Y. Ideda, *Chem. Lett.*, 759 (1977).
(3) T. B. Posner and C. D. Hall, *J. Chem. Soc., Perkin Trans. 2*, 729 (1976).
(4) D. A. Happer, *Aust. J. Chem.*, **29**, 2607 (1973).
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(7) (a) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N.Y., 1972, pp 196–205; (b) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley, New York, N.Y., 1972, pp 80–85.
(8) For a recent report dealing with the ambident nature of heteroatoms see W. P. Meyer and J. C. Martin, *J. Am. Chem. Soc.*, **98**, 1231 (1976).
(9) Pertinent data for five meta-substituted β,β-dichlorostyrenes have also been obtained;[6] inclusion of these points in the analysis gives $\rho = 3.51$ and $r = 0.996$.
(10) The α-*tert*-butylstyrene system (**3**) gives only poor correlations upon Hammett analysis, presumably on account of severe effects precluding the attainment of coplanarity[2a] of the aryl and the 2-(3,3-dimethyl)butenyl groups.
(11) See also the related discussion in ref 5.
(12) S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, "Progress in Physical Organic Chemistry", Vol. 10, A. S. Streitwieser, Jr., and R. W. Taft, Ed., Wiley, New York, N.Y., 1973, Chapter 1.
(13) Ideally, the minimum basis set should also include data for the NR_2 (R = H or CH_3) and F substituents in order to minimize accidental correlations between substituent σ_I and σ_R values.[12] However, the absence of these two data points should not be serious since an entire range of substituents (i.e., OCH_3 to NO_2) is utilized.
(14) Correlations of good precision are those for which $r \leq 0.1$.[12]
(15) The fact that satisfactory correlations are achieved with three different sets of substituent constants is not uncommon;[12] see also J. Hine, "Structural Effects in Equilibria in Organic Chemistry", Wiley, New York, N.Y., 1975, pp 79–81.
(16) The material described in this note was presented at the International Symposium on the Chemistry of Strained Rings, Binghamton, N.Y., May 27–29, 1977.
(17) (a) L. A. Errede and J. P. Cassidy, *J. Org. Chem.*, **28**, 1059 (1963); (b) V. M. Naiden and A. V. Dombrovskii, *J. Gen. Chem. USSR (Engl. Transl.)*, **32**, 1256 (1962); **1**, 2037 (1965); (c) R. Brown, Ph.D. Thesis, University of Maryland, 1968 [*Diss. Abstr. B*, **29**, 3670 (1969)]; A. Merz, *Angew Chem., Int. Ed. Engl.*, **16**, 57 (1977); (d) D. Seyferth, H. D. Simmons, Jr., and G. Singh, *J. Organomet. Chem.* **3**, 337 (1965); (e) A. J. Speziale and K. W. Ratts, *J. Am. Chem. Soc.*, **84**, 854 (1962).

Epoxidation of Allenic Phosphonic Acids. Intramolecular Trapping of Allene Oxides[1]

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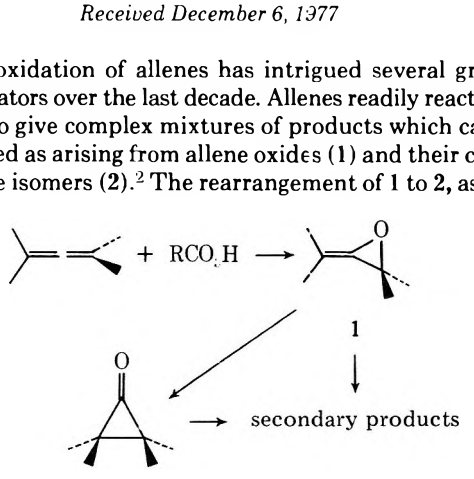
The epoxidation of allenes has intrigued several groups of investigators over the last decade. Allenes readily react with peracids to give complex mixtures of products which can be rationalized as arising from allene oxides (**1**) and their cyclopropanone isomers (**2**).[2] The rearrangement of **1** to **2**, as well



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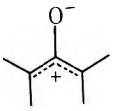
as some of the subsequent reactions of **1** and **2**, have been postulated to involve oxyallyl zwitterion **3**[3] (or its conjugate acid), although recent CNDO/2 calculations suggest another



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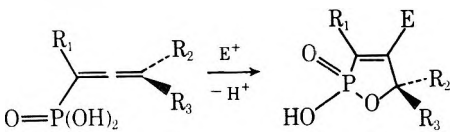
lower energy path for the rearrangement.[4] In two cases, the allene oxides themselves have been isolated.[5] For example, the monoepoxide of 1,3-di-*tert*-butylallene can be isolated, and it rearranges cleanly to 2,3-di-*tert*-butylcyclopropanone with a half-life of ca. 5 h at 100 °C.[5a] The gas-phase reaction of allenes with ground state oxygen atoms has also been rationalized in terms of allene oxides, cyclopropanones, and oxallyl radicals.[6]

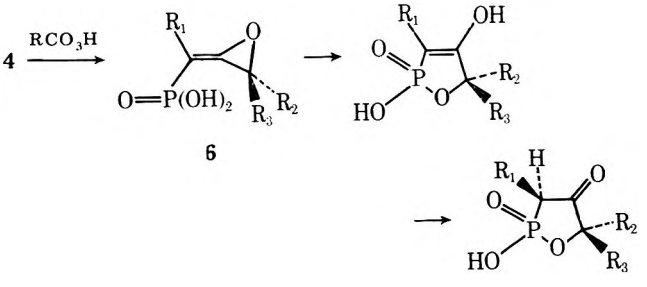
We recently reported that allenic phosphonic acids (**4**) react with electrophiles such as Brönsted acids, bromine, or mercuric salts to form oxaphospholene.[1,7,8]



4 **5**

a, $R_1 = H$; $R_2 = R_3 = CH_3$
b, $R_1 = R_2 = tert$-butyl; $R_3 = H$

From these studies it seemed likely that reaction of **4** with peracids would lead to allene oxide **6**, which might rapidly and cleanly isomerize to 4-keto-1,2-oxaphospholane **7**.[9]



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7

Results and Discussion

When a 20% excess of peracetic acid[10] was added to an aqueous solution of **4a**[7] at 25 °C, ^1H NMR indicated 50% consumption of the starting material after 1.8 h. Two major products were formed: acetone (δ 2.21 (s))[11] and A [δ 1.44 (s, 6 H), 2.84 (d, $J = 14$ Hz, 2 H)[13]] in the ratio 1:3. After 6.3 h, 20% of the starting material remained, and two additional products, B [δ 1.38 (s, 6 H), 3.39 (d, $J = 22$ Hz, 2 H)[13]] and C [δ 2.98 (d, $J = 22$ Hz)[13]], had formed such that the four products were present in essentially equal amounts.[14] After 24 h, starting material (10%) remained, along with A (7%), acetone (20%), B (37%), and C (26%).

Reaction of **4a** with a threefold excess of *m*-chloroperbenzoic acid[15] in chloroform[16] resulted in complete conversion to a stable[17] mixture of A and acetone (3:1) after 5.6 h at 25 °C. Extraction with water gave a solution of A, which hydrolyzed quantitatively to B with a half-life of 20 h at 25 °C. Addition of 1.2 equiv of peracetic acid to the solution of B gave C and acetone in essentially equal amounts, with a comparable half-life. Unfortunately, attempts to isolate A, B, and C from these aqueous solutions gave viscous oils whose NMR spectra suggested that polymerization had occurred.

We have previously shown[18] that phosphonic acids can be esterified with diazomethane (**8**) and under certain conditions carboxylic acids in water may be similarly esterified.[19] The solutions of A, B, and C were separately treated with **8** (large excesses being required for aqueous solutions). Although A and C led to complex mixtures of products, B was esterified

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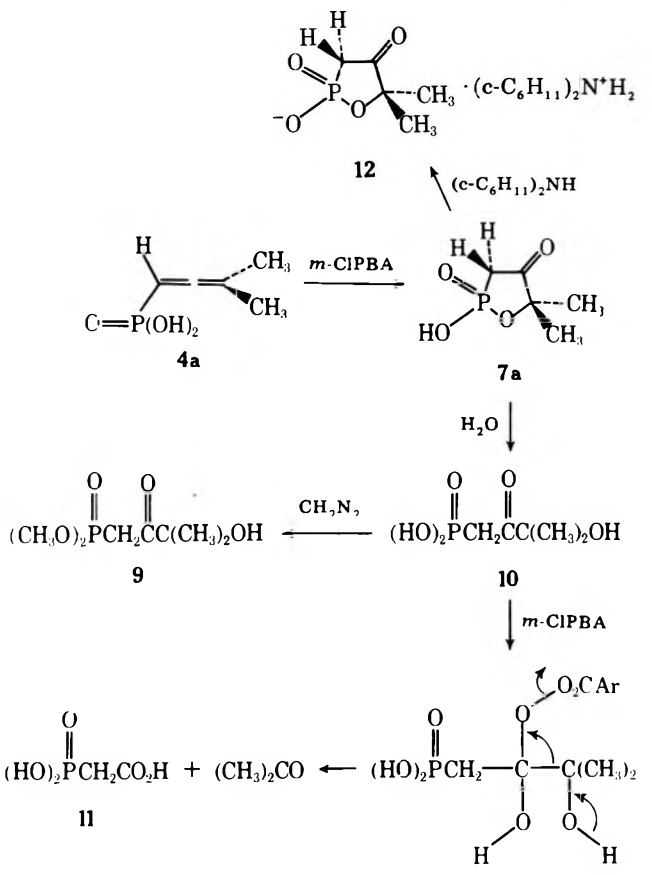
Scheme I

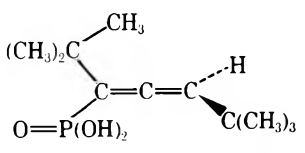


relatively cleanly to give a colorless liquid to which we assign structure **9** based on its ^{1}H NMR spectrum [($CDCl_3$) δ) 1.38 (s, 6 H), 3.47 (d, J = 23 Hz, 2 H), 3.85 (d, J = 11.5 Hz, 6 H), 4.30 (bs, 1 H)] and other data given in the Experimental Section. This assignment then suggests structures **7a, 10,** and **11** for A, B, and C, respectively.[20] More direct evidence for the formation of **7a** came from the isolation of its dicyclohexylamine salt **12**,[21] the properties of which are described in the Experimental Section.

While it is not surprising that compounds **7a, 10,** and **11,** tend to polymerize (or at least associate strongly),[22] it was unexpected that neither **7a, 10,** or even **9** give typical carbonyl derivatives such as 2,4-dinitrophenylhydrazones. This may be due to their neopentyl nature. It is also interesting that the 4-keto group in **7a** greatly facilitates hydrolytic ring opening,[23] while 1,2-oxaphosphol-3-enes show no tendency to ring open even in TFA at 75 °C.[1,7,8]

Two additional observations are worthy of comment at this point. When the dimethyl ester of **4a**[7,18] was allowed to react with 2.5 mol equiv of *m*-chloroperbenzoic acid (necessary for complete consumption of starting material), acetone was the only identifiable product. When cyclization of **6** is prevented by protection of the POH groups, further oxidation of the intermediate to acetone ensues. This also explains the presence of acetone in the original reaction of **4a** with peracid (vide supra).

Equally interesting is the observation that **4b** was totally inert toward *m*-chloroperbenzoic acid after 5 days at 42 °C,



4b

even though 1,3-di-*tert*-butylallene reacts readily.[5a] The phosphoryl substituent apparently deactivates both π bonds, the closer by induction and the further sterically, thereby precluding epoxidation. Oxaphospholene **5a** was also inert toward peracid (73 °C, 24 h).

Experimental Section

General. The instrumentation and general methods were as previously described.[7,8,22]

Reaction of 4a with *m*-Chloroperbenzoic Acid. To a suspension of 590 mg (4.00 mmol) of **4a**[7] in 25 mL of dry chloroform at 24 °C was added a solution of 2.00 g (10.1 mmol) of peracid[15] in 25 mL of dry chloroform at once. The reaction could be followed by ^{1}H NMR as described in the text. The initially heterogeneous mixture[16] became essentially homogeneous after 2 h, remaining so through the end of the reaction. After a total of 5 h, the solution was decanted from a small amount of insoluble material and extracted with 4 × 5 mL of water.[24] To this aqueous solution of **7a** was added 1.00 g (5.5 mmol) of dicyclohexylamine, and the resulting mixture was shaken overnight at 24 °C, then evaporated to dryness at <0.1 mm and 40 °C. The residue was recrystallized from benzene and dried (130 °C, 0.01 mm) to give 285 mg (21%) of **12**: mp 168–170 °C; ^{1}H NMR ($CDCl_3$) δ 0.6–2.3 [envelope with sharp singlet at 1.43, 28 H (theoretical 25)], 2.51 (d, J = 13 Hz) and 2.5–3.0 (envelope) (totalling 4 H), 8.3 (bs, 2 H); IR ($CHCl_3$) 3200–2200 (v br), 1735 (vs), 1455, 1230, 1080, 980, 820 cm^{-1}. Anal. Calcd for $C_{17}H_{32}NO_4P$: C, 59.09; H 9.34. Found: C, 59.10; H, 9.51.[25]

Isolation of 9. A solution of ca. 1.0 g of **7a** in 24 mL of water was prepared as described above. It was heated to 51 °C for 19h causing quantitative hydrolysis to **10.** This reaction can be monitored by ^{1}H NMR as described in the text. Ethereal diazomethane (330 mL of a 1% solution) was added, the ether phase was separated, dried, and evaporated, and the crude **9** was distilled to give 300 mg of a colorless liquid, bp 70 °C (0.05 mm). This product was further purified by HPLC (silica gel, chloroform) to give 95% pure **9,** the ^{1}H NMR data for which are given in the text: IR ($CHCl_3$) 3400 (broad), 1725, 1250 cm^{-1}; MS (20 eV) *m/e* (rel abundance) 211 (1), 192 (6), 151 (19), 150 (68), 124 (15), 111 (100), 110 (34), 80 (25).

Acknowledgment. The HPLC purification of **9** was performed by Mr. Bruce Downs; Messrs. Stephen Gee and John Sullivan prepared the **4a** used in this work.

Registry No.—**4a,** 1831-37-4; **7a,** 65378-71-4; **9,** 65378-72-5; **10,** 65378-73-6; **12,** 65378-74-7.

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(1) Paper 7 in the series on formation and cyclization of allenic phosphonic acids; Paper 5: R. S. Macomber, *J. Org. Chem.*, **42,** 3297 (1977).
(2) See, for example, J. K. Crandall, W. H. Machleder, and S. A. Sojka, *J. Org. Chem.*, **38,** 1149 (1973), and references therein.
(3) A. Liberies, S. Kang, and A. Greenburg, *J. Org. Chem.*, **38,** 1923 (1973).
(4) M. E. Zandler, C. E. Choc, and C. K. Johnson, *J. Am. Chem. Soc.*, **96,** 3317 (1974).
(5) (a) R. L. Camp and F. D. Greene, *J. Am. Chem. Soc.*, **90,** 7349 (1968); (b) J. K. Crandall and W. H. Machleder, *J. Heterocycl. Chem.*, **6,** 777 (1969).
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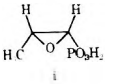
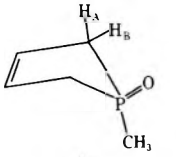
(7) R. S. Macomber and E. R. Kennedy, *J. Org. Chem.*, **41,** 3191 (1976).
(8) R. S. Macomber, *J. Am. Chem. Soc.*, **99,** 3072 (1977).
(9) The obvious similarity of **6** and its isomers to the antibiotic phosphomycin (i) suggests that these compounds may possess similar physiological properties.



(10) Commercially available "40%" material from FMC Corp., 45.5% by iodometric titration.
(11) Addition of authentic acetone increased the intensity of this signal. Separation of the volatile products and solvent by vacuum transfer then treatment with 2,4-dinitrophenylhydrazine gave the 2,4-DNP of acetone, mp 126.0–126.8 °C (lit.[12] 125 °C).
(12) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", 5th ed, Wiley, New York, N.Y., 1964.
(13) When the reaction is carried out in D_2O this signal is rapidly lost due to exchange.
(14) Assuming the δ 2.98 doublet is 2 H (vide infra).
(15) Eastman 85% min; 88% by iodometric titration.
(16) Phosphonic acid **4a** is sparingly soluble in chloroform. But the initial suspension becomes homogeneous as the reaction proceeds.

(17) After 24 h at room temperature there was a slight decrease in the amount of A and a comparable increase in the amount of acetone.
(18) R. S. Macomber, *Synth. Commun.*, **7(6)**, 405 (1977).
(19) E. J. Eisenbraun, R. N. Morris, and G. Adolphen, *J. Chem. Educ.*, **47**, 710 (1970).
(20) Analogous compounds show very similar chemical shifts and P–H coupling constants: ii [K. Moedritzer and P. A. Berger, *J. Org. Chem.*, **42**, 2023 (1977)]; iii and iv [Sadtler Research Labs NMR Standard Spectra 7770, 7771]



ii: δ_A 2.59 (J_{PA} = 14 Hz), δ_B 2.47 (J_{PB} = 8 Hz)

iii: δ_{CH_2} 2.61 ($^3J_{PH}$ = 21 Hz)

iv: δ_{CH_2} 3.59 ($^3J_{PH}$ = 14 Hz)

(21) This technique has been used to isolate salts of other phosphonic acids: R. Rabinowitch, *J. Org. Chem.*, **28**, 2975 (1963).
(22) Compound **5b** was found to form a phosphonic anhydride under certain hydrolysis conditions: R. C. Elder, L. R. Florian, E. R. Kennedy, and R. S. Macomber, *J. Org. Chem.* **38**, 4177 (1973).
(23) The dicyclohexylamine salt of **7a** is stable in water, suggesting that the hydrolytic ring opening is acid catalyzed.
(24) Less than 20 mg of *m*-chlorobenzoic acid is extracted into the water.
(25) Elemental analysis performed by Integral Microanalytical Labs.

Procedure for the Permethylation of Ketones Using Potassium Hydride and Methyl Iodide

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The classical method for the synthesis of permethylated ketones is sequential reaction of the ketone with portions of sodamide and methyl iodide.[1] More recent methods utilize such bases as sodium alkoxides[2] or sodium hydride.[3] In most cases, the overall yield for the replacement of all enolizable hydrogens does not exceed 50%.

We recently required a sample of 2,2,6,6-tetramethylcyclohexanone. The excellent procedure discovered by Charles Brown for using potassium hydride to prepare potassium ketone enolates[4] together with a report[5] that KH reacts with methyl iodide only sluggishly at 50 °C suggested a simple route. Treatment of cyclohexanone with a fourfold excess of KH and methyl iodide at 25 °C might lead directly to the desired ketone. Indeed, with slight modifications of this procedure, the results were sufficiently gratifying that we applied the method to a variety of ketones and report our results here.

Results and Discussion

Reaction of KH with Methyl Iodide. A suspension of KH (10 mmol) in tetrahydrofuran (THF) was maintained at 25 °C and treated with 10 mmol of methyl iodide. Evolution of a gas determined to be methane (GLC retention volume) began immediately. A total of 3.7 mmol of methane was formed in less than 1 min (as measured by a gas buret). No further methane was formed over a 2-h period. GLC analysis of the THF suspension confirmed the presence of the expected 6.3 mmol of residual methyl iodide. Additions of 10 mmol of cyclohexanone to the suspension resulted in the rapid evolution of 6.3 mmol of hydrogen, confirming the presence of 6.3 mmol of residual KH.

Evidently, KH does reduce methyl iodide at room temperature, but the reaction stops far short of completion. We have no direct evidence on the reason for the incomplete reduction, but the following experiment was particularly revealing.

A suspension of 15 mmol of KH in THF was treated with 5 mmol of 2,2,6-trimethylcyclohexanone. Hydrogen (5.0 mmol) was evolved over a 5-min period. Injection of 5 mmol of methyl iodide did not produce any gas evolution (<0.1 mmol). GLC analysis of a small aliquot of the reaction mixture revealed the presence of 4.9 mmol of 2,2,6,6-tetramethylcyclohexanone. At this point, the suspension was treated with an additional 10 mmol of methyl iodide and 3.6 mmol of methane was immediately formed. Again the presence of residual KH (6.4 mmol) and methyl iodide (6.4 mmol) was established.

Based on these results, we make the following points. The incomplete reduction of methyl iodide by KH is probably not due to inhibition by the product KI since KI is also formed (presumably in a similar state) by reaction of the ketone enolate with methyl iodide.[6] The incomplete reduction is probably not due to a trace amount of an inhibitor in the methyl iodide unless the inhibitor is removed by the ketone enolate. The incomplete reduction is not due to the presence of some 30% of a highly reactive form of KH unless this highly reactive form does not preferentially react with the ketone. Most importantly, from our point of view, the potassium enolate of 2,2,6-trimethylcyclohexanone is remarkably reactive to methyl iodide and this reaction is much faster than the reduction of methyl iodide with KH.

Permethylation of ketones. Based on the above results, our original concept was modified slightly so as to minimize competing reduction of methyl iodide. Cyclohexanone was added to a THF suspension containing 4.3 equiv of KH. Methyl iodide (4.3 equiv) was then added dropwise to the

Table I. Methylation of Ketones with KH and Methyl Iodide at 25 °C

Ketone	Registry no.	Product	Registry no.	Yield[a]
Cyclobutanone	1191-95-3	2,2,4,4-Tetramethylcyclobutanone	4298-75-3	(79)
Cyclopentanone	120-92-3	2,2,5,5-Tetramethylcyclopentanone	4541-35-9	100 (83)
Cyclohexanone	108-94-1	2,2,6,6-Tetramethylcyclohexanone	1195-93-3	96 (81)
Cycloheptanone		2,2,7-Trimethylcycloheptanone	40514-75-8	75
Cycloheptanone[b]	502-42-1	2,2,7,7-Tetramethylcycloheptanone	64342-79-6	62 (50)
Acetone	67-64-1	2,2,4-Trimethyl-3-pentanone	5857-36-3	90
Acetone[b]		2,2,4,4-Tetramethyl-3-pentanone	815-24-7	72 (60)
Acetophenone	98-86-2	2,2-Dimethylpropiophenone	938-16-9	100 (81)
4-Heptanone	123-19-3	3,3,5-Trimethyl-4-heptanone	51220-07-6	86 (66)

[a] GLC yields, isolated yields (distillation) in parentheses. [b] Reaction mixture refluxed for 1 h prior to addition of the final equivalent of methyl iodide.

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reaction mixture. GLC analysis established a 96% yield of 2,2,6,6-tetramethylcyclohexanone.

Using this procedure, cyclobutanone, cyclopentanone, cyclohexanone, and acetophenone are nearly quantitatively permethylated in 15 min at 25 °C (see Table I). 4-Heptanone and cycloheptanone give cleanly the trimethylated product and acetone the pentamethylated product under these conditions. In these latter cases, the reason for incomplete methylation is slow reaction of the penultimate methylated ketone with KH. With acetone and cycloheptanone, refluxing the reaction mixture for 1 h followed by cooling and addition of the final equivalent of methyl iodide gives the permethylated ketones in good yields. However, this latter procedure is ineffective with 4-heptanone. In fact, no hydrogen was evolved when a sample of 3,3,5-trimethyl-4-heptanone was refluxed for 6 h with KH and the starting ketone was recovered quantitatively after addition of methyl iodide.

Reduction of 2,2,6,6-Tetramethylcyclohexanone with KH. When reaction mixtures for the permethylation of cyclohexanone were allowed to stir for periods of an hour or more prior to workup, small amounts of a side product identified as the methyl ether of 2,2,6,6-tetramethylcyclohexanol were detected. Evidently, a slow reduction of the permethylated ketone by KH occurs.[7] This was confirmed by stirring mixtures containing equivalent amounts of KH and 2,2,6,6-tetramethylcyclohexanone at room temperature and analyzing quenched aliquots periodically for 2,2,6,6-tetramethylcyclohexanol. Ten percent of the starting ketone was reduced in 5 h and 50% in 24 h.

Experimental Section

^{1}H-NMR spectra were recorded on a Varian T-60 with Me_4Si internal standard. Infrared spectra were recorded using a Perkin-Elmer 237B grating spectrometer. GLC analyses and preparative chromatography were obtained with a Varian 920 using 6 ft × 0.25 in. stainless steel columns packed with 1.5% OV-101 on Chromosorb GHP. THF was distilled from the sodium ketyl of benzophenone just prior to use. KH was obtained as a mineral oil suspension (Alpha) and used directly. Methyl iodide and all ketones were distilled and stored under an argon atmosphere. Caution: the paper by Brown[6] should be consulted before handling KH.

Reaction of KH with Methyl Iodide. A 50-mL round-bottomed flask equipped with a magnetic stirring bar, septum inlet, and mercury bubbler was flushed with argon and attached to a gas buret. The flask was charged with 1.86 mL (10 mmol) of KH suspension and 10 mL of THF. Methyl iodide (0.6 mL, 10 mmol) was injected. A total of 93 mL (3.7 mmol) of gas was evolved in 1 min. No further gas was evolved in 2 h. GLC analysis (2.5% $AgNO_3$, and 7% paraffin on Al_2O_3) of a sample of the gas indicated the presence of methane. 1-Pentane (10 mmol) was added to the reaction mixture as internal standard and GLC analysis (1.5% OV-101) of an aliquot established the presence of 6.3 mmol of methyl iodide.

Permethylation of Ketones. Because of the volatility of methyl iodide, it was found best to use a dry ice condenser on the reaction flask. The following procedure for the permethylation of cyclohexanone is representative of the general technique. A 500-mL round-bottomed flask was equipped with a magnetic stirring bar, septum inlet, and dry ice condenser and flushed with argon. The flask was charged with 40 mL (216 mmol) of KH in mineral oil. The flask was then immersed in a water bath maintained at 25 °C. THF (220 mL) was injected followed by dropwise addition of cyclohexanone (5.2 mL, 50 mmol) over a 5-min period. After 5 min of additional stirring, methyl iodide (13.5 mL, 216 mmol) is added dropwise over a 15-min period. After an additional 15 min of stirring, the reaction mixture is treated cautiously with 15 mL of water. The aqueous layer is extracted with one 15-mL portion of ether and the combined organic layers are dried over anhydrous K_2CO_3. The organic layer is subjected to simple distillation to obtain 6.25 g, 81% yield, of 2,2,6,6-tetramethylcyclohexanone: bp 183–185 °C; ^{1}H NMR (CCl_4, internal Me_4Si) δ 1.6 (s, 6 H), 1.1 (s, 12 H); IR (neat) 1700 cm^{-1} (C=O). Using this procedure, the following compounds were obtained (all new products gave satisfactory C, H elemental analysis):

2,2,4,4-Tetramethylcyclobutanone: isolated yield, 65%; bp 130–133 °C; ^{1}H NMR (CCl_4, internal Me_4Si) δ 1.7 (s, 2 H), 1.2 (s, 12 H); IR (neat) 1780 cm^{-1} (C=O).

2,2,5,5-Tetramethylcyclopentanone: isolated yield, 83%; bp 153 °C; ^{1}H NMR (CCl_4, internal Me_4Si) δ 1.7 (s, 4 H), 1.0 (s, 12 H); IR (neat) 1745 cm^{-1} (C=O).

2,2,7-Trimethylcycloheptanone: isolated by preparative GLC; ^{1}H NMR (CCl_4, internal Me_4Si) δ 2.6–3.0 (m, 1 H) [1.2–2.0 (m, 8 H), 1.0 (s, 6 H), 0.9 (d, 3 H)]; IR (neat) 1710 cm^{-1} (C=O).

2,2,4-Trimethyl-3-pentanone: isolated by preparative GLC; ^{1}H NMR (CCl_4, internal Me_4Si) δ 3.0 (heptet, 1 H, J = 8 Hz), 1.1 (s, 9 H), 1.0 (d, 6 H, J = 8 Hz); IR (neat) 1705 cm^{-1} (C=O).

2,2-Dimethylpropiophenone: isolated yield, 81%; bp (5 Torr) 85–90 °C; ^{1}H NMR (CCl_4, internal Me_4Si) δ 7.5 (m, 2 H), 7.2 (m, 3 H), 1.3 (s, 9 H); IR (neat) 1675 cm^{-1} (C=O).

3,3,5-Trimethyl-4-heptanone: isolated yield, 66%; bp 187 °C; ^{1}H NMR (CCl_4, internal Me_4Si) δ 2.7 (m, 1 H), 1.4 (m, 4 H), 1.0 (s, 6 H), 1.8 (m, 3 H); IR (neat) 1695 cm^{-1} (C=O).

The following compounds were obtained by a modification of the above procedure by which the reaction mixture was heated to reflux for 1 h after addition of one less than the theoretical equivalent of methyl iodide. The reaction flask was then immersed in a water bath at 25 °C and the final equivalent of methyl iodide was injected dropwise. Workup was as described above.

2,2,7,7-Tetramethylcycloheptanone: isolated yield, 50%; bp 195 °C; ^{1}H NMR (CCl_4, internal Me_4Si) δ 1.6 (s, 8 H), 1.1 (s, 12 H).

2,2,4,4-Tetramethyl-3-pentanone: isolated yield, 60%; bp 157 °C; ^{1}H NMR (CCl_4, internal Me_4Si) δ 1.2 (s); IR (neat) 1670 cm^{-1}.

Acknowledgment is made to the National Science Foundation for partial support of this work.

Registry No.—KH, 7693-26-7; methyl iodide, 74-88-4.

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Thiol–Olefin Cooxidation Reaction. 6. A New Convenient Route to 1-Substituted Indenes. Indenone as Dienophile in Diels–Alder Reactions

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A recent publication[1] concerning the use of indenone ketals as dienophiles in a Diels–Alder reaction with butadiene (to give adducts that then serve as starting materials for the synthesis of degradation products of the plant stimulant gibberellic acid) prompts us to report the use of indenone itself in the cycloaddition reaction and its convenient preparation from indene as well as of other 1-substituted indenes (**4**–**6**). The facile conversion of indene by means of the TOCO reaction to a mixture of three isomeric β-hydroxy sulfoxides[2,3] followed by their oxidation to β-keto sulfoxides[4] was coupled with the ready elimination of the sulfoxide moiety to give the 1-substituted indenes as shown in Scheme I.

The formation of **4** requires refluxing overnight in toluene as compared to a 4-h period of reflux for the formation of **5** and **6**. The longer time required for the elimination of the sulfoxide moiety in the case of the formation of **4** suggests the stabilization of **2** by intra- and intermolecular hydrogen bonding.

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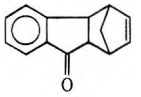
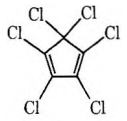
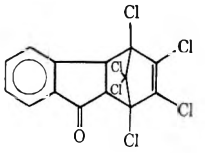
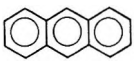
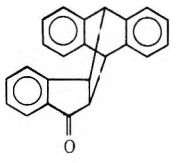
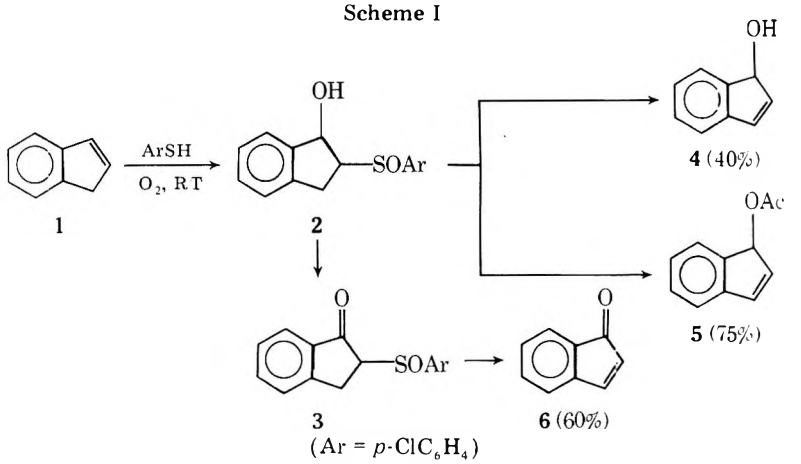
Table I. Diels–Alder Adducts of Indenone 6

Diene	Registry no.	Product	Registry no.	Mp, °C	Yield %
 7	542-92-7	 10	65495-96-7	Liquid	53
 8	97-47-4	 11	65495-97-8	158–60	30
 9	120-12-7	 12	37069-90-2	198–200	68

Scheme I



The conversion of indene to **5** is a one-pot reaction but the intermediate β-acetoxy sulfoxide can also be isolated.

Numerous methods are available for the preparation of substituted indenones,[1,5–8] but there are very few methods available for a specific synthesis of **6**.[7,9,10] Our reaction sequence is highly convenient because **6** can be easily separated from the *p*-chlorophenyl disulfide and other sulfur-containing products. The Diels–Alder reaction can be attained by carrying out the elimination in the presence of dienes and without the need to separate *p*-chlorophenyl disulfide. In this way the chance of dimerization to truxone is reduced. In our hands **4** and **5** fail to give Diels–Alder adducts, even under vigorous conditions (reflux in toluene 48 h), whereas **6** forms Diels–Alder adducts[10] as summarized in Table I.

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Varian A-60A spectrometer using tetramethylsilane as an internal standard. Indene was distilled under vacuum. *p*-Chlorothiophenol was recrystallized from aqueous ethanol. Cyclopentadiene was distilled just before use. Hexachlorocyclopentadiene and anthracene were used directly as supplied commercially. Melting points are uncorrected.

2-(*p*-Chlorophenylsulfinyl)-1-indanone (3). Jones reagent, prepared by dilution with water of a solution of 26.72 g of chromium trioxide in 23 mL of concentrated sulfuric acid to the volume of 100 mL, was added dropwise to a solution of 2 g of **2** in 40 mL of reagent grade acetone until the color of the top layer changed from green to brown. The solvent was removed under vacuum and the residue was extracted with chloroform. The extract was washed with water until the top layer was clear, dried over anhydrous sodium sulfate, and evaporated to give **3** (yield 1.5 g) (75%) recrystallized from 95% ethanol to white needles: mp 160–61 °C (lit.[4] mp 160–62 °C); NMR (Me_2SO-d_6) δ 3.55 (d, 2), 4.9 (t, 1), 7.75 (m, 8).

On addition of a drop of NaOD in D_2O to the Me_2SO-d_6 solution the triplet at δ 4.9 disappeared completely and the doublet at δ 3.55 changed to a singlet.[11]

1-Hydroxyindene (4). A solution of 1 g of **2** in 20 mL of toluene was refluxed overnight. The solvent was removed under vacuum and the residue was chromatographed on 30 g of alumina (F-20). The material was eluted with hexane, a mixture of hexane and benzene, and finally benzene. The hexane fraction gave *p*-chlorophenyl disulfide and the benzene fraction produced **4**: yield 180 mg (40%); mp 57–59 °C (lit.[12] mp 57–58 °C).

1-Acetoxyindene (5). A mixture of 2 g of **2**, 2 g of sodium acetate, 20 mL of acetic anhydride, and 60 mL of toluene was refluxed for 4 h. The solvent was removed under vacuum and the residue was chromatographed on 100 g of silica gel G. The material was eluted with hexane, a mixture of hexane and benzene, and finally benzene. The benzene fraction produced **5**: yield 0.88 g (74%); bp 50–52 °C (3 mm) (lit.[12] bp 118–22 °C (12 mm)); NMR ($CDCl_3$) δ 2.1 (s, 3), 6.2–6.9 (m, 3), 7.2–7.4 (m, 4).

The intermediate β-acetoxy sulfoxide was isolated and characterized as follows. The isomeric mixture of 2 g of **2** was treated overnight with a mixture of 2 g of sodium acetate and 40 mL of acetic anhydride at room temperature. The mixture was concentrated in vacuo and the residue was suspended in benzene. The unreacted sodium acetate was filtered and the removal of benzene gave a gummy product which was crystallized from 95% ethanol to give 1-acetoxy-2-(*p*-chlorophenylsulfinyl)indane: yield 1.74 g (76%); mp 143–45 °C; NMR ($CDCl_3$) δ 1.9 (s, 3), 3.2–3.6 (m, 3), 6.7 (d, 1), 7.2–7.6 (m, 8). Anal. Calcd for $C_{17}H_{15}ClO_3S$: C, 60.89; H, 4.52. Found: C, 60.74; H, 4.56.

1-Indenone (6). A solution of 2 g of **3** in 50 mL of toluene was heated to reflux for 4 h. The solvent was removed under vacuum and

the residue was chromatographed from 60 g of alumina (F-20). The material was eluted with hexane, a mixture of hexane and benzene, and finally benzene. The hexane fraction gave *p*-chlorophenyl disulfide and the benzene fraction produced **6** (yield 0.52 g) (58%), which was characterized by its yellow color, its biting lachrymatory odor, and 2,3-dibromoindanone: mp 62–63 °C (lit.[13] mp 64–65 °C); NMR ($CDCl_3$) δ 6.4–6.9 (m, 2), 7.4–7.8 (m, 4). **6** readily dimerizes to truxone in the presence of a trace of acid catalyst.

Typical Procedure for Diels–Alder Reactions. A solution of 0.5 g (1.7×10^{-3} mol) of **3** and a small excess of diene (3×10^{-3} mol) in 30 mL of toluene was heated to reflux for 8–10 h. The solvent was removed under vacuum and the crude residue was transferred onto a column of 100 g of alumina (F-20) in hexane containing 0.3 to 0.5 mL of toluene. The material was eluted with hexane, 75:25 and 50:50 mixtures of hexane and toluene, and finally toluene. The hexane fraction yielded *p*-chlorophenyl disulfide, the hexane–toluene fraction gave the Diels–Alder adduct in the case of the cyclopentadiene, and the toluene fraction gave the Diels–Alder adduct in the case of hexachlorocyclopentadiene and anthracene.

Cyclopentadiene adduct (10): yield 180 mg (53%); colorless liquid; NMR ($CDCl_3$) δ 1.9 (br s, 2), 2.9–4 (m, 4), 5.3 (q, 1), 5.9 (q, 1), 7.2–7.4 (m, 4). Anal. Calcd for $C_{14}H_{12}O$: C, 85.69; H, 6.26. Found: C, 85.34, H, 6.61.

Hexachlorocyclopentadiene adduct (11): yield 210 mg (30%); mp 158–60 °C; NMR ($CDCl_3$) δ 2.7 (d, 1), 3.2 (d, 1), 7.2–7.5 (m, 4). Anal. Calcd for $C_{14}H_6Cl_6O$: C, 41.78; H, 1.49; Cl, 52.79. Found: C, 42.00; H, 1.59; Cl, 53.09.

Anthracene adduct (12): yield 360 mg (68%); mp 198–200 °C; NMR ($CDCl_3$) δ 3.1 (q, 1), 3.9 (q, 1), 4.6 (d, 1), 4.8 (d, 1), 6.9–7.5 (m, 12). Anal. Calcd for $C_{23}H_{16}O$: C, 89.58; H, 5.22. Found: C, 89.39; H, 5.36.

Acknowledgment. We wish to thank the MHW Laboratories, Phoenix, Arizona 85018, for the microanalysis.

Registry No.—**2,** 62967-56-0; **3,** 62937-76-2; **4,** 61463-21-6; **5,** 35116-20-2; **6,** 480-90-0; 1-acetoxy-2-(*p*-chlorophenylsulfinyl)indine, 65495-98-9; 2,3-dibromoindanone, 50870-59-2.

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Radical Anions of Substituted Cyclobutene-1,2-diones[1]

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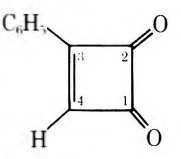
A recent report[2] on the observation of a paramagnetic reduction product of phenylcyclobutene-1,2-dione (**1**) prompts us to describe some observations we have made in this and other systems.

We have observed that the reduction of **1** in a static system at 25 °C yields the spectrum reported by Concepcion and Vincow ($a^H = 11.25, a^C = 8.5, 4.5$ G) in hexamethylphosphoramide (HMPA)–lithium, in dimethyl sulfoxide (Me_2SO)–potassium *tert*-butoxide, or in dimethylformamide (DMF)–electrolysis. We have hesitated upon assigning this species to



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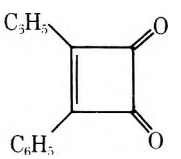


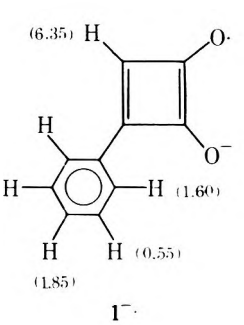
2

$1^{-}\cdot$ for several reasons. The half-life of the species in Me_2SO was several hours which is inconsistent with structure $1^{-}\cdot$, particularly in view of the high spin density of ~11.25/27 on C-4.[3] If the spin densities at C-3 and C-4 were to be equated, it would appear that the semidione function is nearly devoid of spin density. We have been unable to prepare alkyl derivatives in this system, for example, by the treatment of 1,2-dimethylcyclobutene-1,2-dione with basic Me_2SO,[3] but still the reported spectrum indicates little spin delocalization by the aromatic ring. Finally, under flow conditions with basic Me_2SO, **1** was observed to yield an ESR spectrum (Chart I) more consistent with the hyperfine splitting constants (hfsc) expected for $1^{-}\cdot$ and also consistent with the spectrum observed for $2^{-}\cdot$ when **2** is continuously electrolyzed in DMF. Under stopped-flow conditions the species we assign as $1^{-}\cdot$ disappeared in seconds as did $2^{-}\cdot$ when electrolysis was halted. The observed hfs constants for $1^{-}\cdot$ are quite consistent with the Hückel spin density calculations reported by Concepcion and Vincow[2] with all β_{cc} values equal (the predicted values of a^H being[2] $a_4^H = -7.5, a_o^H = -2.05, a_m^H = -0.11$, and $a_p^H = -2.45$ G).[14]

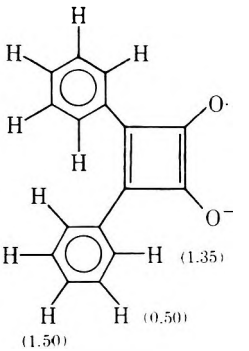
Reduction of **2** with HMPA–lithium or HMPA–(trimethylsilyl)sodium[5] presented some complications which may be related to the observation of the species with a^H = 11–12 G from **1**. With alkali metal reducing systems at 25 °C the radical attributed to $2^{-}\cdot$ was the major species detected, but a second radical anion with a^H = 3.00 (2), 2.4 (4), and 0.8 (4) G was observed. Upon irradiation with a low-pressure UV lamp $2^{-}\cdot$ disappeared and only the spectrum of the second radical anion remained. The second radical anion appears to be benzophenone ketyl but without the usually observed metal hfsc.[6] Reduction of benzophenone (0.25 M) by HMPA–(trimethylsilyl)sodium yielded a spectrum with a^H = 3.5 (2), 2.5 (4), and 0.75 (4) G and a^{Na} = 0.75 G, consistent with literature values of benzophenone ketyl in dimethoxyethane[5] or HMPA.[7]

We presume that the 11.25-G doublet arising from the reduction of **1** and benzophenone ketyl from **2** arise from 1,2 migrations in the cyclobutene-1,2-dione system. Attack by traces of hydroxide ion could initiate a benzilic acid type of rearrangement (Scheme I). Reduction of **1a** to the radical trianion **3** is feasible but now H-4 would be in the nodal plane of the allylic system and a small hfsc would be expected. On the other hand, loss of an electron from **1a** to yield **4** would give a semitrione for which a^H might reasonably be 11 G, and the

Chart I. Observed Hyperfine Splitting Constants



$1^{-}\cdot$



$2^{-}\cdot$, DMF, 25 °C, Bu_4N^+, line width 0.1 G

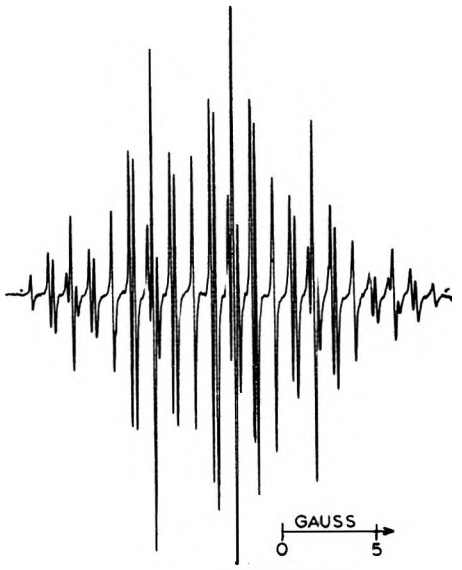
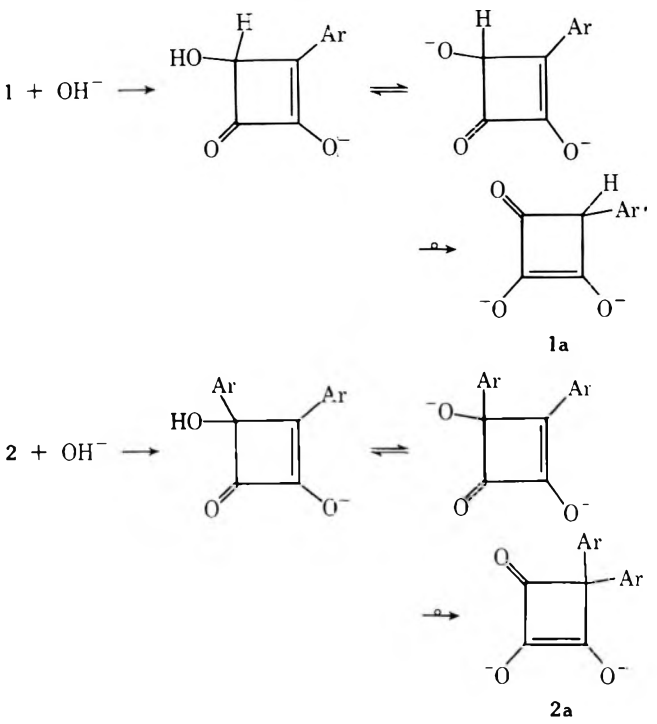
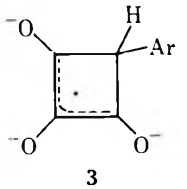


Figure 1. ESR spectrum of 8 at 25 °C observed in HMPA-(trimethylsilyl)sodium at a 0.5 mL/min flow rate through a cell with 0.05-mL dead volume. The initial concentration of 7 was 1×10^{-3} M.

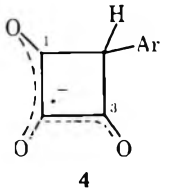
Scheme I



hfsc by the aromatic ring would be absent. In a system such as 4 the magnitude of the hfsc for H-4 will be a function of $(c_1$



3

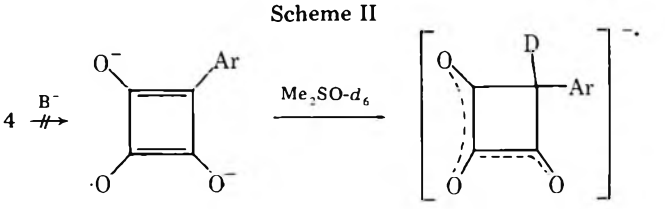


4

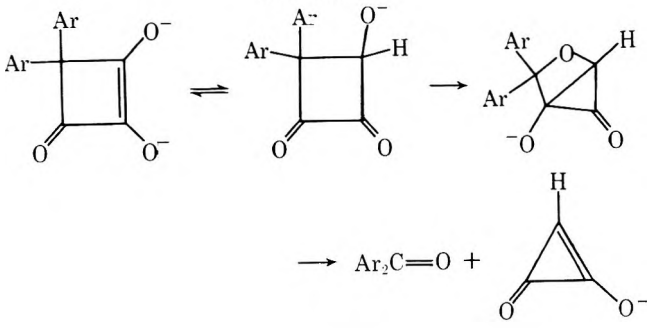
$+ c_3)^2$ where c_1 and c_3 are the coefficients in the singly occupied MO. The absence of hydrogen–deuterium exchange in Me_2SO-d_6 as reported by Concepcion and Vincow[2] can be rationalized with structure 4 in terms of the cyclobutadienoid structure required for this process (Scheme II).

The observation of benzophenone ketyl from 2 is a perplexing observation to rationalize even after **2a** is considered

Scheme II

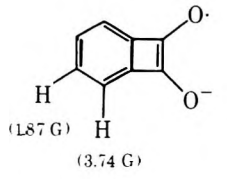


Scheme III

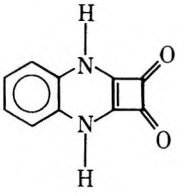


as an intermediate. The possibility exists that it may occur partially or wholly from a photochemical transformation. A Haller–Bauer type cleavage of the carbocyclic ring in **2a** by an oxy anion seems to be the required reaction course. A possible intramolecular formulation is presented in Scheme III.

In the search for other cyclobutene semidiones in addition to the known **6**,[8] we have investigated the reduction of **7**. A

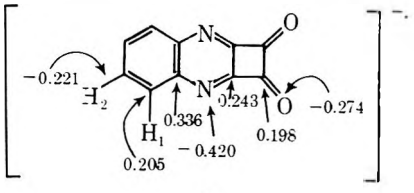


6



7

radical anion was easily detected by treatment with HMPA–lithium in a static system or HMPA-(trimethylsilyl)sodium in a flow system. The hfsc consistent with Figure 1 were a^N = 4.75 (2) G and a^H = 1.25 (2), 0.95 (2) G with a line width of 0.25 G. The persistency of this species as well as the number and magnitude of hfsc suggests that disproportionation or oxidation occurred to give the quinoxaline derivative **8**. Coefficients in the HOMO calculated by the Hückel technique with $\alpha_N = \alpha_O = \alpha_C + 1.2\,\beta_{CC}$, $\beta_{CC} = \beta_{CN}$, and $\beta_{CO} = 1.56\,\beta_{CC}$ as listed in structure **8**, led to predicted hfsc using $Q_{CH}{}^H = -27$ and $Q_N{}^N = +25$ of $c^N = -4.5$, $a_1{}^H = -1.1$, and $a_2{}^H = +1.3$ G.



8

In the quinoxaline radical anion itself the corresponding hfsc are a^N = 5.6 G and a^H = 2.3, 1.0 G, whereas in the phenazine radical anion the assignments are a^N = 5.1, $a_1{}^H$ = 1.9, $a_2{}^H$ = 1.6 G.[9]

Experimental Section

3-Phenylcyclobutene-1,2-dione,[10] 3,4-diphenylcyclobutene-1,2-dione,[11] and 1,2,3,8-tetrahydro-1,2-dioxocyclobuta[*b*]quinoxaline[12] were prepared by literature procedures.

ESR spectra were recorded with a Varian E-3 spectrometer using a flat aqueous sample or flow cells. Spectra were simulated with a

Japan Electron Optics Laboratory Co. JNM-RA-1 spectrum accumulator presuming Lorentzian line shapes.

Static experiments were performed by use of an inverted H-type mixing cell under nitrogen or argon.[13] HMPA was distilled immediately before use from calcium hydride under reduced pressure. Me_2SO was thoroughly dried with molecular sieves before use. For HMPA–lithium reductions a volume of HMPA sufficient to form a 10^{-3} M solution of the ketone was placed in the two arms of the cell and deoxygenated by a stream of nitrogen for 0.5 h. The ketone was added to one arm of the cell and a pellet of freshly cut and cleaned lithium added to the other arm. The nitrogen purge was continued for a few minutes after the lithium solution had turned deep blue. At this point the solutions were mixed and drained into the fused silica cell for measurement. HMPA–(trimethylsilyl)sodium reductions were performed in a similar manner except that sodium methoxide was dissolved in a HMPA solution of hexamethyldisilane (Pierce Chemical Co.) in one arm of the cell. Flow experiments were performed as previously described for the Me_2SO–potassium *tert*-butoxide system using upflow through a Varian V-4549A cell with a dead space of ~0.05 mL. Flow rates could be adjusted by motor driven syringes so that ESR measurements could be made from 0.1 s to a few minutes after mixing.

Registry No.—**1**, 3947-97-5; $1^{-}\cdot$, 65405-28-9; **2**, 24234-76-2; $2^{-}\cdot$, 65405-27-8; **7**, 20420-52-4; **8**, 64014-05-7.

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(7) Sakurai (ref 5) reports a^H = 3.49 (2), 2.38 (4), and 0.75 (4) G without detectable metal hyperfine splitting constants.
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(14) **Note Added in Proof.** Diphenylcyclobutene-1,2-semidione is also formed slowly when diphenylcyclopropenone is treated with potassium *tert*-butoxide in Me_2SO (experimental results with Dr. T. Morita). Under these conditions $2^{-}\cdot$ has a lifetime of hours. The reaction involves an example of carbonyl insertion, $R_2C{=}O + CO + e^- \rightarrow RC(O\cdot){=}C(O^-)R$: see G. A. Russell, D. E. Lawson, and L. A. Cohrymowycz, *Tetrahedron*, **26**, 4697 (1970).

An Ethoxycarbonyl Migration from an Amide Nitrogen to Oxygen[1]

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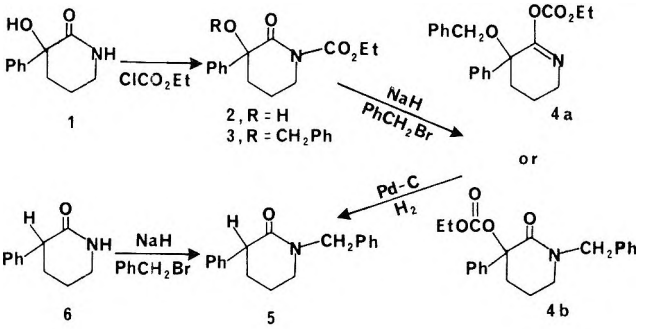
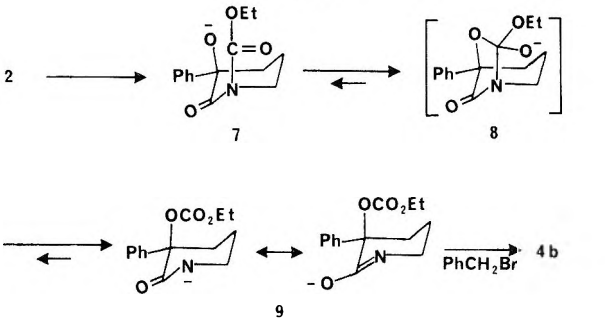
We wish to report what appears to be the first example of an ethoxycarbonyl group migration from an amide nitrogen to oxygen. Previous literature reports have shown that migration of the ethoxycarbonyl group can be a facile process. As early as 1906 it was shown by Blaise and Courtot[2] that an ethoxycarbonyl group could migrate more readily than a methyl group to a positive center. Subsequent reports have been very few in number but have included examples of alkoxycarbonyl shifts to positive, neutral, and negative centers.[3] The only studies that we have seen involving alkoxycarbonyl migration between nitrogen and oxygen are those on the 2-aminophenols,[3,4] *N*-ethoxycarbonylhydrastinine,[5] and substituted isoquinolines,[6] none of which involved an amide nitrogen.

Scheme I



Scheme II



Attempted O-benzylation of **2**, prepared from $ClCO_2Et$ and **1** as shown in Scheme I, did not yield the expected product **3**. The ^{1}H-NMR spectrum of the product was consistent with structure **3**, but the IR spectrum contained carbonyl absorptions at 1750 (carbonate) and 1660 cm^{-1} (lactam or lactim), suggesting a rearranged product such as **4a** or **4b**. The largest fragment in the mass spectrum was *m/e* 263 ($M^+ - 90$). Hydrogenolysis of this product yielded a compound for which the IR spectrum indicated an N-substituted lactam (1640 cm^{-1}),[7] and the ^{1}H-NMR spectrum showed loss of the ethoxycarbonyloxy group and the presence of two types of benzylic protons at δ 4.7 (singlet, 2 H) and 3.7 ppm (multiplet, 1 H). These observations were consistent with structure **5**. Since amides undergo N-alkylation under basic conditions,[8] an unambiguous synthesis of **5** (Scheme I) using 3-phenyl-2-piperidinone (**6**),[9] $PhCH_2Br$, and NaH confirmed the structure assignment. The rearranged product was therefore formulated as structure **4b**. The lack of a parent ion in the mass spectrum of **4b** is consistent with a facile loss of the ethoxycarbonyloxy group via a McLafferty rearrangement, which is not possible in **4a**.

Either an intermolecular or intramolecular mechanism can be envisioned for the conversion of **2** to **4b**. However, it is unlikely that an intermolecular mechanism is operative since none of the O-benzylated product **3** was detected, even though $PhCh_2Br$ was present before NaH addition. A mechanism which is consistent with previous studies on ethoxycarbonyl migrations from nitrogen to oxygen[5,6] is suggested in Scheme II.

As depicted in Scheme II, it is likely that any equilibrium between **7** and **9** favors the delocalized amide anion **9**. Alternatively, it is possible that the equilibrium favors anion **7** and that the $PhCH_2Br$ simply reacts much faster with the amide anion **9**, thus trapping a relatively small fraction of **9** as it is formed to yield **4b**. In order to test this possibility, compound **2** was subjected to the conditions of rearrangement but without $PhCH_2Br$ (Scheme III). In this case the only product formed was **10**, and TLC showed no remaining starting material.

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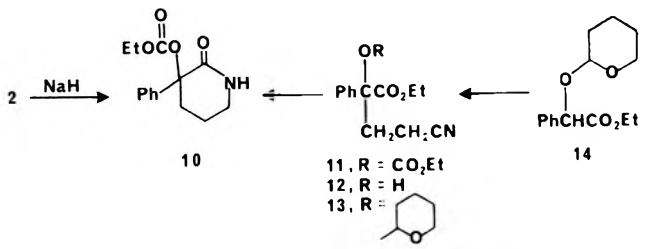
Scheme III



The structure assignment of **10** was confirmed by an alternate synthesis from ethyl 2-phenyl-2-(2-tetrahydropyranyloxy)acetate (**14**).[10] As shown in Scheme III, compound **14** was cyanoethylated with CH_2=CHCN and KO-*t*-Bu to afford **13.** Removal of the THP group with aqueous acid yielded **12,** and **12** was acylated using $ClCO_2Et$ and NaH to give **11.** Hydrogenation of **11** over PtO_2 in acetic acid provided **10.**

These results suggest that any equilibrium between **7** and **9** lies overwhelmingly toward the side of **9.** The driving force for the rearrangement must therefore be formation of the delocalized amide anion **9,** whih is more stable than anion **7.**

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-33 spectrophotometer. The ^{1}H-NMR spectra were obtained on Varian Associates T60 and EM 360 spectrophotometers with 1% Me_4Si as the internal standard. Electron impact mass spectra were recorded using a Varian CH-5 spectrometer. Elemental analyses were performed on a Hewlett-Packard 185B CHN Analyser at the University of Kansas. R_f values were determined using Brinkmann precoated silica gel plates (Silica Gel 60 F-254, 5 × 10 cm, 0.25 mm layer).

1-Ethoxycarbonyl-3-hydroxy-3-phenyl-2-piperidinone (2). A solution of 4.0 g (0.021 mol) of 3-hydroxy-3-phenyl-2-piperidinone (**1**)[10] and 5.7 g (0.052 mol) of $ClCO_2Et$ in 350 mL of toluene was heated at reflux for 24 h and concentrated in vacuo, and the residue was crystallized from Et_2O–hexane to yield 4.2 g (76%) of **2.** Recrystallization from $CHCl_3$–hexane yielded white needles: mp 66–67 °C; IR ($CHCl_3$) 3560 (OH), 1775 (C=O), and 1725 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.4 (s, 5 H, aromatic), 4.4 (q, 2 H, J = 7 Hz, ester CH_2), 4.1 (s, 1 H, OH), 3.8 (m, 2 H, CH_2N), 2.6–1.6 (m, 4 H, $PhCCH_2CH_2$), 1.4 (t, 3 H, J = 7 Hz, ester CH_3); MS (70 eV) *m/e* 263 (M^+). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 64.09; H, 6.60; N, 5.51.

1-Benzyl-3-ethoxycarbonyloxy-3-phenyl-2-piperidinone (4b). To a solution of 0.40 g (0.0015 mol) of **2** and 0.27 g (0.0016 mol) of $PhCH_2Br$ in 10 mL of benzene and 0.5 mL of Me_2SO was added 0.038 g (0.0016 mol) of NaH. The mixture was stirred at 25 °C for 48 h and extracted, respectively, with 10 mL of H_2O, 15 mL of 5% NH_3, and 15 mL of saturated NaCl. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to yield 0.50 g of a pale yellow oil. The oil was chromatographed in equal portions on 2 Brinkmann silica gel plates (20 × 20 cm, 2-mm layer) using 10% Et_2O in $CHCl_3$ as eluent. The major band (R_f 0.58) was isolated to yield 0.40 g (75%) of **4b** as a pale yellow oil: IR (liquid film) 1750 (carbonate) and 1660 cm^{-1} (lactam); ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5 H, aromatic), 4.8 (s, 2 H, $PhCH_2$), 4.2 (q, 2 H, J = 7 Hz, ester CH_2), 3.6–1.4 (m, 6 H, $CH_2CH_2CH_2N$), 1.3 (t, 3 H, J = 7 Hz, ester CH_3); MS (70 eV) *m/e* 263 (M^+ − 90). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.08; H, 6.60; N, 3.60.

1-Benzyl-3-phenyl-2-piperidinone (5). Procedure A. A mixture of 0.35 g (0.0010 mol) of **4b** and 0.2 g of 5% Pd-C (50% wet with H_2O) in 10 mL of absolute EtOH was hydrogenated at 1 atm for 17 h. The mixture was filtered and the filtrate was concentrated in vacuo to yield 0.24 g (71%) of **5** as a clear oil. TLC on silica (10% Et_2O in $CHCl_3$ elution) showed only one spot: R_f 0.54; IR (liquid film) 1640 cm^{-1} (N-substituted lactam); ^{1}H NMR ($CDCl_3$) δ 7.2 (d, 10 H, aromatic), 4.7 (s, 2 H, $PhCH_2$), 3.7 (m, 1 H, PhCH), 3.3 (m, 2 H, CH_2N), 2.4–1.6 (m, 4 H, $PhCCH_2CH_2$); MS (70 eV) *m/e* 265 (M^+). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.27; H, 7.30; N, 5.08.

Procedure B. The general procedure was the same as that for the preparation of **4b,** except that a mixture of 0.10 g (0.00057 mol) of 3-phenyl-2-piperidinone (**6**),[9] 0.11 g (0.00063 mol) of $PhCH_2Br$, 0.015 g (0.00063 mol) of NaH, 5 mL of benzene, and 0.1 mL of Me_2SO was stirred at 25 °C for 12 h. After chromatography the major band (R_f 0.54) was isolated to yield 0.13 g (86%) of **5** as a clear oil. IR and ^{1}H-NMR spectra were identical to the product prepared in procedure A.

3-Ethoxycarbonyloxy-3-phenyl-2-piperidinone (10). Procedure A. A mixture of 0.10 g (0.0038 mol) of **2,** 0.0096 g (0.00040 mol) of NaH, 5 mL of benzene, and 0.1 mL of Me_2SO was stirred at 25 °C for 1 h and extracted with an equal volume of H_2O followed by 5 mL of saturated NaCl, and the organic layer was dried ($MgSO_4$). The solution was concentrated in vacuo to yield 0.10 g of an opaque oil. Addition of 2 mL of Et_2O and cooling yielded 0.07 g (70%) of **10** as a white solid which was recrystallized from $CHCl_3$–Et_2O: mp 155–157 °C; IR (KBr) 3330 (NH), 1745 (carbonate), and 1640 cm^{-1} (lactam); ^{1}H NMR ($CDCl_3$) δ 7.4 (m, 5 H, aromatic), 6.7 (bs, 1 H, NH), 4.2 (q, 2 H, J = 7 Hz, ester CH_2), 3.8–1.5 (m, 6 H, $CH_2CH_2CH_2N$), 1.2 (t, 3 H, J = 7 Hz, ester CH_3); MS (70 eV) *m/e* 263 (M^+). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.49; H, 6.53; N, 5.12.

Procedure B. A mixture of 1.5 g (0.0049 mol) of the nitrile **11** and 0.15 g of PtO_2 in 35 mL of glacial acetic acid was hydrogenated on a Parr shaker at 45 psi for 10 h and filtered, and the filtrate was made basic with 35% NaOH. This solution was extracted with $CHCl_3$ (3 × 35 mL), the extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The residual oil was triturated with Et_2O and cooled to yield a white solid. Fractional recrystallization from $CHCl_3$–hexane yielded 0.20 g (21%) of **1** as the first crop and 0.30 g (23%) of **10** as the second crop. Compound **10** was recrystallized from $CHCl_3$–Et_2O: mp 156.5–157.5 °C; IR and ^{1}H NMR spectra were identical to that for the product in procedure A.

Ethyl 4-Cyano-2-ethoxycarbonyloxy-2-phenylbutyrate (11). A solution of 3.0 g (0.013 mol) of **12** and 0.31 g (0.013 mol) of NaH in 40 mL of benzene and 1 mL of Me_2SO was heated briefly to reflux and cooled to 50 °C, and 1.4 g (0.013 mol) of $ClCO_2Et$ was added. After heating at reflux an additional 1.5 h, the mixture was cooled to 25 °C and stirred overnight. The solution was extracted with 50 mL of H_2O followed by 50 mL of saturated NaCl, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to yield 2.8 g (71%) of **11** as a clear oil: bp 150 °C (.03 mm); IR (liquid film) 1795 (carbonate) and 1750 cm^{-1} (ester); ^{1}H NMR ($CDCl_3$) δ 7.4 (m, 5 H, aromatic), 4.2 (m, 4 H, carbonate and ester CH_2), 3.3–2.3 (m, 2 H, $PhCCH_2$), 2.0 (t, 2 H, CH_2CN), 1.25 (m, 6 H, carbonate and ester CH_3). Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.95; H, 6.30; N, 4.40.

Ethyl 4-Cyano-2-hydroxy-2-phenylbutyrate (12). A solution of 15 g (0.047 mol) of **13** in 250 mL of absolute EtOH and 50 mL of 20% HCl was heated at reflux for 1 h, reduced in vacuo to half volume, made basic with 3 N NaOH, and extracted with Et_2O (3 × 100 mL). The extracts were dried ($MgSO_4$) and concentrated in vacuo. Distillation of the residual oil gave 5.8 g (53%) of **12** as a clear oil: bp 123 °C (0.018 mm); IR (liquid film) 3410 (OH) and 1730 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$) δ 7.3 (m, 5 H, aromatic), 4.2 (q, 2 H, J = 7 Hz, ester CH_2), 3.9 (bs, 1 H, OH), 1.4 (m, 4 H, CH_2CH_2CN), 1.2 (t, 3 H, J = 7 Hz, ester CH_3). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.74; H, 6.43; N, 5.66.

Ethyl 4-Cyano-2-phenyl-2-(2-tetrahydropyranyloxy)butyrate (13). To a stirred solution of 100 g (0.380 mol) of **14**[10] in 80 mL of *t*-BuOH was added 14.2 g (0.130 mol) of KO-*t*-Bu. A solution of 100 g (1.89 mol) of acrylonitrile in 70 mL of *t*-BuOH was added dropwise over 45 min and stirring was continued for 1 h. The reaction mixture was poured into 200 mL of cold 2% HCl and filtered, the filtrate was passed through a bed of alumina on a Buchner funnel, and the solvent was removed in vacuo. The residual oil was placed on a high vacuum rotary evaporator to remove $(CH_3)_3COCH_2CH_2CN$, bp 40 °C (0.2 mm). The residue crystallized upon standing to provide 85.0 g (71%) of **13.** Recrystallization from CH_3OH–H_2O yielded white plates: mp 94–95 °C; IR (KBr) 2225 (CN) and 1725 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.4 (s, 5 H, aromatic), 4.7 (bs, 1 H, OCHRO), 4.4–3.9 (q, 2 H, J = 7 Hz, ester CH_2), 3.9–3.3 (m, 2 H, OCH_2), 2.9–2.2 (m, 4 H, CH_2CH_2CN), 2.2–1.4 (m, 6 H, $CH_2CH_2CH_2$), 1.4–1.0 (t, J = 7 Hz, ester CH_3). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.13; H, 7.30; N, 4.14. Found: C, 68.44; H, 7.40; N, 4.14.

Registry No.—**1,** 65379-06-8; **2,** 65379-07-9; **4b,** 65379-08-0; **5,** 65379-09-1; **6,** 51551-56-5; **10,** 65379-01-3; **11,** 65379-02-4; **12,** 65379-03-5; **13,** 65379-04-6; **14,** 65379-05-7; $ClCO_2Et$, 541-41-3; $PhCH_2Br$, 100-39-0.

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Communications

Conversion of Epoxides to Olefins with Trifluoroacetyl Iodide and Sodium Iodide[1]

Summary: Trifluoroacetyl iodide has been found to react with epoxides in the presence of excess sodium iodide to produce the related olefins in high yield; the reaction stereospecifically generates olefins of the same geometry as the epoxides.

Sir: Several methods of deoxygenating epoxides to produce olefins have been reported. Nonstereospecific procedures include treatment of epoxides with chromous salts[2] or with zinc–copper couple.[3] Stereospecificity is obtained using reagents such as triphenylphosphine selenide,[4] potassium selenocyanate–methanol,[5] hexamethyldisilane–KOMe,[6] and lithium diphenylphosphide.[7] We recently described the conversions of epoxides to *vic*-dihalides with triphenylphosphine dihalides;[8] the dihalides were then reduced to olefins with, for example, zinc. The diastereomer content of the *vic*-dihalide was found to be quite solvent dependent; deviation from the predominant backside displacement of C–O by bromide with increasing solvent polarity was ascribed to internal participation by the bromine which had performed the initial displacement (Scheme I). To the extent that such bridging occurred, the diastereomer of opposite configuration was formed, and the olefin ultimately generated was of the same geometry as that of the initial epoxide.

We wished to construct a product from an epoxide that might react exclusively via an onium ion to convert that epoxide to the olefin of the same geometry. Neighboring iodine is, of course, more proficient in interacting with an adjacent carbonium ion than is bromine. However, triphenylphosphine diiodide could not be made to react with aliphatic epoxides.

It was found that trifluoroacetic anhydride (1 equiv) and sodium iodide (1 equiv) reacted exothermically with (*Z*)-7,8-epoxy-2-methyloctadecane[9] (in 1:1 CH_3CN–THF) to produce a β-iodotrifluoroacetate [NMR (CCl_4) δ 4.06 (m, CHI), 4.72 (m, CHO_2CCF_3)] which on exposure to sodium iodide (3 equiv) in the same solvent system for 24 h spontaneously generated iodine, sodium trifluoroacetate, and the corresponding *Z* olefin in 90% yield. Similarly, the corresponding *E* epoxide upon treatment with trifluoroacetyl iodide (generated in situ) and excess sodium iodide produced the *E* olefin, again in 90% yield. In the absence of more definitive data, it is presumed that the yellow–orange solution of anhydride and sodium iodide contains trifluoroacetyl iodide; the epoxides are stable in solutions containing trifluoroacetic anhydride alone. Identification of the gross structure of the olefins was made by comparison with authentic samples;[8] analysis of geometry was accomplished by epoxidation with *m*-chloroperbenzoic acid, and examination of the resulting epoxides by capillary gas chromatography (DEGS, 4 mm × 46 m, 170 °C, helium carrier at 4 mL/min). Retention times were 10.2 (*trans*-epoxide) and 10.8 min (*cis*-epoxide); the initially employed *cis*-epoxide (97.5% cis) provided 97.7% *cis*-olefin, and the *trans*-epoxide (97.5% trans) provided >98% *trans*-olefin. The conversions of several epoxides to olefins with trifluoroacetyl iodide generated in situ from trifluoroacetic anhydride and NaI are given in Table I. It is apparent that the reaction proceeds in high yield and is stereospecific for the epoxides of 1,2-dialkylethenes.

Scheme I

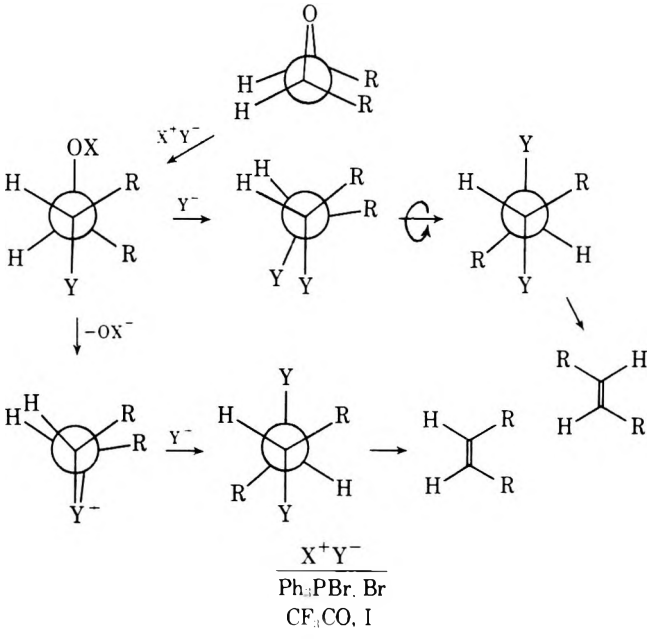

Table I. Reactions of Epoxides with Trifluoroacetyl Iodide

Reactant	Geometry	Product	Geometry	% yield
1,2-Epoxycyclohexane		Cyclohexene		77[a]
1,2-Epoxydecane		1-Decene		91[b]
5,6-Epoxydecane	93% *Z*	5-Decene	93% *Z*	95[b]
5,6-Epoxydecane	94% *E*	5-Decene	95.5% *E*	95[b]
7,9-Epoxy-2-methyloctadecane	97.5% *Z*	2-Methyl-7-octadecene	97.7% *Z*	90[a]
7,8-Epoxy-2-methyloctadecane	97.5% *E*	2-Methyl-7-octadecene	>97% *E*	90[a]

[a] Estimated by GLC. [b] Distilled yield; checked by GLC.

The transformations involved bear comparison with the

familiar Prevost reaction in which olefins react with silver acetate and iodine to produce *vic*-acetates by trans addition. The intermediate iodoacetates solvolyze in acetic acid with carbonyl oxygen participation and replacement of iodide by acetate. The carbonyl oxygen of the trifluoroacetyl group, however, is much less nucleophilic, and excess iodide ion is present. Hence, the trifluoroacetate group is replaced either with the intermediacy of an iodonium ion, as indicated in Scheme I, or directly as part of a concerted elimination process initiated by attack of iodide ion upon bound iodine. Both processes lead to the same stereochemical result.

In a typical experiment, sodium iodide, which has been oven dried at 110 °C overnight (4 equiv), is placed in a reaction vessel fitted with a drying tube. Dry acetonitrile and dry tetrahydrofuran (1 mL/mmol of epoxide) are injected into the reaction vessel. Stirring is initiated and trifluoroacetic anhydride (1 equiv) is injected. After 5 min, the deep yellow solution is cooled in an ice bath, and the epoxide (1 equiv) is injected neat. When the reaction is conducted in this manner, no noticeable evolution of heat occurs. After 5 min, the bath is removed and the mixture is allowed to stir for 24 h. The reaction mixtures were worked up by dilution with aqueous $NaHSO_3$ and extraction into petroleum ether, followed by distillation of the olefins. Current work is directed to examining the scope of the reactions of trifluoroacetyl halides and related compounds with epoxides.

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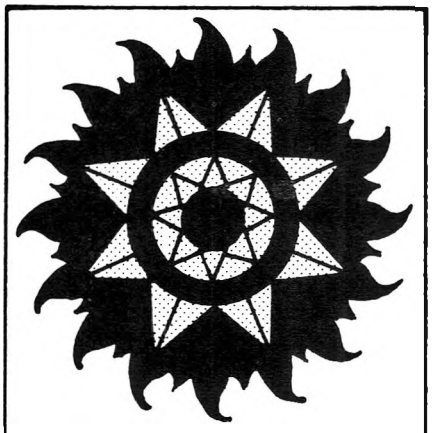

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The past few years have witnessed a dramatic increase in the application of organosilicon compounds as reagents in synthetic organic chemistry.[1] PCR offers a wide range of organosilicon products. Below are listed a few of them with some suggested uses.

1. See, for instance, recent reviews by Chan [*Accts. Chem. Res.*, **10**, 442 (1977)] and by Hudrlik ["New Applications of Organometallic Reagents in Organic Synthesis", D. Seyferth, Ed., Elsevier, Amsterdam, 1976, pp 127-159] and references therein.

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1. D. J. Peterson, *J. Org. Chem.*, 33, 780 (1968). 2. T. H. Chan, E. Chang and E. Vinokur, *Tet. Let.* 1137 (1970). 3. See, for instance, S. Moorhouse and G. Wilkinson, *J. Chem. Soc.*, Dalton Trans. 2187 (1974). 4. C. Burford, F. Cooke, E. Ehlinger & P. Magnus, *J. Am. Chem. Soc.*, **99**, 4536 (1977).

TRIETHYLSILANE

Versatile reducing agent. Will reduce acetals and ketals,[1] aldehydes and ketones[2,3], α,β-unsaturated carbonyl compounds[4,5], acid chlorides,[6] nitriles[7] and isocyanates.[8] Can also be used for the selective cleavage of N-carbobenzoxy derivatives of amino acids and peptides.[9]

25070-4 **Triethylsilane** 25g–$15.00; 100g–$42.00

1. E. Frainnet and C. Esclamadon, *Compt. Rend.*, **254**, 1814 (1962). 2. M. P. Doyle, D. J. DeBruyn, and D. A. Kooistra, *J. Am. Chem. Soc.*, **94**, 3659 (1972). 3. C. T. West, et. al, *J. Org. Chem.*, **38**, 2675 (1963). 4. D. N. Kursanov, et al. *Synthesis*, 420 (1973). 5. I. Ojima, T. Kogura and Y. Nagai, *Tet. Let.*, 5085 (1972). 6. J. D. Citron, *J. Org. Chem.*, **34**, 1977 (1969). 7. J. L. Fry, *J. Chem. Soc. Chem. Comm.*, **45**, (1974). 8 R. F. Borch, *J. Org. Chem.*, **34**, 627 (1969). 9. L. Birkofer, E. Bierwirth and A. Ritter, *Ber.*, **94**, 821 (1961).

TRIMETHYLBROMOSILANE

Finding increased use in biochemical areas such as preparation of phosphoric acids by dealkylation of their esters[1] and preparation of trimethylsilyl derivatives of hydroxysteroids.

27650-1 **Trimethylbromosilane** 25g–$15.00; 100g–$55.00

1. C. E. McKenna, et al, *Tet. Let.*, 155 (1977).

TRIMETHYLSILYL AZIDE

Can be used as a substitute for the explosive hydrazoic acid in the preparation of heterocycles[1,2] and isocyanates.[3]

11013-0 **Trimethylsilyl azide** 10g–$14.00; 50g–$49.25

1. S. S. Washburne, W. R. Peterson, Jr. and D. A. Berman, *J. Org. Chem.*, **37**, 1738 (1972). 2. J. D. Warren, J. H. MacMillan and S. S. Washburne, *J. Org. Chem.*, **40**, 743 (1975). 3. J. H. MacMillan and S. S. Washburne, *J. Org. Chem.*, **38**, 2982 (1973).

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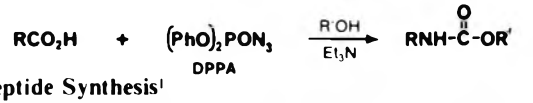
Diphenylphosphoryl azide (DPPA) is a stable, non-explosive liquid with unique applications in organic synthesis, some of which are described below.

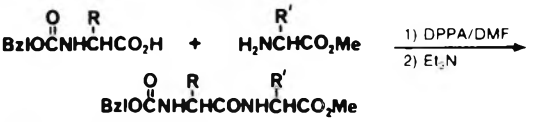
Synthesis of Carbamates[1]

DPPA effects the conversion of carboxylic acids to carbamates under mild conditions without isolation of a potentially explosive carbonyl azide, thus providing a one-pot equivalent of the Curtius reaction



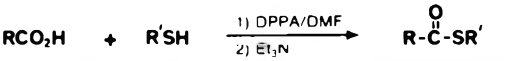
Peptide Synthesis[1]

As an azide transfer reagent, **DPPA** effects the coupling of *N*-acylamino acids or peptides with amino acid or peptide esters without racemization:



Synthesis of Thiol Esters[2]

Treatment of a carboxylic acid and a thiol with **DPPA** and triethylamine affords the thiol ester:



Again, the reaction proceeds with little or no racemization; even a highly functionalized cephalosporin derivative afforded the corresponding thiol ester.

Stereospecific Synthesis of Azides from Alcohols[3]

The reaction of alcohols with **DPPA**, triphenylphosphine and diethyl azodicarboxylate gives azides in 60 to 90% yield without racemization.

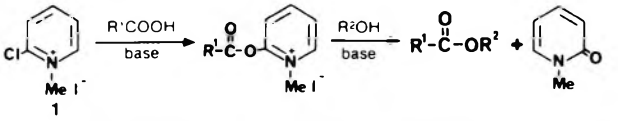
References:

1) T. Shioiri, K. Ninomiya, and S. Yamada, *J. Am. Chem. Soc.*, **94**, 6203 (1972).
2) S. Yamada, Y. Yokoyama, and T. Shioiri, *J. Org. Chem.*, **39**, 3302 (1974).
3) B. Lal, B. Pramanik, M. Manhas, and A. Bose, *Tetrahedron Lett.*, 1977 (1977).

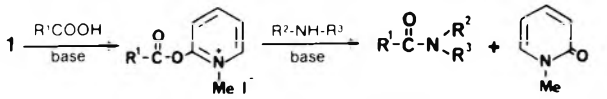
17,875-6 Diphenylphosphoryl azide (DPPA) **25g $24.45**
100g $65.15

Recent reports in the chemical literature have established 1-alkyl-2-halopyridinium salts as effective reagents for the synthesis of carboxylic esters,[1] carboxamides,[2] 2-pyridyl sulfides,[3] lactones,[4] alkyl halides,[5] and carbodiimides.[6]

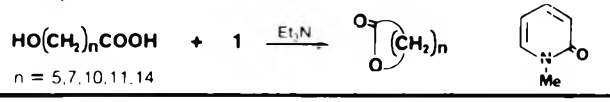
Reactions of carboxylic acids and alcohols with **2-chloro-1-methylpyridinium iodide** (**1**) in the presence of two molar equivalents of tri-*n*-butylamine afforded the corresponding carboxylate esters.[1]



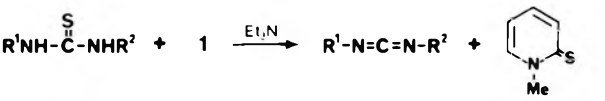
Carboxamides are formed rapidly in high yields by the reactions of free carboxylic acids and amines with **2-chloro-1-methylpyridinium iodide.** This reaction is applicable to both secondary and tertiary alkyl-substituted acids and amines.[2]



Direct lactonization of ω-hydroxy acids has been successfully carried out under mild conditions by treatment with **2-chloro-1-methylpyridinium iodide** in the presence of triethylamine.[4]



Aromatic and aliphatic carbodiimides, which are useful coupling reagents for the synthesis of peptides and nucleotides,[7,8] have been prepared in high yields by treating N,N′-disubstituted thioureas with **2-chloro-1-methylpyridinium iodide** in the presence of triethylamine.[6]



All of the above synthetic transformations using **2-chloro-1-methylpyridinium iodide** proceed in 60-90% overall yield. Reactions of **2-chloro-1-methylpyridinium iodide** can be carried out in a variety of solvents such as toluene, dichloromethane, dimethoxyethane, and pyridine at temperatures ranging from ambient to the boiling point of the solvent.

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19,800-5 2-Chloro-1-methylpyridinium iodide
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