/ VOLUME 43 MAY 12, 1978 NUMBER 10 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

Published by the
AMERICAN CHEMICAL SOCIETY

BOOKS AND JOURNALS DIVISION

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

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

Magazine and Production Department: Bacil Guiley, Head

Research and Development Department: Seldon W. Terrant, Head

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

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

Editorial Information

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

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

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

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

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

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

Subscription and Business Information

1978 subscription prices, printed or microfiche, including postage. Microfiche by air mail; printed by surface mail. Printed edition air mail or air freight rates available from Membership & Subscription Services at the address below.

	U.S.	Foreign
Member	$26.00	$36.00
Nonmember	104.00	114.00
Supplementary material (available in microfiche only)	20.00	38.00

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

Changes of address must include both old and new addresses with ZIP code and a recent mailing label. Send all address changes to the Membership & Subscription Services. Please allow 6 weeks for change to become effective.

Claims for missing numbers will not be allowed if loss was due to failure of notice of change of address to be received in the time specified; if claim is dated, (a) North America: more than 90 days beyond issue date, (b) all other foreign: more than one year beyond issue date; or if the reason given is "missing from files". Hard copy claims are handled by Membership & Subscription Services.

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

To order **single issues or back volumes,** printed or microfiche, contact Special Issue Sales at the ACS Washington address, or call (202) 872-4365. Current year single issue $5.00. Prior year single issue $5.00. Back volume $115.00. Foreign postage additional.

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

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

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

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

Editorial Department
American Chemical Society
P.O. Box 3330
Columbus, Ohio 43210
(614) 421-6940, Ext. 3171

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

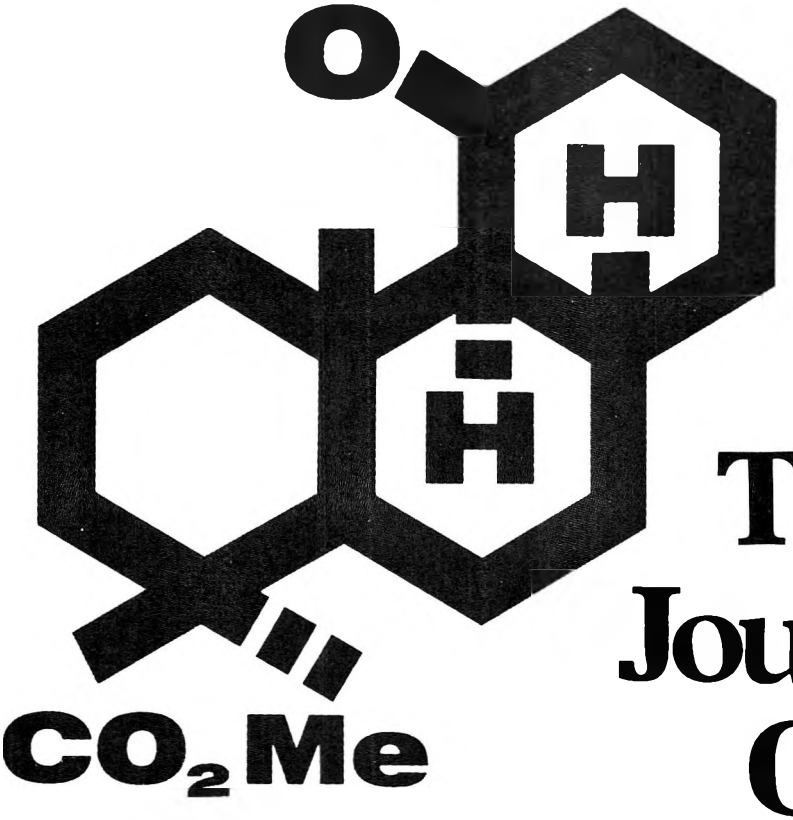
Notice to Authors last printed in the issue of January 6, 1978

JOCEAH 43(10) 1843–2090 (1978)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry

VOLUME 43, NUMBER 10

MAY 12, 1978



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

The Journal of Organic Chemistry

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

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

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

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

Bill me ☐ Bill company ☐ Payment enclosed ☐

Air freight rates available on request.

Name _____

Street _____ Home ☐ Business ☐

City _____ State _____ Zip _____

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

AVAILABLE IN HARD COPY OR MICROFICHE.

Toll Free: New Orders Only
800-424-8001
D.C. 466-7720
Cable Address: INCOMS
Telex: 64539 I.C.S.W.W.

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

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

AUTHOR INDEX

THE JOURNAL OF Organic Chemistry

VOLUME 43, NUMBER 10

MAY 12, 1978

Correlation of Solvent Effects on Rates of Solvolysis and S_N2 Reactions

A. J. Parker,* U. Mayer, R. Schmid, and V. Gutmann

Institute for Inorganic Chemistry, Technical University Vienna, A-1060 Vienna, Austria

Received September 8, 1977

The effect of solvent transfer on rates of some classical S_N1 solvolyses and S_N2 reactions depends on the anion solvating properties of the solvents, as measured either by $\Delta G_{tr}(Cl^-)$ or by the changes in solvent acceptor number [Δ(AN)]. For transfer through high dielectric ($\epsilon > 20$) solvents other than water, the transfer free energies of activation show the approximate linear free-energy relationships, $\Delta G^{\ddagger}_{tr} = n\Delta G_{tr}(Cl^-) = -n'\Delta(AN)$. These very simple relationships are extreme cases of the more precise expressions, $\Delta G^{\ddagger}_{tr}(S_N1) = p\Delta G_{tr}(K^+) + n\Delta G_{tr}(Cl^-) - \Delta G_{tr}(RX) = -p'\Delta(DN) - n'\Delta(AN) - \Delta G_{tr}(RX)$ and $\Delta G^{\ddagger}_{tr}(S_N2) = -n\Delta G_{tr}(Cl^-) - \Delta G_{tr}(RX) = n'\Delta(AN) - \Delta G_{tr}(RX)$. These expressions apply to a greater range of reactions and correlate rates in water and formamide as well as other less structured solvents. Even for "limiting" solvolyses of *tert*-butyl chloride and *p*-methoxyneophyl tosylate, cation solvation plays a significant role in S_N1 but not S_N2 reactions, if transfer is through a sufficiently wide range of low dielectric as well as high dielectric solvents. The usefulness of donor and acceptor numbers, as well as free energies of transfer of K^+ and Cl^- as measures of cation and anion solvating power of solvents, is demonstrated.

Chemists have been seeking a simple method for predicting rates of reactions in different solvents.[1-9] This paper develops the linear free-energy relationships (eq 1 and 2) which, for several reactions in most polar solvents, reduce to the approximate relationships (eq 3). Equation 3 is a relationship of remarkable simplicity and although approximate, predicts several solvent effects on rate in a way that may be acceptable to many chemists.

$$\Delta G^{\ddagger}_{tr}(S_N1) = p\Delta G_{tr}(K^+) + n\Delta G_{tr}(Cl^-) - \Delta G_{tr}(RX) = -p'\Delta(DN) - n'\Delta(AN) - \Delta G_{tr}(RX) \quad (1)$$

$$\Delta G^{\ddagger}_{tr}(S_N2) = -n\Delta G_{tr}(Cl^-) - \Delta G_{tr}(RX) \quad (2a)$$

$$= n'\Delta(AN) - \Delta G_{tr}(RX) \quad (2b)$$

$$\Delta G^{\ddagger}_{tr}(S_N1 \text{ or } S_N2) = \pm n\Delta G_{tr}(Cl^-) = \mp n'\Delta(AN) \quad (3)$$

In eq 1, $\Delta G^{\ddagger}_{tr}(S_N1)$ is the transfer free energy of activation for solvolysis reactions (eq 4) of carbon compounds, RX, and $\Delta G^{\ddagger}_{tr}(S_N2)$ in eq 2 is the transfer free energy of activation for S_N2 reactions of anions Y^- with carbon compounds RX (eq 5). Transfer is from any polar reference solvent, o, to other solvents, s, and the effect (k^s/k^o) of solvent transfer on the rates, k, are related to $\Delta G^{\ddagger}_{tr}$ through eq 6. $\Delta G_{tr}(K^+)$ and $\Delta G_{tr}(Cl^-)$ in eq 1 and 2 are single ion free energies of transfer from the reference solvent to other solvents. They are based on the TATB assumption that $\Delta G_{tr}(Ph_4As^+) = \Delta G_{tr}(Ph_4B^-)$.[10,11] Values of $\Delta G_{tr}(RX)$ are experimentally determined free energies of solvent transfer for carbon compounds, RX. The donor numbers (DN) and acceptor numbers (AN) are empirical parameters reflecting the donor and acceptor properties of the solvents[12] and p, n, p', and n' are sensitivity parameters. The symbolism $RX^{\ddagger}$ and $YRX^{-\ddagger}$ denotes the S_N1 and S_N2 transition states, respectively.

$$RX \rightleftharpoons R^{\delta+} \cdots\cdots X^{\ddagger\delta-} \rightarrow R^+ + X^- \rightarrow, \text{ solvolysis products} \quad (4)$$

$$Y^- + RX \rightarrow YRX^{-\ddagger} \rightarrow YR + X^- \quad (5)$$

$$\Delta G^{\ddagger}_{tr} = -RT \ln (k^s/k^o) \quad (6)$$

Apart from the $\Delta G_{tr}(RX)$ term, eq 1 in part corresponds to the general forms of the multiparameter approaches proposed by Fawcett–Krygowski[13] and Mayer[14] in terms of the donor–acceptor description of solvent effects on equilibrium constants and rates of reaction. In the case of S_N2 reactions at carbon (eq 5) our expression (eq 2) differs from that proposed by Fawcett–Krygowski.[13] Because cations and cationic centers are not involved in such S_N2 reactions we do not agree that solvent donor properties, e.g., cation solvating power, are a factor in determining rates of these reactions.

The transfer free energy of activation is given by eq 7 for S_N1 and by eq 8 for S_N2 reactions.[2]

$$\Delta G^{\ddagger}_{tr}(S_N1) = \Delta G_{tr}(RX^{\ddagger}) - \Delta G_{tr}(RX) \quad (7)$$

$$\Delta G^{\ddagger}_{tr}(S_N2) = \Delta G_{tr}(YRX^{-\ddagger}) - \Delta G_{tr}(RX) - \Delta G_{tr}(Y^-) \quad (8)$$

As several chemists have appreciated,[1-7] these equations allow interpretations of mechanism, but since ΔG_{tr} of transition states cannot be measured independently of a rate constant,

* Author to whom inquiries should be addressed at The School of Mathematical and Physical Sciences, Murdoch University, Murdoch, Western Australia.

they are only of limited value in predicting solvent effects on rate. One approach is to use ΔG_{tr} (model) for a real model solute as an indicator of $\Delta G_{tr}(RX^{\ddagger})$ or $\Delta G_{tr}(YRX^{-\ddagger})$. The work of Abraham[3,4] has been notable in this area and some preliminary developments[1] have been reviewed.[2]

Another approach is to estimate $\Delta G_{tr}(RX^{\ddagger})$ and $\Delta G_{tr}(YRX^{-\ddagger})$ from the general anion and cation solvating properties of the solvents combined with estimates of the sensitivity of these "solutes" to such properties.[15] This recognizes that $YRX^{-\ddagger}$ is an anion and that $RX^{\ddagger}$ is a highly polar species, with well-developed cationic and anionic centers which will respond to the cation and anion solvating power of the solvents. Anion and cation solvating power is measured directly by $\Delta G_{tr}(Cl^-)$(TATB) and $\Delta G_{tr}(K^+)$(TATB), respectively. $\Delta G_{tr}(Cl^-)$ is very appropriate for S_N2 reactions; however, the donor–acceptor approach[12,16] to molecular interactions has some advantages as a measure of ion solvating power in estimating $\Delta G_{tr}(RX^{\ddagger})$ because $RX^{\ddagger}$ is not an ion, but a highly polar "molecule" and there may be some conceptual difficulties in relating $\Delta G_{tr}(K^+)$ or $\Delta G_{tr}(Cl^-)$ for fully solvated ions to solvation of parts of the $RX^{\ddagger}$ dipole.

Acceptor numbers are derived from the NMR chemical shifts of phosphorus which are produced on transfer of Et_3PO through solvents.[12] They are directly observable quantities and prove to be an excellent quantitative empirical solvent parameter for correlating those chemical phenomena which change with the electrophilic or acceptor properties of solvents.[12,16] In the broadest possible sense of the word, acceptor numbers measure the ability of the solvents to "accept" (interact with) electron pairs from suitable donors in a variety of chemical situations.

Donor numbers measure the ability of solvents to donate electron pairs to suitable acceptors[16-19] and have been defined as the negative of the enthalpy of adduct formation between the reference acid $SbCl_5$ and a solvent molecule in highly dilute 1,2-dichloroethane solution.

Despite occasional conceptual difficulties, especially relating to entropic effects,[8] it is an indisputable fact that a remarkable amount of chemical information on systems in solution, be it a ΔG, ΔH, or other property, is correlated by the donor and acceptor numbers of solvents.[16] The precise nature of the acceptor–donor interaction need not be specified. It could be H bonding, formation of an acid–base adduct, an ion–dipole interaction, covalent bonding, ion–ligand coordination, nucleophilic assistance, or electrophilic solvation of a leaving group. The advantage of the donor–acceptor correlations is that they bring many types of anion–molecule, cation–molecule, ion pair–molecule, and molecule–molecule interaction under one umbrella.

The advantage of such a general concept for estimating $\Delta G_{tr}(RX^{\ddagger})$ is obvious. The S_N1 transition state $RX^{\ddagger}$ for solvolysis of RX is indisputably highly dipolar,[3,15] but it is not an ion pair, it is certainly not solvent separated ions, and it is very unlike "normal" polar organic molecules RX. Many chemists do not wish to be drawn into disputes about the type of interaction between solvent and RX in the transition state, but they are very interested in finding the most suitable solvent for a desired reaction. The concept of a donor interaction at $R^{\delta+}$ and an acceptor interaction at $X^{\delta-}$ between $R^{\delta+}\cdots X^{\delta-}$ and solvent does not require definition of the exact nature of $RX^{\ddagger}$, nor does it require a statement as to the precise nature of the interactions.[16]

There are limitations of course. The donor–acceptor correlations break down completely when interactions between soft acceptors (e.g., Cu^+, Tl^+, Zn^{2+}) and soft donors (e.g., *N,N*-dimethylthioformamide) take place. Back-bonding is not modeled by interactions of donors with $SbCl_5$. Acceptor numbers only have validity if they reflect chemical shifts for $Et_3PO\cdots A$ adduct formation, rather than (as with CF_3CO_2H) protonation of triethylphosphine oxide.[12] Solvents which are weaker donors than dichloroethane (heptane) do not of course have meaningful donor numbers, other than to say they are less than zero.

Phenomenological Observations. With the background given above, we will first demonstrate some phenomenological relationships (eq 3) between the transfer free energy of activation of S_N1 and S_N2 reactions, anion solvating power, and solvent acceptor properties. We will then use eq 7 and 8 to see why these relationships develop and why, in some cases, deviations from the linear relationships (eq 3) occur.

Equations 9–12 summarize four relationships between transfer free energies of anions (Y^-)[11,20,21] and cations (M^+)[11,20-23] in high dielectric solvents, excluding soft cations in soft solvents, excluding other situations (e.g., Ag^+ in CH_3CN) where back-bonding is possible and excluding hydrophobic anions or cations (e.g., BPh_4^-, NBu_4^+) in water, where solvation is of the second kind. Some ΔG_{tr} (ion) values are in Tables I and II, but ref 11 and 20 contain additional values which fit eq 9–12.

Equation 9 summarizes the excellent correlation between solvation of potassium cation and solvation of other cations, including soft cations in hard solvents and hard cations in soft solvents.[24,25] As shown in Table III, values of p decrease with decreasing surface charge of the cation ($Zn^{2+} > Cd^{2+} > Ba^{2+} > > Li^+ > Na^+ > K^+ > Cs^+ > Ph_4As^+$). Thus $-\Delta G_{tr}(K^+)$ as recorded in Table II is a good measure of cation solvating power of solvents.[25] The more positive $-\Delta G_{tr}(K^+)$, the stronger the cation solvating power.

$$\Delta G_{tr}(M^+) = p\Delta G_{tr}(K^+) \quad (9)$$

$$\Delta G_{tr}(Y^-) = n\Delta G_{tr}(Cl^-) \quad (10)$$

$$\Delta G_{tr}(M^+) = -p'\Delta(DN) \quad (11)$$

$$\Delta G_{tr}(Y^-) = -n'\Delta(AN) \quad (12)$$

Data in Table I and II in ref 11 and 20 show that anion solvating power is effectively measured by $-\Delta G_{tr}(Cl^-)$ as in eq 10, with sensitivity (n) decreasing with decreasing anionic surface charge ($OAC^- > Cl^- > Br^- > I^- > ClO_4^-$; Table III).

Potassium ion solvating power (and thus general cation solvating power through eq 9) is well measured by solvent donor properties (eq 11), as shown in Figure 1 and Table II. Chloride ion solvating power (and thus general anion solvating power through eq 10) is well measured by solvent acceptor properties (eq 12), as shown in Figure 2 and Table II.

Equations 9–12 are of great value in correlating many aspects of solution chemistry, but in this paper we are concerned only with kinetics of S_N1 and S_N2 reactions. The expressions $-\Delta G_{tr}(K^+)$ or $+1.30\ \Delta(DN)$ are equivalent as measures of the cation solvating power of solvents. Values of $-\Delta G_{tr}(Cl^-)$ or $+1.30\ \Delta(AN)$ are equivalent as measures of anion solvating power, as shown in Table II. We expect that eq 11 or 12 will only give lower limits to $\Delta G_{tr}(M^+)$ or $\Delta G_{tr}(Y^-)$ when transfer is to solvents of very low dielectric constant (<5) like dioxane and ether. This is because Born type solvation is the major contributor to ΔG_{tr}(ion) for such extreme transfers and this is not well measured by donor and acceptor numbers.

S_N2 Reactions. Transfer free energies of activation for many S_N2 reactions like eq 5 have simple linear free-energy relationships (eq 13–15) with $\Delta G_{tr}(Y^-)$, $\Delta G_{tr}(Cl^-)$, and $\Delta(AN)$ as shown in Table IV. Values of n'', n, and n' are in Table III and express the sensitivity of each reaction to solvent transfer.

$$\Delta G^{\ddagger}_{tr}(S_N2) = -n''\Delta G_{tr}(Y^-) \quad (13)$$

$$\Delta G^{\ddagger}_{tr}(S_N2) = -n\Delta G_{tr}(Cl^-) \quad (14)$$

Table I. Free Energies of Transfer of Ions from DMF at 25 °C (kJ g-ion^{-1}). TATB Assumption $\Delta G_{tr}(Ph_4As^+) = \Delta G_{tr}(Ph_4B^-)$

Solvent[a]	ΔG_{tr}[b] (Br^-)	ΔG_{tr}[b] (N_3^-)	ΔG_{tr}[b] (I^-)	ΔG_{tr}[b] (SCN^-)	ΔG_{tr} (NMe_4^+)[d,f]	ΔG_{tr} (Me_3S^+)[e,f]	ΔG_{tr}[b] (Ag^+)
CF_3CH_2OH	−41		−25				66
H_2O	−34	−35	−18	−16	5		17
$HCONH_2$	−24	−23	−11	−12			2
MeOH	−23	−24	−10	−10	11	13	24
NMeF	−19						2[g]
EtOH	−15	−18	−4		15	16	20[i]
Me_2SO	−7	−11	−9[c]	−8[c]	3		−17
$MeNO_2$		−10	−6	−7	6	11	43
PC		−6	−6	−7			33
MeCN	−3	−6	−4	−3	8	11	−5
DMF	0	0	0	0	0	0	0
DMA		−1	−2	1		1	−5
NMePy	1	6	0	3	2		−7[i]
Me_2CO	8	9	8		8	12	25[i]
HMPT		13	12	6			−26[i]
0.70 Me_2SO–H_2O			−9[j]	−8[j]			
0.32 Me_2SO–H_2O		−17[j]	−10[j]	−8.5[j]			

[a] Abbreviations as in Table II. [b] From $\Delta G_{tr}(AgX)$[11,20] − $\Delta G_{tr}(Ag^+)$(TATB), this table. [c] Dubious value because of high solubility of AgX and complex formation. [d] From $\Delta G_{tr}(Me_4NI)$[3] − $\Delta G_{tr}(I^-)$, this table. [e] From $\Delta G_{tr}(Me_3S^+)$ − $\Delta G_{tr}(Ag^+)$[2] + $\Delta G_{tr}(Ag^+)$(TATB), this table. [f] Values are somewhat uncertain because of the high solubility of Me_4NI and Me_3SX in many solvents and the possibility of solvates. This is why we prefer $\Delta G_{tr}(K^+)$ as a measure of cation solvating power. [g] H. Schneider and C. Kalidas, private communication based on the ferrocene assumption, cf. ref 10 and 20. [h] Reference 11. [i] Reference 22. [j] Reference 2.

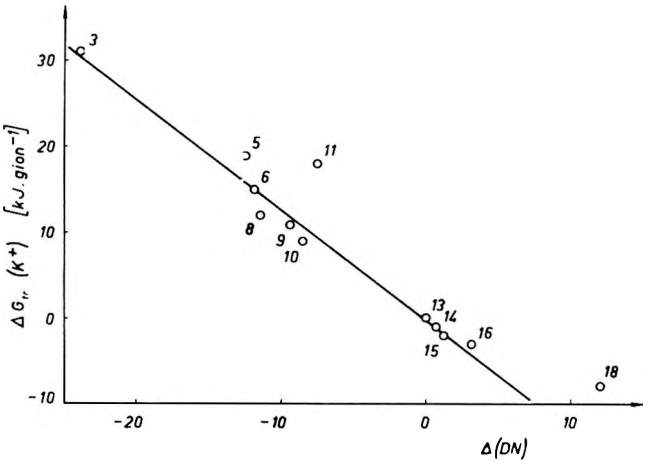


Figure 1. Relationship between potassium cation solvating power and solvent donor properties. Plot of the equation $\Delta G_{tr}(K^+) = -1.30\Delta(DN)$ of eq 9 and 11 and Table II. Solvent data points are numbered as in Table II.

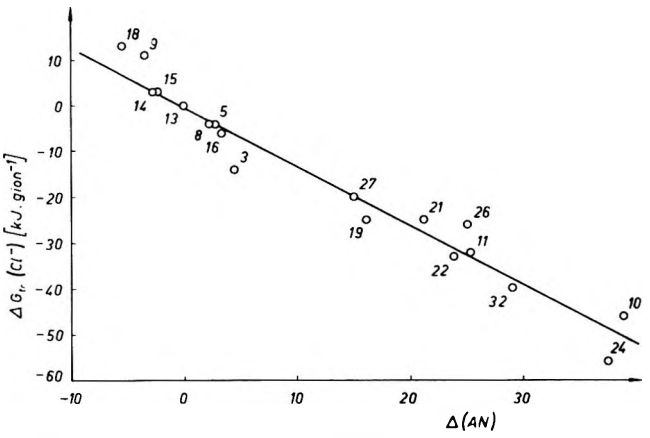


Figure 2. Relationship between chloride anion solvating power and solvent acceptor properties. Plot of the equation $\Delta G_{tr}(Cl^-) = -1.30\Delta(AN)$ of eq 12 and 10 and Table II. Solvent data points are numbered as in Table II.

$$\Delta G^{\ddagger}_{tr}(S_N2) = n'\Delta(AN) \quad (15)$$

Transfer is through any set of polar solvents of high dielectric constant (>10), provided that the observed rate constants are for reaction of free anions Y^-, rather than ion pairs.

As shown in Tables III and IV, the relationship is even simpler for some S_N2 reactions of iodomethane and for most S_NAr reactions in that n'' in eq 13 is unity. Equations 14 and 15 follow as corrolaries of eq 13, through eq 10 and eq 12, respectively. Thus n in eq 14 is n'' (eq 13) × n (eq 10) and n' (eq 15) is n'' (eq 13) × n' (eq 12). This is confirmed in Table III.

The attempted correlations for water and formamide are instructive. As shown in Table IV, water and formamide are quite well correlated by eq 13–15 for reaction 6 of 4-fluoronitrobenzene with azide ion, reaction 5 of 2,4-dinitroiodobenzene with SCN^-, and reaction 3 of iodomethane with SCN^-, where n'' is unity. However, for all other reactions in Table IV, S_N2 reactions in water and formamide are up to 15 kJ mol^{-1} faster in terms of $\Delta G^{\ddagger}_{tr}(S_N2)$ than required by eq 13–15. This is true, even for reactions where n'' is unity, e.g., $CH_3I + Cl^-$ (reaction 1).

We note from Table III that values of n'' in eq 13 of less than unity are observed if the transition state is loose;[26] e.g., for displacement at the methyl of the tosylate by azide ion, n'' is only 0.5, for reaction 4 of *n*-butyl bromide with azide ion, n'' is 0.73, and for reaction of bromomethane with Cl^-, n'' is 0.80. Values of n'' from eq 13 can give valuable mechanistic information as to the tight or loose nature of S_N2 transition states.[2,26]

The choice of eq 13, 14, or 15 for predicting rates of S_N2 reactions, or deriving values of n, n', or n'' to provide mechanistic information as to tightness or looseness, etc., of transition states, will depend on which parameters, $\Delta G_{tr}(Y^-)$, $\Delta G_{tr}(Cl^-)$, or $\Delta(AN)$, are available. Equation 13 has the most direct mechanistic significance, as we will see, but the parameters for eq 14 and 15 are more precise and more are available. Equation 13 of course provides a way of measuring $\Delta G_{tr}(Y^-)$, eq 14 a way of measuring $\Delta G_{tr}(Cl^-)$, and eq 15 a way

Table II. Changes in Anion and Cation Solvating Power and Changes in Acceptor and Donor Properties of Solvents on Transfer from DMF at 25 °C (values in kJ g-ion^{-1})

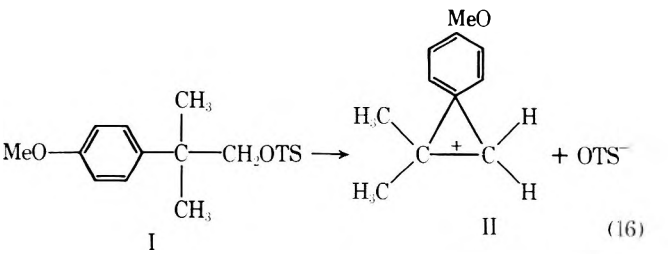
	Solvent[a]	Registry no.	ϵ[b]	Cation solvating power: $+1.30\Delta(DN)$	Cation solvating power: $-\Delta G_{tr}(K^+)$[e]	Anion solvating power: $+1.30\Delta(AN)$[b]	Anion solvating power: $-\Delta G_{tr}(Cl^-)$
1	DCE	107-06-2	10.1	>−35		+1	
2	*n*-Hexane	110-54-3	1.9	>−35[i,k]	ca. −180[j]	>−20[k]	
3	$MeNO_2$	75-52-5	36.7	−31	−31	+6	+14
4	$PhNO_2$	98-95-3	34.8	−29		−2	
5	MeCN	75-05-8	36.0	−16	−19	+4	4
6	TMS	126-33-0	43.3	−15	−15		+4
7	Dioxane	123-91-1	2.2	>−15[k]		>−6[k]	
8	PC	2453-03-4	65.0	−15	−12	+3	+4
9	Me_2CO	67-64-1	20.7	−12	−11	-4_5	−11
10	H_2O	7732-18-5	78.5	−11	−9	+50	+46
11	MeOH	67-56-1	32.6	−10	−18	+32	+32
12	Ether	60-29-7	4.2	>−10[k]		>−15[k]	
13	DMF	68-12-2	36.7	0[g]	0	0[g]	0
14	NMePy	872-50-4	33.0	+1	+1	−4	−3
15	DMA	127-19-5	37.8	+2	+2	-4_5	−3
16	Me_2SO	67-68-5	46.7	+4	+3	$+4_5$	+6
17	Pyd	110-86-1	12.3	+8		−3	
18	HMPT	680-31-9	29.6	+16	+8	−7	−13
19	NMeF	123-39-7	182.4			+21	+25
20	Me_2CHOH	67-63-0	18.3			$+22_5$	
21	EtOH	64-17-5	24.3		−25	+27	+25
22	$HCONH_2$	75-12-7	109.5		−7	+31	+33
23	HOAc	64-19-7	6.3			+48	
24	CF_3CH_2OH	75-89-8	26.1		−45	+48[c]	+56
25	CF_3CO_2H	76-05-1	8.3	>−35[k]	>−45[h]	<+115[d]	
26	0.32 Me_2SO–H_2O					33[m]	26[l]
27	0.89 MeCN–H_2O					20[m]	20[n]
28	0.80 MeCN–H_2O					27[m]	25[n]
29	0.63 MeCN–H_2O					34[m]	32[n]
30	0.51 MeCN–H_2O					35[m]	36[n]
31	0.40 MeCN–H_2O					36[m]	38_5[n]
32	0.30 MeCN–H_2O					38[m]	40[n]
33	0.20 MeCN–H_2O					43[m]	40[n]
34	0.10 MeCN–H_2O					47[m]	44[n]

[a] Abbreviations are: DCE, 1,2-dichloroethane; TMS, tetramethylene sulfone at 30 °C; PC, propylene carbonate; DMF, *N,N*-dimethylformamide; NMePy, *N*-methyl-2-pyrrolidinone; DMA, *N,N*-dimethylacetamide; Me_2SO, dimethyl sulfoxide; HMPT, hexamethylphosphoric triamide; NMeF, *N*-methylformamide. Solvent mixtures: numbers indicate mole fraction of organic solvent component. [b] Reference 12. [c] U. Mayer, private communication. [d] Maximum value, because acceptor number includes chemical shift for protonated Et_3PO averaged with chemical shift of CF_3CO_2H·$OPEt_3$ adduct. [e] Reference 22 and 23. [f] From $\Delta G_{tr}(AgCl)$[11,20] − $\Delta G_{tr}(Ag^+)$(TATB), Table I or ref 23. [g] The donor number of DMF is 26.6 and its acceptor number is 16.0. [h] Estimated from low dielectric constant and low basicity of this solvent. [i] Solvents which are weaker donors than 1,2-dichloroethane should have negative donor numbers. Assignment of DN = 0 in eq 11 therefore indicates a solvating power which is somewhat too high. [j] $\Delta G_{tr}(K^+)$ is 340 kJ g-ion^{-1} for transfer from DMF to the gas phase.[22] A simple Born calculation, using a dielectric constant of 1.9 for hexane, predicts $\Delta G_{tr}(K^+)$ of 180 kJ g-ion^{-1} for transfer from DMF to hexane. [k] It seems unlikely that the donor–acceptor concept for predicting ion solvating power extends to these very low dielectric solvents. We expect weaker ion solvating power than predicted by donor and acceptor numbers. [l] Reference 2. [m] U. Mayer, W. Gerger, and V. Gutmann, *Monatsh. Chem.*, 108, 489 (1977). [n] W. E. Waghorne, Ph.D. Thesis, Australian National University, Canberra, Australia, 1972.

of measuring acceptor numbers indirectly from rate constants in different solvents, should these not be otherwise available, and all three are related through eq 10 and 12.

In summary then, rates of S_N2 reactions between anions and molecules in polar solvents have tolerable linear free-energy relationships with the anion solvating properties and with the acceptor properties of the solvents as recorded in Table II. An example is illustrated in Figure 3 for reaction 6 of Table IV.

S_N1 Solvolysis. Two classical investigations of physical organic chemistry are the solvent effects on the rates of solvolysis of *tert*-butyl chloride and *p*-methoxyneophyl tosylate (eq 16). The solvolysis of *tert*-butyl chloride leads to the Grunwald–Winstein *Y* values[27,28,29] and the solvolysis of *p*-methoxyneophyl tosylate (I) measures "solvent ionizing power".[30,31] The subsequent work by Abraham[3,15] on *tert*-butyl chloride has been particularly illuminating, as have the investigations of Schleyer and co-workers[31] and Rudakov[32] on this and related substrates. It is of interest to simplify these highly sophisticated and successful interpretations for the benefit of nonspecialists, who are familiar with the principles of anions, cation, and molecule solvation, but not the language and concepts of the physical organic chemist. As noted, Fawcett and Krygowski[8] have presented relationships which are closely related to ours, but we consider important new data points and discuss the implications in a somewhat different way.



(16)

***p*-Methoxyneophyl Tosylate.** There is an excellent linear free-energy relationship (eq 17) between $\Delta G_{tr}(Cl^-)$ at 25 °C

Table III. Sensitivities of Anions, Cations, and S_N2 Reactions to Solvent Transfer through High Dielectric Solvents at 25 °C. Values of *n* and *p* in eq 9–15 and 2

Anions[c] Y^-	Registry no.	*n* (eq 10)	*n'* (eq 12[d])	Cations[e] M^+	Registry no.	*p* (eq 9)	*p'* (eq 11[f])
F^-	16984-48-8	1.25	1.62	Zn^{2+}	23713-49-7	5.2	7.5
OAc^-	71-50-1	1.33	1.73	Cd^{2+}	22537-48-0	4.3	6.0
Cl^-	16887-00-6	1.00	1.30	Ba^{2+}	22541-12-4	3_3	4_5
Br^-	24959-67-9	0.74	1.00	Li^+	17341-24-1	2.1	2.9
N_3^-	14343-69-2	0.75	1.0	Na^+	17341-25-2	1.5	2.1
SCN^-	1111-67-8	0.35[a]	0.45	K^+	24203-36-9	1.0	1.30
OTs^-	16722-51-3	0.3–0.4[g]	0.4–0.5[c,g]	Cs^+	18459-37-5	0.7	1.0
I^-	20461-54-5	0.3_5–0.4[a]	0.4–0.5	NMe_4^+	51-92-3	0.5	0.7
ClO_4^-	14797-73-0	0	0	Ph_4As^+	15912-80-8	0.25	0.3
BPh_4^-	4358-26-3	0.0_5	0.0_5				

Registry no. (RX)	Reactants RX + Y^-	*n''* (eq 13[b,c])	*n* (eq 14[b,c])	*n'* (eq 15[b,d])
74-88-4	$CH_3I + SCN^-$	1.0[a]	0.35	0.45
	$CH_3I + Br^-$	1.0	0.7	1.0
	$CH_3I + Cl^-$	1.0	1.0	1.30
74-83-9	$CH_3Br + SCN^-$	1.0[a]	0.35	0.45
	$CH_3Br + Cl^-$	0.80	0.80	1.0
109-65-9	n-$BuBr + N_3^-$	0.73	0.55	0.72
80-48-8	$CH_3OTs + N_3^-$	0.50	0.36	0.54
350-46-9	$4\text{-}NO_2C_6H_4F + N_3^-$	1.0	0.75	1.0
636-98-6	$4\text{-}NO_2C_6H_4I + N_3^-$	1.0	0.75	1.0
709-49-9	$2,4\text{-}(NO_2)_2C_6H_3I + SCN^-$	1.0[a]	0.35	0.45
	$2,4\text{-}(NO_2)_2C_6H_3I + Cl^-$	1.0	1.0	1.30

[a] Significant deviations from the appropriate equations occur for some solvents because of difficulties in measuring solubilities of AgI and AgSCN.[18] [b] Values of $\Delta G^{\ddagger}_{tr}(S_N2)$ calculated from ref 2. [c] Values of $\Delta G_{tr}(Y^-)$ from Table I or from $\Delta G_{tr}(Ag^+) + \Delta G_{tr}(Y^-)$[11,20] $- \Delta G_{tr}(Ag^+)$(TATB), Table I. [d] Values of Δ(AN) from acceptor numbers in Table II. [e] Values of $\Delta G_{tr}(M^+)$ from ref 11 or 23. [f] Donor numbers from Table II. [g] Only three data points available: cf. R. Alexander, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *J. Am. Chem. Soc.*, **89**, 3703 (1967).

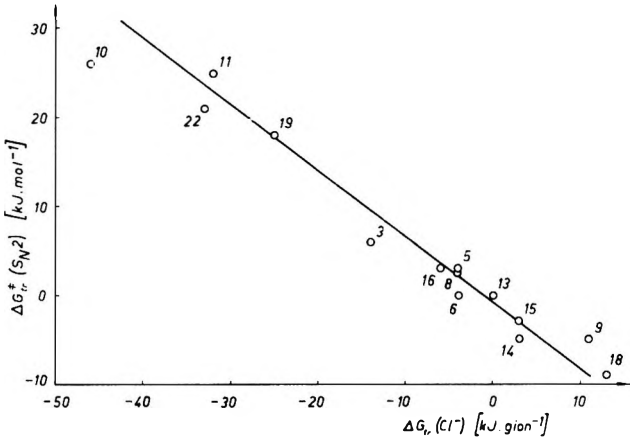


Figure 3. Relationship between transfer free energy of activation $\Delta G^{\ddagger}_{tr}(S_N2)$ and anion solvating power of solvents for transfer of the S_NAr reaction between azide ion and 4-fluoronitrobenzene at 25 °C. Plot of the equation $\Delta G^{\ddagger}_{tr}(S_N2) = -0.75\Delta G_{tr}(Cl^-)$, cf. eq 14 and Table IV.

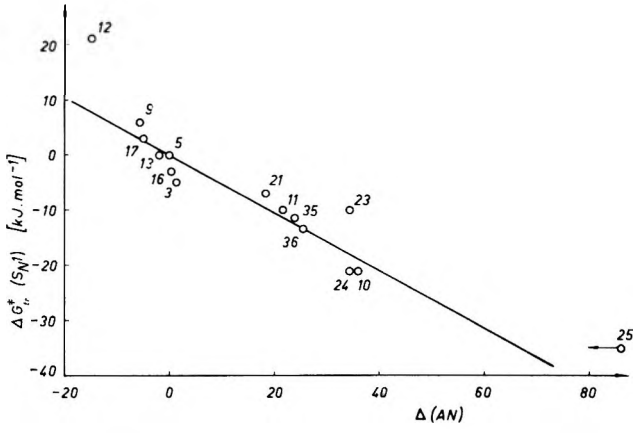


Figure 4. Relationship between transfer free energy of activation and solvent acceptor properties for solvolysis of *p*-methoxyneophyl tosylate at 75 °C. Plot of the eq 18 $\Delta G^{\ddagger}_{tr}(S_N1) = -0.52\Delta(AN)$; cf. Table V. No. 35: mole fraction EtOH in mixture with water = 0.55. No. 36: mole fraction MeOH in mixture with water = 0.64.

(Table II) and the transfer free energy of activation for solvolysis of *p*-methoxyneophyl tosylate at 75 °C (Table V). Even water tolerably satisfies the relationship. The value of *n* is 0.40.

$$\Delta G^{\ddagger}_{tr}(S_N1) = n\Delta G_{tr}(Cl^-) \quad (17)$$

A corrolary of eq 10, 12, and 17 is given by eq 18. As shown in Figure 4 and Table V there is a good correlation between acceptor numbers of pure solvents and alcohol–water mixtures and solvolysis rates ($\Delta G^{\ddagger}_{tr}(S_N1)$) of *p*-methoxyneophyl tosylate. The value of *n'* is 0.52 as required by the special case of eq 12, $\Delta G_{tr}(Cl^-) = -1.30\ \Delta(AN)$, and by $n = 0.4$ in eq 17. The use of acceptor numbers allows us to introduce extra data points for which $\Delta G_{tr}(Cl^-)$ are not available. However these are all for solvents of low dielectric constant, i.e., acetic acid (6.3), ether (4.2), pyridine (12.3), and trifluoroacetic acid (8.3). Substantial positive deviations (up to +13 kJ mol^{-1}) from the requirements of eq 18 are observed in three of the solvents, but pyridine is well correlated in a relationship covering 56 kJ mol^{-1} in $\Delta G^{\ddagger}_{tr}(S_N1)$.

$$\Delta G^{\ddagger}_{tr}(S_N1) = -n'\Delta(AN) \quad (18)$$

Unlike the good correlations with chloride anion solvating power and acceptor number, there is no meaningful rela-

Table IV. Correlation of Solvent Effects on S_N2 Rates through eq 2, 13, 14 or 15. Transfer at 25 °C in kJ mol^{-1} from Dimethylformamide of Reactions RX + Y$^-$ → RY + X$^-$

Solvent[a]	ΔG_{tr}(RX)[b]	$\Delta G^{\ddagger}_{tr}(S_N2)$,[b] (obsd)	$-n''\Delta G_{tr}(Y^-)$[g] (eq 13)	$-n\Delta G_{tr}(Cl^-)$[e] (eq 14)	$+n'\Delta$(AN)[e] (eq 15)	$\Delta G^{\ddagger}_{tr}(S_N2)$ (eq 2a)	$\Delta G^{\ddagger}_{tr}(S_N2)$ (eq 2b)
		Reaction 1: RX = CH_3I; $Y^- = Cl^-$; $n'' = 1.0$; $n = 1.0$; $n' = 1.30$					
H_2O	11	35		46	50	35	39
$HCONH_2$	6	27		33	31	27	25
DMF	0	0		0	0	0	0
DMA	0	−3		−3	−3	−3	−3
MeCN	1	7		4	4	3	3
NMePy	−1	−6		−3	-3_5	−2	-2_5
$MeNO_2$	2	10		14	6	12	4
Me_2CO	−2	0		−11	-4_5	−9	-2_5
MeOH	3	34		32	33	29	30
NMeF		24_5[d]		25	21		
$C_2H_4Cl_2$		5[c]			1		
		Reaction 2: RX = CH_3I; $Y^- = Br^-$; $n'' = 1.0$; $n = 0.75$; $n' = 1.00$					
CF_3CH_2OH		31[f]	41	41	37		
H_2O	11	26	34	34	39	23	28
MeOH	3	24	23	24	25	21	22
$HCONH_2$	6	20	24	24	24	18	18
EtOH	2	20_5[f]	15	18_5	21	17	19
MeCN	1	7[f]	3	3	3	2	2
DMF	0	0	0	0	0	0	0
Me_2CO	−2	−5	−8	−8	-3_5	−6	-1_5
NMePy	−1	−7	−1	−2	−3	−1	−2
		Reaction 3: RX = CH_3I; $Y^- = SCN^-$; $n'' = 1.0$; $n = 0.35$; $n' = 0.45$					
H_2O	11	14	16	16	17_5	5[j]	6.5[j]
MeOH	3	13	10	11	11	8[j]	8[f]
$HCONH_2$	6	10	12	11	11	5[j]	5[j]
NMeF		7_5		8_5	7		
$MeNO_2$	2	5	7	5	2	3	0
MeCN	1	5	3	1_5	1	0	0
DMF	0	0	0	0	0	0	0
DMAC	0	−2	−1	−1	−1	−1	−1
PC		4[f]	7	2	1		
Me_2CO	−2	−2		−4	−2	−2	0
NMePy	−1	−7	−3	−1	−1	0	0
Me_2SO	0	2[f]	+8	+2	$+1_5$	2	1_5
0.70 Me_2SO–H_2O	4_5	7_5	8		6		1_5
0.32 Me_2SO–H_2O	7	8	8_5	9	15_5	2	4_5
		Reaction 4: RX = *n*-BuBr; $Y^- = N_3^-$; $n'' = 0.73$; $n = 0.55$; $n' = 0.72$					
MeOH	1	19	17_5	18	18	17	17
H_2O	>15	15	25	25	28	<10	<13
$HCONH_2$	4	13	17	18	17	14	13
TMS		4_5		2			
Me_2SO	1	2	8	3	2	2	1
DMF	0	0	0	0	0	0	0
MeCN	-0_5	−2	4	2	2	2_5	2_5
DMAC	0	−3	−1	−2	−2	−2	−2
Me_2CO	0	−3	−7	−6	-2_5	−6	-2_5
HMPT	-1_5	−5	−9	−7	−4	−6	-2_5
		Reaction 5: RX = 2,4-$(NO_2)_2C_6H_3I$; $Y^- = SCN^-$; $n'' = 1.0$; $n = 0.35$; $n' = 0.45$					
$HCONH_2$	ca.9[h]	11	12	11	11	2[j]	2[j]
MeOH	>6[h]	10	10	11	11	<5[j]	<5[j]
Me_2SO		3	8[i]	2	1_5		
$MeNO_2$		2	7	5	2		
MeCN		1	3	1	1		
DMF	0	0	0	0	0	0	0
TMS		0		1			
NMePy		−2	−3	−1	−1		
DMAC		−2	−1	−1	−1		
Me_2CO		−6		−4	−2		
		Reaction 6: RX = 4-$NO_2C_6H_4F$; $Y^- = N_3^-$; $n'' = 1.0$; $n = 0.75$; $n' = 1.0$					
H_2O	>15[k]	26[n]	35	35	39	<20[j]	<24[j]
MeOH	7[h]	25	24	24	25	17[j]	18[j]
$HCONH_2$	9[h]	21	23	25	24	16[j]	15[j]
NMeF		18[l,m]		19	16		
$MeNO_2$		6[n]	10	10	4_5		
Me_2SO	0.5[h]	3[n]	11	4_5	3	4[j]	2_5[j]
MeCN	4_5[h]	3[n]	6	3	3	-1_5[j]	-1_5[j]

Table IV (*Continued*)

Solvent[a]	$\Delta G_{tr}(RX)$[b]	$\Delta G^{\ddagger}_{tr}(S_N2)$,[b] (obsd)	$-n''\Delta G_{tr}(Y^-)$[g] (eq 13)	$-n\Delta G_{tr}(Cl^-)$[e] (eq 14)	$+n'\Delta(AN)$[e] (eq 15)	$\Delta G^{\ddagger}_{tr}(S_N2)$ (eq 2a)	$\Delta G^{\ddagger}_{tr}(S_N2)$ (eq 2b)
			Reaction 6 (Continued)				
PC		2_5[n]	6	3	2		
PhCN		1[l]			0		
$PhNO_2$		0[l]			−1		
DMF	0[h]	0	0	0	0	0	0
TMS		0[n]		3			
DMAC		−3	−1	−2	−2		
Me_2CO		−5	−9	−8	-3_5		
NMePy	-1_5[h]	−5	−6	−2	−3	-0_5[j]	−1.5[j]
HMPT	−2[h]	−9[n]	−13	−7	−5	−5[j]	−3[j]

[a] Abbreviations as in Table II. [b] Reference 2, unless stated otherwise. [c] Reference 40. [d] A. J. Parker, *J. Chem. Soc.*, 1328 (1961). [e] Table II. [f] Reference 20. [g] Table I unless stated otherwise. [h] Estimated from ΔG_{tr} for $4\text{-}NO_2C_6H_4I$ and $2,4\text{-}(NO_2)_2C_6H_3Cl$, ref 2. [i] $\Delta G_{tr}(Y^-)$ is uncertain; see Table I. [j] These equations are not expected to apply to these reactions; see text. [k] Both $4\text{-}NO_2C_6H_4F$ and $2,4\text{-}(NO_2)_2C_6H_3Cl$ (ref 2) have solubilities >1 M in DMF and $<10^{-3}$ M in water at 25 °C $\Delta G_{tr}(RX)$ is >15 kJ mol^{-1}. [l] J. Miller and A. J. Parker, *J. Am. Chem. Soc.*, **83**, 117 (1961). [m] Extrapolated from a rate constant measured at 100 °C, assuming same activation energy as for reaction in formamide. [n] Reference 6.

Table V. Correlation of Solvent Effects on Rate of Solvolysis of *p*-Methoxyneophyl Tosylate[k] (ROTs) at 75 °C: Transfer from Acetonitrile

Solvent[a]	$\Delta G^{\ddagger}_{tr}(S_N1)$ (obsd)	$-0.52\Delta(AN)$[f] (eq 18)	$0.40\Delta G_{tr}(Cl^-)$[f] (eq 17)
CF_3CO_2H	−35[d]	−45[g]	
CF_3CH_2OH	−21[e]	−18	−21
H_2O	−21[b,c]	−19	−17
MeOH	−10[c]	−12	−11
HOAC	−10[c]	−18	
EtOH	−7[c]	-9_5	−8
Me_2SO	−3[c]	0	−1
$MeNO_2$	−5[c]	−1	−4
DMF	0[c]	1_5	2
MeCN	0[c]	0	0
Pyd	3[c]	2	
Me_2CO	6[c]	3	6
Ether	21[c]	>8[h]	
0.64 MeOH–H_2O	−13[i]	−13[j]	
0.55 EtOH–H_2O	-11_5[i]	-12_5[j]	

[a] Abbreviations as in Table II, pyd is pyridine. [b] Approximate value, extrapolated from water–solvent mixtures. [c] Reference 30. [d] Estimated from solvolysis of neophyl tosylate in this solvent: A. F. Diaz, I. Lazdins, and S. Winstein, *J. Am. Chem. Soc.*, **90**, 6546 (1968). [e] Estimated from solvolysis of 2-adamantyl tosylate, ref 31. [f] Table II. [g] See footnote *d*, Table II. [h] Footnote *k*, Table II. [i] Calculated from rate constants at 25 and 50 °C given in ref 30. [j] See footnote *m*, Table II. [k] Registry no.: 59024-80-5.

tionship such as eq 19 between $\Delta G^{\ddagger}_{tr}(S_N1)$ for these solvolyses and the cation solvating power of the solvents (Table II). As shown by Fawcett and Krygowski,[8] the dependence of these rates on solvent donor properties is negligible.

$$\Delta G^{\ddagger}_{tr}(S_N1) = p\Delta G_{tr}(K^+) = -p'\Delta(DN) \qquad (19)$$

Solvolysis of *p*-methoxyneophyl tosylate is always faster in the significantly stronger anion solvating solvents (e.g., trifluoroethanol, trifluoroacetic acid) of a set of solvents, irrespective of cation solvating power. Instructive comparisons from Table V are: the similar values of $\Delta G^{\ddagger}_{tr}(S_N1)$ between CH_3NO_2 and Me_2SO, which are two solvents of very different cation solvating, but similar anion solvating properties (Table II); faster solvolysis in ethanol than DMF; and similar rates of solvolysis in water and trifluoroethanol (similar AN) despite a difference of 35 kJ g-ion^{-1} in their ability to solvate K^+ (Table II).

To summarize, rates of solvolyses of *p*-methoxyneophyl tosylate in solvents of high polarity have a linear free-energy relationship with the anion solvating properties, as measured by Δ(AN) or $-\Delta G_{tr}(Cl^-)$ of the solvents. In the language of the physical organic chemists, Figure 4 and Table V establish that electrophilic solvation of the leaving group, rather than solvent ionizing power, is the major factor in determining differences in rates of solvolysis of *p*-methoxyneophyl tosylate. These are limiting solvolyses, with no detectable nucleophilic participation by the solvent. We cannot agree that it is not necessary to account explicitly for electrophilic (anionic) solvation of the leaving group in *these* solvolysis reactions[31] and recall the original Hughes–Ingold formulation[33] of an S_N1 reaction. "S_N1 reactions involve a rate-determining ionization to a cationic intermediate. The solvent functions largely in an electrophilic manner (as an acceptor) to heterolyze the C–X bond and solvate the anion. No covalent interaction between the solvent and cation is required." Certainly this solvolysis fits that description.

***tert*-Butyl Chloride.** $\Delta G^{\ddagger}_{tr}(S_N1)$ for *tert*-butyl chloride solvolysis, as measured by the rate of production of HCl, is analyzed in Table VI. The linear free-energy relationship (eq 17) is less satisfactory than it was for *p*-methoxyneophyl tosylate. Rates of solvolysis by water and formamide are now much faster than required by eq 17. Weak cation solvators of very different anion solvating properties, such as ethanol, methanol, trifluoroethanol, nitromethane, acetonitrile, and acetone, fit a linear relationship of slope 0.5 in eq 17. However solvolysis of *tert*-butyl chloride by solvents which are very strong cation solvators (Table II), such as DMF, *N*-methylpyrrolidine, DMAC, and Me_2SO, are a little faster than required by eq 17.

As noted, eq 18 is a corollary of eq 10, 12, and 17, so like eq 17 it gives a tolerable correlation between solvent acceptor numbers and $\Delta G^{\ddagger}_{tr}(S_N1)$ for solvolysis of *tert*-butyl chloride in solvents of high dielectric constant, other than water. The value of n' is 0.65 in Table VI. The use of acceptor numbers gives much the same deviations as eq 17, but allows inclusion of data points, for ether (4.2), dioxane (2.2), heptane (1.9), nitrobenzene (35), isopropyl alcohol (18.3), acetic acid (6.3), and trifluoroacetic acid (8.3). Many of these are low dielectric solvents (values in parentheses) so only maximum values of their anion solvating power can be estimated from Δ(AN) (Table II). The low dielectric solvents (<10) all actually solvolyze *tert*-butyl chloride *more slowly* than predicted by solvent acceptor numbers in eq 18. The slower than predicted rates are observed whether the low dielectric solvents are poor acceptors and donors, like heptane, strong donors but weak

Table VI. Correlation of Solvent Effects on Rates of Solvolysis of *tert*-Butyl Chloride [p] and *tert*-Butyl Bromide [q] at 25 °C. Transfer from Acetonitrile in kJ mol^{-1} (*t*-BuCl) or DMF (*t*-BuBr)

$$\Delta G^{\ddagger}_{tr}(S_N1) = p\Delta G_{tr}(K^+) + n\Delta G_{tr}(Cl^-) - \Delta G_{tr}(t\text{-BuX}) \quad (1a)$$

$$\Delta G^{\ddagger}_{tr}(S_N1) = -p'\Delta(DN) - n'\Delta(AN) - \Delta G_{tr}(t\text{-BuX}) \quad (1b)$$

Solvent[a]	ΔG_{tr} (*t*-BuX)[b]	$\Delta G^{\ddagger}_{tr}(S_N1)$ (obsd[c])	$n\Delta G_{tr}(Cl^-)$[i] (eq 17)	$-n'\Delta(AN)$[i] (eq 18)	$\Delta G^{\ddagger}_{tr}(S_N1)$ (eq 1a)	$\Delta G^{\ddagger}_{tr}(S_N1)$ (eq 1b)
Reaction: *t*-BuX = *t*-BuCl; $p = 0.20$; $p' = 0.28$; $n = 0.50$; $n' = 0.65$						
H_2O	18	−41[c]	−21	−23	−41	−45
CF_3CO_2H		−32[h]		<−56[g]		<−52
CF_3CH_2OH		−27[h]	−26	−22	>−22	
$HCONH_2$	4[j]	−25[c]	-14_5	-13_5	-20_5	−21.5
MeOH	1	−15[c]	−14	-14_5	−15	−16.5
HOAc	0	−12[c]		−22		<−19
EtOH	0	-9_5[c]	-10_5	−12	-9_5	
Me_2CHOH	0	−6[c]		−9		−10
Me_2SO	1	-5_5[d]	−1	0	−6	−5
$MeNO_2$	1	−4[d]	−5	−1	−3	2
DMF	−1	−1[d]	2	2	−1	−1
DMA	−1[k]	-0_5[d]	3_5	4	−1	2
MeCN	0	0[d]	0	0	0	0
NMePy	−1	1_5[d]	3_5	4	0_5	2
$PhNO_2$	−2	6[d]	3	3	8	5
Me_2CO	−2	8[d]	7_5	4	8_5	5_5
Dioxane	−2	12[d]		>5[f]		>8
Ether	−3	23[d]		>10[f]		>12
n-Heptane	−3	42[d]		>13[f]		>21
0.2 MeOH–H_2O	12[l]	−35[m]		−21[n]		−34[o]
0.4 MeOH–H_2O	8[l]	-29_5[m]		−19[n]		−28[o]
0.6 MeOH–H_2O	6[l]	−24[m]		−17[n]		−24[o]
0.8 MeOH–H_2O	3_5[l]	−19[m]		−16[n]		-20_5[o]
Reaction: *t*-BuX = *t*-BuBr: $p = 0.20$; $p' = 0.28$; $n = 0.35$; $n' = 0.45$ from DMF						
	ΔG_{tr}(*t*-BuX)	$\Delta G^{\ddagger}_{tr}(S_N1)$	$n\Delta G_{tr}(Cl^-)$	$-n'\Delta(AN)$	$\Delta G^{\ddagger}_{tr}(S_N1)$	$\Delta G^{\ddagger}_{tr}(S_N1)$
H_2O	22	−32[b]	−12	-17_5	−32	−37.5
CF_3CH_2OH		−18[e]	−14	−17	>−8	
MeOH	3	−7[b]	−8	−11	−7	−12
EtOH	1	−2[b]	−5	-9_5	−1	
DMF	0	0[b]	0	0	0	0
DMA	0[k]	0[b]	0	1	0	1
NMePy	0	2[b]	1	1	1	1
Me_2CO	-0_5	7[b]	3	1_5	6_5	3_5

[a] Abbreviations as in Table II. [b] Reference 3. [c] Reference 29. [d] Reference 15. [e] F. L. Scott, *Chem. Ind.*, 224 (1959). [f] Recorded acceptor numbers for these low dielectric solvents give maximum estimates of their anion solvating power only (see text and Table II). [g] See footnote d, Table II. [h] Reference 31. [i] From Table II. [j] Estimated from *n*-BuBr, ref 2. [k] Estimated from DMF. [l] Interpolated from M. H. Abraham and G. F. Johnston, *J. Chem. Soc. A*, 1610 (1971) after conversion to mole fraction scale. [m] Interpolated from ref 29. [n] See footnote *m*, Table II. [o] Assuming DN = constant ≈ 18 for MeOH–H_2O mixtures. [p] Registry no.: 507-20-0. [q] Registry no.: 507-19-7.

Table VII. Analysis of Solvent Effects on Rate of Solvolyses of *trans*-4-*tert*-Butylcyclohexyl Tosylate[f] (ROTs) at 75 °C. Transfer from Acetonitrile in kJ mol^{-1}

Solvent[a]	$\Delta G^{\ddagger}_{tr}(S_N1)$ (obsd)	$-0.5\Delta(AN)$[e] (eq 18)	$p\Delta G_{tr}(K^+) - \Delta G_{tr}$(ROTs) (eq 1)	$0.4\Delta G_{tr}$ (K^+)
CF_3CO_2H	−29[d]	<−43	<14	>10
CH_3CO_2H	−18[d]	−16	−2	
Me_2SO	−9[b]	0	−9	−9
EtOH	−7[c]	−8	1	2
DMF	−4[b]	+3	−7	−8
$MeNO_2$	−1[b]	0	−1	+5
MeCN	0[b]	0	0	0
Me_2CO	5[b]	4	1	−3

[a] Abbreviations as in Table II. [b] Reference 42. [c] S. Winstein and N. J. Hollness, *J. Am. Chem. Soc.*, 77, 5562 (1955). [d] Reference 43. [e] Acceptor number from Table II. [f] Registry no.: 7453-05-6.

acceptors, like ether and dioxane, or very strong acceptors but weak donors, like acetic acid and trifluoroacetic acid.

For the same solvents, eq 17 is a little more satisfactory than eq 18.

Other Substrates. $\Delta G^{\ddagger}_{tr}(S_N1)$ for solvolysis of *tert*-butyl bromide is also analyzed in Table VI and *trans*-4-*tert*-butylcyclohexyl tosylate is analyzed in Table VII. Equation 18 is clearly not acceptable as describing solvent effects on

rates of solvolysis of *trans*-4-*tert*-butylcyclohexyl tosylate in DMF and Me_2SO. The solvolyses of *tert*-butyl bromide fit eq 18 in much the same indifferent way as do those of *tert*-butyl chloride, but n' in eq 18 is of course less (0.45) because the larger bromide ion is less responsive to solvent anion solvating properties than is the developing chloride ion in *t*-BuCl‡.

Discussion

It is of interest to examine why we obtain the linear relationships eq 13, 14, 15, 17, and 18 between rates, $\Delta G_{tr}(Y^-)$, $\Delta G_{tr}(Cl^-)$, and acceptor number for several S_N2 and S_N1 reactions in different solvents.[34] Even more interesting are the reasons for the deviations which we have noted: i.e., reaction in water and formamide sometimes but not always faster than required by the relationships; solvolyses in strong cation solvators like DMF and Me_2SO sometimes but not always faster than predicted; and much slower solvolyses in low dielectric solvents with a large range of donor and acceptor properties than required by the relationships.

S_N2 Reactions. Rates of S_N2 reactions in different solvents are determined by the three transfer free energies of eq 8. Two simplifications are possible.

First, if the transition state anion, $YRX^{-\ddagger}$, is large with low surface charge, as for the S_NAr reaction of azide ion with 4-fluoronitrobenzene, and if RX is of similar structure and size to $YRX^{-\ddagger}$ (e.g., 4-fluoronitrobenzene),[2,6] then we use an assumption, familiar for nonaqueous solvent chemists, that $\Delta G_{tr}(YRX^{-\ddagger}) = \Delta G_{tr}(RX)$.[20,35] This "transition state" assumption is valid for formamide as well as other polar solvents of high dielectric constant, but may break down for solvents of low dielectric constant and for water.[20] The equality given above is equivalent to assumptions like $\Delta G_{tr}(Ph_4B^-) = \Delta G_{tr}(Ph_4C)$[20] $\Delta G_{tr}(I_3^-) = \Delta G_{tr}(I_2)$[35] and is conceptually related to the ferrocene assumption,[36] the bis(biphenyl)chromium assumption,[37] and the cobaltocene assumption,[36] which are of the form $\Delta G_{tr}(M^+) = \Delta G_{tr}(M^0)$. The "transition-state assumption",[35] given above, reduces eq 8 to $\Delta G^{\ddagger}_{tr}(S_N2) = -\Delta G_{tr}(Y^-)$ as observed for reactions 3, 5, and 6 in Table IV, over a wide range of solvents. This type of situation is a special case of eq 13 ($n'' = 1$) and is common for aromatic nucleophilic substitution reactions, as shown by their n'' values of unity in Table III and correlations for formamide in Table IV, reactions 5 and 6. It is less common for substitution at saturated carbon, but reactions of iodomethane with large anions such as thiocyanate (reaction 3, Table IV) approximate to it.[2] In these cases, eq 13–15 give a much better correlation than eq 2 for water and formamide as shown in Table IV.

In the second simplification we have the more general case of eq 13. If RX is not large (e.g., CH_3Cl) or if for various reasons the S_N2 transition state is loose ($N_3CH_3OTS^{-\ddagger}$)[26] or if its surface charge is significant ($N_3BuBr^{-\ddagger}$), then $\Delta G_{tr}(RX)$ does not equal $\Delta G_{tr}(YRX^{-\ddagger})$ and the two terms must be considered.[2] The transition state ($YRX^{-\ddagger}$) is an anion, but is larger and has less surface charge than Y^-. Thus it is subject to eq 10 and 12, corresponding less strongly to solvent transfer but in the same way as does Y^-. This corollary is expressed in eq 20, which leads from eq 8 to eq 21 and 22.

$$\Delta G_{tr}(YRX^{-\ddagger}) = n'\Delta G_{tr}(Y^-) \quad (20)$$

$$\Delta G^{\ddagger}_{tr}(S_N2) = n'\Delta G_{tr}(Y^-) - \Delta G_{tr}(Y^-) - \Delta G_{tr}(RX) \quad (21)$$

$$\Delta G^{\ddagger}_{tr}(S_N2) = -n''\Delta G_{tr}(Y^-) - \Delta G_{tr}(RX) \quad (22)$$

$$\text{where } n'' = 1 - n'$$

Equation 2 is a corrolary of eq 22, through eq 10 and 12.

In eq 20, n' values are less than unity and decrease as $YRX^{-\ddagger}$ decreases in surface charge (Table III) relative to Y^-. Thus n'' in eq 22 is also less than unity, but *increases* toward unity as $YRX^{-\ddagger}$ decreases in surface charge. For an anion $YRX^{-\ddagger}$ of comparable low surface charge to ClO_4^-, as shown in Table III, n' in eq 20 will be zero. Thus n'' in eq 22 and eq 13 will be unity. An example is reaction 1 in Table IV. It is important to note that reaction 1 in Table IV is *not* the same situation as discussed above for reaction 3 in Table IV, where n'' was unity because of the equality of $\Delta G_{tr}(RX)$ and $\Delta G_{tr}(YRX^{-\ddagger})$. Although n'' is unity in both cases, the difference lies in the need or otherwise to include $\Delta G_{tr}(RX)$ for transfer to water or formamide in the correlation, i.e., to use eq 2 and 22 or eq 13.

For transfer of the monofunctional type of uncharged reactant RX considered here through solvents other than water and to a lesser extent formamide, $\Delta G_{tr}(RX)$ is often negligible (± 2 kJ mol^{-1}),[2] as shown in Tables IV and VI. If this term is negligible in eq 22, the relationship reduces to eq 13 which, as illustrated for all reactions in Table IV, gives an acceptable approximate linear free-energy relationship for many S_N2 reactions in many solvents. As noted, if eq 3 is valid, then eq 14 and 15 follow as corollaries, via eq 10 and 12, and the success of these relationships is explained.

For transfer to water and formamide, $\Delta G_{tr}(RX)$ in eq 22 is significantly positive (Table IV). This is because hydrophobic, weakly polar species RX are more weakly solvated in highly structured solvents like water and formamide than by other solvents. Solvation of such species in water is by a mechanism known as solvation of the second kind.[11,25,38] Less structured solvents, like DMF, CH_3CN, and methanol, do not use this mechanism and solvate RX more strongly and to a comparable extent (ΔG_{tr} is ± 2 kJ mol^{-1}), so that transfer between them involves little change in free energy.[11]

If the transition state anion ($YRX^{-\ddagger}$) has significant negative surface charge, localized for example on Y and X, then its solvation by water, at least in the region of Y and X, is different from solvation of RX. It is solvation of the first kind[11,38] and so $\Delta G_{tr}(YRX^{-\ddagger})$ is usually more negative than $\Delta G_{tr}(RX)$ on transfer to water. Thus the deviations from eq 13, 14, or 15, shown by reactions 1, 2, and 4 in Table IV, for transfer to water and formamide are explained. For transfer of these reactions to water and to some extent formamide, eq 22 or its corollary eq 2 gives a much better correlation of rates, which are otherwise faster than predicted by eq 13 or by its corollaries, eq 14 and 15. As noted, eq 13–15 give a better correlation of rates than eq 2 for reactions 3, 5, and 6 in water and formamide.

For a variety of reasons,[3,32,33,39] the transition states for highly endoenergetic S_N1 ionizations are regarded as highly dipolar species, having a cationic and anionic center. They have some of the features of the products of ionization, i.e., of a carbonium ion and an anion. Although not implying that the transition state is a fully solvated cation and anion or an ion pair, we expect that the cationic portion of $RX^{\ddagger}$ will be solvated according to the cation solvating power of the solvent. The anionic portion will be solvated according to the anion solvating power of the solvent. As noted, ΔG_{tr} for cationic centers responds to a solvent transfer as indicated by the linear relationship eq 9 and 11, and anionic centers respond to solvent transfer as indicated by eq 10 and 12. Thus $\Delta G_{tr}(RX^{\ddagger})$ will be given by the sum of $p\Delta G_{tr}(K^+) + n\Delta G_{tr}(Cl^-)$, or of $-p'\Delta(DN) - n'\Delta(AN)$. The relationship of eq 1 to eq 7 is now apparent.

In eq 1 the sensitivity to solvent transfer, p, n, p', and n', will be less than for the corresponding real cations and anions because the charged centers in this dipolar transition state are not fully solvated or developed ions. The sensitivity parameters tell us much about mechanism.

(A) *p*-Methoxyneophyl Tosylate. In the case of solvolysis of *p*-methoxyneophyl tosylate, Table V and Figure 4, we encounter a special case of eq 1 which could also be written as eq 23, since $p\Delta G_{tr}(K^+) = p''\Delta G_{tr}(R^+) = -p'\Delta(DN)$ through

eq 9 and 11. In eq 23, R^+ is the carbonium ion II.

$$\Delta G^{\ddagger}_{tr}(S_N1) = p''\Delta G_{tr}(R^+) + n\Delta G_{tr}(Cl^-)$$

$$-\Delta G_{tr}(RX) = p''\Delta G_{tr}(R^+) - n'\Delta(AN) - \Delta G_{tr}(RX) \quad (23)$$

The bridged hydrophobic carbonium ion II has very low surface positive charge and is of comparable large size to the hydrophobic reactant molecule, *p*-methoxyneophyl tosylate (RX).[30] Its small positive surface charge means that cation solvating power is a negligible factor in determining its ΔG_{tr} through many solvents of dielectric constant 20–100 (p in eq 9 is small as for Ph_4As^+),[25] but again like Ph_4As^+[11,25] its bulk and hydrophobic properties are significant factors in determining a large positive $\Delta G_{tr}(RX^{\ddagger})$ for transfer to water. Thus we have a situation like that for the ferrocene–ferricinium couple,[36] the bis(biphenyl)chromium(I)–bis(biphenyl)chromium(0) couple,[37] and the cobaltocene–cobalticene couple,[36] which have been used by electrochemists to estimate ΔG_{tr}(ion) from $\Delta E_{1/2}$ values. The ferrocene-like assumptions that $\Delta G_{tr}(M^0) = \Delta G_{tr}(M^+)$ have proved quite successful.[10,36,37] For the same reasons that lead to the ferrocene assumption, we assume that $p''\Delta G_{tr}(R^+) = \Delta G_{tr}(RX) = \Delta G_{tr}(R^+)$, where R^+ is cation II and RX is *p*-methoxyneophyl tosylate. Thus eq 23 reduces to eq 17 and 18 and the excellent relationship shown in Table V and Figure 4 for transfer between high dielectric solvents, including water, is explained.

It remains to be explain why eq 18 predicts faster solvolyses of *p*-methoxyneophyl tosylate than are observed in solvents of dielectric constant <10. The full implications of ferrocene-like assumptions that $\Delta G_{tr}(M^0) = \Delta G_{tr}(M^+)$ need to be appreciated. The assumption has proved successful for transfer through solvents of dielectric constant 25–60, where $\Delta(1/\epsilon)_{tr}$ is 0–0.024, and thus changes in "Born-like solvation" [25] are negligible. However Born-like solvation can account for >90% of the solvation energy of an ion on transfer from gas phase to high dielectric solvents.[25] Thus we do not believe that $\Delta G_{tr}(M^+) = \Delta G_{tr}(M^0)$ for transfer from solvents of dielectric constant >25 to solvents of ϵ <5. Born calculations suggest that for such a transfer (where $\Delta(1/\epsilon)_{tr}$ is >0.16) $\Delta G_{tr}(M^+)$ is at least 20 kJ g-ion^{-1}, even for transfer of large cations of low surface charge, like ferricinium and Ph_4As^+.[25] The similar solubilities of large polar molecules like ferrocene, *tert*-butyl chloride (Table VI), and 4-iodonitrobenzene[2] in dipolar aprotic solvents of $\epsilon > 25$ and in ether, hexane, and dioxane of $\epsilon < 5$ make it obvious that $\Delta G_{tr}(RX)$ and $\Delta G_{tr}(M^0)$ are <±5 kJ mol^{-1}. Thus $\Delta G_{tr}(M^+)$ is greater than $\Delta G_{tr}(M^0)$ for transfer from high to very low dielectric solvents and the assumption which reduces eq 23 to eq 18 breaks down for such transfers. Then $\Delta G^{\ddagger}_{tr}(S_N1)$, as observed, is more positive (i.e., solvolysis is slower) than predicted by eq 17 and 18 in Table V for solvolysis in ether, acetic acid, and trifluoroacetic acid.

The problem is accentuated by uncertainties as to whether acceptor numbers fully reflect the poor anion solvating power of very low dielectric solvents (Table II), so that other types of correlation may be more successful for such solvents.[15]

Despite these difficulties, three points should be emphasized: eq 17 and 18 correlate rates of this solvolysis to within 3 kJ for 10 of the 13 solvents in Table V, covering 27 kJ mol^{-1} in $\Delta G^{\ddagger}_{tr}(S_N1)$. It is notable that eq 18 correlates solvolysis in pyridine, a solvent of only moderate dielectric constant (12.3) and a strong cation solvator of high donor number. Despite its low dielectric constant and very weak cation solvating properties (Table II), *solvolysis in trifluoroacetic acid is much faster than in any other solvent considered in this paper*. The success of this anion solvator par excellence reemphasizes the overwhelming importance of anion solvating properties in determining rates of this type of solvolysis.

(B) *tert*-Butyl Chloride. Values of $\Delta G^{\ddagger}_{tr}(S_N1)$ calculated from titrimetric rate constants for *solvolysis* have been shown[39] to represent the free energies of activation for *ionization* of *tert*-butyl chloride, without complications such as ion pair return and rate determining (E2C or other) elimination,[40] in polar high dielectric solvents. This S_N1 transition state is highly polar with about 0.8 unit of positive charge spread mainly over the nine hydrogens of $(CH_3)_3C$ and 0.8 unit of negative charge on chlorine.[3,15] The charge separation is about 2.3 Å.[15] It is important to note that much of the positive charge is spread over nine equivalent hydrogen atoms, which are hard acids, and the developing *tert*-butyl carbonium ion has considerably greater surface charge than the developing cation II of *p*-methoxyneophyl tosylate. This highly polar transition state will respond linearly to the changes in cation and anion solvating power on solvent transfer, so that eq 1, a general expression for S_N1 solvolysis reactions, whether limiting or not, is followed.

Ferrocene-like assumptions do not apply to the solvolysis of *tert*-butyl chloride, but, as discussed, do apply to *p*-methoxyneophyl tosylate. The difference between *tert*-butyl chloride (M^0) and *p*-methoxyneophyl tosylate solvolysis is that the developing *tert*-butyl cation (M^+), like Me_3S^+ and NMe_4^+,[2,3] is small enough and of sufficient surface charge to be solvated in water by the first kind of solvation mechanism,[11,25,38] so $\Delta G_{tr}(M^+)$ does not equal $\Delta G_{tr}(M^0)$ in water or formamide, and eq 1, rather than eq 17 or 18, must be used.

The partial success of eq 17 and 18 (Table VI) in correlating rates of solvolysis of *tert*-butyl chloride suggest that $p\Delta G_{tr}(K^+)$, the cation solvating contribution to $\Delta G^{\ddagger}_{tr}(S_N1)$ in eq 1, is usually negligible.

Equations 1, 17, and 18 are applied in Table VI to the solvolysis of *tert*-butyl chloride, using the anion and cation solvating parameters of Table II and observed values for $\Delta G_{tr}(t\text{-BuCl})$. A value of 0.50 was used for n and 0.65 for n'; these fit eq 17 and 18. A value of 0.20 was chosen for p and 0.28 for p', so as to fit the observed $\Delta G^{\ddagger}_{tr}(S_N1)$ and eq 1. Values of $\Delta G^{\ddagger}_{tr}(S_N1)$ observed and calculated from eq 1, 17, and 18 are in Table VI. Agreement is very satisfactory for eq 1, but as noted, deviations from eq 17 and 18 are observed.

Our value of 0.2 for p is supported by the following argument. Values (Table I) of $\Delta G_{tr}(Me_3S^+)$ and $\Delta G_{tr}(Me_4N^+)$, through eq 9 and p in Table III, suggest the approximate relationship $\Delta G_{tr}(Me_4N^+) \approx \Delta G_{tr}(Me_3S^+) \approx (0.5 \pm 0.1)\text{-}\Delta G_{tr}(K^+)$. It has been suggested that Me_4N^+, and more obviously Me_3S^+, model Me_3C^+ in terms of its response to solvent transfer,[2,3] so that $\Delta G_{tr}(Me_4N^+) = \Delta G_{tr}(Me_3S^+) = \Delta G_{tr}(Me_3C^+) = 0.5\Delta G_{tr}(K^+)$ from eq 9. We have noted (n in Table VI) that the partial chloride ion in the transition state t-$BuCl^{-\ddagger}$ seems to have half the response of a fully solvated chloride ion to solvent transfer. If partial Me_3C^+ has the same relative response as partial Cl^- to the fully solvated ion, then $0.5\Delta G_{tr}(Me_3C^+)^{\ddagger} = [(0.5 \times 0.5) \pm 0.1]\Delta G_{tr}(K^+)$, so that a value of 0.2–0.3 for p in eq 1 is reasonable. Such a value makes $p\Delta G_{tr}(K^+)$ in eq 1 a small, even negligible term. Since $\Delta G_{tr}(t\text{-BuCl})$ in eq 1 also usually is small, the success of the approximate relationships eq 17 and 18, as well as eq 1, in correlating many solvolysis rates of *tert*-butyl chloride is readily explained.

The term $0.5\Delta G_{tr}(Cl^-)$ dominates the right hand side of eq 1, even more so since $0.2\Delta G_{tr}(K^+)$ and $\Delta G_{tr}(t\text{-BuCl})$ in eq 1 are of the same sign (Table II and VI) in most solvents, so that the deviation $0.2\Delta G_{tr}(K^+) - \Delta G_{tr}(t\text{-BuCl})$ of eq 17 and 18 from eq 1 is even smaller than each term. The exception is for transfer to water, where $\Delta G_{tr}(t\text{-BuCl})$ is +18 kJ mol^{-1} and $0.2\Delta G_{tr}(K^+)$ is −2 kJ g-ion^{-1} for transfer from acetonitrile to water, so that eq 17 differs from eq 1 by 20 kJ mol^{-1} in its attempt to correlate $\Delta G^{\ddagger}_{tr}(S_N1)$. Equation 18 is even less successful than eq 17. Likewise, eq 18 gives increasing positive deviations for methanol–water mixtures with increasing water

content, whereas excellent agreement is obtained by eq 1.

Having demonstrated the significance of eq 1 in solvolysis of *tert*-butyl chloride, we note that Abraham also showed the occasional influence of $\Delta G_{tr}(t\text{-BuCl})$ in determining rate and developed a very satisfactory linear free-energy relationship (eq 24 and 25). This effectively uses a partial ion pair, $Me_4N^+Cl^-$, as a model for the transition state $t\text{-BuCl}^{\ddagger}$.[3] Equation 25 is valid for polar high dielectric solvents, but like eq 18, shows deviations for low dielectric solvents. Abraham comments that he finds a *poor* relationship, eq 26. This, via eq 9 with $M^+ = Me_4N^+$, is identical to our relationship eq 1, except for different sensitivities. Abraham did not in fact separate $\Delta G_{tr}(Me_4N^+) + \Delta G_{tr}(Cl^-)$ in eq 26 into individual ionic transfers, and so was forced to allocate the *same* sensitivity to anion and cation solvating properties. Thus he was unable to comment on the relative importance of anion and cation solvation in determining $\Delta G^{\ddagger}_{tr}(S_N1)$. His rejection of eq 26 and adoption of eq 25 lead him to conclude that the S_N1 transition state has a structure between reactants and ion pair, not one between ion pair and solvated, separated ions.[41] This question is not answered by our analysis, despite the apparent implications of eq 1 and 23. As noted, we have more confidence in relationships based on separately determined $\Delta G_{tr}(Cl^-)$ and $\Delta G_{tr}(K^+)$ than in $\Delta G_{tr}(Me_3S^+) + \Delta G_{tr}(Cl^-)$, $\Delta G_{tr}(Cs^+) + \Delta G_{tr}(Cl^-)$,[32] $\Delta G_{tr}(Me_4N^+) + \Delta G_{tr}(Cl^-)$, or $\Delta G_{tr}(Me_4N^+Cl^-)$ from solubility and conductance measurements. This is because of the advantages of potentiometry over solubility methods for determining ΔG_{tr} values of these single ions.[22,23,25]

$$\Delta G_{tr}(t\text{-BuCl}^{\ddagger}) = 0.67\Delta G_{tr}(Me_4N^+Cl) \quad (24)$$

$$\Delta G^{\ddagger}_{tr}(S_N1) = 0.67\Delta G_{tr}(Me_4N^+Cl^-) - \Delta G_{tr}(t\text{-BuCl}) \quad (25)$$

$$\Delta G^{\ddagger}_{tr}(S_N1) \approx 0.39\Delta G_{tr}(Me_4N^+) + 0.39\Delta G_{tr}(Cl^-) - \Delta G_{tr}(t\text{-BuCl}) \quad (26)$$

Equation 18 is not adequate for correlating the effects on $\Delta G^{\ddagger}_{tr}(S_N1)$ of transferring the solvolysis of *tert*-butyl chloride from high dielectric to very low dielectric solvents like ether, dioxane, *n*-heptane, acetic acid, and trifluoroacetic acid. The equations predict faster solvolyses than are observed in these low dielectric solvents and this can be explained in part by eq 1, which introduces a term allowing for the poor cation solvating properties of these solvents. Values of $\Delta G_{tr}(t\text{-BuCl})$ are still negligible (Table VI) for transfer to low dielectric solvents, so eq 1 can be written as the approximate relationship eq 27, which improves the correlation significantly for transfer to DMF, DMA, NMePy, and Me_2SO, which are strong cation solvators. The coefficients in eq 27 for Δ(DN) and Δ(AN) follow from p' and n' (Table III) in eq 11 and 12, respectively. However, as shown in Table II, the relationships eq 11 and 12 which lead to eq 27 are very uncertain for low dielectric solvents, and it is not profitable to use eq 27 for solvolysis rates in ether, heptane, and dioxane.

$$\Delta G^{\ddagger}_{tr}(S_N1) = 0.2\Delta G_{tr}(K^+) + 0.5\Delta G_{tr}(Cl^-) = -0.3\Delta(DN) - 0.72\Delta(AN) \quad (27)$$

In summary, eq 1, 27, 17, and 18 give decreasingly less comprehensive correlations of the rates of solvolysis of *tert*-butyl chloride in different solvents. However, even eq 17 and 18 are satisfactory for transfer through a wide range of solvents, where the combined effects of changes in cation solvation and in solvation of *t*-BuCl can be neglected.

We note the success of the reaction field method in explaining solvolysis rates of *tert*-butyl chloride in a limited number of solvents which are weak anion solvators.[15] However, dipole moment, quadrupole moment, molar volume, and refractive index of the transition state and solutes, coupled with the dielectric constant of the solvent, cannot explain the differences between rates of solvolysis of *tert*-butyl chloride in trifluoroacetic acid and nitrobenzene, trifluoroethanol and ethanol, methanol and dimethylformamide, acetonitrile and acetic acid, and Me_2SO–acetonitrile (Table VI). *Anion* solvating power and *cation* solvating power, as distinct from general electrostatic ion solvating power, must be taken into account when considering solvolysis of *tert*-butyl chloride in a wider range of solvents.[8] Anions and cations have specific and different "chemical" interactions with solvents. No theory based on solvent dielectric constant, dipole moment, quadrupole moment, etc., can hope to be generally applicable to the detailed chemistry of ions in solution.[2,13,25]

(C) *tert*-Butyl Bromide and *trans*-4-*tert*-Butylcyclohexyl Tosylate. The analysis for solvolysis rates of *tert*-butyl bromide, in terms of eq 1, is in Table VI. Since bromide, rather than chloride, is now the leaving group, n is only 0.35, rather than 0.5; i.e., the solvolysis is less sensitive than that of *tert*-butyl chloride to anion solvating power. We use $0.2\Delta G_{tr}(K^+)$, assuming the same sensitivity to cation solvating power for *t*-BuBr and *t*-BuCl. The deviations and the correlations in Table VI can be explained in the same way as for the solvolysis of *tert*-butyl chloride.

The analysis of rates of solvolysis of *trans*-4-*tert*-butylcyclohexyl tosylate (ROTs) at 75 °C (Table VII)[42,43] can only be semiquantitative at this time, because $\Delta G_{tr}(ROTs)$ is unknown and there are insufficient data points fitting eq 1 to give accurate values of n and n'. Despite these difficulties, the analysis in Table VII is worthwhile, especially because the data are for solvolysis at a secondary carbon atom. Tables V–VII show three situations. Table V analyzes data for solvolysis at a primary carbon atom, *with full participation from a neighboring 4-methoxyphenyl group.* There is a requirement for extensive solvation of the leaving tosylate ($n' = 0.52$). Table VI analyzes data for solvolysis at the tertiary carbon with less sensitivity to anion solvating power, and Table VII analyzes data for solvolysis of a secondary tosylate, with some neighboring hydrogen participation.[43] Table VII shows a partial analysis in terms of eq 1 and a full analysis in terms of eq 18, with $n' = 0.5$ for this tosylate, as determined by the "fit" for ethanol, nitromethane, acetonitrile, acetone, and acetic acid. Knowing $n'\Delta$(AN) and $\Delta G^{\ddagger}_{tr}(S_N1)$ allows calculation of $p\Delta G_{tr}(K^+) - \Delta G_{tr}(ROTs)$, as shown in Table VII. We expect[2,3] $\Delta G_{tr}(ROTs)$ for transfer through the solvents of Table VII to be no more than ± 2 kJ mol^{-1}, so the significant deviations from eq 18 of up to 14 kJ mol^{-1} for solvolysis in CF_3CO_2H, and ca. -8 kJ mol^{-1} for solvolysis in Me_2SO and DMF are due to a stronger sensitivity of this solvolysis to cation solvating power. As shown in Table VII, a value of $\sim 0.4\Delta G_{tr}(K^+) - 0.5\Delta$(AN) fits the observed values of $\Delta G^{\ddagger}_{tr}(S_N1)$ to eq 1 with modest success. Certainly the need to take account of the cation solvating power of the solvents is apparent for solvolysis of this tosylate.

In summary, the sensitivity to cation solvating power (Table II) of the solvolysis of *p*-methoxyneophyl tosylate (0.1), *tert*-butyl chloride (0.2), and *trans*-4-*tert*-butylcyclohexyl tosylate (0.4) increases in the order of p values (eq 1) shown in parentheses. Thus eq 17 and 18 (i.e., eq 3) are very satisfactory for correlating rates of solvolysis of *p*-methoxyneophyl tosylate, are of some value for correlating solvolysis of the *tert*-butyl halides, but are likely to be of very limited value for solvolysis of secondary halides and tosylates.

The expression $\Delta G^{\ddagger}_{tr} = \pm n\Delta G_{tr}(Cl^-) = \mp n'\Delta$(AN) is a very useful "rule of thumb" for estimating solvent effect on rates of S_N1 and S_N2 reactions of the charge type shown. Care is necessary when considering reactions in structured solvents like water and formamide.

Acknowledgment. This paper was written while one of us (A.J.P.) was a visiting Professor at the Technical University

Vienna. Support by the Bundesministerium für Wissenschaft und Forschung is gratefully acknowledged.

References and Notes

(1) R. Alexander, E. C. F. Ko, A. J. Parker, and T. J. Broxton, *J. Am. Chem. Soc.*, **90**, 5049 (1968).
(2) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).
(3) M. H. Abraham, *J. Chem. Soc., Perkin Trans 2*, 1343 (1972).
(4) M. H. Abraham, *Prog. Phys. Org. Chem.*, **11**, 2 (1974).
(5) E. M. Arnett, W. G. Bentrude, J. J. Burke, and P. Mc.C. Duggleby, *J. Am. Chem. Soc.*, **87**, 1541 (1965).
(6) B. G. Cox and A. J. Parker, *J. Am. Chem. Soc.*, **95**, 408 (1973).
(7) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, N.Y., 1963.
(8) W. R. Fawcett and T. M. Krygowski, *Aust. J. Chem.*, **28**, 2115 (1975).
(9) I. A. Koppel and V. A. Palm, "Advances in Linear Free Energy Relationships", N. B. Chapman and J. Shorter, Ed., Plenum Press, New York, N.Y., 1972, Chapter 5.
(10) B. G. Cox and A. J. Parker, *J. Am. Chem. Soc.*, **95**, 402 (1973).
(11) B. G. Cox, G. R. Hedwig, A. J. Parker, and D. W. Watts, *Aust. J. Chem.*, **27**, 477 (1974).
(12) U. Mayer, V. Gutmann, and W. Gerger, *Monatsh. Chem.*, **106**, 1235 (1975).
(13) T. M. Krygowski and W. R. Fawcett, *J. Am. Chem. Soc.*, **97**, 2143 (1975).
(14) U. Mayer, *Pure Appl. Chem.*, **41**, 291 (1975).
(15) M. H. Abraham and R. J. Abraham, *J. Chem. Soc., Perkin Trans. 2*, 47 (1974).
(16) V. Gutmann, "The Donor Acceptor Approach to Molecular Interactions", Plenum Press, New York, N.Y., 1978.
(17) V. Gutmann, *Electrochim. Acta*, **21**, 661 (1976).
(18) U. Mayer, *Monatsh. Chem.*, in press.
(19) V. Gutmann and R. Schmid, *Coord. Chem. Rev.*, **12**, 263 (1974).
(20) R. Alexander, A. J. Parker, J. H. Sharp, and W. E. Waghorne, *J. Am. Chem. Soc.*, **94**, 1148 (1972).
(21) One of us (A.J.P.) has recalculated $\Delta G_{tr}(X^-)$ from $\Delta G_{tr}(AgX)$ in ref 11 and $20 - \Delta G_{tr}(Ag^+)$ TATB in ref 11 and 22. The results in Tables I and II for anions thus update $\Delta G_{tr}(X^-)$ in ref 20.
(22) D. A. Owensby, A. J. Parker, and J. W. Diggle, *J. Am. Chem. Soc.*, **96**, 2682 (1974).
(23) A. J. Parker, a survey of ΔG_{tr}(cation) measured by solubility, potentiometry, and polarography and converted to TATB assumed values: submitted for publication.
(24) R. Alexander, D. A. Owensby, A. J. Parker, and W. E. Waghorne, *Aust. J. Chem.*, **27**, 933 (1974).
(25) A. J. Parker, *Electrochim. Acta*, **21**, 671 (1976).
(26) E. C. F. Ko and A. J. Parker, *J. Am. Chem. Soc.*, **90**, 6447 (1968). In a loose S_N2 transition state, Y and X are loosely bound to carbon and negative charge is localized on Y and X. There is positive charge on carbon. In a tight transition state, negative charge is dispersed over Y, C, and X with both X and Y interacting strongly with carbon. Thus one observes a spectrum of transition states between tight $Y^{\delta-}CH_3^{\delta-}X^{\delta-}$ and loose $Y^- \cdots {}^+CH_3 \cdots X^-$.
(27) E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, **70**, 846 (1948).
(28) S. Winstein, E. Grunwald, and W. H. Jones, *J. Am. Chem. Soc.*, **73**, 2700 (1951).
(29) A. H. Fainberg and S. Winstein, *J. Am. Chem. Soc.*, **78**, 2770 (1956).
(30) S. G. Smith, A. H. Fainberg, and S. Winstein, *J. Am. Chem. Soc.*, **83**, 618 (1961).
(31) F. L. Schadt, T. W. Bentley, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **98**, 7667 (1976).
(32) E. S. Rudakov, *Dokl. Akad. Nauk SSR*, **212** (2), 417 (1973).
(33) E. D. Hughes and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 603 (1941); *ibid.*, **37**, 657 (1941).
(34) Our discussion is for pure solvents, but we see no reason why, once donor and acceptor numbers and ΔG_{tr}(ion) values become available, the same equations will not apply to mixed solvents. It is not possible to predict donor, acceptor, or ΔG_{tr}(ion) values in mixtures from linear functions of the pure solvent components. Solvent–solvent interactions effectively make each mixture a new solvent, not a mixture with the properties of each component.
(35) A. J. Parker and R. Alexander, *J. Am. Chem. Soc.*, **90**, 3313 (1968).
(36) H. M. Koepp, H. Wendt and H. Strehlow, *Z. Elektrochem.*, **64**, 483 (1960).
(37) G. Gritzner, V. Gutmann, and R. Schmid, *Electrochim. Acta*, **13**, 919 (1968).
(38) H. G. Hertz, *Angew. Chem., Int. Ed. Engl.*, **9**, 124 (1970).
(39) D. J. Raber, R. C. Bingham, J. M. Harris, J. L. Fry, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **92**, 5977 (1970).
(40) A. J. Parker, M. Ruane, D. A. Palmer, and S. Winstein, *J. Am. Chem. Soc.*, **94**, 2228 (1972).
(41) Our approximate but usually adequate relationships eq 17 and 18 use parameters which are widely available and more easily obtained than $\Delta G_{tr}(Me_4N^+Cl^-)$ n eq 25. However, eq 25 is a landmark[3] in the development of our understanding of this classical solvolysis reaction.
(42) P. Beltrame, G. Biale, D. J. Lloyd, A. J. Parker, M. Ruane, and S. Winstein, *J. Am. Chem. Soc.*, **94**, 2240 (1972).
(43) A. F. Diaz, I. Lazdins, and S. Winstein, *J. Am. Chem. Soc.*, **90**, 1904 (1968).

Analytical Solution to the Curtin–Hammett/Winstein–Holness Kinetic System[1]

Jeffrey I. Seeman* and William A. Farone*

Philip Morris Research Center, Richmond, Virginia 23261

Received October 18, 1977

The analytical solution is presented for the kinetic scheme involving a starting material which exists in two isomeric forms, each of which reacts via first-order or pseudo-first-order kinetics to give a different product. This kinetic scheme has been approximated by the well-known Curtin–Hammett (C–H) principle (in terms of product ratios) and by the Winstein–Holness (W–H) equation (in terms of reaction rate). The versatility of the exact solution is discussed especially with regard to the range of validity of the C–H/W–H approximations.

Conformational analysis commands a central role in the understanding of the physical properties and the chemical reactivity of molecules.[2] Almost 25 years ago, Curtin and Hammett,[3] Winstein and Holness,[4] and Eliel and Ro[5] independently considered the chemical consequences of a system in which the starting material exists in two distinct equilibrating forms, each reacting to give a different product (Scheme I).[6]

Scheme I

$$A_1 \xleftarrow{k_{21}} A_2 \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} A_3 \xrightarrow{k_{34}} A_4$$

Two principles dealing with this kinetic scheme were advanced. The Curtin–Hammett (C–H) principle stated that the ratio of the products formed "depends only on the relative energy levels of the transition states by which the products are formed, provided that the activation energy for product formation is large compared to the activation energy for the interconversion of the isomeric starting materials"[7] (eq 1).[8] The Winstein–Holness (W–H) equation approximated the overall rate constant for total product formation as the time-independent quantity shown in eq 2.[4,5,9]

$$\frac{A_4}{A_1} = \frac{k_{23}}{k_{32}}\frac{k_{34}}{k_{21}} = K\frac{k_{34}}{k_{21}} \tag{1}$$

$$k_{WH} = \frac{k_{34}K + k_{21}}{K + 1} \tag{2}$$

The Winstein–Holness relationship and the Curtin–Hammett principle have been valuable approximations be-

0022-3263/78/1943-1854$01.00/0

cause they allow the use of simplified expressions to describe rate and product composition phenomena. The assumption used in both of these treatments is the same, that is, the rate constants for interconversion between the conformational isomers, k_{23} and k_{32}, are significantly larger than the rate constants for reaction, k_{21} and k_{34}.

While the W–H relationship refers to reaction rates and the C–H principle refers to product ratio composition, the two are indeed fundamentally related to each other. These relationships have been extensively used in the literature although only qualitative arguments have been proposed to support the decision to use, or not to use, these relationships for any particular chemical system. We now report the analytical mathematical solution[10] (eq 3–14) to Scheme I and an analysis of the range of validity of the C–H/W–H approximations. This exact solution allows the determination of the concentration of reactants and products (A_i) (C–H principle) and permits the calculation of the rates of formation of A_1 and A_4 (W–H equation), both as a function of time. The exact solution is valid for any system which is represented by Scheme I,[6a] and we will demonstrate its usefulness by delineating the range of k_{ij} which will result in C–H/W–H kinetics and by elucidating those parameters which control the observed kinetics.[11]

$$A_1(t) = bk_{21}e^{\alpha t}/\alpha + k_{21}Ce^{\beta t}/\beta + (A_{10} - bk_{21}/\alpha - k_{21}C/\beta) \quad (3)$$

$$A_2(t) = be^{\alpha t} + Ce^{\beta t} \quad (4)$$

$$A_3(t) = de^{\alpha t} + he^{\beta t} \quad (5)$$

$$A_4(t) = dk_{34}e^{\alpha t}/\alpha + hk_{34}e^{\beta t}/\beta + (A_{40} - dk_{34}/\alpha - k_{34}h/\beta) \quad (6)$$

$$\alpha = [-\Omega + (\Omega^2 - 4\Delta)^{1/2}]/2 \quad (7)$$

$$\beta = [-\Omega - (\Omega^2 - 4\Delta)^{1/2}]/2 \quad (8)$$

$$\Omega = k_{21} + k_{23} + k_{34} + k_{32} \quad (9)$$

$$\Delta = k_{21}k_{34} + k_{21}k_{32} + k_{23}k_{34} \quad (10)$$

$$d = bk_{23}/(\alpha + k_{34} + k_{32}) \quad (11)$$

$$h = Ck_{23}/(\beta + k_{34} + k_{32}) \quad (12)$$

$$C = [A_{30} - A_{20}k_{23}/(\alpha + k_{34} + k_{32})]/k_{23}[1/(\beta + k_{34} + k_{32}) - 1/(\alpha + k_{34} + k_{32})] \quad (13)$$

$$b = A_{20} - C \text{ where } A_{i0} = \text{initial concn of } i \quad (14)$$

The C–H/W–H approximations are valid when $A_3/A_2 = k_{23}/k_{32}$ and is time independent. This relationship implies both eq 1 and 2. The validity of either eq 1 or 2 also implies that A_3/A_2 is constant. More complex results are obtained for sets of k_{ij} for which these requirements are not met. For a system involving non-C–H kinetics, both A_4/A_1 and A_3/A_2 will be time dependent. Thus, a simple experimental test for C–H and W–H kinetics involves the examination of the time dependency of the product mixture and/or the ratio of starting isomers.[6b]

For the purpose of evaluating deviation from C–H kinetics, we have defined the terms Δ_{CH} (eq 15) and Δ_{WH} (eq 16).[6b]

$$\Delta_{CH} = \frac{K(k_{34}/k_{21}) - A_4/A_1}{A_4/A_1} \times 100 \quad (15)$$

$$\Delta_{WH} = \frac{k_{WH} - k_{obsd}}{k_{obsd}} \times 100 \quad (16)$$

$$k_{obsd} = \frac{d(A_1 + A_4)}{dt}(A_2 + A_3)^{-1}$$

For Scheme I kinetics, the absolute magnitude of Δ_{CH} and Δ_{WH} either is close to zero at all times or increases in absolute magnitude monotonically to a limiting value with increasing reaction percentage. It is convenient to arbitrarily assign any value of $|\Delta_{CH}| \geq 5$ and any value of $|\Delta_{WH}| \geq 5$ as non-C–H and non-W–H, respectively. This value was based on a assumed experimental error of 5% expected for many reactions. The maximum value of Δ_{CH} is at reaction completion and was evaluated at infinite time in this work. However, Δ_{WH} is (1) meaningless at $t = \infty$ since the reaction is complete and (2) useless at $t = 0$ since it is exactly zero for all values of the rate constants at 0% conversion. This latter observation indicates that there is no deviation from W–H kinetics at $t = 0$, regardless of the values of k_{ij}, even though major deviations can occur as soon as the reaction begins.

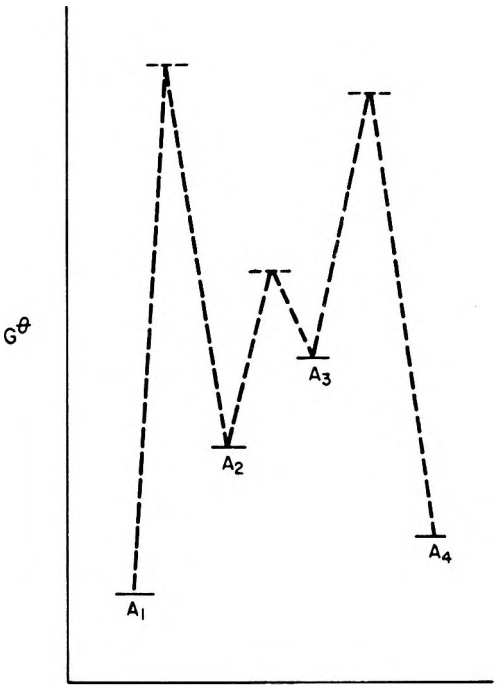


Figure 1. The relative free energies of A_i and the free energies of activation per mole for Scheme I systems when $k_{21} < k_{23} < k_{32}$ and $k_{34} < k_{32}$ (case I).

The chemistry involved in Scheme I kinetics can be illustrated by examining the extreme kinetic situations as shown in Figures 1 and 8. These figures, patterned after the recent observations of Cruickshank et al.,[13] represent the free energy of 1 mol of each of the states concerned without reference to either reaction progress or time; i.e., the horizontal spacing is drawn as such for convenience only. Real chemical compounds are represented by solid lines while transition states are represented by broken lines.

Case I (Figure 1). When $k_{21} \leq k_{23} \leq k_{32}$ and $k_{34} \leq k_{32}$, then eq 3–14 can be used to calculate the reaction profile (cf. Figure 2) and it is possible to compare the results with those obtained using the C–H/W–H approximations. We choose a simplifying procedure to enable us to make these evaluations. A set of values for k_{23} and k_{32} was chosen; then, k_{21} and k_{34} were each varied over eight orders of magnitude in 32 steps. For each set of four rate constants, A_4/A_1 at $t = \infty$ and k_{obsd} at a predetermined reaction time were calculated using eq 3–14. The percentage reaction at this reaction time was also calculated. From these values, Δ_{CH} and Δ_{WH} were determined. These results were automatically tabulated or could be more conveniently displayed in a 40 × 40 matrix grid, the x and y coordinates being k_{21} and k_{34} and the out-of-plane z coordinate being either Δ_{CH} or Δ_{WH}.

For case I kinetics, as for most of the cases that follow Scheme I, certain sets of k_{ij} can result in $\Delta_{CH} \simeq 0$ although

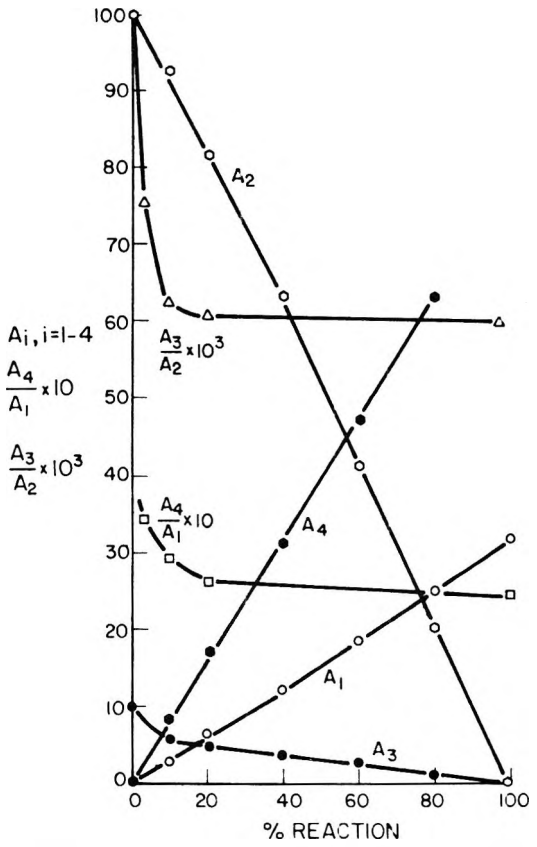


Figure 2. Values of A_i (i = 1–4), A_4/A_1, and A_3/A_2 as a function of percent reaction when $k_{21} = 1.0 \times 10^{-4}$, $k_{23} = 5.64 \times 10^{-4}$, $k_{32} = 5.64 \times 10^{-3}$, and $k_{34} = 4.0 \times 10^{-3}$. Note that A_3/A_2 and A_4/A_1 are both time dependent. The very low value of A_3 at >40% reaction indicates that A_4, which increases continuously throughout the course of the entire reaction, originates actually form A_2.

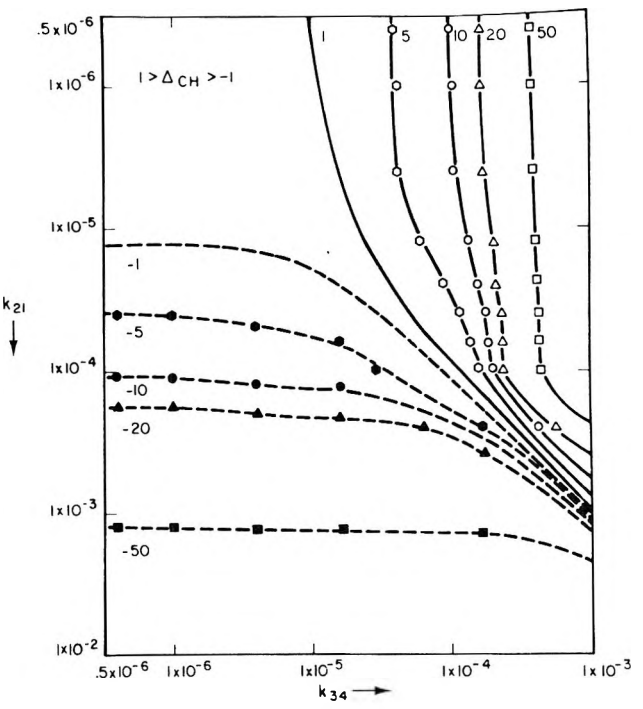


Figure 3. Δ_{CH} contours determined at 100% reaction as a function of k_{21} and k_{34} when $k_{23} = k_{32} = 5.64 \times 10^{-4}$. Note that multiplication of all the k_{ij} by the same constant does not change Δ_{CH}.

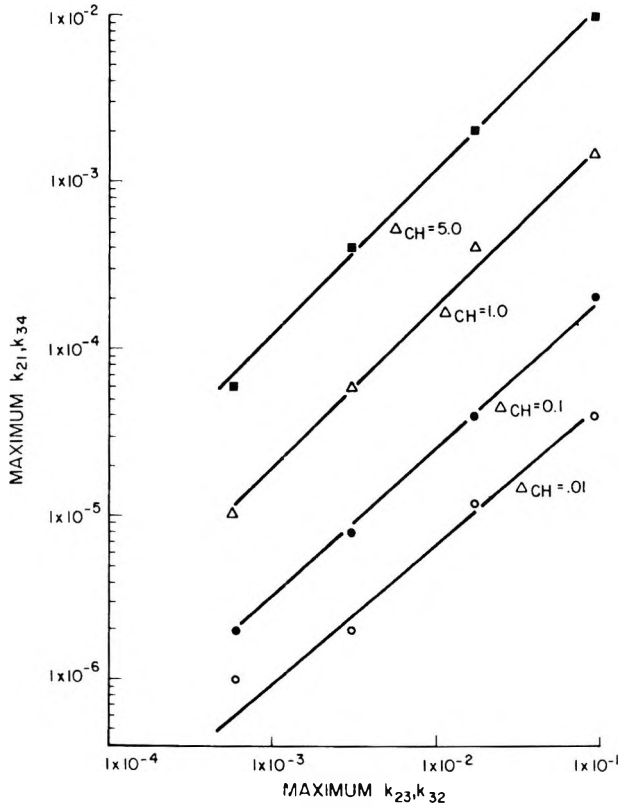


Figure 4. Maximum allowable values of k_{21} and k_{34} as a function of Δ_{CH} when $k_{23} = k_{32}$.

one or more of the basic assumptions seems not to apply. For example, $\Delta_{CH} \simeq 0$ when $k_{21} \simeq k_{34}$, regardless of the values of k_{23} and k_{32}. In this situation the agreement with the C–H/W–H approximations is due to a mathematical degeneracy in the definition of Δ_{CH} and Δ_{WH} and not to a kinetic result which is consistent with the C–H/W–H postulates.

As seen in Figure 3, this results in the diagonal of the matrix becoming identically zero. Results similar to this for other choices of k_{ij} also have zero lines. The zero lines are not always along the diagonal of the matrix but always appear close to it (see below), due to the lack of symmetry caused by $k_{23} \neq k_{32}$ in these cases. The rate of change of Δ_{CH} perpendicular to the matrix diagonal is dependent on the location in the figure, being generally much smaller in absolute magnitude the closer to the upper left-hand corner. This is because the C–H approximation is valid in this region of k_{ij}'s. It should be noted that the values of Δ_{CH} and Δ_{WH} are not symmetrical with an interchange of variables due to the selection of the exact solution as the reference in eq 15 and 16.

For case I kinetics, examination of a wide range of values of $k_{23} = k_{32}$ as described above led to the interesting observation that $\Delta_{CH} < 5$ when $k_{23} > 10k_{21}$ (note that $k_{21} < k_{34}$). Figure 4 illustrates the maximum value of k_{21} as a function of Δ_{CH}. It is interesting that a series of parallel lines results, indicating that similar deviations from C–H kinetics will be obtained for a set of rate constants having the same relative magnitudes proportional to one another.

As k_{34} approaches k_{32} in magnitude. Δ_{CH} increases steadily. When $k_{34} > 0.1\ k_{32}$, then $\Delta_{CH} > 5$. In conclusion, it generally *appears that when the rate of reaction from the less stable of the two isomers (A_2 or A_3) is greater than 0.1 times as fast as the rate of conversion of that compound to its isomer the C–H/W–H kinetics will not approximate the actual chemistry observed.* As k_{34} gets progressively smaller with respect to k_{32}, k_{21} can approach the value of k_{23} and still allow the resultant system to follow the C–H/W–H approximations.

It is interesting that the conclusions from the previous paragraph are valid even when k_{21} approaches, and in some cases is even greater than, k_{23}. This indicates the strong role

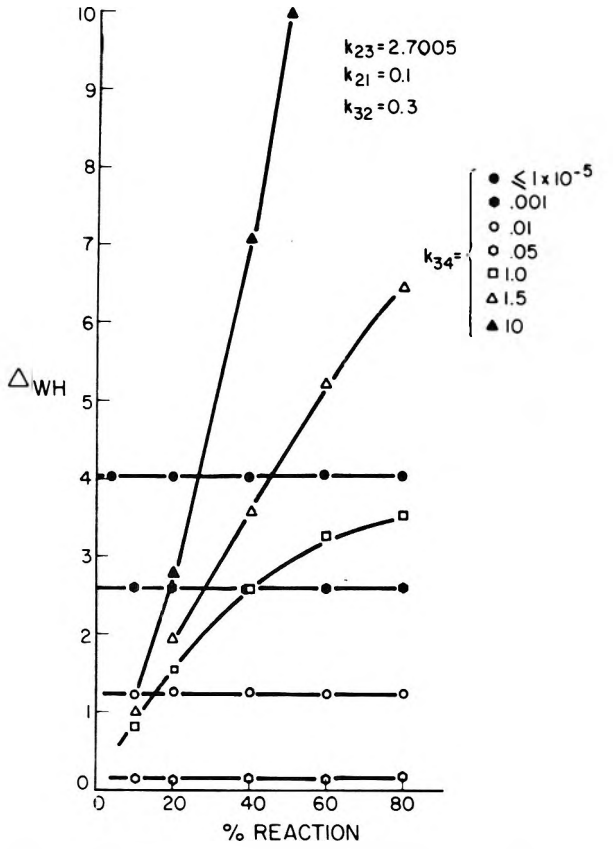


Figure 5. The dependency of Δ_{WH} as a function of reaction completion for sets of k_{ij}. Note that multiplication of all the k_{ij} by the same factor will not change the dependencies shown in this figure but will only change the relationship between percentage completion and time.

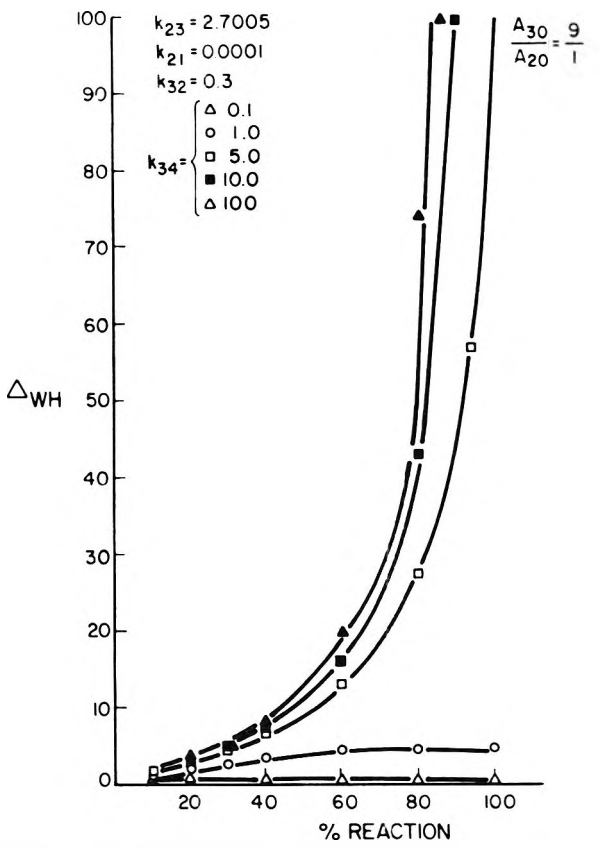


Figure 6. The dependency of Δ_{WH} as a function of reaction completion for sets of k_{ij}. Compare with Figure 5.

that the $A_3 \rightarrow A_4$ transformation exerts on the reaction profile under these special relationships between the k_{ij}'s. The larger k_{32} is with respect to k_{23}, the larger k_{21} can become with respect to k_{23} and still fall within the C–H/W–H approximations. This observation can be explained by realizing that significantly smaller amounts of A_3 with respect to A_2 are available for reaction.

As discussed above Δ_{WH} will be reaction percentage dependent, and this is illustrated in Figures 5 and 6 for sets of case I kinetics. A strong percentage reaction dependency does exist, and the greater the variation from W–H kinetics, the greater the dependency becomes. Thus, when the limiting value of Δ_{WH} is small, the asymptotic value is reached early in the reaction. This observation is a crucial simplifying factor in our comparison of Δ_{CH} and Δ_{WH} as criteria for the kinetic systems.

Since one of the major assumptions in the derivation of both C–H and W–H kinetics is that $k_{23},k_{32} \gg k_{21},k_{34}$, i.e., A_3/A_2 is constant throughout the reaction, it was expected that Δ_{CH} and Δ_{WH} would qualitatively mirror each other in response to variation in the choice of k_{ij}. Such a comparison, however, is complicated by the time dependency discussed at length above; nonetheless, Δ_{CH} and Δ_{WH} did match each others dependence on the set of k_{ij}.

Figures 5 and 6 represent cases having the same k_{23}, k_{32}, and k_{34}, but $k_{21} = 0.1$ in Figure 5 and $k_{21} = 1 \times 10^{-4}$ in Figure 6. Note that Δ_{WH} is independent of percent reaction for certain values of k_{ij} indeed for those values which correspond to C–H kinetics. Also note the degeneracy found in Δ_{WH} (Figure 5), similar to the degeneracy found in Δ_{CH} and discussed above. Also, lowering k_{34} below a certain point in each of these cases has no effect on Δ_{WH}, i.e., Δ_{WH} reaches a limiting value. A comparison of Figures 5 and 6 indicates the important controlling features in W–H kinetics. For example, Figure 5 shows the degeneracy at $k_{34} \simeq 0.05$ (i.e., where Δ_{WH} reaches a minimum value) and the kinetics become strongly non-W–H for $k_{34} \simeq 1$. On the other hand, Figure 6 indicates the degeneracy at $k_{34} \simeq 1 \times 10^{-4}$ but the kinetics are well approximated by W–H for $k_{34} \simeq 1$. Clearly, Figure 6 kinetics are a closer fit to the W–H kinetics than Figure 5 kinetics. This is because the lower value for k_{21} in Figure 6 kinetics biases the system to favor the approximations made in deriving the C–H/W–H equations.

When Δ_{CH} and $\Delta_{WH} \gg 5$, these terms become quantitatively meaningless in a practical sense. The deviations from an assumed kinetics situation for sets of k_{ij} are so great that only qualitative meaning can be placed on large values of these terms. A detailed analysis of non-C–H/W–H kinetics can best be done by the examination of the dependency of A_i as a function of time (percent reaction).

A very large percentage of the literature which cites the Curtin–Hammett principle and/or the Winstein–Holness equation is related to kinetic systems illustrated by case I kinetics. For example, two conformations of the starting material having unequal free energies of formation each give a different product at rates significantly slower than their rates of interconversion. This is illustrated by considering the interconversion–alkylation of the nicotine analogue, 1-methyl-2-phenylpyrrolidine, shown in Scheme II.[14] If $k_{2\rightarrow3},k_{3\rightarrow2} \gg k_{2\rightarrow1},k_{3\rightarrow4}$, then [4]/[1] and [3]/[2] are expected to be constant throughout the course of the reaction and the C–H/W–H approximations are expected to be valid.

Estimates of the rates and barriers for the nitrogen inversions shown in Scheme II can be made on the basis of low-temperature NMR results and strong acid kinetic quenching of the **2** ⇄ **3** mixture. Kinetic studies of the iodomethylation of **2** ⇄ **3** using well-established conductometric techniques allow the determination of the overall pseudo-first-order rate constant for alkylation, and ^2H NMR analysis of the total

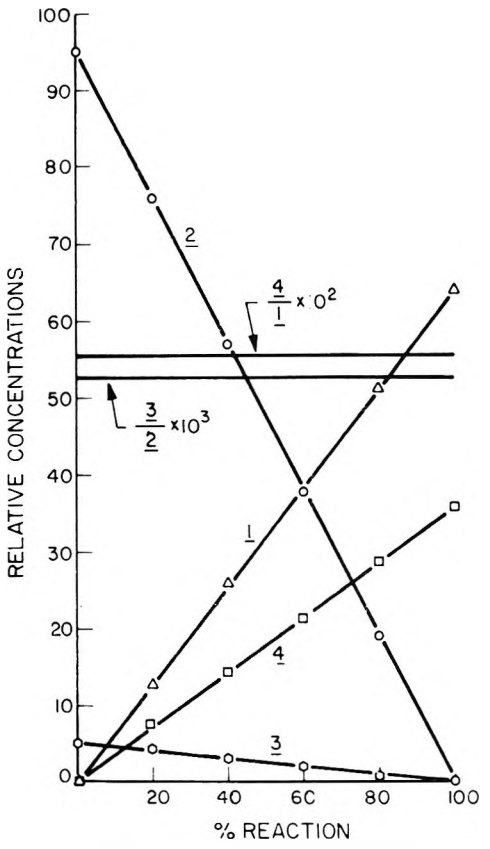
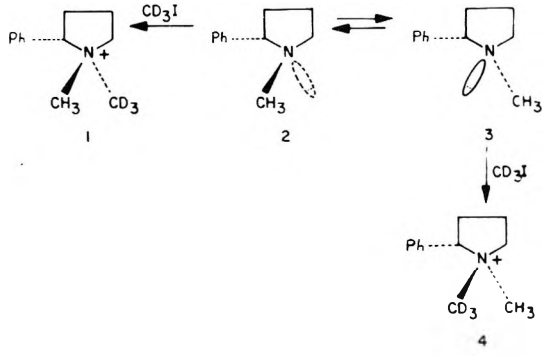


Figure 7. The relative concentrations of 1–4 (see Scheme II) and the ratios of starting materials (3/2) and products (4/1) where $k_{2\rightarrow1} = 3.24 \times 10^{-4}$, $k_{3\rightarrow4} = 3.45 \times 10^{-3}$, $K = k_{2\rightarrow3}/k_{3\rightarrow2} = 5.26 \times 10^{-2}$, and $k_{3\rightarrow2}/k_{3\rightarrow4} > 20$.

Scheme II



reaction mixture resulting from deuteroiodomethylation allowed the determination of the value of 4/1. These determinations allowed the estimates for the rate constants shown in the caption of Figure 7.[14]

The rate constants and subsequent kinetic analysis using the exact solution for Scheme II are shown in Figure 7, which illustrates the compositions and ratios of conformers and products of Scheme II for 1–95% conversion representing over 60 h of reaction time. As expected, 3/2 and 4/1 are clearly time independent. While the rates of isomer interconversion are considerably greater than the rates of alkylation, a time dependency in both the product ratio 4/1 and the "overall rate constant" k_{WH} occurs only at *very low* conversion. This is reasonable, since a small time delay will be required following the initiation of the reaction to allow reequilibration of the isomers. The size of this time delay will be very dependent on the closeness to the C–H/W–H approximations. Thus, no sets of k_{ij} will exactly be described by the C–H/W–H approximations.

A number of kinetic situations can be postulated which by inspection fail to meet the C–H/W–H criteria. Included in these are case II ($k_{23} \leq k_{32} < k_{21}$ and $k_{34} < k_{32}$) and case III ($k_{21} < k_{23} < k_{32} < k_{34}$). Examples of cases II and III in chemical systems in which the $A_2 \rightleftarrows A_3$ represents conformational interconversion are rare, and we will not examine these systems in detail. Suffice it to say that eq 3–14 can be used expeditiously to derive the k_{ij} from kinetic data in these cases. It should be pointed out that systems involving more complex chemical reactions between A_2 and A_3 can be solved exactly using eq 3–14 (see below).

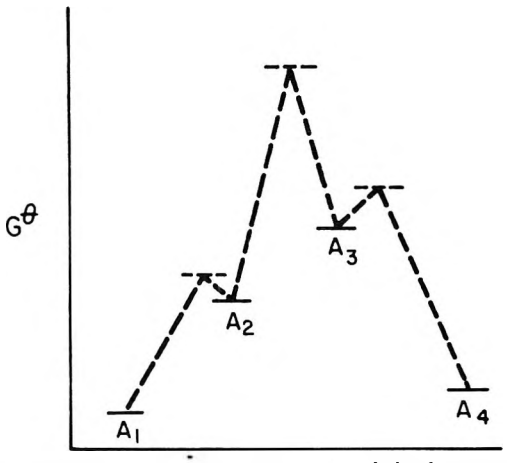


Figure 8. The relative free energies of A_i and the free energies of activation per mole for Scheme I systems when $k_{23} \leq k_{32} < k_{21}$ and k_{34} (case IV).

Case IV (Figure 8; $k_{23} < k_{32} < k_{21}$ and k_{34}). In this case, both reaction rates are greater than the rates of interconversion, and non-C–H/W–H kinetics will be obtained. This case is particularly interesting in that it describes a number of important chemical situations generally labeled as "the fast chemical reaction technique".[15]

The object of this technique is often to determine the conformational equilibrium value for a compound existing in more than one form *and not* to analyze the compound's reactivity. Indeed, assumptions are made with respect to the compound's chemical reactivity and these are basic to the method.

McKenna has described five kinetic cases, three involving intermolecular reactions and two involving intramolecular reactions.[15b] The exact mathematical solution to Scheme I allows a more detailed examination of a number of McKenna's cases. For example, McKenna's case 5 is similar to our case IV in that one is dealing with an intramolecular reaction in which $k_{23},k_{32} \ll k_{21},k_{34}$ (often termed "diffusion controlled"). McKenna concludes that $A_4/A_1 = k_{32}/k_{23}$ even if $k_{21} \neq k_{34}$. An examination of Table I reveals how the exact solution of Scheme I places a more quantitative relationship between the rate constants involved in case IV kinetics.

Consider the situations involving conformational isomers having $\Delta H^{\ddagger}_{inv} = 6$, 10, and 18 kcal/mol being subjected under Scheme I. A number of observations can be made.[6b]

(1) When $\Delta H^{\ddagger}_{inv}$ is sufficiently small and $A_{23} = A_{32}$[6b] is sufficiently large so that $k_{23},k_{32} > 10k_{21},10k_{34}$, then $A_4/A_1 = K(k_{34}/k_{21})$, exactly as expected under C–H conditions (see case I above). For example, the barrier of inversion for nicotine is ca. 6 kcal/mol.[14] According to Table I, lines 1–3, the C–H approximation is valid, A_4/A_1 is time independent, and a kinetic discrimination between the formation of A_1 and A_4 could be directly observed in the product ratio.

(2) When $k_{21},k_{34} \gg k_{23},k_{32}$ (Table I, lines 7–9), then the kinetic system behaves as if A_2 and A_3 are not interconvertible; i.e., the reaction to product occurs so quickly that any depletion of either A_2 (or A_3) would not be replenished from

Table I. Scheme I Kinetics under Fast Chemical Reaction Conditions[c]

Line	k_{21}	k_{23}[a]	k_{32}[a]	k_{34}	$E_{0,inv}$, kcal mol^{-1}	A_4/A_1[b] 10% rxn	50% rxn	94% rxn	100% rxn
1	1×10^{12}	1.15×10^{13}	1.03×10^{14}	1×10^{12}	6	0.111	0.111	0.111	0.111
2	2×10^{12}			1×10^{12}		0.056	0.056	0.056	0.056
3	1×10^{12}			2×10^{12}		0.222	0.222	0.222	0.222
4	1×10^{12}	1.31×10^{10}	1.18×10^{11}	1×10^{12}	10	0.111	0.111	0.111	0.111
5	2×10^{12}			1×10^{12}		0.056	0.065	0.090	0.105
6	1×10^{12}			2×10^{12}		0.211	0.171	0.124	0.118
7	1×10^{12}	1.71×10^{4}	1.54×10^{5}	1×10^{12}	18	0.111	0.111	0.111	0.111
8	2×10^{12}			1×10^{12}		0.057	0.065	0.092	0.111
9	1×10^{12}			2×10^{12}		0.212	0.170	0.118	0.111

[a] Determined using eq 18 with $A = 1 \times 10^{15}$ at 298.16 K. Note that multiplication of all the k_{ij} by the same number changes the product composition with respect to time but not with respect to percent reaction. [b] $A_{30}/A_{20} = k_{23}/k_{32} = 0.11$. [c] Note ref 6.

A_3 (or A_2). Thus, even if $k_{21} \neq k_{34}$, kinetic discrimination will be observed, but only prior to reaction completion. It is interesting to note that A_4/A_1 will be time dependent but equal to $K = k_{23}/k_{32}$ at 100% reaction. Reactivity of this sort may be expected from isomers such as *cis*- and *trans*-*N*-alkyl-2-arylaziridines, known to have $\Delta H^{\ddagger}_{inv} = 18$ kcal/mol.

(3) When $k_{21},k_{34} \sim k_{23},k_{32}$ (Table I, lines 4–6), an intermediate kinetic response is obtained. Neither the C–H approximation nor the kinetic quenching formulation describe A_4/A_1. Here, a kinetic discrimination for reaction can be determined only by application of the exact solution to Scheme I kinetics. This would require, for example, the determination of $K = k_{23}/k_{32}$ and A_4/A_1 at 100% reaction. These experimental values and the application of a numerical technique such as the Newton–Raphson method for extracting roots of an equation would allow the evaluation of k_{34}/k_{21} for the intermediary case.

(4) It is interesting to note that for the examples shown in Table I, lines 1–9, A_4/A_1 at low (<10%) percentage reaction depends primarily on the ratios k_{21}/k_{34} and k_{23}/k_{32} and not on the relative magnitudes of k_{ij}; this is because any imbalance in A_3/A_2 which may occur during the course of the reaction has not yet been able to exert its influence.

(5) When $k_{21} = k_{34}$ for some of the cases in Table I (lines 1, 4, and 7), $A_4/A_1 = 0.111 = k_{23}/k_{32}$. These sets of k_{ij}'s fall along the zero line of the Δ_{CH} matrix, i.e., are degenerate.

(6) We have previously demonstrated that A_4/A_1 is not dependent on the magnitudes of the k_{ij}'s (as the time-percentage reaction dependency is) but only on their relative magnitudes. Thus, Table I is more generally applicable in that multiplication of the k_{ij}'s in one set by the same constant results in the same dependency of A_4/A_1 as a function of reaction percentage.

More complex kinetic schemes may be necessary to describe phenomena associated with biomolecular diffusion-controlled reactions. For example, substrate and reagent mixing and other solution inhomogeneity factors must be included. The treatment shown in Table I is the simplest exact solution possible. If Table I shows the results to be non-C–H, then all more complicated systems will be non-C–H unless there exist fortuitous balancing factors. Hence, the results shown in Table I can be used as approximations for more complex reacting systems.

Reaction Energetics

It must be noted that the C–H/W–H approximations are in terms of the k_{ij} and not activation energies (E_{ij}) and preexponential factors (A_{ij}).[6b] The Arhennius equation (eq 17) and the Eyring equation (eq 18) are the two relationships generally used to relate the rate constants of a reaction to energy and entropy parameters. These two equations are specific formulations of the more general Eyring equation (eq 19). The appropriate rate equation for a particular reaction is dependent on the nature of the reaction, i.e., whether the reaction is unimolecular or bimolecular, whether the transition state complex is linear, nonlinear, etc.[16] In Scheme I, the interconversions $A_2 \rightleftarrows A_3$ signified a unimolecular conformational (or configurational) transformation, and as such eq 18 is suggested by theory.[16] The only assumption that has been made in the derivation of the exact solution in terms of the reactions $A_2 \rightarrow A_1$ and $A_3 \rightarrow A_4$ is that they obey first-order kinetics or pseudo-first-order kinetics. Theory suggests a wide range of values for n in eq 19 for reactions following this assumption, and for the calculation of Δ_{CH} and Δ_{WH} we have chosen[17] the value $n = 0$ as has often been done in the literature.

$$k = A \exp(-E_a/RT) \quad (17)$$

$$k = AT \exp(-E_0/RT) \quad (18)$$

$$k = AT^n \exp(-E_0/RT) \quad (19)$$

Tables II and III demonstrate the important observation that the preexponential factors play a determining role in

Table II. Derivation of the Minimum E_{21} and E_{34} for C–H Acceptability When $E_{23} = E_{32} = 18$ kcal/mol (298 K)[a]

A_{23},A_{32}[b,c]	k_{21},k_{34}[c,d]	A_{21},A_{34}	k_{21}/A_{21}, k_{34}/A_{34}	E_{21},E_{34} for C–H acceptability,[a,d] kcal mol^{-1}
1×10^{5}	$<4 \times 10^{-10}$	1	$<4 \times 10^{-10}$	>12.8
		10	$<4 \times 10^{-11}$	>14.1
		1×10^{2}	$<4 \times 10^{-12}$	>15.5
		1×10^{3}	$<4 \times 10^{-13}$	>16.9
		1×10^{4}	$<4 \times 10^{-14}$	>18.2
		1×10^{5}	$<4 \times 10^{-15}$	>19.6
1×10^{10}	$<4 \times 10^{-5}$	1	$<4 \times 10^{-5}$	>6.0
		10	$<4 \times 10^{-6}$	>7.3
		1×10^{2}	$<4 \times 10^{-7}$	>8.7
		1×10^{3}	$<4 \times 10^{-8}$	>10.1
		1×10^{4}	$<4 \times 10^{-9}$	>11.4
		1×10^{5}	$<4 \times 10^{-10}$	>12.8
1×10^{15}	<4	1×10^{2}	$<4 \times 10^{-2}$	>1.9
		1×10^{3}	$<4 \times 10^{-3}$	>3.3
		1×10^{4}	$<4 \times 10^{-4}$	>4.6
		1×10^{5}	$<4 \times 10^{-5}$	>6.0

[a] The Arrhenius equation is arbitrarily used in these calculations; e.g., $E_a = 18$ kcal/mol implies that $k/A = 5.64 \times 10^{-14}$ at 298 K. [b] $A_{23} = A_{32}$ since the same transition state is involved. [c] Multiplication of all the k_{ij} by the same number changes the product composition with respect to time but not with respect to percent reaction. [d] These are the maximum values possible for k_{21},k_{34} such that $\Delta_{CH} < 5$. Note ref 6.

Table III.[a] **Derivation of the Minimum E_{21} and E_{34} for C-H Acceptability When $E_{23} = E_{32} = 6$ kcal/mol**[b]

A_{23},A_{32}	k_{21},k_{34}	A_{21},A_{34}	k_{21}/A_{21}, k_{34}/A_{34}	E_{21},E_{34} for C-H acceptability,[a] kcal mol^{-1}
10	$<3 \times 10^{-1}$	1	$<3 \times 10^{-1}$	>0.71
		10	$<3 \times 10^{-2}$	>2.07
		1×10^{2}	$<3 \times 10^{-3}$	>3.43
		1×10^{3}	$<3 \times 10^{-4}$	>4.79
		1×10^{4}	$<3 \times 10^{-5}$	>6.15
		1×10^{5}	$<3 \times 10^{-6}$	>7.51
1×10^{10}	$<3 \times 10^{4}$	1×10^{5}	$<3 \times 10^{-1}$	>0.71
1×10^{15}	$<3 \times 10^{9}$	1×10^{10}	$<3 \times 10^{-1}$	>0.71

[a] See Table II footnotes. [b] $E_a = 6$ kcal/mol implies $k/A = 3.83 \times 10^{-5}$.

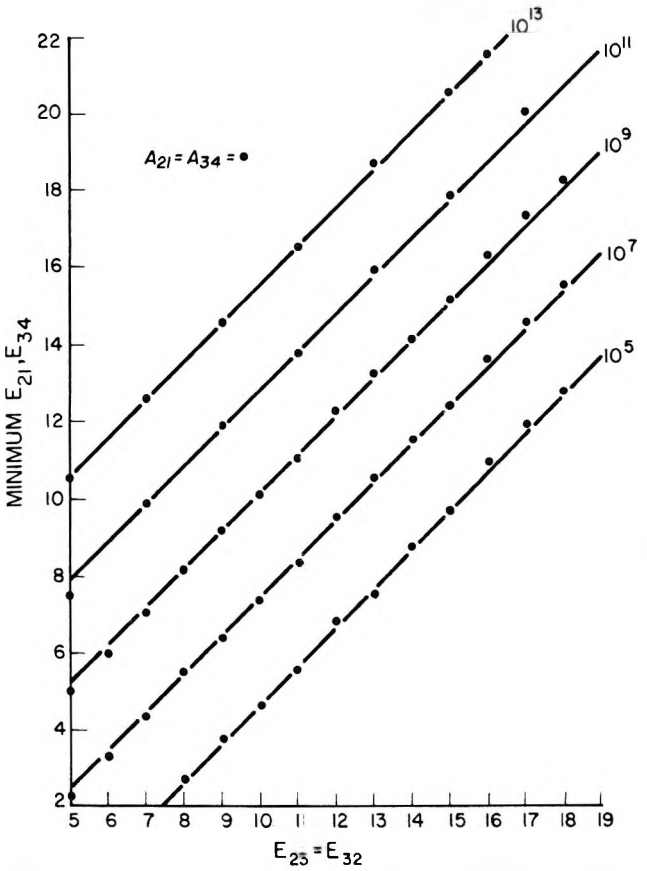


Figure 9. The minimum values of the activation energies E_{21} and E_{34} for C-H acceptability ($\Delta_{CH} < 5$) as a function of the activation energies for isomer interconversion ($E_{23} = E_{32}$). The family of lines represents different values of the preexponential factors $A_{21} = A_{34}$. Note that the free energies of A_2 and A_3 are equal and $A_{23} = A_{32} = 1 \times 10^{-10}$.

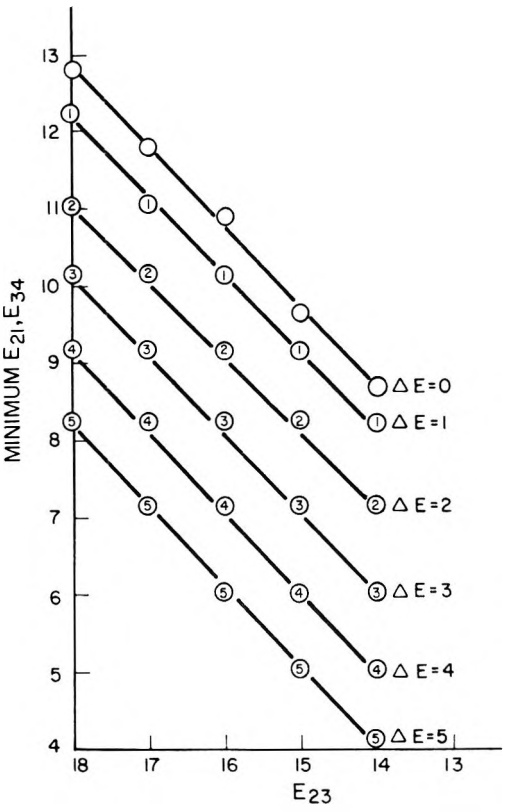


Figure 10. The minimum values of the activation energies E_{21} and E_{34} for C-H acceptability ($\Delta_{CH} < 5$) as a function of the activation energy E_{23} for different values of $\Delta E = E_{23} - E_{32}$. $A_{23} = A_{32} = 1 \times 10^{-10}$; $A_{21} = A_{34} = 1 \times 10^{-5}$. In this figure, the free energy difference between A_2 and A_3 is varied; compare with Figure 9.

these kinetics. While significant statistical errors are associated with the experimental determination of the preexponential factor A, it is clear that the preexponential factors for typical unimolecular reactions[18] (e.g., conformational interconversion) are a number of orders of magnitude greater than the preexponential factors of bimolecular reactions.[19]

These points are illustrated by comparing the results for Scheme I kinetics when $E_a = 18$ kcal/mol (Table II) with those when $E_a = 6$ kcal/mol (Table III). The former is representative of the energy barrier of nitrogen inversion for aziridines[18] and the latter is representative of the inversion barrier of a hindered pyrrolidine, e.g., nicotine.[14] If we assume (1) that the preexponential factor for inversion is 10^{10} and (2) the upper limit for any preexponential factor for the reactions $A_2 \rightarrow A_1$ and $A_3 \rightarrow A_4$ is 10^5, then any reaction having a barrier less than 12.8 kcal/mol will result in non-C-H/W-H kinetics for the aziridines ($\Delta H^{\ddagger}_0 = 18$ kcal/mol) while any barrier less than 0.71 kcal/mol for the substituted pyrrolidine would result in non-C-H/W-H kinetics. Consider the result if one assumes that the preexponential factor for nitrogen interconversion is 10^{15} rather than 10^{10}. Reaction barriers less than 6.0 kcal/mol for aziridines would result in non-C-H/W-H kinetics.

The influence of the preexponential factor in determining reaction profiles can be seen in Figure 9 which shows the minimum values of E_{21},E_{34} for $\Delta_{CH} < 5$ for different values of $A_{21} = A_{34}$ assuming $A_{23} = A_{32} = 1 \times 10^{10}$. The parallel lines are not an obvious consequence of the exact solution (eq 3-14) but are related to the linear relationship found in Figure 4.

We also examined the minimum E_{21},E_{34} allowable and still maintain $\Delta_{CH} < 5$ for sets of E_{23},E_{32} having a constant energy difference $x = E_{23} - E_{32}$ as a function of E_{23} (Figure 10). A series of parallel lines resulted, thus indicating that the actual value of the energy difference between A_2 and A_3 is important for determining the minimum value of E_{21},E_{32} but the location on the energy scale, in an absolute sense, is not.

It is important to stress at this stage that the kinetics are controlled by the rate constants which appear in the rate expressions, and it is from these rate constants measured at various temperatures that the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are calculated. We have attempted to use the designations of E_a, E_0, or $\Delta H^{\ddagger}$ corresponding to the individual author's use in the literature. In some literature cases, it is difficult to determine which equation (e.g., eq 17-19) the author used in derivation of his activation parameters. Although the relationship between these various parameters is well-known, considerable uncertainly exists in the usage of eq 17-19. For example, the value

Table IV.[a] Calculated[b] Percentages of Hydroboration Products for Thujopsene (5) under the Assumption That the Minor Isomer[c] Reacts Faster Than the Major Isomer[c]

$E_{HB,5s\rightarrow 6}$, kcal mol^{-1}	$E_{HB,5s\rightarrow 7}$, kcal mol^{-1}	$k_{5s\rightarrow 6}/k_{5n\rightarrow 7}$	A_{inv}/A_{HB}	% products 6	% products 7
3.7	9.1	1×10^4	1×10^3	96.6	3.4
3.7	9.1	1×10^4	1×10^4	98.8	1.2
5	9.5	2×10^3	1×10^7	95.2	4.8
9	14	4.8×10^3	1×10^3	97.9	2.1
8	13	4.8×10^3	1×10^3	97.9	2.1

[a] Subscripts "inv" and "HB" refer to the ring inversion processes and hydroboration reactions, respectively. [b] $E_{5s\rightarrow 5n} = 11$ kcal mol^{-1}. Calculations were based on eq 17 at 25 °C. Note that multiplication of all k_{ij} by the same number changes the product distribution with respect to time but not with respect to percent reaction. [c] $[k_{5s\rightarrow 5n}/k_{5n\rightarrow 5s} = 0.01]$.

of n in eq 19 is usually assumed to be 0 or 1, but other values are certainly possible and would dramatically effect the derived thermodynamic parameters. The value of κ is, by and large, indeterminate and is generally assumed to be 1, though theory suggests that κ can be considerably larger than 1 (e.g., in unimolecular processes). Tables II and III are meant to *illustrate* the controlling factors in C–H/W–H chemistry in terms of these more widely used activation parameters. Thus, whether or not an aziridine or any other molecule follows C–H/W–H kinetics will be best judged following the experimental determination of the k_{ij} and not by the hypothetical treatment shown in Tables II and III.

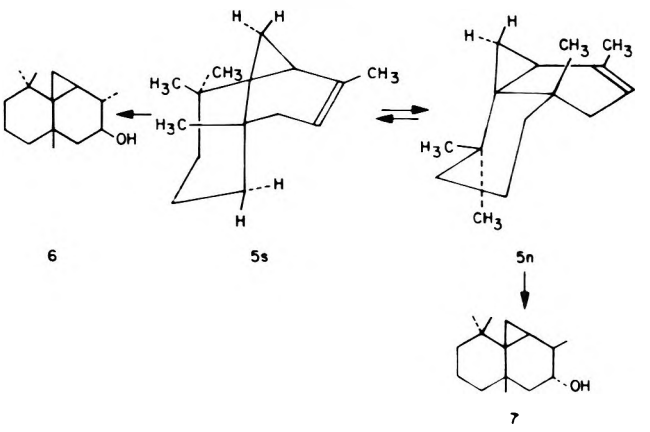
Additional Applications of the Exact Solution. Perhaps the ultimate use of the exact solution (eq 3–14) to Scheme I is the determination of all the rate constants from time–concentration data. The experimental difficulties in determining time–concentration data coupled with the previous unavailability of the exact solution to this kinetic scheme have encouraged various investigators either (1) to use the C–H/W–H approximations or (2) to intuitively cite the probable failure of these approximations for the treatment of their systems. We are unaware of any kinetic treatment of a Scheme I non-C–H/W–H kinetic system.

Numerous examples can be found in the literature in which the C–H/W–H approximations are utilized for various determinations. If appropriate upper (or lower) limits can be made for the reaction rate constants for a chemical system or interest, then the exact solution can predict the appropriateness or inappropriateness of the use of these approximations.

One continuing application of Scheme I kinetics involves the determination of the position of the $A_2 \rightleftarrows A_3$ equilibrium, defined by $K = k_{23}/k_{32}$. For example, the early work on the quaternization of tropines incorporated the assumption that the product ratio A_4/A_1 was dependent only on the free energy difference between the reactant configurational isomers.[20] Such considerations led to incorrect deductions[20] of reactant isomer ratios, since the C–H approximation clearly indicates a dependency not only on K $[=k_{23}/k_{32} = \exp(-\Delta G^0/RT)]$ but also on the ratio of reaction rates k_{34}/k_{21} (see eq 1).

Indeed, numerous examples can be found in the chemical literature in which the C–H principle is interpreted by implying that "the ratio of the products so formed is independent of the relative energy levels of the various starting forms . . .".[7] This interpretation is somewhat misleading as evidenced by eq 1. Indeed, the relative values of k_{23} and k_{32} are always reflected in the relative values of A_1 and A_4: (1) if $k_{21},k_{34} \gg k_{23},k_{32}$, then (kinetic quenching) $A_4/A_1 = A_3/A_2 = k_{23}/k_{32}$ at reaction completion; (2) if $k_{21},k_{34} \ll k_{23},k_{32}$ (C–H/W–H), then eq 1 is valid; and (3) if k_{21} and/or $k_{34} \sim k_{23}$ and/or k_{32}, then eq 3–14 are the simplest descriptors of $A_i(t)$, and A_i are certainly dependent on the relative values of k_{ij}.

Scheme III



To exemplify these concepts, consider the attempt by Acharya and Brown to elucidate the conformational equilibrium position of (−)-thujopsene (**5**).[21,22] Acharya and Brown hypothesized that the steroidal **5s** and nonsteroidal conformations **5n** of (−)-thujopsene would stereospecifically yield alcohols **6** and **7**, respectively, on hydroboration–peroxide oxidation. The isolation of a single alcohol identified as **6** in 96.3% yield formed the basis of their conclusion that thujopsene exists preferentially in the steroidal conformation **5s**.[21]

An alternative hypothesis is that thujopsene exists preferentially (e.g., 100-fold greater) in the nonsteroidal conformation **5n** but the hydroboration rate $k_{5s\rightarrow 6}$ of the steroidal conformer is considerably larger than the rate $k_{5n\rightarrow 7}$ of the nonsteroidal conformer. Utilizing the activation barriers for Scheme III suggested by Acharya and Brown,[21] one can apply eq 3–14 and examine the conditions under which isomer **6** is preferentially formed when conformer **5n** predominates. The results of some of these calculations are illustrated in Table IV, which clearly indicates that if the ratio $k_{5s\rightarrow 6}/k_{5n\rightarrow 7}$ is sufficiently large, product from the "minor" isomer will predominate whether or not the kinetic system can be described by the C–H/W–H approximations. The major conclusion from this treatment is that detailed kinetic studies must be performed in any attempt to correlate product ratio with the equilibrium distribution of isomers.

Considerable interest has been shown for some years in the thermal chemistry of azoalkanes.[23] Engel et al.[23a] recently investigated the thermolysis of a number of *cis*- and *trans*-azoalkanes. They demonstrated that *trans*-dinorbornyldiazene (**8t**) decomposes giving nitrogen and unspecified hydrocarbons, while lower temperature thermolysis of the less stable cis isomer **8c** leads only to the trans compound **8t**. The possibility that some of the nitrogen from **8t** was derived from prior isomerization to **8c** was not mentioned. Equations 3–14, coupled with the thermodynamic parameters reported for these compounds, allow the calculation of the ratio of nitrogen coming directly from the trans isomer **8t** vs. the nitrogen coming from the trans isomer via the cis isomer **8c** (Table V). The relative times for 50% reaction completion are also shown in Table V and can serve as an additional experimental test for the kinetic parameters. Since a significant amount of product does indeed arise via the indirect pathway, the transition state parameters for the transformation of **8t** to prod-

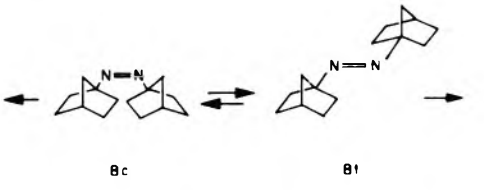


Table V. Calculated[a] Reaction Profiles for the Thermal Decomposition of 8t

Temp, °C	Total N_2 via 8t / Total N_2 via 8c	Rel rxn times[b]
400	1.35	1
300	1.39	1.3×10^3
200	1.53	3.8×10^7
100	1.72	2.5×10^{14}

[a] Based on thermodynamic data cited in ref 23a,d using eq 18. This treatment assumes $A_{8t\rightarrow 8c} = A_{8c\rightarrow 8t}$ and $A_{8c\rightarrow Pdt} = A_{8t\rightarrow Pdt}$. [b] Relative times for 50% destruction of 8.

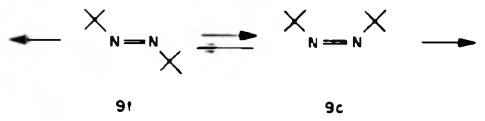
Table VI.[a] Calculated[b] Reaction Profiles for the Thermal Decomposition of 9c and 9t

$\Delta H^{\ddagger}_{9c\rightarrow 9t}$	$\Delta H^{\ddagger}_{9t\rightarrow 9c}$	**9c** → **9t** → N_2[c,d] from −17 °C pyrolysis of **9c**, %	**9t** → **9c** → N_2[d,e] from 183 °C pyrolysis of **9t**, %
20	42.3	96	0.241
21	43.3	89	0.234
22	44.3	54	0.215
23	45.3	14	0.172
24[c,f]	46.3	2.2[c,f]	0.107

[a] The exact solution to Scheme I (eq 3–14) can also serve as the exact solution to lesser included kinetic schemes. In some cases, as exemplified in a number of the calculations performed for Table VI, sets of k_{ij} are obtained in which Scheme I can be approximated by simplier kinetics schemes, e.g., parallel or series first-order reactions (cf. ref 16, Chapter 8). [b] Based on the thermodynamic data cited in ref 23a, assuming $A_{9t\rightarrow 9c} = A_{9c\rightarrow 9t}$. [c] Experimentally, the conversion **9c** → **9t** at −17 °C was not observed. [d] Evaluated at infinite time. [e] The percentage of decomposition occurring via the indirect path (**9t** → **9c** → N_2) compared with the direct path (**9t** → N_2) at >180 °C was not discussed in the literature (cf. ref 23a). [f] Minimum value consistent with experimental data (see footnote c above) assuming an experimental error of 5%.

ucts should be reobtained from experiments that can distinguish these two pathways.

Thermolysis of either *cis*- or *trans-tert*-butyldiazene (**9c** and **9t**) leads only to fragmentation; in neither case was cis–trans isomerization observed.[23a] Equations 3–14 can be utilized to determine the minimum activation enthalpies for cis–trans isomerization such that these processes not be observed; in addition, the likelihood of the sequence **9t** → **9c** → N_2 can be evaluated. These results are shown in Table VI.



9t **9c**

The exact solution for Scheme I kinetics has two additional versatilities: it can be used for systems (1) in which A_2 and A_3 do not necessarily represent conformational isomers but, in a less restrictive sense, interconverting compounds; and (2) in which the initial ratio of concentrations A_{30}/A_{20} is not equal to the equilibrium distribution.[24]

An interesting example incorporating both of these aspects can be found in the recent work of Dolbier and Enoch on the thermochemistry of *cis*- and *trans*-1,1-difluoro-2,3-dimethylcyclopropanes, **10c** and **10t**, respectively.[25] Analysis of this system using the published rate data and eq 3–14 indicates that C–H/W–H kinetics should be obtained if an equilibrium mixture of **10c** and **10t** were pyrolyzed; however, when **10c** and **10t** were pyrolyzed independently, non-C–H/W–H kinetics

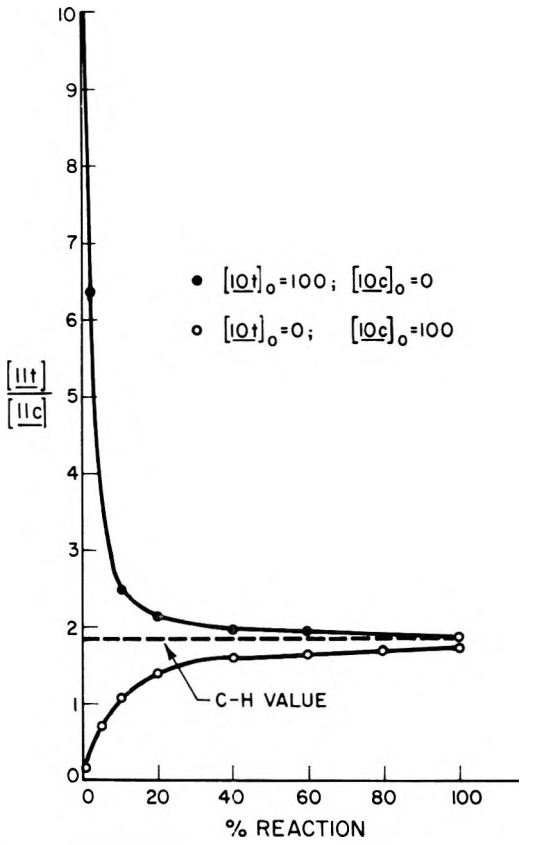
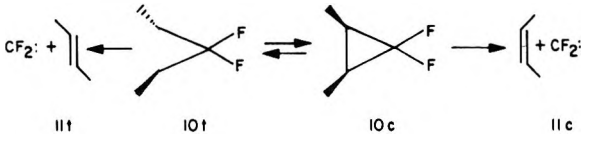


Figure 11. The calculated percentage reaction dependency of the product ratio [11t]/[11c] obtained in the independent pyrolyses of either **10t** or **10c** using rate data obtained from ref 25: $k_{10c\rightarrow 10t} = 3.96 \times 10^{-5}$; $k_{10t\rightarrow 10c} = 2.07 \times 10^{-5}$; $k_{10c\rightarrow 11c} = 1.2 \times 10^{-6}$; $k_{10t\rightarrow 11t} = 1.15 \times 10^{-6}$. The dashed line in the figure represents the C–H value.

should have been obtained (see Figure 11). Note that, as indicated in Figure 11, maximum deviation from C–H kinetics occurs early in the reaction. The use of the exact kinetic solution should allow the most accurate determination of the rate constants and other thermodyanmic properties of this system, as well as substantiate the system's presumed stereospecificity.



11t **10t** **10c** **11c**

Summary and Conclusions

Equations 3–14 form the exact analytical solution to any chemical system represented by Scheme I. The solution can be applied regardless of the relative values of the rate constants k_{ij}. The species A_2 and A_3 can be conformational or configurational isomers or two compounds related by their mutual interconversion through more complex chemistry. Any initial values for the species A_1–A_4 may be used as input; e.g., the initial value A_{30}/A_{20} may not equal the equilibrium value K. If the reactions to A_1 and A_4 from A_2 and A_3, respectively, are bimolecular (or higher order) with respect to a particular reagent, then eq 3–14 can be used *only if* the reactions to product can be treated as pseudo-first-order. The reaction order to A_1 and A_4 need not be identical, however, as the appropriate transformations in the k_{ij} may be made.

Maximum utilization of these results can be had as in any kinetic study if time–concentration data are available. These data would allow the determination of the k_{ij}. However, if only

partial experimental information is available, upper and/or lower limits of some of the rate parameters may be estimated in many cases as described above.

A wide range of values of k_{ij} has been selected and the kinetic results have been evaluated (cases I–IV above). This has allowed the rough generalization that the Curtin–Hammett principle and the Winstein-Holness equation correctly approximate the exact solution *when* $k_{23},k_{32} > 10k_{21},10k_{34}$. However, the more skewed the system, either by grossly differing values of the k_{21},k_{34} or k_{23},k_{32} pairs or by situations in which $A_{30}/A_{20} \approx k_{23}/k_{32}$, the greater the above inequality must be for C–H/W–H acceptability.

The relationships between the rate constants and the thermodynamic parameters (E_a, A, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$) were examined for Scheme I kinetic systems. It was found that the preexponential factor plays a considerable role in determining the kinetic results. This observation was contrasted to the usual view that the activation energies alone controlled the kinetics. An important consequence of the dominating role of the preexponential factor is that chemical systems which undergo intramolecular conversion to product are more likely to be non-C–H/W–H. This is due to the significantly greater value of the preexponential factor for intramolecular processes than for intermolecular processes (from five to ten orders of magnitude larger).[6a,18,19]

The product ratio A_4/A_1 is always partially dependent on the relative energy levels of the starting forms. This dependency is manifested (albeit in a complex fashion) in the appearance of both k_{23} and k_{32} in eq 3–14. Under C–H/W–H conditions, this dependency is simply directly proportional to the ratio k_{23}/k_{32} (cf. eq 1).

It is hoped that these results will not only allow a better appreciation of the Curtin–Hammett and Winstein–Holness concepts but also serve as the basis for more detailed experimentation in complex chemical systems. We are currently examining the utility of the solution and anticipate that these results will indeed be put to significant use exceeding the simple, but important, analyses initially made possible by the long and well-used approximations of Curtin–Hammett and Winstein–Holness.[26,27]

Acknowledgment. We thank Drs. E. B. Sanders and A. Kassman for their continued assistance in this project. We also thank the Philip Morris Research Center Computer Section, and in particular Dr. P. Martin and Mr. D. Clark, for their interest in this investigation. The technical assistance of Mrs. Anne Donathan and Mr. J. Day is gratefully acknowledged. We especially thank Dr. T. S. Osdene for his encouragement. We acknowledge Professor Paul S. Engel for helpful discussions and for supplying us with unpublished results.

Registry No.—**1**, 65414-58-6; **2/3**, 938-36-3; **4**, 65414-59-7; **5**, 470-40-6; **6**, 25966-77-2; **7**, 26039-33-8; **8c**, 59388-64-6; **8t**, 59388-65-7; **9c**, 24577-10-4; **9t**, 15464-01-4; **10c**, 694-20-2; **10t**, 694-21-3; **11c**, 590-18-1; **11t**, 624-64-6.

References and Notes

(1) For the previous paper in this series, see J. I. Seeman, *Synthesis*, 498 (1977).
(2) (a) N. L. Allinger and E. L. Eliel, "Topics in Stereochemistry", Vol. 1–9, Interscience, New York, N.Y., 1967–1976; (b) International Symposium on Conformational Analysis Lectures, *Pure Appl. Chem.*, 465–666 (1971); (c) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, N.Y., 1965; (d) L. M. Jackman and F. A. Cotton, Ed., "Dynamic Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, N.Y., 1975; (e) M. Hanack, "Conformation Theory", Academic Press, New York, N.Y., 1965; (f) E. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962.
(3) (a) D. Y. Curtin, *Rec. Chem. Prog.*, **15**, 111 (1954); (b) L. P. Hammett, "Physical Organic Chemistry", 2nd ed., McGraw-Hill, New York, N.Y., 1970, pp 119–120; (c) D. Y. Curtin and M. C. Crew, *J. Am. Chem. Soc.*, **77**, 354 (1955); (d) ref 2f, pp 149–156, 234–239; (e) ref 2c, pp 28–35.
(4) (a) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955); (b) ref 2c, pp 27–28, 47–50; (c) ref 2f, pp 234–237.
(5) (a) E. L. Eliel and R. S. Ro, *Chem. Ind. (London)*, 251 (1956); (b) E. L. Eliel and C. A. Lukach, *J. Am. Chem. Soc.*, **79**, 5986 (1957); (c) E. L. Eliel, *J. Chem. Educ.*, **37**, 126 (1960); (d) see ref 2c footnote on pp 48–49.
(6) (a) The treatment given herein is also applicable to kinetic systems in which the products are formed via a bimolecular or higher order reaction but follow pseudo-first-order kinetics. (b) Throughout this paper, A_i (i = 1–4) represents the concentration of the chemical entities involved in Scheme I with rate constants k_{ij} for the reaction $A_i \rightarrow A_j$; A_{i0} represents the initial value of A_i. E_{ij}, ΔH_{ij}, and A_{ij} represent the activation energy, the activation enthalpy, and the preexponential factor, respectively, for the $A_i \rightarrow A_j$ transformation.
(7) Reference 2c, p 28.
(8) (a) An extension of the Curtin–Hammett principle to chemical systems involving three or more very rapidly interconverting conformations each reacting slowly to give the same two products with independent rate constants has recently been made[cf. C. Alvarez-Ibarra, F. Fernández-González, A. Garcia-Martinez, R. Pérez-Ossorio, and M. L. Quiroga, *Tetrahedron Lett.*, 2715 (1973), and references cited therein]. (b) For an extension of the Curtin–Hammett principle to systems in which each conformer yields the same two products, see R. O. Hutchins, *J. Org. Chem.*, **42**, 920 (1977).
(9) For an examination of special cases of Winstein–Holness kinetics, see (a) D. C. Best, G. M. Underwood, and C. A. Kinsbury, *J. Org. Chem.*, **40**, 1984 (1975) (note especially footnote 36); (b) E. S. Lewis and M. D. Johnson, *J. Am. Chem. Soc.*, **82**, 5399 (1960).
(10) The method of solution for systems of equations such as these is given in, e.g., R. C. Buck and E. F. Buck, "Introduction to Differential Equations", Houghton Mifflin Co., Boston, Mass., 1976, Chapter 6; E. L. Ince, "Ordinary Differential Equations", Dover Publications, New York, N.Y., 1956, Chapter IX; I. S. Sokolnikoff and R. M. Redheffer, "Mathematics of Physics and Modern Engineering", McGraw-Hill, New York, N.Y., 1958, pp 95–106.
(11) The primary use of the W–H equation has been the extrapolation of k_{ax} and k_{eq} in a conformationally fixed system (e.g., *cis*- and *trans*-4-*tert*-butylcyclohexanol) to a compound (e.g., cyclohexanol) capable of existing in and reacting from two conformations. The inherent assumption in such an analysis is that only two *idealized* conformations are available to the reacting compound. This assumption has been the focus of considerable controversy due to the established importance of substituent-induced conformational changes.[12] Our manuscript does not deal with this extrapolative use of the W–H equation, although it can be used in some cases (i.e., when the W–H approximation to Scheme I fails) to determine the validity of the use of Scheme I to represent a particular chemical system's kinetics. Equations 3–14 will always allow one to derive k_{ij} from time–concentration data for Scheme I systems. However, extrapolations and other uses of these k_{ij} must be evaluated in terms of the assumptions made in the extrapolation procedure. These justifications are independent of the correct derivation of the k_{ij}. For a particularly interesting discussion on the problems that can occur in the extrapolative use of W–H concepts, see H. Kwart and T. Takeshita, *J. Am. Chem. Soc.*, **86**, 1161 (1964).
(12) See, for example, P. J. Halfpenny, P. J. Johnson, M. J. T. Robinson, and M. G. Ward, *Tetrahedron*, **32**, 1873 (1976), and references cited therein.
(13) F. R. Cruickshank, A. J. Hyde, and D. Pugh, *J. Chem. Educ.*, **54**, 288 (1977).
(14) (a) J. F. Whidby and J. I. Seeman, *J. Org. Chem.*, **41**, 1585 (1976); J. I. Seeman, J. F. Whidby, E. Thomas, and W. A. Farone, unpublished results; (b) J. I. Seeman, H. V. Secor, R. L. Bassfield, and J. F. Whidby, *Tetrahedron Lett.*, in press.
(15) (a) D. C. Appleton, J. McKenna, J. M. McKenna, L. B. Sims, and A. R. Walley, *J. Am. Chem. Soc.*, **98**, 292 (1976); (b) J. McKenna, *Tetrahedron*, **30**, 1555 (1974); (c) F. A. L. Anet, I. Yavari, I. J. Ferguson, A. R. Katritzky, M. Moreno-Manas, and M. J. T. Robinson, *J. Chem. Soc., Chem. Commun.*, 399 (1976), and references cited therein; (d) P. J. Crowley, M. J. T. Robinson, and M. G. Ward, *Tetrahedron*, **33**, 915 (1977).
(16) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2nd ed, Wiley, New York, N.Y., 1961, Chapters 4 and 5; note especially Table 2, p 94.
(17) This approach also results in computational simplicity, for the kT^n/h term can be considered "lumped into" the preexponential factor A_{ij}.
(18) (a) J. B. Lambert, *Top. Stereochem.*, **6**, 19–105 (1971); (b) J. M. Lehn, *Top. Curr. Chem.*, **15**, 311 (1970); (c) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2nd ed, Cornell University Press, Ithaca N.Y., 1969, pp 471–473.
(19) (a) A. T. Bottini in "Selective Organic Transformations", Vol. 1, B. S. Thyagarajan, Ec., Wiley, New York, N.Y., 1970, pp 89–142; (b) J. L. Imbach, A. R. Katritzky, and R. A. Kolinksi, *J. Chem. Soc. B*, 556 (1966); (c) H. C. Brown, *J. Chem. Soc.*, 1248 (1956).
(20) (a) J. McKenna, *Top. Stereochem.*, **5**, 275–308 (1970); note especially p 278. (b) For an elegant summary of this work, see G. Fodor, R. V. Chastain, Jr., D. Frehel, M. J. Cooper, N. Mandava, and E. L. Gooden, *J. Am. Chem. Soc.*, **93**, 403 (1971).
(21) S. P. Acharya and H. C. Brown, *J. Org. Chem.*, **35**, 3874 (1970) (note especially ref 14).
(22) See also P. C. Traas, L. M. van der Linde, and H. J. Takken, *Rec. Trav. Chim. Pays-Bas.*, **93**, 264 (1974).
(23) (a) P. S. Engel, R. A. Melaugh, M. A. Page, S. Szilagyi, and J. W. Timberlake, *J. Am. Chem. Soc.*, **98**, 1971 (1976); (b) J. W. Timberlake and A. W. Garner, *J. Org. Chem.*, **41**, 1666 (1976); (c) P. S. Engel and D. J. Bishop, *J. Am. Chem. Soc.*, **97**, 6754 (1975); (d) J. Hinz, A. Oberlinner, and C. Rüchardt, *Tetrahedron Lett.*, 1975 (1973); (e) L. D. Fogel, A. M. Rennert, and C. Steel, *J. Chem. Soc., Chem. Commun.*, 536 (1975), and references cited in these publications.
(24) See, for example, (a) R. Grée and R. Carrié, *J. Chem. Soc., Chem. Com-*

mun., 112 (1975); (b) H. L. Goering, C.-S. Chang, and J. V. Clevenger, J. Org. Chem., 41, 4023 (1976); (c) W. C. Agosta and S. Wolff, J. Am. Chem. Soc., 98, 4182 (1976).
(25) W. R. Dolbier, Jr., and H. O. Enoch, J. Am. Chem. Soc., 99, 4532 (1977).
(26) Following the completion of our work, we became aware that J. M. Lluch, Universidad Autonoma de Barcelona, had also solved kinetic Scheme I exactly (unpublished work). We thank Professor E. L. Eliel for bringing this work to our attention and for helpful discussions.
(27) **Note Added in Proof.** Following acceptance of this paper, N. S. Zefirov reported [*Tetrahedron*, **33**, 2719 (1977)] an analytical expression for A_4/A_1 for Scheme I at reaction completion. This expression does not include arbitrary initial conditions and does not describe the system as a function of time.

Secondary Orbital Interactions Determining Regioselectivity in the Diels–Alder Reaction. 3. Disubstituted Dienes

Peter V. Alston*

E. I. du Pont de Nemours and Company, Organic Chemicals Department, Jackson Laboratory, Wilmington, Delaware 19898

Raphael M. Ottenbrite

Department of Chemistry, Virginia Commonwealth University, Richmond, Virginia 23284

Theodore Cohen

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received October 17, 1977

Frontier molecular orbital theory is used to predict the regioselectivity in the Diels–Alder reactions of disubstituted butadienes. The primary orbital interactions which have been used by several investigators to predict the regioselectivity in the Diels–Alder reaction could not account for the regioselectivity observed with 1,2-disubstituted butadienes. When the secondary orbital interactions were included in the theory, the preferred regioisomer was predicted in every case. The frontier molecular orbitals of the dienes and dienophiles were determined by the CNDO/2, INDO, CNDO/S, and Hückel methods.

The regioselectivity of the Diels–Alder reaction has been successfully rationalized by considering only the interactions between the frontier molecular orbitals (FMO) of the diene and the dienophile.[1-5] This approach is based on the second-order perturbation equation for the energy change which accompanies the orbital interactions of the two molecules involved in a cycloaddition reaction.[6] From this theory several investigations[2-5] have used the following generalizations to predict the regioselectivity: (1) the principle stabilization of the transition state arises from the HOMO–LUMO interaction which is the closest in energy (when the FMO interactions have similar energy separations, both interactions are considered); (2) the larger primary orbital coefficient of the diene will bond preferentially with the larger primary orbital coefficient of the dienophile. In fact, Anh et al.[3] has recently applied this approach to approximately 100 examples of the Diels–Alder reaction.

In previous investigations we have found numerous cases in which this approach failed to predict the regioselectivity that was observed.[1] However, these discrepancies were eliminated when the secondary orbital interactions were considered. Consequently, we have added a third generalization in our approach which is as follows: (3) the secondary orbital coefficient of the dienophile will interact preferentially with the larger secondary orbital coefficient of the diene. By considering which regioisomers are favored by the interactions in generalizations 2 and 3 and the relative importance of these generalizations, the preferred regioisomer can be predicted.

In this paper the above theories have been applied to the uncatalyzed Diels–Alder reactions of disubstituted butadienes. In these cases generalizations 2 and 3 favor different regioisomers and the experimentally preferred regioisomer varies with the substituent combination, thereby allowing a critical evaluation of the two theoretical approaches.

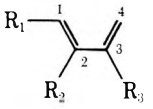
Results and Discussion

CNDO/2 calculations predict that the energy separation between the HOMO of the diene and the LUMO of the dienophile is considerably smaller than the energy separation between the LUMO of the diene and the HOMO of the dienophile for all reactions that have been investigated. Thus, the principle stabilization of the transition state will result from the former MO interaction and the latter can be neglected. Consequently, in the frontier molecular orbital approach the second-order perturbation equation simplifies into eq 1 and 2 for the two possible endo approaches of the dienophile to the diene.[7] In the equations the γ_{cc} values are the atomic orbital transition state resonance integrals for the p_z carbon atomic orbitals. The c values are the atomic orbital coefficients in the respective molecular orbitals and the E values are the energies of the interacting frontier molecular orbitals.

Using CNDO/2 FMO energies and coefficients (Table I), the stabilization energy from the interaction of HOMO of the diene and the LUMO of the dienophile has been calculated for the various reactions. A resonance integral of 7 eV for the primary orbital interactions and a resonance integral of 2.8 eV for the secondary orbital interactions were used in the calculations. The value of 7 eV for the resonance integral of the primary orbital interactions was derived from the concerted transition state that ab initio calculations[8] predicted for the cycloaddition of ethylene to butadiene along with consideration for the narrowing of the FMO energy separation in the transition state and a larger than experimental CNDO/2 energy separation between the interacting MO's. The resonance integral for the secondary orbital interactions was assigned a smaller value because the geometry of the transition state favors the overlap between the primary orbitals at the

0022-3263/78/1943-1864$01.00/0

Table I. Highest Occupied Molecular Orbitals of the Disubstituted Butadienes



R_1	R_2	R_3	MO method	P_z coeff[a] C-1	C-2	C-3	C-4	Energy of HOMO, eV
CH_3	CH_3CONH	H	CNDO/2	0.578	0.357	0.180	0.336	−10.83
			INDO	0.577	0.340	0.169	0.317	−10.17
			CNDO/S	0.596	0.421	0.320	0.503	−8.65
			Hückel	0.622	0.421	0.238	0.466	
CH_3	CH_3O	H	CNDO/2	0.580	0.410	0.225	0.402	−11.38
			INDO	0.585	0.393	0.210	0.380	−10.75
			CNDO/S	0.606	0.456	0.286	0.483	−8.80
			Hückel	0.627	0.434	0.258	0.490	
CH_3	CH_3	H	CNDO/2	0.561	0.456	0.284	0.468	−11.72
			INDO	0.562	0.453	0.296	0.475	−11.29
			CNDO/S	0.588	0.469	0.322	0.514	−8.89
			Hückel	0.592	0.444	0.316	0.546	
C_6H_5S	CH_3O	H	CNDO/2	0.296	0.300	0.094	0.231	−9.93
			Hückel	0.562	0.248	0.307	0.425	
CH_3	C_6H_5	H	CNDO/2	0.563	0.442	0.257	0.432	−11.64
			INDO	0.566	0.440	0.266	0.438	−11.15
			CNDO/S	0.596	0.469	0.311	0.499	−8.94
			Hückel	0.465	0.424	0.227	0.459	
C_6H_5	C_6H_5	H	CNDO/2	0.535	0.445	0.242	0.421	−11.46
			INDO	0.538	0.448	0.250	0.428	−10.92
			CNDO/S	0.589	0.475	0.303	0.495	−8.94
			Hückel	0.446	0.374	0.162	0.376	
H	CH_3O	C_6H_5S	CNDO/2	0.079	0.039	0.140	0.329	−10.50
			Hückel	0.669	0.419	0.254	0.406	
H	Cl	CH_3	CNDO/2	0.519	0.322	0.319	0.497	−12.54
			Hückel	0.579	0.364	0.378	0.602	
H	C_6H_5	CH_3	CNDO/2	0.570	0.357	0.332	0.520	−12.15
			Hückel	0.591	0.335	0.268	0.472	

[a] These are absolute values. The other atomic orbital coefficients are zero for HOMO.

Table II. $HOMO_{diene}$–$LUMO_{dienophile}$ Energy Difference between Regioisomers of the Disubstituted Butadienes

Diene	Registry no.	Dienophile	Registry no.	ΔE ($E_{meta} - E_{para}$), kcal/mol[a,b] Primary	Primary and secondary
1-Methyl-2-acetamido-1,3-butadiene	65442-04-8	Acrolein	107-02-8	6.710	2.182
1-Methyl-2-methoxy-1,3-butadiene	65415-12-5	Methyl acrylate	96-33-3	5.389	0.371
1,2-Dimethyl-1,3-butadiene	4549-74-0	Acrylonitrile	107-13-1	1.844	−1.694
1,2-Dimethyl-1,3-butadiene		Methyl acrylate		2.956	−2.026
1,2-Diphenyl-1,3-butadiene	5731-95-3	Acrylic acid	79-10-7	3.187	−2.536
1-Methyl-2-phenyl-1,3-butadiene	37580-41-9	Acrylic acid		3.764	−1.466
1-Phenylthio-2-methoxy-1,3-butadiene	65415-13-6	Methyl vinyl ketone	78-94-4	1.307	−2.197
2-Methoxy-3-phenylthio-1,3-butadiene	60603-16-9	Methyl vinyl ketone		−2.976	−1.951
2-Methoxy-3-phenylthio-1,3-butadiene		Acrylonitrile		−2.132	−1.336
2-Methyl-3-chloro-1,3-butadiene	1809-02-5	Acrylic acid		−0.733	−0.693
2-Methyl-3-phenyl-1,3-butadiene	18476-73-8	Acrylic acid		−1.527	−0.888

[a] Meta or para to 2-substituent. [b] A negative energy difference favors the meta regioisomer while a positive energy difference favors the para regioisomer.

expense of the secondary orbital overlap.

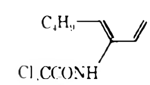
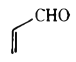
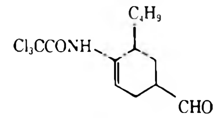
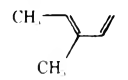
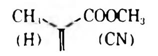
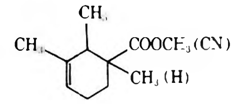
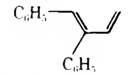
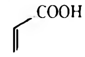
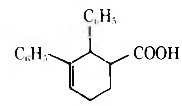
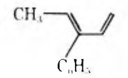
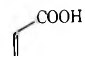
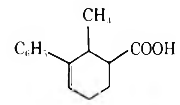
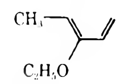
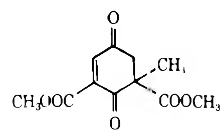
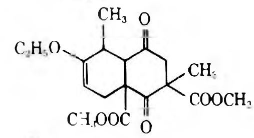
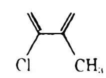
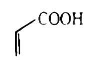
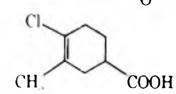
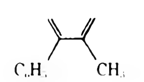
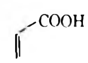
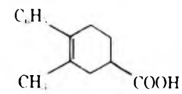
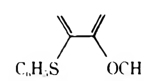
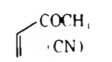
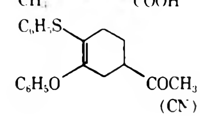
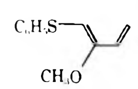
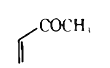
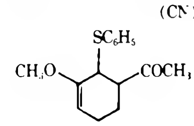
From these stabilization energies the energy difference between the two possible regioisomers in the reactions of the 1,2-disubstituted butadienes was determined (Table II). In all of these reactions the primary orbital interactions favored the para (to the 2-substituent) regioisomer. However, the para regioisomer was preferred in only two of the analogous reactions that were found in the literature (Table III).[9] If the secondary orbital interactions were included in the theory, the experimentally preferred regioisomer was predicted in every case.

Perturbation calculations were also carried out on the reactions of several 2,3-disubstituted butadienes (Table II). In these cases the calculations predicted that the primary interactions will dominate the secondary orbital interactions, in agreement with the experimental results.

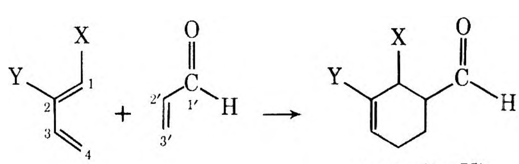
Furthermore, INDO and CNDO/S calculations were carried out on several of the dienes to determine the sensitivity of the coefficient magnitudes to changes in parameterization and the level of approximation. In every case the relative magnitudes of the HOMO coefficients from these SCF MO methods agreed with those of the CNDO/2 method (Table I).

The effect of the interaction between the HOMO of the dienophile and the LUMO of the diene on the theories' pre-

Table III. Preferred Regioisomer in the Diels–Alder Reactions of Disubstituted Butadienes

Diene	Dienophile	Preferred regioisomer	Ref
			*a*
			*b*
			*b*
			*b*
			*b*
			*b*
			*b*
			*c*
			*d*

[a] L. E. Overman and L. A. Clizbe, *J. Am. Chem. Soc.*, **98**, 235 (1976). [b] Y. A. Titov, *Russ. Chem. Rev.*, **31**, 267 (1962). [c] B. M. Trost and A. J. Bridges, *J. Am. Chem. Soc.*, **98**, 5017 (1976). [d] T. Cohen, A. J. Mura, Jr., D. W. Shull, E. R. Fogel, R. J. Ruffner, and J. R. Falck, *J. Org. Chem.*, **41**, 3218 (1976).

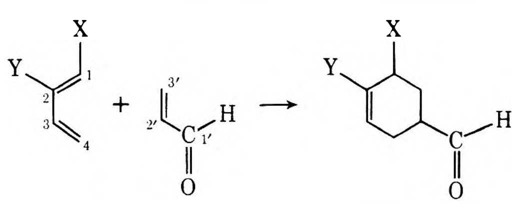


meta (to Y)

$$E_{meta} = 2(c_1c_{2'}\gamma_{cc} + c_4c_{3'}\gamma_{cc} + c_2c_{1'}\gamma'_{cc})^2/$$

primary interactions — secondary interaction

$$(E_{diene}^{HOMO} - E_{dienophile}^{LUMO}) \quad (1)$$



para (to Y)

$$E_{para} = 2(c_1c_{3'}\gamma_{cc} + c_4c_{2'}\gamma_{cc} + c_3c_{1'}\gamma'_{cc})^2/$$

primary interactions — secondary interaction

$$(E_{diene}^{HOMO} - E_{dienophile}^{LUMO}) \quad (2)$$

dictions was examined. No improvement in Anh's theory was found by including this MO interaction. Also, this MO interaction had no effect on the predictions from our approach. Furthermore, the π MO's lying below (subjacent) and above (superjacent) the FMO's were also considered. Though it is difficult to ascertain the importance of the interactions of these MO's in the transition state, no improvement in either theoretical approach could be found by the inclusion of these interactions. Furthermore, the molecular orbital methods did not agree on the actuality of the subjacent and superjacent molecular orbitals. In fact, the CNDO/S calculations which treat the β for σ and π overlap differently had no subjacent and superjacent π MO's which could affect the regioselectivity.

Anh et al.[3,10] has indicated that simple Hückel calculations are superior to CNDO/2 calculations in the prediction of the preferred regioisomer in cycloaddition reactions. Consequently, Hückel calculations were carried out on the disubstituted dienes using Hess and Schaads' parameters[11] for sulfur and Streitwieser's parameters[12] which were found to give good predictions by Anh for all of the other atoms. The Hückel coefficients did not agree with the SCF MO coefficients in three cases (Table I), resulting in incorrect predictions in these cases. However, in defense of the Hückel method these cases contained sulfur or chlorine substituents for which the parameters may not be adequate.

Finally, the geometries used in the SCF MO calculations[13,14] were determined by standard bond angles and bond lengths[13] except for the sulfur–carbon bond and the ∠CSC which were assigned values[15] of 1.75 Å and 109°, respectively. Small changes in these bond angles and bond lengths did not affect

the interpretations. Also, the CNDO/2 method predicts that the preferred conformation of the phenyl group is perpendicular to the plane of the diene moiety for all dienes except 1-phenylthio-2-methoxy-1,3-butadiene. Consequently, this conformation of the phenyl group was used in those calculations.

Conclusion

The regioselectivity in the Diels–Alder reactions of disubstituted butadienes cannot be predicted from the primary orbital interactions. However, by including the secondary orbital interactions in the theory the preferred regioisomer can be predicted in all these cases.[16] Furthermore, we have applied our approach to approximately 100 examples of the Diels–Alder reaction including 1-substituted, 2-substituted, 1,3-disubstituted, and 1,4-disubstituted butadienes as well as the reactions in this paper. In all these other cases, the preferred regioisomer was correctly predicted using CNDO/2 FMO energies and coefficients.

Acknowledgments. The authors thank the Virginia Commonwealth University Computer Center for a generous use of their IBM 370/158 computer. Also, T.C. wishes to thank the National Institutes of Health for partial support (GM-22760).

Registry No.—3-Acetamido-2-methyl-3-cyclohexene-1-carboxaldehyde, 65415-14-7; 4-acetamido-5-methyl-3-cyclohexene-1-carboxaldehyde, 65415-15-8; methyl 3-methoxy-2-methyl-3-cyclohexene-1-carboxylate, 65415-16-9; methyl 4-methoxy-5-methyl-3-cyclohexene-1-carboxylate, 65415-17-0; 2,3-dimethyl-3-cyclohexene-1-carbonitrile, 65415-18-1; 4,5-dimethyl-3-cyclohexene-1-carbonitrile, 65415-19-2; methyl 2,3-dimethyl-3-cyclohexene-1-carboxylate, 65415-20-5; methyl 4,5-dimethyl-3-cyclohexene-1-carboxylate, 65484-18-6 2,3-diphenyl-3-cyclohexene-1-carboxylic acid, 65415-21-6; 4,5-diphenyl-3-cyclohexene-1-carboxylic acid, 65415-22-7; 3-phenyl-2-methyl-3-cyclohexene-1-carboxylic acid, 65415-23-8; 4-phenyl-5-methyl-3-cyclohexene-1-carboxylic acid, 65415-24-9; 2-methoxy-3-phenylthio-4-acetylcyclohexene, 65415-25-0; 1-methoxy-6-phenylthio-4-acetylcyclohexene, 65415-07-8; 1-methoxy-2-phenylthio-5-acetycyclohexene, 60603-21-6; 1-methoxy-2-phenythio-4-acetylcyclohexene, 60603-33-0; 3-methoxy-4-phenylthio-3-cyclohexene-1-carbonitrile, 60603-20-5; 4-methoxy-3-phenylthio-3-cyclohexene-1-carbonitrile, 65415-08-9; 3-methyl-4-chloro-3-cyclohexene-1-carboxylic acid, 35563-73-6; 4-methyl-3-chloro-3-cyclohexene-1-carboxylic acid, 65415-09-0; 3-methyl-4-phenyl-3-cyclohexene-1-carboxylic acid, 65415-10-3; 4-methyl-3-phenyl-3-cyclohexene-1-carboxylic acid, 65415-11-4.

References and Notes

(1) (a) P. V. Alston R. M. Ottenbrite, and D. D. Shillady, *J. Org. Chem.*, **38**, 4075 (1973); (b) P. V. Alston and R. M. Ottenbrite, *ibid.*, **40**, 1111 (1975).
(2) K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975), and references cited therein.
(3) O. Eisentein, J. M. Lefour, N. T. Anh, and F. F. Hudson, *Tetrahedron*, **33**, 523 (1977), and references cited therein.
(4) N. D. Epiotis, *J. Am. Chem. Soc.*, **95**, 5624 (1973).
(5) I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley, New York, N.Y., 1976.
(6) W. C. Herndor, *Chem. Rev.*, **72**, 157 (1972).
(7) A discussion of the endo/exo stereoselectivity of the Diels–Alder reaction is contained in J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967).
(8) (a) R. E. Townsend, G. Ramunni, G. Segal, W. J. Hehre, and L. Salem, *J. Am. Chem. Soc.*, **98**, 2190 (1976). (b) L. A. Burke, G. Leroy, and M. Sana, *Theor. Chim. Acta*, **40**, 313 (1975).
(9) Some of the reactions were studied before the availability of modern separation techniques; consequently, the accuracy of the regioisomer ratios is not very great and the products which are formed by kinetic control have not been verified in these cases. However, more recent experimental data are available for the monosubstituted butadienes.[5] By assuming that the substituent effects are additive, the preferred regioisomer can be predicted for the disubst tuted butadienes from the regioisomer ratios of the monosubstituted butadienes. In every case the predicted and experimental regioisomers were the same.
(10) C. Minot and N. T. Anh, *Tetrahedron*, **33**, 533 (1977).
(11) B. A. Hess, Jr., and L. J. Schaad, *J. Am. Chem. Soc.*, **95**, 3907 (1973).
(12) A. Streitwieser, Jr., "MO Theory for Organic Chemists", Wiley, New York, N.Y., 1961, p 135.
(13) CNDO/2 and INDO methods: J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, N.Y., 1970.
(14) CNDO/S method: G. Keuhnleuz and H. H. Jaffe, *J. Chem. Phys.*, **58**, 2258 (1973).
(15) W. R. Blackmore and S. C. Abrahams, *Acta Crystallogr.*, **8**, 323 (1955).
(16) There are other intermolecular diatomic interactions besides the ones used in our theory which could affect regioselectivity. However, Bachler and Mark [*Theor. Chim. Acta*, **43**, 121 (1976)] have shown by intermolecular perturbation theory that these other interact ons roughly cancel each other out.

Observations Concerning the Scope and Mechanism of Photostimulated Reactions of Aryl Iodides with Diethyl Phosphite Ion. A Remarkable Difference in Behavior between *m*- and *p*-Chloroiodobenzene[1]

Joseph F. Bunnett* and René P. Traber[2]

University of California, Santa Cruz, California 95064

Received August 16, 1977

Extending studies of the photostimulated reactions of diethyl phosphite ion with aryl halides to form diethyl arylphosphonates, we find that sodium and potassium diethyl phosphite serve equally well, that the reaction is suitable for use on a preparative scale, that the ortho, meta, and para isomers of the iodoanisoles and iodotoluenes all react satisfactorily, and that the iodobenzene/bromobenzene reactivity ratio is about 1×10^3. In $S_{RN}1$ reactions of dihalobenzenes with nucleophiles, whether one or two halogen atoms are replaced depends on the nucleophiles and the halogens involved and on their orientation (meta or para in this study); reactions of the chloroiodobenzenes are about the borderline between mono- and disubstitution.

Under photostimulation, aryl iodides react smoothly and quickly with diethyl phosphite ion to form diethyl arylphosphonate esters;[3,4] see eq 1. The reaction occurs in a number of solvents, although ammonia or dimethyl sulfoxide is preferred. Observed quantum yields in Me_2SO greatly exceed unity;[5] that and other facts indicate a chain mechanism, and the radical chain $S_{RN}1$ mechanism[6] is believed to obtain.

$$ArI + (EtO)_2PO^- \xrightarrow{h\nu} ArPO(OEt)_2 + I^- \qquad (1)$$

The propagation cycle for the $S_{RN}1$ mechanism, which was first proposed (though without symbolization) by Kornblum[7] and Russell[8] and their associates for some substitutions at rather specialized aliphatic centers, is sketched in Scheme I.

Scheme I

$$[ArX]^- \cdot \rightarrow Ar \cdot + X^- \qquad (M1)$$

$$Ar \cdot + Y^- \rightarrow [ArY]^- \cdot \qquad (M2)$$

$$[ArY]^- \cdot + ArX \rightarrow ArY + [ArX]^- \cdot \qquad (M3)$$

0022-3263/78/1943-1867$01.00/0

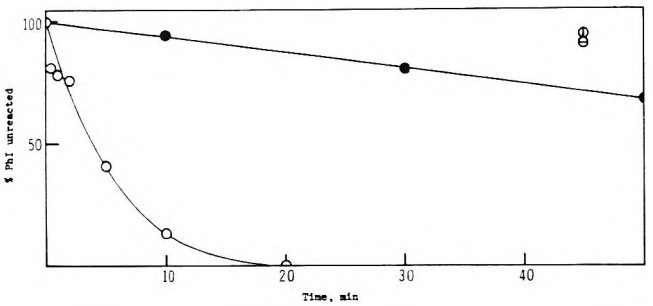


Figure 1. Reactivity of iodobenzene with diethyl phosphite ion in liquid ammonia at reflux: open circles, irradiation without additives; closed circles, irradiation with 0.5 mol % of *p*-dinitrobenzene added; circle with horizontal bar, irradiation with 5 mol % of *p*-dinitrobenzene added; circle with vertical bar, without additives in the dark.

The sum of the three steps of this cycle is, after cancellation of like terms that appear on both sides, merely a substitution ($ArX + Y^- \rightarrow ArY + X^-$) in which nucleophile Y^- replaces nucleofuge X^-. A complete radical chain mechanism also comprises initiation and termination steps. The probable character of these for the reaction of eq 1 is discussed in detail elsewhere.[5]

We now report observations relevant to the scope and mechanism of this reaction.

Results

Preparative Scale Reaction. Inasmuch as previous reactions according to eq 1 had all been conducted on a small scale, about 0.01 mol, an experiment was conducted in which 0.1 mol of iodobenzene and 0.2 mol of $(EtO)_2PO^-K^+$ in 1 L of ammonia were irradiated for 45 min in the Rayonet photochemical reactor. All the iodobenzene was consumed, and 20 g (94%) of pure diethyl phenylphosphonate was obtained. The reaction is thus shown to be useful on a preparative scale. An *Organic Syntheses* procedure on an even larger scale was developed on the basis of this experiment.[9]

Use of Sodium Diethyl Phosphite. In all previous experiments concerning the reaction of eq 1, *potassium* salts of diethyl phosphite or other dialkyl phosphites had been employed. We prepared *sodium* diethyl phosphite in the usual way by reaction of sodium metal with diethyl phosphonate, $(EtO)_2PHO$, in liquid ammonia and found that it reacted with iodobenzene during 45-min irradiation to give diethyl phenylphosphonate in 88% yield. Because this is satisfactory and because sodium metal is easier to handle, sodium diethyl phosphite is the reagent employed in most of the present work.

Behavior of Bromobenzene. The reaction of bromobenzene with diethyl phosphite ion, under photostimulation, is much slower than of iodobenzene. During 4-h irradiation, only 61% of bromide ion was released. GLC examination of the organic products indicated the presence of 59% of diethyl phenylphosphonate as well as residual bromobenzene.

Reactivity of Iodobenzene. A mixture of iodobenzene (0.0455 M) and $(EtO)_2PO^-K^+$ (0.0909 M) in ammonia at reflux was irradiated in the Rayonet reactor with "350 nm" lamps, and samples taken at various times were analyzed by GLC. After 21 min, more than 99% of the iodobenzene had reacted. From experience with the same reaction in Me_2SO solution,[5] one would expect the rate to be independent of iodobenzene concentration but dependent on the first power of $(EtO)_2PO^-K^+$ concentration and, therefore, that a plot of $\ln (b - x)$ vs. time, where b is the initial nucleophile concentration and x is the diethyl phenylphosphonate concentration, would be linear. Such a plot (not shown) was linear from time 2 to 12 min (31–86% reaction) but had a steeper slope for the first 2 min. A second-order kinetic plot, of $\ln (a - x)/(b - x)$ vs. time, where a is the initial iodobenzene concentration, was linear from time 0 to 10 min (to 74% reaction) but was steeper thereafter. We judge this experiment not to be definitive of kinetic order.

The outcome of a group of experiments at similar but not identical concentration levels is shown in Figure 1. Under irradiation, the reaction of iodobenzene with $(EtO)_2PO^-K^+$ was finished in 20 min. In the dark, only 5% of iodide ion was released in 45 min. When 5 mol % of *p*-dinitrobenzene (an efficient inhibitor of many $S_{RN}1$ reactions[7]) was present, an irradiated reaction released only 9% of iodide ion in 45 min. When the *p*-dinitrobenzene presence was reduced to a mere 0.5 mol %, reaction under irradiation was somewhat faster; it went to the extent of 32% in 50 min, but that nevertheless represents strong retardation.

Interpretation of the retarding effect of *p*-dinitrobenzene is not straightforward. On the one hand, it may be acting as a scavenger of electrons or radicals and thereby interfering with perpetuation of the propagation cycle of Scheme I. Alternatively, it or something derived from it may be absorbing photons necessary for initiation. The reaction solutions containing *p*-dinitrobenzene were observed to have yellow to brown-red color.

The influence of dioxygen, a familiar radical scavenger, was assessed by preparing a mixture of $(EtO)_2PO^-K^+$ and iodobenzene in ammonia in the usual way, under N_2, and then bubbling air briskly through it before and during irradiation for 45 min. The usual products were obtained in virtually quantitative yield: iodide ion (98.4%) and diethyl phenylphosphonate (99%). Clearly dioxygen has little, if any, effect.

Reaction in the Presence of Bromide Ion. The reaction of iodobenzene with $(EtO)_2PO^-Na^+$ in ammonia was conducted in the presence of excess KBr in order to see if any incorporation of bromide ion occurred to form bromobenzene. After 5-min irradiation, 81% of iodide ion had been released, 77% of diethyl phenylphosphonate had been formed, but no bromobenzene could be detected.

Reactions of Substituted Iodobenzenes with Diethyl Phosphite Ion. Reactions of *o*- and *m*-iodotoluene and of *o*- and *m*-iodoanisole with $(EtO)_2PO^-Na^+$ in ammonia under irradiation for 60–75 min afforded the corresponding diethyl arylphosphonates according to eq 1 in yields of 71, 91, 85, and 86%, respectively. The corresponding para isomers have already been reported to undergo the same type of reaction, in both cases in 95% yield.[3] Reaction of *o*-iodotoluene with sodium dimethyl phosphite in ammonia during 2-h irradiation afforded dimethyl o-tolylphosphonate in 82% yield. These conversions are all straightforward.

Reactions of Dihalobenzenes with Diethyl Phosphite Ion. Experiments concerning photostimulated reactions of all eight *m*- and *p*-haloiodobenzenes with diethyl phosphite ion are summarized in Table I. About half the data are due to Bunnett and Creary,[3] and about half stem from the present work. Except for two substrates that have low solubility in ammonia and which reacted incompletely despite prolonged irradiation, all these compounds afforded high yields of arylphosphonate esters. In the cases of the diiodobenzenes and the bromoiodobenzenes, both halogen atoms were replaced to afford bis(phosphonate esters); only from *m*-bromoiodobenzene was any monophosphonate ester obtained, and it was a minor by-product. The two fluoroiodobenzenes displayed opposite behavior, giving only the corresponding diethyl fluorophenylphosphonates which represent replacement of iodine but not fluorine.

As for the chloroiodobenzenes, there is a remarkable difference in the behavior of the meta and para isomers. *p*-Chloroiodobenzene affords mainly the corresponding bis(phosphonate ester) accompanied by a mere trace of mono-

Table I. Photostimulated Reactions of Haloiodobenzenes with Diethyl Phosphite Ion[f] in Ammonia

Expt no.	XC_6H_4I	Registry no.	Irradiation time, min[a]	Products,[b] % $C_6H_4[PO(OEt)_2]_2$	Products,[b] % $XC_6H_4PO(OEt)_2$	Recovered XC_6H_4I, %
1[c]	p-$C_6H_4I_2$	624-38-4	205[d]	87	0	
2[c]	m-$C_6H_4I_2$	626-00-6	90	94	0	
3	p-BrC_6H_4I	589-87-7	240[d]	56	0	24
4[c]	m-BrC_6H_4I	591-18-4	60	87	Trace	
5	p-ClC_6H_4I	637-87-6	90	59	Trace	[e]
6a[c]	m-ClC_6H_4I	625-99-0	40	4	89	
6b	m-ClC_6H_4I		60	Trace	91	
7	p-FC_6H_4I	352-34-1	90	0	91	
8[c]	m-FC_6H_4I	1121-86-4	50	0	96	

[a] In the Rayonet photochemical reactor, with 16 "350 nm" lamps. [b] No cine substitution was detectable. [c] Experiments 1, 2, 4, 6a, and 8 are from ref 3. [d] Irradiation prolonged because of low substrate solubility. [e] Detected but not determined. [f] Registry no.: 29800-93-9.

Table II. Competition between Bromo- and Iodobenzene in Photostimulated Reaction with Diethyl Phosphite Ion in Ammonia

Expt no.	PhI,[e] mmol	PhBr,[f] mmol	$(EtO)_2PO^-K^+$, mmol	$PhPO(OEt)_2$, mmol	Irradiation time, s	% I^-	% Br^-	k_{PhI}/k_{PhBr}[a]
11[b]	10	29	29		55[c]	30	0.089	400
12	5	25	18		55[c]	42	0.094	580
13	1	25	20		60	69	0.076	1520
14	1	50	20		60	63	0.056	1770
15	1	75	20		60	77	0.060	2230
16	1	25	20	0.1	30	40	0.044	1160
17	1	25	20	1	30	59	0.056	1590
18	1	25	20	3	60	99	0.094	[d]
19	1	25	20	5	60	69	0.064	1830
20	1	25	20	10	60	98	0.064	[d]
21	1	25	20	10	30	34	0.040	1040
22	1	25	20	10	45	55	0.048	1660

[a] Experimental uncertainty due to titration error estimated as ±10% in the rate ratio. [b] Experiment by Creary. [c] Ammonia volume: 160 mL. [d] Not calculated (too much I^-). [e] Registry no.: 591-50-4. [f] Registry no.: 108-86-1.

phosphonate product. However, m-chloroiodobenzene gives a high yield of the monophosphonate ester, diethyl m-chlorophenylphosphonate, but very little bisphosphonate. This striking difference is susceptible to rational interpretation, as discussed below.

Iodobenzene/Bromobenzene Reactivity Ratio. By means of a direct competition experiment,[10a] Creary[11] estimated the relative reactivity of iodobenzene with respect to bromobenzene to be 400. We have performed several further experiments of the same sort; they are summarized, with Creary's experiment, in Table II. They show iodobenzene to be several hundredfold more reactive than bromobenzene.

In these experiments, the amounts of bromide and iodide ion formed were determined by potentiometric titration with $AgNO_3$. In a typical experiment (experiment 17), 12.42 mL of titrant was required to attain the iodide end point and a further 0.28 mL to the bromide end point. One may ask whether the end points were well enough defined for such small differences to be accurately measurable. The answer is that the end points were indeed sharp and clearly separated. The estimated uncertainty of each end point is ±0.02 mL. Taking this uncertainty into account leads to an estimated uncertainty in the k_{PhI}/k_{PhBr} ratios of about ±10%.

In experiments 11–15, the initial iodobenzene/bromobenzene concentration ratio varied from about 1:3 to 1:75, and the measured reactivity ratio rises steadily from 400 to 2230. We believe the effect to be real, not an experimental artifact.

We thought of the possibility that the reaction product, diethyl phenylphosphonate, might influence the reactivity ratio. In experiments 13 and 16–22, varying amounts of this product were present along with constant amounts of the reactants. Although the measured reactivity ratio varied somewhat among these experiments, there is no correlation of it with the amount of diethyl phenylphosphonate present.

Discussion

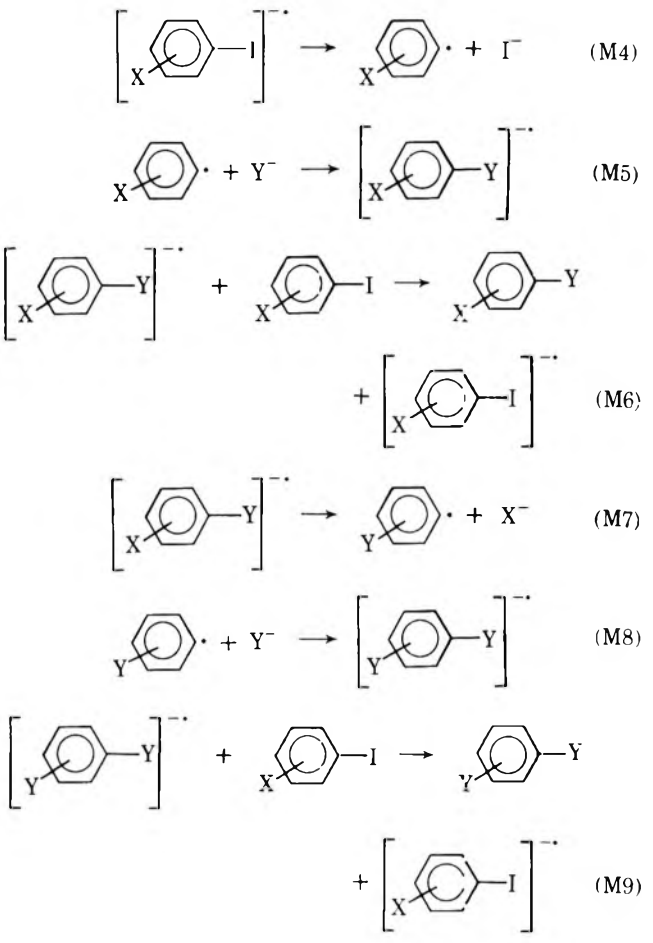
Utility as a Preparative Method. Our work shows that the reaction of eq 1 serves excellently for the preparation of diethyl phenylphosphonate on a 0.1 mol scale. It also shows, extending the experience of Bunnett and Creary,[3] that the method works well with the ortho, meta, and para isomers of the iodoanisoles and the iodotoluenes. It appears to be a method of choice for the preparation of dialkyl arylphosphonates, being experimentally convenient, having wide applicability, and giving excellent yields.

Remarkable Behavior of m-Chloroiodobenzene. In its reaction with $(EtO)_2PO^-K^+$, this dihalobenzene for the most part suffers replacement of iodine but not chlorine, furnishing diethyl m-chlorophenylphosphonate. What makes this reaction remarkable is comparison of it with the reaction of the para isomer with the same reagent and with the photostimulated reaction of m-chloroiodobenzene with thiophenoxide ion in ammonia. In the latter, both halogen atoms are replaced to form mainly m-bis(phenylthio)benzene with very little m-chlorophenyl phenyl sulfide.[16]

In Scheme II, the general $S_{RN}1$ mechanism of Scheme I is elaborated for the somewhat more complex case of an iodohalobenzene reacting with nucleophile Y^-.

Scheme II comprises two parts. Steps M4, M5, and M6 are exactly analogous to the three steps of Scheme I; these constitute a propagation cycle for the replacement of iodine but

Scheme II



not of halogen atom X by nucleophile Y^-. Steps M7, M8, and M9, together with steps M4 and M5, constitute a propagation cycle for the replacement both of iodine and the other halogen by the nucleophile. Steps M7, M8, and M9 are of the same character as steps M4, M5, and M6, respectively, dealing with the involvement of halogen X instead of the depicted iodine atom.

According to the model of Scheme II, the relative rates of steps M6 and M7 determine whether one or both halogens are replaced. (In some cases, the product of monosubstitution, XC_6H_4Y, may, of course, be able to react further with the nucleophile under the reaction conditions.) A major factor determining whether step M6 or M7 is the faster is the rate of the fragmentation that occurs in step M7.

Electrochemical studies have provided some information about factors affecting the frangibility of aryl halide radical anions.[12-14] They show the fragility of carbon–halogen bonds to decrease in the order: C–I > C–Br > C–Cl > C–F. They show the order of frangibility among isomers, $[p\text{-}RC_6H_4X]^{-\cdot} > [m\text{-}RC_6H_4X]^{-\cdot}$, where R is a group with capability to accept electrons mesomerically, such as the benzoyl or the (β-4-pyridyl)vinyl group, $NC_5H_4CH{=}CH{-}$.

Consider now the behavior of *m*-chloroiodobenzene, with respect to the other *m*-haloiodobenzenes in their photostimulated reactions with diethyl phosphite ion in ammonia. As listed in Table I, *m*-diiodobenzene suffers replacement of both iodines without any monosubstitution product being detectable. *m*-Bromoiodobenzene gives mainly disubstitution but a little monosubstitution product is formed. *m*-Chloroiodobenzene gives some disubstitution product but mainly monosubstitution. From *m*-fluoroiodobenzene, only the product of replacement of iodine could be obtained. With respect to the mechanism of Scheme II, the product pattern correlates very well with the indicated order of the fragility of C–X bonds in aryl halide radical anions.

Consider next the behavior of *m*-chloroiodobenzene as compared to *p*-chloroiodobenzene. In photostimulated reaction with diethyl phosphite ion, the para isomer affords mainly the disubstitution product with a mere trace of the monosubstitution product. But the meta isomer gives mainly mono- and little disubstitution product. This is a manifestation of the orientational effect on radical anion frangibility indicated by electrochemical studies. Although to our knowledge *m*- and *p*-chlorophenylphosphonate esters have not been examined by cyclic voltammetry, it would be expected from studies on analogous compounds[12,14] that the radical anion of the para isomer would fragment perhaps two orders of magnitude faster than that of the meta isomer. Observed behavior again finds interpretation in the model of Scheme II. The further implication that the product ratio should depend on the concentration of *m*-chloroiodobenzene, which should affect the absolute rate of step M6 but not M7, has recently been confirmed in experiments of Bunnett and Shafer.[15]

Consider finally the behavior of *m*-chloroiodobenzene with diethyl phosphite ion as compared to that with thiophenoxide ion. With the phosphorus nucleophile, monosubstitution predominates whereas mainly disubstitution occurs with thiophenoxide ion.[16] Bunnett and Creary[3] pointed out that this difference could be understood if step M7 were slower when group –Y were the diethoxyphosphinyl group, $(EtO)_2P(O)$–, than the phenylthio group. They suggested that because the former is more strongly electron attracting the $[m\text{-}ClC_6H_4PO(OEt)_2]^{-\cdot}$ radical anion could be expected to be less frangible than $[m\text{-}ClC_6H_4SPh]^{-\cdot}$. That seems a reasonable proposition.

A complete argument should also take into account the effect of group –Y on the rate of step M6. We have no information about substituent effects on such processes, but we suspect that when –Y is more strongly electron attracting the rate of electron transfer in the indicated sense should be lower. On the other hand, it is conceivable that the rate constant is at or close to the encounter-controlled limit, irrespective of whether –Y is the diethoxyphosphinyl or the phenylthio group.[17]

Iodobenzene/Bromobenzene Reactivity Ratio. In competition experiments, iodobenzene reacts about 1000 times faster than bromobenzene with diethyl phosphite ion. This huge difference contrasts with the approximately eightfold difference observed in the photostimulated reactions of these compounds with acetone enolate ion in ammonia[11] or the 5.6-fold difference in the dark or photostimulated reaction with pinacolone enolate ion in dimethyl sulfoxide solution.[18]

We suppose, in terms of the $S_{RN}1$ mechanism, that the measured reactivity ratios report the relative rate constants for the involvement of iodo- and bromobenzene in step M3, Scheme I. That is an electron-transfer step.

The rate of electronation of iodobenzene by means of the hydrated electron is about thrice as great as for bromobenzene;[19] k_{PhI} is 1.2×10^{10} M^{-1} s^{-1}, essentially at the encounter-controlled limit, and k_{PhBr} is 4.3×10^9 M^{-1} s^{-1}. In tetrahydrofuran solution, rate constants for electron transfer from (ion-paired) sodium naphthalenide to butyl iodide and hexyl bromide[20] are, respectively, 4.6×10^7 and 7.2×10^4 M^{-1} s^{-1}. Rate constants for electron transfer from aromatic hydrocarbon radical anions to other aromatic hydrocarbons are about 3×10^9 M^{-1} s^{-1}, essentially at the encounter-controlled limit, when the standard free energy change is negative, but one or two powers of ten slower when it is positive.[17]

An hypothesis warranting consideration[21] is that step M3 shows selectivity similar to that in reactions of the hydrated

Table III. Preparation and Physical Properties of Phosphonate Esters

Substrate	Registry no.	Mol of reactant used	Irradiation time, min	Halide ion yields, %	Phosphonate ester product: Formula	Registry no.	Yield, %	Mp or bp (Torr), °C	IR, cm^{-1}	^1H NMR, δ (CCl_4)	MS	Ref
o-$CH_3C_6H_4I$[a]	615-37-2	0.023	60	95	*o*-$CH_3C_6H_4PO(OEt)_2$	15286-11-0	71	94–95 (0.2)	1600, 1480, 1450, 1250, 1025, 965, 820, 760	1.33 (t, 6 H), 2.6 (t, 3 H), 4.1 (m, 4 H), 7.3–8.1 (m, 4 H)	228 (M^+), 227, 226 212, 199, 184, 183	*c*
o-$CH_3C_6H_4I$[a,b]		0.023	120	94	*o*-$CH_3C_6H_4PO(OMe)_2$	6840-23-9	82	72–74 (0.09)	1600, 1460, 1245, 1020, 825, 755	2.6 (d, J = 1.5 Hz, 3 H), 3.75 and 3.95 (2 s, 6 H), 7.6–8.3 (m, 4 H)	201, 200, 186	*c*
m-$CH_3C_6H_4I$	625-95-6	0.025	75		*m*-$CH_3C_6H_4PO(OEt)_2$	15286-13-2	91	92–93 (0.02)	1610, 1580, 1250, 1025, 960, 785, 700	1.31 (t, 6 H), 2.45 (s, 3 H), 4.13 (m, 4 H), 7.3–8.0 (m, 4 H)	228 (M^+), 200, 199, 184, 183, 172, 171, 156, 155, 154	*c*
o-$CH_3OC_6H_4I$	529-28-2	0.015	75	99	*o*-$CH_3OC_6H_4PO(OEt)_2$	15286-17-6	85	122–124 (0.14)	1275, 1250, 1050, 1025, 760	1.30 (t, 6 H), 3.88 (s, 3 H), 3.8–4.3 (m, 4 H), 6.8–8.1 (m, 4 H)	244 (M^+), 215, 213 187	*c*
m-$CH_3OC_6H_4I$[a]	766-85-8	0.021	75	98	*m*-$CH_3OC_6H_4PO(OEt)_2$	65442-22-0	86	143 (1.5)	1600, 1580, 1470, 1430, 1250, 1240, 1040, 1025, 965, 790, 695	1.32 (t, 6 H), 3.88 (s, 3 H), 4.1 (m, 4 H), 7.0–7.6 (m, 4 H)	244 (M^+), 216, 215, 200, 188, 187	
p-BrC_6H_4I[d]		0.015	240	71 (I^-) 70 (Br^-)	*p*-$C_6H_4[PO(OEt)_2]_2$	21267-14-1	56	70–71.5				*e*
p-ClC_6H_4I[d]		0.015	90	77 (I^-) 75 (Cl^-)	*p*-$C_6H_4[PO(OEt)_2]_2$		59	70.5–72	1480, 1450, 1390, 1375, 1250, 1145, 1025, 960, 805, 760, 620	1.37 (t, 12 H), 4.2 (m, 8 H), 7.8–8.2 (dd, 4 H)		*e*
m-ClC_6H_4I[d]		0.015	60	97 (I^-) Nil (Cl^-)	*m*-$ClC_6H_4PO(OEt)_2$	23415-71-6	91	107–109 (0.09)	1250, 1145, 1050, 1025, 970, 790, 690, 670		250/248 (M^+), 235/233, 222/220	*f*
p-FC_6H_4I[d]		0.022	90	97 (I^-) Nil[g] (F^-)	*p*-$FC_6H_4PO(OEt)_2$	310-40-7	91	105 (0.65)	1600, 1500, 1445, 1250, 1160, 1130, 1025, 960, 835	1.35 (t, 6 H), 4.1 (m, 4 H), 7.0–7.5 and 7.7–8.2 (2 m, 4 H)	232 (M^+), 204, 188, 187, 176, 160, 159	*h*

[a] Experiment performed with the technical assistance of E. W. Bouldin. [b] $(MeO)_2PHO$ used instead of $(EtO)_2PHO$. [c] Reference 26. [d] See also Table I. [e] P. Tavs, *Chem. Ber.*, **103**, 2428 (1970). [f] D. I. Lobanov, E. N. Tsvetkov, and M. I. Kabachnik, *Zh. Obshch. Khim.*, **39**, 841 (1969). [g] Negative qualitative test with $CaCl_2$. [h] H. Schindlbauer, *Chem. Ber.*, **100**, 3432 (1967).

electron with phenyl halides when the associated free energy change is significantly negative but that selectivity is much greater when the free energy change is near zero or positive. That would amount to postulating a selectivity–reactivity relationship,[22] and whether such relationships exist is a matter of controversy.[10b] An alternative hypothesis is that when the free energy change for step M3 is positive this step may be a quasi-equilibrium within the encounter complex, with step M1 then entering into determination of the apparent electron-transfer rate.

Available polarographic data do not, however, support such interpretations. For polarographic reduction of diethyl phenylphosphonate in dimethylformamide solution with tetraethylammonium iodide supporting electrolyte, $E_{1/2}$ is reported to be −2.04 V vs. the mercury pool,[23] which amounts to about −2.54 V vs. the standard calomel electrode.[24] Inasmuch as $E_{1/2}$ values for reduction of iodo- and bromobenzene are higher (less negative),[25] electron transfer from $[PhPO(OEt)_2]^{-\cdot}$ to either halobenzene should be exoenergetic.

Interpretation of the remarkable difference in iodobenzene/bromobenzene reactivity ratios is a challenge.

Experimental Section

Large-Scale Preparation. To a solution of potassium metal (7.8 g, 0.2 mol) in 1000 mL of liquid ammonia in a 3-L round-bottom flask provided with a well-type condenser and swept by a slow stream of dry N_2, about 27.7 g (0.2 mol) of diethyl phosphonate was added during a period of 5 min. The last increments were added dropwise, and addition was stopped when the blue color was discharged. Iodobenzene (20.4 g, 0.1 mol) was added, and the flask with condenser and stirrer was placed within a Rayonet Model RPR-100 photochemical reactor equipped with fluorescent lamps emitting maximally at 350 nm. Irradiation was conducted for 45 min, with interruption at ca. 15-min intervals to spray the flask exterior with a little 2-propanol and wipe away the frost with a towel. Ammonium nitrate (10 g) and 250 mL of diethyl ether were added, the ammonia was allowed to evaporate, 100 mL of water was added, the ether layer was separated, and the water layer was thrice extracted with 200-mL portions of ether. The combined ether extracts were dried over anhydrous Na_2SO_4, the ether was evaporated, and the residue was distilled; 20.0 g (94%) of diethyl phenylphosphonate, bp 85–87 °C (0.05 Torr), was obtained. The IR spectrum was identical with that of an authentic sample.

Reactions of Substituted Iodobenzenes with Diethyl Phosphite Ion. These reactions were conducted as described above, but on a smaller scale. In general, 250 mL of ammonia was used, in a 500-mL flask, and the molar amount of sodium or potassium diethyl phosphite was about double that of the substrate. Details about the experiments and the properties of the products obtained are set forth in Table III. The observed ^1H NMR spectra are in agreement with the observations of Obrycki and Griffin.[26] Iodide, bromide, or chloride ion in the aqueous layer from product workup was determined by titration with $AgNO_3$.

Competition Experiments (Table II). Reactions were performed in the manner described, with 250 mL of ammonia being used unless otherwise stated. After evaporation of the ammonia and addition of water, the aqueous phase was separated, acidified with HNO_3, and titrated with standard $AgNO_3$ solution. k_{PhI}/k_{PhBr} values were reckoned by means of the expression[10a]

$$k_{PhI}/k_{PhBr} = \ln([PhI]_0/[PhI]_t)/\ln([PhBr]_0/[PhBr]_t)$$

Experiments on the Reactivity of Iodobenzene. Reactions were carried out in the manner described. Samples (ca. 1 mL) were removed at measured times by means of a J tube[27] and added to 1 mL of water, and the mixture was extracted with 1 mL of ether. The ether layer was examined by GLC on a column of 2.5% SE-54 on Chromosorb GAW/DMCS. The peaks for iodobenzene and diethyl phenylphosphonate were corrected for molar response, and the progress of the reaction was judged from their relative magnitudes.

References and Notes

(1) Research supported in part by the National Science Foundation.
(2) Fellow of the Schweizerischen Stiftung für Stipendien auf dem Gebiete der Chemie, 1974–1975.
(3) J. F. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3612 (1974).
(4) J. F. Bunnett, R. G. Scamehorn, and R. P. Traber, *J. Org. Chem.*, **41**, 3677 (1976).
(5) S. Hoz and J. F. Bunnett, *J. Am. Chem. Soc.*, **99**, 4690 (1977).
(6) J. K. Kim and J. F. Bunnett, *J. Am. Chem. Soc.*, **92**, 7463 (1970).
(7) N. Kornblum, R. E. Michel, and R. C. Kerber, *J. Am. Chem. Soc.*, **88**, 5662 (1966); N. Kornblum, *Angew. Chem., Int. Ed. Engl.*, **14**, 734 (1975).
(8) G. A. Russell and W. C. Danen, *J. Am. Chem. Soc.*, **88**, 5663 (1966); **90**, 347 (1968).
(9) J. F. Bunnett and R. H. Weiss, *Org. Synth.*, in press.
(10) (a) J. F. Bunnett in "Investigation of Rates and Mechanisms of Reactions", 3rd ed, Part I, E. S. Lewis, Ed., Wiley, New York, N.Y., 1974, p 159; (b) p 468.
(11) X. Creary, unpublished work in this laboratory.
(12) L. Nadjo and J. M. Saveant, *J. Electroanal. Chem.*, **30**, 41 (1971).
(13) K. Alwair and J. Grimshaw, *J. Chem. Soc., Perkin Trans. 2*, 1150, 1811 (1973).
(14) J. Grimshaw and J. Trocha-Grimshaw, *J. Electroanal. Chem.*, **56**, 443 (1974).
(15) J. F. Bunnett and S. J. Shafer, *J. Org. Chem.*, following paper in this issue.
(16) J. F. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3611 (1974).
(17) L. M. Dorfman, *Acc. Chem. Res.*, **3**, 224 (1970).
(18) R. G. Scamehorn and J. F. Bunnett, *J. Org. Chem.*, **42**, 1449 (1977).
(19) M. Anbar and E. J. Hart, *J. Am. Chem. Soc.*, **86**, 5633 (1964).
(20) S. Bank and D. A. Juckett, *J. Am. Chem. Soc.*, **97**, 567 (1975).
(21) This hypothesis has emerged in discussions with colleagues in this laboratory, especially X. Creary, S. Hoz, and J. Swartz.
(22) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, N.Y., 1963, p 162.
(23) Ya. A. Levin, Yu. M. Kargin, V. S. Galeev, and V. I. Sannikova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 411 (1968); A. V. Il'yasov, Yu. M. Kargin, Ya. A. Levin, I. D. Morozova, B. V. Mel'nikov, A. A. Vafina, N. N. Sotnikova, and V. S. Galeev, *ibid.*, 770 (1971).
(24) P. H. Given, M. E. Peover, and J. Schoen, *J. Chem. Soc.*, 2674 (1958); P. G. Grodzka and P. J. Elving, *J. Electrochem. Soc.*, **110**, 231 (1963).
(25) L. Meites and P. Zuman, "Electrochemical Data", Part I, Vol. A, Wiley, New York, N.Y., 1974, pp 178–181.
(26) R. Obrycki and C. E. Griffin, *J. Org. Chem.*, **33**, 632 (1968).
(27) R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 1407 (1973).

Role of Monosubstitution Product in the Reactions of m-Dihalobenzenes with Diethyl Phosphite Ion to Form Tetraethyl m-Phenylenebisphosphonate. Strong Evidence of Mechanism from Simple Observations[1]

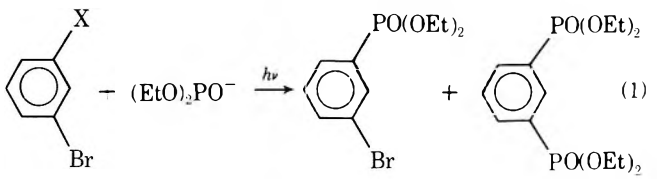
Joseph F. Bunnett* and Sheldon J. Shafer

University of California, Santa Cruz, California 95064

Received August 16, 1977

Interrupted photostimulated reaction of diethyl phosphite ion with m-bromoiodobenzene (**1b**) in liquid ammonia gives much tetraethyl m-phenylenebisphosphonate (**3**), much unreacted **1b**, and a little diethyl m-bromophenylphosphonate (**2**). Inasmuch as **2** is less reactive than **1b** with diethyl phosphite ion under these conditions, **2** cannot be an intermediate on the main route from **1b** to **3**. This result is compatible with the $S_{RN}1$ mechanism but excludes all conceivable alternative mechanisms. Interrupted reaction with m-dibromobenzene (**1a**) affords a similar product mixture but, since **2** is more reactive than **1a** under the more strenuous conditions necessary to get **1a** to react, the failure of **2** to appear as a product of interrupted reaction is of uncertain significance. Experiments specifically to probe one alternative radical chain mechanism offer no support for it.

Under photostimulation, diethyl phosphite ion reacts readily[2] with iodobenzene and more slowly with bromobenzene to form diethyl phenylphosphonate, $C_6H_5PO(OEt)_2$. The same reagent converts m-bromoiodobenzene mainly into tetraethyl m-phenylenebisphosphonate (**3**) (87% yield), only a small amount of monosubstitution product **2** being formed.[2] Titration of samples taken in the course of a reaction showed that the ratio of iodide ion to bromide ion release was virtually constant throughout the process and, thus, that there was no accumulation of **2** at early stages of the reaction.[3]



(1)

1a, X = Br
b, X = I

2 **3**

Analogous behavior has been observed for reactions of certain dihalobenzenes with thiophenoxide ion.[4] In the case of the thiophenoxide reaction with m-chloroiodobenzene, not only is the disubstitution product, $m\text{-}C_6H_4(SPh)_2$, formed preferentially to m-chlorophenyl phenyl sulfide, but the latter reacts demonstrably slower than m-chloroiodobenzene with thiophenoxide ion. The conclusion that m-chlorophenyl phenyl sulfide is not an intermediate on the main route to the disubstitution product is of great significance in regard to reaction mechanism.[4]

We now report an inquiry into the role that **2** may play as an intermediate or by-product in the photostimulated conversion of **1a** and **1b** into **3**. We have also performed some other experiments concerning the mechanism of reaction of aryl halides with diethyl phosphite ion.

Results

Reactions of m-bromoiodobenzene (1b). In the presence of a fourfold excess of sodium diethyl phosphite under irradiation at about 350 nm for 7 min, **1b** reacted incompletely, forming **2** in about 7% yield and **3** in about 60% yield, with about 28% of unreacted **1b** remaining (experiments 1 and 2, Table I). Under the same conditions, **2** reacted only to the extent of 40% (experiment 3), and thus **2** is less reactive than **1b**.

The lesser reactivity of **2** is demonstrated also by the behavior of mixtures of **1b** and **2** under conditions of the same type (experiments 4 and 5). While all or nearly all of the **1b** reacts, virtually all of the **2** introduced is recovered as such, and there is extensive formation of **3**. Undoubtedly some of the **2** was a minor by-product from the reaction of **1b**, but nevertheless experiments 4 and 5 show that while **1b** reacts extensively **2** reacts only to a small extent.[5]

There was negligible reaction of **1b** with $(EtO)_2PO^-Na^+$ in the dark (experiments 16 and 17).

These experiments constitute compelling evidence that **2** is not an intermediate except perhaps to a minor extent in the transformation of **1b** into **3**. They do not exclude the possibility of an alternative stepwise reaction involving first the replacement of bromine to form diethyl m-iodophenylphosphonate and then the replacement of iodine, but strong arguments against such a possibility can be marshaled on other grounds.

Reactions of m-Dibromobenzene (1a). If both halogens in a m-dihalobenzene are the same, uncertainties as to which would be replaced first in a stepwise mechanism disappear.

1a is much less reactive than **1b** with diethyl phosphite ion. Compare experiment 6 with experiment 1 or 2. Under identical conditions, **1a** reacts (forming **3** exclusively) only to the extent of 15% while **1b** is about 70% consumed. In no case did the reaction of **1a** with sodium diethyl phosphite form any detectable amount of **2**.

In experiments 7 and 8, the reactivities of **1a** and **2**, separately, are compared under identical conditions. Whereas **1a** reacts only to the extent of about 30%, **2** is almost wholly consumed.[6] In experiments 9 and 10, which are nearly identical in design, the reactivities of **1a** and **2**, admixed, are compared. In both experiments there was almost total reaction by **2** and scarcely any consumption of **1a**.

The comparative reactivities of **1a** and **2** were also examined under irradiation with lamps that emit maximally at 300 nm. Experiments 12 and 13 show that, separately, **2** is more reactive than **1a**. Experiment 14 shows that, admixed, **2** is again more reactive than **1a**. Experiment 15 demonstrates that extended irradiation of **2** in the absence of the nucleophile causes little change.

It is thus evident that, for reactions of **1a** with diethyl phosphite ion, the monosubstitution product **2** is *more* reactive than the original substrate. One cannot tell from the present data whether or not the absence of **2** as a detectable product from the reaction of **1a** is due to its never being formed or to its rapid transformation, after being formed, to disubstitution product **3**. A more detailed kinetic and product study might, however, enable the question to be answered definitively.

0022-3263/78/1943-1873$01.00/0

Table I. Photostimulated Reactions of *m*-Dihalobenzenes with Sodium Diethyl Phosphite in Liquid Ammonia

Expt no.	Dihalobenzene, mmol	2, mmol	$(EtO)_2PO^-Na^+$, mmol	λ, nm[a]	Irradiation time, min	Materials present after reaction, mmol: Dihalobenzene	2	3
1	**1b**, 5.1		19.4	350	7	1.4	0.3	3.2
2	**1b**, 5.0		22.0	350	7	1.4	0.4	2.8
3[b]		4.8	22.1	350	7		3.0	1.9
4	**1b**, 3.1	2.4	22.0	350	7	0.12	2.7	2.5
5	**1b**, 2.6	2.5	21.3	350	7	0	2.4	2.2
6	**1a**, 5.3		21.0	350	7	4.5	0	0.8
7	**1a**, 5.1		21.9	350	20	3.6	0	1.6
8[c]		4.8	21.8	350	20		0.1	4.3
9	**1a**, 2.7	2.4	22.3	350	20	2.7	0.5	1.9
10	**1a**, 2.5	2.4	22.2	350	20	2.5	0	2.2
11	**1a**, 5.2		21.9	350	120	1.3	0	3.6
12	**1a**, 5.0		20.7	300	20	2.1	0	2.6
13		4.7	21.7	300	20		*d*	4.7
14	**1a**, 2.5	2.4	22.0	300	20	2.1	0	2.9
15		4.6	Nil	300	120		4.3	
16[e]	**1b**, 4.6		20.3	Dark	7.5[f]		*g*	*g*
17[e]	**1b**, 4.6		20.2	Dark	122[f]		*h*	*j*

[a] Broad-bd radiation from fluorescent lamps rated emit maximally at the wavelength listed. [b] In a preliminary experiment, 4.6 mmol of 2 and 20.9 mmol of $(EtO)_2PONa$ scarcely reacted in 7 min, and 94% of unreacted 2 was determined. [c] In a preliminary experiment, 4.9 mmol of 2 and 22.1 mmol of $(EtO)_2PONa$ during 20-min irradiation afforded 9% of 3, and 92% of unreacted 2 was determined. [d] A trace at the appropriate GLC retention time. [e] Experiment by Raymond R. Bard. [f] Time in dark. [g] No detectable formation of halide ion. [h] Iodide ion (1.9%) and bromide ion (1.4%) were determined as products.

Comparison of experiments 7 and 12, Table I, suggests that light of shorter wavelength is more effective for stimulation of the reaction of **1a** with diethyl phosphite ion. However, inasmuch as both sets of fluorescent lamps furnish broad-band radiation and no actinometry was performed, these experiments cannot be regarded as an adequate test of the dependence of quantum yield on wavelength.

Probes of an Alternative Mechanism. For reasons discussed below, we exposed iodobenzene to two sets of conditions under which we thought that diethyl phosphonyl radicals, $(EtO)_2PO\cdot$, might exist transiently. In one experiment, a mixture of iodobenzene, diethyl phosphonate $[(EtO)_2PHO]$, and di-*tert*-butyl peroxide was heated at reflux for 5 h. A large amount of unreacted iodobenzene was found by GLC analysis, but no diethyl phenylphosphonate could be detected. In the other, a solution of diiodine, I_2, in tetrahydrofuran was added slowly with stirring to a solution of iodobenzene and sodium diethyl phosphite in liquid ammonia carefully shielded from external illumination, and the solution was stirred a few minutes longer. Again there was extensive recovery (94%) of iodobenzene, and no trace of diethyl phenylphosphonate could be found.

Preparation of Diethyl *m*-Bromophenylphosphonate (2). Because little or no **2** is formed in the reactions of **1a** and **1b** with diethyl phosphite ion, we were obliged to use another approach in order to obtain quantities sufficient for our studies. The Doak–Freedman synthesis[7] of *m*-bromophenylphosphonic acid (from *m*-bromobenzenediazonium fluoroborate and PCl_3 in ethyl acetate with catalysis by CuBr) served us dependably although the yield was modest (32%). In some cases we experienced difficulty in converting the acid to the acid chloride, $m\text{-}BrC_6H_4POCl_2$. For reasons not well understood, successful conversion to the acid chloride seemed to depend on fastidious recrystallization of the phosphonic acid. Transformation of the acid chloride to **2** was straightforward. The **2** used in the studies reported above was prepared by this route.

Despite its serviceability, the route described was somewhat objectionable because of the difficulties mentioned, the many steps involved, and the low overall yield. We therefore attempted the direct bromination of diethyl phenylphosphonate, a reaction of which we found no mention in the literature. Attempted bromination by means of the *Organic Syntheses* procedure for bromination of nitrobenzene[8] afforded no bromination product. The method of Derbyshire and Waters,[9,10] which employs bromine and silver sulfate in concentrated sulfuric acid, was, however, successful, giving **2** in 66% yield in a short reaction time. The **2** so obtained was, however, not pure. GLC analysis showed the presence of some unbrominated diethyl phenylphosphonate and of some dibrominated material, each to the extent of about 5%. In working with small quantities, we were able to effect a partial separation by distillation, and we believe that a larger quantity could be purified successfully by this means.

Solvent Effects. A problem with use of liquid ammonia as a solvent for $S_{RN}1$ reactions is the limited solubility of some substrates in it. We did a few experiments concerning photostimulated reaction of **1a** with sodium diethyl phosphite in ammonia containing 20% of tetrahydrofuran or dimethyl sulfoxide as cosolvent. Whereas a 32% yield of **3** was obtained in neat ammonia (experiment 7, Table I), three experiments with tetrahydrofuran cosolvent for the same or longer irradiation time gave **3** in yields ranging from 0 to 15%, and one experiment with dimethyl sulfoxide cosolvent gave **3** in 14% yield.

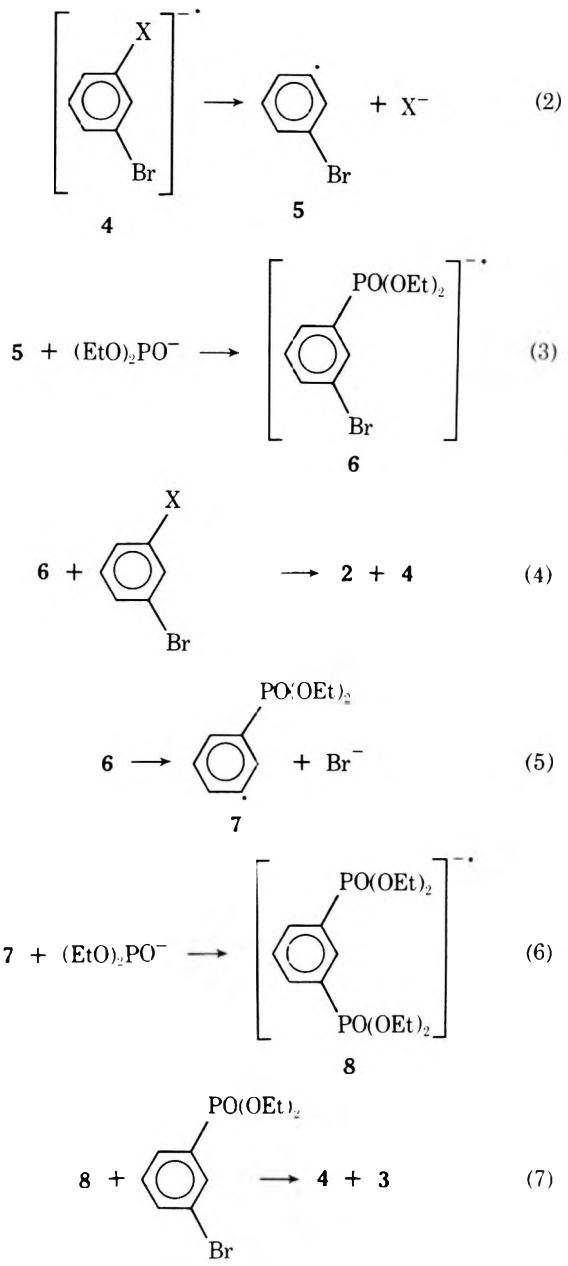
Discussion

We have observed that both **1a** and **1b**, in interrupted photostimulated reactions with excess diethyl phosphite ion according to eq 1, give mainly or entirely disubstitution product **3** with little or none of monosubstitution product **2**, even as substantial amounts of **1a** and **1b** remain unreacted.

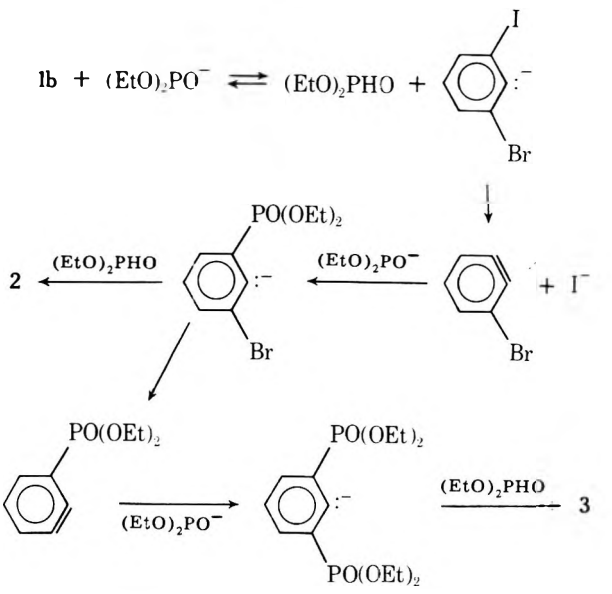
In the case of **1b**, we have shown that **1b** reacts with diethyl phosphite ion faster than does **2**. The fact that little **2** is formed compels the conclusion that **2** is not an intermediate on the main route from **1b** to **3**.

In the case of **1a**, we have found that **2** does react faster than **1a**. That experiment is therefore inconclusive as to whether or not **2** is an intermediate on the pathway from **1a** to **3**. Because of the close analogy between **1a** and **1b** and because of

Scheme I



Scheme II



mechanistic considerations discussed below, we believe that **2** is not an intermediate in this reaction either.

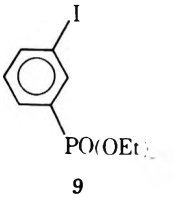
These reactions are presumed to occur by the $S_{RN}1$ mechanism.[11] When that mechanism is applied straightforwardly to the present case, two alternative propagation cycles result, as sketched in Scheme I. One cycle, which leads to monosubstitution product **2**, comprises steps 2–4. The other, leading to disubstitution product **3**, consists of steps 2, 3, and 5–7. This radical chain mechanism must, of course, also involve initiation and termination steps, but they are of little immediate interest. Other work[12] gives some insight into what their nature may be.

The mechanism of Scheme I accommodates naturally the experimental conclusion that **2** is not an intermediate on the main route from **1b** to **3**. The intermediate which represents replacement of iodine but not of bromine is not **2** but **6**, which is the radical anion of **2**. Scheme I provides two pathways for **6** to tread, namely, electron transfer to **1b** (step 4) with formation of **2** and fragmentation to expel bromide ion (step 5) and ultimately to form **3**. Under the conditions employed, the latter pathway was selected about ten times as often as the former.

The reaction of **1a** with diethyl phosphite ion is presumed to occur via the same mechanism. The same crucial intermediate, **6**, is involved regardless of the identity of halogen X. In the partitioning between steps 4 and 5, somewhat less use of step 4 would be anticipated because electron transfer from the hydrated electron to bromobenzene is slower than to iodobenzene.[13] One would therefore expect less formation of **2** than in the reaction of **1b**, but one cannot tell whether this is the reason no **2** could be detected as a product because **2** itself is transformed comparatively rapidly to **3** under the conditions of the reaction with **1a**.

Although the mechanism of Scheme I gives a fine account of the present observations and of others regarding the photostimulated reactions of *m*-dihalobenzenes with dialkyl phosphite ions and is the only conceivable mechanism compatible with the evidence, we must invoke the universal caveat that the evidence may also be consistent with some mechanism as yet unconceived, that is, with a mechanism that no one has thought of or that at least has not come to our attention.

Our finding that **2** is not an intermediate on the main route from **1b** to **3** serves to exclude a great many mechanisms, some rational, some ridiculous, some conceivable, and maybe some as yet unconceived, that would involve **2** as an intermediate. However, the significance of this exclusion is considerably reduced unless stepwise replacement first of bromine, to form intermediate **9**, and then of iodine can also be excluded. We did not investigate the reactivity of **9** with diethyl phosphite ion but, taking note of the greater reactivity of **2** than of **1a**,

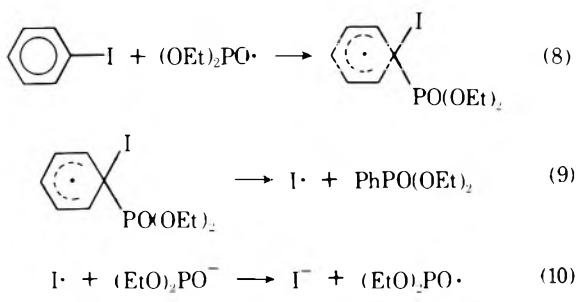


9

we suppose that **9** would be more reactive than **1b**. There is, however, a strong argument against any mechanism that would replace the bromine of **1b** before the iodine, namely, that iodobenzene is enormously more reactive than bromobenzene in photostimulated reaction with diethyl phosphite ion.[14] The greater reactivity of **1b** than of **1a** is a further expression of the same characteristic. The exclusion of reaction via the intermediacy of **9** is therefore strongly supported.

A mechanism of wholly different character that provides for conversion of **1b** to **3** without the intermediacy of **2** is

Scheme III



sketched in Scheme II. It is an aryne mechanism, and a central intermediate is the conjugate base of **2** rather than **2**. Arguments against it can be made, but it is definitively disqualified by the fact (experiment 16) that **1b** does not react detectably with $(EtO)_2PO^-Na^+$ in the dark under the conditions of experiments 1, 2, 4, or 5.

Exclusion of an Alternative Radical Mechanism. Among the many mechanisms excluded by the predominance of a pathway that avoids **2** as an intermediate is a radical chain mechanism, the propagation cycle of which is sketched (for reaction of iodobenzene) in Scheme III. This mechanism finds precedent in mechanisms suggested for substitution reactions in which, it appears, other types of radicals react with aryl halides.[15]

Although a mechanism analogous to that of Scheme III could be written for an aryl bromide, the far greater reactivity of iodo- than of bromobenzene with diethyl phosphite ion would dictate that as applied to **1b** it should involve replacement first of iodine to form **2** and then of bromine. Such a mechanism provides no way for involvement of iodine in the process to trigger the involvement of bromine, as does the mechanism of Scheme I. For that reason alone a mechanism of the type in Scheme III can be rejected.

As mentioned above, we did nevertheless perform further experiments to test the mechanism of Scheme III. The experiment with iodobenzene, diethyl phosphonate, and di-*tert*-butyl peroxide was fashioned after experiments of Jason and Fields[16] who achieved the phosphonation of naphthalene, anthracene, and other polynuclear aromatic hydrocarbons in good yields by refluxing them with diethyl phosphonate and di-*tert*-butyl peroxide. They proposed a radical mechanism involving the attachment of $(EtO)_2PO\cdot$ radicals to ring carbon atoms and then removal of hydrogen atoms. The failure of iodobenzene to react appreciably if at all under those conditions inveighs against the mechanism of Scheme III.

The experiment with iodobenzene, sodium diethyl phosphite, and diiodine in liquid ammonia in the dark was performed with the thought that diiodine might bring about one-electron oxidation of the diethyl phosphite ion, somewhat as in step 10, Scheme III. If diethyl phosphonyl radicals were thereby generated, reaction to form diethyl phenylphosphonate should occur readily if Scheme III were valid, for the conditions are (except for the mode of stimulation) identical with those under which reaction occurs in high yield under illumination. Again, little reaction of the iodobenzene was detected.

Experimental Section

Instrumentation. NMR spectra were determined on a JEOL Minimar 60-MHz instrument. GLC analyses were performed by means of a Hewlett-Packard Model 5750 flame ionization instrument equipped with a 183 cm × 3.2 mm, 10% silicone rubber (UC-W98) on 80–100 mesh WAW DMCS column. Reaction yields were esitmated from peak areas with respect to those of an internal standard, suitable molar response corrections being applied. Photostimulated reactions were carried out in a Rayonet Model RPR-100 reactor equipped with 16 lamps, usually a set rated to emit maximally at 350 nm but sometimes a set rated to emit maximally at 300 nm, as noted in Table I.

Reactions of Substrates with Sodium Diethyl Phosphite. In a three-neck 250-mL round-bottom flask equipped with a dry ice condenser and polyethylene stir bar, and under a dry nitrogen atmosphere, dry ammonia was condensed to the level of 50 mL as marked on the outside of the flask. Then 20–22 mmol of clean sodium metal was added and stirred until dissolved. This solution was then titrated dropwise with diethyl phosphonate, until no blue color remained. Then the substrate or substrates were added, in amounts as noted in Table I. The solution was placed in the photolysis apparatus and stirred gently, and the frost was washed off the flask with acetone. The photolysis was then started. If photolysis was longer than 20 min, it was stopped every 20 min and the frost removed from the outside of the flask by rinsing with acetone. After the photolysis was complete, 1.7 g (21 mmol) of ammonium nitrate and 50 mL of chilled diethyl ether were added. The ammonia was allowed to evaporate, and water was added and then a measured amount of diphenylmethane as internal standard. The crude reaction mixture was subjected to a normal workup. A portion of the resulting ether extract was analyzed by GLC.

Modified Doak–Freedman Synthesis of *m*-Bromophenylphosphonic Acid. *m*-Bromobenzenediazonium tetrafluoroborate (48.59 g, 0.179 mol) was placed in a 1-L, three-neck, round-bottom flask and 279 mL of ethyl acetate was added. The flask was equipped with a mechanical stirrer, thermometer, and a gas outlet into a water trap. After stirring was begun, 15.84 mL (24.93 g, 0.182 mol) of phosphorus trichloride and 4.0 g of copper(I) bromide were added. After some 30 min, a slight darkening of the reaction mixture was noted but no gas evolved. The reaction mixture was then heated with a water bath to 50 °C; then the bath was removed. Gas started to evolve slowly and then rapidly, and the reaction mixture was cooled with an ice bath to prevent foaming. After about 30 min, no more gas could be observed. The reaction was stirred 1 h, and then the heating started again, this time without cooling as gas was evolved slowly. After 30 min more of stirring, the now black solution was quenched carefully with water. The reaction mixture was subjected to steam distillation to remove volatile materials. The remaining solution was concentrated on a rotary evaporator until the solid–aqueous suspension contained only about 50 mL of liquid. The solid was removed by filtration. The crude solid was dissolved in a minimum of 10% sodium hydroxide and an insoluble tar removed by filtration. The solution was again concentrated to about 50 mL and titrated dropwise with concentrated hydrochloric acid until the pH was 4–4.5, as indicated by means of pH 3–5 indicator paper. The resulting crude solid was removed by filtration and added to 60 mL of 6 M hydrochloric acid which was then brought to boiling. The solution of phosphonic acid was then separated from insoluble diarylphosphinic acid, placed in a warm beaker, and allowed to cool slowly. Initially, some granular crystals formed. The hydrochloric acid solution was decanted from this granular solid and allowed to cool. The crystals that formed slowly (plates) were collected on a sintered glass funnel. These crude crystals were recrystallized from 40 mL of 6 M hydrochloric aicd, again with separation of the initial granular crystals from the acid solution. The acid solution was allowed to cool slowly and the resulting crystals (plates) were collected by glass frit filtration and then dried for 15 h under a vacuum (~0.5 mm) at room temperature: yield, 13.48 g (32%); mp 149–151 °C (lit.[7] mp 149–151 °C).

m-Bromophenylphosphonic dichloride was prepared from the phosphonic acid after Denham and Ingham.[17]

Preparation of Diethyl *m*-Bromophenylphosphonate. To a mixture of 2.83 g (3.6 mL, 0.0614 mol) of absolute ethanol and 2.04 g (2.1 mL, 0.0257 mol) of pyridine under a nitrogen atmosphere at 0 °C was added dropwise 3.36 g (0.0123 mol) of *m*-bromophenylphosphonic dichloride. After the addition was complete, the mixture was allowed to warm to room temperature, stirred for 15 min at room temperature, and heated to 50 °C for 30 min. The mixture was cooled, 30 mL of cold diethyl ether was added, and the solution was filtered to remove pyridine hydrochloride. The resulting solution was evaporated until all the ether and ethanol were gone. The resulting viscous liquid was redissolved in cold diethyl ether, and the additional pyridine hydrochloride which separated was removed by filtration. The ether solution was washed with water and the ether removed under vacuum. The crude liquid was distilled at reduced pressure: yield, 2.876 g (79%); bp 110–114 °C (0.2 mm); NMR ($CDCl_3$) δ 1.33 (t, 6 H), 4.18 (quintet, ^{31}P coupling, 4 H), 7.18–8.27 (m, 4 H).

Bromination of Diethyl Phenylphosphonate. In a 100-mL three-neck, round-bottom flask equipped with a Teflon stir bar and a condenser was placed 22.5 mL of 98% sulfuric acid and 2.5 mL of distilled water. To this mixture was added 5.00 g (0.0233 mol) of diethyl phenylphosphonate and then 1.3 mL (4.0 g, 0.0253 mol) of bromine. The reaction mixture was stirred, 4.25 g (0.0136 mol) of silver

sulfate was added, and stirring was continued for 1 h, at which time no bromine was noted in the mixture and a thick yellow suspension was noted. The reaction mixture was poured into 75 mL of cold water and the flask was washed with 15 mL of water. Diethyl ether (100 mL) was added, the resulting two-phase suspension was filtered through a sintered glass funnel to remove silver salts, and the resulting mixture was subjected to a normal workup. Removal of the ether under vacuum left a viscous liquid which was distilled at reduced pressure: bp 119–124 °C (0.6 mm); yield, 4.50 g (66%). The infrared and NMR spectra of this product were virtually identical with those of authentic diethyl *m*-bromophenylphosphonate. However, analysis by means of a Finnigan Model 4000 gas–liquid chromatograph interfaced with a mass spectrometer showed the sample to be contaminated with about 5% diethyl phenylphosphonate and with about 5% of a substance of long retention time with MS characteristic of a dibromo derivative thereof.

Reaction of Iodobenzene with Sodium Diethyl Phosphite and Iodine. Dry ammonia (50 mL) was condensed in a 250-mL, three-neck, round-bottom flask equipped with a polyethylene stir bar and dry ice condenser and under a nitrogen atmosphere. Sodium metal (457 mg, 19.89 mmol) was added to the liquid ammonia. The mixture was stirred and titrated with diethyl phosphonate until no color remained. Then 942 mg (4.62 mmol) of iodobenzene was added. The entire reaction assembly including flask and condenser was covered with aluminum foil to keep light out.

In a vial, 258 mg (1.02 mmol) of iodine was placed and 10 mL of dry tetrahydrofuran (freshly distilled from $LiAlH_4$) was added. The vial was equipped with a stir bar and the solution was stirred until the iodine dissolved. This solution was drawn into a syringe covered with aluminum foil and added dropwise to the stirred liquid ammonia solution. After the addition was complete, the mixture was stirred 3 min and then quenched with 2.1 g of NH_4NO_3 and 50 mL of cold diethyl ether. The aluminum foil was removed and the ammonia was allowed to evaporate. The resulting mixture was subjected to normal workup. GLC analysis showed a 92% recovery of iodobenzene and no trace of diethyl phenylphosphonate.

Reaction of Iodobenzene with Diethyl Phosphonate and Di-*tert*-butyl Peroxide. Iodobenzene (4.08 g, 2.24 mL, 0.02 mol) and diethyl phosphonate (3.16 g, 2.95 mL, 0.0229 mol) were placed in a 25-mL, round-bottom flask equipped with a stir bar and condenser and under a nitrogen atmosphere. Then 1.46 g (1.84 mL, 0.01 mol) of di-*tert*-butyl peroxide was added. The mixture was gently refluxed (at about 111 °C) for 5 h. The reaction mixture was cooled; diethyl ether and water were added and subjected to normal workup. The ether extract was washed with aqueous ferrous ammonium sulfate solution to remove traces of peroxides. GLC analysis of the ether solution showed large quantities of iodobenzene but no trace of diethyl phenylphosphonate.

Solvent Effects. In each of a series of experiments, about 5 mmol of **1a** was allowed to react with about 20 mmol of $(EtO)_2PO^-Na^+$ in 50 mL of ammonia with irradiation by "350 nm" lamps. Three experiments in which 20% tetrahydrofuran was present as cosolvent gave, in irradiation times of 20, 40, and 120 min, respectively, nil, 10, and 15% yields of **3**, with a corresponding amount of unreacted **1a** being present. With 20% dimethyl sulfoxide as cosolvent, a 14% yield of **3** was formed during 20-min irradiation

Registry No.—**1a**, 108-36-1; **1b**, 591-18-4; **2**, 35125-65-6; **3**, 25944-79-0; sodium diethyl phosphite, 2303-76-6; *m*-bromophenylphosphonic acid, 6958-02-0; *m*-bromobenzenediazonium tetrafluoroborate, 500-25-4; *m*-bromophenylphosphonic dichloride, 65442-15-1; diethyl phenylphosphonate, 1754-49-0; iodobenzene, 591-50-4.

References and Notes

(1) Research supported in part by the National Science Foundation.
(2) J. F. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3612 (1974).
(3) J. F. Bunnett, R. G. Scamehorn, and R. P. Traber, *J. Org. Chem.*, **41**, 3677 (1976).
(4) J. F. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3611 (1974).
(5) A preliminary experiment mentioned in footnote *b*, Table I, indicated extremely low reactivity for **2**. We suspect that an adventitious impurity may have inhibited that reaction.
(6) A preliminary experiment mentioned in footnote *c*, Table I, indicated much lower reactivity for **2**. This experiment was performed about the same time as that mentioned in footnote *b*, and again interference by an adventitious impurity is suspected.
(7) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **73**, 5658 (1951).
(8) J. R. Johnson and C. G. Gauerke, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1941, p 123.
(9) D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.*, 573 (1950).
(10) P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution", Butterworths, London, 1959, p 110.
(11) J. K. Kim and J. F. Bunnett, *J. Am. Chem. Soc.*, **92**, 7463, 7464 (1970).
(12) S. Hoz and J. F. Bunnett, *J. Am. Chem. Soc.*, **99**, 4690 (1977).
(13) M. Anbar and E. J. Hart, *J. Am. Chem. Soc.*, **86**, 5633 (1964).
(14) J. F. Bunnett and R. P. Traber, *J. Org. Chem.*, preceding paper in this issue.
(15) L. Benati, C. M. Camaggi, and G. Zanardi, *J. Chem. Soc., Perkin Trans. 1*, 2817 (1972); J. R. Shelton and A. L. Lipmar, Jr., *J. Org. Chem.*, **39**, 2386 (1974); M. Fiorentino, L. Testaferri, M. Tiecco, and L. Troisi, *Chem. Commun.*, 316, 317 (1977); *J. Chem. Soc., Perkin Trans. 2*, 87 (1977).
(16) E. F. Jason and E. K. Fields, *J. Org. Chem.*, **27**, 1402 (1962).
(17) J. M. Denham and R. K. Ingham, *J. Org. Chem.*, **23**, 1298 (1958).

Effect of Substrate Concentration on Partitioning between Mono- and Disubstitution in Photostimulated Reactions of *m*-Haloiodobenzenes with Diethyl Phosphite Ion[1]

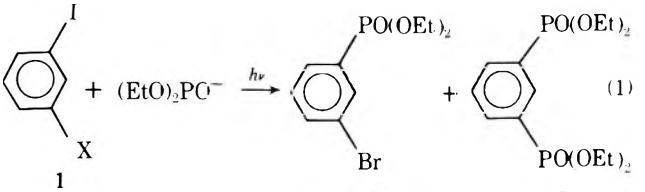
J. F. Bunnett* and Sheldon J. Shafer

University of California, Santa Cruz, California 95064

Received August 16, 1977

The reactions of *m*-bromoiodobenzene (**1a**) and *m*-chloroiodobenzene (**1b**) with diethyl phosphite ion give mixtures of a monosubstitution product, in which only iodine is replaced, and a disubstitution product, in which both halogens are replaced. These products are, respectively, a diethyl *m*-halophenylphosphonate and tetraethyl *m*-phenylenebisphosphonate. Mainly monosubstitution occurs with **1b** and mainly disubstitution with **1a**. As expected from the $S_{RN}1$ radical chain mechanism, the ratio of monosubstitution to disubstitution product from either substrate increases linearly with increasing substrate concentration.

m-Bromoiodobenzene (**1a**) and *m*-chloroiodobenzene (**1b**) react rapidly with diethyl phosphite ion in liquid ammonia under irradiation to form one or both of two products, one representing replacement only of iodine and the other representing replacement of both halogens by the nucleophile;[2-5] see eq 1. These products are, respectively, a diethyl *m*-halophenylphosphonate (**2a** or **2b**) and tetraethyl *m*-phenylenebisphosphonate (**3**).



a, X = Br; b, X = Cl

0022-3263/78/1943-1877$01.00/0

Table I. Photostimulated Reactions of *m*-Haloiodobenzenes with Diethyl Phosphite Ion in Liquid Ammonia

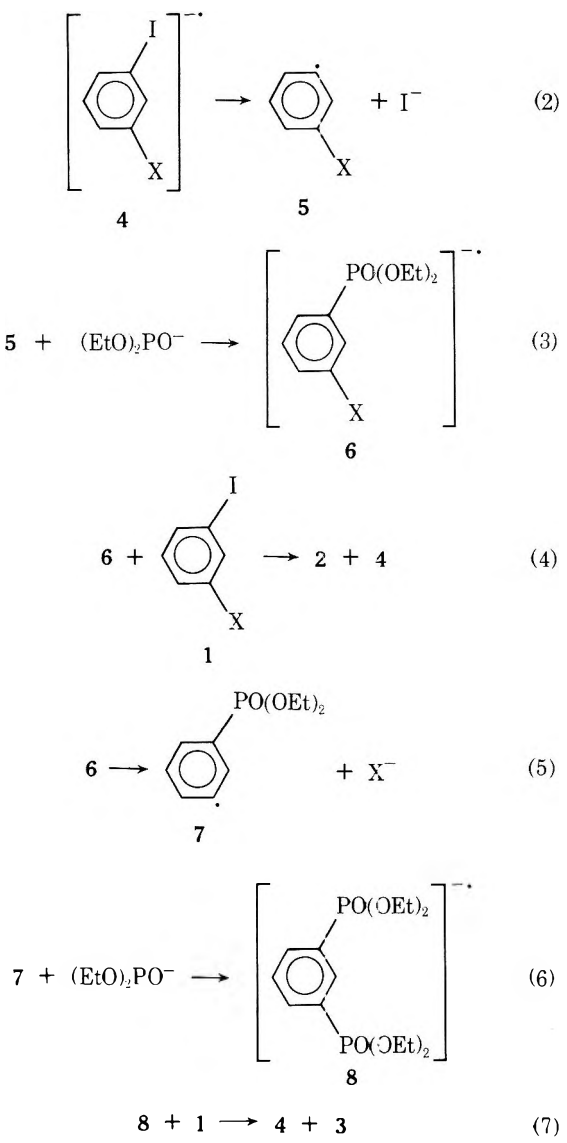
Expt. no.	Substrate	[Substrate], M	Irradiation time, min	Unreacted subtrate, %	Product yields, % 2[a]	3
1[b]	**1a**	0.101	7	28	8	56
2		0.052	5	22	6	58
3		0.027	2	31	3	55
4		0.014	1.0	39	1.5	58
5		0.007	0.8	26	1.0	63
6		0.007	0.7	63	0.6	30
7		0.007	1.0	11	*c*	83
8		0.051	7	14	6	59
9		0.026	7	0	2	96
10	**1b**	0.100	10	7	96	0
11		0.026	2.5	2	91	3
12		0.012	1.2	2	86	7
13		0.008	0.9	2	80	13

[a] Product **2** is **2a** from **1a** or **2b** from **1b**. [b] From ref 5. [c] Present in trace amount but not measured.

From **1a**, the chief product is bisphosphonate ester **3** in about 90% yield, monophosphonate ester **2a** having been reported only to the extent of about 8%. However, from **1b** the principal product is monophosphonate ester **2b** with bisphosphonate ester **3** having been sometimes observed[2] and sometimes not.[3]

These reactions are thought to occur by the $S_{RN}1$ mechanism.[6] This is a radical chain mechanism. The propagation steps relevant to the present reactions are presented in Scheme I. According to this mechanism, the formation of monophosphonate ester **2a** or **2b** is attributed to the cycle of steps 2–4, while the formation of bisphosphonate ester **3** is ascribed to the repeating sequence of steps 2, 3, and 5–7.

Scheme I



(2) (3) (4) (5) (6) (7)

In terms of Scheme I, the formation mainly of disubstitution product **3** from *m*-bromoiodobenzene (**1a**) but mainly of monosubstitution product **2b** from *m*-chloroiodobenzene (**1b**) is explicable mainly in terms of the effect of C–X bond strength on the frangibility of radical anion **6** in step 5. Electrochemical studies have shown that the radical anions of aryl bromides fragment, into halide ion and aryl radical, much faster than do the radical anions of aryl chlorides.[7] Fragmentation step 5 is much faster when X is bromine than chlorine, and, therefore, the extended propagation cycle leading from **1a** to **3** is favored over the shorter cycle that leads to **2**.

Strictly speaking, however, it is the relative rates of steps 4 and 5 that determine the relative amounts of mono- and disubstitution products, according to the mechanism of Scheme I. Whereas step 5 is unimolecular, step 4 is bimolecular, for it involves electron transfer from radical anion **6** to substrate molecule. This mechanism would therefore call for the partitioning between mono- and disubstitution products to depend on the concentration of substrate, with a larger percentage of monosubstitution product being obtained at higher substrate concentrations.

We now report an experimental test of this expectation. We have examined the effect of substrate concentration on the partitioning between products for reactions both of **1a** and of **1b**.

Results

Our principal experimental results are summarized in Table I. Experiments 1–5, inclusive, constitute a rational set concerning *m*-bromoiodobenzene (**1a**). The yield of monosubstitution product **2a** drops steadily as the substrate concentration is diminished. Experiments 10–13, inclusive, constitute a corresponding set concerning *m*-chloroiodobenzene (**1b**). Again the yield of monosubstitution product **2b** decreases as the substrate concentration is decreased. There is a corresponding increase in the yield of disubstitution product **3**.

The photostimulated reaction of iodobenzene with potassium diethyl phosphite in dimethyl sulfoxide solution, to form diethyl phenylphosphonate, has been found to proceed at a rate independent of iodobenzene concentration but dependent on about the 0.84 power of light intensity.[8] Those observations were made under conditions such that nearly every incident photon was absorbed. The present reaction mixtures were probably similarly opaque. If a similar rate law obtains for the

reactions of eq 1, a shorter time should be necessary at lower substrate concentration to realize a given percentage of conversion of reactants to products.

Because **2a** is known to be capable of reacting under the conditions of these experiments to form **3**, albeit slower than **1a**, it was deemed desirable to terminate each experiment with **1a** at a time at which a substantial amount of **1a** remained unreacted so that conversion of **2a** to **3** could be minimized. It is for this reason that a shorter irradiation time was used with each decrease in substrate concentration, both for the set of experiments 1–5 and for the set of experiments 10–13. Within the former set, in each case about 30% of the substrate remained unreacted.

These concerns were less pressing for reactions of **1b**, for we found that, although **2b** does react with diethyl phosphite ion under photostimulation to form **3**, the reaction is very slow and would have made negligible progress during the very short reaction times involved in our principal experiments. Accordingly, the fact that reactions of **1b** were carried nearly to completion is no cause for worry. Actually, the employment of ever shorter irradiation times within experiments 10–13 was probably unnecessary.

That these concerns were justified in respect to reactions of **1a** is shown by comparison of experiment 9 with experiment 3. The product ratio, **3/2a**, is about 18 when the reaction is conducted only to the extent of about 69% but climbs to 48 when the reaction is conducted for 3.5 times as long, with complete consumption of the substrate. It is probable that in experiment 9 there was some transformation of **2a** to **3** in the later minutes of irradiation.

Experiments 5–7 were conducted with nearly identical reactant concentrations and with irradiation times, respectively, of 48, 40, and 60 s. The percentage of conversion of **1a** to products varies considerably within this set of experiments and is not uniformly related to the measured irradiation times. We suspect that this minor irregularity is to be attributed to short induction periods stemming from the presence of varying amounts of adventitious impurities in ostensibly identical reaction mixtures.

It may be noted in Table I that **1b** appears to be somewhat more reactive than **1a**. Compare especially experiment 11 with experiment 3 or experiment 12 with experiment 4.

Discussion

The $S_{RN}1$ propagation mechanism of Scheme I provides, as we have seen,[5] a straightforward rationalization of the facts that **2a** is not an intermediate on the main route from **1a** to **3** and that **1a** gives mainly disubstitution product **3** while **1b** gives mainly monosubstitution product **2b**.

However, the mechanism of Scheme I also *requires* that the partitioning of reaction between mono- and disubstitution products be related to substrate concentration in the sense that relatively more monosubstitution product should be formed at higher concentrations of substrate. Our results show that requirement to be satisfied both for reactions of **1a** and of **1b**.

Furthermore, the mechanism of Scheme I calls for a quantitative relationship of product ratio to substrate concentration. Inasmuch as product partitioning should be decided by competition between steps 4 and 5

$$d[2]/d[3] = k_4[6][1]/k_5[6] = (k_4/k_5)[1] \quad (8)$$

Integrating

$$[2]_t/[3]_t = (k_4/k_5) \int [1] \quad (9)$$

Since substrate concentration did not remain constant within any experiment, one must consider the shape of the integral, $\int [1]$, in eq 9. Providing that each experiment is carried to the same fraction of completion, each integral will have a similar relationship to the original concentration of substrate **1a** or **1b**, and therefore the ratio of mono- to disubstitution product within any such set of experiments should be approximately linearly related to initial substrate concentration.

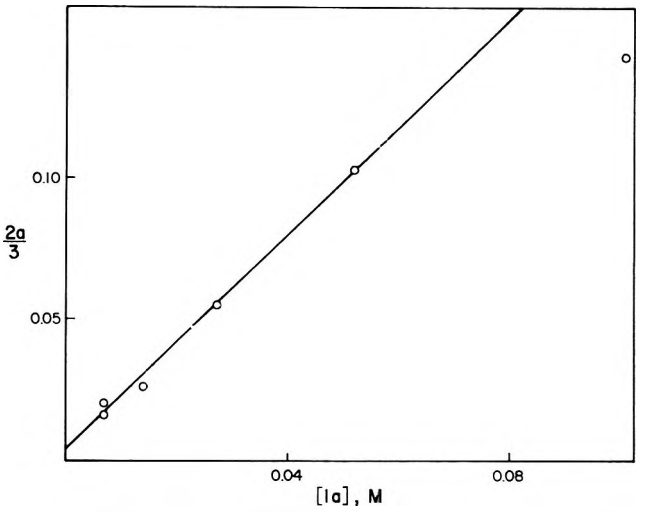


Figure 1. The monosubstitution/disubstitution product ratio (**2a/3**), as a function of **1a** concentration, for reactions of *m*-bromoiodobenzene with diethyl phosphite ion. Data of experiments 1–6, inclusive.

In Figure 1 we present a plot of data from experiments 1–6, inclusive, the product ratio, **2a/3**, against **1a** concentration. The expected linearity is observed except for the point for experiment 1. A similar plot for the data of experiments 11–13 is also linear.

The fact that partitioning between mono- and disubstitution products conforms both qualitatively and quantitatively to the requirements of the mechanism of Scheme I provides further strong support for the $S_{RN}1$ mechanism.

Experimental Section

The experiments summarized in Table I were conducted according to the procedures used in the principal experiments of an accompanying report.[5] The concentration of $(EtO)_2PO^-Na^+$ was throughout about 0.42 M. In a further experiment, 4.96 mmol of diethyl *m*-chlorophenylphosphonate (**2b**) and 21.5 mmol of sodium diethyl phosphite in 50 mL of ammonia under N_2 were irradiated in the Rayonet reactor with "350 nm" lamps for 60 min; by GLC it was determined that 17% of **3** had been formed and that 83% of the **2b** remained unreacted.

Registry No.—**1a**, 591-18-4; **1b**, 625-99-0; **2a**, 35125-65-5; **2b**, 23415-71-6; **3**, 25944-79-0; $(EtO)_2PO^-Na^+$, 2303-76-6.

References and Notes

(1) Research supported in part by the National Science Foundation.
(2) J. F. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3612 (1974).
(3) J. F. Bunnett and F. P. Traber, *J. Org. Chem.*, first of three papers in this issue.
(4) J. F. Bunnett, R. G. Scamehorn, and R. P. Traber, *J. Org. Chem.*, **41**, 3677 (1976).
(5) J. F. Bunnett and S. J. Shafer, *J. Org. Chem.*, preceding paper in this issue.
(6) J. K. Kim and J. F. Bunnett, *J. Am. Chem. Soc.*, **92**, 7463 (1970).
(7) L. Nadjo and J. M. Savéant, *J. Electroanal. Chem.*, **30**, 41 (1971); K. Alwair and J. Grimshaw, *J. Chem. Soc., Perkin Trans. 2*, 1150, 1811 (1973); J. Grimshaw and J. Trocha-Grimshaw, *J. Electroanal. Chem.*, **56**, 443 (1974).
(8) S. Hoz and J. F. Bunnett, *J. Am. Chem. Soc.*, **99**, 4690 (1977).
(9) The substantial linearity of five points in Figure 1 is more remarkable than the deviation of one. Experimental uncertainties include the exact volume of solvent employed as well as the usual amount of random error in GLC analysis.

Acylanthranils. 6. Role of Steric Hindrance in the Reaction of Electrophilic Reagents with Linear Primary Aliphatic Amines[1]

L. A. Errede

Central Research Laboratories, 3M Company, Saint Paul, Minnesota 55101

Received March 17, 1977

The product distributions obtained in the reactions of acetylanthranil (1) with amines 2 having the generic formula $H_2N(CH_2)_nH$ indicate that reaction via pathway A to give the corresponding acetamidine salt 3, which requires only minutes for completion, is favored when $n < 4$, but that reaction via pathway B to give the corresponding diamide 4, which requires hours for completion, is favored when $n \geq 4$. It is postulated that this crossover in selectivity at $n = 4$ is caused by steric hindrance owing to a coiled configuration on the part of the $H_2N(CH_2)_4$ segment held together by intramolecular van der Waals forces. This coiled configuration also appears to account for the small, but measurable, decrease in pK_a for those amines with $n \geq 4$.

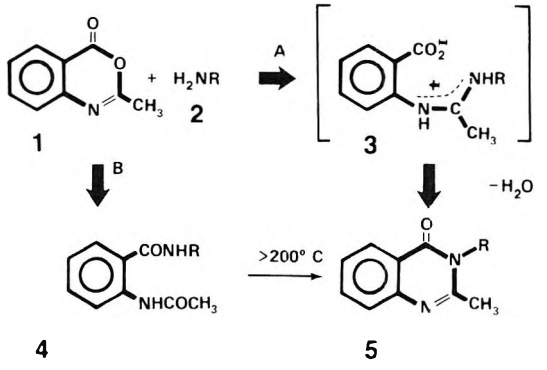
It was reported that the reaction of acetylanthranil (1) with amines 2 in nonpolar solvents such as benzene or diethyl ether occurs via alternate pathways[2] to give either the corresponding acetamidine intermediate 3 via pathway A or the corresponding benzamide 4 via pathway B. Primary amines follow pathway A unless some form of steric hindrance precludes addition to the 2 position of 1, which serves to restrict interaction to the slower alternative pathway B to give 4 as discussed previously.[3,4] Secondary amines, however, follow pathway B exclusively. It was shown that even pseudosecondary amines (i.e., a primary amine such as anthranilic acid or ethanolamine, which can form a five- or six-membered ring by intramolecular hydrogen bonding with the polar group at the β position) follow pathway B in a nonpolar solvent.[5] In a polar solvent, however, these amines behave like normal primary amines and follow pathway A, because the formation of the cyclic configuration is precluded by intermolecular association with the solvent.[5] Tertiary amines do not react with 1 except to serve as an excellent solvent for reaction with other nucleophiles such as water, which gives o-acetamidobenzoic acid.[2,4]

It was noted[4] that reaction with primary aromatic amines neat usually requires 2–3 h for completion, whereas the corresponding reaction with methyl-, ethyl-, and *n*-propylamines is complete within 10 min. This difference in reactivity with amines that follow pathway A was ascribed to the relative difference in basicity for the aromatic (pK_a ca. 5) and the aliphatic (pK_a ca. 11) amines.[4] It was decided, therefore, to investigate whether or not the rate of reaction with the amines $H_2N(CH_2)_nH$ via pathway A would increase with *n* in accordance with the expected electropositive contribution of the polymethylene chain to the nucleophilic center.

Results and Discussion

Acetylanthranil (1) was made to react in benzene at room temperature with the set of linear aliphatic amines **2a–h**, wherein $n = 0, 1, 2, 3, 4, 6, 10$, and 12, respectively. The approximate time required for reaction completion was noted and the product mixtures obtained thereby were separated according to the materials balance procedure described previously.[2] This procedure accounted for more than 95% of the reactants, which were added in equivalent amounts. The percent acetylanthranil isolated as **3**, **4**, and **5** was then used to calculate the corresponding selectivity ratio for reaction via pathway A to pathway B, i.e., k_A/k_B = (**3** and/or **5**)/**4**. The materials balance data are collected in Table I and the supporting characterization data are collected in Table II. Unreacted acetylanthranil was either recovered per se (example **2a**) or isolated as o-acetamidobenzoic acid (**6**) which was produced by reaction with water as part of the post reaction separation procedure (examples **2g** and **2h**).

Scheme I



Instead of the expected monotonic increase in reactivity without change in selectivity as a function of *n*, Table I shows that the members of the subset with $n < 4$ follow pathway A, whereas those with $n \geq 4$ follow pathway B. Moreover the former, with the exception of ammonia, required only minutes for reaction completion, whereas the latter required hours. The sharp changes in selectivity and reactivity are especially interesting because both observations infer some form of steric hindrance in this reaction, which is associated with the segment $H_2N(CH_2)_4$–.

The results obtained with ammonia, however, were unique and apparently contradictive. The reaction of 1 in benzene saturated with anhydrous ammonia at room temperature was pseudo-first-order and the half-life of 1 under these conditions was 32 h.[4] About 35% was recovered unchanged after 48 h and the rest was isolated as 2-methylquinazol-4-one (**5a**). The isolation of this product in good yield shows that the reaction follows pathway A exclusively as expected for an amine that does not exhibit steric hindrance, such as methylamine, but the unusually slow rate of reaction is characteristic of amines that exhibit considerable steric hindrance, such as *tert*-butylamine. Because these two observations appear to be inconsistent, more investigation at a later time is required for clarification.

The unexpected observation of a change in selectivity at $n = 4$ from pathway A, which gives **3** as a precipitate, to pathway B, which gives **4** as a soluble product, offered the additional possibility for following the reactions that go via pathway B spectrophotometrically instead of gravimetrically. Our attempts to do so by IR and/or NMR analysis verified that reaction of 1 with an equivalent amount of an amine **2** having $n \geq 4$ requires 2–6 h for completion and that the reaction is second order (i.e., in a given experiment, the rates of disappearance of the reactants 1 and 2 are both equal to the rate of formation of the product **4**). The reproducibility of the calculated rate constants in a set of repeat experiments with a given amine, however, was not good enough to verify or deny

0022-3263/78/1943-1880$01.00/0

Table I. Products Obtained in the Reaction of 1 with $H_2N(CH_2)_nH$ in Benzene at Room Temperature

Amine	Registry no.	n	pK_a[f]	Time allowed for reaction	% 1 isolated as 4	3	5	Selectivity A/B = (3 and/or 5)/4
2a	7664-41-7	0	9.26	2 days[a]	0	0	65	>50/1[b]
2b	74-89-5	1	10.66	1 h[c]	0	100	0	>50/1
2c	75-04-7	2	10.81	1 h[c]	0	100	0	>50/1
2d	107-10-8	3	10.71	4 h[c]	7	93	0	17/1[d]
2e	109-73-9	4	10.61	1 day[e]	100	0	0	<1/25
2f	111-26-2	6	10.56	1 day[e]	96	0	4	1/24
2g	2016-57-1	10	10.64	5 h[e]	96	0	0	<1/25
2h	124-22-1	12	10.63	5 h[e]	97	0	0	<1/25

[a] This rate of reaction ($T_{1/2}$ = 32 h) is unusually slow for an amine that follows pathway A. We have observed that the rate of reaction is fast in polar solvents, but the products depend on the choice of solvent. The reaction of 1 with NH_3, which is unusually complicated, will be discussed fully in a subsequent publication. [b] The remaining 35% was recovered as unreacted 1. [c] Precipitation of 3 was complete within 10 min indicating reaction completion within this time interval. [d] Reaction was complete within 10 min in n-propylamine neat,[4] and the selectivity was >50/1. [e] Subsequent attempts to follow reaction kinetically by IR and/or NMR analysis indicated that reaction was complete within 2–6 h. [f] pK_a values taken from ref 18 and 19.

Table II. Characterization Data for Products 3, 4, and 5 Noted in Table I

Product	n	Mp, °C	Key IR absorption bands
Acetamidines (3) from amine			
2b	1	136–7	3.2–4.4, 6.3
2c	2	109–10	3.0–4.4, 6.3
2d	3	118–20	3.2–4.3, 6.3
2-Methylquinazolones (5) from			
2a	0	240–1	6.0, 6.2
2d	3	81–2	6.0, 6.2
o-Acetamidobenzamides (4) from			
2d	3	125–7	3.1, 6.1, 6.2, 6.3, 6.5
2e	4	133–4	3.1, 6.1, 6.2, 6.3, 6.5
2f	6	99–100	3.1, 6.0, 6.1, 6.2, 6.3, 6.5
2g	10	85–90	3.1, 6.0, 6.1, 6.2, 6.3, 6.5
2h	12	84–7	3.1, 6.0, 6.1, 6.2, 6.3, 6.5

the expected dependence of rate on n, because the range in calculated rate constants for a given amine was at least as great as the range in average rate constants for the set. It was decided, therefore, to defer publication of these data until the required quantitative reproducibility could be established and the work repeated.

Meanwhile the cause for the qualitative change in selectivity from pathway A to B at n = 4 became more interesting to us than the original objective. Accordingly, the literature was reexamined to see if similar aberrations in the reactions of the linear aliphatic amines $H_2N(CH_2)_nH$ were observed with other electrophiles.

It was noted by Hall et al.[6a,b] that the base strength of these amines does not increase monotonically as a function of n from 1 to 5. Later Brown[6c] noted that the irregularity in chemical behavior when n is 3 or 4 is fairly general and even appears in the gas-phase dissociation of the corresponding addition compounds with trimethylboron. He ascribed[6c] this irregularity primarily to an entropy effect, owing to steric preclusion of certain configurations when $n > 2$.

Although many papers[9,10] and excellent review articles[11-14] have been written about the relative basicity of amines in terms of parameters that reflect Brown's "B-Strain Theory",[15] Trotman-Dickenson's "Solution Theory",[16] and Taft's "σ^* Values",[17a] little further attention was given to the amines $H_2N(CH_2)_nH$, except to note[12] that the pK_a values for this series from n = 1 to 22 fall in the range of 10.7 ± 0.2. Apparently the variance in this set of pK_a values was not considered worthy of further consideration[12,14] since a large change in n causes at most only a small change in pK_a. This attitude is indeed justified, but only if the reported data either deviates randomly about the line pK_a = 10.7 ± 0.2, reflecting experimental error, or increases monotonically from 10.5 to 10.9, reflecting the expected influence of induction within the homologous series. Neither is the case, however, as can be seen from Figure 1, which plots the pK_a data for these amines, taken from ref 18 and 19 as a function of n. In contrast to either alternative condition, it is noticed that the pK_a values rise smoothly from 9.26 at n = 0 to a maximum of 10.81 at n = 2 and then fall to an asymptotic line given by 10.62 ± 0.3, from n = 4 to at least n = 22, the highest member of this series for which a pK_a value is reported. The pK_a values for the members below n = 4 are outside the limits of reproducibility indicated by the data given for the members with $n \geq 4$. This reconsideration of the data suggests that this observed distribution of pK_a as a function of n may be a manifestation of some real factor that suppresses the expected increase in base strength as noted by others.[6]

In contrast to the abnormal behavior of the amines in solution, gas-phase protonation of $H_2N(CH_2)_nH$ appears to be quite normal. It was reported by Aue[20] that the free energy and enthalpy of these reactions with methyl-, ethyl-, n-propyl, and n-butylamine exhibit a simple monotonic increase from n = 1 to 4, indicating that the chemical aberration may be peculiar to the solvated state at relatively lower temperatures.

One would expect the pK_a values in water for the set of amines $H_2N(CH_2)_nH$ to approach rapidly an asymptotic limit as shown by the dotted line in Figure 1 and given by the equation:

$$pK_a^* = 9.26 + 1.40 \sum_{1}^{n} 1/n^3$$

where 9.26 is the pK_a value for n = 0, 1.40 is the difference in pK_a values for n = 0 and 1 (i.e., the first and second members, respectively), and pK_a^* is the idealized value for the $(n + 1)$th

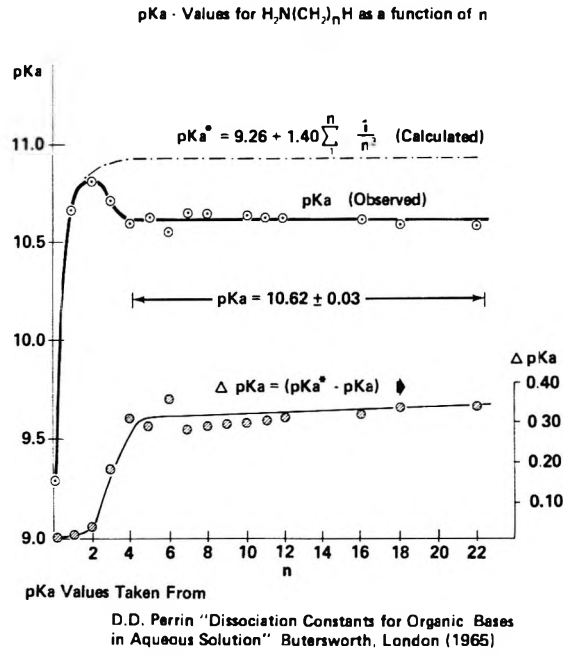


Figure 1.

member of this series. This equation is analogous to that which relates the bond dissociation energies (BDE) for the corresponding bonds in the homologous series $R(CH_2)_nH$ in terms of n,[21] namely:

$$E_n = E_0 + \Delta E_0^1 \sum_1^n 1/n^3$$

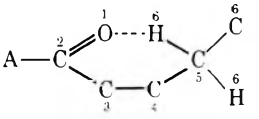
where E_0 is the BDE for the first member, ΔE_0^1 is the corresponding difference for the first and second members, and E_n is the value for the $(n + 1)$th member.

The difference between the calculated idealized pK_a* and the experimentally observed pK_a (i.e., $\Delta pK_a = pK_a^* - pK_a$) approaches rapidly an asymptotic limit of about 0.3 pK_a units, which corresponds to a difference in free energy of less than 0.5 kcal. This difference is constant over the range $n = 4$ to 22 as shown in Figure 1. Since significant increases in ΔpK_a occur only at $n = 3$ and 4, it is concluded that these are the methylene groups primarily responsible for the chemical aberration and that consequently the aberration must be associated with some configuration peculiar to the $H_2N(CH_2)_4$ segment, which might somehow impede the approach of an electrophilic center to the amino group.

If this postulation is correct then one should observe a sharp change in selectivity at about $n = 3$ or 4, when this set of amines with the general formula $H_2N(CH_2)_nH$ is made to react with acetylanthranil in a nonpolar solvent. This is exactly what was observed within the set given by the members $n = 0$, 1, 2, 3, 4, 6, 10, and 12. The data collected in Table I show that reaction in benzene at room temperature follows pathway A exclusively, when n is 0, 1, and 2 (i.e., A/B > 50/1), but that reaction via pathway B is measurable at $n = 3$ (i.e., A/B = 17/1) and is the dominant pathway for all values of n > 3 (i.e., A/B < 1/24). This change in selectivity at $n = 4$ corresponds exactly to the first member of this series that manifests maximum ΔpK_a as a function of n as shown in Figure 1. This infers that both effects are manifestations of the same cause, which exhibits its full impact when $n > 3$. Since reaction of a primary amine with acetylanthranil via pathway B is associated with some form of steric hindrance, it implies that here too steric hindrance is somehow responsible for the sharp change in selectivity at $n = 4$. This crossover in selectivity cannot be ascribed to the usual solvent or temperature effects since the same solvent, benzene, and the same temperature, room temperature, were used in each experiment. It is concluded, therefore, that the chemical aberration is due to steric hindrance manifested by the $H_2N(CH_2)_4$ segment, which is precluded (or mitigated, considerably) when $n < 4$.

It is difficult to imagine how the $H_2N(CH_2)_4$ segment might exhibit steric hindrance in this reaction unless it attains a five- or six-membered ring configuration, which is geometrically similar to that of a cyclic secondary amine as described in the first paragraph for ethanolamine and for anthranilic acid. In these two examples, however, the integrity of the pseudocyclic amine structure was maintained by intramolecular hydrogen bonding, which is not available to the $H_2N(CH_2)_4$ segment. If these linear aliphatic primary amines do assume cyclic configurations in solution, then their integrity must be maintained only by intramolecular forces of the van der Waals type, which are very small indeed. Consequently the effect of this weak intramolecular assoication would be felt only in solution at lower temperatures where "balling" would be abetted by gentle collisions with surrounding solvent molecules. In the gas phase, however, the energy state is such that the weak force of intramolecular association is easily overcome by thermal effects and the molecule assumes an open configuration, which is more accessible to a proton. Consequently the chemistry in the gas phase should be quite "normal" as reported by Aue,[2c] whereas in solution it manifests the slight aberration first observed by others.[6]

The hypothesis that the $H_2N(CH_2)_n$ segments assume a coiled configuration in solution, which serves to impede reaction with an electrophilic reagent, bears formal resemblance to Newman's "Rule of Six",[17b] which states that in reactions involving addition to a center of unsaturation, the greater the number of atoms in the 6 position, the greater will be the steric hindrance to attack at the center of unsaturation of molecules such as



where A is HO, R_2N, R, or H. Newman[17b] pointed out that the coiled position is effective in hindering attack at the center of unsaturation because (1) the space about the center of unsaturation is partially blocked by the physical presence of the hydrocarbon coil, and (2) when addition occurs from the open direction, the increased spatial requirements involved in going from the ground state to the tetrahedral configuration of the intermediate state are more easily met in an uncoiled, rather than a coiled, configuration.

The idea that intramolecular association to form a six-membered ring can influence the chemistry of organic compounds was first suggested by Dippy,[22] who proposed that intramolecular hydrogen bonding of the carboxyl group with the hydrogen atom of the CH_3 was responsible for the abnormal increase in the ionization constant of butyric acid over propionic acid. Brown[6c] suggested that this might also obtain in the linear aliphatic amine series, but he pointed out correctly that the effect is too small to be attributed to intramolecular hydrogen bonding and suggested therefore that it might be attributable to an entropy effect that favors dissociation of the protonated form.

Although Brown's explanation is valid for reversible reactions that involve dissociation, it is not valid for nonreversible reactions that go in the forward direction, such as the reactions of 1 with $H_2N(CH_2)_nH$ to give either the corresponding 3 or 4 via pathways A or BZrespectively. If steric hindrance is to influence the selectivity in these reactions, it must do so in the forward direction, since the reverse possibility is excluded by definition. It is postulated therefore that this steric hindrance

is caused by the amine in its coiled configuration, which resembles geometrically a cyclic secondary amine.

It was shown that intramolecular hydrogen bonding is indeed strong enough to ensure the integrity of a cyclic configuration in the cases of anthranilic acid and ethanol amine[5] in nonpolar solvents. A key question now is whether or not the weak force of van der Waals attraction is also sufficiently great to hold long chain aliphatic amines in the postulated cyclic configuration.

More experiments are required to test further the hypothesis that these amines indeed manifest a form of "Newman Steric Hindrance" and also to help clarify the unique but mutually inconsistent results on selectivity and reactivity noted with ammonia.

Experimental Section

General Procedure. Reaction of acetylanthranil (**1**) with the amine **2** was made to occur in benzene at room temperature. The products **3**, **4**, and **5** were separated and identified according to the chemical procedure described previously.[1,2] The materials balance of products with reactants was usually about 95%. The selectivity for reaction via pathway A relative to pathway B was calculated from the product distribution according to the equation: A/B = (**3** and/or **5**)/**4**. The data for these reactions are collected in Table I. The characterization data for the corresponding products, **3**, **4**, and **5**, are collected in Table II. The details for reaction of ammonia (**2a**), methylamine (**2b**), and ethylamine (**2c**) in benzene, at room temperature, and *n*-propylamine (**2d**) neat, at 0 °C, are given in ref 4. The details for reaction of **1** with **2d**, *n*-butylamine (**2e**), *n*-hexylamine (**2f**), *n*-decylamine (**2g**), and *n*-dodecylamine (**2h**) in benzene, at room temperature, are given below:

Reactions of 1 with $H_2N(CH_2)_nH$ in Benzene at Room Temperature. i. With *n*-Propylamine (2d) to Give 3d and Some 4d. A solution of acetylanthranil (5 g) in benzene (50 cm^3) was mixed at room temperature with a solution of *n*-propylamine (**2d**) (2.0 g) in benzene (50 cm^3). Precipitation began to occur within 20 min and appeared to be complete within 4 h. The precipitate (1.9 g; mp 118–120 °C) was separated by filtration and identified as *N*-(2-carboxyphenyl)-*N'*-(*n*-propyl)acetamidine (**3d**) by its IR spectrum, Table II. The mother liquor was evaporated to dryness under vacuum. The residue (5.2 g) was leached sequentially with dilute aqueous base and then with dilute aqueous acid. The base–acid insoluble residue (0.5 g; mp 125–127 °C) was identified as *o*-acetamido-*N*-(*n*-propyl)-benzamide (**4d**) by its IR spectrum. The aqueous extracts were allowed to remain at room temperature overnight, during which time a white crystalline solid (3.0 g; mp 81–82 °C) separated from the alkaline solution. This precipitate was identified as *N*-(*n*-propyl)-2-methylquinazol-4-one (**5d**) by its IR spectrum. It was demonstrated that **5d** is formed from **3d** in aqueous solution by dissolving a 1-g sample of **3d** in dilute aqueous base at room temperature to give a clear solution from which **5d** (0.1 g) precipitated within 4 h.

ii. With *n*-Butylamine (2e) to Give 4e. A solution of **1** (1.6 g) and *n*-butylamine (0.8 g) in benzene (10 cm^3) was allowed to react overnight at room temperature. The reaction mixture was separated as described in i. The only product isolated (2.2 g; mp 132.5–133 °C) was *o*-acetamido-*N*-(*n*-butyl)benzamide (**4e**) which was identified by its IR spectrum and its mp (Table II).

iii. With *n*-Hexylamine (2f) to Give 4f and Some 5f. A solution of **1** (5 g) and *n*-hexylamine (**2f**) (3.0 g) in benzene (50 cm^3) was allowed to react at room temperature overnight. The reaction mixture was separated as described in i. The major component (7.5 g; mp 99–100 °C, after recrystallization from methanol) was isolated as the insoluble fraction after sequential extraction with dilute aqueous base and aqueous acid. It was identified as (o-acetamido)-*N*-(*n*-hexyl)-benzamide (**4f**) by its IR spectrum (Table II). Neutralization of the aqueous acid extract with base gave a white precipitate (0.3 g; mp 64–66 °C) which was identified as *N*-(*n*-hexyl)-2-methylquinazol-4-one (**5f**) by its IR spectrum.

iv. With *n*-Decylamine (2g) to Give 4g. A solution of **1** (5 g) and *n*-decylamine (4.8 g) in benzene (30 cm^3) was allowed to react for 5 h at room temperature. The clear solution produced thereby was separated as described under i, and o-acetamido-*N*-(*n*-decyl)benzamide, (**4g**) (9.4 g; mp 85–90 °C) was the only product isolated. It was identified by its IR spectrum (Table II). Unreacted **1** was isolated as *o*-acetamidobenzoic acid (0.5 g; mp 185–186 °C).

v. With *n*-Dodecylamine (2h) to Give 4h. A solution of **1** (1.6 g) and *n*-dodecylamine (2.0 g; Armeen-12D) in benzene (40 cm^3) was allowed to react for 5 h at room temperature. The solution was separated as described under i, and *o*-acetamido-*N*-(*n*-dodecyl)benzamide (**4h**) (3.5 g; mp 84–87 °C) was the only product isolated. It was identified by its IR spectrum (Table II). Unreacted **1** was isolated as *o*-acetamidobenzoic acid (0.1 g; mp 186–187 °C).

Acknowledgment. The author is indebted to Dr. J. J. McBrady for interpretation of the IR spectra.

Registry No.—**1**, 525-76-8; **3b**, 65452-95-1; **3c**, 61047-28-7; **3d**, 34242-12-1; **4d**, 59525-19-8; **4e**, 59525-20-1; **4f**, 65452-96-2; **4g**, 65452-97-3; **4h**, 65452-98-4; **5a**, 1769-24-0; **5d**, 50677-60-6; **5f**, 65452-99-5.

References and Notes

(1) Presented before the 172nd National Meeting of the American Chemical Society, San Francisco, California, September, 1976, Abstract No. Orgn. 116.
(2) Part 2: L. A. Errede, J. J. McBrady, and H. T. Olen, *J. Org. Chem.*, **41**, 1765 (1976).
(3) Part 3: L. A. Errede, H. T. Olen, and D. R. Yarian, *J. Org. Chem.*, **42**, 12 (1977).
(4) Part 4: L. A. Errede, J. J. McBrady, and H. T. Olen, *J. Org. Chem.*, **42**, 656 (1977).
(5) Part 5: L. A. Errede and J. J. McBrady, *J. Org. Chem.*, **42**, 3863 (1977).
(6) (a) N. F. Hall and M. R. Sprinkle, *J. Am. Chem. Soc.*, **54**, 3469 (1932); (b) C. H. Hoerr, M. R. McCorkle, and A. W. Ralston, *ibid.*, **65**, 328 (1943); (c) H. C. Brown, M. D. Taylor, and S. Sujishi, *ibid.*, **73**, 2464 (1951).
(7) (a) H. K. Hall, *J. Am. Chem. Soc.*, **78**, 2570 (1966); (b) *ibid.*, **79**, 5441 (1957).
(8) S. R. Palet, *J. Phys. Colloid. Chem.*, **51**, 1028 (1947).
(9) E. Folkers and O. Runquist, *J. Org. Chem.*, **29**, 830 (1964).
(10) G. N. Chremos and H. K. Zimmerman, *Chimia*, **18**, 265 (1964).
(11) V. Gold, *Prog. Stereochem.* **3**, 169 (1962).
(12) J. Clark and D. D. Ferrin, *Q. Rev., Chem. Soc.*, **18**, 295 (1964).
(13) N. V. Sidgwich, "The Organic Chemistry of Nitrogen", Clarenden Press, Oxford, 1966, p 103.
(14) J. W. Smith, "The Chemistry of the Amino Group", S. Patai, Ed., Interscience, London, 1968, Chapter IV.
(15) H. C. Brown, *Rec. Chem. Prog.*, **14**, 83 (1953).
(16) A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1293 (1949).
(17) (a) R. W. Taft, Jr., "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, Chapter 13, p 556; R. W. Taft, Jr., Chapter 13, p 556; (b) M. S. Newman, Chapter 4, p 201.
(18) A. Albert and E. P. Sergent, "The Determination of Ionization Constants", 2nd ed, Chapman and Hall, London, 1971.
(19) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution", Buttersworths, London, 1965.
(20) D. H. Aue, *J. Am. Chem. Soc.*, **98**, 318 (1976).
(21) (a) L. A. Errede, *J. Phys. Chem.*, **64**, 1031 (1960); (b) ibid., **65**, 2262 (1961); (c) *J. Org. Chem.*, **27**, 3425 (1962).
(22) J. F. J. Dippy, *J. Chem. Soc.*, 1222 (1938); *Chem. Rev.*, **25**, 151 (1939).

Acylanthranils. 7. Influence of the End Group on Selectivity in the Reaction of ω-Substituted Linear Aliphatic Amines with Acetylanthranil[1]

L. A. Errede* and J. J. McBrady

Central Research Laboratories, 3M Company Saint Paul, Minnesota 55101

Received April 15, 1977

The reaction of acetylanthranil (**1**) with the amines $H_2N(CH_2)_4(CH_2)_{n-4}Z$ (**2a, 2b, 3c**) follows pathway B when Z is H (**2a**), but it follows pathway A when Z is a polar group such as OH (**2b**) or CO_2H (**2c**). This remote control on reaction selectivity at the other extremity is attributed to steric hindrance to reaction with **1** imparted by the $H_2N(CH_2)_4$– segment, which is held in the form of a six-membered Newman coil by the force of intramolecular association of the van der Waals type when Z is H, but which is overcome by intermolecular hydrogen bonding when Z is a OH or CO_2H. The reaction follows pathway B, however, when the terminal group is esterified.

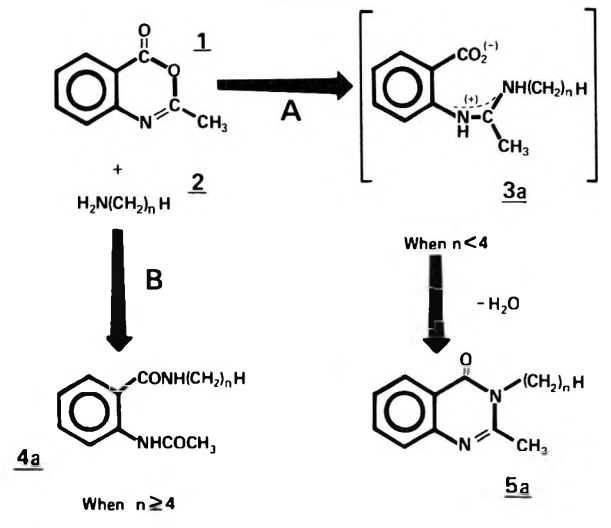
It was observed[2,3] that the pK_a value for the amines in the homologous series $H_2N(CH_2)_nH$ (**2a**) does not increase with n to an asymptotic limit as expected but rather peaks at $n = 2$ and then falls to a lower value, which remains relatively constant over the range from $n = 4$ to 22. This observation led to the speculation[3] that only the third and/or fourth methylene groups are responsible for this deviation from ideality, since increasing the chain further does not increase the deviation.

Hard evidence in support of this speculation was noted in the product distributions obtained in the reaction of acetylanthranil (**1**) with the amines **2a** neat or in an organic solvent.[3] Those amines with $n < 3$ followed pathway A exclusively to give the corresponding *N*-(2-carboxyphenyl)acetamidine salt **3** or its cyclodehydration product **5**; whereas those amines with $n > 3$ followed pathway B exclusively to give the corresponding *o*-acetamidobenzamide **4** as shown in Scheme I. Although reaction with *n*-propylamine (**2a**; $n = 3$) was dominated by pathway A, reaction via the alternate pathway was somewhat competitive. The exact selectivity ratio, however, depended on the reaction conditions.

Since reaction via pathway B is followed only by those amines that exhibit some form of steric hindrance,[4,5] it was suggested[3] that this crossover in reaction selectivity at $n = 4$ is also caused by steric hindrance and that it is imparted by the segment $H_2N(CH_2)_4$–. It was postulated[3] that it does so by forming in solution a six-membered coil similar to that described by Newman[6] in his "Rule of Six" to explain the marked decrease in reactivity exhibited by carbonyl compounds that can close a six-membered ring by intramolecular association.

It was shown[7] that a similar pseudoheterocyclic secondary amine configuration can indeed exhibit steric hindrance in the reaction with acetylanthranil, if the integrity of this configuration is maintained by intramolecular hydrogen bonding. Thus, amines such as ethanolamine and anthranilic acid, which associate by intramolecular hydrogen bonding in nonpolar solvents, react with acetylanthranil in benzene via pathway B, but in pyridine or in acetic acid they react via pathway A, owing to intermolecular association of the β-substituted amines with the solvent, which precludes the formation of the cyclic configuration and hence precludes the steric hindrance.[7]

Scheme I



The question now is whether or not the weak force of intramolecular association of the van der Waals type is also sufficient to ensure the integrity of the pseudocyclic configuration in benzene solution. In such a coiled configuration, the $H_2N(CH_2)_4$– segment like the above resembles geometrically, but not electronically, heterocyclic secondary amines, which are known to react with **1** via pathway B owing to steric hindrance.

It was postulated[3] that this small force is sufficient to restrict in aqueous solution the free rotation of the tetramethylene segment about the amino group to which it is attached and therefore to influence disproportionately the steric requirement for hydration of the free amine form, relative to that of the ammonium ion form to account for the entropy effect suggested by Brown.[2c] In contrast to the chemical aberration noted in aqueous solution, the affinity of the amines $H_2N(CH_2)_nH$ for a proton in the gas phase is quite normal as pointed out by Aue.[8] This observation is not unexpected or inconsistent, since these molecules in the gas phase are in a higher energy state, which is sufficient to overcome the weak force of intramolecular association that supports the coiled configuration in aqueous solution. Consequently the methylene chain in the gas phase should remain in a more open or extended configuration, which does not interfere with the approach of a proton or enhance dissociation of the ammonium ion as is assumed to be the case in aqueous solution.

If this postulation is correct, then the sets of amines $H_2N(CH_2)_nZ$, where the ω group Z is a polar group, such as OH (**2b**) or CO_2H (**2c**), should not exhibit the chemical aberration that is exhibited in solution at room temperature by the set **2a**, where Z = H. The relatively strong force of intermolecular hydrogen bonding with the sets **2b** and **2c** should easily overcome the weaker force of intramolecular van der Waal's association extant in the set **2a** to ensure that the amines **2b** and **2c** remain in open configuration, especially in a polar solvent, as shown in Scheme II. Accordingly, long-chain aliphatic amines with a polar substituent in the ω positions should behave chemically toward electrophilic reagents like simple short-chain aliphatic amines such as ethylamine.

Support for this premise can be found in the data published by Girault and Rumpt, who reported[9] in 1958 that unlike the amines $H_2N(CH_2)_nH$ the pK_a values for the amines $H_2N(CH_2)_nOH$ (**2b**) ($n = 0$ to 6) increase monotonically from 5.96 for $n = 0$ to 10.62 for $n = 6$. On the basis of these data, however, one cannot say unequivocally that the chemical

0022-3263/78/1943-1884$01.00/0

Table I. Products Isolated from the Reaction of 1 with $H_2N(CH_2)_nZ$, 2

Amine Series	Reaction conditions: n	Z	Solvent	Temp, °C	Time	% units of 1 isolated as: 4	3	5	Calcd selectivity A/B = (3 and/or 5)/4
2a	<4	H	Benzene	rt	4 h	0	*a*	*a*	>16/1[a]
	≥4	H	Benzene	rt	1 day	*a*	0	0	>1/23[a]
2b	2	OH	Neat	rt	1 day	*b*	0	0	>1/25[b]
	2	OH	Pyridine	rt	1 day	0	0	*b*	<50/1[b]
	3	OH	c	80	20 min	*b*	0	*b*	2/1[b]
	3	OH	Pyridine	rt	1 day	*b*	0	*b*	17/1[b]
	3	OH	Neat	rt	1 day	0	0	*b*	>50/1[b]
	6	OH	c	100	1 h	0	0	62	>50/1[d]
2c	2	CO_2H	Acetic acid	Reflux	3 h	0	0	100	>50/1
			Pyridine	rt	1 day	0	0	95	>50/1
	3	CO_2H	Acetic acid	rt	1 wk	0	0	80	>50/1[e]
			Pyridine	rt	1 day	0	0	100	>50/1
	5	CO_2H	Acetic acid	rt	1 wk	0	0	80	>5/1[f]
			Pyridine	rt	1 day	0	0	100	>50/1
2d	6	*g*	c	100	4 h	90	0	0	<1/25

[a] Data taken from ref 3. [b] Data taken from ref 7. [c] 1 made to react with an equivalent weight of amine by fusion at the temperature indicated. [d] 17% of the units of 1 isolated as 6-(*o*-acetamidobenzcarboxy)-*n*-hexylamine, **2d**, and 16% isolated as **4d**, the *o*-acetamidobenzamide of **2d**. [e] 14% of the units of 1 were isolated as *o*-acetamidobenzoic acid. [f] 20% of the units of 1 were isolated as *o*-acetamidobenzoic acid, indicative that these reactions (notes e and f) were not yet complete when terminated. [g] The group is *o*-$(CH_3CONH)PhCO_2$.

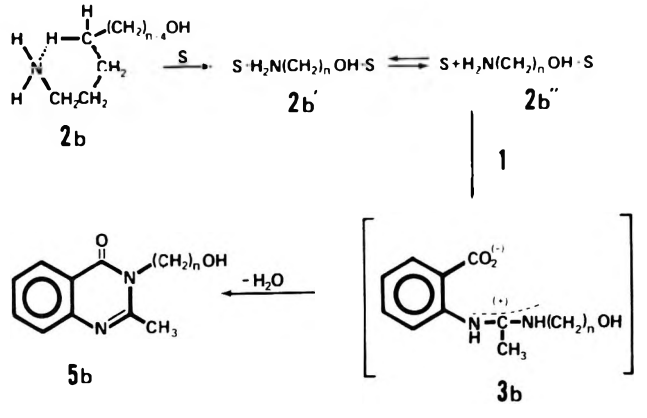
Table II. Characterization Data for Reaction Products 4 and 5 in Table I

Product	Registry no.	mp, °C	Key IR[a] abs bands in μm	NMR[b] data in τ values
Amide				
4d (*n* = 6) from amine **2d** (*n* = 6)	65453-00-1 65453-01-2	144–5	3.0, 3.1, 5.8, 6.0, 6.2, 6.3, 6.6	($CDCl_3$) 1.2–3.0 (cpx, Ar, −1.2 and 3.5 (br, NH), 5.63 (t, CH_2O), 6.52 (q, CH_2NH), 7.75 and 7.80 (s, CH_3), 8.0–8.6 $(CH_2)_4$
Quinazolones				
5b (*n* = 6) from amine **2b** (*n* = 6)	65452-92-8 4048-33-3	120–1	2.9, 6.1, 6.3	($CDCl_3$) 1.6–2.7 (cpx, Ar), 5.88 (t, CH_2N), 6.32 (t, CH_2O), 7.34 (s, CH_3), 7.63 (s, OH), 8.0–8.6 $(CH_2)_4$
5c (*n* = 2) from amine **2c** (*n* = 2)	65452-93-9 107-95-9	218–20	3.3–4.3, 5.9, 6.3, 6.4	
5c (*n* = 3)	65452-94-0	114–5 ⎫ 141–2[d] ⎭	3.0–4.3, 5.7, 5.9, 6.1, 6.3, 6.4	(Me_2SO-d_6) 1.7–2.6 (cpx, Ar), 5.88 (t, CH_2N), 7.33 (s, CH_3), 7.57 (t, $CH_2C{=}O$), 8.06 (cpx, CH_2)
5c (*n* = 5)	65453-02-3	179–80	3.2–4.3, 5.8, 6.0, 6.3, 6.4	
Amine				
2d (*n* = 6)[c]		Oil	3.1 br, 5.8, 6.1, 6.3, 6.6	

[a] br = broad. [b] cpx = complex, br = broad, t = triplet, q = quartet, s = singlet. [c] o-$(CH_3COHN)PhCO_2(CH_2)_6NH_2$, i.e., the o-acetamidobenzoate of amine **2b** (*n* = 6). [d] Hydrates.

aberration in pK_a as a function of *n* noted in the set **2a** was avoided in the set **2b** because steric hindrance to formation of the ammonium ion was avoided or that the reverse reaction was suppressed by avoiding the entropy effects noted by Brown,[2c] or both, since pK_a is only a measure of the equilibrium state of the system.

Scheme II

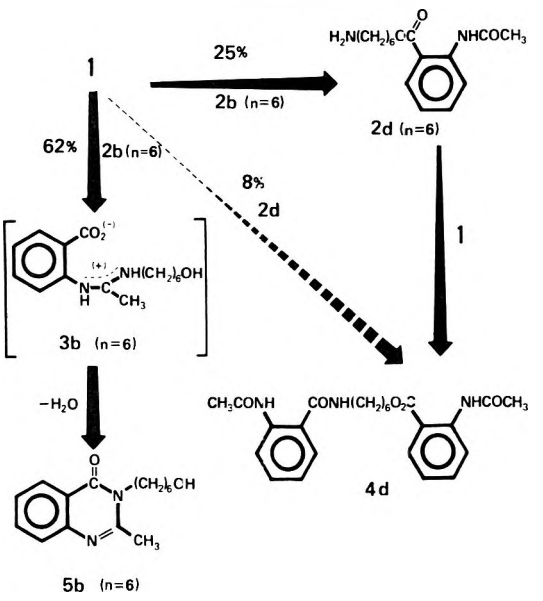


The product distribution obtained in the reaction of amines with acetylanthranil is a more definitive test, since the products are formed irreversibly and therefore the reaction selectivity will indicate the presence or absence of steric hindrance to the forward reaction only. Accordingly, acetylanthranil was made to react with the amino alcohols $H_2N(CH_2)_nOH$ (**2b**) (*n* = 2, 3, and 6). These results are collected in Table I for easy comparison with results obtained earlier[3] with the amines $H_2N(CH_2)_nH$ (**2a**). The corresponding characterization data for the products of reaction with **2b** are collected in Table II.

In contrast to the results obtained with **2a**, the data show that the amino alcohols **2b** follow pathway A preferentially for the values of *n* > 2 and even for *n* = 2 when the reaction is carried out in a polar solvent as mentioned earlier.

To make certain that this remote control on reaction selectivity of the amino group in the ω position is not unique to ω-substituted amino alcohols, acetylanthranil was made to

Scheme III



react with the carboxylic acids $H_2N(CH_2)_nCO_2H$ (**2c**) (n = 2, 3, and 5). Again the reaction products were separated and identified and the selectivity was calculated from the product distribution as described previously.[9] These data are also collected in Table I and the characterization data for the products isolated are collected in Table II. As expected, the selectivity data show that all the amines in the set **2c** follow pathway A preferentially. This uniform result is in sharp contrast to that obtained with the set **2a**, which shows crossover in selectivity from pathway A to B at n = 4.

That this remote control over reaction selectivity is attributable to intermolecular hydrogen bonding by the polar groups at the terminal positions is demonstrated further by the results obtained with 6-(2-acetamidobenzcarboxy)-n-hexylamine (**2d**) (n = 6), which was isolated as a component of the complicated product mixture obtained when 6-amino-n-hexanol-1 (**2b**) (n = 6) was made to react with an equivalent amount of acetylanthranil by fusion at 100 °C. In this reaction 62% of the acetylanthranil units was isolated as N-(6-hydroxyhexamethylene)-2-methylquinazol-4-one (**5b**) (n = 6), 17% as 6-(2-acetamidobenzcarboxy)-n-hexylamine (**2d**) (n = 6), and 16% as **4d**, the o-acetamidobenzamide of **2d**. The formation of these products can be rationalized as outlined in Scheme III. That **4d** (n = 6) was indeed formed from **2d** (n = 6) was demonstrated when **2d** (n = 6) was made to react with an equivalent amount of **1** by fusion at 100 °C to give **4d** (n = 6) as the major product of reaction, exclusive of the alternative possible product [i.e., the 2-acetamidobenzoate ester of **5b** (n = 6)]. This result indicates that selectivity reverts to pathway B, inferring steric hindrance, when the possibility for intermolecular hydrogen bonding is decreased owing to esterification of the terminal OH group.

The results obtained in this investigation are consistent with the hypothesis that the amines $H_2N(CH_2)_4(CH_2)_{n-4}Z$ exhibit steric hindrance to reaction with electrophiles when Z is H owing to the $H_2N(CH_2)_4$– segment, which assumes a six-membered Newman coil configuration. When Z is a polar substituent, however, the intramolecular force that holds the cyclic configuration is overcome by intermolecular hydrogen bonding so that the amine can now react with the electrophilic reagent without steric hindrance.

Experimental Procedures

The general procedure for reaction of acetylanthranil (**1**) with aliphatic amines **2** and the separation and identification of the products **3**, **4**, and **5** are described in preceding publications.[3,5,7] The materials balance of products with reactants was usually more than 90% so that reliable calculation of the reaction selectivity could be made from the corresponding product distribution as noted in Table I. Characterization data for the products isolated are collected in Table II. Specific details and slight modifications in procedure to accommodate the bifunctional amines investigated are noted below.

A. Reaction of 1 with the Amines $H_2N(CH_2)_nH$ (2a) in Benzene. These procedures are described in ref 3.

B. Reaction of 1 with the Amines $H_2N(CH_2)_nOH$ (2b). (i) ethanolamine **2b** (n = 2) is described in ref 7; (ii) 3-amino propanol (**2b**) (n = 3) is described in ref 7; (iii) 6-amino-n-hexanol-1 (**2b**) (n = 6).

Acetylanthranil (5 g) and 6-amino-n-hexanol-1 (**2b**; n = 6) (5 g) were warmed on a steam bath for 1 h. The solution was allowed to cool to room temperature overnight. The solid product was ground to a fine powder and then leached sequentially with cold dilute aqueous base and aqueous acid. The IR and NMR spectra of the insoluble residue (1.1 g) indicated that this material was **4d** (n = 6), i.e., the 2-acetamidobenzamide derivative of 6-(2-acetamidobenzcarboxy)-n-hexylamine (**2d**) (n = 6). Recrystallization of this amido ester from methanol gave **4d** (n = 6) in the form of colorless crystals (mp 144–145 °C). The assigned structure of the recrystallized product was verified by its NMR and IR spectra (Table II). The aqueous acid extract was made alkaline with dilute aqueous base and a viscous orange oil (1.6 g) separated from solution. The IR spectrum (Table II) of this oil indicated that this product was 6-(2-acetamidobenzcarboxy)-n-hexylamine (**2d**) (n = 6). A sample of the oil (1 g) was fused with an equal weight of acetylanthranil to give **4d** (n = 6) in good yield (1.5 g; mp 142–144 °C) (no depression with the above sample). The aqueous alkaline mother liquor from which **2d** (n = 6) was separated was allowed to remain at room temperature overnight, during which time N-(6-hydroxy-n-hexyl)2-methylquinazol-4-one (**5b**) (n = 6) separated in the form of a white powder (4.8 g; mp 120–121 °C). The assigned structure was confirmed by its IR and NMR spectra (Table II). Thus 62% of the acetylanthranil units were isolated as **5b** (n = 6), 17% as **2d** (n = 6), and 16% as **4d** (n = 6).

C. Reactions with the Amines $H_2N(CH_2)_nCO_2H$, (2c). i. 3-Aminopropionic Acid (n = 2). A solution of **1** (5 g) and 3-aminopropionic acid (**2c**) (n = 2) (5 g) in acetic acid (60 cm^3) was allowed to react at reflux for 3 h. The solution was cooled to room temperature and then added to 500 cm^3 of cold water to cause precipitation of the product as a white powder (8 g), which was soluble in $NaHCO_3$. Recrystallization from hot water gave the product in the form of white crystals (7.2 g; mp 218–220 °C) which were identified as N-(2-carboxyethyl)-2-methylquinazol-4-one (**5c**) (n = 2) by its IR spectrum (Table II) and by its elementary analysis. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.49; NE, 232.2. Found: C, 62.1; H, 5.3; N, 12.1; NE, 228.

The quinazolone carboxylic acid was also obtained in good yield when the reaction was repeated using pyridine as solvent at room temperature. The reaction mixture was separated essentially as described in detail for reaction of **1** with **2c** (n = 5).

ii. 4-Aminobutyric Acid (n = 3). A solution of **1** (5 g) and 4-aminobutyric acid (**2c**) (n = 3) (5 g) in acetic acid (50 cm^3) was allowed to react at room temperature for 1 week. The excess solvent was removed at about 10 mmHg pressure in a rotary film evaporator. The nonvolatile product was leached with water to dissolve the acetamidine salt, leaving a powdery residue (0.8 g; mp 182–183 °C), which was indentified as o-acetamidobenzoic acid by its IR spectrum and mixture melting point with an authentic sample. The mother liquor was allowed to remain at room temperature overnight. During this time the acetamidine salt was converted to the corresponding quinazolone carboxylic acid, which precipitated from solution as a white powder. The powder was recrystallized from hot water to give the product in the form of white crystals (6.5 g), which melted at 114–115 °C with evolution of a gas, solidifed, and remelted at 141–142 °C. A sample was fused at 120 °C until bubbling was completed to give a white solid that remelted at 140 °C. The IR and NMR spectra, Table II, indicated that the sample melting at 114 °C and that at 141 °C were hydrates of N-(3-carboxypropyl)-2-methylquinazol-4-one (**5c**) (n = 3).

Thus 14% of the acetylanthranil units were recovered as acetylanthranilic acid, indicating incomplete reaction, and 80% were recovered as the quinazolone carboxylic acid **5c** (n = 3).

Conversion of **1** to the quinazolone carboxylic acid was 90% complete when the reaction was allowed to occur overnight in pyridine at room temperature. The product was isolated essentially as described in detail for reaction of **1** with **2c** (n = 5).

iii. 6-Aminocaproic Acid (n = 5). A solution of **1** (5 g) and 6-aminocaproic acid (**2c**) (n = 5) (4.0 g) in acetic acid (30 cm^3) was al-

lowed to react at room temperature for 1 week; the reaction mixture was separated essentially as described in detail for reaction of **1** with **2c** (n = 3). About 20% of the acetylanthranil units were recovered as o-acetamidobenzoic acid (mp 185–186 °C) and the rest was isolated as N-(5-carboxy-n-pentyl)-2-methylquinazol-4-one (**5c**) (n = 5) (mp 179–180 °C). The assigned structure was verified by its IR spectrum and by its NE (calcd 274; obsd 277).

Another solution of **1** (5 g) and **2c** (n = 5) in pyridine (40 cm^3) was allowed to react at room temperature overnight. During this time the quinazolone product separated as a white powder (4.8 g; mp 169–171 °C), which was removed by filtration. The mother liquor was evaporated to dryness at 60 °C (10 mmHg). The nonvolatile semisolid residue was leached with water to remove pyridine. The IR spectrum of the crystalline residue (3.1 g; mp 172–175 °C) was essentially the same as that fraction melting at 169–171 °C (no depression in melting point with a mixed sample). The two fractions were combined and recrystallized from hot water to give N-(5-carboxy-n-pentyl)-2-methylquinazol-4-one (**5c**) (n = 5) in the form of white crystals (7.3 g; 179–180 °C). The IR spectrum of this sample was identical to that obtained via reaction in acetic acid.

Registry No.—**1**, 525-76-8; **2c** (n = 3), 56-12-2; **2c** (n = 5), 60-32-2; o-acetamidobenzoic acid, 89-52-1.

References and Notes

(1) Presented before the 172nd National Meeting of the American Chemical Society at San Francisco, California, September, 1976, Abstract No. Orgn 116.
(2) (a) N. F. Hall and M. R. Sprinkle, *J. Am. Chem. Soc.*, **54**, 3469 (1932); (b) C. H. Hoerr, M. R. McCorkle, and A. W. Ralston, *ibid.*, **65**, 328 (1943); (c) H. C. Brown, M. D. Taylor, and S. Sujishi, *ibid.*, **73**, 2464 (1951).
(3) Part 6: L. A. Errede, *J. Org. Chem.*, this issue.
(4) Part 3: L. A. Errede, H. T. Oien, and D. R. Yarian, *J. Org. Chem.*, **42**, 12 (1977).
(5) Part 4: L. A. Errede, J. J. McBrady, and H. T. Oien, *J. Org. Chem.*, **42**, 656 (1977).
(6) M. S. Newman, Ed., *"Steric Effects in Organic Chemistry"*, *Wiley*, New York, N.Y., 1956, Chapter 4, p 201.
(7) Part 5: L. A. Errede and J. J. McBrady, *J. Org. Chem.*, **42**, 3863 (1977).
(8) D. H. Aue, *J. Am. Chem. Soc.*, **98**, 318 (1976).
(9) G. Girault and P. Rumpf, *C. R. Hebd. Seances Acad. Sci.*, **246**, 1705 (1958).
(10) Part 2: L. A. Errede, J. J. McBrady, and H. T. Oien, *J. Org. Chem.*, **41**, 1765 (1976).

Acylanthranils. 8. Question of Newman Steric Hindrance in the Reaction of Linear Aliphatic Amines with Acetylanthranil[1]

L. A. Errede* and G. V. D. Tiers

Central Research Laboratories, 3M Company, Saint Paul, Minnesota 55101

Received July 8, 1977

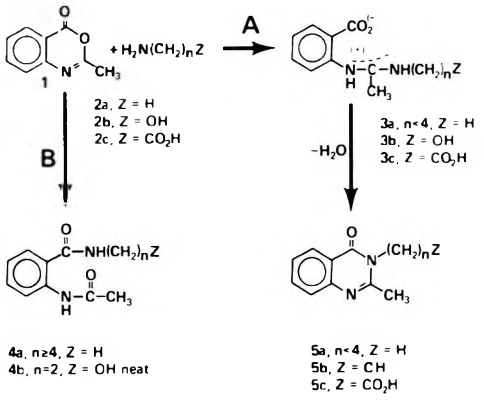
Although hydrocarbon amines with the general formula $H_2N(CH_2)_4R$ (**2**) react "abnormally" with acetylanthranil (**1**) to give the corresponding o-acetamidobenzamide (**4**), analogous amines that do not have a hydrogen atom at the critical fourth carbon position removed from the amino group react "normally" with **1** to give the corresponding acetamidine salt **3**. These results support the premise that the "abnormal" selectivity is caused by the aminotetramethylene segment, which forms a six-membered Newman coil due to intramolecular van der Waals attraction of hydrogen for nitrogen.

It was reported[2,3] that the reaction selectivity of acetylanthranil with the linear aliphatic amines $H_2N(CH_2)_nH$ is dependent upon the number of methylene groups in the aliphatic chain. When $n < 3$ the reaction follows pathway A exclusively to give the corresponding acetamidine intermediate **3** or its cyclodehydration product **5**, but when $n > 3$ the reaction follows pathway B exclusively to give the corresponding o-acetamidobenzamide (**4**) as shown in Scheme I. Reaction with n-propylamine (**2a**) (n = 3) follows both pathways in the relative ratio of A/B > 17/1.

Since pathway B is associated with amines that exhibit steric hindrance to reaction with other electrophiles, whereas pathway A is associated with amines that do not,[4] it was suggested[3] that steric hindrance is also responsible for the sharp crossover in reaction selectivity with **1** at n = 4, and it was postulated further that this steric hindrance is caused by the $H_2N(CH_2)_4$– segment, which is held in the form of a six-membered ring by the small force of intramolecular association of the van der Waals type[3] as shown in Figure 1. Such a configuration is similar to that proposed by Newman[5] in his "Rule of Six" to explain the observed marked decrease in rate of saponification for amides and esters of aliphatic acids with more than three carbon atoms in the chain.

Support of this point of view is found in the observation[6] that the long-chain aliphatic amines $H_2N(CH_2)_nOH$ (**2b**) and $H_2N(CH_2)_nCO_2H$ (**2c**) react with **1** via pathway A, showing that interaction with **1** occurs without steric hindrance, when the long-chain amine has a polar group in the ω position. This remote control by the polar substituent, OH or CO_2H, on the reaction selectivity of the NH_2 group at the other extremity is attributed to the intermolecular hydrogen bonding, especially in a polar solvent, which serves to overcome the weak force of intramolecular van der Waals association that supports the Newman coil. Thus, the ω-substituted amine is kept in a more open configuration, which enables interaction to occur with **1** via pathway A as described previously.[6] Analogous results were obtained[7] with anthranilic acid (**2d**) and with ethanolamine (**2b**) (n = 2). In nonpolar solvents, or neat, these amines interacted with **1** via pathway B, owing to intramolecular hydrogen bonding that formed six- and five-membered rings, respectively. In polar solvents, such as pyridine or acetic acid, however, these amines interacted with **1** via pathway A, since the ring structure that imparted steric hindrance in the

Scheme I



0022-3263/78/1943-1887$01.00/0

Table I. Product Distributions Obtained in the Reaction of 1 with H_2NR in Diethyl Ether

Amine	Registry no.	R	% 1 units isolated as 4	3	5	Selectivity at rt A/B = (3 and/or 5)/4
2a ($n < 3$)		$(CH_2)_nH$	0	*a*	0	>50/1[a]
2a ($n = 3$)		$(CH_2)_3H$	*a*	*a*	0	>17/1[a]
2a ($n > 3$)		$(CH_2)_4(CH_2)_{n-1}H$	*a*	0	0	<1/24[a]
2b ($n = 6$)		$(CH_2)_6OH$	0	0	*b*	>50/1[b]
2c ($n = 5$)		$(CH_2)_5CO_2H$	0	0	*b*	>50/1[b]
2e	919-30-2	$(CH_2)_3Si(OEt)_3$	0	95	0	>50/1
2f	65452-64-4	$(CH_2)_3Si[OSi(OCH_3)_3]_3$	16[c]	0	80[c]	~5/1[c]
2g	78-81-9	$CH_2CH(CH_3)_2$	*d*	*d*	0	23/1[d]
2h	5813-64-9	$CH_2C(CH_3)_3$	*d*	*d*	0	12/1[d]
2i ($n = 2$)	753-90-2	CH_2CF_3	0	99	0	>50/1
2i ($n = 3$)	422-03-7	$CH_2CF_2CF_3$	0	0	95	>50/1
2i ($n = 6$)	355-34-0	$CH_2(CF_2)_4CF_3$	0	0	99	>50/1
2j	5332-73-0	$CH_2CH_2CH_2OCH_3$	40[c]	0	40[c]	~1/1[c]
2k	109-85-3	$CH_2CH_2OCH_3$	50[c]	0	25[c]	~1/2[c]

[a] Data taken from ref 2. [b] Data taken from ref 3. [c] Product mixture isolated as an oil. The product distribution (i.e., selectivity) was estimated from its IR and NMR spectra. [d] Data taken from ref 5.

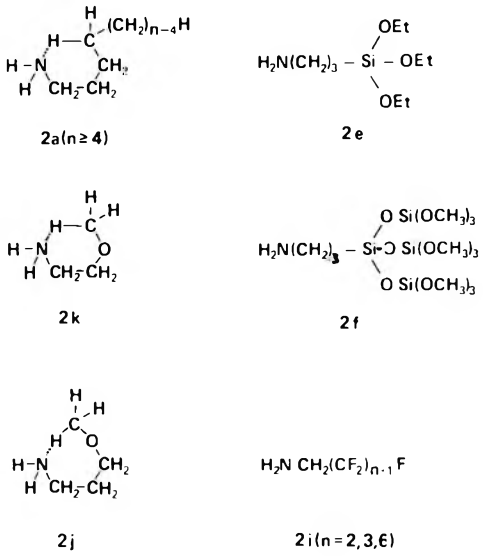


Figure 1.

nonpolar solvents now was precluded by intermolecular hydrogen bonding at the extremities.

A similar mitigating effect of a polar group in the ω position on the chemistry of long-chain aliphatic amines is evidenced when one compares the reactions of the amines $H_2N(CH_2)_nH$[3] and $H_2N(CH_2)_nOH$[7] with hydronium ions in aqueous solution. The pK_a values of the amines $H_2N(CH_2)_nH$ as a function of n show a maximum[3] of 10.81 at $n = 2$ followed by a smooth decrease to the line 10.62 ± 0.03 for all values of $n > 3$, whereas the pK_a values for the amines $H_2N(CH_2)_nOH$ show no such maximum[8] but rather increase monotonically from 5.96 at $n = 0$ to 10.62 at $n = 6$.

Although these results are consistent with the postulation that the change in chemistry as a function of n is caused by the formation of a Newman coil as shown in Figure 1, they do not implicate specifically intramolecular van der Waals attraction of the nitrogen atom with a hydrogen atom on the fourth methylene group. A more definitive test of this hypothesis is the product distribution obtained when acetylanthranil is made to react with similar long-chain aliphatic amines that have no hydrogen atom in this critical position. If this hypothesis is correct then the product distribution obtained with these amines will indicate that reaction occurs predominantly via pathway A instead of B despite the fact that these amines may have rather bulky substituents elsewhere than at the α-carbon atom.

A few amines of this type were available to us for testing with acetylanthranil. Accordingly, the respective material balances were completed as described previously[4,9] and the corresponding reaction selectivities calculated therefrom are collected in Table I for easy comparison with results obtained in earlier studies. The corresponding characterization data of new products and derivatives thereof are collected in Table II.

The data show that triethoxy-3-amino-*n*-propylsilane (**2e**), which has oxygen atoms in each of the three critical positions, as shown in Figure 1, follows pathway A instead of B to give the corresponding acetamidine salt intermediate **3e** in 95% yield, despite the fact that the $-Si(OEt)_3$ group in the fourth position is bulkier than a $-CH_3$ group, which caused reaction with *n*-butylamine to follow pathway B exclusively.

A sample of **3e** was converted in good yield to the corresponding quinazolone **5e** by fusion above 100 °C to confirm the assigned structure.

Even the amine, tris(trimethylsilyloxy)-3-amino-*n*-propylsilane (**2f**) favored pathway A over pathway B in the ratio of about 5/1, despite the enormous umbrella-like bulk of the $-Si[OSi(OCH_3)_3]_3$ group in the fourth position. In this case the product mixture was isolated as an oil that could not be separated chemically owing to the hydrolytic instability of the trimethylsilyloxy group. The IR and NMR spectra of this oil, however, indicated that cyclodehydration of **3f** had occurred to give the corresponding quinazolone **5f** and that the ratio of **5f** to **4f**, the *o*-acetamidobenzamide product obtained via pathway B, was 5/1.

These results indicated that an H atom located on the fourth carbon position removed from the amino group is virtually a necessary condition for "abnormal" reaction of linear aliphatic amines with acetylanthranil via pathway B, while mere bulkiness has relatively little effect, unless of course it is on N itself or the α-carbon atom as reported previously.[4] Similar results were noted earlier with C_4 and C_5 amines; both isobutyl- and neopentylamines[5] (**2g** and **2h**), which have no fourth carbon position, followed A preferentially, whereas the corresponding straight chain C_4 and C_5 amines followed pathway B despite their relative less "bulky" geometry.

To test the six-ring hypothesis further, acetylanthranil was allowed to react with a set of fluorocarbon amines of generic formula $H_2NCH_2(CF_2)_nF$ (**2i**). These have no H atom at the critical fourth carbon position for ring formation and consequently should not exhibit the crossover in selectivity with increase in chain length.

Table II. Characterization Data for Products 3, 4, and 5 Listed in Table I

Product	Mp, °C	Key IR abs bands in μm	NMR[b] data (Me_2SO-d_6) in τ values
Acetamidines, **3**			
From amine **2g**	78–83	2.9–4.0, 6.1, 6.3, 6.5	
From amine **2i** (n = 2)	107–8	3.2–4.3 6.1, 6.3, 6.5	
2-Methylquinazolones, **5**			
From **3g**	185–200	6.0, 6.3	
From **3i** (n = 2)	92–3	6.0, 6.3	
From **2i** (n = 3)	106–7	6.0, 6.3	
From **2i** (n = 6)	100–2	6.0, 6.3	1.7–2.5 (cpx, Ar), 4.86 (t, CH_2N), 7.33 (s, CH_3)
From **2k**	72–4[a]	6.0, 6.3	
2-Acetamidobenzamides, **4**			
From **2k**	83–5[a]	3.1, 6.1, 6.2, 6.3, 6.5	−1.2 and 1.3 (2, NH), 1.4–2.9 (cpx, Ar)
From **3i** (n = 2) (trace)	191–194	3.1, 6.1, 6.3, 6.5	6.49 (cpx, $NHCH_2CH_2O$), 6.69 (s, CH_3O), 7.84 (s, $CH_3C{=}O$)

[a] Isolated from the product mixture obtained as an oil by repeated recrystallization from hexane and manual separation of two distinctly different crystalline types to give small samples of **5k** and **4k** for identification purposes. [b] cpx = complex, t = triplet, s = singlet.

The data are summarized in Tables I and II. The results obtained with the first two members of this set (i.e., 1,1-dihydroperfluoroethylamine (**2i**) (n = 2) and 1,1-dihydroperfluoro-n-propylamine (**2i**) (n = 3)) showed that fluorocarbon amines with less than four carbon atoms react like their hydrocarbon counterparts to give the corresponding acetamidine salt **3** via pathway A, but at a slower rate owing to the decreased basicity of the amine. Significantly, no crossover in selectivity was noted when 1,1-dihydroperfluoro-n-hexylamine (**2i**) (n = 6) was made to react with **1**. The "normal" pathway was followed and the correspoinding quinazolone **5i** (n = 6) was isolated in good yield as the only product of the reaction.

One might expect to find borderline cases that manifest intermediate selectivity when gross structural changes modify the ability of the molecule to form or hold the coiled structure illustrated with **2a**. One such change is replacement of a methylene group by an ether link.

Acetylanthranil was allowed to react with the amino ether $H_2N(CH_2)_3OCH_3$ (**2j**) which lacks a hydrogen atom in the "critical" fourth position. A product mixture of **5j** and **4j** was obtained which indicated that reaction occurred via both pathways at comparable rates. While the analogous five ring would seem untenable due to the six-bond oppositions required, a seven-membered ring analogous to the coil form of **2a** would not suffer from that objection, though perhaps it would be partially destabilized by entropy effects related to ring size and the flexibility of the ether link. Some support for this view is provided by results with the lower amino ether $H_2N(CH_2)_2OCH_3$ (**2k**) for which was found only a small preference for the "abnormal" pathway B. This is consistent with the above suggestion but not decisive.

Taken as a whole these results support the premise[2,3] that aliphatic hydrocarbon amines with the segment $H_2N(CH_2)_4$–, which can form a coiled six-membered configuration by intramolecular association, do indeed exhibit Newman "Rule-of-Six" steric hindrance to reaction with electrophilic reagents.

Experimental Section

General Procedure. Acetylanthranil was allowed to react at ca. 25 °C with an equivalent amount of a chosen amine in diethyl ether and the products were separated according to the scheme described in detail in a previous publication.[9] Samples of the acetamidine salt **3** when isolated were converted to the corresponding quinazolone **5** by fusion or by solution in dilute aqueous base as described previously.[10] The percentage of acetylanthranil units isolated as the products **3**, **4**, and **5** and the corresponding reaction selectivities, **A/B** = (**3** and/or **5**)/**4**, calculated therefrom are collected in Table I. The characterization data for the products isolated in these reactions and the quinazolones produced by cyclodehydration of the acetamidines isolated are collected in Table II.

Amines Used. Tri(ethoxy)-3-aminopropylsilane (**2e**) was obtained as a commercial sample "A-1100" from Union Carbide Corp. Tris-(trimethylsilyloxy)-3-aminopropylsilane (**2f**) was obtained from D. N. Vivona of the 3M Co., who had prepared the amine from **2e**. His preparation is described in a recent patent.[11] The fluorocarbon amine, 1,1-dihydroperfluoroethylamine (**2i**) (n = 2), was obtained from Dr. T. S. Reid of the 3M Co., who prepared the compound by reduction of perfluoroacetonitrile according to the procedure of Bissel and Finger;[12] 1,1-dihydroperfluoro-n-propylamine (**2i**) (n = 3) was prepared by Dr. D. R. Husted (now deceased) of the 3M Co., according to the procedure of Husted and Ahlbrecht;[13] 1,1-dihydroperfluoro-n-hexylamine (**2i**) (n = 6) was synthesized by M. L. Sandberg of the 3M Co. via catalytic reduction of perfluoro-n-hexanonitrile according to the procedure of Husted and Ahlbrecht.[14] The amino ethers, 3-methoxy-n-propylamine (**2j**) and 2-methoxyethylamine (**2k**), were from American Cyanamid Co. and Eastman Organic Chemicals Co., respectively.

Acknowledgment. The authors are indebted to Dr. J. J. McBrady for interpretation of the IR and NMR spectra.

Registry No.—**1**, 525-76-8; **3g**, 34264-52-3; **3i** (n = 2), 65452-65-5; **4i** (n = 2), 65452-71-3; **4k**, 65452-70-2; **5g**, 391-03-7; **5i** (n = 2), 65452-66-6; **5i** (n = 3), 65452-67-7; **5i** (n = 6), 65452-68-8; **5k**, 65452-69-9.

References and Notes

(1) Presented before the 172nd National Meeting of the American Chemical Society at San Francisco, Sept. 1976, Abstract No. Orgn. 116.
(2) H. C. Brown, M. D. Taylor, and S. Sujishi, *J. Am. Chem. Soc.*, **73**, 2464 (1951).
(3) Part 6: L. A. Errede, *J. Org. Chem.*, this issue.
(4) Part 4: L. A. Errede, J. J. McBrady, and H. T. Oien, *J. Org. Chem.*, **42**, 656 (1977).
(5) M. S. Newman, "Steric Effects in Organic Chemistry", Wiley, New York, N.Y., 1956 p 201.
(6) Part 7: L. A. Errede and J. J. McBrady, *J. Org. Chem.*, this issue.
(7) Part 5: L. A. Errede and J. J. McBrady, *J. Org. Chem.*, **42**, 3863 (1977).
(8) G. Girault and P. Rumpf, *C. R. Hebd. Seances Acad. Sci.*, **246**, 1705 (1958).
(9) Part 2: L. A. Errede, J. J. McBrady, and H. T. Oien, *J. Org. Chem.*, **41**, 1765 (1976).
(10) Part 1: L. A. Errede, *J. Org. Chem.*, **41**, 1763 (1976).
(11) C. M. Smith and G. V. D. Tiers, U.S. Patent 3 888 891 (1975).
(12) E. R. Bissel and M. Finger, *J. Org. Chem.*, **24**, 1256 (1959).
(13) D. R. Husted and A. H. Ahlbrecht, *J. Am. Chem. Soc.*, **75**, 1605 (1953).
(14) D. R. Husted and A. H. Ahlbrecht, U.S. Patent 2 691 043 (1954).

Kinetic and Product Study of the Thermolyses of Several Nitrones and *O*-Alkyloximes

Jose A. Villarreal, Thomas S. Dobashi, and Edward J. Grubbs*

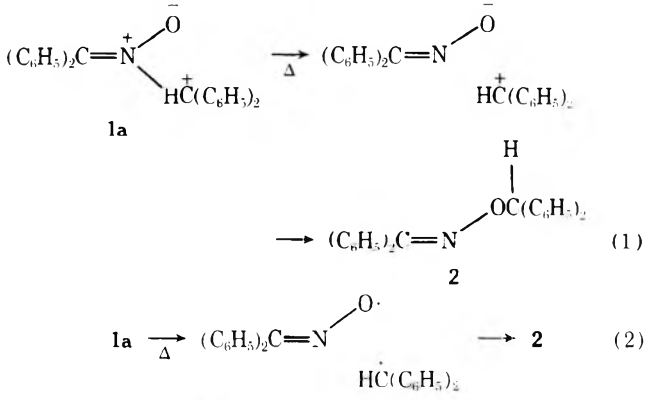
Department of Chemistry, San Diego State University, San Diego, California 92182

Received July 27, 1977

The products from the thermal decompositions of *N*-benzhydryl-α,α-diphenylnitrone (**1a**) in diethylcarbitol, in *tert*-butyl alcohol, and in *N*,*N*-dimethylacetamide have been determined. The products from the thermolyses of *N*-(*p*-methylbenzhydryl)-α,α-diphenylnitrone (**1b**), *N*-benzhydryl-α,α-bis(*p*-chlorophenyl)nitrone (**1c**), and *N*-benzhydryl-α,α-bis(*p*-methylphenyl)nitrone (**1d**) in diethylcarbitol have also been isolated and identified. Rates and activation parameters for thermal decompositions have been measured. The alkylation of (*Z*)-benzaldoxime anion with chlorotriphenylmethane has been repeated. The structure of the product is shown to be (*Z*)-*O*-triphenylmethylbenzaldoxime [(*Z*)-**6**] and not a nitrone as previously reported. The geometrically isomeric *p*-methylbenzophenone *O*-triphenylmethyloximes [(*E*)-**9** and (*Z*)-**9**] have been prepared and characterized. Thermal geometric equilibrations of (*Z*)-**6** and its isomer (*E*)-**6** as well as of (*Z*)-**9** and (*E*)-**9** are described. The mechanisms of these thermal processes are discussed in light of these experiments.

In several recent publications[2-4] we presented evidence bearing on specific stereochemical and kinetic properties of intermediates which are formed during the thermal decompositions of *N*-benzhydryl-α,α-diarylnitrones. In the present report we summarize kinetic and product data which support the mechanistic course of these reactions which was proposed earlier.[5] Some observations regarding the thermal behavior of *O*-alkyloximes are also presented.

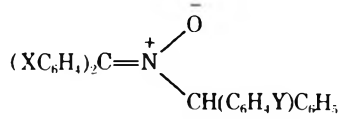
The stereochemical course[2,4] of the nitrone to *O*-alkyloxime rearrangements as well as crossover studies[3] rule out a concerted process[6] as a major mechanistic path. At the inception of the present study it was hoped that a detailed kinetic and product study would provide a basis for distinguishing between two[7] alternate likely mechanistic routes (eq 1 and 2).



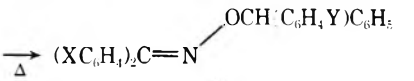
1a

2 (1)

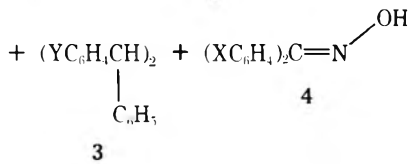
(2)



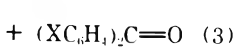
1a, X = Y = H
b, X = H; Y = *p*-CH_3
c, X = *p*-Cl; Y = H
d, X = *p*-CH_3; Y = H



2



3 **4**



(3)

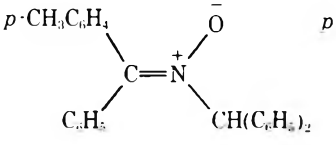
5

The kinetic investigation provides moderate support for the homolytic pathway and the results of the product analyses clearly require radical intermediates in these decompositions.

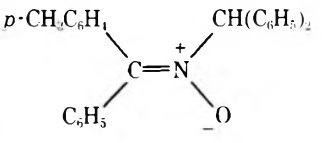
Results

Products from Nitrone Decompositions. The thermal decompositions of four nitrones gave some or all of the products[8] shown in eq 3. Complete (99%) decomposition typically required a minimum of 40 h at 144 °C. The results are shown in Table I.

Kinetics of Nitrone Decompositions. Kinetic data are summarized in Table II. The rate plots for disappearance of nitrones **1a–d** show excellent linearity in accord with the first-order rate law. Included in the table are rate constants for the thermal decompositions (in diethylcarbitol) of the geometrically isomeric nitrones **1e** and **1f**.[9]

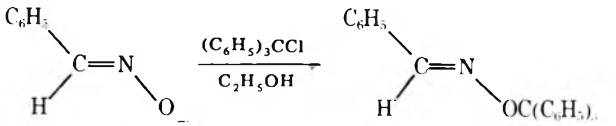


1e

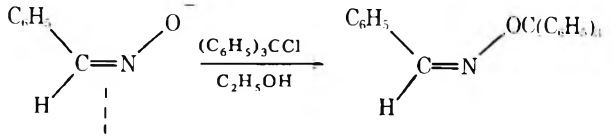


1f

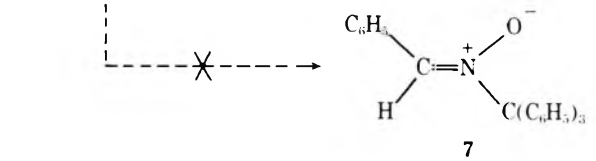
Preparation and Thermolyses of *O*-Alkyloximes. The geometrically isomeric *O*-tritylbenzaldoximes [(*E*)-**6** and (*Z*)-**6**] were prepared as described previously by Buehler.[10] Alkylation of the two oxime anions with chlorotriphenylmethane afforded the geometrically pure *O*-trityloximes. The



(*E*)-**6**



(*Z*)-**6**



7

0022-3263/78/1943-1890$01.00/0

Table I. Products from the Thermolyses of Various Nitrones at 144 °C

Nitrone	Solvent	Concn[a]	% yield 2	% yield 3[b]	% yield 4	% yield 5	Product balance[c]	% reaction
1a	DEC[d]	0.0037	43.9	34.8	22.0		72.2	99.2
1a	*t*-BuOH	0.0036	99.4				99.4	99.99
1a	DMA[e]	0.0083	50.0	38.7	26.9		82.8[f]	78.8
1b	DEC	0.0028	39.1	34.6	58.0		85.5	99.0
1c	DEC	0.0046	29.5	27.4	40.3	13.7	70.2	98.8
1d	DEC	0.0038	27.3	32.9	24.1	22.8	67.2	98.8

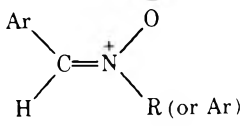
[a] Initial nitrone concentration. [b] Based on 1 mol of **3** from 2 mol of **1**. [c] Percent of moles of unrecovered **1** accounted for in the products. [d] Diethyl carbitol. [e] *N,N*-Dimethylacetamide. [f] 21.4% of the starting nitrone was reisolated from this reaction.

Table II. Rate Constants[a] and Activation Parameters[b] for the Decomposition of Various Nitrones

Compd	Registry no.	Solvent	Temp, °C	10^3[1], M[c]	% reaction	10^5k, s^{-1}	E_a, kcal/mol	$\Delta S^{\ddagger}$, eu
1a	5076-57-3	DEC	130	3.20	61.5	0.579		
				2.52	79.7	0.594		
			144	2.15	64.4	2.86	38.8 ± 0.3	11.0 ± 0.8
				2.44	75.1	2.88		
				2.13	75.1	2.89		
				2.26	61.5	2.93		
				0.434	71.9	3.01		
				0.437	71.2	3.01		
			160	2.11	37.0	15.3		
				2.00	70.0	16.7		
				2.37	46.0	17.0		
		t-BuOH	130	3.44	62.4	0.250		
				0.733	59.7	0.232		
				0.745	60.5	0.236		
			144	2.41	69.9	1.26	40.9 ± 0.4	14.5 ± 0.8
				3.50	61.0	1.28		
				2.58	88.0	1.32		
				0.906	75.4	1.30		
				0.664	72.2	1.34		
				0.596	72.2	1.35		
			160	3.07	77.0	7.66		
				2.84	77.8	7.97		
				0.930	82.7	8.13		
				0.650	74.9	8.22		
		DMA	130	3.43	76.0	0.357		
				3.30	76.0	0.360		
			144	3.22	68.3	1.78	39.1 ± 0.3	10.7 ± 0.7
				3.64	69.9	1.80		
				0.926	68.3	1.84		
				0.902	69.9	1.90		
			160	3.10	78.1	10.5		
				3.34	78.1	10.6		
1b		DEC	130	2.69	85.8	0.694		
	5076-55-1			2.66	86.2	0.715		
			144	3.23	72.6	3.09	37.9 ± 0.2	9.2 ± 0.6
				3.21	72.8	3.10		
				2.39	64.2	3.22		
				2.45	66.0	3.32		
			160	3.03	46.5	17.4		
				2.27	69.3	17.9		
				2.76	74.4	18.9		
1c		DEC	144	1.94	77.5	2.60		
	5076-58-4			1.71	79.0	2.71		
				0.528	77.5	2.60		
				0.529	71.8	2.61		
1d	5120-68-3	DEC	144	2.36	60.9	1.66		
				2.29	62.4	1.71		
				0.630	62.7	1.73		
				0.793	63.8	1.78		
1e	42270-99-5	DEC	144	3.3	75.0	2.98[d] (2.60)[e]		
1f	42271-00-1	DEC	144	3.3	75.0	1.76[d] (2.65)[e]		

[a] Average precision (probable error) of k was ±1%. [b] The errors listed for E_a and $\Delta S^{\ddagger}$ are standard errors. [c] Initial nitrone concentration. [d] Rate constants determined from slopes of plots corresponding to 0–10% reaction. [e] Rate constants determined from slopes of plots corresponding to 35–65% reaction.

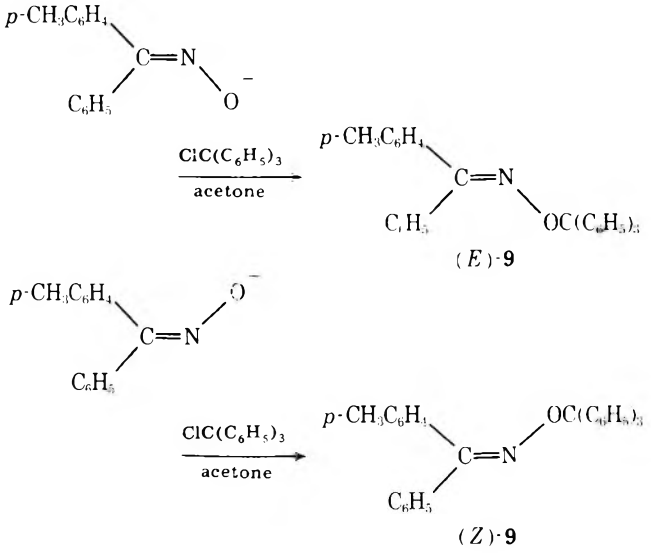
product of the second alkylation shown was originally assigned a nitrone structure.[10] That this assignment was incorrect can be shown by the following observations. The ultraviolet spectrum reported for 7 [λ_{max} 252 nm (log ϵ 4.23)] is inconsistent with that expected for this compound. Nitrones having the general structure 8 are known to have intense π–π^* transitions with maxima in the region of about 290–340 nm.[11,12] Also the NMR spectrum of a nitrone of general structure 8 is expected to show two low-field protons (sepa-



8

rated from and lower than the remaining aromatic protons).[13–15] This is not observed for the alkylation product from the (*Z*)-oxime anion. That the correct structure is (*Z*)-**6** is confirmed by the dipole moment comparisons shown in Table III. It is clear that the nitrone 7 would be expected to have a dipole moment several times larger than that exhibited by (*Z*)-**6**. The geometric assignments for **6** rest on firm ground since stereospecific O-alkylations[5] and arylations[15] of isomeric oxime anions have been previously observed.

The isomeric *p*-methylbenzophenone *O*-trityloximes [(*F*)-**9** and (*Z*)-**9**] were similarly prepared by alkylation of the corresponding oxime anions with chlorotriphenylmethane.



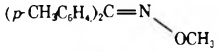
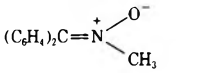
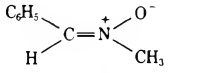
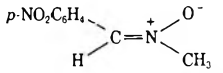
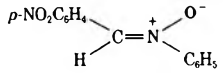
(*E*)-**9**

(*Z*)-**9**

Samples of (*Z*)-**6** and separately (*E*)-**6** were sealed in glass tubes under vacuum and heated. The products were chromatographically separated on alumina-packed columns eluting with benzene–hexane mixtures.[16] Starting with either isomer, an equilibrium mixture (*E*)-**6**/(*Z*)-**6** of 9.8 ± 0.1 was obtained at 200 °C.[17] No other product was observed in these melts. Geometric equilibration was complete within 30 min at 200 °C. The equilibration data at this temperature led to a free-energy difference between (*E*)-**6** and (*Z*)-**6** of approximately 2 kcal/mol.

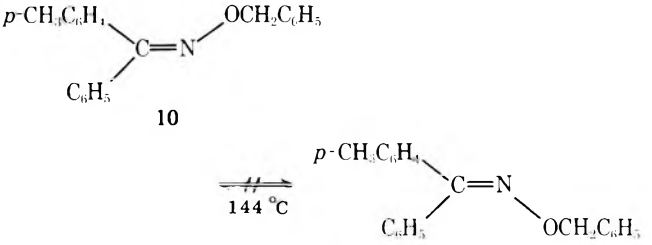
The thermal *E* ⇌ *Z* equilibration of (*E*)-**9** and (*Z*)-**9** were observed in melts after about 6 h at 180 °C and after 96 h in *tert*-butyl alcohol at 144 °C.[18] The NMR and IR spectra of the recovered samples were identical with those of a 50:50 mixture of pure isomers. The EPR spectrum determined during the thermal isomerization of (*Z*)-**9** in the melt (180 °C) consisted of three lines of equal intensity. The nitrogen hyperfine coupling constant was 31.4 ± 0.6 G. No additional coupling to hydrogen was observable.

Table III. Dipole Moments of Several Nitrones and *O*-Alkyloximes

Compd	Registry no.	μ, D	Solvent	Ref
(*E*)-**6**		0.84 (0.86)	Benzene	*a*
	65311-13-9	1.16	Benzene	*a*
	7500-79-0	4.31	Benzene	*a*
(*Z*)-**6**		1.23 (1.34)	Benzene	*a*
		3.49	Benzene	11
		6.20	Dioxane	11
		6.32	Dioxane	11

[a] These values were determined in the course of this work. Dielectric constants of solutions were measured using a Dipolmeter Type DM 01 (Wissenshaftlich-Technische Werkstätten GmbH, Weilheim, Germany). The Guggenheim method [E. A. Guggenheim, *Trans. Faraday Soc.*, **74**, 2193 (1952)] was employed for obtaining dipole moments.

The thermal configurational stability of *p*-methylbenzophenone (*Z*)-*O*-benzyloxime (**10**)[19] was also tested. The *O*-

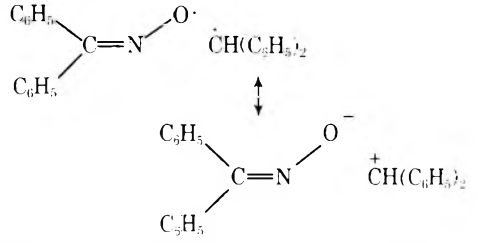


benzyloxime was heated in *tert*-butyl alcohol at 144 °C for 116 h under sealed tube conditions. After removal of the solvent, spectroscopic analysis showed that no detectable isomerization or decomposition had occurred.

Discussion

The products of the thermal decompositions of **1a** and its methyl- and chloro-substituted analogues are more diverse than originally reported by Cope.[6] Only in *tert*-butyl alcohol is the N to O rearrangement essentially free of side products. The production of a substantial quantity of *sym*-tetraarylethane (**2**) from each of the nitrones studied provides evidence for the intermediacy of benzhydryl radicals. Also, the formation of diarylketoximes[20] (**4**) is most easily explained on the basis of hydrogen atom abstraction by iminoxy radicals. An alternative source of the oximes, namely, proton transfer to an oxime anion (eq 1), is inconsistent with the absence of this product only in *tert*-butyl alcohol. Rather, since *tert*-butyl alcohol is a notoriously poor hydrogen atom donating solvent, recombination of iminoxy radicals with benzhydryl radicals appears to become the dominant reaction course. The almost quantitative formation of *O*-benzhydryloxime in *tert*-butyl alcohol cannot be attributed to an unusually efficient cage effect, since the fraction of the total *O*-ether product generated which is formed via an intermolecular process is actually greater for *tert*-butyl alcohol than for the other two solvents (see accompanying paper). It should be noted that traces of tetraphenylethane were isolated under similar conditions during crossover studies in *tert*-butyl alcohol (ac-

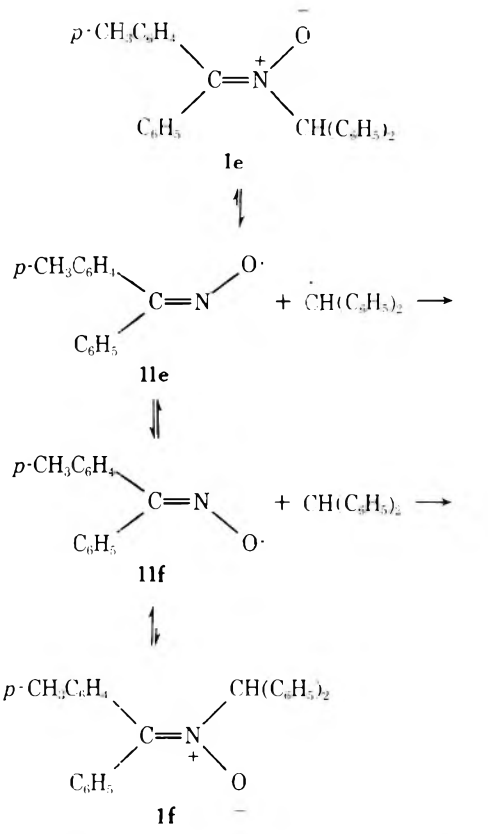
companying paper). It would be reasonable to assume that the use of efficient radical scavengers during decompositions in *tert*-butyl alcohol would trap the free radicals in competition with recombination to give *O*-benzhydryloximes. Such experiments have not yet been performed with this system. The undecomposed nitrone might have been expected to behave as a reasonably good spin trap. In fact, nitroxide radicals attributed to reactions between **1a** and benzhydryl radicals have been observed for decompositions of **1a** either in the melt or in diethylcarbitol.[5b] If such processes are taking place in *tert*-butyl alcohol, only very small quantities of nitroxide must be forming or the process is rapidly reversible. Perhaps more interesting is the basis for the inability of iminoxy–iminoxy and benzhydryl–benzhydryl dimerization processes to compete with benzhydryl–iminoxy radical combinations. Although radical–radical terminations are believed to have very low activation energies, a benzhydryl–iminoxy recombination may be more nearly a diffusion-controlled process because of resonance stabilization of the transition state as shown. This possibility is being subjected to experimental tests.



The first-order rate constants (Table II) for the decomposition of the nitrones in diethylcarbitol at 144 °C differ by less than a factor of 2. In addition, the rate constants for the decomposition of **1a** in each of the three solvents vary over a range of only 2.2 at 144 °C. The small variation in rate with changing substituents and solvents is more compatible with a radical or concerted process than an ionic route such as eq 1.

The net effects expected for an ionic process with the substituent changes made in **1c** and **1d** are difficult to assess. The substituents in **1c** and **1d** are both probably capable of stabilizing the ground state via resonance. But if oxime anion formation were nearly complete in a transition state, the *p*-chloro substituents would presumably stabilize and the *p*-methyl substituents destabilize the activated complex. The net effect anticipated from the substitution of H by methyl in the benzhydryl portion of the nitrone is less ambiguous. This substitution would be expected to lead to a considerable rate enhancement if a benzhydryl cation were substantially formed in the transition state. In diethylcarbitol at 144 °C the rate ratio for **1b**/**1a** is only 1.1. This value is comparable to *p*-methyl substitution effects in the radical decompositions of *tert*-butyl arylperacetates ($k_{p\text{-}CH_3}/k_H \sim 2$)[22] and in the homolyses of azocumenes ($k_{p,p'\text{-}CH_3}/k_H \sim 1.7$).[23]

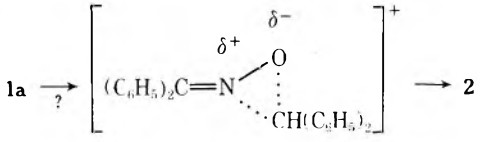
Only the rate plots for the decompositions of nitrones **1e** and **1f** show curvature. The final "slopes" (35–65% reaction) are essentially identical and reflect the fact that at this stage of the reaction, geometric equilibration[24] of the starting nitrones is largely complete. These nitrones have been shown spectroscopically (NMR analysis of reisolated nitrone) to equilibrate during the decompositions, finally reaching a 50:50 ± 2% composition. If one concludes (from the data from the present study and from the others referred to herein) that the initial step in the decomposition of **1e** and **1f** is the formation of iminoxy radicals and benzhydryl radicals, then the free-energy difference between the two iminoxy radicals, **11e** and **11f**, in diethylcarbitol can be estimated. If the usual assumption is made that the activation energy is negligible for the recombination of radicals (in this case to reform **1e** and



1f), then the difference between the "initial" rate constants (obtained during the first 10% of the decomposition) can be ascribed to differences in the free energies of the two iminoxy radicals. This value at 144 °C is 437 cal, corresponding to an equilibrium constant of 1.70. A similar observation has been made for the iminoxy radicals formed in *tert*-butyl alcohol, where k was found to be 1.4.[4]

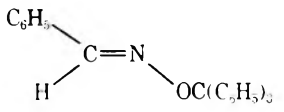
The rates and activation parameters for decomposition–rearrangement of **1a** were determined in three solvents varying substantially in hydrogen-bonding capability and polarity.[25] The essential invariance in rates and activation parameters is most easily accommodated by a homolytic dissociation.

On the basis of product studies, only for the decomposition of **1a** in *tert*-butyl alcohol is a cyclic concerted rearrangement

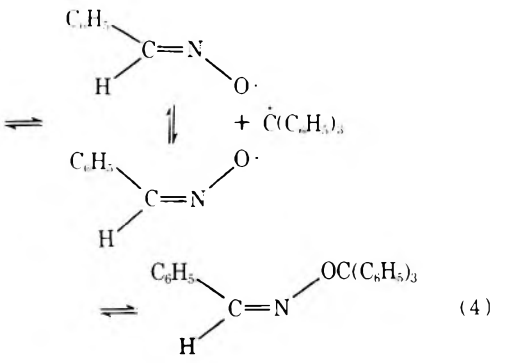


to **2** a viable mechanistic option. However, the nearly identical activation parameters for the decomposition of **1a** in the three solvents renders this possibility highly unlikely. Also, the high degree of intermolecularity for the rearrangement in *tert*-butyl alcohol (see accompanying paper) relegates a concerted process to a minor competing role if at all existent.

The *O*-trityloximes (*E*)-**6**, (*Z*)-**6**, (*E*)-**9**,[27] and (*Z*)-**9** were shown to undergo geometric equilibration in the melt or/and in solution at temperatures ranging from 144 to 200 °C. The most likely course of these isomerizations is again a homolysis of the N–O bond, followed by rapid geometric isomerization of the iminoxy radicals[4] and recombination as shown in eq 4 and 5. Were a nondissociative (rotational or lateral shift) mechanism operative, the *O*-benzhydryl analogues of **9** would be expected to undergo a similar geometric isomerization. But the *O*-benzhydryl derivatives have been shown to be completely configurationally stable under the above conditions.[4] Similarly, the (*Z*)-benzyl derivative, **10**, was shown to be

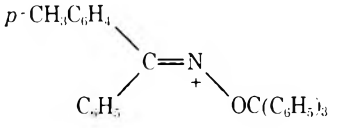


(*E*)-**6**

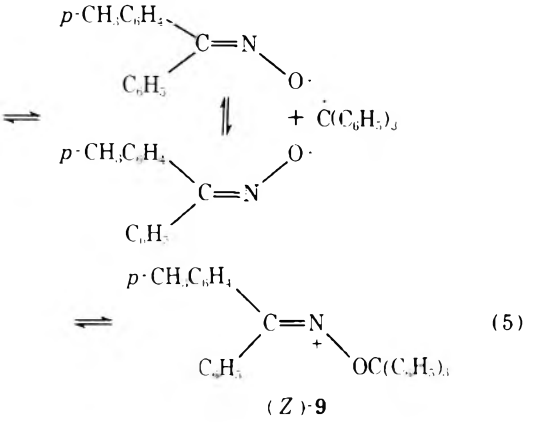


(4)

(*Z*)-**6**



(*E*)-**9**



(5)

(*Z*)-**9**

configurationally stable. The remarkable configurational stability of benzophenone *O*-methyloxime derivatives has been previously reported.[28] Thus, in contrast with *O*-methyl, benzyl, and benzhydryl derivatives, the stability of the developing trityl radical appears to be responsible for lowering the activation energy and promoting the homolysis. It is possible that trityloxyphenyl nonbonded interactions in **9** raise ground-state free energies and thereby accelerate the homolysis. But the facile isomerization of (*E*)-**6** (possessing only a trityloxy–hydrogen interaction) suggests that this factor is of relatively minor importance. The observation of the iminoxy radicals in isomerizing melts at 180 °C by electron-spin resonance supports the above mechanistic proposal.

Conclusions

The available evidence now indicates that the nitrone decompositions and the *O*-trityloxime isomerizations are initiated by a homolysis of C–N or a C–O bond producing reasonance-stabilized iminoxy and alkyl radicals. Conceivably the formation of these radicals could be formed in a reversible electron-transfer step following a heterolysis as in eq 1. Bilevitch and co-workers[29] have reported ESR evidence for such an electron transfer between trityl cations and *tert*-butoxy anions with resultant formation of the ether. The absence of

$$(C_6H_5)_3C^+ + (CH_3)_3CO^- \rightarrow (C_6H_5)_3C\cdot + \cdot OC(CH_3)_3 \rightarrow (C_6H_5)_3COC(CH_3)_3$$

appreciable substituent or solvent effects in the nitrone decompositions diminishes the likelihood that such a multistep process is operative in these reactions.

Experimental Section[30]

***p*-Methylbenzophenone (*Z*)-*O*-Trityloxime [(*Z*)-9].** *p*-Methylbenzophenone (*Z*)-oxime[2,4] (0.917 g, 4.34 mmol) in 20 mL of absolute ether was converted to its sodium salt with metallic sodium. The ether was removed using dry nitrogen and 15 mL of acetone was distilled into the reaction flask. An equivalent of chlorotriphenylmethane was added and the mixture was stirred under nitrogen for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure, dissolved in boiling CCl_4, and filtered. The filtrate was again concentrated to an oil and then crystallized from 9:1 dioxane–water and again from petroleum ether (bp 60–80 °C), affording 0.576 g (29%) of (*Z*)-9, mp 171.5–173 °C. The important spectral features are as follows: NMR ($CHCl_3$) δ 7.60–6.90 (m, 24 H, aromatic), 2.42 (s, 3 H, *p*-CH_3); UV (C_2H_5OH) λ_{max} 263.5 nm (log ε 4.16).

Anal. Calcd for $C_{33}H_{27}NO$: C, 87.38; H, 6.00; N, 3.09. Found: C, 87.46; H, 6.32; N, 3.33.

***p*-Methylbenzophenone (*E*)-*O*-Trityloxime [(*E*)-9].** The *E* isomer was prepared from the (*E*)-oxime[2,4] as described for (*Z*)-**9**. It was obtained in 25% yield following crystallizations (of the CCl_4-extracted oil) from hexane and then from absolute ethanol, mp 124–134 °C. The important spectral features are as follows: NMR ($CHCl_3$) δ 6.83–7.50 (m, 24 H, aromatic), 2.26 (s, 3 H, *p*-CH_3); UV (C_2H_5OH) λ_{max} 266.5 nm (log ε 4.20).

Anal. Calcd for $C_{33}H_{27}NO$: C, 87.38; H, 6.00; N, 3.09. Found: C, 87.17; H, 6.06; N, 3.29.

(*Z*)-*O*-Tritylbenzaldoxime [(*Z*)-6] (previously assigned structure **7**) was prepared as described by Buehler[31] in 52% yield: mp 144–145.5 °C (lit.[31] mp 143–144 °C); UV (C_2H_5OH) λ_{max} 251 nm (log ε 4.24) [lit.[31] λ_{max} 252 nm (log ε 4.23)].

(*E*)-*O*-Tritylbenzaldoxime [(*E*)-6] was prepared as previously described[31] in 63% yield: mp 120.5–121.5 °C (lit.[31] mp 118 °C); UV (C_2H_5OH) λ_{max} 260 nm (log ε 4.26) [lit.[31] λ_{max} 260 nm (log ε 4.27)].

4,4′-Dimethylbenzophenone *O*-Methyloxime. To a mixture of 5.06 g (22.4 mmol) of 4,4′-dimethylbenzophenone oxime and 39.7 g (0.280 mol) of iodomethane was slowly added 7.28 g (31.4 mmol) of silver oxide. The mixture was heated under reflux for 1 h and filtered. The residue was washed with 50 mL of ether. The combined filtrate was concentrated, whereupon the product crystallized. The *O*-methyloxime was then recrystallized four times from absolute ether, affording 2.04 g (38%) of colorless crystals, mp 99–100 °C. The NMR spectrum (CCl_4) shows the following: δ 6.58–7.40 (m, 8 H, aromatic), 3.87 (s, 3 H, OCH_3), 2.32 and 2.37 (2 s, 3 H, 3 H, *p*-CH_3).

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.40; H, 7.16; N, 5.86. Found: C, 80.26; H, 7.30; N, 5.62.

***N*-Methyl-α,α-diphenylnitrone.** Samples of 1.47 g (17.6 mmol) of *N*-methylhydroxylamine hydrochloride and 3.81 g (17.6 mmol) of benzophenone imine hydrochloride were mixed in 35 mL of 90–100 °C petroleum ether under nitrogen. Ammonia was bubbled through the stirred mixture for 45 min. The mixture was then boiled under reflux for 12 h. The mixture was filtered. Concentration and cooling of the filtrate afforded 1.56 g (42%) of the nitrone, mp 98–100 °C (lit.[32] mp 102–103 °C). The NMR spectrum (CCl_4) shows the following: δ 7.90 (m, 2 H, ortho protons on α-phenyl cis to oxygen), 7.38 (m, 8 H, aromatic), and 3.56 (s, 3 H, NCH_3).

The preparations of *N*-benzhydryl-α,α-diphenylnitrone (1a) and the substituted analogues 1b–d were previously described.[33]

Thermal Configurational Stability of *p*-Methylbenzophenone (*Z*)-*O*-Benzyloxime[19] (10). The *O*-benzyloxime (33.7 mg) was placed in a Pyrex tube (8 × 200 mm). Dry *tert*-butyl alcohol (2 mL) was added. The solution was degassed and the tube was sealed under vacuum and heated at 144 °C for 116 h. The tube was opened, the solvent was evaporated, and the NMR ($CDCl_3$) of the residue was determined.

The Thermal Isomerizations of *p*-Methylbenzophenone (*E*)- and (*Z*)-*O*-Trityloximes [(*E*)-9 and (*Z*)-9]. The pure *O*-trityloximes [degassed solutions (~0.03 M in *tert*-butyl alcohol)] were separately heated at 144 °C for 96 h. The resulting solutions were concentrated to remove solvent. The NMR and IR spectra of the residues were then determined.

The Thermal Isomerization (*E*)- and (*Z*)-*O*-Triphenylmethylbenzaldoxime [(*E*)-6 and (Z)-6]. Samples of (*E*)-**6** and separately (*Z*)-**6** were heated for various periods of time at temperatures of 200 °C of ~145 °C. The products were chromatographically separated on alumina-packed columns eluting with hexane–benzene mixtures.

General Procedures for Kinetic Experiments. Rate constants were measured for the disappearance of the nitrone by following the decrease in its maximum absorbance at about 310 nm. A solution (~10 mL) of the nitrone was prepared with freshly distilled solvent. About 1 mL of solution was pipetted into each of ten Pyrex tubes. The solutions in the tubes were degassed and then sealed under vacuum and placed simultaneously in a constant temperature (±0.1 °C) oil bath.

Tubes were removed from the oil bath at approximately equal time intervals and quenched in an ice–water mixture. The first (zero time) tube in a given run was generally quenched 15–30 min after the time of immersion of all the tubes. From five to ten tubes were used for each kinetic run. Infinity absorptions were obtained for each solvent and for each nitrone.

After all the quenched tubes had been opened and allowed to thermally equilibrate (~1 h) to room temperature in a desiccator, aliquots (~1 mL) were weighed by difference into volumetric flasks and then diluted with chloroform (ACS reagent grade) at room temperature. Absorbances were measured at 25.0 °C with a Beckman Model DU spectrophotometer.

The first-order rate constant, which is the slope of the plot of ln ($A - A_\infty$) vs. t (A is the absorbance at time t, and A_∞ is the absorbance at $t = \infty$), was calculated by method of least squares. The Arrhenius activation energy, E_a, was calculated from the least-squares slope of the plot of ln k vs. $1/T$.

Acknowledgments. This investigation was supported by the Research Corporation (Frederick Gardner Cottrell Grant), the San Diego State University Foundation, and the National Cancer Institute, National Institutes of Health, and U.S. Public Health Service (Grant No. CA-10741-04).

Registry No.—(*Z*)-**6**, 23057-28-5; (*E*)-**6**, 10229-67-1; (*Z*)-**9**, 65311-11-7; (*E*)-**9**, 65311-12-8; **10**, 42449-53-6; *p*-methylbenzophenone (*Z*)-oxime, 2998-92-7; chlorotriphenylonethane, 76-83-5; *p*-methylbenzophenone (*E*)-oxime, 2998-91-6; 4,4′-dimethylbenzophenone oxime, 1714-49-4; iodomethane, 74-88-4; *N*-methylhydroxylamine hydrochloride, 4229-44-1; benzophenone imine hydrochloride, 5319-67-5.

References and Notes

(1) Abstracted in part from the Ph.D. Theses of J. A. Villarreal and of T. S. Dobashi, University of California, San Diego, and San Diego State University, 1973.
(2) T. S. Dobashi and E. J. Grubbs, *J. Am. Chem. Soc.*, **95**, 5070 (1973).
(3) J. A. Villarreal and E. J. Grubbs, *J. Am. Chem. Soc.*, **96**, 7594 (1974).
(4) T. S. Dobashi, D. R. Parker, and E. J. Grubbs, *J. Am. Chem. Soc.*, **99**, 5382 (1977).
(5) (a) E. J. Grubbs, J. A. Villarreal, J. D. McCullough, Jr., and J. S. Vincent, *J. Am. Chem. Soc.*, **89**, 2234 (1967); (b) J. S. Vincent and E. J. Grubbs, *ibid.*, **91**, 2022 (1969).
(6) A. C. Cope and A. C. Haven, *J. Am. Chem. Soc.*, **72**, 4896 (1950).
(7) A less likely alternative to eq 1 with the charges reversed on the intermediates would also be amenable to kinetic probes.
(8) Product mixtures were chromatographed over alumina and/or Florisil columns. Separated components were compared with authentic samples by means of mixed melting points and infrared spectra.
(9) These nitrones were employed in a study of the stereochemical course of N to O rearrangements.[2,4] Complete quantitative product analyses were not performed for these decompositions, since only geometric compositions of the *O*-benzhydryloximes and recovered nitrones were of interest.
(10) E. Buehler, *J. Org. Chem.*, **32**, 261 (1967).
(11) T. Kubota, M. Yamakawa, and Y. Mori, *Bull. Chem. Soc. Jpn.*, **36**, 1552 (1963).
(12) Note for example that (*Z*)-*N*-*tert*-butyl-α-phenylnitrone exhibits the absorption at 293.5 nm.[13]
(13) M. H. Goodrow, J. A. Villarreal, and E. J. Grubbs, *J. Org. Chem.*, **39**, 3447 (1974).
(14) K. Koyano and H. Suzuki, *Bull. Chem. Soc. Jpn.*, **42**, 3306 (1969).
(15) E. J. Grubbs, R. J. Milligan and M. H. Goodrow, *J. Org. Chem.*, **36**, 1780 (1971).
(16) Pure samples of (*E*)-**6** and (*Z*)-**6** were shown to be stable under the chromatographic separation conditions.
(17) Total recovery of the *O*-trityloximes after heating and separating amounted to at least 96%
(18) Quantitative rates of approach to equilibrium have not been determined.
(19) T. S. Dobashi, M. H. Goodrow, and E. J. Grubbs, *J. Org. Chem.*, **38**, 4440 (1973).
(20) The formation of diaryl ketones, **5** (Table I), was observed in only two instances. The origin is not known with certainty. Hydrolysis of oximes via adventitious contamination by water is one possible source. In fact, benzophenone oximes are known to be sensitive to exposure to ordinary atmospheric conditions and decompose fairly readily to the corresponding ketone and nitric acid.[21] The autocatalytic nature of these decompositions suggests the intervention of radical intermediates.
(21) A. H. Blatt, Ed., "Organic Syntheses", Collect. Vol. 2, Wiley, New York, N.Y., 1943, p 71.
(22) P. D. Bartlett and C. Rüchardt, *J. Am. Chem Soc.*, **82**, 1756 (1960).
(23) J. R. Shelton, C. K. Liang, and P. Kovacic, *J. Am. Chem. Soc.*, 90, 354 (1968).
(24) The geometric equilibration is a result of torsional rotation[19] and recombination of benzhydryl radicals with geometrically isomerizing iminoxy radicals.[2]
(25) An extrapolation of dielectric constant data[26] to 144 °C for dimethylacetamide yields a value of about 16. Those for *tert*-butyl alcohol and diethylcarbitol using similar extrapolations are approximately 3.
(26) G. R. Leader and J. F. Gormley, *J. Am. Chem. Soc.*, **73**, 5731 (1951).
(27) The melting point range for this isomer suggests the presence of a contaminant. However, repeated recrystallizations from different solvents failed to narrow this range. The elemental analyses are in satisfactory agreement with the theoretical values. And thin layer as well as column chromatographic probes revealed only one component. Furthermore, spectra of equilibrium mixtures of (*E*)-**9** and (*Z*)-**9** reached from either starting *O*-trityloxime were identical.
(28) D. Y. Curtin, E. J. Grubbs, and C. G. McCarty, *J. Am. Chem. Soc.*, **88**, 2775 (1966).
(29) K. A. Bilevitch, N. N. Bubnov, and O. Yu. Okhlobystin, *Tetrahedron Lett.*, 3465 (1968).
(30) Melting points and boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 621 recording spectrophotometer. Ultraviolet spectra were measured using either a Cary Model 14 or a Beckman Model DU spectrophotometer. NMR spectra were obtained on a Varian Model A-60. Mass spectra were determined with a Hitachi Perkin-Elmer Model RMU-6E spectrometer and the EPR spectrum obtained using a Varian E-3 spectrometer equipped with a Varian E-4557-9 variable-temperature controller. Analyses were performed by C. F. Geiger Laboratories and by M. H. W. Laboratories.
(31) E. Buehler, *J. Org. Chem.*, **32**, 261 (1967).
(32) L. Semper and L. Lichtenstadt, *Ber. Dtsch. Chem. Ges.*, **51**, 933 (1918).
(33) E. J. Grubbs, J. D. McCullough, Jr., B. H. Weber, and J. R. Maley, *J. Org. Chem.*, **31**, 1098 (1966).

An Investigation of the Inter- vs. Intramolecularity of the Thermal Rearrangement of *N*-Benzhydryl-α,α-diphenylnitrone to Benzophenone *O*-Benzhydryloxime

Jose A. Villarreal and Edward J. Grubbs*

Department of Chemistry, San Diego State University, San Diego, California 92182

Received September 27, 1977

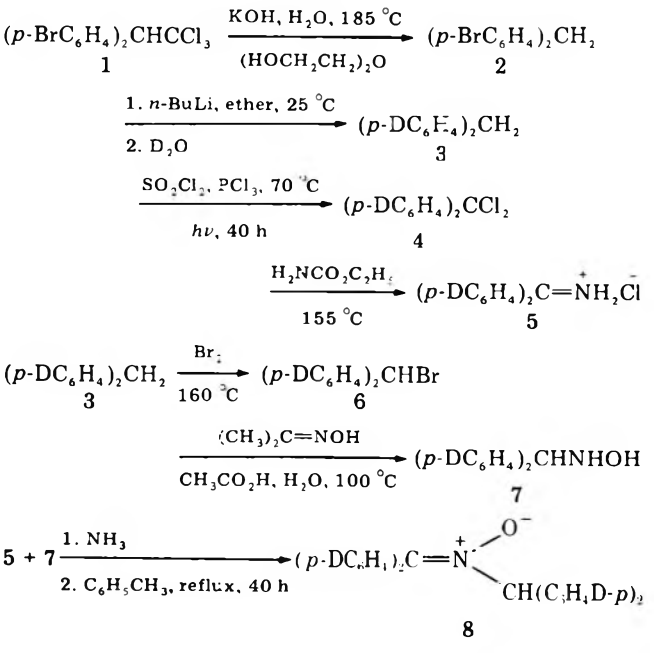
The synthesis of *N*-(benzhydryl-*p,p'*-d_2)-α,α-diphenyl-*p,p'*-d_2-nitrone (8) is described. Thermal decompositions of mixtures of 8 and the undeuterated analogue 9 have been conducted in diethylcarbitol, in *tert*-butyl alcohol, and in dimethylacetamide. On the basis of mass spectral analyses of the product (benzophenone *O*-benzhydryloxime), the extent of intermolecularity in the N to O rearrangement has been determined. Solvent effects on the partitioning of the radical intermediates is discussed. Evidence is also presented for iminoxy benzhydryl radical recombination at nitrogen to regenerate nitrone.

The currently available data[2] bearing on the thermal rearrangement of *N*-benzhydryl-α,α-diarylnitrones to the corresponding *O*-benzhydryloximes indicate that the principal mechanistic route involves the formation of iminoxy and benzhydryl radicals. In this report we describe the preparation of para-tetradeuterated *N*-benzhydryl-α,α-diphenylnitrone (8). Thermal decompositions of mixtures of 8 and the undeuterated analogue 9 are also described. The results allow an assessment of the inter- vs. intramolecular partitioning of this rearrangement.

Results

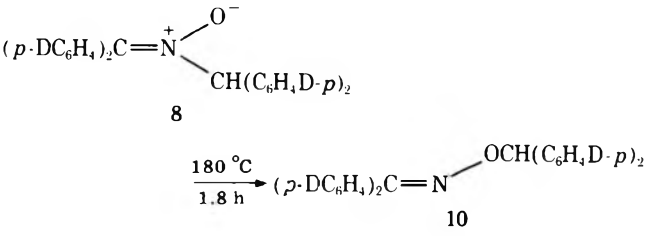
Syntheses. The synthesis of *N*-(benzhydryl-*p,p'*-d_2)-α,α-diphenyl-*p,p'*-d_2-nitrone (8) is illustrated in Scheme I. The starting trichloride was easily prepared by the acid-catalyzed alkylation of bromobenzene by chloral hydrate,[3] but in low (9%) yield. Conversion of the trichloride 1 to 4,4'-dibromodiphenylmethane (2) proceeded in high (85%) yield as previously described by Galun, Kaluszyner, and Bergmann.[4] This dibromide was treated with butyllithium in hexane, the concentration of which was determined by a double titration technique.[5] Adventitious contamination by water during the deuterolysis step led to less than complete dideuteration. Nonetheless, approximately 93% of theoretical maximum deuterium content was introduced into the two para positions. The chlorination of 3 proceeded in 74% yield. Conversion of 4 to the imine hydrochloride 5 was accomplished in 40% yield using ethyl carbamate.[6] Bromination of 3 provided 6 in 86% yield. The alkylation of acetone oxime by 6 and in situ hydrolysis afforded the deuterated *N*-benzhydrylhydroxylamine (7) in 43% yield. Finally, condensation in toluene of 7 and the imine liberated from 5 by ammonia provided the desired labeled nitrone 8 in 30% yield.

Scheme I



Combustion analysis of 8 showed it to have 17.63 atom % excess of deuterium (average of two analyses). Since the theoretical for fully tetradeuterated nitrone is 19.05 atom %, this represents 92.5% of complete para deuteration. This is in excellent agreement with the value obtained for 3. Thus no deuterium was lost in the intervening synthetic steps. The mass spectra of 8 (using mass spectra of the undeuterated analogue 9 to correct for naturally occurring isotope contributions) indicated that 8 was composed of 81.33% tetra-, 17.56% tri, and 1.11% dideuterated species.

A sample of the *O*-benzhydryl isomer of 8 was prepared by heating 8 in the melt at 180 °C, followed by chromatography and crystallization.



Crossover Experiments. Mixtures of the deuterated and undeuterated nitrones 8 and 9 were decomposed in degassed solutions prepared from diethylcarbitol, *tert*-butyl alcohol, and *N,N*-dimethylacetamide. The products were separated chromatographically and the isotopic composition of either the *O*-benzhydryloxime or recovered nitrone was then determined mass spectroscopically.[7] The product analyses for these decompositions are summarized in Table I.

The degree of intramolecularity, α, was determined by comparing the mole fraction of dideuterated species (*m/e* 365) found in the *O*-ether or nitrone with that expected from a purely statistical recombination of benzhydryl and iminoxy radicals. The degree of intramolecularity is defined by

$$\alpha = (X_{365} - D_{365})/(C_{365} - D_{365}) \quad (1)$$

where X_{365} is the mole fraction of dideuterated species in the isolated nitrone or *O*-ether, D_{365} is the mole fraction of dideuterated species which would be formed from a completely statistical recombination of radicals, and C_{365} is the mole fraction of dideuterated species in the starting mixture of nitrones 8 and 9. The general methods and discussion of ap-

0022-3263/78/1943-1896$01.00/0

Table I. Product Analyses from Decompositions of Mixtures of 8 and 9 at 144 °C in Several Solvents

Run no.	Weights of 8 and 9, mg	Solvent	Vol, mL	% reaction[a]	*O*-Ether,[b] mg	Nitrone,[c] mg	Tetraphenylethane, mg
I	10.2, 10.4	DEC[d]	20	99.9	9.8		3.5
II	10.2, 9.9	*t*-BuOH	20	99.9	17.0		0.2
III	10.0, 10.1	DMA[e]	20	99.9	8.6		3.9
IV	9.9, 10.1	*t*-BuOH	20	50		9.8	

[a] Based upon kinetic data. [b] Weight of *O*-benzhydryloxime. [c] Weight of recovered nitrone. [d] Diethylcarbitol. [e] *N,N*-Dimethylacetamide.

Table II. Distribution of Ion Species from *O*-Benzhydryloximes and Nitrone Isolated from the Decomposition of Mixtures of 8 and 9

Run no.[a]	Product analyzed	Fraction of ions with *m/e* 363	364	365	366	367	
I	*O*-Ether[b]	0.3397	0.0331	0.2862	0.0626	0.2784	*X*[c]
		0.4977	0.0	0.0058	0.0882	0.4085	*C*[c]
		0.2477	0.0494	0.4530	0.0450	0.2048	*D*[c]
II	*O*-Ether	0.3023	0.0387	0.3710	0.0534	0.2346	*X*
		0.5101	0.0	0.0054	0.0860	0.3985	*C*
		0.2602	0.0494	0.4528	0.0428	0.1949	*D*
III	*O*-Ether	0.3343	0.0331	0.2806	0.0652	0.2869	*X*
		0.5084	0.0	0.0055	0.0863	0.3998	*C*
		0.2585	0.0494	0.4528	0.0431	0.1962	*D*
IV	Nitrone	0.3969	0.0162	0.1846	0.0727	0.3297	*X*
		0.4976	0.0	0.0056	0.0882	0.4086	*C*
		0.2476	0.0494	0.4530	0.0450	0.2049	*D*

[a] Corresponds to experiments summarized in Table I. [b] *O*-Benzhydryloxime. [c] Values in successive rows opposite *X*, *C*, and *D* correspond to fractional distributions calculated for previously defined X_m, C_m, and D_m.

Table III. Summary of Crossover Experiments[a] Corresponding to Total Decompositions of Mixtures of 8 and 9 at 144 °C

Solvent	Nitrone concn, M[b]	Total *O*-ether yield[c]	α[d]	Yield of intramol *O*-ether[e]	Yield of intermol *O*-ether[f]	Yield of coupling product[g]
DEC[h]	0.00284	0.476	0.373	0.178	0.298	0.37
t-BuOH	0.00276	0.846	0.183	0.155	0.691	0.02
DMA[i]	0.00278	0.426	0.385	0.164	0.262	0.42

[a] Based upon data in Tables I and II. [b] Initial concentration of the mixture. [c] Fraction of nitrone converted to benzophenone *O*-benzhydryloxime. [d] Degree of intramolecularity in N to O rearrangement. [e] Fraction of nitrone converted to *O*-ether by an intramolecular process; equal to product of total *O*-ether yield and α. [f] Difference between total *O*-ether yield and the intramolecular *O*-ether yield. [g] Fraction of nitrone converted to 1,1,2,2-tetraphenylethane based upon 1 mol of tetraphenylethane from 2 mol of nitrone. [h] Diethylcarbitol. [i] *N,N*-Dimethylacetamide.

proximations for obtaining such values from mass spectral intensities have been described by Biemann.[8] Mass spectra of undeuterated nitrone and *O*-ether were used to correct mass spectral intensities of isotopically labeled samples for isotopic natural abundances. The value of α is the fraction of the *O*-benzhydryloxime product or the fraction of recovered nitrone which is not formed by a statistical recombination of benzhydryl and iminoxy radicals. In the case of the reisolation of unrearranged nitrone, the magnitude of α is influenced by the fact that a portion of the nitrone never undergoes homolysis.

The value of α can theoretically be calculated from the equation

$$\alpha = (X_m - D_m)/(C_m - D_m) \quad (2)$$

for any value of m in the range of 365–367. However, $|X_m - D_m|$ and $|C_m - D_m|$ have the largest values for $m = 365$.[9]

The distribution of ion species derived from products (nitrone or *O*-ether) shown in Table I are presented in Table II. Necessary control experiments (employing mass spectral analyses) with nitrones and *O*-ethers of known isotopic composition demonstrated that neither isotopic scrambling nor structural isomerization occur during the isolation and separations following partial or total decompositions of nitrone mixtures.

The intra- vs. intermolecularity of the N to O rearrangements under conditions effecting total decompositions of nitrones is given in Table III.

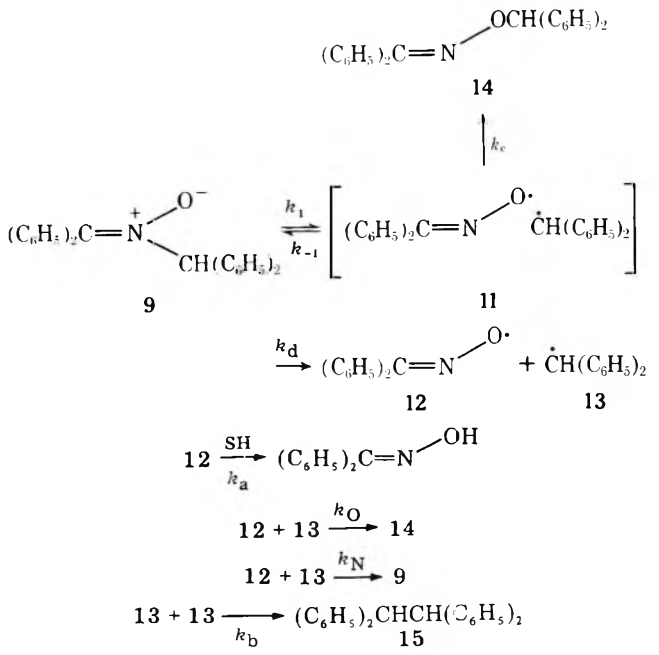
Discussion

The data and data summary in Tables I–III demonstrate that in all solvents employed, the major portion of benzophenone *O*-benzhydryloxime from rearrangement of nitrone is formed via an intermolecular process. Thus, in diethylcarbitol 62.5% of the *O*-ether isolated is produced intermolecularly; in dimethylacetamide the corresponding value is 68.1%, and in *tert*-butyl alcohol it is 81.7%.

The substantial intermolecularity of the N to O rearrangement together with the isolation of tetraphenylethane in each case provide evidence for the initial formation of benzhydryl and iminoxy radicals from homolysis of the nitrone C–N bond.

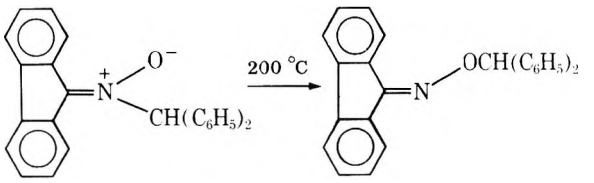
The fraction of nitrone converted to *O*-benzhydryloxime by an intermolecular process is clearly solvent dependent.[10] By contrast, the fraction of nitrone converted to *O*-benzhydryloxime via an intramolecular route is nearly independent

Scheme II



of the nature of the solvent (at least at this elevated temperature of 144 °C), the value being 16.5 ± 1%. These results can be explained in terms of the behavior of the radical pair initially formed in these solvents. The options available to the radical pair are outlined (using undeuterated structures for simplicity) in Scheme II. The radical pair, **11**, is initially formed via C–N homolysis within a solvent cage. This caged pair of radicals can collapse to *O*-benzhydryloxime (giving intramolecularly formed **14**) before they diffuse (k_d) and become free radicals or they can recombine at nitrogen, regenerating nitrone. The fraction of radical pairs that eventually collapse to the cage product, **14**, prior to diffusion, is nearly identical in the three solvents at this elevated temperature.[11] The bulk of the remaining radical pairs, **11**, are converted to free radicals. The free benzhydryl and iminoxy radicals thus formed by the diffusion process can recombine at oxygen to form "intermolecular *O*-ether" or at nitrogen. That the latter as well as the former occurs can be deduced from the data in Table II, wherein reisolated nitrone was analyzed mass spectrometrically after 50% decomposition. Using eq 1, α is found to be 0.60. The coupling of benzhydryl radicals to form tetraphenylethane and the abstraction of hydrogen atoms from the solvent[13] (primarily by iminoxy radicals to form benzophenone oxime) are, however, processes which compete with the bimolecular recombination of these two free radicals. The hydrogen atom donating abilities of the three solvents are reflected in the yield of benzophenone oxime. Under conditions comparable to those employed for the crossover studies, the yields of benzophenone oxime in diethylcarbitol and in DMA were 22 and 27%, respectively; in *tert*-butyl alcohol, the yield was virtually zero.[14] Thus the diminished yields of intermolecularly formed *O*-benzhydryloxime in diethylcarbitol and in DMA is a result of extensive destruction of free iminoxy radicals via hydrogen-atom transfer from the solvents.

The crossover experiments discussed above show that free benzhydryl and iminoxy radicals are generated to a major extent during the decomposition of *N*-benzhydryl-α,α-diphenylnitrone. The intramolecularly formed rearrangement product presumably originates from cage recombination of the radical pair at oxygen, an irreversible process at the operating temperature.[2a,c] The possibility that a small amount of this product is formed by way of a fully concerted mechanism[15] cannot be excluded. In this regard it is interesting to note the following. Nitrone **16** has been decomposed in a solution of hexachlorobutadiene at 200 °C.[2d] During the decomposition, CIDNP (emission) was observed for the benzhydryl proton of the rearrangement product **17**, formed in



52% yield. Thus, caged radical recombination is implicated during the thermolysis of this nitrone, which is closely related to the substrate in the present study.

A full report describing the kinetic partitioning of processes available to the benzhydryl–iminoxy radical pair, **11**, will be published at a later time.

Experimental Section[16]

1,1-Bis(4-bromophenyl)-2,2,2-trichloroethane (1)[3] was converted to **4,4′-dibromodiphenylmethane (2)** by a previously described method.[4]

Diphenylmethane-*4,4′-d*$_2$ (3) was prepared from 4,4′-dibromodiphenylmethane via a metal–halogen exchange (using butyllithium) followed by deuterolysis. A 96.0-g (0.295 mol) sample of the dibromide in 1500 mL of anhydrous ether was treated with 320 mL of a 1.68 M solution (0.538 mol) of butyllithium in hexane over a period of 30 min. The reaction was carried out under an atmosphere of nitrogen while stirring the mixture continuously. Following an additional 25-min period of stirring, an excess of 99.5 mol % pure deuterium oxide was added dropwise with cooling and stirring. The reaction mixture was filtered and concentrated to about 100 mL. The concentrate was then distilled affording 36.4 g (79.6%) of **3**, bp 146–157 °C (27–30 mm). This product was combined with 5.8 g of **3** similarly obtained and redistilled to give 36.1 g of **3** as a colorless liquid, bp 105–108 °C (3.3 mm). Diphenylmethane reportedly distills at 149 °C (29 mm).[17] The NMR spectrum (CCl_4) is as follows: δ 3.90 (s, 2 H, CH_2) and 7.12 (m, ~8 H, aromatic). Duplicate combustion analyses of the product indicated 15.45 and 15.55 atom % excess D (theoretical for fully dideuterated diphenylmethane is 16.67%).

Dichlorodiphenylmethane-*4,4′-d*$_2$ (4). A mixture of 18.2 g (0.107 mol) of dideuteriodiphenylmethane, 35 mL (0.433 mol) of freshly distilled sulfuryl chloride, and 1.4 mL (0.016 mol) of phosphorus trichloride was placed in a 250-mL quartz flask equipped with a condenser and acidic gas trap. The mixture was placed in a Rayonet photochemical reactor fitted with 253.7-nm lamps. The solution was stirred and irradiated for 40 h at about 70 °C. The reaction mixture was distilled affording 18.8 g (74%) of a light-yellow liquid, bp 138–145 °C (2.4 mm). Dichlorodiphenylmethane reportedly distills at 164–167 °C (12 mm).[18] The IR spectrum (neat) showed the C–D stretches at 2260 and 2280 cm^{-1}. The NMR spectrum (CCl_4) showed only a symmetrical multiplet at δ 7.40.

Benzophenone Imine-4,4′-*d*$_2$ hydrochloride (5) was prepared from **4** using a method previously described for the undeuterated analogue.[19] The crude hydrochloride was purified by sublimation [185 °C (1 mm)]. The white crystalline product was obtained in 40% yield and used directly as described below.

Bromodiphenylmethane-*4,4′-d*$_2$ (6) was prepared by brominating **3** as described for the undeuterated analogue.[20] The product (obtained in 86% yield) distilled as a yellow liquid, bp 135–145 °C (0.9 mm). Bromodiphenylmethane distills at 183 °C (23 mm).[7] The infrared spectrum (neat) showed C–D stretches at 2260 and 2280 cm^{-1}. The NMR spectrum (CCl_4) was as follows: δ 6.17 (s, 1 H, CBrH) and 7.42 (m, ~8 H, aromatic).

***N*-Benzhydrylhydroxylamine-*4,4′-d*$_2$ (7)** was prepared from **6** as described for the undeuterated analogue.[21] The colorless product (obtained in 43% yield) crystallized from cyclohexane, mp 76.5–77.5 °C. The reported[21] melting point of the undeuterated compound is 75 °C.

***N*-(Benzhydryl-*p,p′-d*$_2$)-α,α-diphenyl-*p,p′-d*$_2$-nitrone (8)** was prepared by condensing 0.031 mol of **5** and 0.031 mol of **7** in 57 mL of toluene essentially as described for the undeuterated nitrone.[6a] The crude oily solid product mixture was dissolved in 85 mL of hot ethanol. The pale yellow crystalline product (6.8 g) was collected and dried, mp 157–165 °C. This material was further purified by chromatography on Florisil. In a typical purification, 2.21 g of crude product was chromatographed on a 3.4 × 19 cm column of Florisil (75 g). Hexane

through benzene–hexane (1:4) eluted 0.220 g of deuterated benzophenone *N*-benzhydrylimine.[22] Benzene–hexane (3:2) eluted 0.460 g of nitrone contaminated with the *N*-benzhydrylimine and a yellow substance, and benzene–hexane (4:1) eluted 0.246 g of slightly discolored nitrone. Pure nitrone was eluted as a white solid (1.255 g) by benzene and benzene–ether (19:1). Colorless fractions of nitrone thus obtained were recrystallized twice from absolute ethanol, affording 3.44 g (30.4%) of **8**, mp 167–169 °C. The reported melting point of the undeuterated nitrone is 165–167 °C.[15] The important spectral features of **8** are as follows: IR (KBr) 2280 (C–D stretch) and 1220 cm^{-1} (N → O); NMR ($CDCl_3$) δ 6.45 (s, 1 H, benzhydryl C–H), 7.33 (m, ~14 H, aromatic), and 8.08 (d, 2 H, o-H of α-phenyl ring cis to oxygen).

Combustion analyses of **8** indicated 17.60 and 17.65 atom % excess D (theoretical for fully tetradeuterated nitrone is 19.05 atom %). The mass spectrum (19 eV) of **8** shows peaks at *m/e* 365, 366, 367, 368, and 369. No peaks were present between the parent ion region (*m/e* 363–367) and the region *m/e* 347–351 which corresponds to the loss of oxygen. Corrections for natural isotope contributions by comparison with an undeuterated sample (possessing peaks at *m/e* 363, 364, and 365) were made. The calculated distribution (average of three spectra) of deuterated species in **8** was thus found to be 1.11% di-, 17.56% tri-, and 81.33% tetradeuterated (all ±0.11%). The atom % excess D calculated from the mass spectral data is 18.11.

Benzophenone-*p,p'-d*$_2$ *O*-(Benzhydryl-*p,p'-d*$_2$)oxime (10). A 67-mg sample of the deuterated nitrone was heated in an evacuated tube at 180 °C for 1.8 h. The product mixture was chromatographed twice over columns (~1 × 7 cm) of alumina. Hexane–benzene (4:1) eluted a colorless oil which crystallized from absolute ethanol, affording 50 mg (75%) of **10** as a white solid, mp 101.5–103.5 °C. The reported melting point of the undeuterated analogue is 101.5–102 °C.[15] Hexane–benzene (49:1) and ether also eluted 4 and 6 mg, respectively, of deuterated tetraphenylethane and benzophenone oxime.

The important spectral features of **10** are as follows: IR (KBr) 2260 and 2290 cm^{-1} (C–D stretch); NMR ($CDCl_3$) δ 5.55 (s, 1 H, benzhydryl C–H), 7.32 (m, ~16 H, aromatic). The mass spectrum (17 eV) of **10** showed peaks at *m/e* 365, 366, 367, 368 and 369 in the parent ion region. The calculated distribution (average of three spectra) of deuterated species in **10** was 1.07% di-, 17.85% tri-, and 81.08% tetradeuterated (all ±0.10%).

Crossover Experiments. Approximately equimolar amounts of deuterated and undeuterated nitrones (typically about 10 mg of each) were weighed into Pyrex tubes. The appropriate solvent (freshly distilled) was added with a pipet. The solutions were then degassed and sealed under vacuum. The tubes were heated in a constant temperature bath at 144 ± 0.1 °C. After a time required for 99.9% reaction, the *O*-benzhydryloxime product was isolated quantitatively by chromatography on alumina. Hexane–benzene (4:1) eluted this product. Mass spectral analyses were then used to determine the extent of crossover. In the decomposition corresponding to 50% disappearance of nitrone, it was necessary to first chromatograph the decomposition mixture on Florisil in order to isolate the undecomposed nitrone which is unstable on alumina.

Acknowledgments. The authors wish to thank Professor G. Spiteller of the University of Göttingen for numerous mass spectral determinations. This investigation was supported by the National Cancer Institute, National Institute of Health, and U.S. Public Health Service (Grant No. CA-10741-04).

Registry No.—**2**, 1941-86-2; **3**, 65311-45-7; **4**, 65311-46-8; **5**, 65311-47-9; **6**, 65311-48-0; **7**, 65311-49-1; **8**, 65311-50-4; **9**, 5076-57-3; **10**, 65311-51-5; benzophenone *O*-benzhydryloxime, 65311-52-6.

References and Notes

(1) Abstracted in part from the Ph.D. Thesis of J. A. Villarreal, University of California, San Diego, and San Diego State University, 1973.
(2) See (a) E. J. Grubbs, J. A. Villarreal, J. D. McCullough, Jr., and J. S. Vincent, *J. Am. Chem. Soc.*, **89**, 2234 (1967); (b) J. S. Vincent and E. J. Grubbs, *ibid.*, **91**, 2022 (1969); (c) T. S. Dobashi, D. R. Parker, and E. J. Grubbs, *ibid.*, **99**, 5382 (1977); (d) D. G. Morris, *Chem. Commun.*, 221 (1971); and the accompanying paper in this issue.
(3) K. Brand and D. Krücke-Amelung, *Ber. Dtsch. Chem. Ges.*, **72**, 1029 (1939).
(4) A. B. Galun, A. Kaluszyner, and E. D. Bergmann, *J. Org. Chem.*, **27**, 1426 (1962).
(5) R. G. Jones and H. Gilman, *Org. React.*, **6**, 353 (1951).
(6) (a) E. J. Grubbs, J. D. McCullough, Jr., B. H. Weber, and J. R. Maley, *J. Org. Chem.*, **31**, 1098 (1966); (b) A. Hantzsch and F. Kraft, *Ber. Dtsch. Chem. Ges.* **24**, 3511 (1891).
(7) The isotopic compositions of isolated tetraphenylethane samples were not determined, and no attempt was made to isolate benzophenone oxime from these crossover mixtures.
(8) K. Biemann, "Mass Spectrometry: Organic Chemical Applications", McGraw-Hill, New York, N.Y., 1962, pp. 59–39, 212–227.
(9) A propagation of error treatment shows that the standard error of α calculated for *m* = 363 or 367 is four times larger on the average than for *m* = 365.
(10) The fraction of nitrone converted to *O*-benzhydryloxime by an intermolecular process also depends upon the initial concentration of nitrone mixture as will be described in a later publication.
(11) The viscosities of these solvents are very low at 144 °C. The value for DMA at 144 °C is approximately 4.3 × 10^{-3} p.[12] Those for *tert*-butyl alcohol and diethyl carbitol, based upon extrapolations, appear to be somewhat smaller.
(12) J. N. Friend and W. D. Hargreaves, *Philos. Mag.*, **37**, 201 (1946).
(13) Presumably some of the benzophenone oxime can also be formed via direct solvent hydrogen atom abstraction by the iminoxy radical in **11** prior to diffusion.
(14) See J. A. Villarreal, T. S. Dobashi, and E. J. Grubbs, *J. Org. Chem.*, proceeding paper in this issue.
(15) A. C. Cope and A. C. Haven, Jr., *J. Am. Chem. Soc.*, **72**, 4896 (1950).
(16) Melting points and boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 621 recording spectrophotometer. NMR spectra were determined on a Varian Model A-60 spectrometer. Deuterium analyses were performed by J. Nemeth, University of Illinois. Mass spectra were obtained by Dr. G. Spiteller, University of Göttingen. Solvents were dried over sodium or calcium oxide (*tert*-butyl alcohol) and distilled under nitrogen.
(17) H. Adkins and R. Conner, *J. Am. Chem. Soc.*, **53**, 1091 (1931).
(18) M. G. Voronkov and E. P. Popova, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 689 (1966); *Chem. Abstr.*, **67**, 81865u (1967).
(19) A. Hantzsch and F. Kraft, *Ber. Dtsch. Chem. Ges.*, **24**, 3511 (1891).
(20) J. F. Norris, R. Thomas, and B. M. Brown, *Ber. Dtsch. Chem. Ges.*, **43**, 2940 (1910).
(21) O. Exner, *Chem. Listy*, **50**, 779 (1956); *Chem. Abstr.*, **50**, 15477h (1956).
(22) The origin of this side product is under investigation.

Synthesis of Nitronyl Alcohols and Their Benzoate Esters

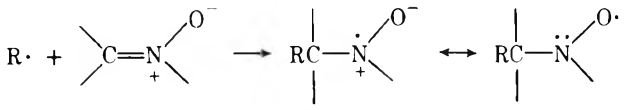
Edward G. Janzen* and Robert C. Zawalski[1]

Department of Chemistry, University of Georgia, Athens, Georgia 30602, and The Guelph-Waterloo Center for Graduate Work in Chemistry, University of Guelph, Guelph, Ontario N1G 2W1 Canada

Received October 6, 1977

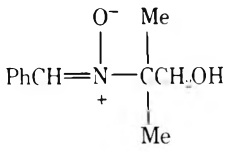
The synthesis of six new nitronyl alcohols is reported: $PhCH{=}N^{+}(O^{-})C(CH_3)_2(CH_2)_mOH$, in which $m = 1, 2$, and 3; and $PhCH{=}N^{+}(O^{-})C(CH_3)_n(CH_2OH)_p$, in which $n + p = 3$ and $0 \leq n \leq 3$ and $0 \leq p \leq 3$. All are produced by condensation of benzaldehyde and the appropriately substituted hydroxylamine derived from the nitro alcohol of the corresponding structure. The synthesis of the benzoates of the nitronyl alcohols starting from the benzoates of the corresponding nitro alcohols is also described.

The addition of radicals to nitrones produces nitroxides.[2]

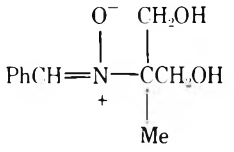


This reaction seems to be fairly general for radicals with the unpaired electron centered on carbon (carbon-centered radicals[3]) and also for oxygen-centered radicals.[4] Because the ESR spectrum of the nitroxides produced should be in principle unique for each radical trapped, the addition reaction is useful in detecting low concentrations of reactive free radicals which cannot be detected directly by ESR methods. This technique has been named spin trapping.[3,5] The potential applications and limitations of this method are under investigation in these laboratories.

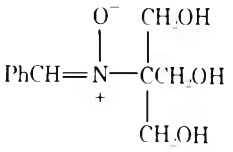
It is obvious that a water-soluble nitrone would be desirable for free-radical studies in aqueous solution. The extensively studied α-phenyl-*tert*-butylnitrone (PBN) dissolves very slowly in water up to about 0.1 M. One would expect improved water solubility with retention of stability on spin trapping when the *tert*-butyl methyl hydrogens are replaced by hydroxy groups (I–III). The synthesis of these compounds as well



I

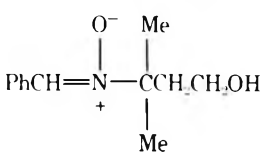


II

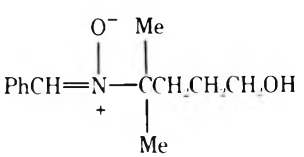


III

as their benzoate esters is described in this paper. Also, the preparation of two phenylnitrones with an extended methylene chain will be given (IV and V).

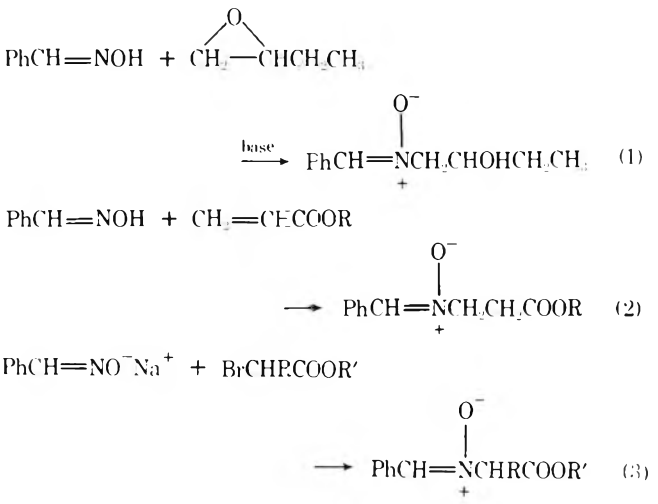


IV



V

Apparently these *N*-*tert*-alkylnitronyl alcohols have not been previously prepared, although a few other nitronyl alcohols and esters have been reported. The following reactions were used to prepare the nitronyl alcohols reported in the literature.[6-8]

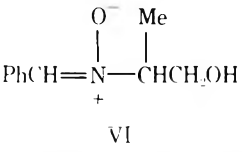


(1)

(2)

(3)

The synthesis of VI is also included here.



VI

General Approach to the Synthesis of Nitronyl Alcohols. The nitronyl alcohols reported here were synthesized by the condensation of benzaldehyde with the appropriately substituted hydroxylamine. The substituted hydroxylamine

is obtained from the zinc/ammonium chloride reduction of the appropriate nitro alcohol. The nitro alcohols needed for the synthesis of I, II, and III were prepared from formaldehyde and the appropriate nitroalkane. However, they can also be obtained commercially. The nitro alcohols for IV and V were prepared by special methods. In every case the nitronyl alcohol benzoate ester was made by the condensation of benzaldehyde with the hydroxylamine of the nitro alcohol benzoate ester.

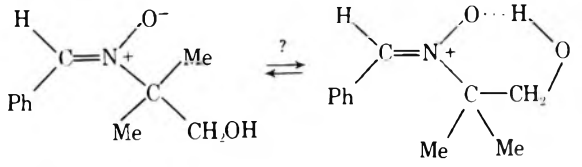
Synthesis. α-Phenyl-*N*-(1-hydroxy-2-methyl-2-propyl)nitrone (I). Since this compound bears a close resemblance to PBN, the name "hydroxy PBN" or HOPBN will be used. HOPBN can be prepared from formaldehyde, 2-nitropropane, and benzaldehyde in good yield. The assignment of structure is based on NMR, IR, and UV spectroscopy. In $CDCl_3$ the following assignments are made: multiplet at δ

* Address correspondence to the University of Guelph.

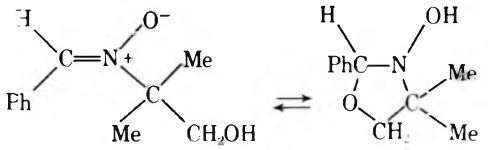
0022-3263/78/1943-1900$01.00/0

8.23 due to the ortho protons of the phenyl group, multiplet at δ 7.40 due to the meta, para, and vinyl protons, broad singlet at δ 4.45 due to the hydroxy proton, singlet at δ 3.73 due to the methylene protons, and singlet at δ 1.55 due to the protons of the two methyl groups. Integration is consistent with this assignment. The spectrum in the region of the phenyl group is identical with that of PBN and frequently has diagnostic value for identifying the presence of N-substituted phenylnitrones, particularly in polar solvents like D_2O or Me_2SO-d_6.[9] In polar solvents the ortho protons are strongly deshielded, appearing at δ 8.4, whereas the meta and para protons appear at δ 7.1–7.4. This separation frequently allows resolution of the vinyl proton singlet at δ 7.4–7.8. In KBr absorptions due to the OH and C=N stretch are found at 3180 and 1591 cm^{-1}, respectively. The ultraviolet spectrum of HOPBN is identical with that of PBN: λ_{max} 298 (ethanol), 305 (hexane) nm (ϵ_{max} ca. 15 000). The two broad, moderately intense absorptions have been reported to be characteristic of N-alkylated phenylnitrones.[10]

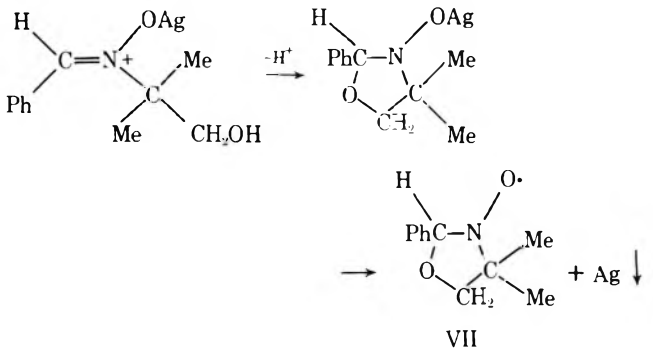
The question as to the possibility of intramolecular H bonding in this compound is under investigation.



HOPBN is a stable white crystalline solid completely soluble in water. No evidence for the cyclic hydroxylamine isomer has been found. Thus, although aliphatic hydroxylamines



react instantly with alcoholic silver nitrate at room temperature upon mixing to yield a dark gray, silver precipitate, pure samples of HOPBN (or PBN) do not produce precipitates in the presence of silver ions. However, when followed by ESR spectroscopy, a small amount of nitroxide is observed upon mixing HOPBN with alcoholic silver nitrate at room temperature. This signal increases with time. The same result is obtained with lead tetraacetate. Further studies of this reaction are under way. The Lewis acid centers probably facilitate cyclization by coordination with the nitronyl oxygen. The structural assignment of VII is based on the synthesis of the amine precursor.[11]



VII

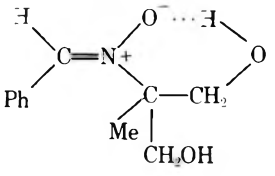
The benzoate ester of I was prepared by reducing the benzoate ester of 2-methyl-2-nitropropanol to the hydroxylamine followed by condensation with benzaldehyde. This method appears to be quite general for the preparation of nitronyl benzoates. Attempts to synthesize the benzoate ester of I directly from HOPBN were unsuccessful.

$$NO_2CMe_2CH_2OH \xrightarrow{BzCl} NO_2CMe_2CH_2OBz \xrightarrow{Zn}$$

$$HONHCMe_2CH_2OBz \xrightarrow{PhCHO} PhCHN(O)CMe_2CH_2OBz$$

The acetate ester of 2-methyl-2-nitropropanol did not survive the Zn/NH_4Cl reduction. Hydrolysis occurred, producing I upon reaction with benzaldehyde.

α-Phenyl-*N*-(1,3-dihydroxy-2-methyl-2-propyl)nitrone (II). The name "dihydroxy PBN" or $(HO)_2$PBN will be used for this compound. $(HO)_2$PBN was prepared from nitroethane, formaldehyde, and benzaldehyde in relatively poor overall yield. This compound is a white low-melting hygroscopic solid. The structural assignment is based on NMR spectroscopy. In D_2O the vinyl proton peak falls between the ortho and meta/para multiplets. The peaks for the methyl and hydroxy protons are singlets with the correct relative areas. Of interest is the fact that the diastereotopic methylene protons appear as two triplets with different chemical shifts. The possibility of intramolecular H bonding of one hydroxymethylene group is under investigation.



II

The dibenzoate ester of II was prepared from the dibenzoate ester of 2-methyl-2-nitro-1,3-propanediol.

α-Phenyl-*N*-(2-hydroxymethyl-1,3-dihydroxy-2-propyl)nitrone (III). $(HO)_3$PBN was prepared from nitromethane, formaldehyde, and benzaldehyde in moderately low yield. The compound is a white crystalline solid. The structural assignment is based on NMR, IR, and UV spectroscopy and elemental analysis (see Experimental Section). The NMR spectrum of $(HO)_3$PBN differs from that of $(HO)_2$PBN in that both the hydroxy and methylene protons appear as singlets in this case. No evidence for a difference in chemical shift for one methylene group as compared to the other two is available at this time.

The tribenzoate ester of III was prepared from the tribenzoate ester of 2-hydroxymethyl-2-nitro-1,3-propanediol.

α-Phenyl-*N*-(4-hydroxy-2-methyl-2-butyl)nitrone (IV). Since this compound still bears a close resemblance to PBN, except that instead of a *tert*-butyl group a *tert*-pentyl group is attached to the nitrogen atom of the nitrone, the term "hydroxy PPN" or HOPPN will be used to designate ω-hydroxy-α-phenyl-*N*-(*tert*-pentyl)nitrone. The synthesis of HOPPN was accomplished by condensation of benzaldehyde with the substituted hydroxylamine obtained from reduction of 3-nitro-3-methylbutanol. The latter was made from the hydrolysis of 3-methyl-3-nitrobutyl acetate produced in the peracid oxygenation of 5-methyl-5-nitro-2-hexanone. A 13% overall yield was obtained.

$$NO_2CHMe_2 \xrightarrow{CH_2=CHCOCH_3} NO_2CMe_2CH_2CH_2COCH_3$$

$$\xrightarrow{CF_3COOH} NO_2CMe_2CH_2CH_2OCOCH_3$$

$$\xrightarrow{NaOH} NO_2CMe_2CH_2CH_2OH \xrightarrow[NH_4Cl]{Zn} HONHCMe_2CH_2CH_2OH$$

$$\xrightarrow{PhCHO} PhCH{=}\overset{+}{N}(O^-)CMe_2CH_2CH_2OH$$

α-Phenyl-*N*-(5-hydroxy-2-methyl-2-pentyl)nitrone (V). Since the hydroxyalkyl group in this compound is *tert*-hexyl, the term "hydroxy PHN" or HOPHN will be used to designate ω-hydroxy-α-phenyl-*N*-(*tert*-hexyl)nitrone. The synthesis of HOPHN was accomplished by condensation of benzaldehyde with the substituted hydroxylamine obtained from the reduction of 4-nitro-4-methylpentanol. The latter was made by reduction of 4-nitro-4-methylpentanal with sodium cyanoborohydride. A 15% overall yield was obtained. Structure assignment was by NMR spectroscopy.

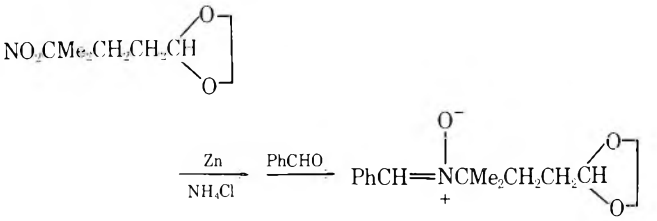
$$NO_2CHMe_2 \xrightarrow{CH_2=CHCHO} NO_2CMe_2CH_2CH_2CHO$$

$$\xrightarrow{NaCNBH_3} NO_2CMe_2CH_2CH_2CH_2OH$$

$$\xrightarrow[NH_4Cl]{Zn} HONHCMe_2CH_2CH_2CH_2OH$$

$$\xrightarrow{PhCHO} PhCH{=}\overset{+}{N}(O^-)CMe_2CH_2CH_2CH_2OH$$

An attempt was made to obtain the nitrone by protecting the aldehydic function from the zinc/NH_4Cl reduction of the nitro group. Although the expected protected phenylnitrone was obtained, hydrolysis destroyed the nitrone function. This method was not successful in producing HOPHN. The assignment of structure was based on NMR spectroscopy.



α-Phenyl-*N*-(1-hydroxy-2-propyl)nitrone (VI). The condensation of benzaldehyde with the hydroxylamine ob-

$$PhCHO + HONHCHMeCH_2OH \longrightarrow PhCH{=}\overset{+}{N}(O^-)CHMeCH_2OH$$

VI

tained from 2-nitropropanol produced VI in 55% overall yield. Structural assignment was based on NMR spectroscopy.

Experimental Section

Synthesis of α-Phenyl-*N*-(1-hydroxy-2-methyl-2-propyl)-nitrone (I). To a cooled flask containing 2-methyl-2-nitropropanol (5.95 g, 0.05 mol) in 150 mL of ethanol was added ammonium chloride (3.25 g, 0.061 mol) in 50 mL of distilled water. Fine zinc powder (13 g, 0.2 mol) was added over a period of 15 min with stirring and continued cooling (<30 °C). After stirring for 4 h the zinc salts were filtered off and washed with hot 95% ethanol (2 × 100 mL) and hot chloroform (2 × 100 mL). The light green filtrate (the blue color comes from the nitroso function) was concentrated to 50 mL by rotoevaporation and extracted with chloroform (4 × 100 mL). The combined extracts were concentrated to 100 mL and used in the next step.

Benzaldehyde (5.25 g, 0.05 mol) was added to the above chloroform solution, and the mixture was gently refluxed for 3.5 h. After cooling, drying over anhydrous $MgSO_4$, and concentrating by rotoevaporation, a solid paste was recovered which after two recrystallizations from cold CCl_4 yielded a fine white powder (5.2 g, 55% yield overall): mp 75–76 °C; NMR ($CDCl_3$) δ 8.23 (m, 2 H, C_6H_5 ortho), 7.40 (m, 4 H, C_6H_5 2 meta and 1 para, 1 vinyl), 4.45 (s, broad, 1 H, CH_2OH), 3.73 (s, 2 H, CH_2OH), 1.55 (s, 6 H, $2CH_3$); IR (KBr) 3180 (OH), 1591 (C=N) cm^{-1}; UV λ_{max} 298 (EtOH), 305 (hexane) nm (ϵ_{max} ca. 15 000). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.22; H, 7.88; N, 7.34.

Synthesis of α-Phenyl-*N*-(1,3-dihydroxy-2-methyl-2-propyl)nitrone (II). Reduction of 2-methyl-2-nitro-1,3-propanediol to the hydroxylamine derivative and condensation with benzaldehyde were accomplished on a 0.05-mol scale by the procedure used for the preparation of I. Two recrystallizations from cold benzene yielded low-melting white crystals (1.6 g, 15.3% yield overall): mp 52–55 °C (hygroscopic); NMR (D_2O) δ 8.18 (m, 2 H, C_6H_5 ortho), 7.38 (m, 4 H, C_6H_5 2 meta and 1 para, 1 vinyl), 4.10 (s, broad, 2 H, $2CH_2OH$), 3.98 (m, 4 H, $2CH_2OH$), 1.41 (s, 3 H, CH_3); IR (film) 3280 (OH), 1588 (C=N) cm^{-1}; UV (EtOH) λ_{max} 296 nm. An analytically pure sample suitable for elemental analysis could not be prepared.

Synthesis of α-Phenyl-*N*-(2-hydroxymethyl-1,3-dihydroxy-2-propyl)nitrone (III). Reduction of 2-hydroxymethyl-2-nitro-1,3-propanediol to the hydroxylamine derivative and condensation with benzaldehyde by the method used for I gave white powdery crystals after four recrystallizations from methanol/petroleum ether (2.48 g, 22% overall yield): mp 89–91 °C; NMR (D_2O) δ 7.70 (m, 2 H, C_6H_5 ortho), 7.20 (s, 1 H, vinyl), 7.0 (m, 3 H, C_6H_5 meta and 1 para), 4.45 (s, 6 H, $3CH_2OH$); IR (KBr) 3380–3190 (broad OH), 1590 (C=N) cm^{-1}; UV (EtOH) λ_{max} 298 nm (ϵ_{max} ca. 15 000). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.49; H, 6.60; N, 6.15.

Synthesis of α-Phenyl-*N*-(4-hydroxy-2-methyl-2-butyl)nitrone (IV). To a solution of trifluoroperacetic acid (32.5 g, 0.25 mol) in methylene chloride prepared from trifluoroacetic anhydride and 90% hydrogen peroxide by the method of Emmons and Pagano[12] was added 5-methyl-5-nitro-2-hexanone (prepared from the Michael addition of 2-nitropropane to vinyl methyl ketone) dropwise with cooling over a period of 1 h. The mixture was allowed to stand overnight and was then poured into 500 mL of water. The organic layer separated and was extracted with 10% $NaHCO_3$ (2 × 100 mL) and saturated NaCl (100 mL). Rotoevaporation yielded a white sweet-smelling slurry, which from NMR spectroscopy was estimated to contain 66% of 3-methyl-3-nitrobutyl acetate. The mixture was refluxed in methanolic KOH for 2 days. The dark tarry mixture was filtered through glass wool, concentrated to 100 mL under vacuum, and extracted with ether (5 × 100 mL). The ether extract was concentrated to 100 mL, filtered through glass wool, and rotoevaporated to yield a dark brown oil. This was heated to boiling in 50% H_2O/EtOH and treated with charcoal (Norit). After filtering and concentrating to 50 mL on the rotoevaporator, extraction with chloroform yielded 3-methyl-3-nitrobutanol (4.25 g, 12.8% yield) as a pale yellow oil: NMR ($CDCl_3$) δ 4.50 (s, broad, 1 H, OH), 3.70 (t, J = 6 Hz, 2 H, CH_2OH), 2.23 (t, J = 6 Hz, OCH_2CH_2), 1.65 (s, 6 H, $2CH_3$); IR (neat) 3350 (OH), 1551 (NO_2) cm^{-1}.

Reduction to the hydroxylamine was accomplished by the standard procedure used in the preparation of I.

The resulting chloroform solution of the hydroxylamine derivative was gently refluxed with benzaldehyde (3.40 g, 0.32 mol) for 3 h. Rotoevaporation yielded a green oil, and TLC on silica gel indicated the presence of two components. The mixture was separated on a 11 × 1 in silica gel (60–200 mesh) column using ethyl acetate/chloroform (50:50) as elutant. The nitronyl alcohol was collected within the 250–330-mL fraction of elutant (flow rate, 1 cm^3/min). Rotoevaporation followed by vacuum desiccation yielded the nitronyl alcohol as a clear viscous oil (0.85 g, 12.9%): NMR ($CDCl_3$) δ 8.18 (m, 2 H, C_6H_5 ortho), 7.48 (s, 1 H, vinyl), 7.23 (m, 3 H, C_6H_5 2 meta and 1 para), 4.55 (s, broad, 1 H, OH), 3.47 (t, J = 5 Hz, 2 H, CH_2OH), 2.29 (t, J = 5 Hz, 2 H, CH_2CH_2O), 1.61 (s, 6 H, $2CH_3$); IR (neat) 3350 (OH), 1584 (C=N) cm^{-1}; UV (EtOH) λ_{max} 298 nm (ϵ_{max} ca. 15 000).

Synthesis of α-Phenyl-*N*-(5-hydroxy-2-methyl-2-pentyl)-nitrone (V). In a well-ventilated hood freshly prepared 4-methyl-4-nitropentanal (5.3 g, 0.064 mol) from 2-nitropropane and acrolein was added to cooled 50% aqueous methanol (100 mL) at pH 4 (H_2SO_4). This was followed by the addition of sodium cyanoborohydride (4.04 g, 0.065 mol) in small portions over 30 min with periodic additions of H_2SO_4 to maintain pH 4. After stirring for 4 h at room temperature, the deep brown liquid was diluted with 250 mL of H_2O and extracted with chloroform (4 × 100 mL). A pale yellow oil (8.0 g, 84%) was isolated by rotoevaporation: NMR ($CDCl_3$) δ 4.25 (s, broad, 1 H, OH), 3.65 (t, J = 5 Hz, 2 H, CH_2OH), 1.90 (m, 2 H, CH_2), 1.61 (s, 6 H, $2CH_3$), 1.50 (m, 2 H, CH_2); IR (neat) 3345 (OH) and 1550 (NO_2) cm^{-1}, with no trace of carbonyl absorption.

Reduction to the hydroxylamine derivative was accomplished by the procedure used in the preparation of I. The resulting green oil was eluted through a 10 × 1 in silica gel (200 mesh) column using 25% ethyl acetate in chloroform. The nitronyl alcohol was collected in the fraction between 300 to 380 mL of elutant (flow rate, 1 mL/min). Evaporation of the solvent followed by 24 h of vacuum desiccation yielded the nitrone as a colorless jelly (2.05 g, 14.53% overall): NMR (CCl_4) δ 8.20 (m, 2 H, C_6H_5 ortho), 7.38 (s, 1 H, vinyl), 7.25 (m, 3 H, C_6H_5 2 meta and 1 para), 3.65 (s, broad, 1 H, OH), 3.40 (t, J = 4 Hz,

2 H, CH_2OH), 1.80 (m, 2 H, CH_2), 1.45 (s, 6 H, $2CH_3$). 1.35 (m, 2 H, CH_2); IR (neat) 3350 (OH), 1585 (C=N) cm^{-1}; UV (EtOH) λ_{max} 298 nm (ϵ_{max} ca. 15 000).

Synthesis of the Ethylene Glycol Acetal of V. A mixture of 4-methyl-4-nitropentanal (25 g, 0.17 mol), ethylene glycol (10.78 g, 0.18 mol), and 0.5 g of *p*-toluenesulfonic acid in 50 mL of benzene was vigorously refluxed under a Dean-Stark trap for 3 h. The solution was cooled, diluted to 150 mL with benzene, extracted with saturated $NaHSO_3$ (2 × 50 mL) and saturated NaCl, and rotoevaporated, and the oil recovered was distilled under vacuum (120 °C at 6 mm). The dioxolane was isolated as a colorless liquid (25.3 g, 78.8%): IR 1546 (NO_2) cm^{-1}, with no carbonyl absorption.

Reduction to the hydroxylamine and condensation with benzaldehyde were on a 0.1-mol scale following the procedure used in the preparation of I. The crude nitrone was isolated as a green oil, which solidified upon refrigeration. Recrystallization from hexane/petroleum ether yielded pure white crystals (19.9 g, 76%): mp 64–65 °C; NMR ($CDCl_3$) δ 8.25 (m, 2 H, C_6H_5 ortho), 7.45 (s, 1 H, vinyl), 7.30 (m, 3 H, C_6H_5 2 meta and 1 para), 4.84 (t, J = 4 Hz, 1 H, methine), 3.85 (m, 4 H, acetal), 2.0 (m, 2 H, CH_2), 1.65 (m, 2 H, CH_2), 1.60 (s, 6 H, $2CH_3$); IR (KBr) 1585 (C=N) cm^{-1}. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.50; H, 8.03; N, 5.32. Found: C, 68.48; H, 8.01; N, 5.29.

Synthesis of the Benzoate Ester of Nitrone I. Pyridine (3.9 g, 0.05 mol) was added to 2-methyl-2-nitropropanol (5.95 g, 0.05 mol) and benzoyl chloride (7.0 g, 0.05 mol) in 50 mL of dry benzene. After refluxing vigorously for 1 h the solution was cooled and extracted with 1 N HCl (2 × 100 mL), 1 N KOH (2 × 100 mL), and 50 mL of saturated NaCl. Rotoevaporation yielded the benzoate as a sweet-smelling yellow oil (9.8 g, 95%): IR (neat) 1728 (C=O), 1549 (NO_2) cm^{-1}.

Reduction to the hydroxylamine derivative and condensation with benzaldehyde were accomplished by following the procedure used for I. The crude nitronyl ester was recrystallized from cold benzene to yield white crystals (7.12 g, 48% overall): mp 95–96 °C; NMR ($CDCl_3$) δ 8.32 (m, 2 H, C_6H_5 ortho, nitrone), 7.90 (m, 2 H, C_6H_5 ortho, ester), 7.60 (s, 1 H, vinyl), 7.40 (m, 6 H, $2C_6H_5$ 4 meta and 2 para), 4.69 (s, 2 H, CH_2O), 1.75 (s, 6 H, $2CH_3$); IR (KBr) 1732 (C=O), 1684 (C=N) cm^{-1}. Anal. Calcd for $C_{18}N_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.59; H, 6.44; N, 4.80.

Synthesis of the Dibenzoate Ester of Nitrone II. Pyridine (7.8 g, 0.10 mol) was added to 60 mL of dry benzene containing 2-methyl-2-nitro-1,3-propanediol (6.75 g, 0.05 mol) and 2 equiv of benzoyl chloride (14.5 g, 0.10 mol). The turbid solution was refluxed for 6 h, cooled, diluted with 100 mL of benzene, and extracted with 1 N HCl (2 × 100 mL), 1 N KOH (2 × 100 mL), and 100 mL of saturated NaCl. Rotoevaporation yielded a crude solid which recrystallized from ethyl acetate/petroleum ether to yield white crystals of the dibenzoate (13.2 g, 84.9%): mp 85–86 °C; NMR ($CDCl_3$) δ 8.23 (m, 4 H, $2C_6H_5$ ortho), 7.65 (m, 6 H, $2C_6H_5$ 4 meta and 2 para), 4.97 (s, 4 H, $2CH_2O$), 1.90 (s, 3 H, CH_3); IR (KBr) 1732 (intense 2C=O), 1547 (NO_2) cm^{-1}.

Reduction to the hydroxylamine derivative and condensation with benzaldehyde were accomplished by the procedure used in the preparation of I. From 10.5 g of the nitro alcohol was obtained 12.6 g (89.5%) of nitronyl ester as fine white crystals: mp 154–155 °C (ethyl acetate); NMR ($CDCl_3$) δ 8.30 (m, 2 H, C_6H_5 ortho, nitrone), 7.95 (m, 4 H, $2C_6H_5$ ortho, ester), 7.63 (s, 1 H, vinyl), 7.40 (m, 6 H, $3C_6H_5$ 2 meta and 2 para), 4.88 (m, 4 H, $2CH_2O$). 1.85 (s, 3 H, CH_3); IR (KBr) 1730 (intense C=O). 1588 (C=N) cm^{-1}. Anal. Calcd for $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.35. Found: C, 71.88; H, 5.60; N, 3.32.

Synthesis of the Tribenzoate Ester of Nitrone III. A solution of commercial 2-hydroxymethyl-2-nitro-1,3-propanediol (3.0 g, 0.02 mol) in 50 mL of dry benzene was added to 3 equiv of benzoyl chloride (8.43 g, 0.06 mol) in dry pyridine (4.68 g, 0.06 mol). The mixture was refluxed for 3 h, cooled, washed with 100 mL of water, and extracted with 1 N HCl (2 × 50 mL), 1 N KOH (2 × 50 mL), and saturated NaCl solution. Rotoevaporation yielded a crude yellow solid which after two recrystallizations from ethyl acetate/pentane gave the tribenzoate as white crystals (2.34 g, 25%): mp 110–111 °C; NMR ($CDCl_3$) δ 8.10 (m, 6 H, $3C_6H_5$ ortho), 7.60 (m, 9 H, $3C_6H_5$ 6 meta and 3 para), 5.08 (s, 6 H, $3CH_2O$); IR (KBr) 1739 (very intense C=O), 1550 (NO_2) cm^{-1}.

Reduction to the hydroxylamine derivative was by the procedure used for I except that dioxane/water was used instead of ethanol/water. The condensation with benzaldehyde gave a white solid (1.60 g, 61%) which was recrystallized twice from ethyl acetate/pentane to yield the nitronyl ester as fine white crystals: mp 123–124 °C; NMR ($CDCl_3$) δ 8.26 (m, 2 H, C_6H_5 ortho, nitrone), 7.80 (m, 6 H, $3C_6H_5$ ortho, ester), 7.65 (s, 1 H, vinyl), 7.30 (m, 12 H, $4C_6H_5$ 8 meta and 4 para), 5.08 (s, 6 H, $3CH_2O$); IR (KBr) 1733 (intense C=O), 1593 (C=N) cm^{-1}. Anal. Calcd for $C_{31}H_{27}NO_7$: C, 70.84; H, 5.18; N, 2.67. Found: C, 70.78; H, 5.12; N, 2.61.

Synthesis of α-Phenyl-*N*-(1-hydroxy-2-propyl)nitrone (VI). This nitronyl alcohol was prepared by the same procedure used for I by starting with commercial 2-nitropropanol (5.25 g, 0.05 mol). Two recrystallizations of the crude product from ethyl acetate/petroleum ether gave pure white crystals (4.94 g, 55% overall): mp 139–140 °C; NMR ($CDCl_3$) δ 8.18 (m, 2 H, C_6H_5 ortho), 7.53 (m, 4 H, C_6H_5 2 meta and 1 para, 1 vinyl), 3.90 (m, 4 H, CH_2OH, methyne, CH_2OH), 1.31 (d, J = 10 Hz, 3 H, CH_3); IR (KBr) 3280 (OH), 1595 (C=N) cm^{-1}; UV (EtOH) λ_{max} 298 nm (ϵ_{max} ca. 15 000). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.96; H, 7.36; N, 7.75.

Acknowledgment. This work was supported by the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made.

Registry No.—I, 55277-95-7; I benzoate, 63829-80-1; II, 65102-43-4; II dibenzoate, 65102-44-5; III, 65102-45-6; III tribenzoate, 65138-31-0; IV, 65102-46-7; V, 65102-47-8; V ethylene glycol acetal, 65102-48-9; VI, 63829-45-8; 2-methyl-2-nitropropanol, 76-39-1; 2-methyl-2-nitro-1,3-propanediol, 77-49-6; 2-hydroxymethyl-2-nitro-1,3-propanediol, 126-11-4; 5-methyl-5-nitro-2-hexanone, 4604-49-3; 3-methyl-3-nitrobutyl acetate, 65102-49-0; 3-methyl-3-nitrobutanol, 65102-50-3; 4-methyl-4-nitropentanal, 57620-49-2; ethylene glycol, 107-21-1; benzoyl chloride, 98-88-4; 2-nitropropanol, 2902-96-7; *p*-formaldehyde, 30525-89-4; 2-nitropropane, 79-46-9; nitroethane, 79-24-3; nitromethane, 75-52-5; benzaldehyde, 100-52-7; 2-hydroxyamino-2-methylpropanol, 4706-13-2; 2-hydroxyamino-2-methyl-1,3-propanediol, 24395-58-2; 2-hydroxyamino-2-hydroxymethyl-1,3-propanediol, 65102-51-4; 3-hydroxyamino-3-methylbutanol, 65102-52-5; 4-hydroxyamino-4-methylpentanol, 65102-53-6; 2-hydroxyaminopropanol, 39796-64-0; 2-methyl-2-nitropropyl benzoate, 65102-54-7; 2-hydroxyamino-2-methylpropyl benzoate, 63829-78-7; 2-methyl-2-nitro-1,3-propanediol dibenzoate, 65102-55-8; 2-hydroxyamino-2-methyl-1,3-propanediol dibenzoate, 65102-56-9; 2-hydroxymethyl-2-nitro-1,3-propanediol tribenzoate, 65102-57-0; 2-hydroxyamino-2-hydroxymethyl-1,3-propanediol tribenzoate, 65102-58-1.

Supplementary Material Available: Syntheses of 2-methyl-2-nitropropanol, 2-methyl-2-nitro-1,3-propanediol, and 2-hydroxymethyl-2-nitro-1,3-propanediol (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) Taken from the Ph.D. Dissertation of R. C. Zawalski, "An Electron Spin Resonance Study of the Free Radical Reactivity of Nitronyl Alcohols and Nitronyl Benzoate Esters", University of Georgia, 1976.
(2) M. Iwamura and N. Inamoto, *Bull. Chem. Soc. Jpn.*, **40**, 702, 703 (1967); **43**, 856, 860 (1970).
(3) (a) E. G. Janzen and B. J. Blackburn, *J. Am. Chem. Soc.*, **90**, 5909 (1968); **91**, 4481 (1969); (b) E. G. Janzen and J. L. Gerlock, *ibid.*, **91**, 3108 (1969); *Nature (London)*, **222**, 867 (1969); (c) E. G. Janzen and I. G. Lopp, *J. Magn. Reson.*, **7**, 107 (1972); (d) E. G. Janzen and J. I-P. Liu, *ibid.*, **9**, 510, 513 (1973); (e) E. G. Janzer and I. G. Lopp, *J. Phys. Chem.*, **76**, 2056 (1972); (f) E. G. Janzen, I. G. Lopp, and T. V. Morgan, *ioid.*, **77**, 139 (1973); (g) E. G. Janzen, T. Kasai, and K. Kuwata, *Bull. Chem. Soc. Jpn.*, **46**, 2061 (1973); (h) E. G. Janzen and C. A. Evans, *J. Am. Chem. Soc.*, **97**, 205 (1975); (i) E. G. Janzen, D. E. Nutter, and C. A. Evans, *J. Phys. Chem.*, **79**, 1983 (1975).
(4) E. G. Janzen, C. A. Evans, and Y. Nishi, *J. Am. Chem. Soc.*, **94**, 8236 (1972); E. G. Janzen and C. A. Evans, *ibid.*, **95**, 8205 (1973).
(5) E. G. Janzen, *Acc. Chem. Res.*, **4**, 31 (1971).
(6) W. Kliegel, *Justus Liebigs Ann. Chem.*, **733**, 92 (1970).
(7) L. B. Volodarski and A. Ya. Tiknonev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1218 (1972); *Zh. Org. Khim.*, **9**, 770 (1973).
(8) T. Polonski and A. Chimiak, *J. Org. Chem.*, **41**, 2092 (1976).
(9) E. Buehler, *J. Org. Chem.*, **32**, 261 (1967).
(10) W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 5739 (1957); K. Koyano and H. Suzuki, *Tetrahedron Lett.*, 1859 (1968).
(11) E. G. Janzen, R. L. Dudley, and R. C. Zawalski, *J. Am. Chem. Soc.*, in preparation.
(12) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 4557 (1955).

Rates of Acid-Catalyzed Hydration of Isomeric Z/E Alkenes. Effects of Steric Crowding on Additions to Alkenes†

Willy K. Chwang and Thomas T. Tidwell*

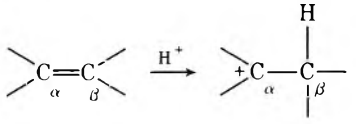
Department of Chemistry, University of Toronto, Scarborough College, West Hill, Ontario, Canada M1C 1A4

Received November 15, 1977

Rates of acid-catalyzed hydration of *Z*/*E* isomers of 2-butene, 3-hexene, 2,5-dimethyl-3-hexene, and 2,2,5,5-tetramethyl-3-hexene were measured at 25 °C in H_2O or 20% EtOH–80% aqueous H_2SO_4. The reactions proceeded by rate-determining protonation on carbon with rate ratios *Z*/*E* of 2.1, 1.2, 0.50, and 3.8, respectively. The results indicate little loss of steric strain in the transition state for protonation and are compared with the corresponding ratios in other electrophilic additions.

The reactivities of isomeric cis and trans olefins have been a topic of continuing interest in the study of electrophilic reactions.[1] In particular the relative reactivities of the isomeric 1,2-di-*tert*-butylethylenes have been used as a criterion of mechanism in the addition of *p*-chlorophenylsulfenyl chloride,[2a] mercuric acetate,[2b] bromine,[2c] and chlorine.[2d] These studies were intended to disclose whether bridged or open transition states occurred in these reactions. The reactivity of these isomers in catalytic hydrogenation was also used to study the mechanism of that process.[2e] However, rates of protonation, the prototype of an electrophilic reaction proceeding through an open transition state, have not been available for these compounds.

We have confirmed by a study of structural effects upon reactivities of alkenes in acid-catalyzed hydration reactions[3] that this reaction proceeds through $A_{SE}2$ rate-determining protonation on carbon (eq 1) and have established that the



(1)

effect of substituents on the reaction may be quantitatively correlated by eq 2 for 1,1-disubstituted alkenes.

$$\log k_2 = \rho\Sigma\sigma_p^+ + C \qquad (2)$$

When β substituents (eq 1) are also present the addition of terms to account for the effects of the β substituent on the ground-state stability of the alkenes and on the developing charge in the ion allows these compounds to be included in the correlation as well.

It appeared, therefore, highly desireable to utilize the mechanistic understanding gained of the hydration reaction for an analysis of the reactivity of geometrically isomeric alkenes, in particular the 1,2-di-*tert*-butylethylenes. We had previously collected the data available on the isomeric 2-butenes and 3-hexenes,[3d] but nothing had been reported on the higher homologues of this series.

Results

Hydration of the isomeric 2-butenes and 3-hexenes could be followed by observing the disappearance of the ultraviolet end absorption of the alkene chromophores in aqueous sulfuric acid as we have done previously.[3] However, the isomeric 1,2-diisopropyl- and 1,2-di-*tert*-butylethylenes were insufficiently soluble in this medium to utilize this method. Therefore rates were carried out in 20% ethanol–80% aqueous sulfuric acid, a medium for which the acidity function H_0 is available.[4] For comparison of the rates on a common basis the rates of the 3-hexenes were determined in each medium, and the relative reactivity factor for these substrates was used to calculate rates for all the substrates in aqueous sulfuric acid. The observed rates are collected in Tables I and II and are summarized in Table III with derived slopes and intercepts of log *k* vs. H_0 plots, solvent isotope effects, and *Z*/*E* rate ratios.

Our rates for (*Z*) and (*E*)-3-hexene in H_2SO_4 may be compared to data of Yates et al.[5a] in both cases and Modena et al.[5b] in the latter. Minor differences occur, with our rates being slightly greater in all cases, and the rates of Yates et al. being rather closer to ours than to those of Modena et al. The most significant differences are in the slopes of the log *k* vs. H_0 plots for the *E* isomer (−1.14[5b] as compared to our value of −1.35) and the fact that Yates et al. report $k(Z)/k(E) = 0.84$, whereas we find a value of 1.2. An objective assessment of the relative reliabilities of the sets of data does not appear practical, but our data are internally consistent, and in any event the differences between the different laboratories are minor.

The UV absorption decreased by at least 90% during the course of each of the reactions, indicating large equilibrium constants for hydration. However, in the case of the 1,2-diisopropyl and 1,2-di-*tert*-butylethylenes after about 5 half-lives for hydration a slow increase in the UV absorption became noticeable. In the case of the 1,2-di-*tert*-butylethylenes this eventually increased to a value greater than the absorption of the original alkenes. When 2,2,5,5-tetramethyl-3-hexanol (**1**), the expected product of direct hydration, was subjected to the reaction conditions the UV absorption increased with the approximate first-order rate constant of 3.2×10^{-5} s^{-1} at 25 °C in 20% EtOH–80% H_2SO_4 containing 13.9 equiv H^+ kg^{-1}. The same rate constant was observed for the slow increase in absorption beginning with either of the isomeric di-*tert*-butylethylenes.

Reaction of (*E*)-1,2-di-*tert*-butylethylene with a solution of 33% 14 M H_2SO_4 and 67% dioxane at 85 °C for 22 h led to a product mixture containing about 10% starting material and 90% 2,3,5,5-tetramethyl-2-hexene (**2**).[6] When the *Z* isomer was subjected to the same conditions the VPC trace of the product mixture showed the presence of about 5% starting material, 5% *E* isomer, and 90% **2**.

Repetition of the isomerization with *E* alkene in D_2SO_4 for 2 h led to the isolation of **2** whose NMR spectrum showed a sharp *t*-Bu peak but with considerably diminished and broadened signals for the vinyl methyl and CH_2 protons. The integrals of the last two peaks decreased by 80 and 72%, respectively, relative to the *tert*-butyl group. The mass spectrum of the undeuterated **2** showed the molecular ion at *m/e* 140 and strong signals at 125 ($M^+ - CH_3$), 83 ($M^+ - t$-Bu), and 69 (perhaps $MeC^+HCH{=}CHMe$). The deuterated material showed strong signals at *m/e* 156–160, 149–151, 134–136, 93–95, and 76–78. This indicated the presence of two species, one containing 16–20 deuteriums and the other 9–11. As

† Dedicated to Professor M. S. Newman on the occasion of his 70th birthday.

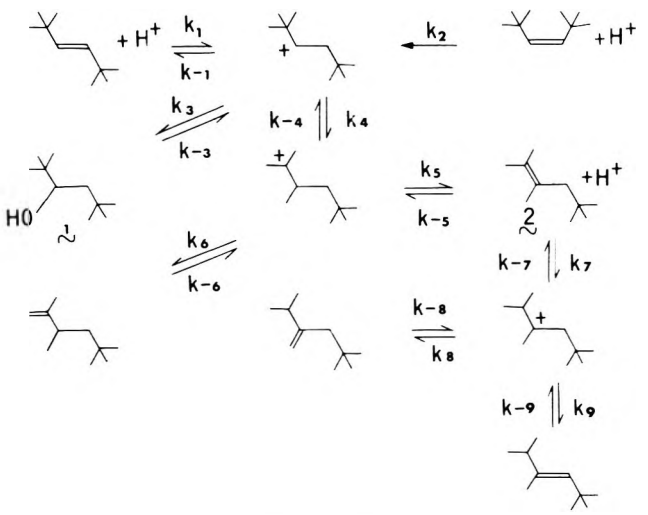
0022-3263/78/1943-1904$01.00/0

Table I. Rates of Hydration of Alkenes in Aqueous H_2SO_4 (25 °C)

Alkene	Registry no.	$[H_2SO_4]$(M)[a]	H_0[b]	k_{obsd}, s^{-1}
EtCH=CHEt[c] (Z)	7642-09-3	8.63	−4.19	0.760×10^{-2}
		8.09	−3.91	0.269×10^{-2}
		7.47	−3.57	0.960×10^{-3}
		6.92	−3.28	0.407×10^{-3}
		8.82 (D_2SO_4)		0.972×10^{-2}
		6.93 (D_2SO_4)		0.350×10^{-3}
EtCH=CHEt[d] (E)	13269-52-8	8.63	−4.19	0.594×10^{-2}
		8.09	−3.91	0.219×10^{-2}
		7.47	−3.57	0.792×10^{-3}
		6.92	−3.28	0.347×10^{-3}
		8.82 (D_2SO_4)		0.829×10^{-2}
		6.93 (D_2SO_4)		0.336×10^{-3}
MeCH=CHMe[e] (Z) (2)	590-18-1	8.63	−4.19	0.793×10^{-2}
		8.09	−3.91	0.282×10^{-2}
		7.47	−3.57	0.928×10^{-3}
		6.92	−3.28	0.344×10^{-3}
		8.82 (D_2SO_4)		0.694×10^{-2}
MeCH=CHMe[f] (E)	624-64-6	8.63	−4.19	0.354×10^{-2}
		8.09	−3.91	0.130×10^{-2}
		7.47	−3.57	0.456×10^{-3}
		6.92	−3.28	0.183×10^{-3}
		8.82 (D_2SO_4)		0.449×10^{-2}

[a] Measured by titration. [b] Interpolated from standard tables. [c] $\log k = -1.39H_0 - 7.96$ ($r = 0.999$). [d] $\log k = -1.35H_0 - 7.89$ ($r = 0.999$). [e] $\log k = -1.49H_0 - 8.34$ ($r = 1.000$). [f] $\log k = -1.40H_0 - 8.35$ ($r = 0.999$).

Scheme I



outlined in the discussion this may be interpreted in terms of Scheme I.

The k_2 values calculated from extrapolation of the log k_{obsd} vs. H_0 plots to $H_0 = 0$ are somewhat less than those we derived earlier.[3d] As we have discussed before,[3e] this arises from the steep dependence of rate on acidity shown by these alkenes.

The solvent isotope effects (Table IV) are compared at equal molarities. As we have noted before,[3e] this is reasonable inasmuch as the acidity functions of H_2SO_4 and D_2SO_4 are essentially identical at the same molarity except in very dilute acids and above 97% acid.

Discussion

The dependence of the rates on acidity and the reactivities of the alkenes are consistent with the reactions proceeding by rate-determining protonation on carbon to give carbonium ions (the $A_{SE}2$ mechanism, eq 1). This is supported by the results obtained on a wide variety of other alkenes of diverse structural types.[3] As we have noted elsewhere[3e] solvent isotope effects vary within a considerable range for alkene protonations and are not an unambiguous criterion of mechanism. The values found here are within the limits reported for others reacting by the $A_{SE}2$ route.

The initial decrease in absorption in each case suggests that following the rate-determining steps the resulting carbonium ions then undergo hydration to the corresponding carbinols. This is in accord with the generally observed 1,2 additions of a variety of electrophiles which has been noted for these compounds. For example, HBr-catalyzed addition of acetic acid to the 2-butenes and 3-hexenes,[7] trifluoroacetic acid addition to the 3-hexenes,[8] bromination of the 1,2-diisopropylethylenes,[2c] and chlorination[2d] of the 1,2-di-*tert*-butylethylenes occur predominantly by this route.

The initial sharp drop in the ultraviolet absorption during reaction of the 1,2-di-*tert*-butylethylenes implies that the hydration product **1** is initially formed, although this material was not actually isolated. The slower formation of a substance with a stronger UV absorption at the same rate from either *E* or *Z* alkene, or authentic **1**, and the isolation of **2** strongly supports this pathway, as shown in Scheme I.

The possibility must be considered that the (*Z*)-di-*tert*-butyl alkene is being rapidly converted to the *E* isomer so that the observed rate of reaction of the *Z* isomer corresponds to consumption of the *E* isomer. However, that $k(Z)/k(E)$ for the 1,2-di-*tert*-butylethylene has a close correspondence to k_2/k_1 (Scheme I) is supported by several lines of evidence. The fact that $k(Z)$ exceeds $k(E)$ by a factor of 3.8 (Table III) shows that isomerization of *Z* to *E* is not extensive, as this process if complete would result in identical observed rate constants beginning with either isomer. The presence of some residual *Z* isomer after 90% conversion to **2** also indicates that the conversion of *Z* to *E* is not a major route, and the fact that when the *E* isomer is converted to **2** to the extent of 25% in D_2SO_4 the recovered *E* isomer contains only 2% deuterium indicates that $k_4 > k_{-1}$ (Scheme I).

The deuterium distribution of **2** formed in D_2SO_4 is highly revealing as to the course of the reaction. Much of **2** contains 9–11 atoms *D*, but the NMR spectrum of the product shows a sharp *tert*-butyl signal, indicating that none of **2** with a partially deuterated *tert*-butyl group is present. The absence of mass spectral peaks corresponding to the incorporation of

Table II. Rates of Reaction of Alkenes in 20% EtOH–80% H_2SO_4 (25 °C)

Alkene	Registry no.	Equiv H^+, kg^{-1}[a]	H_0	k_{obsd}, s^{-1}
t-BuCH=CH-*t*-Bu (*Z*)[b]	692-47-7	11.3	−4.51	1.61×10^{-2}
		10.6	−3.95	2.67×10^{-3}
		10.0	−3.62	1.14×10^{-3}
		9.65	−3.39	4.92×10^{-4}
		10.9 (D_2SO_4)		4.31×10^{-3}
t-BuCH=CH-*t*-Bu (*E*)[c]	692-48-8	12.0	−5.07	1.93×10^{-2}
		11.3	−4.51	4.86×10^{-3}
		10.6	−3.95	6.61×10^{-4}
		10.0	−3.62	2.82×10^{-4}
		10.9 (D_2SO_4)		1.46×10^{-3}
		10.7 (D_2SO_4)		1.06×10^{-3}
i-PrCH=CH-*i*-Pr (*Z*)[d]	10557-44-5	11.3	−4.51	2.29×10^{-3}
		10.6	−3.95	4.61×10^{-4}
		10.3	−3.62	2.26×10^{-4}
		9.65	−3.39	1.19×10^{-4}
		10.9 (D_2SO_4)		1.16×10^{-3}
		10.2 (D_2SO_4)		2.94×10^{-4}
i-PrCH=CH-*i*-Pr (*E*)[e]	692-70-6	11.3	−4.51	5.64×10^{-3}
		10.6	−3.95	8.37×10^{-4}
		10.0	−3.62	4.96×10^{-4}
		9.65	−3.39	2.14×10^{-4}
		10.9 (D_2SO_4)		2.47×10^{-3}
		10.7 (D_2SO_4)		1.44×10^{-3}
EtCH=CHEt (*Z*)[f]		11.3	−4.51	1.23×10^{-2}
		10.6	−3.95	2.07×10^{-3}
		9.65	−3.39	7.11×10^{-4}
		9.08	−3.05	2.43×10^{-4}
		10.9 (D_2SO_4)		4.26×10^{-3}
		10.7 (D_2SO_4)		2.82×10^{-3}
EtCH=CHEt (*E*)[g]		11.3	−4.51	1.05×10^{-2}
		10.6	−3.95	1.94×10^{-3}
		9.65	−3.39	5.31×10^{-4}
		9.08	−3.05	2.06×10^{-4}
		10.9 (D_2SO_4)		4.15×10^{-3}
		10.7 (D_2SO_4)		2.51×10^{-3}

[a] Determined by titration. [b] $\log k = -1.33H_0 - 7.80$ ($r = 0.999$). [c] $\log k = -1.30H_0 - 8.26$ ($r = 0.997$). [d] $\log k = -1.13H_0 - 7.78$ ($r = 0.999$). [e] $\log k = -1.23H_0 - 7.83$ ($r = 0.992$). [f] $\log k = -1.13H_0 - 7.04$ ($r = 0.995$). [g] $\log k = -1.15H_0 - 7.20$ ($r = 0.999$).

Table III. Comparative Rates and Isotope Effects of Protonation of Alkenes RCH=CHR

R	k_{H^+}/k_{D^+}[a]		k_2[b]	
	Z	*E*	*Z*	*E*
Me	1.56	1.04	4.53×10^{-9}	4.48×10^{-9}
Et	1.14	1.06	1.10×10^{-8}	1.27×10^{-8}
i-Pr	0.92	0.96	2.77×10^{-9}	6.82×10^{-9}
t-Bu	1.47	1.05	1.95×10^{-8}	5.88×10^{-9}

[a] Average of all values in aqueous H_2SO_4 and in 20% EtOH–80% aqueous H_2SO_4 solutions calculated as k_{obsd} [HA]/k_{obsd} [DA] at the molarities of DA reported in Tables I and II using rates of HA interpolated to the same molarity. [b] $k_2 = k_{obsd}/h_0$ at $h_0 = 1$; rates not statistically corrected. For R = *i*-Pr and *t*-Bu rates are for aqueous H_2SO_4 solution estimated from the observed rates in 20% EtOH–80% H_2SO_4 by multiplying the rate ratio of the alkene to (*E*)-3-hexene at 11.3 equiv H^+ kg^{-1} in 20% EtOH by the k_2 value of (*E*)-3-hexene. At $H_0 = 0$ the average of the rates in H_2O–H_2SO_4 of the (*E*)- and (*Z*)-3-hexenes is 0.16 times the rates in 20% EtOH.

12–15 deuteriums is in accord with this conclusion. This result could occur by conversion of the initial *secondary* ion to a *tertiary* ion via k_4 and then rapid interconversion of *tertiary* ions via k_5–k_9 and their reversal. Some of **2** contained 16–19 atoms *D* and was thus approaching complete deuteration. This could occur by an occasional reformation of the *secondary* ion from the *tertiary* ion via k_{-4} followed by either deprotonation (k_{-1}) or hydride migration to give the isomeric *secondary* ion with the same carbon skeleton. Rapid conversion to a *tertiary* ion and complete equilibration of the hydrogens would then follow.

The rates of reaction suggest that several competing structural factors on reactivity are operative. The 3-hexenes tend to be more reactive than the 2-butenes, suggesting a greater electron donation by the ethyl groups relative to methyl. (*Z*)-1,2-Diisopropylethylene is distinctly the least reactive of the group, giving rise to the only $k(Z)/k(E)$ ratio less than 1.0. (*Z*)-1,2-Di-*tert*-butylethylene is the most reactive of the group, suggesting some relief in the transition state of the 10 kcal/mol steric strain[9] present in the ground state of this molecule. For RCH=CHOEt the *t*-Bu/Me rate ratio is 1.2 for the *Z* isomers and 0.6 for the *E* isomers, and the *Z*/*E* ratios are 7.1, 5.7, 3.8, and 3.2 for R = *t*-Bu, *i*-Pr, Et, and Me, respectively.[10a] Steric hindrance to solvation in the developing cation might have been expected to be a significant factor, as the solvation energy from interaction of solvent with the π cloud in (*E*)-1,2-di-*tert*-butylethylene has been found to be negligible for DMF solvent.[10b,c] However, in MeOH solvent steric hindrance does not appear to reduce the solvation energy.[10b,c] In the present case the change in solvation energy between the ground state and transition states is the significant quantity, and no major change between the different pairs is noticeable.

Correlation of the rates by the extended version of eq 2 used for 1,2-disubstituted alkenes[3c] is straightforward and these substrates fit the correlation within the limits previously established. Even for these crowded substrates an explicit term to account for ground state strain is unnecessary.

The most surprising feature of this work is the low $k(Z)/$

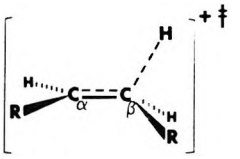
Table IV. Relative Reactivities ($k(Z)/k(E)$) of Isomeric Alkenes toward Various Electrophiles

Alkene	Electrophile				
	H_3O^+[a]	ArSCl[b]	$Hg(OAc)_2$	Br_2	Cl_2
t-BuCH=CH-*t*-Bu	3.8	1.58 × 10^5	>100[d]	51.9[e]	0.37[c]
i-PrCH=CH-*i*-Pr	0.50	9.7		0.42[c]	
EtCH=CHEt	1.2	9.2	6.2[f]	1.1[e,h]	
MeCH=CHMe	2.1	3.1	3.4[g]	1.3[e,h]	1.3[i]

[a] This work. [b] G. H. Schmid, C. L. Dean, and D. G. Garratt, *Can. J. Chem.*, **54**, 1253 (1976). [c] Reference 2d. [d] Reference 2b, and R. D. Bach and R. F. Richter, *Tetrahedron Lett.*, 4099 (1973). [e] K. Yates and R. S. McDonald, *J. Org. Chem.*, **38**, 2465 (1973), and ref 2c. [f] H. J. Bergman, G. Collin, G. Just, G. Müller-Hagen, and W. Pritzkow, *J. Prakt. Chem.*, **314**, 285 (1972). [g] J. Halpern and H. B. Tinker, *J. Am. Chem. Soc.*, **89**, 6427 (1967). [h] G. A. Olah and T. R. Hockswender, Jr., *J. Am. Chem. Soc.*, **96**, 3574 (1974); see also J. E. Dubois and G. Mouvier, *Bull. Soc. Chim. Fr.*, 1426 (1968). [i] M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 4285 (1965).

$k(E)$ ratio of only 3.8 for the 1,2-di-*tert*-butylethylenes. This ratio is much less than those observed for arylsulfenyl halide addition, bromination, or oxymercuration (Table IV) (reactions that we have concluded proceed through bridged intermediates for these but not all substrates).[11] It might well have been anticipated that protonation of the 1,2-di-*tert*-butylethylenes would have led to an even greater $k(Z)/k(E)$ ratio than for the reactions leading to bridged transition states. Thus formation of an open ion (Scheme I) might allow relief of a great deal of the 10 kcal/mol strain present in the *Z* isomer, particularly since alkene hydrations are proposed to have late transition states.[12]

The transition state model[13] below for this reaction may help to explain this result. During protonation there is probably little twisting around the central C–C bond as there is still significant double bond character remaining. The R group on C_β is depressed from the plane of the groups on C_α, but at the same time the decreasing C_α–C_β–R angle tends to minimize any movement of the R groups away from one another in the transition state. Only in the fully formed intermediate can significant rotation around the central C–C bond occur with concomitant reduction of the R–R repulsion.



As for the reactions involving bridged transition states we have suggested that steric approach control is the decisive rate-determining factor.[2a] Thus in the *E* isomer both sides of the molecule are blocked to attack of the electrophile, whereas in the *Z* isomer one side of the molecule is unhindered. This factor appears to be much less important in protonations, possibly due to a combination of lower steric requirement for the electrophile and because of a more open direction of approach.

Experimental Section

(*E*)- and (*Z*)-2-Butene were obtained from Matheson Gas Products and the isomeric 3-hexenes and 2,5-dimethyl-3-hexenes and (*E*)-2,2,5,5-tetramethyl-3-hexene were obtained from Chemical Samples Co. (*Z*)-2,2,5,5-Tetramethyl-3-hexene was obtained by hydrogenation of 2,2,5,5-tetramethyl-3-hexyne over Raney nickel.[9] Deuterated acids and solvents were obtained from Aldrich-Diaprep.

Kinetics were performed by injecting 10-μL samples of 0.3 M solutions of the alkenes in MeOH into 3 mL of the acid solution in 1-cm cells thermostated at 25 °C in a Cary 118 spectrophotometer and monitoring the decrease in absorbance at 197.5 nm. Solutions of 20% EtOH–80% H_2SO_4 were prepared as described.[4] Deuterated solutions were prepared by dilution of D_2SO_4 with D_2O or EtOD. Acid concentrations were measured by titration with standard NaOH and were converted to weight percentages using standard tables.[3,4] At least two runs were made at each acidity.

The product study of (*E*)-2,2,5,5-tetramethyl-3-hexene was carried out by heating 0.35 g (2.5 mmol) of the alkene in a mixture of 10 mL of dioxane and 5 mL of 14 M H_2SO_4 in a sealed ampule at 85 °C for 22 h. The mixture was then extracted with ether, washed with NaCl and $NaHCO_3$ solutions, and dried over Na_2CO_3. After evaporation of volatile solvent the residue was analyzed by gas chromatography using a 3 M × 10 mM 20% FFAP column at 120 °C and 60 mL/min He. The major product, retention time 15 min, showed a mass spectrum (70 eV) with peaks (rel heights) at *m/e* 140 (M^+, 10), 125 ($M^+ - CH_3$, 43), 97 (16), 84 (23), 83 ($M^+ - t$-Bu, 68), 82 (12), 71 (11), 70 (72), 69 (100), 37 (t-Bu^+, 40), and 55 (40) and NMR (CCl_4) δ 0.88 (s, 9, *t*-Bu), 1.68 (s, 9, 3 vinyl Me), and 2.00 (s, 2, CH_2-*t*-Bu) and was identified as 2,3,5,5-tetramethyl-2-hexene (**2**) by comparison of the NMR with that of an authentic sample.[6] Approximately 10% of the starting material was still present.

Treatment of the *Z* isomer under the same conditions led to a product mixture consisting of 90% of **2** and peaks in the gas chromatogram corresponding to 5% each of the (*Z*)- and (*E*)-2,2,5,5-tetramethyl-3-hexenes. Comparable results were obtained with either isomer when the dioxane was absent from the reactant mixture.

The *E* alkene (0.35 g, 2.5 mmol) was also heated with a mixture of 4 mL of 18 M D_2SO_4, 1 mL of D_2O, and 10 mL of dioxane for 2 h at 85 °C. After extraction the mixture was separated by gas chromatography as above and found to consist of about 75% starting material and 25% of the material with the same retention time as **2**. The mass spectrum (70 eV) of the former indicated the incorporation of 2% deuterium. The NMR of the latter corresponded to that of **2**, but the vinyl methyl and methylene absorptions had broadened and diminished in area by 80 and 72%, respectively, in their areas relative to the *t*-Bu peak in the undeuterated material. The mass spectrum (70 eV) showed peaks (rel heights) at *m/e* 160 (2), 159 (3), 158 (4), 157 (3), 156 (1), 151 (7), 150 (3), 149 (5), 148 (2), 136 (3), 135 (5), 134 (3), 96 (13), 95 (43), 94 (57), 93 (38), 92 (20), 91 (10), 78 (14), 77 (23), 76 (18), 75 (11), 74 (8), 66 (19), 65 (18), 62 (18), 61 (15), and 57 (100).

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Research Council of Canada for support of this research.

References and Notes

(1) For general reviews, see: (a) R. Bolton in "Comprehensive Chemical Kinetics", Vol. 9, C. H. Bamford and C. F. H. Tipper, Ed., Elsevier, New York, N.Y., 1973; (b) P. D. B. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems", Elsevier, Amsterdam, 1966; (c) G. H. Schmid and D. G. Garratt in "Chemistry of the Alkenes", Vol. 2, Supplement A, J. Zabicky, Ed., Wiley-Interscience, New York, N.Y., 1977; (d) T. Okuyama and T. Fueno, *Kagaku No Ryoiki*, **29**, 17 (1975).
(2) (a) C. L. Dean, D. G. Garratt, T. T. Tidwell, and G. H. Schmid, *J. Am. Chem. Soc.*, **96**, 4958 (1974); (b) R. D. Bach and R. F. Richter, *J. Org. Chem.*, **38**, 3442 (1973); (c) K. Yates and R. S. McDonald, *J. Am. Chem. Soc.*, **93**, 6297 (1971); (d) R. Fahey, *ibid.*, **88**, 4681 (1966); (e) H. H. Kung, R. J. Pellet, and R. L. Burwell, Jr., *ibid.*, **98**, 5603 (1976).
(3) Literature data are summarized in the references below, especially the last: (a) K. Oyama and T. T. Tidwell, *J. Am. Chem. Soc.*, **98**, 947 (1976); (b) W. K. Chwang, P. Knittel, K. M. Koshy, and T. T. Tidwell, *ibid.*, **99**, 3395 (1977); (c) S. Y. Attia, J. P. Berry, K. M. Koshy, Y.-K. Leung, E. P. Lyznicki, Jr., V. J. Nowlan, K. Oyama, and T. T. Tidwell, *ibid.*, **99**, 3401 (1977); (d) P. Knittel and T. T. Tidwell, *ibid.*, **99**, 3408 (1977); (e) W. K. Chwang, V. J. Nowlan, and T. T. Tidwell, *ibid.*, **99**, 7233 (1977); (f) V. J. Nowlan and T. T. Tidwell, *Acc. Chem. Res.*, **10**, 252 (1977).
(4) A. J. Kresge, and H. J. Chen, *J. Am. Chem. Soc.*, **94**, 8192 (1972).
(5) (a) K. Yates, G. H. Schmid, T. W. Regulski, D. G. Garratt, H.-W. Leung, and R. McDonald, *J. Am. Chem. Soc.*, **95**, 160 (1973); (b) G. Modena, F. Rivetti, G. Scorrano, and U. Tonellato, *ibid.*, **99**, 3392 (1977).
(6) J. E. Dubois, J. S. Lomas, and D. S. Sagatys, *Tetrahedron Lett.*, 1349 (1971); the identification of **2** was kindly confirmed by Dr. Lomas by a comparison of NMR spectra.
(7) D. J. Pasto, G. R. Meyer, and B. Lepeska, *J. Am. Chem. Soc.*, **96**, 1858 (1974).
(8) P. E. Peterson and G. Allen, *J. Org. Chem.*, **27**, 1505 (1962).
(9) R. B. Turner, D. E. Nettleton, Jr., and M. Perelman, *J. Am. Chem. Soc.*, **80**, 1430 (1958); W. H. Puterbaugh and M. S. Newman, *ibid.*, **81**, 1611 (1959).
(10) (a) T. Okuyama, T. Fueno, H. Nakatsuji, and J. Furukawa, *J. Am. Chem. Soc.*, **89**, 5826 (1967); (b) P. P. S. Saluja, T. M. Young, R. F. Rodewald, F. H.

Fuchs, D. Kohli, and R. Fuchs, *ibid.*, **99**, 2949 (1977); R. Fuchs and P. P. S. Saluja, *Can. J. Chem.*, **54**, 3857 (1976).
(11) (a) T. R. Cerksus, V. M. Csizmadia, G. H. Schmid, and T. T. Tidwell, *Can. J. Chem.*, **56**, 205 (1978); (b) G. H. Schmid and T. T. Tidwell, *J. Org. Chem.*, **43**, 460 (1978); (c) I. C. Ambidge, S. K. Dwight, C. Rynard, and T. T. Tidwell, *Can. J. Chem.*, **55**, 3086 (1977).
(12) Y. Chiang, A. J. Kresge, and J. R. Wiseman, *J. Am. Chem. Soc.*, **98**, 1564 (1976).
(13) For a summary of theoretical treatments of the alkene protonation transition state see ref 3e and 3f.

Reaction of Singlet Oxygen with 2-Methylnorbornadiene and 2-Methylidenenorbornene. Evaluation of Electronic and Steric Effects on the Course of Hydroperoxidation

Charles W. Jefford* and Christian G. Rimbault

Département de Chimie Organique, Université de Genève 30, 1211 Genève 4, Switzerland

Received August 30, 1977

The dye-sensitized photooxygenation of 2-methylnorborna-2,5-diene (**5**) and 2-methylidenenorborn-5-ene (**6**) has been studied. Olefin **5** gave the expected allylically rearranged exo and endo hydroperoxides in a ratio of 7.3:1. Olefin **6** gave the allylically rearranged hydroperoxide (98%) together with the exo and endo epoxides deriving from the methylidene function (2%). The rates of photooxygenation of **5** and **6** were compared with those obtained with 2-methylnorborn-2-ene (**1**), 2-methylidenenorbornane (**2**), 1-methylcyclopentene (**7**), and methylidenecyclopentane (**8**). The partial rates for oxygen attack on the exo faces of the bicyclic olefins were found to parallel the ionization potentials of the reacting double bonds. An interpretation of electronic and steric effects was made in terms of the formation of an activated complex arising from the interaction of the HOMO of the olefin with the LUMO of singlet oxygen.

Norbornene is a substrate par excellence for the study of the mechanism of reactions occurring at the double bond. Norbornene itself is slowly oxidized by singlet oxygen, but cannot give hydroperoxide in an ene-type reaction as the allylic carbon–hydrogen bond lies in the nodal plan of the double bond.[1] However, 2-methylnorbornene (**1**) and 2-methylidenenorbornane (**2**) react readily to give the allylic hydroperoxides.[2]

Compounds **1** and **2**, unlike simple olefins, only undergo the "ene" reaction in one direction. Furthermore, the approach of the oxygen molecule is differentiated by the exo and endo faces of the norbornyl skeleton. By studying rates of photooxygenation and product analyses of **1** and **2** together with their 7,7-dimethyl derivatives **3** and **4** (Table I) we discovered that, while the endo sides in the series **1**–**4** are really indistinguishable, the partial rates for the exo side varied significantly.[3]

The presence of methyl at C(7) depressed the rate of attack by oxygen much more at an internal than an external double bond. We concluded that steric hindrance in the ground-state structures is an important rate-determining factor for the hydroperoxidation reaction. We deduced that steric strictures operate in the formation of the carbon–oxygen bond, but not in the abstraction of the allylic hydrogen atom, and further that the former event precedes the latter. As a consequence the transition state should have dipolar character; partial negative charge would accumulate on the terminal oxygen atom counterbalancing positive charge dispersed hyperconjugatively over the allylic portion (Figure 1). There are two important corollaries, if this picture is correct. The first is that when steric and statistical differences are negligible for a pair of competing "ene" modes, then the products should be partitioned according to the relative importance of the Markownikoff effects. The second is that, as oxygen behaves as an electrophile, rates ought to be determined by the relative energies of the respective frontier orbitals.

In this paper we examine the validity of this second corollary by modifying the molecular orbital levels of the reacting olefin by introducing a second double bond, but which is essentially inert to singlet oxygen. The substrates chosen are

Scheme I

5 **9** **10**

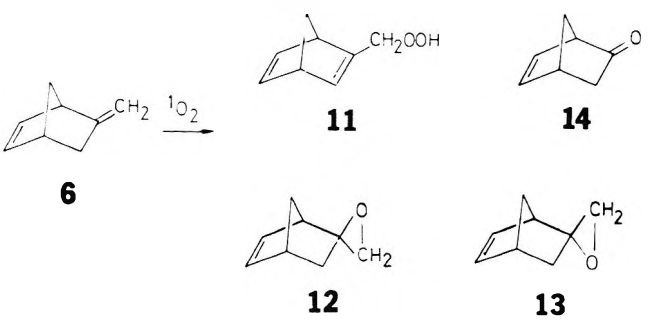
2-methylnorbornadiene (**5**) and 2-methylidenenorbornene (**6**). The kinetics and stereochemistry of the photooxygenation of **5** and **6** are compared with the monoolefinic parents **1** and **2** together with the monocyclic olefins, 2-methylcyclopentene (**7**) and 2-methylidenecyclopentane (**8**).

Results

Product Analyses. Photooxygenation of 2-methylnorbornadiene gave, after reduction with triphenylphosphine or sodium borohydride, a mixture of the expected exo and endo allylic alcohols **9** and **10** in a ratio of 7.33:1 in a yield of 88% (Scheme I).

2-Methylidenenorborn-5-ene (**6**) under similar conditions gave the expected hydroperoxymethyl derivative **11**. However, the *exo*- and *endo*-epoxides **12** and **13** were also obtained together with traces of norborn-2-en-2-one (**14**) (Scheme II). As the photooxygenation leading to primary products was slow, the reaction was stopped after 2% conversion of **6**; the relative percentages of the products so obtained were 98% (**11**), 0.2%

Scheme II



6 **11** **14** **12** **13**

0022-3263/78/1943-1908$01.00/0

Table I. Relative Rates of Photooxygenation of 2-Methylnorbornene, 2-Methylidenenorbornane, and Their 7,7-Dimethyl Derivatives

	1[a]	3[b]	2[c]	4[d]
k_{rel}(total)	40.0	1.0	13.0	3.4
k_{rel}(exo)	39.4	0.16	12.5	1.4
k_{rel}(endo)	0.6	0.84	0.5	2.0

[a] Registry no. 694-92-8. [b] Registry no. 514-14-7. [c] Registry no. 497-35-8. [d] Registry no. 471-84-1.

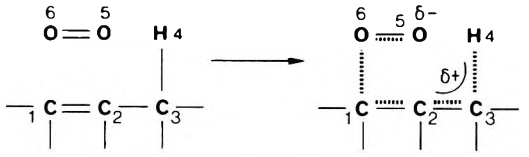
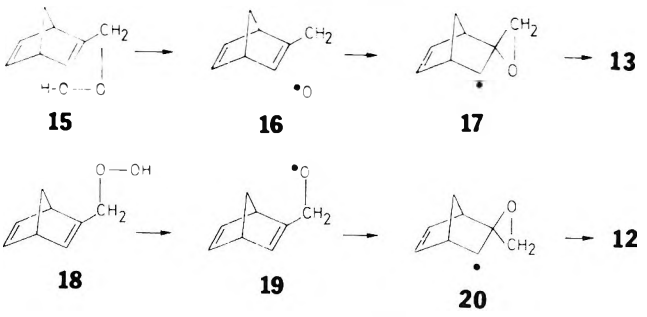


Figure 1. Creation of dipolar transition state leading to allylically rearranged hydroperoxide.

(12), and 1.8% (13). The assignment of structures to 12 and 13 was made by comparison with authentic samples prepared independently.[4]

No equilibration between 12 and 13 occurred under the conditions of gas-phase chromatography. Moreover, the ratio was invariant with the amount of 6 consumed and therefore it can be assumed that they arise from secondary reactions of hydroperoxide 11. This assumption was confirmed by irradiating 11 under nitrogen instead of oxygen. A mixture of the 13 and 12 epoxides was obtained in a ratio of 5.6:1. The predominance of the endo isomer (13) can be attributed to the preferred conformation of the hydroperoxide in which the hydroxy grouping points toward the endo side of the diene moiety (15). This conformation should be favored over others, e.g., 18, by virtue of intramolecular hydrogen bonding. Homolysis of the oxygen–oxygen bond in 15 will furnish the oxy radical 16 which on rapid closure gives the homoallylic radical 17, whence 13 (Scheme III). In similar fashion, the less favored

Scheme III



conformational isomer 18 generates the radicals 19 and 20, which furnish the *exo*-epoxide 12.

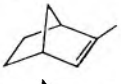
Kinetics. The total rates of photooxygenation of the six olefins were determined by measuring the disappearance of substrate. For the purposes of comparison, rates were partitioned into relative rates for exo and endo attack. As the products resulted from kinetic control, the exo/endo isomer ratio gives the partial rates directly. The exo/endo ratio for 6 was estimated by assuming that the proportionality which pertains to the pair of olefins 1 and 2 also holds for the pair 5 and 6 (Table II).

Discussion

On inspecting Table II, it is seen that the monocyclic olefins react faster than their bicyclic counterparts. There also appears to be an inconsistency for the bicyclic partners. On going from the norbornene 1 to the norbornadiene 5, the rate increases some 2.5 times, whereas on passing from the norbornane 2 to the norbornene 6 the rate actually decreases fourfold. These different rates can be usefully analyzed by considering the frontier orbitals of the reactants.

The approach of the singlet oxygen molecule to the olefin will result in a mutual perturbation of the appropriate frontier orbitals.[6,7] Two limiting approaches may be considered. In the first, the whole allylic fragment is attacked by both ends of the oxygen molecule; an ene-type mechanism operates and the hydroperoxide is formed with allylic shift (Figure 2a). In the second, the oxygen molecule adds end-on to the double bond creating a perepoxide, which subsequently rearranges to the allylic hydroperoxide (Figure 2b). Since oxygen is an electrophile, the dominant interaction will be that between the lowest unoccupied molecular orbital (LUMO) of oxygen and

Table II. Relative Rates of Photooxygenation of Some Cyclic Monoolefins Together with Their Ionization Potentials

No.	Substrate	Registry no.	Exo/endo isomer ratio	k_{rel} (total)	k_{rel} (exo)	k_{rel} (endo)	k_{rel} (exo′)	ln k_{rel} (exo′)	IP, eV
6		694-91-7	3.0[a]	1	0.75	0.25	1	0	9.31[c]
2			28[b]	4.3	4.15	0.15	5.5	1.7	9.02[c]
8		1528-30-9	1	15.5	7.75	7.75	10.3	2.33	9.15[d]
1			66[b]	13.5	13.3	0.2	17.7	2.87	8.57[e]
5		5235-55-2	7.3	34.0	30	4	40.0	3.69	8.42[e]
7		693-89-0	1	507	253	253	338	5.82	8.55[d]

[a] By extrapolation, see text. [b] Obtained from ref 1 and 3. [c] Obtained from ref 5. [d] See ref 23. [e] Determined by E. Haselbach (University of Basel).

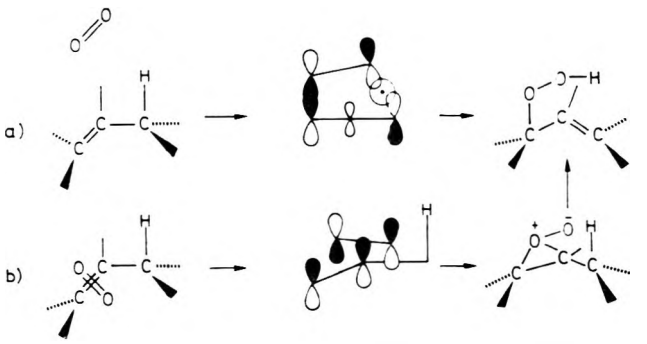


Figure 2. Alternative transition states leading to allylic hydroperoxidation. (a) The concerted ene reaction. (b) Cheletropic reaction generating transient perepoxide.

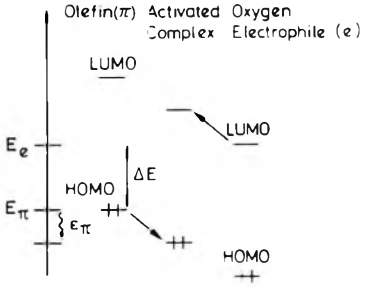


Figure 3. Interaction of the HOMO of the olefin with the LUMO of singlet oxygen to form the activated complex.

the highest occupied molecular orbital (HOMO) of the allylic or, to simplify matters, the double bond portions respectively (Figures 2a and 2b).[3-10]

The stabilization (ϵ_π) attained on forming the activated complex will be a linear measure of the rate of reaction.

$$\text{rate} = f(\epsilon_\pi),\ \epsilon_\pi = -\mathcal{H}^2/\Delta E$$

Moreover, the extent of the lowering of the HOMO level (ϵ_π) of the olefin is determined by the closeness of the energy gap (ΔE) existing between the respective orbitals of the olefin (E_π) and oxygen (E_e) before interaction (Figure 3). The numerator of the perturbation expression also shows that the size of the stabilization depends on the square of the hamiltonian ($\mathcal{H}$), namely on the matching of symmetries and the overlap capabilities of the interacting orbitals. For practical purposes, ionization potentials (IP) and electron affinities (EA) can represent the energies of the HOMO and LUMO levels, respectively.[11,12]

$$\text{rate} \propto \mathcal{H}^2/[\text{IP}_{\text{HOMO}} - \text{EA}_{\text{LUMO}}] \qquad (1)$$

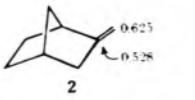
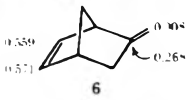
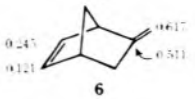
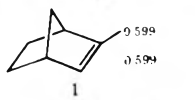
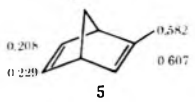
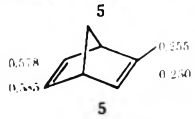
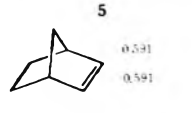
As oxygen is used throughout, the value of its electron affinity is not needed. Assuming that the numerator of eq 1 is constant for a series of olefins, their ionization potentials should constitute a reliable index of their rates of photooxygenation. As we shall see later, the application of this empirical expression furnishes information on electronic and steric effects.

For the bicyclic dienes, a sizable splitting exists between the pairs of ionization potentials, 0.38 eV for **6** and 0.68 eV for **5**, indicating a strong interaction between the homoconjugated orbitals.[13] Although the systems themselves are not appreciably stabilized, the reactivity of the allylic double bonds is significantly altered. When two doubly occupied molecular orbitals interact, the lower-lying level is stabilized while the higher is destabilized, the effect being greater the closer the levels in energy.[14] Accordingly, the experimental ionization potentials can be assigned to each of the homoconjugated double bonds (π_A and π_B) (Table III). Since it is only the allylic fragment (which contains π_B) which can react, the frontier orbital implicated in the reaction will be the HOMO for **5**, but the next HOMO for **6**. For the bicyclic series the denominator of eq 1 is a minimum for **5** and a maximum for **6**, so that the reactivity rates (k) should increase in the order

$$k_6 < k_2 < k_1 < k_5$$

which is in fact the case.

Table III. Ionization Potentials and Electron Densities of Norbornane-Type Olefins

Olefin		Electron density[a] π_A	Electron density[a] π_B	IP obsd, eV
 2	HOMO		1.33	9.02
 6	HOMO	1.28	0.14	8.93
 6	Next HOMO	0.15	1.28	9.31
 1	HOMO		1.40	8.57
 5	HOMO	0.19	1.41	8.42
 5	Next HOMO	1.35	0.23	9.10
	HOMO		1.40	8.97[b]

[a] Calculated by MINDO/3. [b] Reference 14a.

Strictly speaking, the numerator also affects the rate; however, MINDO/3 calculations indicate, notwithstanding their drawbacks, that the electron densities in the π_B part are relatively unchanged for the pairs **1/5** and **2/6** (Table III). The calculations are less than satisfactory for the IP's, but this is less important, as the experimental values are available. Therefore, for each pair, the numerator of eq 1 remains the same.

Nevertheless, discrepancies in the rates still remain. The sequence of ionization potentials certainly parallels the rates found for the bicyclic olefins, but for a constant IP the methylidene derivatives react faster than their endocyclic isomers. Moreover, the monocyclic reference compounds react even faster still, much more so than their ionization potentials would indicate. A way of reconciling these differences is to assume that the simplest structures, the references **7** and **8**, are reacting normally and that photooxygenation of the bicyclic olefins is sterically retarded.

A semiquantitative measure of steric effects is obtainable by plotting the logarithm of rates against ionization potentials, or rather the logarithms of the exo partial rates, assuming the exo faces of the substrates to have more in common topographically than the endo faces. If it is assumed that for each pair of olefins (**7/8, 2/6,** and **1/5**) the exo steric environment is the same, then three parallel straight lines are obtained (Figure 4). Olefins **7** and **8** are conformationally mobile and thus the fit of both partners in the activated complex is as good as it can be. However, on passing to the rigid methylidene derivatives, **2/6,** approaching oxygen now experiences hindrance by the C(7) syn hydrogen atom (Figure 5); the fit is less good and

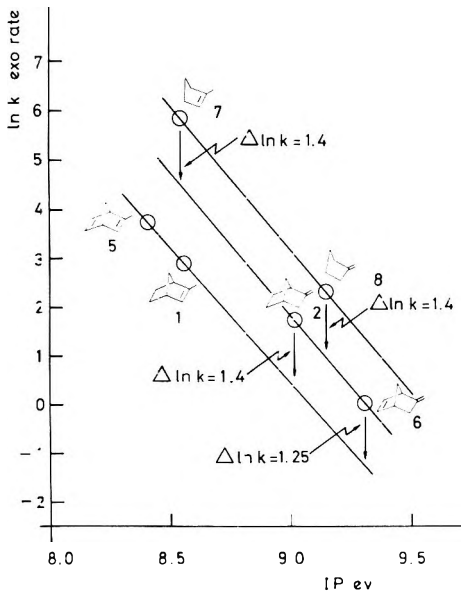


Figure 4. Correlation of the rate of exo photooxygenation with the ionization potential of the reacting double bond (π_B) for some cyclic and bicyclic olefins.

Figure 5. Different steric impediments due to the C(7) *syn*-hydrogen atom experienced by oxygen approaching (a) the midpoint of an external double bond and (b) an internal double bond in the norbornane-type skeleton.

the depression in rate of $\Delta \ln k \sim 1.4$ is about the same for both. If the oxygen is obliged to insert itself deeper into the bicyclic skeleton (Figure 5), as is the case for the pair of norbornenes **1**/**5**, the extra hindrance arising from the C(7) hydrogen atom occasions a further slowing in rate of about $\Delta \ln K \sim 1.25$–1.4. This steric trend is corroborated by the exo/endo ratios found for the epoxidation of methylidenenorbornane and norbornene, viz. 6.7 and 200, respectively.[15]

Conclusion

This study shows that hydroperoxidation of an olefin by singlet oxygen is well described as a typical electrophilic reaction, the rate of which is controlled by the HOMO of the active double bond. To a first approximation the rate of photooxygenation is inversely proportional to the ionization potential of the double bond. For a series of olefins, any deviations from the predicted rate can be ascribed to the operation of steric effects. Although the model was based on an activated complex leading to perepoxide, the use of an ene-type transition state would entail similar electronic and steric arguments leading to the same conclusions.[24]

Experimental Section

General. The details of the chromatographic, spectroscopic, and photooxygenation procedures as well as the preparation of 2-methylnorbornene (**1**) and 2-methylidenenorbornane (**2**) have already been described.[3]

Olefins. 1-Methylcyclopentene (**7**) was purchased from Fluka, Buchs. Methylidenecyclopentane (**8**) was prepared by the Wittig reaction.[16] **2-Methylidenenorborn-5-ene (6).** The commercial product (purchased from Aldrich Chemical Co.) was rid of minor quantities (~5%) of its isomer **5** by GLC at 100 °C (5% FFAP on Chromosorb G). **2-Methylnorborna-2,5-diene (5).**[25] A solution of 18.4 g of freshly distilled and degassed norborna-2,5-diene (0.2 mol) in 50 mL of ether was added to 20.8 g of *N*-butyllithium (0.3–5 mol) in 250 mL of ether at 0 °C.[17] After stirring overnight, the violet-colored solution was added slowly under nitrogen to 60 g of methyl iodide (0.42 mol) in dry ether at −78 °C. The temperature was allowed to rise to 25 °C over 1 h and the solution was poured into ice–water. The organic layer was separated, washed, dried, and evaporated. Fractional distillation followed by preparative GLC (20% Apiezon on Chromosorb W) gave 3.8 g of **6** (18% yield): NMR (CCl_4) δ 1.85 (d, 3 H), 1.95 (m, 2 H), 3.2 (m, 1 H), 3.5 (m, 1 H), 6.1 (m, 1 H), 6.8 (m, 2 H); MS (*m/e*) 106 (M^+, 79), 105 (58), 91 (100), 91 (100), 66 (53).

Photooxygenations. Determination of Relative Rates (Table II). The competition method, based on the disappearance of olefin, requires no calibration since only ratios of concentrations are measured.[18] Moreover, the products are often unstable under GLC conditions, whereas the olefins are quite stable. A pair of olefins of roughly similar reactivity is dissolved in a standard solution of acetonitrile containing methylene blue. An inert standard is also added. Typically the mixture consists of ~1 mmol of each olefin and 0.5 mmol of benzene in 2 mL of solvent. The solution is then placed in the reaction vessel under oxygen, irradiated, and stirred to 0 °C.[19] Small samples are taken at regular intervals and analyzed by GLC. Oxygen uptake is measured volumetrically. For a competition reaction between two olefins, A and B, the rate (k) can be expressed as follows:

$$A + O_2 \xrightarrow{k_A} AO_2$$

$$B + O_2 \xrightarrow{k_B} BO_2$$

If the oxygen concentration is constant then $k_A/k_B = \ln (A_0/A_t)/\ln (B_0/A_t)$ where A_0 and B_0 are the starting concentrations and A_t and B_t are the concentrations after time t.

Product Analyses. 2-Methylnorborna-2,5-diene (5). A solution of 0.48 g of **5** in 3 mL of acetonitrile (plus methylene blue) under an atmosphere of oxygen was irradiated at 0 °C until 95% reaction. Reduction was effected with sodium borohydride in methanol, giving 0.493 g of crude product which was purified by GLC (20% on Chromosorb W). The exo and endo allylic alcohols **9** and **10** were obtained in a ratio of 7.3:1 in a 72% yield. The distinction between **9** and **10** was made by NMR spectroscopy. Isomer **9** shows a W-type coupling between the anti C(7) and endo C(3) protons which is absent in isomer **10**.[20] The exo and endo dispositions of the hydroxyl groups were further confirmed by using shift reagent.

Exo Isomer (9):[28] NMR ($CDCl_3$) δ 1.74 (d of t of d, 1 H), 1.9 (d of t of t, 1 H) [C(7) anti and C(7) syn, $^3J_{7\epsilon,1}$ = 1.5 Hz, $^4J_{7a,3}$ = 1.5 Hz, $^2J_{7a,7s}$ = 9.0 Hz], 2.8 (m, 1 H), 3.12 (m, 1 H), 4.02 (m, 1 H), 4.98 (s, 1 H), 6.06 (d, 1 H); IR (film) 3500–3200, 3065, 2980, 1320, 1100, 1039, 890, 760, 720 cm^{-1}.

Endo Isomer (10): NMR ($CDCl_3$) δ 1.48 (d of t, 1 H), 1.72 (d of t of t, 1 H) [C(7) anti and C(7) syn, $^3J_{7a,1}$ = 1.8 Hz, $^3J_{7s,1}$ = 1.5 Hz, $^2J_{7a,7s}$ = 9.0 Hz]. 3.04 (m, 1 H), 3.16 (m, 1 H), 4.56 (m, 1 H), 5 and 5.06 (two s, 2 H), 6.14 and 6.40 (d of d, 2 H).

2-Methylidenenorborn-5-ene (6). Olefin **6** (0.6 g, 5.6 mmol) in 3 mL of acetonitrile was irradiated for 2 h at 0 °C. After 80% absorption of 1 equiv of oxygen, the solvent was evaporated and the residue extracted with pentane. After further evaporation, column chromatography over silica gel (eluting with pentane/ether) effected removal of olefin **6** (15 mg). Subsequent thin-layer chromatography (silica gel, eluting with hexane/ether) gave exo-epoxide **12** (R_f 0.409, traces), *endo*-epoxide **13** (R_f 0.337, 15 mg), norbornenone **14** (R_f 0.313, traces), and lastly hydroperoxide **11** (R_f 0.297, 85 mg). After a 2% conversion of olefin **6** the percentage ratios of products were 0.2, 1.8, ~0.1, and 98%.

1-Hydroperoxymethylnorborna-2,5-diene (11): NMR ($CDCl_3$) δ 2.1 (s, 1 H), 3.3 (m, 2 H), 4.7 (d, 1 H), 6.75 (m, 1 H), 6.9 (m, 2 H), 8.25 (s, 1H); IR (CCl_4) 3540 (m), 1675 (m), 1260 (w) cm^{-1}, MS (*m/e*) 138 (M^+, 0.85), 120 (13), 91 (40), 66 (29), 18 (100). Treatment of **11** with triphenylphosphine in ether gave the corresponding alcohol. It was purified by chromatography over silica gel and identified by comparison with an authentic sample.[21]

Epoxides 12 and 13. These were identified with authentic samples.[4]

Norborn-5-en-2-one (14). This was identified by oxidizing 2-hydroxynorborn-5-ene.[22]

Acknowledgments. We thank the Swiss National Science Foundation for support of this work (Grant No. 2.238.0.74). We thank J. C. Perlberger for carrying out the MINDO/3 calculations.

Registry No.—**9**, 56682-78-1; **10**, 65102-12-7; **11**, 65102-13-8.

References and Notes

(1) C. W. Jefford and A. F. Boschung, *Helv. Chim. Acta*, **57**, 2257 (1974).
(2) C. W. Jefford, M. H. Laffer, and A. F. Boschung, *J. Am. Chem. Soc.*, **94**, 8904 (1972).
(3) C. W. Jefford and A. F. Boschung, *Helv. Chim. Acta*, **57**, 2242 (1974).
(4) R. S. Bly, C. M. du Bose, Jr., and G. B. Konizer, *J. Org. Chem.*, **33**, 2188 (1968).
(5) S. A. Cowling, R. A. W. Johnstone, A. A. Gorman, and P. G. Smith, *Chem. Commun.*, 627 (1973).
(6) R. F. Hudson, *Angew. Chem.*, **85**, 63 (1973); K. Fukui, *Bull. Chem. Soc. Jpn.*, **39**, 498 (1966); W. C. Herndon, *Chem. Rev.*, **72**, 157 (1972); E. Heilbronner and H. Bock, "Das HMO-Modell und seine Anwendung", Verlag Chemie Weinheim, Bergstrasse, 1968; M. J. S. Dewar, *Angew. Chem., Int. Ed. Engl.*, **10**, 761 (1971).
(7) G. Klopman, Ed., "Chemical Reactivity and Reaction Paths", Wiley-Interscience, New York, N.Y., 1974.
(8) S. Inagaki and K. Fukui, *Bull Chem Soc. Jpn.*, **46**, 2240 (1973); K. Fukui, *Acc. Chem. Res.*, **4**, 57 (1971).
(9) H. R. Pfaendler, H. Tanida, and E. Haselbach, *Helv. Chim. Acta*, **57**, 383 (1974).
(10) S. Inagaki, S. Yamabe, H. Fujimoto, and K. Fukui, *Bull. Chem. Soc. Jpn.*, **45**, 3510 (1972).
(11) R. Sustmann, *Pure Appl. Chem.*, **40**, 569 (1975).
(12) K. Houk, *Acc. Chem. Res.*, **8**, 361 (1975).
(13) R. Hoffmann, *Acc. Chem. Res.*, **4**, 1 (1971).
(14) P. Bischof, J. A. Hashmall, E. Heilbronner, and V. Hornung, *Helv. Chim. Acta*, **52**, 1745 (1969); E. Heilbronner and H. D. Martin, *ibid.*, **55**, 1490 (1972); M. J. S. Dewar and J. S. Wasson, *J. Am. Chem. Soc.*, **92**, 3506 (1970); E. Haselbach, E. Heilbronner, and G. Schröder, *Helv. Chim. Acta*, **54**, 153 (1971); D. Chadwick, D. C. Frost, and L. Weiler, *J. Am. Chem. Soc.*, **93**, 4962 (1971); P. Bruckmann and M. Kiessinger, *Angew. Chem., Int. Ed. Engl.*, **11**, 524 (1972).
(15) H. C. Brown, J. H. Kawakami, and S. Ikegami, *J. Am. Chem. Soc.*, **92**, 6914 (1970).
(16) J. M. Conia and J. C. Limasset, *Bull. Soc. Chim. Fr.*, **6**, 1936 (1967).
(17) R. G. Jones, *Org. React.*, **6**, 352 (1951).
(18) K. R. Kopecky and H. J. Reich, *Can. J. Chem.*, **43**, 2265 (1965).
(19) A. I. M. Keulemans, "Gas Chromatography", Vol. 32, Reinhold, New York, N.Y., 1957.
(20) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964); C. W. Jefford and W. Wojnarowsky, *Helv. Chim. Acta*, **53**, 1194 (1970).
(21) An authentic sample has been prepared by reduction of 2-aldehydo-2,5-norbornadiene with lithium aluminum hydride. Spectral data were in complete agreement with those reported (cf. ref 29).
(22) S. J. Cristol and P. K. Freeman, *J. Am. Chem. Soc.*, **83**, 4427 (1961).
(23) F. Freeman, *Chem. Rev.*, **75**, 439 (1975).
(24) For similar conclusions, see: L. A. Paquette, D.C. Liotta, C. C. Liao, T. G. Wallis, N. Eickman, J. Clardy, and R. Gleiter, *J. Am. Chem. Soc.*, **98**, 6413 (1976); L. A. Paquette, D. C. Liotta, and A. D. Baker, *Tetrahedron Lett.*, 2681 (1976).
(25) The reported synthesis was realized according to the method of M. J. Maskornick, E. I. Du Pont de Nemours & Co., private communication, 1973. This diene has also been prepared by cycloaddition of acetylene and methylcyclopentadiene (cf. ref 25) or between propyne and cyclopentadiene (cf. ref 27).
(26) J. Hyman, E. Freireich, and R. E. Lidov (to Shell Development Company), U.S. Patent 2 875 256; *Chem. Abstr.*, **53**, 13082d (1959).
(27) C. A. Cohen, French Patent 1 478 766 (1967); *Chem. Abstr.*, **68**, 12554a (1968).
(28) Spectral data for allylic alcohol 9 are in complete agreement with those reported (cf. ref 29).
(29) I. Tabushi, K. Yamamura, and J. Ueda, *J. Am. Chem. Soc.*, **97**, 4039 (1975).

Oxidation of a Bicyclobutane-Bridged Diene with $^1O_2$ and O_3. Wittig Reactions of the Corresponding Enone and Dione

R. F. Heldeweg, H. Hogeveen,* and E. P. Schudde

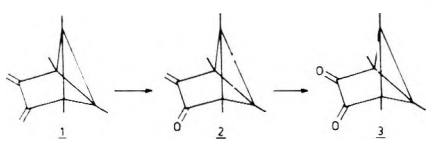
Department of Organic Chemistry, University of Groningen, Groningen, The Netherlands

Received June 13, 1977

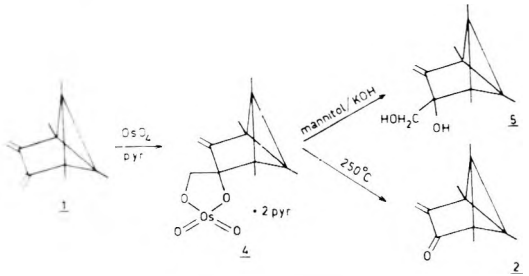
Oxidation of 1,2,5,6-tetramethyl-3,4-dimethylenetricyclo[3.1.0.0^{2,6}]hexane upon treatment with OsO_4, $^1O_2$, and O_3 is reported. The corresponding bicyclobutane-bridged α,β-unsaturated ketone and α-diketone are used as starting materials in Wittig reactions, which in one case result in cyclopropane formation.

Oxidation of organic compounds constitutes a subject with numerous ramifications.[1-5] Hydrocarbon oxidation using transition-metal compounds, peracids, and peroxides together with photosensitized oxygenations and ozonization rank among the frequently employed methods in this area in which phase-transfer catalysis[6] and crown ether chemistry[7] are of increasing importance.

In view of the intriguing reactivity of tricyclic diene 1,[8,9] e.g., in Diels–Alder reactions, we aimed at synthesizing the corresponding enone **2** and diketone **3** from **1**. Two types of ketone preparation involving carbon–carbon bond breaking, one-step and two-step cleavage reactions, are opportune. Apart from realization of the diene → enone → dione transformations, attention has to be paid to keep the bicyclobutane moiety intact. Generally speaking this leaves out the modes of oxidation which involve the use of acids and those in which the presence of certain transition metals is required. In the present paper the results of some oxidation reactions (e.g., O_3, $^1O_2$) of compound **1** are described, together with those of the Wittig reactions of enone **2** and dione **3**.



Oxidation of 1. A. Osmium Tetroxide. The highly poisonous osmium tetroxide can be employed to convert olefins to glycols or ketones, depending upon reaction conditions; the initially formed adducts in many cases are of sufficient stability to permit their isolation.[10,11] Upon addition of osmium tetroxide at room temperature to diene **1** in ether containing pyridine (10:1), a brown precipitate was formed immediately. To this compound structure **4** is tentatively assigned. Supporting data for the proposed structure were obtained by performing a reductive cleavage of **4** by mannitol in an alkaline solution, leading to glycol **5**, and a pyrolysis at 250 °C, affording α,β-unsaturated ketone **2**, which was trapped at −196 °C. However, this expensive route did not allow a large scale preparation of **2** and was abandoned for this reason.

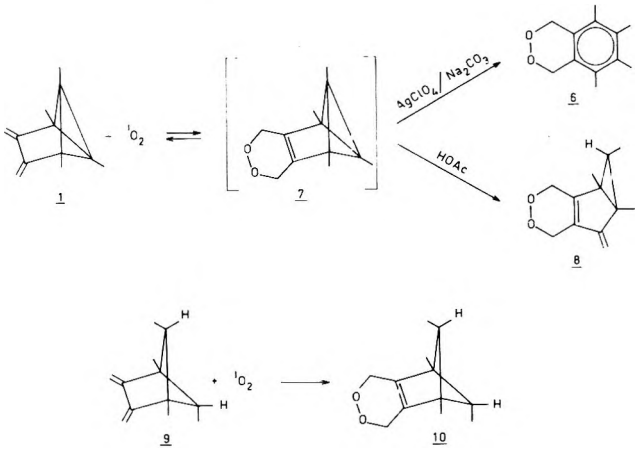


B. Singlet Oxygen. Rearrangements of [2 + 4] adducts from singlet oxygen ($^1O_2$) and conjugated dienes[12] to α,β-unsaturated [2 + 2] adducts are known in the literature.[13-15]

0022-3263/78/1943-1912$01.00/0

Furthermore, fragmentation of dioxetanes is a common process.[16,17] In view of these data, singlet oxygen addition to diene **1** was investigated. However, no reaction between $^1O_2$ and **1** was observed at room temperature ($^1O_2$ was generated in a methylene blue sensitized reaction). When this experiment was repeated after addition of a catalytic amount of silver perchlorate together with sodium carbonate to the methylene chloride solution, diene **1** was rapidly converted to peroxide **6**.[18,19] Because of the fact that $AgClO_4/Na_2CO_3$ was not found to accelerate the addition of $^1O_2$ to other conjugated dienes (cyclohexadiene and **9**), the smooth formation of aromatic compound **6** may indicate that a benzvalene (**7**) participates in an equilibrium which exists under the prevailing experimental conditions. Since it has been reported[20] that, apart from their behavior towards $AgClO_4/Na_2CO_3$, benzvalenes are extremely sensitive to acids, $AgClO_4/Na_2CO_3$ was replaced by acetic acid (20 mol %) in another $^1O_2$ experiment. As expected,[20] a homofulvene (**8**) could be isolated in this case, which reinforces the idea of a preequilibrium in the singlet oxygen reaction. The hope of being able to prove this experimentally by performing the reaction of **1** with $^1O_2$ at −70 °C and running the ^1H NMR spectra of the sample at the same temperature was not fulfilled, however.

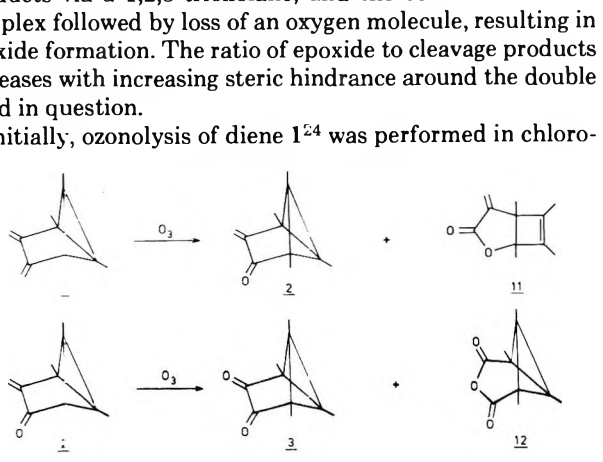
It is of interest to note that bicyclic diene **9** does react with



$^1O_2$ at room temperature, leading to **10**.[21] Although the observed difference[22] between **1** and **9** is intriguing, no progress was made in this approach as far as the synthesis of **2** and **3** is concerned.

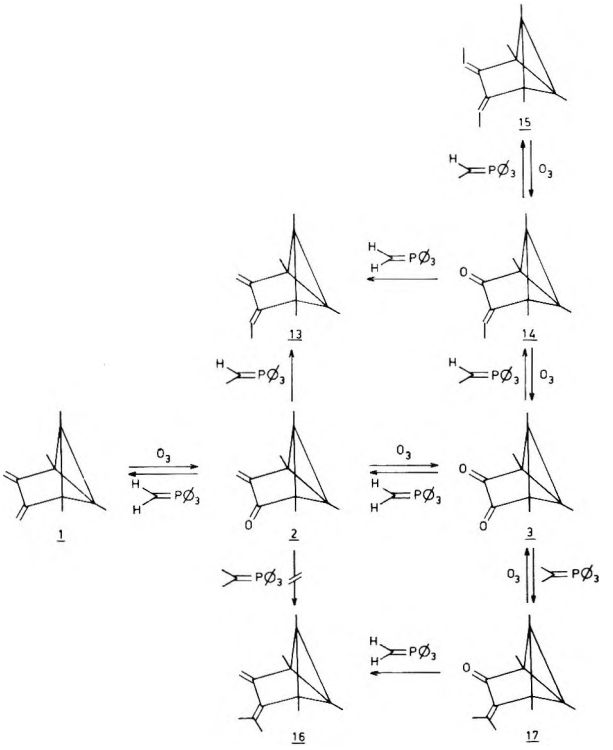
C. Ozonolysis. In a third attempt to convert **1** to **2** and subsequently to **3**, we made use of O_3. There are reasons to assume that the initial interaction between a carbon π system and ozone leads to the reversible formation of a π complex,[23] the fate of which depends on the character of the organic substrate. The possibilities are in principle the entrance into a 1,3-dipolar cycloaddition, leading ultimately to ozonolysis products via a 1,2,3-trioxolane, and the conversion to a σ complex followed by loss of an oxygen molecule, resulting in epoxide formation. The ratio of epoxide to cleavage products increases with increasing steric hindrance around the double bond in question.

Initially, ozonolysis of diene **1**[24] was performed in chloroform at room temperature. Ozone was added until no ^1H NMR signals due to olefinic protons of the diene could be observed anymore. Two products were formed in a 1:4 ratio and identified as the α,β-unsaturated ketone **2** and the rearranged ester **11**, respectively. When the ozonolysis was carried out in the presence of Na_2CO_3 or pyridine, the product ratio changed to 1:1 in the former and 4:1 in the latter case. Ozonolysis of ketone **2** under similar conditions in chloroform containing pyridine was performed: again two products were isolated from the reaction mixture, the α-diketone **3**[25] and the anhydride **12**, which were formed in a 9:2 ratio. Bicyclic diene **9** reacts with ozone in a different manner: epoxides are formed exclusively.[21] Data provided by Story and Burgess[28] support the idea that most abnormal ozonolysis products are in fact normal Baeyer–Villiger products generated by the action of the peracid formed in the reaction. Actually, in our case the *m*-chloroperbenzoic acid oxidation of **2** leads to **11** and that of **3** to **12**. Thereupon, more detailed investigations led to the conclusion that both **2** and **3** can be made the sole identifiable products in their respective reaction steps: the former by performing the reaction at low temperatures in methylene chloride and pyridine, and the latter by performing the ozonolysis of **2** in methanol at room temperature followed by addition of dimethyl sulfide.[29] Of course, the Baeyer–Villiger reactions mentioned earlier make it possible to synthesize exclusively both **11**[30] and **12**.



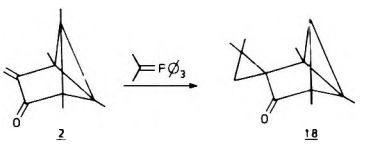
Wittig Reactions of 2 and 3. Investigations concerning the chemical aspects of diene **1**[18,19,32] made it desirable to have a route to substituted dienes at one's disposal. Of course, both enone **2** and dione **3** can in principle take part in Wittig reactions. Experiments performed in this area are jointly represented in Scheme I. The reaction between enone **2** and iso-

Scheme I

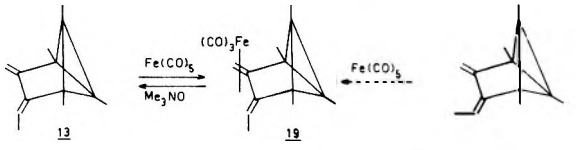


propylidenetriphenylphosphorane took an unexpected course: instead of the corresponding diene **16**, a cyclopropane-containing product (**18**) was isolated. The formation of a cyclopropane derivative has been reported by Freeman[33] in the reaction between methylidenetriphenylphosphorane and mesitoylphenylethylene, in which attack at the carbonyl carbon is sterically hindered. However, steric effects alone are not enough as a motive for cyclopropane formation in our case

since **17** could be prepared in high yield from **3**, in which case the ylide was given no alternative. Hence, as to be expected,



steric and electronic aspects of both reactants affect the outcome of the reaction. On the basis of the observed mode of attack of **2** by isopropylidenetriphenylphosphorane, one may wonder whether in **13** and **14** the methyl substituent is in a syn or anti position. Addition of successive portions of $Eu(fod)_3$ gave rise to ^1H NMR shift enhancements which indicate the substituent to be in a syn position in **14**. A second method to solve syn–anti problems in conjugated dienes rests on the principle of complexation[34] followed by decomplexation:[35] the fact that **13** as a starting material proved to be identical with the diene obtained by oxidation of **19** is in agreement with the



presence of a syn-methyl group in **13** (the synthesis and chemical aspects of the iron tricarbonyl complex of **1** have been reported[36]).

Experimental Section

General Remarks. Melting points are uncorrected. Mass spectra were run on a AEI MS-902. Infrared spectra (Nujol mull) were recorded on a Perkin-Elmer Infracord 257 spectrophotometer. ^1H NMR spectra were taken with a Jeol C-60 HL spectrometer with deuteriochloroform as the solvent and Me_4Si as an internal reference. ^{13}C NMR spectra were run on a Varian XL-100 with deuteriochloroform as the solvent and Me_4Si as an internal reference. Preparative TLC was performed with aluminium oxide (Merck; 10–40 μm, not activated).

OsO_4 Addition to 1. To a solution of diene **1** (0.160 g, 1.00 mmol) in ether (10 mL) and pyridine (1.0 mL) was added OsO_4 (0.254 g, 1.00 mmol) while stirring at room temperature. A brown precipitate was formed immediately, which in part was filtered. This solid material (0.217 g) was heated at 250 °C under reduced pressure (1.0 mm) for 10 min, and both enone **2** (22 mg) and pyridine (49 mg) were trapped at −196 °C. Spectroscopic data of **2** were identical with those of material obtained from ozonolysis of **1**.

Mannitol (1.0 g) and aqueous potassium hydroxide (10%, 10 mL) were added to the remaining suspension, and the mixture was stirred overnight at room temperature. The aqueous layer was extracted with methylene chloride (3 × 5 mL), and the combined organic layers were subsequently dried over anhydrous potassium carbonate. Evaporation of the solvent under reduced pressure followed by preparative TLC (methylene chloride) afforded **5** as a colorless viscous oil (58 mg, 0.30 mmol): ^1H NMR δ 1.09 (s, 3 H), 1.11 (s, 3 H), 1.31 (s, 3 H), 1.35 (s, 3 H), 3.54 (broad s, 2 H), 4.67 (s, 1 H), and 4.87 (s, 1 H); IR 1650 and 3400 (broad) cm^{-1}; MS Calcd exact mass, *m/e* 194.131 (M^+); MS Found, *m/e* 194.135. When pyridine was omitted no **5** could be obtained.

$^1O_2$ Addition to Diene 1. A solution of diene **1** (1.60 g, 10.0 mmol) and methylene blue (50 mg) in methylene chloride (150 mL) continuously saturated with oxygen was irradiated at room temperature for 48 h with a high-pressure mercury arc (Hanau S81) using a saturated aqueous solution of potassium bichromate as a filter. Diene **1** was completely recovered upon filtration through Al_2O_3 followed by evaporation of the solvent. When the reaction was carried out at −70 °C no spectroscopic indication (^1H NMR) for the presence of **7** in the reaction mixture could be obtained. In the presence of $AgClO_4$ (41 mg, 0.20 mmol) and Na_2CO_3 (1.0 g) the experiment was repeated at room temperature under otherwise identical conditions. After 90 min **1** was completely converted. The usual workup followed by crystallization from *n*-pentane afforded **6** (1.78 g, 9.27 mmol; 93%): mp 160.5–161.5 °C; H NMR δ 2.08 (s, 6 H), 2.22 (s, 6 H), and 5.09 (s, 4 H); IR 800, 970, 995, and 1045 cm^{-1}; MS *m/e* 192 (M^+). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.61; H, 8.29.

When acetic acid (0.12 g, 2.0 mmol) was added to the solution instead of $AgClO_4/Na_2CO_3$, diene **1** was found to be completely transformed to homofulvene **8** within 2.5 h under otherwise identical conditions. Compound **8** was purified by preparative TLC (*n*-pentane): ^1H NMR δ 0.92 (distorted q, J = 6 Hz, 1 H), 1.03 (distorted d, J = 6 Hz, 3 H), 1.10 (s, 3 H), 1.20 (s, 3 H), and 4.67–4.83 (6 H); IR 890, 990, and 1600 cm^{-1}; MS Calcd exact mass, *m/e* 192.115 (M^+); MS Found, *m/e* 192.116.

When cyclohexadiene or bicyclic diene **9** was allowed to react with $^1O_2$ at room temperature under the conditions mentioned above, it was found that the presence of $AgClO_4/Na_2CO_3$ did not alter the reaction rates of the $^1O_2$ addition.[21,37]

Synthesis of 1,2,5,6-Tetramethyl-4-methylenetricyclo[3.1.0.0^{2,6}]hexan-3-one (2). Procedure I. At room temperature ozone was added at a rate of 1.5 g/h (oxygen flow of 20 L/h through a Fischer OZ III "Ozone Generator") to a stirred solution of **1** (0.800 g, 5.00 mmol) in $CHCl_3$ (10 mL) until no ^1H NMR signals due to olefinic protons of the diene could be observed anymore. Two products were formed in a 1:4 ratio (^1H NMR), isolated (GLC; SE-30 column all temperatures below 200 °C), and identified as **2** and **11**, respectively. Enone **2**: mp 45.0–45.5 °C; ^1H NMR δ 1.16 (s, 3 H), 1.27 (s, 3 H), 1.51 (s, 6 H), 4.84 (s, 1 H), and 5.67 (s, 1 H); ^{13}C NMR δ 3.3, 4.4, 7.2, 30.9, 41.3, 50.9, 106.1, 149.3, and 210.3; IR 1650 and 1720 cm^{-1}; MS *m/e* 178 (M^+); UV (ethanol) λ_{max} 215 nm (log ε 3.7) and 314 (1.3). Anal. Calcd for $C_{11}H_{14}O$: C, 81.48; H, 8.64. Found: C, 81.00; H, 8.62.

Lactone **11**: mp 55.0–56.0 °C; ^1H NMR δ 1.22 (s, 3 H), 1.38 (s, 3 H), 1.55 (broad s, 6 H), 5.53 (s, 1 H), and 6.28 (s, 1 H); ^{13}C NMR δ 7.9, 8.5, 15.0 (2C), 53.4, 87.8, 120.3, 141.0, 142.1, 143.6, and 170.5; IR 1650 and 1750 cm^{-1}; MS *m/e* 178 (M^+). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.16; H, 7.87. Found: C, 74.00; H, 7.92.

Procedure II. When the ozonolysis was carried out in the presence of Na_2CO_3 (1.0 g) under otherwise identical conditions, the ratio of compounds **2** and **11** changed to 1:1 (^1H NMR).

Procedure III. Addition of pyridine (1.0 mL) instead of Na_2CO_3 (procedure II) afforded **2** as the major product (the ratio of compounds **2** and **11** was 4:1, respectively), as determined by ^1H NMR spectroscopy.

Procedure IV. Diene **1** (28.8 g, 180 mmol) dissolved in CH_2Cl_2 (750 mL) containing pyridine (36 mL) was ozonolyzed (O_2 flow >80 L/h) at −60 °C for 2 h and 53 min under vigorous mechanical stirring. The solution was allowed to warm to room temperature overnight, and subsequently methylene chloride and pyridine were removed by evaporation under reduced pressure. *n*-Hexane (100 mL) was added to the residue, the mixture was stirred for 2 h, and water (50 mL) was introduced. The reaction mixture was filtered through Celite-535, the layers were separated, and the organic phase was washed with water (3 × 10 mL) and a saturated aqueous solution of NaCl (2 × 10 mL) and dried over anhydrous sodium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded crude **2** (29.7 g), which was estimated to be about 60% pure (^1H NMR). Enone **2** was purified by distillation under reduced pressure (30–40 °C, 0.01 mm): yield 53% (15.5 g, 95.7 mmol), purity 85% (^1H NMR). Analytically pure enone **2** was obtained by crystallization from *n*-pentane followed by sublimation at 35 °C. The fact that none or at the most only negligible amounts of **11** are formed makes this procedure the one of choice for the synthesis of **2**.

Procedure V. According to the method reported by Thompson,[38] the concept of reductive decomposition of the trioxolane at low temperatures was investigated. Employing triphenylphosphine or dimethyl sulfide, no improvements concerning the yield of **2** or the workup procedure were made compared with procedure IV.[39]

Preparation of 1,2,5,6-Tetramethyltricyclo[3.1.0.0^{2,6}]hexane-3,4-dione (3). Procedure I. Analogous to procedure III, enone **2** (0.810 g, 5.00 mmol) was ozonolyzed in $CHCl_3$ (10 mL) containing pyridine (1.0 mL). Two products were formed, isolated (repeated fractional crystallizations from ether followed by sublimations), and identified as α-diketone **3** and anhydride **12**, which were present in the reaction mixture in a 9:2 ratio, respectively. Diketone **3**: mp 142.5–143.0 °C; ^1H NMR δ 1.30 (s, 6 H) and 1.67 (s, 6 H); ^{13}C NMR δ 3.5, 4.6, 28.7, 51.6, and 194.6; IR 1750 cm^{-1}; UV–vis (ethanol) λ_{max} 272 nm (log ε 1.1) and 436 (1.4); MS *m/e* 164 (M^+). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.06; H, 7.36. Found: C, 72.92; H, 7.33.

Anhydride **12**: mp 154.0–155.0 °C; ^1H NMR δ 1.30 (s, 6 H) and 1.54 (s, 6 H); ^{13}C NMR δ 3.7, 10.0, 31.6, 41.9, and 169.6; IR 1770 and 1800 cm^{-1}; MS *m/e* 180 (M^+). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.73; H, 6.72. Found: C, 66.68; H, 6.71.

Procedure II. Enone **2** (4.82 g, 30.0 mmol) dissolved in dry methanol (125 mL) was ozonolyzed (O_2 flow 10 L/h; i.e., 1.2 g of O_3 per hour) at room temperature for 72 min. Subsequently ozone was removed

by a stream of nitrogen, and dimethyl sulfide (3.0 mL) was added to the solution. Stirring was continued for 1 h. Evaporation of the solvent under reduced pressure ($T \leq 40$ °C) followed by column (diameter = 2.5 cm) chromatography (Merck, activity II–III, 50 g of Al_2O_3; ether,) of crude **3** (dissolved in CH_2Cl_2) afforded **3**, which was crystallized from ether, yield 43% (2.13 g, 13.0 mmol). This procedure constitutes the best method for the synthesis of **3**, with no **12** being formed.

Syntheses of 11 and 12. When **2** (0.162 g) or **3** (0.164 g) dissolved in $CHCl_3$ (5 mL) was treated with *m*-chloroperbenzoic acid (0.150 g) in the presence of Na_2CO_3 (1.0 g) at room temperature, the exclusive formation of **11** and **12**, respectively, was observed (^{1}H NMR).

Wittig Reactions: General Procedures. Method A. To a stirred suspension of phosphonium salt (5.00 mmol) in dry THF (50 mL) was added *n*-BuLi (2.8 mL, 1.8 N in *n*-hexane) under a nitrogen atmosphere at room temperature. A solution of the substrate (5.00 mmol) in THF (2 mL) was subsequently introduced. The workup procedure consisted of addition of water (100 mL), extraction with *n*-pentane (2 × 50 mL), drying of the combined organic layers over anhydrous potassium carbonate, filtration, evaporation of the solvent under reduced pressure, and preparative TLC (*n*-pentane).

Method B. In this case the ylide was added to the organic substrate in THF (30 mL). The workup was according to method A above.

Tetracyanoethylene (TCNE) Adducts. All newly synthesized dienes were for analytical purposes converted to their polycyclic TCNE adducts, which isomerized to aromatic compounds prior to melting.[8,19] General procedure: to a solution of the diene (0.20 mmol) in chloroform (5 mL) was added TCNE (0.025 g, 0.20 mmol) at room temperature; after stirring for 10 min the solvent was evaporated, and the obtained solid material was crystallized from ether; the polycyclic TCNE adduct was heated as such at 100 °C for 15 min, followed by crystallization from ether.

Ozonolysis of Substituted Enones. In a way essentially analogous to the one reported for the synthesis of **3** from **2** according to procedure II, all newly prepared enones were ozonolyzed to **3**, in qualitative experiments, in order to obtain confirmable information about their polycyclic skeleton.

Synthesis of 13 from 2 (Method A). Reaction time: 30 min at room temperature. Using the phosphonium bromide, compound **13** was isolated in 73% yield as a colorless liquid (0.635 g, 3.65 mmol): ^{1}H NMR δ 1.10 (s, 3 H), 1.36 (s, 9 H), 1.83 (d, J = 7 Hz, 3 H), 4.40 (s, 1 H), 4.86 (s, 1 H), and 5.68 (q, J = 7 Hz, 1 H); IR 1640 and 3080 cm^{-1}; MS *m/e* (M^-) 174.

Polycyclic TCNE adduct: ^{1}H NMR δ 1.06 (s, 3 H), 1.15 (s, 3 H), 1.45 (s, 3 H), 1.47 (s, 3 H), 1.62 (d, J = 7 Hz, 3 H), and 3.0–3.5 (m, 3 H); IR 1660 and 2240 cm^{-1}.

Aromatic TCNE adduct: mp 190.5–191.5 °C; ^{1}H NMR δ 1.68 (d, J = 7 Hz, 3 H), 2.17 (s, 3 H), 2.20 (s, 9 H), 3.54 and 3.74 (AB system, J_{AB} = 17 Hz, 2 H), and 3.95 (q, J = 7 Hz, 1 H); IR 2250 cm^{-1}; MS *m/e* 302 (M^+). Anal. Calcd for $C_{19}H_{18}N_4$: C, 75.47; H, 6.00. Found: C, 75.39; H, 5.98.

Synthesis of 14 from 3 (Method B). Reaction time: 15 min at room temperature. An 81% yield of **14** as a viscous oil (0.717 g, 4.07 mmol) was obtained using the phosphonium bromide: ^{1}H NMR δ 1.05 (s, 3 H), 1.45 (s, 3 H), 1.51 (s, 6 H), 1.84 (d, J = 8 Hz, 3 H), and 6.05 (q, J = 8 Hz, 1 H); IR 1650 and 1710 cm^{-1}; MS *m/e* 176 (M^+). Induced downfield shifts varied linearly with the ratio [Eu(fod)$_3$]/[**14**] in the range 0.0–0.7, $\Delta\delta_H$ = 7.0 ppm and $\Delta\delta_{CH_3}$ = 2.0 ppm at [Eu(fod)$_3$]/[**14**] = 0.7 (H and CH_3 are the substituents of the terminal sp^2 carbon atom), in agreement with the presence of the CH_3 group in the syn position in **14**.

Preparation of 13 from 14 (Method A). Reaction time: 15 min at room temperature. Using the phosphonium iodide, compound **13** was isolated in 69% yield (0.598 g, 3.44 mmol). The spectroscopic data were in agreement with those of material obtained using **2** as the starting material.

Synthesis of 15 from 14 (Method A). Reaction time: 1 h at room temperature. A 73% yield of **15** as a colorless liquid (0.683 g, 3.63 mmol) was isolated using the phosphonium bromide: ^{1}H NMR δ 1.35 (s, 6 H), 1.38 (s, 6 H), 1.84 (d, J = 7 Hz, 6 H), and 5.53 (q, J = 7 Hz, 2 H); IR 1635 and 3040 cm^{-1}; MS *m/e* 138 (M^+).

Polycyclic TCNE adduct: ^{1}H NMR δ 1.12 (s, 6 H), 1.45 (s, 3 H), 1.48 (s, 3 H), 1.63 (d, J = 7 Hz, 6 H), and 3.25 (q, J = 7 Hz, 2 H); IR 1650 and 2250 cm^{-1}.

Aromatic TCNE adduct: mp 192.0–193.0 °C; ^{1}H NMR δ 1.71 (d, J = 7 Hz, 6 H), 2.25 (s, 12 H), and 4.03 (q, J = 7 Hz, 2 H); IR 2260 cm^{-1}; MS *m/e* 316 (M^+). Anal. Calcd for $C_{20}H_{20}N_4$: C, 75.92; H, 6.37. Found: C, 75.69; H, 6.42.

Preparation of 17 from 3 (Method B). Reaction time: 15 min at room temperature. A 79% yield of **17** as a viscous oil (0.752 g, 3.96 mmol) was obtained employing the phosphonium bromide: ^{1}H NMR δ 1.06 (s, 3 H), 1.41 (s, 3 H), 1.45 (s, 6 H), 1.88 (s, 3 H), and 2.07 (s, 3 H); IR 1650 and 1700 cm^{-1}; MS *m/e* 190 (M^+).

Synthesis of 16 from 17 (Method A). Reaction time: 1 h under reflux. Using the phosphonium iodide, compound **16** was isolated as a colorless liquid in 72% yield (0.679 g, 3.61 mmol): ^{1}H NMR δ 1.08 (s, 3 H), 1.33 (s, 3 H), 1.37 (s, 6 H), 1.94 (broad s, 6 H), 4.73 (s, 1 H), and 4.98 (s, 1 H); IR 1640 and 3080 cm^{-1}; MS *m/e* 188 (M^+).

Polycyclic TCNE adduct: ^{1}H NMR δ 1.01 (s, 3 H), 1.16 (s, 3 H), 1.44 (s, 6 H), 1.57 (s, 6 H), and 3.18 (s, 2 H); IR 1650 and 2260 cm^{-1}.

Aromatic TCNE adduct: mp 191.5–192.5 °C; ^{1}H NMR δ 1.70 (s, 6 H), 2.20 (s, 3 H), 2.25 (s, 9 H), and 3.76 (s, 2 H); IR 2260 cm^{-1}; MS *m/e* 316 (M^+). Anal. Calcd for $C_{20}H_{20}N_4$: C, 75.92; H, 6.37. Found: C, 75.58; H, 6.42.

Preparation of 2 from 3 (Method B). Reaction time: 15 min at room temperature. Employing the phosphonium iodide gave an 84% yield (0.684 g, 4.22 mmol). The spectroscopic data were in agreement with those of material obtained from the ozonolysis of **1**.

Synthesis of 1 from 2 (Method A). Reaction time: 15 min at room temperature. Using the phosphonium iodide, compound **1** was isolated in 78% yield (0.621 g, 3.88 mmol). The spectroscopic data were in agreement with those of authentic material.[9]

Preparation of 18 from 2 (Method A). Reaction time: 6 h under reflux. A 57% yield of **18** (0.578 g, 2.83 mmol) was isolated employing the phosphonium bromide: ^{1}H NMR δ 0.74 (s, 2 H), 1.07 (s, 6 H), 1.17 (s, 3 H), 1.21 (s, 3 H), 1.42 (s, 3 H), and 1.48 (s, 3 H); ^{13}C NMR δ 2.6, 3.5, 4.8, 10.3, 19.7, 22.9, 23.5, 25.3, 29.7, 31.9, 38.0, 38.8, 52.2, and 216.4; IR 1735 and 3050 cm^{-1}; MS Calcd exact mass, *m/e* 204.151 (M^+); MS Found, *m/e* 204.154. Anal. Calcd for $C_{14}H_{20}O$: C, 82.31; H, 9.87. Found: C, 82.79; H, 10.01.

Preparation of the $Fe(CO)_3$ Complex 19. Diene **13** (0.696 g, 4.00 mmol) was heated with iron pentacarbonyl (1.60 g, 8.00 mmol) at 70 °C for 24 h under a blanket of nitrogen. The mixture was cooled and filtered, and excess iron pentacarbonyl was removed by distillation under reduced pressure. Preparative TLC (*n*-pentane) afforded **19** as an orange liquid (0.347 g, 1.11 mmol; 28%): ^{1}H NMR δ 0.45 (d, J = 2.5 Hz, 1 H), 1.11 (q, J = 7.0 Hz, 1 H), 1.16 (s, 3 H), 1.37 (s, 3 H), 1.49 (s, 3 H), 1.57 (s, 3 H), 1.66 (d, J = 7.0 Hz, 3 H), and 2.05 (d, J = 2.5 Hz, 1 H); IR 1980 and 2060 cm^{-1}; MS *m/e* 314 (M^+) (peaks at *m/e* 286, 258, and 230 indicate the successive loss of CO ligands).

Oxidation of 19. Complex **19** (0.347 g, 1.11 mmol) was heated in benzene (5 mL) at 40 °C for 2 days in the presence of Me_3NO[35] (3.0 g) in a nitrogen atmosphere. The mixture was cooled and filtered, and the solvent was evaporated under reduced pressure. Preparative TLC (*n*-pentane) yielded only diene **13** (48 mg, 0.28 mmol; 25%).

Registry No.—**1**, 50590-86-8; **2**, 56745-77-8; **3**, 56745-78-9; **4**, 65121-37-1; **5**, 65102-61-6; **6**, 65102-62-7; **8**, 65102-63-8; **11**, 56745-76-7; **12**, 56745-79-0; **13**, 65102-64-9; **13**-TCNE, 65121-38-2; **14**, 65102-65-0; **15**, 65102-66-1; **15**-TCNE, 65102-70-7; **16**, 65102-67-2; **16**-TCNE, 65102-71-8; **17**, 65102-68-3; **18**, 65102-69-4; **19**, 65120-34-5; OsO_4, 20816-12-0; $Fe(CO)_5$, 13463-40-6; O_2, 7782-44-7

References and Notes

(1) *Oxidation 1969–1971*, **1** (1969).
(2) *Oxidation 1969–1971*, **2** (1971).
(3) L. J. Chinn, "Selection of Oxidants in Synthesis: oxidation at the carbon atom", Marcel Dekker, New York, N.Y., 1971.
(4) *Oxid. Org. Chem. 1965–1973*, Part A, (1965).
(5) *Oxid. Org. Chem. 1965–1973*, Part B, (1973).
(6) C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971).
(7) D. J. Sam and H. E. Simmons, *J. Am. Chem. Soc.*, **94**, 4024 (1972).
(8) H. Hogeveen and P. W. Kwant, *Tetrahedron Lett.*, 3747 (1973).
(9) H. Hogeveen and P. W. Kwant, *J. Org. Chem.*, **39**, 2624 (1974).
(10) R. Criegee, B. Marchand, and H. Wannowius, *Justus Liebigs Ann. Chem.*, **550**, 99 (1942).
(11) J. S. Baran, *J. Org. Chem.*, **25**, 257 (1960).
(12) On the basis of a MINDO/3 study it was recently concluded that the addition of $^1O_2$ to butaciene does not proceed via a synchronous pericyclic mechanism but rather involves the formation of a peroxirane or zwitterion: M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **99**, 2338 (1977).
(13) H. H. Wassermann, K. Stiller, and M. B. Floyd, *Tetrahedron Lett.*, 3277 (1968).
(14) J. Rigaudy, R. Dupont, and Nguyen Kim Cuong, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **269**, 416 (1969).
(15) J. Rigaudy, P. Capdevielle, and M. Maumy, *Tetrahedron Lett.*, 4997 (1972).
(16) D. R. Kearns, *Chem. Rev.*, **71**, 395 (1971).
(17) H. Wynberg and H. Numan, *J. Am. Chem. Soc.*, **99**, 603 (1977).
(18) H. Hogeveen and W. F. J. Huurdeman, *Tetrahedron Lett.*, 1255 (1974).
(19) H. Hogeveen, W. F. J. Huurdeman, and E. P. Schudde, Tetrahedron Lett., 4211 (1974).
(20) W. F. J. Huurdeman, Thesis, University of Groningen, 1976; H. Hogeveen and W. F. J. Huurdeman, *J. Am. Chem. Soc.*, **100**, 860 (1978).
(21) D. M. Kok, unpublished results.

(22) H. Hogeveen, W. F. J. Huurdeman, and D. M. Kok, *J. Am. Chem. Soc.*, **100**, 871 (1978).
(23) P. S. Bailey, F. E. Potts, and J. W. Ward, *J. Am. Chem. Soc.*, **92**, 230 (1970).
(24) R. F. Heldeweg and H. Hogeveen, *Tetrahedron Lett.*, 1517 (1975).
(25) Because of the fact that the UV spectrum of **1** shows the presence of an absorption at λ_{max} 250 nm (*n*-hexane), it is reasonable to assign an essentially planar structure to the diene moiety of this hydrocarbon.[9] In view of Leonard's work,[26] the intercarbonyl angle in the case of diketone **3** is likely to be larger than 10° [λ_{max} 436 nm (ethanol)].[27]
(26) N. J. Leonard and P. M. Mader, *J. Am. Chem. Soc.*, **72**, 5388 (1950).
(27) A structure determination using x-ray techniques has been performed by Dr. A. L. Spek, Laboratorium voor Struktuurchemie, Transitorium III, Utrecht, The Netherlands: the intercarbonyl angle was found to be 14° (to be published).
(28) P. R. Story and J. R. Burgess, *Tetrahedron Lett.*, 1287 (1968).
(29) J. J. Pappas, W. P. Keaverney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).
(30) Although the α-methylene-γ-butyrolactone structural unit is encountered in a group of naturally occurring cytotoxic sesquiterpenes,[31] compound **11** was found to be inactive against leukaemia in mice L 1210 (performed by the European Organization for Research on Treatment of Cancer in cooperation with the National Cancer Institute at Bethesda through the courtesy of Dr. L. M. van Putten). The possible activity against P 388 is at present being tested. Compound **11** bears the international registration number NSC 264928.
(31) P. A. Grieco, *Synthesis*, 67 (1975).
(32) H. Hogeveen and P. W. Kwant, *Acc. Chem. Res.*, **8**, 413 (1975).
(33) J. P. Freeman, *Chem. Ind. (London)*, 1254 (1959).
(34) J. E. Mahler and R. Fettit, *J. Am. Chem. Soc.*, **85**, 3955 (1963).
(35) Y. Shvo and E. Hazum, *J. Chem. Soc., Chem. Commun.*, 336 (1974).
(36) J. Elzinga and H. Hogeveen, *Tetrahedron Lett.*, 2383 (1976).
(37) G. O. Schenck and D. E. Dunlap, *Angew. Chem.*, **68**, 248 (1956).
(38) W. S. Knowles and Q. E. Thompson, *Chem. Ind. (London)*, 121 (1959).
(39) Tetracyanoethylene cannot be used in this case (compare with ref 8): C. Criegee and P. Günther, *Chem. Ber.*, **96**, 1564 (1963).

Cyclopropane and Allene Analogues of a Bicyclobutane-Bridged Diene

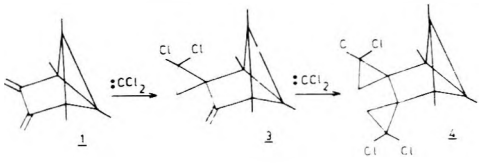
R. F. Heldeweg and H. Hogeveen*

Laboratory of Organic Chemistry, University of Groningen, Groningen, The Netherlands

Received June 13, 1977

Bicyclobutane-bridged diene **1**, 1,2,5,6-tetramethyl-3,4-dimethylenetricyclo[3.1.0.0^{2,6}]hexane, was used as starting material in the syntheses of cyclopropanes and allenes. These compounds were prepared by performing modifications of the butadiene moiety in **1**. First of all, dihalocarbene additions were carried out under phase-transfer conditions. Reduction of the geminal dihalocyclopropanes with sodium in liquid ammonia afforded cyclopropanes. Allenes were prepared by treating the geminal dibromocyclopropanes with methyllithium. Reactions of the allene and cyclopropane analogues of **1** with tetracyanoethylene are reported.

The bicyclobutane-bridged diene 1,2,5,6-tetramethyl-3,4-dimethylenetricyclo[3.1.0.0^{2,6}]hexane, **1**,[1,2] has recently been found to be extremely reactive in Diels–Alder cycloadditions.[3] Compound **1** is also easily available in large amounts.

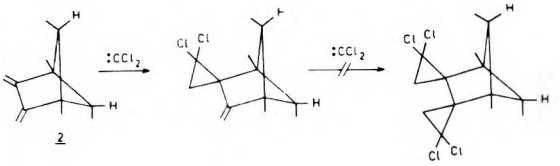


These two facts led us to consider the use of **1** as starting material in the syntheses of small ring compounds and reactive multiple bonds.

In order to minimize the risks of bicyclobutane rearrangements during modifications of the carbon–carbon double bonds of the diene moiety of **1** into allenes or cyclopropanes, it was evident that reaction paths involving the use of transition metals or acids had to be avoided. Our hope was that the transformations would occur at reasonably low temperatures and via synthesis of a common precursor or directly from the diene. Since allenes can easily be synthesized from geminal dihalocyclopropanes and alkyllithium compounds[4–8] and, moreover, reductions of geminal dihalocyclopropanes yield cyclopropanes,[4,5] geminal dihalocyclopropanes in principle constitute the desired type of precursor and our attention was drawn to their preparation.

Dihalocarbene generation under phase-transfer conditions proved to be a versatile method which facilitated the synthesis of a substantial number of geminal dihalocyclopropanes. Although the reaction of dichlorocarbene generated according to classical methods with conjugated olefins usually does not occur beyond the addition of 1 equiv, mono and multiple additions are easily accomplished with dichlorocarbene generated under phase-transfer catalysis conditions.

Dihalocarbene Additions. According to the general procedure as reported by Makosza and Warzyniewicz,[9] diene **1** was allowed to react with dichlorocarbene at room temperature under vigorous stirring. Within 1 h **1** was converted to the bis adduct (80%), of which only the trans isomer appeared to be present. This is due to the fact that one of the chlorine atoms erects a barrier at the cis side in the mono adduct. The smooth formation of the bis adduct mentioned above is in sharp contrast with the unsuccessful attempts to prepare a bis adduct in the case of diene **2**,[10] in which compared with **1** the central bicyclobutane C–C bond has been opened, therewith in principle allowing the methyl groups in question to exert more steric influence on chemical events at the diene moiety.

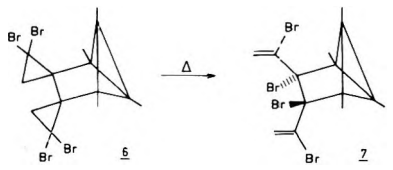


A modification of the organic phase, *n*-pentane and chloroform in a 3:1 ratio, made it possible to synthesize and isolate the mono adduct **3** (76%) of dichlorocarbene and diene **1** under otherwise identical conditions.

The same method allows the generation of the dibromocarbene adducts. The yields of the adducts are lower than those achieved in the corresponding dichlorocarbene reactions. Furthermore, the mono and bis adducts of dibromocarbene and **1** (compounds **5** (38%) and **6** (28%), respectively) were found to be less stable than their chloro analogues. Thermal disrotatory ring opening[11,12] takes place very easily, especially in the case of **6**, leading to a compound which we tentatively assign as structure **7**.

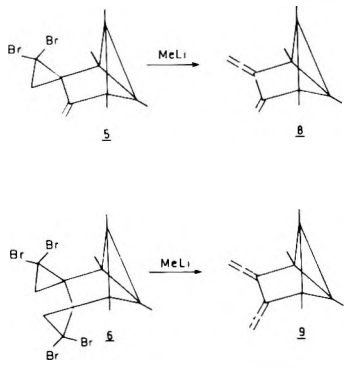
Synthesis of a Mono- and Bisallene. The treatment of geminal dibromocyclopropanes with methyllithium is known to provide a widely applicable route to allenes.[4,8] Intramo-

0022-3263/78/1943-1916$01.00/0



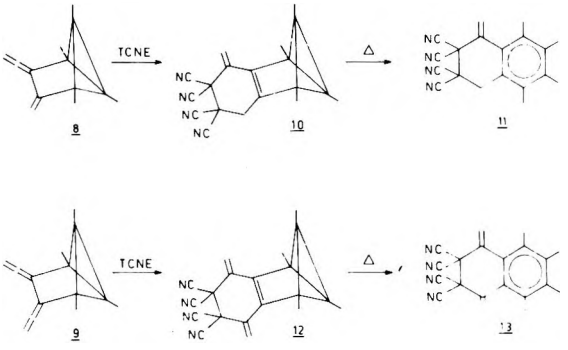
lecular reactions may cause complications, however, when the bromides involved are derivatives of vinylcyclopropane or bicyclopropane: Skattebøl obtained cyclopentadienes in the former and fulvenes in the latter case as the major products.[8]

Because of these findings a risk of intramolecular mishaps existed also in the planned conversion of **5** to monoallene **8** and

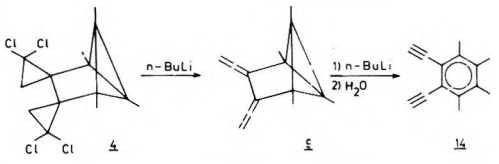


of **6** to bisallene **9**. However, when methyllithium was added at low temperature (−50 °C) to ether solutions of either **5** or **6** followed by workup at room temperature, the allenes **8** and **9** were isolated as the major product. Although the formation of minor amounts of a cyclopentadiene and a fulvene, respectively, cannot rigorously be excluded, there were no spectroscopic indications for their presence in the reaction mixtures immediately after workup.

The allenes were allowed to react with tetracyanoethylene (TCNE) at room temperature, and after isomerization of the bicyclobutane moieties the aromatic cycloadducts **11** and **13** were subjected to elemental analyses.

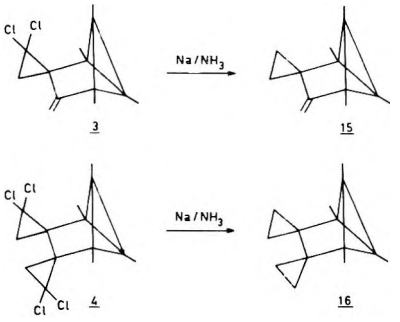


When the chloro analogues **3** and **4** were treated likewise with methyllithium, the starting materials were recovered unchanged. Neither was compound **8** formed from **3** using *n*-butyllithium. However, bis adduct **4** did undergo the desired reaction on addition of *n*-butyllithium, but the reaction mixture consisted of **4**, bisallene **9**, and o-diethynylbenzene derivative **14**. The intermediacy of **9** in the conversion of **4** to

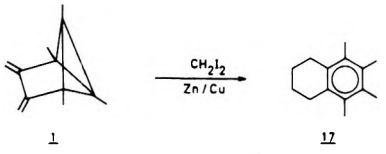


14 was shown by an experiment in which a large excess of *n*-butyllithium was added to a sample of pure bisallene **9**, prepared from **6**, affording exclusively **14**.[13] The allene–acetylene equilibrium can be set up by the use of catalytic amounts of strong bases. No equilibrium is obtained when large quantities of base are used, but all the material is tied up as the alkali salt of the terminal acetylene.[14]

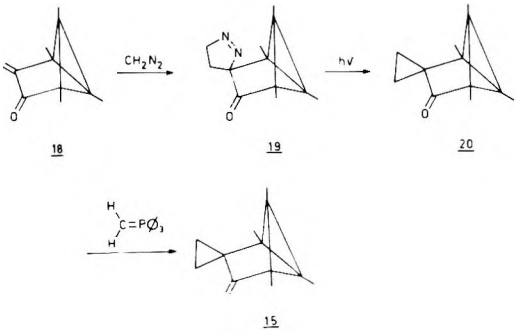
Synthesis of a Mono- and Bicyclopropane. The Na/NH_3 type of reduction[15] was tried on **3**, **4**, **5**, and **6**. This approach turned out to be successful in all cases, and both the bicyclobutane-bridged vinylcyclopropane **15** and bicyclopropane **16** were isolated. Since these compounds can be synthesized in higher yields and, moreover, are easier to handle, the geminal dichlorocyclopropanes **3** and **4** are preferable to the corresponding dibromo compounds **5** and **6** as starting materials.



Attempts to prepare **15** and **16** directly from diene **1** according to the method published by Simmons and Smith[16] failed due to isomerization of the bicyclobutane moiety. The tetraline derivative **17** was isolated in spite of the presence of dimethoxyethane, which was recommended to prevent Lewis acid catalyzed rearrangements under the prevailing conditions (Simmons–Smith reagent/diene **1**, 3:1).

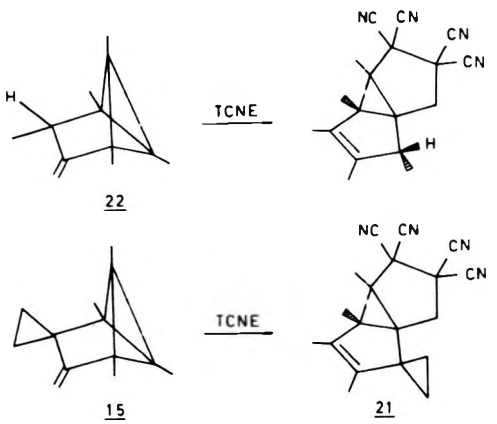


Diazomethane addition to unsaturated ketone **18**[21] followed by the photochemically induced loss of nitrogen and a Wittig reaction provides another route to **15** which proceeds in a high



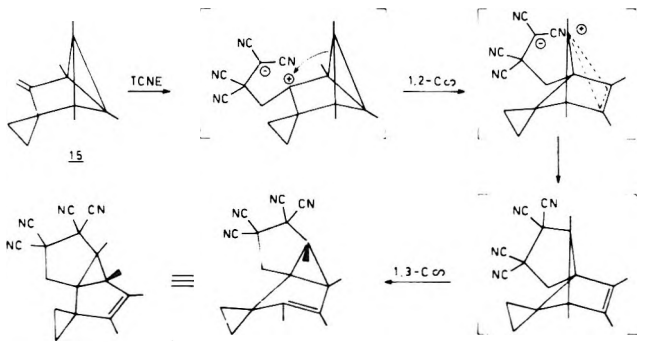
overall yield;[17] the method described earlier is, however, superior for reasons of simplicity.

In the literature[18] the initial formation of a [2 + 2] adduct from vinylcyclopropane and TCNE has been reported; the product isomerizes thermally to a seven-membered ring. Although **15** contains a vinylcyclopropane moiety, its reaction with TCNE takes a different course involving a rearrangement of the bicyclobutane skeleton. In chloroform the conversion of **15** to **21** is complete within 3 min at room temperature. The behavior of **15** toward TCNE bears a close resemblance to that of **22**.[19] Although in contrast to the latter reaction an intermediate adduct was not observed by NMR spectroscopy, the addition of TCNE to **15** leading to **21** is likely to occur along an analogous pathway.

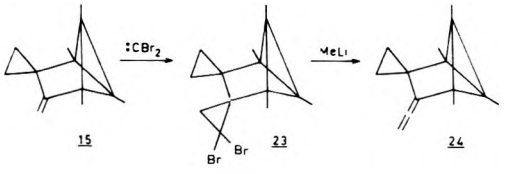


22 15 21

No reaction between TCNE and 16 was observed at temperatures up to 150 °C.

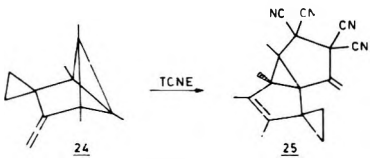


Synthesis of a Cyclopropylallene. In order to complete the class of allene and cyclopropane modifications of **1**, the synthesis of the cyclopropylallene **24** starting from **15** via the dibromocarbene adduct **23** was attempted. No attempts were made to purify and completely characterize **23**. Compound



15 23 24

24 could actually be isolated after addition of methyllithium to a solution of crude **23**, but difficulties were encountered in its reaction with TCNE. The immediate addition of TCNE did take place at −20 °C, but the 1:1 adduct which is thought to have structure **25** decomposed during workup.



24 25

Conclusion

Of the newly prepared compounds, allenes **8** and **9** decompose rapidly within a few days at room temperature and, moreover, are difficult to purify. However, compounds **15** and **16** deserve further experimental and theoretical attention since they possess a considerable amount of strain energy, are easily synthesized, and are fairly stable at room temperature. Experiments to exploit their chemical reactivity are being performed.

Experimental Section

General Remarks. Melting points are uncorrected. Mass spectra were run on a AEI MS-902. Infrared spectra (Nujol mull) were recorded on a Perkin-Elmer Infracord 257 spectrophotometer. ^{1}H NMR spectra were taken with a Jeol C-60 HL spectrometer with deuteriochloroform as the solvent and Me_4Si as an internal reference. ^{13}C NMR spectra were run on a Varian XL-100 with deuteriochloroform as the solvent and Me_4Si as an internal reference. Preparative TLC was performed with aluminium oxide (Merck; 10–40 μm, not activated).

Synthesis of Spiro[2,2-dichlorocyclopropane-1,3'-1',2',5',6'-tetramethyl-4'-methylenetricyclo[3.1.0.0^{2,6}]hexane] (3). Chloroform (25 mL), *n*-pentane (75 mL), diene **1** (4.0 g, 25 mmol), a 50% aqueous solution of sodium hydroxide (100 g), and triethylbenzylammonium chloride (1.0 g) were combined and stirred vigorously at room temperature for 1 h. Then water (200 mL) and chloroform (100 mL) were added, the organic layer was separated, washed with water (3 × 20 mL), and dried over anhydrous potassium carbonate, and the solvent was evaporated. A mixture of **1** and **3** was obtained, from which **1** was removed by vacuum distillation. Compound **3** (4.6 g, 19 mmol; 76%) was pure enough to be used in further experimental work: mp 58.0–59.0 °C; ^{1}H NMR δ 1.07 (s, 3 H), 1.14 (s, 3 H), 1.33 (s, 3 H), 1.45 (s, 3 H), 1.70 and 1.80 (AB system, J_{AB} = 8 Hz, 2 H), 4.48 (s, 1 H), and 4.73 (s, 1 H); ^{13}C NMR δ 2.4, 3.2, 7.5, 8.6, 26.0, 27.4, 28.7, 42.2, 45.5, 46.6, 64.7, 99.0, and 157.6; IR 1660 cm^{-1}; MS Calcd exact mass, *m/e* 242.063 (M$^+$); MS Found, *m/e* 242.065.

Preparation of *d,l*-Dispiro[2,2-dichlorocyclopropane-1,3'-1',2',5',6'-tetramethyltricyclo[3.1.0.0$^{2',6'}$]hexane-4',1''-2'',2''-dichlorocyclopropane] (4). Compound **4** was prepared analogously to the synthesis of **3**. However, instead of *n*-pentane (75 mL) additional chloroform was used (75 mL). After evaporation of the organic solvent a solid material resided which was recrystallized from *n*-pentane. An 80% yield of **4** (6.5 g, 20 mmol) was obtained: mp 140.0–140.5 °C; ^{1}H NMR δ 1.06 (s, 6 H), 1.48 (s, 6 H), and 1.81 and 2.07 (AB system, J_{AB} = 9 Hz, 4 H); ^{13}C NMR δ 3.0, 9.2, 27.0, 27.1, 44.1, 47.0, and 64.6; MS (M$^+$) *m/e* 324, 326, 328, 330, and 332. Anal. Calcd for $C_{14}H_{16}Cl_4$: C, 51.56 H, 4.95; Cl, 43.49. Found: C, 51.48; H, 4.95; Cl, 43.55.

Synthesis of Spiro[2,2-dibromocyclopropane-1,3'-1',2',5',6'-tetramethyl-4'-methylenetricyclo[3.1.0.0$^{2',6'}$]hexane] (5). Mono adduct **5** was prepared in a similar manner as **3**. Instead of chloroform (25 mL) bromoform (25 mL) was used. Both **1** and excess bromoform were removed by distillation (T < 35 °C) under reduced pressure. For reasons of stability crude **5** (viscous oil) was stored in the dark while cool, yield 38% (2.4 g, 9.5 mmol): ^{1}H NMR δ 1.11 (s, 3 H), 1.15 (s, 3 H), 1.33 (s, 3 H), 1.46 (s, 3 H), 1.90 and 2.36 (AB system, J_{AB} = 7 Hz, 2 H), 4.47 (s, 1 H), and 4.75 (s, 1 H); IR 1650 cm^{-1}; MS (M$^+$) *m/e* 330, 332, and 334.

Preparation of *d,l*-Dispiro[2,2-dibromocyclopropane-1,3'-1',2',5',6'-tetramethyltricyclo[3.1.0.0$^{2',6'}$]hexane-4',1''-2'',2''-dibromocyclopropane] (6). Bis adduct **6** was synthesized in a way analogous to the preparation of **4**. Instead of chloroform (100 mL) bromoform (100 mL) was used. Excess bromoform was removed by distillation under reduced pressure (T < 35 °C). After crystallization from *n*-pentane **6** was obtained in 28% yield (3.5 g, 6.9 mmol): ^{1}H NMR δ 1.12 (s, 6 H), 1.55 (s, 6 H), and 2.04 and 2.42 (AB system, J_{AB} = 9 Hz, 4 H); MS (M$^+$) *m/e* 500, 502, 504, 506, and 508.

Prior to melting, compound **6** underwent ring opening on heating at 60 °C for 5 min, affording **7** as a viscous oil: ^{1}H NMR δ 1.03 (s, 6 H), 1.36 (s, 6 H), 4.78 (s, 2 H), and 5.33 (s, 2 H); MS (M$^+$) *m/e* 500, 502, 504, 506, and 508.

Synthesis of 1,2,5,6-Tetramethyl-3-methylene-4-vinylidenetricyclo[3.1.0.0^{2,6}]hexane (8) from 5. A solution of **5** (0.664 g, 2.00 mmol) in ether (25 mL) kept under a nitrogen atmosphere was cooled (−50 °C), and subsequently methyllithium (1.4 mL, 1.5 N in ether) was added by means of a syringe. Then the mixture was allowed to warm to room temperature and water (25 mL) was added. The two layers were separated, and the organic layer was collected, dried over anhydrous potassium carbonate, and evaporated, leaving crude allene **8** which was purified by preparative TLC (*n*-pentane). An isolated yield of 27% of **8** (0.083 g, 0.54 mmol) was obtained. For reasons of stability compound **8**, a colorless mobile oil, was used immediately or stored at low temperature in the dark: ^{1}H NMR δ 1.16 (s, 6 H), 1.43 (s, 6 H), 4.96 (s, 1 H), and 5.21 and 5.25 (two partially overlapping s, 3 H); IR 1650 and 1960 cm^{-1}; MS *m/e* 172 (M$^+$).

Preparation of 10. To a solution of **8** (0.070 g, 0.41 mmol) in chloroform (10 mL) was added TCNE (0.051 g, 0.40 mmol) at room temperature. After stirring for 10 min the solvent was evaporated (T < 35 °C) and the residing solid was crystallized from *n*-pentane. Adduct **10** (0.097 g, 0.32 mmol) was isolated in 80% yield; it rearranged to compound **11** before melting: ^{1}H NMR δ 1.13 (s, 3 H), 1.35 (s, 3 H), 1.55 (s, 6 H), 3.37 (s, 2 H), and 5.88 (apparent s, 2 H); IR 1625 and 2260 cm^{-1}.

Synthesis of 11. When **10** (0.097 g, 0.32 mmol) was heated at 100 °C a rearrangement took place which was complete within 5 min and afforded **11** in a quantitative yield: ^{1}H NMR δ 2.22 (s, 3 H), 2.31 (s, 6 H), 2.42 (s, 3 H), 3.77 (s, 2 H), 5.87 (d, J = 2 Hz, 1 H), and 6.46 (d, J = 2 Hz, 1 H); IR 1625 and 2260 cm^{-1}; MS m/e 300 (M$^+$). Anal. Calcd for $C_{19}H_{16}N_4$: C, 75.98; H, 5.37; N, 18.65. Found: C, 75.76; H, 5.42; N, 18.79. Compound **11** decomposed at temperatures above 225 °C.

Synthesis of 1,2,5,6-Tetramethyl-3,4-divinylidenetricyclo[3.1.0.0^{2,6}]hexane (9) from 6. Both the preparation and the purification of **9** were carried out according to the procedures described previously for monoallene **8**. Using **6** (1.000 g, 1.984 mmol) as the starting material, bisallene **9** (0.212 g, 1.15 mmol) was isolated as a colorless mobile oil in a 58% yield and for reasons of stability it was used immediately or stored at low temperature in the dark: ^{1}H NMR δ 1.12 (s, 6 H), 1.41 (s, 6 H), and 5.06 (s, 4 H); IR 1970 cm^{-1}; MS m/e 184 (M$^+$).

Preparation of 12. Starting from **9** (0.212 g, 1.15 mmol), adduct **12** (0.281 g, 0.901 mmol) was prepared and purified in the way mentioned in the case of **10** (80% yield); **12** rearranged to **13** prior to melting: ^{1}H NMR δ 1.34 (s, 6 H), 1.57 (s, 6 H), and 5.90 (apparent s, 4 H); IR 1620 and 2260 cm^{-1}.

Synthesis of 13. Compound **12** (0.281 g, 0.901 mmol) isomerized on heating at 100 °C for 10 min. The aromatic compound **13** was isolated in quantitative yield: ^{1}H NMR δ 2.32 (s, 6 H), 2.45 (s, 6 H), 5.88 (d, J = 2 Hz, 2 H), and 6.48 (d, J = 2 Hz, 2 H); IR 1625 and 2260 cm^{-1}; MS m/e 312 (M$^+$). Anal. Calcd for $C_{20}H_{16}N_4$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.61; H, 5.10; N, 18.06. Compound **13** decomposed at temperatures above 225 °C.

Formation of 1,2-Diethynyl-3,4,5,6-tetramethylbenzene (14). To a cold (−50 °C) solution of **4** (1.63 g, 5.00 mmol) in ether (25 mL) kept under a nitrogen atmosphere was added n-butyllithium (6.0 mL, 1.8 N in n-hexane). After warming to room temperature water (25 mL) was introduced and the organic layer was collected and evaporated. ^{1}H NMR spectroscopy indicated the presence of **9** and **14** (1:2 ratio) and starting material (30%).

When pure **9** (0.184 g, 1.00 mmol), prepared from **6**, was treated with an excess of n-butyllithium (10 mL, 1.8 N in n-hexane) under otherwise identical conditions, only **14** could be observed by ^{1}H NMR spectroscopy after workup. Compound **14** was purified by preparative TLC (n-pentane) followed by crystallization from n-pentane. A 73% yield of **14** (0.133 g, 0.731 mmol) was isolated: ^{1}H NMR δ 2.12 (s, 6 H), 2.35 (s, 6 H), and 3.40 (s, 2 H); IR 2120 cm^{-1} MS m/e 182 (M$^+$). Anal. Calcd for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 92.27; H, 7.74. After melting at 114.5–115.5 °C, compound **14** decomposed at a slightly higher temperature.

Synthesis of Spiro[cyclopropane-1,3′-1′,2′,5′,6′-tetramethyl-4′-methylenetricyclo[3.1.0.0$^{2',6'}$]hexane] (15). Ammonia (250 mL) was condensed at −50 °C in a dry reaction vessel containing **3** (4.86 g, 20.0 mmol), and the vessel was equipped with a cold-finger condenser. The ammonia inlet was replaced with a stopper, and sodium (1.84 g, 80.0 mg-atom), cut into small pieces, was introduced in portions throughout the reaction. After addition of the total amount of sodium the reaction mixture was stirred at −50 °C until the solution decolorized. Then the condenser was removed and the ammonia allowed to evaporate. Ether (100 mL) and water (100 mL) were added, and the aqueous layer was extracted with ether (2 × 200 mL). The organic layers were combined and dried over anhydrous potassium carbonate, and the solvent was subsequently evaporated, leaving crude **15** which was distilled under reduced pressure at 28–33 °C (1.0 mm). A 76% yield of **15**, a colorless liquid (2.64 g, 15.2 mmol), was obtained: ^{1}H NMR δ 0.40 (m, 2 H), 0.68 (m, 2 H), 0.76 (s, 3 H), 1.13 (s, 3 H), 1.38 (s, 6 H), 4.07 (s, 1 H), and 4.38 (s, 1 H); ^{13}C NMR δ 2.6, 4.9, 7.1, 9.4, 25.7, 30.1, 40.1, 46.1, 89.9, and 164.2; IR 1650 and 3050 cm^{-1}; MS m/e 174 (M$^+$).

Since no satisfactory elemental analysis could be obtained, compound **15** was also synthesized in an independent way using diazomethane (see below).

Preparation of Dispiro[cyclopropane-1,3′-1′,2′,5′,6′-tetramethyltricyclo[3.1.0.0$^{2',6'}$]hexane-4′,1″-cyclopropane] (16). In the manner described for the conversion of **3** to **15**, compound **4** (6.52 g, 20.0 mmol) afforded **16** upon reduction with sodium (3.68 g, 160 mg-atom) in liquid ammonia at −50 °C. An 84% yield of **16**, a colorless liquid (3.14 g, 16.7 mmol), was isolated after distillation under reduced pressure at 30–35 °C (1.0 mm): ^{1}H NMR δ −0.17 (m, 4 H), 0.28 (m, 4 H), 0.72 (s, 6 H), and 1.32 (s, 6 H); ^{13}C NMR δ 3.0, 3.5, 5.6, 21.0, 31.8, and 43.5; IR 3050 cm^{-1}; MS Calcd exact mass, m/e 188.156 (M$^+$); MS Found, m/e 188.158.

Na/NH$_3$ Reductions of 5 and 6. Using **5** or **6** as the starting material, **15** and **16**, respectively, were synthesized in a way essentially identical with the method described above. After distillation under reduced pressure compound **5** (0.664 g, 2.00 mmol) afforded **15** (72%) and compound **6** (0.504 g, 1.00 mmol) gave **16** (79%).

Preparation of 17. A mixture of methylene iodide (1.90 g, 7.10 mmol), a zinc–copper couple prepared according to Shank and Shechter[16] (4.68 g, 7.20 mg-atom), diene **1** (400 mg, 2.50 mmol), anhydrous ether (2.5 mL), dimethoxyethane (0.5 mL), and a crystal of iodine was heated under reflux for 6 h in a nitrogen atmosphere. The solution was then washed with a saturated ammonium chloride solution (3 mL) and water (3 mL). Evaporation of the solvent afforded a complex reaction mixture. Preparative TLC (n-pentane) made it possible to isolate and characterize one of the components (**17**); the melting point (78.0–78.5 °C) and spectroscopic data of **17** (MS, IR, and ^{1}H NMR) are in agreement with those of authentic material.[20] No indication for the presence of **15** or **16** was obtained by ^{1}H NMR spectroscopy. The yield of **17** was 24% (0.112 g, 0.596 mmol).

Alternative Synthesis of 15 Using Diazomethane. To a solution of diazomethane in ether (20 mL, 0.25 N) was added enone **18** (0.810 g, 5.00 mmol) under stirring at room temperature. After about 2 h the solution lost its characteristic color and the solvent was evaporated, leaving **19** in quantitative yield: ^{1}H NMR δ 0.93 (s, 3 H), 1.18 (s, 3 H), 1.50 (s, 3 H), 1.65 (s, 3 H), and 4.3–4.8 (ABCD system, 4 H); ^{13}C NMR δ 2.4, 3.1, 4.3, 6.0, 21.2, 26.3, 28.5, 41.5, 52.4, 77.0, 100.1, and 211.5; IR 1540 and 1730 cm^{-1}.

Using a high-pressure mercury arc, compound **19** (0.998 g, 4.89 mmol) dissolved in benzene or chloroform (150 mL) was irradiated for 3 h. Evaporation of the solvent afforded **20** (0.848 g, 4.82 mmol) as a waxy solid in quantitative yield: ^{1}H NMR δ 0.56 (s, 4 H), 0.87 (s, 3 H), 1.09 (s, 3 H), and 1.49 (s, 6 H); IR 1735 cm^{-1}; MS m/e 174 (M$^+$).

To a suspension of methyltriphenylphosphonium iodide (2.02 g, 5.00 mmol) in dry tetrahydrofuran (50 mL) was added n-BuLi (2.8 mL, 1.8 N in n-hexane) under a nitrogen atmosphere at room temperature. A solution of **20** (0.848 g, 4.82 mmol) in tetrahydrofuran (2 mL) was subsequently introduced, and the reaction mixture was stirred for 15 min at room temperature. Water (100 mL) was added and the aqueous layer was extracted with n-pentane (2 × 50 mL). The combined organic layers were dried over anhydrous potassium carbonate, and the solvent was evaporated, leaving crude **15** which was identical with the material prepared by Na/NH$_3$ reduction of **3**. Preparative TLC (n-pentane) afforded 89% of **15** (0.738 g, 4.29 mmol).

Synthesis of 21. To a stirred solution of **15** (0.696 g, 4.00 mmol) in chloroform (25 mL) was added TCNE (0.512 g, 4.00 mmol) at room temperature. After 15 min the solvent was evaporated and the resulting crude **21** was crystallized from ether, yield 83% (0.998 g, 3.30 mmol): mp 154.0–154.5 °C; ^{1}H NMR δ 0.5–1.0 (m, 4 H), 1.28 (q, J = 0.5 Hz, 3 H), 1.41 (s, 3 H), 1.65 (s, 3 H), 1.70 (q, J = 0.5 Hz, 3 H), and 2.55 and 2.75 (AB q, J_{AB} = 7.5 Hz, 2 H); ^{13}C NMR δ 5.8, 6.5, 8.4, 11.3, 12.4, 12.8, 30.8, 38.6, 41.5, 45.5, 47.2, 47.5, 52.5, 110.4, 110.9, 111.2, 112.7, 132.5, and 136.6; IR 1660 and 2240 cm^{-1}; MS m/e 302 (M$^+$). Anal. Calcd for $C_{19}H_{18}N_4$: C, 75.47; H, 6.00; N, 18.53. Found: C, 75.20; H, 5.92; N, 18.24.

No indication for an intermediate adduct was obtained from ^{1}H NMR spectra recorded during an experiment performed at low temperature (T = −40 °C).

Attempted Addition of TCNE to 16. Under the conditions mentioned above **16** was not found to react with TCNE. Even at higher temperatures (T < 150 °C and hexachlorobuta-1,3-diene as the solvent) no formation of an adduct was observed by ^{1}H NMR spectroscopy.

Synthesis of Spiro[cyclopropane-1,3′-1′,2′,5′,6′-tetramethyl-4′-vinylidenetricyclo[3.1.0.0$^{2',6'}$]hexane] (24). Under phase-transfer conditions dibromocarbene was allowed to react with compound **15** (0.870 g, 5.00 mmol) in the way indicated earlier (synthesis of **6**). Excess bromoform was removed by distillation under reduced pressure (T < 35 °C). By ^{1}H NMR spectroscopy signals due to olefinic protons in **15** were shown to be absent and, furthermore, absorptions due to the four methyl groups in **23** (δ 1.07, 1.27, 1.33, and 1.50) were observed. Under a nitrogen atmosphere methyllithium (4.0 mL, 1.5 N in ether) was added to a solution of **23** in ether (25 mL) at −50 °C followed by workup as reported previously (preparation of **8**). Preparative TLC (n-pentane) afforded 27% of **24** as a colorless mobile oil (0.247 g, 1.33 mmol): ^{1}H NMR δ 0.25–0.55 (m, 4 H), 0.73 (s, 3 H), 1.12 (s, 3 H), 1.38 (s, 6 H), and 4.90 (s, 2 H); IR 1965 and 3050 cm^{-1}; MS Calcd exact mass, m/e 186.141 (M$^+$); MS Found, m/e 186.144.

Addition of TCNE to 24. Upon addition of TCNE (0.170 g, 1.33 mmol) to a solution of **24** (0.247 g, 1.33 mmol) in chloroform (0.3 mL) kept in a NMR tube at −40 °C a reaction took place leading to a product (**25**) containing olefinic protons [δ 5.47 (d, J = 2.5 Hz) and 6.02 (d, J = 2.5 Hz)]. However, when the temperature was raised to

room temperature the adduct decomposed. Upon addition of more TCNE the formation of yet another adduct (presumably 2:1) was observed (also at −40 °C) suggesting the presence of a vinylcyclopropane moiety in the initially formed adduct **25**. Because of the encountered difficulties in workup no adduct was isolated.

Registry No.—**1**, 50590-86-8; **3**, 65103-68-6; **4**, 65103-69-7; **5**, 65103-70-0; **6**, 65103-71-1; **7**, 65103-72-2; **8**, 65103-73-3; **9**, 65103-74-4; **10**, 65103-75-5; **11**, 65103-76-6; **12**, 65103-77-7; **13**, 65103-78-8; **14**, 65103-79-9; **15**, 65103-80-2; **16**, 65103-81-3; **17**, 19063-11-7; **18**, 56745-77-8; **19**, 65103-82-4; **20**, 65103-83-5; **21**, 65103-84-6; **23**, 65103-85-7; **24**, 65103-86-8; **25**, 65103-87-9; chloroform, 67-66-3; bromoform, 75-25-2; diazomethane, 334-88-3.

References and Notes

(1) H. Hogeveen and P. W. Kwant, *Tetrahedron Lett.*, 3747 (1973).
(2) H. Hogeveen and P. W. Kwant, *J. Org. Chem.*, **39**, 2624 (1974).
(3) W. F. J. Huurdeman, Thesis, University of Groningen, 1976.
(4) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **76**, 6162 (1954).
(5) W. von E. Doering and P. M. LaFlamme, *J. Am. Chem. Soc.*, **78**, 5447 (1956).
(6) W. von E. Doering and P. M. LaFlamme, *Tetrahedron Lett.*, 75 (1958).
(7) L. Skattebøl, *Acta Chem. Scand.*, **17**, 1683 (1963).
(8) L. Skattebøl, *Tetrahedron Lett.*, 1107 (1967), and references cited therein.
(9) M. Makosza and W. Wawrzyniewicz, *Tetrahedron Lett.*, 4659 (1969).
(10) D. Kok, unpublished results.
(11) E. V. Dehmlow and J. Schonefeld, *Justus Liebigs Ann. Chem.*, **744**, 42 (1971).
(12) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, N.Y., 1970.
(13) The isomerization of the bicyclobutane moiety eventually leading to the formation of an aromatic compound is not entirely clear.
(14) J. Bainvel, B. Wojtkowiak, and R. Ramonet, *Bull. Soc. Chim. Fr.*, 978 (1963).
(15) A. Beverloo, M. C. Dieleman, P. E. Verkade, K. S. de Vries, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **81**, 1033 (1962).
(16) H. E. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, *Org. React.*, **20**, 1 (1973), and references cited therein.
(17) T. L. Jacobs, *Heterocycl. Compd.*, **5**, 72 1957.
(18) S. Sarel, A. Felzenstein, and J. Yovell, *J. Chem. Soc., Chem. Commun.*, 753 (1974).
(19) R. F. Heldeweg, H. Hogeveen, and C. Zwart, *Tetrahedron Lett.*, 2535 (1977).
(20) D. Hausigk, *Synthesis*, 307 (1971).
(21) For the synthesis of **18**, see R. F. Heldeweg, H. Hogeveen, and E. P. Schude, *J. Org. Chem.*, this issue, companion paper.

Photoinduced Decomposition of Peracetic Acid in Benzene

Yoshiro Ogata* and Kohtaro Tomizawa

Contribution No. 243 from the Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya, Japan

Received September 8, 1977

The decomposition of peracetic acid in benzene, which was initiated by two light sources (at 2537 Å or over 2900 Å), showed preferential reaction of methyl radical with benzene, affording toluene, rather than reaction of hydroxyl radical, affording phenols. Analysis of simple products including methane, ethane and water showed that induced decomposition of peracid by methyl and hydroxyl radicals is the major pathway rather than aromatic radical substitution. The formation of biphenyl by phenyl radical coupling or addition of phenyl radical to benzene is not important.

The interaction between radicals and aromatic hydrocarbons may involve two reactions, i.e., radical addition and hydrogen atom abstraction, and radical addition is said to predominate in solution.[1,2] The reaction of methyl radical with benzene affords mainly toluene via addition and dehydrogenation,[1,2] while hydroxyl radical gives phenols and coupling products.[3-5]

The thermal decomposition of peracetic acid in benzene has been studied kinetically[6] but is only limited information on the decomposition mechanism and products. The photolysis of peracetic acid in cyclohexane was reported to give mainly cyclohexanol which suggests induced decomposition of peracid by cyclohexyl radical.[7]

Our previous study[8] suggested that the photolysis of peracetic acid in toluene involved the induced decomposition of peracid by CH_3·, HO·, and $PhCH_2$· radicals and the extent of the induced decomposition varied with wavelength of light.

The present paper discloses the mechanism of photoinduced decomposition of peracetic acid in benzene, where more induced decomposition occurs than in toluene.

Results

The photolysis of peracetic acid in benzene with 2537 Å or >2900 Å light afforded carbon dioxide, oxygen, methane, ethane, water, methanol, methyl acetate, toluene, phenol, and biphenyl (trace). The yield of phenol with 2537 Å light increases with a decrease in peracid concentration, while only a trace of phenol is formed at >2900 Å independent of the peracid concentration. Trace amounts of xylenes and methylbiphenyls (M^+ 168, *m/e* 152, 153, 165, 167, 168 and no peak of *m/e* 91 corresponding to $PhCH_2$)[9] were obtained in both photolyses.

Estimation of CO_2 and O_2. CO_2 (1 mol) was evolved from 1 mol of peracid decomposed with 2537 Å light, but the yield of CO_2 was 5–10% lower at >2900 Å (Tables I and II). The yield of O_2 was 5–15% of peracid decomposed at 2537 Å and >2900 Å.

Products. The time dependence of yields was studied in order to know primary products and the possibility of further reaction. These results are shown in Tables I (2537 Å) and II (>2900 Å). As is apparent from the tables, the yield of H_2O, methane, and toluene increases as the photolysis proceeds, i.e., the concentration of peracid decreases. The yield of phenol is relatively high at 2537 Å, while only a trace was detected at >2900 Å.

Analogously to toluene,[8] the yield of MeOH decreases as the photolysis proceeds. The MeOH initially formed being esterified to methyl acetate with acetic acid.

The effects of the concentrations of peracid and radicals on the yields were studied to estimate the reactivity of methyl and hydroxyl radicals, and the results are shown in Tables III (2537 Å) and IV (>2900 Å).

The effects of peracid concentration on the yields (Tables III and IV) were similar as observed in the time dependence (Tables I and II). The remarkable difference between 2537 Å and >2900 Å was observed in the yields of H_2O, CH_4, C_2H_6, and PhOH. That is, at 2537 Å, the yield of H_2O is high (relative to >2900 Å) and the yield of CH_4 is less than that of C_2H_6. Whereas at >2900 Å, the yield of H_2O is low and the yield of CH_4 is greater than that of C_2H_6. In addition, the yield of

0022-3263/78/1943-1920$01.00/0

Table I. Time Dependence of Product Yields on Irradiation (2537 Å) Time in Photolysis of Peracetic Acid[c] in Benzene

Time, h	[CH_3CO_3H decomposed] × 10^4 mol (%)	Products × 10^4 mol (%)										
		CO_2[a]	O_2[b]	H_2O[a]	CH_4[a]	C_2H_6[b]	MeOH[a]	MeOAc[a]	PhMe[a]	Xylene[b]	PhOH[a]	PhPh[b]
0.5	3.135	3.079	Trace	0.429	0.509	0.690	0.640	0.014	0.210	0.016	0.017	0.011
	(8.5)	(98.2)		(13.7)	(16.2)	(44.0)	(20.4)	(0.4)	(6.7)	(1.0)	(0.2)	(0.7)
1.0	5.141	5.017	0.084	0.952	0.866	1.089	0.897	0.037	0.562	0.044	0.105	0.015
	(13.9)	(97.6)	(3.3)	(18.5)	(16.9)	(42.4)	(17.5)	(0.7)	(10.9)	(1.7)	(2.0)	(0.6)
3.0	13.79	14.10	0.396	3.092	2.372	2.835	2.045	0.142	1.808	0.139	0.441	0.026
	(37.3)	(102.3)	(5.7)	(22.4)	(17.2)	(41.1)	(14.8)	(1.0)	(13.1)	(2.0)	(3.2)	(0.4)
4.5	18.18	17.89	0.658	4.861	3.240	3.748	2.227	0.340	2.800	0.193	0.791	0.028
	(49.2)	(98.4)	(7.2)	(26.7)	(17.8)	(40.6)	(12.3)	(1.9)	(15.4)	(2.1)	(4.4)	(0.3)
7.0	24.45	23.94	0.949	6.936	4.460	4.831	2.245	0.645	3.888	0.308	1.208	0.088
	(66.1)	(97.9)	(7.8)	(28.4)	(18.2)	(39.5)	(9.2)	(2.6)	(15.9)	(2.5)	(4.9)	(0.3)

[a] % = [yield]/[peracid decomposed] × 100. [b] % = 2 × [yield]/[peracid decomposed] × 100. Experimental error was within ±5% by GLC analysis. [c] Initial concentration of peracid = 3.699 mmol/25 mL (0.148 M).

Table II. Time Dependence of Product Yields on Irradiation (>2900 Å) Time in Photolysis of Peracetic Acid[c] in Benzene

Time, h	[CH_3CO_3H decomposed] × 10^4 mol (%)	Products × 10^4 mol (%)										
		CO_2[a]	O_2[b]	H_2O[a]	CH_4[a]	C_2H_6[b]	MeOH[a]	MeOAc[a]	PhMe[a]	Xylene[b]	PhOH[a]	PhPh[b]
1.0	2.608	2.283	0.009	0.146	1.149	0.239	0.491	0.003	0.118	0.009		
	(7.1)	(87.5)	(0.7)	(5.6)	(44.1)	(18.4)	(18.8)	(0.1)	(4.5)	(0.7)		
2.0	4.931	4.455	0.041	0.518	2.239	0.422	0.908	0.018	0.333	0.018	0.002	0.001
	(13.3)	(90.3)	(1.7)	(10.5)	(45.4)	(17.1)	(18.4)	(0.4)	(6.8)	(0.7)	(0.1)	(0.1)
4.0	9.575	8.546	0.148	1.631	4.493	0.813	1.540	0.056	0.831	0.027	0.006	0.005
	(25.9)	(89.3)	(3.1)	(17.0)	(46.9)	(17.0)	(16.1)	(0.6)	(8.7)	(0.6)	(0.1)	(0.1)
6.0	13.27	12.26	0.380	2.696	6.108	1.083	2.006	0.122	1.084	0.033	0.024	0.008
	(35.9)	(92.4)	(5.7)	(20.3)	(46.0)	(16.3)	(15.1)	(0.9)	(8.2)	(0.5)	(0.2)	(0.1)
9.0	17.98	16.46	0.788	3.848	8.553	1.424	2.411	0.223	1.881	0.058	0.047	0.013
	(48.6)	(91.6)	(8.8)	(21.4)	(47.6)	(15.8)	(13.4)	(1.2)	(10.5)	(0.6)	(0.3)	(0.2)
12.0	21.71	20.46	1.220	4.928	10.56	1.811	2.872	0.239	2.338	0.078	0.080	0.022
	(58.7)	(94.3)	(11.2)	(22.7)	(48.6)	(16.7)	(13.2)	(1.1)	(10.8)	(0.7)	(0.4)	(0.2)

[a] % = [yield]/[peracid decomposed] × 100. [b] % = 2 × [yield]/[peracid decomposed] × 100. Experimental error was within ±5% by GLC analysis. [c] Initial concentration of peracid = 3.699 mmol/25 mL (0.148 M).

PhOH increases with decreasing peracid concentration at 2537 Å, while only a trace of PhOH is observed at >2900 Å. The difference may be due to the concentration of produced radicals.

Discussion

Initial Process. As reported previously with toluene,[8] in view of the extinction coefficient of benzene ($\epsilon_{2537Å}$ = 90 and $\epsilon_{>2900Å} \approx 0$)[10] and peracetic acid ($\epsilon_{<2537Å} < 25$,[11] $\epsilon_{2900Å}$ = 2.4, $\epsilon_{3000Å}$ = 1.23, and $\epsilon_{3600Å}$ = 0.046),[8] the 2537 Å light should be absorbed predominantly by benzene, since the extinction coefficient of benzene is ca. 5 times as large as that of peracid and benzene is in a large excess. Then excited benzene must transfer energy to peracid as toluene does,[8] producing two radicals (eq 1–3). On the other hand, the >2900 Å irradiation excites mainly peracetic acid resulting in the O–O cleavage (eq 4), because the extinction coefficient of peracid is much higher than that of benzene at >2900 Å.

$$PhH \xrightarrow{h\nu\ (2537\ Å)} [PhH]^* \quad (1)$$

$$[PhH]^* + CH_3CO_3H \rightarrow PhH + [CH_3CO_3H]^* \quad (2)$$

$$[CH_3CO_3H]^* \rightarrow CH_3CO_2\cdot + HO\cdot \rightarrow CH_3\cdot + CO_2 + HO\cdot \quad (3)$$

$$CH_3CO_3H \xrightarrow{h\nu\ (>2900\ Å)} CH_3CO_2\cdot + HO\cdot \rightarrow CH_3\cdot + CO_2 + HO\cdot \quad (4)$$

The rate of radical production by eq 1–3 with 2537 Å may be greater than that by eq 4 with >2900 Å, since half-time of decomposition is ca. 4.2 h with 2537 Å and ca. 9.5 h with >2900 Å. This is due to the higher extinction coefficient of benzene than that of peracetic acid and also to a large excess of benzene. Therefore, this high relative absorbance at 2537 Å (where total light would be absorbed within a pathlength of 2 cm) indicates the possibility of producing high local concentrations of the radicals relative to the >2900 Å photolysis. This would certainly have an effect on yields of radical–radical coupling products.

Induced Decomposition of Peracid by Radicals. As reported previously with toluene,[8] $CH_3\cdot$ and HO· radicals formed in eq 3 and 4 may induce the following reactions.

$$PhH + R\cdot \rightarrow Ph\cdot + RH \quad (5)$$

$$CH_3CO_3H + R\cdot \rightarrow CH_3CO_3\cdot + RH \quad (6)$$

$$CH_3CO_2OH + CH_3\cdot \rightarrow CH_3CO_2\cdot + CH_3OH \quad (7)$$

$$R = CH_3 \text{ and } HO$$

The direct H-atom abstraction by radicals (eq 5) may occur.[12] However, this reaction is not important since the yield of the coupling product (e.g., biphenyl) is very low even at high concentrations of peracid (Tables III and IV).

In the 2537 Å photolysis, the total yields of CH_4 and H_2O are ca. 46–60% per peracid decomposed and the total yields of products bearing phenyl group are 11–27% as shown in Table III. The total yields of CH_4 and H_2O in the >2900 Å photolysis are ca. 58–73% and the total yields of products bearing phenyl group are ca. 4–16% (Table IV). Therefore,

Table III. Effect of Peracetic Acid Concentration on Product Yields in Irradiation (2537 Å) of Peracetic Acid in Benzene

$[CH_3CO_3H]^a$ × 10 M	$[CH_3CO_3H$ decomposed] × 10^4 mol (%)	Products × 10^4 mol (%)									
		O_2[b]	H_2O[c]	CH_4[c]	C_2H_6[b]	MeOH[c]	MeOAc[c]	PhMe[c]	Xylene[b]	PhOH[c]	PhPh[b]
4.372	84.91	2.428	25.65	14.29	17.90	18.99	2.700	7.727	0.403	0.403	0.055
	(77.7)	(5.7)	(30.2)	(16.8)	(42.2)	(22.4)	(3.2)	(9.1)	(1.0)	(0.6)	(0.1)
3.240	54.65	1.465	15.65	10.16	11.41	10.25	1.459	5.771	0.281	0.312	0.082
	(67.5)	(5.4)	(28.6)	(18.6)	(41.8)	(18.8)	(2.7)	(10.6)	(1.0)	(0.6)	(0.3)
2.665	57.51	2.088	19.13	10.46	11.58	10.93	1.984	6.688	0.316	0.719	0.101
	(86.3)	(7.3)	(33.3)	(18.2)	(40.3)	(19.8)	(3.5)	(11.6)	(1.1)	(1.3)	(0.4)
1.874	36.96	1.464	11.30	7.266	7.000	6.180	1.005	5.463	0.224	1.087	0.052
	(78.9)	(7.9)	(30.6)	(19.7)	(37.9)	(16.7)	(2.7)	(14.8)	(1.2)	(2.9)	(0.3)
1.197	23.94	0.903	8.216	5.214	4.715	3.347	0.491	3.871	0.138	1.183	0.037
	(80.0)	(7.5)	(34.3)	(21.8)	(39.4)	(14.0)	(2.1)	(16.2)	(1.2)	(4.9)	(0.3)
0.942	19.34	0.838	6.303	4.094	3.695	2.798	0.414	3.050	0.120	1.400	0.017
	(82.1)	(8.7)	(32.6)	(21.2)	(38.2)	(14.5)	(2.1)	(15.8)	(1.2)	(7.2)	(0.2)
0.391	7.354	0.346	2.519	1.624	1.359	1.174	0.134	1.025	0.044	0.480	0.012
	(75.2)	(9.4)	(34.3)	(22.1)	(37.0)	(16.0)	(1.8)	(13.9)	(1.2)	(6.5)	(0.3)
0.176	3.535	0.201	1.320	0.787	0.667	0.427	0.067	0.663	0.024	0.241	0.008
	(80.3)	(11.4)	(37.4)	(22.3)	(37.7)	(12.1)	(1.9)	(18.8)	(1.4)	(6.8)	(0.4)

[a] Initial concentration. [b] % = 2 × [yield]/[peracid decomposed] × 100. [c] % = [yield]/[peracid decomposed] × 100. Experimental error was within ±5% by GLC analysis.

Table IV. Effect of Peracetic Acid Concentration on Product Yields in Irradiation (>2900 Å) of Peracetic Acid in Benzene

$[CH_3CO_3H]^a$ × 10 M	$[CH_3CO_3H$ decomposed] × 10^4 mol (%)	Products × 10^4 mol (%)									
		O_2[b]	H_2O[c]	CH_4[c]	C_2H_6[b]	MeOH[c]	MeOAc[c]	PhMe[c]	Xylene[b]	PhOH[c]	PhPh[b]
4.372	65.39	3.845	11.92	26.18	6.461	12.15	2.256	2.138	0.016	0.098	0.134
	(59.8)	(11.8)	(18.2)	(40.0)	(19.8)	(18.6)	(3.5)	(3.3)	(0.1)	(0.2)	(0.4)
3.240	44.30	2.997	8.258	18.79	4.191	7.194	1.444	1.741	0.053	0.089	0.071
	(54.7)	(13.5)	(18.6)	(42.4)	(18.9)	(16.2)	(3.3)	(3.3)	(0.2)	(0.2)	(0.3)
2.665	44.20	3.346	10.40	18.72	3.803	7.850	1.114	2.475	0.066	0.141	0.066
	(66.3)	(15.1)	(23.5)	(42.4)	(17.2)	(17.8)	(2.5)	(5.6)	(0.3)	(0.3)	(0.3)
1.874	26.68	1.717	5.963	11.85	2.180	3.975	0.758	2.644	0.111	0.125	0.017
	(57.0)	(12.9)	(22.4)	(44.4)	(16.3)	(14.9)	(2.8)	(9.9)	(0.8)	(0.5)	(0.1)
1.197	17.54	1.058	4.257	8.088	1.243	2.703	0.217	1.775	0.080	0.074	0.021
	(58.6)	(12.1)	(24.3)	(46.1)	(14.2)	(15.4)	(1.2)	(10.1)	(0.9)	(0.4)	(0.2)
0.942	13.01	0.727	2.970	5.989	0.920	1.941	0.215	1.443	0.082	0.047	0.012
	(55.2)	(11.2)	(22.8)	(46.0)	(14.2)	(14.9)	(1.7)	(11.1)	(1.3)	(0.4)	(0.2)
0.391	6.720	0.439	1.696	3.156	0.452	0.816	0.088	0.892	0.035	0.028	0.008
	(68.7)	(13.1)	(25.2)	(47.0)	(13.4)	(12.2)	(1.3)	(13.3)	(1.0)	(0.4)	(0.3)
0.176	2.781	0.168	0.719	1.299	0.184	0.345	0.031	0.394	0.017	0.008	0.003
	(63.1)	(12.1)	(25.9)	(46.7)	(13.3)	(12.4)	(1.1)	(14.2)	(1.2)	(0.3)	(0.2)

[a] Initial concentration. [b] % = 2 × [yield]/[peracid decomposed] × 100. [c] % = [yield]/[peracid decomposed] × 100. Experimental error was within ±5% by GLC analysis.

CH_3· and HO· must abstract H atom from peracid, because the quantities of H atoms available from benzene are insufficient for the CH_4 and H_2O produced.

Furthermore, as shown in Tables I and II, the yield of H_2O increases with decomposing peracid. The yield of CH_4 at 2537 Å is lower than that of H_2O after 1-h irradiation, while the yield of CH_4 at >2900 Å is much higher than that of H_2O at any reaction time. These results suggest that radicals CH_3· and HO·, which were directly formed by eq 3 and 4, couple to give C_2H_6, H_2O_2, and CH_3OH, and alternatively they decompose CH_3CO_3H (eq 6 and 7) to give CH_4, H_2O, CH_3OH, and (H_2O_2). Thus induced decompositions (eq 6 and 7) reduce the concentration of HO· compared with that of CH_3· because CH_3CO_3· and CH_3CO_2· (eq 6 and 7) give CH_3· alone. Therefore, the yield of H_2O will be lower than that of CH_4 although the H-atom abstraction by HO· is preferred to that by CH_3·.[13]

Acetylperoxy radical (CH_3CO_3·) by eq 6 should decompose to give CH_3·, CO_2, and O_2 as reported previously;[14] CH_3· thus formed may repeatedly be used in the induced reaction, since CH_3· will again be produced by a radical attack on peracetic acid.

Coupling of Radicals. Ethane may be formed by radical coupling ($2CH_3$· → C_2H_6). Table V shows that the ratio $[C_2H_6]/[CO_2]$ (≈0.19 with 2537 Å and ≈0.075 with >2900 Å) is greater than that with toluene (≈0.16 with 2537 Å and ≈0.065 with >2900 Å). This fact reveals that coupling of CH_3· is favored in benzene, because ring H atoms are difficult to abstract compared with the methyl H atoms of toluene.

As stated above, the induced decomposition (eq 6) and thus radical concentration are related to the wavelength used, e.g., the higher absorbance at 2537 Å may give higher (local) concentrations of radicals relative to the >2900 Å photolysis. As shown in Table V, the ratio $[C_2H_6]/[CO_2]$ is higher at 2537 Å. This is due to the high concentration of CH_3· radical at 2537 Å, which again accelerates the formation of CH_3· by induced

Table V. Decomposition of Peracetic Acid in Benzene vs. Toluene

Temp, °C	$[CH_3CO_3H]^a$ × 10^2 M	CO_2/ $[CH_3CO_3H$ decomposed]	CH_4/CO_2	C_2H_6/CO_2	$(CH_4 + C_2H_6)/CO_2$
rt[b]	9.42	0.98	0.216	0.195	0.606
rt[b]	3.91	0.97	0.228	0.191	0.610
rt[b]	1.76	1.01	0.220	0.189	0.598
rt[c]	9.42	0.89	0.517	0.080	0.677
rt[c]	3.91	0.93	0.505	0.072	0.649
rt[c]	1.76	0.91	0.513	0.073	0.659
rt[d]	6.50	1.01	0.40	0.16	0.72
rt[d]	3.70	1.02	0.44	0.16	0.76
rt[e]	10.6	0.89	0.70	0.064	0.83
rt[e]	6.8	0.91	0.65	0.057	0.76
85.0[f]	2.30	0.07	0.72		
65.0[g]	7.60		0.293	0.024	0.340

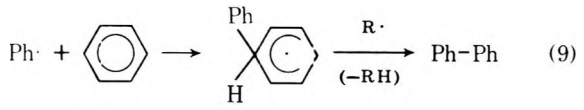
[a] Initial concentration. [b] With 2537 Å light irradiation. [c] With >2900 Å light irradiation. [d] Data summarized for photolysis of peracetic acid in toluene with 2537 Å light by Y. Ogata and K. Tomizawa, *J. Org. Chem.* **43**, 261 (1978). [e] Data summarized for photolysis of peracetic acid in toluene with >2900 Å light by Y. Ogata and K. Tomizawa, *J. Org. Chem.*, **43**, 261 (1978). [f] Data reported for thermal decomposition of peracetic acid in toluene by F. W. Evans and A. H. Sehon, *Can. J. Chem.*, **41**, 1826 (1963). [g] Data reported for thermal decomposition of diacetyl peroxide in benzene by M. Levy and M. Szwarc, *J. Am. Chem. Soc.*, **76**, 5981 (1954).

decomposition of peracid (eq 6) and eventually leads to the high ratio.

This is apparent from the formation of methanol. The total yields of methanol and methyl acetate were 14–25% at 2537 Å and 13–22% at >2900 Å with benzene, while those yields were 2.4–10.7% at 2537 Å and 5.6–8.5% at >2900 Å with toluene. The increase of total yields in benzene compared with that in toluene may be due to the decrease of the reactivity of radical on benzene, i.e., the acceleration of coupling of CH_3· and HO· radicals and an induced reaction (eq 7).

In contrast, there is obtained only a trace of biphenyl which is formed by coupling (eq 8) and/or addition (eq 9).

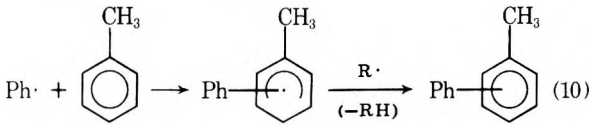
$$2Ph\cdot \longrightarrow Ph\text{-}Ph \qquad (8)$$



(9)

Coupling (eq 8) is less probable than the addition (eq 9) in view of the low concentration of phenyl radical which is formed by the ring H atom abstraction.

Methylbiphenyls detected by GC–MS may also be formed similarly (eq 10).

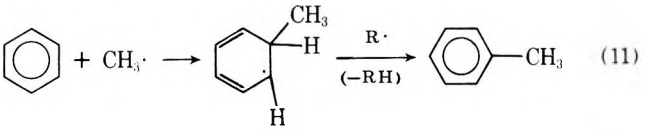


(10)

Addition and Abstraction by Radicals. The formation of CH_4 or H_2O) via abstraction of ring H atoms by CH_3· and HO· radicals is unlikely, so that toluene, xylene, and phenol may be formed by addition of the appropriate radical to benzene (eq 11–13).

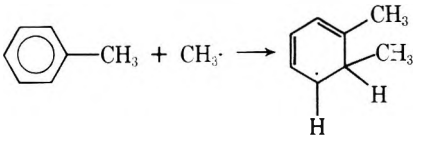
As to the formation of xylenes, eq 12a is preferred to eq 12b, since intermediate **1** is converted readily to toluene in the presence of radicals, xylenes formed in this photolysis include *o*-, *m*- and *p*-xylenes, and there is no evidence for the presence of dimethyldihydrobenzene (**2**) by means of GC–MS.

The photolysis of methylmercuric iodide in benzene with 3130 Å light gave toluene (ca. 40%) and xylenes (ca. 1%).[15] The lower yield in our photolysis (Tables III and IV) is attributed to the variety of reactants for attack of CH_3·, i.e., peracetic acid (induced reaction shown in eq 6 and 7), CH_3· and HO· (coupling), and benzene (addition), in contrast to the simple reactant (benzene alone) in methylmercuric iodide photolysis.

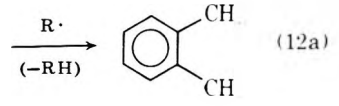


(11)

1 (or para isomer)

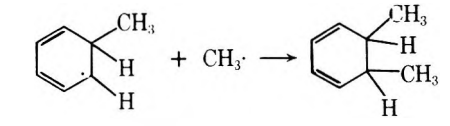


(or meta or para isomer)

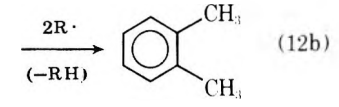


(12a)

(or meta or para isomer)

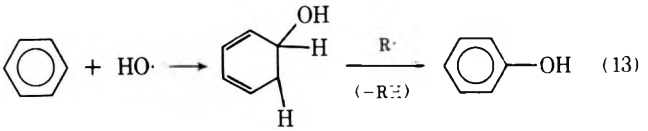


1 (or para isomer) **2**



(12b)

(or para isomer)



(13)

An increase of the yield of toluene was observed at lower peracid concentration (Tables III and IV). With increasing peracid concentration, the concentration of radicals generated by photolysis (eq 1–4) and also by induced decomposition (eq 6 and 7) increases, hence coupling is more important than addition, whereas with lowering peracid concentration, the extent of coupling decreases and hence the extent of addition increases.

The yield of phenol at 2537 Å is less than that of toluene and the yield increases with a decrease of peracid concentration. The concentration of HO· is lower than that of CH_3· because of the occurrence of eq 6 and 7 and hence the yield of phenol is lower than that of toluene. The proportionality of the yield

of phenol and $1/[CH_3CO_3H]$ may be due to a similar reason as that given for toluene as stated above.

The very low yield of phenol at >2900 Å (Table IV) is attributable to the facile reaction of HO· with peracid (eq 6) and/or its reaction with benzene to abstract H atom forming stable H_2O rather than addition to benzene. On the other hand, the high relative yield of phenol at 2537 Å compared with the >2900 Å photolysis may be due to higher concentration of HO· (directly formed) on account of the higher absorbance at 2537 Å. The increase of the yield of phenol with decreasing peracid concentration may be due to the increasing ratio of addition vs coupling.

As stated above, the yields of aromatic products, i.e., toluene, xylenes, phenol, and biphenyl, are low on the basis of peracetic acid decomposed. This is due to the low reactivity of benzene to radicals (CH_3· and HO·) which attacks preferentially peracid by abstracting atoms, as reported in the reaction of peracetic acid with *tert*-butoxy radical,[14] thus CH_3· and HO· abstract H atom of CH_3CO_3-**H** to give CH_4 and H_2O, respectively, and CH_3· abstracts HO· of CH_3CO_2-OH to form methanol.

For the formation of O_2 there are two conceivable mechanisms, i.e., dark disproportionation of peracid (eq 14) and decomposition of peroxyacetyl radical (eq 15).[14]

$$2CH_3CO_3H \rightarrow 2CH_3CO_2H + O_2 \quad (14)$$

$$2CH_3CO_3\cdot \rightarrow 2CH_3\cdot + 2CO_2 + O_2 \quad (15)$$

Equation 14 does not evolve CO_2, so that is not in accord with our results (Tables I and II); hence the formation of O_2 may be due to eq 15. O_2 evolved by eq 15 may react rapidly with alkyl radical (CH_3·) to give peroxy radical (CH_3OO·) and/or may escape out of the solution. When the concentration of CH_3· is high, the reaction of CH_3· with O_2 is probable and thus methylperoxy radicals formed may react with themselves and peroxyacetyl radicals to form CH_3OH, CH_3CO_2H, O_2, etc., as reported previously.[14] In fact, an increase of concentrations of peracid at 2537 Å in our photolysis increased the yield of CH_3OH by the reaction of CH_3· with O_2 and/or coupling of CH_3· with HO· and/or induced decomposition (eq 7). On the other hand, the higher yield of O_2 at lower concentration of peracid may be due to the evolution of O_2 from the solution without reacting with CH_3·.

The concentration of radicals formed by eq 4 is low at >2900 Å compared with that at 2537 Å; therefore, the possibility of reaction of O_2 with CH_3· is lower than that at 2537 Å and hence the yield of O_2 evolved is higher than that at 2537 Å. Tables III and IV show that this is the case.

Conclusions

(i) The decomposition of peracid by excited energy transfer (eq 1–3) is more effective at 2537 Å than that by the direct decomposition (eq 4) at >2900 Å, so that the contribution of induced decomposition (eq 6) at 2537 Å may be less than that at >2900 Å. This less contribution of induced decomposition (eq 6) may be due to the increased coupling at 2537 Å caused by the higher concentrations of radicals. Therefore, the evolution of O_2 at >2900 Å is greater than that at 2537 Å.

(ii) The reaction of radicals with peracid, i.e., induced decomposition, is preferred to the reaction with benzene.

(iii) The yield of toluene, a product via addition of CH_3· to benzene, is ca. 9–18% (2537 Å) and 3–14% (>2900 Å), while the yield of xylenes from toluene[8] is 10–14% (2537 Å) and 5–7% (>2900 Å).

Experimental Section

Materials. Peracetic acid was prepared by the reaction of acetic anhydride (205 g) with 60% aqueous H_2O_2 added with concentrated H_2SO_4 (0.5 mL) at 35–40 °C.[16] Benzene was purified by distillation over P_2O_5. A water-free peracetic acid–benzene solution was prepared by the method of Hormer[17] and was immediately irradiated after the estimation of peracid concentration.

Apparatus. GLC analyses were performed on a Yanagimoto gas chromatograph with FID and TCD, Model G 180. A Shimadzu GC-MS 7000 gas chromatograph–mass spectrometer was used to determine gaseous products and identify the photolysis products. A Halos low-pressure 30 W Hg lamp and a Halos high-pressure 300 W Hg lamp were used as light sources. All experiments were carried out in a cylindrical quartz vessel (2 × 12 cm) or a cylindrical Pyrex vessel (2 × 12 cm).

Analyses of Gaseous Products. The gaseous products evolved by photolysis were collected in a gas buret (300 mL) connected with a capillary tube to the photolysis system. Analysis of gaseous products was carried out by two methods: (A) Analysis of CO_2 was carried out by the measurement of the gas volume absorbed in 33% aqueous KOH and then analysis of O_2 was done by absorption with aqueous alkaline pyrogallol.[18] Gaseous products remaining in the gas buret were analyzed by GC–MS and GLC with columns packed with Porapak T (80–100 mesh, 2.5 mm × 2 m) and Porapak QS (80–100 mesh, 2.5 mm × 2 m); the mass analysis of CH_4 and C_2H_6 was done by the comparison of peaks with those of authentic samples.[19] (B) Analyses of O_2 and CH_4 were carried out by GLC with a column packed with Molecular Sieve 5A (80–100 mesh, 2.5 mm × 2 m) with thermal conductivity detector (TCD) using He as a carrier gas. Analyses of CO_2, CH_4, and C_2H_6 were performed by GLC with a column packed with Porapak QS with TCD.

Another estimation of CO_2 was done also by acidimetry with 10^{-2} N $Ba(OH)_2$ in which the gas had been bubbled with N_2 as a carrier.

Photolysis of a Mixture of Peracetic Acid and Benzene. A mixture of peracetic acid and benzene was photolyzed in a quartz cell with a 30 W low-pressure Hg lamp or in a Pyrex cell with a 300 W high-pressure Hg lamp through a water jacket (18–20 °C). After estimation of peracid remaining in the solution, a constant amount of Me_2SO–benzene was added to the photolyzate to avoid contamination by GLC thermolysis products of peracid.[20] Gaseous products evolved were analyzed by the above method and the products in the solutions were analyzed by GLC with TCD and FID (Porapak QS, Bentone 34-DIDP, PEG 20M Chamelite CS, and Apiezon Grease L). The same mixtures of peracetic acid–benzene as used in photolysis were kept standing under the same conditions (in the dark) without irradiation. After the same treatments as used in the photolysis, the solutions were analyzed by GLC. The yields of photolysis products were corrected by the observed yields (trace) of the dark reaction.

Registry No.—Peracetic acid, 79-21-0; benzene, 71-43-7; toluene, 108-88-3.

References and Notes

(1) M. Levy, M. Steinberg, and M. Szwarc, *J. Am. Chem. Soc.*, **76**, 3439 (1954).
(2) M. Levy and M. Szwarc, *J. Am. Chem. Soc.*, **76**, 5981 (1954).
(3) J. R. L. Smith and R. O. C. Norman, *J. Chem. Soc.*, 2897 (1963).
(4) K. Omura and T. Matsuura, *Tetrahedron*, **24**, 3475 (1968).
(5) C. R. E. Jefcoate, J. R. L. Smith, and R. O. C. Norman, *J. Chem. Soc. B*, 1013 (1969).
(6) F. W. Evans and A. H. Sehon, *Can. J. Chem.*, **41**, 1826 (1963).
(7) D. L. Heywood, B. Phillips, and H. A. Stansbury, Jr., *J. Org. Chem.*, **26**, 281 (1961).
(8) Y. Ogata and K. Tomizawa, *J. Org. Chem.*, **43**, 261 (1978).
(9) E. Stenhagen, S. Abrahamson, and F. W. McLefferty, "Registry of Mass Spectral Data", Vol. 1, Wiley, New York, N.Y., 1974, pp 556 and 557.
(10) S. L. Murov, "Handbook of Photochemistry", Marcel Dekker, New York, N.Y., 1973, p 3.
(11) O. H. Wheeler and L. A. Kaplan, "Organic Electron Spectral Data", Vol. 3, Interscience, New York, N.Y., 1966.
(12) M. Cher, *J. Phys. Chem.*, **68**, 1316 (1964).
(13) J. K. Kochi, "Free Radicals", Vol. 1, Wiley, New York, N.Y., 1973, pp 70–83.
(14) (a) N. A. Clinton, R. A. Kenley, and T. G. Traylor, *J. Am. Chem. Soc.*, **97**, 3746 (1975); (b) N. A. Clinton, R. A. Kenley, and T. G. Traylor, *ibid.*, **97**, 3752 (1975); (c) R. A. Kenley and T. G. Traylor, *ibid.*, **97**, 4700 (1975).
(15) G. E. Corbett and G. H. Williams, *J. Chem. Soc.*, 3437 (1964).
(16) Y. Ogata and K. Aoki, *J. Org. Chem.*, **31**, 4181 (1966).
(17) L. Hormer and E. Jurgens, *Chem. Ber.*, **90**, 2184 (1957).
(18) K. Hata, N. Sugiyama, T. Kobayashi, M. Ohta, and M. Ohki, "Kagaku Zikken-Ho", Tokyo Kagaku Dozin, Tokyo, 1974, pp 348 and 349.
(19) E. Stenhagen, S. Abrahamson, and F. D. McLefferty, "Registry of Mass Spectral Data", Vol. 1, Wiley, New York, N.Y., 1974, pp 1 and 2.
(20) Private communication by Dr. Y. Sawaki.

Role of Glucose and Related Compounds in Micellar and Nonmicellar Nucleophilic Reactions

Clifford A. Bunton,* Gianfranco Savelli,[1] and Luis Sepulveda[2]

Department of Chemistry, University of California, Santa Barbara, California 93106

Received July 5, 1977

The decomposition of 2,4-dinitrofluorobenzene (DNF) and 2,4-dinitrochlorobenzene (DNC) in aqueous NaOH and cetyltrimethylammonium bromide (CTABr) is speeded by added glucose and the kinetic form and spectral evidence suggest that an intermediate ether is formed and decomposes to 2,4-dinitrophenoxide ion. This intermediate is also formed in the absence of CTABr. The reaction in CTABr is also speeded by methyl α-glucoside and sorbose. The rate constants for the reaction of DNF with OH^- and the anion of the sugar and the decomposition of the ether can be separated by following the reactions at an isosbestic point and at λ_{max} for 2,4-dinitrophenoxide ion. Meisenheimer complexes are detected spectrally in reactions of glucose, sorbose, and sorbitol in the presence of CTABr, and the sorbitol complex is long-lived. Glucose also speeds the reaction of DNF in micelles of *p*-octyloxybenzyltrimethylammonium bromide. Glucose inhibits the reactions of glycyl glycinate with DNF in CTABr and of *p*-nitrophenyl diphenyl phosphate with fluoride and hydroxide ion. These polyols inhibit reaction by a medium effect, but their anions may react nucleophilically.

The effect of chemically inert solutes on micellar catalysis in water has been studied extensively,[3] and generally both electrolytes and nonpolar solutes decrease catalysis.[5,8,9] The effect of added electrolytes can be rationalized in terms of a competition between an inert counterion and a reactive ion for the micelle with some possible effect due to changes in micellar structure.[8,10] Nonionic hydrophilic solutes disrupt micelles, and hydrophobic solutes enter them and reduce the surface charge. Both effects should reduce micellar catalysis. Several monosaccharides apparently increase the catalysis by micellized cetyltrimethylammonium bromide (CTABr) of the reaction of 2,4-dinitrochlorobenzene (DNC) with hydroxide ion.[11] This interesting observation was unexpected and appeared to be an important exception to the well-documented examples of inhibition of micellar catalysis by inert solutes.[5-7] It was suggested that the sugars had a physical effect on the micellar structure but no evidence was given.

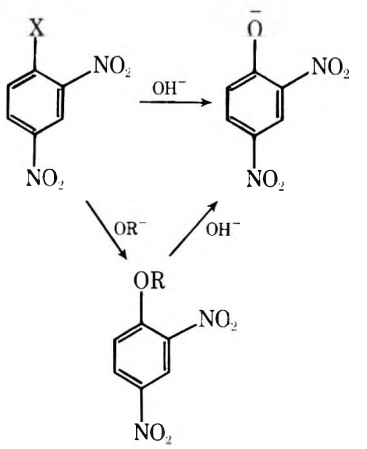
Alkoxide ions are good nucleophiles, even in water,[12] and the 1-hydroxyl groups of sugars have $pK_a \sim 12$,[13,14] so that at high pH an alkoxide ion might react with the halonitrobenzene. Attack of alkoxide ion occurs readily in water at high pH with both DNC and 2,4-dinitrofluorobenzene (DNF) in the presence of β-trifluoroethanol, propargyl alcohol, or choline, and with DNF the formation of the intermediate is much faster than its subsequent decomposition to products, although this is not so with DNC.[15]

The anion of a micellar bound sugar should be a good nucleophile. For example, micelles of alkyl(2-hydroxyethyl)-dimethylammonium bromide and related compounds are effective nucleophiles at high pH in nucleophilic aromatic substitution,[15] addition to carbocations, and dephosphorylation and deacylation.[16] It therefore seems probable that the rate enhancements reported in ref 11 are due to a chemical intervention by the sugar and not to a physical effect on the micelle.

If the beneficial effect of a sugar upon micellar catalysis has a physical origin it should be observed with a variety of nucleophiles, such as fluoride ion or amines, which react at relatively low pH, but if the sugar acts as a nucleophile the effect should be seen only at high pH where the sugar is partly ionized.

We therefore examined the effects of added D-glucose upon the micellar-catalyzed reactions of hydroxide ion and glycylglycine with DNF[17] and hydroxide and fluoride ion with *p*-nitrophenyl diphenyl phosphate.[18] Rates are increased when the sugar can react as a nucleophile, otherwise we observe inhibition.

D-Glucose was used in most experiments, but we used other



X = Cl, F
R = CH_2CF_3, $CH_2C{\equiv}CH$, $CH_2CH_2N^+Me_3$, glucosyl, $CH_2CH_2N^+Me_2C_{16}H_{33}$

polyols including methyl α-glucoside, whose 1-hydroxyl group is blocked. Glucose also speeds the reaction of DNF in aqueous sodium hydroxide and reaction intermediates are detected spectrally in the presence and absence of micelles.

Experimental Section

Materials. The reactants and CTABr were purified following procedures already described.[15] *p*-Octyloxybenzyltrimethylammonium bromide (OOBTABr) was prepared by reducing *p*-octyloxybenzoic acid to the alcohol ($LiAlH_4$), converting the alcohol into the bromide (PBr_3/Et_2O), and quaternizing the bromide with Me_3N in MeCN. The bromide was precipitated (Et_2O) and recrystallized (Me_2CO–Et_2O). This surfactant in water had cmc = 6.9×10^{-3} M, and there was no minimum in a plot of surface tension against concentration. (Found: C, 60.3; H, 9.1; N, 3.7; Br, 22.1. $C_{18}H_{32}NOBr$ requires: C, 60.3; H, 9.0; N, 3.9; Br, 22.3.)

Kinetics. All the reactions were followed spectrophotometrically at 25.0 °C, using solutions made up so that CO_2 was excluded. Solutions were freshly made up because glucose is unstable at high pH, and its decomposition is speeded by micelles of CTABr.[11] The reaction of glyclyglycine with DNF was followed at 355 nm, and that of *p*-nitrophenyl diphenyl phosphate with OH^- or F^- was followed at 403 nm. The formation of 2,4-dinitrophenoxide ion from DNF was followed at 358 nm, but we observed isosbestic points for the reaction of DNF in NaOH with several sugars both in water and in the presence of CTABr (cf. ref 15). Isosbestic points were at the following wavelengths: for DNF with glucose 329–330 mm, methyl α-glucoside 330 nm, and sorbose 327 nm, and for DNC with glucose 330 nm. We obtained good first-order rate constants for the reactions of DNF when reaction was followed at the isosbestic point but generally not when it was followed at 358 nm. However, the final part of these runs followed a first-order rate equation.

There was also a species with λ_{max} at 495 nm which built up during

0022-3263/78/1943-1925$01.00/0

Table I. pK_a of Glucose [a]

[glucose], M	pK_a	[glucose], M	pK_a
0.01	12.38	0.15	12.30 (12.28)
0.03	12.31	0.30	(12.24)
0.07	12.30 (12.23)	0.50	(12.20)
0.10	12.32		

[a] At 23 °C with stoichiometric concentration of NaOH of 0.01 M. The values in parentheses were obtained using 0.02 M NaOH.

Table II. Inhibition of Glucose of the Reaction of *p*-Nitrophenyl Diphenyl Phosphate with Hydroxide Ion[a]

[glucose], M	10^3k_ψ, s^{-1}	[glucose], M	10^3k_ψ, s^{-1}
	3.80	0.05	2.33
0.01	3.42	0.07	2.27
0.03	2.78	0.10	2.17

[a] At 25.0 °C in 0.01 M NaOH.

Table III. Effect of Glucose on the Reaction of DNF with Hydroxide Ion [a]

[glucose], M	$10^3(k_1^{OH}[OH^-] + k_1^{GO}[GO^-])$ s^{-1} [b]	$10^3k_2[OH^-]$ s^{-1} [c]
	2.58[d]	
0.01	5.32	0.23
0.02	8.50	
0.03	8.03	0.14
0.07	7.87	0.097
0.10	6.89	0.064
0.15	6.47	0.050
0.30	5.14	
0.50	3.90	
0.70	3.94	

[a] At 25.0 °C with 0.02 M NaOH. [b] Followed at the isobestic point at 329 nm. [c] Final part of the reaction followed at 358 nm. [d] 10^3k_ψ = 2.4 for reaction followed at 358 nm.[18]

reaction. The absorbance in this region was small for reactions of DNF in the presence of glucose and sorbose, but it was large in the presence of sorbitol.

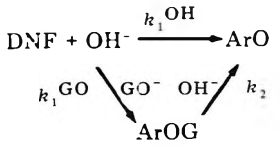
Acid Dissociation of Glucose. We calculated the pK_a of glucose from the change of pH when glucose is added to dilute NaOH using a Thomas high pH glass electrode and a Corning Model 12 pH meter with an expanded scale. Our values are classical and assume no effect of glucose on K_w for water. Within experimental error the pK_a values do not depend on the concentration of added glucose and decrease slightly with increasing initial concentration of hydroxide ion (Table I). Our pK_a values agree reasonably well with literature values of 12.43 at 18 °C and 12.18 at 16.5–19 °C.[13,14]

Results

The general approach was to follow three types of reactions: Type 1 reactions were run at relatively low pH using nucleophiles other than hydroxide or alkoxide ion, for example, fluoride ion or amine. Type 2 reactions involve attack of hydroxide or alkoxide ion, but here only the first step of reaction was followed. In Type 3 reactions attack of alkoxide ion gives an intermediate which generates the final detectable products in a second step, e.g., attack upon a halonitrobenzene gives an aryl ether which then decomposes to a dinitrophenoxide ion.[15]

Reactions in the Absence of Surfactant. As an example of a type 2 reaction we examined the effect of glucose upon the decomposition of *p*-nitrophenyl diphenyl phosphate in aqueous sodium hydroxide (Table II). There is a small rate retardation suggesting that glucose (GOH) has a negative solvent effect which overcomes any contribution due to reaction between substrate and GO^- (the reaction of hydroxide ion is slowed by addition of organic solvents[19]).

Scheme I



A type 3 reaction was that of DNF in hydroxide ion. Addition of small amounts of glucose speeds the reaction of DNF in 0.02 M sodium hydroxide followed at the isosbestic point (Table III). In this table the term $k_1^{OH}[OH^-] + k_1^{GO}[GO^-]$ is the first-order rate constant for the postulated attack by OH^- and GO^- (where GO^- is an anion of glucose). The rate constants go through a maximum with increasing glucose concentration, which is the result of attack by the reactive alkoxide ion, GO^-, and a negative solvent effect by glucose. Reactions at the higher glucose concentration (>0.1 M), followed at the isobestic point, were first order for only 2 half-lives, suggesting that more than one intermediate might be formed, and there was a small shift in the isosbestic point during reaction.

The final part of the reaction followed at 358 nm was first order, and the first-order rate constant for this step is $k_2[OH^-]$ (Table III).

Kinetic Analysis of Reaction of DNF in Aqueous Hydroxide Ion. Although there is evidence for formation of a small amount of Meisenheimer complex in reactions of DNF with glucose in CTABr we detected no such complex in water where the reaction follows Scheme I.

The overall first-order rate constant is determined by following reaction at the isobestic point, whereas reaction followed at 358 nm has a complex kinetic form (cf. ref 15). On the assumption that an intermediate ether is formed the value of $k_2[OH^-]$ for decomposition of the intermediate, ArOG, is estimated by following the final part of the reaction at 358 nm after all the DNF has disappeared.

The first-order rate constant for disappearance of DNF is $k_1^{OH}[OH^-] + k_1^{GO}[GO^-]$, where $[OH^-]$ and $[GO^-]$ are the actual concentrations of the ions in the reaction solution. In principle we can separate these constants using the concentrations of OH^- and GO^- calculated from the pK_a of glucose, but there are several problems. (i) Glucose in relatively high concentration has a medium effect on the reactions, cf. Tables II and III, and probably on its own acid dissociation. (ii) Although the 1-hydroxyl group of glucose is the most acidic there may be contributions from reactions of the other hydroxyl groups, for example, methyl α-glucoside reacts with DNF. But in 0.01 M glucose $[GO^-]$ = 0.0044 M from the data in Table I, and if k_1^{OH} has the same value as in water $k_1^{GO} \sim 0.75$ M^{-1} s^{-1}. Thus the anion of glucose is more nucleophilic than OH^- for which k_1^{OH} = 0.13 M^{-1} s^{-1} (Table III), and our results establish that at high pH glucose is an effective nucleophile, despite the statements to the contrary in ref 11.

The intermediate is much less reactive to hydroxide ion than is DNF, and the decrease of $k_2[OH^-]$ with increasing glucose can be ascribed to a medium effect of glucose and a decreasing concentration of hydroxide ion.

In this treatment we have neglected the role of the α and β epimers of glucose. They and the open chain compound will be in equilibrium in our reaction conditions, but the reactions of their alkoxide ions toward DNF generate different nonequilibriating ethers, which could decompose to dinitrophenoxide ion at different rates. However, the rates of attack of hydroxide upon various 2,4-dinitrophenyl ethers do not depend markedly upon the alkyl group (cf. ref 15 and references cited therein), so that the existence of epimeric inter-

Table IV. Inhibition by Glucose of the Reaction of Glycylglycine [b] with DNF [a,c]

[glucose], M	10^2k_ψ, s^{-1}	[glucose], M	10^2k_ψ, s^{-1}
	2.71	0.07	1.43
0.01	2.22	0.10	1.28
0.03	1.78		

[a] At 25.0 °C, pH 9.5 with 0.015 M borate buffer, 0.025 M glyclyglycine, and 0.025 M CTABr. [b] Registry no. 556-50-3. [c] Registry no. 70-34-8.

Table V. Inhibition by Glucose [d] of the Reactions of *p*-Nitrophenyl Diphenyl Phosphate [e] with Fluoride [f] and Hydroxide Ion [a,g]

	10^2k_ψ, s^{-1}	
[glucose], M	NaF[b]	NaOH[c]
	2.84	7.78
0.01	2.69	5.33
0.02		4.56
0.03	2.08	4.78
0.05	1.70	4.13
0.07	1.64	3.58
0.10	1.52	3.17

[a] At 25.0 °C. [b] 0.01 M NaF at pH 9.0, 0.015 M borate buffer, and 0.002 M CTABr. [c] 0.01 M NaOH in 0.003 M CTABr. [d] Registry no. 50-99-7. [e] Registry no. 10359-36-1. [f] Registry no. 16984-48-8. [g] Registry no. 14280-30-9.

Table VI. Effect of Glucose on the Reaction of Hydroxide Ion with 2,4-Dinitrochlorobenzene [a,d]

	10^3k_ψ, s^{-1}	
[glucose], M	330 nm[b]	358 nm[c]
0.01	3.39	5.26
0.02	5.13	6.25
0.04	6.73	7.50
0.07	7.70	6.07
0.10	6.71	5.40
0.15	5.42	4.33

[a] At 25.0 °C with 0.05 M NaOH in 0.02 M CATBr, $10^3k_\psi = 4.2$ s^{-1} in the absence of glucose. [b] Isosbestic point. [c] λ_{max} for 2,4-dinitrophenoxide ion. [d] Registry no. 97-00-7.

mediates should not seriously complicate our kinetic analysis based on Scheme I.

Micellar-Catalyzed Reactions

Inhibiting Effects of Glucose. It is convenient to consider first type 1 and 2 reactions, because their rates in aqueous CTABr are reduced by added glucose. This is shown by the results for the type 1 reactions of glycylglycine with DNF in CTABr[17] (Table IV) and of fluoride ion with *p*-nitrophenyl diphenyl phosphate (Table V) and for the type 2 reaction of *p*-nitrophenyl diphenyl phosphate with hydroxide ion (Table V).

In these reactions small amounts of glucose are effectively reducing micellar catalysis. Glucose is very hydrophilic and can exert an appreciable effect on water structure and disrupt the micelles. Attack by glucose upon the phosphoryl group is apparently unimportant.

Catalysis by Glucose of Reactions in CTABr. The reactions of DNF and DNC at high pH fall into type 3, and repetitive scanning of the reaction mixture in the ultraviolet region shows that an intermediate builds up and decays during reaction. We follow disappearance of substrate at the isosbestic point for the intermediate ether and 2,4-dinitrophenoxide ion and appearance of 2,4-dinitrophenoxide ion

Table VII. Effects of Glucose on the Reaction of DNF in Hydroxide and CTABr [a]

[glucose], M	$10^3(k_1^{OH}[OH^-] + k_1^{GO}[GO^-])$, s^{-1} [b]	$10^3k_2[OH^-]$, s^{-1} [c]
	100	
0.01	240	3.92
0.02	285	
0.03	282	1.33
0.05	324	
0.07	308	0.63
0.10	334	
0.15	323	0.35
0.20	275	0.22
0.40	183	0.09

[a] At 25.0 °C with 0.01 M NaOH and 0.025 M CTABr. [b] Followed at 330 nm. [c] Followed at 358 nm.

Table VIII. Decomposition of the Ether Intermediate [a,b]

[glucose], M	$10^3k_2[OH^-]$, s^{-1}
0.01	12.7
0.02	11.6
0.04	9.32

[a] At 25.0 °C; reaction followed at 358 nm in 0.05 M NaOH and 0.02 M CTABr. [b] Registry no. 25775-97-7.

formed directly or via the intermediate at 358 nm.

The reaction followed at the isosbestic point is first order with respect to DNC, but that followed at 358 nm is only approximately so, and first-order plots were linear for less than 2 half-lives. In addition the values of k_ψ obtained at the two wavelengths do not agree (Table VI).

The attack of hydroxide or alkoxide ion upon DNF should be much faster than upon an intermediate 2,4-dinitrophenyl ether, cf. Table III and ref 15. The general approach is similar to that described for reaction in the absence of CTABr. Reactions are followed both at the isosbestic point and at 358 nm, and the results are in Table VII.

For reactions of both DNC and DNF the rate constants for disappearance of substrate ($k_1^{OH}[OH^-] + k_1^{GO}[GO^-]$) go through maxima with added glucose, suggesting that it introduces a new reaction path but also has a negative solvent effect.

The second step of the reaction, decomposition of the intermediate, was followed in 0.05 M NaOH for comparison with the observations on the reaction of DNC. Under these conditions the first step of the reaction of DNF is too fast to be followed by conventional methods, but the first-order rate constant, $k_2[OH^-]$ (Table VIII), is slightly larger than the rate constant for disappearance of DNC (Table VI). Aryl ethers are often more reactive to nucleophiles than the corresponding chlorides.[15]

Separation of Rate Constants of First Step. The initial reaction of DNF gives 2,4-dinitrophenoxide ion directly, plus an ether which slowly goes to phenoxide ion. Therefore the overall reaction followed at 358 nm is not first order with respect to DNF and in principle the steps in Scheme I can be separated using a simulator (Appendix) and fitting the variation of 2,4-dinitrophenoxide ion with time to rate constants for the various steps. (In this approach the value of $k_2[OH^-]$ was that determined directly from the last part of the reaction.)

For reaction in CTABr these individual rate constants are in Table IX, and their sum agrees reasonably well with the values determined directly. The rate of attack of hydroxide ion upon DNF decreases steadily with increasing glucose which decreases the concentration of hydroxide ion.

Table IX. Separation of Rate Constants in Reaction of DNF [a]

[glucose], M	$10^3k_1^{OH}[OH^-]$, s^{-1}	$10^3k_1^{GO}[GO^-]$, s^{-1}	Sum Obsd [b]	Sum Calcd
0.01	211	66.7	240	278
0.03	183	142	282	325
0.07	113	217	308	330
0.15	58.3	239	323	297
0.20	41.7	233	275	275

[a] At 25.0 °C in 0.01 M NaOH and 0.025 M CTABr. [b] Table VII.

Table X. Effect of β-Methyl Glucoside [d] on Decomposition of DNF in CATBr [a,e]

[glucoside], M	$10^3(k_1^{OH}[OH^-] + k_1^{RO}[RO])$, s^{-1} [b]	$10^3k_2[OH^-]$, s^{-1} [c]
	100	
0.01	107 (105)	0.16
0.02	(112)	
0.03	121 (118)	
0.05	119 (131)	
0.07	(139)	0.12
0.10	169	0.16
0.15		0.16

[a] At 25.0 °C with 0.01 M NaOH and 0.025 M CTABr. [b] Followed at 330 nm; the values in parentheses were obtained at 358 nm. [c] Followed at 358 nm. [d] Registry no. 709-50-2. [e] Registry no. 57-09-0.

Table XI. Effect of Sorbose [b] on the Decomposition of DNF [a]

[sorbose], M	10^3k_ψ, s^{-1}	[sorbose], M	10^3k_ψ, s^{-1}
0.01	175	0.05	133
0.02	233	0.07	132
0.03	151	0.07	132

[a] At 25.0 °C in 0.025 M CTABr and 0.01 M NaOH, for reaction followed at 327 nm; in the absence of sorbose $10^3k_\psi = 100\ s^{-1}$. [b] Registry no. 87-79-6.

We were also able to fit the kinetic form of the reaction of DNF in 0.01 M glucose and 0.02 M NaOH in water, followed at 358 nm, using the simulator (cf. ref 15), and estimated the following values of $k_1^{OH}[OH^-] = 3.0 \times 10^{-3}$ and $k_1^{GO}[GO^-] = 1.3 \times 10^{-3}\ s^{-1}$. They are in fair agreement with the first-order rate constant of $5.32 \times 10^{-3}\ s^{-1}$ for disappearance of DNF followed at the isosbestic point of 329 nm.

Effect of α-Methyl Glucoside on Reaction of DNF. Glucose is probably most reactive at the 1-hydroxyl group but there may be contributions from reaction at other positions, because methyl α-glucoside speeds the decomposition of DNF giving an intermediate which decomposes to 2,4-dinitrophenoxide ion (Table X).

In α-methyl glucoside the 6-hydroxyl group should be the most accessible, but reaction of cycloamyloses occurs at the 2-hydroxyl group.[23]

Effects of Other Polyols and Formation of Meisenheimer Complexes. Meisenheimer complexes are formed in some of these reactions, because we observe absorbances at 495 nm which go through maxima in reactions of DNF with glucose or sorbose in CTABr. Cyclic Meisenheimer complexes of 1,2 diols with 2,4-dinitrobenzenes have extinction coefficients at this wavelength of ca. 26 000.[21] If we use this value we estimate that in 0.025 M CTABr and 0.01 M NaOH the reaction of DNF with 0.1 M glucose or sorbose gives a maximum of ca. 5% of Meisenheimer complex. We neglect this relatively small contribution to the overal reaction in our kinetic treatment (Scheme I). We see no absorbance at 495 nm in reactions of methyl α-glucoside with DNF.

Table XII. Effect of Sorbitol [b] on the Decomposition of DNF [a]

[sorbitol], M	10^3k_ψ, s^{-1} λ 358 nm	λ 495 nm	[sorbitol], M	10^3k_ψ, s^{-1} λ 358 nm	λ 495 nm
0.01	104	91	0.05		185
0.02	100	91	0.07	183	207
0.03	121	94	0.10	210	233

[a] At 25.0 °C in 0.025 M CTABr and 0.01 M NaOH. [b] Registry no. 50-70-4.

Table XIII. Catalysis of the Reaction of DNF with Hydroxide Ion by OOBTABr [a,b]

10^3[OOBTABr], M	10^3k_ψ, s^{-1}	10^3[OOBTABr], M	10^3k_ψ, s^{-1}
	1.2	25	34.0
6	1.56	30	35.0
10	9.26	40	35.3
20	23.5	60	33.3

[a] At 25.0 °C in 0.01 M NaOH. [b] Registry no. 69405-78-3.

Table XIV. Effect of Glucose on the Decomposition of DNF in OOBTABr [a]

[glucose],	$10^3(k_1^{OH}[OH^-] + k_1^{GO}[GO^-])$, s^{-1} [b]	$10^3k_2[OH^-]$, s^{-1} [c]
0.01	88.9	1.77
0.02	107.0	1.04
0.03	112.0	
0.05	126.0	
0.07	128.0	0.46

[a] At 25.0 °C with 0.01 M NaOH and 0.03 M OOBTABr. [b] Followed at 330 nm. [c] Followed at 358 nm.

Sorbose behaves very much like glucose in that the disappearance of DNF followed at the isosbestic point of 327 nm follows first-order kinetics. The rate constants are in Table XI. The reaction followed at λ_{max} for 2,4-dinitrophenoxide ion is not first order, as expected if it involves formation of an intermediate ether plus a small amount of Meisenheimer complex.

With sorbitol there is ca. 50% formation of a Meisenheimer complex absorbing at 495 nm, based on an extinction coefficient of 26 000.[21] This complex is long lived under our reaction conditions (0.1 M sorbitol, 0.01 M NaOH, and 0.025 M CTABr)[22] but it decomposes at low pH. The reaction is first order when followed at either 358 or 495 nm and the rate constants are similar (Table XII) suggesting that the products do not interconvert extensively during the reaction.

The rate enhancements by sorbitol are similar to those found with sorbose, and the only difference is that this open chain polyol forms a cyclic complex much more readily than do the cyclic sugars, even though both glucose and sorbose can have hydroxyls in a cis 1,2 arrangement.

Reaction in Other Cationic Micelles. These rate enhancements by polyols should be general for reactions in solutions of other cationic surfactants, as shown for OOBTABr (Tables XIII and XIV).

In the absence of glucose the micellar catalysis is approximately half that of CTABr, but added glucose gives very similar rate enhancements of the first step of the reaction, followed at the isosbestic point (330 nm), and there is a second

slow decomposition of an intermediate (Scheme I) which can be followed at 358 nm (Table XIV). The rate constants for this second step decrease as expected with increasing glucose concentration.

Chemical and Physical Effects of Sugars and Related Polyols. Glucose and related compounds increase reaction rates in cationic micelles only when they can react as nucleophiles and introduce a new reaction path which involves an alkoxide ion which is more reactive than hydroxide. This situation is observed in reactions of DNC and DNF but not in dephosphorylation or in reactions followed at relatively low pH.

There is always an additional inhibitory effect which is similar to, but larger than, that of hydrophilic monohydric alcohols.[5-7,17b]

Our evidence relates only to glucose and its methyl glucoside, sorbose, and sorbitol but the effects seem to be general; for example, the largest rate enhancements of the decomposition of DNC in CTAB were by fructose which is more acidic than either glucose or arabinose.[13,14] There is no evidence that these rate enhancements have a physical origin as suggested in ref 11.

The rate reductions which we observe in those systems in which the alkoxide ion of the polyol does not act as a nucleophile are similar to those found on addition of simple monohydric alcohols.[17b] The driving force for micellization, i.e., the hydrophobic effect, depends on the water structure, which is disrupted by polar hydroxylic solutes. As noted in ref 11, glucose and related compounds have marked physical effects on micellar catalysis, but these always appear to be inhibitory, and the rate enhancements observed here and reported in ref 11 are occasioned by introduction of a new chemical reaction.

Acknowledgments. Support of this work by the National Science Foundation and the Arthritis, Digestive and Metabolic Diseases Institute of the U.S. Public Health Service is gratefully acknowledged.

Appendix

The kinetic simulation followed the approach used earlier,[15] except that a digital rather than an analogue system was used. The design of the simulator is described elsewhere.[24]

References and Notes

(1) On leave from the Institute of Chemistry, University of Perugia, Perugia, Italy with support of the National Research Council of Italy, and a Nato Research Grant.
(2) On leave from the Faculty of Sciences, University of Chile, Santiago, Chile.
(3) For discussion of micellar catalysis see ref 4–7.
(4) E. H. Cordes, Ed., "Reaction Kinetics in Micelles", Plenum Press, New York, N.Y., 1973.
(5) E. H. Cordes and C. Gitler, *Prog. Bioorg. Chem.*, **2**, 1 (1973).
(6) E. J. Fendler and J. H. Fendler, "Catalysis in Micellar and Macromolecular Systems", Academic Press, New York, N.Y., 1975.
(7) C. A. Bunton, *Prog. Solid State Chem.*, **8** 239 (1973); J. B. Jones, Ed., "Application of Biomedical Systems in Chemistry", Part II, Wiley, New York, N.Y., 1976, Chapter 4.
(8) C. A. Bunton, ref 4, p 73.
(9) For exceptions to this generalization see ref 8 and 10.
(10) C. A. Bunton, M. J. Minch, L. Sepulveda, and J. Hidalgo, *J. Am. Chem. Soc.*, **95**, 3262 (1973); C. A. Bunton, M. Minch, and L. Sepulveda, *J. Phys. Chem.*, **75**, 2708 (1971); C. A. Bunton, A. A. Kamego, M. J. Minch, and J. L. Wright, *J. Org. Chem.*, **40**, 1321 (1975); M. J. Blandamer and D. J. Reid, *J. Chem. Soc., Faraday Trans. 1*, **71**, 2156 (1975).
(11) M. J. Blandamer, G. H. Beatham, C. H. Branch, and D. J. Reid, *J. Chem. Soc., Faraday Trans. 1*, **72**, 2139 (1976).
(12) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **84**, 2910 (1962); T. C. Bruice, T. H. Fife, J. J. Bruno, and N. E. Brandon, *Biochemistry*, **1**, 7 (1962).
(13) L. Michaelis and P. Rona, *Biochem. Z.*, **49**, 232 (1913); G. Thamsen, *Acta Chem. Scand.*, **6**, 270 (1952).
(14) B. Capon and W. G. Overend, *Adv. Carbohydr. Chem.*, **15**, 32 (1960).
(15) C. A. Bunton and S. Diaz, *J. Am. Chem. Soc.*, **98**, 5663 (1976).
(16) C. A. Bunton, L. Robinson, and M. Stam, *J. Am. Chem. Soc.*, **92**, 7393 (1970); C. A. Buntor and L. G. Ionescu, *ibid.*, **95**, 2912 (1973); C. A. Bunton and S. Diaz, *J. Org. Chem.*, **41**, 33 (1976); C. A. Bunton and C. H. Paik, *ibid.*, **41**, 40 (1976); K. Martinek, A. V. Levashov, and I. V. Berezin, *Tetrahedron Lett.*, 1275 (1975).
(17) (a) D. G. Herries, W. Bishop, and F. M. Richards, *J. Phys. Chem.*, **68**, 1842 (1964); (b) C. A. Bunton and L. Robinson, *J. Am. Chem. Soc.*, **92**, 356 (1970).
(18) C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34**, 773 (1969).
(19) C. A. Bunton, S. J. Farber, and E. J. Fendler, *J. Org. Chem.*, **33**, 29 (1968).
(20) C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34**, 780 (1969).
(21) R. J. Pollitt and B. C. Saunders, *J. Chem. Soc.*, 1132 (1964).
(22) Micellar effects upon rate and equilibrium constants for the formation of Meisenheimer complexes are discussed comprehensively in ref 6, Chapter 6.
(23) D. W. Griffiths and M. L. Bender, *Adv. Catal.*, **23**, 209 (1973).
(24) C. Magagnosc, D. Shindell, and D. Purich, *J. Chem. Educ.*, submitted.

Host–Guest Complexation. 8. Macrocyclic Polyethers Shaped by Two Rigid Substituted Dinaphthyl or Ditetralyl Units[1,2]

Donald J. Cram,* Roger C. Helgeson, Stephen C. Peacock, Lester J. Kaplan, Linda A. Domeier, Patrice Moreau,[3a] Kenji Koga,[3b] James M. Mayer, Y. Chao, Merrell G. Siegel, Dale H. Hoffman, and G. Dotsevi Y. Sogah[3c]

Contribution No. 3863, Department of Chemistry, University of California, Los Angeles, California 90024

Received August 5, 1977

Reported here are the syntheses and characterization of a large number of stereoisomeric macrocyclic polyethers (hosts) that contain rigid chiral units for studies of chiral recognition in molecular complexation with racemic alkylammonium salts (guests). These macrocyclic compounds contain six oxygens hexagonally arranged and held together by four ethylene (E) units and two differently substituted 1,1′-dinaphthyl units (D) bound to oxygen in their 2,2′ positions to give the general structure $D(OEOEO)_2D$. Also reported are similarly shaped compounds in which 1,1′-ditetralyl units (T) are bound to oxygen in their 2,2′ positions to give the general structures $T(OEOEO)_2D$ and $T(OEOEO)_2T$. The general shape of these compounds with all oxygens coplanar and turned inward places the naphthalene or tetralin rings in planes perpendicular to the plane of the macroring, with the two aryl rings protruding from each face of the macroring. Between the walls formed by these rigid units are chiral cavities, which are shaped further by substituents in the 3,3′ positions of the dinaphthyl or ditetralyl units. These 3,3′ substituents include CH_3, CH_2Cl, CH_2OH, $C(CH_3)_2OH$, $CH(CH_3)_2$, $CH_2OCH_2CO_2CH_3$, CH_2,OCH_2CO_2H, $CH_2N(CH_2CH_2)_2O$, and Br. Substituents in the 6 position of the dinaphthyl unit diverge from the macroring and the cavities, and are used to manipulate solubility properties or to bond the hosts to solid supports. They are remote from the macroring binding sites and chiral barriers. These 6 substituents include Br, $Si(CH_3)_2OCH_3$, $COCH_3$, CO_2CH_3, CO_2H, $CH_2CO_2CH_3$, CH_2CH_2OH, $CH{=}CH_2$, $SO_3Ba_{1/2}$, and $C(CH_3)_3$. Optical resolutions of 3,3′-dimethyl-2,2′-dihydroxy-1,1′dinaphthyl and of 3,3′-dicarboxy-2,2′-dihydroxy-1,1′-dinaphthyl are reported Catalytic reductions of the enantiomers of 2.2′-dihydroxy-1,1′-dinaphthyl, 3,3′-dimethyl-2,2′-dihydroxy-1,1′-dinaphthyl, and dinaphthyl-containing macrocyclic polyethers converted the 1,1′-dinaphthyl units into the 5,5′,6,6′,7,7′,8,8′-octahydro-1,1-dinaphthyl (1,1′-ditetralyl) units with full preservation of configuration. The configurational stabilities to heat and catalysts and the maximum rotations of compounds containing chiral units were determined. The critical ring-closing steps were conducted without high dilution and went in yields that varied between about 17 and 64%. They were conducted under conditions that fully preserved the configurations of the chiral units. Generalizations useful in developing synthetic strategies emerged from this work: (1) Substituents in the 3 position of the dinaphthyl system had to be introduced before ring closure. (2) Alkyl, CH_2OH, $(CH_3)_2COH$, Br, and $CH_2N(CH_2CH_2)_2O$ substituents did not interfere with the ring-closing reactions. (3) Electrophilic substitution reactions of the macrocyclic ethers occurred in the 6 positions of the dinaphthyl and in the 3 positions of the ditetralyl units. (4) Only the Mannich reaction on 2,2′-dihydroxy-1,1′-dinaphthyl (dinaphthol) could be used to introduce substituents directly into the 3 positions of the dinaphthyl unit. (5) The chiral diphenolic starting materials and the macrocycles were configurationally stable to the conditions of the reactions to which they were submitted with the exception of the Mannich reaction. (6) The ring closures were the most satisfactory when $D(OEOEOTs)_2$ or $T(OEOEOTs)_2$ was treated with $D(OH)_2$ or $T(OH)_2$ in refluxing THF–KOH. The symmetry properties and shapes of the host compounds reported here are discussed.

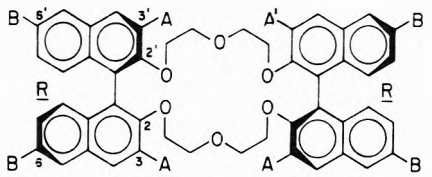
Paper 7 of this series[4] reports the syntheses of a variety of macrocyclic host compounds containing one, two, or three chiral 1,1-dinaphthyl units incorporated into ring systems. Ether oxygen or pyridine nitrogen-containing units attached to the 2,2′ positions of the dinaphthyl group (or groups) were used to complete the cycles. The dinaphthyl units act as chiral barriers, and the heteroatoms provide binding sites for hydrogen bonding to the ammonium ions of amine salts, which are the guests in complexation.

Molecular models (Corey–Pauling–Koltun, or CPK) of hosts that contain two dinaphthyl units and six ether oxygens such as 1 indicate that the six oxygens in their more stable gauche conformations are about equally spaced from one another in a plane. The four naphthalene rings occupy four different planes each of which is perpendicular to that of the macrocycle. Two of the aromatic rings are above and tangent to the macroring and two are below and tangent to the macroring. Thus the space above and below the macroring is divided into two chiral cavities by the naphthalene rings which act as walls or steric barriers. Systems containing two cavities on each face are referred to as dilocular, since the substituents attached to an alkylammonium ion complexed on one face must be distributed in these two cavities. Dilocular hosts possess shapes remarkably dependent on the relative configurations of the two dinaphthyl units. When they possess the same configuration as in 1, the naphthalene walls occupy parallel planes, the cavities are of about equal size, and the molecule is chiral. When the two dinaphthyl units possess opposite configurations, the naphthalene walls occupy planes that converge, as in 2. On each face, one of the cavities is large and the other is small. If the dinaphthyl units are similarly substituted, these compounds are meso and achiral.

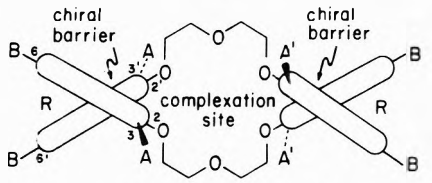
The shapes of the cavities are subject to the number and nature of substituents A and A′ attached at the 3 and 3′ positions of the naphthalene rings in 1 and 2. Such substituents extend the chiral barriers and converge on the molecular parts of guests bound by the oxygens of the macroring. Substituents B and B′ attached to the 6 positions of the naphthalene rings in 1 and 2 diverge from the binding site and have little effect on the shapes of the cavities. Substituents in these positions can be used to manipulate the physical properties of such hosts or to attach them to solid supports.

The degree and direction of chiral recognition in complexation exhibited by dilocular hosts such as 1 have been reported to depend on substituents A.[2a,b,5] Dilocular hosts such as 1 have been attached through B substituents to solid supports for optical resolution of guests by chromatography.[2c,d] This paper reports the syntheses of compounds 1 and 2 in which substituents A and B have been extensively varied. Also reported are cycles in which the outer benzene rings of 1 and 2 have been reduced to their tetrahydro derivatives. The first Results section deals with the starting materials for ring clo-

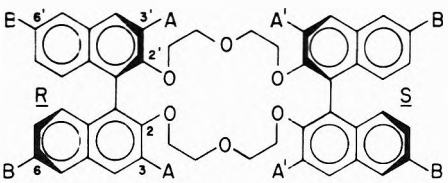
0022-3263/78/1943-1930$01.00/0



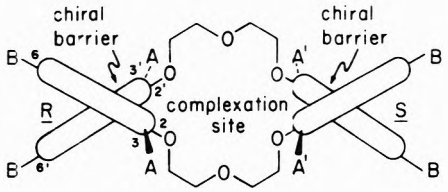
1



1 (projection formula)



2

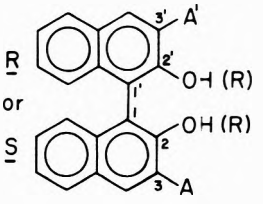


2 (projection formula)

sures. The second section describes the syntheses of the ring systems, and the manipulation of substituents once the rings are closed. The third section reports on how the dinaphthyl can be converted to ditetralyl units either before or after the rings are closed, and how both types of units can be incorporated into the same compounds. The first section under Discussion reports on the configurational stability of compounds that contain the dinaphthyl and ditetralyl units. The second section points to the symmetry properties and shapes of the host compounds of this paper. The results of complexation of many of these host compounds are described in future papers of this series.

Results

Dinaphthols, Ditetralols, and Derivatives. Use of 4-(butoxymethyl)morpholine[6] in a modified Mannich reaction



3, A=A'=H
4, A=A'=$CH_2N(CH_2CH_2)_2O$
5, A=H, A'=$CH_2N(CH_2CH_2)_2O$
6, A=A'=$CH_2N(CH_3)_2$
7, A=A'=CH_2OAc, R=Ac
8, A=CH_2OAc, R=H
A'=$CH_2N(CH_2CH_2)_2O$
9, A=A'=CH_2OH
10, A=H, A'=CH_2OH
11, A=CH_2OH, A'=$CH_2N(CH_2CH_2)_2O$
12, A=A'=CH_2Br
13, A=A'=CH_3
14, A=CH_3, A'=CH_2OH
15, A=CH_3, A'=$CH_2N(CH_2CH_2)_2O$
16, A=A'=CO_2H
17, A=A'=CO_2CH_3
18, A=A'=$C(CH_3)_2OH$
19, A=A'=CH_3, R=$(CH_2CH_2O)_2H$
20, A=A'=CH_3, R=$(CH_2CH_2O)_2Ts$
21, A=A'=H, R=$(CH_2CH_2O)_2Ts$

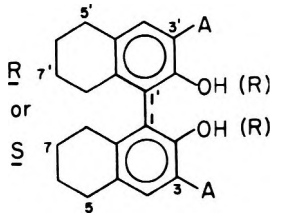
(160 °C) with 2,2'-dihydroxy-1,1'-dinaphthyl (**3**) gave mainly disubstituted product **4** (61%) but a small amount of monosubstituted compound **5** (15%) as well. Similarly, the bisamine **6** was prepared (33%).[7] When heated in acetic anhydride, **4** gave tetraacetate **7** (46%) and monoacetate **8** (39%), reduction of which with $LiAlH_4$ gave tetrol **9**[8] (98%) and triol **11** (75%), respectively. Applications of similar procedures to aminodiol **5** gave triol **10** (80%). Substitution of propionic anhydride at reflux for acetic anhydride gave a better conversion to the tetraester, reduction of which gave tetrol **9** in 85% overall yield.

Key intermediate 3,3'-dimethyl-2,2'-dihydroxy-1,1'dinaphthyl (**13**) was prepared in several ways. Treatment of tetrol **9** with HBr in AcOH gave dibromide **12** (85%), reduction of which with $LiAlH_4$ gave **13** (98%). Direct but not exhaustive catalytic reduction of tetrol **9** with palladium and hydrogen gave diol **13** (33%) as well as incompletely reduced triol **14** (32%). Direct reduction of diaminodiol **4** with palladium and hydrogen produced **13** (44%) as well as aminodiol **15** (20%).

Racemic dimethyldiol **13** was resolved easily through the cinchonine and strychnine salts of its phosphoric acid diester, the former of which produced a 34% yield (racemate = 100%) of optically pure (+)-(*R*)-**13**, and the latter a 20% yield of optically pure (−)-(*S*)-**13**. The absolute configurations of these enantiomers were determined by their synthesis from optically pure diacids (+)-(*R*)-**16** and (−)-(*S*)-**16** (respectively) of established absolute configurations.[9] An improved preparation of **16**[10] (41%) and its optical resolution to give its pure enantiomers[10] are also reported here, (+)-(*R*)-**16** in 34% and (−)-(*S*)-**16** in 30% yield. Reduction with $LiAlH_4$ of (+)-(*R*)-**16** of maximum rotation gave (+)-(*R*)-**9** (77%) and of (−)-(*S*)-**16** gave (−)-(*S*)-**9** (79%). Hydrogenolysis of each enantiomer with hydrogen and palladium gave (+)-(*R*)-**13** (94%) and (−)-(*S*)-**13** (98%), respectively. The four separately prepared samples of one or the other enantiomers of dimethyldiol **13** gave rotations of essentially the same values (disregarding signs), which points to their optical purities (see Experimental Section). Treatment of optically pure diacid (+)-(*R*)-**16** gave diester (+)-(*R*)-**17**[9a] (76%), reduction of which with $LiAlH_4$ gave (+)-(*R*)-**9** (63%), of essentially the same rotation observed for the compound prepared from diacid (+)-(*R*)-**16** directly. Diester (+)-(*R*)-**17** with CH_3Li gave tetrol (+)-(*R*)-**18** (87%) as a benzene solvate.

As starting materials for directed ring closures (next section) involving two different kinds of biarylol units, $OCH_2CH_2OCH_2CH_2OH$ "arms" were attached at the 2,2' positions of the 3,3'-dimethyl-1,1'-dinaphthyl system. Treatment of optically pure (−)-(*S*)-3,3'-dimethyl-2,2'-dihydroxy-1,1'-dinaphthyl [(−)-(*S*)-**13**)] with NaH and $ClCH_2CH_2OCH_2CH_2OTHP$[4] (THP is the tetrahydropyranyl protecting group) gave the corresponding bis(THP) derivative, which was cleaved with acid to give dimethyldiol, (+)-(*S*)-**19** (90%). Similarly, (+)-(*R*)-**13** was converted to (−)-(*R*)-**19** (68%). These two diols were converted to their respective ditosylates, (+)-(*S*)-**20** (92%) and (−)-(*R*)-**20** (93%), whose rotations were equal in magnitude and opposite in sign. Of all the dinaphthyl compounds prepared, only **19** and **20** coupled the (*R*) configuration with a (−) rotation and the (*S*) configuration with a (+) rotation. The ditosylates without the 3-methyl groups substituted in the naphthalene ring (**21**) were reported previously.[4]

Catalytic reduction of certain of the above 1,1'-dinaphthyl derivatives with platinum and hydrogen in glacial acetic acid gave the corresponding 1,1'-ditetralyl derivatives. As expected both on steric and electronic grounds, the outer aromatic rings were reduced selectively to leave the biphenyl moiety intact. Importantly for our purposes, when conducted at 25 °C, the reduction went with no loss in optical purity. Thus reduction of optically pure (+)-(*R*)-2,2'-dihydroxy-1,1'-dinaphthyl



22, A=H
23, A=CH_3
24, A=H, R=$(CH_2CH_2O)_2Ts$
25, A=CH_3, R=$(CH_2CH_2O)_2H$
26, A=CH_3, R=$(CH_2CH_2O)_2Ts$
27, A=B-

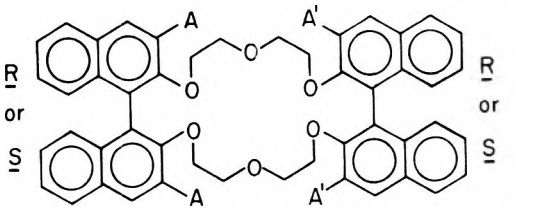
[(+)-(*R*)-**3**] at 25 °C over a 7-day period gave (+)-(*R*)-**22** (92%) as sharp-melting crystals. Similar reduction of optically pure (−)-(*S*)-**3** at 65 °C over a 3-day period gave (−)-(*S*)-**22** (92%) which melted over a 3 °C range, and whose rotations at four wavelengths were 8 ± 1% lower in magnitude than those for (+)-(*R*)-**22**. Apparently at 65 °C for three days, 4% of the material at some stage underwent inversion of configuration. The configurational stability to heat of compounds containing the 2,2′-disubstituted-1,1′-ditetralyl unit are discussed in a future section of this paper.

As a further test of the stereospecificity of the reduction reaction, optically pure dimethyldiol, (+)-(*R*)-**13**, was converted to its ditetralyl derivative (+)-(*R*)-**23** by two different routes. In the first, (+)-(*R*)-**13** was reduced directly to (+)-(*R*)-**23** (94%) to give a sharp-melting solid. In the second, the two phenolic hydroxyl groups of (+)-(*R*)-**13** were methoxymethylated to give the derivative with the more bulky and nonketolizable OCH_2OCH_3 groups. This derivative was then reduced with platinum and hydrogen in glacial acetic acid at 25 °C and the mixed acetal protective groups were removed to give (+)-(*R*)-**23** (81% overall) of the same melting point and rotation as that produced by direct reduction. These results make it highly unlikely that any racemization occurs during reductions conducted at 25 °C. Attempts to rearomatize **22** to give **3** under mild conditions failed.

Other 1,1′-dinaphthyl compounds with ether groups appended in the 2,2′ positions were similarly reduced to their 1,1′-ditetralyl derivatives. Thus the two hydroxyl groups of optically pure (−)-(*S*)-**3** were converted to OCH_2CH_2O-CH_2CH_2OH groups as before,[4] and this polyetherdiol was reduced and tosylated to give (−)-(*S*)-**24** (69% overall). Similarly, optically pure dimethyl two "armed" diol (+)-(*S*)-**19** was reduced to (+)-(*S*)-**25** (98%), and (−)-(*R*)-**19** gave (−)-(*R*)-**25**. These reduced diols were converted to their ditosylates, (+)-(*S*)-**26** and (−)-(*R*)-**26**, in 97 and 70% yields, respectively. The magnitudes of the optical rotations of these two sets of enantiomers were in satisfactory agreement with one another considering rotations were taken on incompletely chemically purified materials (all were glasses, and only a few milligrams were purified for analysis). Interestingly, the coupling of the (*R*) configuration with levorotatory character was carried over from **19** and **20** to their corresponding ditetralyl derivatives, **25** and **26**.

The substitution patterns in the bromination of 2,2′-dihydroxy-1,1′-ditetralyl [(+)-(*R*)-**22**] proved to be simpler than those observed with 2,2′-dihydroxy-1,1′-dinaphthyl (**3**). With the former compound (optically pure) bromination in CH_2Cl_2 at −30 °C gave (+)-(*R*)-**27** (98%) as a sharp melting solid. Bromination of **3** in CH_2Cl_2 at reflux led to 5,5′,6,6′-tetrabromo-2,2′-dihydroxy-1,1′-dinaphthyl (**28**), 81%, identified by its analysis and ^1H NMR and mass spectra. Bromination of 2,2′-dimethoxy-1,1′-dinaphthyl[12] gave 4,4′,6,6′-tetrabromo-2,2′-dimethoxy-1,1′-dinaphthyl, 91%, identified by its analysis and ^1H NMR and mass spectra.[13]

Macrocyclic Polyethers Containing Substituted Dinaphthyl Units. In the following ring-closing reactions, yields



(RR)(SS)-**29**, A=CH_3, A'=H
(RS)(SR)-**29**, A=CH_3, A'=H
(+)-(RR)-**29**, A=CH_3, A'=H
(−)-(SS)-**29**, A=CH_3, A'=H
(+)-(SR)-**29**, A=CH_3, A'=H
(RR)(SS)-**30**, A=CH_2OH, A'=H
(RS)(SR)-**30**, A=CH_2OH, A'=H
(+)-(RR)-**30**, A=CH_2OH, A'=H
(+)-(RR)-**31**, A=CH_2Cl, A'=H
(RR)(SS)-**32**, A=A'=CH_3
(RS)-**32**, A=A'=CH_3
(+)-(RR)-**32**, A=A'=CH_3
(−)-(SS)-**32**, A=A'=CH_3
(+)-(RR)-**33**, A=$C(CH_3)_2OH$, A'=H
(+)-(RR)-**34**, A=$CH(CH_3)_2$, A'=H
(RR)(SS)-**35**, A=$CH_2OCH_2CO_2CH_3$, A'=H
(RS)(SR)-**35**, A=$CH_2OCH_2CO_2CH_3$, A'=H
(+)-(RR)-**35**, A=$CH_2OCH_2CO_2CH_3$, A'=H
(RS)(SR)-**36**, A=$CH_2OCH_2CO_2H$, A'=H
(RR)(SS)-**36**, A=$CH_2OCH_2CO_2H$, A'=H
(+)-(RR)-**36**, A=$CH_2OCH_2CO_2H$, A'=H
(RR)(SS)-**37**, A=A'=CH_2OH
(RS)-**37**, A=A'=CH_2OH
38, A=A'=$CH_2N(CH_2CH_2)_2O$

were not maximized nor were high dilution conditions employed. Dry THF and KOH (35%) as a reaction medium (at reflux) in general gave the highest yields.

Because of the high chiral recognition in complexation exhibited by the dimethyl substituted cycles **29**,[2b] all of its stereoisomers were prepared and characterized. Treatment of the racemic two-armed ditosylate[4] **20** with racemic diol **3** in DMF–NaH led to a mixture of diastereomers that was separated by chromatography to give (*R,S*),(*S,R*)-**29** (12%) and (*R,R*),(*S,S*)-**29** (8%), both of which were high melting solids. The ^1H NMR spectral chemical shift of the methyl groups of the (*R,R*),(*S,S*) isomer occurred at 0.1 ppm higher field than that for the (*R,S*),(*S,R*) isomer. Molecular models (CPK) of (*R,R*),(*S,S*)-**29** indicate that conformations are available which allow the methyl groups attached to one naphthalene ring to approach the face of a transannular naphthalene ring. In models of (*R,S*),(*S,R*)-**29**, these conformations are not available. The spectra of the two diastereomers differed even more in the OCH_2 region. Optically pure (*R,R*)-**29** was prepared in 32% yield from (*R*)-**3** and (*R*)-**20** in THF, KOH, and H_2O, whereas (*S,S*)-**29** was obtained (64%) from (*S*)-**3** and (*S*)-**20** (minimum of water). Optically pure (*S,R*)-**29** (16%) was prepared similarly from the reaction of optically pure dimethyldiol (*S*)-**13** and optically pure two-armed ditosylate, (*R*)-**21**. Comparisons of the ^1H NMR spectra of those isomers made by the stereodirected syntheses with those prepared from racemic materials identified the configurations of the two racemates. Although the two racemates were crystalline solids melting well over 200 °C, the (*S,R*), (*R,R*), and (*S,S*) enantiomers could not be induced to crystallize. They were purified carefully by both absorption and gel permeation chromatography, and the (*R,R*) and (*S,S*) isomers possessed rotations of the same magnitude but of opposite sign. The magnitude of rotation of (*S,R*)-**29** was much smaller than that of its diastereomers, a fact which correlates with its more "meso-like" structure.

Treatment of racemic tetrol **9** with racemic two-armed ditosylate **21** likewise produced (*R,R*),(*S,S*)-**30** (16%) and (*R,S*),(*S,R*)-**30** (8%) both as high melting solids with different ^1H NMR spectra. From (*R*)-**9** and (*R*)-**21**, (*R,R*)-**30** was prepared as a glass (28%) whose ^1H NMR spectrum served to differentiate between the two racemates. As expected, the greater acidity of the two phenolic hydroxyl groups of tetrol **9** led to their alkylation in the presence of 2 equiv of base in preference to the CH_2OH groups in the production of **30**. Treatment of (*R,R*)-**30** with thionyl chloride gave dichloride

(*R,R*)-**31** (76%), reduction of which with $LiAlH_4$ gave (*R,R*)-**29** (80%). The optical rotations of the two samples of (*R,R*)-**29** prepared by the two entirely different routes are in exact agreement with one another at λ 578 nm and have the exact magnitude as that of (*S,S*)-**29** at this wavelength. Furthermore, the magnitudes of the optical rotations of (*R,R*)-**29** prepared from dichloride (*R,R*)-**31** were the same at λ 546 and at λ 436 nm as the sample of (*S,S*)-**29** prepared by the other route.

The four stereoisomeric tetramethyl compounds **32** were also prepared, but in lower yields for the ring closures. From the reaction of racemic dimethyldiol **13** with racemic two-armed ditosylate **20** was isolated a 10% yield of the (*R,R*)-(*S,S*)-**32** and a 7% yield of (*R,S*)-**32**, both of which are high melting solids. These two compounds were also prepared in 5 and 4% respective yields by the reaction of diethylene glycol ditosylate with **13**. A smaller cycle closed by the reaction of one molecule of each reactant with one another was also produced in 8% yield. From (*R*)-**13** and (*R*)-**20**, (*R,R*)-**32** was obtained (28%), and from (*S*)-**13** and (*S*)-**20**, (*S,S*)-**32** was produced (28%). These compounds are also glasses and possess rotations of almost identical magnitude. They possess ^1H NMR spectra identical to that of (*R,R*),(*S,S*)-**32** but distinctly different from that of (*R,S*)-**32**. These comparisons were used to assign the configurations to the racemate [(*R,R*),(*S,S*)-**32**] and to the *meso* compound [(*R,S*)-**32**].

Isopropyl groups were introduced as substituents into the 3,3′ positions of the dilocular system as follows. Treatment of the tertiary diol (+)-(*R,R*)-**18** with the two-armed ditosylate (+)-(*R*)-**21** gave diol (+)-(*R,R*)-**33** (28%). This compound was dehydrated by heating it at 175 °C with pyridine-treated alumina,[14] and the two 2-propenyl groups were reduced to two isopropyl groups with hydrogen and palladium to give (+)-(*R,R*)-**34** (75%).

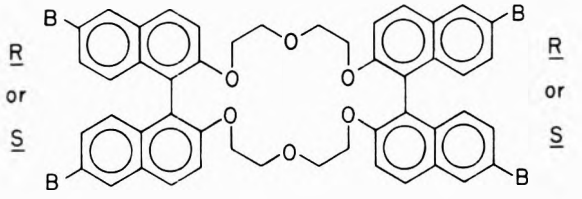
Carboxyl-terminated side chains were introduced into the hosts with the cyclic diols **30** as starting materials. For example, (*R,R*),(*S,S*)-**30** when mixed with NaH followed by methyl bromoacetate gave diester (*R,R*),(*S,S*)-**35** (71%). Similarly, (*R,S*),(*S,R*)-**30** gave (*R,S*),(*S,R*)-**35** (50%) and (*R,R*)-**30** gave (*R,R*)-**35** (77%). Hydrolysis of diesters (*R,S*),-(*S,R*)-**35**, (*R,R*),(*S,S*)-**35**, and (*R,R*)-**35** gave the corresponding diacids (*R,S*),(*S,R*)-**36** (94%), (*R,R*),(*S,S*)-**36** (83%), and (*R,R*)-**36** (76%).

Tetrols **37** are potential starting materials for preparation of polycyclic hosts in which four bridges link two dinaphthyl units. A mixture of the diastereomeric cyclic tetrols **37** was produced by treatment of racemic open-chain tetrol **9** with diethylene glycol ditosylate in THF–KOH. The two diastereoisomers produced were separated by chromatography and exhibited identical melting points. When mixed, the diastereomers gave a 20 °C melting point depression. They also exhibited different chromatographic behavior and ^1H NMR spectra. Their configurational identification made use of the fact that one was a racemate [(*R,R*),(*S,S*)-**37**] and the other a meso compound [(*R,S*)-**37**].

The structures were assigned to these diastereomers by a new partitioning method. Each was distributed between two layers composed of a mixture of $CDCl_3$, CD_3CO_2D, D_2O, (+)-α-phenylethylammonium bromide, and $NaPF_6$, whose composition was adjusted to allow nearly half of the host to be in each layer (^1H NMR spectra). The amine salt remained almost completely in the D_2O-rich layer. The layers were separated, the host was isolated from each layer, and optical rotations were taken on the four host samples produced. The rotation of product isolated from the $CDCl_3$-rich layer was positive and from the D_2O-rich layer was negative for the sample originally of the (*R,R*),(*S,S*) configuration. Zero rotation was observed for the product isolated from each layer when the (*R,S*) material was used. The yield of (*R,R*),(*S,S*)-**38** isolated from the original reaction mixture was 10%, and the yield of (*R,S*)-**38** was also 10%.

In a similar ring-closing reaction, racemic diaminodiol **4** was treated with diethylene glycol ditosylate in THF–*t*-BuOK. A 36% yield of 2,3,4,5-di-1,2-(3-*N*-morpholinomethylnaphtho)-1,6,9-trioxaundeca-2,4-diene was isolated and characterized (cyclic product of reaction of 1 mol of diethylene glycol ditosylate and of **4**). Also produced was a 51% yield of a sharp-melting compound which appeared to be either (*R,R*),(*S,S*)-**38** or (*R,S*)-**38**. The configuration was not determined, but the compound probably possesses the (*R,R*),-(*S,S*) configuration. Molecular models (CPK) of each diastereoisomer indicate the meso or (*R,S*) isomer to be somewhat more sterically congested than the (*R,R*) isomer.

Fortunately the dilocular systems were subject to direct electrophilic substitution, the 6 positions being the point of attack. The various stereoisomers of parent compound **39**



(RR)(SS)-**39**, B=H
(RS)-**39**, B=H
(+)-(RR)-**39**, B=H
(-)-(SS)-**39**, B=H
(RR)(SS)-**40**, B=Br
(RS)-**40**, B=Br
(+)-(RR)-**40**, B=Br
(RS)-**41**, B=$Si(CH_3)_2OCH_3$
(RR)(SS)-**42**, B=CH_3CO
(-)-(SS)-**42**, B=CH_3CO
(RR)(SS)-**43**, B=CO_2CH_3
(RR)(SS)-**44**, B=CO_2H
(-)-(SS)-**45**, B=$CH_2CO_2CH_3$
(SS)-**46**, B=CH_2CH_2OH
(-)-(SS)-**47**, B=$CH=CH_2$
(-)-(SS)-**48**, B=$SO_3(Be)_{\frac{1}{2}}$
(-)-(SS)-**49**, B=$C(CH_3)_3$

listed were available from a previous study.[4] The chiral isomers used were optically pure and were freed from their crystalline solvates before use. Bromination of (*R,R*),(*S,S*)-**39** with excess bromine at 2 °C gave tetrabromide (*R,R*),(*S,S*)-**40** (88%). That the compound contained four bromine atoms was demonstrated by its analysis and mass spectrum. Similarly, (*R,S*)-**39** gave (*R,S*)-**40** (90%), and (*R,R*)-**39** gave (*R,R*)-**40**. The splitting patterns of the aryl protons in the ^1H NMR spectra of these compounds demonstrated the 6 positions were substituted. As a model reaction for attachment of dilocular systems to silica gel,[2c] (*R,S*)-**40** was tetralithiated with butyllithium, and this organometallic was added to a very large excess of dichlorodimethylsilane followed by methanol. Thus four dimethylmethoxysilyl groups were introduced into the 6 positions of the naphthalene rings to give (*R,S*)-**41** (84%).

Acetylation of (*R,R*),(*S,S*)-**39** with acetyl chloride in nitrobenzene at 25 °C gave the tetraacetyl derivative, (*R,R*),-(*S,S*)-**42** (93%). Similarly, (*S,S*)-**39** gave (*S,S*)-**42** (89%). The aryl proton splitting pattern in the ^1H NMR spectrum of this isomer was uniquely interpretable on the basis of substitution in the 6 positions of the naphthalene rings. Oxidation of (*R,R*),(*S,S*)-**42** with NaOBr and esterification of the tetraacid product gave tetraester (*R,R*),(*S,S*)-**43** (77%), whose ^1H NMR spectrum confirmed the substituents occupied the 6 positions. Hydrolysis of this tetraester gave tetracarboxylic acid (*R,R*),(*S,S*)-**44** (77%). This compound was almost totally insoluble in organic solvents but was readily soluble in aqueous alkali. The symmetrical distribution of the four CO_2^- groups prevented the salt from being a soap. Thus the highly lipophilic host **39** can be converted into a highly hydrophilic host by introduction of four carboxylate ions in the 6 positions.

Tetraacetyl compound (*S,S*)-**42** was used to prepare the

tetravinyl compound (*S,S*)-**47.** This compound was prepared for use as a highly chiral cross-linking agent for use in the polymerization of styrene and other vinyl monomers. Polymers cross-linked with (*S,S*)-**47** are visualized as containing chiral cavities potentially useful for resolving racemates by chromatography.[15]

Oxidative rearrangement[13] of (*S,S*)-**42** was accomplished with thallium trinitrate in methanol–perchloric acid–CH_2Cl_2. Tetraester (*S,S*)-**45** was produced in 98% yield, reduction of which gave tetrol (*S,S*)-**46** (90%). This compound was converted to its tetratosylate, which without characterization was treated with *t*-BuOK–Me_2SO to give the tetravinyl compound (*S,S*)-**47** (47%).

Sulfonation of (*S,S*)-**39** gave the tetrasulfonic acid characterized as its barium salt, (*S,S*)-**48** (50%). The aryl proton splitting pattern in the ^1H NMR spectrum of this compound established that sulfonation had occurred in the 6 position. This barium salt was converted to its lithium salt (a nonsoap), which was readily soluble in water and totally insoluble in organic media. This material was used in chiral recognition experiments conducted in aqueous media with chiral alkylammonium salts.[17]

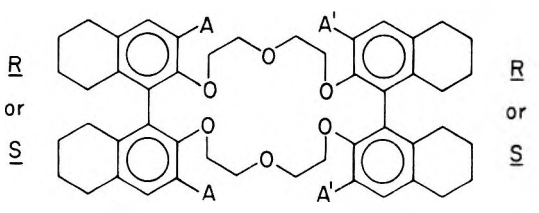
Attachment of long hydrocarbon chains (e.g., $C(CH_3)_2(CH_2)_{16}CH_3$) to the 6 position of these dilocular hosts would not only make them extremely lipophilic but also would produce high molecular weight waxes potentially useful as liquid phases for optical resolution in GLC chromatography. As a model experiment for attachment of such chains to these hosts, (*S,S*)-**39** was treated at −78 °C in dry CH_2Cl_2 with *t*-BuCl and $AlCl_3$ to give (*S,S*)-**49** (45%). The aromatic proton splitting pattern in the ^1H NMR spectrum of this compound was too complicated to be interpreted. However, it was similar enough to those of **45** and **47** that contain $CH_2CO_2CH_3$ and $CH{=}CH_2$ groups respectively in their 6 positions to make it clear that the four *tert*-butyl groups had entered the 6 positions as well.

Macrocyclic Polyethers Containing Ditetralyl Units. Molecular models of hosts containing the 2,2′-disubstituted 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-dinaphthyl (ditetralyl) unit are very similar in shape to those containing the dinaphthyl unit. However, their π base properties and aromatic substitution patterns were expected to be different from their parent dinaphthyl compounds. Therefore syntheses were undertaken of hosts containing two of these units and six oxygens incorporated into 22-membered macrocyclic rings.

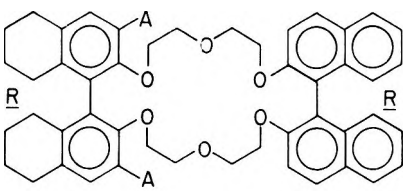
Two general approaches proved viable. In the first, the cycles containing two dinaphthyl units were reduced directly to produce cycles containing two ditetralyl units. In the second and more flexible approach, the rings were assembled by combining ditetralyl with dinaphthyl units to give hosts containing one unit of each type.

Reduction of unsubstituted bisdinaphthyl host (−)-(*S,S*)-**39**[4] with hydrogen in platinum–acetic acid at 25 °C for several days gave (−)-(*S,S*)-**50** in yields of 95–99%. Unlike the starting material, this product crystallized without forming a solvate. The same compound, (−)-(*S,S*)-**50,** of the same rotation was obtained in 54% yield by treatment of diol (−)-(*S,S*)-**22** with the reduced two-armed ditosylate (−)-(*S*)-**24** (THF–KOH). The enantiomer, (+)-(*R,R*)-**50,** was obtained by similar reduction of the cycle containing one dinaphthyl and one ditetralyl unit [(+)-(*R,R*)-**55**] whose synthesis is described later in this section. The rotations and melting points of the two enantiomers corresponded, a fact that indicates the reductions occurred without loss of optical purity. Similarly, dimethyl bisdinaphthyl host (+)-(*R,R*)-**29** was reduced to the dimethyl bisditetralyl host (+)-(*R,R*)-**51** (70%). The same compound was prepared by ring closing the ditetralyl two-armed ditosylate (+)-(*R*)-**24** with dimethyldiol (+)-(*R*)-**13** to make (+)-(*R,R*)-**57** which was reduced to (+)-(*R,R*)-**51.** The fact that the rotations of the two samples of (+)-(*R,R*)-**51** were within 2% of one another indicates that no loss of optical purity occurred during the reactions. Similarly, tetramethyl bisdinaphthyl system (+)-(*R,R*)-**32** was reduced to (+)-(*R,R*)-**52** (88%). The ^1H NMR and mass spectra of these reduced compounds and their elemental analyses indicated that only the outer rings underwent catalytic reduction. This result correlates with the facts that these outer rings are much less sterically hindered than the inner biphenyl systems, which appear to resist reduction. Reduction of the outer rings of **50** allows substituents to be introduced directly into the 3 position of the cycles. Thus bromination of (−)-(*S,S*)-**50** gave (+)-(*S,S*)-**53** (96%).

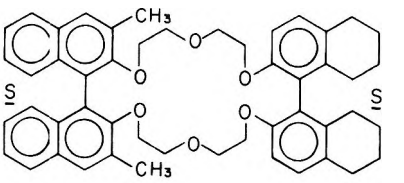
Ring closure of dibromodiol (+)-(*R*)-**27** and dinaphthyl two-armed ditosylate (+)-(*R*)-**21**[4] gave the dibromocycle (+)-(*R,R*)-**54** (68%) which contains one ditetralyl and one dinaphthyl unit. Lithiation of this substance and protonation of the organometallic produced gave (+)-(*R,R*)-**55** (96%), catalytic reduction of which gave (+)-(*R,R*)-**50** (92%). Dimethylditetralol, (+)-(*R*)-**23,** and dinaphthyl two-armed ditosylate (+)-(*R*)-**21** cyclized to produce (+)-(*R,R*)-**56** (70%), which contains a dimethylditetralyl unit on one side of the macrocycle and a dinaphthyl unit on the other. The isomer of this compound in which the methyl groups are on the dinaphthyl unit, (−)-(*S,S*)-**57,** was produced in 42% yield by treating dimethyldinaphthyl two-armed ditosylate (+)-(*S*)-**20** with ditetralol (−)-(*S*)-**22.**



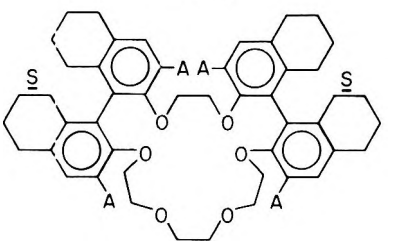
(−)-(SS)-50, A=A'=H (+)-(RR)-52, A=A'=CH_3
(+)-(RR)-50, A=A'=H (+)-(SS)-53, A=A'=Br
(+)-(RR)-51, A=CH_3, A'=H



(+)-(RR)-54, A=Br (+)-(RR)-56, A=CH_3
(+)-(RR)-55, A=H



(−)-(SS)-57



(−)-(SS)-58, A=H
(+)-(SS)-59, A=Br

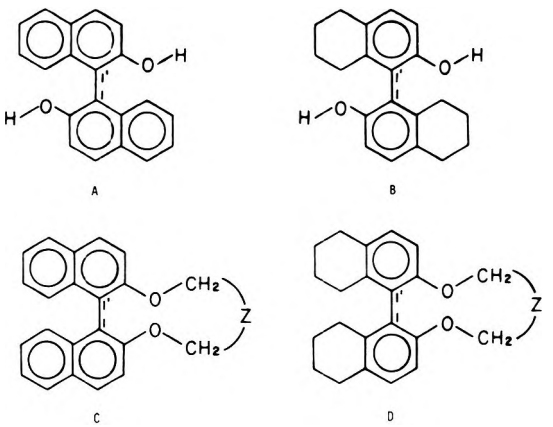
The isomer of **39** containing two dinaphthyl units of the (*S*) configuration connected by one $-OCH_2CH_2O-$ and one $-O(CH_2CH_2O)_3-$ bridge was catalytically reduced to give (−)-(*S,S*)-**58** (85%). Bromination of this compound gave (+)-(*S,S*)-**59** (94%) in which the bromine atom specifically entered the 3,3′ position of the ditetralyl units (^{1}H NMR spectra).

Discussion

Configurational Stabilities of Compounds Containing the Ditetralyl Units. Since many of the hosts described here were prepared for quantitative chiral recognition studies, their optical purities are important. Thus questions of what reaction conditions might induce reversal of the configurations of the dinaphthyl or ditetralyl units had to be answered. Studies already showed the cyclic hosts containing the dinaphthyl units were stable to temperatures of more than 200 °C.[4] Here we describe comparisons of the configurational stabilities of both the starting materials and cycles that contain the ditetralyl and dinaphthyl units. When heated in butanol at 118 °C for 24 h (+)-(*R*)-2,2′-dihydroxy-1,1′-dinaphthyl [(+)-(*R*)-**3**] lost ~1% of its rotation, whereas (+)-(*R*)-2,2′-dihydroxy-5,5′,6,6′,7,7′8,8′-octahydro-1,1′-dinaphthyl [(+)-(*R*)-**22**] lost ~2% of its rotation. When heated for 24 h at 100 °C in dioxane–water, 1.2 M in HCl, (+)-(*R*)-**3** lost 56% of its rotation whereas (+)-(*R*)-**22** lost <1% of its rotation. When heated at 118 °C for 24 h in butanol, 0.7 M in KOH, (+)-(*R*)-**3** lost 20% of its rotation, whereas (+)-(*R*)-**22** lost 7% of its rotation. Care was taken in the isolation of the compounds after treatment to avoid optical fractionation (rotations were taken on total samples). Small amounts of the rotational losses could reflect slight compound decomposition. Interestingly, the ditetralyl unit appears somewhat more configurationally stable to base and particularly to acid than the dinaphthyl unit. This latter fact correlates with the expectation that direct protonation of a 1,1-dinaphthyl system in the 1 or 1′ positions to give a configurationally unstable cation[4] occurs more readily than protonation in the 1 or 1′ positions of a 1,1′-ditetralyl system.[4]

The optical stabilities of bisdinaphthyl system (+)-(*R,R*)-**39** and bisditetralyl system (+)-(*R,R*)-**50** were compared by heating each in ampules at 226 °C in diphenyl ether for 1 week and reisolating the compounds. During the reisolation, traces of solvent and decomposition products were removed (silica gel chromatography). Since both compounds were glasses and total samples were used, no fractionation occurred. The rotations of the respective starting materials and recovered cycles were within 3% of one another, which indicates the compounds were essentially optically stable at this temperature for this time period.

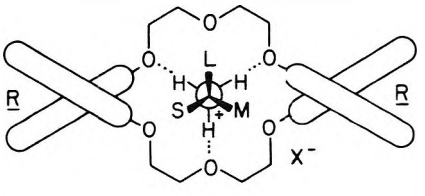
A comparison of CPK molecular models of dinaphthol **3** and ditetralol **22** suggests that the barriers to rotation in the two units should be somewhere nearly comparable. In both compounds, the transition states for racemization undoubtedly involve conformations A and B rather than C and D. The protons in A and B might well be in the 1 or 1′ positions, rather than on oxygen. Incorporation of the dinaphthyl and ditetralyl units in cycles containing 22-ring members or less forces racemization to occur via conformations C and D. Molecular model (CPK) examinations provide this conclusion and indicate that C and D are much higher energy than A and B.



The important question arises as to whether adsorption on platinum during catalytic reduction of the enantiomers of dinaphthyl **3** to those of ditetralol **22** also catalyzes the interconversion of enantiomers at some stage. Conceivably transition states for stereoisomer interconversion (e.g., A and B) that are much more planar than starting materials might be stabilized by adsorption on a platinum surface. Alternatively, platinum might transfer hydrogen atoms reversibly to the 1,1′ positions to produce short-lived intermediates with lower rotation barriers than those of A–D. Although such catalysis might exist, the barriers to interconversion must remain high enough to have allowed the reductions of dinaphthol **3** and dimethyldinaphthol **13** when carried out at 25 °C to have gone with negligible configurational loss. The evidence for this conclusion was discussed in an earlier section.

The question remains whether the *cycles* containing dinaphthyl units underwent configuration modification during reduction to ditetralyl units through stabilization of planar structures (e.g., C and D). Evidence that the cycles were stable to the conditions used in the reduction reactions is found in the fact that the same (or enantiomeric) compounds assembled in different reaction sequences gave rotations whose magnitudes were very close to one another. In the sequences compared, catalytic reduction in one of the two sequences was carried out before ring closure and the other after ring closure. In the first example, cycle (−)-(*S,S*)-**39** was reduced to (−)-(*S,S*)-**50**, which gave the same magnitude of rotation and mp as (+)-(*R,R*)-**50** obtained by a route that involved (+)-(*R,R*,)-**22** as one starting material. In the second example, cycle (+)-(*R,R*)-**29** was reduced to (+)-(*R,R*)-**51**, which gave a rotation only 2% higher than that obtained for a sample of (+)-(*R,R*)-**51** prepared from (+)-(*R*)-**24** (which contains a ditetralyl unit) as one starting material. In the latter synthetic route, the intermediates and the final product were not crystalline and the purification procedures depended on chromatographic procedures in which fractionation of enantiomers is highly improbable.

Symmetry Properties and Shapes of Host Compounds. These macrocyclic polyethers were prepared for study as host compounds for their chiral recognition properties in the complexation of enantiomeric primary amine salts as guests. Structure **60** is an idealized representation of the sterically

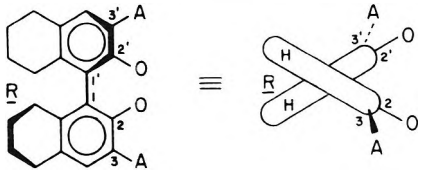


60

more stable diastereomeric complex between (*R,R*)-**39** and $LMSC^*NH_3{}^+X^-$, in which L is a large, M a medium, and S a small group. All of the hosts reported here possess three oxygens that can be spaced to hydrogen bond, in the tripod-like arrangement of structure **60**, with the NH_3^+ group of the guest (CPK models). Such an arrangement in a complex makes the C–N bond of the guest perpendicular to the best plane of the oxygens of the host. The L, M, and S groups are

distributed in the two chiral cavities between the naphthalene walls that protrude from that face of the complex from which the N–C bond protrudes.

In the following projection formulas of hosts whose syntheses have been described here, the presence of C_2 axes in the compounds they represent are indicated by the symbols ⊥ or ⌒, and planes of symmetry by the symbol ▮. The presence of the hosts of a ditetralyl unit substituted in the 3 positions by A groups is indicated by partial structures **61**.

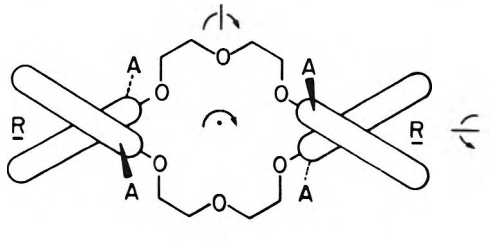


61

Hosts that contain at least one C_2 axis form the same complex when a guest is attached to either face. Such hosts are said to be nonsided, since each side is the stereochemical equivalent of the other. Hosts that contain three mutually perpendicular C_2 axes (D_2 symmetry) possess two cavities on each face between their naphthalene walls which although chiral are the stereochemical equivalent of one another. As a result, superimposable complexes are produced when L is distributed in any of the four cavities on the two faces of a host with D_2 symmetry. For example, if L were distributed in the lower and S and M in the upper cavity by conformational reorganization (180° rotation of the guest only about the C–N bond) in complex **60**, the new complex would be superimposable on the original by rotation of the whole new complex 180° around the C–N bond.

The shapes and symmetry properties of these macrocycles are affected both by the substituents in the 3 positions of the aryl units and by reduction of the outer rings of the dinaphthyl units. Structure **62** which possesses D_2 symmetry represents the shapes of several compounds reported here. In (*R,R*)-**32**, the A's are methyl groups, which are coplanar with their attached naphthalene rings and bonded oxygens. Thus the methyl groups extend the chiral barriers and decrease the cavity sizes.

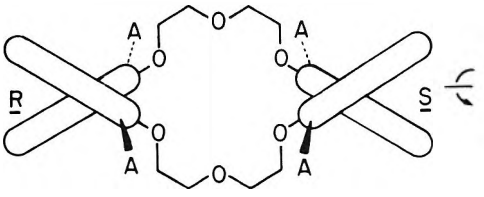
In CPK molecular models of host **62** with A = H, we estimated that each naphthalene ring protruding from each face occupies ~65° of the 360° of that cylinder of space whose axis is perpendicular to the best plane of the oxygens and is centered equidistant from all six oxygen atoms turned inward. In the model used for this estimate, each oxygen was equidistant from its two nearest oxygen neighbors. Since two naphthalene rings protrude from each face, in **62** with A = H each cavity exposes ~115° of the cylinder.[4] Examination of models of **62** with A = CH_3 (*R,R*-**32**) suggests that each 3-methylnaphthyl group occupies about ~80°, which leaves only about 100° for each of the two cavities on each face. In **62** with A = CH_2OH (*R,R*-**37**), the two OH groups on each face are close enough to hydrogen bond one another with no conformation adjustments except those involving rotations about the CH_2–O and O–H bonds. In such a conformation, no space is available for an alkylammonium ion guest. The close proximity of these pairs of $ArCH_2OH$ groups to one another suggests that the gas liberated when the racemate (*R,R*),-(*S,S*)-**37** melts at 170 °C is water and that the high temperature introduces two extra CH_2OCH_2 groups into the cycle. Interestingly, the mass spectrum of the cycle gives a strong M^+ minus $2H_2O$ peak. When the CH_2OH groups are turned outward, away from the axis of the cylinder, their space occupation of the cavities is only slightly greater than those of CH_3 groups. When the A groups of **62** are Br [(*R,R*)-**53**], again only about 100° of the cylinder is left for each cavity.



62

D_2-symmetry

Structure **63** is the meso form of **62**. The naphthalene walls and their A substituents that protrude from each face converge on one another. When A = H as in (*R,S*)-**39**, ~60° of the cylinder is available in one cavity, ~170° remaining in the other. When A = CH_3 as in (*R,S*)-**32**, the methyl groups are close to touching one another. Only about 30° of the cylinder remains open to the small cavity, but the other cavity remains at ~170°. In **63** with A = CH_2OH [(*R,S*)-**37**], the OH groups

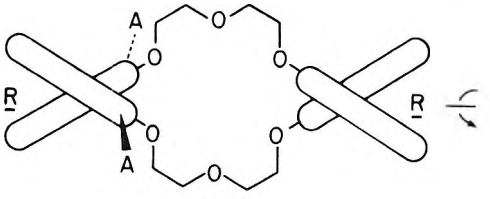


63

One mirror plane plus a C_2 axis

on the same face in the proper conformation can easily hydrogen bond one another. The gas liberated when (*R,S*)-**37** melts at 168–170 °C is probably water, a fact that correlates with the appearance in the mass spectrum of an ion with M^+ minus $2H_2O$. The (*R,S*) four-stranded cycle that possibly is formed looks in CPK models about comparably compressed to that of the (*R,R*) configuration.

Compound **64** with A = CH_3 [(*R,R*)-**29**] is chiral and possesses a C_2 axis, which means the two faces are stereochemically equivalent and the guest is nonsided. The larger of the

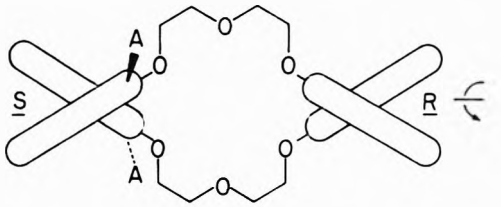


64

One C_2 axis

two cavities has available 115° and the smaller 100° of the imaginary cylinder of space. When A = CH_2OH [(*R,R*)-**30**] with the OH group turned outward, the cavity sizes are close to those of the compound with A = CH_3. With A = $C(CH_3)_2OH$ [(*R,R*)-**33**], either a CH_3 or OH is turned inward, and the smaller of the two cavities shrinks to ~90° or less, depending on whether an OH or CH_3 is turned toward the opposite naphthalene wall. When A = $CH(CH_3)_2$, the smaller of the cavity sizes can be as large as 100° with H turned inward, but as small as 60° with CH_3 inward.

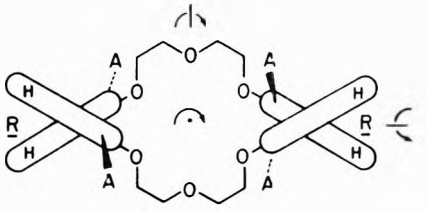
When A = H in **65**, the structure contains a mirror plane and a C_2 axis, as in (*R,S*)-**39**. However, when A = CH_3 as in (*S,R*)-**29**, the compound is chiral, possesses a C_2 axis, and is therefore nonsided. The two cavities on each face are different from those of any of the other compound. The smaller of the two has available only 45% of the cylinder and the larger 170° of the cylinder.



65
One C_2 axis

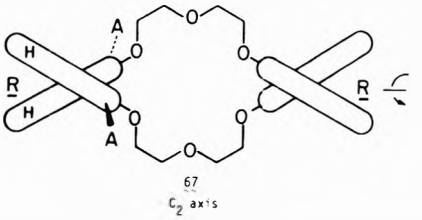
The compounds that contain two ditetralyl units with similar substituents (A groups) in their 3 positions are represented by projection structure **66.** Like structure **62, 66** exhibits D_2 symmetry which means all four cavities are chiral and are stereochemically equivalent to one another. Most importantly, the molecules represented by **66** are nonsided. The substitution of these ditetralyl for the dinaphthyl units has in CPK molecular models only minor effects on their shapes and cavity sizes. *Provided the four methylene groups of the ditetralyl units are in the proper conformations,* the dihedral angles between the planes of the diphenyl part unit can be as small as the 60° estimated for the dinaphthyl units. This allows the two oxygens attached to each biaryl unit to be as close to one another as the oxygens of *gauche*-ethylene glycol. Again given the proper conformations, the dihedral angle appears able to be as large as ~120° without causing bond angle deformations of any consequence. When in the conformation with all oxygens turned inward and close together, the macroring places the oxygen's unshared electron pairs in positions that resemble those of 18-crown-6 (CPK molecular models). The main difference in shape between compounds **66** and **62** (provided the A groups are the same) occurs only in those parts of the cavities most distant from the axis of the imaginary cylinder. The saturated portions of the tetralin rings are thicker than the corresponding unsaturated portions of the naphthalene rings. Therefore the effects of the spacial differences between the ditetralyl and dinaphthyl systems on host–guest relationships are expected to be small except when guests possess large groups that extend far from the axis of the cylinder in the complexes. However, the basicities of the aryl oxygens and the π base strengths of the two types of units are expected to be somewhat different.

Compounds (*R,R*)-**50** (A = H), (*R R*)-**52** (A = CH_3), and (*R,R*)-**53** (A = Br) (actually the *S,S* isomer was prepared) all conform to the general structure, **66.** Systems that lose two of

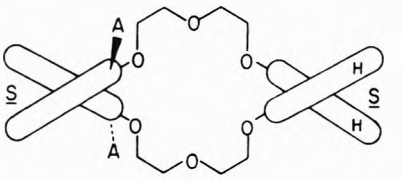


66
D_2-symmetry

their C_2 axes by combining a dinaphthyl with a ditetralyl unit are represented by general structures **67** and **68.** Compounds (*R,R*)-**54** (A = Br), (*R,R*)-**55** (A = H), and (*R,R*)-**56** (A = CH_3) all possess the general shape of **67,** whereas (*S,S*)-**57** conforms



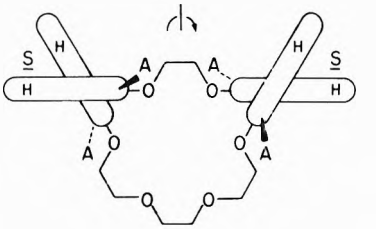
67
C_2 axis



68
C_2 axis

to the general shape of **68** in which A = CH_3. The cavity sizes in all of these compounds are estimated to be similar to those of the corresponding dinaphthyl parent compounds.

Compounds (*S,S*)-**58** (A = H) and (*S,S*)-**59** (A = Br) possess entirely different shapes than **62–66.** The two ditetralyl groups in these compounds are attached by one ethylene glycol unit and by a triethylene glycol unit. They possess the general shape suggested by **69,** which is chiral, but possess a C_2 axis



69
C_2 axis

and are therefore nonsided. The compound with A = H possesses cavities in CPK models similar to those of the parent bisdinaphthyl system.[4] The smaller of the two cavities on one face has ~55° of the imagined cylinder available whereas the larger has ~ 175°. When A = Br, the smaller cavity is narrowed to ~30°, and the larger to ~160°.

These results demonstrate feasibility for synthesizing a variety of potential host compounds whose symmetry properties, shapes, hydrophilicity, and lipophilicity are subject to manipulation. The syntheses reported here are highly modular. A few rigid units with different shapes and symmetry properties have been strung together with more flexible spacing and binding units to provide desired compounds. These syntheses make possible a semisystematic attack on the problem of host–guest complexation phenomena.

Experimental Section

General. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. All ^1H NMR chemical shifts are given as δ in ppm from internal Me_4Si unless otherwise indicated and were recorded on a Varian HA-100 or T-60 spectrometer. Optical rotations were obtained with a Perkin-Elmer 141 polarimeter in a 1 dm thermostated cell. Gel permeation chromatograms were run on a $\frac{3}{8}$ in. by 20 ft column of styragel 100-Å beads in CH_2Cl_2 (30–70 μm particle size, exclusion limit of 1500 molecular weight) at a flow rate of 4 mL m^{-1} and a pressure of 200–400 lb/in.^{2}. Mass spectra were taken at 70 eV on an AEI Model MS-9 double-focusing spectrometer. All chemicals were reagent grade. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Dimethylformamide (DMF) was distilled from CaH_2 prior to use. All reactions that involved KOH, KO-*t*-Bu, $LiAlH_4$, or NaH were conducted in an inert atmosphere. All organic solutions were dried with magnesium sulfate. All noncrystalline macrocycles, once synthesized, were air sensitive and were therefore stored under argon at 0 °C.

3,3′-Bis(*N*-morpholinomethyl)-2,2′-dihydroxy-1,1′-dinaphthyl (4) and 3-*N*-Morpholinomethyl-2,2′-dihydroxy-1,1′-dinaphthyl (5). A solution of 100 g (0.35 mol) of 2,2′-dihydroxy-1,1′-dinaphthyl (**3**) in 850 g (4.9 mol) of 4-(butoxymethyl)morpholine[6] was heated at 160 °C under N_2 for 5 days (a precipitate of **4** started to form after 6 h). The reaction mixture was cooled, 300 mL of benzene was added with stirring, and after the mixture had stood 10 h at 25 °C the solid was collected, washed with 300 mL of ether, and dried at 25 °C (30 mm) to give 104 g (61%) of **4.** A sample of 5 g of this material was recrystallized from $CHCl_3$ and EtOAc to give 4.5 g of **4,** mp 300 °C. The 60 MHz ^1H NMR spectrum in $CDCl_3$ gave δ 7.60 (m, ArH, 4 H), 7.05

(m, ArH, 6 H), 3.98 (ABq, J_{AB} = 14 Hz, $ArCH_2N$, 4 H), 3.64 (m, OCH_2, 8 H), and 2.60 (m, NCH_2, 8 H). The mass spectrum gave M^+ 484. Anal. Calcd for $C_{30}H_{32}O_4N_2$: C, 74.36; H, 6.66; N, 5.78. Found: C, 74.23; H, 6.75; N, 5.66.

From the filtrate of the original reaction by chromatography was obtained **5** in 15% yield, mp 226–228 °C. Anal. Calcd for $C_{25}H_{23}O_3N$: C, 77.90; H, 6.01. Found: C, 77.84; H, 5.99.

3,3′-Bis(dimethylaminomethyl)-2,2′-dihydroxy-1,1′-dinaphthyl (6). Application of the same procedure to 42.9 g (0.15 mol) of 2,2′-dihydroxy-1,1′-dinaphthyl and 131 g (1 mol) of dimethylaminoisobutoxymethane[7] in 400 mL of isobutyl alcohol gave after 9 days at 160 °C 19.8 g (33%) of diamine **6**, mp 256–258 °C, M^+ 400. Anal. Calcd for $C_{26}H_{28}N_2O_2$: C, 77.97; H, 7.05. Found: C, 78.20; H, 6.88.

3,3′-Diacetoxymethyl-2,2′-diacetoxy-1,1′-dinaphthyl (7). A solution of 50 g (0.105 mol) of **4** in 1200 mL of acetic anhydride was refluxed for 8 days. The solution was cooled and evaporated at 30 mm, and the residue was dissolved in 150 mL of benzene. The residue was chromatographed on 1 kg of silica gel in hexane–benzene (2:1, v:v). Elution of the column with hexane–benzene mixtures eluted the desired product, **7**, which was recrystallized from ether to give 24.5 g (46%) of tetraacetate, mp 113–114 °C. Anal. Calcd for $C_{30}H_{26}O_8$: C, 70.03; H, 5.09. Found: C, 70.18; H, 5.18. Further elution of the column with ether–benzene produced 3-acetoxymethyl-3′-*N*-morpholinomethyl-2,2′-dihydroxy-1,1′-dinaphthyl (**8**), which was recrystallized from benzene–ether to give 16.5 g (39%), mp 115–117 °C. Anal. Calcd for $C_{28}H_{27}NO_5$: C, 73.51; H, 5.95. Found: C, 73.72; H, 6.04. Substitution of propionic anhydride at reflux for 4 days for acetic anhydride gave an 85% yield of the corresponding tetraester, which without characterization was converted to tetrol **9** (see next section).

3,3′-Bis(hydroxymethyl)-2,2′-dihydroxy-1,1′-dinaphthyl (9). To a refluxing suspension of 10.0 g (0.21 mol) of $LiAlH_4$ suspended in 1.5 L of dry ether was added dropwise 18.5 g (0.036 mol) of tetraacetate **7** dissolved in 100 mL of THF. The mixture was refluxed for 6 h and cooled, and ethanol was added dropwise at 0 °C to decompose excess reagent. To the mixture was added 400 mL of 15% hydrochloric acid and 300 mL of THF. The solution was stirred for 12 h and the organic layer was washed with 10% $NaHCO_3$ solution, and dried. The ether was evaporated at 30 mm, and the concentrated solution (250 mL) was refluxed with continuous replacement of THF by benzene. Tetrol **9** crystallized from hot benzene to give 12.5 g (98%), mp 222–224 °C (lit.[8] mp 231 °C), M^+ 346. Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.44; H, 5.35.

3-Hydroxymethyl-2,2′-dihydroxy-1,1′-dinaphthyl (10). Application of the above procedures to 3-*N*-morpholinomethyl-2,2′-dihydroxy-1,1′-dinaphthyl **5** gave triol **10** (80%), mp 206–207 °C, M^+ 316. Anal. Calcd for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10. Found: C, 79.70; H, 5.29.

3-Hydroxymethyl-3′-*N*-morpholinomethyl-2,2′-dihydroxy-1,1′-dinaphthyl (11). Application of the above procedure to compound **8** gave triol **11** (75%), mp 190–192 °C, M^+ 415. Anal. Calcd for $C_{26}H_{25}O_4N$: C, 75.16; H, 6.06. Found: C, 75.07; H, 5.95.

3,3′-Bis(bromomethyl)-2,2′-dihydroxydinaphthyl (12). A slow stream of dry HBr was bubbled through a stirred suspension of 8.5 g of tetrol **9** in 120 mL of glacial acetic acid. After 10 min, the solid dissolved, the temperature increased, and a heavy precipitate formed. The mixture after standing 1 h was filtered and the filtrate was evaporated. The residue and filtrate were dissolved in 500 mL of ether and the solution was washed with water and then with a saturated solution of $NaHCO_3$. The solution was dried and evaporated to give 11 g of solid. One crystallization of this material from benzene gave 9.5 g (85%) of **12**: mp 215–216 °C; ^1H NMR (CD_3COCD_3) δ 8.05 (s, ArH^4, 2 H), 7.84 (q, ArH^5, 2 H), 7.22 (m, $Ar^{6,7}$, 4 H), 6.94 (m, ArH^8, 2 H), 4.84 (s, $ArCH_2Br$, 4 H); M^+ 472. Anal. Calcd for $C_{22}H_{16}O_2Br_2$: C, 55.96; H, 3.41. Found: C, 55.94; H, 3.53.

3,3′-Dimethyl-2,2′-dihydroxy-1,1′-dinaphthyl (13). To a suspension of 3.0 g of $LiAlH_4$ in 350 mL of dry ether was added 7.08 g of the above dibromide **12** dissolved in 100 mL of THF. The mixture was refluxed for 4 h and stirred at 25 °C for 12 h more. At 0 °C, 25 mL of 95% ethanol was cautiously added, followed by 300 mL of 15% hydrochloric acid and 100 mL of THF. The layers were separated and the organic layer was washed twice with 10% $NaHCO_3$ solution and with water and was dried and evaporated. The residue was crystallized from benzene to give 4.7 g (98%) of dimethyldiol **13**, mp 205 °C. The ^1H NMR spectrum in $CDCl_3$ gave δ 7.76 (m, $ArH^{4,5}$, 4 H), 7.17 (m, ArH, 6 H), 5.05 (s, OH, 2 H), and 2.47 (s, CH_3, 6 H); mass spectrum M^+ 314. Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.98; H, 5.85.

Dimethydiol **13** was also prepared by catalytic reduction of tetrol **9**. A solution of 6.0 g of **9** in 60 mL of 95% ethanol was stirred with 3.0 g of 10% palladium on charcoal under 1 atm of hydrogen for 8 h. The mixture was filtered and the filtrate was evaporated under vacuum and chromatographed on 100 g of silica gel. Elution of the column with benzene gave dimethyldiol **13**, 1.83 g (33%), mp 205 °C, undepressed by admixture with an authentic sample. Elution with 1:1 (v:v) benzene–CH_2Cl_2 gave 1.9 g (32%) of 3′-hydroxymethyl-3-methyl-2,2′-dihydroxy-1,1′-dinaphthyl (**14**): mp 204 °C (from benzene); M^+ 330; ^1H NMR ($CDCl_3$) δ 7.82 (m, $ArH^{4,5}$, 4 H), 7.16 (m, ArH, 6 H), 4.93 (s, $ArCH_2$, 2 H), and 2.50 (s, CH_3, 3 H). Anal. Calcd for $C_{22}H_{18}O_3$: C, 79.98; H, 5.49. Found: C, 79.96; H, 5.68.

Elution of the column with 98:2 (v:v) CH_2Cl_2–isopropyl alcohol gave 1.0 g (17%) of starting tetrol, **9**.

Reduction of diaminediol **4** gave dimethyldiol **13** and 3-*N*-morpholinomethyl-3′-methyl-2,2′-dihydroxy-1,1′-dinaphthyl (**15**). A mixture of 2.0 g of diaminediol **4**, 80 mL of glacial acetic acid, 120 mL of 95% ethanol, and 1.0 g of 10% palladium on charcoal was stirred under 1 atm of H_2 for 15 h. The product was isolated by chromatography on 100 g of silica gel. Benzene eluted 0.56 g (44%) of dimethyldiol **13**, mp 206 °C, undepressed by admixture with an authentic sample. Elution of the column with 1:1 benzene–CH_2Cl_2 gave 0.280 g (20%) of aminodiol **15**, mp 185 °C, from CH_2Cl_2–ether: M^+ 399; ^1H NMR ($CDCl_3$) δ 7.72 (m, $ArH^{4,5}$, 4 H), 7.16 (m, ArH, 6 H), 3.96 (s, $ArCH_2N$, 2 H), 3.66 (t, CH_2O, 4 H), 2.60 (t, CH_2N, 4 H), and 2.49 (s, CH_3, 3 H). Anal. Calcd for $C_{26}H_{25}O_3N$: C, 78.17; H, 6.31. Found: C, 78.09; H, 6.37.

Optical Resolution of 3,3′-Dimethyl-2,2′-dihydroxy-1,1′-dinaphthyl (13). A slurry of 146 g of racemic **13**, 750 mL of CH_2Cl_2, and 84.5 g of $POCl_3$ was stirred under N_2 and 111.3 g of triethylamine was added slowly at a rate that maintained gentle reflux. After addition was complete, the solution was stirred an additional hour and extracted twice with 300 mL of water. The solution was dried and evaporated and the crude chlorophosphate was stirred with 750 mL of THF and 200 mL of water at 50 °C for 1 h. To this solution, 700 mL of ethyl acetate was added, the layers were separated, and the organic layer was washed with 200 mL of water and with 200 mL of brine, dried, and evaporated under vacuum to produce white crystals of the phosphoric acid diester of weight 129 g (75%), mp >300 °C, M^+ 376.

A mixture of 60 g (0.160 mol) of the above acid ester, 47.0 (0.160 mol) of cinchonine, and 800 mL of methanol was warmed to reflux, and to the solution was added 149 mL of water. The solution was cooled to 25 °C, and the crystalline salt that separated was collected, washed, and dried to give 40.8 g of salt (38% based on racemate = 100%). This material was recrystallized three times from methanol–water to give 32.0 g (30%) of salt: $[\alpha]^{25}_{578}$ −291°, $[\alpha]^{25}_{546}$ −339°, $[\alpha]^{25}_{436}$ −632° (c 1.1, DMF).

The (−)-salt, 40.0 g (0.06 mol), was shaken with 1 L of ether and 500 mL of 5 M hydrochloric acid. The resulting slurry was extracted with ether in a continuous extractor until all solids dissolved (4 days). The ether layer was evaporated to give a white foam: weight 21.5 g (95%); $[\alpha]^{25}_{436}$ −1121°, $[\alpha]^{25}_{546}$ −650°, $[\alpha]^{25}_{578}$ −561° (c 1.0, MeOH); mp >300 °C. In 200 mL of dry THF was suspended 2.0 g (0.53 mol) of $LiAlH_4$, and dropwise a 50 mL of THF solution of this acid diester was added at a rate to maintain a gentle reflux. The reaction mixture was cooled to 25 °C and stirred for 8 h. Excess reducing agent was destroyed by adding cautiously 10 ml of ethyl acetate. The aluminum salts produced were treated in succession with 2 mL of water, 2 mL of 40% NaOH solution, and 3 mL of water. The salts were filtered and washed with fresh THF. The organic layers were combined and evaporated under vacuum. The resulting oil was dissolved in CH_2Cl_2, washed with water and brine, and dried. Evaporation of the solvent at reduced pressure gave 14.9 g (90%) of white crystals, recrystallization of which from benzene gave dimethyldiol, (+)-(*R*)-**13**, which after heating for 8 h at 110 °C (0.05 mm) to remove benzene gave mp 200–201 °C: ^1H NMR ($CDCl_3$) δ 7.76 (m, ArH, 4 H), 7.17 (m, ArH, 6 H), 5.05 (s, OH, 2 H), 2.47 (s, 6 H); M^+ 314; $[\alpha]^{25}_{436}$ +131.3°, $[\alpha]^{25}_{546}$ +45.7°, and $[\alpha]^{25}_{578}$ +37.3° (c 1.0, $CHCl_3$). Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.92; H, 5.85.

The mother liquors from the above cinchonine salt formation and purification were evaporated under vacuum to a gel, which when dried at 100 °C under vacuum gave 68.2 g of fine powder. This material was suspended in 1 L of 5 M HCl solution and continuously extracted with ether until a homogeneous aqueous solution was obtained. The ether was evaporated to yield a white foam, weight 34.8 g (58% of original acid), $[\alpha]^{25}_{436}$ +923° (73% optically pure).

In 52 mL of hot ethanol, 2.0 g (0.053 mol) of the above (+)-acid and 1.77 g (0.053 mol) of strychnine were mixed to give a solution. When cooled, fine white crystals separated, which were recrystallized from methanol–water to give 2.0 g (48%) of salt, $[\alpha]^{25}_{436}$ +672.0° (c 1.0, DMF), which did not change on further recrystallization. This salt (1.0 g) was converted to its acid by the same procedure as that used

for the cinchonine salt to give 0.47 g (89%) of (+)-acid diester, $[\alpha]^{25}_{436}$ +1218°, $[\alpha]^{25}_{546}$ +869°, $[\alpha]^{25}_{578}$ +566° (c 1.0, MeOH). Recrystallization of this material from methanol did not change these rotations. By the same procedure used for the (−)-acid diester, 0.300 g of this (+)-acid diester was converted to 0.224 g of dimethyldiol (−)-(*S*)-**13**, which after recrystallization from benzene and drying for 8 h at 110 °C (0.05 mm) to remove benzene gave 0.203 g (82%) of white crystals: $[\alpha]^{25}_{436}$ −129.8°, $[\alpha]^{25}_{546}$ −45.1°, and $[\alpha]^{25}_{578}$ −36.9° (c 1.0, $CHCl_3$); mp 200–202 °C; ^1H NMR ($CDCl_3$) δ 7.72 (m, ArH, 4 H), 7.17 (m, ArH, 6 H), 2.48 (s, CH_3, 6 H); M^+ 314. Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 84.01; H, 5.70.

2,2′-Dihydroxy-1,1′-dinaphthyl-3,3′-dicarboxylic Acid (16). A mixture of 3-hydroxy-2-naphthoic acid (72 g, 0.383 mol) and NaOH (14.4 g, 0.36 mol) in 1 L of water was heated to reflux in a 12-L flask. With vigorous stirring and refluxing, a hot solution of $FeCl_3$·$6H_2O$ (108 g, 0.4 mol) in 200 mL of water was added dropwise (15 min). The mixture foamed as greenish-brown precipitates separated. After being stirred at reflux for 45 min, the mixture was cooled and a solution of 80 g (2 mol) of NaOH in 1 L of water was added, followed by 600 mL of concentrated hydrochloric acid. The mixture was stirred for 20 min, and the yellow precipitate that separated was filtered, washed with 350 mL of 10% HCl and 600 mL of H_2O, and dried. To a hot solution of the 73.5 g of dried solid in 370 mL of THF was added 59.8 g (0.59 mol) of triethylamine. The solution produced large brown plates when cooled to 25 °C for 1 day and to 0 °C for 1 day, which were collected and washed with cold THF to give 47 g of salt. This material was dissolved in 200 mL of 5% aqueous NaOH, and the resulting solution was washed once with ether. The aqueous layer was filtered, and the filtrate was acidified with concentrated hydrochloric acid to pH ~1. The deposited solid (**16**) was collected, water washed, and dried to give a yellow powder (29.5 g, 41%), mp >285 °C. This material was used directly in the following optical resolution.

Resolution of 2,2′-Dihydroxy-1,1′-dinaphthyl-3,3′-dicarboxylic Acid (16). To a suspension of 61.2 g (0.164 mol) of racemic **16** in 700 mL of methanol was added a solution in 20 mL of methanol of 50.0 g (0.345 mol) of optically pure L-leucine methyl ester, $[\alpha]^{25}_{589}$ +15.3° (neat). The reddish-brown solution was heated on a steam bath for 5 min and cooled to 25 °C for 1 day and to 0 °C for 1 day. The salt that separated was filtered, washed with a small amount of methanol, and dried to give 50.3 g (92%) of yellow crystals. The crystals were powdered in a mortar, and the powder was digested in three successive portions of 200 mL of hot methanol at reflux with stirring for 1 h. The rotations (c 0.3, MeOH) and weights of the solids obtained at each stage were as follows: before digestion, $[\alpha]^{25}_{578}$ +99.7°, weight 50.0 g; first digestion, $[\alpha]^{25}_{578}$ +117.8°, weight 43 g; second digestion, $[\alpha]^{25}_{578}$ +124.9°, weight 39.6 g; third digestion, $[\alpha]^{25}_{578}$ +123.0°, weight 37.5 g. The final powder was dissolved in 200 mL of water containing 6 g of NaOH. The resulting solution was washed with ether, filtered, and acidified to pH 1 to give a yellow precipitate, which was collected, washed, and dried at ca. 110 °C under vacuum to give (+)-(*R*)-**16**, 20.9 g (34%, racemate = 100%). An analytical sample was recrystallized from glacial acetic acid and had to be dried at 138 °C for 24 h at 0.05 mm to free it of solvent: needles; mp >285 °C; $[\alpha]^{25}_{578}$ +194°, $[\alpha]^{25}_{589}$ +185° (c 1.08, pyridine), reported[10a] $[\alpha]^{15}_{589}$ +179° (pyridine). Anal. Calcd for $C_{22}H_{14}O_6$: C, 70.58; H, 3.77. Found: C, 70.48; H, 3.94.

The mother liquor from the original salt was evaporated to a brown oil which was mixed with 60 mL of methanol and filtered from an insoluble yellow powder (which was methanol washed), and the oil was evaporated. The residual salt was converted back (see above) to diol diacid **16** enriched in the (−) isomer, 29.1 g. To a suspension of 29.0 g of this powder in 200 mL of methanol was added 23.5 g (0.233 mol) of triethylamine, and the resulting hot clear dark-red solution was allowed to stand at 25 °C for 2 days. The solid that separated was air dried (36.5 g) and recrystallized from 365 mL of methanol containing 3 mL of triethylamine to give 29.6 g of large plates of the salt. This material was converted to its acid (see above) to give after drying at 110 °C under vacuum for 24 h (−)-(*S*)-**16** as a yellow powder: 18.2 g (30%, racemate = 100%); mp >285 °C; $[\alpha]^{25}_{546}$ −246°, $[\alpha]^{25}_{578}$ −203°, $[\alpha]^{25}_{589}$ −190° (c 0.750, pyridine), reported[10b] $[\alpha]^{20}_{589}$ −171° (pyridine). The ^1H NMR spectra in dimethylacetamide of the two enantiomers were identical to one another.

(+)-(*R*)-3,3′-Bis(hydroxymethyl)-2,2′-dihydroxy-1,1′-dinaphthyl, (+)-(*R*)-9, and (−)-(*S*)-9. A solution of the above diacid diol (+)-(*R*)-**16** (7.49 g or 20 mmol) in 60 mL of THF was added to a suspension of $LiAlH_4$ (6.08 g or 160 mmol) in 200 mL of THF, which was refluxed for 9 h. The cooled reaction mixture was stirred with 90 mL of 50% hydrochloric acid and 100 mL of ether. The organic layer was separated, and the aqueous layer was extracted with a mixture of ether–THF. The combined organic layers were washed with brine, dried, and evaporated with added benzene to give a yellow solid. Recrystallization of this material from THF–benzene gave prisms (solvate) which when dried at 138 °C at 0.05 mm for 24 h gave (+)-(*R*)-**9**: 5.35 g (77%); mp 192–195 °C; $[\alpha]^{25}_{546}$ +78.7° (c 1.2, THF). Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.28; H, 5.24. Found: C, 76.39; H, 5.36.

A similarly conducted reduction of optically pure (−)-(*S*)-**16** gave (−)-(*S*)-**9** in 79% yield: mp 190–193 °C; $[\alpha]^{25}_{546}$ −77.8° (c 1.1, THF). This material gave M^+ 349 and the same ^1H NMR spectrum in CD_3COCD_3 as (*R*)(*S*)-**9** as follows: δ 7.98 (s, Ar^4H, 2 H), 7.80 (m, Ar^5H, 2 H), 7.18 (m, ArH, 6 H), and 4.92 (s, CH_2, 4 H).

(+)-(*R*)-3,3′-Dimethyl-2,2′-dihydroxy-1,1′-dinaphthyl, (+)-(*R*)-13, from (+)-(*R*)-2,2′-Dihydroxy-1,1′-dinaphthyl-3,3′-dicarboxylic Acid, (+)-(*R*)-16, and (−)-(*S*)-13 from (−)-(*S*)-16. Diacid diol (+)-(*R*)-**16**, $[\alpha]^{25}_{589}$ +185° (c 1.08, pyridine), was reduced to tetrol (+)-(*R*)-**9** by the above procedure and the tetrol reduced to dimethyldiol (+)-(*R*)-**13** as follows. A mixture of 1 g (2.9 mmol) of (+)-(*R*)-**9**, 60 mL of ethyl acetate, and 1 g of 10% palladium on charcoal was reduced at 25 °C for 20 h under 3 atm of H_2 on a Parr apparatus. The mixture was filtered and evaporated and the product was chromatographed on 60 g of silica gel in CH_2Cl_2 to give product recrystallized from benzene and dried at 110 °C at 0.05 mm for 8 h to remove benzene to give 0.85 g (94%) of (+)-(*R*)-**13**: mp 197–199 °C; $[\alpha]^{25}_{436}$ +125.0°, $[\alpha]^{25}_{546}$ +44.2°, $[\alpha]^{25}_{578}$ +36.3° (c 1, $CHCl_3$). The ^1H NMR spectrum and TLC behavior of this material were identical to those of (+)-(*R*)-**13** prepared by direct resolution.

Similarly, diacid diol (−)-(*S*)-**16**, $[\alpha]^{25}_{589}$ −190° (c 1, pyridine), was reduced to tetrol (−)-(*S*)-**9**, 1.0 g (2.9 mmol) of which was hydrogenated to give 0.89 g (98%) of dried (8 h at 110 °C (0.05 mm)) (−)-(*S*)-**13**, which gave: mp 199–121 °C; $[\alpha]^{25}_{436}$ −128.8°, $[\alpha]^{25}_{546}$ −45.1°, and $[\alpha]^{25}_{578}$ −36.8° (c 1, $CHCl_3$).

(+)-(*R*)-3,3′-Dicarbomethoxy-2,2′-dihydroxy-1,1′-dinaphthyl, (+)-(*R*)-17. To a solution of 5.48 g (14.6 mmol) of diacid diol (+)-(*R*)-**16** (see above), $[\alpha]^{25}_{578}$ +190° (c 1.1, pyridine), in 70 mL of THF was added a solution of CH_2N_2 in 70 mL of ether (prepared from 7.0 g or 47 mmol of *N*-methyl-*N*-nitrosourea). Excess CH_2N_2 was decomposed immediately with 4 mL of AcOH, and the solution was evaporated to dryness. The residual solid was dissolved in CH_2Cl_2, and the solution was washed successively with water, saturated aqueous $NaHCO_3$, water, and brine. The solution was dried and evaporated, and 6.9 g of residual solid was chromatographed on silica gel in $CHCl_3$. The diester product [(+)-(*R*)-**17**] was recrystallized from benzene–pentane to give transparent plates, drying of which at 110 °C under vacuum converted them to nontransparent plates (4.5 g, 76%): mp 243–245 °C (lit.[9a] 239–240 °C); $[\alpha]^{25}_{436}$ +675°, $[\alpha]^{25}_{546}$ +227°, $[\alpha]^{25}_{578}$ +184°, $[\alpha]^{25}_{589}$ +172° (c, 0.815, THF), reported[9a] $[\alpha]^{25}_{589}$ +159° (c 1.0, THF). This material gave M^+ 402, and the ^1H NMR ($CDCl_3$) (60 MH_2) δ 6.00 (s, CH_3, 6 H), 2.85–2.55 (m, ArH, 6 H), 2.0–2.3 (m, ArH, 2 H), 1.33 (s, ArH, 2 H), −0.7 (s, OH, 2 H). Anal. Calcd for $C_{24}H_{18}O_6$: C, 71.63; H, 4.51. Found: C, 71.66; H, 4.65.

Reduction of this diester with $LiAlH_4$ gave (+)-(*R*)-**9** in 63% yield, mp 191–193.5 °C; $[\alpha]^{25}_{546}$ +77.1°, $[\alpha]^{25}_{578}$ +63.8° (c, 1.24, THF), whose ^1H NMR spectrum was identical to that of the sample prepared directly from (+)-(*R*)-**16** (see above).

(+)-(*R*)-3,3′-Di(2-hydroxy-2-propyl)-2,2′-dihydroxy-1,1′-dinaphthyl, (+)-(*R*)-18. To a solution of 5.0 g (12.4 mmol) of (+)-(*R*)-3,3′-dicarbomethoxy-2,2′-dihydroxy-1,1′-dinaphthyl [(+)-(*R*)-**17**], $[\alpha]^{25}_{578}$ +184° (c 1.0, THF), in 300 mL of dry THF at 0 °C under N_2 was added 70 mL of CH_3Li (1.6 M in hexane) in a single portion. The mixture was stirred for 1 h at 25 °C, CH_3OH was added dropwise to decompose the excess CH_3Li, the solution was diluted with 150 mL of water, and 12 M hydrochloric acid was added dropwise with stirring until a pH of 4 was attained. The mixture was shaken with 400 mL of CH_2Cl_2 and 600 mL of $NaHCO_3$ saturated aqueous solution; the organic layer was dried and evaporated under reduced pressure. The residue was crystallized from benzene to give 5.2 g (87%) of light-yellow needles that were dried at 25 °C and atmospheric pressure, mp ~175 °C (decompose), of a 1:1 benzene solvate of (+)-(*R*)-**18**: M^+ 402; ^1H NMR (CD_3COCD_3) δ 7.92 (m, ArH, 4 H), 7.20 (m, ArH, 6 H), 1.83 (s, CH_3, 12 H); $[\alpha]^{25}_{546}$ +132°, $[\alpha]^{25}_{578}$ +109°, and $[\alpha]^{25}_{589}$ +103°. When heated at 110 °C (0.05 mm) for 8 h, the solvate showed significant decomposition (TLC and ^1H NMR). A sample dried at 0.05 mm for 48 h at 25 °C gave an analysis consistent with 0.5 mol of benzene of solvation. Anal. Calcd for $C_{26}H_{26}O_4$·$0.5C_6H_6$: C, 78.88; H, 6.62. Found: C, 78.82; H, 6.62.

(+)-(*S*)-3,3′-Dimethyl-2,2′-bis(5-hydroxy-3-oxa-1-pentyloxy)-1,1′-dinaphthyl [(+)-(*S*)-19] and (−)-(*R*)-19. In 150 mL of dry DMF (stored under 4A molecular sieves) at 50 °C was dissolved 20 g (63.7 mmol) of (−)-(*S*)-3,3′-dimethyl-2,2′-dihydroxy-1,1′-dinaphthyl [(−)-(*S*)-**13**]. $[\alpha]^{25}_{578}$ −36.9°, $[\alpha]^{25}_{436}$ −129.8° (c 1.0, $CHCl_3$). Under dry N_2, 6.4 g (128 mmol) of a 50% NaH dispersion in oil was carefully added. After H_2 evolution ceased, 26.5 g (127 mmol) of 2-

(2-chloroethoxy)ethyl 2-tetrahydropyranyl ether[4] in 50 mL of dry DMF was added. The resulting mixture was stirred at 70 °C for 40 h and then an additional 0.65 g (13 mmol) of NaH and 2.65 g (12.7 mmol) of the above chloro ether were added. The mixture was stirred for an additional 2 days, and mixed with 600 mL of water. After standing 24 h, the water was decanted from the precipitated oil, which was shaken with 200 mL of CH_2Cl_2 and 200 mL of water. The organic layer was washed with three 200-mL portions of water, dried, and filtered through a column of 50 g of activated alumina (MCB), which was subsequently washed free of product with CH_2Cl_2. The resulting solution was evaporated to 150 mL, and 150 mL of methanol and 10 mL of concentrated hydrochloric acid were added. After stirring for 2 h at 25 °C, the mixture was shaken with 100 mL of $NaHCO_3$ in water to neutralize the acid, the aqueous layer was saturated with NaCl and washed twice with CH_2Cl_2, the combined CH_2Cl_2 solutions were washed twice with water and dried, and the solvent was evaporated. The residue was magnetically stirred and heated at 120 °C for 2 h (0.1 mm) and cooled, and the mineral oil was rinsed from the oil with three successive 20 mL pentane portions. The product was dried to give 28.4 g (90%) of (+)-(*S*)-**19** as a soft white glass dried at 75 °C at 50 μm for 24 h: ^1H NMR ($CDCl_3$) δ 8, 2.53 (s, CH_3, 6 H), 3.17 (m, CH_2O-CH_2CH_2O, 12 H), 3.50 (m, $ArOCH_2$ and OH, 6 H), 7.09 (m, ArH, 6 H), 7.74 (m, ArH, 4 H); $[\alpha]^{25}_{578}$ +106.4°, $[\alpha]^{25}_{546}$ +124.4°, $[\alpha]^{25}_{436}$ +246.3° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.37; H, 7.00.

Similarly, from (+)-(*R*)-3,3′-dimethyl-2,2′-dihydroxy-1,1′-dinaphthyl, (+)-(*R*)-**13**, $[\alpha]^{25}_{436}$ +125.0° (*c* 1, $CHCl_3$), (−)-(*R*)-**19** was prepared in 68% yield (15.4 g scale), M^+ 462, whose ^1H NMR spectrum was identical to its enantiomer.

(+)-(*S*)-3,3′-Dimethyl-2,2′-bis(5-tosyloxy-3-oxa-1-pentyloxy)-1,1′-dinaphthyl [(+)-(*S*)-20], (−)-(*R*)-20, and (*RS*)-20. To a solution of 20.0 g (40.8 mmol) of diol (+)-(*S*)-**19** in 75 mL of dry pyridine cooled to −20 °C was added 20 g (105 mmol) of tosyl chloride in 50 mL of dry pyridine at −20 °C. The mixture was swirled for 1 min and stored at −20 °C for 48 h. The mixture was poured onto 500 g of crushed ice, and the aqueous layer was decanted from the precipitated oil. The oil was dissolved in CH_2Cl_2 and washed with water, cold 5% hydrochloric acid, and 5% aqueous $NaHCO_3$. The solution was dried and evaporated under vacuum to give after drying at 40 °C (0.1 mm) for 30 h 30.2 g (92%) of (+)-(*S*)-**20** as a white glass: ^1H NMR ($CDCl_3$) δ 2.36 (s, *p*-CH_3, 6 H), 2.46 (s, 3-CH_3, 6 H), 2.90–4.00 (m, OCH_2, 16 H), 6.90–7.40 (m, ArH, 10 H), 7.57–7.87 (m, ArH, 8 H); $[\alpha]^{25}_{578}$ +69.3°, $[\alpha]^{25}_{546}$ +80.8°, $[\alpha]^{25}_{436}$ +158° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{44}H_{46}O_{10}S_2$: C, 66.15; H, 5.80. Found: C, 66.16; H, 5.91.

Similarly, from (−)-(*R*)-**19** (see above) was prepared 22.9 g (93%) of (−)-(*R*)-**20**, $[\alpha]^{25}_{578}$ −69.7° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{44}H_{46}O_{10}S_2$: C, 66.14; H, 5.80. Found: C, 66.27; H, 6.05.

Similarly from (*R*),(*S*)-13 was prepared (*R*),(*S*)-19 (59%), which was converted to (*R*),(*S*)-**20** (90%), which was a glass, and possessed an ^1H NMR spectrum identical to that of (+)-(*S*)-**20**. Anal. Calcd for $C_{44}H_{46}O_{10}S_2$: C, 66.15; H, 5.80. Found: C, 66.40; H, 6.16.

(+)-(*R*)-2,2′-Dihydroxy-5,5′,6,6′,7,7′,8,8′,-octahydro-1,1′-dinaphthyl [(+)-(*R*)-22) and (−)-(*S*)-22. A mixture of 10.0 g (0.0275 mol) of (+)-(*R*)-2,2′-dihydroxy-1,1′-dinaphthyl [(+)-(*R*)-**3**], $[\alpha]^{25}_{589}$ +34.2° (*c* 1.0, $CHCl_3$), 1.2 g of PtO_2, and 250 mL of glacial acetic acid was shaken in a Parr apparatus under 3 atm of hydrogen at 25 °C for 7 days. The mixture was filtered through a Celite pad, and the filtrate was shaken with 400 mL of $CHCl_3$ and 1.5 L of water. The organic layer was washed with two 1-L portions of water and 1 L of 10% $NaHCO_3$ solution, dried, and evaporated. The residue was dissolved in 50 mL of CH_2Cl_2 and the solution was passed through a 150-g silica gel column. The product eluted with 2 L of CH_2Cl_2 and was crystallized from heptane to give 9.7 g (96%) of (+)-(*R*)-**22**: mp 165–166 °C; M^+ 294; ^1H NMR ($CDCl_3$) δ 6.90 (ABq, ArH, 4 H), 4.60 (s, OH, 2 H), 2.70 (m, $ArCH_2$, 4 H), 2.20 (m, $ArCH_2$, 4 H), and 1.66 (m, CCH_2CH_2C, 8 H); $[\alpha]^{25}_{436}$ +137.3°, $[\alpha]^{25}_{546}$ +65.2°, $[\alpha]^{25}_{578}$ +55.5°, $[\alpha]^{25}_{589}$ + 52.8° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.40; H, 7.38.

Similarly (−)-(*S*)-**3** of $[\alpha]^{25}_{589}$ −34.3° (*c* 1.0, $CHCl_3$) was reduced at 25 °C to (−)-(*S*)-**22** (95%): M^+ 294; ^1H NMR identical to its enantiomer; $[\alpha]^{25}_{578}$ −55.5°; mp 165–166 °C.

A similar conversion was applied to 5.0 g of (−)-(*S*)-**3** of $[\alpha]^{25}_{589}$ −34.3° (*c* 1.0, $CHCl_3$), except the reaction was conducted at 65 °C for 3 days. The product, 4.7 g (92%), gave: mp 164–167 °C; M^+ 294; ^1H NMR identical to its enantiomer; $[\alpha]^{25}_{436}$ −125°, $[\alpha]^{25}_{546}$ −60.1°, $[\alpha]^{25}_{578}$ −50.5°, and $[\alpha]^{25}_{589}$ −49.4° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.59; H, 7.53. Found: C, 81.70; H, 7.54. These rotations are 8 ± 1% below those observed for (+)-(*R*)-**22**, a fact compatible with 4% of the material undergoing inversion at some stage during the reduction at this higher temperature.

(+)-(*R*)-3,3′-Dimethyl-5,5′,6,6′,7,7′,8,8′-octahydro-2,2′-dihydroxy-1,1′-dinaphthyl [(+)-(*R*)-23]. A mixture of 3 g (9.5 mmol) of optically pure (+)-(*R*)-3,3′-dimethyl-2,2′-dihydroxy-1,1′-dinaphthyl [(+)-(*R*)-**13**], $[\alpha]^{25}_{578}$ +37.3° (*c* 1, $CHCl_3$), 0.25 g of PtO_2, 100 mL of glacial acetic acid, and 20 mL of ethyl acetate was shaken in a Parr apparatus under 3 atm of H_2 for 6 days. The product was isolated as in the reduction of (+)-(*R*)-**3** but was crystallized from hexane to give 2.9 g (94%) of (+)-(*R*)-**23** as white needles: mp 164–166 °C; M^+ 322; $[\alpha]^{25}_{436}$ +190°, $[\alpha]^{25}_{546}$ +94°, and $[\alpha]^{25}_{578}$ +84° (*c* 1.04, THF); ^1H NMR ($CDCl_3$) δ 6.88 (s, ArH, 2 H), 4.57 (s, OH, 2 H), 2.72 (m, $ArCH_2$, 4 H), 2.21 (m, $ArCH_2$, 4 H), 2.20 (s, $ArCH_3$, 6 H), and 1.68 (m, CCH_2CH_2C, 8 H). Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.83; H, 7.92.

The same compound, (+)-(*R*)-**23**, was prepared from the same (+)-(*R*)-**13** by first protecting the two OH groups with OCH_2OCH_3 groups to inhibit possible racemization, reducing the tetraether, and deprotecting the reduced product. To a solution of 3 g (9.5 mmol) of (+)-(*R*)-**13** in 150 mL of THF under N_2 at 25 °C was added 2 g of NaH as a 50% oil dispersion. The mixture was stirred 15 min, 3 g (37.5 mmol) of chloromethyl methyl ether was added, and the mixture was stirred for 12 h. The excess NaH was decomposed by dropwise addition of CH_3OH; the resulting solution was shaken with CH_2Cl_2 and H_2O (400 mL of each). The organic layer was dried and evaporated under vacuum to an oil. An ^1H NMR spectrum of this product (a small mineral oil contaminant) in $CDCl_3$ gave δ 7.78 (m, ArH, 4 H), 7.22 (m, ArH, 6 H), 4.52 (AB quartet, OCH_2, 4 H), 2.80 (s, OCH_3, 6 H), and 2.53 (s, $ArCH_3$, 6 H). This protected (tetraether) phenol was reduced similarly to its parent (+)-(*R*)-**13**, and the reduced product was chromatographed in benzene on 100 g of silica gel made up in cyclohexane. Elution of the column with 2 L of benzene gave mineral oil, whereas elution with 2 L of 19:1 (v:v) benzene to ether gave the tetraether as a colorless oil. Its ^1H NMR spectrum in $CDCl_3$ gave δ 6.82 (s, ArH, 2 H), 4.80 (s, OCH_2, 4 H), 2.90 (s, OCH_3, 6 H), 2.72 (m, $ArCH_2$, 4 H), 2.22 (m, $ArCH_2$, 4 H), 2.21 (s, $ArCH_3$, 6 H), and 1.68 (m, CCH_2CH_2C, 8 H). This oil was mixed with 200 mL of $CHCl_3$, 300 mL of CH_3OH, and 5 mL of concentrated hydrochloric acid, and the mixture was stirred for 18 h at 25 °C. A saturated aqueous solution of $NaHCO_3$ (800 mL) was cautiously added, the mixture was shaken, and the organic layer was dried and evaporated under vacuum. The residue was crystallized from hexane to give 2.5 g (81% overall) of white needles of (+)-(*R*)-**23**, mp 164–166 °C, whose ^1H NMR spectrum was identical to that of directly prepared material, and which gave $[\alpha]^{25}_{436}$ +190°, $[\alpha]^{25}_{546}$ +94°, and $[\alpha]^{25}_{578}$ +80° (*c* 1.08, THF).

(−)-(*S*)-2,2′-Bis(5-tosyloxy-3-oxa-1-pentyloxy)-5,5′,6,6′,-7,7′,8,8′-octahydro-1,1′-dinaphthyl [(−)-(*S*)-24]. The diol, (*S*)-2,2′-bis(5-hydroxy-3-oxa-1-pentyloxy)-1,1′-dinaphthyl (20.9 g or 45.2 mmol), prepared as before[4] from optically pure (−)-(*S*)-2,2′-dihydroxy-1,1′-dinaphthyl [(−)-(*S*)-**3**] was dissolved in 250 mL of glacial acetic acid. Platinum oxide (250 mg) was added and the mixture was stirred under 1 atm of H_2 for 4 days at 25 °C. The solution was filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2, and the solution was washed with aqueous $NaHCO_3$, dried, and evaporated to give 21.0 g (99%) of the corresponding octahydrodiol as a viscous oil. This material was dissolved in 50 mL of dry pyridine, the solution was cooled to 0 °C, and 20 g (105 mmol) of tosyl chloride in 30 mL of dry pyridine cooled to 0 °C was added. The solutions were mixed and allowed to stand at −20 °C for 5 days and then poured onto 500 g of crushed ice. The mixture was brought to 25 °C, the water was decanted, and the precipitated oil was dissolved in CH_2Cl_2. The solution was washed with cold 5% hydrochloric acid and water, dried, and evaporated under vacuum to give 34.0 g (98%) of a viscous white gum. A small sample was purified by silica gel TLC to give (−)-(*S*)-**24**: ^1H NMR ($CDCl_3$) δ 1.67 (m, CCH_2CH_2C, 8 H), 2.17 (m, $ArCH_2$, 4 H), 2.42 (s, $ArCH_3$, 6 H), 2.70 (m, $ArCH_2$, 4 H), 3.40 (m, CH_2OCH_2, 8 H), 3.90 (m, $ArOCH_2$ and CH_2OTs, 8 H), 6.67 and 7.00 (d, d, diphenyl ArH, 4 H), 7.32 and 7.75 (d, d, tosyl ArH, 8 H); $[\alpha]^{25}_{578}$ −26.2° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{42}H_{50}O_{10}S_2$: C, 64.76; H, 6.47. Found: C, 64.71; H, 6.63.

(+)-(*S*)-3,3′-Dimethyl-2,2′-bis(5-hydroxy-3-oxa-1-pentyloxy)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1-dinaphthyl [(+)-(*S*)-25] and (−)-(*R*)-25. A mixture of 100 mL of glacial acetic, 10 g of diol (+)-(*S*)-**19** (see above), and 0.10 g of PtO_2 was stirred under 1 atm of H_2 at 25 °C for 3 days. The mixture was filtered, the acetic acid was evaporated under reduced pressure, and the residue was distributed between CH_2Cl_2 and aqueous $NaCHO_3$. The organic layer was washed with water, dried, and evaporated under vacuum to give after drying under vacuum 10 g (98%) of (+)-(*S*)-**25** as a white glass: ^1H NMR ($CDCl_3$) δ 1.67 (m, CCH_2CH_2C), 2.20 (m, $ArCH_2$, 4 H), 2.27 (s, $ArCH_3$, 6 H), 2.70 (m, $ArCH_2$, 4 H), 3.93 (m, OCH_2, 16 H), 6.85 (s, ArH, 2 H); $[\alpha]^{25}_{589}$ +25.0°, $[\alpha]^{25}_{578}$ +26.3° (*c* 1.0, $CHCl_3$). An analytical sample

was prepared by TLC on silica gel. Anal. Calcd for $C_{30}H_{42}O_6$: C, 72.26; H, 8.49. Found: C, 72.40; H, 8.51.

Similarly 17.0 g of (−)-(*R*)-**19** (see above) was reduced to give 20.0 g (98%) of (−)-(*R*)-**25**: $[\alpha]^{25}_{589}$ −24.0° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.67 (m, CCH_2CH_2C, 8 H), 2.18 (m, $ArCH_2$, 4 H), 2.25 (s, CH_3, 6 H), 2.68 (m, $ArCH_2$ and OH, 6 H), 3.25–3.84 (m, OCH_2, 16 H), 6.86 (s, ArH, 2 H). A small sample was purified by preparative TLC on silica gel for analysis. Anal. Calcd for $C_{30}H_{42}O_6$ C, 72.26; H, 8.49. Found: C, 72.27; H, 8.23.

(−)-(*R*)-3,3′-Dimethyl-2,2′-bis(5-tosyloxy-3-oxa-1-pentyloxy)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-dinaphthyl [(−)-(*R*)-26) and (+)-(*S*)-26. From 17.4 g (34.5 mmol) of diol (−)-(*R*)-**25** and 15.0 g (78.7 mmol) of tosyl chloride in 50 mL of pyridine for 3 days at −20 °C was obtained product which was filtered through 100 g of alumina in CH_2Cl_2. The product, (−)-(*R*)-**26**, 27 g (97%), was a white glass: ^1H NMR ($CDCl_3$) δ 1.35 (m, CCH_2CH_2C, 8 H), 2.15 (m, $ArCH_2$, 4 H), 2.18 (s, CH_3 of naphthyl, 6 H), 2.40 (s, CH_3 of tosyl, 6 H), 2.72 (m, $ArCH_2$, 4 H), 3.17–4.08 (m, OCH_2, 16 H), 6.83 (s, diphenyl ArH, 2 H), 7.27 (d, tosyl ArH, 4 H), 7.58 (d, tosyl ArH, 4 H); $[\alpha]^{25}_{589}$ −14.4° $[\alpha]^{25}_{578}$ −14.0° (c 0.5, $CHCl_3$). An analytical sample was prepared by TLC on silica gel. Anal. Calcd for $C_{44}H_{54}O_{10}S_2$: C, 65.48; H, 6.74. Found: C, 65.24; H, 6.77.

Similarly, from 10 g of diol (+)-(*S*)-**25** was prepared 11.2 g (70%) of (+)-(*S*)-**26** as a white glass, $[\alpha]^{25}_{578}$ +13.4° (c 0.5, $CHCl_3$), whose ^1H NMR spectrum was essentially identical to that of its enantiomer. An analytical sample was prepared by TLC on silica gel. Anal. Calcd for $C_{44}H_{54}O_{10}S_2$: C, 65.48; H, 6.74. Found: C, 65.62; H, 6.70.

(+)-(*R*)-3,3′-Dibromo-2,2′-dihydroxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-dinaphthyl, (+)-(*R*)-27. To a solution of 4.6 g (16 mmol) of (+)-(*R*)-**22**, $[\alpha]^{25}_{546}$ +65.2° (c 1.1, $CHCl_3$), in 150 mL of CH_2Cl_2 at −30 °C was added 5.8 g (36 mmol) of Br_2 in a single portion. The mixture was stirred for 15 min, 200 mL of $NaHSO_3$ saturated aqueous solution was added, and the mixture was allowed to warm to 25 °C and was stirred for 1 h. The CH_2Cl_2 layer was separated, washed with 10% $NaHCO_3$ (300 mL), dried, and evaporated and the residue was crystallized from heptane to give 6.9 g (98%) of (+)-(*R*)-**27**: mp 142–143 °C; M^+ 450 (^{79}Br); ^1H NMR ($CDCl_3$) δ 7.18 (s, ArH, 2 H), 5.17 (s, OH, 2 H), 2.70 (m, $ArCH_2$, 4 H), 2.20 (m, $ArCH_2$, 4 H), and 1.66 (m, CCH_2CH_2C, 8 H); $[\alpha]^{25}_{436}$ +65.0°, $[\alpha]^{25}_{546}$ +35.3°, $[\alpha]^{25}_{578}$ +30.5°, and $[\alpha]^{25}_{589}$ +29.2° (c 1.05, $CHCl_3$). Anal. Calcd for $C_{20}H_{20}Br_2O_2$: C, 53.12; H, 4.46. Found: C, 53.24; H, 4.46.

5,5′,6,6′-Tetrabromo-2,2′-dihydroxy-1,1′-dinaphthyl (28).[13] To a solution of 2,2′-dihydroxy-1,1′-dinaphthyl (5.72 g or 0.020 mol) in 200 mL of CH_2Cl_2 was added Br_2 (10 mL, 31.96 g or 0.20 mol) in one portion, and the resulting solution was held at reflux for 19 h. The solution was cooled, washed with two 100-mL portions of 20% aqueous $NaHSO_3$, with 5% aqueous $NaHCO_3$, and with water. The solution was dried and evaporated to give a white solid purified by trituration with CH_2Cl_2: 9.75 g (81%); M^+ 598 (^{79}Br) ^1H NMR (CD_3COCD_3) δ 6.88, 6.97 (d of d, half of A_2B_2q, $J_{7,8}$ = 9 Hz, $J_{4,8}$ of the epi H^1s = 0.9 Hz, H_8, 2 H), 7.34, 7.42 (d, half of A_2B_2q, $J_{7,8}$ = 9 Hz, H_7, 2 H); 7.37, 7.46 (d, half of A_2B_2q, $J_{3,4}$ = 9.5 Hz, H_3, 2 H), 8.22, 8.32 (d of d, half of A_2B_2q, $J_{3,4}$ = 9.5, H_3, J_{epi} = 0.9 Hz, H_4, 2 H). Anal. Calcd for $C_{20}H_{10}Br_4O_2$: C, 39.91; H, 1.68. Found: C, 39.52; H, 2.12.

4,4′,6,6′-Tetrabromo-2,2-dimethoxy-1,1-dinaphthyl.[13] To 1.57 g (0.005 mol) of 2,2′-dimethoxy-1,1-dinaphthyl,[12] mp 195 °C, in 80 mL of $CHCl_3$ was added at 25 °C dropwise a solution of 2 mL or 6.2 g of Br_2 (0.0388 mol) in 20 mL of $CHCl_3$. After the resulting solution has stood 18 h it was treated with 25 mL of 20% aqueous $NaHSO_3$ with cooling. The resulting mixture was shaken with water and CH_2Cl_2, the organic phase was washed with aqueous K_2CO_3 solution, dried, and evaporated under vacuum. The product was chromatographed on 200 g of neutral alumina, and the product was eluted with 25% (v) CH_2Cl_2 in pentane to give 2.86 g (91%) of product, which was recrystallized from CCl_4–ethanol and dried at 135 °C (1 mm): mp 225–227 °C; M^+ 626 (^{79}Br); ^1H NMR ($CDCl_3$) δ 3.68 (s, CH_3O, 6 H), 6.81, 6.90 (half of ABq, J = 9 Hz, H_8, 1 H), 7.20, 7.29 (d, d, J = 2 Hz, H_7 coupled to H_5, half of ABq coupled to H_8, J = 9 Hz, H_7, 1 H), 7.68 (s, H_3, 2 H), 8.35 (d, J = 2 Hz, H_5 coupled to H_7, 2 H). Anal. Calcd for $C_{22}H_{14}Br_4O_2$: C, 41.94; H, 2.24. Found: C, 41.69; H, 2.47.

(*R,R*),(*S,S*)-2,3,4,5-Di-1,2-(3-methylnaphtho-13,14,15,16-di(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(*R,R*),(*S,S*)-29], (*R,S*),(*S,R*)-29, (−)-(*R,S*)-29, (+)-(*R,R*)-29, and (−)-(*S,S*)-29. To a solution of 0.570 g of **3** in 15 mL of dry DMF stirred at 25 °C under N_2 was added 0.22 g of NaH (57% dispersion in mineral oil), followed by 1.6 g of two-armed dimethyl ditosylate **20**, in 25 mL of dry DMF. The mixture was stirred at 45 °C until it became homogeneous and then at 60 °C for 48 h. The mixture was cooled, the solvent was evaporated under reduced pressure, and the residue was shaken with CH_2Cl_2 and water. The organic layer was washed with water and brine, dried, and evaporated, and the residue was dried as a foam at 80 °C and 50 μm for 3 h, weight 1.3 g. This material was chromatographed on 200 g of silica gel. Hexane eluted unreacted 3 (0.13 g or 23%), whereas 2:3 hexane–CH_2Cl_2–methane eluted first (*R,S*),(*S,R*)-**29** (mp 249 °C, 0.176 g, 12%, from CH_2Cl_2), then a mixture of diastereomers (0.12 g, 8%), and finally (*R,R*),(*S,S*)-**29** (mp 222–223 °C, 0.147 g, 10%, from CH_2Cl_2). Both diastereomers gave M^+ 740. The ^1H NMR spectrum in $CDCl_3$ of the (*R,S*),(*S,R*) isomer gave δ 7.72 (m, ArH, 8 H), 7.36 (s, ArH, 2 H), 7.12 (m, ArH, 12 H), 3.96 (m, CH_2O, 4 H), 3.69 (m, CH_2O, 4 H), 3.33 (m, CH_2O, 4 H), 2.88 (m, CH_2O, 4 H), and 2.50 (s, CH_3, 6 H); that of the (*R,R*),(*S,S*) isomer gave δ 7.80 (m, ArH, 8 H), 7.38 (s, ArH, 2 H), 7.09 (m, ArH, 12 H), 4.00 (m, OCH_2, 4 H), 3.50 (m, CH_2O, 8 H), 3.04 (m, CH_2O, 4 H), and 2.40 (s, CH_3, 6 H). Anal. Calcd for each isomer $C_{50}H_{44}O_6$: C, 81.06; H, 5.99. Found for (*R,S*),(*S,R*)-**29**: C, 80.84; H, 6.23. Found: C, 80.63; H, 6.12.

Procedure II (see below) was applied to 1.80 g of optically pure (−)-(*S*)-**13** and 4.40 g of optically pure (−)-(*R*)-**19** (two-armed ditosylate) to give 0.68 g (16%) of (+)-(*S,R*)-**29** as a foam, $[\alpha]^{25}_{589}$ +41.4°, $[\alpha]^{25}_{578}$ +44.2°, $[\alpha]^{25}_{546}$ +53.4°, and $[\alpha]^{25}_{436}$ +142.3° (c 1, $CHCl_3$). The ^1H NMR spectrum of this compound was identical to that of (*R,S*),(*S,R*)-**29** but different from that of (*R,R*),(*S,S*)-**29.** Anal. Calcd for $C_{50}H_{44}O_6$: C, 81.06; H, 5.99. Found: C, 81.12; H, 6.20.

Procedure I. Isomer (+)-(*R,R*)-**29** was synthesized from optically pure binaphthol (+)-(*R*)-**3** and dimethyl two-armed ditosylate (−)-(*R*)-**20** as follows. To 1 L of THF, 6.04 g (0.021 mol) of (+)-(*R*)-**3**, $[\alpha]^{25}_{589}$ +34.1° (c 1.0, $CHCl_3$), and 2.8 g (0.0042 mol) of KOH (85%) dissolved in 30 mL of water were added and the solution was held at reflux 30 min. Optically pure (−)-(*R*)-**20** [$[\alpha]^{25}_{578}$ −69.7°, c 1.0, $CHCl_3$] was added and the mixture was refluxed for 180 h. The reaction mixture was evaporated under reduced pressure and shaken with water–CH_2Cl_2; the CH_2Cl_2 layer was water washed, dried, and evaporated to give 5.6 g of oil. This oil was chromatographed on 250 g of neutral alumina and eluted with 1:10 (v:v) acetone–CCl_4, the last 900 mL of 1600 mL of which gave 4.97 g (32%) of product as a white foam: M^+ 740, M^{2+} 370, gel permeation column retention volume 152 mL of CH_2Cl_2; $[\alpha]^{25}_{578}$ +152° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.8–6.9 (m, ArH, 22 H), 4.20–2.85 (m, CH_2O, 16 H), 2.35 (s, CH_3, 6 H). Anal. Calcd for $C_{50}H_{44}O_6$: C, 81.06; H, 5.99. Found: C, 81.10; H, 6.13.

Procedure II. A mixture of 100 mL of THF, 1.0 g of optically pure binaphthol, (−)-(*S*)-**3** (0.0032 mol, $[\alpha]^{25}_{589}$ −34.3°, c 1.0, $CHCl_3$), and 0.40 g (0.0064 mol) of KOH (85%) was stirred for 1 h and then 2.54 g (0.0032 mol) of optically pure (+)-(*S*)-**20** (dimethyl two-armed ditosylate, $[\alpha]^{25}_{578}$ +70.0°, c 1.0, $CHCl_3$) in 100 mL of THF was added; the mixture was refluxed under N_2 for 175 h. The crude product (2.62 g) was isolated as before and purified by gel permeation chromatography to give 1.50 g (64%) of (−)-(*S,S*)-**29** as a white foam; M^+ 740, M^{2+} 370, gel permeation retention volume 152 mL of CH_2Cl_2; $[\alpha]^{25}_{436}$ −380°, $[\alpha]^{25}_{546}$ −171°, $[\alpha]^{25}_{578}$ −152° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.80–6.90 (m, ArH, 22 H), 4.2–2.85 (m, CH_2O, 16 H), 2.35 (s, CH_3, 6 H). Anal. Calcd for $C_{50}H_{44}O_6$: C, 81.06; H, 5.99. Found: C, 81.38; H, 6.03.

(*R,R*),(*S,S*)-2,3,4,5-Di-1,2-(3-hydroxymethylnaphtho)-13,-14:15,16-di(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(*R,R*),(*S,S*)-30], (*R,S*),(*S,R*)-30, and (+)-(*R,R*)-30. A solution of 23 g of tetrol **9** in 2 L of THF, 5.4 g of NaOH in 60 mL of H_2O, and 56 g of 2,2′-di(5-tosyloxy-3-oxa-1-pentyloxy)-1,1′-dinaphthyl (**21**)[14] was stirred under N_2 at reflux for 100 h. The crude product was isolated as in procedure I and chromatographed on 1.5 kg of alumina. The column was washed with 3 L of ether, and the products were eluted with ether–isopropyl alcohol mixtures to give 17.0 g (33%) of crude **30.** The faster moving diastereomer was fractionally crystallized from CH_2Cl_2–ethyl acetate to give (*R,S*)-,(*S,R*)-**30:** 4.25 g (8%); mp 197–198 °C; M^+ 772; ^1H NMR ($CDCl_3$) δ 8.00–6.98 (m, ArH, 22 H), 4.94 (m, $ArCH_2$, 4 H), and 4.40–2.76 (m, OCH_2, 16 H). Anal. Calcd for $C_{50}H_{44}O_8$: C, 77.70; H, 5.74. Found: C, 77.50; H, 5.96.

Fractional crystallization of the slower moving racemate from CH_2Cl_2 and ethyl acetate gave 8.5 g (16%) of (*R,R*),(*S,S*)-**30:** mp 230–231 °C; M^+ 772; ^1H NMR ($CDCl_3$) δ 7.80 (m, ArH, 8 H), 7.18 (m, ArH, 14 H), 4.70 (m, $ArCH_2$, 4 H), and 4.22–3.78 (m, OCH_2, 16 H). Anal. Calcd for $C_{50}H_{44}O_8$: C, 77.70; H, 5.74. Found: C, 77.48; H, 6.01.

By the same procedure from optically pure (+)-(*R*)-**21**[14] and (+)-(*R*)-**9** (see above) was produced in 28% yield (+)-(*R,R*)-**30** as a glass, pure to TLC, $[\alpha]^{25}_{578}$ +120°, $[\alpha]^{25}_{546}$ +115°, $[\alpha]^{25}_{436}$ +318° (c 1.0, $CHCl_3$). The ^1H NMR spectra of (+)-(*R,R*)-**30** and that of (*R,R*),-(*S,S*)-**30** (see above) were identical but decidedly different from that of (*R,S*),(*S,R*)-**30** (see above).

(+)-(*R,R*)-2,3,4,5-Di-1,2-(3-chloromethylnaphtho)-13,14:15,16-di(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene, (+)-(*R,R*)-31. To a solution of 0.90 g (1.2 mmol) of (+)-(*R,R*)-**30** in 40 mL of benzene was added 4.0 g (34 mmol) of thionyl chloride in a single portion. The solution was stirred at 25 °C for 10 h and evaporated at 30 mm of pressure and 60 °C. The residue was dissolved in 50 mL of CH_2Cl_2 and the solution was extracted with 30 mL of 10% $NaHCO_3$. The organic layer was dried and concentrated to 15 mL, and the residue was chromatographed on 50.0 g of silica gel. Elution of the column with 2 L of CH_2Cl_2 gave 0.72 g (76%) of (+)-(*R,R*)-**31** as a glass, which was dried at 50 μm and 50 °C for 10 h. The compound gave the ^1H NMR spectrum in $CDCl_3$ of δ 8.05–6.90 (m, ArH, 22 H), 4.70 (ABq, $ArCH_2$, 4 H), and 4.16–2.78 (m, OCH_2, 16 H); $[\alpha]^{25}_{589}$ +116°, $[\alpha]^{25}_{578}$ +122°, $[\alpha]^{25}_{546}$ +145°, and $[\alpha]^{25}_{436}$ +335°. Anal. Calcd for $C_{50}H_{42}Cl_2O_6$: C, 74.15; H, 5.24. Found: C, 74.50; H, 5.26.

(+)-(*R,R*)-Dimethyldinaphtho-22-crown-6 [(+)-(*R,R*)-29] from (+)-(*R,R*)-31. To a solution of 1.5 g (39 mmol) of $LiAlH_4$ in 150 mL of THF under N_2 was added 0.7 g (0.87 mmol) of (+)-(*R,R*)-**31** in 20 mL of THF. The mixture was refluxed for 3 h and cooled to 5 °C and the excess $LiAlH_4$ was decomposed by dropwise addition of water. Ether (150 mL) and 100 mL of 6 N hydrochloric acid were added and the resulting mixture was stirred at 25 °C for 6 h. The organic layer was separated, and the aqueous phase was extracted with 100 mL of ether. The combined organic extracts were washed with 100 mL of 10% $NaHCO_3$ solution, dried, and concentrated to 30 mL. The residue was chromatographed on 50 g of neutral alumina. Elution of the column with 2.5 L of ether gave 0.51 g (80%) of (+)-(*R,R*)-**29** as a colorless glass, dried at 50 μm and 100 °C for 5 h. The ^1H NMR spectrum in $CDCl_3$ gave δ 8.00–6.90 (m, ArH, 22 H), 4.24–2.90 (m, OCH_2, 16 H), and 2.40 (s, CH_3, 16 H); $[\alpha]^{25}_{589}$ +145°, $[\alpha]^{25}_{578}$ +152°, $[\alpha]^{25}_{546}$ +170°, and $[\alpha]^{25}_{436}$ +381° (*c* 1.0, $CHCl_3$).

(*R,R*),(*S,S*)-2,3,4,5,13,14,15,16-Tetra-1,2,(3-methylnaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(*R,R*),(*S,S*)-32], (*R,S*)-32, (+)-(*R,R*)-32, and (−)-(*S,S*)-32. From 0.942 g of racemic **13**, 2.4 g of racemic **20**, and 0.377 g of KOH in 60 mL of THF and 1 mL of water refluxed for 40 h was obtained an isomeric mixture that was chromatographed on 400 g of silica gel. Benzene elution of the chromatogram and recrystallization of the product gave 0.155 g (7%) of (*R,S*)-**32**: mp 314–315 °C; M^+ 768; ^1H NMR ($CDCl_3$) δ 7.73 (d, $ArH^{4,5}$, 8 H), 7.10 (m, ArH, 12 H), 3.68 (m, CH_2O, 8 H), 3.26 (m, CH_2O, 4 H), 2.86 (m, CH_2O, 4 H), and 2.52 (s, CH_3, 12 H). Anal. Calcd for $C_{52}H_{48}O_6$: C, 81.22; H, 6.29. Found: C, 81.01; H, 6.28. Elution of the chromatographic column with 20:1 (v:v) benzene–ether gave (*R,R*),(*S,S*)-**32**, which after recrystallization from CH_2Cl_2–ether gave: 0.22 g (10%); mp 158–160 °C; M^+ 768; ^1H NMR ($CDCl_3$) δ 7.70 (m, $ArH^{4,5}$, 8 H), 7.12 (m, ArH, 12 H), 3.50 (m, CH_2O, 8 H), 2.92 (m, CH_2O, 8 H), 2.45 (d, CH_3, 12 H). Anal. Calcd for $C_{52}H_{48}O_6$: C, 81.22; H, 6.29. Found: C, 80.93; H, 6.28.

When racemic **13** was treated similarly with diethylene glycol ditosylate, (*R,S*)-**32** (4%), mp 314–315 °C, (*R,R*),(*S,S*)-**32** (5%), mp 158–160 °C, and (*R*),(*S*)-2,3,4,5-di-1,2-(3-methylnaphtho)-1,6,9-trioxaundeca-2,4-diene (8%), mp 285 °C (from benzene), were produced. This monolocular material gave: M^+ 384; ^1H NMR ($CDCl_3$) δ 7.72 (m, $Ar^{4,5}$, 4 H), 7.20 (m ArH, 6 H), 4.06 (m, CH_2O, 4 H), 3.28 (t, CH_2O, 4 H), and 2.58 (s, CH_3, 6 H). Anal. Calcd for $C_{26}H_{24}O_3$: C, 81.22; H, 6.29. Found: C, 81.45; H, 6.44.

From a mixture of 8.60 g (0.0274 mol) of (+)-(*R*)-**13**, $[\alpha]^{25}_{578}$ +37.3° (*c* 1.0, $CHCl_3$), 21.9 g (0.027 mol) of (−)-(*R*)-**20**, $[\alpha]^{25}_{578}$ − 67.9 °C (*c* 1.0, $CHCl_3$), 4.2 g (0.0636 mol) of KOH (85%) in 75 mL of water, and 1.5 L of THF at reflux for 231 h was obtained by procedure I (and a CH_2Cl_2 solution filtration through 50 g of alumina to remove polymer) 6.4 g of crude product. This material was chromatographed on 300 g of alumina and eluted with the last 900 mL of 1.8 L of acetone–CCl_4 (1:10, v:v) to produce 5.8 g (28%) of (+)-(*R,R*)-**32** as a glass: M^+ 768; ^1H NMR ($CDCl_3$) δ 7.8–6.9 (m, ArH, 20 H), 4.2–2.8 (m, CH_2O, 16 H), 2.35 (s, CH_3, 6 H); $[\alpha]^{25}_{436}$ +321°, $[\alpha]^{25}_{546}$ +156.5°, $[\alpha]^{25}_{578}$ +135° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{52}H_{48}O_6$: C, 81.23; H, 6.28. Found: C, 80.92; H, 6.14.

Similarly, (−)-(*SS*)-**32** was prepared as a glass (28%), $[\alpha]^{25}_{578}$ −134° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{52}H_{48}O_6$: C, 81.23; H, 6.28. Found: C, 81.38; H, 6.02.

(+)-(*R,R*)-2,3,4,5-Di-1,2-[3-(2-hydroxy-2-propyl)naphtho]-13,14:15,16-di(1,2-naphtho)-1,6,9,12,16,20-hexaoxacyclodocosa-2,4,13,15-tetraene, (+)-(*R,R*)-33. From 3.6 g (9 mmol) of (+)-(*R*)-3,3′-(2-hydroxy-2-propyl)-2,2′-dihydroxy-1,1′-dinaphthyl (see above), 7.0 g (9 mmol) of optically pure (+)-(*R*)-2,2′-di(5-tosyloxy-3-oxa-1-pentyloxy)-1,1′-dinaphthyl,[4] 750 mL of THF, and 20 mL of water (procedure I) after 7 days of reflux was obtained crude material that was chromatographed on 100 g of activity 1 neutral alumina (in ether). The column was washed with 300 mL of ether, and the product was eluted with 49:1 (v:v) ether–isopropyl alcohol to give 2.1 g (28%) of (+)-(*R,R*)-**33** as a white foam; M^+ 828 (weak), $M^+ - H_2O$ 810 (strong), $M^+ - 2H_2O$ 792 (strong); ^1H NMR ($CDCl_3$) δ 7.78 (m, ArH, 8 H), 7.12 (m, ArH, 14 H), 3.55 (m, OCH_2, 16 H), 1.60 (s, CH_3, 6 H), and 1.70 (s, CH_3, 6 H); $[\alpha]^{25}_{436}$ +222°, $[\alpha]^{25}_{546}$ +88°, $[\alpha]^{25}_{578}$ +73°, $[\alpha]^{25}_{589}$ +589° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{54}H_{52}O_8$: C, 78.24; H, 6.32. Found: C, 78.20; H, 6.43.

(+)-(*R,R*)-2,3,4,5-Di-1,2-(3-isopropylnaphtho)-13,14,15,16-di-(1,2-naphtho)-1,6,9,12-hexaoxacyclodocosa-2,4,13,15-tetraene, (+)-(*R,R*)-34. To a solution of 0.450 (0.54 mmol) of (+)-(*R,R*)-**33** (see above) in 25 mL of CH_2Cl_2 was added 7 g of neutral alumina, activity 1, pretreated with 2% pyridine.[14] The suspension was evaporated at 25 °C (30 mm), and the residue was heated at 175 °C for 5 h under 30 mm of pressure. The solid was extracted five times with 50-mL portions of CH_2Cl_2 at 25 °C, and the combined extracts were evaporated. The residue was dissolved in 50 mL of ethyl acetate and hydrogenated under 2 atm of H_2 with 1 g of 10% Pd on C in a Parr apparatus for 30 min. The suspension was filtered, the filtrate was evaporated, and the residue was dissolved in CH_2Cl_2 and chromatographed on 50 g of neutral activity 1 alumina in ether. Elution of the column with 1.5 L of ether gave 325 mg (75%) of (+)-(*R,R*)-**34** as a white foam: M^+ 796; ^1H NMR ($CDCl_3$) δ 7.80 (m, ArH, 8 H), 7.14 (m, ArH, 14 H), 3.38 [m, OCH_2, $CH(CH_3)_2$, 18 H] and 1.39 (d, CH_3, 12 H); $[\alpha]^{25}_{436}$ +207°, $[\alpha]^{25}_{546}$ +86°, $[\alpha]^{25}_{578}$ +71°, and $[\alpha]^{25}_{589}$ +67° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{54}H_{52}O_6$: C, 81.38; H, 6.58. Found: C, 81.46; H, 6.57.

(*R,R*),(*S,S*)-2,3,4,5-Di-1,2-[3-(2,5-dioxa-4-oxohexa)]-13,14,-15,16-di(1,2-naphthol)-1,6,9,12,16,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(*R,R*),(*S,S*)-35], (*R,S*),(*S,R*)-35, and (+)-(*R,R*)-35. To a solution of (*R,R*),(*S,S*)-**30**, 2.4 g or 3.1 mmol, in 200 mL of THF under N_2 was added NaH (2.0 g, 42 mmol) as a 50% mineral oil dispersion. The mixture was stirred for 15 min, methyl bromoacetate (3.0 g, 20 mmol) in 10 mL of THF was added, and the mixture was refluxed for 18 h. The reaction mixture was cooled, filtered, and evaporated under reduced pressure. The residue was shaken with 200 mL each of water and CH_2Cl_2, the water layer was extracted with CH_2Cl_2, and the combined organic layers were dried and evaporated under reduced pressure. The residue in 10 mL of benzene was chromatographed on 100 g of silica gel (cyclohexane). The column was washed with 500 mL of cyclohexane, 1 L of benzene, and 2 L of 49:1 (v:v) benzene–ether to give impurities, and the product was eluted with 2 L of 9:1 (v:v) benzene–ether as 2.0 g (71%) of a colorless oil: M^+ 916; ^1H NMR ($CDCl_3$) δ 7.90 (m, ArH, 8 H), 7.20 (m, ArH, 14 H), 4.72 (broad s, $ArCH_2$, 4 H), 4.03 (s, OCH_2O, 4 H), 3.63 (s, CH_3O, 6 H), and 4.22–2.90 (m, OCH_2CH_2O, 16 H). Anal. Calcd for $C_{56}H_{52}O_{12}$: C, 73.35; H, 5.72. Found: C, 73.29; H, 5.75.

By the same procedure, (*R,S*),(*S,R*)-**30** was converted to (*R,S*),-(*S,R*)-**35** (50%) which was a glass: M^+ 916; ^1H NMR ($CDCl_3$) δ 8.07–6.85 (m, ArH, 22 H), 4.97 (s, $ArCH_2$, 4 H), 4.20 (s, CH_2CO_2, 4 H), 3.66 (s, OCH_3, 6 H), and 4.40–2.50 (m, OCH_2CH_2O, 16 H). Anal. Calcd for $C_{56}H_{52}O_{12}$: C, 73.35; H, 5.72. Found: C, 73.30; H, 5.60.

Similarly, (+)-(*R,R*)-**30** (see above) was converted to (+)-(*R,R*)-**35** (77%) which was a glass: $[\alpha]^{25}_{589}$ +110°, $[\alpha]^{25}_{578}$ +116°, $[\alpha]^{25}_{546}$ +137°, $[\alpha]^{25}_{436}$ +311° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) identical to (*R,R*),(*S,S*)-**35**. Anal. Calcd for $C_{56}H_{52}O_{12}$: C, 73.35; H, 5.72. Found: C, 73.19; H, 5.59.

(*R,S*),(*S,R*)-2,3:4,5-Di-1,2-[3-(2,5-dioxa-4-oxopenta)]-13,14:15,16-di(1,2-naphtho)-1,6,9,12,16,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(*R,S*),(*S,R*)-36), (*R,R*),(*S,S*)-36, and (+)-(*R,R*)-36. To a solution of diester (*R,S*),(*S,R*)-**35** (see above) (0.6 g, 0.65 mmol) in 60 mL of ethanol was added NaOH (2.0 g, 50 mmol) in 10 mL of water. The solution was refluxed for 12 h, concentrated at 60 °C (30 mm) to about 5 mL, and diluted with water to 100 mL. The suspension was extracted with two 50-mL portions of CH_2Cl_2; the aqueous layer was acidified with HCl to pH 1. The mixture was stirred with 200 mL of CH_2Cl_2 until the two phases were transparent (2 h). The layers were separated, and the aqueous layer was extracted with 50 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with water, dried, and evaporated to give 550 mg (94%) of product as a white powder: M^+ 888; ^1H NMR δ 8.10–6.90 (m, ArH, 22 H), 5.00 (broad s, $ArCH_2$, 4 H), 4.22 (broad s, CH_2CO_2, 4 H), 4.30–2.80 (m, OCH_2CH_2O, 16 H). Anal. Calcd for $C_{54}H_{48}O_{12}$: C, 72.96; H, 5.44. Found: C, 72.90; H, 5.32.

Similarly, (*R,R*),(*S,S*)-**35** (see above) was hydrolyzed to (*R,R*),-(*S,S*)-**36** (83%), which was a colorless glass: M^+ 888; ^1H NMR (CD_3CO_2D) δ 8.15–6.80 (m, ArH, 22 H), 4.80 (s, $ArCH_2$, 4 H), 4.18 (s, OCH_2CO_2, 4 H), and 4.20–2.75 (m, OCH_2CH_2O, 16 H). Anal. Calcd for $C_{54}H_{48}O_{12}$: C, 72.96; H, 5.44. Found: C, 73.12; H, 5.51.

Similarly, (+)-(*R,R*)-**35** (see above) was converted to (+)-(*R,R*)-**36** (76%): glass; $[\alpha]^{25}_{589}$ +104°, $[\alpha]^{25}_{578}$ +110°, $[\alpha]^{25}_{546}$ +131°, and $[\alpha]^{25}_{436}$

+304° (c 1.0, THF); ^{1}H NMR δ 8.15–6.35 (m, ArH, 22 H), 4.68 (broad s, $ArCH_2$, 4 H), 3.98 (broad s, OCH_2CO_2, 4 H), and 430–2.80 (m, OCH_2CH_2O, 16 H). Anal. Calcd for $C_{54}H_{48}O_{12}$: C, 72.96; H, 5.44. Found: C, 73.10; H, 5.56.

(*R,R*),(*S,S*)-2,3,4,5,13,14,15,16-Tetra-1,2-(3-hydroxymethylnaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(*R,R*),(*S,S*)-37] and (*R,S*)-37. From 5.5 g (10.1 mmol) of tetrol **9**, 4.1 g (10 mmol) of diethylene glycol ditosylate, 1.15 g (20.3 mmol) of KOH in 210 mL of THF, and 16 mL of water refluxed under N_2 for 5 days was obtained 5.5 g of crude product (procedure I). Chromatography of this material on silica gel with 20:1 (v:v) ether–methanol gave after further chromatography on alumina 0.50 g (10%) of (*R,R*),(*S,S*)-**37**: mp 168–170 °C (bubbles); M^+ 832 (weak) $M^+ - 2H_2O$ 796; ^{1}H NMR ($CDCl_3$) δ 7.76 (m, ArH, 8 H), 7.10 (m, ArH, 12 H), 4.76 (s, $ArCH_2$, 8 H), 3.36–2.96 (m, OCH_2CH_2O, 16 H). Anal. Calcd for $C_{52}H_{48}O_{10}$: C, 74.98; H, 5.81. Found: C, 74.86; H, 6.00.

Further elution of the silica gel column with 92% ether–8% methanol (v:v) gave 0.52 g (10%) of (*R,S*)-**37**: mp 168–170 °C (bubbles); $M^+ - 2H_2O$ 796; ^{1}H NMR ($CDCl_2$) δ 7.80 (m, ArH, 8 H), 7.10 (m, ArH, 12 H), 4.80 (broad s, $ArCH_2$, 8 H), 3.83–2.48 (complex m, OCH_2CH_2O, 16 H). Anal. Calcd for $C_{52}H_{48}O_{10}$: C, 74.98; H, 5.81. Found: C, 75.14; H, 6.00.

These two diastereomers give a mmp 148–160 °C (bubbles). Thorough mixing of (*R,R*),(*S,S*)-**37** (83 mg), 0.20 mL of $CDCl_3$, 0.40 mL of CD_3CO_2D, 0.11 mL of D_2O, 20.2 mg of optically pure (+)-α-phenylethylammonium bromide, and 10 mg of $NaPF_6$ gave two layers, whose ^{1}H NMR spectra indicated the macrocycle was 40% in the aqueous-rich and 60% in the chloroform-rich phase. The amine salt was almost completely in the aqueous layer. The macrocycle in each layer was isolated. Material from the $CDCl_3$ layer gave $[\alpha]^{25}_{578}$ +0.1 ± 0.05° (c 2, $CHCl_3$), and that from the water layer gave $[\alpha]^{25}_{578}$ −0.2 ± 0.1° (c 2. $CHCl_3$). A similar distribution experiment performed with (*R,S*)-**37** gave optical rotations of 0.0°.

2,3,4,5,13,14,15,16-Tetra-1,2-(3-*N*-morpholinomethylnaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene (38). From 19.36 g (40 mmol) of diaminodiol **4**, 29 g (80 mmol) of *t*-BuOK, and 16.56 g (40 mmol) of diethylene glycol ditosylate in 800 mL of THF held at 25 °C for 12 h and at reflux for 90 min was isolated (procedure I) 34.8 g of material which was chromatographed on 900 g of neutral alumina with ether as eluting agent. Fractions 3–7 (500-mL fractions) contained 2,3:4,5-di-1,2-(3-*N*-morpholinomethylnaphtho)-1,6,9-trioxaundeca-2,4-diene which after further purification by alumina chromatography gave 7.9 g (36%) of pure material as an oil, dried at 60 °C (20 mm) for 24 h, M^+ 554. Anal. Calcd for $C_{34}H_{38}O_5N_2$: C, 73.64; H, 6.86. Found: C, 73.92; H, 7.08. Fractions 9–14 of the original chromatograph column contained **38**, which precipitated as a microcrystalline material on evaporation of the ether solution: weight 11.2 g (51%); mp 130–132 °C; M^+ 1108; one component on TLC. Anal. Calcd for $C_{68}H_{76}O_{10}N_4$: C, 73.64; H, 6.86. Found: C, 73.32; H, 7.16. The configuration of this material was not determined.

(*R,R*),(*S,S*)-2,3,4,5,13,14,15,16-Tetra-1,2-(6-bromonaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(*R,R*),(*S,S*)-40], (*R,S*)-40, and (+)-(*R,R*)-40. Cycle (*R,R*),(*S,S*)-bisdinaphthyl-22-crown-6 [(*R,R*),(*S,S*)-**39**)],[4] 6.82 g (9.57 mmol) in 400 mL of CH_2Cl_2, was stirred under argon at 2 °C. Bromine (4.0 mL or 78.4 mmol) dissolved in 100 mL of CH_2Cl_2 was added dropwise (30 min) with stirring. After an additional 30 min, 50 mL of a 10% $NaHSO_3$ solution was added, the organic phase was separated, anhydrous K_2CO_3 was added, and the mixture was refluxed for 10 min and filtered. The filtrate was filtered through a 100-g column of activity IV alumina, and the column filtrate was evaporated to leave a light yellow oil. This material crystallized from CH_2Cl_2–ether (1:1, v:v), and the solid that separated was collected and slurried with hot ethyl acetate, cooled, and filtered to give 8.65 g (88%) of white crystals of (*R,R*),(*S,S*)-**40**: mp 299–300 °C; ^{1}H NMR ($CDCl_3$) δ 7.25 (d, ArH^3, $J_{3,4}$ = 9 Hz, 4 H), 7.80 (d, ArH^4, 4 H), 7.97 (d, ArH^5, $J_{5,7}$ = 2 Hz, 4 H), 7.20 (d of d, ArH^7, $J_{7,8}$ = 9 Hz, 4 H), 6.85 (d, ArH^8, 4 H), 3.81 (m, $ArOCH_2$, 8 H), and 3.17 (m, CH_2OCH_2, 8 H). Anal. Calcd for $C_{48}H_{26}Br_4O_6$: C, 56.06; H, 3.58. Found: C, 56.25; H, 3.50.

Similarly, (*R,S*)-**39** gave (*R,S*)-**40** in 90% yield, mp 334–335 °C (from $CHCl_3$–heptane), M^+ 1024. Anal. Calcd for $C_{48}H_{36}Br_4O_6$: C, 56.06; H, 3.53. Found: C, 56.30; H, 3.57.

Similarly, optically pure (+)-(*R,R*)-**39**[4] gave (+)-(*R,R*)-**40** (91%): mp 179–180 °C (from $CHCl_3$–heptane); $[\alpha]^{25}_{589}$ +108°, $[\alpha]^{25}_{578}$ +124°, $[\alpha]^{25}_{546}$ +148° (c 1.0, $CHCl_3$). Anal. Calcd for $C_{48}H_{36}Br_4O_6$: C, 56.06; H, 3.53. Found: C, 56.27; H, 3.12.

(*R,S*)-2,3,4,5,13,14,15,16-Tetra-1,2-(6-dimethylmethoxysilylnaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(*R,S*)-41]. In a dry system under pure dry argon was placed 250 mL of pure dry 1,2-dimethoxymethane (distilled from CaH_2) containing a trace amount of triphenylmethane indicator. A few drops of butyllithium solution in hexane were added until a pink color persisted. Then 6 mL of a 2.2 M solution of butyllithium in hexane (13.2 mmol) was added dropwise under argon to the solution stirred at −75 °C. Tetrabromide (*R,S*)-**40** (2.05 g) was added and the resulting mixture was stirred for 3 h at −75 °C and then added rapidly under argon to 12 g of dichlorodimethylsilane stirred at −75 °C. The stirred mixture was allowed to warm to 25 °C, and after 4 h at 25 °C the mixture was heated to reflux for 10 h. The mixture was cooled and filtered, the filter cake was washed with dry 1,2-dimethoxyethane, and the solvent was evaporated under reduced pressure to give a glass, which was stirred with 25 mL of dry methanol. The resulting solution was evaporated and the residue was chromatographed on silica gel in CH_2Cl_2 to give 1.8 g (84%) of (*R,S*)-**41**: mp 95–96 °C; M^+ 1064. Anal. Calcd for $C_{60}H_{72}Si_4O_{10}$: C, 67.67; H, 6.77. Found: C, 67.45; H, 6.89.

(*R,R*),(*S,S*)-2,3,4,5,13,14,15,16-Tetra-1,2-(6-acetylnaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(*R,R*),(*S,S*)-42]. Anhydrous $AlCl_3$ (10.68 g or 80 mmol) and acetyl chloride (3.14 g or 40 mmol) were added to 50 mL of nitrobenzene (distilled from P_2O_5 and stored over 4 Å molecular sieves) at 25 °C. The solution was stirred at 25 °C for 15 min, 1.0 g (1.4 mmol) of (*R,R*),(*S,S*)-**39**[4] was added, and the mixture was stirred at 25 °C for 2 h. The reaction mixture was poured onto a mixture of ice and hydrochloric acid, and the mixture was shaken with CH_2Cl_2. the water layer was extracted with CH_2Cl_2, and the combined organic phases were dried and evaporated (in vacuum), and the residue was chromatographed on 75 g of low activity silica gel with CH_2Cl_2–ethanol (98:2, v:v) as eluting agent to give 1.15 g (93%) of product, which was rechromatographed on 75 g of silica gel to give with 200:1 (v:v) CH_2Cl_2–ethanol, (*R,R*),(*S,S*)-**42**, which was dissolved in 40 mL of hot $CHCl_3$ and crystallized by the addition of 5 mL of ether to give 630 mg (51%) of pure product: mp 340–341 °C (decomposition); IR spectrum (KBr), carbonyl absorption at 1680 cm^{-1}. Anal. Calcd for $C_{48}H_{40}O_6$: C, 76.35; H, 5.49. Found: C, 76.10; H, 5.64.

Similarly, 2.0 g of optically pure (−)-(*S,S*)-**39**[4] was converted to 2.2 g (89%) of (−)-(*S,S*)-**42** (without chromatography, but precipitated with ether from nitrobenzene–CH_2Cl_2), 258–262 °C. An analytical sample recrystallized from ether–$CHCl_3$ gave: mp 264–265 °C dec; $[\alpha]^{25}_{578}$ −87°, $[\alpha]^{25}_{546}$ −105° (c 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.67 (s, CH_3, 12 H), 3.19 (m, $ArOCH_2$, 8 H), 3.83 (m, CH_2OCH_2, 8 H), 7.03 (d, $J_{7,8}$ = 9 Hz, 4 H), 7.34 (d, $J_{3,4}$ = 9 Hz, 4 H), 7.70 (d of d, $J_{7,8}$ = 9 Hz, $J_{5,7}$ = 2 Hz, 4 H), 8.08 (d, $J_{3,4}$ = 9 Hz, 4 H), 8.48 (d, $J_{5,7}$ = 2 Hz, 4 H); M^+ 880; IR spectrum (KBr), carbonyl absorption at 1670 cm^{-1}. Anal. Calcd for $C_{48}H_{40}O_6$: C, 76.35; H, 5.49. Found: C, 76.35; H, 5.69.

(*R,R*),(*S,S*)-2,3,4,5,13,14,15,16-Tetra-1,2-(6-carbomethoxynaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(*R,R*),(*S,S*)-43]. A solution of 16 g of KOH (85%) and 11.2 g of NaOH in 72 mL of water was cooled to 0 °C and 8.0 mL (24.8 g or 155 mmol) of Br_2 was added. Tetraacetylcycle (*R,R*),(*S,S*)-**42** (1.2 g or 1.36 mmol) was added to the stirred solution followed by 120 mL of purified dioxane (refluxed 24 h with Na followed by distillation). The vigorously stirred solution was heated slowly to reflux (30 min), held there for 2 h, cooled, and mixed with 100 mL of 10% aqueous $NaHSO_3$. The solvent was evaporated at reduced pressure and the residue was dissolved in 80 mL of water. The solution was acidified with 15 mL of 20% aqueous H_2SO_4 to a pH of 1. The heavy precipitate of tetraacid was collected and washed with acetone and water to give 1.234 g of crude material, which was mixed with 350 mL of dry methanol and 56 drops of concentrated H_2SO_4. The mixture was stirred at reflux for 5 days, the methanol was about 75% evaporated, and the resulting solution was shaken with water and CH_2Cl_2. The organic layer was washed with water, dried, and evaporated under reduced pressure, and the residue was chromatographed on 300 g of silica gel deactivated with 15% water with CH_2Cl_2 as the developer to give 1.1 g of crude diester, which was recrystallized from CH_2Cl_2–acetone to give 1.0 g (77%) of (*R,R*),(*S,S*)-**43**: mp 300–301 °C; M^+ 994; ^{1}H NMR ($CDCl_3$) δ 7.30 (d, ArH^3, $J_{3,4}$ = 9 Hz, 4 H), 8.04 (d, ArH^4, 4 H), 8.60 (d, ArH^5, $J_{5,7}$ = 2 Hz, 4 H), 7.72 (d of d, ArH^7, $J_{7,8}$ = 9 Hz, 4 H), 7.02 (d, ArH^8, 4 H), 3.87 (m, $ArOCH_2$, 8 H), 3.17 (m, CH_2OCH_2, 8 H), and 3.88 (s, CH_3, 12 H). Anal. Calcd for $C_{56}H_{48}O_{14}$: C, 71.18; H, 5.12. Found: C, 71.08; H, 5.10.

(*R,R*),(*S,S*)-2,3,4,5,13,14,15,16-Tetra-1,2-(6-carboxynaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(*R,R*),(*S,S*)-44]. A mixture of 0.769 g (0.813 mmol) of (*R,R*),(*S,S*)-**43** and 150 mL of a 0.5 M LiOH solution of 50% purified dioxane–water (v) was heated at reflux for 12 h and the solvent was evaporated under reduced pressure to 30 mL. This solution was acidified with 120 mL of 1 N HCl, and the mixture was boiled to coagulate the product which was collected and water washed. The product was dissolved in 10 mL

of 0.25 M aqueous NaOH, the solution was washed twice with CH_2Cl_2, and the product was again precipitated and coagulated with 1 N HCl solution to pH 1.5. The product was collected and washed with 1 N HCl solution and dried at 0.1 mm at 165 °C for 24 h to give 0.557 g (77%) of (*R,R*),(*S,S*)-**44**; ^{1}H NMR (2.5 M NaOD in D_2O) δ 2.89 (m, OCH_2O, 8 H), 3.70 (m $ArOCH_2$, 8 H), 6.98 (d, ArH^3, $J_{3,4}$ = 9 Hz, 4 H), 7.40 (d, ArH^8, $J_{7,8}$ = 9 Hz, 4 H), 7.63 (d of d, ArH^7, $J_{7,8}$ = 9 Hz, $J_{5,7}$ = 1.3 Hz, 4 H), 8.28 (d, ArH^4, $J_{3,4}$ = 9 Hz, 4 H), and 8.54 (d, ArH^5, $J_{5,7}$ = 1.3 Hz, 4 H). Anal. Calcd for $C_{52}H_{40}O_{14}$: C, 70.26; H, 4.54. Found: C, 70.28; H, 4.71.

(−)-(*S,S*)-2,3,4,5,13,14,15,16-Tetra-1,2-[6-(3-oxa-2-oxobuta)-naphtho]-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(−)-(*S,S*)-45]. Thallium trinitrate (4.2 g or 9.5 mmol)[16] was dissolved in a mixture of 83 mL of methanol and 70% aqueous perchloric acid (16 mL) cooled in an ice bath. A solution of optically pure tetraacetylcycle (−)-(*S,S*)-**42** (2.04 g or 2.32 mol) in 25 mL of CH_2Cl_2 was added. The initially homogeneous mixture was stirred for 1 h at 4 °C and 3 h at 25 °C and filtered from the precipitated thallous nitrate. The filtrate was diluted with 200 mL of water and extracted with 200 mL of CH_2Cl_2 twice, and the combined organic layers were dried. Evaporation of the solvent and drying of the residue under vacuum at 75 °C gave (−)-(*S,S*)-**45** as a foam; 2.27 g (98%); M^+ 1000; ^{1}H NMR ($CDCl_3$) δ 3.0–3.4 (m, och_2O, 8 H), 3.6–4.0 (m, $ArOCH_2$, 8 H), 3.67 (s, OCH_3, 6 H), 3.72 (s, $ArCH_2$, 4 H), 7.0–7.4 (m, ArH, 12 H), 7.7–8.0 (m, ArH, 8 H). Recrystallization of a small sample of the material from ether–chloroform gave mp 174–175 °C. Anal. Calcd for $C_{60}H_{56}O_{14}$: C, 71.99; H, 5.64. Found: C, 71.75; H, 5.85.

(*S,S*)-2,3,4,5,13,14,15,16-Tetra-1,2-[6-(3-oxapropana)naphtho]-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(*S,S*)-46]. Ester (−)-(*S,S*)-**45**, 1.65 g, was reduced with $LiAlH_4$ in THF in the usual way to give 1.3 g (90%) of (*S,S*)-**46** as a white foam: M^+ 888; ^{1}H NMR ($CDCl_3$) δ 1.67 (s, OH, 4 H), 2.92 (t, $ArCH_2CH_2$, J = 6 Hz, 8 H), 3.85 (t, $ArCH_2CH_2$, J = 6 Hz, 8 H), 3.0–3.4 (m, $ArOCH_2$, 8 H), 3.6–4.0 (m, OCH_2O, 8 H), 7.0–7.4 (m, ArH, 12 H), 7.7–8.0 (m, ArH, 8 H). An analytical sample was chromatographed on silica gel with gradient elution from CH_2Cl_2 to 6% methanol–CH_2Cl_2 (v), followed by drying at 160 °C (0.1 mm). Anal. Calcd for $C_{56}H_{56}O_{10}$: C, 75.65; H, 6.35. Found: C, 75.67; H, 6.34.

(−)-(*S,S*)-2,3,4,5,13,14,15,16-Tetra-1,2-(6-vinylnaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(−)-(*S,S*)-47]. To a solution of crude tetrol (*S,S*)-**46** (200 mg, 0.23 mmol) in 3 mL of puridine at 0 °C was added 300 mg or 1.6 mmol of tosyl chloride, and the solution was allowed to stand at 0 °C for 48 h. The tetratosylate was isolated in the usual way to give 0.310 mg or 0.21 mmol (88%) of crude product used directly in the next step. This material was dissolved in 4 mL of Me_2SO (4 mL distilled from BaO and stored over 4 Å molecular sieves) and 112 mg (1 mmol) of *t*-BuOK was added to give a dark brown mixture that was stirred for 2 h at 25 °C. The mixture was shaken with 25 mL of 10% hydrochloric acid and 40 mL of CH_2Cl_2. The organic layer was washed with water, dried, and evaporated under reduced pressure to give a brown oil that was chromatographed on 7 g of silica gel in CH_2Cl_2 to give 80 mg (47%) of (−)-(*S,S*)-**47** as a colorless glass, dried at 25 °C (0.1 mm): M^+ 816; $[\alpha]^{25}_{578}$ −52°, $[\alpha]^{25}_{546}$ −62°, $[\alpha]^{25}_{435}$ −175° (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 3.1–3.4 (m, $ArOCH_2$, 8 H), 3.7–4.0 (m, CH_2OCH_2, 8 H), 5.23, 5.71, and 6.84 (d of d, $CH{=}CH_2$ J = 1 and 11 Hz; J = 11 and 17 Hz, respectively, 4 H each), 7.0–7.5 (m, ArH, 12 H), 7.7–8.0 (m, ArH, 8 H). For analysis the sample was dried at 140 °C (0.1 mm) for 72 h. Anal. Calcd for $C_{56}H_{48}O_6$: C, 82.35; H, 5.92. Found: C, 82.25; H, 6.02.

(−)-(*S,S*)-2,3,4,5,13,14,15,16-Tetra-1,2-(6-barium sulfonatonaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(−)-(*S,S*)-48]. Optically pure bisdinaphtho-22-crown-6 [(−)-(*S,S*)-**39**][4], 5.0 g or 7.02 mmol, was added at 25 °C with stirring to 25 mL of concentrated H_2SO_4. After 2 h of stirring at 25 °C the mixture was homogeneous and light brown. After 22 h of additional stirring at 25 °C, the solution was poured slowly into 125 mL of distilled water at 0 °C with stirring at 0 °C (ice bath). The solution was neutralized to pH 7.4 with $Ba(OH)_2{\cdot}8H_2O$. Because of the massive precipitate of $BaSO_4$ it was necessary to filter at an intermediate stage and then the neutralization was continued. The final mixture was heated to coagulate the $BaSO_4$ and the mixture was filtered through a fritted glass filter. The filter cake was thoroughly washed with boiling distilled water, and the clear filtrate was evaporated under reduced pressure to give 4.5 g (50% of (−)-(*S,S*)-**48**. An analytical sample of this salt dissolved in H_2O was purified by gel permeation chromatography (Bio-Gel P_2, 100–200 mesh, exclusion limit, 2600). The neutral UV-active fractions were combined and evaporated to dryness to give white crystals: mp >360 °C; $[\alpha]^{25}_{589}$ −165.5°, $[\alpha]^{25}_{578}$ −180.0°, $[\alpha]^{25}_{546}$ −216.4° (*c* 1.2, H_2O); ^{1}H NMR (D_2O) δ relative to $(CH_3)_2CO$ as internal standard 0.46 (broad s, OCH_2O, 8 H), 1.32 (broad s, $ArOCH_2$, 8 H), 4.66 (d, $J_{7,8}$ = 9 Hz, ArH^8, 4 H), 5.08 (m, ArH^3 + ArH^7, 8 H), 5.97 (d, $J_{3,4}$ = 10 Hz, ArH^4, 4 H), and 6.24 (s, ArH^5, 4 H). Anal. Calcd for $C_{48}H_{36}S_4O_{18}Ba_2$: C, 43.22; H, 2.78; Ba, 21.20. Found: C, 43.50; H, 3.02; Ba, 21.20.

An aqueous solution containing 1.5 g (1.1 mmol) of (−)-(*S,S*)-**48** in distilled water was passed through 10 g of Dowex 50 cationic exchange resin. The UV-active effluent was evaporated, and the remaining tetrasulfonic acid liquid was dried at 40 °C for 4 h. This material gave a neutralization equivalent with LiOH in distilled water to a phenolphthalein end point of 255 (Calcd 258) and was neutralized likewise to give after evaporation and drying 1.2 g (98%) of the tetralithium salt of the tetrasulfonic acid, whose ^{1}H NMR spectrum in D_2O was superimposable on that of the Ba salt.

(−)-(*S,S*)-2,3,4,5,13,14,15,16-Tetra-1,2-(6-*tert*-butylnaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(−)-(*S,S*)-49]. A solution of 391 mg (0.54 mmol) of optically pure (−)-(*S,S*)-**39**[4] in 5 mL of dry CH_2Cl_2 was cooled to −78 °C, and 0.51 g (5.4 mmol) of *tert*-butyl chloride was added followed by 0.72 g (5.4 mmol) of $AlCl_3$. The reaction mixture was stirred for 6 h at −78 °C and quenched with water. The mixture was shaken with CH_2Cl_2 and water, the organic phase was dried, and the solvent was evaporated under reduced pressure to give 0.40 g of crude product as a foam. This material was chromatographed on silica gel with CH_2Cl_2 as the mobile phase to give 230 mg (45%) of product, which after crystallization from ethanol–$CHCl_3$ gave (−)-(*S,S*)-**49**: mp 289–291 °C; M^+ 936; ^{1}H NMR ($CDCl_3$) δ 1.25 (s, CH_3, 36 H), 3.20 (m, CH_2OCH_2, 8 H), 3.8 (m, $ArOCH_2$, 8 H), 6.92 to 7.26 (m, ArH, 12 H), and 7.70 to 7.88 (m, ArH, 8 H). The aryl splitting pattern resembles that of tetraester **45** and that of tetravinyl compound **47**. The compound gave $[\alpha]^{25}_{589}$ −116.9°, $[\alpha]^{25}_{578}$ −122.4°, $[\alpha]^{25}_{546}$ −146.2°, $[\alpha]^{25}_{436}$ −342.3° (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{64}H_{72}O_6$: C, 82.01; H, 7.74. Found: C, 81.75; H, 7.91.

(−)-(*S,S*)-2,3,4,5,13,14,15,16-Tetra-1,2-(5,6,7,8-tetrahydronaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(−)-(*S,S*)-50]. A 2.0-g sample (23 mmol) of (−)-(*S,S*)-**39**, $[\alpha]^{25}_{578}$ −221° (*c* 1.0, $CHCl_4$),[4] was dissolved with heating in 350 mL of glacial acetic acid–ethyl acetate (6:1, v:v) and 0.50 g of PtO_2 was added. The solution was hydrogenated in a Parr apparatus at 25 °C under 3 atm of hydrogen for 5 days. The solution was filtered, the solvent was evaporated under reduced pressure, and the residue in $CHCl_3$ was extracted with 10% $NaHCO_3$ to remove the acetic acid. Evaporation of the filtrate gave 2.0 g (98%) of product as white needles, which were recrystallized from cyclohexane to give (−)-(*S,S*)-**50**: mp 235–236 °C; M^+ 728; ^{1}H NMR ($CDCl_3$) δ 1.7 (m, CCH_2CH_2C, 16 H), 2.2 (m, CH_2 at C-8 of tetralin, 8 H), 2.8 (m, CH_2 at C-5 of tetralin, 8 H), 3.4 and 3.7 (m, m, OCH_2CH_2O, 16 H), 6.5 (d, ArH^3, 4 H), 6.9 (d, ArH^4, 4 H); $[\alpha]^{25}_{578}$ −55°, $[\alpha]^{25}_{546}$ −62°, $[\alpha]^{25}_{436}$ −106° (*c* 1.0 $CHCl_3$). Anal. Calcd for $C_{48}H_{56}O_6$: C, 79.09; H, 7.74. Found: C, 79.15; H, 7.96.

This same compound, (−)-(*S,S*)-**50**, was prepared in 54% yield by the ring-closing reaction of 1.1 g (3.7 mmol) of reduced diol (−)-(*S*)-**22**, $[\alpha]^{25}_{578}$ −55.5° (*c* 1.0 $CHCl_3$), with the reduced two-armed ditosylate (−)-(*S*)-**24**, $[\alpha]^{25}_{578}$ −26.2° (*c* 1.0, $CHCl_3$), in 300 mL of refluxing THF–H_2O (99:1, v:v) containing 0.42 g (7.5 mmol) of KOH (4 day reaction time). The cyclic product, after alumina chromatography and recrystallization from cyclohexane, gave mp 235–236 °C, an ^{1}H NMR spectrum identical with that of (−)-(*S,S*)-**50** prepared from (−)-(*S,S*)-**39**, and $[\alpha]^{25}_{578}$ −55°, $[\alpha]^{25}_{546}$ −62 °, and $[\alpha]^{25}_{436}$ −105° (*c* 1.0, $CHCl_3$).

(+)-(*R,R*)-2,3,4,5-Di-1,2-(3-methyl-5,6,7,8-tetrahydronaphtho)-13,14,15,16-di-1,2-(5,6,7,8-tetrahydronaphtho)-1,6,9,12,-17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(+)-(*R,R*)-51]. Procedure III. A sample of 1.23 g (1.66 mmol) of (+)-(*R,R*)-**29**, $[\alpha]^{25}_{578}$ +144.5° (*c* 1, $CHCl_3$), was dissolved with heating in 50 mL of glacial acetic acid, and 297 mg of PtO_2 was added. The mixture was stirred at 85 °C under 1 atm of H_2 for 5 days and filtered. The filtrate was evaporated under reduced pressure, and the residue in ether was passed through a short alumina column to remove the acetic acid. The material was then chromatographed in CH_2Cl_2 on silica gel to give 1.17 g (70%) of (+)-(*R,R*)-**51** as a white foam (dried at 50 °C (0.1 mm) for 20 h): M^+ 756; $[\alpha]^{25}_{578}$ +35.4°, $[\alpha]^{25}_{546}$ +39.2°, $[\alpha]^{25}_{436}$ +63.7° (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.7 (m, CCH_2CH_2C, 16 H), 2.2 (s and m superimposed, CH_3 and CH_2 at C-8 of tetralin ring, 14 H), 2.8 (m, CH_2 at C-5 at tetralin ring, 8 H), 3.4 and 3.7 (m, OCH_2CH_2O, 16 H), 6.5–7.0 (s at 6.8 superimposed on q, ArH, 6H). Anal. Calcd for $C_{50}H_{60}O_6$: C, 79.33; H, 7.99. Found: C, 79.31; H, 7.92.

In an alternative synthesis of (+)-(*R,R*)-**51** in which none of the intermediates were characterized, optically pure (+)-(*R*)-**3** was converted to (+)-(*R*)-bis-2,2′-bis(5-hydroxy-3-oxa-1-pentyloxy)-1,1′-dinaphthyl,[4] $[\alpha]^{25}_{578}$ +22.1° (*c* 1, $CHCl_3$), which was catalytically

reduced in acetic acid with PtO_2 and H_2 at 50 °C for 2 days to give (*R*)-2,2′-bis(5-hydroxy-3-oxa-1-pentyloxy)-5,5′-6,6′,7,7′,8,8′-octahydro-1,1′-dinaphthyl (68%) which was tosylated to give the ditosylate (*R*)-**24**, 45% (^{1}H NMR identical to (*S*)-**24**, see above). This material was ring closed by procedure II with (+)-(*R*)-**13** (optically pure) to give (+)-(*R,R*)-**57** (72%) (^{1}H NMR identical to (−)-(*S,S*)-**57**, see below) which was reduced in acetic acid, H_2, and PtO_2 at 80–90 °C for 5 days to give (+)-(*R,R*)-**51** (43%), $[\alpha]^{25}_{578}$ +34.8°, $[\alpha]^{25}_{546}$ +38.5°, $[\alpha]^{25}_{436}$ +62.0° (*c* 1.92, $CHCl_3$). These rotations are 98, 98, and 97% respectively of the sample of (+)-(*R,R*)-**51** prepared from (+)-(*R,R*)-**29**.

(+)-(*R,R*)-2,3,4,5,13,14,15,16-Tetra-1,2-(3-methyl-5,6,7,8-tetrahydronaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(+)-(*R,R*)-52]. A 2.0-g sample (12.6 mmol) of (+)-(*R,R*)-**32**, $[\alpha]^{25}_{578}$ +134.8° (*c* 1.0, $CHCl_3$), 250 mL of glacial acetic acid, and 660 mg of PtO_2 was stirred at 60 °C. The product was isolated as in procedure III to give 1.84 g (88%) of (+)-(*R,R*)-**52** as a white foam: M^+ 784; $[\alpha]^{25}_{578}$ +22.2°, $[\alpha]^{25}_{546}$ +23.3°, $[\alpha]^{25}_{436}$ +33.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.6 (m, CCH_2CH_2C, 16 H), 2.2 (m and s, $ArCH_2$ at C-8 of decalin and $ArCH_3$, 20 H), 2.7 (m, $ArCH_2$ at C-5 of decalin, 8 H), 3.3 and 3.7 (m, m, OCH_2CH_2O, 16 H), 6.8 (s, ArH, 4 H). Anal. Calcd for $C_{52}H_{64}O_6$: C, 79.55; H, 8.21. Found: C, 79.33; H, 8.01.

(+)-(*S,S*)-2,3,4,5,13,14,15,16-Tetra-1,2-(3-bromo-5,6,7,8-tetrahydronaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(+)-(*S,S*)-53]. To a solution of 141 mg (0.194 mmol) of (−)-(*S,S*)-**50** (see above) dissolved in 10 mL of CH_2Cl_2 was added 0.05 mL of Br_2. The solution was immediately covered with foil and cooled to −45 °C for 1 h, by which time starting material had disappeared (TLC). After an additional 45 min, the reaction mixture was added to 10 mL of 10 aqueous $NaHSO_3$. The mixture was shaken, the aqueous layer was washed with CH_2Cl_2, and the combined organic layers were washed with water, dried, and evaporated to give (+)-(*S,S*)-**53** as a white foam which was dried at 50 °C (0.1 mm) for 24 h, 0.193 mg (96%). The material gave: M^+ 1040 (part of an isotopic cluster); $[\alpha]^{25}_{578}$ +98.1°, $[\alpha]^{25}_{546}$ +114°, $[\alpha]^{25}_{436}$ +223° (c 0.81, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.7, 2.2, and 2.7 [m, $(CH_2)_4$, 32 H], 3.4 and 3.7 (m, OCH_2CH_2O, 16 H), 7.3 (s, ArH, 4 H). Anal. Calcd for $C_{48}H_{52}O_6Br_4$: C, 55.19; H, 5.02. Found: C, 55.34; H, 5.05.

(+)-(*R,R*)-2,3,4,5-Di-1,2-(3-bromo-5,6,7,8-tetrahydronaphtho)-13,14,15,16-di(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(+)-(*R,R*)-54]. To a stirred solution of 7.3 g (16 mmol) of dibromodiol (−)-(*R*)-**27** (see above) and 14.2 g (18 mmol) of the optically pure two-armed ditosylate (+)-(*R*)-**21**[4] in 1 L of THF under N_2 was added 1.8 g (36 mmol) of KOH in 30 mL of water. The mixture was refluxed for 7 days and the crude product was isolated in the usual way and chromatographed on 300 g of neutral activity I alumina in ether. The column was eluted with 5 L of ether to give 9.6 g (68%) of (+)-(*R,R*)-**54** as a white foam: M^+ 876 (^{79}Br); $[\alpha]^{25}_{436}$ +66°, $[\alpha]^{25}_{546}$ +20°, and $[\alpha]^{25}_{578}$ +16° (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.80 (m, ArH, 4 H), 7.24 (m, ArH, 10 H), 3.50 (m, OCH_2CH_2O, 16 H), 2.70 (m, $ArCH_2$, 4 H), 2.10 (m, $ArCH_2$, 4 H), and 1.62 (m, CCH_2CH_2C, 8 H). Anal. Calcd for $C_{48}H_{46}Br_2O_6$: C, 65.16; H, 5.28. Found: C, 65.78; H, 5.48.

(+)-(*R,R*)-2,3,4,5-Di-1,2-(5,6,7,8-tetrahydronaphtho)-13,14,15,16-di(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(+)-(*R,R*)-55]. To a stirred solution of 1.5 g (1.7 mmol) of dibromocycle (+)-(*R,R*)-**54** (see above) in 200 mL of dry THF stirred under N_2 at −78 °C was added 20 mL of butyllithium (1.6 M in hexane). The mixture was stirred for 45 min, CH_3OH was added dropwise (20 mL), and the solution was allowed to warm to 25 °C. The crude product was isolated by the usual extraction–evaporation method to give a white solid which when crystallized from CH_2Cl_2–hexane gave 1.18 g (96%) of (+)-(*R,R*)-**55**: mp 211–212 °C, M^+ 720; $[\alpha]^{25}_{436}$ +251°, $[\alpha]^{25}_{546}$ +116°, and $[\alpha]^{25}_{578}$ +99° (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.82 (m, ArH, 4 H), 6.96 (m, ArH, 12 H), 3.50 (m, OCH_2CH_2O, 16 H), 2.74 (m, $ArCH_2$, 4 H), 2.18 (m, $ArCH_2$, 4 H), and 1.68 (m, CCH_2CH_2C, 8 H). Anal. Calcd for $C_{48}H_{48}O_6$: C, 79.97; H, 6.71. Found: C, 80.22; H, 6.96.

(+)-(*R,R*)-2,3,4,5,13,14,15,16-Tetra-1,2-(5,6,7,8-tetrahydronaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(+)-(*R,R*)-50]. A mixture of 300 mg (0.42 mmol) of (+)-(*R,R*)-**55** and 100 mg of PtO_2 and 50 mL of glacial acetic acid was hydrogenated at 25 °C for 5 days. The product was isolated as in procedure III to give 280 mg (92%) of white crystalline (+)-(*R,R*)-**50** (from CH_2Cl_2–hexane), mp 234–235 °C, whose ^{1}H NMR spectrum and TLC behavior were identical to that of (−)-(*S,S*)-**50** (see above), $[\alpha]^{25}_{436}$ +102°, $[\alpha]^{25}_{546}$ +60°, $[\alpha]^{25}_{578}$ +53° (*c* 1.0, $CHCl_3$).

(+)-(*R,R*)-2,3,4,5-Di-1,2-(3-methyl-5,6,7,8-tetrahydronaphtho)-13,14,15,16-di(1,2-naphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(+)-(*R,R*)-56]. To a stirred solution of 3.8 g (11.8 mmol) of reduced optically pure dimethyldiol, (+)-(*R*)-**23**, in 600 mL of THF under N_2 was added 1.35 g (24 mmol) of KOH in 10 mL of water. The mixture was stirred for 15 min at 25 °C, 9.5 g (12.3 mmol) of optically pure dinaphthyl two-armed ditosylate [(+)-(*R*)-**21**][4] in 400 mL of THF was added, and the mixture was refluxed for 7 days. The crude product was isolated as in procedure I and was chromatographed on 200 g of alumina in ether with ether as developer to give 6.2 g (70%) of product as a white foam after drying at 60 °C (0.1 mm) for 24 h. This (+)-(*R,R*)-**56** gave: M^+ 748; $[\alpha]^{25}_{436}$ +244°, $[\alpha]^{25}_{546}$ +110°, $[\alpha]^{25}_{578}$ +93°, and $[\alpha]^{25}_{589}$ +83° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.80 (m, ArH, 10 H), 7.08 (m, ArH, 10 H), 3.50 (m, OCH_2CH_2O, 16 H), 2.72 (m, $ArCH_2$, 4 H), 2.18 (s, $ArCH_3$, 6 H), 2.14 (m, $ArCH_2$, 4 H), and 1.64 (m, CCH_2CH_2C, 8 H). Anal. Calcd for $C_{50}H_{52}O_6$: C, 80.18; H, 7.00. Found: C, 80.09; H, 7.03.

(−)-(*S,S*)-2,3,4,5-Di-1,2-(3-methylnaphtho)-13,14,15,16-di-1,2-(5,6,7,8-tetrahydronaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(−)-(*S,S*)-57]. To a solution of reduced ditetralyldiol (−)-(*S*)-**22**, $[\alpha]^{25}_{578}$ −49.4° (*c* 1.0, $CHCl_3$), in 150 mL of dry THF under N_2 was added 0.50 g (7.6 mmol) of KOH (85%), the mixture was refluxed for 30 min, and 2.62 g (3.4 mmol) of optically pure dimethyldinaphthyl two-armed ditosylate (+)-(*S*)-**20** ($[\alpha]^{25}_{578}$ +70.0°, *c* 1.0, $CHCl_3$) in 50 mL of dry THF was added. The mixture was refluxed for 160 h, and the crude product was isolated as in procedure I to give 1.45 g of material that was submitted to gel permeation chromatography to give after drying at 60 °C (0.1 mm) for 24 h 1.06 g (42%) of (−)-(*S,S*)-**57** as a white foam: M^+ 748; $[\alpha]^{25}_{436}$ −88.6°, $[\alpha]^{25}_{546}$ −47.6°, $[\alpha]^{25}_{578}$ −41.0°, and $[\alpha]^{25}_{589}$ −39.4°; ^{1}H NMR ($CDCl_3$) δ 7.9, 6.8 (m, m, ArH, 14 H), 3.1–4.0 (m, OCH_2CH_2O), 2.95 (m, $ArCH_2$, 4 H), 2.50 (s, CH_3, 6 H), 2.23 (m, $ArCH_2$, 4 H), 1.93 (m, CCH_2CH_2C, 8 H). Anal. Calcd for $C_{50}H_{52}O_6$: C, 80.18; H, 6.99. Found: C, 80.07; H, 7.03.

(−)-(*S,S*)-2,3,4,5,10,11,12,13-Tetra-1,2-(5,6,7,8-tetrahydronaphtho)-1,6,9,14,17,20-hexaoxacyclodocosa-2,4,10,12-tetraene [(−)-(*S,S*)-58]. A mixture of 1.013 g (1.41 mmol) of (−)-(*S,S*)-2,3,4,5,10,11,12,13-tetra-1,2-naphtho-1,6,9,14,17,20-hexaoxacyclodocosa-2,4,10,12-tetraene [$[\alpha]^{25}_{578}$ −223°, *c* 4.5, $CHCl_3$],[4] 48 mg of PtO_2, and 70 mL of glacial acetic acid was heated at 75–85 °C under 1 atm of H_2 with stirring for 7 days. The product was isolated as in procedure III and purified by chromatography on silica gel–CH_2Cl_2 to give 820 mg (85%) of (−)-(*S,S*)-**58**: M^+ 728; $[\alpha]^{25}_{578}$ −106°, $[\alpha]^{25}_{546}$ −121°, $[\alpha]^{25}_{436}$ −223° (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.7 (m, CCH_2CH_2C, 16 H), 2.2, 2.8 (m, m, $ArCH_2$, 16 H), 3.2, 3.5, 3.9 (m, OCH_2CH_2O, 16 H), 6.2–7.0 (m, ArH, 8 H). Anal. Calcd for $C_{48}H_{56}O_6$: C, 79.09; H, 7.74. Found: C, 79.10; H, 7.80.

(+)-(*S,S*)-2,3,4,5,10,11,12,13-tetra-1,2-(3-bromo-5,6,7,8-tetrahydronaphtho)-1,6,9,14,17,20-hexaoxacyclodocosa-2,4,10,12-tetraene [(+)-(*S,S*)-59]. To a solution of 581 mg (0.798 mmol) of (−)-(*S,S*)-**58** (see above) in 25 mL of CH_2Cl_2 in a foil-wrapped flask and cooled to −50 °C was added with stirring 0.25 mL of bromine. After 2 h, 15 mL of a 10% aqueous solution of $NaHSO_3$ was added, the layers were shaken, and the aqueous layer was washed with 10 mL of CH_2Cl_2. The combined organic layers were washed with water, dried, and evaporated under reduced pressure to give a white foam of (+)-(*S,S*)-**59**: 588 mg (94%); M^+ 1040 (isotopic cluster); $[\alpha]^{25}_{578}$ +47.6°, $[\alpha]^{25}_{546}$ +55.4°, $[\alpha]^{25}_{436}$ +109.6° (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.7, 2.1 and 2.7 [m, $(CH_2)_4$, 32 H], 3.4 and 3.8 (m, OCH_2CH_2O, 16 H), 7.3 (d, ArH, 4 H). Anal. Calcd for $C_{48}H_{52}Br_4O_6$: C, 55.19; H, 5.02. Found: C, 55.52; H, 5.03.

Optical Stability to Heat of (−)-(*S,S*)-2,3,4,5,13,14,15,16-Tetra-1,2-(5,6,7,8-tetrahydronaphtho)-1,6,9,12,17,20-hexaoxacyclodocosa-2,4,13,15-tetraene [(−)-(*S,S*)-(50)]. A 77.8-mg sample of (−)-(*S,S*)-**50** was dissolved in 15 mL of diphenyl ether which had been passed through an alumina column. The rotations of the solution were measured at 25 °C in a 1-mL, 1-dm cell, α^{25}_{578} −0.110°, α^{25}_{546} −0.124°, α^{25}_{436} −0.168° (observed). An 8-mL aliquot of this solution was transferred to a thick-walled glass ampule which was evacuated, passed through two freeze–thaw cycles, frozen a third time, and sealed, all under high vacuum. The ampule was heated to 175 °C for 1 week and cooled and the rotations were measured, $[\alpha]^{25}_{578}$ −0.106°, $[\alpha]^{25}_{546}$ −0.122°, $[\alpha]^{25}_{436}$ −0.162°. The already heated material was transferred to a fresh ampule, similarly sealed and heated at 200 °C for 1 week and 223 °C for 1 week and the rotations were measured, $[\alpha]^{25}_{578}$ −0.106°, $[\alpha]^{25}_{546}$ −118°, $[\alpha]^{25}_{436}$ −156°. The already heated material was similarly recycled and held at 253 °C for 5 days to give $[\alpha]^{25}_{578}$ −0.106°, $[\alpha]^{25}_{546}$ −0.119°, and $[\alpha]^{25}_{436}$ −0.156°. These experiments demonstrate these ditetralyl systems are configurationally stable to temperatures as high as 250 °C for as long as 5 days.

In a similar experiment, (+)-(*R,R*)-**50** of rotation $[\alpha]^{25}_{578}$ +57.8° (*c* 0.83 $CHCl_3$) was heated in a sealed tube in diphenyl ether at 226

°C for 1 week. The material was reisolated and subjected to silica gel chromatography (a small amount of open-chain material was removed), and the (+)-(*R*,*R*)-**50** recovered gave $[\alpha]^{25}_{578}$ +60.2° (*c* 1.04, $CHCl_3$).

In an identical and parallel experiment, the bisdinaphthyl system (+)-(*R*,*R*)-**39** of rotation $[\alpha]^{25}_{578}$ +209° (*c* 1.0, CH_2Cl_2) was found to decrease in rotation to $[\alpha]^{25}_{578}$ +202° (*c* 1.1, CH_2Cl_2). During silica gel purification, again a small amount of open-chain material was removed.

Configurational Stability to Heat of (+)-(*R*)-2,2′-Dihydroxy-1,1′-dinaphthyl [(+)-(*R*)-3] and of (+)-(*R*)-2,2′-Dihydroxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-dinaphthyl [(+)-(*R*)-22]. The general procedures involved dissolving 100-mg samples of each diol in the appropriate solutions in parallel experiments and heating each solution with stirring under N_2 in the same oil bath. The optical purity of the isolated product was then determined. Neutral, acidic, and basic conditions were all examined.

A. Neutral Conditions. The diols were heated in 10 mL of butanol at 118 °C for 24 h, and the solutions were cooled and evaporated under reduced pressure to give white solids that were dried at 110 °C (0.05 mm) for 8 h. The total samples were dissolved and their rotations were taken.

B. Acidic Conditions. The diols were heated at 100 °C for 24 h in a solution of purified dioxane (12 mL) and 10 mL of 1.2 M aqueous hydrochloric acid. The solutions were cooled and shaken with 50 mL of $CHCl_3$ and 300 mL of water and the organic layer was dried and evaporated under reduced pressure to give a pale yellow foam dried at 110 °C (0.05 mm) for 8 h. Total samples were dissolved and their rotations were taken.

C. Basic Conditions. The diols were heated at 118 °C for 26 h in 10 mL of butanol that was 0.7 M in KOH. The solutions were cooled and shaken with 50 mL of $CHCl_3$ and 300 mL of dilute hydrochloric acid and the organic layer was washed with water, dried, and evaporated under reduced pressure. Each residue was dissolved in 10 mL of CH_2Cl_2 and chromatographed on 20 g of silica gel in CH_2Cl_2. The 500 mL of column eluate (CH_2Cl_2) was evaporated under reduced pressure to give white solids that were dried 8 h at 110 °C (0.05 mm).

Comparisons of the optical rotations before and after the heat treatments are as follows: Diol (+)-(*R*)-**3**, $[\alpha]^{24}_{589}$ +34.2° (*c* 1.0, THF), initial rotation gave after the above treatments: neutral conditions, $[\alpha]^{25}_{589}$ +33.7° (*c* 1.0, THF) or 1% loss in rotation; acidic conditions, $[\alpha]^{25}_{589}$ +14.9° (*c* 1.0, THF) or 56% loss in rotation; basic conditions, $[\alpha]^{25}_{589}$ +27.2° (*c* 1.0, THF) or 20% loss in rotation. Reduced diol, (+)-(*R*)-**22**, initial rotation $[\alpha]^{25}_{589}$ +52.8 (*c* 1.0, $CHCl_3$), gave after the above treatments: neutral conditions, $[\alpha]^{25}_{589}$ +51.6° (*c* 1.0, $CHCl_3$), 2% loss in rotation: acidic conditions, $[\alpha]^{25}_{589}$ +52.5° (*c* 1.0, $CHCl_3$), <1% loss in rotation; basic conditions, $[\alpha]^{25}_{589}$ +49.1° (*c* 1.0, $CHCl_3$), 7% loss in rotation.

Registry No.—(±)-**3**, 41024-90-2; (+)(*R*)-**3**, 18531-94-7; (−)(*S*)-**3**, 18531-99-2; (±)-**4**, 55442-26-7; (±)-**5**, 55442-27-8; (±)-**6**, 55442-28-9; (±)-**7**, 55442-29-0; (±)-**8**, 65355-15-9; (±)-**9**, 55515-95-2; (+)(*R*)-**9**, 42167-07-7; (−)(*S*)-**9**, 42167-06-6; (±)-**10**, 55442-32-5; (±)-**11**, 55442-31-4; (±)-**12**, 55442-33-6; (±)-**13**, 55442-34-7; (±)(*R*)-**13**, 55515-98-5; (−)(*S*)-**13**, 55515-99-6; (±)-**13** phosphoric acid diester, 65355-16-0; (+)(*R*)-**13** phosphoric acid diester cinchonine, 65391-02-8; (+)(*R*)-**13** phosphoric acid diester, 65391-01-7; (−)(*S*)-**13** phosphoric acid diester, 39648-68-5; (+)(*R*)-**13** strychnine, 65355-10-4; (+)(*R*)-**13** CH_2OCH_3 diether, 65355-11-5; (±)-**14**, 55442-35-8; (±)-**15**, 55442-36-9; (±)-**16**, 65390-98-9; (+)(*R*)-**16** L-leucine methyl ester, 65355-12-6; (+)(*R*)-**16**, 18531-92-5; (−)(*S*)-**16**, 42167-04-4; (+)-(*R*)-**17**, 18531-91-4; (+)(*R*)-**18**, 65355-13-7; (+)(*S*)-**19**, 65390-99-0; (−)(*R*)-**19**, 65391-00-6; (±)-**19**, 55442-38-1; (±)-**20**, 55442-39-2; (+)-(*S*)-**20**, 65337-83-9; (−)(*R*)-**20**, 65337-84-0; (±)-**21**, 55441-94-6; (+)(*R*)-**21**, 55821-78-8; (+)(*R*)-**22**, 65355-14-8; (−)(*S*)-**22**, 65355-00-2; (+)(*R*)-**23**, 65355-01-3; (+)(*R*)-**24**, 65355-02-4; (−)(*S*)-**24**, 65355-03-5; (+)(*S*)-**25**, 65355-04-6; (−)(*R*)-**25**, 65355-05-7; (−)(*R*)-**26**, 65355-06-8; (+)(*S*)-**26**, 65355-07-9; (+)(*R*)-**27**, 65355-08-0; (±)-**28**, 65355-09-1; (*R*,*S*),(*S*,*R*)-**29**, 55516-17-1; (*R*,*R*),(*S*,*S*)-**29**, 55516-16-0; (+)(*S*,*R*)-**29**, 65390-97-8; (+)(*R*,*R*)-**29**, 55516-22-8; (−)(*S*,*S*)-**29**, 55321-98-2; (*R*,*S*),(*S*,*R*)-**30**, 55442-69-8; (*R*,*R*),(*S*,*S*)-**30**, 55516-19-3; (+)(*R*,*R*)-**30**, 55516-20-6; (+)(*R*,*R*)-**31**, 55516-21-7; (*R*,*S*)-**32**, 55516-15-9; (*R*,*R*),(*S*,*S*)-**32**, 55442-67-6; (+)(*R*,*R*)-**32**, 65337-85-1; (−)(*S*,*S*)-**32**, 65390-94-5; (+)(*R*,*R*)-**33**, 65354-98-5; (+)(*R*,*R*)-**34**, 65354-99-6; (*R*,*R*),(*S*,*S*)-**35**, 55442-70-1; (*R*,*S*),(*S*,*R*)-**35**, 55516-23-9; (+)(*R*,*R*)-**35**, 55516-24-0; (*R*,*S*),(*S*,*R*)-**36**, 55442-71-2; (*R*,*R*),(*S*,*S*)-**36**, 65390-95-6; (+)-(*R*,*R*)-**36**, 55516-25-1; (*R*,*R*),(*S*,*S*)-**37**, 55442-64-3; (*R*,*S*)-**37**, 55527-98-5; (*R*,*R*),(*S*,*S*)-**38**, 65390-96-7; (*R*,*R*),(*S*,*S*)-**39**, 41024-97-9; (*R*,*S*)-**39**, 41024-94-6; (+)(*R*,*R*)-**39**, 41024-95-7; (−)(*S*,*S*)-**39**, 41024-93-5; (*R*,*R*)(*S*,*S*)-**40**, 55516-26-2; (*R*,*S*)-**40**, 55516-27-3; (+)-(*R*,*R*)-**40**, 55130-93-3; (*R*,*S*)-**41**, 55516-28-4; (*R*,*R*),(*S*,*S*)-**42**, 55442-74-5; (−)(*S*,*S*)-**42**, 65390-91-2; (*R*,*R*),(*S*,*S*)-**43**, 65354-86-1; (*R*,*R*)(*S*,*S*)-**44**, 55442-79-0; (−)(*S*,*S*)-**45**, 65354-87-2; (*S*,*S*)-**46**, 65354-88-3; (−)(*S*,*S*)-**47**, 65354-89-4; (−)(*S*,*S*)-**48**, 65354-90-7; (−)-(*S*,*S*)-**49**, 65354-91-8; (−)(*S*,*S*)-**50**, 65354-92-9; (+)(*R*,*R*)-**50**, 65390-92-3; (+)(*R*,*R*)-**51**, 65354-93-0; (+)(*R*,*R*)-**52**, 65354-94-1; (+)(*S*,*S*)-**53**, 65354-95-2; (+)(*R*,*R*)-**54**, 65354-96-3; (+)(*R*,*R*)-**55**, 65354-97-4; (+)(*R*,*R*)-**56**, 65378-55-4; (+)(*R*,*R*)-**57**, 65390-93-4; (−)(*S*,*S*)-**57**, 65354-80-5; (−)(*S*,*S*)-**58**, 65354-81-6; (+)(*S*,*S*)-**59**, 65354-82-7; 4-(butoxymethyl)morpholine, 5625-84-3; dimethylaminoisobutoxymethane, 50339-64-5; cinchonine, 118-10-5; 3-hydroxy-2-naphthoic acid, 92-70-6; L-leucine methyl ester, 2666-93-5; 2-(2-chloroethoxy)-ethyl-2-tetrahydropyranyl ether, 54533-84-5; tosyl chloride, 98-59-9; chloromethyl methyl ether, 107-30-2; (*S*)-2,2′-bis(5-hydroxy-3-oxa-1-pentyloxy)-1,1′-dinaphthyl, 65390-89-8; 4,4′,6,6′-tetrabromo-2,2-dimethoxy-1,1-dinaphthyl, 65354-83-8; 2,2′-dimethoxy-1,1-dinaphthyl, 2960-93-2; (*R*),(*S*)-2,3:4,5-di-1,2-(3-methylnaphtho)-1,6,9-trioxaundeca-2,4-diene, 55442-68-7; 2,3:4,5-di-1,2-(3-*N*-morpholinomethylnaphtho)-1,6,9-trioxaundeca-2,4-diene, 55442-62-1; dichlorodimethylsilane, 75-78-5; *tert*-butyl chloride, 507-20-0; (+)-(*R*)-bis-2,2′-bis(5-hydroxy-3-oxa-1-pentyloxy)-1,1′-dinaphthyl, 65390-90-1; (*R*)-2,2′-bis(5-hydroxy-3-oxa-1-pentyloxy)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1-dinaphthyl, 65354-85-0; (−)-(*S*,*S*)-2,3,4,5,10,11,12,13-tetra-1,2-naphtho-1,6,9,14,17,20-hexaoxacyclodocosa-2,4,10,12-tetraene, 55515-84-9.

References and Notes

(1) This work was supported by a grant from the National Science Foundation, GP-33533X, and by the U.S. Public Health Service, Research Grant No. GM12640-12 from the Department of Health, Education, and Welfare.

(2) Some of these results were outlined in communications: (a) R. C. Helgeson, J. M. Timko, P. Moreau, S. C. Peacock, J. M. Mayer, and D. J. Cram, *J. Am. Chem. Soc.*, **96**, 6762 (1974); (b) S. C. Peacock and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, 282 (1976); (c) G. D. Y. Sogah and D. J. Cram, *J. Am. Chem. Soc.*, **97**, 1259 (1975); (d) G. D. Y. Sogah and D. J. Cram, *ibid.*, **98**, 3038 (1976).

(3) (a) C. N. R. S. Postdoctoral Fellow 1972–1973; (b) Public Health Service International Postdoctoral Research Fellow, 1971–1972; (c) African-American Institute, AFGRAD, Fellow.

(4) E. P. Kyba, G. W. Gokel, F. de Jong, K. Koga, L. R. Sousa, M. G. Siegel, L. Kaplan, G. D. Y. Sogah, and D. J. Cram, *J. Org. Chem.*, **42**, 4173 (1977).

(5) (a) G. W. Gokel, J. M. Timko, and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, 444 (1975); (b) F. de Jong, M. G. Siegel, and D. J. Cram, *ibid.*, 551 (1975); (c) M. Newcomb, G. W. Gokel, and D. J. Cram, *ibid.*, **96**, 6810 (1974).

(6) A. J. Isbell and D. W. Wood, *J. Chem. Eng. Data*, **75**, 575 (1962).

(7) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, 532 (1923).

(8) T. M. Harris and C. R. Hauser, *J. Org. Chem.*, **29**, 1391 (1964).

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

(10) (a) K. Weil and W. Kuhn, *Helv. Chim. Acta*, **27**, 1648 (1944); (b) W. M. Stanley and R. Adams, *Recl. Trav. Chim. Pays-Bas*, **48**, 1035 (1929); (c) H. J. Barber and K. Gaimster, *J. Appl. Chem.*, 2, 565 (1952).

(11) E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, T. L. Tarnowski, S. S. Moore, and D. J. Cram, *J. Am. Chem. Soc.*, **99**, 2564 (1977).

(12) E. D. Bergmann and I. Shahak, *J. Chem. Soc.*, 1418 (1959).

(13) We warmly thank Dr. G. W. Gokel for preparing these compounds.

(14) E. von Rudloff, *Can. J. Chem.*, **39**, 1860 (1961).

(15) References 2c and 2d and references cited therein.

(16) (a) A. McKillop, J. D. Hunt, E. C. Taylor, and F. Kienzle, *Tetrahedron Lett.*, 5275 (1970); (b) A. McKillop, B. Swain, and E. C. Taylor, *J. Am. Chem. Soc.*, **95**, 3340 (1973).

(17) L. J. Kaplan and D. J. Cram, unreported results.

Formation of the Lithium Enolate of *N,N*-Dimethyl-2-trimethylsilylacetamide. Reaction with Carbonyl Compounds and Epoxides

Richard P. Woodbury and Michael W. Rathke*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

Received October 7, 1977

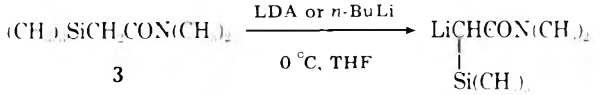
Addition of *N,N*-dimethyl-2-trimethylsilylacetamide to either lithium diisopropylamide or *n*-butyllithium generates the lithium enolate **4**, which was isolated as a white solid. The enolate is stable for several days in THF solution at 25 °C. Reaction of the enolate with aldehydes or ketones gives α,β-unsaturated amides. Reaction of the enolate with epoxides gives products corresponding to addition followed by 1,4 migration of the trimethylsilyl grouping from carbon to oxygen.

The lithium enolates of α-trimethylsilyl esters, **1**, react with aldehydes or ketones to give excellent yields of α,β-unsaturated esters.[1] We recently reported that enolates of *N,N*-dialkylamides have appreciably greater stability than the corresponding ester enolates.[2] Consequently, it seemed likely that enolates of α-trimethylsilylamides, **2**, would have synthetic advantages over **1**. We report here the results of a study on the formation and stability of **2**, together with information on its reactions with aldehydes, ketones, and epoxides.

1 **2**

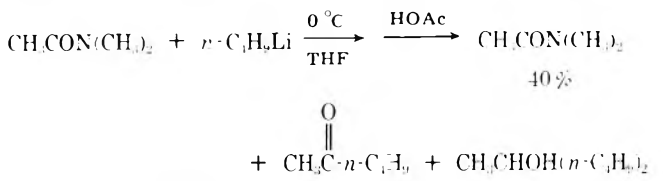
Results and Discussion

Formation and Isolation of Lithio-*N,N*-dimethyl-2-trimethylsilylacetamide. Addition of *N,N*-dimethyl-2-trimethylsilylacetamide, **3**, to THF solutions of lithium diisopropylamide, LDA, at 0 °C formed the lithium enolate, **4**.

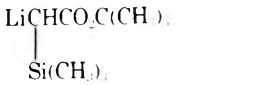


3 **4**

Quenching the reaction mixture with acetic acid gave a quantitative recovery of **3**. Surprisingly, the same results were obtained using *n*-butyllithium as the base. Presumably, the bulky trimethylsilyl grouping of **3** prevents addition of *n*-butyllithium to the carbonyl group. Thus, addition of the less hindered *N,N*-dimethylacetamide to solutions of *n*-butyllithium in THF gave predominantly addition products. The ability to generate **4** by means of *n*-butyllithium may be of synthetic advantage when amine-free solutions are required.

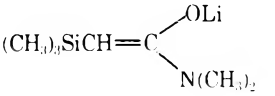


Solutions of **4** prepared by either method are stable for several days at room temperature. For example, quenching the reaction mixtures after 6 days returns 90–95% of **3**. In contrast, the corresponding ester enolate, **5**, must be generated at dry ice temperature and undergoes rapid self-condensation on warming to room temperature.[1a]



5

Addition of **3** to solutions of LDA in pentane gave a white precipitate assumed to be an amine complex of **4**. Removal of solvent and diisopropylamine under reduced pressure gave **4** as a white solid in 95% yield. Quenching weighed samples of **4** with glacial acetic acid gave 99–100% recovery of **3** (GLC). The solid turns brown on exposure to air; however, samples stored in sealed bottles have remained colorless for several months. The solid is soluble in dry pyridine and ^{1}H-NMR and ^{13}C-NMR spectra were obtained with the solution. For comparison, the ^{1}H-NMR[2] and ^{13}C-NMR data for the lithium enolate of *N,N*-dimethylacetamide, **6**, in pyridine solution



4

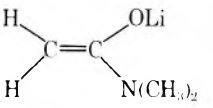
^{1}H NMR δ 2.90 (s, 1 H), 2.76 (s, 6 H), 0.33 (s, 9 H)

^{13}C NMR δ 174.69 (C_1), 56.00 (C_2), 39.34 (NCH_3), 2.35 ($SiCH_3$)

3

^{1}H NMR δ 2.80 (s, 3 H), 2.73 (s, 3 H), 1.96 (s, 2 H), 0.13 (s, 9 H)

^{13}C NMR δ 171.10 (C_1), 37.72 (NCH_3), 34.46 (NCH_3), 24.67 (C_2), 0.56 ($SiCH_3$)



6

^{1}H NMR: δ 3.16 (d, 1 H), 2.93 (d, 1 H), 2.63 (s, 6 H)

^{13}C NMR δ 169.39 (C_1), 55.99 (C_2), 39.53 (NCH_3)

were also obtained. We note that the two *N*-methyl groupings, which are nonequivalent in **3**, are equivalent by both ^{1}H and ^{13}C NMR in the enolates **4** and **6**. Presumably, this is indicative of a lessened resonance interaction of the nitrogen electron pair in the enolates. Considering the similarity of the spectra of **4** to those of **6** (for which an oxygen–lithium structure was proposed[2]) an oxygen–lithium bonded structure for **4** seems likely.

Reaction of 4 with Aldehydes and Ketones. THF solutions of **4** were prepared by reaction of **3** with LDA at 0 °C and treated with an equivalent amount of an aldehyde or ketone. Quenching after 15 min, followed by GLC analysis, gave the results shown in Table I. Good yields of α,β-unsaturated amides were obtained with ketones and with nonenolizable aldehydes. However, the enolizable aldehydes, acetaldehyde,

0022-3263/78/1943-1947$01.00/0

Table I. Reaction of Lithio-*N,N*-dimethyltrimethylsilylacetamide (4) with Carbonyl Compounds

Carbonyl	Registry no.	Product	Yield, %[a]
CH_3COCH_3	67-64-1	$(CH_3)_2C{=}CHCON(CH_3)_2$	86
CH_3COCH_3		$(CH_3)_2C{=}CHCON(CH_3)_2$	94 (82)[b]
c-$C_6H_{10}O$	108-94-1	c-$(C_6H_{10}){=}CHCON(CH_3)_2$	94 (85)
c-$C_6H_{10}O$		c-$(C_6H_{10}){=}CHCON(CH_3)_2$	92[c]
C_6H_5CHO	100-52-7	$C_6H_5CH{=}CHCON(CH_3)_2$	85
$C_6H_5CH{=}CHCHO$	14371-10-9	$C_6H_5CH{=}CHCH{=}CHCON(CH_3)_2$	90 (89)
CH_3CHO	79-07-0	$CH_3CH{=}CHCON(CH_3)_2$	10
CH_3CHO		$CH_3CH{=}CHCON(CH_3)_2$	9[b]
CH_3CH_2CHO	123-38-6	$CH_3CH_2CH{=}CHCON(CH_3)_2$	15

[a] GLC yield, isolated yields in parentheses. [b] Reaction at dry ice temperature. [c] 4 prepared by reaction of *n*-butyllithium with 3.

and propionaldehyde gave only negligible yields. In these cases, major amounts (70–80%) of the starting amide 3 were found in the quenched reaction mixture together with a variety of higher boiling products. Presumably, 4 reacts with these aldehydes mainly by enolization.

$$4 + RCH_2CHO \rightarrow RHC{=}CHOLi + 3$$

Attempts to overcome this problem by reaction of the aldehyde with 4 at dry ice temperature were unsuccessful. However, slightly higher yields of the corresponding α,β-unsaturated amide from the reaction with acetone were obtained at dry ice temperature (see Table I).

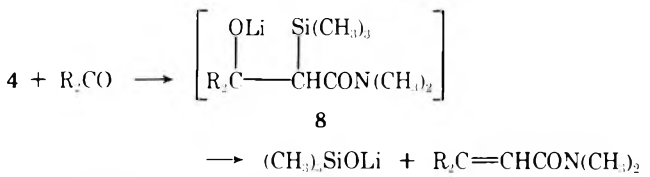
The reagent adds in a 1,2 fashion with the α,β-unsaturated aldehyde, *trans*-cinnamaldehyde.

$$4 + C_6H_5CH{=}CHO \rightarrow C_6H_5CH{=}CHCH{=}CHCON(CH_3)_2$$

7

The product (7) is a 60:40 mixture of *trans*-2,*trans*-4 and *cis*-2,*trans*-4 isomers. Consequently, although the stereochemistry of the original double bond is retained, there appears to be little stereoselectivity in the formation of the new double bond. Similar observations have been made for the corresponding reactions of aldehydes with the ester enolate 1.[1b] Finally, the reaction appears to work equally well with amine-free 4 prepared by reaction of 3 with *n*-butyllithium, as judged by the results obtained with cyclohexanone (Table I).

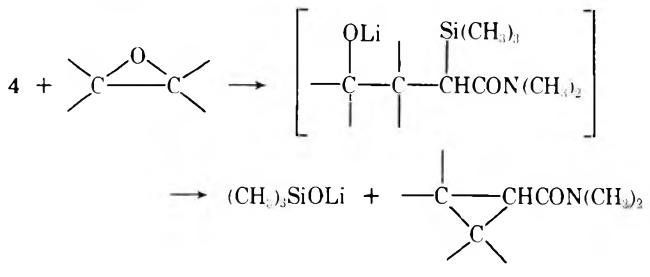
Reaction of 4 with Epoxides. Reaction of 4 with carbonyl compounds presumably occurs by an initial addition to the carbonyl grouping followed by a fast 1,2 elimination of lithium trimethylsilyloxide.[3] A similar sequence with epoxides would give cyclopropanes by a 1,3 elimination.[4] We note that such a reaction with the ester enolate 5 is unlikely to succeed be-



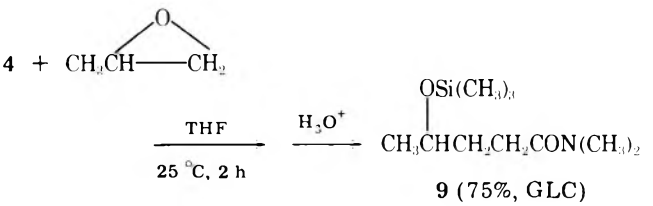
8

cause of the low reactivity of epoxides and the instability of 5.[1a]

A THF solution of 4 was treated with an equivalent amount



of propylene oxide. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by GLC analysis of quenched aliquots. After 2 h, starting material was consumed, and a single product, 9, was present



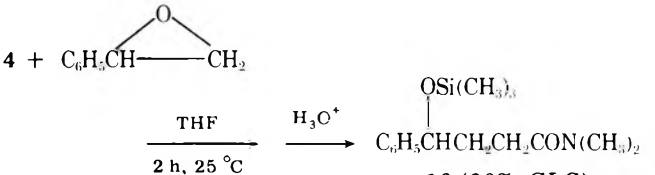
9 (75%, GLC)

in 75% yield. The structure of 9 was deduced from its ^{1}H-NMR spectrum and by synthesis from the corresponding alcohol.

$$CH_3CHOHCH_2CH_2CON(CH_3)_2 + (CH_3)_3SiCl \xrightarrow{Et_3N} 9$$

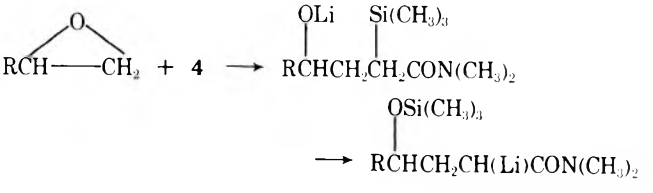
Refluxing reaction mixtures of 4 and propylene oxide for periods of several days led to a gradual loss of 9, but only much higher boiling products were formed with no evidence for cyclopropane compounds.

Reaction of 4 with styrene oxide proceeded similarly and a 90% yield (GLC) of the corresponding product, 10, was obtained.



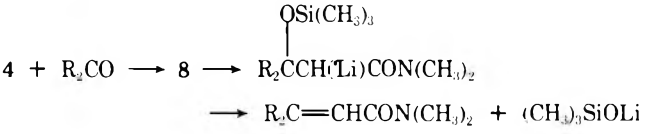
10 (90%, GLC)

These results are rationalized by assuming an initial addition of 4 at the less substituted side of the epoxide, followed by a 1,4 migration of silicon from carbon to oxygen to form the amide enolate, 11. That 11 is inert to cyclopropane formation



11

was confirmed by refluxing a reaction mixture containing 9 and LDA. Complete recovery of 9 was obtained by quenching after 12 h. Although the lack of cyclopropane formation is discouraging, we note that the results possibly represent the first observation of a 1,4 migration of silicon from carbon to oxygen[5] and also are suggestive that the reaction of 4 with



carbonyl compounds proceeds by initial 1,3 migration of silicon followed by elimination.

Experimental Section

^{1}H-NMR spectra were recorded on a Varian T-60 with Me_4Si internal standard. ^{13}C-NMR spectra were recorded with a Varian CFT-20 spectrometer using external D_2O for locking signal. GLC analyses were performed with a Varian 920 using 6 ft × 0.25 in. stainless steel columns packed with 3% carbowax 20M on non-acid-washed Chromosorb G support. *n*-Butyllithium (Aldrich) was titrated before use by the procedure of Watson and Eastham.[6] Diisopropylamine was distilled from CaH_2 and stored under nitrogen. THF was distilled from the sodium ketyl of benzophenone just prior to use. All other reagents were obtained commercially and used directly.

Preparation of Lithio-*N,N*-dimethyl-2-trimethylsilylacetamide (4). A 50-mL round-bottom flask equipped with magnetic stirrer, septum inlet, and mercury bubbler was flushed with argon and charged with 10 mL of pentane and 6.3 mL (10 mmol) of a solution of *n*-butyllithium in hexane. The flask was immersed in an ice–water bath and 1.4 mL (10 mmol) of diisopropylamine was injected. The cooling bath was removed, and after 5 min of stirring at 25 °C, volatile material was removed under vacuum. The white residue of LDA was dissolved in 20 mL of THF and the flask was immersed in an ice–water bath. *N,N*-Dimethyl-2-trimethylsilylacetamide,[7] 1.6 mL (10 mmol), was injected dropwise. After 10 min of stirring in the ice bath, the colorless solution of **4** was used directly for reaction with carbonyl compounds or epoxides.

Stability Studies of 4. A solution of **4** was prepared as described above and warmed to room temperature. Aliquots (0.5 mL) were removed periodically and quenched by addition of 0.02 mL of glacial acetic acid. The mixture was centrifuged and analyzed by GLC for recovered **3**. The recovery of **3** was 100% after 1 h, 95% after 3 days, and 92% after 6 days. The initially colorless reaction mixture was light yellow after 6 days.

Preparation of 4 for NMR Analyses. A 0.5 M solution of LDA in pentane was prepared as described above and maintained at 0 °C. *N,N*-Dimethyl-2-trimethylsilylacetamide (1.6 mL, 10 mmol) was added dropwise and a white precipitate formed immediately. After 15 min of stirring at 0 °C, the solvent and amine were removed under vacuum to obtain a white residue of **4** weighing 1.57 g (95% yield). The solid was dissolved in 10 mL of dry pyridine and NMR spectra were obtained.

Reaction of 4 with Aldehydes and Ketones. A solution of **4** (10 mmol) in THF prepared as described above and maintained at ice–water temperature was treated with 10 mmol of the aldehyde or ketone. The solution was then warmed to 25 °C and allowed to stir for 15 min. At the end of this period, the reaction mixture was quenched by addition of 5 mL of 2 M HOAC. The separated organic layer was analyzed by GLC for α,β-unsaturated amide. The solvent was stripped off and the product was isolated. The following α,β-unsaturated amides were prepared. *N,N*-Dimethyl-3-methyl-2-butenoamide (from **4** with acetone): ^{1}H NMR (CCl_4, internal Me_4Si) δ 5.63 (s, 1 H), 2.87 (s, 6 H), 1.83 (d, 3 H), 1.77 (d, 3 H). *N,N*-Dimethyl-2-cyclohexylideneacetamide (from **4** with cyclohexanone): ^{1}H NMR (CCl_4 internal Me_4Si) δ 5.35 (s, 1 H), 2.88 (s, 6 H), 2.54 (m, 2 H), 2.10 (m, 2 H), 1.57 (m, 5 H); IR (CCl_4) 1640 (C=O), 1625 cm^{-1} (C=C). *N,N*-Dimethyl-5-phenyl-*cis*-2,*trans*-4-pentadienoamide (from **4** with *trans*-cinnamaldehyde): mp 39–41 °C (lit.[8] mp 38–40 °C); ^{1}H NMR (CCl_4 internal Me_4Si) δ 7.8 (d, d, 1 H, J = 15, 11 Hz), 7.3 (m, 5 H), 6.0 (d, d, 1 H, J = 11, 1 Hz), 3.1 (bs, 6 H). *N,N*-Dimethyl-5-phenyl-*trans*-2,*trans*-4-pentadienoamide (from **4** with *trans*-cinnamaldehyde): mp 98–100 °C (lit.[8] mp 100–102 °C); ^{1}H NMR (CCl_4, internal Me_4Si) δ 7.4 (m, 6 H), 6.9 (m, 2 H), 6.45 (d, 1 H, J = 15 Hz), 3.1 (bs, 6 H). The products from reaction of **4** with benzaldehyde, acetaldehyde, and propanal were identified by comparison with authentic samples (GLC retention times).

Reaction of 4 with Propylene Oxide. A solution of **4** (10 mmol) in THF was prepared as described above and maintained at 25 °C. Propylene oxide (0.76 mL, 11 mmol) was injected and the solution was stirred for 2 h. The reaction mixture was then quenched with 0.6 mL (11 mmol) of glacial acetic acid. GLC analysis revealed the only traces of **3** and the presence of *N,N*-dimethyl-4-trimethylsiloxypentanoamide (**9**) in 75% yield. Pure samples of **9** were obtained by preparative GLC: ^{1}H NMR (CCl_4, internal Me_4Si) δ 3.81 (m, 1 H), 2.94 (s, 3 H), 2.84 (s, 3 H), 2.21 (t, 2 H), 1.60 (m, 2 H), 1.10 (d, 3 H), 0.10 (s, 9 H).

Reaction of 4 with Styrene Oxide. Using the procedure described above for propylene oxide, GLC analysis indicated the formation of *N,N*-dimethyl-4-phenyl-4-trimethylsiloxybutanoamide (**10**) in 90% yield. Pure samples of **10** were obtained by preparative GLC: ^{1}H NMR (CCl_4, internal Me_4Si) δ 7.16 (s, 5 H), 4.75 (t, 1 H), 2.94 (s, 6 H), 2.27 (t, 2 H), 1.94 (m, 2 H), 0.10 (s, 9 H); IR (CCl_4) 1645 cm^{-1} (C=O).

Acknowledgment is made to the National Science Foundation for partial support of this work.

Registry No.—**3**, 23184-28-3; **4**, 65378-64-5; **6**, 56579-98-7; **9**, 65378-65-6; **10**, 65378-66-7; *N,N*-dimethyl-3-methyl-2-butenoamide, 42902-94-3; *N,N*-dimethyl-2-cyclohexylideneacetamide, 65378-67-8; *N,N*-dimethyl-5-phenyl-*cis*-2,*trans*-4-pentadienoamido, 65378-68-9; *N,N*-dimethyl-5-phenyl-*trans*-2,*trans*-4-pentadienoamido, 21497-23-4; propylene oxide, 75-56-9; styrene oxide, 96-09-3.

References and Notes

(1) (a) S. L. Hartzell, D. F. Sullivan, and M. W. Rathke, *Tetrahedron Lett.*, 1403 (1974); (b) K. Shimoji, H. Taguchi, K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **96**, 1620 (1974).
(2) R. P. Woodbury and M. W. Rathke, *J. Org. Chem.*, **42**, 1688 (1977).
(3) Alcohol products analogous to **8** have been isolated after short reaction times (at −78 °C) of the ester enolate **5** with cyclohexanone.[1a]
(4) Reaction of epoxides with phosphorus ylides analogous to **4** at 200 °C is reported to give cyclopropanes: D. B. Denny, J. J. Vill, and M. J. Boskin, *J. Am. Chem. Soc.*, **84**, 3944 (1962).
(5) It is, of course, possible that the rearrangement is an intermolecular process. We have no evidence bearing on this point.
(6) S. C. Watson, and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967).
(7) *N,N*-Dimethyl-2-trimethylsilylacetamide was prepared as described by: M. W. Rathke and R. P. Woodbury, *J. Org. Chem.*, **42**, 3961 (1977).
(8) D. H. R. Barton, G. Hewitt, and P. G. Sammes, *J. Chem. Soc. C*, **1**, 16 (1969).

Preparation of Simple Chiral Allenes. Reaction of Propargylic Carbamates with Lithium Dialkylcuprates

W. H. Pirkle* and Charles W. Boeder

Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

Received September 19, 1977

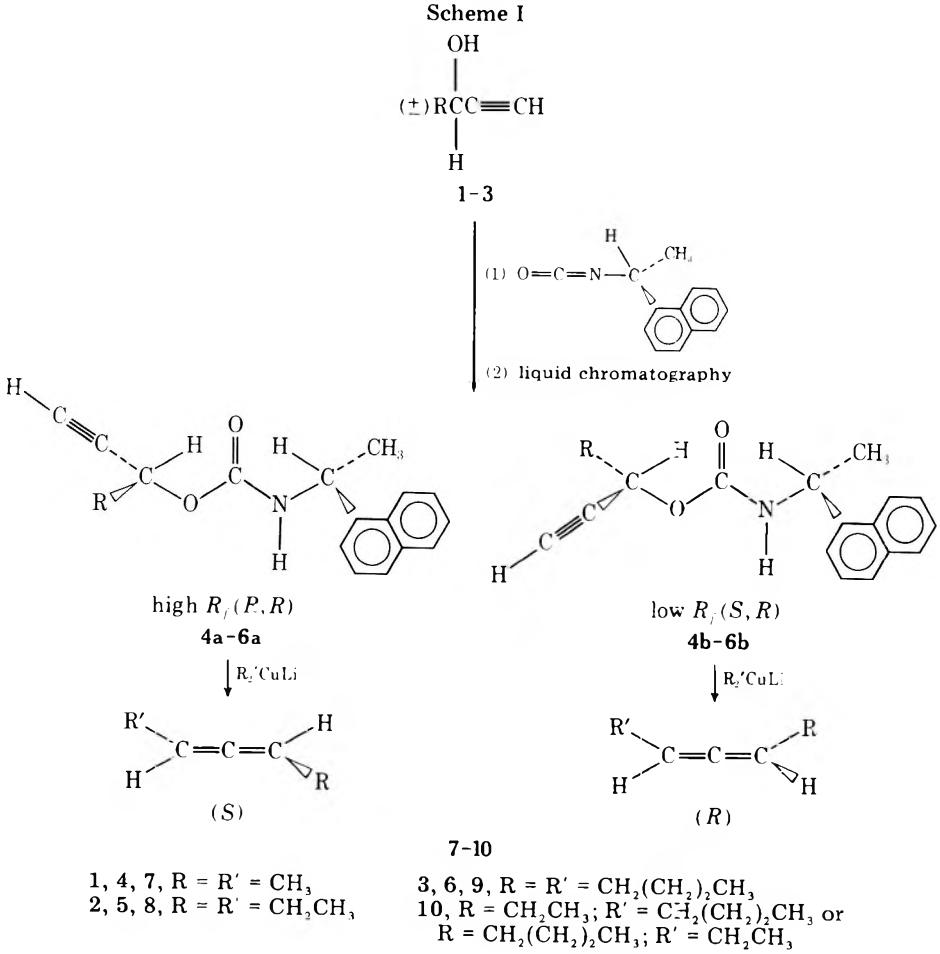
The diastereomeric carbamates derived from (*R*)-1-[1-naphthyl]ethyl isocyanate and racemic secondary propargylic alcohols such as 1-butyn-3-ol, 1-pentyn-3-ol, or 1-heptyn-3-ol are readily separable by multigram HPLC. Once separated, these diastereomers react with dialkylcuprates at low temperature to afford 1,3-dialkylallenes in high yields and with substantial enrichment (60–80% ee) in one enantiomer. Both enantiomers of the allene may be obtained; absolute configurations are predictable.

In the absence of additional functional "handles" for resolution, chiral allenes of high enantiomeric purity are not generally obtainable.[1] For example, partial hydroboration of a racemic allene with an asymmetric dialkylborane affords but modest enantiomeric enrichment of the residual allene.[2] While cycloelimination reactions leading to chiral allenes have been reported,[3,4] resolution of the chiral precursors may be tedious and the resulting allenes may be of but low enantiomeric purity.[3] Corey and Borden have prepared 1,3-di-*tert*-butylallene of high enantiomeric purity from a chiral propargyl alcohol.[5] However, this reaction, which also affords substantial amounts of an achiral acetylene, has not been shown to be generally useful as a preparative method for allenes. A preparative procedure of documented generality has been reported by Crabbé; the reaction of propargylic acetates with lithium dialkylcuprates efficiently affords a variety of allenes.[6,7] Importantly, Crabbé showed in one instance that a chiral acetate afforded an optically active allene, albeit in modest enantiomeric purity. This reaction can be considerably improved; the present report describes several such modifications that convert Crabbé's original approach to a simple and convenient method for efficiently obtaining either enantiomer of a chiral allene in relatively high enantiomeric purity.

Scheme I outlines the synthesis of enantiomerically enriched 1,3-dialkylallenes starting from racemic propargylic alcohols. The diastereomeric carbamates derived from racemic propargylic alcohols such as **1–3** and (*R*)-1-[1-naphthyl]ethyl isocyanate are readily separable by multigram HPLC. After separation, lithium dialkylcuprates react with these diastereomers at −78 °C to afford chiral allenes having a substantial degree of enantiomeric enrichment. Our modification simplifies the resolution of the chiral precursor, makes it unnecessary to retrieve the chiral alcohol from the resolving agent, and obviates the need to convert the alcohol to acetate. Use of reaction temperatures lower than those used by Crabbé results in enhanced enantiomeric purities.

For example, high R_f (*R*,*R*) carbamate diastereomer **6a**

Scheme I



1, **4**, **7**, R = R′ = CH_3
2, **5**, **8**, R = R′ = CH_2CH_3
3, **6**, **9**, R = R′ = $CH_2(CH_2)_2CH_3$
10, R = CH_2CH_3; R′ = $CH_2(CH_2)_2CH_3$ or R = $CH_2(CH_2)_2CH_3$; R′ = CH_2CH_3

0022-3263/78/1943-1950$01.00/0

Table I. Synthesis of Chiral 1,3-Dialkylallenes by the Reaction of Lithium Dialkylcuprates with Propargyl Esters at −78 °C

Lithium cuprate	Registry no.	Ester	Registry no.	Allene	Registry no.	Inverse addition $[\alpha]^{25}_D$	Inverse addition % yield[a]/% ee[g]	Normal addition $[\alpha]^{25}_D$	Normal addition % yield/% ee
Di-*n*-butyl	24406-16-4	**6a**	65391-25-5	(*S*)-**9**	65253-19-2	+34.7 (5, $CHCl_3$)	78/51	+54.5 (3.6, $CHCl_3$)	76/80
		6b	65337-07-7	(*R*)-**9**	65253-20-5	−33.4 (7, $CHCl_3$)	75/49	−51.2 (5.5, $CHCl_3$)	76/75
		6b		(*R*)-**9**		−2.5 (3.3, $CHCl_3$)	77/5[b]		
		11	65252-17-0	(*S*)-**9**		+26.2 (5, $CHCl_3$)	60/39		
		12	65253-18-1	(*S*)-**9**		+30.5 (1.1, $CHCl_3$)	73/45		
		5a	65337-08-8	(*S*)-**10**	20431-70-3	+27.9 (4.6, $CHCl_3$)	74/34	+42.4 (4.2, $CHCl_3$)	77/52
		5b	65335-09-9	(*R*)-**10**	65337-12-4	−49.4 (5, $CHCl_3$)	79/61	−40.2 (4.2, $CHCl_3$)	79/50
Diethyl	38297-20-0	**5a**		(*S*)-**8**	20431-62-3	+62.8 (4, $CHCl_3$)	73/60	+33.8 (2, $CHCl_3$)	72/33
		5b		(*R*)-**8**	34862-66-3	−62.6 (5.1, $CHCl_3$)	71/60	−28.0 (1.2, $CHCl_3$)	72/27
		5b		(*R*)-**8**				−26.4 (1, $CHCl_3$)	74/26[c]
		6a		(*S*)-**10**		+53.2 (4.3, $CHCl_3$)	70/66	+21.4 (3.5, $CHCl_3$)	72/26
		6b		(*R*)-**10**		−27.7 (4.3, $CHCl_3$)	73/34	−27.4 (4.7, $CHCl_3$)	73/34
Dimethyl	15681-48-8	**4a**[d]	65337-10-2	*e*					
		6b		*e*					
		13	65337-11-3	(*R*)-**7**	20431-56-5	−29.7 (2.6, Et_2O)	30/19[d,f]		
Di-*tert*-butyl	23402-75-7	**6a**		*e,f*					
1-Pentynyl(*n*-butyl)	39697-41-1	**6a**		(*S*)-**9**					<15/-[e,f]
SPh(*n*-butyl)	53128-68-0	**6b**		(*R*)-**9**		−53.4 (1.6, $CHCl_3$)	20/82[g]		

[a] Determined by GLPC. [b] Reaction time of 3 h at −30 to −40 °C. [c] Carbamate at −78 °C when added. [d] Di-*n*-butyl ether used as solvent. [e] Recovered starting material. [f] Reaction time of 18 h. [g] Reaction time of 24 h.

(relative and therefore absolute configurations assigned by NMR differences between **6a** and **6b**[8]) reacts with lithium di-*n*-butylcuprate at −78 °C to afford (*S*)-(+)-1,3-di-*n*-butylallene whereas (*S,R*) diastereomer **6b** similarly affords (*R*)-(−)-1,3-di-*n*-butylallene. Enantiomeric purities of 75–80% have been attained. Table I summarizes the yields and estimated enantiomeric purities[9] for allenes prepared in the course of this study.

An important and unanticipated finding is that the optical yield of the reaction depends upon the order in which reagents are mixed and that the optimum mixing order is not the same for all cuprates. This "mixing order" effect[12] on allene enantiomeric purity is greater in magnitude than the small but real variations in enantiomeric purity encountered between two diastereomers using a given mixing order.[13] The difference in stereospecificity between a pair of diastereomers was most pronounced during the "crossing" experiments that led to 3,4-nonadiene. That such differences may occur is clear in principle. However, we presently have no insight into the actual origin of these differences. Indeed, there is little detailed understanding of the mechanism of this multistep allene-forming reaction.[6]

It is evident from data in Table I that the nature of the leaving group also influences the enantiomeric yield of the reaction. Using similar conditions, the enantiomeric purities of the allenes derived from inverse addition of lithium di-*n*-butylcuprate to the tosylate (**11**), acetate, (**12**), and carbamate(s) (**6a** (or **6b**)), respectively of resolved 1-heptyn-3-ol, were observed to increase in the order 39, 45, and 51% (or 49%). It would appear that poorer leaving groups afford higher enantiomeric yields. Similarly, less reactive cuprates may also afford higher enantiomeric yields.[14] For example, the mixed lithium thiophenoxy(*n*-butyl)cuprate did react with carbamate **6b** to afford 1,3-di-*n*-butylallene of greater enantiomeric purity (82% ee) than that obtained using optimal conditions with di-*n*-butylcuprate (76% ee). However, the yield of allene was much reduced (20%) and most of the starting carbamate was recovered. Lithium dimethylcuprate was also found to be unreactive toward propargyl carbamate **4a.** However, this reagent does react with the tosylate (**13**) of (*S*)-1-butyn-3-ol to afford (*R*)-(−)-1,3-dimethylallene albeit in low yield and enantiomeric purity.

In summary, racemic secondary propargylic alcohols can be readily resolved as diastereomeric carbamates by multigram HPLC. These carbamates react with lithium dialkylcuprates at −78 °C to afford chiral allenes of high enantiomeric purity and in high yield. This reaction sequence represents a simple and convenient two-step synthesis of chiral allenes from readily available starting materials.

Experimental Section

Cuprous iodide was purified by a method previously described.[15] Ethyllithium was prepared in diethyl ether in a manner analogous to Gilman's preparation of *n*-butyllithium.[16] *n*-Butyllithium in hexane was obtained from Ventron Corp. Racemic propargylic alcohols were either prepared by the addition of the appropriate aldehyde to ethynylmagnesium bromide[17] or were purchased from Farchan Acetylenes. Lithium dialkylcuprates were prepared as previously described: dimethyl,[18] diethyl,[18] di-*n*-butyl,[18] di-*tert*-butyl,[19] thio-

phenoxy (*n*-butyl),[19] and 1-pentynyl (*n*-butyl).[20] Alcohols (*S*)-**1** and (*R*)-**3** were prepared from **4b** and **6a** respectively by trichlorosilane cleavage.[21]

Carbamates 4–6. These diastereomers were prepared and separated as previously described.[8] Chromatographic separation of the propargylic carbamate diastereomers is general and facile, increasing in ease for higher members of the series.

(*R*)-1-Heptynyl 3-Acetate (12). To a cold (0 °C) stirred solution of (*R*)-**3** (4 mmol) in diethyl ether (10 mL) was added *n*-butyllithium in hexane (4 mmol). After stirring for 10 min, acetyl chloride (4.2 mmol) was added dropwise and the mixture was stirred for 2 h. The reaction mixture was extracted with 10% $NaHCO_3$ (2 × 10 mL) and dried ($MgSO_4$) and the ether was removed under reduced pressure to afford **12** (95%) as a colorless liquid: NMR (CCl_4) δ 0.9 (triplet, 3, CH_3), 1.4 (multiplet, 4, $CH_2CH_2CH_2CH_3$), 1.7 (multiplet, 2, $HOCHCH_2$), 2.0 (singlet, 3, CO_2CH_3), 2.27 (doublet, 1, C≡CH), 5.2 (dt, 1, HOCH).

Allenes. All allenes were prepared by either (or both) of the procedures described below for the preparation of 1,3-di-*n*-butylallene.

A. Normal Addition. Carbamate **6a**, 1.04 g (3.5 mmol), in diethyl ether (25 mL) was added dropwise over a 10-min period to a stirred solution of di-*n*-butylcuprate (3.5 mmol) in diethyl ether (15 mL) cooled with acetone–dry ice. After being stirred for an additional 7 h at −78 °C, the cooling bath was removed and the reaction mixture was allowed to come to 0 °C, quenched with saturated aqueous NH_4Cl (20 mL), and stirred for 15 min to allow the copper salts to precipitate. The mixture was filtered and the organic layer was separated, washed with saturated aqueous NH_4Cl (20 mL), dried ($MgSO_4$), and concentrated at reduced pressure. Molecular distillation of the residue afforded 0.4 g (76%) of (*S*)-(+)-1,3-di-*n*-butylallene: $[\alpha]^{25}_D$ +54.5° (3.6, $CHCl_3$); IR (film) 1945 cm^{-1} (allene); NMR)ccl_4) δ 0.9 (triplet, 6, CH_3), 1.3 (multiplet, 8, $CH_2CH_2CH_2CH_3$), 1.95 (multiplet, 4, C=CCH_2), 4.95 (quintet, 2, HC=C).

B. Inverse Addition. Lithium di-*n*-butylcuprate (3.5 mmol) in diethyl ether (15 mL) cooled to −78 °C was added portionwise over 5 min to cold (−78 °C) stirred solution of carbamate **6a**, 1.08 g (3.5 mmol). The reaction mixture was stirred for 7 h at −78 °C and allene was isolated by a workup identical to that above. (*S*)-(+)-1,3-Di-*n*-butylallene, 0.39 g (74%), $[\alpha]^{25}_D$ +34.7° (5, $CHCl_3$), was obtained.

1,3-Dimethylallene (7). This allene was prepared from **13** as described in Table I. The allene was identical to authentic material by GLPC and gave the same methoxymercuration adduct.[2]

1,3-Diethylallene (8). This allene was prepared in various yields and enantiomeric purities as shown in Table I: IR (film) 1945 cm^{-1} (allene); NMR (CCl_4) δ 1.0 (triplet, 6, CH_3), 2.0 (multiplet, 4, CH_2CH_3), 5.1 (quintet, 2, HC=C).

3,4-Nonadiene (10). This allene was prepared in various yields and enantiomeric purities as shown in Table I: IR (film) 1955 cm^{-1} (allene); NMR (CCl_4) δ 0.97 (triplet, 6, CH_3), 1.32 (multiplet, 4, $CH_2CH_2CH_2CH_3$), 1.9 (multiplet, 4, C=CCH_2), 4.8 (quintet, 2, HC=C).

Acknowledgment. This work has been partially funded by grants from the National Science Foundation and the National Institutes of Health.

Registry No.—(±)-**1**, 65337-13-5; (±)-**2**, 65253-21-6; (±)-**3**, 51586-58-4; (*R*)-**3**, 51703-65-2; (*R*)-1-[1-naphthyl]ethyl isocyanate, 42340-98-7.

References and Notes

(1) For a review of synthetic approaches to chiral allenes, see R. Rossi and P. Diversi, *Synthesis*, 25 (1973).
(2) W. L. Waters, W. S. Linn, and M. C. Caserio, *J. Am. Chem. Soc.*, **90**, 6741 (1968); W. R. Moore, H. W. Anderson, and S. D. Clark, *ibid.*, **95**, 835 (1973).
(3) J. M. Walbrick, J. W. Wilson, and W. M. Jones, *J. Am. Chem. Soc.*, **90**, 2895 (1968).
(4) R. J. Convers, PhD Thesis, University of Illinois, Urbana, Ill., 1974.
(5) W. T. Borden and E. J. Corey, *Tetrahedron Lett.*, 313 (1969).
(6) J. L. Luche, E. Barreiro, J. M. Dollat, and P. Crabbé, *Tetrahedron Lett.*, 4615 (1975).
(7) It has been recently reported [M. M. Midland, *J. Org. Chem.*, **42**, 2650 (1977)] that trialkylboranes act upon acetylide ions derived from propargylic acetates to efficiently afford allenes. The stereochemistry of this reaction has not yet been reported.
(8) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **42**, 1839 (1977).
(9) Some of the estimations of enantiomeric purity are based upon the assumption that all simple chiral allenes should have approximately the same maximum molecular rotation. This assumption seems reasonable on the basis of Brewster's model of optical activity.[10] Brewster's calculation of the maximum specific rotation to be expected for 1,3-dimethylallene ($[\alpha]_D$ +174°) receives considerable support from our recent experimental determination ($[\alpha]_D$ ±157°) of this rotation.[11] Experimentally determined maximum molecular rotations for 1,3-dimethylallene and 1,3-diethylallene are 107 and 100°, respectively.[11] For the purpose of this paper, we have used ±100° as the molecular rotation expected for an enantiomerically pure 1,3-di-*n*-alkylallene.
(10) J. H. Brewster, "Topics in Stereochemistry", Vol. 2, Wiley, New York, N.Y., 1967.
(11) W. H. Pirkle and C. W. Boeder, *J. Org. Chem.*, **42**, 3697 (1977).
(12) While the origin of this effect cannot be stated with certainty, it may reflect different solution structures for the cuprates.
(13) This small difference between allene enantiomeric purities suggests that structural variation of the chiral amine portion of the carbamate could lead to allenes having still greater enantiomeric purities.
(14) Since the degree of stereospecificity shown by a reaction is a consequence of the energy difference between the diastereomeric transition states, very low activation energies preclude large energy differences between the alternate pathways. When both activation energies are large, the difference between the pathways may be, but is not necessarily, large enough to afford significant stereoselectivity.
(15) G. B. Kauffman and L. A. Teter, *Inorg. Synth.*, 7, 9 (1963).
(16) H. Gilman, "Organic Reactions", Vol. 8, Wiley, New York, N.Y., 1954, p 285.
(17) L. Skattebøl, E. R. H. Jones, and M. C. Whiting, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1967, p 792.
(18) C. R. Johnson and G. A. Dutra, *J. Am. Chem. Soc.*, **95**, 7777 (1973).
(19) G. H. Posner, C. E. Whitten, and J. J. Sterling, *J. Am. Chem. Soc.*, **95**, 7788 (1973).
(20) J. P. Marino and D. M. Floyd, *J. Am. Chem. Soc.*, **96**, 7138 (1974).
(21) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **42**, 2781 (1977).

Preparation of *exo*-Tricyclo[3.3.2.0^{2,4}]decan-9-one and Related Compounds

Ioannis M. Takakis and William C. Agosta*

Laboratories of The Rockefeller University, New York, New York 10021

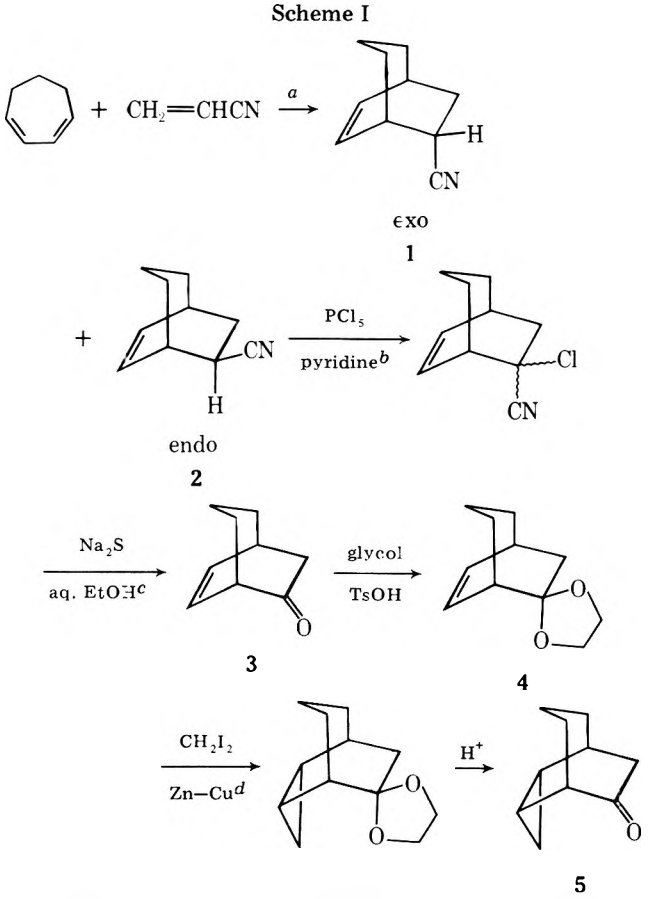
Received October 17, 1977

Synthesis of *exo*-tricyclo[3.3.2.0^{2,4}]decan-9-one (**5**) through efficient (92%) Simmons–Smith reaction of olefinic ketal **4** is described. Efforts to extend this work to ketals **16** and **17** led unexpectedly to selective cyclopropanation anti to the ketal function and formation of **27** and **28**, respectively. Improvements in the preparation of various known intermediates are reported, including a doubling of the yield (to 50%) in oxidation of cycloheptatriene to tropone.

As part of a study of the photochemistry of tricyclic ketones we required *exo*-tricyclo[3.3.2.0^{2,4}]decan-9-one (**5**). In this report we describe convenient preparation of this substance along with other related synthetic transformations. Many of the compounds involved have been recorded previously, but we were able to make material improvements in some earlier preparations, provide two stereochemical assignments, and also uncover two examples of the Simmons–Smith reaction that specifically furnish an unexpected stereoisomer. There have been recent publications in related

0022-3263/78/1943-1952$01.00/0

Scheme I

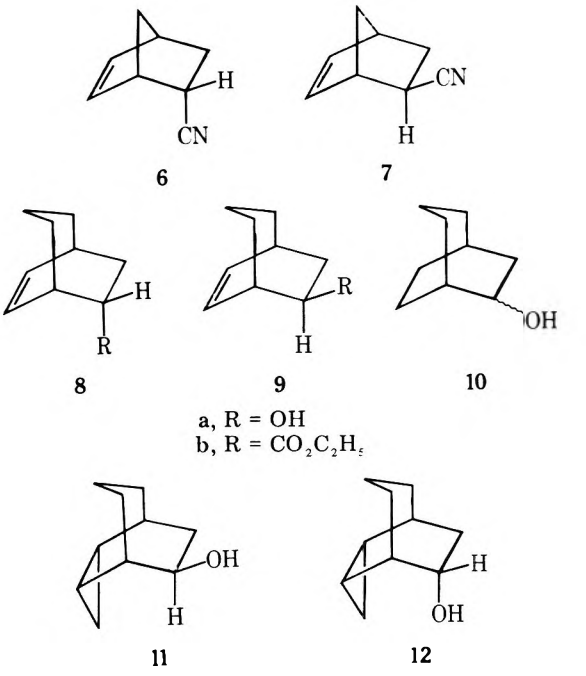


[a] Reference 3. [b] Reference 6. [c] Reference 12. [d] References 14 and 19.

areas,[1,2] and our observations may be of some general interest. The preparation of **5** is summarized in Scheme I, and only those steps requiring specific comment are discussed below.

We have separated and characterized the two diastereomeric Diels–Alder adducts **1** and **2**, previously known only as a mixture,[3] and assigned their stereochemistry on the basis of differences in their NMR spectra. The olefinic resonance in one (assigned as **2**) appears at δ 6.32 (m, 2 H), while in the other (assigned as **1**) the two protons are shifted downfield and separated, 6.42 and 6.52 (dd, $J_1 = J_2 = 8$ Hz, 1 H, for each signal). A similar spectral difference is seen in the related *endo*- and *exo*-5-norbornene-2-carbonitriles (**6** and **7**, respectively), where the olefinic protons of **6** appear downfield ~0.1 ppm relative to their positions in **7**.[4] In support of this assignment for **1** and **2** is the further observation that the proton α to the cyano group resonates at 2.96 in **1** and at 2.76 in **2**. In the related alcohols the carbinyl proton of **8a** appears 0.17 ppm downfield from that of **9a**. Studies of other bicyclic systems have shown that the relative chemical shift of such protons in epimers is a useful and reliable indication of stereochemistry.[5]

Previous work had shown that for the alcohols **8a** and **9a**, the ethyl esters **8b** and **9b**, and the saturated alcohols **10** the exo isomer (as **8a** and **8b**) is the more stable in each case.[6,7] Attempts to confirm the configurational assignment of **1** and **2** by base-catalyzed equilibration were thwarted, however, since the observed equilibrium mixture contained 50 ± 1% of each isomer. It has been suggested that the controlling factor in determining the relative stability of the two isomers of **10** is the sizable interaction of the hydroxyl group of the endo isomer with hydrogens of the trimethylene bridge.[7] In models it is clear that such interactions in **2** should be much less severe than in **9a** or **9b** because of the cylindrical symmetry of the cyano group. One final point of interest in **1** and **2** concerns

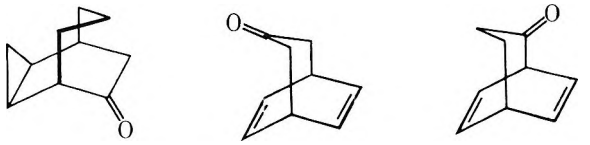


the applicability of the Alder–Stein rules[8] to the Diels–Alder reaction in which they are formed. Alder previously pointed out[9] that the rules worked poorly for the addition of cyclic dienes to acrylonitrile, since the reaction with cyclopentadiene gave **6** and **7** in the ratio 60:40,[10] and since the two adducts with 1,3-cyclohexadiene were formed in essentially equal amounts. This trend is continued in the reaction of acrylonitrile with 1,3-cycloheptadiene; the configurational assignment made above leads to the conclusion that the epimer predicted by the Alder–Stein rules (**1**) is actually the minor product in this case (**1:2** ~ 35:65).

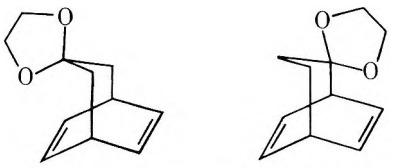
The mixture of nitriles **1** and **2** was converted to ketone **3**[6] through chlorination with phosphorus pentachloride[11] and subsequent hydrolysis in aqueous alcoholic sodium sulfide.[12] In our hands these more recently developed conditions for hydrolysis of the chloronitrile were preferable to the previously employed[6] potassium hydroxide in aqueous dimethyl sulfoxide. In line with observations in related systems,[1,13,14] neither **3** nor the major alcohol formed on its reduction under a variety of conditions, **9a**,[6] was reactive in the Simmons–Smith reaction. Even under forcing conditions, for example, **9a** yielded only a minute amount of **11**.[15] Only in **8a** can the hydroxyl group facilitate cyclopropanation,[14,16,17] and indeed **8a**[6] did react satisfactorily to form **12**. Unfortunately, however, this unsaturated alcohol is not readily available from **3**.[6] A useful solution to this practical problem involved conversion of **3** to its ethylene ketal **4**, which underwent smooth, stereoselective cyclopropanation in 92% yield on treatment with a large excess of zinc–copper couple and methylene iodide.[18] The specific procedure used, which is very convenient since it requires only commercially available zinc–copper, was based on earlier, detailed studies.[19]

Reduction of tricyclic ketone **5** with sodium in alcohol or with lithium aluminum hydride in ether furnished **11** and **12** in the ratio ~3:1, and this correlation provides proof that the inefficient cyclopropanation of **9a** mentioned above proceeds by exo attack.

The efficacious Simmons–Smith reaction of **4**, along with the earlier observations noted above, suggested that an appropriate functional group located on the three-carbon bridge would direct and accelerate cyclopropanation of a bicyclo[3.2.2]nonene from the endo side and thus provide a synthetic approach to the tricyclic ketone **13**. This reasoning led to our preparation of the two isomeric bicyclononenones **14** and **15**, ketones previously described by Baker,[21] and explo-



13 14 15

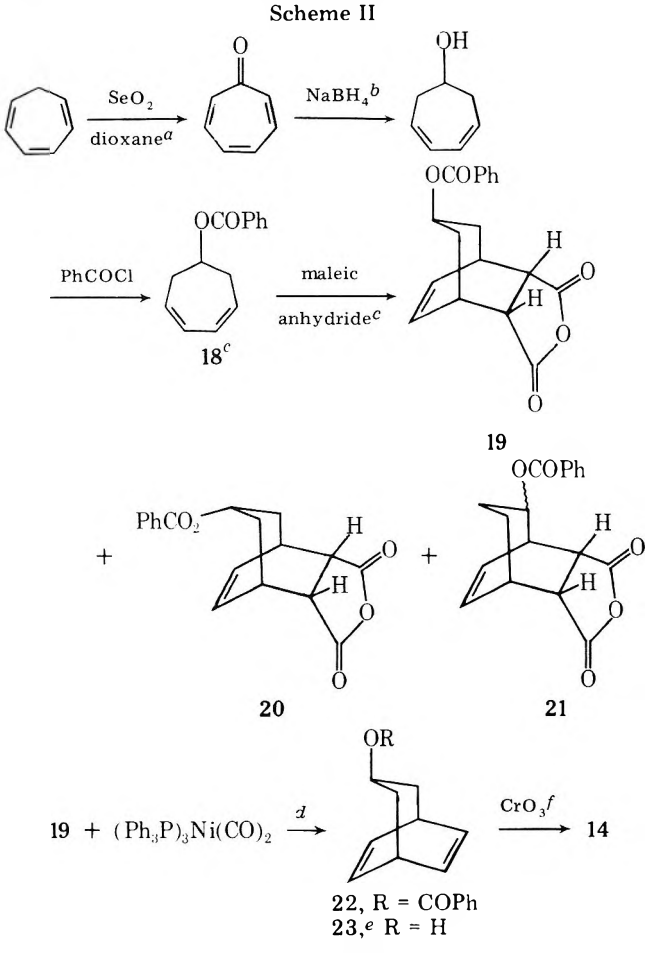


16 17

ration of the Simmons–Smith reaction with the derived ketals **16** and **17**. Preparation of these compounds is shown in Scheme II and makes use of intermediates reported by Baker[21] and others as indicated. Again, only those transformations requiring special comment are discussed below.

The selenium dioxide oxidation of cycloheptatriene to tropone was originally reported to give a 25% yield,[22] and this or a lower yield has been obtained subsequently by others.[21,23] We have reliably obtained a 50% yield in this transformation through use of purified dioxane as solvent, vigorous stirring, and careful control of the reaction temperature at 90 ± 0.5 °C for 21 h; the improvement in yield should enhance the value of this convenient one-step preparation of tropone. We have confirmed the interesting observation first made by Baker[21] that addition of maleic anhydride to **18** furnishes not only the expected adducts **19** and **20**, but also the isomeric adduct **21**. Transformation of one of these adducts (**19**) to dienone **14** is

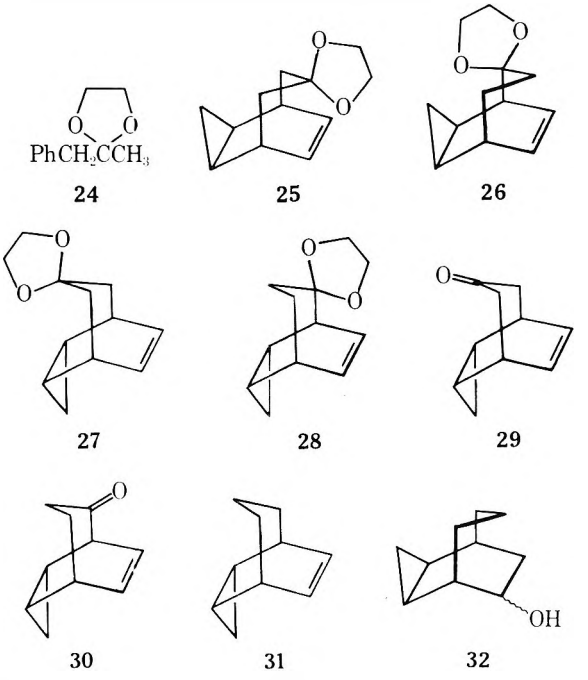
Scheme II



[a] References 21, 22, and 23; see text. [b] Reference 23. [c] Reference 21. [d] Reference 24. [e] From saponification of **22**. [f] Reference 26.

illustrated in Scheme II. For preparative purposes these reactions were also performed on the mixture **19–21** to give both **14** and **15**. Various of the individual steps were carried out on purified materials derived from one or the other of the individual benzoates **19–21**, and the resulting intermediates were identical with those found by Baker.[21] In place of the previously used[21] electrolytic oxidative bisdecarboxylation of these ester anhydrides **19–21**, we found it advantageous to treat them with dicarbonylbis(triphenylphosphine)nickel,[24] a procedure which yielded 92–97% of the desired diene benzoates (as **22**) on a 5-g scale. Ketalization of **14** required particular attention; either excessive acid or prolonged reaction times led to increasing amounts of the ketal of phenylacetone (**24**), through opening of the bicyclic system and aromatization. Mild conditions, either with a quite limited amount of *p*-toluenesulfonic acid or alternatively with pyridinium chloride as catalyst, gave ketal **16** as desired. As is mechanistically reasonable, no similar problem was encountered in ketalization of **15**.

Cyclopropanation of ketals **16** and **17** proceeded to give products originally presumed to be the endo cyclopropanes **25** and **26** respectively. This view was reinforced by the finding that the alcohol **23** failed to undergo the Simmons–Smith reaction under comparable conditions. This latter result seemed reasonable, since the expected dominant conformation of **23** holds the hydroxyl group equatorial and away from both double bonds, as shown. In the reactive ketals, however, the two half-chair conformations of the three-carbon bridge are



equivalent, and one of the double bonds will always have a nearby oxygen atom to facilitate cyclopropanation. The apparent wisdom of these considerations notwithstanding, the Simmons–Smith products from **16** and **17** were shown unequivocally to be **27** and **28** by conversion of each ketal to tricyclic ketone **5**. Ketones **29** and **30** obtained from the ketals underwent Wolff–Kishner reduction to give the same hydrocarbon **31**. A control experiment showed that **30** was thermally stable at 195–200 °C in diethylene glycol, thus ruling out the possibility that the configuration of the three-membered ring was inverted in the course of the Wolff–Kishner reduction. Hydroboration[25] of **31** yielded **11** selectively and **11** was oxidized to **5** using chromic oxide in pyridine.[26] The formal possibility that it is the Simmons–Smith reaction of **4** rather than that of **16** and **17** that leads to the unanticipated stereochemical result may be dismissed on the

basis of the spectroscopic properties of various intermediates. A striking example is the large downfield chemical shift of the methylene protons of the cyclopropane ring of **12** and of the ethylene ketal of **5** in comparison with their position in **11**.[27] No such difference in NMR spectra would be expected for the two epimers represented in **32**.

We conclude then that, although **16** and **17** show reactivity in the Simmons–Smith reaction greater than that expected for unactivated simple olefins, they are exceptional in that the stereochemistry of this process is not that required by intramolecular assistance of the sort seen in **4** and in earlier work by others.[1,14,16,17] It appears that the relative positions of the ketal grouping and double bond in both **16** and **17** are such that this sort of intramolecular assistance in cyclopropanation is unfavorable; the observed enhanced reactivity may be due to a directive effect of the second double bond or to intermolecular assistance, but further information is needed to explain this behavior of **16** and **17** satisfactorily. For the present our observations provide a cautionary note on assignment of stereochemistry solely on the basis of stereoselective Simmons–Smith cyclopropanation.

Experimental Section

Materials and Equipment. All analytical and preparative VPC separations were performed on a Varian Aerograph Model 920 single-column gas chromatograph equipped with a thermal conductivity detector. Helium was used as the carrier gas at ~65 lb pressure. Injection port and detector temperatures were kept constant at 200–210 and 210–220 °C, respectively. Chromatograms were recorded with a Servo Writer II (Texas Instruments, Inc.) operating at a constant speed of 8 in./h. The following columns were used: A, 16 g of 20% Carbowax 20M, 5 ft; B, 33 g of 20% DEGS, 11 ft; C, 25% QF-1, 10 ft; D, 28 g of SILAR 10-C, 10 ft. All columns were constructed of standard aluminum tubing having $^3/_{16}$-in. i.d. Chromosorb P, mesh 60/80, was used as the solid support in all, except in column C, where chromosorb W, mesh 45/60, was employed. Yields were determined either by weighing the collected fractions or by weighing cutout traces of the peaks. Retention times were measured at the interval between the injection point and the maximum of a given peak. VPC data are reported as follows: retention time in minutes, column temperature in degrees centigrade, flow rate in milliliters per minute. NMR spectra were obtained on a Varian T-60A (60 MHz), or on a Varian HR-220 (220 MHz) spectrometer operating in either continuous wave mode or in Fourier Transform (FT) mode. NMR spectra were recorded in CCl_4 solution containing ~1% tetramethylsilane (Me_4Si) as an internal reference (0 ppm). Infrared spectra (CCl_4 solution) were recorded on a Perkin-Elmer Model 621 grating infrared spectrophotometer. A mass spectrum was obtained on a Du Pont 21-492 double-focusing mass spectrometer with a resolution of 10^4 with an AEI DS-30 data system. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus. Melting points are corrected, and boiling points are reported uncorrected. Solutions were dried over anhydrous Na_2SO_4 or $MgSO_4$. Exceptions to the above are noted.

***exo*- and *endo*-6-Cyanobicyclo[3.2.2]non-8-ene (1 and 2).** A mixture of the epimeric nitriles was prepared in 78% yield as described by Alder.[3] VPC analysis of a crude sample on column A (182 °C, 167 mL/min) indicated two products which were isolated and identified as the following: *endo*-8-cyanobicyclo[3.2.2]non-6-ene (**2**) (14 min, 51%): mp 65.5–67.0 °C; IR 3045 (m), 2933 (s), 2879 (m), 2864 (m), 2243 (m), 1646 (w), 1472 (m), 1465 (m), 1455 (m), 1448 (m), 942 (w), 933 (m), 721 (m), 708 (s), 660 (w) cm^{-1}; NMR (220 MHz) δ 1.44–1.75 (m, 4 H), 1.75–2.08 (m, 3 H), 2.20 (ddd, J = 13.5, 12, 6.5 Hz, 1 H), 2.54 (m, 1 H), 2.67 (m, 1 H), 2.76 (ddd, J = 12, 10, 6 Hz, 1 H), 6.32 (m, 2 H); *exo*-8-cyanobicyclo[3.2.2]non-6-ene (**1**) (20 min, 27%): mp 57.5–58.5 °C; IR 3046 (m), 2935 (s), 2860 (m), 2242 (m), 1654 (w), 1466 (w), 1452 (m), 1448 (m), 941 (m), 713 (s) cm^{-1}; NMR (220 MHz) δ 1.30–1.73 (m, 6 H), 1.98 (ddd, J = 14, 5, 5 Hz, 1 H), 2.21 (ddd, J = 14, 10, 1.5 Hz, 1 H), 2.56 (m, 1 H), 2.78 (m, 1 H), 2.96 (ddd, J = 10, 5, 1.5 Hz, 1 H), 6.42 (dd, J = 8, 8 Hz, 1 H), 6.52 (dd, J = 8, 8 Hz, 1 H).

Equilibration of **1** with a catalytic amount of potassium *tert*-butoxide in THF[28] and subsequent VPC analysis on column A gave equal amounts of **1** and **2** (50 ± 1%).

Bicyclo[3.2.2]non-8-en-6-one (3). A solution of 6-chloro-6-cyanobicyclo[3.2.2]non-8-ene (22.5 g, 124 mmol),[6] $Na_2S{\cdot}9H_2O$ (44.7 g, 186 mmol), and 95% aqueous ethanol (150 mL) was heated at reflux for 17 h.[12] The cooled orange mixture was added to water (200 mL) and extracted with 100 mL of ether (8×). The combined ether extracts were washed with brine and dried. Concentration, followed by sublimation at 115–150 °C (17 mm), gave 8.0 g (47%) of a white solid. The physical and spectroscopic characteristics of **3** were the same as those reported.[6]

***exo*- and *endo*-Bicyclo[3.2.2]non-8-en-6-ol (8a and 9a).** Reduction of **3** (1.00 g, 7.36 mmol) with sodium (7.50 g, 326 mmol), in dry, absolute ethanol (100 mL) and purification by sublimation (aspirator) gave 957 mg (96%) of a white solid. VPC of a crude sample on column A (150 °C, 122 mL/min) indicated complete conversion and two products which were isolated and identified on the basis of their previously reported IR spectra.[6] For exo-bicyclo[3.2.2]non-8-en-6-ol (**8a**) (30 min, 35%): NMR (220 MHz) δ 1.22–1.67 (m, 8 H), 2.25 (dd, J = 14.6, 8.2 Hz, 1 H), 2.40 (m, 2 H), 4.08 (d, J = 8.1 Hz, 1 H), 6.00 (dd, J = 8.0, 8.0 Hz, 1 H), 6.19 (dd, J = 8.0, 8.0 Hz, 1 H). For *endo*-bicyclo[3.2.2]non-8-en-6-ol (**9a**) (37 min, 61%): NMR (220 MHz) δ 1.23–1.68 (m, 5 H), 1.68–1.93 (m, 3 H), 2.24 (ddd, J = 14, 10, 7 Hz, 1 H), 2.42 (m, 2 H), 3.91 (ddd, J = 10, 5, 5 Hz, 1 H), 5.92 (m, 2 H).

Bicyclo[3.2.2]non-8-en-6-one Ethylene Acetal (4). A mixture of **3** (4.91 g, 361 mmol), ethylene glycol (10 mL), and *p*-toluenesulfonic acid monohydrate (292 mg) in benzene (200 mL) was heated at reflux with continuous removal of water. Fresh acid (187 mg) was added after 20 h and heating continued for 30 additional h. The mixture was worked up in the usual fashion and distilled to give 6.50 g (100%) of a colorless liquid, bp 77–79 °C (0.80–0.85 mm). A sample purified further by VPC on column A had the following properties: IR 3042 (m), 2929 (s), 2875 (s), 1648 (w), 1446 (m), 1380 (m), 1360 (m), 1198 (m), 1135 (s), 1105 (s), 1039 (s), 967 (m), 948 (m), 844 (m), 712 (s) cm^{-1}; NMR (60 MHz), δ 0.958–2.69 with major absorptions at 1.56, 1.96, 2.29 (m, 10 H), 3.76 (br s, 4 H), 5.91 (m, 2 H).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.17; H, 8.97.

General Cyclopropanation Procedure. All Simmons–Smith reactions were carried out as reported in the literature,[14] except that a large excess of diiodomethane (Aldrich) and a zinc–copper couple (Ventron-Alfa) were used.[19] In a typical run, a mixture of zinc–copper couple (5–6 equiv) and a few crystals of iodine in anhydrous ether was heated at reflux for ~0.5 h. At the end of this period, a solution of the olefinic compound (1 equiv) and diiodomethane (3–4 equiv) in a small amount of anhydrous ether was added dropwise over 0.5 h. The mixture was heated for 24–48 h, cooled to 0–5 °C, and quenched with saturated aqueous NH_4Cl. The two layers were separated, and the aqueous layer was extracted with ether (3–4×). The combined ether extracts were washed with 10% aqueous Na_2CO_3 and with brine. After drying and concentration, the crude product was purified by distillation or by preparative VPC.

***exo*-Tricyclo[3.3.2.0^{2,4}]decan-*exo*-9-ol (12).** Treatment of **8a** (50 mg, 362 mmol) with diiodomethane (292 mg, 1.09 mmol) and zinc–copper couple (142 mg, 2.17 mmol) in ether (5 mL) for 21 h and purification of the crude product by VPC on column A gave 23 mg (42%) of a white solid: mp 157–161 °C (sealed tube); IR 3620 (m), 3384 (br, s), 3082 (w), 3006 (s), 2923 (s), 1468 (m), 1465 (m), 1448 (m), 1322 (w), 1182 (m), 1086 (w), 1071 (w), 1061 (m), 1033 (s), 1011 (s), 940 (m) cm^{-1}; NMR (220 MHz) δ 0.438 (ddd, J = 8.5, 8.5, 5.5 Hz, 1 H), 0.784 (dddd, J = 13, 8.5, 4.5, 2 Hz, 1 H), 0.903 (dddd, J = 13, 8.5, 4.5, 1.5 Hz, 1 H), 1.26 (ddd, J = 5.5, 4.5, 4.5 Hz, 1 H), 1.32–1.97 (m, 9 H), 2.11 (m, 1 H), 2.23 (m, 1 H), 3.90 (dddd, J = 8, 4, 4, 2 Hz, 1 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.71; H, 10.61.

***exo*-Tricyclo[3.3.2.0^{2,4}]decan-9-one Ethylene Acetal.** A mixture of **4** (2.96 g, 16.4 mmol), diiodomethane (12.9 g, 48.2 mmol), and zinc–copper couple (6.31 g, 96.5 mmol) in ether (40 mL) was treated as described above. Microdistillation gave 2.93 g (92%) of a colorless liquid: bp 106–110 °C (1.4 mm). An analytical sample purified by VPC on column A had the following characteristics: IR 3090 (w), 3014 (m), 3001 (m), 2954 (s), 2931 (s), 2900 (s), 2880 (s), 2856 (m), 1466 (m), 1447 (m), 1437 (m), 1371 (m), 1127 (s), 1108 (s), 1072 (m), 1057 (s), 1043 (m), 1031 (m), 1016 (w), 985 (m) cm^{-1}; NMR (60 MHz, with $CHCl_3$ as internal reference) δ 0.346 (m, 1 H), 0.942 (m, 3 H), 1.27–2.40 with d, J = 4 Hz at 1.72 (m, 10 H), 3.77 (br s, 4 H).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.43. Found: C, 74.14; H, 9.50.

Bicyclo[3.2.2]non-8-en-6-one tosylhydrazone was prepared in 90% yield according to a procedure of Cope:[29] mp 195–198 °C (dec); IR ($CHCl_3$) 3294 (w), 3220 (w), 3022 (m), 2937 (s), 2860 (m), 1632 (w), 1598 (w), 1388 (m), 1335 (m), 1166 (s), 1092 (m), 812 (m), 658 (m), 545 (m) cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 0.933–2.02 with major absorption at 1.52 (m, 6 H), 2.02–2.82 with s at 2.42 (m, 7 H), 3.08 (m, 1 H), 6.05 (m, 2 H), 7.22 (d, J = 8 Hz, 2 H), 7.78 (d, J = 8 Hz, 2 H).

Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.14; H, 6.62; N, 9.21. Found: C, 63.18; H, 6.76; N, 9.24.

Tropone. The procedure used for the preparation of **14** was essentially that of Radlick[22] with the following modifications: Spectral grade dioxane (Scintrex Reagent from J. T. Baker), cycloheptatriene (43.0 g, 97% from Aldrich), and a freshly opened bottle of selenium dioxide (55.0 g, from MCB) were used. The mixture was thermostated at 90 ± 0.5 °C (oil bath) with vigorous stirring for 21 h. Distillation on a simple head gave a small amount of cycloheptatriene and 24.1 g (50%) of a pale yellow liquid: bp 110 °C (11 mm) [lit.[14] bp 91–92 °C (4 mm)]. The yield was found to be reproducible on this scale.

3-Benzoyloxybicyclo[3.2.2]nona-6,8-diene (22). Anhydride **19** (5.00 g, 16.0 mmol)[21] was treated with dicarbonylbis(triphenylphosphine)nickel (20.5 g, 32.1 mmol) in dry diglyme (200 mL) at vigorous reflux for 65 h.[24] The cooled, black mixture was concentrated in vacuo, diluted with chloroform (200 mL), and filtered through Celite. Chloroform was removed and the yellow-green residue was diluted with pentane (1000 mL) to precipitate unreacted starting material and/or impurities. The solution was filtered, and the filtrate was washed with 200 mL of water (3×), dried, and concentrated. The yellow semisolid was dissolved in a small amount of 7:3 (v:v) petroleum ether/benzene and chromatographed over a 44 × 4 (i.d.) cm silica gel (activity I, 260 g) column to give 17.8 g (87% recovery) of the catalyst (eluted with 1500 mL of 7:3 petroleum ether/benzene) and a white solid (eluted with 1500 mL of benzene) which after drying at 40 °C (0.1 mm) weighed 3.55 g (92%); the melting point and spectral characteristics were the same with those reported for **22**.[21] In another run using twice the amount of catalyst indicated above while keeping the other reagents constant, a 97% yield of **22** was realized.

In similar fashion mixtures of **19** and the isomeric 2-benzoate anhydride yielded **22** and the 2-benzoate diene. Purification of the latter product by preparative VPC gave material identical with that previously reported.[21]

Bicyclo[3.2.2]nona-6,8-dien-3-one Ethylene Acetal (16). Ketone **14** obtained by hydrolysis of **22** and subsequent oxidation[21] was ketalized with minimal rearrangement by treatment (3.44 g, 25.6 mmol) with ethylene glycol (10 mL) using pyridinium chloride (304 mg) as catalyst[30] in benzene (75 mL) for 39 h. Distillation gave 3.76 g of a colorless liquid (82%): bp 64–65 °C (0.40 mm). VPC on column A (150 °C, 109 mL/min) revealed three peaks identified as starting **14** (30 min, 4.4%), **24** (35 min, 8.1%), and **16** (54 min, 70%). For **16**: IR (CS_2) 3047 (m), 2947 (s), 2928 (s), 2873 (m), 1610 (w), 1372 (m), 1361 (w), 1157 (m), 1101 (s), 1068 (m), 1058 (m), 948 (m), 780 (s) cm^{-1}; NMR (60 MHz) δ 1.72, (d, J = 4 Hz, 4 H), 3.02 (m, 2 H), 3.69 (s, 4 H), 6.15 (m, 4 H).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.25; H, 7.98.

Ketalization was also carried out successfully using very small amounts of *p*-toluenesulfonic acid and by controlling the reaction period. However, use of ordinary conditions and amounts of this acid led to a 78% yield of **24**, acid hydrolysis of which gave phenylacetone.

Bicyclo[3.2.2]nona-6,8-dien-2-one Ethylene Acetal (17). A 52:48 mixture of **14** and **15**[21] (3.32 g, 24.7 mmol) was treated with ethylene glycol (7.0 mL) and *p*-toluenesulfonic acid (203 mg) in benzene (150 mL) for 24 h. Concentration of the solution gave 3.89 g (88%) of a viscous oil. VPC on column D (150 °C, 71 mL/min) indicated **24** (51 min, 48%) and **17** (82 min, 40%). For **17**: IR (CS_2) 3045 (m), 2955 (s), 2926 (s), 2873 (s), 1609 (w), 1372 (m), 1352 (m), 1296 (m), 1282 (m), 1222 (m), 1129 (m), 1098 (s), 1067 (s), 1055 (m), 1033 (m), 950 (s), 909 (m), 895 (m), 725 (s), 693 (m), 671 (m), 658 (m) cm^{-1}; NMR (60 MHz) δ 1.28–1.97 (m, 4 H), 2.88 (m, 2 H), 3.75 (br s, 4 H), 6.08 (m, 4 H).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.12; H, 7.87.

***exo*-Tricyclo[3.3.2.0^{2,4}]dec-9-en-7-one Ethylene Acetal (27).** A mixture of **16** (413 mg, 2.32 mmol), diiodomethane (2.48 g, 9.27 mmol), and zinc–copper couple (0.91 g, 14 mmol) in ether (15 mL) was heated at reflux for 24 h. VPC on column A (initial column temperature 150 °C, raised to 170 °C after 90 min, 109 mL/min) showed three peaks, two of which were identified as **24** (35 min, 7.1%) and **27** (77 min, 68%); the third (127 min, 25%) remains unidentified. Preparative VPC gave 193 mg (43%) of **27**: IR (CS_2) 3074 (w), 3037 (m), 3002 (m), 2970 (m), 2943 (s), 2916 (s), 2871 (m), 1154 (m), 1113 (s), 1094 (s), 1052 (m), 1029 (s), 828 (s), 764 (m), 752 (m) cm^{-1}; NMR (60 MHz) δ 0–0.583 (m, 2 H), 1.10 (m, 2 H), 1.88 (d, J = 4 Hz. 4 H), 2.55 (m, 2 H), 3.78 (br s, 4 H), 5.66 (m, 2 H).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.81; H, 8.21.

***exo*-Tricyclo[3.3.2.0^{2,4}]dec-9-en-7-one (29).** Hydrolysis of **27** (30.5 mg, 0.159 mmol) with an equivolume solution of 10% aqueous HCl–methanol, followed by preparative VPC on column A, gave 14.5 mg (62%) of a white solid: mp 46–49 °C (sealed tube); IR (CS_2) 3077 (w), 3042 (m), 3007 (s), 2912 (s), 1698 (s), 1411 (m), 1385 (m), 1327 (m), 1191 (m), 1153 (m), 1032 (s), 1028 (s), 829 (s), 814 (w), 779 (m), 722 (m) cm^{-1}; NMR (60 MHz) δ 0.062–0.612 (m, 2 H), 1.14 (m, 2 H), 2.51 (m, 4 H), 2.71 (m, 2 H), 5.84 (m, 2 H).

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.81; H, 8.16.

***exo*-Tricyclo[3.3.2.0^{2,4}]dec-9-en-6-one Ethylene Acetal (28).** Cyclopropanation of **17** (430 mg, 2.41 mmol) was carried out as for **16**. An analytical sample purified by VPC on column A had the following properties: IR (CS_2) 3076 (w), 3041 (m), 3003 (m), 2953 (m), 2912 (s), 2874 (s), 1290 (m), 1115 (s), 1100 (s), 1088 (s), 1061 (s), 1043 (m), 1034 (m), 956 (s), 881 (m), 827 (m), 740 (m), 719 (m) cm^{-1}; NMR (60 MHz) δ 0.117–0.617 (m, 2 H), 0.617–1.38 (m, 2 H), 1.38–2.28 (m, 4 H), 2.53 (m, 2 H), 3.83 (br s, 4 H), 5.60 (m, 2 H).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.00; H, 8.24.

***exo*-Tricyclo[3.3.2.0^{2,4}]dec-9-en-6-one (30).** Crude **28** was hydrolyzed to give (after purification by VPC on column A) 266 mg of a white solid (74%, based on **17**): mp 33–35 °C (sealed tube); IR (CS_2) 3076 (w), 3042 (m), 3004 (m), 2952 (m), 2922 (s), 2859 (m), 1701 (s), 1412 (m), 1226 (m), 1160 (m), 1151 (m), 1032 (m), 1027 (m), 889 (m), 881 (m), 727 (m), 722 (m), 702 (s) cm^{-1}; NMR (60 MHz) δ 0.500 (m, 2 H), 1.18 (m, 2 H), 2.00 (m, 2 H), 2.65 (m, 3 H), 3.10 (m, 1 H), 5.75 (m, 2 H).

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.02; H, 8.15.

***exo*-Tricyclo[3.3.2.0^{2,4}]dec-9-ene. (31). A. From 29.** The modified Wolff–Kishner reduction[31] of **29** (231 mg, 1.56 mmol), followed by VPC purification on column A, gave 180 mg of a white solid (86%): mp 78–80.5 °C (sealed tube); IR (CS_2) 3073 (w), 3033 (m), 3000 (s), 2915 (s), 2851 (s), 1652 (w), 1432 (w), 1384 (m), 1323 (m), 1108 (w), 1094 (w), 1059 (m), 1040 (w), 1027 (m), 923 (m), 875 (m), 831 (m), 748 (m), 726 (w), 713 (s), cm^{-1}; NMR (60 MHz) δ 0.012–0.595 (m, 2 H), 0.920 (m, 2 H), 1.48 (m, 6 H), 2.50 (m, 2 H), 5.50 (m, 2 H).

Anal. Calcd for $C_{10}H_{14}$: C, 89.49; H, 10.51. Found: C, 89.42; H, 10.38.

B. From 30. Similar treatment of **30** (241 mg, 1.63 mmol) and purification gave 162 mg of **31** (74%). In a control experiment, no change was observed in **30** after heating it in diethylene glycol at 195–200 °C for 1.5 h.

***exo*-Tricyclo[3.3.2.0^{2,4}]decan-*endo*-9-ol (11). A. From 31.** Hydroboration of **31** (742 mg, 5.53 mmol) with diborane in THF[25] gave 0.80 g of a white solid. A small sample (purified by VPC on column A) and a large excess of bis(trimethylsilyl) acetamide were sealed in a tube and heated at 75–78 °C (oil bath) for 40 h. The cooled tube was unsealed; the solution was shaken with water (~10 min) and extracted with ether (4×). The combined ether extracts were washed with water and brine, and dried. Removal of ether gave a viscous oil which was purified by VPC on column B and subsequently hydrolyzed. An analytical sample purified by VPC on column B had the following characteristics: mp 177–179 °C (sealed tube); IR 3620 (m), 3418 (br, s), 3078 (w), 3007 (s), 2929 (s), 1469 (m), 1461 (m), 1447 (m), 1217 (w), 1085 (s), 1071 (s), 1061 (m), 1025 (m), 1009 (s), 994 (m), 946 (m) cm^{-1}; NMR (220 MHz) δ 0.379 (m, 2 H), 0.902 (m, 2 H), 1.19–2.10 (m, 9 H), 1.83 (m, 2 H), 3.76 (ddd, J = 10, 6, 4, Hz, 1 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H. 10.59. Found: C, 78.77; H, 10.58.

B. From 9a. A mixture of **9a** (102 mg, 0.738 mmol), diiodomethane (592 mg, 2.21 mmol), and zinc–copper couple (289 mg, 4.42 mmol) in ether (10 mL) was heated at reflux for 63 h. Preparative VPC on column A (168 °C, 162 mL/min) gave 19 mg of two unidentified products A (9.4 min) and B (10 min), 24 mg of starting **8b** (16 min) and 4.9 mg (5.7% yield, based on unrecovered **9a**) of a white solid (33 min). The IR and NMR spectra of the latter, were identical with those of **11** described above.

***exo*-Tricyclo[3.3.2.0^{2,4}]decan-9-one (5). A. From its Ethylene Acetal.** The acetal (2.90 g, 14.9 mmol) was hydrolyzed with 10% aqueous HCl–methanol solution. Preparative VPC on column A gave 2.09 g of a white solid (93%): mp 141–142 °C; IR 3072 (w), 3009 (m), 2929 (s), 2862 (m), 1717 (s), 1461 (m), 1443 (m), 1412 (m), 1380 (w), 1342 (w), 1313 (w), 1214 (m), 1187 (w), 1088 (m), 1024 (m) cm^{-1}; NMR (220 MHz, $CHCl_3$ as internal reference) δ 0.329 (m, 1 H), 0.471 (ddd, J = 8, 8, 6.5 Hz, 1 H), 1.06 (m, 2 H), 1.23–2.16 with d, J = 4 Hz, at 1.93 (m, 8 H), 2.34 (m, 1 H), 2.65 (m, 1 H); mass spectrum m/e 150.1026 (M^+, calcd for $C_{10}H_{14}O$, 150.1044).

B. From 12. Oxidation[26] of **12** (279 mg, 1.83 mmol) followed by VPC isolation on column A gave 212 mg of a white solid (77%) which had identical melting point and spectral characteristics with those of **5** described above.

C. From 11. Similarly, crude **11** (0.80 g) from hydroboration of **31** was oxidized[27] to 664 mg of **5** (80%, based on **31**).

Reduction of 5. A. With Sodium in Ethanol. Ketone **5** (196 mg, 1.30 mmol) was reduced with sodium (1.34 g, 58.2 mmol) in dry, absolute ethanol (15 mL), as described above for **3**. The crude sample was purified by VPC on column A to give 167 mg (one peak) of **11** and **12** (84%), treatment of which with bis(trimethylsilyl) acetamide (see above) gave a viscous liquid. VPC on column B (110 °C, 71 mL/min) indicated two products, A (50 min, 76%) and B (54 min, 24%). Each product was isolated and hydrolyzed to the corresponding alcohol. The IR spectra of the alcohols from A and B were identical with those of **11** and **12**, respectively.

B. With Lithium Aluminum Hydride. Ketone **5** (188 mg, 1.25 mmol) was reduced with excess lithium aluminum hydride in ether to give a white solid which after purification by VPC on column A weighed 144 mg (75%). Analysis via the trimethylsilyl ethers as described above indicated **11** (73%) and **12** (27%).

Acknowledgments. We thank Mr. William Rosenstein for technical assistance, Mr. S. T. Bella for microanalyses, and the National Science Foundation for support of this research through Grant CHE74-21436. The 220-MHz NMR spectra were obtained on an instrument at The Rockefeller University and operated by a consortium supported in part by NSF Grant PCM74-12247.

Registry No.—**1**, 65311-25-3; **2**, 65375-83-9; **3**, 29415-86-9; **4**, 65311-26-4; **5**, 65311-27-5; **8a**, 29577-00-2; **8b**, 23217-50-7; **9a**, 30365-09-4; **11**, 65311-28-6; **12**, 65375-84-0; **14**, 26788-91-0; **15**, 26760-27-0; **16**, 65311-29-7; **17**, 65311-30-0; **19**, 63072-75-3; **22**, 65311-31-1; **24**, 4362-18-9; **27**, 65311-32-2; **28**, 65311-33-3; **29**, 65366-49-6; **30**, 65311-34-4; **31**, 65311-35-5; 6-chloro-6-cyanobicyclo[3.2.2]non-8-ene, 29415-85-8; ethylene glycol, 107-21-1; exo-tricyclo[3.3.2.$0^{2,4}$]decan-9-one ethylene acetal, 65311-36-6; bicyclo[3.2.2]non-8-en-6-one tosylhydrazone, 65311-37-7; tropone, 539-80-0; cycloheptatriene, 544-25-2.

References and Notes

(1) A. de Meijere, C. Weitemeyer, and O. Schallner, *Chem. Ber.*, **110**, 1504 (1977).
(2) L. G. Kozar, R. D. Clark, and C. H. Heathcock, *J. Org. Chem.*, **42**, 1386 (1977).
(3) K. Alder, S. Hartung, and G. Hausmann, *Chem. Ber.*, **89**, 1972 (1956).
(4) J. C. Davis, Jr., and T. V. Van Auken, *J. Am. Chem. Soc.*, **87**, 3900 (1965).
(5) This effect is seen in **6** and **7**[4] as well as other 2-substituted 5-norbornenes. For discussion, see L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Oxford, 1969, pp 84, 230, and 231, and references cited therein.
(6) J. Braband, M. Muehlstaedt, and G. Mann, *Tetrahedron*, **26**, 3667 (1970).
(7) M. Hartmann, *Ann.*, **724**, 102 (1969).
(8) K. Alder and G. Stein, *Ann.*, **514**, 1 (1934); *Angew. Chem.*, **50**, 510 (1937); J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961), and references cited therein.
(9) K. Alder, K. Heimbach, and R. Reubke, *Chem. Ber.*, **91**, 1516 (1958).
(10) See also in this regard Y. Kobuke, T. Fueno, and J. Furukawa, *J. Am. Chem. Soc.*, **92**, 6548 (1970).
(11) P. K. Freeman, D. M. Balls, and D. J. Brown, *J. Org. Chem.*, **33**, 2211 (1968).
(12) D. A. Evans, W. L. Scott, and L. K. Truesdale, *Tetrahedron Lett.*, 121 (1972).
(13) R. E. Pincock and J. I. Wells, *J. Org. Chem.*, **29**, 965 (1964).
(14) H. E. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, *Org. React.*, **20**, 1 (1973).
(15) The stereochemistry of **11** is demonstrated below.
(16) S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.*, **83**, 3235 (1961); W. G. Dauben and G. H. Berezin, *ibid.*, **85**, 468 (1963).
(17) D. A. Lightner and W. A. Beavers, *J. Am. Chem. Soc.*, **93**, 2677 (1971).
(18) A report of similar use of a ketal to facilitate cyclopropanation of a rigid β,γ-unsaturated ketone appeared during the course of this work (ref 1).
(19) I. M. Takakis, Dissertation, New York University, 1976; Y. E. Rhodes and I. M. Takakis, manuscript in preparation.
(20) R. H. Shapiro, *Org. React.*, **23**, 405 (1976).
(21) A. J. Baker, A. M. Chalmers, W. W. Flood, D. J. MacNichol, A. B. Penrose, and R. A. Raphael, *J. Chem. Soc., Chem. Commun.*, 166 (1970). See also A. M. Chalmers, Dissertation, University of Glasgow, 1967; W. W. Flood, Dissertation, University of Glasgow, 1971; A. F. Cameron and G. Ferguson, *J. Chem. Soc. B*, 943 (1970); A. M. Chalmers and A. J. Baker, *Tetrahedron Lett.*, 211 (1977). We are indebted to Dr. Baker (University of Glasgow) for correspondence and the generous provision of experimental details and spectroscopic data prior to their publication.
(22) P. Radlick, *J. Org. Chem.*, **29**, 960 (1964).
(23) D. I. Schuster, J. M. Palmer, and S. C. Dickerman, *J. Org. Chem.*, **31**, 4281 (1966).
(24) B. M. Trost and F. Chen, *Tetrahedron Lett.*, 2603 (1971). For additional examples, see K. Wiesner, P. Ho, R. C. Jain, S. F. Lee, S. Oida, and A. Philipp, *Can. J. Chem.*, **51**, 1448 (1973); W. G. Dauben, G. T. Rivers, R. J. Twieg, and W. T. Zimmerman, *J. Org. Chem.*, **41**, 887 (1976).
(25) H. C. Brown, "Organic Syntheses via Boranes", Wiley, New York, N.Y., 1975; H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 1241 (1961).
(26) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
(27) Similar differences have been noted previously in the NMR spectra of lower homologues of **11** and **12**, the bicyclo[3.2.2.$0^{2,4}$]nonan-6-ols: G. R. Wenzinger and J. A. Ors, *J. Org. Chem.*, **39**, 2060 (1974); P. E. Schueler and Y. E. Rhodes, *ibid.*, **39**, 2063 (1974); ref 17. The photochemical behavior of **5**, which will be discussed elsewhere, is also compatible only with the assigned stereochemistry (I. M. Takakis, unpublished observations).
(28) N. L. Allinger and W. Szkrybalo, *J. Org. Chem.*, **27**, 4601 (1962).
(29) A. C. Cope, D. L. Nealy, P. Scheiner, and G. Wood, *J. Am. Chem. Soc.*, **87**, 3130 (1965).
(30) R. Rausser, A. M. Lyncheski, H. Harris, R. Grocela, N. Murrill, E. Bellamy, D. Ferchinger, W. Gebert, H. L. Herzog, E. B. Hershberg, and E. P. Olivetu, *J. Org. Chem.*, **31**, 26 (1966).
(31) R. K. Murray, Jr., and K. A. Babiak, *J. Org. Chem.*, **38**, 2556 (1973).

Stereoselective Total Syntheses of the Fungitoxic Hydroquinones (±)-Zonarol and (±)-Isozonarol

Steven C. Welch* and A. S. C. Prakasa Rao

Department of Chemistry, University of Houston, Houston, Texas 77004

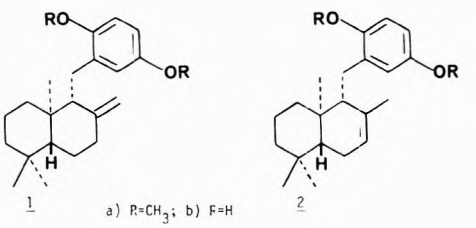
Received October 31, 1977

Stereoselective and regioselective total syntheses of two naturally occuring fungitoxic hydroquinones (±)-zonarol (**1b**) and (±)-isozonarol (**2b**) are described. The key features of these syntheses are: (a) the dehydration of tertiary alcohol **6** to alkene **7** without rearrangement utilizing dimethyl sulfoxide at 155 °C; (b) the conjugate addition of 2,5-dimethoxyphenylmagnesium bromide Grignard reagent to enone **9b**; and (c) ether cleavage of compounds **1a** and **2a** utilizing lithium *n*-butyl mercaptide in hexamethylphosphoric triamide at 150 °C for 24 h to afford the respective natural products.

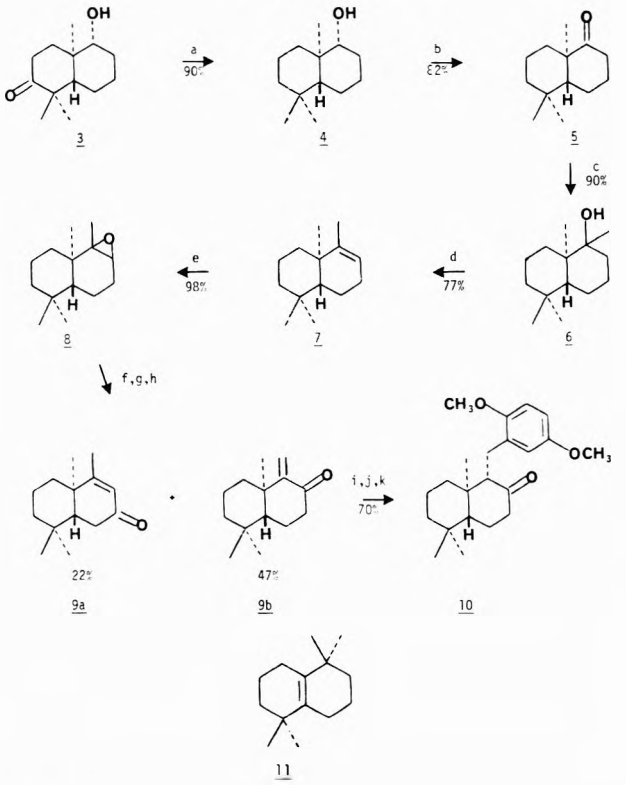
The two naturally occurring fungitoxic hydroquinones zonarol (**1b**) and isozonarol (**2b**) were isolated from brown seaweed *Dictopteris undulata* found in the Pacific Ocean near Southern California and the Gulf of California.[1-3] The structure and absolute stereochemistry of these merosesquiterpenoids[4] were rigorously defined by degradation and spectroscopy.[1-3] These two marine natural products were found to be active against the following pathogenic fungi: *Phytophthora cinnamoni*, *Rhizoctonia solani*, *Sclerotinia sclerotiorum*, and *Sclerotium rolfsii*.[1] We wish to report,

0022-3263/78/1943-1957$01.00/0

Scheme I



Scheme II



[a] N_2H_4, KOH, DEG, Δ. [b] CrO_3, H_2SO_4, H_2O, acetone. [c] CH_3Li, Et_2O, 0 °C. [d] Me_2SO, 155 °C. [e] *m*-CPBA Na_2HPO_4, $CHCl_3$. [f] LiN(*n*-Pr)$_2$, THF, Δ, 6 h. [g] $CrO_3 \cdot Pyr_2$, CH_2Cl_2. [h] Chromatography, Ξ. Merck, silica gel-60, 15% Et_2O–85% petroleum ether (bp 30–60 °C) eluent. [i] 2,5-Dimethoxyphenylmagnesium bromide, DME. [j] Ac_2O [k] KOH, CH_3OH.

herein, the full details of the first stereoselective and regioselective total syntheses of both (±)-zonarol (**1b**) and (±)-isozonarol (**2b**).[5]

Results and Discussion

The starting material chosen for these syntheses is readily available ketol **3** previously prepared by Heathcock and coworkers.[6] Ketol **3** is prepared from 2-methyl-1,3-cyclohexanedione and ethyl vinyl ketone in three synthetic stages in 46% overall yield. Haung-Minlon modification of the Wolff–Kishner reduction of ketol **3** using hydrazine hydrate in diethylene glycol (DEG) in the presence of potassium hydroxide at 200 °C gives alcohol **4** in 90% yield.[7] Oxidation of alcohol **4** with Jones' reagent in acetone affords ketone **5** in 82% yield.[8] Addition of excess methyllithium in ether at 0 °C to ketone **5** produces a mixture of tertiary alcohols **6** in 90% yield. Dehydration of tertiary alcohols **6** utilizing standard reagents ($SOCl_2$, pyridine; or $POCl_3$, pyridine; or I_2, benzene; or H_2SO_4, pentane; or *p*-TsOH, benzene) gives only substantial quantities of the corresponding symmetrical rearrangement product **11**. This troublesome rearrangement can be circumvented by performing the dehydration in anhydrous dimethyl sulfoxide at 155 °C for 16 h.[9] This latter reaction converts tertiary alcohols **6** to trisubstituted alkene **7** without any trace of the rearrangement product in 77% yield. Epoxidation of alkene **7** with *m*-chloroperbenzoic acid in chloroform in the presence of disodium hydrogen phosphate gives an equimolar mixture of epoxides **8** (α/β, respectively) in 98% yield.[10] Epoxide ring opening by treatment of oxiranes **8** with lithium di-*n*-propylamide in refluxing tetrahydrofuran for 6 h produces a mixture of allylic alcohols.[11] Oxidation of this mixture of allylic alcohols with Collins' reagent[12] then affords an easily separable mixture of enones **9a** and **9b** (ratio 32:68, respectively) in 69% yield. Enones **9a** and **9b** are easily separated by column chromatography on E. Merck silica gel-60 using 15% ether–85% petroleum ether (bp 30–60 °C) as the eluent. Enone **9a** displays a one proton quartet (J = 2 Hz) at δ 5.53 ppm, whereas enone **9b** shows a two-proton AB quartet (J_{AB} = 2 Hz) with each doublet centered at δ 4.93 and δ 5.36 ppm, respectively. When the epoxidation of alkene **7** to oxirane **8** is carried out in dry ether the ratio of epoxides is 30:70 (α/β, respectively). When this mixture of epoxides is carried through the same reaction sequence to enones **9a** and **9b** the ratio of enones **9a**/**9b** changes to 56:44, respectively, in 69% yield. Enone **9b** was previously prepared by Eschenmoser et al. as well as White et al. via different synthetic routes.[13] Generation of the Grignard reagent of 1-bromo-2,5-dimethoxybenzene[14] utilizing standard methods (Mg turnings, I_2 catalyst, DME or THF) is rather difficult and capricious; however, when the magnesium metal is prepared by Rieke's method ($MgCl_2$ + 2K, DME),[15] then the Grignard reagent forms readily in 1,2-dimethoxyethane (DME). Addition of copper(I) iodide (in catalytic amount) followed by enone **9b** and quenching with freshly distilled acetic anhydride affords a crude enol acetate by conjugate addition and enolate anion trapping.[16] Treatment of this crude enol acetate with potassium hydroxide in methanol then produces ketone **10** (mp 108–109 °C) in 70% overall yield from enone **9b**. Enolate anion trapping with acetic anhydride facilitates the isolation and purification of the final product, ketone **10**. Quenching the conjugate addition reaction at 0 °C with dilute hydrochloric acid solution gives ketone **10** in somewhat lower yields. Nuclear magnetic resonance data (CCl_4) of ketone **10** indicate the presence of three aromatic protons (m, δ 6.67), two methoxyl groups (s, δ 3.72 and s, δ 3.76), and three quaternary methyl groups (s, δ 0.97; s, δ 0.90; and s, δ 0.80 ppm).

A Wittig reaction on ketone **10** utilizing methylenetriphenylphosphorane in anhydrous dimethyl sulfoxide at 80 °C for 24 h affords (±)-zonarol dimethyl ether (**1a**, mp 117–118 °C) in 93% yield.[17] Cleavage of dimethyl ether **1a** to (±)-zonarol (**1b**) is smoothly accomplished in 90% yield with lithium *n*-butyl mercaptide in hexamethylphosphoric triamide at 150 °C for 24 h. Other reagents and conditions (NaSEt, DMF[18]; LiI·3H_2O, collidine[19]; and CH_3MgI, Δ[20]) give an equimolar mixture of the monomethyl ethers. Treatment of ketone **10** with excess methyllithium in ether at 0 °C followed by dehydration of the resulting tertiary alcohol by heating in anhydrous dimethyl sulfoxide at 155 °C for 16 h gives (±)-zonarol dimethyl ether (**1a**) and (±)-isozonarol dimethyl ether (**2a**) (ratio 1:4.8, respectively) in 67% yield. After separation (chromatography over 15% silver nitrate on silica gel) (±)-isozonarol dimethyl ether (**2a**) was then smoothly converted to (±)-isozonarol (**2b**) by treatment with lithium *n*-butyl mercaptide in hexamethylphosphoric triamide at 150 °C for 24 h. Both synthetic (±)-zonarol dimethyl ether (**1a**) and (±)-isozonarol dimethyl ether (**2a**) were identical (IR, NMR, GLC, and TLC) with the respective dimethyl ethers prepared from natural zonarol (**1b**) and isozonarol (**2b**).[21]

Experimental Section

Melting points were determined on a Fisher-Johns and/or Büchi melting point apparatus and are uncorrected. Analyses were per-

formed by Spang Microanalytical Laboratory, Ann Arbor, Mich. 48106.

Silica gel PF 254-366 (E. Merck No. 7748) and Silica gel 60 (E. Merck No. 7734, 70–230 mesh) available from Brinkmann Instruments were used for thin-layer and column chromatography, respectively.

Analytical gas-phase chromatography (GLC) was performed using the following types of columns and flow rates: (A) 5-ft stainless steel, 0.125-in. column packed with 3% SE-30 on Varaport 30, 100/120 mesh (Varian), flow rate 15 mL/min at ambient temperature; (B) 6-ft stainless steel, 0.125-in. column packed with 5% OV-17 on Varaport-30, 80/100 mesh (Varian), flow rate 15 mL/min at ambient temperature.

Infrared (IR) spectra were recorded on a Perkin-Elmer 237B. Solid samples were recorded in spectroquality carbon tetrachloride or chloroform using 0.10-mm sodium chloride cells. Liquid samples were sometimes taken as thin films between sodium chloride plates.

Nuclear magnetic resonance (NMR) spectra were measured on a Varian Associates Model T-60 spectrometer. All reactions were performed under an atmosphere of dry nitrogen. The equipment was dried in an oven at 120 °C for several hours, then allowed to cool in an atmosphere of dry nitrogen. All liquid transfers were made with nitrogen-filled syringes.

The petroleum ether used was Baker Analyzed Reagent, bp 30–60 °C. The terms "dry tetrahydrofuran", "dry 1,2-dimethoxyethane", and "dry diethyl ether" refer to purification of the commercial materials by distillation from lithium aluminum hydride under nitrogen. "Dry benzene", "dry hexamethylphosphoric triamide", and "dry di-*n*-propylamine" were obtained by distillation of the commercial materials from calcium hydride. "Dry dichloromethane" was obtained by distillation of the solvent from phosphorus pentoxide. Dimethyl sulfoxide was triple distilled from calcium hydride–sodium amide (98:2) onto freshly activated molecular sieves type 4A. The nomenclature utilized is that preferred by Chemical Abstracts.[22]

(1α,4aβ,8aα)-Decahydro-5,5,8a-trimethyl-1-naphthalenol (4). Haung-Minlon modification of Wolff–Kishner reduction was utilized. Hydrazine hydrate (14.42 g, 0.45 mol) and potassium hydroxide (22.44 g, 0.4 mol) in diethylene glycol (100 mL) were added to ketone 3 (20 g, 95 mmol) and heated under nitrogen atmosphere for 2 h at 150 ± 5 °C. Then the temperature was raised to 200 °C to remove excess hydrazine and water, and heating was continued for another 4 h. The reaction mixture was then cooled to room temperature, diluted with dilute hydrochloric acid, and extracted with ether (3 × 200 mL). The combined ethereal extracts were washed with water (3 × 50 mL) and saturated sodium chloride solution (50 mL), then dried ($MgSO_4$), filtered, and concentrated in vacuo to give 18 g (90%) of alcohol **4:** bp 70 ± 2 °C (0.1 mm); IR (CCl_4) 3400–3600 (OH), 1370, 1390 cm^{-1} (*gem*-dimethyl); NMR (CCl_4) δ 0.87 (s, 9, CH_3), 3.00 ppm (m, 1, oxymethine). Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found C, 79.69; H, 12.33.

***trans*-Octahydro-5,5,8a-trimethyl-1(2*H*)-naphthalenone (5).** Saturated alcohol 4 (17.5 g, 89.5 mmol) was dissolved in reagent acetone (100 mL), cooled to 0–5 °C, and Jones reagent was added dropwise until the reaction mixture remained orange. After stirring for an additional 20 min, the reaction was quenched with isopropyl alcohol, diluted with water (400 mL), and then extracted with ether (3 × 150 mL). The combined ethereal extracts were washed with water (3 × 50 mL) and saturated sodium chloride solution (50 mL), dried ($MgSO_4$), filtered, and then evaporated in vacuo to give 16 g of crude ketone **5.** This material was purified by column chromatography on silica gel (400 g) using 15% ether–85% petroleum ether as the eluent collecting 250-mL fractions. Fractions 6–10 were combined to give 13 g (82%) of pure ketone **5:** bp 65 ± 5 °C (0.3 mm) (bulb to bulb); IR (film) 1705 cm^{-1} (CO); NMR (CCl_4) δ 0.90 (bs, 6, CH_3), 1.13 ppm (s, 3, CH_3). Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.39; H, 11.53.

Decahydro-1,5,5,8a-tetramethyl-1-naphthalenol (6). Saturated ketone 5 (8.7 g, 45 mmol) was dissolved in freshly distilled dry ether (100 mL), cooled to 0 °C (ice bath) and methyllithium in ether (25 mL, 2 M, 50 mmol) was added dropwise over a period of 30 min and then stirred for 4 h. The reaction mixture was poured into ice water (400 mL) and extracted with ether (3 × 100 mL). The combined ethereal extracts were washed with water (3 × 60 mL) and saturated sodium chloride solution (50 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give 9 g of crude alcohol **6.** The material was purified by passing through a column of silica gel and eluting with 1:1 ether/petroleum ether to give 8.4 g (90%) of pure tertiary alcohol **6:** IR (film) 3485–3530 cm^{-1} (OH).

***trans*-1,2,3,4,4a,7,8,8a-Octahydro-1,1,4a,5-tetramethylnaphthalene (7).** Tertiary alcohol 6 (8.4 g, 40 mmol) was dissolved in dry dimethyl sulfoxide (50 mL) and heated at 155 °C under nitrogen for 16 h. The reaction mixture was then cooled to room temperature, diluted with water (300 mL), and extracted with 1:1 ether/pentane (3 × 100 mL). The combined ether–pentane extracts were washed with water (3 × 25 mL) and saturated sodium chloride solution (50 mL), then dried ($MgSO_4$), filtered, and concentrated in vacuo to give 7.05 g of crude olefin 7. This material was purified by distillation to give 5.93 g (77%) of alkene **7:** bp 62–65 °C (0.2 mm) (bulb to bulb); IR (CCl_4) 1630 cm^{-1} (C=C); NMR (CCl_4) δ 0.87 (s, 3, CH_3), 0.88 (s, 3, CH_3), 1.00 (s, 3, CH_3), 5.10 ppm (bs, 1, alkene proton).

Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.48; H, 12.62.

Decahydro-4,4,7a,7b-tetramethyloxireno[*a*]naphthalene (8). To a solution of *m*-chloroperbenzoic acid (2.5 g, 85%, 12 mmol) in reagent grade chloroform (50 mL) was added disodium hydrogen phosphate (3.41 g, 24 mmol). This mixture was cooled to 0 °C (ice bath) and alkene 7 (1.92 g, 10 mmol) in chloroform (10 mL) was added dropwise with stirring for 2 h. The reaction was monitored by thin-layer chromatography (TLC, 10% ether–90% petroleum ether). Disodium hydrogen phosphate was filtered and washed with chloroform. The combined chloroform layers were washed with 10% sodium hydroxide solution (2 × 25 mL), water (3 × 25 mL), and saturated sodium chloride solution (25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give crude epoxide 6 (2.3 g). This material was distilled (bulb to bulb), bp 65–68 °C (0.3 mm), to give 2.11 g (98%) of epoxide **8:** IR (CCl_4) 1240, 855 cm^{-1} (epoxide); NMR (CCl_4) δ 0.83 (s, 6, CH_3), 1.03 (s, 3, CH_3), 1.12 (s, 3, CH_3), 2.67 ppm (s, 1, oxymethine). Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.80; H, 11.69.

***trans*-Octahydro-5,5,8a-trimethyl-1-methylene-2(1*H*)-naphthalenone (9b) and *trans*-4a,5,6,7,8,8a-Hexahydro-4,4a,8,8-tetramethyl-2(1*H*)-naphthalenone (9a).** Freshly distilled di-*n*-propylamine (4.86 g, 6.58 mL, 48 mmol) was dissolved in dry tetrahydrofuran (100 mL) and cooled to 0 °C (ice bath). *n*-Butyllithium (24 mL, 2 M, 48 mmol) was added dropwise with stirring. After 10 min the ice bath was removed and epoxide 8 (3.02 g, 16 mmol) in dry tetrahydrofuran (20 mL) was added dropwise over a period of 10 min. The resulting mixture was then heated at reflux for 6 h. The reaction mixture was cooled in an ice bath, quenched with 10% hydrochloric acid (400 mL), and extracted with ether (3 × 100 mL). The ether extract was washed with water (3 × 50 mL) and saturated sodium chloride solution (50 mL), then dried ($MgSO_4$), filtered, and evaporated in vacuo to give 3.6 g of crude allylic alcohols.

To a solution of pyridine (15.5 g, 15.8 mL, 0.196 mol) in dry methylene chloride (75 mL), under nitrogen, cooled to 0 °C (ice bath) was added anhydrous chromium trioxide (9.8 g, 98 mmol) in small amounts. This mixture was then allowed to stir for 30 min. The crude allylic alcohol (3.4 g, 16.35 mmol) dissolved in dry methylene chloride (25 mL) was added over a period of 10 min and then allowed to stir for about 1 h at room temperature. A very dark solid separated as the reaction proceeded. The total reaction mixture then was filtered through a short column of either silica gel or Florisil and eluted with methylene chloride (500 mL). The total eluent was washed with 10% hydrochloric acid solution (4 × 50 mL), water (3 × 50 mL), and saturated sodium chloride solution (50 mL), then dried ($MgSO_4$), filtered, and evaporated in vacuo to give 2.87 g of crude ketones.

This mixture (4.7 g, combined from several experiments) was chromatographed on silica gel (250 g) and eluted with 15% ether–85% petroleum ether. Fractions 6 to 16 gave 2.35 g (47%) pure enone **9b,** distilled bulb to bulb at 65 °C (0.5 mm): IR (CCl_4) 1685 (C=O), 1600 cm^{-1} (C=C); NMR (CCl_4) δ 0.97 (s, 3, CH_3), 1.00 (s, 3, CH_3), 1.05 (s, 3, CH_3), 4.93, 5.36 ppm (dd, 2, $=CH_2$). Fractions 20 to 30 gave **9a** 1.16 g (22%), distilled bulb to bulb at 65–68 °C (0.5 mm); IR (CCl_4) 1670 (C=O), 1615 cm^{-1} (C=C); NMR (CCl_4) δ 0.92 (s, 3, CH_3), 0.96 (s, 3, CH_3), 1.13 (s, 3, CH_3), 5.53 ppm (bs, 1, —COCH=). Analysis of ketone **9b** was reported in the literature. Analysis of ketone **9a:** Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found C, 81.60; H, 10.88.

(1α, 4aβ, 8aα)-1-[(2,5-Dimethoxyphenyl)methyl]octahydro-5,5,8a-trimethyl-2(1*H*)-naphthalenone (10). Freshly cut potassium metal (2.737 g, 70 mg atom), anhydrous magnesium chloride (analytical grade dried under vacuum at 150 °C for 2 h, 3.427 g, 36 mmol), and potassium iodide (6 g, 36 mmol) were mixed under dry nitrogen atmosphere in 1,2-dimethoxyethane (100 mL) and heated under reflux for 3 h. The reaction mixture became a dark and viscous liquid; then 2,5-dimethoxy-1-bromobenzene (7.6 g, 35 mmol) was added and the mixture was allowed to reflux for another 2 h. The reaction mixture then was cooled to 0 °C; copper(I) iodide (1.4 g) was added and the mixture was stirred for 5 min. Enone **9b** (1.5 g, 7.3 mmol) dissolved in 1,2-dimethoxyethane (20 mL) was added dropwise and stirred for 15 min at 0 °C (ice bath) and for 30 min at room temperature. The

reaction was then quenched with acetic anhydride (20 mL) and stirred overnight. The reaction mixture was then diluted with saturated ammonium chloride solution (400 mL) and extracted with ether (4 × 100 mL). The combined ethereal extracts were washed with water (3 × 50 mL) and saturated sodium chloride solution (100 mL), then dried ($MgSO_4$), filtered, and evaporated in vacuo to give dark brown oil (7 g). This crude material was treated for 20 h at room temperature with 10% alcoholic potassium hydroxide solution (100 mL). Most of the alcohol was removed in vacuo, then diluted with water (200 mL) and extracted with ether (3 × 100 mL). The combined ethereal extracts were washed with water (3 × 50 mL) and saturated sodium chloride solution (50 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give a brown oil. This material was distilled (bulb to bulb) to remove low boiling material such as 1,4-dimethoxybenzene and unreacted 2,5-dimethoxybromobenzene, bp 70–98 °C (0.7 mm). Residue, 2.35 g (94%), was recrystallized from petroleum ether to give 1.74 g (70%) of pure ketone **10**: mp 108–109 °C; IR (CCl_4) 1710 (C=O), 1605, 1585 (aromatic), 1040 (aromatic methoxyl), 855 cm^{-1} (aromatic 1,4-disubstitution); NMR (CCl_4) δ 0.80 (s, 3, CH_3), 0.90 (s, 3, CH_3), 0.97 (s, 3, CH_3), 2.66 (bs, 2, benzylic), 3.72 (s, 3, OCH_3), 3.76 (s, 3, OCH_3), and 6.67 ppm (m, 3, aromatic). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.61; H, 9.66.

(±)-Zonarol Dimethyl Ether (1a). Sodium hydride (57% oil dispersion, 0.421 g, 10 mmol) was washed with dry *n*-pentane several times to remove oil and then flushed with nitrogen. Dimethyl sulfoxide [10 mL, triple distilled from $CaH_2/NaNH_2$ (98:2, respectively)] and then distilled onto freshly activated molecular sieves type 4A] was introduced and heated at 80 °C for 30 min until the evolution of hydrogen was complete. Methyltriphenylphosphonium bromide (3.572 g, 10 mmol) was added as a solid and stirred for 10 min. The reaction mixture became deep orange in color. At this stage, ketone **10** (0.689 g, 2 mmol) dissolved in hot dimethyl sulfoxide (5 mL) was added and stirred at 80 °C for 24 h. The reaction mixture was then cooled to room temperature, diluted with water (150 mL), and extracted with ether (3 × 100 mL). The combined ethereal extracts were washed with water (3 × 25 mL) and saturated sodium chloride solution (50 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give a solid which was passed through a column of silica gel to remove triphenylphosphine oxide. The resulting material, 0.718 g, was recrystallized from pentane to give white crystalline solid, (±)-zonarol dimethyl ether (**1a**) (0.636 g, 93%), mp 117–118 °C: IR (CCl_4) 1640 (C=C), 1585 (aromatic), 1040 (aromatic methoxyl) 855 cm^{-1} (aromatic 1,4-disubstitution); NMR (CCl_4) δ 0.83 (s, 3, CH_3), 0.86 (s, 3, CH_3), 0.90 (s, 3, CH_3), 2.66 (d, 2, benzylic), 3.60 (s, 3, aromatic methoxyl), 3.76 (s, 3, aromatic methoxyl), 4.63 (d, 2, $=CH_2$), 6.53 ppm (m, 3, aromatic). Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.74; H, 10.07.

(±)-Isozonarol Dimethyl Ether (2a). To a solution of ketone **10** (0.344 g, 1 mmol) in anhydrous ether (10 mL) was added methyllithium in ether (2 mL, 2 mol, 4 mmol) at 0 °C and stirred for 4 h at room temperature; excess methyllithium was quenched by adding ice water (20 mL), and the mixture was extracted with ether (3 × 20 mL). The combined ethereal extracts were washed with water (2 × 10 mL) and saturated sodium chloride solution (10 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give 0.37 g of crude alcohol: IR (CCl_4) 3400–3600 (OH), 1600, 1580 cm^{-1} (aromatic); NMR (CCl_4) δ 0.90 (s, 9, CH_3), 1.05 (s, 3, CH_3), 3.7 ppm (s, 3, aromatic methoxyl), (s, 3, aromatic methoxyl), 6.67 (m, 3, aromatic). The above crude alcohol (0.37 g) was dissolved in dry dimethyl sulfoxide (10 mL) and heated at 150 °C for 18 h. The mixture was cooled to room temperature, diluted with water (50 mL), and extracted with ether (3 × 25 mL). The combined ethereal extracts were washed with water (2 × 10 mL) and saturated sodium chloride solution (25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give a gummy material. This material was passed through a column of silica gel to remove dimethyl sulfoxide and then chromatographed on 15% silver nitrate silica gel (20 g, 75 mL column volume) with 15% ether–85% petroleum ether as eluent; fractions 3 and 4 gave 0.185 g of (±)-isozonarol dimethyl ether (**2a**) and fractions 6 and 7 gave 0.036 g of (±)-zonarol dimethyl ether (**1a**). (±)-Isozonarol dimethyl ether could not be crystallized (dried by vacuum, 0.1 mm, 24 h): IR (CCl_4) 1660 (C=C), 1610, 1585 (aromatic), 1050 (aromatic methoxyl), 865 cm^{-1} (aromatic, 1,4-disubstitution); NMR (CCl_4) δ 0.90 (s, 9, CH_3), 2.61 (m, 2, benzylic), 3.70 (s, 3, aromatic methoxyl), 3.77 (s, 3, aromatic methoxyl), 5.30 (bs, 1, —C=CH), 6.63 ppm (m, 3, aromatic). Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.49; H, 10.12.

(±)-Zonarol (1b). Lithium hydride (0.079 g or 0.15 g of 57% oil dispersion, 10 mmol) was freed from oil with pentane and flushed with dry nitrogen. Hexamethylphosphoric triamide (HMPA, 3 mL, refluxed over CaH_2 and distilled onto freshly activated molecular sieves type 4 A) was added and stirred. To this slurry, *n*-butyl mercaptan (0.901 g, 1.11 mL, 10 mmol) was added dropwise and stirred until hydrogen evolution was complete (10 min). Pure (±)-zonarol dimethyl ether (0.172 g, 0.5 mmol) in HMPA (4 mL) was added and the solution was heated at 150 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with 10% hydrochloric acid solution (50 mL), and extracted with ether (3 × 30 mL). The combined ethereal extracts were washed with water (3 × 10 mL) and saturated sodium chloride solution (25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give 0.27 g of crude product. This material was purified by passing through a column of silica gel and eluting with 35% ether–65% petroleum ether to give 0.152 g (90%) of pure (±)-zonarol (**1b**) as a gummy material: bp 155–160 °C (0.01 mm); IR ($CHCl_3$) 3300–3600 (OH), 1660 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.80 (s, 3, CH_3), 0.83 (s, 3, CH_3), 0.90 (s, 3, CH_3), 2.70 (d, 2, benzylic), 4.76 (d, 2, $=CH_2$), 6.56 ppm (m, 3, aromatic). Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.22; H, 9.55.

(±)-Isozonarol (2b). Lithium hydride (0.04 g, 0.07 g of 57%, 5 mmol) was washed with pentane to remove mineral oil and was flushed with dry nitrogen. Hexamethylphosphoric triamide (HMPA, 2 mL) was added and stirred. To this slurry, *n*-butyl mercaptan (0.451 g, 0.535 mL, 5 mmol) was added dropwise and stirred until the evolution of hydrogen had stopped (10 min). (±)-Isozonarol dimethyl ether (0.069 g, 0.2 mmol) in HMPA (2 mL) was added and heated at 145 ± 5 °C for 26 h. The reaction mixture was cooled to room temperature, diluted with 10% hydrochloric acid solution and extracted with ether (3 × 25 mL). The combined ethereal extracts were washed with water (3 × 10 mL) and saturated sodium chloride solution (25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to give 0.075 g of crude product. This material was purified by chromatography on silica gel, eluting with 65% petroleum ether–35% ether. Fractions 6 to 10 gave 0.05 g (86%) of pure (±)-isozonarol (**2b**): bp 155–165 °C (0.01 mm); IR ($CHCl_3$) 3225–3600 (OH), 1620, 1580 cm^{-1} (aromatic); NMR ($CDCl_3$) δ 0.90 (s, 9, CH_3), 2.60 (m, 2, benzylic), 5.40 (bs, 1, —C=CH—), 6.67 ppm (m, 3, aromatic). Anal. Calcd for $C_{23}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.05; H, 9.46.

1,2,3,4,5,6,7,8-Octahydro-1,1,5,5-tetramethylnaphthalene (11). To a solution of tertiary alcohol **6** (1.1 g, 4 mmol), in dry benzene (50 mL), a crystal of *p*-toluenesulfonic acid was added and the solution was allowed to reflux for 4 h. The reaction mixture was then cooled to room temperature, washed with saturated sodium bicarbonate solution (25 mL), water (25 mL), and saturated sodium chloride solution (25 mL), filtered through $MgSO_4$, and evaporated in vacuo to give 0.95 g of crude product. This material was distilled bulb to bulb at 45 ± 5 °C (0.1 mm) to give 0.85 g (80%) of colorless alkene **11**: IR (CCl_4) 1675 (C=C), 1375, 1355 cm^{-1} (*gem*-dimethyl); NMR (CCl_4) δ 1.00 ppm (s, 12, CH_3). Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: 87.39; H, 12.61.

Acknowledgment. We graciously thank the Robert A. Welch Foundation (Grant No. E-518), The National Institute of General Medical Sciences (Grant No. GM18759), and the Link Foundation for support of this research program.

Registry No.—**1a**, 63757-96-0; **1b**, 63813-82-1; **2a**, 63757-97-1; **2b**, 63813-83-2; **3**, 52782-49-7; **4**, 65516-59-8; **5**, 65556-24-3; **6** isomer 1, 65516-60-1; **6** isomer 1 2,3-dehydro deriv, 65516-65-6; **6** isomer 2, 65516-61-2; **6** isomer 2 2,3-dehydro deriv, 65516-64-5; **7**, 65516-62-3; **8** isomer 1, 65556-25-4; **8** isomer 2, 65556-27-6; **9a**, 65516-63-4; **9b**, 65556-26-5; **10**, 65516-66-7; **11**, 56239-59-9; 2,5-dimethoxy-1-bromobenzene, 25245-34-5; decahydro-1-(2,5-dimethoxybenzyl)-2,5,5,8a-tetramethyl-2-naphthol, 65516-67-8.

References and Notes

(1) W. Fenical and O. McConnell, *Experientia*, **31**, 1004 (1975); W. Fenical, J. J. Sims, D. Squatrito, R. M. Wing, and P. Radlick, *J. Org. Chem.*, **38**, 2383 (1973).
(2) G. Cimino, P. DeLuca, S. DeStefano, and L. Minale, *Tetrahedron*, **31**, 271 (1975).
(3) Personal communication with Professor W. Fenical regarding the absolute configuration of both zonarol (**1b**) and isozonarol (**2b**).
(4) The term "meroterpenoids" (from which merosesquiterpenoids is derived) was coined by Professor J. W. Conforth, *Chem. Br.*, **4**, 102 (1968), and refers to natural y occurring compounds arising from mixed biogenesis.
(5) For a preliminary report on these syntheses, see S. C. Welch and A. S. C. P. Rao, *Tetrahedron Lett.*, 505 (1977).
(6) J. S. Dutcher, J. G. Macmillan, and C. H. Heathcock, *J. Org. Chem.*, **41**, 2663 (1976).
(7) D. Todd, *Org. React.*, **4**, 378 (1948); Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946); **71**, 3301 (1949).
(8) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem.*

Soc., 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).
(9) V. J. Traynelis, W. L. Hergenrother, H. T. Hanson, and J. A. Valicenti, *J. Org. Chem.*, **29**, 123 (1964).
(10) No attempt was made to separate these epoxides. The stereochemistry was assigned on the basis of precedent and the epoxide ring opening was expected to generate (after oxidation) easily separable enone **9b** as the major product; see ref 6.
(11) J. K. Crandall and L. C. Crawley, *Org. Synth.*, **53**, 17 (1973); C. L. Kissel and B. Rickborn, *J. Org. Chem.*, **37**, 2060 (1972); R. P. Thummel and B. Rickborn, *J. Am. Chem. Soc.*, **92**, 2064 (1970).
(12) J. C. Collins and W. W. Hess, *Org. Synth.*, **52**, 5 (1972); R. Ratcliffe and R. Rodehorst, *ibid.*, **55**, 84 (1976); N. H. Andersen and H. Uh, *Synth. Commun.*, **3**, 115 (1973).
(13) E. Roman, A. J. Frey, P. A. Stadler, and A. Eschenmoser, *Helv. Chem. Acta*, **40**, 1900 (1957); R. W. Skeean, G. L. Trammell, and J. D. White, *Tetrahedron Lett.*, 525 (1976).
(14) D. F. MacSweeney and R. Ramage, *Tetrahedron*, **27**, 1481 (1971).
(15) R. D. Rieke and P. M. Hudnall, *J. Am. Chem. Soc.*, **94**, 7178 (1972); R. D. Rieke and S. E. Bales, *J. Chem. Soc., Chem. Commun.*, 879 (1973).
(16) R. E. Ireland, S. W. Baldwin, and S. C. Welch, *J. Am. Chem. Soc.*, **94**, 2056 (1972).
(17) A. Maercker, *Org. React.*, **14**, 270 (1965).
(18) G. I. Feutrill and R. N. Mirrington, *Tetrahedron Lett.*, 1327 (1970); *Aust. J. Chem.*, **25**, 1719, 1713 (1972).
(19) I. T. Harrison, *Chem. Commun.*, 616 (1969).
(20) R. Mechoulan and Y. Gaoni, *J. Am. Chem. Soc.*, **87**, 3273 (1965).
(21) We are grateful to Professor W. Fenical for providing natural samples of zonarone and isozonarone which were converted to the respective methyl ethers (**1a** and **1b**) by reduction ($NaBH_4$, CH_3OH) and *O*-alkylation (CH_3I, CaO, Me_2SO, room temperature, 24 h).
(22) The names of each of the compounds were obtained from Professor Kurt L. Loening, Director of Nomenclature, Chemical Abstracts Service, Columbus, Ohio, 43210.

Stereoselective Biomimetic Total Synthesis of 6α-Methyl-19-norsteroids

Marinus B. Groen and Filippus J. Zeelen*

Organon Scientific Development Group, Oss, The Netherlands.

Received November 1, 1977

Cyclization of the chiral substrate 3-methyl-2-[(*E*)-6′-(*m*-methoxyphenyl)-3′-heptenyl]-2-cyclopenten-1-ol (**6**) was investigated. In addition to high stereo- and regioselectivity almost complete optical induction by the methyl substituent was observed: with stannic chloride at −70 °C ~75% of the tetracyclic products consisted of 3-methoxy-6α,17-dimethyl-1,3,5(10),13(17)-gonatetraene (**8a**). This compound was converted into the 3-methyl ethers of *dl*-6α-methylestrone (**11**) and *dl*-6α-methylestradiol-17β (**13**), thus giving access to 6α-methyl-19-norsteroids.

In the last decade the biomimetic polyene cyclization reaction has proved to be a fruitful approach to the total synthesis of polycyclic natural products.[1] Practical applications for the synthesis of steroids were most extensively explored by Johnson and co-workers.[1a,b] One of the many contributions by this group was a stereospecific total synthesis of *dl*-estrone.[2]

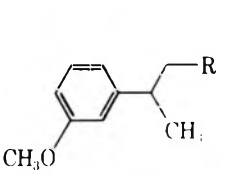
In this paper we report an extension of the latter synthesis, starting with a polyolefinic substrate which carries a methyl substitutent at the pro-C-6 atom.[3] The purpose of this modification was (a) to see whether the newly introduced chiral center would effect asymmetric induction in the cyclization and (b) to examine the practicality of this synthesis as a route to 6α-methyl-19-norsteroids.[17]

The substrate used in the *dl*-estrone synthesis[2] lacks a stable chiral center, leading to racemic products.[4] The presence of a stable chiral center in the substrate allows early resolution (an important condition for an efficient steroid synthesis) and formation at will of the steroid with the natural or unnatural configuration depending on which enantiomer of the substrate is used, *provided a high degree of optical induction by the chiral center takes place.* Examples of optical induction in the biomimetic synthesis of 11α-methyl- and 11α-hydroxyprogesterone were reported by the Stanford group.[3a,b] In the present case the chiral center is further removed from the reaction center so that optical induction is not an a priori obvious matter.

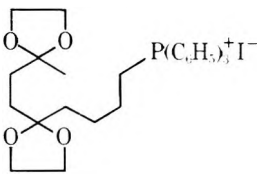
6α-Methyl-19-norsteroids were shown to be compounds with potent hormonal activity.[5] They have been prepared by partial synthesis via a somewhat troublesome route[6] and in racemic form via a Smith–Torgov type total synthesis.[5] Interestingly the latter synthesis produces 6β-methylestradiol derivatives as the major initial products, whereas the 6α isomers are the biologically more active ones.[7]

Synthesis of the Substrate

Methyl 3-(*m*-methoxyphenyl)butyrate (**1**) was prepared in 68% yield by addition of lithium dimethylcuprate to methyl *m*-methoxycinnamate. This synthesis is shorter than the published one[5] and more versatile allowing the introduction of alkyl groups other than methyl by a proper choice of the organometallic reagent. It should be noted that **1** is an asymmetric compound and therefore, at least in principle, resolvable.

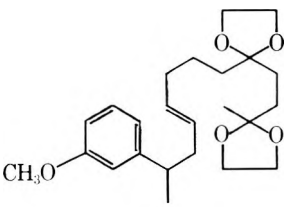


1, R = $COOCH_3$
2, R = CHO

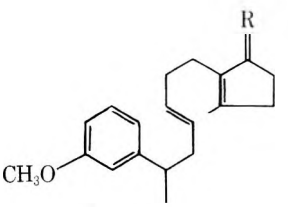


3

Elegant asymmetric syntheses of β-substituted acids[8a] and aldehydes[8b] have been reported. The aldehyde **2**, obtained by reduction of **1** with diisobutylaluminium hydride in 72% yield, was condensed with the phosphorane derived from **3**[9] employing Wittig–Schlosser conditions.[10] The olefin **4** was



4



5, R = O
6, R = H(OH)

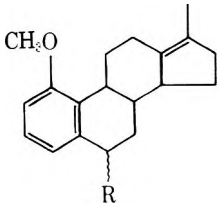
isolated in 80% yield (over 95% trans isomer by NMR analysis). Acid-catalyzed hydrolysis followed by base-catalyzed cyclodehydration produced the cyclopentenone **5** in 84% yield.

The ketone **5** was reduced with lithium aluminum hydride to the substrate **6** in quantitative yield. Due to its instability **6** was subjected to cyclization immediately after workup.

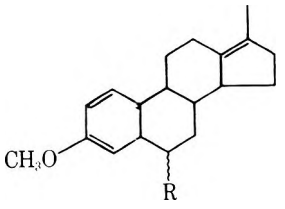
0022-3263/78/1943-1961$01.00/0

Cyclization Studies

The substrate **6** was cyclized with stannic chloride (3–5 equiv) in dichloromethane (30 min, −70 °C). The reaction mixture showed essentially two spots on TLC. These corresponded with a less and a more polar fraction isolated in 12 and 64% yield by column chromatography, consisting of the 1-methoxy (**7a, 7b**) and 3-methoxy isomers (**8a, 8b**), respectively.



7a, R = α-CH_3
b, R = β-CH_3



8a, R = α-CH_3
b, R = β-CH_3

Crystallization of the less polar fraction from methanol afforded its major component (9.5% yield based on **6**), mp 94.5–96.5 °C, which was assigned structure **7a.** The proton NMR spectrum showed inter alia a doublet at δ 1.27 (J = 6.8 Hz) for the 6α-CH_3 group and a doublet of doublets at δ 6.94 (J = 8 and 2.5 Hz) for the proton at C-4. The latter represents a downfield shift of over 0.2 ppm with respect to the 6-unsubstituted case. This shift is characteristic for a 6α-methyl substituent.[5]

Examination of the NMR spectrum of the mother liquor revealed the presence of a second methyl signal centered at δ 1.30 (d, J = 7 Hz), attributed to the 6β-isomer **7b.** Integration and taking into account the amount of **7a** isolated showed that the **7a/7b** ratio originally must have been ca. 9:1.

Crystallization of the more polar fraction from methanol afforded nearly pure **8a,** mp 37–42 °C, in 53% yield based on **6.** The proton NMR spectrum showed inter alia a doublet at δ 1.31 (J = 7 Hz) for the 6α-CH_3 group and a broadened doublet (J = 2.5 Hz) at δ 6.83 for the proton at C-4. These values compare well with reported data.[5] The stereochemistry was proven unambiguously by the conversion of **8a** into compounds with known structure (vide infra). The NMR spectrum of the mother liquor showed an additional doublet centered at δ 1.28 attributed to the 6β-isomer **8b** (cf. ref 5). The original mixture was determined to be a 9:1 mixture of **8a** and **8b.**

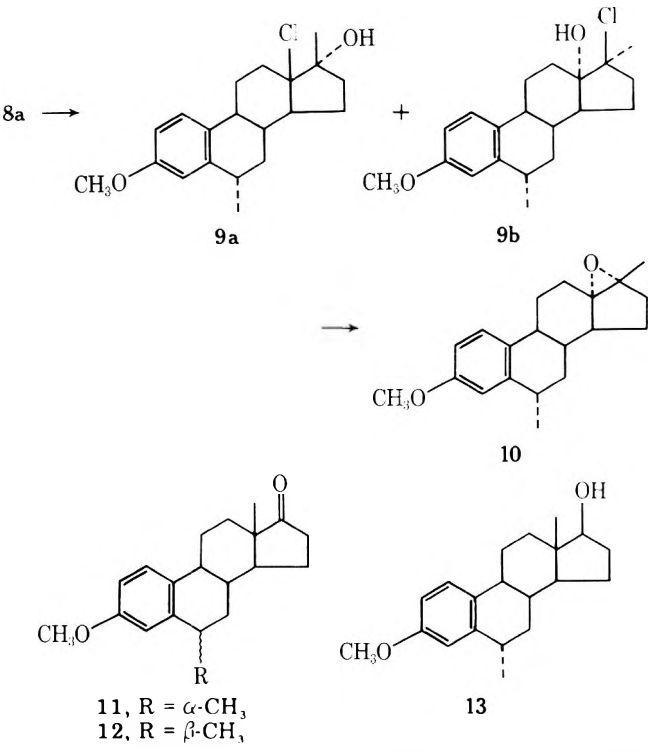
The cyclization of **6** was also carried out with formic acid at ca. 5°C. This afforded **7a** plus **7b** in 19% yield and **8a** plus **8b** in 52.5% yield. As in the previous experiment the **7a/7b** and **8a/8b** ratio's were ca. 9:1.

Pure **8a** was converted into a mixture of chlorohydrins (**9a, 9b**) by reaction with *N*-chlorosuccinimide in 2:1 *tert*-butyl alcohol/water. In situ treatment with KOH afforded the α-epoxide **10** in 54% yield, mp 149–151 °C.

The somewhat disappointing yield could be traced to the first step. A sample of pure chlorohydrin[11] was isolated by chromatography over deactivated alumina (ca. 50% yield). Subsequent treatment with base employing the same conditions as above afforded **10** in practically quantitative yield.

The epoxide **10** was converted into the methyl ether of *dl*-6α-methylestrone (**11**) in 64% yield with boron trifluoride in toluene or dichloromethane. This compound, mp 110–112 °C, was spectroscopically (NMR, IR) identical to authentic **11** (*d* enantiomer),[12] but different from authentic **12.**[13] Thus the structure of **11** and hence that of **8a** were unequivocally established.

The mother liquor of **8a** (enriched in **8b**) was also carried through the reaction sequence described above. The NMR spectrum of the reaction product clearly showed the presence



9a **9b** **10**

11, R = α-CH_3
12, R = β-CH_3 **13**

of both **11** (13-CH_3 at δ 0.89) and **12** (13-CH_3 at δ 0.92), but the latter product could not be obtained in a pure state.

Reduction of **11** with lithium aluminum hydride afforded the known racemic estradiol derivative **13,** whose physical data agreed with those reported.[5]

Discussion

The synthesis of the substrate **6** closely follows the reported procedure[2] and requires no comment. The low-temperature cyclization of **6** with $SnCl_4$ showed high regioselectivity, the para/ortho ratio (=**8a** + **8b**/**7a** + **7b**) being ca. 5 at −70 °C. As expected this ratio was affected by temperature and catalyst decreasing to 2.7 at 5 °C with formic acid. No doubt the para/ortho ratio can be improved by conducting the cyclization at lower temperature and by the use of bulkier ether substituents as was demonstrated by Johnson.[2]

More significant for our purpose is the great preponderance of 6α- over 6β-methyl-substituted cyclization products (9:1 ratio). This implies that cyclization of the (*S*) enantiomer of **6,** which can be obtained from (*S*)-**1,** must lead predominantly to products with the natural steroid configuration. It can be deduced that in that case the 6α-substituted products **7a** and **8a** will have the natural configuration and those with the 6β-methyl substituent **7b** and **8b** the unnatural one. Since the latter products can easily be removed by crystallization it follows that the work described here lends itself to the *total asymmetric synthesis of steroids with natural configuration* by the simple expedient of resolution (or asymmetric synthesis) at a *very early stage.*[14]

Whereas generally good yields were obtained in the synthesis leading to **8a** further conversion into **11** suffered from relatively low yields. This was especially so for the formation of the chlorohydrins (**9a, 9b**). It was found that in this reaction step considerable amounts of polar by-products (up to 30% yield) were formed. We believe that these products[15] arise by initial α attack of the Cl^+ ion followed by proton elimination and hydrolysis.[16]

In spite of these complications, which need further exploration, already the overall yield of the total synthesis described here compares favorably with the previously reported Smith–Torgov route.[5] Moreover it complements the latter in that 6α- rather than 6β-methylestrone derivatives are ob-

tained as the principal products. In fact apart from a single reference in the patent literature[7] no satisfactory synthesis for this class of compounds appears to have been reported (for an alternative unpublished synthesis, ref 12).

Experimental Section

Boiling points and melting points, determined in capillary tubes, are uncorrected. Infrared spectra were recorded in dichloromethane solution on a Perkin-Elmer 357 grating spectrometer. Proton NMR spectra were recorded in deuteriochloroform solution with tetramethylsilane as internal standard on a Varian A 60 D or a Bruker HX-90E instrument.

Microanalyses were performed by Dr. W. McMeekin, Analytical Department, Organon Laboratories, Newhouse, Scotland. For column chromatography Woelm silica gel 90–230 mesh and Woelm aluminum oxide were used.

Unless stated otherwise reaction mixtures were worked up by addition of water followed by three extractions with ether. The combined extracts were washed with water and dried over anhydrous sodium sulfate. After filtration solvents were removed in vacuo on a rotary evaporator. The residues were chromatographed over 20–30-fold by weight silica gel.

***dl*-3-(*m*-Methoxyphenyl)butanal (2).** A solution of lithium dimethylcuprate was prepared by addition of 40 mL of methyllithium (2 M solution, 0.080 mol) in ether to 7.6 g (0.040 mol) of cuprous iodide in 70 mL of dry ether under nitrogen at 0 °C.

A solution of 4.8 g (0.025 mol) of methyl *m*-methoxycinnamate in 20 mL of ether was added dropwise and the resulting mixture was stirred for 1 h at 0 °C. The crude product was chromatographed with 8:2 hexane–ethyl acetate to give 3.65 g (68% yield) of methyl 3-(*m*-methoxyphenyl)butyrate (1). This was dissolved in 36 mL of dry toluene and cooled to −78 °C under nitrogen. A solution of diisobutylaluminum hydride in toluene (17.5 mL, 1.2 M, 20% excess) was added dropwise at <−70 °C. The reaction mixture was stirred for 25 min at −70 °C and then poured onto 70 mL of 2 N sulfuric acid. The mixture was allowed to warm up to room temperature and the organic layer was separated, dried (anhydrous Na_2SO_4), and concentrated in vacuo. The residue was chromatographed with 9:1 hexane–ethyl acetate and distilled in vacuo to give 2.25 g of **2** (72% yield): bp 92–94 °C (0.8 mm); NMR δ 1.32 (d, J = 7 Hz, 3 H, $CHCH_3$), 2.67 (m, 2 H, CH_2CHO), 3.35 (m, 1 H, ArCH–), 3.80 (s, 3 H, OCH_3), 6.6–7.4 (m, 4 H, aromatic H's), 9.70 (t, J = 2 Hz, 1 H, CHO); IR 2839 (OCH_3), 1725, 2720, 2821 cm^{-1} (CHO). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; O, 17.96. Found: C, 74.24; H, 7.79; O, 18.19.

***dl*-(*E*)-2-(*m*-Methoxyphenyl)-9,12-bis(ethylenedioxy)-4-tridecene (4).** A suspension of 6.32 g (0.01 mol) of the phosphonium salt **3** in 20 mL of dry THF was cooled in an ice bath under nitrogen, while 11 mL of a 1.0 M solution of phenyl lithium in ether was added dropwise (a red coloration indicating formation of the ylid started after addition of ca. 1 mL). The resulting red solution was stirred for 15 min without cooling and then cooled to −70 °C. A solution of 1.6 g (9 mmol) of aldehyde **2** in 5 mL of dry THF was added dropwise and after 5 min 18 mL of 1 M phenyllithium in ether was added. The resulting red solution was warmed to −30 °C. After 5 min at −30 °C the reaction was quenched with 1 mL of methanol. Normal workup and chromatography with 8:2 hexane–ethyl acetate afforded 2.9 g (79% yield) of **4** as a colorless oil: NMR δ 1.22 (d, J = 7 Hz, 3 H, protons at C-1), 1.31 (s, 3 H, protons at C-13), 1.70 (s, 4 H, protons at C-10 and C-11), 2.7 (m, 1 H, ArCH–), 3.80 (s, 3 H, OCH_3), 3.92 (br s, 8 H, OCH_2CH_2O), 5.36 (m, 2 H, olefinic protons), 6.6–7.4 (m, 4 H, aromatic protons), 1.3–2.4 (m, 8 H); IR 971 cm^{-1} (trans CH=CH). Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97; O, 19.78. Found: C, 71.09; H, 9.07; O, 19.89.

***dl*-3-Methyl-2-[(*E*)-6′-(m-methoxyphenyl)-3′-heptenyl]-2-cyclopenten-1-one (5).** A solution of 2.9 g (7.2 mmol) of **4** in 130 mL of 2:1 95% ethanol–0.2 N hydrochloric acid was heated at 55–60 °C for 1.5 h. Subsequently 11.5 mL of 2 N aqueous potassium hydroxide was added and the resulting mixture was heated at reflux for 2 h. The reaction mixture was concentrated in vacuo to ca. 50 mL and was further worked up in the normal manner. Chromatography with 8:2 hexane–ethyl acetate gave 1.8 g (84% yield) of **5** as a viscous colorless oil: NMR δ 1.20 (d, J = 7 Hz, 3 H, $ArCHCH_3$), 1.98 (br s, 3 H, allylic methyl), 3.78 (s, 3 H, OMe), 5.32 (m, 2 H, CH=CH), 6.5–7.3 (m, 4 H, aromatic protons), 1.9–2.9 (m, 11 H); IR 1695, 1645 (cyclopentenone), 969 cm^{-1} (trans CH=CH). Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78; O, 10.72. Found: C, 80.60; H, 8.86; O, 10.50.

***dl*-3-Methyl-2-[(*E*)-6′-(*m*-methoxyphenyl)-3′-heptenyl]-2-cyclopenten-1-ol (6).** A solution of 1.8 g (6 mmol) of **5** in 60 mL of dry ether was cooled to −20 °C. Lithium aluminum hydride (0.45 g, 12 mmol) was added in portions, with stirring. The mixture was allowed to warm up to 0 °C over 30 min. The excess of hydride was destroyed by addition of saturated sodium sulfate solution. The ether layer was decanted from precipitated salts, which were extracted with two more portions of ether. The combined ether solutions were dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo (<25 °C). This left 1.8 g (99% yield) of **6** as a colorless oil, which was immediately used in the next step.

***dl*-1- and -3-Methoxy-6α,17-dimethyl-1,3,5(10),13(17)-gonatetraene (7a and 8a). a. With Stannic Chloride.** A solution of stannic chloride (2.8 mL, 5 equiv) in 150 mL of dry dichloromethane was cooled to −70 °C under nitrogen. A solution of 1.80 g (6.0 mmol) of **6** in 60 mL of dichloromethane was added dropwise with stirring over 1 h and the resulting red solution was stirred for another 30 min at −70 °C. A solution of 6.0 g of NaOH in 30 mL of 80% ethanol was added dropwise (temperature <−60 °C) followed by water. The mixture was allowed to warm up to room temperature; the organic phase was separated and dried over anhydrous K_2CO_3. The solvent was stripped off and the residue was chromatographed with 9:1 hexane–toluene. First 1-methoxy isomers (**7a, 7b**) were eluted (0.198 g, 12% yield). Crystallization from methanol gave 0.133 g of **7a**, mp 94.5–96.5 °C, and a second crop of 0.027 g, mp 87–91 °C (9.5% yield). The mother liquor contained about equal amounts of **7a** and **7b**. Further elution produced the 3-methoxy isomers (**8a, 8b**) as an oil (1.08 g, 64% yield). Crystallization from methanol gave 0.90 g (53% yield) of crystalline **8a**, mp 37–42 °C. Repeated crystallization afforded an analytically pure sample, mp 45–46 °C. The mother liquor consisted of **8a** and **8b**, which could not be separated.

b. With Formic Acid. A solution of 0.85 g (2.83 mmol) of **6** in 50 mL of dichloromethane was added dropwise with stirring to 25 mL of 98% formic acid at ca. 5 °C After the addition was completed (ca. 1 h) the pale yellow reaction mixture was stirred for 15 min at 5 °C and then diluted with water. The organic phase was separated, washed with water and aqueous sodium bicarbonate, and dried over anhydrous K_2CO_3. The products were isolated and purified as in a. Thus were obtained **7a** + **7b** (9:1 mixture) in 19% yield (0.15 g) and **8a** + **8b** in 52.5% yield (0.42 g) also as a 9:1 mixture **7a:** NMR δ 1.27 (d, J = 6.8 Hz, 3 H, 6α-CH_3), 1.65 (br s, 3 H, 17-CH_3), 3.80 (s, 3 H, OCH_3), 6.71 (dd, J = 7.5 and 2 Hz, H at C-2), 6.94 (dd, J = 8 and 2.5 Hz, H at C-4), 7.15 (t, J = 7.5 Hz, H at C-3), 0.5–3.3 (m, 14 H). **8a:** NMR δ 1.31 (d, J = 7 Hz, 3 H, 6α-CH_3), 1.63 (br s, 3 H, 17-CH_3), 3.77 (s, 3 H, OCH_3), 6.72 (dd, J = 8.5 and 2.5 Hz H at C-2), 6.83 (d, J = 2.5 Hz, H at C-4), 7.23 (d, J = 8.5 Hz, H at C-1), 0.7–3.2 (m, 14 H). Anal. Calcd for $C_{20}H_{26}O$: C, 85.05; H, 9.28; O, 5.67. Found for **7a:** C, 84.98; H, 9.15; O, 5.70. Found for **8a:** C, 85.07; H, 9.42; O, 5.76.

***dl*-3-Methoxy-6α,17-dimethyl-13α,17α-epoxy-1,3,5(10)-gonatriene (10).** To a solution of 0.282 g (1.0 mmol) of **8a** in 10 mL of *tert*-butyl alcohol was added with stirring and cooling in ice 5 mL of water, 0.50 g of powdered calcium carbonate, and 0.54 g (4 mmol) of *N*-chlorosuccinimide. The mixture was stirred for 1 h at 5 °C. In one experiment the reaction mixture was worked up at this point and chromatographed over neutral alumina (activity grade IV) to give **9a** and **9b** in ca. 50% yield. Otherwise 3 mL of 40% aqueous KOH was added and the resulting mixture was stirred for 30 min at 5 °C. Water and dichloromethane were added and the organic phase was separated and dried over anhydrous K_2CO_3. The solvent was stripped off and the residue was chromatographed over base-washed alumina (activity grade IV) with 2:1 hexane–dichloromethane. A small amount of starting material was eluted followed by 0.161 g of **10** (54% yield) and 0.10 g of more polar by-products. Analytically pure **10**, mp 149–151 °C, was obtained by recrystallization from methanol. The mixture of **9a** and **9b** redissolved in 2:1 *tert*-butyl alcohol–water and treated as above afforded **10** in quantitative yield: NMR δ 1.36 (s, 3 H, 17-CH_3), 1.32 (d, J = 7 Hz, 3 H, 6α-CH_3), 3.83 (s, 3 H, OCH_3), 6.7–7.4 (m, 3 H, aromatic protons), 0.85–3.3 (m, 14 H). Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78; O, 10.72. Found: C, 80.50; H, 8.88; O, 10.94.

***dl*-3-Methoxy-6α-methyl-1,3,5(10)-estratrien-17-one (11)** A solution of 0.217 g (0.73 mmol) of **10** in 23 mL of toluene was treated with 0.2 mL of boron trifluoride etherate and shaken for 1 min. The purple reaction mixture was shaken with aqueous K_2CO_3 until the color had disappeared. Normal workup and chromatography with 9:1 hexane–ethyl acetate afforded 0.138 g (64% yield) of **11** as an oil which crystallized on standing. An analytical sample had mp 110–112 °C (from methanol): NMR δ 0.89 (s, 3 H, 13-CH_3), 1.34 (d, J = 7 Hz, 3 H, 6α-CH_3), 3.79 (s, 3 H, OCH_3), 6.6–7.3 (m, 3 H, aromatic protons), 0.8–3.3 (m, 14 H). Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78; O, 10.72. Found: C, 80.53; H, 8.61; O, 10.77.

***dl*-3-Methoxy-6α-methyl-1,3,5(10)-estratrien-17β-ol (13).** A 20-mg sample of **11** was reduced with lithium aluminum hydride in ether. Normal workup and crystallization from ether afforded 18 mg

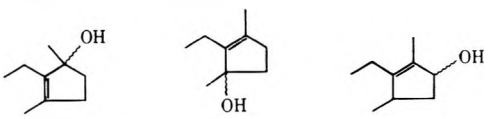
(90% yield) of pure **13**: mp 174–176 °C (lit.[5] mp 173–176 °C); NMR identical to reported data.[5]

Acknowledgment. We thank Professor W. S. Johnson for stimulating discussions. He guided us on the way which led to the initiation of this study. We acknowledge the assistance of Mr. B. Hindriken.

Registry No.—**1**, 65452-45-1; **2**, 65452-46-2; **3**, 33548-59-3; **4**, 65452-47-3; **5**, 65452-48-4; **6**, 65452-49-5; **7a**, 65452-50-8; **7b**, 65484-12-0; **8a**, 65452-51-9; **8b**, 65452-52-0; **9a**, 65452-53-1; **9b**, 65452-54-2; **10**, 65452-55-3; **11**, 65452-56-4; **12**, 65452-57-5; **13**, 5753-83-3; lithium dimethylcuprate, 15681-48-8; methyl *m*-methoxycinnamate, 15854-56-5.

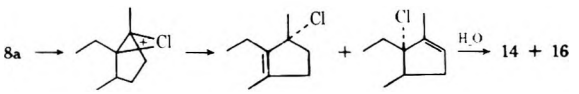
References and Notes

(1) For recent reviews on this subject see: (a) W. S. Johnson, *Bioorg. Chem.*, **5**, 51 (1976); (b) W. S. Johnson, Angew. Chem., **88**, 33 (1976); (c) E. E. van Tamelen, *Acc Chem. Res.*, **8**, 152 (1975).
(2) (a) P. A. Bartlett and W. S. Johnson, *J. Am. Chem. Soc.*, **95**, 7501 (1973); (b) P. A. Bartlett, J. I. Brauman, W. S. Johnson, and R. A. Volkmann, *ibid.*, **95**, 7502 (1973).
(3) Pro-C-6 refers to the carbon atom which is to become C-6 (steroid numbering) following Johnson's nomenclature: (a) W. S. Johnson and G. E. DuBois, *J. Am. Chem. Soc.*, **98**, 1038 (1976); (b) W. S. Johnson, S. Escher, and B. W. Metcalf, *ibid.*, **98**, 1039 (1976).
(4) A chiral center is present in the form of an allylic alcohol or its derivative, which is lost upon cyclization. It was suggested[2a] that optical induction by this chiral center might take place, but investigations to that effect showed only minimal retention of optical activity: W. S. Johnson, J. A. M. Peters, N. P. van Vliet, and F. J. Zeelen, to be published
(5) G. H. Douglas, G. C. Buzby, Jr., C. R. Walk, and H. Smith, *Tetrahedron*, **22**, 1019 (1966).
(6) C. C. Bolt, A. J. van den Broek, G. H. Visser, H. P. de Jongh, and C. M. Siegmann, *Recl. Trav. Chim. Pays-Bas*, **90**, 849 (1971).
(7) Japanese Patent Publication 2282 (1963), Teikoku Horm. Manufacturing Comp.; *Chem. Abstr.*, **59**, 11607 (1963).
(8) (a) A. I. Meyers and C. E. Whitten, *J. Am. Chem. Soc.*, **97**, 6266 (1975); (b) S. Hashimoto, S. Yamada, and K. Koga, *ibid.*, **98**, 7450 (1976).
(9) W. S. Johnson, M. B. Gravestock, and B. E. McCarry, *J. Am. Chem. Soc.*, **93**, 4332 (1971).
(10) Reaction conditions for this and the following steps in the synthesis were taken with some modifications from Johnson's work.[2,9]
(11) The NMR spectrum of this sample showed inter alia singlets at δ 1.49 and 1.64 (ca. 4:1 ratio) which tentatively may be assigned to the 17-CH_3 group of **9a** and **9b**, respectively.
(12) Authentic *d*-11, mp 89–90 °C, was prepared from 6α-methyl-4-estrene-3,17-dione[6] by microbiological aromatization (Arthrobacter Simplex) followed by methylation.
(13) Authentic *d*-**12**, mp 106–107 °C, was prepared by methylation of 6β-methylestrone: E. Velarde, J. Iriarte, H. J. Ringold, and C. Djerassi, *J. Org. Chem.*, **24**, 311 (1959).
(14) By the same token steroids with the unnatural configuration may be obtained by starting with (*R*)-**6**.
(15) NMR evidence suggest the following partial structures:



14 15 16

The NMR spectrum showed inter alia signals at δ 1.7 (br s, allylic methyl in **15** and **16**), 1.34 (s, CH_3CO in **14**), and 4.56 (br d, J = 5 Hz, HCOH in **16**).
(16) We propose the following mechanism:



17 18 19

(17) A similar total synthesis of thiophene analogues of 6α-alkyl-19-norsteroids was reported recently: A. A. Macco, R. J. de Brouwer, and H. M. Buck, *J. Org. Chem.*, **42**, 3196 (1977).

Total Synthesis of (±)-Cedrol and (±)-Cedrene via an Intramolecular Diels–Alder Reaction

Edward G. Breitholle and Alex G. Fallis*

Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland, Canada A1B 3X7

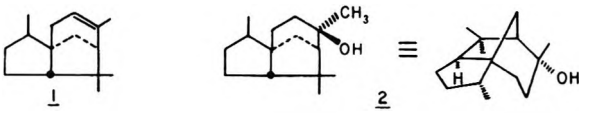
Received September 21, 1977.

A total synthesis of racemic cedrol and cedrene is described in which a key step is the intramolecular Diels–Alder reaction of alkyl cyclopentadiene **3** to give the tricyclic olefin **4**. Oxidation of this material followed by ring expansion gives cedrone (**6**), which is converted to the sesquiterpenes. Modification of the functionality of the starting materials will permit the application of this general route to diverse tricyclic systems.

Cedar-wood oil contains the interesting sesquiterpenes α-cedrene (**1**) (accompanied by ~15% of the β isomer) and its crystalline hydration product cedrol (**2**), both of which possess the relatively rare tricyclo[5.3.1.0^{1,5}]undecane skeleton.[1] In addition, several related more highly oxygenated members of this family such as shellolic acid[2] and other lac resin and vetiver oil components[3] are known. Interest in these tricyclic sesquiterpenes is widespread and a number of diverse syntheses have been reported since the original total synthesis of Stork and Clarke.[4] However, all of these recent synthetic studies[5] have attempted to mimic, to some extent, the bio-

synthesis of cedrene and, thus, have utilized a series of carbonium ion intermediates of the general type illustrated.

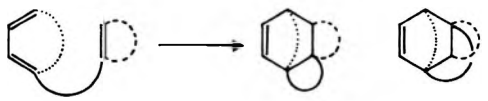
We report herein a total synthesis of (±)-cedrol (**2**) and (±)-cedrene (**1**) via an intramolecular Diels–Alder reaction



1 2

of an alkyl cyclopentadiene. The stereoselective route is direct and should be suitable for the construction of related compounds.[6]

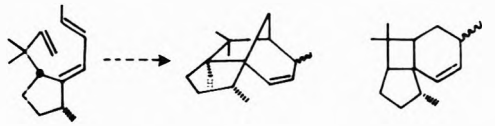
The Diels–Alder reaction occupies a position of prominence in the arsenal of the synthetic organic chemist as a consequence of its good yields, mild reaction conditions, predictability, and high stereoselectivity. In view of both the steric and electronic requirements for this cycloaddition, intramolecular applications provide access to diverse systems which are otherwise difficult to prepare.[7] Thus, complex multicyclic



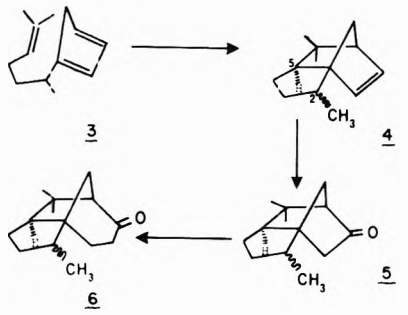
arrays (as illustrated) can be envisaged, when both the diene and dienophile components are themselves cyclic, and with

0022-3263/78/1943-1964$01.00/0

Scheme I



Scheme II



appropriate ring systems the opportunity to prepare stereoselectively a variety of tricyclic sesquiterpenes is apparent.

Several possible approaches to the cedrene nucleus may be envisaged. Retrograde analysis of the cedrene skeleton reveals that a "paper" Diels–Alder route should be the sequence in Scheme I. The simplicity of this approach has certain appeal; however, our studies on other internal Diels–Alder systems, earlier work by House and Cronin[8] with acyclic dienes, and a careful examination of molecular models indicate that the unsaturated compound is too rigid to permit the required alignment of the π systems for the reaction to be successful. Indeed, it appears that to the extent that any monomeric product is formed the undesired cyclobutane compound will be favored due to the preferred orientation of the dienophile.

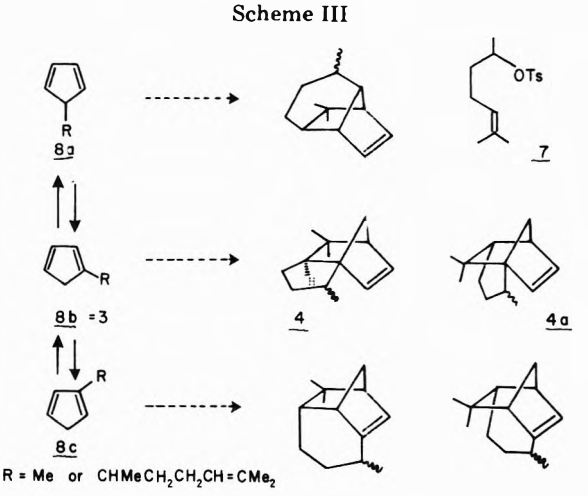
Thus, the approach selected (Scheme II) is based on the generation of a suitable tricyclo[5.2 1.0^{1,5}]dec-8-ene system (i.e., **4**) which by ring expansion and functional-group manipulation could be converted to cedrene. An attractive route to this intermediate is by internal cycloaddition of the alkyl cyclopentadiene **3**. The sequence takes advantage of the rapid isomerization of 5-alkyl- to 1-alkylcyclopentadienes at room temperature[9] and, although the double bond is trisubstituted, necessitating forcing conditions for the reaction, it was anticipated, due to the stereochemical constraints of the system, that the cyclopentane side chain would have the correct exo orientation[10] and that hydroboration would give the desired ketone **5** for ring expansion to cedrone (**6**).

Results and Discussion

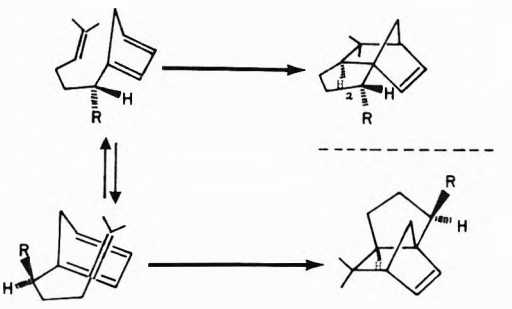
A commercial sample of 6-methyl-5-hepten-2-one was reduced with lithium aluminum hydride in diethyl ether and the resulting alcohol[11] treated with tosyl chloride in pyridine to afford the tosylate **7** in 93% overall yield. Separate treatment of the alcohol with triphenylphosphine dibromide gave the corresponding bromide (74%). It is well established, from previous studies with methyl cyclopentadiene,[9] that the initial product from alkylation of sodium cyclopentadiene **8a** isomerizes rapidly at room temperature to **8b** and more slowly to **8c**. Thus, alkylation of sodium cyclopentadiene[12] with tosylate **7** in tetrahydrofuran at 0 °C for 30 min followed by 4 h at room temperature afforded, after workup, the isomer **8b** (85% yield).[13] Detectible amounts of the isomers **8a** and **8c** were not present based on the ^{1}H NMR spectrum. This spectrum displayed a multiplet at δ 2.80 due to the two allylic cyclopentyl hydrogens and a complex signal from δ 5.8 to 6.5 representing the three vinyl ring hydrogens consistent with structure **8b**.

Although the desired isomer **8b** had been obtained, the thermal conditions required for the Diels–Alder reaction will

Scheme III



Scheme IV



shift the equilibrium, and thus consideration of the possible intramolecular cycloaddition products which may result is warranted. These are depicted in Scheme III. It will be noted that monomeric tricyclic products from **8c** are unlikely, since both possible structures violate Bredt's rule. The desired product **4** from **8b** will clearly be favored, since the geometry of the system precludes the efficient overlap of the reacting centers required for the twistane structure **4a**. However, if sufficient **8a** is present it would cyclize to the undesired structure, although for this to occur the Diels–Alder reaction must be more rapid than isomerization to **8b** which seems unlikely under the temperature conditions found to be required.

Cyclization of **8** was effected by heating a dilute solution in hexamethylphosphoramide or tri-*n*-butylamine at 205 ± 5 °C for 7 h to give the tricyclic olefin **4** in 36% yield after column chromatography. Alternatively the reaction was conducted in a sealed tube in xylene at 155 °C for 50 h. Based on unreacted starting material this was the most efficient process affording the desired product in 74% yield, but attempts to push the reaction to completion including the use of metal catalysts were unsuccessful. It appears that the equilibrium position between the open precursor and the Diels–Alder adduct cannot be easily shifted under the temperature and pressure conditions available.

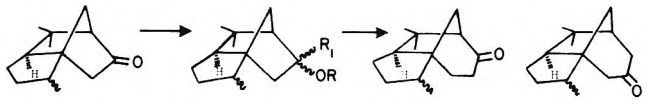
The isomeric internal Diels–Alder structures are excluded by the ^{1}H NMR spectrum of the cyclization product which is consistent with **4**. The olefinic signals appeared as an unsymmetrical multiplet at δ 6.01 representing the AB portion of an ABX system, while the single allylic bridgehead proton (X) gave rise to a broad resonance at δ 2.27 ($W_{1/2}$ = 6 Hz). The methyl signals appeared as singlets at δ 0.80 and 1.05 due to the endo and exo geminal group and as a doublet at δ 0.91 (J = 6.5 Hz) representing the secondary methyl function. Although **4** was homogeneous by both GLC and TLC, the proton noise-decoupled ^{13}C NMR spectrum indicated it was an epimeric mixture at C_2 (~1:1).[14] This spectrum confirmed the

single mode of attachment of the cyclopentane side chain, and the success of the synthesis indicated this was exo.

Unfortunately, there does not appear to be a simple method of controlling the stereochemistry at C_2 during the reaction. An unsubstituted alkyl cyclopentadiene (R = H) may react from either of the two conformations shown. These are equivalent except for the orientation of the double bond with respect to the cyclopentadiene methylene and cyclization will give rise to an enantiomeric mixture (the two products are nonsuperimposable mirror images). In our case (R = CH_3), since there is not a significant conformational energy difference due to the nonbonded interactions present in the precursor (between the methyl group and the methylene bridge), even optically active **8b** will afford a diastereomeric mixture.

Hydroboration of **4** in dimethoxyethane proceeded as expected to give after oxidative workup and treatment with Jones' reagent the desired ketone **5** whose infrared spectrum contained a strong carbonyl band at 1735 cm^{-1} typical of a cyclopentanone. No evidence for the positional isomer due to attack at the more hindered center was obtained. Previous work with norbornanone[15] suggested that ring expansion of this ketone should give predominantly the required ketone **6** as an epimeric mixture.

Ketone **5** was inert to diazomethane even under Lewis acid catalyzed conditions and, since conventional cyanohydrin formation failed, the trimethylsilylcyanohydrin **9** was prepared using the general procedure of Evans and co-workers[16] with trimethylsilylcyanide and zinc iodide at room temperature. The nitrile displayed a very weak infrared band at 2220 cm^{-1} in addition to intense absorptions at 860 and 1260 cm^{-1} due to the trimethylsilyl function. The primary amine **10** obtained upon lithium aluminum hydride reduction was treated with nitrous acid to give the ring-expanded ketones in 73% overall yield from **5**. This product contained a variable amount (15–25%) of the positional isomer **11** which was separated by TLC.[17]



5 9 R = $SiMe_3$, R_1 = CN 6 11

10 R = H, R_1 = CH_2NH_2

Stereoselective addition of methyllithium[4] to the epimeric cedrone mixture **6** gave a 1:1 mixture of (±)-cedrol (**2**) and (±)-*epi*-cedrol. These alcohols were separated by GLC and the spectral (^1H NMR, IR, MS) and chromatographic properties (GLC, TLC) of the synthetic cedrol were indistinguishable from an authentic sample of the natural material. The cedrol was converted to (±)-α-cedrene (**1**) and (±)-β-cedrene in quantitative yield (ratio 80:20) by dehydration[19] in pyridine containing thionyl chloride at 5 °C to complete the synthesis.

Extension of this route using modified side chains should provide access to a variety of more highly oxygenated cedrenoids as well as the related tricyclo[6.2.1.$0^{1,6}$]undecane ring system possessed by isolongifolene.

Experimental Section

Melting points were determined on a Fisher-John's melting point apparatus and are uncorrected. Microanalyses were performed by Atlantic Microlab Inc., Atlanta, Georgia.

Infrared spectra were recorded neat, unless otherwise indicated, on a Perkin-Elmer 237B or 451 grating spectrophotometer and were calibrated with the 2850- and 1601-cm^{-1} bands of polystyrene film. Proton magnetic resonance spectra were measured using a Varian Model EM-360 spectrometer in carbon tetrachloride solutions, unless otherwise stated, containing tetramethylsilane as an internal standard. Band positions are reported in parts per million downfield from Me_4Si (δ scale). Mass spectra were determined on a Hitachi Perkin-Elmer EMU 6E instrument using a ionization energy of 70 eV.

The GLC analyses were conducted on a Varian Aerograph gas chromatograph Model 1720 with helium as a carrier gas on a 10 ft × 0.25 in. 13% SE-30 column supported on Chromosorb W (AW-DMCS) (70–80 mesh) (A) or on a 8 ft × 0.25 in. 20% Carbowax 20 M column supported on Chromosorb W (AW-DMCS) (70–80 mesh) (B).

Solutions in organic solvents were dried over anhydrous magnesium sulfate and stripped of solvent with a Büchi rotary evaporator connected to a water aspirator.

6-Methyl-5-hepten-2-ol. A solution of 6-methyl-5-hepten-2-one (10 g, 68 mmol, Aldrich) in dry ether (50 mL) contained in a dropping funnel was added slowly to a 500-mL three-necked round-bottom flask, equipped with a reflux condenser fitted with a calcium chloride drying tube, containing a suspension of lithium aluminium hydride (2.66 g, 70 mmol) in anhydrous ether (110 mL). The resulting mixture was refluxed for 12 h and the excess reagent destroyed by the careful addition of aqueous ethyl acetate. The reaction mixture was diluted with cold 2 M sulfuric acid (150 mL). The organic layer was separated and the aqueous layer extracted with ether (2 × 45 mL). The combined ether extracts were washed with saturated aqueous sodium chloride solution and dried, the solvent was removed under reduced pressure, and the residual oil was purified by distillation [bp 33–35 °C (0.35 mm), lit.[11] bp 91 °C (34 mm)] to give the alcohol: 8.7 g (100%); IR (neat) 3320–3350 (br, OH) cm^{-1}; ^1H NMR δ 5.0 (1 H, br t, J = 7 Hz, CH=C), 4.16 (1 H, s, OH), 3.65 (1 H, sextet, J = 6.5 Hz, CHO), 1.64 (3 H, s, CH_3C=C), 1.55 (3 H, s, CH_3C=C), 1.09 (3 H, d, J = 6.5 Hz, CH_3CH) ppm; mass spectrum M* 128.

6-Methyl-5-heptene 2-*p*-toluenesulfonate (7). *p*-Toluenesulfonyl chloride (9.55 g, 50 mmol) was added in small increments to a cold solution (ice bath) of the methylheptenol (5.0 g, 39 mmol) in pyridine (22 mL), and stirring was continued for 21 h at ~5 °C (cold room). The white reaction mixture was transferred to a separatory funnel, ice-cold 40% aqueous hydrochloric acid (125 mL) was added, and the aqueous material was extracted with ether (2 × 100 mL). These combined extracts were washed with water and brine and then dried, and the solvent was removed under reduced pressure to give the tosylate **7**, 10.33 g (93.5%), as a clear light-yellow oil: IR (neat) 1597 (Ph) 1195, 1180 (–SO_3R) cm^{-1}; ^1H NMR δ 7.63 (2 H, d, J = 9 Hz, ArH α to SO_3), 7.18 (2 H, d, J = 9 Hz, ArH α to CH_3), 4.83 (1 H, br t, J = 7 Hz, CH=C), 4.47 (1 H, sextet, J = 6.5 Hz, CHO), 2.33 (3 H, s, CH_3Ar), 1.59 (3 H, s, CH_3C=C), 1.45 (3 H, s, CH_3C=C), 1.18 (3 H, d, J = 6.5 Hz, CH_3CH) ppm.

Anal. ($C_{15}H_{22}O_3S$) C, H, S.

2-Bromo-6-methyl-5-heptene. To triphenylphosphine (4.19 g, 16 mmol, BDH) suspended in cold (ice bath) dry acetonitrile (70 mL) a solution of bromine (2.56 g, 16 mmol) in acetonitrile (15 mL) was added dropwise followed by pyridine (1.3 mL, 16 mmol). The reaction, after stirring for 15 min in the ice bath, was warmed to room temperature, and a solution of 6-methyl-5-hepten-2-ol (2.0 g, 16 mmol) in acetonitrile (20 mL) was added over 15 min. The resulting clear solution was stirred at room temperature for 1 h, the solvent was removed and the resulting solid was extracted between ethyl acetate and water. The organic layer was dried and the residue after filtration and concentration distilled [bp 32–38 °C (0.75 mm)] to give the bromide: 2.3 g (74%); ^1H NMR δ 5.01 (1 H, br t, $J \approx 7$ Hz, CH=C), 4.00 (1 H, m, $J \approx 6.5$ Hz, CHBr), 1.60, 1.71 (9 H, CH_3) ppm; mass spectrum M* 190.

Preparation of 1,5-Dimethyl-4-hexenyl-2′-cyclopentadiene (8). (A) Sodium spheres (2.88 g, 0.125 mol, MCB) were refluxed in dry xylene (35 mL) under nitrogen until sodium sand had formed. After cooling to room temperature the xylene was decanted, and the sand was washed with dry tetrahydrofuran (2 × 25 mL) and suspended in tetrahydrofuran (75 mL). Freshly distilled cyclopentadiene (~10 mol) was added to the stirred mixture in four portions, resulting in a deep red-purple solution in which all the sodium had been consumed (~3 h).[12] The solution was cooled in an ice bath, and the tosylate **7** (31.3 g, 0.11 mol) in dry tetrahydrofuran (100 mL) was added dropwise over 0.5 h. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirring continued for a further 4 h. The light-brown mixture was transferred to a separatory funnel, diluted with brine (100 mL), and extracted with ether (4 × 700 mL), the combined extracts were washed with brine and dried, and the solvent was removed to afford an oil which was purified by column chromatography on silica gel (10:1) elution with *n*-hexane to give the hydrocarbon **8**, 16.5 g (85%), as a clear oil: IR 1660, 1601 (C=C) cm^{-1}; ^1H NMR 5.8–6.5 (3 H, m, cyclopentadiene), 5.02 (1 H, br t, $J \approx 6$ Hz, CH=CMe_2), 2.80 (2 H, d of m $J \approx 5$, 1.3, 1 Hz, C=CCH_2C=C), 1.09 (3 H, d, J = 7 Hz, CH_3CH), 1.55, 1.63 [6 H, s, $(CH_3)_2C$=C] ppm; mass spectrum M* 176.

An analytical sample was obtained by preparative GLC (column A).

Anal. ($C_{13}H_{20}$) C, H.

(B) Similar reaction of sodium cyclopentadiene with the bromide required 104 h at room temperature in THF and after column chromatography afforded the triene 8 in 69% yield.

(C) Cyclopentadienylmagnesium bromide was prepared according to the method of Brieger[20] and reacted over 15 h at room temperature with tosylate in diethyl ether under nitrogen to give 8 in 65% yield after standard workup and chromatography.

(D) Lithium cyclopentadiene was generated from methyllithium and cyclopentadiene and reacted with the tosylate (4 h, 0–25 °C) to give a 57% yield of the alkyl cyclopentadiene after chromatography.

Preparation of 2,6,6-Trimethyltricyclo[5.2.1.0^{1,5}]dec-8-ene (4). (A) A solution of alkylcyclopentadiene 8 (18.41 g, 0.105 mol) in dry hexamethylphosphoramide (HMPA, 100 mL) was added over a 2-h period to a hot solution of HMPA (110 mL) maintained under N_2 in a silicone oil bath at 205 ± 5 °C in a 500-mL three-necked flask equipped with a condenser and pressure-equalizing dropping funnel. Heating was continued for a further 5 h, the reaction was cooled to room temperature, and the resulting black solution was diluted with brine (250 mL) and extracted with ethyl acetate (3 × 90 mL). The combined extracts were washed with water (5 × 100 mL), dried, and concentrated, and the oily residue was passed through a silica gel column (8:1) eluting with *n*-hexane. These fractions were combined and distilled [bp 53–56 (0.2 mm)] to give the tricyclic olefin **4**: 6.5 g (36%); IR (neat) 3040 (CH=C), 1550 (w, C=C) cm^{-1}; ^{1}H NMR δ 6.01 (2 H, m, CH=CH), 2.27 (2 H, br s, $w_{1/2}$ = 6 Hz, CH), 0.81 (3 H, s, CH_3), 1.07 (3 H, S, CH_3), 0.91 (3 H, d, J = 6.5 Hz, CH_3CH) ppm; ^{13}C NMR ($CDCl_3$) δ 139.56, 139.11, 136.03, 135.58 (C=C for each epimer); mass spectrum M* 176.

Anal. ($C_{13}H_{20}$) C, H.

(B) The triene 8 (0.161 g, 0.915 mmol) in dry xylene (4.5 mL) was sealed in a Carius tube and heated at 155 ± 3 °C for 51 h. The tube was opened, solvent was removed, and the product was isolated in 37% yield (74% based on unreacted starting material) by preparative GLC (column A).

(C) A solution of the triene 8 (0.271 g, 1.54 mmol) in dry tri-*n*-butylamine (15 mL) was added over a 0.5-h period to a hot solution of tri-*n*-butylamine (40 mL) maintained under N_2 in a silicone oil bath at 210 ± 5 °C in a 100-mL three-necked flask equipped with a condenser and pressure-equalizing dropping funnel. Heating was continued for a further 3.5 h, the cooled reaction mixture was poured into ice-cold 50% aqueous hydrochloric acid, and the product was extracted with ether (2 × 50 mL). The combined extracts were washed with dilute hydrochloric acid, 10% aqueous sodium bicarbonate solution (25 mL), and brine, dried, and concentrated to give an oily residue. The tricyclic olefin 4 was purified by preparative GLC, 0.079 g (29%, ~55% based on unchanged starting material) (column A).

Preparation of 2,6,6-Trimethyltricyclo[5.2.1.0^{1,5}]decan-8-one (5). To a cold (0 °C) solution of the alkene 4 (1.7 g, 9.7 mmol) in dry dimethoxyethane (12 mL) under nitrogen, in a 100-mL three-necked flask equipped with a reflux condenser and pressure-equallizing dropping funnel maintained in an ice bath, was added sodium borohydride (0.53 g, 14 mmol). Freshly distilled boron trifluoride etherate (1.97 mL, 16 mmol) in dimethoxyethane was added dropwise to the cold solution over a 10-min period. The reaction mixture was allowed to warm to room temperature, and stirring was continued for a total of 20 h. The reaction was then cooled in an ice bath and the excess reagent destroyed by careful addition of water (~1.5 mL) and this was followed by aqueous sodium hydroxide solution (3 M, 5 mL) and aqueous hydrogen peroxide (30%, 5 mL) dropwise. The reaction was refluxed gently for 45 min, aqueous 10% sodium sulfite solution was added to destroy the excess peroxide (negative starch/KI test), diluted with water, and extracted with ethyl acetate (4 × 50 mL). The combined extracts were washed with brine (50 mL), dried, and concentrated to give an oil (1.7 g). This alcohol was dissolved in dry acetone and cooled to 0 °C (ice bath), and Jones' reagent was introduced dropwise to the stirred solution until a faint-yellow color persisted. A few drops of isopropyl alcohol were added to utilize excess oxidant, and the mixture was poured into ether–brine. The aqueous layer was extracted with ether (3 × 35 mL), and the combined extracts were washed with water and brine, dried, and concentrated to afford the ketone as an oil (1.59 g, 86%). This material was shown to be homogeneous by GLC analysis (column A) and was used without further purification: IR (neat) 1735, (CCl_4), 1745 cm^{-1}; NMR δ 0.96 (9 H, br s with two sharp shoulders), 1.03, 0.98 (CH_3); 75 mg of ketone plus 40 mg of Eu(fod)$_3$ resolved the methyl signals and confirmed that the diastereomeric ratio was 1:1; mass spectrum M* 192.

The ketone was further characterized as its 2,4-DNP derivative, crystallized from aqueous methanol, mp 164–166 °C.

Anal. ($C_{19}H_{24}N_4O_4$) C, H, N.

Preparation of Silyl Cyanohydrin (9). Anhydrous zinc iodide (10 mg) and trimethylsilylcyanide (0.92 g, 9.2 mmol) were added to the tricyclic ketone **5** (1.70 g, 8.85 mmol) maintained under nitrogen. The resulting solution was stirred at room temperature for 5.5 h and then concentrated under reduced pressure to give the cyanohydrin ether: 2.51 g (97%); IR (neat) 2220 (w, C≡N) cm^{-1}; ^{1}H NMR δ 0.30 [9 H, s, $(CH_3)_3Si$] ppm; mass spectrum M* 291.

Preparation of Amino Alcohol 10. Lithium aluminum hydride (10.4 g, 0.011 mol) was suspended in anhydrous ether (12 mL) under N_2 in a 50-mL three-necked flask equipped with a magnetic stirring bar, reflux condenser, and pressure-equalizing dropping funnel. An ether solution (10 mL) of the cyanohydrin ether **9** (2.66 g, 9.14 mmol) was added dropwise so that gentle reflux was maintained. Stirring was continued for 10 h at room temperature, excess hydride was destroyed by careful addition of water (~1 mL), 15% aqueous sodium hydroxide solution (1 mL), and water (1 mL), and the reaction was stirred until a granular white precipitate was formed. After filtration, the ether solution was washed with brine, dried, and concentrated to give the aminomethyl alcohol **10**: 1.81 g (89%); IR (neat) 3330 (br OH), 3120–3280 (br NH_2) cm^{-1}.

The amine hydrochloride was prepared by bubbling hydrochloric acid through an ether solution of the amine and collecting the precipitate: mp 205 °C, sublimed 250–260 °C; ^{1}H NMR (Me_2SOd_6) δ 8.10 (3 H, br s, NH_3^+), 4.95 (1 H, br s, OH), 2.80 (2 H, s, CH_2N) ppm. An analytical sample was recrystallized from methanol–diethyl ether (1:8).

Anal. ($C_{14}H_{26}ONCl$) C, H, N.

Preparation of 2,6,6-Trimethyltricyclo[5.3.1.0^{1,5}]undecan-8-one (6). An aqueous solution (3 mL) of sodium nitrite (0.38 g, 5.5 mmol) was added dropwise to a cold (ice bath) solution of the amino alcohol **10** (0.91 g, 4.08 mmol) in water (7 mL) containing glacial acetic acid (0.35 mL, 6.0 mmol). The reaction was stirred for 2 h at 0 °C and 6 h at room temperature. water was added, and the reaction was then extracted with ether (3 × 25 mL). The combined extracts were washed with aqueous 10% sodium bicarbonate solution and brine, dried, and concentrated to give the ketones as an oil (0.7 g, 83.3%). The analysis indicated that 15–25% (depending on run) of the positional isomer **11** was present. They were separated from the epimeric cedrones by TLC (six elutions with 20% chloroform–*n*-hexane). The upper band contained ketone **11**: IR (neat) 1706 (C=O) cm^{-1}; ^{1}H NMR δ 0.88 (3 H, d, J = 6.5 Hz, CH_3CH), 1.13 (3 H, s, CH_3), 1.02 (3 H, s, CH_3) ppm; mass spectrum M* 206.

The epimeric cedrones (**6**) were extracted from the lower band: IR (neat) 1705 (C=O) cm^{-1}; ^{1}H NMR δ 0.97 (9 H, br s with shoulders, CH_3) ppm; mass spectrum M* 206.

The diastereomer could be separated by preparative GLC (column B, 187 °C), the cedrone possessing the longer retention time.

Preparation of (±)-*epi*-Cedrol and (±)-Cedrol (2). A dry ether solution (5 mL) of the epimeric cedrones (0.33 g, 1.6 mmol) was added slowly to a methyllithium solution (10 mL, 11 mmol). The resulting solution was refluxed under nitrogen for 2 h, cooled, quenched carefully with water, diluted with ether, and extracted, and the combined ether extracts were washed with brine, dried, and concentrated to give the cedrols as a semicrystalline residue, 0.284 g (80%). The alcohols were separated by preparative GLC (column B, 177 °C), the (±)-*epi*-cedrol being eluted first.

(±)-*epi*-cedrol recrystallized from aqueous methanol: mp 107–109 °C; IR (Nujol) 3450 (br, OH); ^{1}H NMR δ 0.83 (3 H, d, J = 6 Hz, CH_3CH), 0.92 (3 H, s, *endo*-CH_3), 1.19 (3 H, s, *exo*-CH_3), 1.23 (3 H, s, CH_3COH) ppm; mass spectrum M* 222.

Anal. ($C_{15}H_{26}O$) C, H, O.

(±)-Cedrol recrystallized from aqueous methanol; mp 94–96 (lit.[4] (+)-cedrol mp 86–87 °C); IR (nujol) 3330 (br, OH) cm^{-1}; ^{1}H NMR δ 0.82 (3 H, d, J = 6 Hz, CH_3CH), 0.97 (3 H, s, *endo*-CH_3), 1.18 (3 H, s, *exo*-CH_3), 1.26 (3 H, s, CH_3COH) ppm; mass spectrum M* 222. These spectral features were the same as an authentic sample of commercial cedrol.

The total ketone mixture from the ring expansion was also treated with methyllithium and the resulting alcohols were separated by GLC (column B), or alternatively the positional isomers were first separated from the cedrols by TLC eluting with 50% chloroform–*n*-hexane.

Preparation of (±)-α-Cedrene (1) and (±)-β-Cedrene.[19] Thionyl chloride (0.1 mL) was added to a cold (0 °C) pyridine solution (1 mL) of (±)-cedrol (15 mg, 0.07 mmol), and the reaction was stirred under nitrogen for 1.5 h. Water was added and the mixture was extracted with ether (3 × 15 mL); these extracts were washed with cold aqueous 10% hydrochloric acid and brine, dried, and concentrated

to afford a quantitative conversion to (±)-α- and (±)-β-cedrene (80:20). They could be separated by GLC (column B, 146 °C): ^{1}H NMR δ 0.82 (3 H, d, J = 6.5 Hz, CH_3CH), 0.92 (3 H, s, *endo*-CH_3), 0.98 (3 H, s, *exo*-CH_3), 5.15 (0.8 H, br s, HC=C, α), 4.49 (0.2 H, br s, CH_2=C, β) ppm; mass spectrum M* 204.

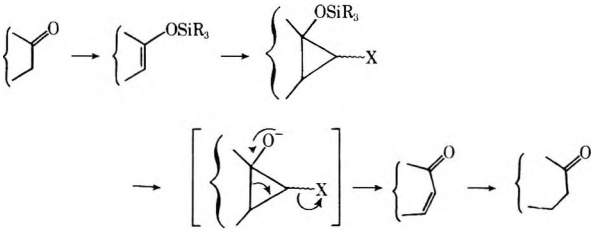
These results compared favorably with an authentic sample of cedrol, which under the conditions described above afforded the α- and β-cedrenes in an 83:17 ratio. The spectral features of the synthetic cedrene were in excellent agreement with an authentic sample of α-cedrene (Aldrich) shown by GLC and NMR analysis to contain 14% of the β isomer.

Acknowledgment. We are grateful to Memorial University of Newfoundland for financial support of this research.

Registry No.—**1**, 22567-43-7; **2**, 22567-44-8; **4** epimer 1, 65391-62-0; **4** epimer 2, 65391-63-1; **5** epimer 1, 65391-64-2; **5** epimer 2, 65391-65-3; **5**-DNP, 65442-01-5; **6** epimer 1, 50896-63-4; **6** epimer 2, 50896-62-3; **7**, 4582-61-0; **8b**, 65378-59-8; **9**, 65378-60-1; **10**, 65378-61-2; **10** HCl, 65378-62-3; **11**, 65378-63-4; 6-methyl-5-hepten-2-one, 110-93-0; 6-methyl-5-hepten-2-ol, 1569-60-4; *p*-toluenesulfonyl chloride, 98-59-9; 2-bromo-6-methyl-5-heptene, 4434-77-9; cyclopentadiene, 542-92-7; sodium cyclopentadiene, 4984-82-1; cyclopentadienyl bromide, 41851-49-4; lithium cyclopentadiene, 16733-97-4; trimethylsilylcyanide, 7677-24-9; (±)-*epi*-cedrol, 65391-66-4; (±)-β-cedrene, 65450-98-8.

References and Notes

(1) G. Stork and R. Breslow, *J. Am. Chem. Soc.*, **75**, 3291, 3292 (1953); Pl. A. Plattner, A. Fürst, A. Eschenmoser, W. Keller, H. Klau, St. Meyer, and M. Rosner, *Helv. Chim. Acta*, **36**, 1845 (1953); Pl. A. Plattner, A. Fürst, St. Meyer, and W. Keller, *ibid.*, **37**, 266 (1954).
(2) P. Yates and G. F. Field, *J. Am. Chem. Soc.*, **82**, 5764 (1960).
(3) R. Kaiser and P. Naegeli, *Tetrahedron Lett.*, 2009 (1972); A. N. Singh, A. D. Upadhye, V. V. Mhasker, S. Dev, A. V. Pol, and V. G. Naik, *Tetrahedron*, **30**, 3689 (1974).
(4) G. Stork and F. H. Clarke, Jr., *J. Am. Chem. Soc.*, **77**, 1073 (1955); **83**, 3114 (1961).
(5) E. J. Corey, N. N. Girotra, and C. T. Mathew, *J. Am. Chem. Soc.*, **91**, 1557 (1969); T. G. Crandall and R. G. Lawton, *ibid.*, **91**, 2127 (1969); E. Demole, P. Enggist, and C. Borer, *Helv. Chim. Acta*, **54**, 1845 (1971); N. H. Anderson and D. D. Syrdal, *Tetrahedron Lett.*, 2455 (1972); E. J. Corey and R. D. Balanson, *Tetrahedron Lett.*, 3153 (1973); P. T. Lansbury, V. R. Haddon, and R. C. Stewart, *J. Am. Chem. Soc.*, **96**, 896 (1974).
(6) A portion of our work has appeared in preliminary form: E. G. Breitholle and A. G. Fallis, *Can. J. Chem.*, **54**, 1991 (1976); presented in part at the International Symposium on Stereochemistry, Abstract M1, Kingston, Ontario, Canada, June 27–July 2, 1976. At the outset it appeared that α-pompene was also a member of this tricyclic family; however, its structure has been revised; A. Matsuo, T. Maeda, M. Nakayama, and S. Hayashi, *Tetrahedron Lett.*, 4131 (1973); A. Matsuo, H. Nozak, M. Nakayame, Y. Kushi, S. Hayashi, and N. Kaminjo, *Tetrahedron Lett.*, 241 (1975).
(7) R. G. Carlson, *Annu. Rep. Med. Chem.*, **9**, 270 (1974); W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, **16**, 10 (1977).
(8) H. O. House and T. H. Cronin, *J. Org. Chem.*, **30**, 1061 (1965).
(9) S. McLean and P. Haynes, *Tetrahedron*, **21**, 2329 (1965); see also J. Backes, R. W. Hofmann, and F. W. Steuber, *Angew. Chem., Int. Ed. Engl.*, **14**, 553 (1975).
(10) Cf. E. J. Corey and R. S. Glass, *J. Am. Chem. Soc.*, **89**, 2600 (1967); A. Krantz and C. Y. Lin, *ibid.*, **95**, 5662 (1973).
(11) O. Wallach, *Justus Liebigs Ann. Chem.*, **275**, 171 (1893); J. Mori, *Tetrahedron*, **31**, 3011 (1975).
(12) R. B. King and F. G. A. Stone, *Inorg. Synth.*, **7**, 99 (1963).
(13) Attempted use of thallium cyclopentadiene was unsuccessful.
(14) We are grateful to A. W. McCulloch and J. A. Walter, National Research Council of Canada, Halifax, Nova Scotia, for obtaining this spectrum.
(15) G. Fachinett, F. Pictra, and A. Marsili, *Tetrahedron Lett.*, 393 (1971); M. A. McKinney and P. P. Patel, *J. Org. Chem.*, **38**, 4059 (1973).
(16) D. A. Evans, G. L. Carroll, and L. K. Truesdale, *J. Org. Chem.*, **39**, 914 (1974).
(17) This sequence would be improved if formation of the unwanted ketone could be suppressed. This should be feasible as outlined, since the carbon bearing oxygen is locked in position in the starting ketone and final product. After completion of the synthesis but before this was a workable alternative, others reported a closely related ring expansion for the system X = H using ferric chloride which should be applicable to the present case.[18]



(18) Y. Ito, S. Fujii, and T. Saegusa, *J. Org. Chem.*, **41**, 2073 (1976); cf. G. Stork and T. L. MacDonald, *J. Am. Chem. Soc.*, **97**, 1264 (1975).
(19) E. V. Rudloff, *Can. J. Chem.*, **39**, 1860 (1961).
(20) G. Brieger, *J. Am. Chem. Soc.*, **85**, 3783 (1963).

Synthesis of Garosamine and of Related Amino Sugars. An Efficient Tetrahydrooxazine Ring Opening

John J. Wright* and Charles L. Luce

Chemical Research Schering Corporation, Bloomfield, New Jersey 07003

Received October 27, 1977

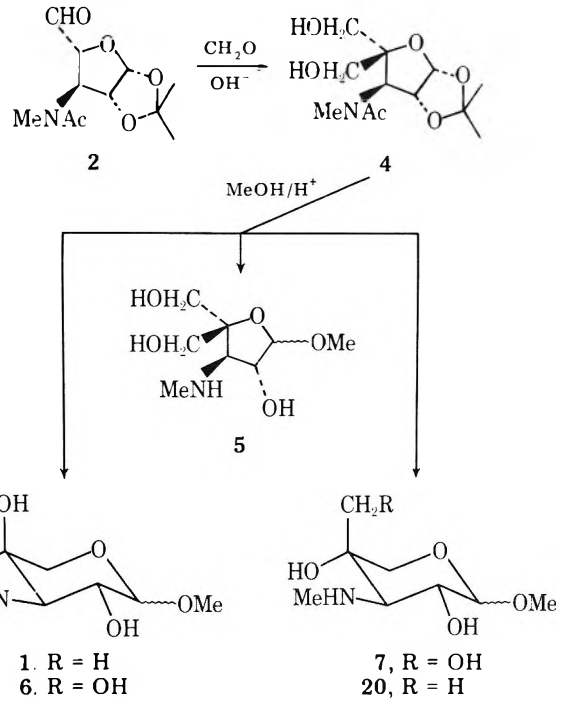
Garosamine, a component of the antibiotic gentamicin, and a series of related amino sugars have been synthesized from glucose by a stereospecific route involving a versatile tricyclic intermediate. A new oxidative tetrahydrooxazine ring-opening reaction is also reported.

The synthesis of branched chain amino sugars has been the focus of attention of a number of research groups in recent years because of the common occurrence of these compounds in nature in association with antibiotics. Synthetic approaches to these compounds have usually employed the addition of organometallic reagents, diazoalkanes, and enolate salts to cyclic ketones with varying degrees of stereochemical control. Such an approach was used in a previous synthesis of the methyl glycoside of garosamine (1),[1] a component monosaccharide of the gentamicin antibiotics.[2] Because of our interest in synthetic approaches to aminoglycoside antibiotics,[3] we required an efficient and stereospecific synthesis of garosamine and of structurally related amino sugars. We wish to report such a synthesis and also the development in the course of this work of a novel tetrahydrooxazine ring-opening reaction.

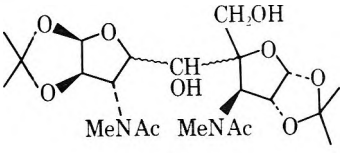
We had observed in a related study that the aldehyde **2** is prone to undergo aldol condensations leading, for example, after borohydride reduction of the initially formed aldol condensation product, to the dimeric compound **3**, of undetermined stereochemistry at position 4 of both furanosyl rings. Exploitation of the reactivity of a related aldehyde in the synthesis of apiose has been reported.[4] Our planned synthesis is outlined in Scheme I.

0022-3263/78/1943-1968$01.00/0

Scheme I



In view of the above observation, the aldehyde **2** was expected to undergo aldol condensation with formaldehyde under mildly alkaline conditions to give, after reduction of the intermediate β-hydroxy aldehyde, the diol **4.** Methanolysis (6 N HCl) of **4** was expected to give an equilibrium mixture of the furanosyl and pyranosyl glycosides **5, 6,** and **7** in which

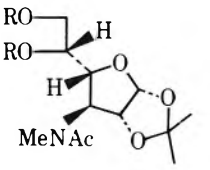


3

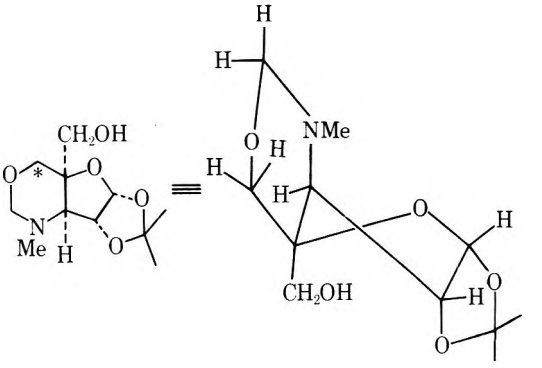
6, the pyranosyl anomeric mixture with the hydroxymethyl group in an equatorial position, was expected to predominate. It should be noted that the starting aldehyde epimeric at C-4 would serve equally well for the purpose as the same enolate ion would be involved in the aldol condensation step.

The unknown amino sugar **6** formally corresponds to methyl garosaminide in which the C-methyl group is functionalized with a hydroxyl group and constituted in itself a desired target compound.

1,2:5,6-Diisopropylidene-3-methylamino-3-*N*-acetyl-α-D-galactofuranoside (**8**) was prepared in high overall yield from diisopropylidene glucose by modification of existing routes.[5,6] Selective hydrolysis in aqueous acetic acid of the 5,6-isopropylidene group gave the crystalline diol **9,** mp 114–118 °C, in 82% yield. Periodate oxidation of the diol gave aldehyde **2** which was not isolated but which was treated with excess aqueous formaldehyde under alkaline conditions (pH 10.5). Over several hours at 40 °C a clean conversion into a single product (mp 79–80 °C) was observed in 90% yield after crystallization. Examination of the mass and ^{1}H NMR spectra allowed the assignment of structure **10** to this material. The expected aldol reaction clearly took place and was followed by cross-Cannizzaro reduction with excess formaldehyde to generate diol **4.** Under the mildly basic conditions of this reaction, neighboring group-assisted hydrolysis of the acetamide group occurred to give the methylamino compound **12** which condensed rapidly with excess formaldehyde to give **10.** In accordance with this mechanism, the diol intermediate **4** could be obtained in high yield by keeping the pH near 8. When sodium borohydride was added to the reaction mixture some

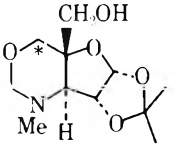


8, R = R = isopropylidene
9, R = R = H

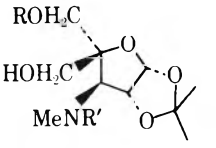


10

of the dimethylamino analogue **13** was obtained, mp 64–66 °C.



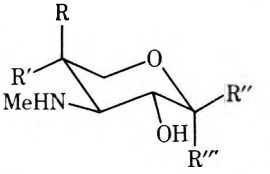
11



12, R = R′ = H
13, R = H; R′ = Me
23, R = tetrahydropyranyl; R′ = H

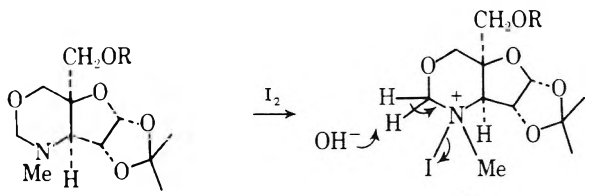
Although two isomeric forms of the tricyclic alcohol **10** having either a cis or a trans ring junction are possible in principle, examination of models and of the ^{1}H NMR spectrum strongly suggested that only the cis ring junction would be formed, as drawn, because of constraints imposed by the 1,2-isopropylidene group. The small coupling constant (~0.5 Hz) between H-2 and H-3 in **10** and in all the 1,2-isopropylidene derivatives in this series is characteristic of a T_2[3] twist conformation of the furanose ring[7] in which the torsional angle between H-2 and H-3 is close to 90°. Only the hydroxymethyl group cis to the amine group can be involved in the tetrahydrooxazine ring when the furanose has this conformation. Proof of this assignment was obtained by chemical correlation vide infra. The remarkable ease of hydrolysis of the amide **4** presumably arises from catalytic participation by the neighboring *cis*-hydroxymethyl group.

Methanolysis (6 N HCl in methanol) of **4** gave an anomeric mixture of the desired pyranosides (**14** and **15**) which were separable by partition chromatography on silica gel in a combined yield of 70%. Proof of the stereochemistry at position 4 of both anomers was obtained from circular dichroism measurements of the cuproammonium complexes (TaCu) in solution. Only vicinal amino alcohols can form strong complexes with tetramine copper[8] and the sign of the Cotton effect

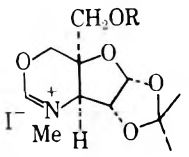


14, R = OH; R′ = CH_2OH; R″ = H; R‴ = OMe
15, R = OH; R′ = CH_2OH; R″ = OMe; R‴ = H
16, R = CH_2OH; R′ = OH; R″ = H; R‴ = OMe
17, R = CH_2OH; R′ = OH; R″ = OMe; R‴ = H
18, R = OH; R′ = Me; R″ = H; R‴ = OMe

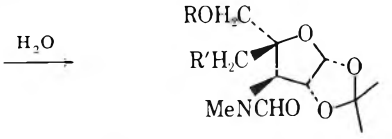
Scheme II



10, R = H
21, R = tetrahydropyranyl
24, R = CONHPh



29, R = H
30, R = tetrahydropyranyl
31, R = CONHPh



19, R = H; R′ = OH
22, R = tetrahydropyranyl; R′ = OH
25, R = CONHPh; R′ = OH
26, R = CONHPh; R′ = I
27, R = CONHPh; R′ = H

at 280 nm is diagnostic for the chirality of the complex.[9] The value for $[\theta]_{280}$ of −7100 obtained for **14** and of −5350 for **15** corresponds in each case to a δ chelate in which the vicinal amino and alcohol groups form a positive torsional angle. Whereas in **14** and **15** both possible sites of complexation would lead to such a chelate, both components of the alternative anomeric mixture **16** and **17** have the alternative stereochemistry at C-4 and formation of both λ and δ chelates would be possible for each anomer making approximately equal and opposite contributions to the magnitude of the Cotton effect. This would lead in each case to a value for $[\theta]_{280}$ near zero. In agreement with the assignment of structures **14** and **15** to the products, a value for $[\theta]_{230}$ of −7960 was obtained for β-methyl garosaminide (**18**) obtained from natural sources.

The ready formation of the tricyclic alcohol **10** offered the opportunity to modify selectively the groups corresponding to the geminal hydroxymethyl groups of the intermediate **4**, thereby providing a stereospecific route to a number of branched chain amino sugars. For this purpose procedures were required to open the tetrahydrooxazine ring in the presence of the isopropylidene group. Attempts to hydrolyze this ring selectively under mildly acidic conditions were not successful. In addition, methanolysis of **10** in 6 N methanolic hydrochloric acid did not provide the expected methyl glycosides **14** and **15** but gave products which incorporated the *O*,*N*-methylene group originally derived from formaldehyde either through retention of the tetrahydrooxazine ring or from initial cleavage to formaldehyde followed by recondensation.

It was necessary, therefore, to devise a method to open the tetrahydrooxazine ring under neutral or mildly basic conditions. This was achieved by the action of iodine and sodium acetate in aqueous methanol. The oxidative cleavage of **10** by this method proceeded smoothly under mildly basic conditions to give the ring-opened *N*-formyl compound **19** in 91% yield in 30 min at room temperature. Prolonged treatment led to the formation of traces of the product of formamide hydrolysis. This reaction appears to be general for related systems, proceeding efficiently also in the five-membered oxazolidine ring system.[10] The postulated mechanism is outlined in Scheme II.

Methanolysis of the *N*-formyl derivative **19** under conditions identical to that of **4** gave rise to the same anomeric mixture of methyl glycosides **14** and **15**.

The stereochemistry of the ring junction in the tricyclic alcohol **10** was determined by conversion of **10** into methyl garosaminide. Formal transformation of the methylene group marked with an asterisk in **10** into a methyl group would lead, after methanolysis, to methyl garosaminide (**1**) if the ring junction were cis as shown. If the junction were trans, the unknown isomer **20** would result. To this end, the hydroxymethyl group in **10** was first blocked as its tetrahydropyranyl ether to give **21** as an inseparable diastereomeric mixture. Oxidative ring cleavage provided the *N*-formyl analogue **22** in 91% yield after chromatography. Attempts to convert the hydroxymethyl group generated in this reaction into a methyl group proved difficult because of steric hindrance to displacement reaction at that neopentyl-like site. Thus, lithium triethylborohydride reduction of the mesylate derivative proved unsuccessful. Similarly attempted displacement of the mesylate group with iodide ion led to recovered starting material and treatment with hydrazine gave only the product of sulfur–oxygen cleavage of the sulfonate group and de-*N*-formylation (**23**).

A successful displacement was, however, achieved in moderate yield with triphenylphosphite methiodide, although acidic conditions generated by this reagent led to hydrolysis of the tetrahydropyranyl ether blocking group. In an alternate procedure, the alcohol group in **10** was blocked as the phenylcarbamate by reaction with phenyl isocyanate in pyridine and oxidative ring cleavage then proceeded smoothly as before to give the required *N*-formyl derivative **25**. In this compound, as in all the *N*-formyl derivatives, the ^{1}H NMR spectrum reflected the presence in solution of nearly equal proportions of the two amide rotamers. Treatment of **25** with triphenylphosphite methiodide in dry dimethylformamide at 80 °C gave the iodide **26** in 44% yield and reduction of this material with tri-*n*-butylstannane proceeded smoothly in benzene at reflux to provide the desired methyl analogue **27**.

Attempts to generate the iodo derivative **26** directly from **24** by oxidation with iodine in aprotic solvents via displacement on carbon of a postulated intermediate imminium salt (**31**) were unsuccessful. This was presumably due in part to the considerable steric hindrance at the site of displacement.

As the phenylcarbamate group proved resistant to hydrolysis by methanolic hydrochloric acid, compound **27** was deblocked in two successive stages; treatment with ethanolic hydrazine hydrate was followed by methanolysis. The product obtained in 80% yield was an anomeric mixture of α- and β-methyl garosaminides (**1**) identical with authentic material in all chromatographic and analytical aspects.

This transformation constitutes a stereospecific synthesis of garosamine and also confirms the initial assignment of cis stereochemistry to the ring junction in **10**. Clearly chemical manipulation of this tricyclic intermediate will lead therefore to a variety of branched chain amino sugars of known relative (and absolute) stereochemistry of utility in the synthesis of new aminoglycoside antibiotics.

Experimental Section

^{1}H-NMR spectra were obtained at 60 or 100 MHz using either a Varian A60A or a XL 100-15 spectrometer. Chemical shifts in $CDCl_3$ are reported in ppm downfield from internal Me_4Si. IR spectra were recorded with either a Perkin-Elmer 221 or an Infracord 137 spectrometer. Mass spectra were recorded with a Varian CH5 spectrometer. CD spectra were recorded on a Cary 61 spectrometer.

Preparation of *N*-Methyl-*N*-acetyl-3-amino-3-deoxy-1,2:5,6-diisopropylidene-α-D-galactofuranose (8). *N*-Acetyl-3-

amino-3-deoxy-1,2:5,6-diisopropylidene-α-D-galactofuranose (5 g) was dissolved in dry DMF (20 mL). Sodium hydride (750 mg) and methyl iodide (3.5 g) were added and the whole solution was stirred for 5 h. Ethanol was added until effervescence ceased, the solution was filtered, and the filtrate was reduced to dryness under reduced pressure. The residue was taken up in chloroform and filtered and ether was added to induce crystallization of the title compound (4.5 g, 85%): mp 140–141 °C; $[\alpha]^{26}_D$ +8.5° (0.4, methanol); NMR ($CDCl_3$) δ 1.32, 1.38, 1.45, 1.58 (4 s, 12 H, isopropylidene CH_3,s), 2.09 (s, 3 H, $COCH_3$), 3.08 (s, 3 H, NCH_3), 4.84 (dd, 1 H, J = 4, 1 Hz, H-2), 6.08 (d, 1 H, J = 4 Hz, H-1); mass spectrum m/e 315 (M^+), 300 ($M - 15$)$^+$. Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.2; H, 7.9; N, 4.5. Found: C, 56.9; H, 7.8; N, 4.62

Preparation of *N*-Methyl-*N*-acetyl-3-amino-3-deoxy-1,2-iospropylidene-α-D-galactofuranose (9). *N*-Methyl-*N*-acetyl-3-amino-3-deoxy-1,2:5,6-di-isopropylidene-α-D-galactofuranose (10.0 g) was dissolved in 50% aqueous acetic acid and left at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel in 7.5% methanol in chloroform to give the title compound (7.6 g, 87%): mp 114–118 °C; $[\alpha]^{26}_D$ +23.4° (0.3, $CHCl_3$); NMR ($CDCl_3$) δ 1.33 (s, 3 H, C-CH_3), 1.58 (s, 3 H, $COCH_3$), 4.9 (d, 1 H, J = 4 Hz, H-2), 6.08 (d, 1 H, J = 4 Hz, H=1); mass spectrum m/e 275 (M^+). Anal. Calcd for $C_{12}H_{21}NO_6$: C, 52.4; H, 7.6; N, 5.1. Found: C, 52.3; H, 7.9; N, 5.0.

Starting material (1.1 g) was also recovered.

4-Hydroxymethyl-3,5-*O*,*N*-methylene-1,2-isopropylidene-3-methylamino-3-deoxy-α-D-xylofuranoside (10). *N*-Acetyl-*N*-methyl-1,2-isopropylidene-3-amino-3-deoxy-α-D-galafuranoside (9) (7.6 g) was dissolved in water (70 mL) and sodium metaperiodate (6.23 g) was added. After 20 min, ethylene glycol (0.5 mL) was added followed after 10 min by an 37% aqueous solution of formaldehyde (40 mL). Sodium bicarbonate (2.5 g) was added and the pH of the resulting solution was adjusted to 10.5 with 1 N sodium hydroxide solution. After 4 h at 40 °C, a further 20 mL of formaldehyde solution was added and the reaction mixture was left at 40 °C for a further 30 min. The solution was extracted with chloroform to give the title compound essentially pure (6.7 g). Chromatography on silica gel gave analytical grade material (6.1 g, 90%): mp 79–80 °C (from diethyl ether–hexane); $[\alpha]^{26}_D$ −52.9°; NMR ($CDCl_3$) δ 1.33 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 2.34 (s, 3 H, N-CH_3), 2.48 (s, 1 H, OH), 2.81 (broad s, 1 H, H-3), 4.68 (broad d, 1 H, J = 5 Hz, H-2), 6.07 (d, 1 H, J = 5 Hz, H-1); mass spectrum m/e 245 (M^+), 230 ($M - 15$)$^+$. Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.9; H, 7.8; N, 5.7. Found: C, 53.6; H, 8.0; N, 5.5.

4-Hydroxymethyl-1,2-isopropylidene-3-*N*-formyl-3-*N*-methyl-3-amino-3-deoxy-α-D-arabinofuranoside (19). The tricyclic alcohol (10) (2.9 g) was dissolved in 25% aqueous methanol and treated with sodium acetate (15 g) and iodine (15 g). After 30 min, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with an aqueous solution of sodium thiosulfate and water and dried. The whole was concentrated to dryness to give the title compound (2.3 g, 91%) as a gum: $[\alpha]^{26}_D$ +30.6° (0.3, ethanol); NMR ($CDCl_3$) 1.33 (s, 3 H, C-CH_3), 1.58 (s, 3 H, c-CH_3), 2.92, 3.12 (2 s, 3 H, N-CH_3, rotamers); 4.2 (m, 1 H, H-3), 4.9, 5.14 (2 dd, 1 H, J = 1.5, 4 Hz, H-2, rotamers), 5.99, 6.08 (2 d, 1 H, H-1, rotamers), 8.1 (s, 1 H, CHO); mass spectrum m/e 261 (M^+). Anal. Calcd for $C_{11}H_{19}NO_6$: C, 50.6; H, 7.3; N, 5.4. Found: C, 50.4; H, 7.4; N, 5.1.

Methyl 3-Methylamino-3-deoxy-4-hydroxymethyl-2- and β-L-arabinopyranoside. The *N*-formyl derivative (19) (2.1 g) was heated at reflux in 6 N methanolic hydrochloric acid for 3 h. The solvent was removed under vacuum and the residue was chromatographed on silica gel in the lower phase of a chloroform–methanol–10% ammonium hydroxide (2:1:1) solvent mixture to give first the α glycoside as a gum (0.54 g) (15): $[\theta]_{280}$ (TaCu) −5350; 100 MHz NMR (D_2O) δ 2.45 (s, 3 H, NCH_3), 4.52 (s, 3 H, OCH_3), 4.25 (d, 1 H, J = 8 Hz, H-1); mass spectrum m/e 207 (M^+), 208 ($M + 1$)$^+$.

Subsequently isolated also as a gum was the β glycoside (14) (0.69 g): $[\theta]_{280}$ (TaCu) −7100; 100 MHz NMR (D_2O) δ 2.45 (s, 3 H, NCH_3), 2.72 (d, 1 H, J = 10.5 Hz, H-3), 3.41 (s, 3 H, OCH_3), 3.77 (dd, 1 H, J = 4, 10.5 Hz, H-2), 3.8 (d, 1 H, J = 12.5 Hz, H-5 eq), 4.75 (d, 1 H, J = 4 Hz, H-1); mass spectrum m/e 207 (M)$^+$, 208 ($M + 1$)$^+$.

Tetrahydropyranyl Ether (21). The tricyclic alcohol (10) (0.75 g) was dissolved in dry benzene. Dihydropyran (0.56 mL) and trifluoracetic acid (0.26 mL) were added and the solution was left at room temperature for 18 h. The benzene solution was washed with saturated aqueous sodium bicarbonate and water and dried ($MgSO_4$) and the solvent was removed under vacuum. Chromatography on silica gel in 1% methanol in chloroform gave the tetrahydropyranyl derivative (0.9 g, 93%) characterized as a diastereoisomeric mixture: $[\alpha]^{26}_D$ −39.2°; 100 MHz NMR (CDCl) δ 1.32 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 2.36, 2.38 (2 s, 3 H, NCH_3, rotamers), 3.01, 3.04 (2 s, 1 H, H-3, rotamers), 4.65 (m, 2 H, H-2 and OCHO), 6.04 (2 d, 1 H, J = 5 Hz, H-1). Anal. Calcd for $C_{16}H_{27}NO_6 \cdot \frac{1}{2}H_2O$: C, 56.8; H, 8.3; N, 4.1. Found: C, 57.0; H, 85; N, 3.9.

4-Hydroxymethyl-5-*O*-tetrahydropyranyl-1,2-isopropylidene-3-*N*-formyl-3-*N*-methyl-3-amino-3-deoxy-α,D-arabinofuranoside (22). The tetrahydropyranyl ether 21 (2.7 g) in 25% aqueous methanol was treated with sodium acetate (anhydrous) (4.0 g) and iodine (2.0 g). After 17 h at room temperature, the reaction mixture was partitioned between chloroform and saturated sodium thiosulfate solution. The chloroform layer was washed with water, dried over $MgSO_4$ and evaporated to dryness, to give essentially pure title compound as a gum (91%): $[\alpha]^{26}_D$ −10.6°; NMR ($CDCl_3$) δ 1.2 (s, 3 H, CH_3); 1.6 (m, 12 H, CH_3 and CH_2), 2.93, 3.06 (2 s, 3 H, NCH_3, rotamers), 5.0 (m, 1 H, H-2, rotamers), 6.08 (m, 1 H, H-1); mass spectrum m/e 330 ($M - 15$)$^+$. Anal. Calcd for $C_{16}H_{27}NO_7$: C, 55.6; H, 7.8; N, 4.0. Found: C, 55.4; H, 7.9; N, 3.8.

Reaction of Phynyl Isocyanate with Tricyclic Alcohol (10). Tricyclic alcohol 10 (1 g) and phenyl isocyanate (0.50 g) were dissolved in pyridine (10 mL) and left at room temperature for 18 h. The solvent was removed under high vacuum and the residue was chromatographed on silica gel to give compound 24 as a gum (1.35 g, 92%): $[\alpha]^{26}_D$ −28° (0.4, ethanol); NMR ($CDCl_3$) δ 1.3 (s, 3 H, CCH_3), 1.58 (s, 3 H, CCH_3), 2.35 (s, 3 H, NCH_3), 2.87 (broad singlet, 1 H, H-3), 4.64 (d, 1 H, J = 4.5 Hz, H-2), 6.05 (d, 1 H, J = 4.5 Hz, H-1), 7.35 (m, 5 H, Ar); mass spectrum m/e 364 (M)$^+$, 349 ($M - 15$)$^+$. Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.4; H, 6.6; N, 7.7. Found: C, 59.7; H, 6.8; N, 7.5.

4-Hydroxymethyl-5-*O*-phenylcarbamoyl-1,2-isopropylidene-3-*N*-formyl-3-*N*-methyl-3-amino-3-deoxy-β-L-arabinofuranose (25). The phenylurethane 24 (5.0 g) was dissolved in 25% water in methanol (160 mL) and treated with sodium acetate (10 g) and iodine (10 g). After 2.5 h a further 5 g of each inorganic reagent was added. After a further 30 min, the whole was poured into water (300 mL) and extracted with ethyl acetate (2 × 250 mL). The organic layer was washed with an aqueous solution of sodium thiosulfate and water and dried. The whole was concentrated to dryness and the residue was crystallized from a chloroform–hexane mixture (86%): mp 175–176 °C; $[\alpha]^{26}_D$ −34.90° (0.5, ethanol); NMR ($CDCl_3$) δ 1.33 (s, 3 H, CCH_3), 1.63 (s, 3 H, CH_3), 2.9, 3.04 (2 s, 3 H, NCH_3, rotamers), 4.88, 5.1 (two broad doublets, 1 H, H-2, rotamers), 6.05, 6.16 (2 broad doublets, 1 H, H-1, rotamers), 8.1 (2 s, 1 H, CHO, rotamers); mass spectrum m/e 380 (M^+). Anal Calcd for $C_{18}H_{24}N_2O_7 \cdot \frac{1}{2}H_2O$: C, 55.5; H, 6.4; N, 7.2. Found: C, 55.6; H, 6.25; N, 7.03.

4-Iodomethyl-5-*O*-phenylcarbamoyl-1,2-isopropylidene-3-*N*-formyl-3-*N*-methyl-3-deoxy-α-D-arabinofuranoside (26). The phenylcarbamoyl derivative 25 (2 g) in dry DMF (25 mL) was heated at 80 °C for 18 h with triphenylphosphite methiodide (8.0 g). The cooled reaction mixture was poured in 1 N aqueous potassium hydroxide and extracted with chloroform. The extracts were washed with water, dried, and concentrated to leave an oily residue. Chromatography of the residue on silica gel in benzene–ethyl acetate (1:1) gave the title compound (1.1 g, 44%) as an oil: $[\alpha]^{26}_D$ −20.3°c (0.5, ethanol); NMR ($CDCl_3$) 1.3 (s, 3 H, CCH_3), 1.65 (s, 3 H, CCH_3), 2.9, 3.05 (2 s, 3 H, NCH_3, rotamers), 3.3 (m, 2 H, CH_2I), 5.0 (2 d, 1 H, J = 4 Hz, H-2, rotamers), 6.1 (2 d, 1 H, J = 4 Hz, rotamers), 8.10, 8.16 (2 s, 1 H, rotamers, CHO); mass spectrum m/e 490 (M^+). Anal. Cald for $C_{18}H_{23}N_2O_6I$: C, 44.1; H, 4.7. Found: C, 44.4; H, 4.9.

5-*O*-Phenylcarbamoyl-1,2,isopropylidene-4-*C*-methyl-3-*N*-methyl-amino-3-*N*-formyl-3-deoxy-β-L-arabinofuranoside (27). The iodo derivative 26 (1.0 g) was dissolved in dry benzene (10 mL) and heated at reflux with tri-*n*-butylstannane (1.2 mL) for 6 h. The solvent was removed by evaporation under high vacuum to give an oily residue which was triturated with petroleum ether and the residue was chromatographed on silica gel in benzene–ethyl acetate (1:1) to give the title compound (0.63 g, 85%): $[\alpha]^{26}_D$ −35.4° (0.5, ethanol); NMR ($CDCl_3$) 1.3 (s, 3 H, CCH_3), 1.35 (s, 3 H, CCH_3), 1.66 (s, 3 H, CCH_3), 2.90, 2.98 (2 s, 3 H, NCH_3, rotamers), 4.9 (m, 1 H, H-2, rotamers), 6.0 (t, 1 H, H-1, rotamers), 8.1 (broad singlet, 1 H, CHO); mass spectrum m/e 364 (M^+). Anal. Calcd for $C_{18}H_{24}N_2O_6 \cdot \frac{1}{2}H_2O$: C, 57.9; H, 6.7; N, 7.5. Found: 58.1; H, 6.7; N, 7.1.

Methyl Garosaminides (1). The phenylcarbamoyl derivative (0.5 g) was heated under reflux with 10% hydrazine hydrate in ethanol for 5 h. The solvent and excess hydrazine hydrate were removed by evaporation under high vacuum. The residue was taken up in 6 N methanolic hydrochloric acid and heated at reflux for 3 h. Evaporation of the solvent and chromatography of the residue on silica gel in the lower phase of a chloroform–methanol–7% ammonium hyroxide (2:1:1) solvent system gave methyl garosaminide as an anomeric mixture (0.21 g) (80%) identical in all respects with authentic material.

Garosamine Hydrochloride. The synthetic methyl garosaminide anomeric mixture was heated for 2 h in 6 N aqueous hydrochloric acid.

Evaporation of the solvent gave garosamine hydrochloride identical with authentic material.

Acknowledgments. We thank our colleagues for helpful discussions and Messrs. J. Morton, J. McGlotten, and P. Bartner for spectral data.

Registry No.—**4,** 65483-48-9; **8,** 65483-49-0; **9,** 65483-50-3; **10,** 65483-51-4; **13,** 65483-52-5; **14,** 65483-53-6; **15,** 65483-54-7; **19,** 65483-55-8; **21,** 65483-56-9; **22,** 65483-57-0; **24,** 65483-58-1; **25,** 65483-59-2; **26,** 65483-60-5; **27,** 65504-54-3; garosamine, 29914-71-4; *N*-acetyl-3-amino-3-deoxy-1,2:5,6-diisopropylidine-α-D-galactofuranose, 19131-09-0.

References and Notes

(1) W. Meyer zu Reckendorf and E. Bischof, *Chem Ber.*, **105,** 2546 (1972).
(2) D. J. Cooper, P. J. L. Daniels, M. D. Yudis, H. M. Marigliano, R. D. Guthrie, and S. T. K. Bukhari, *J. Chem Soc.*, 3126 (1971).
(3) J. J. Wright, P. J. L. Daniels, and A. K. Mallams, *Chem. Commun.*, 676 (1973).
(4) R. Schaffer, *J. Am. Chem. Soc.*, **81,** 5452 (1959).
(5) W. Meyer zu Reckendorf, "Methods in Carbohydrate Chemistry", Vol. 6, R. L. Whistler and J. N. BeMiller, Ed., Academic Press, New York, N.Y., 1972, p 129.
(6) J. S. Brimacombe, P. A. Gent, and M. Stacey, *J. Chem. Soc.*, 567 (1968).
(7) R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLaughlan, *J. Chem. Soc.*, 3699 (1962).
(8) S. Umezawa, T. Tsuchiya, and K. Tatsuta, *Bull. Chem. Soc. J.*, **39,** 1235 (1966).
(9) S. T. Bukari, R. D. Guthrie, A. I. Scott, and A. D. Wrixon, *Tetrahedron*, **26,** 3653 (1970).
(10) J. J. Wright, unpublished observations.

Poly(iminomethylenes). 6.[1] Synthesis and Polymerization of α- and β-D-Glucopyranosyl Isocyanide

Roeland J. M. Nolte, Jean A. J. van Zomeren, and Jan W. Zwikker*

Department of Organic Chemistry of the University, Croesestraat 79, Utrecht, The Netherlands

Received September 6, 1977

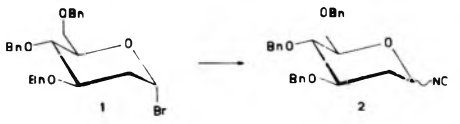
Both anomers of 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl isocyanide have been synthesized starting from 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide. This bromide was converted into the β-azide which after hydrogenation to the amine and formylation afforded *N*-formyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosylamine. Dehydration of the latter compound gave the isocyanides in an α to β ratio of 1:9. Polymerization of the isocyanides was performed with nickel chloride. From the optical rotations it was concluded that the helical polymers obtained from the anomeric monomers are opposites in a screw sense.

Poly(isocyanides), more systematically named poly(iminomethylenes), $[RN{=}C{<}]_n$, are rigid rod polymers[2] with a helical configuration.[3,4] In general, they are easily prepared from the monomeric isocyanides, RN=C, with nickel chloride or a nickel(II) complex as catalyst.[5,6] Stereoselective formation of either a right-handed (*P*) or left-handed (*M*) helix can be expected when the monomeric isocyanide is one enantiomer of R*N=C, in which R* is chiral.

Because of their ready availability and optical purity natural compounds often are the starting materials of choice for stereoselective syntheses. Our first entry into this field was the synthesis of a poly(iminomethylene) derived from L-histidine.[1] In the present paper we wish to report the synthesis of such polymers derived from glucose. An additional motive for the synthesis of these compounds is the fact that polymer-bounded sugars[7] and especially sugar residues linked to polymer-bounded amino acids may be interesting models in immunological studies.[8]

Results and Discussion

Reaction of silver cyanide with benzyl protected glucopyranosyl halides (**1**) was recently reported[9] to give formerly unknown isocyano sugars (**2**).



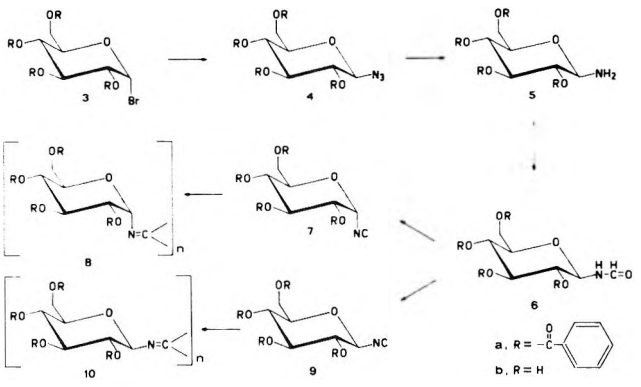
In our hands, however, this reaction afforded unseparable mixtures of α and β anomers and other unidentified products.

We have synthesized the α and β anomers of D-glucopyranosyl isocyanide, compounds **7** and **9,** via amine **5** and N-substituted formamide **6** according to Scheme I.

A convenient route for the synthesis of per-*O*-acylglycosylamines is provided by the reduction of the corresponding *O*-acylglycosyl azides.[10] Sproviero[11] synthesized 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl azide (**4a**) in 66% yield from 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**3a**) by a nucleophilic displacement reaction with sodium azide in boiling acetonitrile. We have carried out this reaction by using phase-transfer catalysis in a mixture of chloroform and water. Compound **4a** was isolated in quantitative yield; its β-D-gluco configuration was confirmed by the ^{1}H-NMR spectrum, in which the signal for the anomeric proton appeared as a doublet at 4.95 ppm ($J_{1,2}$ = 8.7 Hz).

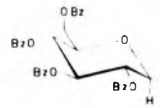
Catalytic hydrogenation of the glycosyl azide **4a** over palladium on carbon afforded 1,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosylamine (**5a**) as a white foam. The latter amine was converted into its debenzoylated form (**5b**) by reaction with sodium methanolate in methanol. The infrared absorption spectrum of **5b** showed that this compound was uncontaminated by *N*-benzoylglucopyranosylamine,[12] proving that in the reduction step no O → N benzoyl migration had oc-

Scheme I



0022-3263/78/1943-1972$01.00/0

Table I. Optical Rotation Data of Poly(iminomethylenes) [RN=C<]$_n$, and Monomers, RN=C

R	Monomer $[\alpha]^{22}_D$[a]	Polymer $[\alpha]^{22}_D$[a]	Contribution of helix to $[\alpha]$	Screw sense of helix
	+70.4°[b]	>+80°[c]	(+)	*M*
	+44.7°[d]	0.0°[e]	(−)	*P*

[a] In chloroform; the rotation of the polymer is expressed per repeating unit. [b] *c* 1.47. [c] *c* 0.42. [d] *c* 2.52. [e] *c* 0.73.

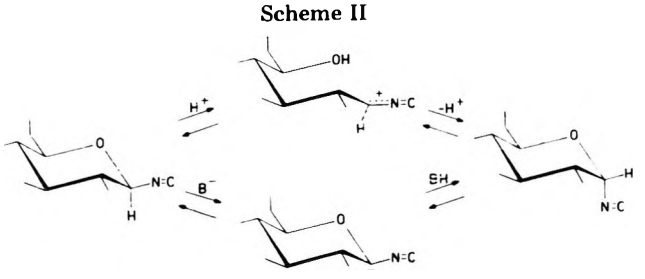
curred.[11] On treatment with formic acetic anhydride, the glycosylamine **5a** gave *N*-formyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosylamine (**6a**). In the infrared and NMR spectra of **6a** the characteristic absorptions of the *N*-formyl function were partly masked by absorption peaks of the benzoyl protecting groups. After removal of the latter groups to give free *N*-formylglucopyranosylamine (**6b**) the former absorptions became visible. The coupling constant $J_{1,2}$ in the ^{1}H-NMR spectrum of **6b** amounted to 8.4 Hz. This is indicative of a β-D-gluco configuration.[13] In view of its axial position the signal of the anomeric proton appeared at a rather low field (δ 5.08 ppm). The low field shift is probably due to the electron-withdrawing character of the *N*-formyl group attached to the anomeric center. A similar chemical shift value has been found for the anomeric proton in 2-acetamido-1-*N*-(4-L-aspartyl)-2-deoxy-β-D-glucopyranosylamine.[13]

The glycosyl isocyanides **7a** and **9a** were obtained in 90% yield by dehydration of the *N*-formylglucopyranosylamine **6a** using phosphorus oxychloride and triethylamine as the dehydrating agent.[14] Substitution of pyridine for triethylamine as the base lowered the yield to 15%. Other dehydrating agents like thionyl chloride in *N,N*-dimethylformamide[15] and triphenylphosphine–carbon tetrachloride[16] gave no or only traces of isocyanide. Compounds **7a** and **9a** were separated by column chromatography and isolated as almost odorless, white solids in a ratio of 1:9. They were soluble in apolar solvents, moderately soluble in alcohols, and insoluble in water. The infrared absorption spectra of the solids showed characteristic isocyanide stretching vibrations at 2124 cm^{-1} (α anomer) and 2142 cm^{-1} (β anomer). In the ^{13}C-NMR spectra of **7a** and **9a** the ^{13}C resonances of the isocyano carbons were observed at 166.1 and 165.1 ppm, respectively.[9] The structure of isocyanides **7a** and **9a** was further established by elemental analysis, ^{1}H NMR, and mass spectroscopy.

Compound **9a** could be converted into free β-D-glucopyranosyl isocyanide (**9b**) without affecting the NC function. Aliphatic isocyanides with free hydroxylic groups have not been described before.[17]

The isolation of both α- and β-isocyanide from *N*-formyl-β-D-glucopyranosylamine might indicate anomerization of these compounds under the reaction conditions employed. Anomerization is conceivable to occur through acid- and base-catalyzed pathways (Scheme II).

Scheme II



Preliminary experiments, however, showed that neither triethylammonium chloride nor triethylamine could effect anomerization of **7a** and **9a**. Elevated temperatures and strong bases like 1,8-bis(dimethylamino)naphthalene ("proton sponge") and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) were ineffective as well. Enhancement of the electron-withdrawing effect of the isocyano group through coordination of **7a** and **9a** to copper(II) tetrafluoroborate and subsequent treatment with strong base was not successful either. The results above suggest that anomerization is most likely to occur in some stage of the dehydration of the *N*-formylglucopyranosylamine by phosphorus oxychloride.

Both glycosyl isocyanides **7a** and **9a** were polymerized by 1 mol % nickel chloride[5] in chloroform–methanol 1:1 (v/v). Under these conditions the rate of polymerization of **7a** was very slow, probably as a result of steric hindrance; its isocyano group is in axial position. As judged by TLC, polymerization of **7a** was accompanied by anomerization. The poly(iminomethylenes) were isolated as creamish brown solids. They were soluble in apolar solvents and insoluble in alcohols and water. Their infrared absorption spectra showed partly obscured –N=C< stretching vibrations at approximately 1640 cm^{-1}. The polymers showed an intrinsic viscosity in the order of 0.025 dL/g (toluene, 30.0 °C). Applying the Mark–Houwink equation as determined[2] for poly(1-phenylethyliminomethylene), a molecular weight of 6000 is calculated. Higher degrees of polymerization can be expected at higher isocyanide catalyst ratios.[18]

Removal of the protecting groups in **10a** and subsequent ultrafiltration and freeze drying of the resulting solution afforded poly(β-D-glucopyranosyliminomethylene), **10b**, as a light-brown solid. In its infrared spectrum a distinct –N=C< stretching vibration was visible at 1630 cm^{-1}. Compound **10b** was soluble only in water.

In earlier papers[3,4] we showed that poly(iminomethylenes) have a helical configuration. On polymerization of a chiral isocyanide an excess of one screw sense can be expected. The preferred screw sense can be predicted by application of our S–M–L rule which will be described in a forthcoming paper.[19] S–M–L stands for small, medium, and large in isocyanide C(S)(M)(L)–N=C, respectively. The reverse direction of rotation S → M → L in **7** and **9** gives rise to an opposed screw sense of their polymers, viz., right handed (*P*) for **10a** and left handed (*M*) for **8a**. We know[4] that a *P* screw gives rise to a (−) contribution to the optical rotation. Since the side chain in polymer **10a** will probably have the same sign of optical rotation as in the monomer, the contributions by main chain and side chain are opposing. The total rotation can be expected to be small; in fact, it is not significantly different from zero (Table I). In polymer **8a** the contributions by main chain and side chain are both predicted to be (+). The experimental value of 80° (Table I) is probably still somewhat too low for pure **8a**. Because of the anomerization mentioned above, our sample of **8a** will contain **10a** or be a copolymer of **7a** and **9a**.

Experimental Section

General. Melting points were determined on a Mettler FP5/FP51 photoelectric melting point apparatus. Rotations were measured on a Perkin-Elmer 141 polarimeter. Infrared (IR) spectra were recorded on a Perkin-Elmer 457 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on Varian EM-390 and Varian CFT-20 instruments, respectively. Chemical shifts (δ) are given in ppm downfield from internal tetramethylsilane or sodium 2,2,3,3-tetradeutero-3-(trimethylsilyl)propionate. Abbreviations used are: s = singlet, d = doublet, m = multiplet, br = broad. Mass spectra were recorded on an AEI MS-902 mass spectrometer. Elemental analyses were carried out by the Element Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands, under supervision of W. J. Buis. TLC was performed on silica (Schleicher and Schüll TLC Ready Plastic Foil FR-1500) and detection was effected by UV and/or spraying with 20% sulfuric acid in methanol and charring at 120 °C for 10 min. Column chromatography was performed on silica (Merck Kieselgel 60, 230–400 mesh).

2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl Bromide (3a). This compound was prepared as described in the literature.[20]

2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl Azide (4a). To a solution of 13.2 g (20 mmol) of **3a** in 100 mL of chloroform was added 26 g (400 mmol) of sodium azide in 100 mL of water and 300 mg of benzyltriethylammonium chloride. The mixture was vigorously stirred for 2 h at 70 °C. Hereafter another 26 g of sodium azide and 300 mg of benzyltriethylammonium chloride were added and stirring was continued until TLC (benzene–isopropyl alcohol, 100:1) indicated complete conversion of **3a** (6–15 h). The aqueous layer was separated and extracted twice with chloroform. The combined organic layers were washed, dried over sodium sulfate, and concentrated in vacuo to give 12.6 g of white solid **4a**. Recrystallization from absolute ethanol afforded a purified sample: mp 113–114 °C; $[\alpha]^{22}_D$ −0.54° (c 5.0, $CHCl_3$) [lit. $[\alpha]^{22}_D$ +42.0° (c 1.0, $CHCl_3$);[11] to us this value seems less reliable]; IR (KBr) 2120 (N_3), 1725 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.90 and 7.40 (2 × m, 20, benzoyl), 6.00–6.40 (m, 3, H-2,3,4), 4.95 (d, $J_{1,2}$ = 8.7 Hz, 1, H-1), 4.80–4.40 (m, 2, H-6,6′), 4.40–4.15 (m, 1, H-5). Anal. Calcd for $C_{34}H_{27}N_3O_9$: C, 65.70; H, 4.38; N, 6.76; O, 23.16. Found: C, 65.54; H, 4.23; N, 6.82; O, 23.19.

2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosylamine (5a). An amount of 15.8 g (25.4 mmol) of **4a** in 350 mL of ethyl acetate was hydrogenated over 1.8 g of 10% palladium on carbon under a slow stream of hydrogen. When TLC (chloroform–methanol, 25:1) showed that starting material was no longer present, the reaction mixture was filtered and used directly for the synthesis of **6a**. For characterization a sample was drawn and evaporated to give a white foam: IR (KBr) 3350 (NH_2), 1725 cm^{-1} (C=O) and absence of N_3; ^{1}H NMR ($CDCl_3$) δ 7.95 and 7.35 (2 × m, 20, benzoyl), 6.05–5.25 (m, 3, H-2,3,4), 4.70–4.35 (m, 2, H-6,6′), 4.55 (d, $J_{1,2}$ = 8.1 Hz, 1, H-1), 4.30–4.05 (m, 1, H-5). A broad signal at δ 2.30 was attributed to the NH_2 group, although the integration value was too low for two protons.

***N*-Formyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosylamine (6a).** To the solution of **5a** in ethyl acetate was added at room temperature 17 mL (210 mmol) of formic acetic anhydride. After 6 h TLC (chloroform–methanol, 25:1) revealed the complete conversion of **5a**. The volatile compounds were removed under reduced pressure followed by several codistillations with absolute ethanol in vacuo. After drying in vacuo (0.02 mm) 16.0 g (100%) of **6a** was obtained. For analytical purposes a small amount was recrystallized from absolute ethanol: mp 178.5–179.5 °C; $[\alpha]^{22}_D$ +61.1° (c 1.0, $CHCl_3$); IR (KBr) 3400 (NH), 1720 (C=O benzoyl), 1690 cm^{-1} (C=O formyl); ^{1}H NMR ($CDCl_3$) δ 8.15 (s, 1, CHO), 7.95 and 7.30 (2 × m, 21, benzoyl and NH), 6.20–5.45 (m, 3, H-2,3,4), 5.60 (d, $J_{1,2}$ = 9.0 Hz, 1, H-1), 4.80–4.20 (m, 3, H-5,6,6′). Anal. Calcd for $C_{35}H_{29}NO_{10}$: C, 67.41; H, 4.69; N, 2.25; O, 25.66. Found: C, 67.06; H, 4.83; N, 2.13; O, 25.89.

***N*-Formyl-β-D-glucopyranosylamine (6b).** To a suspension of 520 mg (0.83 mmol) of **6a** in 100 mL of dry methanol was added a solution of sodium methanolate in methanol until the reaction mixture had pH 8 (wet indicator paper). After being stirred for 2 h at room temperature TLC (chloroform–methanol, 25:1) indicated that conversion was complete. The reaction mixture was neutralized by Dowex 50W (H^+) resin, filtered, and concentrated in vacuo (0.02 mm) to yield 172 mg (100%) of **6b**: IR (KBr) 3300–3400 (OH, NH), 1680 cm^{-1} (C=O formyl); ^{1}H NMR (D_2O) δ 8.30 (s, 1, CHO formyl), 5.08 (d, $J_{1,2}$ = 8.4 Hz, 1, H-1), 3.90–3.30 (m, 6, remaining CH's).

α and β-Anomers of 2,3,4,6-Tetra-*O*-benzoyl-D-glucopyranosyl isocyanide (7a and 9a). An amount of 2.5 g (4.0 mmol) of **6a** was suspended in 20 mL of triethylamine and 10 mL of methylene chloride; 4.8 g (31 mmol) of phosphorus oxychloride was added dropwise with stirring at 0 °C. The mixture was stirred overnight at room temperature. Subsequently, 25 mL of methylene chloride was added and the mixture was poured into an ice-cold saturated solution of sodium bicarbonate in water. The layers were separated and the aqueous layer was extracted three times with 25 mL of methylene chloride. The combined organic layers were washed with water, dried over sodium sulfate, and evaporated to dryness in vacuo, yielding a crude mixture of **7a** and **9a**. This mixture was separated by chromatography on a column of silicagel (30 cm long, 4 cm i.d.) with chloroform as eluent. In this way 0.12 g of **7a**, 0.17 g of a mixture of **7a** and **9a**, and 1.78 g of **9a** were obtained. Total yield 86%.

Pure **7a** had mp 54–56 °C: $[\alpha]^{22}_D$ +70.4° (c 1.5, $CHCl_3$); IR (KBr) 2124 ± 1 (NC, CO was used for calibration), 1725 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 8.00 and 7.35 (2 × m, 20, benzoyl), 6.25 (d of d, 1) and 5.85 (d of d, 1, H-3,4), 5.90 (d, $J_{1,2}$ = 4.5 Hz, 1, H-1), 5.50 (d of d, 1, H-2), 5.00–4.40 (m, 3, H-5,6,6′); ^{13}C NMR ($CDCl_3$) δ 166.1 (NC), 165.7, 165.2, 165.1 and 164.8 (C=O), 133.8, 133.5, 133.2, and 133.1 (arom C-4), 129.9–129.5 and 128.4–128.0 (2 × m, remaining arom C's), 78.8 (C-2), 71.5 (C-1), 69.6 (C-3), 69.4 (C-5), 67.9 (C-4), 61.8 (C-6). ^{13}C assignments were made by comparison with reported values of per-*O*-acetylglucopyranose[21] and isocyanides;[22] the position of C-6 was confirmed by an ^{1}H off-resonance decoupling experiment.

Pure **9a** had mp 88–90 °C: $[\alpha]^{22}_D$ +44.7° (c 2.5, $CHCl_3$); IR (KBr) 2142 ± 1 (NC), 1725 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 8.00 and 7.45 (2 × m, 20, benzoyl), 6.05–5.65 (m, 3, H-2,3,4), 5.20 (d, $J_{1,2}$ = 8.4 Hz, 1, H-1), 4.80–4.45 (m, 2, H-6,6′), 4.45–4.15 (m, 1, H-5); ^{13}C NMR ($CDCl_3$) δ 165.1 (NC), 165.9, 165.4, 164.8, and 164.6 (C=O), 133.6, 133.5, 133.4, and 133.1 (arom C-4), 129.8–129.7 and 128.3–128.1 (2 × m, remaining arom C's); 79.6 (C-2), 74.9 (C-1), 72.1 (C-3), 71.6 (C-5), 68.4 (C-4), and 62.3 (C-6). ^{13}C assignments are tentative vide supra; MS *m/e* 605 (M^+), 428 (M − benzoic acid − HC(O)NC), 361 (M − 2 benzoic acid), 352 (M − benzoic acid anhydride − HCN), 334 (M − 2 benzoic acid − HCN), 321 (M − $PhCOOCH_2$· − benzoic acid − −HCN). Anal. Calcd for $C_{35}H_{27}NO_9$: C, 69.42; H, 4.49; N, 2.31; O, 23.78. Found: C, 69.47; H, 4.77; N, 2.35; O, 23.41.

β-D-Glucopyranosyl Isocyanide (9b). Debenzoylation of **9a** as described for **6a** afforded **9b** in quantitative yield. The product was isolated by freeze drying: IR (KBr) 3400 (OH), 2150 cm^{-1} (NC), no C=O present; ^{1}H NMR (CD_3OD) δ 4.60 (H-1, partly masked by solvent), 3.85–3.25 (m, remaining H's).

Polymerization of 2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl Isocyanide (9a). To a solution of 1.59 g (2.63 mmol) of **9a** in 4 mL of chloroform was added a solution of 6.1 mg (0.026 mmol) of nickel chloride hexahydrate in 4 mL of methanol. The mixture was stirred for 2 days at room temperature. The solvent was removed under diminished pressure and the resulting red-brown solid was dissolved in 15 mL of chloroform. This solution was added dropwise, with vigorous stirring, to 500 mL of methanol–water 4:1. The precipitate was filtered off and dried in vacuo yielding 1.56 g (98%) of pale yellow **10a**: $[\alpha]^{22}_D$ 0.0° (c 0.7, $CHCl_3$); IR (KBr) 1730 (C=O), 1640 cm^{-1} (N=C); ^{1}H NMR ($CDCl_3$) δ 7.9 ($\Delta\nu_{1/2}$ 45 Hz) and 7.4 ($\Delta\nu_{1/2}$ 45 Hz) (2 × br, 20, benzoyl), 5.8 ($\Delta\nu_{1/2}$ 105 Hz, br, 4, tentative assignment H-1,2,3,4), 4.6 ($\Delta\nu_{1/2}$ 90 Hz, br, 3, tentative assignment H-5,6,6′). Anal. Calcd for $C_{35}H_{27}NO_9$: C, 69.42; H, 4.49; N, 2.31; O, 23.78. Found: C, 68.63; H, 4.64; N, 2.67; O, 24.06.

Polymerization of 2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl Isocyanide (7a). A procedure analogous to that described for the polymerization of **9a** was followed, except that the temperature of the reaction mixture was kept at 45 °C. After a reaction time of 7 days a 35% yield of polymer was obtained: $[\alpha]^{22}_D$ +80° (c 0.42, $CHCl_3$). After another 5 days the yield had increased to 88%: $[\alpha]^{22}_D$ +71°. Spectroscopic properties as for **10a**.

Poly(β-D-glucopyranosyliminomethylene) (10b). To a solution of 162 mg (0.27 mmol) of **10a** in 40 mL of dry THF was added sodium methanolate in methanol until the reaction mixture had pH 8. After being stirred for 2 h at room temperature, TLC revealed complete removal of the benzoyl groups. Diluted hydrochloric acid was added dropwise until the mixture had pH 6. After removal of the organic solvents in vacuo, the residue was diluted with water and after several extractions with ether subjected to ultrafiltration (Diaflo Ultra-Filter, UM-2). Freeze drying of the resulting solution afforded 35 mg (68%) of a creamish powder: $[\alpha]^{22}_D$ 0° (c 0.7, D_2O); IR (KBr) 3500–3200 (OH), 1630 cm^{-1} (NC); ^{1}H NMR (D_2O) δ 5.1 (H-1, partly masked by solvent), 4.4 ($\Delta\nu_{1/2}$ 20 Hz, br) and 4.1 ppm ($\Delta\nu_{1/2}$ 30 Hz, br, remaining protons).

Acknowledgments. The authors thank Professor W. Drenth and Dr. J. F. G. Vliegenthart for their helpful discussions and interest in the present work. The assistance of Dr. J. Haverkamp and Dr. J. P. Kamerling in the interpretation of ^{13}C-NMR and mass spectra is gratefully acknowledged.

Registry No.—**3a,** 1428-11-2; **4a,** 33639-93-9; **5a,** 33639-91-7; **6a,** 65293-31-4; **6b,** 65293-32-5; **7a,** 65375-78-2; **8a,** 65292-96-8; **9a,** 65375-79-3; **9b,** 65292-94-6; **10a,** 65292-93-5; **10b,** 65292-95-7; sodium azide, 26628-22-8; formic acetic anhydride, 2258-42-6.

References and Notes

(1) Part 5: J. M. van der Eijk, R. J. M. Nolte, and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **97**, 46 (1978).
(2) F. Millich, *Adv. Polym. Sci.*, **19**, 118 (1975).
(3) R. J. M. Nolte, A. J. M. van Beijnen, and W. Drenth, *J. Am. Chem. Soc.*, **96**, 5932 (1974).
(4) A. J. M. van Beijnen, R. J. M. Nolte, W. Drenth, and A. M. F. Hezemans, *Tetrahedron*, **32**, 2017 (1976).
(5) R. J. M. Nolte, R. W. Stephany, and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **92**, 83 (1973).
(6) R. J. M. Nolte and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **92**, 788 (1973).
(7) Polystyrene bounded sugars have been described in: (a) B. Helferich and H. J. Hofmann, *Chem. Ber.*, **85**, 175 (1952); (b) B. Helferich and K.-H. Jung, *Hoppe-Seyler's Z. Physiol. Chem.*, **311**, 54 (1958).
(8) L. Berrens, "The Chemistry of Atopic Allergens", Karger, Basel, 1971.
(9) P. Boullanger and G. Descotes, *Tetrahedron Lett.*, 3427 (1976); the ^{13}C-NMR resonance of the isocyano carbon in compound **2**, reported in this paper, is probably incorrect; see ref 22.
(10) F. Micheel and A. Klemer, *Adv. Carbohydr. Chem.*, **16**, 85 (1961).
(11) J. F. Sproviero, A. Salinas, and E. S. Bertiche, *Carbohydr. Res.*, **19**, 81 (1971).
(12) R. S. Tipson, A. S. Cerezo, V. Deulofeu, and A. Cohen, *J. Res. Natl. Bur. Stand., Sect. A*, **71**, 53 (1967).
(13) L. Dorland, B. L. Schut, J. F. G. Vliegenthart, G. Strecker, B. Fournet, G. Spik, and J. Montreuil, *Eur. J. Biochem.*, **73**, 93 (1977).
(14) I. Ugi and R. Meyr, *Angew. Chem.*, **70**, 702 (1958).
(15) H. M. Walborsky and G. E. Niznik, *J. Org. Chem.*, **37**, 187 (1972).
(16) R. Appel, R. Kleinstück, and K.-D. Ziehn, *Angew. Chem.*, **83**, 143 (1971).
(17) I. Ugi, "Isonitrile Chemistry", Academic Press, New York, N.Y., 1971.
(18) A. J. Naaktgeboren, R. J. M. Nolte, and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, in the press.
(19) A. J. M. van Beynen, R. J. M. Nolte, J. W. Zwikker, and W. Drenth, *J. Mol. Catal.*, in press.
(20) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.*, **72**, 2200 (1950).
(21) D. E. Dorman and J. D. Roberts, *J. Am. Chem. Soc.*, **93**, 4463 (1971).
(22) R. W. Stephany, M. J. A. de Bie, and W. Drenth, *Org. Magn. Reson.*, **6**, 45 (1974).

Substituted Coumarins and Azacoumarins. Synthesis and Fluorescent Properties

Ronald L. Atkins* and Dan E. Bliss

Organic Chemistry Branch, Chemistry Division, Code 3856, Research Department
Naval Weapons Center, China Lake, California 93555

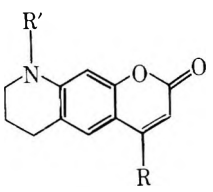
Received August 30, 1977

A number of new substituted 7-amino- and 8-aza-7-amino coumarins have been synthesized. Substituent effects on fluorescence properties (maxima and quantum yields) are reported. Substitution by fluorine in the 4-methyl position and by nitrogen in the benzo ring has been found to reduce fluorescence quantum yields. Nitrogen substitution in the benzo ring provides a blue shift in the fluorescence while fluorine substitution at the 4-methyl position gives pronounced red shifts.

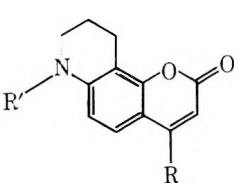
Recent synthesis programs in this laboratory have resulted in the preparation of a large number of substituted coumarins and azacoumarins for use as emission sources for dye laser applications. The effects of substituents on the lasing characteristics of these compounds have been reported.[1-4] This report describes the synthesis of several new laser dyes and the effects of substituents on their fluorescence maxima and fluorescence quantum yields.

The new coumarin dyes prepared in the present work are shown below. Results are summarized in Table I. The syntheses led to several new results of chemical interest.

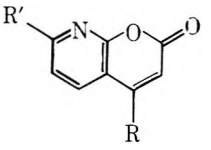
Synthesis. The preparation of 8-aza-7-hydroxy-4-methylcoumarin (**3c**) by the method of von Pechmann[5,6] from 2,6-dihydroxypridine (**4**) and ethyl acetoacetate gave in addition to the desired product small amounts of the bis addition product 10-aza-2,8-dioxo-4,6-dimethyl-2*H*,8*H*-benzo[1,2-*b*:5,4-*b*]dipyran (**5**) (detected by mass spectroscopy; M^+ ion at *m/e* 243). Merchant and co-workers[7] also noted the formation of trace amounts of a similar bis addition product in the reaction of ethyl acetoacetate with resorcinol. When the condensation of 2,6-dihydroxypyridine (**4**) is carried out in



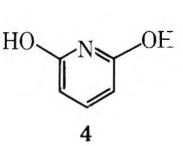
1a. R = CH_3; R′ = H
b. R = CF_3; R′ = H
c. R = CH_3; R′ = CH_3
d. R = CF_3; R′ = CH_3



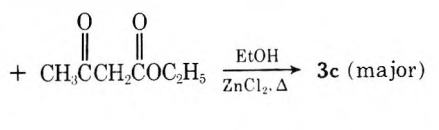
2a. R = CH_3; R′ = H
b. R = CF_3; R′ = H
c. R = CH_3; R′ = CH_3
d. R = CF_3; R′ = CH_3

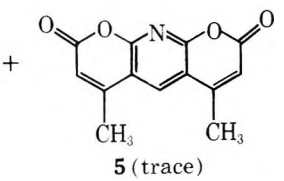


3a. R = CH_3; R′ = NH_2
b. R = CH_3; R′ = $N(CH_3)_2$
c. R = CH_3; R′ = OH
d. R = CF_3; R′ = 
e. R = CH_3; R′ = 



4





5 (trace)

Table I. Substituted Amino-, Hydroxy-, 8-Aza-7-amino-, and 8-Aza-7-hydroxycoumarins

Compd	Registry no.	Yield %	Mp °C	Recrystallization solvent	Fluores max in ethanol, (exc., nm)	Quantum yield ϕ_{fluor}	Molecular formula	Anal. % (theory) C	H	N	F
1a	62669-73-2	55	236–238	Ethanol	450 (380)	0.92	$C_{13}H_{13}NO_2$	72.27 (72.54)	5.96 (6.09)	6.35 (6.51)	
1b	53518-16-4	76	229–230	Ethanol	522 (406)	0.85	$C_{13}H_{10}F_3NO_2$	57.92 (58.00)	3.59 (3.74)	5.08 (5.20)	21.09 (21.17)
1c	65292-83-3	67	145–148	Acetonitrile	458 (378)	1.00	$C_{14}H_{15}NO_2$	72.99 (73.34)	6.37 (6.59)	6.06 (6.11)	
1d	53518-19-7	87	197–198	Acetonitrile	522 (413)	0.75	$C_{14}H_{12}F_3NO_2$	59.46 (59.36)	4.25 (4.24)	5.13 (4.96)	19.94 (20.14)
2a	65292-84-4	78	148–151	Methanol	455 (372)	0.67	$C_{13}H_{13}NO_2$	72.39 (72.54)	5.90 (6.08)	6.47 (6.51)	
2b	53518-17-5	39	187–188	Ethanol	537 (405)	0.64	$C_{13}H_{10}F_3NO_2$	57.89 (58.00)	3.69 (3.74)	5.15 (5.20)	21.34 (21.17)
2c	65292-85-5	50	126–128	Methanol	468 (375)	0.73	$C_{14}H_{15}NO_2$	73.03 (73.34)	6.38 (6.59)	6.14 (6.11)	
2d	65292-86-6		134–136	Methanol	537 (410)	0.33	$C_{14}H_{12}F_3NO_2$	58.96 (58.95)	4.45 (4.95)	4.95 (4.90)	20.00 (19.98)
3a	65292-87-7	63	330–340	Me_2SO	370 (340)		$C_9H_8N_2O_2$	61.33 (61.36)	4.61 (4.58)	16.07 (15.90)	
3b	57980-06-0	13	157–160	Benzene/ Hexane	422 (365)	0.60	$C_{11}H_{12}N_2O_2$	64.61 (64.69)	6.03 (5.92)	13.71 (13.72)	
3c	57980-05-9	15	295–297	Me_2SO	412 (356)	0.76	$C_9H_7NO_3$	60.90 (61.01)	4.00 (3.98)	8.03 (7.91)	
3d	58721-73-6	95	218–220	Acetonitrile	478 (380)	0.20	$C_{18}H_{11}F_3N_2O_3$	52.33 (52.01)	3.77 (3.69)	9.30 (9.33)	19.14 (18.98)
3e	57980-07-1	99	188–189	Benzene	425 (358)	0.54	$C_{13}H_{14}N_2O_3$	66.34 (63.41)	5.69 (5.73)	11.22 (11.38)	

the presence of excess ethyl 4,4,4-trifluoroacetoacetate, 10-aza-2,8-dioxo-4,6-bis(trifluoromethyl)-2*H*,8*H*-benzo[1,2-*b*:5,4-*b*]dipyran, (**6**), the bis addition compound, is the principal product (50% yield).

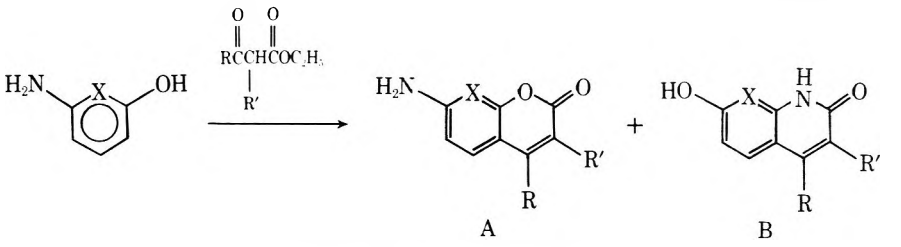
In the preparation of 7-amino-4-methylcoumarin (**7**) from

6

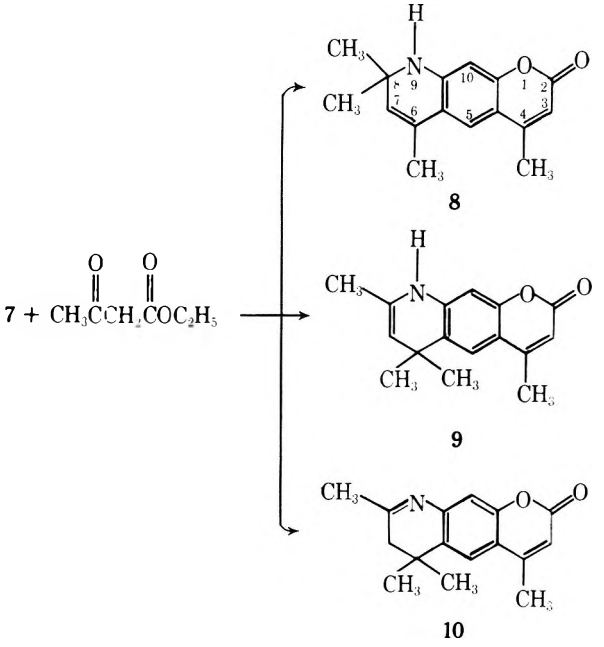
ethyl acetoacetate and *m*-aminophenol, a second strongly fluorescing coumarin was isolated. This material had also been prepared by von Pechmann and was reported to be 2-keto-4,6,6,8-tetramethyl-6,7-dihydro-2*H*-pyrano[3,2-*g*]quinoline (**10**).[8]

This assignment is incorrect. The product exhibits a sharp absorption in the IR at 3310 cm^{-1} indicative of the secondary amine moiety. The ^1H-NMR spectrum (see Experimental Section) which eliminates **10** does not allow a definitive choice between **8** and **9**. NMR analysis employing the shift reagent $Eu(fod)_3$ which associates with the carbonyl oxygen made possible the assignment of all proton absorptions. However,

Table II. Reaction of β-Ketoesters with *m*-Aminophenol and 6-Amino-2-pyridinol



Experiment	X	R	R′	Reaction conditions	Coumarin (A) No. (%)	Quinolone (B) No. (%)
(1)	C	CH_3	CH_3	Neat	11 (46)	12 (trace)
(2)	C	CH_3	H	Neat	7 (trace)	13 (60)
(3)	C	CF_3	H	Neat	14 (major)	15 (10)
(4)	C	CH_3	H	$ZnCl_2$/EtOH	7 (16)	13 (25)
(5)	C	CF_3	H	$ZnCl_2$/EtOH	14 (42)	15 (trace)
(6)	N	CF_3	H	Neat	16 (61)	17 (15)
(7)	N	CH_3	CH_3	Neat	18 (major)	19 (20)



a choice between 8 and 9 still could not be made since the geminal dimethyl group and vinylmethyl (the 6-methyl in 8 or the 8-methyl in 9) are essentially equidistant from the site of $Eu(fod)_3$ association.

Measurement of the nuclear Overhauser effect enhancements of the ring protons proved definitive. Saturation of the geminal dimethyl resonance resulted in the enhancement of the N–H integral and the dihydro ring vinyl proton integrals. Saturation of the 4-methyl absorption revealed enhancement of H-3 and H-5, while saturation of the dihydro ring vinyl methyl absorption resulted in observation of enhanced absorption of H-5 and the dihydro ring vinyl hydrogen. These data are consistent only with structure 8.

Product 8 is most likely formed by the Michael-type addition of the intermediate 7-amino-4-methylcoumarin (7) to mesityl oxide. The mesityl oxide most likely is formed under the reaction conditions employed from acetone (the acetone derived by retrogression from ethyl acetoacetate). Knoevenagel[9] has reported a similar 1,4-Michael addition of aniline to mesityl oxide (formed *in situ* from acetone) giving 1,2-dihydro-2,2,4-trimethylquinoline. This mechanistic path is further supported by the reaction of mesityl oxide with 7 to yield 8.

A convenient method for preparation of courmarins and quinolones is to omit catalyst and solvent and simply heat the precursor aminophenol with the β-keto ester.[10,11] This method, however, can lead to mixtures of coumarins and quinolones in contrast to von Pechmann's procedure which provides primarily coumarins. While the reaction is regiospecific in that ring formation is ortho to the reacting functional group and para to the second giving 7-substituted products, no 5-substituted products are obtained, it is nonselective with respect to the functional groups.

Several examples illustrate this reaction feature (Table II). When *m*-aminophenol is heated in the presence of ethyl 2-methylacetoacetate, Table II, reaction 1, the major product is 7-amino-2,3-dimethylcoumarin (11) formed in 46% yield. A trace amount of the isomeric 7-hydroxy-2,3-dimethylquinolone (12) was isolated from the base-soluble extract of the reaction mixture.[12] However, when *m*-aminophenol is heated in the presence of an equimolar amount of ethyl acetoacetate, the only isolable addition product is 7-hydroxy-4-methylquinolone (13). Only a trace amount of coumarin 7 (detected by TLC analysis of the reaction mixture) was formed.

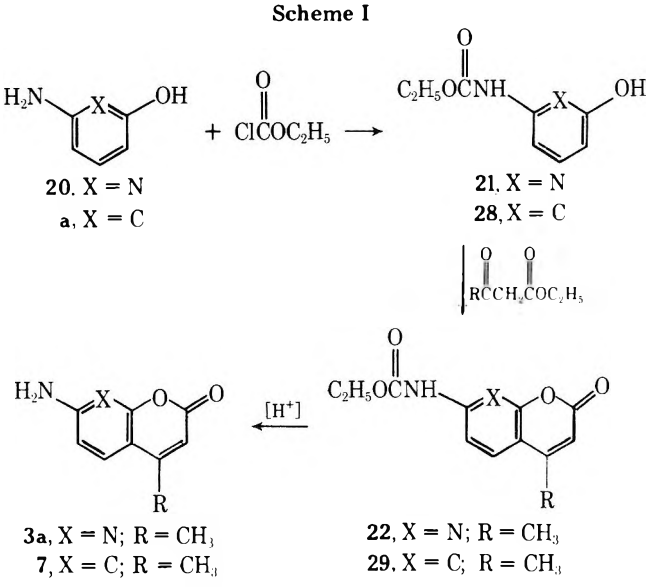
When the condensation of *m*-aminophenol and ethyl 4,4,4-trifluoroacetoacetate is carried out in absolute ethanol at reflux in the presence of anhydrous zinc chloride (von Pechmann conditions) the addition occurs at the hydroxyl group giving 14. Only a trace of quinolone is observed (Table II, reaction 5). Evidently the zinc chloride complexes with the amino group and thus facilitates condensation via the hydroxyl group. However, when the condensation of *m*-aminophenol with ethyl 4,4,4-trifluoroacetoacetate is carried out in the absence of solvent (Table II, reaction 3), the major product is the coumarin 14. A 10% yield of quinolone 15 was recovered from the base-soluable extract.[12]

Similar results are obtained with 6-amino-2-pyridinol (20). When 20 is heated in the presence of ethyl 4,4,4-trifluoroacetoacetate a 76% yield of addition products is obtained giving approximately a 4:1 ratio of quinolone to coumarin, Table II, reaction 6.[12] A similar product distribution is realized when 20 is allowed to react with ethyl 2-methylacetoacetate,[12] Table II, reaction 7.

Since reaction of 20 with β-keto esters gives mixtures of quinolones and coumarins, it was necessary to modify the reaction sequence in order to obtain pure 7-aminocoumarins in good yields. This was accomplished by first deactivating the amino substituent through formation of its urethane derivative. Reaction of this intermediate gives exclusively the coumarin derivative (Scheme I). The free amino compound is then liberated by mild acid hydrolysis.[13]

While urethane derivative 21 gave reasonable yields of coumarin upon reaction with β-keto esters, 6-acetamido-2-

Scheme I



pyridinol (**23**) fails to give the desired product. Prolonged heating of **23** in the presence of excess ethyl acetoacetate resulted in the recovery of starting material.

A convenient procedure for the methylation of functional groups (amino, hydroxyl, amide) in these systems has been developed. Where other procedures such as reductive methylation with sodium cyanoborohydride or hydrogen (platinum catalyst) failed, simply heating the precursor in the presence of excess trimethyl phosphate gives the desired product in good to excellent yields,[14] see for example the prepartion of **1c** and **1d.**

In the preparation of 7-hydroxy- and 5-hydroxy-5,6,7,8-tetrahydroquinolines it was found that when the hydrogenation of the heteroring was carried out in neutral media, no acid catalyst,[15] uptake of hydrogen was quantitative (although longer reaction times were required) and a cleaner product resulted.

Fluorescence. Substituent effects on the fluorescence maxima of these systems parallel those observed in other coumarin dyes. A large bathochromic shift of 82 nm is seen in changing the 4-methyl group in **2a** to a trifluoromethyl group in **2b.** Similar shifts are observed in other pairs, i.e., **1a–b, 1c–d.** The red shift is not of the same magnitude in the azacoumarins. A shift of 53 nm is obtained with **3d** compared to **3e.**

Varying the substituent in the 7 position does not result in large shifts in these compounds and does not seem to follow a predictable pattern. Compounds **2b** and **2d** for example both have fluorescence maxima at 537 nm. The alkylation seemingly has no effect. However, compound **1a** exhibits a red shift of 8 nm upon methylation of the nitrogen to give **1c,** and methylation of **2a** results in a 13-nm red shift in **2c.** The azacoumarins all exhibit pronounced hypsochromic shifts when compared to their carbon analogues.

The quantum yields of fluorescence are generally high for the substituted 7-amino-4-methylcoumarins. In all cases substitution by fluorine at the 4-methyl position results in a diminished quantum yield of fluorescence. In the azacoumarin series the quantum yields are less than in the carbon series, and again substitution of fluorine in the 4-methyl group lowers the quantum yield still further, i.e., compounds **3e** and **3d.**

These factors work in concert in the 4-trifluoromethyl-8-azacoumarins and these compounds exhibit low quantum yields of fluorescence. The fluorinated bis adduct **6** shows very poor fluorescence and at liquid nitrogen temperature in absolute ethanol exhibits strong phosphorescence. To the contrary, the pseudo-bis adduct **8** fluoresces strongly at 470 nm with high stability and exhibits lasing action over a 25-nm range (455–480 nm). Surprisingly, **8** also shows strong phosphorescence in ethanol at liquid nitrogen temperature indicating efficient intersystem crossing to the triplet state, a process generally regarded to be highly deleterious to lasing.

Experimental Section

Proton and ^{13}C-NMR spectra were obtained with a Varian XL-100 FT spectrometer and are referenced to tetramethylsilane as an internal standard. IR spectra (KBr discs) were obtained with a Perkin-Elmer 137 spectrometer. UV absorbance data were measured on a Cary-14 spectrometer. Fluorescence spectra and quantum yields were determined using a Turner Model 210 spectrofluorometer utilizing quinine sulfate as a quantum yield standard. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E spectrometer. Melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

7-Hydroxyquinoline (23). This compound was prepared from *m*-aminophenol via the Skraup quinoline synthesis using the procedure of Bradford *et al.*[16]

7-Hydroxy-1,2,3,4-tetrahydroquinoline (24). 7-Hydroxyquinoline (4.0 g, 27.6 mmol) and PtO_2 (0.3 g) were suspended in 150 mL of 95% ethanol containing 1 mL of concentrated HCl. Hydrogenation (Parr apparatus, room temperature, 50 lb H_2 pressure) was continued until the theoretical amount of H_2 was absorbed (4 h). Filtration and concentration gave 5.04 g of red oil. Water (50 mL) was added and the resulting suspension was made basic (dilute NH_3). Extraction with ether (4 × 75 mL) drying ($CaCl_2$), and concentration gave 3.5 g of oil (90%) which solidified upon standing (mp 70–80 °C): NMR ($CDCl_3$) δ 1.8–2.4 (m, 2H, $CH_2\mathbf{CH_2}CH_2$), 2.76 (t, 2, J = 7 Hz, $\mathbf{NCH_2}CH_2$), 3.38 (t, 2, J = 6 Hz, $CH_2\mathbf{CH_2}Ar$), 4.8 (bs, 2, **OH** and **NH**), 6.16 (d, 1, J_{para} = 2 Hz, H-8), 6.33 (d of d, 1, J_{para} = 2 Hz, J_{ortho} = 8 Hz, H-5), 7.05 (d, 1, J_{ortho} = 8 Hz, H-6). In subsequent preparations the HCl was omitted. While the hydrogenation generally took two or three times longer, the product (obtained in quantitative yield) was of sufficient purity for use without further purification.

2-Keto-4-methyl-6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]quinoline (1a). Ethyl acetoacetate (7.78 g, 60 mmol), **24** (7.9 g, 53 mmol), and anhydrous zinc chloride (11 g, 80 mmol) were added to absolute ethanol (100 mL). The resulting mixture was heated at reflux 15 h. A yellow solid had precipitated. More solid was deposited upon cooling to room temperature. Filtration gave 5.62 g. Pouring the mother liquors into ice water (100 mL) yielded an additional 0.75 g of yellow solid. The crude yield was 55%. Two recrystallizations from ethanol gave yellow needles, mp 236–238 °C; NMR (Me_2SO-d_6): δ 2.78 (m, 2, $CH_2\mathbf{CH_2}CH_2$), 2.30 (s, 3, 4-Me), 2.72 (t, 2, J = 6.2 Hz, $CH_2\mathbf{CH_2}Ar$), 3.29 (t, 2, J = 6.2 Hz, N-$\mathbf{CH_2}CH_2$), 5.82 (s, 1, H-3), 6.31 (s, 1, H-5), 6.81 (bs, 1, N-**H**), 7.21 (s, 1, H-10); IR: 3425 cm^{-1} (N-H); 1710 cm^{-1} (C=O).

2-Keto-4-trifluoromethyl-6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]quinoline (1b). 7-Hydroxy-1,2,3,4-tetrahydroquinoline (2.38 g, 16 mmol), ethyl 4,4,4-trifluoroacetoacetate (2.9 g, 16 mmol), anhydrous zinc chloride (6.0 g), and dry ethanol (50 mL) were mixed and the resulting mixture was heated at reflux for 18 h under a dry N_2 atmosphere with stirring. A solid deposited on cooling. Filtration gave yellow crystals: 3.5 g (76%); mp 229–230 °C; NMR ($CDCl_3$) δ 1.64–1.88 (m, 2, $CH_2\mathbf{CH_2}CH_2$), 2.62 (t, 2, J = 6 Hz, $CH_2\mathbf{CH_2}Ar$), 3.23 (t, 2, J = 6 Hz, $\mathbf{NCH_2}CH_2$), 6.23 (bs, 2, C-5 and C-8), 7.06 (bs, 1, H-3); IR 3450 (NH), 1720 cm^{-1} (C=O), mass spectrum *m/e* 269, M^+.

2-Keto-4,9-dimethyl-6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]quinoline (1c). Trimethyl phosphate (1.0 g, 7.1 mmol) and **1a** (1.0 g, 4.65 mmol) were heated in an oil bath at 200 °C for 30 min. The resulting dark oil set to a solid mass upon cooling. Crystallization from acetonitrile (10 mL) gave yellow-green plates (0.7 g, mp 145–148 °C) of the desired product (67% yield): NMR ($CDCl_3$) δ 1.75–2.2 (m, 2, $CH_2\mathbf{CH_2}CH_2$), 2.32 (d, 3, J = 0.6 Hz, 4-Me), 2.81 (t, 2, J = 7 Hz, $CH_2\mathbf{CH_2}Ar$), 3.40 (t, 2, J = 6.5 Hz $\mathbf{NCH_2}CH_2$), 2.98 (s, 3, NMe), 6.0 (q, 1, J = 0.6 Hz, H-3), 6.48 (s, 1, H-5), 7.18 (s, 1, H-6); IR 1724 cm^{-1} (C=O), N-H absent.

2-Keto-4-trifluoromethyl-9-methyl-6,7,8,9-tetrahydro-2*H*-pyrano[3,2-*g*]quinoline (1d). Trimethyl phosphate (30 mL) and **1b** (2.5 g) were heated at reflux for 4 h. Cooling gave yellow crystals (2.3 g, 87%) which recrystallized from acetonitrile gave golden needles (mp 197–198 °C): NMR ($CDCl_3$) δ 1.86–2.10 (m, 2, $CH_2\mathbf{CH_2}CH_2$), 2.80 (t, 2, J = 6 Hz, $CH_2\mathbf{CH_2}Ar$), 3.01 (s, 3, $\mathbf{NCH_3}$), 3.41 (t, 2, J = 6 Hz, $\mathbf{NCH_2}CH_2$), 6.36 and 6.44 (two s, each 1 H, C-5 and C-10), 7.20 (bs, 1, H-3); mass spectrum *m/e* 283, M^+.

5-Hydroxy-1,2,3,4-tetrahydroquinoline, (25). 5-Hydroxyquinoline (5.0 g, 35 mmol) suspended in 100 mL of 95% ethanol con-

taining 6 mL of concentrated HCl was hydrogenated in the presence of PtO_2 (0.5 g) in a Parr apparatus (room temperature, 50 lb H_2) until the theoretical amount of H_2 was absorbed. Filtration and concentration gave a dark oil. Water (100 mL) was added and the resulting solution was neutralized by addition of 1 N NaOH (70 mL). The solution was extracted with ether (5 × 100 mL) and dried ($CaSO_4$). Filtration and concentration gave 5 g of a brown oily solid. The brown solid was washed with $CHCl_3$ (100 mL) and dried to give 4.8 g of a tan solid (95%): mp 110–112 °C; IR 3180 cm^{-1} (NH); NMR ($CDCl_3$) δ 1.92 (m, 2, $CH_3CH_2CH_2$), 2.65 (6, 2, J = 7 Hz, NCH_2CH_2), 3.22 (t, 2, J = 5.5 Hz, CH_2CH_2Ar), 4.76 (bs, 2, NH and OH), 6.09 (d, 2, J = 8 Hz, H-6 and H-8), 6.80 (t, 1, J = 8 Hz, H-7).

2-Keto-4-methyl-7,8,9,10-tetrahydro-2*H*-pyrano[2,3-*f*]quinoline (2a). Ethyl acetoacetate (5.2 g, 40 mmol), **25** (5.5 g, 37 mmol), and anhydrous zinc chloride (6.8 g, 50 mmol) were added to 50 mL of absolute ethanol. The resulting mixture, protected from moisture with a positive dry N_2 atmosphere, was heated at reflux for 20 h. The cooled reaction solution was poured onto 100 g of crushed ice. A viscous oil separated and gave 1.4 g of yellow solid upon rubbing with a glass rod. The remaining organic phase was dissolved in hot ethanol and gave a second crop of product (2.1 g). A third crop of yellow solid (3.1 g) was recovered from the combined aqueous phase extracts and acetone washings of the gummy solids adhering to the reaction flasks. Yield of crude product was 78%. Two recrystallizations (MeOH) gave yellow needles (mp 149–151 °C); NMR ($CDCl_3$) δ 1.9 (m, 2, $CH_2CH_2CH_2$), 2.3 (s, 3, 4-Me), 2.9 (t, 2, J = 6.4 Hz, CH_2CH_2Ar), 3.38 (t, 2, J = 5.8 Hz, NCH_2CH_2), 4.5 (bs, 1, NH), 6.0 (s, 1, H-3), 6.41 (d, 1, J = 8.5 Hz, H-5), 7.27 (d, 1, J = 8.5 Hz, H-6); IR 3436 (NH), 1724 cm^{-1} (C=O).

2-Keto-4-trifluoromethyl-7,8,9,10-tetrahydro-2*H*-pyranol[2,3-*f*]quinoline (2b). Ethyl 4,4,4-trifluoroacetoacetate (6.63 g, 36 mmol), **25** (6.36 g, 36 mmol), anhydrous $ZnCl_2$ (10 g), and absolute ethanol (75 mL) were heated at reflux for 20 h (dry N_2 atmosphere). The cooled solution was concentrated, taken up in 75 mL of $CHCl_3$, washed with 1 N NaOH (2 × 50 mL) and water (50 mL), and dried ($MgSO_4$). Filtration and concentration gave 4.0 g (39%) of yellow solid, mp 187–188 °C (ethanol): IR 3310 (NH), 1710 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 1.84 (p, 2, J = 6 Hz, $CH_2CH_2CH_2$), 2.73 (t, 2, J = 6 Hz, NCH_2CH_2), 3.31 (t, 2, J = 6 Hz, CH_2CH_2Ar), 3.54 (bs, 1, NH), 6.29 (s, 1, H-3), 6.58 (d, 1, J_{ortho} = 9 Hz, H-6), 7.19 (d of q, 1, J_{ortho} = 9 Hz, J_{CF_3} = 1.8 Hz, H-5).

2-Keto-4,7-dimethyl-7,8,9,10-tetrahydro-2*H*-pyrano[2,3-*f*]quinoline (2c). Trimethyl phosphaste (1.0 g, 7 mmol) and **2a** (0.83 g, 3.8 mmol) were mixed and heated at 195 °C for 1 h in an oil bath. The resulting dark oil was dissolved in 20 mL of methylene chloride and chromatographed on a 15 × 3 cm alumina column ($MeCl_2$ eluant). The first yellow band (0.7 g) was recrystallized from MeOH (10 mL) to give 0.44 g (50%) of the desired product: mp 126–128 °C; NMR ($CDCl_3$) δ 1.78 (m, 2, $CH_2CH_2CH_2$), 2.34 (d, 3, J = 0.6 Hz, 4-Me), 2.7–3.1 (m, 2, CH_2CH_2Ar), 3.2 (s, 3, NMe), 3.39 (t, 2, J = 6 Hz, NCH_2CH_2), 6.1 (bs, 1, H-3), 6.62 (d, 1, J = 9.4 Hz, H-5), 7.38 (d, 1, J = 9.4 Hz, H-6); IR 1740 cm^{-1} (C=O), NH absent.

2-Keto-7-methyl-4-trifluoromethyl-7,8,9,10-tetrahydro-2*H*-pyrano[2,3-*f*]quinoline (2d). The methylation of **2b** was carried out as in preparation **2c** to give the desired product as yellow needles (mp 134–136 °C): NMR ($CDCl_3$) δ 2.0 (m, 2, $CH_2CH_2CH_2$), 2.92 (t, 2, J = 7 Hz, CH_2CH_2Ar), 3.08 (s, 3, NMe), 3.36 (t, 2, J = 7 Hz, NCH_2CH_2), 6.44 (s, 1, H-3), 6.65 (d, 1, J_{ortho} = 9 Hz, H-8), 7.44 (d of q, 1, J_{ortho} = 9 Hz, J_F = 1.0 Hz, H-7); IR 1738 cm^{-1} (C=O), N–H absent.

3-Hydroxyphenylurethane (28). Ethyl chloroformate (10 g, 92 mmol) was added in one portion to a stirred suspension of *m*-aminophenol (10 g, 92 mmol) in 400 mL of dry diethyl ether. A white precipitate (the amine hydrochloride) formed immediately. The reaction mixture was stirred an additional 2 h at room temperature. The hydrochloride was removed by filtration. Evaporation of the solvent left 8 g of grey solid. Crystallization from benzene/cyclohexane (200 and 400 mL, respectively) gave upon cooling (0 °C) 7.0 g (84% yield) of colorless needles: mp 94–95 °C; IR 3260 (NH), 1700 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.30 (t, 3, J = 7 Hz, OCH_2CH_3), 4.21 (q, 2, J = 7 Hz, OCH_2CH_3), 6.59 (bm, 4, NH, OH, H-4, and H-6), 7.06 (t, 1, J = 8 Hz, H-7), 7.30 (s, 1, H-2).

7-Carbethoxyamino-4-methylcoumarin (29). Ethyl acetoacetate (5.62 g, 43 mmol) and **28** (6.5 g, 36 mmol) suspended in 88 mL of 70% H_2SO_4 were stirred 4 h at room temperature. The clear yellow solution was poured into 400 mL of ice water, giving a voluminous white crystalline precipitate. The solid filtered and crystallized from 400 mL of absolute ethanol to give 7.4 g (83% yield) of colorless needles: mp 186–188 °C; NMR (Me_2SO-d_6) δ 1.39 (t, 3, J = 7 Hz, CH_2CH_3), 2.32 (d, 3, J = 1.4 Hz, 4-Me), 3.83 (q, 2, J = 7 Hz, CH_2CH_3), 5.54 (q, 1, J = 1.4 Hz, H-3), 6.52 (d of d, 1, J_{ortho} = 7.4 Hz, J_{para} = 2 Hz, H-5), 6.65 (d, 1, J_{para} = 2 Hz, H-8), 6.76 (d, 1, J_{ortho} = 7.4 Hz, H-6), 8.80 (bs, 1, NH). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 62.95; H, 5.29; N, 5.65.

7-Amino-4-methylcoumarin (7). 7-Carbethoxyamino-4-methylcoumarin (**29**) (7.0 g, 28 mmol) was heated at reflux 4 h in 25 g of concentrated H_2SO_4 and 25 g of glacial acetic acid. On cooling a yellow precipitate was deposited. The mixture was poured into 100 mL of ice water and let stand overnight. The resulting suspension was made slightly basic with 50% NaOH with cooling by addition of ice chips. The yellow precipitate was filtered and washed with ice water (3 × 50 mL). Crystallization from ethanol yielded three crops of yellow needles (4.9 g, 99%), mp 220–224 °C (lit.[18] mp 223 °C).

6-Carbethoxyamino-2-pyridinol (26). 2-Amino-6-hydroxypyridine (11 g, 100 mmol) and ethyl chloroformate were stirred at room temperature for 20 h in a solution of 400 mL of dry ether and 100 mL of dry tetrahydrofuran containing 10 g (100 mmol) of triethylamine. Filtration of the reaction mixture gave 12.5 g of grey solid which was identified as a mixture of triethylamine hydrochloride and unreacted 2-amino-6-hydroxypyridine by TLC. Evaporation of the mother liquors gave 6.7 g (37%) of small colorless needles (mp 70–72 °C) which darkened appreciably upon exposure to light: IR 3420 (OH), 3310 and 3205 (NH), 1755 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.34 (t, 3, J = 7 Hz, CH_2CH_3), 4.37 (q, 2, J = 7 Hz, CH_2CH_3), 4.69 (bs, 2, NH and OH), 6.45 (d, 1, J = 8 Hz, H-3 or H-5), 6.48 (d, 1, J = 8 Hz, H-3 or H-5), 7.50 (t, 1, J = Hz, H-4). Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.67; H, 5.56; N, 15.32.

8-Aza-7-amino-4-methylcoumarin (3a). Ethyl acetoacetate (4.55 g, 35 mmol) and **26** (5.0 g, 27.5 mmol) were mixed and heated at 130 °C with stirring for 16 h. After 15 min of heating a clear solution resulted. A yellow solid formed as heating was continued. After cooling the excess ester was removed by rotoevaporation. The resulting yellow solid was crystallized from Me_2SO to give 2.3 g of yellow solid (mp 230–235 °C). The mother liquors were diluted with 200 mL of distilled water to give an additional 2 g of yellow solid. The combined material, isolated in 63% yield, was 8-aza-7-amino-4-methylcoumarin as confirmed from spectral data. Apparently the reaction conditions were sufficient to effect hydrolysis of the carbethoxy group: IR 1670 cm^{-1} (C=O). The NH absorption bands are not evident in KBr nor do they appear in a Nujol mull. The carbamate carbonyl is absent. NMR (Me_2SO-d_6) δ 2.33 (s, 3, 4-Me), 6.12 (s, 1, H-3), 6.26 (d, 1, J_{ortho} = 8.5 Hz, H-5), 7.77 (d, 1, J_{ortho} = 8.5 Hz, H-6); upon addition of D_2O the 7-amino protons appeared as a broad singlet at 3.50; MS *m/e* 231, M^+.

8-Aza-7-hydroxy-4-methylcoumarin (3c). Ethyl acetoacetate (2.60 g, 20 mmol), **4** (2.22 g, 20 mmol), and anhydrous $ZnCl_2$ were mixed and heated at reflux in 25 mL of anhydrous methanol under a dry N_2 atmosphere with stirring for 8 h. After standing at room temperature a red-orange solid was deposited (0.48 g), 15%: mp 295–297 °C (Me_2SO); NMR (Me_2SO-d_6) 2.40 (d, 3, J = 0.8 Hz, 4-Me), 3.22 (bs, 1, OH), 6.18 (q, 1, J = 0.8 Hz, H-3), 6.66 (d, 1, J_{ortho} = 4 Hz, H-5), 8.04 (d, 1, J_{ortho} = 4 Hz, H-6); IR 1750 cm^{-1} (C=O).

2-Hydroxy-6-morpholinopyridine (27). 2-Chloro-6-hydroxypyridine (4.0 g, 31 mmol) was heated at reflux (87 °C) in 25 mL of morpholine for 96 h. Upon cooling morpholine hydrochloride, 3.5 g (mp 160–165 °C (lit.[17] mp 175 °C)) precipitated. The hydrochloride was filtered and the green mother liquors were concentrated to give a green solid. The solid was dissolved in 100 mL of benzene, treated with decolorizing charcoal, and filtered. The emerald green solution deposited crystals upon cooling (10 °C), 5.1 g (mp 136–140 °C, 91% yield). Recrystallization from acetonitrile did not improve the melting point: NMR (Me_2SO-d_6) δ 3.35 (m, 4, CH_2OCH_2), 3.69 (m, 4, CH_2NCH_2), 5.92 (d, 1, J = 4 Hz, H-2 or H-4), 6.09 (d, 1, J = 4 Hz, H-2 or H-4), 7.39 (t, 1, J = 4 Hz, H-3); MS *m/e* 180, M^+; IR NH absent.

8-Aza-7-morpholino-4-trifluoromethylcourmarin (3d). Ethyl 4,4,4-trifluoroacetoacetate (5 mL) and **27** (2.0 g, 11 mmol) were heated at reflux for 60 h. The volatile material was removed by rotoevaporation to give crystalline material. Recrystallization from acetonitrile (75 mL) gave gold needles: 3.2 g (95%, mp 218–220 °C); NMR (acetone-d_6) δ 3.02 (s, 8, morpholine protons), 6.57 (s, 1, H-3), 6.94 (d, J_{ortho} = 4.5 Hz, H-6), 7.90 (d of q, 1, J_{ortho} = 4.5 Hz, J_F = 1.0 Hz, H-5); IR 1728 cm^{-1} (C=O).

8-Aza-7-dimethylamino-4-methylcoumarin (3b). 2-Dimethylamino-6-hydroxypyridine (1.1 g, 8 mmol) was heated at 150 °C in the presence of excess ethyl acetoacetate (10 mL) for 66 h. The excess ethyl acetoacetate was removed by rotoevaporation to give a dark oil. Addition of methanol (5 mL) gave a yellow solid. The solid was crystallized from benzene/hexane to give 210 mg (13%) of the desired product as yellow crystals (mp 157–160 °C): NMR ($CDCl_3$) δ 2.24 (d, 1, J = 0.6 Hz, 4-Me), 3.12 (s, 6, NMe_2), 5.94 (q, 1, J = 0.6 Hz, H-3), 6.38 (d, 1, J_{ortho} = 4 Hz, H-5), 7.62 (d, 1, J_{ortho} = 4 Hz, H-6).

Table III. NOE Enhancement Factors

Saturated group	Enhancement[a]				
	H-5	N-H	H-10	H-3	H-7
Geminal dimethyl	1.00	1.16	1.00	0.95	1.23
6-Me	1.19	1.04	0.92	1.00	1.17
4-Me	1.34	0.97	0.97	1.54	1.00

[a] The enhancement ratio was determined from the ratio of the integral obtained with the secondary irradiation frequency on to the integral obtained with the secondary irradiation frequency off, both values being the average value obtained for at least five integrations.

8-Aza-4-methyl-7-morpholinocoumarin (3e). Ethyl acetoacetate (5.1 g, 40 mmol) and **27** (2.0 g, 11 mmol) were mixed and heated at reflux for 60 h to give a dark oil. The volatile materials were removed by rotoevaporation giving 3.6 g of semicrystalline black solid. This solid was washed with ether (100 mL) and twice recrystallized from benzene to give tan needles: mp 188–189 °C; IR 1735 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.36 (d, 3, J = 0.7 Hz, 4-Me), 3.76 (m, 8, morpholino protons), 6.04 (d, 1, J = 07 Hz, H-3), 6.54 (d, 1, J = 4.2 Hz, H-5), 7.69 (d, 1, J = 4.2 Hz, H-6).

10-Aza-2,8-dioxo-4,6-bis(trifluoromethyl)-2*H*,8*H*-benzo-[1,2-*b*:5,4-*b*]dipyran (6). 2,6-Dihydroxypyridine was heated at 135 °C in excess ethyl 4,4,4-trifluoroacetoacetate (66 h). The product crystallized as colorless needles: mp 280–282 °C (Me_2SO); 5.36 g (50% yield); IR 1780 cm^{-1} (C=O); MS m/e 351, M^+; NMR (Me_2SO-d_6) δ 7.10 (s, 2, H-3 and H-7), 8.32 (broad s. 1, H-5). Anal. Calcd for $C_{13}H_3F_6NO_4$: C, 44.47; H, 0.86; F, 32.18; N, 3.99. Found: C, 44.42; H, 0.82; F, 32.18; N, 3.99.

2,6-Dihydroxypyridine (4). 2,6-Dihydroxypyridine hydrochloride (10.0 g, 68 mmol) was suspended in 400 mL of water and the pH was adjusted to 3.5 by addition of concentrated aqueous ammonia. The flocculent white solid was filtered, dried in vacuo, and used immediately without further purification.

6-Acetamido-2-pyridinol (30). This compound was prepared by the method of Buo-Hoi, Gauthier, and Xuong[18] in 50% overall yield starting from 6-amino-2-pyridinol.

Attempted Preparation of 7-Acetamido-8-aza-4-methylcoumarin (31). Ethyl acetoacetate (1.72 g; 13.2 mmol) and **30** (2.0 g; 13.2 mmol) were heated at 170 °C (oil bath) for 16 h. The pyridinol had not gone into solution. Mesytelene (5 mL) was added and the reaction mixture was heated an additional 20 h at 170 °C. Upon cooling, 2.1 g of solid separated. NMR and IR showed this to be recovered **24**, contaminated with a small amount of mesytelene.

2-Keto-4,6,8,8-tetramethyl-8,9-dihydro-2*H*-pyrano[3,2-*g*]-quinoline (8). *m*-Aminophenol (10 g; 92 mmol) and ethyl acetoacetate were mixed. Upon heating to 150 °C a clear solution was obtained. As heating continued a yellow precipitate formed. Heating was continued for a total of 6 h. The precipitate was filtered from the hot solution and washed with cyclohexane. A further 2.2 g of yellow solid was obtained from the cooled filtrate. Crystallization from methanol gave beautiful golden needles (mp 270–274 °C (lit.[8] mp 268 °C)): NMR (Me_2SO-d_6) δ 1.68 (s, 6, 8-*gem*-dimethyls), 2.29 (d, 3, J = 2 Hz, 6-Me), 2.72 (d, 3, J = 1.6 Hz, 4-Me), 5.8 (bs, 1, H-7), 6.25 (q, 1, J = 1.6 Hz, H-3), 6.71 (s, 1, H-10), 7.1 (bs, 1, NH), 7.48 (s, 1, H-5); IR 3311 (NH), 1695 cm^{-1} (C=O); MS m/e 255, M^+. Anal. Calcd: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.67; H, 6.87; N, 5.45. The nuclear Overhauser effect enhancements[19] are given in Table III. The spectra were obtained at 80 °C from a 100% Me_2SO-d_6 sample degassed by five freeze cycles and sealed under vacuum.

Registry No.—**4**, 626-06-2; **6**, 65292-88-8; **7**, 26093-31-2; **8**, 65392-09-8; **23**, 580-20-1; **24**, 58196-33-1; **25**, 61468-43-7; **26**, 65292-89-9; **27**, 65292-90-2; **28**, 7159-96-8; **29**, 58632-48-7; **30**, 770-20-7; ethyl acetoacetate, 141-97-9; ethyl 4,4,4-trifluoroacetoactate, 372-31-6; trimethyl phosphate, 512-56-1; 5-hydroxyquinoline, 578-67-6; *m*-aminophenol, 591-27-5; 2-amino-6-hydroxypyridine, 5154-00-7; 2-chloro-6-hydroxypyridine, 16879-02-0; morpholine, 110-91-8; 2-dimethylamino-6-hydroxypyridine, 65292-91-3; 2,6-dihydroxypyridine·HCl, 10357-84-3; ethyl chloroformate, 541-41-3; ethyl 2-acetopropionate, 609-14-3.

References and Notes

(1) E. J. Schimitschek, J. A. Trias, P. R. Hammond, and R. L. Atkins, *Opt. Commun.*, **11**, 352 (1974).
(2) P. R. Hammond, A. N. Fletcher, R. A. Henry, and R. L. Atkins, *Appl. Phys.*, **8**, 311 (1975).
(3) P. R. Hammond, A. N. Fletcher, R. A. Henry, and R. L. Atkins, *Appl. Phys.*, **8**, 315 (1975).
(4) E. J. Schimitschek, J. A. Trias, P. R. Hammond, R. A. Henry, and R. L. Atkins, *Opt. Commun.*, **16**, 313 (1976).
(5) H. von Pechmann and C. Duisberg, *Chem Ber.*, **16**, 2119 (1883).
(6) S. M. Sethna and R. Phadke, *Org React.*, **7**, 1 (1953).
(7) J. R. Merchant, J. R. Patell, and S. M. Thakkar, *Indian J. Chem.*, **12**, 657 (1974).
(8) H. von Pechmann and O. Schwarz, *Chem. Ber.*, **32**, 3699 (1899).
(9) E. Knoevenagel *et al.*, *Chem. Ber.*, **56**, 2414 (1923).
(10) R. A. Henry and P. R. Hammond, *J. Heterocycl. Chem.*, **14**, 1109 (1977).
(11) L. L. Woods and M. M. Fooladi, *J. Chem. Eng. Data*, **13**, 440 (1968).
(12) Experiment was performed by Dr. R. A. Henry of this Laboratory. Details are available in Naval Weapons Center Technical Publications 5768, Part 1, September 1975.
(13) J. E. Pretka, U. S. Patent 3 008 969 (1961).
(14) P. R. Hammond and R. L. Atkins, *J. Heterocycl. Chem.*, **12**, 1061 (1975).
(15) C. J. Cavallito and T. H. Haskell, *J. Am. Chem. Soc.*, **66**, 1166 (1944).
(16) L. Bradford, T. J. Elliot, and F. M. Reese, *J. Chem. Soc.*, 437 (1947).
(17) L. Knorr, *Justus Liebigs Ann. Chem.*, **301**, 1 (1898).
(18) N. P. Buo-Hoi, M. Gauthier, and M. Dat Xuong, *Bull. Soc. Chim. Fr.*, 52 (1965).
(19) F. A. L. Anet and R. Anet, "Determination of Organic Structures by Physical Methods", Vol. 3, F. C. Nachod and J. J. Zuckerman, Ed., Academic Press, New York, N.Y., 1973, pp 344–420.

Syntheses of [1-(Alkylthio)]- and (1-Mercapto)cycloalkanephosphonic Esters by the Reactions of Cycloalkanethiones with Trialkyl Phosphites

Shigeo Yoneda, Tokuzo Kawase, and Zen-ichi Yoshida*

Department of Synthetic Chemistry, Kyoto University, Yoshida, Kyoto 606, Japan

Received September 29, 1977

Cycloalkanethiones reacted with trialkyl phosphites to give [1-(alkylthio)]- and/or (1-mercapto)cycloalkanephosphonic esters. The reaction mechanism is discussed in terms of a concerted one via the betaine intermediate. These sulfur-containing esters are easily converted to cycloalkanephosphonic esters in good yields by Raney nickel treatment.

The chemistry of thiocarbonyl compounds[1] has attracted much attention owing to their interesting reactivities and preparative significance. Especially, the reactions of thiocarbonyl compounds with organophosphorus compounds such as phosphites and phosphines have been the focus of interest in the past several years, because phosphines and phosphites

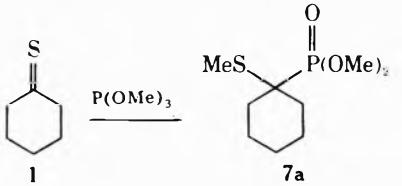
0022-3263/78/1943-1980$01.00/0

are known to demonstrate both "carbophilicity" and "thiophilicity"[2] toward organosulfur compounds. There have been several noteworthy reports on the reactions of thiocarbonyl compounds with phosphines or phosphites. Middleton and Scharkey[3] reported the reactions of hexafluorothioacetone and thiofluorenone with trialkyl phosphites to give corresponding phosphoranes. The formation of 1,3-dithiacyclohexylidenephosphorane from 1,3-dithiacyclohexane-2-thione and trimethyl phosphite was also reported by Corey and Märkl.[4] On the other hand, in his preceding papers, Corey et al.[5,6] reported the formation of olefins by the reactions of substituted ethylene trithiocarbonates and thionocarbonates with trialkyl phosphites. By similar reaction of 1,3-dithiole-2-thiones with phosphines and phosphites, many tetrathiafulvalene derivatives have been synthesized.[7] Thiocarbonyl compounds employed in those works were aromatic thiones,[3,7] perfluorothione,[3] and cyclic trithiocarbonates.[4-7] All these reactions could be explained to take place by initial thiophilic attack of phosphines and phosphites at the thiocarbonyl sulfur atom.

We have studied the reactions of cycloalkanethiones with trialkyl phosphites and succeeded in synthesizing new sulfur-containing phosphonic esters, [1-(alkylthio)]- and (1-mercapto)cycloalkanephosphonic esters. This reaction is obviously explained by carbophilic attack of phosphites at the thiocarbonyl carbon atom.

Results and Discussion

The reaction of cyclohexanethione (1) with 4 equiv of trimethyl phosphite in toluene at reflux temperature has been carried out. After a complete fading of the pink color of **1**, the workup of the reaction mixture gave a 51% yield of *O,O*-dimethyl [1-(methylthio)]cyclohexanephosphonate (**7a**). The



1 7a

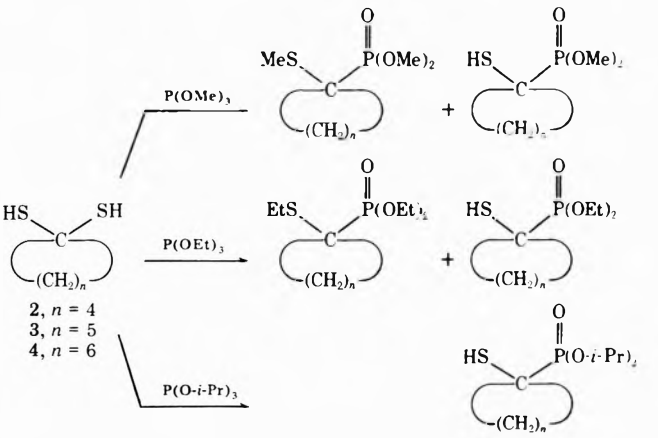
structure of **7a** was determined by the NMR and IR spectra. In the NMR spectrum of **7a**, the protons of the methyl group attaching to the sulfur atom appeared as a singlet at δ 2.20 and those attached to the oxygen atom as a doublet at δ 3.86 with J_{P-H} = 10.1 Hz. For comparison, the methyl resonances in dimethyl cyclohexanephosphonate appear as a doublet at δ 3.77 with J_{P-H} = 10.0 Hz. The infrared spectrum of **7a** revealed a strong band at 1240 cm^{-1} which is characteristic of a P=O double bond. Desulfurization of **7a** with Raney nickel in ethanol afforded dimethyl cyclohexanephosphonate, which was identical with the authentic sample.

In our preceding communication,[8] cyclohexanedithiol (**3**) was employed as a precursor of cyclohexanethione (**1**), since heating of **3** is known to afford **1** by an elimination of hydrogen sulfide. Thus, in this study *gem*-dithiols were also used in most cases as starting materials, because they are more available than cycloalkanethiones.

When a solution of cyclopentanedithiol (**2**) and 4 equiv of trimethyl phosphite in toluene was refluxed, hydrogen sulfide evolved and the color of the solution turned to pink. After the subsequent decolorization was complete, distillation gave *O,O*-dimethyl [1-(methylthio)]cyclopentanephosphonate (**5a**) in 56% yield, the formation of which was confirmed by comparing the spectral data of the product (**5a**) to those prepared from cyclopentanethione. The evolution of hydrogen sulfide and the pink coloration indicate the formation of cyclopentanethione in the reaction (Scheme I).

The reaction of **2** with triethyl phosphite gave a mixture of two sulfur-containing phosphonic esters, which were distilled

Scheme I



5, n = 4 **6**, n = 4
7, n = 5 **8**, n = 5
9, n = 6 **10**, n = 6

a, R = Me; **b**, R = Et; **c**, R = *i*-Pr

as a mixture and analyzed by gas chromatography. The second fraction was *O,O*-diethyl [1-(ethylthio)]cyclopentanephosphonate (**5b**). The structures were determined by the elemental analyses and spectral data. The NMR spectrum consisted of a quartet at δ 2.86 (2 H, J = 7.5 Hz, SCH_2CH_3), double quartets at δ 4.08 and 4.16 (4 H, J_{H-H} = 7.2 Hz, J_{P-H} = 8.5 Hz, $POCH_2CH_3$), and two triplets at δ 1.20 (3 H, J = 7.5 Hz, SCH_2CH_3) and 1.32 (6 H, J = 7.2 Hz, $POCH_2CH_3$). The infrared spectrum revealed an absorption at 1235 cm^{-1} due to a P=O double bond. These spectral features were totally consistent with the assignment of **5b**. The first fraction was *O,O*-diethyl (1-mercapto)cyclopentanephosphonate (**6b**). In the NMR spectrum of **6b**, the mercapto proton appeared as a broad singlet at δ 2.24, the methylene protons as double quartets at δ 4.11 and 4.19, and the methyl protons as a triplet at δ 1.34, respectively. The infrared spectrum of **6b** clearly exhibited an absorption at 2505 cm^{-1} assigned to the S–H stretching.

The reaction of **2** with triisopropyl phosphite gave only *O,O*-diisopropyl (1-mercapto)cyclopentanephosphonate (**6c**) in good yield (83%), but no ester having an alkylthio group. Similarly to **6b**, in the NMR spectrum the mercapto proton appeared at δ 2.28 and in the infrared spectrum a weak band at 2510 cm^{-1} assigned to the S–H stretching.

In the reactions giving mercaptophosphonic esters **6b** and **6c**, the generation of corresponding olefins was detected by a usual method.

The reaction of **3** with trialkyl phosphites was briefly reported in our preceding communication,[8] and a detailed description of the procedure and the characterization of the products were described in the Experimental Section.

The reaction of cycloheptanedithiol (**4**) with trialkyl phosphites was carried out under similar reaction conditions as mentioned above. The evolution of hydrogen sulfide and the pink coloration were also observed, and the reactions were stopped after decolorization was complete. The results are summarized in Scheme I and Table I.

As seen in Table I, the reactions proceeded rather slowly in benzene, toluene, and xylene, though the use of such solvents makes the workup of the reaction mixture easier. By addition of a small amount of ethanol to toluene, the reaction of **3** with trimethyl phosphite was accelerated to give *O,O*-dimethyl [1-(methylthio)]cyclohexanephosphonate (**7a**) together with trace of *O,O*-dimethyl (1-mercapto)cyclohexanephosphonate (**8a**). In the case of utilizing ethanol itself as a solvent, **8a** was more favorably obtained than **7a**.[18]

The mechanistic interpretation of the reactions of cycloalkanethiones (cycloalkanedithiols) with trialkyl phos-

Table I. Reaction Conditions and Yields of Products in the Reaction of Cycloalkanedithiols with Trialkyl Phosphites

Substrates (*gem*-dithiols)	Registry no.	Reactants (phosphites)	Registry no.	Reaction time, h	Solvents	Yield, % Alkylthio	Yield, % Mercapto
Cyclopentanedithiol (2)	1687-46-3	$P(OMe)_3$	121-45-9	10	Toluene	56	0
		$P(OEt)_3$	122-52-1	12	Toluene	20[a]	26[a]
		$P(O\text{-}i\text{-}Pr)_3$	116-17-6	10	Toluene	0	83
Cyclohexanedithiol (3)	3855-24-1	$P(OMe)_3$		20	Benzene	59	0
				20	Toluene	70	0
				10	Xylene	68	0
				5	Toluene (ethanol)	63	Trace
				5	Ethanol	23	39[b]
		$P(OEt)_3$		20	Toluene	20[a]	30[a]
		$P(O\text{-}i\text{-}Pr)_3$		20	Toluene	0	89
				5	Ethanol	0	85
		$P(OCr)_3$[c]	51666-84-3	20	Toluene	65	0
Cycloheptanedithiol (4)	65392-29-2	$P(OMe)_3$		48	Toluene	48	0
		$P(OEt)_3$		40	Toluene	23[a]	21[a]
		$P(O\text{-}i\text{-}Pr)_3$		48	Toluene	0	76

[a] Determined by gas chromatography. [b] 7.6% of the ethyl ester was contained. [c] Cr = $-CH_2CH{=}CHCH_3$.

phites is outlined in Scheme II. The reaction would be initiated by removal of hydrogen sulfide from cycloalkanedithiols, which might be accelerated by the action of phosphites as base. The resulting cycloalkanethiones A might immediately react with phosphites. Though trialkyl phosphites mostly behave as thiophilic reagents toward thiocarbonyl groups, in this case the phosphorus atom of phosphite seems to attack directly at the carbon atom of the thiocarbonyl group. This carbophilic attack of phosphites would form the betaine intermediate B. Addition of a small amount of polar solvent such as ethanol would stabilize the betaine intermediate B and make the reaction proceed more rapidly.

In the reaction of thiobenzophenone with trialkyl phosphites, Ogata et al.[9] suggested a reaction intermediate similar to B. The intermediate, they suggested, is not a zwitterion but a biradical, since the migration of alkylcarbonium ions in an ionic intermediate such as that of the Arbusov reaction was not observed. In our experiments, however, the intermediate should be a zwitterion type (B), because the migration of an alkyl group in an ionic intermediate occurred.

From the intermediate B the migration of the alkyl group or proton would afford the phosphonic esters containing a sulfur atom as the alkylthio or mercapto group. When phosphites were trimethyl and/or triethyl phosphites, the negatively charged sulfur atom of the betaine intermediate B would intramolecularly interact with alkyl groups from the backside and result in the formation of phosphonic esters bearing an alkylthio group. This migration is similar to that of the Arbusov reaction, in which halide anion is known to attack at the alkyl group from the backside and result in the formation of alkyl halide and phosphonic esters. However, when triethyl and/or triisopropyl phosphites were employed, these backside attacks of negatively charged sulfur would be hindered by methyl groups, and, therefore, the proton migration would take place via a concerted mechanism. In the proton migration a stepwise mechanism involving the carbonium ion also might be excluded for the following reasons: (1) in nonpolar solvents such as benzene, toluene, and xylene, the formation of the carbonium ion would unlikely take place; (2) in spite of the order of increasing stability of carbonium ions ($i\text{-}Pr^+ > Et^+ > Me^+$), the product ratios of alkylthio- to mercaptophosphonic esters decrease in this series.

In connection with the study of whether the migration took place concerted or stepwise, the reaction of 3 with tricrotyl phosphite was examined. As shown in Scheme III, the phosphite attacked at the carbon atom of the thiocarbonyl group and formed the betaine intermediate C. If the migration occurs stepwise, as the crotyl carbonium ion is known to be stable, the products must be the mercapto type phosphonic ester and/or the mixture of crotylthio and methylallylthio type esters. But, only one kind of alkylthio type phosphonic ester was obtained. In the NMR spectrum the methyl protons ap-

Scheme II

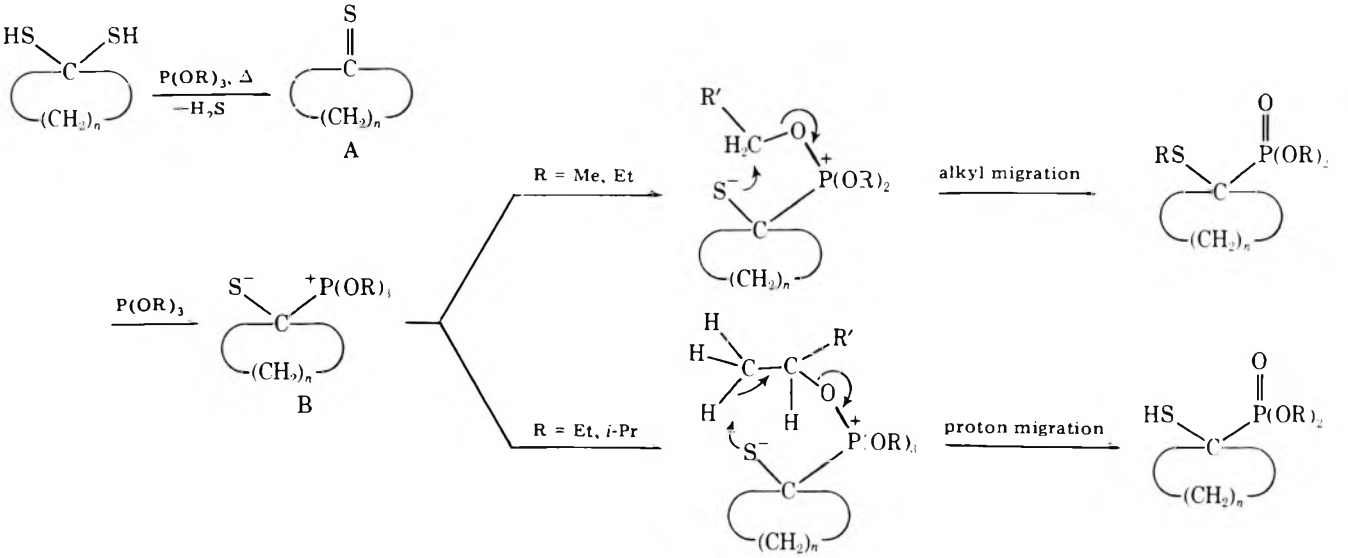
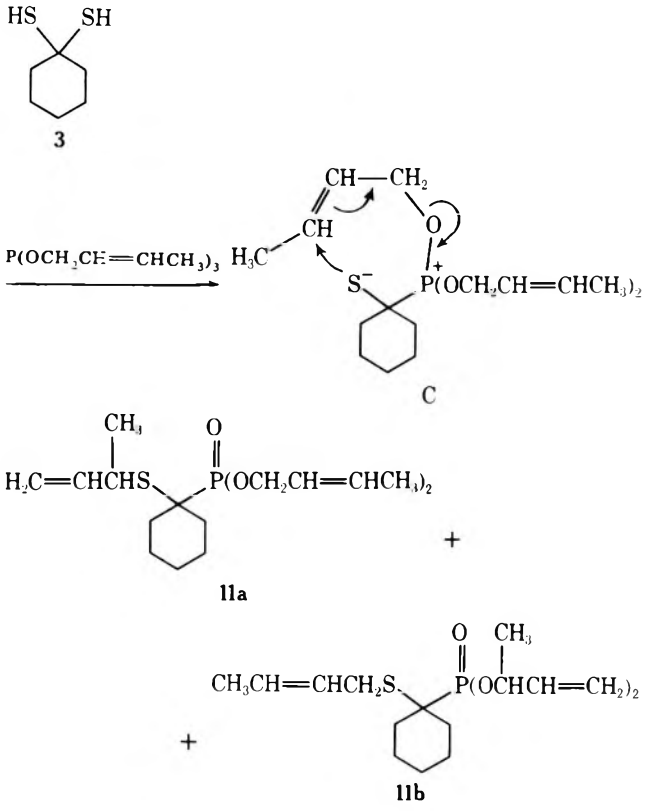


Table II. Yields of Cycloalkanephosphonic Esters by Desulfurization of [1-(Alkylthio)]- and (1-Mercapto)cycloalkanephosphonic Esters with Raney Nickel

Substrates	Registry no.	Products	Registry no.	Yield, %[a]
5a	65392-30-5	**16a**	26580-25-6	82 (46)
5b + 6b[b]	65392-31-6 (**5b**) 65392-32-7 (**6b**)	**16b**	65392-40-7	79 (37)
6c	65392-33-8	**16c**	65392-41-8	89 (74)
7a	55499-38-2	**17a**	1641-61-8	78 (55)
7b + 8b[b]	55499-40-6 (**7b**) 55499-39-3 (**8b**)	**17b**	7413-09-4	92 (46)
8c	55499-41-7	**17c**	7351-26-0	82 (73)
9a	65392-34-9	**18a**	26580-34-7	84 (41)
9b + 10b[b]	65392-35-0 (**9b**) 65392-36-1 (**10b**)	**18b**	65392-42-9	80 (33)
10c	65392-37-2	**18c**	65392-43-0	82 (63)

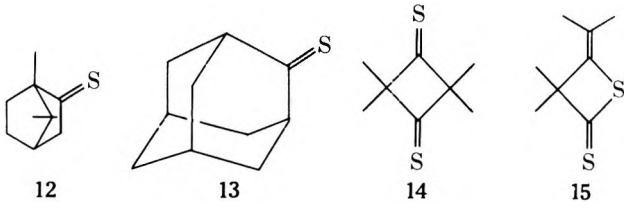
[a] Numbers in parentheses indicate the overall yield of cycloalkanephosphonic esters from *gem*-dithiols. [b] Mixtures of ethyl esters (having the ethylthio and mercapto group) were directly used.

Scheme III

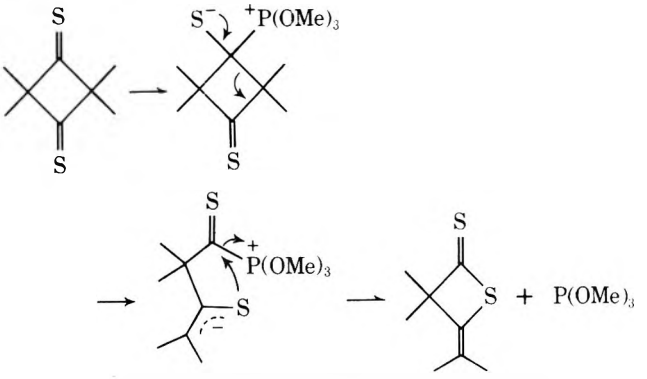


peared clearly as a doublet at δ 1.37 and the infrared spectrum revealed a characteristic band for the terminal olefin at 910 cm^{-1}, which means that the alkyl group attaching to the sulfur atom is not crotyl ($-CH_2CH{=}CHCH_3$) but methylallyl [$-CH(CH_3)CH{=}CH_2$]. Furthermore, the reaction of **3** with trimethylallyl phosphite was also examined. As expected, only one kind of alkylthio type ester was obtained. In the NMR spectrum the methylene protons appeared as a doublet at δ 3.36 (J = 7.0 Hz), which means that the alkyl group attached to the sulfur atom is not methylallyl but crotyl. Therefore, it is reasonably considered that the migration took place via a cyclic concerted mechanism. That is to say, the attack of the negatively charged sulfur atom occurred on the carbon atom of the C=C double bond, just as in the thio-Claisen rearrangement, not directly on the carbon atom adjacent to oxygen.

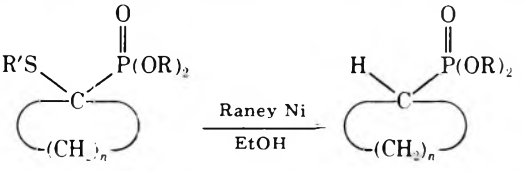
Though the reactions of other cycloalkanethiones such as thiocamphor (**12**), adamantanethione (**13**), and 2,2,4,4-tetramethylcyclobutane-1,3-dithione (**14**) with trimethyl



phosphite were carried out, the expected reaction did not occur. In the case of the former two thiones, **12** and **13**, this is explainable by steric hindrance to attack by phosphite. The reaction of **14** gave the dithiolactone **15** quantitatively, which is different from the result of the reaction of tetramethylcyclobutanedione with trimethyl phosphite.[10] The formation of **15** from **14** is explained by the following scheme.



These phosphonic esters are the new type esters in the view of bearing sulfur as alkylthio or mercapto groups. Our sulfur-containing phosphonic esters were easily converted to cycloalkanephosphonic esters in good yields by Raney nickel desulfurization. The results are summarized in Table II. In the case of diethyl esters, the mixture of two type esters was directly used. The overall yield from *gem*-dithiols **2**–**4** did not



vary whether sulfur-containing esters were isolated before reduction or not. In general, the phosphonic esters have been previously prepared from alkyl halides and phosphites by the Arbusov reaction, but the yields of cycloalkanephosphonic esters are known to be low because of the side reaction (e.g., removal of hydrogen halide), especially in the use of secondary alkyl halides.[11] In our reactions, phosphonic esters were obtained in good yields as shown in Table II.

Experimental Section

The infrared spectra were recorded on a Hitachi EPI-G3 grating infrared spectrophotometer; the ^1H NMR spectra were recorded on a Varian Associates AH-100 spectrometer. The chemical shifts are given in parts per million relative to internal Me_4Si. Mass spectra were taken on a Hitachi RMU-6C mass spectrometer. Elemental analyses were carried out at the Elemental Analytical Center of Kyoto University. Gas–liquid chromatography was carried out with a Shimazu gas chromatograph Model GC-6A, using the stainless steel column packed with 20% silicone DC-550 on Celite 545.

Materials. Cyclohexanethione was prepared as described by Mayer et al.,[12] and cyclohexanedithiol and cyclopentanedithiol were prepared from 1-morpholinocyclohexene and -cyclopentene according to the literature of Djerassi and Tursch.[13] Cycloheptanedithiol was similarly prepared from 1-morpholinocycloheptene with hydrogen sulfide in 73% yield [62–63 °C (2.0 mmHg)]. Thiocamphor,[14] adamantanethione,[15] and 2,2,4,4-tetramethylcyclobutane-1,3-dithione[16] were prepared by the reported methods. Trimethyl phosphite and triethyl phosphite were commercial materials and were used after distillation. Triisopropyl and tricrotyl phosphites were prepared utilizing the procedure of Ford-Moore and Perry[17] from phosphorus trichloride and the corresponding alcohols, bp 60–61 °C (10 mmHg) and 104–105 °C (2.5 mmHg), respectively.

Reaction of Cyclohexanethione (1) with Trimethyl Phosphite. A mixture of cyclohexanethione (1.14 g) and trimethyl phosphite (5.0 g, 4 equiv) in 30 mL of toluene was heated at reflux under nitrogen overnight, producing a colorless solution. After removal of toluene and excess trimethyl phosphite, the oily residue was distilled to give 1.21 g (57%) of **7a** as a colorless liquid: bp 112–113 °C (2.5 mmHg); IR (neat) 1230 (P=O), 1180, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45–1.95 [m, 10 H, $-(CH_2)_5-$], 2.20 (s, 3 H, SCH_3), and 3.86 (d, 6 H, J = 10.1 Hz, $POCH_3$); MS *m/e* 238. Anal. Calcd for $C_9H_{19}O_3PS$: C, 45.37; H, 8.04; P, 13.00. Found: C, 45.08; H, 8.38; P, 13.38.

General Procedure for Reaction of the Cycloalkanedithiols 2–4 with Trialkyl Phosphites. A mixture of the 0.01 mol of the cycloalkanedithiol (**2**–**4**) and 0.04 mol of trialkyl phosphite in 30 mL of toluene was heated at reflux under nitrogen for 20–50 h. After removal of toluene and excess trialkyl phosphite, the residue was distilled under vacuum to give a colorless viscous liquid. In the reactions with triethyl phosphite, the distillates were [1-(ethylthio)]- and (1-mercapto)cycloalkanephosphonic esters, which were separated by gas chromatography, and yields were determined.

The boiling points, IR, ^1H NMR, and mass spectral (MS) data, and the results of elemental analyses are as follows.

***O,O*-Dimethyl [1-(methylthio)]cyclopentanephosphonate (5a):** bp 103–104 °C (4.0 mm); yield 56%; IR (neat) 1240 (P=O), 1180, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47–2.26 [m, 8 H, $-(CH_2)_4-$], 2.23 (s, 3 H, SCH_3), and 3.85 (d, 6 H, J = 11 Hz, $POCH_3$); MS *m/e* 224. Anal. Calcd for $C_8H_{17}O_3PS$: C, 42.85; H, 7.64; P, 13.81. Found: C, 42.98; H, 7.84; P, 13.57.

***O,O*-Diethyl [1-(ethylthio)]cyclopentanephosphonate (5b):** bp 102–103 °C (2.5 mm) as a mixture of **5b** and **6b**; yield 20%; IR (neat) 1235 (P=O), 1162, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3 H, J = 7.5 Hz, SCH_2CH_3), 1.32 (t, 6 H, J = 7.2 Hz, $POCH_2CH_3$), 1.5–2.2 [m, 8 H, $-(CH_2)_4-$], 2.86 (q, 2 H, J = 7.5 Hz, SCH_2CH_3), and 4.08 (dq, 4 H, J_{H-H} = 7.2 Hz, J_{P-H} = 8.5 Hz, $POCH_2CH_3$); MS *m/e* 266. Anal. Calcd for $C_{11}H_{23}O_3PS$: C, 49.61; H, 8.70; P, 11.63. Found: C, 49.36; H, 8.99; P, 11.83.

***O,O*-Diethyl (1-mercapto)cyclopentanephosphonate (6b):** yield 26%; IR (neat) 2505 (SH), 1235 (P=O), 1160, and 1030 cm^{-1}; ^1H NMR (CCl_4) δ 1.34 (t, 6 H, J = 7.1 Hz, $POCH_2CH_3$), 1.5–2.3 [m, 8 H, $-(CH_2)_4-$], 2.24 (br s, 1 H, SH), and 4.11 and 4.19 (dq, 4 H, J_{H-H} = 7.1 Hz, J_{P-H} = 8.5 Hz, $POCH_2CH_3$); MS *m/e* 238. Anal. Calcd for $C_9H_{19}O_3PS$: C, 45.36; H, 8.04; P, 13.00. Found: C, 45.36; H, 7.96; P, 13.04.

***O,O*-Diisopropyl (1-mercapto)cyclopentanephosphonate (6c):** bp 107–109 °C (3.2 mm); yield 83%; IR (neat) 2510 (SH), 1245 (P=O), and 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 [d, 12 H, J = 6.5 Hz, $POCH(CH_3)_2$], 1.55–2.20 [m, 8 H, $-(CH_2)_4-$], 2.28 (s, 1 H, SH), and 4.78 and 4.86 [dsep, 2 H, J_{H-H} = 6.5 Hz, J_{P-H} = 8 Hz, $POCH(CH_3)_2$]; MS *m/e* 266. Anal. Calcd for $C_{11}H_{23}O_3PS$: C, 49.61; H, 8.70; P, 11.63. Found: C, 49.30; H, 8.54; P, 11.91.

***O,O*-Dimethyl [1-(methylthio)]cyclohexanephosphonate (7a):** bp 102–104 °C (1.5 mm); yield 70%. All spectral and elemental data were identical with those of the product of the reaction of cyclohexanethione with trimethyl phosphite.

***O,O*-Diethyl [1-(ethylthio)]cyclohexanephosphonate (7b):** bp 114–115 °C (2.3 mm) as a mixture of **7b** and **8b**; yield 20%; IR (neat) 1240 (P=O), 1165, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3 H, J = 7.5 Hz, SCH_2CH_3), 1.35 (t, 6 H, J = 7.0 Hz, $POCH_2CH_3$), 1.45–1.98 [m, 10 H, $-(CH_2)_5-$], 2.78 (q, 2 H, J = 7.5 Hz, SCH_2CH_3), and 4.15 and 4.23 (dq, 4 H, J_{H-H} = 7.0 Hz, J_{P-H} = 8 Hz, $POCH_2CH_3$); MS *m/e* 280. Anal. Calcd for $C_{12}H_{25}O_3PS$: C, 51.41; H, 8.99; P, 11.05. Found: C, 51.01; H, 8.82; P, 11.39.

***O,O*-Diethyl (1-mercapto)cyclohexanephosphonate (9b):** yield 30%; IR (neat) 2500 (SH), 1245 (P=O), 1165, and 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (t, 6 H, J = 7.0 Hz, $POCH_2CH_3$), 1.5–1.93 [m, 10 H, $-(CH_2)_5-$], 1.93 (s, 1 H, SH), and 4.18 and 4.26 (dq, 4 H, J_{H-H} = 7.0 Hz, J_{P-H} = 8.0 Hz, $POCH_2CH_3$); MS *m/e* 251. Anal. Calcd for $C_{10}H_{21}O_3PS$: C, 47.60; H, 8.39; P, 12.28. Found: C, 47.71; H, 8.64; P, 12.47.

***O,O*-Diisopropyl (1-mercapto)cyclohexanephosphonate (8c):** bp 114–115 °C (2.5 mm); yield 89%; IR (neat) 2500 (SH), 1245 (P=O), and 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 [d, 12 H, J = 7 Hz, $POCH(CH_3)_2$], 1.46–1.90 [m, 10 H, $-(CH_2)_5-$], 1.91 (s, 1 H, SH), and 4.67 and 4.73 [dsep, 2 H, J_{H-H} = 7 Hz, J_{P-H} = 7.5 Hz, $POCH(CH_3)_2$]; MS *m/e* 280. Anal. Calcd for $C_{12}H_{25}O_3PS$: C, 51.41; H, 8.98; P, 11.05. Found: C, 51.56; H, 9.23; P, 11.16.

***O,O*-Dicrotyl [1-(methylallylthio)]cyclohexanephosphonate (11a):** bp 149–150 °C (4.0 mm); yield 65%; IR (neat) 3080, 3015, 1675, 1630, 1245 (P=O), and 910 cm^{-1} (terminal vinyl); ^1H NMR (CCl_4) δ 1.37 [d, 3 H, J = 7.5 Hz, $SCH(CH_3)CH=CH_2$], 1.41–2.25 [m, 16 H, $-(CH_2)_5-$ and $OCH_2CH=CHCH_3$], 4.05–4.81 [m, 5 H, $OCH_2CH=CHCH_3$ and $SCH(CH_3)CH=CH_2$], 4.83–5.21 [m, 2 H, $SCH(CH_3)CH=CH_2$], 5.51–5.85 [m, 5 H, $OCH_2CH=CHCH_3$ and $SCH(CH_3)CH=CH_2$]; MS *m/e* 385. Anal. Calcd for $C_{18}H_{31}O_3PS$: C, 60.30; H, 8.71; P, 8.64. Found: C, 60.19; H, 8.85; P, 8.71.

***O,O*-Dimethylallyl [1-(crotylthio)]cyclohexanephosphonate (11b):** bp 110–111 °C (0.5 mm); yield 58%; IR (neat) 3080, 3013, 1670, 1630, 1240 (P=O), and 910 cm^{-1}; ^1H NMR (CCl_4) δ 1.38 [d, 6 H, J = 7.4 Hz, $OCH(CH_3)CH=CH_2$], 1.45–2.08 [m, 13 H, $-(CH_2)_5-$ and $SCH_2CH=CHCH_3$], 3.36 (d, 2 H, J = 7.0 Hz, $SCH_2CH=CHCH_3$), 4.15–4.67 [m, 2 H, $OCH(CH_3)CH=CH_2$], 4.57–6.23 [m, 8 H, $OCH(CH_3)CH=CH_2$ and $SCH_2CH=CHCH_3$]; MS *m/e* 385. Anal. Calcd for $C_{18}H_{31}O_3PS$: C, 60.30; H, 8.71; P, 8.64. Found: C, 60.47; H, 8.93; P, 8.50.

***O,O*-Dimethyl [1-(methylthio)]cycloheptanephosphonate (9a):** bp 126–128 °C (2.0 mm); yield 48%; IR (neat) 1240 (P=O), 1180, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45–1.85 [m, 12 H, $-(CH_2)_6-$], 2.21 (s, 3 H, SCH_3), and 3.81 (d, 6 H, J = 10.0 Hz); MS *m/e* 252. Anal. Calcd for $C_{10}H_{21}O_3PS$: C, 47.60; H, 8.39; P, 12.28. Found: C, 47.83; H, 8.54; P, 11.98.

***O,O*-Diethyl [1-(ethylthio)]cycloheptanephosphonate (9b):** bp 132–134 °C (2.5 mm) as a mixture of **9b** and **10b**; yield 23%; IR (neat) 1235 (P=O), 1160, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3 H, J = 7.5 Hz, SCH_2CH_3), 1.32 (t, 6 H, J = 7.0 Hz, $POCH_2CH_3$), 1.45–1.93 [m, 12 H, $-(CH_2)_6-$], 2.78 (q, 2 H, J = 7.5 Hz, SCH_2CH_3), and 4.11 and 4.19 (dq, 4 H, J_{H-H} = 7.0 Hz, J_{P-H} = 8.0 Hz, $POCH_2CH_3$); MS *m/e* 294. Anal. Calcd for $C_{13}H_{27}O_3PS$: C, 53.04; H, 9.24; P, 10.52. Found: C, 52.75; H, 9.48; P, 10.73.

***O,O*-Diethyl (1-mercapto)cycloheptanephosphonate (10b):** yield 21%; IR (neat) 2505 (SH), 1245 (P=O), 1160, and 1038 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (t, 6 H, J = 7.0 Hz, $POCH_2CH_3$), 1.50–1.95 [m, 12 H, $-(CH_2)_6-$], 2.25 (s, 1 H, SH), and 4.19 and 4.27 (dq, 4 H, J_{H-H} = 7.0 Hz, J_{P-H} = 8.0 Hz, $POCH_2CH_3$); MS *m/e* 266. Anal. Calcd for $C_{11}H_{23}O_3PS$: C, 49.61; H, 8.70; P, 11.63. Found: C, 49.89; H, 8.96; P, 11.52.

***O,O*-Diisopropyl (1-mercapto)cycloheptanephosphonate (10c):** bp 141–142 °C (2.9 mm); yield 76%; IR (neat) 2500 (SH), 1240 (P=O), and 990 cm^{-1}; ^1H NMR (CCl_4) δ 1.32 [d, 12 H, J = 6.5 Hz, $POCH(CH_3)_2$], 1.42–2.20 [m, 12 H, $-(CH_2)_6-$], 2.11 (s, 1 H, SH), and 4.69 and 4.76 [dsep, 2 H, J_{H-H} = 6.5 Hz, J_{P-H} = 7.5 Hz, $POCH(CH_3)_2$]; MS *m/e* 294. Anal. Calcd for $C_{13}H_{27}O_3PS$: C, 53.04; H, 9.24; P, 10.52. Found: C, 53.32; H, 9.42; P, 10.61.

Reaction of Cyclohexanedithiol (3) with Trimethyl Phosphite in Ethanol. A mixture of **3** (1.48 g) and trimethyl phosphite (5.0 g) in 20 mL of ethanol was heated at reflux under nitrogen for 5 h. After concentration, the residue was distilled to afford 1.4 g of a mixture of **7a** and **8a**, which was separated by gas chromatography, and yields were determined. The yield of **7a** was 23%, and all spectral data were identical with **7a**.

***O,O*-Dimethyl (1-mercapto)cyclohexanephosphonate (8a):** mp 31–32 °C; yield 39%; IR (neat) 2510 (SH), 1230 (P=O), 1180, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43–1.98 (m, 10 H, $-(CH_2)_5-$], 1.93 (s, 1 H, SH), and 3.85 (d, 6 H, J = 10.0 Hz, $POCH_3$); MS *m/e* 224. Anal. Calcd for $C_8H_{17}O_3PS$: C, 42.85; H, 7.64; P, 13.81. Found: C, 42.83; H, 7.66; P, 13.68.

Reaction of 2,2,4,4-Tetramethylcyclobutane-1,3-dithione with Trimethyl Phosphite. A mixture of **14** (1.37 g) and 4 equiv of tri-

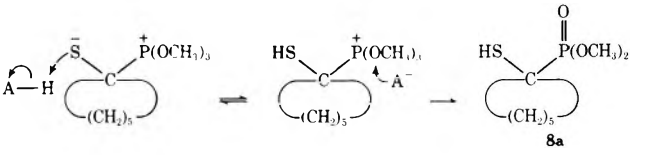
methyl phosphite in 20 mL of toluene was heated at reflux under nitrogen for 3 h. After concentration, the residue was chromatographed on silica with the elution of benzene to give 1.35 g of orange liquid, whose spectral data were all identical with the authentic sample **15**.[13]

Reduction by Raney Nickel. To a suspended solution of 10–15 g of Raney nickel (W-2 type) in 50 mL of ethanol was added a solution containing phosphonic esters **5**–**10** (1.5–2.0 g in 5 mL of ethanol). The reaction mixture was heated at reflux for 20 h. After filtration of nickel, the filtrate was concentrated and the residue was distilled to afford cycloalkanephosphonic esters **16**–**18**. The yields were summarized in Table I.

Registry No.—**1**, 2720-41-4; **8a**, 65392-38-3; **11a**, 55499-42-8; **11b**, 65392-39-4; **14**, 10181-56-3; **15**, 10181-61-0; 1-morpholinocycloheptene, 7182-03-3.

References and Notes

(1) (a) A. Schönberg and A. Wagner, *Methoden Org. Chem. (Houben-Weyl)*, **9**, 699 (1954); (b) R. Mayer, J. Morgenstern, and J. Fabian, *Angew. Chem., Int. Ed. Engl.*, **3**, 277 (1964); (c) D. Paquer, *Int. J. Sulfur Chem., Part B*, **7**, 269 (1972); (d) *ibid.*, **8**, 173 (1973); (e) S. Oae, Ed., "Organic Chemistry of Sulfur", Plenum Press, London, 1974, Chapter 5; (f) for reviews on periodical reports, see S. McKenzie, "Organic Compounds of Sulfur, Selenium and Tellurium", Vol. 1, The Chemical Society, Burlington House, London, 1960, p 181, and F. Duus in Vol. 2, p 200, and Vol. 3, p 219.
(2) D. B. Denny and M. J. Boskin, *J. Am. Chem. Soc.*, **82**, 4736 (1960).
(3) W. J. Middleton and W. H. Scharkey, *J. Org. Chem.*, **30**, 1384 (1965).
(4) E. J. Corey and G. Märkl, *Tetrahedron Lett.*, 3201 (1967).
(5) E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.*, **85**, 2677 (1963).
(6) E. J. Corey, F. A. Carey, and R. A. E. Winter, *J. Am. Chem. Soc.*, **87**, 934 (1965).
(7) (a) H. D. Hartzler, *J. Am. Chem. Soc.*, **92**, 1412 (1970); (b) S. Hünig, G. Kliesslich, H. Quast, and D. Schentzow, *Justus Liebigs Ann. Chem.*, 310 (1973); (c) H. D. Hartzler, *J. Am. Chem. Soc.*, **95**, 4379 (1973); (d) M. G. Miles, J. S. Wager, J. D. Wilson, and A. R. siecle, *J. Org. Chem.*, **40**, 2577 (1975); (e) Z. Yoshida T. Kawase, and S. Yoneda, *Tetrahedron Lett.*, 331 (1975); (f) C. U. Pittman, Jr., M. Narita, and Y. F. Liang, *J. Org. Chem.*, **41**, 2855 (1976).
(8) Z. Yoshida, T. Kawase, and S. Yoneda, *Tetrahedron Lett.*, 235 (1975).
(9) Y. Ogata, M. Yamashita, and M. Mizutani, *Tetrahedron*, **30**, 3709 (1974).
(10) W. G. Bentrude and E. R. Witt, *J. Am. Chem. Soc.*, **85**, 2522 (1963).
(11) H. Krauch and W. Kunz, "Organic Name Reactions", Wiley, New York, N.Y., 1964, p 17; G. M. Kosolapoff, *Org. React.*, **6**, 276 (1951).
(12) R. Mayer and H. Berthold, *Chem. Ber.*, **96**, 3096 (1963).
(13) C. Djerassi and B. Tursch, *J. Org. Chem.*, **27**, 1041 (1962).
(14) D. Paquer, Thes s Université de Caen, Caen, France, 1968.
(15) J. W. Griedanus, *Can. J. Chem.*, **48**, 3530 (1970).
(16) E. U. Elam and H. E. Davis, *J. Org. Chem.*, **32**, 1562 (1967).
(17) A. H. Ford-Moore and B. J. Perry, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 955.
(18) When the other solvents having an active hydrogen were used in the reaction of cyclohexanedithiol with trimethyl phosphite, **8a** was also obtained in considerable yields [**7a**, 33.3%, and **8a**, 50.3% (isobutyl alcohol); **7a**, 36.8%, and **8a**, 33.8% (acetonitrile); **7a**, 29.4%, and **8a**, 35.6% (propionitrile)]. The favorable formation of **8a** might possibly be explained by the following reaction scheme.



Facile and Selective Chlorination–Cleavage of Some Cyclanones and Cyclanols with the CCl_4–KOH–*t*-BuOH Reagent. In Situ Conversion of Estrones and Estradiols into Dichlorodoisynolic Acids[1a]

Cal Y. Meyers* and Vera M. Kolb[1b]

Department of Chemistry and Biochemistry, Southern Illinois University, Carbondale, Illinois 62901

Received September 13, 1977

Studies of the reactions of ketones and alcohols with CCl_4–KOH–*t*-BuOH have been extended to include cyclanones and cyclanols represented by a series of estrogens. With this reagent estrone (**1**) and estrone 3-methyl ether (**4**) were rapidly and selectively converted into the corresponding 16,16-dichlorodoisynolic acids (**3**, **6**). The in situ reaction pathway consists of D-ring *gem*-α-dichlorination followed by ring cleavage. Similar treatment of estradiol (**2**) and estradiol 3-methyl ether (**5**) also provided these respective products, but at much slower rates because the initial slow oxidation step is rate determining. However, because this step involves a free-radical chain mechanism initiated by dioxygen, the conversion of **5** was greatly accelerated when contact with air was unrestricted. Reaction of **2** could not be accelerated this way because its phenolic moiety functions as a built-in inhibitor of this oxidation process.

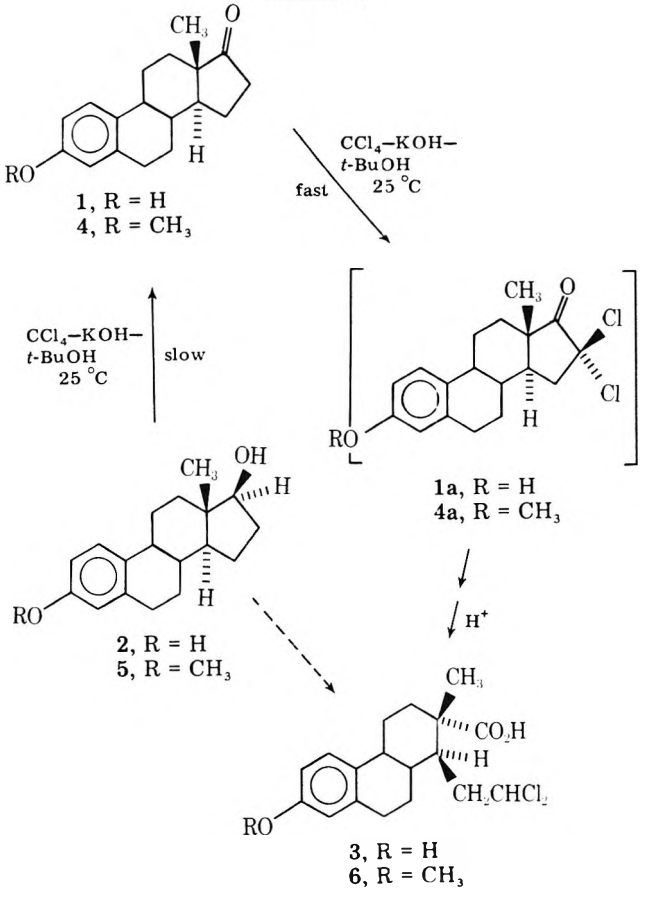
In the course of our recent investigations of the reactions of ketones and alcohols with CCl_4-powdered KOH–*t*-BuOH, the use of estrones and estradiols as substrates was considered a valuable excursion because they represent a common class of cyclanones and cyclanols, respectively (Scheme I). It was already recognized that ketones possessing α-H's are easily α chlorinated with this reagent; rapid subsequent reactions, however, generally lead to the formation of a variety of products.[2-6] While ketones whose carbonyl function is sterically hindered, e.g., mesityl alkyl ketones, are still quite easily converted into α-chlorinated ketones, the latter do not undergo further reaction.[7] Secondary alcohols are initially oxidized with this reagent into ketones which, as already indicated, are α chlorinated in this medium.[2,5,6,8] Sterically hindered alcohols, e.g., neopentyl alcohol and di-*tert*-butylcarbinol, react slowly or not at all with this reagent at moderate temperatures.[2,6,8]

Results

Estrone (**1**) and estrone 3-methyl ether (**4**) are ketones whose carbonyl is hindered from attack mainly on one face. This degree of steric hindrance in **1** and **4** prevented neither the formation nor subsequent reaction of their α-chlorinated derivatives. Thus, both ketones underwent facile conversion with CCl_4–KOH–*t*-BuOH at 25 °C into the *gem*-α-dichloro ketones (**1a**, **4a**) which, however, could not be detected per se because they were rapidly cleaved into 16,16-dichlorodoisynolic acid (**3**) and 16,16-dichlorodoisynolic acid 3-methyl ether (**6**), respectively. Neither product has previously been reported. Within 1 h at room temperature **4** was converted into **6** in 75–80% yield; the white crystalline product, mp 157–158 °C, was analytically pure. The phenolic ketone **1**, similarly treated for 1.5 h, was converted into **3** in yields estimated to be at least 90%; however, the crystalline product, mp 155–157 °C, in this case was contaminated with material suspected to

0022-3263/78/1943-1985$01.00/0

Scheme I

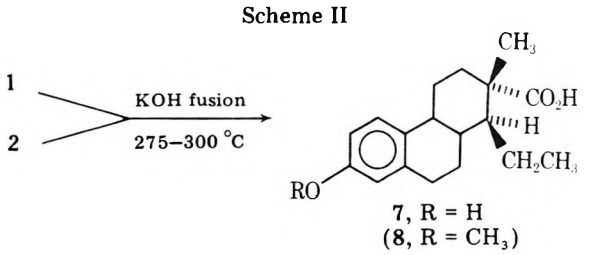


be the 2-aldehyde and 2-carboxylic acid derivatives of **3**. These reactions of both **1** and **4** were conducted in systems continuously flushed with nitrogen or with air. However, little if any variation in reaction rate or product composition could be discerned in either case.

Estradiol (**2**) and estradiol 3-methyl ether (**5**) are secondary alcohols whose carbinol OH, but not α-H, is hindered. These steroidal alcohols slowly underwent reaction with CCl_4–KOH–*t*-BuOH, first being converted into the corresponding estrones, **1** and **4**, and then into the respective dichlorodoisynolic acids, **3** and **6**. After being treated under nitrogen for 5 h at 25 °C, the 3-methoxy alcohol (**5**) was recovered to the extent of 84% and **6** was isolated in 14% yield. Based on consumed substrate, however, the conversion was close to 87%, which suggested that this transformation could be improved by enhancing the rate of the initial, slow oxidation step.[3,6,8] Such a modification was easily effected by carrying out the reaction in a system open to air; after 5 h at 25 °C these reactions provided **6** in yields averaging 30%, and unchanged **5** was recovered to the extent of 50–60%. The phenolic alcohol **2** provided results surprisingly different from those of its methoxy counterpart. Thus, **2** not only was considerably less reactive, but its reactivity was not enhanced by the presence of dioxygen; less than 10% of **2** was consumed during 5 h at 25 °C in reactions maintained under nitrogen *or* open to air.

The facile D-ring cleavage effected in these reactions via the *gem*-α-dichloroestrone intermediates (**1a, 4a**) is quite striking in light of the fact that estrone and estradiol themselves are rather resistant to base-induced cleavage. As illustrated in Scheme II, fusion with KOH is required to convert these estrogens into doisynolic acid (**7**).[6–11] Moreover, as a result of this vigorous process, yields are minimal, chiral modification can accompany the cleavage, and 3-methoxy substrates undergo conversion into 3-hydroxy products (when 3-methoxy products are desired, methylation is generally

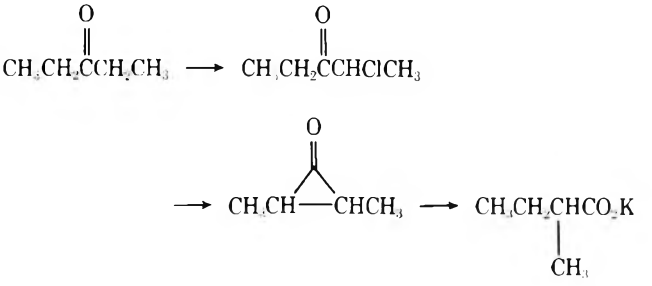
Scheme II



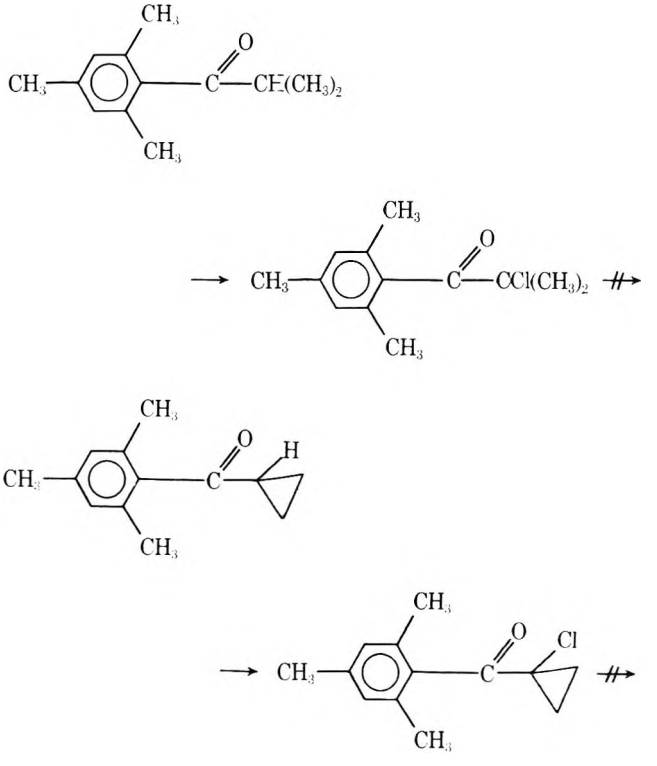
performed *after* the cleavage acids are isolated from the KOH fusion mixtures).[11,12] By comparison, the conversions of the 3-methoxy substrates **4** and **5** into **6** with CCl_4–KOH–*t*-BuOH were carried out at 25 °C, the methoxy group was retained, and chirality was preserved.

Discussion

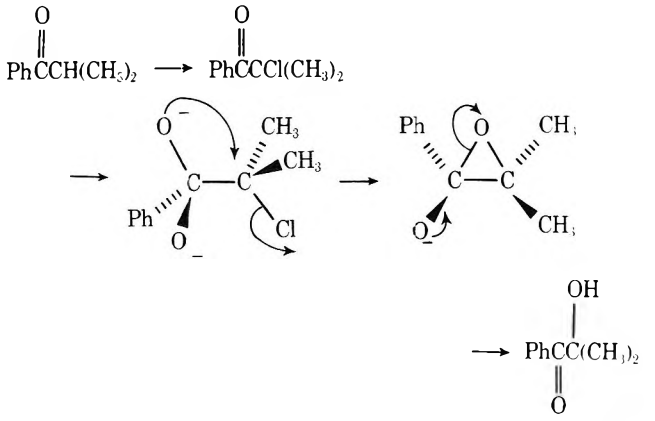
Cyclanones 1 and 4. We have found that in their reactions with CCl_4–KOH–*t*-BuOH, ketones generally fall into four categories:[2–7] (**a**) those having α- and α'-H's, whose α-chloro derivative is formed but rapidly undergoes Favorskii rearrangement, e.g.,



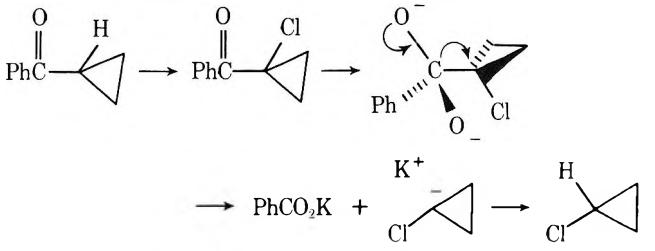
(**b**) those having an α-H but no α'-H and a sterically blocked carbonyl, whose α-chloro derivative is formed and is resistant to further reaction, e.g.,



(**c**) those having an α-H but no α'-H, whose α-chloro derivative is formed but is rapidly converted into the α-hydroxy derivative, e.g.,



(d) Those having an α-H but no α′-H, whose α-chloro derivative is formed but undergoes cleavage, e.g.,



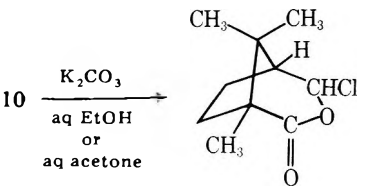
Cyclanones 1 and 4 possess α-H's but no α′-H. Thus, the α-chlorination–Favorskii rearrangement of category a, which is most commonly observed with ketones treated with this reagent, cannot be considered in the cases of 1 and 4.

While molecular models suggest that the carbonyl of these rigid, trans-fused α-methyl ketones may be considerably hindered from attack, steric hindrance of the degree illustrated in category b evidently is not exhibited by 1 and 4 whose α-chloro derivatives underwent rapid transformation.

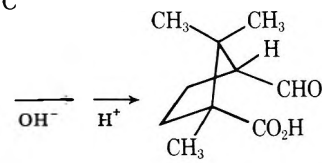
Unhindered ketones possessing only α-H's are usually converted with this reagent into α-chlorinated ketones which undergo either α hydroxylation, category c, or cleavage, category d. These two pathways are not generally competitive; α-hydroxy ketones are usually formed exclusively. However, this α-hydroxylation reaction proceeds via an epoxide intermediate whose formation requires 1,3 elimination of Cl^- from a transition characteristic of S_N2 displacement reactions. When such a transition is not easily attained, the generally disfavored cleavage pathway may be followed, often exclusively as illustrated in the example of α-chlorocyclopropyl phenyl ketone. The unusual stability of the 1-chlorocyclopropyl anion,[13] augmented by the reduced ring strain in cyclopropanes which may be effected by metallation,[14] are factors which would accelerate the cleavage reaction in this example.

Similarly, α hydroxylation of α-chlorinated 1 and 4 is disfavored; in these rigid cyclic structures the transitional antiperiplanar geometry, required for displacement of Cl^- leading to epoxide formation, is not easily accommodated. Moreover, cleavage of these monochlorinated cyclopentanones is relatively slow, and in these systems gem dichlorination can and does occur rapidly. The *gem*-α-dichlorocyclanones **1a** and **4a**, therefore, are formed. They cannot be isolated, however, because they undergo cleavage at a rate which is apparently accelerated by the formation of stabilized α,α-dichlorocarbanions and by the concomitant alleviation of ring strain and unfavorable vicinal interactions between the *gem*-dichloro substituents and *gem*-dioxyanions. In these reactions, then, 1 and 4 follow the pathway first observed with camphor (**9**).[2,4,6] Similar facile base-induced cleavage of *gem*-α-dichlorocyclobutanones has been reported.[15] The dichlorination–cleavage pathway followed by cyclanones **1**, **4**, and **9** is illustrated in Scheme III.

As illustrated in Scheme III, dichlorination–cleavage of **9** into the dichlorocyclopentanoic acid **10** with this reagent proceeds with little if any epimerization of the two chiral centers.[4] Thus, the fact that the dichloromethyl and carboxyl substituents of **10** are in a cis juxtaposition was demonstrated by the conversion of this acid into the chlorolactone **11** (α-chloro-α-campholide) and then into the known product, **12** (camphoric acid *sec*-semialdehyde).[16]



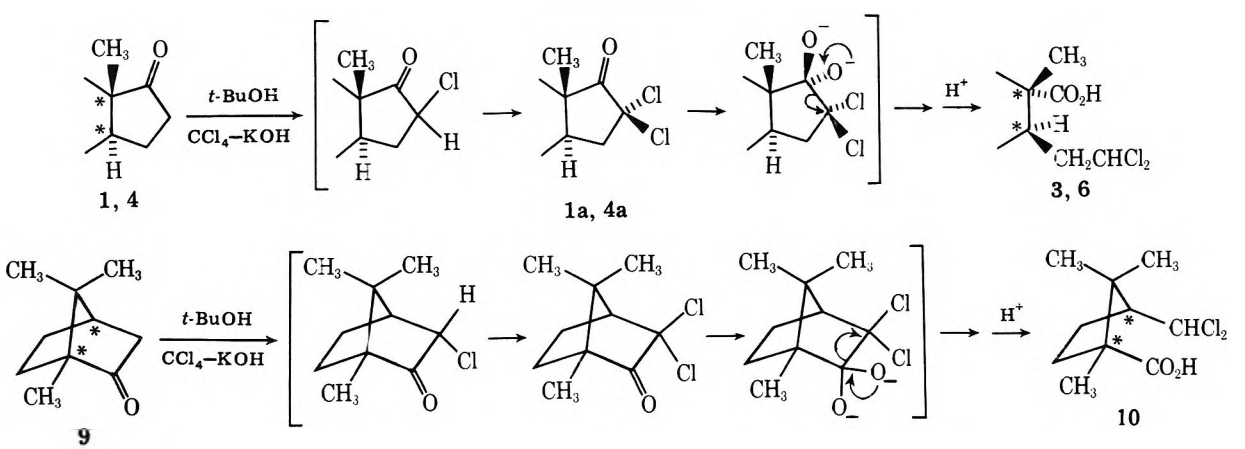
11
mp 135 °C



12
mp 126 °C

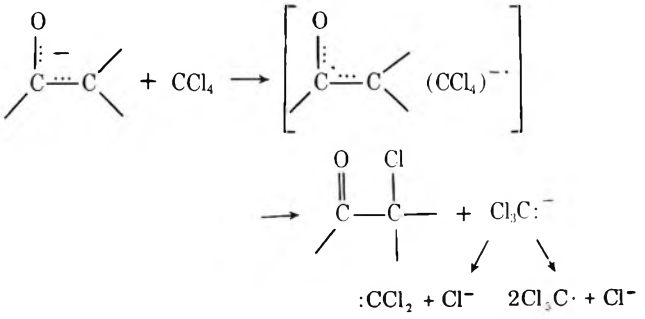
Likewise, 1 and 4 apparently underwent dichlorination–cleavage with this reagent without suffering epimerization of the corresponding chiral centers. In each case the NMR spectrum of the cleavage product exhibited only one sharp singlet representing the methyl on the cyclohexanoic acid ring. Moreover, in those instances where the reactions were quenched prior to completion, the recovered ketone was identical to the original substrate (IR, NMR, mmp).

Scheme III



There seemed to be little difference between the reactivities of estrones **1** and **4**; the conversion of each proceeded to the extent of at least 80% within about 1 h at 25 °C. Furthermore, neither reaction exhibited much sensitivity to dioxygen, so that it mattered little if these reactions were carried out under a blanket of nitrogen or in a system open to air. These results are consistent with data suggesting that α chlorination of ketones with this reagent involves the reaction of enolate anions with CCl_4 in a discrete electron transfer/chlorine atom transfer step proceeding through a radical/anion–radical pair (RARP) mechanism, which is neither a radical chain process nor one that requires initiation by dioxygen.[6,17]

As shown in the equation, the coformation of $Cl_3C:^-$ in the chlorination step leads to the generation of $:CCl_2$ as well as $\cdot CCl_3$.[2,6,17] Under the reaction conditions neither of these species is reactive with the 3-methoxy ketone (**4**) or its product (**6**); the latter, therefore, was formed and isolated in a high state of purity. Phenoxides, however, are quite reactive with $:CCl_2$ and with $\cdot CCl_3$–CCl_4 under these conditions.[6,17,18] It was

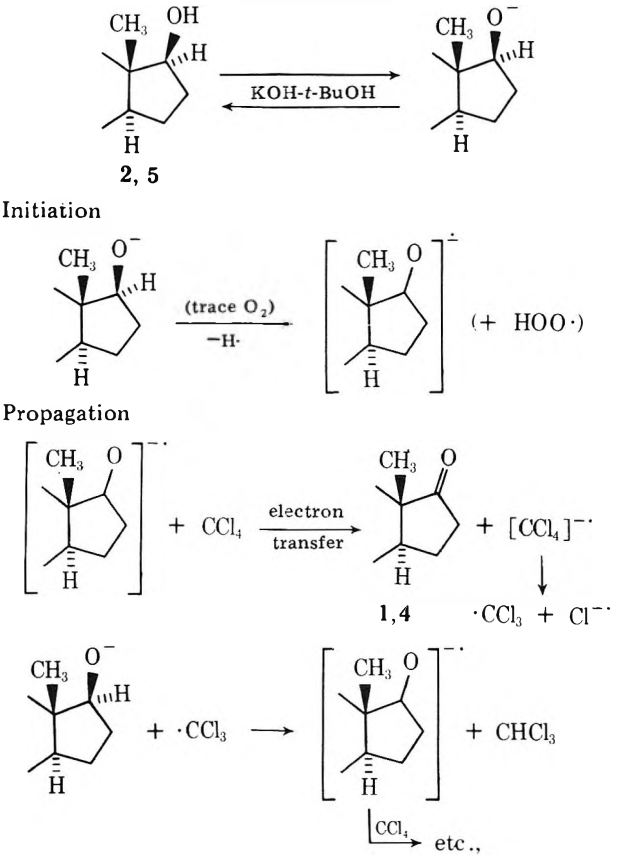


not suprising, then, that the conversion of the phenolic ketone (**1**) into **3** was accompanied by the formation of small amounts of by-products spectrally characteristic of the 2-aldehyde and 2-carboxylic acid derivatives of **3** which might be expected from these minor secondary reactions.

Cyclanols 2 and 5. Alcohols **2** and **5** underwent reaction with CCl_4–KOH–*t*-BuOH quite slowly relative to the reactions of the corresponding ketones, **1** and **4**, with this reagent. This result is reasonable because in these in situ transformations of the alcohols in the initial step, oxidation to ketones, is low with this reagent and, therefore, is rate determining.[3,5,6,8] Steric hindrance may be a factor retarding the rate of these oxidations. Thus, neopentyl alcohol reacts with this reagent at a respectable rate only when the mixture is warmed,[2,3] and isopropyl alcohol reacts faster than di-*tert*-butylcarbinol which exhibits no reactivity even at elevated temperatures.[8] On the other hand, phenylcarbinols are especially reactive, even when hindered (e.g., benzhydrol). There is sufficient evidence now to indicate that alcohols, via their oxyanions/oxyanion radicals, undergo a free-radical chain reaction with CCl_4, a process responsible for their oxidation with this reagent.[6,8] The oxidation of cyclanols **2** and **5** into cyclanones **1** and **4** by this pathway is illustrated in Scheme IV. The fact that these carbinols are relatively hindered and that neither their oxyanions nor oxyanion radicals are especially stabilized may reinforce each other in retarding the rate of these oxidations by this process.

These radical-chain oxidations are initiated by dioxygen and propagated by $\cdot CCl_3$ which is subsequently generated. The number of propagating chains in such a process is closely related to the amount of dioxygen available. Consistent with this mechanism, therefore, is the fact that the reaction of methoxy alcohol **5** (25 °C, 5 h) proceeded much faster in an atmosphere of air (44% reaction) than in an atmosphere of nitrogen (16% reaction). Less obvious, but also consistent with this mechanism, is the fact that *phenolic* alcohol **2** was considerably *less* reactive than its methoxy alcohol counterpart and that its reactivity was indifferent to the amount of dioxygen present,

Scheme IV



viz., less than 10% of **2** underwent reaction during treatment for 5 h at 25 °C in a system maintained under nitrogen *or* open to air. In these reactions a phenolic moiety is essentially all in the form of its phenoxy anion, a function known to inhibit autoxidation and free-radical chain reactions.[19] Moreover, we have found that $\cdot CCl_3$ in CCl_4 solution undergoes a radical-chain addition reaction with a variety of phenoxy anions,[6,17,18] a reaction which would interfere with other chain reactions propagated with $\cdot CCl_3$. The oxidation of **2**, therefore, suffers inhibition by these processes because its phenolic moiety functions as a "built-in" inhibitor.

A comparison of the reactions and reactivity of the CCl_4–KOH–*t*-BuOH reagent with those of alkaline potassium hypochlorite revealed that these two reagents perform differently.[2,3,5] Thus, while camphor is easily α,α dichlorinated with the CCl_4 reagent (vide supra), it is completely recovered, unchanged, when refluxed for 6 h with 1*N* KOH–1*N* KOCl in aqueous dioxane (even though its enolate anion is formed under these conditions).[20] Moreover, while phenolic carbinols are oxidized to the *corresponding* phenolic aldehydes or ketones with the CCl_4 reagent, they primarily undergo ring polychlorination when treated with alkaline hypochlorite.[21] These results indicate that the selective dichlorination–cleavage reactions of the cyclanone and cyclanol systems described here cannot be carried out successfully with alkaline hypochlorite.

Bioassay

Doisynolic acid (**7**) and its methyl ether (**8**) are reported to exhibit estrogenic activity in rats equal to or greater than that of estrone itself.[22] Halogenation of a steroid may enhance, reduce, or change the nature of its activity depending on the steroidal structure, the position of substitution, and the stereochemistry associated with the substitution.[23] The effect of 16,16-dichloro substitution on the activity of **8** was found to be interesting in several aspects. Thus, **6** exhibited estro-

genic *and* anti-estrogenic activity in the mouse-uterine weight assay when tested at the standard screening dosage level of 25 mg/kg. At the reduced dosage level of 8 mg/kg, however, estrogenic activity was maintained but anti-estrogenic activity no longer was exhibited.[24]

Experimental Section

Commercial-grade KOH pellets (85%) were freshly powdered (mortar and pestle) and used immediately. Both CCl_4 and *t*-BuOH were spectroquality. All TLC's were developed with benzene–EtOAc (7:3, v/v), sprayed with 50% H_2SO_4, then heated at 100 °C. NMR spectra were taken on a Varian A-56/60 spectrometer; IR spectra were taken on Beckman IR-5A or IR-10 spectrophotometers; pK_a and neutralization equivalent measurements were determined on a Corning Model 12 pH meter, and melting points were determined on a Thomas–Hoover capillary melting point apparatus and are not corrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

16,16-Dichlorodoisynolic Acid 3-Methyl Ether (6). (a) From Estrone 3-Methyl Ether (4). A solution of 570 mg (2.00 mmol) of estrone 3-methyl ether (**4**; mp 170–171 °C [from MeOH], prepared by the Jones oxidation of estradiol 3-methyl ether [**5**; G. D. Searle and Co.]) in 30 mL of CCl_4 was added to a mixture of 4 g of well-powdered KOH and 16 mL of *t*-BuOH magnetically stirred and maintained under N_2. The reaction was immediately exothermic and the colorless mixture became yellow, gradually deepening to orange. Within 10 min the temperature of the mixture fell to 25 °C and remained constant. After 1 h the mixture was poured into ice–water and extracted several times with ether. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated, leaving 100 mg of a viscous oil containing at least five components (TLC) which were not characterized. The aqueous layer and water washings were combined, acidified (HCl) to pH <1, and extracted several times with ether. The combined extracts were washed with aqueous $NaHCO_3$ (vide infra), dried ($MgSO_4$), and evaporated leaving 550 mg (1.48 mmol, 74%) of a crystalline solid, mp 147–148 °C, whose TLC exhibited one major green spot and four barely detectable other spots. Trituration with and recrystallization from ether provided white crystals (TLC pure, one green spot): mp 157–158 °C; NMR ($CDCl_3$) δ 1.15 (s, 3, CCH_3), 3.77 (s, 3, OCH_3), 5.82 (t, J = 6 Hz, 1, $CHCl_2$), 6.53 (d, J = 3 Hz, 1, C-4 H), 6.61 (split d, J = 8 Hz, 3 Hz, 1, C-2 H), 7.08 (d, J = 8 Hz, 1, C-1 H), and 10.92 (s, 1, CO_2H); IR (Nujol) ν 3333–2250 (broad, OH), 1681 (intense, CO_2H), 1282 (v str, OC–O), 737 and 727 cm^{-1} (med, Cl–C–Cl); pK_a 3.65 (in 48% EtOH, 25 °C; average of several values determined with 4.9×10^{-4} M solutions titrated with 10^{-2} N NaOH);[25] neutralization equivalent Calcd for $C_{19}H_{24}O_3Cl_2$: 371. Found: 360 ± 3.

Anal. Calcd for $C_{19}H_{24}O_3Cl_2$: C, 61.46; H, 6.52; Cl, 19.10. Found: C, 61.53; H, 6.63; Cl, 19.04.

The aqueous $NaHCO_3$ washings were combined, acidified (HCl) to pH <1, and extracted several times with ether; the combined ethereal extracts were dried ($MgSO_4$) and evaporated to provide 50 mg of crystalline material (mp 68–135 °C) about one-half of which was **6** (TLC, IR).[26] Including this additional amount the total yield approached 78%. Several preparations carried out under similar conditions provided almost identical results. In addition, two runs carried out in systems opened to air (25 °C, 1 h) afforded yields of about 75%. The same sample of recrystallized product did not always exhibit the same mp, which ranged from 157–158 °C (most frequently) to 164–166 °C.

(b) From Estradiol 3-Methyl Ether (5). To a stirred solution of 572 mg (2.00 mmol) of estradiol 3-methyl ether (**5**; Searle, mp 118–120 °C) in 30 mL of CCl_4 and 16 mL of *t*-BuOH, maintained under N_2, was added 4.0 g of well-powdered KOH in one portion. The stirred mixture exhibited only a very small exotherm and became slightly yellow. Stirring was continued for 5 h (25 °C) after which time the pale yellow mixture was added to ice–water and extracted several times with ether. The combined ethereal extracts were dried ($MgSO_4$) and evaporated leaving 480 mg (1.68 mmol, 84%) of recovered **5** (IR, mp, mmp). The aqueous residue was acidified (HCl) to pH <1 and extracted with ether, and the extracts were washed with aqueous $NaHCO_3$. The ethereal layer was dried ($MgSO_4$) and evaporated to provide 100 mg (0.27 mmol, 13.5%) of crude product, mp 149–156 °C; IR and NMR spectra were identical to those of the product prepared in (a). The aqueous $NaHCO_3$ washings were acidified to pH <1 with HCl and extracted with ether, and the extracts were dried ($MgSO_4$) and evaporated; only a few milligrams of material were obtained from this fraction.[26]

When this reaction was carried out similarly (25 °C, 5 h) but in a vessel opened to air the yield was improved considerably, to about 30%, while correspondingly less starting material (50–60%) was recovered.

16,16-Dichlorodoisynolic Acid (3). (a) From Estrone (1). To a vigorously stirred solution of 540 mg (2.00 mmol) of estrone (**1**; Upjohn, mp 253–258 °C) in 30 mL of CCl_4 and 16 mL of *t*-BuOH maintained under N_2 was added 4.0 g of well-powdered KOH in one portion. The mixture immediately became quite warm and attained a reddish brown coloration. The exotherm soon subsided and the mixture, at 25 °C, was stirred for a total of 1.5 h and then poured into ice–water. The mixture was acidified (HCl) to pH <1 and extracted with ether, several drops of 2-octanol being added to break the thick emulsion which formed during the extraction. The combined ethereal extracts were washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated, leaving 430 mg of solid material whose NMR spectrum ($CDCl_3$–acetone-d_6: δ 1.23 (s, CCH_3), 5.92 (t, J = 6 Hz, $CHCl_2$)) was characteristically similar to that of **6** but, in addition, exhibited small changes in the aromatic H pattern; likewise, its IR spectrum (Nujol: ν 3400 (Ar–OH), 3200–2450 (broad, CO_2H), 1681 (str, CO_2H), 1282 (med, OC–O), and 727 cm^{-1} (med, Cl–C–Cl)) reflected the pattern of that exhibited by **6**. The combined aqueous $NaHCO_3$ washings were acidified with HCl to pH <1 and extracted with ether; evaporation of the dried extracts provided a solid, 270 mg (after being washed with pentane), whose NMR and IR spectra were very similar to those just described.[26] The absence of starting material was evidenced by the NMR spectra of the two fractions. While the total weight of product, 700 mg, represented a yield of 98%, this material was impure **3**; the presence of the 2-aldehyde and 2-carboxylic acid derivatives of **3** was suggested by the NMR spectrum (δ 7.52 (m, Ar–H ortho to CHO or CO_2H), and 10.40 (s, O=CH or CO_2H)).

This reaction (with 270 mg [1.00 mmol] of **1**, 15 mL of CCl_4, 10 mL of *t*-BuOH, and 2.0 g of powdered KOH) was repeated but in a system opened to air. After 1.5 h at 25 °C the mixture was quenched with ice–water and extracted with CCl_4 three times. The residual aqueous layer was acidified with HCl to pH <1 and the precipitated solid material was separated by filtration, washed with water, and dried in vacuo (25 °C, 16 h), providing 430 mg of a crystalline solid, mp 155–157 °C. Its IR and NMR spectra were almost identical to those described above, indicating the absence of **1**, but suggesting the presence of somewhat more aldehyde contaminent. No further attempt was made to purify **3** prepared in these reactions.

(b) From Estradiol (2). To a vigorously stirred solution of 544 mg (2.00 mmol) of estradiol (**2** [17β]; Schering, mp 174–175 °C) in 30 mL of CCl_4 and 16 mL of *t*-BuOH maintained under N_2 was added 4.0 g of powdered KOH. The colorless mixture became light orange immediately on contact with the KOH, although no exotherm was evident. After being stirred for 5 h at 25 °C the mixture was poured into ice–water and extracted several times with CCl_4, and the aqueous residue was acidified to pH <1 with HCl which provided a mass of precipitated crystals. This mixture was extracted with ether and the combined extracts were dried ($MgSO_4$) and evaporated to leave 560 mg of a solid composed of (IR, NMR) at least 90% of recovered **2** and less than 10% of **3** (the characteristic CO_2H bands and the CCH_3 singlet of the latter were barely discernable in these spectra).

The same reaction was carried out but in a system opened to air, again for 5 h at 25 °C. The mixture seemed to be somewhat deeper orange-brown than that noted above, but similar workup provided about the same amount of solid whose spectra were almost identical to those described above; again, about 90% of **2** was recovered and no more than 10% of **3** was detected.

Acknowledgment. Gratitude is extended to Drs. R. E. Beyler and H. I. Hadler for providing the steroidal substrates used in this study and for their stimulating discussions. V.M.K. is grateful to the Yugoslav–American Commission for Educational Exchange for providing her with financial support.

Registry No.—**1**, 53-16-7; **2**, 50-28-2; **3**, 65311-07-1; 3 2-aldehyde derivative, 65311-08-2; **3** 2-carboxylic-acid derivative, 65311-09-3; **4**, 1624-62-0; **5**, 1035-77-4; **6**, 65311-10-6.

References and Notes

(1) (a) Taken in part from the Ph.D. Dissertation of V.M.K., Southern Illinois University, Carbondale, 1976; (b) Fulbright predoctoral Fellow, 1973–1976.
(2) C. Y. Meyers, A. M. Malte, and W. S. Matthews, *J. Am. Chem. Soc.*, **91**, 7510 (1969).
(3) W. S. Matthews, Ph.D. Dissertation, Southern Illinois University, Carbondale, 1972.

(4) C. Y. Meyers and A. M. Malte, U.S. Patent 3 896 164 (1975).
(5) C. Y. Meyers and W. S. Matthews, U.S. Patent 3 953 494 (1976).
(6) The reactions of ketones, alcohols, and sulfones with perhalomethanes in KOH–*t*-BuOH are reviewed by C. Y. Meyers, W. S. Matthews, L. L. Ho, V. M. Kolb, and T. E. Parady in "Catalysis in Organic Syntheses", G. V. Smith, Ed., Academic Press, New York, N.Y., 1978.
(7) V. M. Kolb and C. Y. Meyers, 170th National Meeting of the American Chemical Society, Chicago, Ill., August 1975, Abstracts ORGN-88.
(8) C. Y. Meyers, V. M. Kolb, and A. J. Aksamit, 172th National Meeting of the American Chemical Society, San Francisco, Calif., August 1976, Abstracts ORGN-48.
(9) D. W. MacCorquodale, S. A. Thayer, and E. A. Doisy, *J. Biol. Chem.*, **99**, 327 (1933); D. W. MacCorquodale, L. Levin, S. A. Thayer, and E. A. Doisy, *ibid.*, **101**, 753 (1933); U. S. Patent 2 069 096 (1937).
(10) W. Holweg and H. H. Inhoffen, German Patents 705 862 (1941) and 719 572 (1942).
(11) K. Miescher, *Helv. Chim. Acta*, **27**, 1727 (1944); J. Heer, J. R. Billeter, and K. Miescher, *ibid.*, **28**, 1342 (1945); K. Miescher *Chem. Rev.*, **43**, 367 (1948). Miescher clarified the structural identification of the acidic products from the KOH fusion reactions and was responsible for selecting the name "doisynolic acid".
(12) L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, N.Y., 1959, pp 488 ff.
(13) C. Y. Meyers and V. M. Kolb, International Symposium, Chemistry of Strained Rings, SUNY-Binghamton, N.Y., May 1977, Abstracts p 28.
(14) J. D. Dill, ref 13, Abstracts p 37, for example, reported a strain energy (kcal/mol) of 26.5 for cyclopropane compared to 18.5 for cyclopropyllithium.
(15) J. M. Conia and J. R. Salaun, *Acc. Chem. Res.*, **5**, 33 (1972); P. R. Brook and A. J. Duke, *J. Chem. Soc. C*, 1764 (1971).
(16) C. Y. Meyers and A. M. Malte, unpublished results. It should be noted that the formation of the potassium salt of **10** by the method illustrated in Scheme III is *not* accompanied by its conversion into **11** or **12** because under these conditions this salt precipitates as it is formed and is, therefore, not reactive.
(17) C. Y. Meyers, T. E. Parady, V. M. Kolb, and D. H. Hua, 174th National Meeting of the American Chemical Society, Chicago, Ill., August 1977, Abstracts ORGN-58.
(18) J. A. Tykal, Ph.D. Dissertation, Southern Illinois University, Carbondale, 1972; C. Y. Meyers and J. A. Tykal, American Chemical Society Midwest Regional Meeting, Manhattan, Kans., Oct. 1968, Abstracts ORGN-32.
(19) C. Walling, "Free Radicals in Solution", Wiley, New York, N.Y., 1957, pp 430 ff.
(20) For example, camphor underwent 25% α-D/H exchange within an hour when refluxed with NaOD–D_2O and 100% exchange during a few hours of reflux (ref 3).
(21) C. Y. Meyers, *J. Org. Chem.*, **26**, 1046 (1961).
(22) E. Tschapp, *Helv. Physiol. Pharmacol. Acta*, **4**, 271, 401 (1946); see also ref 11 and 12.
(23) J. A. Vida, "Androgens and Anabolic Agents", Academic Press, New York, N.Y., 1969, for example, describes the effects of fluoro, chloro, bromo, and iodo substitution on the activity of a variety of androgens.
(24) The assays of **6** were carried out at G. D. Searle and Co. We are grateful to Dr. Kurt Rorig for this service and for providing us with these results.
(25) The related dichloromethylcyclopentanecarboxylic acid (**10**), similarly derived from camphor, exhibited pK_a values of 6.25 in 50% EtOH and 5.30 in water (25 °C).[16]
(26) Evidently **6**, because of its high molecular weight and nonphenolic character, is not very polar and therefore is not readily neutralized in ethereal solution by treatment with aqueous $NaHCO_3$. The corresponding phenolic carboxylic acid (**3**) under the same conditions is more readily neutralized.

Identity of the Stereochemistry of Dinosterol and Gorgosterol Side Chain[1]

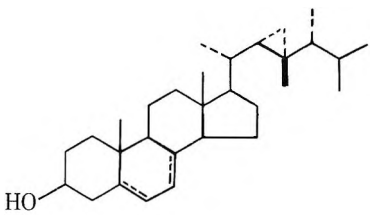
J. Finer,[2a] J. Clardy,*[2a,3] A. Kobayashi,[2b] M. Alam,[2b] and Y. Shimizu*[2b]

Ames Laboratory-USERDA and Department of Chemistry, Iowa State University, Ames, Iowa 50011, and Department of Pharmacognosy, College of Pharmacy, University of Rhode Island, Kingston, Rhode Island 02881

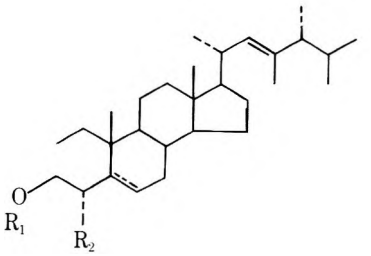
Received July 21, 1977

The structure of dinosterol, a peculiar sterol isolated from the dinoflagellate *Gonyaulax tamarensis*, was confirmed by x-ray crystallography. The proven identity of the stereochemistry of the side chain provided further support for the suspected close biogenetic relationship of dinosterol with gorgosterol and acanthasterol.

A difficult but intriguing problem in the study of marine animal constituents is the metabolite transfer inherent in the marine food chain and symbiosis. More often than not, it is difficult to determine whether an isolated compound is biosynthesized by the organism itself or is of dietary origin, either intact or partially transformed. A most intriguing example is gorgosterol **1** and its derivatives isolated from soft coral or gorgonians.[4] Their structures are unique not only for the presence of a cyclopropane ring but also for the unprecedented C-23 alkylated side chain. The abnormal side chain seems to be formed by methylation at C-24 followed by a second methylation at Δ^{22} and a third alkylation leading to the cyclopropane ring (Scheme I). In fact, Kanazawa et al.[5] isolated from a soft coral, *Sarcophyta elegans*, 23ξ,24ξ-dimethylcholesta-5,22-dien-3β-ol (**2**) which fits well into this scheme. A double bond isomer of gorgosterol, acanthasterol (**3**), was also isolated from the crown-of-thorns starfish, *Acanthaster planci*.[6] Since starfish are known to transform exogenous Δ^5 sterols to Δ^7 sterols,[7] it was immediately speculated that acanthasterol was of dietary origin. Indeed the crown-of-thorns starfish is known to feed on soft corals. As to the origin of gorgosterol in soft corals, Ciereszko et al.[8] already speculated that it might have come from symbiotic dinoflagellates, *Zooxanthellae*, which sometimes constitute a substantial part of the total body weight. The extract of the washed-out zooxanthellae was found to give a mass spectrum peak *m/e* 426 corresponding to gorgosterol. It was also noticed



1 Δ^5
3 Δ^7



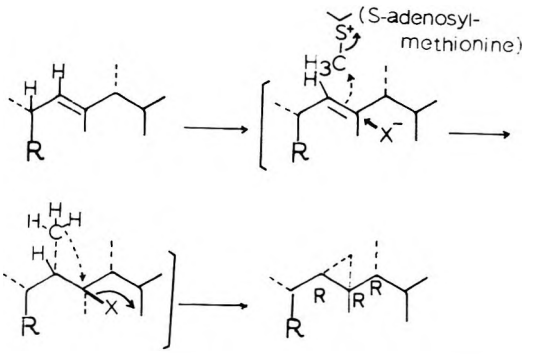
2 Δ^5, R_1, R_2 = H
4 5α, R_1 = H; R_2 = CH_3
5 R_1 = *p*-I-C_6H_3CO; R_2 = CH_3

that the anaerobically kept zooxanthellae gave a *m/e* 428 peak of "dihydrogorgosterol".[8]

In view of the above-mentioned observation and the fact

0022-3263/78/1943-1990$01.00/0

Scheme I



that dinoflagellates along with diatoms constitute the very basis of marine life, we have been investigating the steroidal components of unialgal cultures of dinoflagellates. In a previous communication[9] we reported the presence of dinosterol (**4**, $C_{30}H_{52}O$, mol wt 428) as the major sterol with a lesser amount of cholesterol in the toxic dinoflagellate, *Gonyaulax tamarensis*. The structure of dinosterol was determined as 4α,23,24ξ-trimethyl-5α-cholest-22-en-3β-ol by spectroscopic data and chemical correlation. The structure strongly implies that dinosterol is an intermediate to gorgosterol analogues or a compound just off the main metabolic stream. Significantly, the same sterol has been isolated from a soft coral, *Plexaura homomalla* and *Pseudoplexaura porosa*.[10]

To prove the close association of the dinoflagellate sterol with gorgosterol, it was felt to be very important to compare the stereochemistry of C-24 of both compounds and also to determine the geometry of C-22 double bond.

The *p*-iodobenzoate of dinosterol, **5**, crystallized from ethyl acetate as well formed rectangular solids, mp 217–221 °C. Preliminary x-ray photographs indicated orthorhombic symmetry and the systematic extinctions conformed to the common space group $P_{2_12_12_1}$. Accurate cell constants, determined by least-squares fitting of 15 high angle 2θ values, are $a = 8.081$ (2), $b = 10.658$ (3), and $c = 40.212$ (7) Å. All unique data with $\theta \leq 114°$ were collected using graphite monochromated Cu Kα (1.54178 Å) x rays. A total of 2738 reflections were measured and after correction for Lorentz–polarization and background corrections, 1889 (60%) were judged observed ($F_o \geq 3\sigma(F_o)$).

The iodine atom was located in the three-dimensional Patterson synthesis[11] and the remaining nonhydrogen atoms were located in a subsequent I-phased electron density synthesis. Hydrogen atoms were located and full-matrix least-squares refinement proceeded routinely. Correction for anomalous scattering from the iodine gave a conventional discrepancy index of 0.049 for the structure shown and 0.080 for its enantiomer.[12]

Figure 1 is a computer-generated perspective drawing of the final x-ray model less hydrogens. The configuration of the C-22 double bond is *E* and C-24 has the *R* absolute configuration. The molecular geometry agrees well with generally accepted values.[13]

The absolute configuration of gorgosterol was established as 22*R*, 23*R*, 24*R*.[4] Both dinosterol and gorgosterol have the same stereochemistry at C-24, i.e., brassicasterol type. The *E* form of the dinosterol double bond was anticipated considering the mechanism for the three-membered ring formation (Scheme I). The stereochemistry at C-20 was found to be the normal *R* configuration as assigned previously by the chemical correlation of dinosterol with stigmasterol.[9] Furthermore the projected figure shows that the side chain in this crystalline form is taking the right-handed rotamer position, the least energetic conformer as recently suggested by Nes et al.[14]

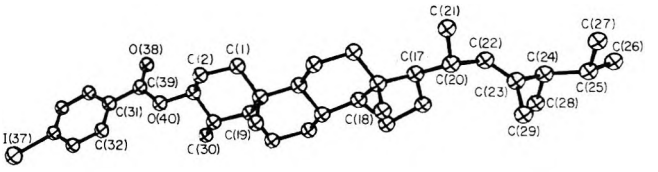


Figure 1. Computer generated perspective drawing of dinosterol *p*-iodobenzoate.

Our results strengthen the previous assertion that dinoflagellates are a primary source of novel sterols found in marine organisms. It is worth noting that the presence of a 4α-methyl group in dinosterol indicates that C-23 methylation in dinosterol may occur at an early stage.

Experimental Section

Low-resolution mass spectra were taken with a DuPont 21-490B model and high-resolution mass spectrum with a CEC 21-110B mass spectrometer. The ^1H NMR spectrum was measured on a Varian HA-100 spectrometer. Melting points were measured on a Fisher-Johns apparatus and were uncorrected. Gas liquid chromatography (GLC) was done with a Varian 1400 model equipped with a 6-ft column.

Culture of *Gonyaulax tamarensis*. An isolated sample obtained at the height of the bloom at Ipswitch, Massachusetts, in September 1972, was used as the seed culture. Large-scale culture of the organism was done in 20-L carboys using a culture medium based upon Guillard F.[15]

Sea water collected at the Beaver Tail Point, Jamestown, R.I., was stored in a dark room at 12 °C for more than 2 weeks and was then filtered through a charcoal layer (Fisher Scientific, coconut charcoal). The filtered sea water was further passed through a Millipore filter (0.22 μm). The filtrate was added with the inorganic ingredients and autoclaved for 15 min. After cooling the organic ingredients were added through a Millipore filter (0.22 μm). The sterile culture medium (12 L) was inoculated with 1 L of the seed culture. The culture bottle was kept under fluorescent illumination at 12 °C without agitation.

After 4 weeks when the population of the organism reaches about 5000–10000/mL, the organism was collected by centrifugation with a Szent-Gyorgi-Blum's continuous system at 5 °C.

Extraction and Isolation of Dinosterol 4. (a) The reddish brown dinoflagellate cells (370×10^6) were digested with 5% ethanolic KOH solution for 3 h on a steam bath. The mixture was extracted with ether (3×50 mL). The ethereal extract was chromatographed on a silica gel 60 prepacked column (1.5×18 mm, E. Merck) using methanol–chloroform as eluting solvents. The dinosterol fraction (7.0 mg) was eluted just after phytol slightly overlapped with cholesterol. Rechromatography on the same column gave a chromatographically pure fraction (TLC and GLC). Recrystallization from MeOH gave needles: mp 220–222 °C; $[\alpha]_D$ ±5° (c 0.6, $CHCl_3$); $C_{30}H_{52}O$ (calcd. *m/e* 428.4041; found: *m/e* 428.4054), *m/e* 428 (26), 387 (15), 370 (10), 316 (65), 303 (24), 287 (100), 271 (67); ^1H NMR δ 0.70 (3 H, s), 0.90 (3 H, d, $J = 7$ Hz), 0.84 (3 H, s), 0.85 (3 H, d, $J = 7$ Hz), 0.94 (6 H, d, $J = 6.5$ Hz), 0.95 (3 H, d, $J = 7$ Hz), 3.10 (1 H, m), 4.87 (1 H, q, $J = 1.2, 10$ Hz). Gas liquid chromatography relative retention time to cholesterol 1.59 (1% OV-17, 240 °C).

The cholesterol fraction (10.5 mg), mp 146–147 °C, gave a single peak in the GLC system. A specimen recrystallized from methanol showed the IR and mass spectrum identical with those of an authentic sample of cholesterol.

(b) The algal cells were extracted with chloroform. The chloroform extract was directly chromatographed with the chromatographic system described in (a) without prior saponification. Dinosterol and cholesterol were obtained in a same proportion (GLC) as isolated in procedure (a) indicating the absence of the preferentially esterified forms of a sterol in the organism.

Dinosterol *p*-Iodobenzoate (5). To a solution of 1 mg of dinosterol in pyridine (0.5 mL) was added 20 mg of *p*-iodobenzoyl chloride. After 2 days at room temperature, the mixture was diluted with ice–water and extracted with ether. After the usual procedure, a crystalline residue was recrystallized from $CHCl_3$ to needles: mp 217–221 °C; *m/e* 658 (17, M^+), 345 (21), 516 (69), 317 (21), 271 (100), 231 (38), 139 (81).

Registry No.—**1**, 29782-65-8; **4**, 58670-63-6; **5**, 65495-99-0; *p*-iodobenzoyl chloride, 1171-02-0.

Supplementary Material Available: A listing of fractional coordinates and temperature factors (Table I), bond lengths (Table II), and bond angles (Table III) of dinosterol (6 pages). Ordering information is given on any current masthead page.

References and Notes

(1) This work was supported by HEW Grant FD-00619 and Sea Grant URI R/D-3.
(2) (a) Iowa State University; (b) University of Rhode Island.
(3) Camille and Henry Dreyfus Teacher-Scholar Grant Awardee 1972–1977. Department of Chemistry, Cornell University, Ithaca, N.Y.
(4) K. C. Gupta and P. J. Scheuer, *Steroids*, **13**, 343 (1969); R. L. Hale, J. Leclercq, B. Tursch, C. Djerassi, R. A. Gross, Jr., A. J. Weinheimer, K. Gupta, and P. J. Scheuer, *J. Am. Chem. Soc.* **92**, 2179 (1970); N. C. Ling, R. L. Hale, and C. Djerassi, *ibid.*, **92**, 5281 (1970). Also 23-demethylgorgosterol: F. J. Schmitz and T. Pattabhiraman, *ibid.* **92**, 6073 (1970).
(5) A. Kanazawa, S. Teshima, T. Ando, and S. Tomita, *Suisan Gakkaishi*, **40**, 729 (1974); A. Kanazawa, T. Ando, and S. Teshima *ibid.*, **43**, 83 (1977).
(6) K. C. Gupta and P. J. Scheuer, *Tetrahedron*, **24**, 5831 (1968); Y. M. Sheikh, C. Djerassi, and B. M. Tursch, *Chem. Commun*, 217 (1971).
(7) See L. J. Goad, I. Rubinstein and A. G. Smith, *Proc. R. Soc. London, Ser. B*, 180, 223 (1972), and references therein.
(8) L. S. Ciereszko, M. A. Johnson, R. W. Schmitz, and C. K. Kooms, *Comp. Biochem. Physiol.*, **24**, 899 (1968).
(9) Y. Shimizu, M. Alam, and A. Kobayashi, *J. Am. Chem. Soc.* **98**, 1059 (1976).
(10) S. Popov, R. M. K. Carlson, A. Wegmann, and C. Djerassi, *Steroids*, **28**, 699 (1976).
(11) The following library of crystallographic programs was used: C. R. Hubbard, C. O. Quicksall and R. A. Jacobson, "The Fast Fourier Algorithm and the Programs ALFF, ALFFDP, ALFFT, and FRIEDEL", USAEC Report IS-2625, Iowa State University, Institute for Atomic Research, Ames, Iowa, 1971; W. R. Busin, K. O. Martin and H. A. Levy, "A Fortran Crystallographic Least Squares Program", USAEC Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965; C. Johnson, "ORTEP, A Fortran Thermal-Ellipsoid Plot Program," U.S. Atomic Energy Commission Report ORNL-3794, Oak Ridge, Tenn., 1965.
(12) W. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).
(13) Additional crystallographic details can be found in the Supplemental Material.
(14) W. R. Nes, T. E. Varkey, and K. Krevitz, *J. Am. Chem. Soc.*, **99**, 260 (1977).
(15) R. R. L. Guillarc, "Symposium on Marine Microbiology", C. Oppenheimer, Ed., C. C. Thomas Publishing Co., New York, N.Y., 1963 p 93.

Studies in Protoberberine Alkaloids. 14. Use of a Mixture of Phosphorus Pentabromide and Phosphorus Pentoxide As a Cyclizing Reagent in Protoberberine Synthesis

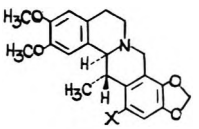
Bantwal R. Pai,* Sankaran Natarajan, Govindarajan Manikumar, Rangaswamy Rajaraman, and Hosbett Suguna

Department of Chemistry, Presidency College, Madras-600 005, India

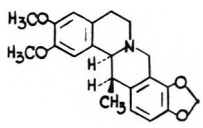
Received August 5, 1977

Cyclization of 1-(2-bromo-α-methyl-4,5-methylenedioxybenzyl)-2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**3**) with a mixture of PBr_5 and P_2O_5 (followed by reduction with $NaBH_4$ in MeOH) led to the formation of 13β-methyl-13aαH-tetrahydropseudoepiberberine (**7**), 4-bromo-13β-methyl-13aαH-tetrahydropseudoepiberberine (**17**), 13α-methyl-13aαH-tetrahydropseudoepiberberine (**8**), and 4-bromo-13α-methyl-13aαH-tetrahydropseudoepiberberine (**18**). Similarly the *N*-formyl derivative **4** gave 13β-methyl-13aαH-tetrahydropseudocoptisine (**9**), 13α-methyl-13aαH-tetrahydropseudocoptisine (**10**), 4-bromo-13α-methyl-13aαH-tetrahydropseudocoptisine (**19**), and 4-bromo-13α-methyl-13aαH-tetrahydropseudocoptisine (**20**).

Our attempts to synthesize thalictrifoline (**1**), base II (**2**), and other related alkaloids by a modified procedure of Shamma et al.[1] were not successful owing to an unexpected but novel rearrangement during the course of the Mannich reaction.[2] It was then planned to use the Bischler–Napieralsky reaction for the cyclization of 1-(2-bromo-α-methyl-4,5-methylenedioxybenzyl)-2-formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**3**) and its bismethylenedioxy analogue **4** to get the required 13-methyltetrahydroprotoberberines.

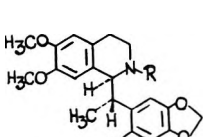


1 X = H
11 X = Br

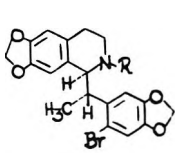


2

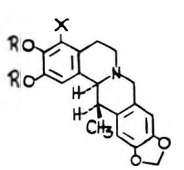
The tetrahydroisoquinolines **5** and **6** gave the corresponding *N*-formyl derivatives **3** and **4** when heated with formic acid and triethylamine. The *N*-formyl derivative **3** was then refluxed with freshly distilled phosphorus oxychloride in benzene and the quaternary salt formed was directly reduced with sodium borohydride in methanol. A mixture of two products was obtained the constituents of which were separated by chromatography and identified from their spectral, physical, and analytical data as the diastereoisomeric 13-methyltetrahydropseudoprotoberberines viz. 13β-methyl-13aαH-tetrahydropseudoepiberberine (**7**) and 13α-methyl-13aαH-tetrahydropseudoepiberberine (**8**). Similarly, when the *N*-formyl derivative **4** was cyclized using $POCl_3$, a mixture of two products was obtained and these were identified as 13β-methyl-13aαH-tetrahydropseudocoptisine (**9**) and 13α-methyl-13aαH-tetrahydropseudocoptisine (**10**). The structures of compounds **7**, **8**, **9**, and **10** were confirmed by comparison with authentic synthetic samples prepared as reported earlier.[1,3] Identical results were obtained when distilled $POBr_3$[4] was used for cyclization in the place of $POCl_3$.



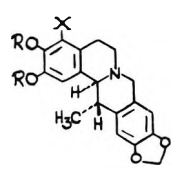
3 R = CHO
5 R = H



4 R = CHO
6 R = H



7 R = CH_3; X = H
9 R+R = CH_2; X = H
17 R = CH_3; X = Br
19 R+R = CH_2; X = Br



8 R = CH_3; X = H
10 R+R = CH_2; X = H
18 R = CH_3; X = Br
20 R+R = CH_2; X = Br

0022-3263/78/1943-1992$01.00/0

Table I

Compd	Registry no.	TLC[a] R_f	Mp, °C	Chemical shift of the C–Me doublet δ, ppm	Rate of methiodide formation $k \times 10^{-4}$, s^{-1} (31.5 °C)	pK_a values
A (17)	65366-50-9	0.9	146	0.93	1.3	7.00 ± 0.05
B (7)	24306-61-4	0.8	197–198	0.93	1.2	
C (18)	65366-51-0	0.5	160	1.47	99.6	7.60 ± 0.05
D (8)	24314-69-0	0.4	132	1.48	60.3	
E (19)	65366-52-1	0.9	205–206	0.93	6.4	
F (9)	65391-28-8	0.8	195	0.94	9.5	
G (20)	65366-53-2	0.5	179	1.43	98.7	
H (10)	65391-29-9	0.4	131	1.44	69.00	

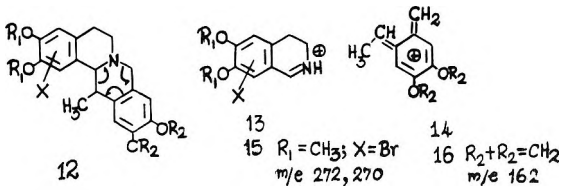
[a] Solvent system, $CHCl_3$/MeOH/EtOAc 40:1:2.5.

However, when an undistilled sample of $POBr_3$ was used for the cyclization of **3**, in addition to the two compounds **7** and **8**, a third compound was obtained in low yields. Analytical and NMR spectral data indicated this compound to be a bromo-substituted tetrahydroprotoberberine and structure **11** was tentatively assigned to it and it was expected to give thalictrifoline (**1**) on debromination. Hoping to improve the yield of this bromo compound a mixture of PBr_5 and P_2O_5 was employed in the cyclization step. When compound **3** was cyclized using this mixture and the resulting quaternary salts were reduced with $NaBH_4$ in MeOH four products were isolated. The mixture was separated by chromatography and the four products were designated as A, B, C, and D, respectively, in the order of their increasing polarity on TLC. (Compound C was found to be identical with the bromo compound obtained earlier during $POBr_3$ cyclization of **3**.) The *N*-formyl derivative **4** also under the same conditions of cyclization and reduction led to four products viz. E, F, G, and H. Some of the physical and spectral data of these compounds are given in Table I. Compounds B, D, F, and H were found to be identical with **7**, **8**, **9**, and **10**, respectively. Compounds A, C, E, and G gave **7**, **8**, **9**, and **10**, respectively, on reductive debromination.

Compounds A and C both analyzed well for the molecular formula $C_{21}H_{22}NO_4Br$ and this was confirmed by their mass spectra (M^+ at *m/e* 433 and 431). Their NMR spectra showed the presence of bromine in one of the two aromatic rings by showing signals for only three aromatic protons. The NMR spectrum in $CDCl_3$ (60 MHz) of compound A showed the following signals: δ 0.93 (3 H, d, J = 7 Hz, $CHCH_3$), 2.78–3.35 (5 H, m), 3.75 (2 H, bs, C_8H), 3.97 (6 H, s, $2OCH_3$), 6.08 (2 H, s, OCH_2O), 6.67 (1 H, s, ArH), 6.77 (1 H, s, ArH), 6.90 (1 H, s, ArH). The NMR spectrum of compound C in $CDCl_3$ (100 MHz) showed the following signals: δ 1.47 (3 H, d, J = 7 Hz, $CHCH_3$), 2.75–3.20 (5 H, m), 3.71 (1 H, d, J = 16 Hz, C_8H), 3.73 (1 H, s, $C_{13a}H$), 4.16 (1 H, d, J = 16 Hz, C_8H), 3.83 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 5.88 (2 H, s, OCH_2O), 6.52 (1 H, s, ArH), 6.69 (1 H, s, ArH), 6.76 (1 H, s, ArH). The chemical shift of the CCH_3 doublet[5] and the presence of a broad singlet in compound A and an AB quartet in compound C for the C_8-methylene protons[6] indicated the *trans*- and *cis*-quinolizidine geometry of compounds A and C, respectively. These assignments are supported by their TLC R_f values, rate of methiodide formation, and pK_a values (cf. ref 1).

The position of bromine in compounds A and C could be partially assigned from an inspection of their mass spectra. All 13-methyltetrahydroprotoberberines give rise to two intense characteristic fragments in their mass spectra arising out of a retro Diels–Alder type ring opening as shown.[7]

Thus compounds of the type **12** would give rise to ions **13** and **14**. Compounds A and C both exhibit prominent peaks at *m/e* 272, 270 and 162, which could be only due to ions **15** and **16**, indicating the presence of bromine in ring *A*.



Of the two possible positions 1 and 4 for bromine in ring *A* position 4 is preferred on stereochemical considerations and the most probable structure for compounds A and C could be represented by **17** and **18**. Compounds E and G, whose NMR and mass spectral data were similar to compounds A and C, were assigned structures **19** and **20**, respectively. X-ray crystallographic studies of these bromo compounds (which are in progress) will settle conclusively the position of bromine.

Experimental Section

Melting points are uncorrected. UV spectra were run on a Beckman DK2A spectrophotometer. EtOH (95%) solutions were used unless otherwise stated. IR spectra were run on a Perkin-Elmer Infracord and Model 421 IR spectrophotometers. Chemical shifts are quoted in ppm downfield from Me_4Si used as internal reference. Mass spectra are from a Varian Mat CH7 mass spectrometer. Elemental analyses were performed by Ciba-Geigy Research Centre, Bombay.

1-(2-Bromo-α-methyl-4,5-methylenedioxybenzyl)-2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (3). Anhydrous formic acid (3 g) was added to triethylamine (1.7 g) at 0 °C. To this mixture was added 1-(2-bromo-α-methyl-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline[2] (**5**) (3 g) and the mixture was refluxed at 145 °C for 2 h in an oil bath. The solution was cooled, poured into water, and extracted with chloroform. The $CHCl_3$ extract was washed with water, dried (Na_2SO_4), and distilled to yield a gum which was crystallized from ethyl acetate: 2.5 g; mp 205 °C; IR (KBr) 1670 cm^{-1} (CO); NMR ($CDCl_3$ + Me_2SO-d_6) δ 1.17, 1.28 (2d, 3 H, $CHCH_3$), 3.89 (s, 6 H, 2 OCH_3), 6.00 (s, 2 H, OCH_2O), 6.65–7.00 (m, 4 H, aromatic protons). Anal. Calcd for $C_{21}H_{22}NO_5Br$: C, 56.24; H, 4.91; N, 3.13. Found: C, 56.43; H, 5.02; N, 3.32.

1-(2-Bromo-α-methyl-4,5-methylenedioxybenzyl)-2-formyl-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline (4). This compound was prepared from 1-(2-bromo-α-methyl-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6,7-methylenedioxyisoquinoline[2] (**6**) by the procedure described above for compound **3**. It was crystallized from ethyl acetate: mp 195 °C; IR (Nujol) 1640 cm^{-1} (CO); mass spectrum *m/e* 229, 227, and 204. Anal. Calcd for $C_{20}H_{18}NO_5Br$: C, 55.55; H, 4.17; N, 3.24. Found: C, 55.81; H, 4.50; N, 3.30.

Cyclization of 3 Using a Mixture of PBr_5 and P_2O_5. To a solution of the *N*-formyl derivative **3** (2 g) in dry benzene (150 mL) was added PBr_5 (3 g) and P_2O_5 (6 g) and the mixture was shaken and left aside at room temperature overnight. It was then refluxed for 10 min and cooled. *n*-Hexane (100 mL) was added and after shaking and leaving for some time the clear supernatant liquid was decanted. The residue was dissolved in cold methanol (150 mL) and neutralized with aqueous sodium hydroxide solution (40%). $NaBH_4$ (1 g) was added in small portions. After 2 h the solvent was removed and the residue was treated with water (100 mL). The aqueous solution was then extracted with $CHCl_3$; the $CHCl_3$ extract was washed with water, dried (Na_2SO_4), and evaporated. The crude product was chromatographed over silica gel (30 g) and eluted with benzene. Fractions (20 mL) were collected and monitored by TLC on silica gel plates using $CHCl_3$/

MeOH/EtOAc (40:1:2.5) as the solvent system and the following compounds were isolated.

1. 4-Bromo-13β-methyl-13aαH-tetrahydropseudoepiberberine (17). Fractions 3–7 were combined and evaporated and the solid obtained was crystallized from benzene–hexane to yield pale yellow needles: 30 mg; mp 146 °C; IR (KBr) 2900–2750 cm^{-1} (Bohlmann bands); UV (EtOH) 288 nm (log ε 3.88); NMR data as given in the discussion; mass spectrum *m/e* 433 and 431 (M^+), 272, 270 and 162. Anal. Calcd for $C_{21}H_{22}NO_4Br$: C, 59.55; H, 5.08; N, 3.23. Found: C, 59.42; H, 5.05; N, 3.27.

2. 13β-Methyl-13aαH-tetrahydropseudoepiberberine (7). Fractions 9–16 were combined and evaporated to yield a solid which was crystallized from benzene as yellow needles: 300 mg; mp 197–198 °C; found to be identical (IR, mp, mmp, and spectra) with an authentic sample prepared as reported.[1]

3. 4-Bromo-13α-methyl-13aαH-tetrahydropseudoepiberberine (18). Fractions 20–30 were combined and evaporated to give a yellow residue. This was crystallized from benzene–hexane as yellow needles: 420 mg; mp 160 °C; UV (EtOH) 288 nm (log ε 3.88); NMR data as given in the discussion; mass spectrum *m/e* 433 and 431 (M^+), 272, 270, and 162. Anal. Calcd for $C_{21}H_{22}NO_4Br$: C, 59.55; H, 5.08; N, 3.23. Found: C, 59.34; H, 5.35; N, 3.22.

4. 13-α-Methyl-13aαH-tetrahydropseudoepiberberine (8). Fractions 31–34 gave a compound which was crystallized from benzene as colorless crystals: 60 mg; mp 132 °C; found to be identical with an authentic sample.[1]

Cyclization of 4 Using PBr_5 and P_2O_5. The *N*-formyl derivative **4** was cyclized as described above and the products were separated by chromatography.

1. 4-Bromo-13β-methyl-13aαH-tetrahydropseudocoptisine (19). Fractions 4–8 were combined and evaporated to give a colorless solid which was crystallized from benzene as colorless crystals: 55 mg; mp 205–206 °C; IR (Nujol) 2800–2700 cm^{-1} (Bohlmann bands); UV (EtOH) 292 nm (log ε 4.00); NMR ($CDCl_3$) δ 0.93 (d, 3 H, J = 7 Hz, $CHCH_3$), 2.20–4.20 (8 H), 5.93 (s, 2 H, OCH_2O), 6.05 (s, 2 H, OCH_2O), 6.57, 6.67, 6.70 (3s, 3 H, aromatic protons); mass spectrum, *m/e* 417, 415 (M^+), 256, 254, and 162. Anal. Calcd for $C_{20}H_{18}NO_4Br$: C, 57.70; H, 4.33; N, 3.36. Found: C, 57.81; H, 4.30; N, 3.36.

2. 13β-Methyl-13aαH-tetrahydropseudocoptisine (9). Fractions 10–16 were combined and crystallized from benzene as pale yellow crystals: 380 mg; mp 195 °C; identical with an authentic sample.[3]

3. 4-Bromo-13α-methyl-13aαH-tetrahydropseudocoptisine (20). Fractions 18–27 when combined and evaporated gave a yellow solid which was crystallized from benzene–hexane as yellow crystals: 400 mg; mp 179 °C; UV (EtOH) 291 nm (log ε 3.98); NMR ($CDCl_3$) δ 1.43 (d, 3 H, J = 7 Hz, $CHCH_3$), 2.57–3.00 (4 H), 3.30–4.35 (4 H), 5.92 (s, 2 H, OCH_2O), 6.01 (s, 2 H, OCH_2O), 6.52 (1 H, aromatic proton), 6.73 (s, 2 H, aromatic protons); mass spectrum *m/e* 417, 415 (M^+), 256, 254, and 162. Anal. Calcd for $C_{20}H_{18}NO_4Br$: C, 57.69; H, 4.33; N, 3.37. Found: C, 57.40; H, 4.30; N, 3.64.

4. 13α-Methyl-13aαH-tetrahydropseudocoptisine (10). Fractions 30–35 gave a compound which was crystallized from benzene–hexane as colorless needles: 75 mg; mp 131 °C. This compound was identical with an authentic synthetic sample.[3]

Catalytic Debromination of 17, 18, 19, and 20. The bromo compounds (250 mg each) were dissolved in methanol (75 mL) and Pd-C (10%, 150 mg) was added to the solution and hydrogenated at room temperature in a paar reduction apparatus for 5 h. The catalyst was then filtered off, the solution was neutralized with dilute NH_4OH solution, and the methanol was distilled off. The residue was then extracted with $CHCl_3$, and the $CHCl_3$ layer was washed with water, dried (Na_2SO_4), and evaporated. The solid residue was crystallized. Thus compounds **17**, **18**, **19**, and **20** gave **7**, **8**, **9**, and **10**, respectively.

Acknowledgment. We are grateful to Dr. K. Nagarajan for his interest and helpful criticisms. S.N. and H.S. thank the C.S.I.R. (India) for a Pool Officership and Postdoctoral Fellowship. R.R. thanks the Government of Tamil Nadu, India for deputation to do research. G.M. thanks the Professor T. R. Govindachari 30th Birthday Commemmoration Committee for financial assistance. The authors thank Dr. R. S. Grewal (Director) and Dr. S. Selvavinayakam, Ciba-Geigy Research Centre, Bombay for spectral and analytical data.

Registry No.—**3**, 65366-54-3; **4**, 65366-55-4; **5**, 65366-56-5; **6**, 65366-57-6; PBr_5, 7789-69-7; P_2O_5, 1314-56-3.

References and Notes

(1) M. Shamma, C. D. Jones, and J. A. Weiss, *Tetrahedron*, **25**, 4347 (1969).
(2) S. Natarajan, B. R. Pai, R. Rajaraman, C. S. Swaminathan, K. Nagarajan, V. Sudarsanam, D. Rogers, and A. Quick, *Tetrahedron Lett.*, 3573 (1975); S. Natarajan, B. R. Pai, R. Rajaraman, H. Suguna, C. S. Swaminathan, K. Nagarajan, and V. Sudarsanam, *J. Chem. Soc., Perkin Trans. 1*, submitted.
(3) T. R. Govindachari, K. Nagarajan, S. Natarajan, and B. R. Pai, *Indian J. Chem.*, **9**, 1313 (1971).
(4) $POBr_3$ was prepared as reported in "Inorganic Synthesis", Vol II, C. Firnelius, Ed., McGraw-Hill New York, N.Y., 1946, p. 151. $POBr_3$ was used earlier successfully for the synthesis of some 9,10-substituted tetrahydroprotoberberines in this laboratory—Cf. R. Rajaraman, B. R. Pai, M. S. Premila and H. Suguna, *Indian J. Chem.*, **15B**, 878 (1977).
(5) C.-K. Yu, D. B. MacLean, R. G. A. Rodrigo, and R. H. F. Manske, *Can. J. Chem.*, **48**, 3673 (1970); T. R. Govindachari, K. Nagarajan, R. Charubala, B. R. Pai, and P. S. Subramanain, *Indian J. Chem.*, **8**, 769 (1970).
(6) M. Cushman, J. Gentry, and F. W. Dekow, *J. Org. Chem.*, **42**, 1111 (1977). The authors thank the referee for bringing this recent article to their notice.
(7) M. Ohashi, J. M. Wilson, H. Budzikiewicz, M. Shamma, W. A. Slusarchyk, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 2807 (1963).

Studies in Protoberberine Alkaloids. 15. Some Aspects on the Rate of Methiodide Formation in Protoberberine Chemistry

Bantwal R. Pai,* Sankaran Natarajan, Hosbett Suguna, and Govindarajan Manikumar

Department of Chemistry, Presidency College, Madras-5, India

Received August 26, 1977

The rates of methiodide formation of several synthetic tetrahydroprotoberberines and some 13-methyltetrahydroprotoberberines have been determined. The effect of the substitution pattern and the geometry of fusion of the **B/C** ring system on the rate constants of the compounds studied is briefly discussed. It is also observed that alkaloids having free phenolic hydroxyl groups have larger reaction rates when compared to their O-alkyl derivatives.

Two important methods being used at present to assign conformation to quinolizidine and indolizidine systems are a study of their NMR spectra[1] and determination of their rate of quaternization with methyl iodide.[2] In the course of our work on protoberberine alkaloids we had prepared a large number of synthetic tetrahydroprotoberberines and a few 13-methyltetrahydroprotoberberines. We established the structures and stereochemistry of these compounds on the basis of their IR, NMR, and mass spectral data. Thus a variety of substrates of known stereochemistry were readily available to us and we thought it worthwhile to study their rate of quaternization with a view to study the limitations of this

0022-3263/78/1943-1994$01.00/0

Table I

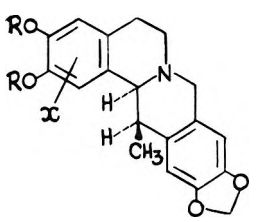
	trans-Quinolizidines				*cis*-Quinolizidines			
	1a[b]	**3a**[c]	**1b**[d]	**3b**[e]	**2a**[f]	**4a**[g]	**2b**[h]	**4b**[i]
$k \times 10^4$ s^{-1} 31.5 °C	1.3 (1.3)[a]	6.4	1.2	9.5	99.62 (341)[a]	98.70	60.32	69.07

[a] Rate constants reported by Shamma et al.[2] for these compounds determined at 25 °C. [b] Registry no. 24306-61-4. [c] Registry no. 65391-28-8. [d] Registry no. 65494-22-6. [e] Registry no. 65442-06-0. [f] Registry no. 24314-69-0. [g] Registry no. 65391-29-9. [h] Registry no. 65442-05-9. [i] Registry no. 65494-23-7.

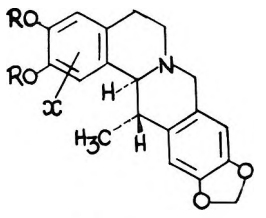
method if any which have not been commented upon by earlier workers. Our observations of the *cis*- and *trans*-quinolizidines of the 13-methyltetrahydroprotoberberines are in general agreement with the earlier findings of Shamma et al.[2] However, we noticed certain aspects which we feel are important and should be taken into consideration in the interpretation of the results of rate of quaternization.

Table I gives the rate constants for the methiodide formation of four 13-methyltetrahydroprotoberberines[2,3] (**1a, 2a, 3a,** and **4a**) and their corresponding bromo derivatives[4] (**1b, 2b, 3b,** and **4b**). It is clear that the *cis*-quinolizidine compounds react at a much faster rate than their corresponding trans compounds. The value of k for the trans compound studied (**1a**) does not change significantly with temperature and the most likely conformation is that represented by A. The cis compound can exist in conformations B and C[5] and is perhaps an equilibrium mixture in solution. At lower temperatures C is expected to be in preponderance, where the lone pair on nitrogen is sterically not hindered, while at higher temperatures the major conformation perhaps has to move to B where the axial methyl group comes in proximity to the nitrogen lone pair and thus makes the rate of quaternization slower. This is evident from the rate constants of **2a** at two different temperatures.

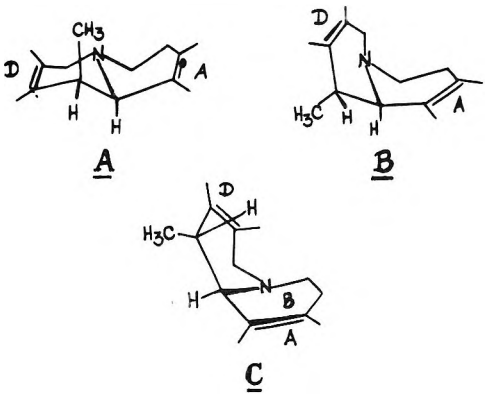
It is also noted from Table I that for the *trans*-quinolizidine compounds the rate constants do not change much when there is a bromine atom present in ring **A** (compare the rates of **1a** and **3a** with those of **1b** and **3b**). However, there is an appreciable decrease in the rate of methiodide formation of the *cis*-quinolizidine compounds as is evident when the rate constants of **2a** and **4a** are compared with those of **2b** and **4b.** In these bromo compounds the position of bromine is not yet settled between the two possibilities of 1 and 4. Bromine in position 1 in the case of cis compounds may cause distortion in the geometry to produce more hindrance to the nucleophilic nitrogen resulting in the rate being decreased.



1a R=CH$_3$; X=H
1b R=CH$_3$; X=Br
3a RR=CH$_2$; X=H
3b RR=CH$_2$; X=Br



2a R=CH$_3$; X=H
2b R=CH$_3$; X=Br
4a RR=CH$_2$; X=H
4b RR=CH$_2$; X=Br



A **B** **C**

The kinetic data on the quaternization of the tetrahydroprotoberberines **5, 6, 7, 8, 9,** and **10** are presented in Table II. All these compounds have relatively lower reaction rates comparable to the *trans*-quinolizidine conformers of the 13-methyl series. Hence in accordance with the general view all these compounds may be said to exist in solution with their **B/C** rings in trans fusion. The rate of quaternization of the tertiary nitrogen in these compounds would depend upon the

Table II

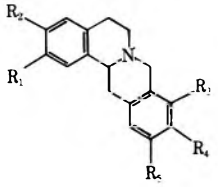
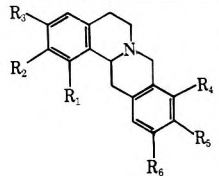
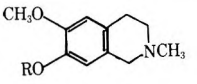
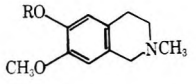
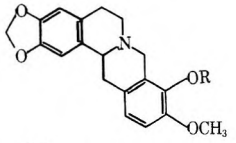
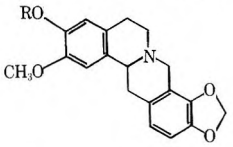
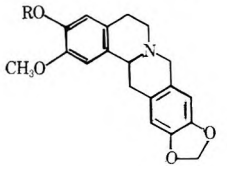
(±)-Compound		Registry No.	Substituents R$_1$	R$_2$	R$_3$	R$_4$	R$_5$	$k \times 10^4$ s^{-1} at 31.5 °C
	**(5)**	53898-94-5	OCH_3	OCH_3	H	OCH_2O		17.9
	(6)	38853-67-7	OCH_3	OCH_3	OCH_2O		H	7.2
	(7)	36295-42-8	OCH_2O		H	OCH_2O		10.67
	(8)	4312-32-7	OCH_2O		OCH_2O		H	7.34
	(9)	28319-96-4	OCH_2O		H	OCH_3	OCH_3	21.11
	(10)	29074-38-2	OCH_2O		OCH_3	OCH_3	H	18.69

Table III

(±)-Compound		Registry no.	Substituents R$_1$	R$_2$	R$_3$	R$_4$	R$_5$	R$_6$	$k \times 10^4$ s^{-1} at 31.5 °C
	**(11)**	17383-17-9	H	OCH_2O		OH	OCH_3	H	29.52
	(12)	7762-76-7	H	OCH_3	OCH_3	OH	OCH_3	H	32.00
	(13)	60229-61-0	H	OCH_3	OH	H	OCH_2O		40.30
	(14)	33746-81-5	OH	OCH_3	H	H	OCH_3	OCH_3	44.00
	(15)		OH	OCH_3	OCH_3	OCH_3	OCH_3	H	(78.00)[a]
	(16)		OH	OCH_3	OCH_3	OCH_3	OH	H	(85.00)[a]

[a] Rate constants reported by Shamma et al.[2] for these compounds.

Table IV

Compd	R	Registry no.	$k \times 10^4$ s^{-1} at 31.5 °C
	H	450-14-6	172.7
	CH_2Ph	15778-79-7	67.2
	H	13871-59-5	216.4
	CH_2Ph	56633-08-0	61.4
	H		29.5
	CH_3		18.7
	H	41431-80-5	14.0
	CH_3		7.2
	H		40.3
	CH_3		18.0

basicity also. So the effect of substitution pattern on the basicity of nitrogen becomes another important factor, besides stereochemical considerations of the different conformations. Here it must be borne in mind however that the stereochemistry by itself can influence the basicity. Table II indicates a trend toward faster rates for the 10,11-substituted compounds, compared to those of the corresponding 9,10-substituted ones as is revealed by the comparison of the pairs **5–6, 7–8,** and **9–10.** It is to be noted that all these compounds are likely to have trans conformation and the differences in their rates are only due to the varying substitution pattern.

In Table III are given the rates of quaternization of a few tetrahydroprotoberberines (**11, 12, 13,** and **14**) which contain a phenolic group. All four compounds have faster rates of quaternization than those compounds in Table II. Their rate constants, particularly of compounds **13** and (±)-caseadine (**14**), approach more toward the values that would be expected for the *cis*-quinolizidines of the 13-methyl series.

Shamma and co-workers[2] reported that the higher rates of quaternization of capaurine (**15**) and capaurimine (**16**) were indicative of the predominance of *cis*-quinolizidine conformations and this was borne out by x-ray crystallographic studies.[6] However, a scrutiny of Table IV (which gives the kinetic data for some phenolic bases and their corresponding *O*-alkylated compounds) indicates that the rate of quaternization is considerably enhanced by the presence of free phenolic hydroxyl groups. The tetrahydroprotoberberines listed therein have the stable trans configuration (cf. Shamma[7]). The nature of the substituents, whether they are free phenolic or *O*-alkylated, will not alter the stereochemistry of **B/C** ring fusion. So, the difference in the rate for this set of compounds can be ascribed only to the presence or absence of a phenolic substituent. Hence, in our view the rates of quaternization have to be used with caution to assign conformation in the quinolizidine and indolizidine systems having free phenolic groups.

Acknowledgment. We are most grateful to Professor Maurice Shamma for helpful criticism and inspiration for this work. We extend our thanks to Dr. K. Nagarajan for his interest in this work. S. N. and H. S. thank the C.S.I.R. (India) for a Pool Officership and a Postdoctoral Fellowship. G. M. thanks the "Professor T. R. Govindachari 60th Birthday Commemmoration Committee" for financial assistance.

References and Notes

(1) C.-K. Yu, D. B. MacLean, R. G. A. Rodrigo, and R. H. F. Manske, *Can. J. Chem.*, **48,** 3673 (1970); T. R. Govindachari, K. Nagarajan, R. Charubala, B. R. Pai, and P. S. Subramanian, *Indian J. Chem.*, **8,** 769 (1970); M. Cushman, J. Gentry, and F. W. Dekow, *J. Org. Chem.*, **42,** 1111 (1977); M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Am. Chem. Soc.*, **86,** 3364 (1964).
(2) M. Shamma, C. D. Jones, and J. A. Weiss, *Tetrahedron*, **25,** 4347 (1969).
(3) T. R. Govindachari, K. Nagarajan, S. Natarajan, and B. R. Pai, *Indian J. Chem.*, **9,** 1313 (1971).
(4) B. R. Pai, S. Natarajan, G. Manikumar, R. Rajaraman, and H. Suguna, *J. Org. Chem.*, preceding paper in this issue.
(5) P. W. Jeffs, *Experientia*, **21,** 690 (1965).
(6) T. Kametani, M. Ihara, T. Honda, H. Shimanouchi, and Y. Sasada, *J. Chem. Soc. C*, 2541 (1971).
(7) M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, N.Y., 1972, pp 293–295.

Unusual Regioselectivity in the Di-π-methane Rearrangement. Inhibition and Control by Electron-Donating Substituents. Mechanistic and Exploratory Photochemistry[1,2]

Howard E. Zimmerman* and William T. Gruenbaum

Chemistry Department, University of Wisconsin, Madison, Wisconsin 53706

Received October 17, 1977

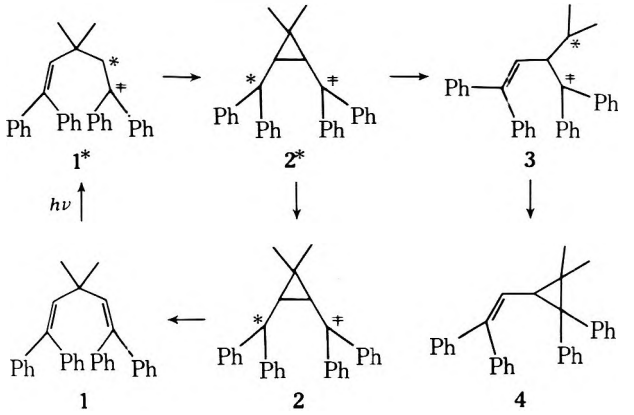
1,1-Bis(*p*-methoxyphenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene and 3,3-dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)-1,4-pentadiene were synthesized and their photochemistry was studied. The excited singlets underwent the di-π-methane rearrangement, while the triplets proved unreactive. In the case of the dianisyl diene unusual regioselectivity was observed in which 2,2-dimethyl-1,1-diphenyl-3-[2,2-bis(*p*-methoxyphenyl)vinyl]cyclopropane predominated 3.3:1 over 1,1-bis(*p*-methoxyphenyl)-2,2-dimethyl-3-(2,2-diphenylvinyl)cyclopropane. This suggests that ionic factors may dominate over odd-electron stabilization in control of regioselectivity in the di-π-methane rearrangement. The reaction quantum yield was determined to be $\phi = 0.097$ for the dianisyl diene and $\phi = 0.044$ for the tetraanisyl diene. The rates of excited singlet rearrangement and decay to ground state were determined. Markedly lower rates of rearrangement were encountered for the anisyl systems compared with the parent 1,1,5,5-tetraphenyl-3,3-dimethyl-1,4-pentadiene. Additionally, the photochemistry of 1,1-bis(*p*-*N*,*N*-dimethylaminophenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene was explored. Here the vinylcyclopropane with the vinyl group bearing the dimethylaminophenyl groups proved to be the exclusive product, again suggesting ionic control of the reaction regioselectivity.

Eleven years ago we reported the occurrence of a general photochemical rearrangement of systems in which an sp^3-hybridized carbon bears two π moieties; we termed this the di-π-methane rearrangement. We proposed the general mechanistic sequence depicted in Scheme I.[3,4] In the intervening years, our investigations of the reaction mechanism have included stereochemistry,[5,6] multiplicity,[5a,6,8] excited-state reaction-rate measurement[6,9] and reaction regioselectivity.[6,9a,10] Our efforts and those of the literature[6] have been pleasingly consonant with the mechanism proposed.

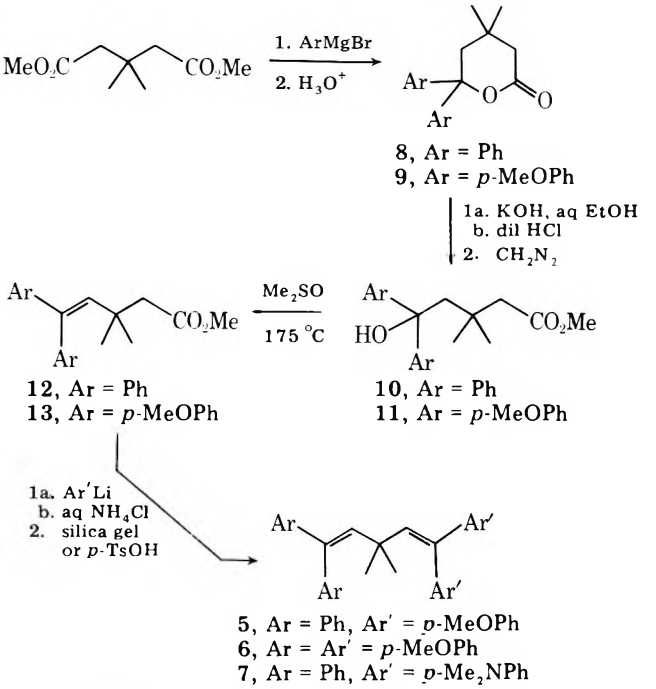
In this mechanism, the asterisk and double dagger of Scheme I have been depicted as odd electrons and the diradical character of the reacting species was emphasized. Nevertheless, despite the success of this picture, it was deemed of interest to determine if there was appreciable ionic character observable in the reaction. Thus, the photochemistry of 1,1-bis(*p*-methoxyphenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene (**5**), 3,3-dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)-1,4 pentadiene (**6**), and 1,1-bis(*p*-*N*,*N*-dimethylaminophenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene (**7**) was examined.

Synthesis of Photochemical Reactants. The syntheses of 1,1-bis(*p*-methoxyphenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene (**5**), 3,3-dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)-1,4-pentadiene (**6**), and 1,1-bis(*p*-*N*,*N*-dimethylaminophenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene (**7**) were carried out as delineated in Scheme II and described in the Experimental Section. Treatment of methyl and ethyl 3,3-dimethylglutarate with aryllithium and Grignard reagents did not lead to 1,5-diol precursors of the dienes of interest; rather, the diaryl δ-lactones **8** and **9** resulted. Thus, the sequence utilizing the Me_2SO elimination[11] of the δ-hydroxy esters **10** and **11** proved both convenient and necessary.

Scheme I. Resonance Version of the Di-π-methane Rearrangement



Scheme II. Syntheses of *p*-Methoxy and *p*-*N*,*N*-Dimethylamino Substituted Dienes



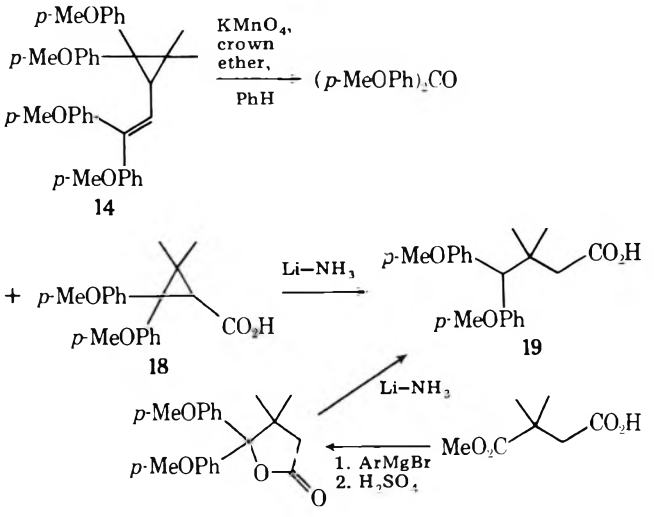
Results

Exploratory Photolyses. The exploratory runs were made both in benzene and *tert*-butyl alcohol solvent using a 450-W medium-pressure lamp, immersion well, and Pyrex filter. Each of the three dienes—the dianisyl diene **5**, the tetraanisyl diene **6**, and the bis(dimethylaminophenyl) diene **7**—led nicely to photochemical products with irradiations up to ~40% conversion. Beyond this, secondary photochemistry was encountered.

From the tetraanisyl diene **6**, a single photoproduct resulted. Typically, irradiation of 265 mg of tetraanisyl diene

0022-3263/78/1943-1997$01.00/0

Scheme III. Structure Elucidation of Tetraanisyl Photoproduct 14



6 afforded 81 mg of photoproduct **14**, mp 149–150 °C, along with 125 mg of recovered diene reactant.

In the case of dianisyl diene **5** two photoproducts were isolated by column chromatography. In a typical run, irradiation of 780 mg of dianisyl diene **5** led to 257 mg of photoproduct **15** and 77 mg of photoproduct **16**, together with 297 mg of recovered reactant. The ratio of major to minor photoproduct thus proved to be 3.3:1, a value not far from that observed in quantum yield runs made to much lower conversion (vide infra).

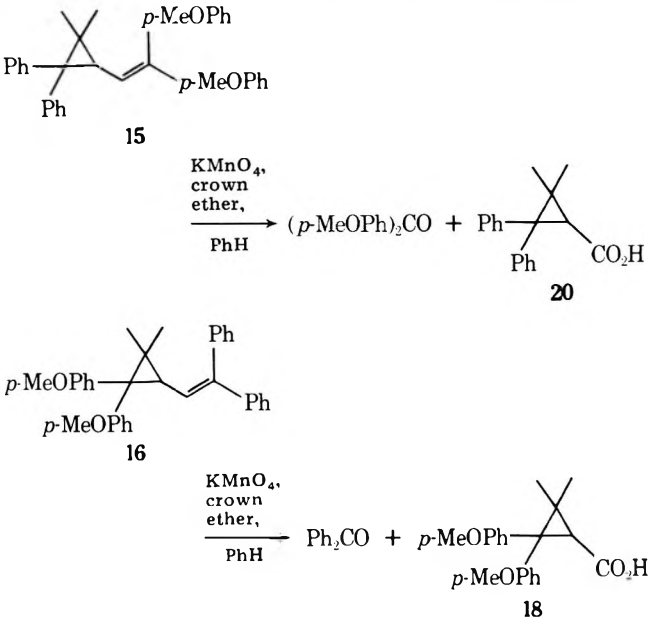
Finally, photolysis of 47 mg of bis(dimethylaminophenyl) diene **7** to complete conversion afforded 21 mg of a single photoproduct (**17**).

Elucidation of Photoproduct Structures. In the case of photoproduct **14**, derived from tetraanisyl diene **6**, a vinylcyclopropane structure (note **14** in Scheme III) was strongly suggested by the NMR spectrum. Thus an AB quartet, corresponding to the τ 4.57 vinyl and the τ 7.99 cyclopropyl methine, was observed. This is closely analogous to the NMR situation observed for similar vinylcyclopropanes.[8a,10b] Also, there were observed two three-hydrogen singlets ascribed to nonequivalent methyl groups, two three-hydrogen singlets and one six-hydrogen singlet corresponding to the four methoxy groups, and also aromatic absorption. These NMR features supported the structural assignment, but unambiguous proof was desired. This was obtained by Sam–Simmons[12] "purple benzene" oxidation of photoproduct **14** (note Scheme III) to give 4,4′-dimethoxybenzophenone and 2,2-bis(*p*-methoxyphenyl)-3,3-dimethylcyclopropanecarboxylic acid (**18**), whose structure was suggested by its NMR spectrum and confirmed by lithium–ammonia degradation to 4,4-bis(*p*-methoxyphenyl)-3,3-dimethylbutanoic acid (**19**) as depicted in Scheme III. The structure of the latter compound was established by independent synthesis (note Scheme III again).

Turning now to the photoproducts obtained from dianisyl diene **5**, we again noted the characteristic AB quartet, two nonequivalent methyls, two nonequivalent methoxy groups, and aromatic hydrogens for each photoproduct. The major photoproduct exhibited its vinyl hydrogen absorption at τ 4.52, which was remarkably close to the τ 4.57 shift for the tetraanisylvinylcyclopropane **14**. In the case of the minor photoproduct, the vinyl absorption at τ 4.30 was strongly reminiscent of the τ 4.25 vinyl peak in the NMR spectrum of the known 2,2-dimethyl-1,1-diphenyl-3-(2,2-diphenylvinyl)cyclopropane (**4**).[8a]

The upfield shift expected for a vinyl hydrogen β to an electron donor suggested that the major photoproduct contained a dianisylvinyl moiety, while the minor photoproduct had a diphenylvinyl group. The degradative scheme using "purple benzene"[12] oxidation was again employed in each case. The major photoproduct **15** afforded 4,4′-dimethoxybenzophenone and 3,3-dimethyl-2,2-diphenylcyclopropanecarboxylic acid (**20**)[8a] as shown in Scheme IV. The minor photoproduct **16** led to benzophenone and 2,2-bis(*p*-methoxyphenyl)-3,3-dimethylcyclopropanecarboxylic acid (**18**). This, too, is shown in Scheme IV.

Scheme IV. Degradation of Dianisyl Diene Photoproducts



Finally, the single photoproduct **17** derived from irradiation of the bis(dimethylaminophenyl) diene **7** revealed an NMR spectrum showing the typical AB quartet, the nonequivalent pair of methyl groups, and aromatic absorption. Also, there were observed two six-hydrogen singlets ascribed to the four *N*-methyl groups. Additionally, the vinyl portion of the AB quartet was centered at τ 4.73, still further upfield from that observed in the anisyl-substituted vinyl groups, indicating the presence of the electron-donating dimethylaminophenyl groups on the double bond. These data lead us then to 2,2-dimethyl-1,1-diphenyl-3-[2,2-bis(*p*-*N*,*N*-dimethylaminophenyl)vinyl]cyclopropane (**17**).

Quantum Yield Determinations. These determinations were made both on the black box apparatus and the semimicrooptical bench described by us earlier.[13,14] In using the former, filter solutions were employed giving 272- and 310-nm light with band widths of 50 nm baseline to baseline; ferrioxalate actinometer was employed.[15] Details are given in the Experimental Section. The usual precautions were taken as previously described[16] for quantum yield determinations. Assay of product was by isolation with gravimetric determination or by high-speed liquid chromatography. The results of direct irradiations are summarized in Table I.

Sensitized runs were made with acetophenone and with benzophenone. In the benzophenone runs benzhydrol was also added, since to the extent that energy transfer was occurring, benzopinacol formation would be inhibited relative to runs omitting the di-π-methane reactant. In these runs, quenching of the benzophenone–benzhydrol reaction was observed and yet no reaction of the diene occurred. It can thus be concluded that despite energy transfer to the di-π-methane dienes, no rearrangement of triplet occurs. These runs are also included in Table I.

Emission Measurements and Single Photon Counting Determination of Excited-State Rate Constants. With the quantum yields in hand, we turned our attention toward a

Table I

Reactants (M)	λ_{irrad}, nm	Φ_r	% conversion
5 (0.000 25)	285	0.085,[a] 0.025[b]	5.6
5 (0.000 87)	272	0.070,[a] 0.023[b]	8.8
5 (0.001 49)	310	0.071,[a] 0.017[b]	6.0
5 (0.000 813), $PhCOCH_3$ (0.309)	331	<0.004[c]	0
6 (0.001 23)	272	0.040[d]	3.3
6 (0.001 53)	310	0.042[d]	6.7
6 (0.001 80)	310	0.051[d]	3.4
6 (0.000 705), Ph_2CO (0.0449)	345	0.002[c]	0
7 (0.000 92)	310	<0.0054[c]	0
7 (0.000 493)	310	0.0027[e]	9.2
Ph_2CO (0.0110), Ph_2CHOH (0.005 45)	345	0.123[f]	24.0
Ph_2CO (0.0110), Ph_2CHOH (0.005 45), **5** (0.000 545)	345	0.031[f]	8.0
Ph_2CO (0.0110), Ph_2CHOH (0.005 45), **6** (0.000 400)	345	0.039[f]	18.0

[a] Formation of dianisylvinyl product **15**. [b] Formation of diphenylvinyl product **16**. [c] Limit of detection. [d] Formation of tetraanisyl product **14**. [e] Formation of bis(dimethylaminophenylvinyl) product **17**. [f] Formation of benzopinacol.

Table II. Results of Emission and Single-Photon Counting Studies

Compd	λ_{em},[a] nm	M	k_{dt}^{77}, s^{-1}	τ^{77}, ns	k_{dt}^{RT}, s^{-1}	τ^{RT}, ps	k_r^{RT}, s^{-1}
Dianisyl diene **5**	330	95	3.7×10^8	2.7	3.5×10^{10}	28	3.4×10^9
Tetraanisyl diene **6**	335	75	5.2×10^8	1.9	3.9×10^{10}	25	1.7×10^9
Dimethylaminophenyl diene **7**	360	70	2.9×10^8	3.5	2.0×10^{10}	50	5.4×10^7
1,1-Dianisylethylene **21**	325	77	2.26×10^8	4.4	1.7×10^{10}	57	
1,1,5,5-Tetraphenyl-3,3-dimethyl-1,4-pentadiene **26**[b]	310	225	8.1×10^9	0.12	1.8×10^{12}	0.55	1.4×10^{11}

[a] λ_{em} refers to wavelength of maximum emission in nanometers. [b] Reference 9b.

more meaningful measure of molecular reactivity, namely the rates with which the excited states rearrange.

It was first necessary to inspect the fluorescence behavior of the di-π-methane diene reactants. 1,1-Dianisylethylene (**21**) was included for comparison. The compounds under study showed similar absorption and emission spectra. The emission was typically diarylvinyl-like with little difference between the dienes and the monoethylenic models. Note Table II. The small shift in wavelength between absorption and emission curves, along with the overlap of these showing a common 0–0 energy difference, indicated emission from S_1 and absence of emission from exciplexed species of either the inter- or intramolecular varieties.

It was important to ascertain that no self-quenching of excited singlets was occurring under experimental conditions. The case of the bis(dimethylaminophenyl) diene **7** was most critical, since its photochemical reactivity was lowest (vide supra). At very low concentration, fluorescence intensity is linear with concentration and deviations due to self-quenching are readily detected. However, in the medium concentration range, we have noted[16,17] that fluorescence emitted mid-cell at 90° increases with concentration until a maximum intensity is obtained at a 0.87 absorbance, whereupon the intensity diminishes. A complex function of concentration is obtained[16] as given in the equation

$$I_f = KI_0\phi_f A \times 10^{-(A/2)} \quad (1a)$$

where A is the absorbance, I_f is the fluorescence intensity at 90° through a slit placed midway along the cell depth, ϕ_f is the fluorescence efficiency, I_0 is the light intensity, and K is an instrumental constant. While our previous study[16] utilized a complete plot of this function to test lack of self-quenching, a convenient two-point test is provided by the equation

$$A_1 10^{-A_1/2} = A_2 10^{-A_2/2} \quad (1b)$$

Here we select as A_1 the optical density used for the single-photon counting studies. One then solves eq 1b for A_2 and determines if a solution of this absorbance really does emit with the same intensity as that with absorbance A_1. This test applied to the diene of present interest showed absence of self-quenching.

With static emission information in hand, we were able to turn our attention to single-photon counting measurements. The primary data derivable are the rate of excited singlet decay (i.e., k_{dt}) and the corresponding excited singlet lifetimes (i.e., $\tau = 1/k_{dt}$). The method used has been described by us previously[9b] and is detailed as necessary in the Experimental Section.

As has been observed in a number of instances in the past, the room-temperature decay rates proved too rapid, especially in the case of the methoxy dienes, to measure directly at room temperature. As before[9b] it was observed that the decay rates decreased dramatically with decrease in temperature and were quite measureable at 77 K. These rates are summarized in Table II.

Previously we have noted that the ratio of fluorescence intensities at two temperatures gives the inverse of the ratio of the two rates of decay; note the equation

$$k_{dt}^{RT}/k_{dt}^{77} = I_f^{77}/I_f^{RT} = M \quad (2)$$

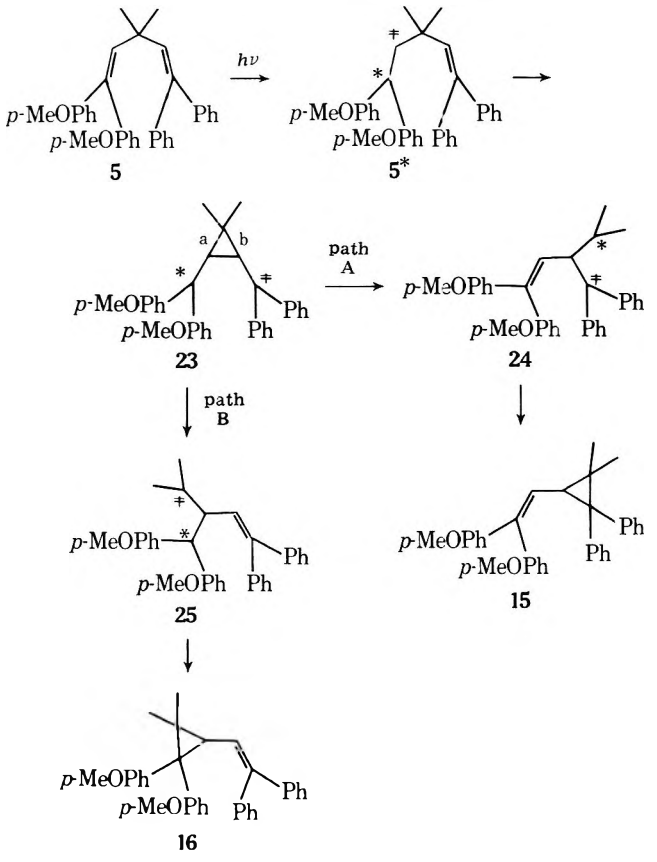
We should note that eq 2 is derived[9b] with the assumption that the rate of fluorescence k_f is temperature independent. While this cannot be taken to be invariably the case, it has proven[9b,17] valid for systems of the type presently under study. The ratio in eq 2, termed[9b] the magic multiplier M, is obtained experimentally from the ratio of fluorescence intensities at the two temperatures.

With M available and with the low-temperature decay rates measureable, one can thus calculate the very rapid room-temperature rates of decay (i.e., the k_{dt}^{RT}'s). Both the M's and the k_{dt}^{RT}'s are included in Table II.

Interpretative Discussion

The first observation to be made is that the di-π-methane rearrangement proceeds to afford the usual vinylcyclopropane

Scheme V. Mechanism of the Reaction



type product and does this via the singlet excited state as expected[8] for acyclic systems.

Unexpected and striking is the regioselectivity encountered. With the usual formulation, where the free valences in the cyclopropyldicarbinyl species 2 (note Scheme I) are represented as odd-electron centers, one would have anticipated a preference for path B in Scheme V rather than the observed path A, since *p*-methoxyphenyl is known[18,19] to stabilize odd-electron centers in excited states better than phenyl and *p*-*N*,*N*-dimethylaminophenyl would be expected to behave similarly. We have noted,[8c,9b] however, that the S_1 excited state consists heavily of ionic terms of the type $\chi_1^{\alpha}(i)\chi_1^{\beta}(j)$, where the χ's refer to atomic orbitals of the system, i and j are two electrons, and α and β refer to the electron spin.[20-22] Thus S_1 states are likely to be quite polarizable; and the dot–dot representation of the excited states, while convenient, should not be construed to exclude polarization.

Also, we need to recognize that the qualitative resonance picture (e.g., note Scheme V) used conveniently is not inconsistent with the Möbius cyclic orbital array **22** (Figure 1), which we have used previously[8a] to rationalize the reaction stereochemistry and photochemical allowedness. Thus, the resonance picture in Scheme V merely dissects the two main mechanistic processes of the rearrangement, namely vinyl–vinyl bridging and accompanying three-ring reopening, for convenience in presentation and to allow consideration in traditional organic terms.

At this point there are two experimental observations which are particularly striking and deserve discussion. One is the rate inhibition by anisyl and dimethylaminophenyl substitution (note Table II) and the other is the regioselectivity encountered wherein electron-donating aryl groups preferentially appear on the double bond of the photoproduct.

In our previous studies[9b,10b] we have suggested that π–π bridging is rate limiting. We have also suggested that one significant mode of S_1 decay derives from such bridging, followed by internal conversion of the cyclopropyldicarbinyl diradical (here 2*) to its ground-state counterpart (i.e., 2), which then reverts to diene reactant 1 by Grob fragmentation. Inspection of Table II reveals that for the presently studied molecules k_{dt}, the total rate of singlet decay, is not appreciably more rapid than that of an isolated dianisylethylene excited singlet. This contrasts with such systems as 1,1,5,5-tetraphenyl-3,3-dimethyl-1,4-pentadiene (**26**),[8a,9b] where an ultrarapid decay is encountered with a lifetime of 0.55 ps. Thus in the present anisyl and dimethylaminophenyl systems a slow rate of bridging seems the likely source of a low S_1 reaction rate rather than any exceptional amount of return of bridged diradical to reactant. Hence the effect of these electron-donating groups must be in the bridging process.

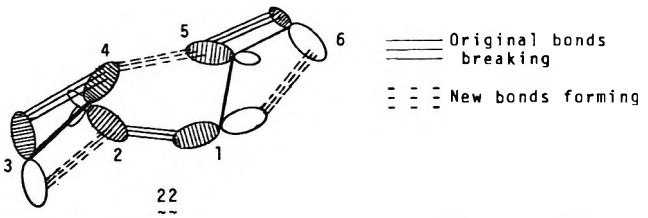


Figure 1. Möbius orbital array in the di-π-methane rearrangement.

SCF–CI calculations[1b,23] reveal that the dramatic rate inhibition derives from excessive stabilization of the vertical excited states for these molecules with considerably less stabilization of the cyclopropyldicarbinyl diradical by these electron-donating aryl groups.

The regioselectivity provides evidence that in the three-ring opening of the cyclopropyldicarbinyl diradical the carbinyl carbon destined to become the final vinyl group becomes much less electron rich. This leads to stabilization by anisyl and other donating groups. Conversely, the carbon destined to become a three-ring atom becomes more electron rich with consequent stabilization by electron-withdrawing groups. SCF–CI calculations[1] show the cyclopropyldicarbinyl diradical to be electron rich at the carbinyl carbons before opening; however, one might expect such a diradical to be quite polarizable.[23]

In this discussion we recognize that the excited state has all gradations of charge separation possible, and that the less than complete regioselectivity for anisyl suggests that we are not dealing with a heavily polar species.

Thus, we can formulate the reaction mechanism as in Scheme V, where the free valences are represented by an asterisk and a double dagger. The significance of these two symbols is not constant along the reaction coordinate, and one might equally validly use the dot–dot formulation presented by us in earlier publications.

Conclusion

In conclusion, we comment that again our mechanistic reasoning in photochemistry has involved the implicit concept that excited-state transformations are controlled by the demand of these species for minimum energy pathways along the excited-state hypersurface.[24] While consideration of ways in which these excited states can convert themselves into ground-state counterparts is of interest, this seems to be related to the photochemical course of a reaction only in a secondary fashion.[25]

Experimental Section[30]

3,3-Dimethyl-5,5-diphenyl-5-hydroxypentanoic Acid Lactone. Phenylmagnesium bromide prepared from 42 mL (0.40 mol) of bromobenzene in 200 mL of anhydrous ether and 9.52 g (0.39 mol) of magnesium turnings was transferred under nitrogen to a constant-pressure addition funnel and added over 2.0 h to a solution of 34.3 g (0.18 mol) of dimethyl 3,3-dimethylglutarate in 400 mL of anhydrous

ether. The reaction was stirred for 1.0 h, quenched with cold 10% sulfuric acid, ether extracted, washed with 5% aqueous sodium bicarbonate solution and with saturated sodium chloride solution, dried over magnesium sulfate, and concentrated under vacuum to a yellow oil. Crystallization from hexane gave 10.0 g of 3,3-dimethyl-5,5-diphenyl-5-hydroxypentanoic acid lactone. A second crop of lactone was obtained after removal of anisole and unreacted dimethyl 3,3-dimethylglutarate by vacuum distillation. The product was recrystallized from hexane to mp 90.5–91.5 °C (lit.[31] mp 90.0–91.0 °C), giving a total of 20.0 g (80% based on unrecovered starting material).

The spectral data were: IR ($CHCl_3$) 3.32, 3.36, 3.47, 5.77, 6.26, 6.69, 6.90, 7.27, 7.41, 7.58, 7.61, 7.9, 8.0–8.3, 8.73, 9.15, 9.45, 10.00, 10.92, 14.43, 15.25 μm; NMR ($CDCl_3$) τ 8.97 (s, 6 H, $C(CH_3)_2$), 7.85 (s, 2 H, CH_2), 7.43 (s, 2 H, CH_2), 2.73 (s, 10 H, arom).

Methyl 3,3-Dimethyl-5,5-diphenyl-5-hydroxypentanoate. A solution of 4.98 g (0.0178 mol) of 3,3-dimethyl-5,5-diphenyl-5-hydroxypentanoic acid lactone, 2.35 g of potassium hydroxide, and 300 mL of 95% ethanol was refluxed for 2.5 h, concentrated under vacuum, taken up in ether and water, and acidified to a methyl orange end point with 10% hydrochloric acid. The ether layer was dried over magnesium sulfate and concentrated under vacuum to 4.84 g (91%) of white crystalline 3,3-dimethyl-5,5-diphenyl-5-hydroxypentanoic acid, mp 114–117 °C, which was used without further purification.

The spectral data were: IR ($CHCl_3$) 2.71, 2.76–4.0, 5.92, 6.26, 6.71, 6.91, 7.15, 7.29, 7.70, 8.0–8.3, 8.55, 8.98, 9.42, 9.73, 9.97, 10.24, 14.43, 15.43 μm; NMR ($CDCl_3$) τ 9.22 (s, 6 H, $C(CH_3)_2$), 7.52 (s, 2 H, CH_2), 7.47 (s, 2 H, CH_2), 3.93 (br s, 2 H, CO_2H and CPh_2OH), 2.97–2.45 (m, 10 H, arom).

A solution of 9.20 g (0.031 mol) of 3,3-dimethyl-5,5-diphenyl-5-hydroxypentanoic acid in 100 mL of ether was added over 15 min to an ether solution of diazomethane generated from 16.8 g of DuPont EXR-101 (*N,N'*-dinitroso-*N,N'*-dimethylterephthalimide with 30% inert filler) as described by Moore and Reed.[32] After 7 h of stirring, excess diazomethane was removed with a stream of nitrogen. The white solid residue was dissolved in ether, filtered, and concentrated to a colorless oil. Recrystallization from hexane gave 8.52 g (89%) of methyl 3,3-dimethyl-5,5-diphenyl-5-hydroxypentanoate, mp 70–70.5 °C.

The spectral data were: IR ($CHCl_3$) 2.91, 3.21, 3.25, 3.31, 3.37, 3.48, 5.86, 6.25, 6.71, 6.91, 7.18, 7.30, 7.41, 7.50, 7.72, 8.28, 8.69, 8.83, 9.40, 9.63, 9.72, 9.97, 10.22, 10.82, 11.29, 11.71, 14.34, 15.39 μm; NMR ($CDCl_3$) τ 9.22 (s, 6 H, $C(CH_3)_2$), 7.48 (s, 4 H, two CH_2), 6.42 (s, 3 H, CO_2CH_3), 5.97 (s, 1 H, OH), 2.93–2.42 (m, 10 H, arom).

Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.90; H, 7.74. Found: C, 77.06; H, 7.82.

Methyl 3,3-Dimethyl-5,5-diphenyl-4-pentenoate. Following the general method of Traynelis,[11] a solution of 0.642 g (2.05 mmol) of methyl 3,3-dimethyl-5,5-diphenyl-5-hydroxypentanoate and 2.8 mL of dimethyl sulfoxide was heated at 175 °C for 2 h, diluted with water, ether extracted, dried over magnesium sulfate, and concentrated to an oil residue which was immediately chromatographed on a 2.5 × 40 cm silica gel[33] column. Elution with 2 L of 5% ether gave: fraction 1, 300 mL, nil; fraction 2, 1000 mL, 0.550 g (91%) of methyl 3,3-dimethyl-5,5-diphenyl-4-pentenoate, a colorless oil; fraction 3, 700 mL, nil.

The spectral data were: IR ($CHCl_3$) 3.35, 5.78, 6.26, 6.71, 6.82, 6.93, 7.31, 7.42, 7.60, 7.72, 8.0–8.4, 8.62, 9.02, 9.48, 9.8, 10.02, 14.43 μm; NMR (CCl_4) τ 8.97 (s, 6 H, $C(CH_3)_2$), 7.78 (s, 2 H, CH_2), 6.42 (s, 3 H, CO_2CH_3), 3.90 (s, 1 H, vinyl), 2.90–2.68 (m, 10 H, arom).

Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.49; H, 7.40.

1,1-Bis(*p*-methoxyphenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene. A solution of 0.500 g (1.70 mmol) of methyl 3,3-dimethyl-5,5-diphenyl-4-pentenoate in 75 mL of anhydrous ether was added over 10 min to a solution of *p*-methoxyphenyllithium prepared from 2.5 mL (19.8 mmol) of *p*-bromoanisole in 60 mL of ether and 16.8 mmol of *n*-butyllithium in 8.4 mL of hexane. The reaction was stirred for 4 h, quenched with cold saturated ammonium chloride solution, ether extracted, dried over magnesium sulfate, and concentrated to a yellow oil. The crude oils from two similar runs (total mass of starting ester used was 1.00 g (3.40 mmol)) were combined and chromatographed on a 2.5 × 85 cm silica gel column.[33] Elution proceeded as follows: fraction 1, 800 mL, hexane, nil; fraction 2, 2000 mL, hexane, 2.63 g of anisole; fraction 3, 1000 mL, 0.5% ether in hexane, nil; fraction 4, 1000 mL, 0.5% ether, 0.072 g of bianisole: fraction 5, 500 mL, 0.5% ether, nil; fraction 6, 4700 mL, 0.5–2.0% ether, 1.42 g (91%) of 1,1-bis(*p*-methoxyphenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene as a colorless glass.

The spectral data were: IR ($CHCl_3$) 3.32, 3.36, 3.38, 3.47, 3.50, 6.23, 6.36, 6.63, 6.83, 6.94, 7.07, 7.28, 7.77, 8.04, 8.24, 8.51, 8.69, 9.02, 9.34, 9.69, 11.4, 12.05, 14.4 μm; NMR (CCl_4) τ 8.98 (s, 6 H, $C(CH_3)_2$), 6.34, (s, 3 H, OCH_3), 6.30 (s, 3 H, OCH_3), 4.21 (s, 1 H, $-CH{=}CAr_2$), 4.10 (s, 1 H, $-CH{=}CPh_2$), 3.44–2.84 (m, 18 H, arom); UV (95% EtOH) 245 nm (ε 30 600).

Anal. Calcd for $C_{33}H_{32}O_2$: C, 86.05; H, 7.00. Found: C, 85.98; H, 7.11.

5,5-Bis(*p*-methoxyphenyl)-3,3-dimethyl-5-hydroxypentanoic Acid Lactone. *p*-Methoxyphenylmagnesium bromide prepared from 16.0 mL (0.125 mol) of *p*-bromoanisole in 100 mL of anhydrous tetrahydrofuran and 2.91 g (0.120 mol) of magnesium turnings was added over 45 min to a solution of 9.47 g (0.050 mol) of dimethyl 3,3-dimethylglutarate in 120 mL of anhydrous tetrahydrofuran. The reaction was stirred for 5 h, quenched with cold 3% sulfuric acid, ether extracted, washed with saturated sodium chloride solution and with water, dried over magnesium sulfate, and concentrated under vacuum to 19.9 g of yellow oil. Removal of additional volatile material by vacuum distillation left 16.2 g of yellow oil which was chromatographed on a 4 × 78 cm column of silica gel.[33] Elution with 4 L of hexane, 2 L of 2.5%, 2 L of 5%, 3 L of 10%, 2 L of 12.5%, 4 L of 15%, 1 L of 17.5%, and 1 L of 20% ether in hexane, and 1 L of 5% chloroform, 25% ether, and 70% hexane gave in 1000-mL fractions: fractions 1–4, 1.38 g of a mixture of anisole and bianisole; fractions 5–10, 3.13 g of a mixture containing unreacted dimethyl 3,3-dimethylglutarate and bianisole; fraction 11, 0.172 g of material containing ~0.08 g of 5,5-bis(*p*-methoxyphenyl)-3,3-dimethyl-5-hydroxypentanoic acid lactone; fractions 12–14, 7.31 g of 5,5-bis(*p*-methoxyphenyl)-3,3-dimethyl-5-hydroxypentanoic acid lactone; fractions 15–16, 2.57 g of a mixture of 1.99 g of lactone and 0.58 g of 5,5-bis(*p*-methoxyphenyl)-3,3-dimethyl-4-pentenoic acid; fractions 17–18, 0.419 g of the pentenoic acid. Crystallization of fractions 11–14 from hexane gave 9.35 g (55%) 5,5-bis(*p*-methoxyphenyl)-3,3-dimethyl-5-hydroxypentanoic acid lactone as a white crystalline solid, mp 88.5–89.5 °C.

The spectral data were: IR ($CHCl_3$) 3.31, 3.36, 3.51, 5.79, 6.21, 6.63, 6.84, 6.95, 7.30, 7.42, 7.7, 7.85, 8.05, 8.25, 8.49, 9.36, 9.70, 10.07 μm; NMR ($CDCl_3$) τ 8.95 (s, 6 H, $C(CH_3)_2$), 7.83 (s, 2 H, CH_2), 7.48 (s, 2 H, CH_2), 6.25 (s, 6 H, OCH_3), 3.21–2.64 (q, 8 H, arom).

Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.36; H, 7.18.

The structure of 5,5-bis(*p*-methoxyphenyl)-3,3-dimethyl-4-pentenoic acid was assigned on the basis of the spectral data: IR ($CHCl_3$) 2.8–3.9, 3.32, 3.36, 3.51, 5.88, 6.22, 6.35, 6.72, 6.83, 7.06, 7.27, 7.31, 7.77, 8.05, 8.25, 8.53, 9.04, 9.67, 12.05 μm; NMR (CCl_4) τ 8.92 (s, 6 H, $C(CH_3)_2$), 7.72 (s, 2 H, CH_2), 6.31 (s, 3 H, OCH_3), 6.24 (s, 3 H, OCH_3), 4.02 (s, 1 H, vinyl), 3.40–2.80 (m, 8 H, arom).

Methyl 5,5-Bis(*p*-methoxyphenyl)-3,3-dimethyl-5-hydroxypentanoate. An ether solution of 5,5-bis(*p*-methoxyphenyl)-3,3-dimethyl-5-hydroxypentanoic acid was prepared by refluxing a mixture of 14.6 g (0.043 mol) of 5,5-bis(*p*-methoxyphenyl)-3,3-dimethyl-5-hydroxypentanoic acid lactone, 15.0 g of potassium hydroxide, 15 mL of water, and 500 mL of 95% ethanol for 2.0 h, concentrating to near dryness under vacuum, dissolving the residue in water, acidifying to the methyl orange end point with 10% hydrochloric acid, and extracting with ether. The resulting solution was added over 90 min to an ether solution of diazomethane generated from 23.7 g of DuPont EXR-101 (*N,N'*-dinitroso-*N,N'*-dimethylterephthalimide with 30% inert filler) as described by Moore and Reed.[32] After 4 h of stirring, excess diazomethane was removed with a stream of nitrogen. The residue was dissolved in ether, filtered, and concentrated under vacuum to 16.0 g (99%) of methyl 5,5-bis(*p*-methoxyphenyl)-3,3-dimethyl-5-hydroxypentanoate, pure by NMR, which was used without further purification.

The spectral data were: IR ($CHCl_3$) 2.95, 3.34, 3.39, 3.41, 3.44, 3.53, 5.80, 6.25, 6.38, 6.65, 6.85, 6.95, 7.09, 7.21, 7.33, 7.45, 7.59, 7.79, 8.05, 8.20, 8.49, 8.54, 8.93, 9.70, 12.02 μm; NMR (CCl_4) 9.24 (s, 6 H, $C(CH_3)_2$), 7.58 (s, 2 H, CH_2), 7.54 (s, 2 H, CH_2), 6.40 (s, 3 H, CO_2CH_3), 6.28 (s, 6 H, $C_6H_4OCH_3$), 3.35–2.65 (q, 8 H, arom).

Methyl 5,5-Bis(*p*-methoxyphenyl)-3,3-dimethyl-4-pentenoate. A mixture of 15.7 g (0.042 mol) of methyl 5,5-bis(*p*-methoxyphenyl)-3,3-dimethyl-5-hydroxypentanoate and 60 mL of dimethyl sulfoxide[11] was heated at 176 °C for 2.5 h, cooled, and partitioned between water and ether. The ether phase was washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated to a yellow oil which was immediately chromatographed on a 2.5 × 45 cm silica gel column.[33] Elution with 2.0 L of 1% ether in hexane gave 13.4 g (90%) of methyl 5,5-bis(*p*-methoxyphenyl)-3,3-dimethyl-4-pentenoate as a colorless oil.

The spectral data were: IR ($CHCl_3$) 3.36, 3.50, 5.75, 6.22, 6.35, 6.63, 6.84, 6.93, 7.76, 8.00, 8.5, 8.9, 9.65, 12.05 μm; NMR (CCl_4) 8.98 (s, 6 H,

$C(CH_3)_2$), 7.80 (s, 2 H, CH_2), 6.42 (s, 3 H, CO_2CH_3), 6.29 (s, 3 H, $C_6H_4OCH_3$), 6.21 (s, 3 H, $C_6H_4OCH_3$), 4.07 (s, 1 H, vinyl), 3.42–2.95 (m, 8 H, arom).

Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.55; H, 7.33.

3,3-Dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)-1,4-pentadiene. A solution of 4.27 g (12.0 mmol) of methyl 5,5-bis(*p*-methoxyphenyl)-3,3-dimethyl-4-pentenoate in 75 mL of anhydrous ether was added over 30 min to a solution of *p*-methoxyphenyllithium prepared from 5.0 mL (38.9 mmol) of *p*-bromoanisole in 45 mL of ether and 39 mmol of *n*-butyllithium in 27 mL of hexane. The reaction was stirred for 2.5 h, quenched with cold saturated ammonium chloride solution, ether extracted, dried over magnesium sulfate, and concentrated under vacuum to 8.98 g of yellow oil which was chromatographed on a 4 × 80 cm silica gel column.[33] Elution with 4 L of hexane, 1 L of 0.5%, 2 L of 1.0%, 1 L of 1.5%, 8 L of 2.5%, 4 L of 10%, 1 L of 12%, 1 L of 15%, and 1 L of 20% ether in hexane proceeded as follows (1000-mL fractions): fraction 1 (4000 mL), 1.23 g of anisole; fractions 2–3, nil; fractions 4–5, 0.196 g of bianisole; fractions 6–8, nil; fractions 9–12, 0.686 g of 3,3-dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)-1,4-pentadiene; fractions 13–14, 0.091 g of overlap; fractions 15–19, 5.42 g of 3,3-dimethyl-1,1-5,5-tetrakis(*p*-methoxyphenyl)pent-4-en-1-ol; fraction 20, nil. The combined yield of pentadiene and pentenol was 95%. The pentenol was dehydrated (vide infra) without further purification. Crystallization from ether–hexane gave white crystals, mp 183–186 °C.

The spectral data were: IR ($CHCl_3$) 2.86, 3.34, 3.39, 3.41, 3.45, 3.53, 6.25, 6.38, 6.65, 6.77, 6.85, 6.96, 7.19, 7.30, 7.81, 8.06, 8.23, 8.50, 8.55, 8.96, 9.22, 9.73, 11.49, 12.03, 12.44 μm; NMR ($CDCl_3$) τ 9.20 (s, 6 H, $C(CH_3)_2$), 7.42 (s, 2 H, CH_2), 6.51 (s, 6 H, OCH_3), 6.22 (s, 3 H, OCH_3), 6.16 (s, 3 H, OCH_3), 5.29 (s, 1 H, OH), 4.12 (s, 1 H, vinyl), 3.48–2.19 (m, 16 H, arom).

A solution of 1.54 g (3.50 mmol) of 3,3-dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)pent-4-en-1-ol in 10 mL of chloroform was added to a solution of 0.073 g of *p*-toluenesulfonic acid in 100 mL of chloroform, stirred at room temperature for 1.0 h, and poured into aqueous sodium bicarbonate solution. The organic layer was dried over sodium sulfate and concentrated to 1.67 g of material containing no trace of starting alcohol (NMR analysis). Chromatography of the crude product on a 2.5 × 80 cm silica gel[33] column eluting with 2 L of hexane, and 4 L of 1.5% and 4 L of 2.5% ether proceeded as follows: fraction 1, 6000 mL, nil; fraction 2, 3000 mL, 1.42 g (96%) of 3,3-dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)-1,4-pentadiene, a colorless glass; fraction 3, 1000 mL, nil.

The spectral data were: IR ($CHCl_3$) 3.32, 3.37, 3.51, 6.23, 6.37, 6.64, 6.83, 6.94, 7.07, 7.28, 7.77, 8.0–8.3, 8.52, 8.68, 9.04, 9.68 μm; NMR (CCl_4) τ 9.00 (s, 6 H, $C(CH_3)_2$), 6.33 (s, 6 H, OCH_3), 6.31 (s, 6 H, OCH_3), 4.29 (s, 2 H, vinyl), 3.49–3.00 (m, 16 H, arom); UV (95% EtOH) 244 (ε 31 600), 264 nm (ε 27 800).

Anal. Calcd for $C_{35}H_{36}O_4$: C, 80.74; H, 6.97. Found: C, 80.93; H, 7.09.

1,1-Bis(*p*-*N*,*N*-dimethylaminophenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene. A solution of 0.831 g (2.83 mmol) of methyl 3,3-dimethyl-5,5-diphenyl-4-pentenoate in 25 mL of anhydrous ether was added over 10 min to a solution of *p*-*N*,*N*-dimethylaminophenyllithium prepared from 1.58 g (7.9 mmol) of *p*-bromo-*N*,*N*-dimethylaniline in 25 mL of anhydrous ether and 7.5 mmol of *n*-butyllithium in 5.2 mL of hexane. The reaction was stirred for 90 min, quenched with cold saturated aqueous ammonium chloride solution, ether extracted, dried over magnesium sulfate, and concentrated under vacuum to 1.96 g of material which was chromatographed on a 2.5 × 45 cm silica gel column.[33] Elution with 1 L of hexane and 0.5 L of 1%, 1 L of 3%, and 1 L of 6% ether in hexane proceeded as follows: fraction 1, 1000 mL, nil; fraction 2, 800 mL, 0.384 g of aryl coupling products; fraction 3, 1500 mL, 1.23 g (89%) of the dehydrated product, 1,1-bis(*p*-*N*,*N*-dimethylaminophenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene, a clear, viscous oil.

The spectral data were: IR ($CHCl_3$) 3.38, 3.50, 3.57, 6.21, 6.43, 6.58, 6.68, 6.85, 6.92, 7.38, 8.59, 8.87, 10.00, 10.24, 10.56, 11.23, 11.59 μm; NMR (CCl_4) τ 8.97 (s, 6 H, $C(CH_3)_2$), 7.17 (s, 6 H, two of the *N*-CH_3 groups), 7.15 (s, 6 H, two *N*-CH_3 groups), 4.27 (s, 1 H, -CH=CAr_2), 4.08 (s, 1 H, -CH=CPh_2), 2.8–3.6 (m, 18 H, arom); UV (95% EtOH) 262 nm (ε 26 400).

Anal. Calcd for $C_{35}H_{38}N_2$: C, 86.37; H, 7.87. Found: C, 86.08; H, 7.61.

Exploratory Photolysis of 1,1-Bis(*p*-methoxyphenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene. A solution of 0.510 g (1.11 mmol) of 1,1-bis(*p*-methoxyphenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene in 1.0 L of *tert*-butyl alcohol was purged with purified nitrogen[34] for 1 h before and during photolysis. The diene solution was irradiated for 0.5 h with a 450-W medium-pressure mercury lamp through a Pyrex filter. Removal of solvent under vacuum left a yellow oil which was chromatographed on a 2.5 × 125 cm silicic acid[35] column. Elution proceeded as follows: fraction 1, 5000 mL, 0–1% ether in hexane, nil; fraction 2, 1300 mL, 1%, 0.432 g of the starting diene; fraction 3, 550 mL, 1%, 0.005 g of starting diene and 0.029 g of 2,2-dimethyl-1,1-diphenyl-3-[2,2-bis(*p*-methoxyphenyl)vinyl]cyclopropane; fraction 4, 900 mL, 1%, 0.028 g of 2,2-dimethyl-1,1-diphenyl-3-[2,2-bis(*p*-methoxyphenyl)vinyl]cyclopropane; fraction 5, 1300 mL, 1%, 0.015 g of 1,1-bis(*p*-methoxyphenyl)-2,2-dimethyl-3-(2,2-diphenylvinyl)cyclopropane. Yield of major product is 11% and yield of minor product is 3%.

The spectral data for 2,2-dimethyl-1,1-diphenyl-3-[2,2-bis(*p*-methoxyphenyl)vinyl]cyclopropane were: IR ($CHCl_3$) 3.28, 3.34, 3.40, 3.41, 3.53, 6.25, 6.35, 6.64, 6.70, 6.85, 6.94, 7.12, 7.28, 7.78, 8.05, 8.26, 8.50, 8.53, 9.01, 9.26, 9.70, 12.12, 14.35 μm; NMR (CCl_4) τ 9.01 (s, 3 H, CH_3), 8.71 (s, 3 H, CH_3), 7.86 (d, J = 10 Hz, 1 H, cyclopropyl methine), 6.28 (s, 3 H, OCH_3), 6.16 (s, 3 H, OCH_3), 4.52 (d, J = 10 Hz, 1 H, vinyl), 3.36–2.48 (m, 18 H, arom).

Anal. Calcd for $C_{33}H_{32}O_2$: C, 86.05; H, 7.00. Found: C, 85.94; H, 7.02.

The spectral data for 1,1-bis(*p*-methoxyphenyl)-2,2-dimethyl-3-(2,2-diphenylvinyl)cyclopropane were: IR ($CHCl_3$) 3.28, 3.34, 3.39, 3.41, 3.53, 6.25, 6.64, 6.71, 6.85, 6.95, 7.14, 7.28, 7.78, 8.05, 8.25, 8.53, 9.00, 9.70, 12.00 μm; NMR (CCl_4) τ 9.04 (s, 3 H, CH_3), 8.72 (s, 3 H, CH_3), 7.98 (d, J = 10 Hz, 1 H, cyclopropyl methine), 6.37 (s, 3 H, OCH_3), 6.28 (s, 3 H, OCH_3), 4.30 (d, J = 10 Hz, vinyl), 3.52–2.60 (m, 18 H, arom).

Anal. Calcd for $C_{33}H_{32}O_2$: C, 86.05; H, 7.00. Found: C, 86.20; H, 7.08.

Exploratory Photolysis of 3,3-Dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)-1,4-pentadiene. A solution of 0.265 g (0.51 mmol) of the diene in 125 mL of benzene was purged with purified nitrogen[34] for 30 min before and during photolysis. The diene solution was irradiated for 30 min through a 1-mm Pyrex filter with a 450-W medium-pressure mercury lamp. Removal of solvent under vacuum left an orange oil which was chromatographed on a 2.5 × 45 cm silicic acid[35] column. Elution with 9 L of 0.0–2.5% ether in hexane gave nil; 2 L of 2.5% gave 0.125 g (47%) of the starting diene; 2 L of 2.5–5.0% gave 0.081 g (31%) of 1,1-bis(*p*-methoxyphenyl)-2,2-dimethyl-3-[2,2-bis(*p*-methoxyphenyl)vinyl]cyclopropane. Recrystallization from hexane gave the vinylcyclopropane as white needles, mp 149–150 °C.

The spectral data were: IR ($CHCl_3$) 3.34, 3.39, 3.41, 3.44, 3.53, 6.25, 6.64, 6.85, 6.95, 7.14, 7.27, 7.39, 7.78, 8.03, 8.53, 9.01, 9.68, 11.99 μm; NMR (CCl_4) τ 9.03 (s, 3 H, CH_3), 8.75 (s, 3 H, CH_3), 7.99 (d, J = 10 Hz, 1 H, cyclopropyl CH), 6.40 (s, 3 H, OCH_3), 6.30 (s, 6 H, two OCH_3), 6.21 (s, 3 H, OCH_3), 4.57 (d, J = 10 Hz, 1 H, CH=CAr_2), 2.72–3.71 (m, 16 H, arom).

Anal. Calcd for $C_{35}H_{36}O_4$: C, 80.74; H, 6.97. Found: C, 80.66; H, 6.91.

Exploratory Photolysis of 1,1-Bis(*p*-*N*,*N*-dimethylaminophenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene. A solution of 0.047 g (0.097 mmol) of 1,1-bis(*p*-*N*,*N*-dimethylaminophenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene in 125 mL of benzene was purged with purified nitrogen[31] for 1.0 h before and during photolysis. The solution was irradiated for 70 min through a Pyrex filter with a Hanovia 450-W medium-pressure lamp. Removal of solvent in vacuo and elution of the crude product through a 2 × 12 cm silicic acid column yielded 0.021 g (45%) of 2,2-dimethyl-1,1-diphenyl-3-[2,2-bis(*p*-*N*,*N*-dimethylaminophenyl)vinyl]cyclopropane in 200 mL of 5% ether in hexane. No starting diene or isomeric vinylcyclopropane was detected.

Spectral data for the bis(dimethylaminophenyl)vinyl product are as follows: NMR (CCl_4) τ 9.01 (s, 3 H, CH_3), 8.74 (s, 3 H, CH_3), 7.81 (d, J = 10 Hz, 1 H, cyclopropyl methine), 7.20 (s, 6 H, NCH_3), 7.10 (s, 6 H, NCH_3), 4.73 (d, J = 10 Hz, 1 H, vinyl), 3.6–2.5 (m, 18 H, arom).

Anal. Calcd for $C_{35}H_{38}N_2$: exact mass, 486.30330. Found: exact mass, 486.30350.

4,4-Bis(*p*-methoxyphenyl)-3,3-dimethyl-4-hydroxybutanoic Acid Lactone. A solution of 4.49 g (0.026 mol) of 3-carbomethoxy-3-methylbutanoic acid[36] in 60 mL of anhydrous tetrahydrofuran was added over 100 min to a solution of *p*-methoxyphenylmagnesium bromide prepared from 11.6 mL (0.090 mol) of *p*-bromoanisole in 100 mL of anhydrous tetrahydrofuran and 2.19 g (0.090 mol) of magnesium turnings, stirred for 14 h, quenched with cold 7% sulfuric acid, partitioned between ether and saturated sodium chloride solution, dried over magnesium sulfate, and concentrated under vacuum to 12.6 g of orange oil. Removal of anisole by vacuum distillation yielded 7.92

g of material which was chromatographed on a 4 × 73 cm silica gel column.[33] Elution with 3 L of hexane, 1 L of 2.5%, 1 L of 5%, 1 L of 7.5%, 2 L of 10%, 2 L of 12.5%, 3 L of 15%, and 1 L of 25% ether in hexane, and 1 L of 2% methanol, 38% ether, and 60% hexane proceeded as follows (500-mL fractions): fractions 1–5, 1.21 g of anisole; fractions 6–9, 0.140 g of bianisole; fractions 10–11, 0.082 g of overlap; fractions 12–13, 0.326 g of 4,4-bis(*p*-methoxyphenyl)-2,2-dimethyl-4-hydroxybutanoic acid lactone; fraction 14, 0.594 g of 2,2-dimethyllactone and 0.100 g of the expected 4,4-bis(*p*-methoxyphenyl)-3,3-dimethyl-4-hydroxybutanoic acid lactone; fraction 15, 0.30 g of 2,2-dimethyllactone and 0.75 g of 3,3-dimethyllactone; fraction 16, 0.090 g of 2,2-dimethyllactone and 1.42 g of 3,3-dimethyllactone; fraction 17, 1.15 g of 3,3-dimethyllactone; fractions 19–26, 0.050 g, unidentified. The major product (3.42 g, 40%), 4,4-bis(*p*-methoxyphenyl)-3,3-dimethyl-4-hydroxybutanoic acid lactone, was recrystallized from hexane to give white prisms, mp 114–115 °C.

The special data were: IR ($CHCl_3$) 3.32, 3.36, 3.39, 3.50, 5.66, 6.20, 6.32, 6.62, 6.82, 6.92, 7.04, 7.17, 7.26, 7.70, 8.0–8.3, 8.46, 8.94, 9.64, 9.75, 10.02, 10.19, 10.81, 10.96, 12.06 μm; NMR ($CDCl_3$) τ 8.78 (s, 6 H, $C(CH_3)_2$), 7.56 (s, 2 H, CH_2), 6.22 (s, 6 H, OCH_3), 3.15–2.49 (q, 8 H, arom).

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.83; H, 6.71.

The minor product (1.31 g, 15%), 4,4-bis(*p*-methoxyphenyl)-2,2-dimethyl-4-hydroxybutanoic acid lactone, was recrystallized from hexane as white prisms, mp 129–130 °C.

The spectral data were: IR ($CHCl_3$) 3.38, 3.53, 5.70, 6.22, 6.33, 6.63, 6.83, 7.04, 7.19, 7.26, 7.72, 8.02, 8.13, 8.47, 8.95, 9.66, 10.03, 10.21, 10.82, 10.99, 12.11 μm; NMR ($CDCl_3$) τ 8.85 (s, 6 H, $C(CH_3)_2$), 7.12 (s, 2 H, CH_2), 6.24 (s, 6 H, OCH_3), 3.06–2.57 (q, 8 H, arom).

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.55; H, 7.01.

4,4-Bis(p-methoxyphenyl)-3,3-dimethylbutanoic Acid. Lithium wire (0.014 g, 2.0 mmol) was added in four pieces to 0.280 g (0.86 mmol) of 4,4-bis(*p*-methoxyphenyl)-3,3-dimethylbutanoic acid lactone dissolved in a mixture of 10 mL of ether, 10 mL of tetrahydrofuran, and 60 mL of liquid ammonia. The intense blue color persisted after addition of the fourth piece of lithium. The reaction was stirred for an additional 20 min, then quenched with excess solid ammonium chloride. Evaporation of ammonia left a white solid which was taken up in ether and water. The water layer was extracted with more ether and the combined organic layer was dried over magnesium sulfate and concentrated to 0.28 g of colorless oil, pure by NMR. Recrystallization from hexane gave 4,4-bis(*p*-methoxyphenyl)-3,3-dimethylbutanoic acid as white needles, mp 74–74.5 °C.

The spectral data were: IR ($CHCl_3$) 2.8–4.0, 3.37, 3.51, 5.88, 6.21, 6.33, 6.64, 6.83, 6.94, 7.11, 7.29, 7.68, 7.9–8.3, 8.48, 8.97, 9.67 μm; NMR ($CDCl_3$) τ 8.84 (s, 6 H, $C(CH_3)_2$), 7.70 (s, 2 H, CH_2), 6.25 (s, 6 H, OCH_3), 6.04 (s, 1 H, $(p\text{-}CH_3OC_6H_4)_2CH$), 3.24–2.60 (q, 8 H, arom), 0.3 (br s, 1 H, COOH).

Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.33; H, 7.40.

Characterization of 2,2-Dimethyl-1,1-diphenyl-3-[2,2-bis(p-methoxyphenyl)vinyl]cyclopropane. A solution of 0.090 g (0.195 mmol) of 2,2-dimethyl-1,1-diphenyl-3-[2,2-bis(*p*-methoxyphenyl)-vinyl]cyclopropane in 15 mL of benzene was added to a solution of 0.427 g of dicyclohexyl-18-crown-6 and 0.172 g of potassium permanganate in 40 mL of benzene (the Sam–Simmons reagent[12]), stirred at room temperature for 37 h, poured into 100 mL of 0.5% hydrochloric acid, ether extracted, washed with water, dried over magnesium sulfate, and concentrated to 0.559 g of yellow oil which was partitioned between ether and 5% aqueous sodium hydroxide solution. The organic phase was washed again with sodium hydroxide solution, dried, and concentrated to an oily residue. Crystallization of the oil from ether–hexane gave 0.020 g (44%) of 4,4′-dimethoxybenzophenone as white needles, the melting point and spectral data of which were identical with that of commercially available 4,4′-dimethoxybenzophenone. The alkaline phase was neutralized to the methyl orange end point with 10% hydrochloric acid, ether extracted, dried, and concentrated to a white solid which gave 0.021 g (40%) of 3,3-dimethyl-2,2-diphenylcyclopropanecarboxylic acid after crystallization from ether–hexane. The melting point and spectral data were identical with the values reported previously.[8a]

Characterization of 1,1-Bis(p-methoxyphenyl)-2,2-dimethyl-3-(2,2-diphenylvinyl)cyclopropane. A solution of 0.048 g (0.10 mmol) of 1,1-bis(*p*-methoxyphenyl)-2,2-dimethyl-3-(2,2-diphenylvinyl)cyclopropane in 10 mL of benzene was added to the Sam–Simmons reagent[12] prepared from 0.153 g of dicyclohexyl-18-crown-6 and 0.064 g of potassium permanganate in 15 mL of benzene, stirred for 22 h, poured into 1% hydrochloric acid, ether extracted, dried over magnesium sulfate, and concentrated to 0.193 g of colorless oil which was chromatographed on a 2.5 × 88 cm column of silicic acid.[35] Elution proceeded as follows: fraction 1, 4500 mL, 0–1% ether in hexane, nil; fraction 2, 1800 mL, 1–2%, 0.011 g (60%) of benzophenone; fraction 3, 5100 mL, 2–40%, 0.045 g of material including some unreacted vinylcyclopropane; fraction 4, 1700 mL, 40–60%, 0.022 g (67%) of 2,2-bis(*p*-methoxyphenyl)-3,3-dimethylcyclopropanecarboxylic acid; fraction 5, 1600 mL, 60–100%, 0.015 g of crown ether. Crystallization from hexane gave 2,2-bis(*p*-methoxyphenyl)-3,3-dimethylcyclopropanecarboxylic acid as white prisms, mp 182–183 °C.

The spectral data were: IR ($CHCl_3$) 2.9–3.6, 3.21, 3.31, 3.36, 3.41, 3.52, 5.87, 6.22, 6.32, 6.61, 6.83, 6.94, 7.27, 7.78, 8.00, 8.13, 8.51, 8.99, 9.64, 10.81 μm; NMR ($CDCl_3$) τ 8.92 (s, 3 H, CH_3), 8.54 (s, 3 H, CH_3), 7.76 (s, 1 H, CH), 6.26 (s, 6 H, OCH_3), 3.28–2.68 (m, 8 H, arom), 2.5–0.5 (1 H, CO_2H, detectable only with integrator).

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.42; H, 6.76.

Characterization of 1,1-Bis(p-methoxyphenyl)-2,2-dimethyl-3-[2,2-bis(p-methoxyphenyl)vinyl]cyclopropane. A solution of 0.135 g (0.26 mmol) of 1,1-bis(*p*-methoxyphenyl)-2,2-dimethyl-3-[2,2-bis(*p*-methoxyphenyl)vinyl]cyclopropane in 10 ml of benzene was added to the Sam-Simmons reagent[12] prepared from 0.436 g of dicyclohexyl-18-crown-6 and 0.118 g of potassium permanganate in 40 ml of benzene, stirred for 40 h, poured into 2% hydrochloric acid, ether extracted, dried over sodium sulfate, and concentrated under vacuum to 0.544 g of clear, viscous oil which was partitioned between ether and 5% aqueous sodium hydroxide solution. The ether layer was dried over sodium sulfate and concentrated under vacuum to 0.471 g of material from which 0.057 g (95%) of 4,4′-dimethoxybenzophenone was obtained by crystallization from hexane. The aqueous layer was acidified to the methyl orange end point with 10% hydrochloric acid, ether extracted, dried over sodium sulfate, concentrated under vacuum, and crystallized from ether–hexane to give 34 mg (40%) of 2,2-bis(*p*-methoxyphenyl)-3,3-dimethylcyclopropanecarboxylic acid.

Characterization of 2,2-Bis(p-methoxyphenyl)-3,3-dimethylcyclopropanecarboxylic Acid. Lithium wire (0.007 g, 1.0 mmol) was added to a solution of 0.023 g (0.07 mmol) of 2,2-bis(*p*-methoxyphenyl)-3,3-dimethylcyclopropanecarboxylic acid in 4 mL of anhydrous ether, 4 mL of tetrahydrofuran, and 20 mL of liquid ammonia. The reaction was stirred for 40 min, then quenched with excess solid ammonium chloride. Evaporation of the ammonia left a white slurry which was dissolved in ether and water. The aqueous layer was saturated with sodium chloride and extracted with ether. The combined ether layers were dried over magnesium sulfate, filtered, and concentrated to 0.021 g of clear, colorless oil. Crystallization from hexane gave 5 mg of the starting cyclopropanecarboxylic acid. The mother liquors were crystallized from hexane to give 15 mg (65%) of 4,4-bis(*p*-methoxyphenyl)-3,3-dimethylbutanoic acid identical in all respects with independently synthesized material (vide supra).

Photolysis Equipment for Quantum Yield Determinations. Quantum yield irradiations were performed on the "black box" apparatus or on the microoptical bench.[13] Light output was measured by ferrioxalate actinometry.[15] The light absorbed in the reaction cell was determined by the splitting ratio technique.[13]

For direct "black box" photolyses, the solution filters used were the following. Filter A: (a) 1.74 M nickel sulfate hexahydrate in 5% sulfuric acid; (b) 1.0 M cobalt sulfate heptahydrate in 5% sulfuric acid; (c) 0.0013 M stannous chloride dihydrate in 15% hydrochloric acid; this combination gave a transmission maximum at 310 nm (40% transmission) and was opaque above 345 nm and below 275 nm. Filter B: (a) 2.0 M nickel sulfate hexahydrate in 5% sulfuric acid; (b) 0.8 M cobalt sulfate heptahydrate in 5% sulfuric acid; (c) 0.0002 M bismuth trichloride in 10% hydrochloric acid; this combination gave a transmission maximum at 272 nm (40% transmission) and was opaque above 305 nm and below 245 nm. For the microbench runs, the monochromator inlet slit was set at 5.4 mm and the exit slit at 2.9 mm, giving a band pass of 22 nm at half-peak height.

For sensitized "black box" runs, the solution filters used were as follows. Filter C: (a) 1.0 M nickel sulfate hexahydrate in 10% sulfuric acid; (b) 1.0 M cobalt sulfate heptahydrate in 10% sulfuric acid; (c) 0.047 M stannous chloride dihydrate in 15% hydrochloride acid; this combination gave a transmission maximum at 331 nm (17% transmission) and was opaque above 365 nm and below 312 nm. Filter D: (a) 0.1 M nickel sulfate hexahydrate in 10% sulfuric acid; (b) 0.4 M cobalt sulfate heptahydrate in 10% sulfuric acid; (c) 0.1 M stannous chloride dihydrate in 15% hydrochloric acid; this combination gave a transmission maximum at 345 nm (40% transmission) and was opaque above 380 nm and below 320 nm.

Direct Quantum Yields. 1,1-Bis(*p*-methoxyphenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene. Run 1 was performed on the microoptical bench, runs 2 and 3, on the black box apparatus.[13] All employed dry *tert*-butyl alcohol as solvent. Each solution was purged with purified nitrogen[34] for 1.0 h before and during irradiation. Runs 1 and 2 were analyzed with high-pressure liquid chromatography using a 2 ft × ⅛ in. column packed with a silicic acid like material developed in these laboratories[37] and eluting with 1.4% ether in hexane. 4-Bromobenzophenone was used as an internal standard. In run 3, the photoproducts were isolated by chromatography on a 2.5 × 45 cm silicic acid[35] column, eluting with 1% ether in hexane. The composition of the fraction containing the photoproducts was determined by manual integration of the vinyl hydrogen peaks in the expanded (108-Hz sweep width) τ 5.0–6.1 region of the 100-MHz NMR spectrum. Data for the individual quantum yields are as follows.

Run 1: monochromator set at 285 nm; starting diene used, 1.0×10^{-2} mmol in 40 mL; 5.1×10^{-2} mEinsteins absorbed; dianisylvinylcyclopropane formed, 4.3×10^{-3} mmol, $\Phi = 0.085$; diphenylvinylcyclopropane formed, 1.3×10^{-3} mmol, $\Phi = 0.025$; 5.6% conversion.

Run 2: filter B; starting diene, 6.45×10^{-1} mmol in 750 mL; 6.1×10^{-1} mEinsteins; dianisylvinylcyclopropane, 4.2×10^{-2} mmol, $\Phi = 0.070$; diphenylvinylcyclopropane, 1.4×10^{-2} mmol, $\Phi = 0.023$; 8.8% conversion.

Run 3: filter A; starting diene, 1.12 mmol in 750 mL; 7.7×10^{-1} mEinsteins; dianisylvinylcyclopropane, 5.7×10^{-2} mmol, $\Phi = 0.071$; diphenylvinylcyclopropane, 1.3×10^{-2} mmol, $\Phi = 0.017$; 6.0% conversion.

Sensitized Quantum Yield. 1,1-Bis(*p*-methoxyphenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene. A solution of 0.280 g (0.61 mmol) of 1,1-bis(*p*-methoxyphenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene, 30.0 mL of acetophenone, and 720 mL of *tert*-butyl alcohol was purged with purified nitrogen[34] for 1.0 h before and during photolysis. The solution was irradiated in the "black box" apparatus[13] through filter combination C with 1.60 mEinsteins of light. Removal of solvent and acetophenone in vacuo left 0.286 g of material. Analysis by NMR spectroscopy showed only starting diene and a trace of acetophenone. No vinylcyclopropanes were detected, and assuming that 3.0 mg could be detected, $\Phi_{sens} < 4 \times 10^{-3}$.

Direct Quantum Yields. 3,3-Dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)-1,4-pentadiene. All three runs were performed on the "black box" apparatus.[13] Each 750-mL *tert*-butyl alcohol solution was purged with purified nitrogen[34] for 1.0 h before and during irradiation. Run 1 was analyzed using high-pressure liquid chromatography (vide supra), eluting with 10% ether in hexane. 4-Methoxybenzophenone was used as an internal standard. Runs 2 and 3 were analyzed by the silicic acid chromatography–NMR integration technique described above. Data for the individual quantum yields are as follows.

Run 1: filter B; starting diene used, 9.2×10^{-1} mmol; 7.6×10^{-1} mEinsteins absorbed; vinylcyclopropane formed, 3.0×10^{-2} mmol, $\Phi = 0.040$; 3.3% conversion.

Run 2: filter A; starting diene, 1.15 mmol; 1.87 mEinsteins; vinylcyclopropane, 7.9×10^{-2} mmol, $\Phi = 0.042$; 6.7% conversion.

Run 3: filter A; starting diene, 1.35 mmol; 9.1×10^{-1} mEinsteins; vinylcyclopropane, 4.6×10^{-2} mmol, $\Phi = 0.051$; 3.4% conversion.

Sensitized Quantum Yield. 3,3-Dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)-1,4-pentadiene. A solution of 0.275 g (0.529 mmol) of 3,3-dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)-1,4-pentadiene and 6.12 g of benzophenone in 750 mL of *tert*-butyl alcohol was purged with purified nitrogen[34] for 1.0 h before and during photolysis. The solution was irradiated in the "black box" apparatus[13] through filter D with 3.36 mEinsteins of light. Removal of solvent under vacuum left a colorless oil from which benzophenone crystallized. Chromatography on a 2.5 × 45 cm silicic acid[35] column eluting with 4.0 L of 0.5% ether in hexane removed benzophenone from the photolysate. Further elution with 1 L of 5% and 1 L of 10% ether in hexane gave 0.273 g of colorless oil. Analysis by NMR showed no evidence of vinylcyclopropane. Assuming that 3.0 mg could be detected, $\Phi_{sens} < 1.7 \times 10^{-3}$.

Direct Quantum Yields. 1,1-Bis(*p*-*N*,*N*-dimethylaminophenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene. Both runs utilized the "black box" apparatus[13] and filter combination A. Each 750-mL *tert*-butyl alcohol solution was purged with purified nitrogen[34] for 1.0 h before and during photolysis. Both runs were analyzed by the silicic acid[35] chromatography–NMR integration technique described above. Data for the individual quantum yields are as follows.

Run 1: starting diene used, 6.9×10^{-1} mmol; 1.14 mEinsteins absorbed; vinylcyclopropane formed, $<6.2 \times 10^{-3}$ mmol; $\Phi < 5.4 \times 10^{-3}$.

Run 2: starting diene, 3.7×10^{-1} mmol; 15.0 mEinsteins absorbed; vinylcyclopropane, 4.1×10^{-2} mmol; $\Phi = 2.7 \times 10^{-3}$.

Energy Transfer Tests. Quenching of Benzophenone Triplets by 1,1-Bis(*p*-methoxyphenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene and by 3,3-Dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)-1,4-pentadiene. The irradiations were carried out on the "black box" apparatus[13] using filter D. A solution of 0.500 g (2.74 mmol) of benzophenone and 0.250 g (1.36 mmol) of benzhydrol in 250 mL of *tert*-butyl alcohol was purged with purified nitrogen[34] for 1.0 h before and during the irradiation. Similarly, a solution of 0.500 g of benzophenone, 0.250 g of benzhydrol, and 0.063 g (0.136 mmol) of 1,1-bis(*p*-methoxyphenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene in 235 mL of *tert*-butyl alcohol and a solution of 0.500 g of benzophenone, 0.250 g of benzhydrol, and 0.052 g (0.100 mmol) of 3,3-dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)-1,4-pentadiene in 235 mL of *tert*-butyl alcohol were purged and irradiated. Chromatography of each photomixture on a 2.5 × 45 cm silicic acid[35] column, eluting with 1% ether, completely separated benzopinacol from the other components.

Run 1: no quencher; 2.40 mEinsteins absorbed; benzophenone recovered, 0.380 g; benzpinacol, 0.108 g; $\Phi = 0.123$; 0% quenching.

Run 2: quencher, 1,1-bis(*p*-methoxyphenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene; 2.41 mEinsteins; benzophenone, 0.460 g; benzpinacol, 0.027 g; $\Phi = 0.031$; 75% quenching.

Run 3: quencher, 3,3-dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)-1,4-pentadiene; 2.41 mEinsteins; benzophenone, 0.410 g; benzpinacol, 0.034 g; $\Phi = 0.039$; 68% quenching.

Emission Studies. Purification of Solvent. Isopentane and methylcyclohexane were purified by repeated washings with 10% fuming sulfuric acid until the washings were colorless, washing with water, refluxing with 10% sulfuric acid saturated with potassium permanganate for 3–6 h, washing again with water, drying over phosphorus pentoxide, and passing through a 2.0 × 80 cm column of alumina containing 10% silver nitrate.[38] The early and late fractions were discarded. Solvents prepared in this manner were transparent in the ultraviolet and emission free.

Single-Photon Counting. The apparatus and procedure have been described in detail previously.[9b] The method uses a high-pressure (~80 psi) nitrogen flash lamp with a half-width of ~2 ns when run at 20–40 kHz, a 1P28 photomultiplier to trigger the start of a time-to-amplitude converter, monochromators before and after the sample, an RCA 8850 photomultiplier and Ortec model 463 constant fraction timing discriminator to signal emergence of a single photon, and a 12 bit Northern Scientific A/D converter interfaced with a PDP8/I–FPP12 minicomputer. The minicomputer was used as a 512-word multichannel analyzer and to do on-line deconvolution by reiterative convolution as previously described.[9b] Independent studies[39] establish a 16-ps error limit. Experiments were run for a time sufficient to collect a minimum of 2000 counts in the highest channel (about 300 000 counts in 512 channels), when collecting at 5% of the 22-kHz lamp frequency. The 5% factor assures that few double photons are collected. Excitation was generally at 280 nm. Optical densities were adjusted to 1.6–2.0 at the excitation wavelength. All runs were performed at 77 K in 4:1 methylcyclohexane–isopentane solvent. The data are reported as follows: compound, average lifetime, average rate of decay, number of runs, estimated error in rates.

1,1-Bis(*p*-methoxyphenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene; 2.7 ns, $k_{dt}^{77} = 3.7 \times 10^8$ s^{-1}, five runs, 5%.

3,3-Dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)-1,4-pentadiene: 1.9 ns, $k_{dt}^{77} = 5.2 \times 10^8$ s^{-1}, 5 runs, 5%.

1,1-Bis(*p*-*N*,*N*-dimethylaminophenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene: 3.5 ns, $k_{dt}^{77} = 2.9 \times 10^8$ s^{-1}, 13 runs, 15%.

1,1-Bis(*p*-methoxyphenyl)ethylene: 4.4 ns, $k_{dt}^{77} = 2.3 \times 10^8$, one run.

Magic Multipliers. For each compound, the fluorescence spectrum was recorded in 4:1 methylcyclohexane–isopentane solution at 77 and 295 K under otherwise identical conditions using an Aminco–Kiers spectrofluorometer with a Hanovia 901C-1 150-W xenon lamp. Concentrations were adjusted to give an optical density in the range of 0.8–1.2, thus minimizing scatter. An excitation wavelength of 280 nm was used for each compound. The magic multipliers were obtained from a single sample by integrating the emission intensities obtained at the two temperatures. Values obtained were as follows: 1,1-bis(*p*-methoxyphenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene, $M = 95$ (2 runs); 3,3-dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)-1,4-pentadiene, $M = 75$ (two runs); 1,1-bis(*p*-N,N-dimethylaminophenyl)-3,3-dimethyl-5,5-diphenyl-1,4-pentadiene, $M = 70$ (two runs); 1,1-bis(*p*-methoxyphenyl)ethylene, $M = 77$ (two runs).

Acknowledgment. Support of this research by the National Science Foundation, by NIH Grant GM07487, and by the U.S. Army Research Office is gratefully acknowledged.

Registry No.—**5,** 65366-58-7; **6,** 65366-59-8; **7,** 65366-60-1; **8,** 53392-28-2; **9,** 65366-61-2; **10,** 56405-96-0; **11,** 65392-12-3; **12,** 56405-97-1; **13,** 65366-62-3; **14,** 65366-63-4; **15,** 65366-64-5; **16,** 65366-65-6; **17,** 65366-66-7; **18,** 65366-67-8; **19,** 65366-68-9; **21,** 4356-69-8; dimethyl 3,3-dimethylglutarate, 19184-67-9; *p*-methoxyphenyllithium, 14774-77-7; *p*-methoxyphenyl bromide, 104-92-7; 3,3-dimethyl-1,1,5,5-tetrakis(*p*-methoxyphenyl)pent-4-en-1-ol, 65392-13-4; *p*-*N*,*N*-dimethylaminophenyllithium, 13190-50-6; 3-carbomethoxy-3-methylbutanoic acid, 32980-26-0; 4,4-bis(*p*-methoxyphenyl)-3,3-dimethyl-4-hydroxybutanoic acid lactone, 65366-69-0; 4,4-bis(*p*-methoxyphenyl)-2,2-dimethyl-4-hydroxybutanoic acid lactone, 65366-70-3; Ph_2CO, 119-61-9; Ph_2CHOH, 91-01-0; 3,3-dimethyl-5,5-diphenyl-5-hydroxypentanoic acid, 65366-71-4; 5,5-bis(*p*-methoxyphenyl)-3-dimethyl-4-pentenoic acid, 65366-72-5.

References and Notes

(1) (a) This is paper 111 of the present series; (b) for a preliminary communication describing a part of these results, see H. E. Zimmerman, W. T. Gruenbaum, R. T. Klun, M. G. Steinmetz, and T. R. Welter, *J. Chem. Soc., Chem. Commun.*, 228 (1978).

(2) For the previous paper (110) on Mechanistic and Exploratory Organic Photochemistry, see H. E. Zimmerman and T. P. Cutler, *J. Chem. Soc., Chem. Commun.*, 232 (1978). In our previous papers we erroneously referred to this as a *J. Am. Chem. Soc.* publication forthcoming.

(3) H. E. Zimmerman and G. L. Grunewald, *J. Am. Chem. Soc.*, **88,** 183 (1966).

(4) H. E. Zimmerman, R. W. Binkley, R. S. Givens, and M. A. Sherwin, *J. Am. Chem. Soc.*, **89,** 3932 (1967).

(5) (a) H. E. Zimmerman and A. C. Pratt, *J. Am. Chem. Soc.*, **92,** 6267 (1970); (b) H. E. Zimmerman, P. Baeckstrom, T. Johnson, and D. W. Kurtz, *ibid.*, **96,** 1459 (1974); (c) H. E. Zimmerman, J. D. Robbins, R. D. McKelvey, C. J. Samuel, and L. R. Sousa, *ibid.*, **96,** 4630 (1974); (d) H. E. Zimmerman, T. P. Gannett, and G. E. Keck, *J. Am. Chem. Soc.*, **100,** 323 (1978); (e) note also the elegant studies by Mariano[7] dealing with di-π-methane reaction stereochemistry.

(6) S. S. Hixson, P. S. Mariano, and H. E. Zimmerman, *Chem. Rev.*, **73,** 531 (1973).

(7) (a) P. S. Mariano and R. B. Steitle, *J. Am. Chem. Soc.*, **95,** 6114 (1973); (b) P. S. Mariano and J. K. Ko, *ibid.*, **95,** 8670 (1973).

(8) (a) H. E. Zimmerman and P. S. Mariano, *J. Am. Chem. Soc.*, **91,** 1718 (1969); (b) H. E. Zimmerman and G. E. Samuelson, *ibid.*, **91,** 5307 (1969); (c) H. E. Zimmerman and G. A. Epling, *ibid.*, **94,** 8749 (1972).

(9) (a) H. E. Zimmerman and A. A. Baum, *J Am. Chem. Soc.*, **93,** 3646 (1971); (b) H. E. Zimmerman, D. P. Werthemann, and K. S. Kamm, *ibid.*, **96,** 439 (1974).

(10) (a) H. E. Zimmerman and A. C. Pratt, *J. Am. Chem. Soc.*, **92,** 6259 (1970); (b) H. E. Zimmerman and B. R. Cotter, *ibid.*, **96,** 7445 (1974).

(11) V. J. Traynelis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *J. Org. Chem.*, **27,** 2377 (1962).

(12) D. J. Sam and H. E. Simmons, *J. Am. Chem. Soc.*, **94,** 4024 (1972).

(13) H. E. Zimmerman, *Mol. Photochem.*, **3,** 281 (1971).

(14) Reference 13 contains several typographical errors. The nickel sulfate, cobalt sulfate, cupric sulfate filter transmits at 295–345 nm. The ultraviolet transparent epoxy cement contains anhydride hardener, stannous octoate, and epoxide in a 100:1:250 ratio. Finally, the height of the black box upper compartment (dimension d in Figure 3) is 28 cm.

(15) C. H. Hatchard and C. A. Parker, *Proc. R. Soc. London, Ser. B,* **140,** 470 (1953).

(16) H. E. Zimmerman and L. M. Tolbert, *J. Am. Chem. Soc.*, **97,** 5497 (1975).

(17) H. E. Zimmerman, K. S. Kamm, and D. P. Werthemann, *J. Am. Chem. Soc.*, **97,** 3718 (1975).

(18) H. E. Zimmerman, R. D. Rieke, and J. R. Scheffer, *J. Am. Chem. Soc.*, **89,** 2033 (1967).

(19) H. E. Zimmerman and C. M. Moore, *J. Am. Chem. Soc.*, **92,** 2023 (1970).

(20) (a) L. Salem, *Science,* **191,** 822 (1976); (b) L. Salem and C. Rowland, *Angew. Chem., Int. Ed. Engl.*, **11,** 92 (1972)

(21) J. Slater, "Quantum Theory of Molecules and Solids", Vol. 1, McGraw-Hill, New York, N.Y. 1963, p 67.

(22) J. Michl, *Mol. Photochem.*, **4,** 243 (1972).

(23) L. Salem and C. Rowland, *Angew. Chem., Int. Ed. Engl.*, **11,** 92 (1972).

(24) (a) H. E. Zimmerman, *Tetrahedron, Suppl. 2,* **19,** 393 (1963); (b) *Science,* **153,** 3738 (1965).

(25) We have classified photochemical reactions into a variety leading directly to the ground state and another which does not.[26,27] In the case of the former, we have noted that a photochemical reaction will be "allowed" when there is a one-electron degeneracy somewhere along the reaction coordinate and that at this point an easy transition to ground state becomes available.[28] Thus the two considerations, ease of motion along the excited-state surface and ease of loss of electronic excitation, are related.[29]

(26) H. E. Zimmerman and D. I. Schuster, *J. Am. Chem. Soc.*, **84,** 4527 (1962).

(27) Note also L. Salem, *J. Am. Chem. Soc.*, **96,** 3486 (1974), for a more recent discussion and inclusion of symmetry assignments to the cases described.

(28) H. E. Zimmerman, *J. Am. Chem. Soc.*, **88,** 1566 (1966).

(29) Loss of electronic excitation has been nicely discussed by J. Michl; note ref 22.

(30) All melting points were determined on a hot-stage apparatus calibrated with known compounds.

(31) W. G. Brown and F. Greenberg, *J. Org. Chem.*, **28,** 599 (1963).

(32) J. A. Moore and D. E. Reed, "Organic Synthesis", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 351.

(33) All chromatography on silica gel employed Vycor glass columns slurry packed in hexane with Grace grade 62 (60–200 mesh) silica gel with 2% by weight of Sylvania no. 290 phosphor (calcium silicate doped with manganese and lead) added to allow monitoring of elution by quenching of the red phosphor luminescence upon observation using an ultraviolet lamp with filter

(34) L. Meites and T. Meites, *Anal. Chem.*, **20,** 984 (1948).

(35) For chromatography columns of silicic acid. Vycor glass columns were slurry packed with a mixture of 80% Mallinckrodt CC-7 (200–325 mesh), 18% Eagle-Picher Celatom, and 2% Sylvania no. 290 red phosphor in hexane.

(36) H. LeMoal, A. Foucaud, R. Carrie, D. Danion, and C. Fayat, *Bull. Soc. Chim. Fr.*, 828 (1964).

(37) H. E. Zimmerman and T. R. Welter, unpublished results.

(38) E. C. Murray and R. N. Keller, *J. Org. Chem.*, **34,** 2234 (1969).

(39) H. E. Zimmerman and T. P. Cutler, *J. Chem Soc., Chem. Commun.*, submitted for publication.

Effect of Additives and Solvents on the Fate of the Primary Photoproduct of 1,3-Dicarbonyl Compounds[1]

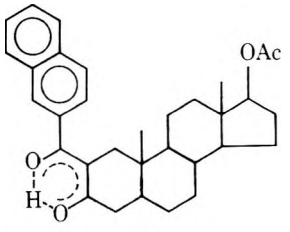
D. Veierov,*[2] T. Bercovici, Y. Mazur, and E. Fischer

Departments of Organic and Structural Chemistry, The Weizmann Institute of Science, Rehovot, Israel

Received August 31, 1977

The primary photoproduct of the chelated enol tautomer of the title compounds is a nonchelated enol. Primary and tertiary amines added at up to equimolar concentrations greatly enhance the rate of the secondary thermal reactions, i.e., re-formation of the chelated enol, and tautomerization to the diketone. Triethylamine enhances the quantum yield of photoketonization. Ethanol added at up to 0.5 M concentrations also enhances the rate of the thermal re-formation of the starting compound. Differences between the solvents hexane, cyclohexane, benzene, and acetonitrile are marginal. It is suggested that the unchelated enol transient undergoes efficient formation of a complex with the amines and, to a much smaller extent, with ethanol. The rates of the spontaneous reactions of these complexes differ greatly from those of the free transient.

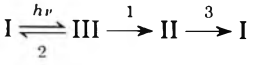
In our previous paper[1] we showed that the primary photoproduct of solutions of the (stable) chelated enols I in aliphatic hydrocarbons is a short-lived nonchelated enol III which then either reverts thermally to I or tautomerizes to the corresponding diketone II. (Both II and III may exist in several conformeric forms, Chart I). In steady irradiation experiments one observes only the so-called photoketonization I → II. Since in most cases I is thermodynamically more stable, II eventually reverts to I, but at rates much smaller than III → II. If the mechanism of photoketonization is indeed as indicated in Scheme I, the overall quantum yield of I → II will depend on the ratio of the rates of the thermal steps 1 and 2. Since these reactions involve either formation of an H bond (III → I) or a proton transfer (III → II), one may expect them to be sensitive to additives such as amines, alcohols, or acetonitrile and to be affected by the nature of the solvent used.



Ih

The results may in turn extend our knowledge of the postulated nonchelated enol III. Compounds a–h described earlier[1] were investigated in this context, but only b and c were studied in greater detail. As will be shown, the rates of all three thermal reactions, III → II, III → I, and II → I, are enhanced by amines and ethanol, while acetonitrile has little effect. The absorption spectra of I are in no case affected by the additives.

Scheme I



Experimental Section

Photochemical and Spectrophotometric Methods. These were essentially as described.[1] The light intensity during irradiations was varied by using wire mesh screens of known transmission. After each experiment, the cell was rinsed with hydrochloric acid, followed by water, acetone, and finally benzene, before drying.

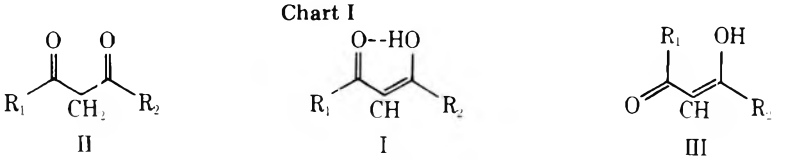
Compounds, Solvents. The compounds have been described.[1] *n*-Heptane, cyclohexane, and benzene were dried by passing them through columns filled with Woelm basic alumina and kept over Molecular Sieves. Absolute ethanol, triethylamine, and *n*-hexylamine were purified by standard methods.[3a]

Results

Steady Irradiation Experiments. Photoketonization. The relative rates of photoketonization I → II were studied spectrophotometrically in the presence of varying concentrations of additives.

(a) Triethylamine, TEA. Freshly prepared concentrated solutions of TEA in the respective hydrocarbon solvent were added to 10^{-4} to 10^{-5} M solutions of the compounds to give final TEA concentrations of up to 10^{-4} M. Under these conditions the absorption spectrum above 200 nm is not affected by TEA (Figure 1). The solutions were irradiated in 10-mm cells at a wavelength determined by the absorption of the respective compound: 254 nm with compounds a and f, 295–410 nm with b–e, and 313 nm with g and h. As shown in Figure 1, almost complete conversion into the ketone can be obtained. The relative rates of photoconversion were measured in a range of TEA concentrations. In these experiments, Figure 2, the extent of photoconversion never exceeded 20%. The spectral changes in the absence and presence of TEA were identical. Isosbestic points were observed up to high extents of photoketonization and also during the subsequent slow thermal reversion to the enol I. Threefold to tenfold variations in the light intensity affected neither the nature nor the quantum yield of the reaction in any of the eight compounds. The quantum yield of I → II was enhanced by TEA, the extent varying widely with the compound (Figure 2). In those compounds in which the quantum yield is very small in the absence of TEA, addition of the latter caused a maximal 40–

Chart I



	a	b	c	d	e	f	g
R_1	methyl	methyl	methyl	methyl	phenyl	ethoxy	ethoxy
R_2	methyl	phenyl	2-naphthyl	2-anthryl	phenyl	methyl	phenyl

0022-3263/78/1943-2006$01.00/0

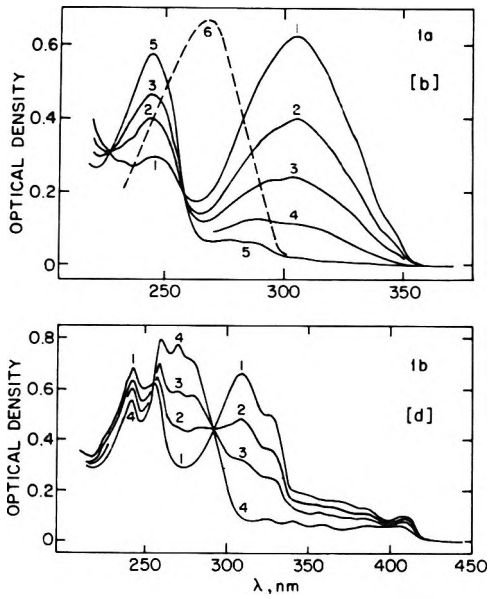


Figure 1. Photoketonization: (a) Spectral changes induced by irradiation of a cyclohexane solution of b (3.70×10^{-5} M) and TEA (4.0×10^{-6} M): (curve 1) before irradiation, (curves 2–5) after 0.75, 1.5, 3, and 6 min of irradiation, respectively, (curve 6) absorption spectrum of IIIb, from flash measurements. (b) Spectral changes induced by irradiation of a cyclohexane solution of [d] (1.9×10^{-5} M) and TEA (1.9×10^{-6} M): (curve 1) before irradiation, (curves 2–4) following 0.5, 1.5, and 4.5 min of irradiation.

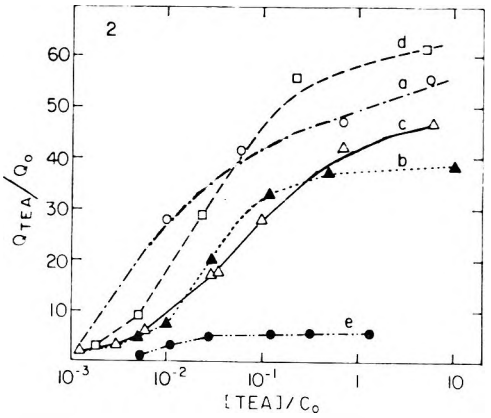


Figure 2. The ratio of the quantum yields in the presence (Q_{TEA}) and absence (Q_0) of TEA as a function of the ratio of concentrations of TEA and of the compound, C_0. Compounds as indicated for each curve.

60-fold increase (compounds a–d, where $Q_{I \rightarrow II} \approx 10^{-3}$) or a sixfold increase (compound e, $Q_{I \rightarrow II} \approx 5 \times 10^{-4}$). In fact, the spectra shown in Figure 1 could only be taken in the presence of TEA. In contrast, the rate of photoketonization in the two ketoesters f and g ($Q_{I \rightarrow II} = 0.10$–$0.15$) and in the steroid diketone h ($Q_{I \rightarrow II} = 4 \times 10^{-5}$) is hardly affected by TEA. Some results are summarized in Table I. The relative rate of photoketonization was found to be independent of the actual concentrations of either the enol or TEA in the approximate range 10^{-6} to 10^{-4} M, and to vary only with the ratio of the concentrations, [TEA]/[compound] (Figure 2). This point was checked by measuring the rates in cells of 100, 10, and 1 mm light path, using such concentrations of the compound and of TEA that the absorption spectra were the same in all three cells.

(b) 1-*n*-Hexylamine, HA. Addition of this primary amine, whose pK_b is similar to that of TEA, caused only a slight decrease in the rates of photoketonization, at concentrations up to equimolar with the two compounds investigated, b and c

Table I. Quantum Yields of the Photoketonization I → II in the Absence (Q_0) and Presence of TEA (Q_{TEA}) (Approximate Maximal Values, cf. Figure 2)

Compd	$10^3 \times Q_0$	$10^2 \times Q_{TEA}$
a	1.3	8
b	1.2	5
c	1.9	9
d	0.66	5
e	0.46	0.3

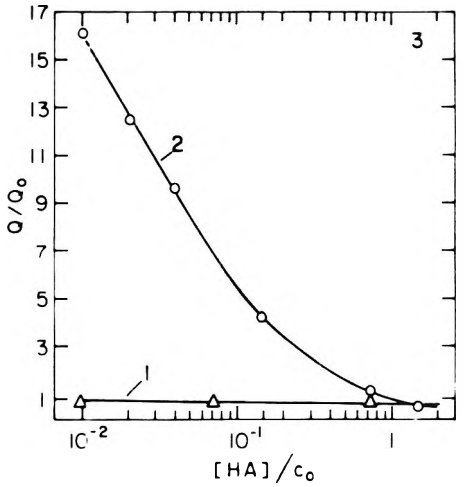


Figure 3. The effect of hexylamine, HA, on the relative quantum yield of photoketonization, Q/Q_0, of compound c in cyclohexane ($C_0 = 3.8 \times 10^{-5}$ M) in the absence (curve 1) or presence (curve 2) of TEA (1.4×10^{-6} M). Abscissa: the ratio of the concentrations of hexylamine and the compound.

(4–5×10^{-5} M in cyclohexane). However, when added together with TEA in cases where the latter sharply enhances the rates, HA reduces these rates and at sufficiently high concentrations may completely cancel the enhancement caused by TEA (Figure 3). The actual rate of photoketonization is determined only by the ratio [HA]/[TEA], irrespective of the order in which the amines were added or any previous irradiation in the presence of TEA only.

(c) Acetonitrile, CH_3CN,[4] did not affect the rates of photoketonization of b and c in cyclohexane even at 1 M.

(d) Ethanol. Ethanol attenuates the photoketonization rate of Ia–Ic both in the absence and in the presence of TEA. Thus, with a 5×10^{-5} M solution of b in cyclohexane, a tenfold decrease of the rate Ib → IIb was achieved by adding ethanol to a final concentration of 0.5 M. In the presence of 5×10^{-6} M TEA a similar decrease is achieved by 0.15 M ethanol. Clearly the ethanol concentrations required to affect the photoketonization rates are four to five orders of magnitude higher than those of TEA. The ketoesters f and g show a completely different behavior; even when *dissolved* in ethanol their rates of photoketonization are similar to those observed in cyclohexane.

Flash Experiments. Formation and Decay of the Nonchelated Enol, III. Flash photolysis of solutions of enols I results in the transient formation of nonchelated enols, III, which decay in parallel paths to I and II.[1] In analogy with the steady irradiation experiments described in the previous paragraph we studied the effect of the same additives on the extent of the photoformation of III and, as far as possible, on the rates of its decay along both paths. The concentration of the III isomer was estimated[1] from the attenuation of the absorbance due to the depletion of I 1 ms after the flash (duration <0.05 ms). Solutions of b (ca. 10^{-5} M) and c (ca. 4×10^{-6} M) were measured at 335 and 350 nm, respectively.

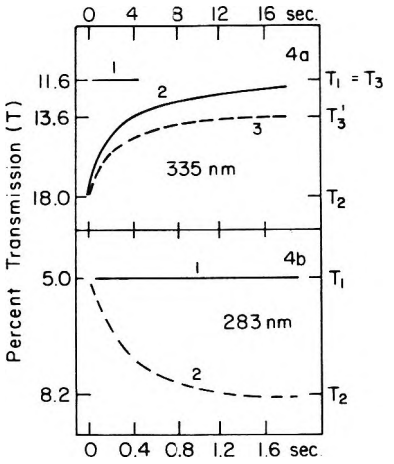


Figure 4. Flash photolysis of a *n*-heptane solution of b (1.2×10^{-5} M) in the absence and presence of TEA (4.5×10^{-6} M). (a) Time dependence of the optical transmission T at 335 nm, where only Ib absorbs: (curve 1) transmission before the flash, (curve 2) following a flash in the absence of TEA (top time scale), (curve 3) the same as curve 2 in the presence of TEA (bottom time scale!). (b) Time dependence of the transmission at 283 nm, following the flash: (curve 1) without TEA, (curve 2) with TEA (bottom time scale!). Cf. also Figure 1a.

Neither the two amines at up to 10^{-5} M nor ethanol had any appreciable effect on the extent of I depletion in cyclohexane solutions, nor was there any marked difference between solutions in *n*-heptane, absolute ethanol, or acetonitrile. In both b and c the equilibrium enol–ketone is practically completely in favor of the enol I in all solvents used here. The time-resolved decay curves at various wavelengths help to understand the nature of the changes following the initial photoformation of III. At a wavelength where only I absorbs, one observed the re-formation of I from III, while at the isosbestic wavelength of the system I $\rightleftharpoons$ III, at which II absorbs much less, it is possible to follow the reaction III $\rightarrow$ II independently of any interconversion III $\rightarrow$ I. In compounds a–e dissolved in either heptane, benzene, acetonitrile, 5% ethanol in heptane, or 5×10^{-6} M hexylamine in heptane, the only process observable in the flash apparatus is the regeneration of I, in accordance with the very low quantum yield (about 10^{-3}) of ketonization to II observed in steady irradiation experiments. However, addition of TEA to solutions of a (1.4×10^{-5} M), b (1.2×10^{-5} M), or c (8×10^{-6} M) in heptane caused a different behavior. The absorbance of I was not recovered completely, and solutions measured in the Cary 14 a few minutes after flashing still showed partial conversion into the corresponding II form. (Complete reversion to I took place only after an hour or so.) Figure 4 furnishes a characteristic example, observed in a heptane solution of b, before and after addition of TEA (cf. also Figure 1a). The absorption at 335 nm, where only I absorbs, is seen to be reduced immediately after the flash to a similar extent both with and without TEA. However, in the absence of TEA the original absorption T_1 recovers completely within about 20 s ($T_3 = T_1$) while in its presence recovery is much faster but only partial, to T'_3 (Figure 4a). The difference $T'_3 - T_3$ increases with the concentration of TEA. At the isosbestic wavelength of the I $\rightleftharpoons$ III system, 283 nm (Figure 4b), one observes in the presence of TEA a gradual decay of the absorption, starting immediately after the flash, while in the absence of TEA a horizontal line is of course obtained. From these and similar results we conclude that TEA enhances the otherwise very inefficient spontaneous conversion III $\rightarrow$ II. Hexylamine, added on top of TEA, attenuated the difference $T'_3 - T_3$ in Figure 4a and $T_2 - T_1$ in Figure 4b. The correlation between the results of the steady and flash irradiation experiments is thus satisfactory.

Table II. Rate Constants of the Spontaneous Reaction III → I at Room Temperature in Various Solvents[a]

Compd	Solvent	k, s^{-1}
a	H	0.27
	AN	0.92
	H + E	690
b	CH	0.33
	B	0.17
	AN	0.87
	H + E	290
c	CH	0.34
	B	0.14
	AN	0.99
	H + E	340
d	CH	0.49
	B	0.34
	AN	1.1
	H + E	350
e	CH	70
	B	9
	0.5% E in CH	110
	1.5% E in CH	700
h	CH	0.83
	B	0.10
	AN	0.69
	H + E	140
g	H	0.11
	H + E	2.8

[a] Concentrations were $2.5–8 \times 10^{-6}$ M. Solvents: H = *n*-heptane, CH = cyclohexane, B = benzene, AN = acetonitrile, H + E = 5% ethanol in heptane.

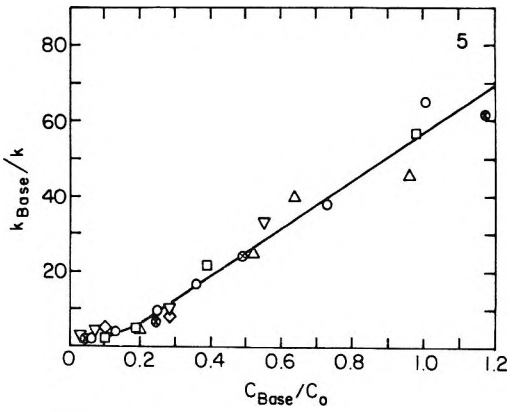


Figure 5. The base-induced enhancement of the rate of the thermal conversion III $\rightarrow$ I in *n*-heptane solutions of compounds a, 8.3×10^{-6} M (triangles), b (circles), and c, 3.5×10^{-6} M (squares). Regular symbols denote solutions with hexylamine, twisted or X-ed symbols denote solutions with triethylamine. Abscissa: ratio of concentrations of base and compound; ordinate: ratio of reaction rate constants in the presence and absence of the respective base.

The solvent dependence of the rate of spontaneous isomerisation III $\rightarrow$ I was studied in a series of solvents by looking at the kinetics of regeneration of I after a short light flash. Table II summarizes the results in heptane, benzene, acetonitrile, and 0.5–5% ethanol in *n*-heptane. Differences between the three solvents studied are seen to be small, but 5% ethanol in *n*-heptane enhances the rate up to 1000-fold as do 5 equiv of hexylamine or TEA. Figures 5 and 6 show the detailed variation of the rate of re-formation of I, after the flash, with the concentration of added base.

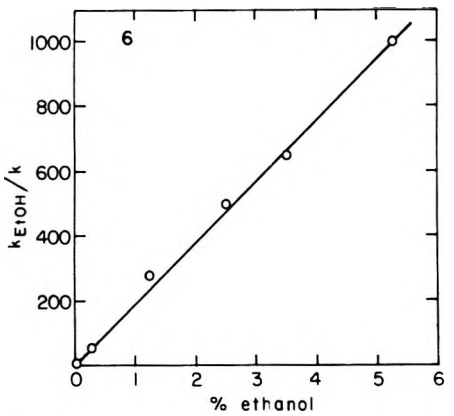


Figure 6. The effect of ethanol on the rate of the reaction IIIb → Ib in a 3.5×10^{-5} M solution of b in *n*-heptane. k and $k_{ethanol}$ denote the rate constants in the absence and presence of ethanol, respectively.

Discussion

If we assume the correctness of the mechanism proposed earlier,[1] i.e, Scheme I, the results lead to the following conclusions: (a) the primary photoreaction I → III is not affected by the additives nor by the solvents investigated, indicating that no "productive" interaction between the additives and I takes place in the ground or excited states; (b) the secondary thermal reactions I ← III → II are strongly enhanced by hydrogen donors or acceptors (the two amines and ethanol) but not by using a medium of high dielectric constant per se (acetonitrile); (c) TEA specifically enhances III → II in those cases where the photoketonization yield is small in the absence of additives, thereby increasing this yield dramatically, while ethanol preferentially enhances III → I, causing a decrease in photoketonization yield; (d) to a lesser extent II → I is also enhanced by all three additives. As a working hypothesis we may assume that III interacts strongly with the additives Ad by means of its free CO and OH groups, while I, in which these groups are neutralized by the chelate bond between them, does not interact. The complexes [III–Ad] thus formed from III undergo isomerization to I and tautomerization to II just like III but at much higher rates, $k'_1 \gg k_1, k'_2 \gg k_2$, so that already at rather low extents of complexation the reactions of the complex will predominate and the extent of photoketonization will be determined by k'_2/k'_1 for each additive. In fact, the possibility cannot be excluded that, at least in compounds b and c, the observed very inefficient photoketonization in the absence of additives is actually due to spurious impurities, at concentrations as low as 10^{-7}–10^{-8} M, acting as additives in the above sense.

The question thus arises by which mechanism complexes of III with amines and alcohols can undergo conversion into I and II much more efficiently than III itself and why TEA preferentially enhances III → II. With regard to the hydrogen transfer from oxygen to carbon involved in ketonization, we assume that in III the conjugation effect of the adjacent keto group on the hydroxy group makes the latter a better proton donor. This assumption is supported by the observation[5,6] that the so-called "fixed trans enols" which contain a keto group

Scheme II

$$\begin{array}{c} \text{III} + \text{Ad} \\ \downarrow \\ \text{I} \overset{k_1}{\longleftarrow} \text{III} \overset{k_2}{\longrightarrow} \text{II};\ \text{I} + \text{Ad} \overset{k'_1}{\longleftarrow} [\text{III–Ad}] \overset{k'_2}{\longrightarrow} \text{II} + \text{Ad} \end{array}$$

where Ad may be HA, TEA, or ethanol

conjugated to a hydroxy group, but unable to form an H bond with it, are much stronger acids than the chelated enolic forms of β-diketones. Thus a $pK_a = 5.2$ was reported for dimedon and 2.8 for methylketene dimer,[5] as against 8.09 for Ia and 8.13 for If.[6] One may therefore expect that partial or even complete proton transfer takes place from the enolic OH groups to the amine,[7] which may then act as a transfer agent. This role of the nitrogen may be similar to that suggested by us[1] for the etheric oxygen in the 3-keto esters. Indeed in these compounds, g and f, the photoketonization yield is high from the start and not affected by TEA, meaning that the ratio k'_2/k'_1 is barely influenced by the additive, while it is enhanced about 50-fold in compounds a–d. The fact that in compound e this ratio is affected much less, and in compound h not at all, indicates that in these two compounds additional factors are involved. In e the rate of IIIe → Ie is particularly high, and it appears that the second aromatic group preferentially enhances k_1. In h the large steroid group may invoke steric factors[8] which enhance the energy of the transition state responsible for the reaction IIIh → IIh. As to the isomerization III → I, if it involves rotation about a quasisingle bond,[1] the rates observed ($k = 0.1$–$1\ s^{-1}$, Table II) are rather slow for such a process and indicate that either the bond order is appreciably above unity because of contributing bipolar mesomeric forms or some other factor is involved.

The reaction III → I involves a decrease in the number of degrees of freedom, and its rate may be determined largely by the activation entropy.[9] In the complex with an amine, in which the molecule probably exists as a negative ion, rotation is more facile, be it because of the lower bond order or because in the strongly polar complex the tendency is to minimize the extent of charge separation as achieved in the U form characteristic for the salts of 1,3-diketones.[10]

Schematically, if we denote the chelated enol ROH, the nonchelated (unstable) enol $\overline{\text{ROH}}$, and the amine A, the situation may be described by the following

$$\overline{\text{ROH}} \xrightarrow{+A} [\overline{\text{ROH}}\text{–A}] \rightarrow [\rightarrow \overline{\text{RO}}^{-}\text{–AH}^{+}]$$

$$\rightarrow [\text{RO}^{-}\text{–AH}^{+}] \rightarrow [\text{ROH–A}] \xrightarrow{-A} \text{ROH}$$

The short but barriered direct route is thus replaced by the multistep route in which smaller barriers have to be overcome. The difference between the primary and the tertiary amine may be due to steric factors. However, another reason may be that the primary amine can act either as a proton acceptor (from OH) or donor to form a hydrogen bond with the keto group. As such it may promote proton transfer from one oxygen to the other, in competition with the transfer from oxygen to carbon. A somewhat similar mechanism has been suggested for the proton transfer reactions in acetyl-acetone dissolved in secondary amines.[11]

The enhancement of the rate of III → I by ethanol is probably due to $k'_1 \gg k_1$ in a similar complex between III and ethanol. However, in this case much larger concentrations of additive are required, indicating that the complexes with ethanol are much weaker than those with amines. A possible role of ethanol as an acid catalyst cannot be ruled out but appears improbable in view of the fact[1] that the nonchelated enols III are themselves rather strong acids, certainly much stronger than ethanol.

It is interesting to note that k_1 in benzene solutions is considerably smaller than in heptane or cyclohexane (Table II). This attenuation of rotation about the quasisingle bond may be due to formation of complexes, in which "the positive end of the molecular dipole (of the solute) is situated above the plane of the aromatic ring" (of the solvent).[12]

Finally[13] a word about the possible role of water. Obviously

the usual procedures of drying solvents and cells cannot prevent the presence of water in the solutions at concentrations at least as high as those of the compounds and the amines, i.e., 10^{-3}–10^{-5} M. In the absence of experiments under "superdry" conditions it is not possible to assess the effect of such water traces. However, the very pronounced effect of amines on the kinetics observed in solutions containing such water traces remains an experimental fact. In nonpolar solvents it is reasonable that the compounds studied, as well as the amines, form associates with these traces of water.

Registry No.—Ia, 1522-20-9; Ib, 1704-14-9; Ic, 65311-55-9; Id, 65311-56-0; Ie, 1704-15-0; Ig, 1522-33-4; Ih, 65311-57-1; IIa, 123-54-6; IIb, 93-91-4; IIc, 13298-50-5; IId, 50593-99-2; IIe, 120-46-7.

References and Notes

(1) Previous paper: D. Veierov, T. Bercovici, E. Fischer, Y. Mazur, and A. Yogev, *J. Am. Chem. Soc.*, **99**, 2723 (1977).
(2) Part of a Ph.D. Thesis by D. V., approved by the Weinberg Graduate School of the Weizmann Institute of Science, Rehovot, 1974.
(3) (a) D. D. Perrin, W. L. F. Armarego, and D. A. Perrin in "Purification of Laboratory Chemicals", Pergamon, Oxford, 1966, pp 45–47 and 351; (b) J. W. Smith in "The Chemistry of the Amino Group", S. Patai, Ed., Interscience, London, 1968, pp 174 and 175.
(4) Dielectric constant at 20 °C = 37.5.
(5) E. S. Gould, "Mechanism and Structure in Organic Chemistry", Holt, Rinehart and Winston, New York, N.Y., 1959, pp 212 and 216.
(6) G. S. Hammond in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, pp 445–450.
(7) M. D. Joesten and L. J. Schaad, "Hydrogen Bonding", Marcel Dekker, New York, N.Y., 1974, p 12.
(8) (a) C. J. Collins and J. F. Eastham in "The Chemistry of the Carbonyl Group", Vol. 1, S. Patai, Ed., Interscience, London, 1966, pp 789 and 790 and references cited therein; (b) M. Hanack, "Conformation Theory", Academic Press, New York, N.Y., pp 267–269 and references cited therein.
(9) S. T. Yoffe, P. V. Petrovsky, Ye. I. Goryunov, T. V. Yershova, and M. I. Kabachnik, *Tetrahedron*, 2783 (1972).
(10) H. E. Zaugg and A. D. Schaefer, *J. Am. Chem. Soc.*, **87**, 1857 (1965).
(11) L. W. Reeves and W. G. Schneider, *Can. J. Chem.*, **36**, 793 (1958).
(12) M. T. Rogers and J. L. Burdett, *Can. J. Chem.*, **43**, 1516 (1965), and references cited therein.
(13) We are grateful to one of the referees for pointing out a possible role of water traces.

Photochemistry of Epoxides. 4. Photoreduction of a Monoepoxide of *endo*-Dicyclopentadiene[1a]

Donald R. Paulson,* A. Spencer Murray,[1b] and Eric J. Fornoret[1c]

Department of Chemistry, California State University, Los Angeles, Los Angeles, California 90032

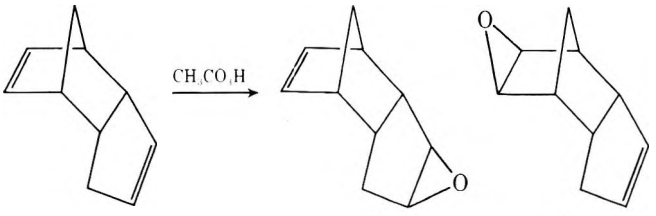
Received November 1, 1977

Two monoepoxides of *endo*-dicyclopentadiene have been prepared by peracetic acid oxidation. Acetone sensitized photolysis of *endo*-4-oxatetracyclo[6.2.1.$0^{2,7}$.$0^{3,5}$]undec-9-ene (**1**) results in efficient photoreduction of the double bond via a free-radical mechanism. Photolysis of model compounds indicates that there is no interaction between the triplet state excited olefin and the epoxy moiety.

Photochemical $2\pi + 2\pi$ intramolecular cyclizations have been used extensively in the synthesis of polycyclic molecules.[2] Recently, $2\pi + 2\sigma$ photochemical cyclizations have been reported by Prinzbach and others.[3] As a continuation of our studies into the photochemical interaction of olefinic and epoxide moieties,[4] we have investigated the acetone sensitized photolysis of the monoepoxides of dicyclopentadiene. These molecules were chosen for study because the close proximity of the olefinic π bond and the carbon–carbon σ bond of the epoxy group might make them amenable to $2\pi + 2\sigma$ intramolecular photocyclization.

Peracetic acid epoxidation of *endo*-dicyclopentadiene gave two monoepoxides in a 1:1.5 ratio. The major product is assigned as *endo*-9-oxatetracyclo[5.3.1.$0^{2,6}$.$0^{8,10}$]undec-3-ene (**2**) while the minor product is assigned as *endo*-4-oxatetracyclo[6.2.1.$0^{2,7}$.$0^{3,5}$]undec-9-ene (**1**). The structures of these two epoxides were first correctly assigned by Alder and Stein.[5] However, they did not obtain a pure sample of epoxide **1**. The assigned structures are readily confirmed by infrared and NMR analysis. Epoxide **1** shows strong absorption at 835 cm^{-1} which is characteristic of the epoxycyclopentane system[6] while epoxide **2** shows strong absorption at 850 cm^{-1} which is characteristic of the 2,3-epoxybicyclo[2.2.1]heptane system.[6] The NMR spectrum of epoxide **2** has an AB pattern centered at δ 1.1 for the protons at C_{11}. This clearly indicates an *exo*-nornornyl epoxy group.[7] The remainder of the spectral data is consistent with the assigned structures (see Experimental Section).

The photochemistry of **1** and **2** was then investigated. Epoxide **2** was found to be essentially inert in both polar and nonpolar solvents using a wide variety of sensitizers and exciting wavelengths. In marked contrast, however, photolysis of **1** in degassed acetone solutions with a 450 W Hanovia medium pressure lamp equipped with a Pyrex filter resulted in formation of **3**[6] in 18–36% yield, **4** (and **4′**) in 14–33% yield, and 2,5-hexandione in 2–10% yield. Low concentrations of **1** (0.01 M) favored **3** while higher concentrations of **1** (0.5 M) favored **4** (**4′**).



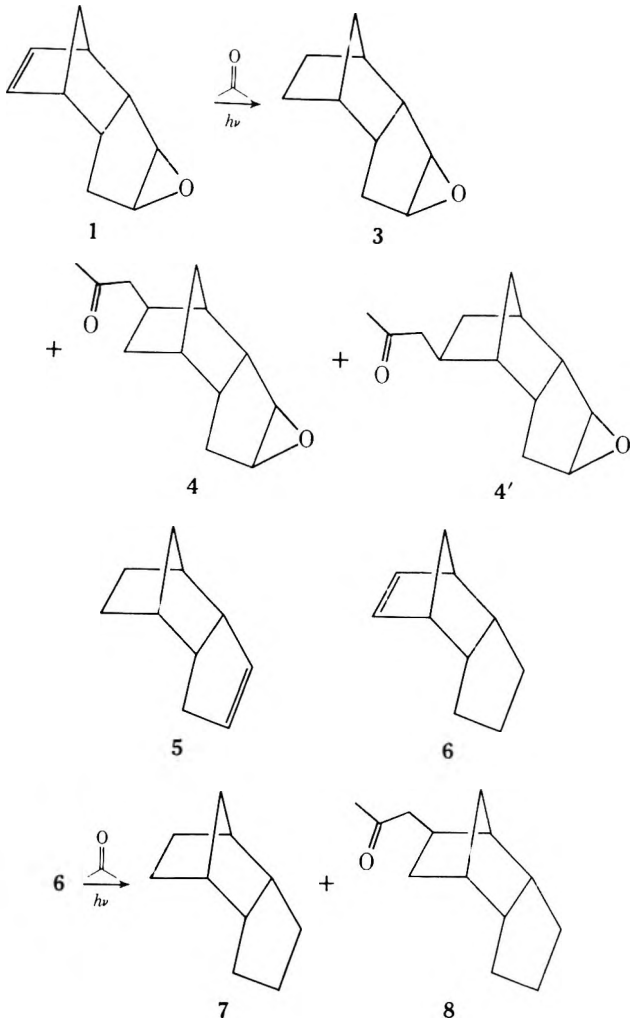
1 **2**

The infrared spectrum of **3** has a strong band at 838 cm^{-1} as expected for an epoxycyclopentane system. We were unable to completely separate **4** and **4′**. However, the infrared spectrum displays a carbonyl band at 1710 cm^{-1} and a strong epoxy cyclopentane band at 837 cm^{-1}. The NMR shows the methyl ketone at δ 2.10.

In order to determine the effect, if any, of the epoxide functional group upon the photoreactivity of **1** and **2**, the photolysis of **5**[6] and **6**[8] was investigated.

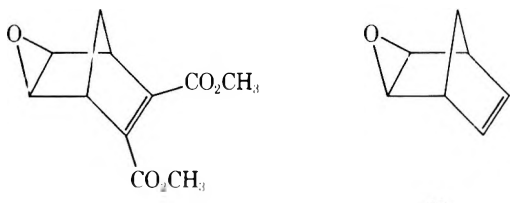
In analogy to epoxide **2**, compound **5** was found to be essentially inert to a wide variety of photochemical conditions. However, photolysis of **6** in acetone solution resulted in the formation of **7**[9] (14–28%), **8** (30–48%), and 2,5-hexandione

0022-3263/78/1943-2010$01.00/0



(1–2%). Again, low concentrations of **6** favored formation of the photoreduced compound **7** while higher concentrations of **6** favored the acetonyl addition compound **8**. Thus the photochemistry of this system is unaltered by the presence of the epoxide functionality.

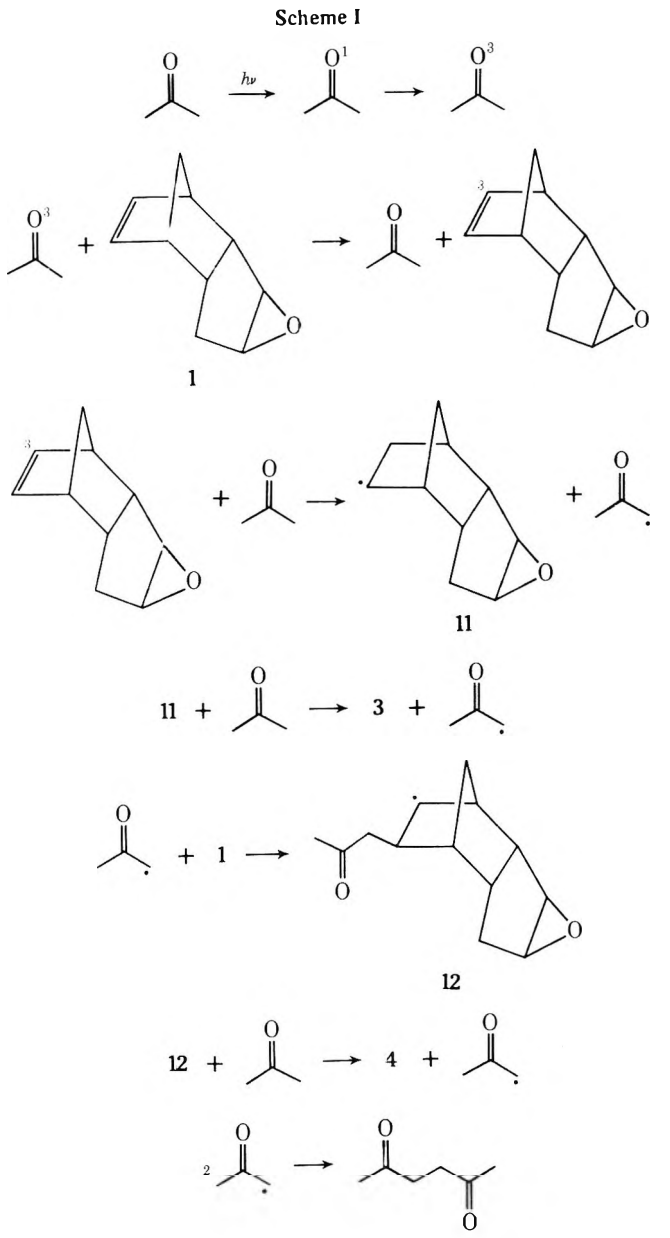
In contrast to our results, compound **9** undergoes competitive $2\pi + 2\sigma$ cyclization and photoreduction[3] while in our system only photoreduction was observed. The difference in reactivity between **1** and **9** is probably due to an excited state of much lower energy in **9**, due to the extended conjugation. Thus the hydrogen abstracting ability of the triplet excited state of **9** would be greatly diminished over that of **1** and cyclization can now effectively compete with hydrogen abstraction. In accord with this explanation, photolysis of **10** in acetone yielded only the photoreduction product.[10]



9 **10**

Mechanistically the reaction probably proceeds through a photosensitized free-radical chain process. The mechanism is shown below; however, other possible sensitized mechanisms could also be postulated. The reaction is initiated by energy transfer from triplet state acetone to yield triplet state **1**. Hydrogen abstraction from acetone by triplet state **1** produces **11** and an acetonyl radical. A second hydrogen abstraction produces **3** and another acetonyl radical. The 2,5-

Scheme I



hexandione arises via radical coupling of two acetonyl radicals. A radical coupling between **11** and an acetonyl radical could account for the formation of **4** (**4′**); however, it is not reasonable for the major product in a free-radical transfer process to occur via a termination step. A more plausible pathway would be the addition of acetonyl radicals to the double bond to produce **12** followed by another abstraction from acetone giving **4**. The exo face is usually the preferred position of attack on norbornene systems by free radicals.[1]

Similar photoreactions to those described here have been reported. Sauers has observed both acetonyl radical addition and photoreduction of several norbornenes by photolysis in acetone.[12] Srinivasin and Hill report[13] an acetonyl addition to cyclobutene under similar conditions. Using considerably higher concentrations than used in the present study, Sharf[14] has observed acetonyl addition and dimerization of tetracyclic homologues of norbornene during photolysis in acetone. These reactions presumably proceed by the same mechanism as those in the present study. The balance between photoreduction, acetonyl addition, and dimerization appears to be a delicate function of the olefin concentration. At very high concentrations (5–10 M) acetone sensitization results in mainly dimerization while at moderate concentrations (~1 M) acetonyl addition products predominate. Finally, at very

low concentrations of olefins, the simple photoreduction becomes a major process.

The possibility still existed that the $2\pi + 2\sigma$ cycloaddition of 1 was a viable reaction but one that proceeded an order of magnitude slower than the abstraction of hydrogen from the acetone sensitizer. In view of the known resistance of cyclopropyl groups to hydrogen abstraction,[15] it was felt that dicyclopropyl ketone (DCK) might be an ideal sensitizer to effect the desired cycloaddition. However, irradiation of 1 in the presence of DCK did not result in any photoreaction of 1. This lack of photoreactivity could be due to a triplet energy of DCK that is too low to efficiently generate norbornene triplets.

Photolysis of dicyclopentadiene (1%) in the presence of DCK produced the expected intramolecular cycloaddition product[16] in excellent yield. Photolysis of norbornene in 10% DCK/benzene yielded the norbornene dimers in a 1:8 ratio in agreement with that reported for acetone sensitization.[17] Furthermore, there was no photoreduction of the norbornene as occurs in the case of acetone sensitization.

These results indicate that DCK is an excellent triplet sensitizer for norbornene type molecules since it does not produce concurrent photoreduction of the alkene. Finally, these results show that intramolecular $2\pi + 2\sigma$ photocyclization will not occur from the triplet state of 1 even when the photoreduction route is completely suppressed.

Experimental Section

Infrared spectra were obtained with a Perkin-Elmer Model 137 spectrophotometer. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer. Melting points were taken in a Hoover-Thomas Capillary Melting Point Apparatus and are uncorrected. Gas chromatography (GPC) was performed on F & M Model 700 and Model 701 gas chromatograph. The analytical column was 10 ft × ⅛ in. 15% carbowax 20 M on 60–80 Chromosorb W; the preparative column was 10 ft × ⅜ in. 15% carbowax 20 M on 60–80 Chromosorb W. Percentage composition data were estimated by peak areas. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

Epoxidation of Dicyclopentadiene. To an ice-cold mechanically stirred mixture of 15.0 g (0.133 M) of *endo*-dicyclopentadiene and 105 g of anhydrous sodium carbonate in 225 mL of methylene chloride was added dropwise 24.9 g (0.131 M) of 40% peracetic acid which had been pretreated with a small amount of sodium acetate. After addition was complete the mixture was stirred at room temperature until the solution gave a negative starch–iodide test (~20 h). The solid salts were removed by suction filtration and washed well with an additional 250 mL of solvent. The solvent was removed from the filtrate by flask evaporation to give 20 g of crude product. GLC analysis of the crude product showed unreacted dicyclopentadiene and two products in the ratio of 1:1:1.5. Column chromatography of 4.0 g of crude product over silica gel using benzene as eluent gave 1.0 g of pure 1 and 1.2 g of pure 2. The minor product 1 was identified as *endo*-4-oxatetracyclo[6.2.1.$0^{2,7}$.$0^{3,5}$]undec-9-ene, mp 85–86 °C. The infrared spectrum (CCl_4) of 1 displays strong bands at 725 and 835 cm^{-1} and weak absorption at 1625 cm^{-1}. The NMR spectrum shows (CCl_4) 4-proton multiplet at δ 1.1–2.1, 6-proton multiplet at 2.3–3.3, and a 2-proton multiplet (CH=CH) centered at 6.04. Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.36; H, 8.26.

The major product was identified as *endo*-9-oxatetracyclo[5.3.1.$0^{2,6}$.$0^{8,10}$]undec-3-ene (2).[5] mp 76–78 °C (lit.[5] mp 79–80 °C). The infrared spectrum (CCl_4) shows absorption at 1640 (weak), 850, and 706 cm^{-1}. The NMR (CCl_4) shows an AB pattern (J = 9.0 Hz) centered at δ 1.098, a 10-proton multiplet from 2.1–3.3, and a 2-proton broad singlet at 5.6.

Photolysis of 1. A. Preparative. A 1.0-g sample of epoxide 1 was dissolved in 100 mL of spectral grade acetone, degassed for 10 min by bubbling nitrogen through the solution and photolyzed for 100 min with a Hanovia 450 W medium pressure lamp equipped with a Pyrex filter. The acetone was removed by flash evaporation to give a gummy mass which was extracted with petroleum ether. The petroleum ether was removed by flash evaporation to give 0.54 g of greenish yellow oil. GPC analysis showed three volatile products in the ratio of 6:1:3.8. The three products were separated by preparative GPC.

The major product was identified as *endo*-4-oxatetracyclo[6.2.1.$0^{2,7}$.$0^{3,5}$]undecane (3) by direct comparison with an authentic sample.[6]

Table I

[1], M	% 3	% 2,4-hexandione	% 4 (4′)
0.017	36	11	14
0.034	34	6	
0.068	30	5	19
0.136	23	2	
0.204	18	2	33

Table II

[6], M	% 7	% 8
0.018	28	36
0.068	22	48
0.340	14	45

The second product was identified as 2,4-hexandione by direct comparison with an authentic sample.

The third product is assigned as a mixture of the two *exo*-acetonyl compounds 4 and 4′. They could not be separated by GPC or column chromatography. The sample shows IR (CCl_4) band at 1725 (C=O) and 838 cm^{-1} (epoxide). The NMR spectrum (CCl_4) showed a 3-proton singlet at δ 1.90 (CH_3C=O). They are assigned the *exo*-acetonyl stereochemistry based on analogy to free-radical additions to norbornene systems.[11]

Photolysis of 0.5 g of 1 in 50 mL of degassed DCK or 50 mL of 10% DCK/benzene with a 450 W medium pressure Hanovia lamp equipped with a Pyrex filter resulted in no detectable volatile products.

B. Chemical Yield Studies. Samples of varying concentration were photolyzed in degassed acetone solutions using a merry-go-round apparatus and either Rayonet RPR-3000 Å bulk in Pyrex tubes or Rayonet RPR -2537 Å bulbs in quartz tubes. The overall results were essentially the same. Table I lists the maximum yields (calculated using eicosane as internal standard) which were obtained of the three photoproducts at 2537 Å.

Photolysis of Bicyclo[5.2.1.$0^{2,6}$]dec-8-ene (6). A 1.0-g sample of 6[8] was dissolved in 100 mL of spectral grade acetone, degassed for 10 min by bubbling nitrogen through the solution, and photolyzed for 90 min with a Hanovia 450 W medium pressure lamp equipped with a Pyrex filter. Nitrogen was bubbled through the solution throughout the irradiation. The acetone was removed by rotary evaporation to give a yellow oil. GPC analysis showed two photoproducts and unreacted 6 in the ratio of 1:2:1. The products were isolated by column chromatography over silica gel using benzene as eluent. A trace of 2,4-hexanedione was also isolated. The minor product was identified as bicyclo[5.2.1.$0^{2,6}$]decane (7) by comparison with an authentic sample.

The major product was assigned as *exo*-8-acetonyltricyclo[5.2.1.$0^{2,6}$]decane (8). The exo stereochemistry is assigned base on analogy to other norbornyl systems.[11] Compound 8 has a strong infrared hand at 1710 cm^{-1} (C=O). The NMR spectrum shows two distinct features of interest: a three-proton singlet at δ 2.01 and a broad two-proton doublet at δ 2.23 (J = 2.0 Hz) indicating an acetonyl group attached to a tertiary carbon. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.90; H, 10.55.

B. Chemical Yield Studies. Samples of varying concentrations were photolyzed in degassed acetone solutions using a merry-go-round apparatus and Rayonet RPR-3000 Å lamps. Table II lists the maximum yields (calculated using *n*-dodecane as internal standard) which were obtained of the two photoproducts.

Photolysis of Dicyclopentadiene. A 20-μL sample of dicyclopentadiene in 2 mL of DCK was degassed by bubbling nitrogen for 3 min and then irradiated at 3000 Å in a Pyrex tube. The only observed product was the intramolecular $2\pi + 2\pi$ cycloaddition product, identified by comparison with an authentic sample.[16]

Photolysis of Norbornene. A solution of 0.5 g of norbornene, 1.5 mL of benzene, and 100 μL of DCK was degassed by bubbling nitrogen for 3 min and irradiated in a Pyrex tube at 3000 Å. The reaction was followed by GPC. The only observable products were the two norbornene dimers (8:1 ratio).[17]

Acknowledgment. This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society, the California State University, Los Angeles Foundation, and by Research Grant RR08101-04, Minority Student Training for Biomedical Research (MBS) from the National Institutes of Health.

Registry No.—1, 52154-83-3; 2, 52154-84-4; 3, 65437-13-0; 4, 65392-50-9; 4′, 65392-49-6; 6, 2826-19-9; 8, 65392-48-5; *endo*-dicyclopentadiene, 1755-01-7; nonbornene, 498-66-8.

References and Notes

(1) (a) This paper was presented in part at the 8th Western Regional Meeting of the American Chemical Society, San Francisco, Calif., October 1972; (b) NSF Undergraduate Research Participant, Summer, 1972; (c) MBS trainee, 1975.
(2) See, for example: O. L. Chapman and G. Levy, "Organic Photochemistry", Vol. 1, Marcel Dekker, New York, N.Y., 1967, pp 283–321; P. E. Eaton, *Acc. Chem. Res.*, **1**, 50 (1968); P. de Mayo, *ibid.*, **4**, 41 (1971).
(3) H. Prinzbach, *Pure Appl. Chem.*, **16**, 17 (1968); H. Prinzbach and W. Auge, *Angew. Chem., Int. Ed. Engl.*, **8**, 209 (1969), and references contained therein.
(4) D. R. Paulson, F. Y. N. Tang, and R. H. Sloane, *J. Org. Chem.*, **38**, 3967 (1973).
(5) K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, **485**, 223 (1931).
(6) A. J. Durbetaki, *J. Org. Chem.*, **26**, 1017 (1961).
(7) J. Meinwald, S. S. Labana, L. L. Labana, and G. H. Wahl, Jr., *Tetrahedron Lett.*, 1789 (1965); K. Tori, K. Kitahonoki, Y. Takano, H. Tonida, and T. Tsuji, *ibid.*, 559 (1964).
(8) R. Wilder, C. Culberson, and G. T. Youngblood, *J. Am. Chem. Soc.*, **81**, 655 (1959).
(9) P. v. R. Schleyer, M. M. Donaldson, R. D. Nicholas, and C. Cupas, *Org. Synth.*, **42**, 8 (1962).
(10) A. Padwa and W. Koehn, *J. Org. Chem.*, **38**, 4007 (1973).
(11) P. D. Bartlett, G. N. Fickes, F. C. Haupt, and F. Hegelson, *Acc. Chem. Res.*, **3**, 177 (1970).
(12) R. R. Sauers, W. Schinski, and M. M. Mason, *Tetrahedron Lett.*, 4763 (1967), and references contained therein.
(13) R. Srinivasin and K. A. Hill, *J. Am. Chem. Soc.*, **88**, 3765 (1966).
(14) H. D. Scharf, *Tetrahedron*, **23**, 3057 (1967).
(15) W. E. Falconer, J. H. Knox, and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 782 (1961); T. Berces and A. F. Trotman-Dickenson, *ibid.*, 4281 (1961).
(16) G. O. Schenk and R. Steinmetz, *Chem. Ber.*, **96**, 520 (1963).
(17) D. R. Arnold, D. J. Trecker, and E. B. Whipple, *J. Am. Chem. Soc.*, **87**, 2569 (1965).

Nuclear Magnetic Resonance Spectroscopy. Carbon-13 and Nitrogen-15 Spectra of the Penicillins and Cephalosporins

Jonathan W. Paschal and Douglas E. Dorman*

The Lilly Research Laboratories, Indianapolis, Indiana 46206

Puliyer R. Srinivasan and Robert L. Lichter

Department of Chemistry, Hunter College of the City University of New York, New York, New York 10021

Received September 1, 1977

^{13}C and ^{15}N NMR spectra of a selection of penicillin and cephalosporin antibiotics are reported and evaluated. The ^{13}C data seem in broad accord with the present theory of ^{13}C chemical shifts. ^{15}N chemical shifts are complicated by solvent effects, and correlations with structure are frequently difficult to recognize. While ^{15}N chemical shifts show no obvious relationship to biological activity, some correlations are possible in the case of ^{13}C.

The contributions of nuclear magnetic resonance (NMR) spectroscopy to studies of the structure and conformations of penicillins and cephalosporins have been many and varied.[1] Because of the relative simplicity of these molecules, routine ^1H NMR spectra usually suffice to elucidate their structures. Nuclear Overhauser enhancement (NOE) measurements provide further information regarding configuration and conformations in these systems.[1] In the rare cases wherein ^1H NMR spectroscopy fails to distinguish structural possibilities, the ^{13}C NMR spectra can be used.[2] As part of a general exploration of the applicability of ^{15}N NMR spectroscopy to organic and biological chemistry, we have measured the ^{15}N NMR spectra of a number of penicillin and cephalosporin derivatives.[3] The purpose of the present paper is to report these results and to provide additional data regarding ^{13}C chemical shifts in these systems.

Experimental Section

Spectra were measured at natural abundance on JEOL PFT-100 multinuclear spectrometers, using the SD-HC heteronuclear decoupler. Data were collected into the JEOL EC-100 computer. Operating frequencies were 10.09 MHz for ^{15}N and 25.03 MHz for ^{13}C spectra. ^{15}N spectra were accumulated over a 4-KHz sweep width in 8 K of memory, using 15–25° tip angles and 1.2–2.0 s repetition rates. Depending on sample, accumulation times ranging from 6 to 16 h were required to obtain satisfactory signal-to-noise ratios. Data were collected and transformed under conditions which would be expected to lead to 0.7–2.0 Hz line broadening.

Whenever possible, spectra were measured in neutral or near-neutral aqueous solutions. Enough D_2O (10%) was added to provide internal lock. Carbon chemical shifts were measured relative to internal 1,4-dioxane and adjusted to the Me_4Si scale by the relation: $\delta_C(Me_4Si) = \delta_C(diox) + 67.4$. ^{15}N chemical shifts were measured relative to external NH_4Cl (2.9 M) dissolved in 1 M HCl.

^{13}C and ^{15}N resonance assignments are based on chemical shifts,[4] off-resonance and single-frequency decoupling experiments,[4] relative peak heights,[3] and partial exchange experiments.[5]

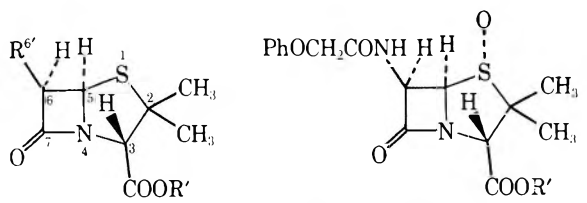
Results and Discussion

Penicillins. The structures of the penicillins studied in this work appear in Figure 1. ^{15}N chemical shift data for both the free antibiotics and their methyl esters are presented in Table I. Inasmuch as the ^{15}N spectra of the free antibiotics were measured in aqueous solutions at pH ~6, the carboxylic acid may be assumed to be fully deprotonated.

For the free penicillins, the lactam resonance appears at about 144 ppm. In penicillin V α-sulfoxide, the N(4) resonance is substantially shielded (125.9 ppm), as might be expected from the usual γ effect of oxygen in ^{15}N chemical shifts.[6,7] Because the rigid penicillin nucleus prevents the oxygen from approaching N(4) closely, this shielding cannot be due to a steric effect. This is in agreement with other studies[4b] which show that steric interactions are not essential to the shielding effects of γ heteroatoms.

Except for the example of hetacillin, the lactam nitrogen chemical shifts in these penicillins appear to be relatively insensitive to changing substitution at N(6′). The case of hetacillin is unique in that N(6′) is incorporated into a lactam ring which bears bulky substituents. In those β lactams which have been studied by x-ray crystallography,[8] the amide N–H has been shown to be projected above the β-lactam ring. In an

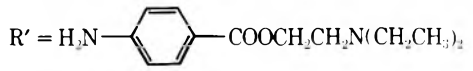
0022-3263/78/1943-2013$01.00/0



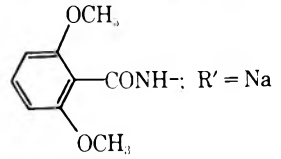
penicillin V α-sulfoxide

Penicillin G, R = $PhCH_2CONH$–; R′ = K

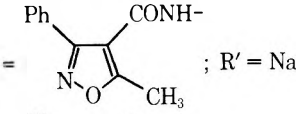
Procaine penicillin G, R = $PhCH_2CONH$–;



Penicillin V, R = $PhOCH_2CONH$–; R′ = Na

Methicillin, R =  ; R′ = Na

Ampicillin, R = $PhCH(NH_2)CONH$–; R′ = Na

Oxacillin, R =  ; R′ = Na

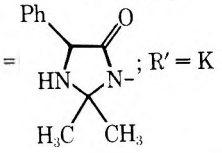
Hetacillin, R =  ; R′ = K

Figure 1. Structures of penicillin derivatives studied in this work.

Table I. ^{15}N-NMR Chemical Shifts in Penicillin Derivatives

Penicillin derivatives	Registry no.	N(4)	N(6′)	Other	Solvent
Methyl esters					
Penicillin G	653-89-4	134.3	85.1		C_6D_6
Penicillin V	2315-05-1	134.8	80.5		1,4-Dioxane
Penicillin V α-sulfoxide	25547-92-6	117.3	78.9		1,4-Dioxane
Methicillin	22668-52-6	136.8	83.4		C_6D_6
Ampicillin	65404-78-6	135.4	78.2	1.1	C_6D_6
Oxacillin	27605-29-4	135.4	87.7	274.9	CH_2Cl_2–C_6D_6
Hetacillin	4052-65-7	124.9	78.4	35.8	CH_2Cl_2–C_6D_6
Salts					
Penicillin G, K	113-98-4	143.7	90.7		H_2O
Penicillin G, K		142.6	86.6		Me_2SO
Penicillin G, procaine	54-35-3	137.1	87.3	45.2, 25.9	Me_2SO
Penicillin V, Na	1098-87-9	143.1	85.5		H_2O
Penicillin V α-sulfoxide, Na	65338-34-3	125.9	82.5		H_2O
Methicillin, Na	132-92-3	144.5	95.8		H_2O
Ampicillin, Na	69-52-3	144.5	87.6	9.6	H_2O
Oxacillin, Na	1173-88-2	144.1	92.1	262.3	H_2O
Hetacillin, K	5321-32-4	132.1	86.0	48.6	H_2O

analogous conformation, the geminal dimethyl group of the side chain of hetacillin would be expected to interact sterically with the thiazolidine ring and its substituents. We suggest that conformational differences resulting from these interactions account for the unusual ^{15}N chemical shifts in hetacillin.

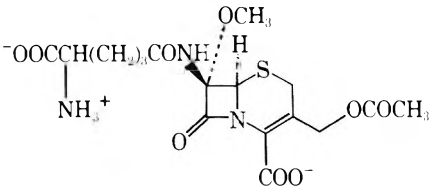
In the methyl esters of these penicillins, the lactam nitrogens are seen to come into resonance approximately 8–10 ppm higher field than in the parent antibiotics. The lactam resonance of procaine penicillin G also occurs at unusually high field. These changes are likely due to differences in the charge on the adjacent carboxylate group, in analogy to the observed changes at the β carbon of carboxylic acids.[9] In cases wherein this charge is present, the lactam nitrogen comes into resonance at relatively lower field than when the charge is absent, as in the esters, or dispersed through ion pairing, as in procaine penicillin G.

As might be expected, the chemical shift of N(6′) is much more dependent upon the identity of the amide. Some of the observed chemical shift differences can be interpreted in the light of our present understanding of ^{15}N chemical shifts. Thus, the upfield positions of N(6′) in penicillin V and ampicillin relative to penicillin G most probably result from the γ heteroatoms included in the side chains of these derivatives.[7] Other changes in the chemical shift of N(6′) are not easily explained in terms of the present theory of ^{15}N chemical shifts. Thus, the effect of the sulfoxide oxygen of penicillin V sulfoxide relative to the parent antibiotic does not correlate well with the δ effect observed in other systems;[7,10] possibly this relatively shielded position of the N(6′) resonance of the sulfoxide results from increased electronegativity[7] of the γ substituent (i.e., sulfoxide vs. sulfide). Also, the N(6′) resonances of methicillin and oxacillin are deshielded relative to penicillin G; this is opposite the shielding effect usually observed in amides in which the carbonyl is in conjugation with an aromatic group.[6] Finally, the amide nitrogen of hetacillin comes into resonance slightly upfield of that of ampicillin, even though the former has two additional β substituents. In ^{15}N chemical shifts, the β effect has been found to be strongly deshielding in nature.[6,7] The discrepancy here is likely due to the fact that N(6′) in hetacillin is incorporated into a lactam, making direct comparison with the other analogues impossible.

The chemical shifts of the amide nitrogens of the methyl esters are all shielded relative to the free penicillins, the shift differences ranging from 3.6 ppm (penicillin V α-sulfoxide) to 12.4 ppm (methicillin). Most of these differences can be ascribed to solvent effects (vide infra).

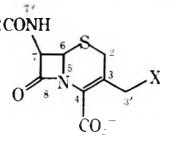
Cephalosporins. In Table II are gathered the ^{13}C and ^{15}N chemical shift data for the cephalosporins examined in this study. Because the cephalosporin nucleus has two sites of substitution (C-3′ and N-7′), it was considered likely that the ^{15}N chemical shifts would vary over a greater range than observed for the penicillins. Accordingly, some effort was made to standardize the conditions of measurement, and all the data shown in Table II were obtained from the carboxylate salt of the cephalosporanic acid dissolved in aqueous solutions at pH values between 4 and 7. In a separate study,[11] it was determined that the ^{13}C NMR spectrum of cephalosporin C (8) was invariant in this pH range, and this was assumed to obtain also for the ^{15}N chemical shifts.

Compounds 1 through 8 differ only in the structure of the amide substituent, R. It is obvious that throughout most of this series, the ^{13}C NMR spectrum is essentially insensitive to this variation. Introduction of a methoxyl group at carbon 7 (**9**) leads to the expected large changes in the chemical shifts of the resonances of carbons 7 (α effect) and 6 (β effect).[4a] The upfield shift at C(3) parallels that associated with α haloge-



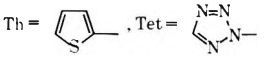
9

Table II. $^{13}C^{a}$ and $^{15}N^{b}$ Chemical Shifts in Cephalosporins

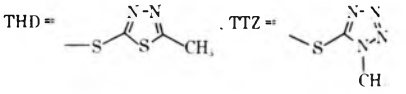


	Registry no.	R[c]	X[d]	C(2)	C(3)	C(3′)	C(4)	4-CO_2^-	N(5)	C(6)	C(7)	N(7′)	CO	C(8)
1	27267-35-2	H	OAc	26.3	117.1	64.9	132.3	169.1	129.3	57.6	58.5	89.6	165.4[e]	165.5[e]
2	32178-86-2	CH_3	OAc	26.3	116.9	65.0	132.3	169.2	129.7	58,0	59.9	87.5	175.5	165.9
3	859-07-4	$PhCH_2$	OAc	26.3	116.9	65.0	132.3	169.2	129.7	58.2	60.0	86.7	176.0	165.5
4	10390-44-0	$PhOCH_2$	OAc	26.3	117.0	65.0	132.3	169.1	129.3	58.0	59.4	81.1	172.7	165.1
5	27910-26-5	PhC(OH)H–	OAc	26.3	116.8	65.0	132.3	169.0	129.6	58.1	59.6	81.4	176.2	165.2
6	153-61-7	$ThCH_2$	OAc	26.3	116.9	65.0	132.3	169.1	129.3	58.1	60.0	85.5	174.8	165.4
7	43141-96-4	$TetCH_2$	OAc	26.3	117.2	65.0	132.3	169.2	129.1	57.8	60.0	83.5	168.2	165.1
8	47580-44-9	AAA	OAc	26.3	116.9	65.0	132.3	169.3	129.4	58.0	59.9	87.1	177.3	165.7
9	32178-82-8	7-OMe, AAA	OAc	26.5	116.7	64.8	132.4	168.8	n.a.[f]	63.4	95.7	n.a.[f]	178.1	161.1
10	34691-02-6	$ThCH_2$	H	29.3	123.2	19.4	127.5	170.6	n.a.	57.7	59.6	n.a.	174.6	165.0
11	5935-65-9	$ThCH_2$	OH	26.2	122.1	61.8	130.3	169.8	n.a.	58.2	59.9	n.a.	174.9	165.5
12	26722-85-0	$ThCH_2$	SCH_3	27.7	120.9	36.1	130.4	169.5	n.a.	58.6	59.8	n.a.	174.4	165.1
13	13057-93-7	$ThCH_2$	PYR	25.9	113.1	62.6	135.9	167.9	130.8	58.3	60.4	85.9	174.5	165.4
14	26970-95-6	$ThCH_2$	THD	27.7	119.1	38.7	131.9	168.4	n.a.	58.5	59.9	n.a.	174.3	165.3
15	33305-26-2	$TetCH_2$	THD	27.7	119.6	38.8	132.0	168.5	130.7	58.1	59.9	83.7	168.1	165.0
16	65338-32-1	PhC(OH)H–	TTZ	27.4	118.9	37.2	131.7	168.4	n.a.	58.2	59.5	n.a.	176.2	165.0
17	10209-11-7	$PhOCH_2$	H	29.3	123.4	19.4	127.6	170.4	n.a.	57.5	59.0	n.a.	172.3	164.7
18	27725-35-8	$PhC(NH_2)H$–	H	29.2	122.7	19.3	127.4	170.6	129.9	57.8	59.1	83.7	176.9	164.8

[a] In ppm from Me_4Si. [b] In ppm from NH_4Cl. [c] Abbreviations used: Ph = phenyl,



AAA = $HOOCC(NH_2)H(CH_2)_3$–. [d] PYR = pryidinium



[e] May be interchanged in assignment. [f] n.a. = not available.

nation of ketones.[4a] In analogy to the penicillins, variation of the structure of the amide substituent effects little change in the chemical shift of the lactam nitrogen. In fact, the variations in the N(5) chemical shifts in compounds **1**–**8** can be taken as a measure of the experimental error in these spectra.

Of greatest interest, however, are the chemical shift changes observed at the amide nitrogen, N(7′). Throughout the series of compounds **1**–**8**, the chemical shift of this nucleus varies over a range of approximately 8.5 ppm, thereby making it a sensitive measure of variations in the structure of R. The N(7′) chemical shift difference between **1** and **2** is small, consistent with the usually small differences between formamides and other amides.[6,7] The similarities in the chemical shifts of the N(7′) resonances of **2**, **3**, and **8** indicate that in these systems, the γ effects of phenyl and methylene groups are very small. As before, however, the addition of a γ heteroatom brings about large shielding effects at the amide nitrogen, the largest changes being observed for the highly electronegative oxygen atoms of **4** and **5**, although the smaller changes observed for nitrogen and sulfur (**7** and **6**, respectively) must be considered experimentally significant. These results are again in broad accord with the usual correlation between the magnitude of the γ effect and the electronegativity of the γ substituent.[4b,7]

Compounds **6** and **10**–**14** form another series in which only one of the substituents on the cephalosporin nucleus is varied, this time the one attached to C(3′). Practical problems and deficiencies in supply prevent our reporting ^{15}N data for more than two compounds in this series. As might have been expected, the chemical shifts of the amide nitrogen and the three carbons of the β-lactam ring are relatively unchanged through this series. Somewhat more surprising is the small change in the chemical shift of N(5) for X equal to acetate and pyridinium (**6** and **13**, respectively). This point will receive further comment below.

The identity of X has a much larger effect on the chemical shifts of nearby carbons. Comparison of the spectra of this series shows that carbon 2 varies through a range of 3.4 ppm. Relating these chemical shifts to that of C(2) in **10** (X = H), it can be seen that these changes are due to γ substitution and that the magnitude of the shift is again related to the electronegativity of the atom attached to C(3′). When this atom is oxygen (**6**, **11**) or positively charged nitrogen (**13**), the γ effect is approximately 3 ppm; for the less electronegative sulfur (**12**, **14**), the shift is nearer 1.5 ppm.

Somewhat more dramatic effects are seen in the resonances of carbons 3 and 4. In **10** (X = H), the chemical shifts of these carbons differ by approximately 4 ppm. The addition of electronegative substituents at C(3′) increases this chemical shift difference, a phenomenon which is generally associated with increasing polarization of the π-electron clouds.[4a] For electronegative substituents such as acetate and pyridinium, the differences in the chemical shifts of carbons 3 and 4 exceed 15 ppm. Concurrent, but smaller, upfield shifts are seen to occur in the carboxylate (C-4′) resonances. The importance of this bond polarization to the activity of these compounds is suggested by the fact that the two compounds showing the greatest differences between the chemical shifts of carbons 3 and 4 (*cf.* **6** and **13**) are among the most successful cephalosporin antibiotics presently available commercially.

While there are presently rather few data available, it seems

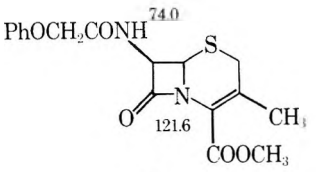
Table III. ^{15}N Data for the Acid and Sodium Salt Forms of 15

	N(5)	N(7′)	Other	Solvent
Salt[a]	130.7	83.7	204.9, 251.6	H_2O
Salt	130.8	82.1	205.7	Me_2SO
Acid	125.1	81.3	205.3	Me_2SO

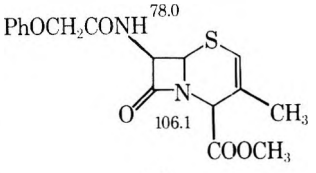
[a] Registry no. 65338-33-2.

evident from Table II that the range of chemical shifts shown by the lactam nitrogen of cephalosporins will be disappointingly small. Thus, throughout Table II, which includes compounds with X varying from H to pyridinium, the N(5) chemical shifts vary by less than 2 ppm. The contrast between this result and those discussed above for carbons 3 and 4 suggests that the effect of X is not efficiently transmitted *through* the carbon–carbon double bond to the lactam nitrogen.

When the double bond is removed from conjugation with this nitrogen, however, the chemical shift is strongly affected. Thus, the N(5) resonances of **19** and **20** differ by 15.5 ppm, a



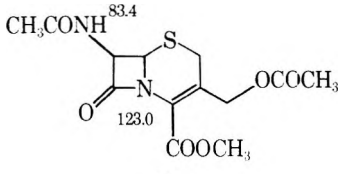
19



20

shift similar in both direction and magnitude to the chemical shift differences of the nitrogens of aniline and cyclohexylamine.[3,6,7] Also intriguing is the difference of 4 ppm in the amide nitrogen chemical shifts of **19** and **20.** This is a shift of surprising magnitude for a nitrogen so remote from the point at which the two structures differ. Most probably, the changes in these chemical shifts are influenced by the different interannular angles of the Δ^2- and Δ^3-cephem systems.[8]

In the penicillins, large changes were observed at both nitrogens in going from the free antibiotics in aqueous solution to the methyl esters in organic solvents. Comparison of the ^{15}N spectra of **2** and **21** provides a measure of the effect of the



21

analogous change in the cephalosporins. For the lactam nitrogen, this chemical shift difference is 6.7 ppm, which compares reasonably with the changes observed in the penicillins (7.2–9.4 ppm). For the amide nitrogen, the difference is 4.1 ppm, which again is similar to the previous examples. In an attempt to distinguish between the effects of differing charges on the carboxylate group and solvent effects, we measured the spectrum of **15** in both its acid and salt forms in dimethyl sulfoxide (Me_2SO) solution. The data in Table III show that the spectra of the salt of **15** in Me_2SO and water are quite similar, only the amide resonance being significantly different. This change in the chemical shift of N(7′), as well as that observed when **15** is converted to its acid form, is probably due to small changes in the solvation of the molecule. In contrast, the lactam nitrogen is seen to be shifted upfield by 5.7 ppm in the acid relative to the salt (Table III). This shift, which we believe results primarily from the change in charge on the carboxylate group, compares closely with the 6.7-ppm shift difference noted above for the lactam nitrogens of **2** and **21.** On the basis of these results, we believe that while the differences in the N(5) chemical shifts of the penicillins (Table I) can be ascribed primarily to ionization effects, the large changes in the amide nitrogen chemical shifts are largely due to solvent effects.

Conclusions

It is to be expected that ^1H NMR spectroscopy[1] will continue to be the predominantly used method in problems of structure elucidation and conformational analysis of the penicillins and cephalosporins. The greater expense of ^{13}C NMR spectroscopy in both time and money will probably result in its being reserved for rather specialized structure problems.[2,12] The present requirement for relatively large samples for ^{15}N NMR spectroscopy will make its use even more selective.

However, in structures with relatively few protons, especially at centers generally regarded as important to the biological activity, ^{13}C and ^{15}N NMR spectroscopy can provide detailed information regarding the electron distribution throughout the molecule. In some cases, there appears at least a broad correlation between carbon chemical shifts and the activities of the β-lactam antibiotics, as seen above in the cases of **6** and **13.** In a phenomenon as complex as biological activity, however, such correlations cannot be expected to be generally successful. At present, for example, there is nothing obvious in the ^{13}C or ^{15}N NMR spectra of **18** which can be correlated with its commerical success.

Many of the sources of ^{15}N chemical shifts are not well understood at present. It is apparent from the above discussion that generalizations derived from simpler systems do not necessarily apply to compounds of biological and commercial importance. Perhaps it is best to recognize the present empirical state of ^{15}N NMR spectroscopy, collecting data when possible, but without prejudicing ourselves about the type of answers we expect.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. In addition, the work at Hunter College was supported by the U.S. Public Health Service Grant GM-21148 from the Division of General Medical Sciences, the CUNY Faculty Research Award Program, the Research Corporation, and Eli Lilly and Company. Funds for the spectrometer were provided in part by NSF Instrument Grant GP-37025. We are grateful to Professor A. K. Bose for providing many of the samples used in this study.

References and Notes

(1) P. V. Demarco and R. Nagarajan in "Cephalosporins and Penicillins. Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, N.Y., 1972, Chapter 8.
(2) S. Kukolja, N. D. Jones, M. O. Chaney, T. K. Elzey, M. R. Gleissner, J. W. Paschal, and D. E. Dorman, *J. Org. Chem.*, **40**, 2388 (1975).
(3) R. L. Lichter and D. E. Dorman, *J. Org. Chem.*, **41**, 582 (1976).
(4) (a) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972; (b) E. L. Eliel et al., *J. Am. Chem. Soc.*, **97**, 322 (1975).
(5) R. A. Newmark and J. R. Hill, *J. Magn. Reson.*, **21**, 1 (1976).
(6) R. L. Lichter in "Determination of Organic Structures by Physical Methods", Vol. 4, F. C. Nachod and J. J. Zuckerman, Ed., Academic Press, New York, N.Y., 1971, Chapter 4.
(7) R. L. Lichter and J. D. Roberts, *J. Am. Chem. Soc.*, **94**, 2495 (1972).
(8) R. M. Sweet in ref 1, Chapter 7.
(9) R. Hagen and J. D. Roberts, *J. Am. Chem. Soc.*, **91**, 4504 (1969).
(10) D. E. Dorman and J. W. Paschal, *J. Am. Chem. Soc.*, **98**, 6885 (1976).
(11) J. W. Paschal and D. E. Dorman, unpublished results.
(12) C. R. Harrison and P. Hodge, *J. Chem. Soc., Perkin Trans. 1*, 1772 (1976).

Synthesis, Carbon-13 Nuclear Magnetic Resonance, and Mass Spectral Studies of 3-Aroyloxy-3,5,5-trimethyl-1-pyrazoline *N*-Oxides

Elie Abushanab,* Iou-Iou Sytwu,[1] August Zabbo, and Leon Goodman

Departments of Medicinal Chemistry and Chemistry, University of Rhode Island, Kingston, Rhode Island 02881

Received September 23, 1977

A new oxidative method for the synthesis of 1-pyrazolines (**2**) from 2-pyrazolines (**1**) utilizing benzoyl peroxides was discovered. Oxidation of **2** with *m*-chloroperbenzoic acid resulted in the formation of the corresponding 1- and 2-oxides (**3** and **4**). Chemical degradation of **4** and ^{13}C NMR and mass spectral fragmentation studies of **2**, **3**, and **4** led to unequivocal assignment of the position of the N-oxide function.

The recent interest in the chemistry of the azoxy function is partly related to its occurrence in natural products with potent physiological activity. Cyasin[2] a potent carcinogen[3] and elaiomycin[4] a tuberculostatic agent[5] serve as examples. Furthermore, azoxides are believed to be hydrolytic metabolic intermediates responsible for the biological activity of the clinically useful nitrosoureas.[6] Our interest in 3-aroyloxy-1-pyrazoline *N*-oxides as potential anticancer agents is based on the rationale that related azoxides could be generated upon the in vivo hydrolysis of these compounds.

Unlike previous reports on the preparation of cis[7] and trans[7a,8] azoxyalkanes, synthetic methods for 3-oxysubstituted azoxides are rather limited. Methoxide fragmentation of a nitrosourethanocyclopropane furnished a 3-methoxy-1-pyrazoline 1-oxide.[9] Silver ion assisted displacement of bromide in phenylbromomethyldiazene 1-oxide by oxygen nucleophiles afforded the corresponding substituted compounds.[8] Peracid oxidation of 3-acetoxy- and 3-benzoyloxy-3,5,5-trimethyl-1-pyrazolines (**2a** and **2b**) furnished, depending on the peracid used, the corresponding 1- and 2-oxides.[10] It is this latter method that was used in the present work to prepare the title compounds.

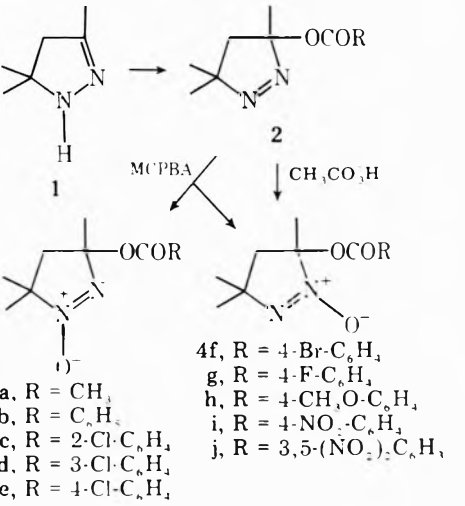
Freeman synthesized **2a** and **2b** by oxidation of the 2-pyrazoline (**1**) with lead tetraacetate and lead tetrabenzoate, respectively.[10] The instability of lead salts of substituted benzoic acids[11] did not allow the use of this method for the preparation of a variety of aromatic esters whose rates of hydrolysis could have interesting biological implications. However, a new method for oxidation of such 2-pyrazolines was discovered when it was noted that treatment of **1** with an equimolar quantity of benzoyl peroxide, with the aid of illumination, yielded the known **2b**.[10] This same method permitted the synthesis of the substituted 3-benzoyloxy-1-pyrazolines (**2c–i**) as shown in Scheme I. The benzoyl peroxides were prepared by treatment of the corresponding acid chloride with sodium or hydrogen peroxide.[12]

The reactions were carried out in chloroform or benzene at room temperature and gave 40–60% yields of the product. It is believed that this oxidation takes place via radical intermediates as depicted in Scheme II.

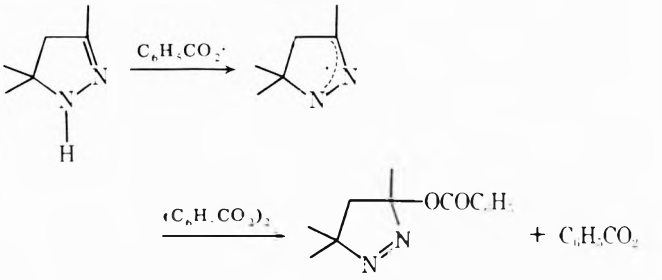
Similar oxidations have been reported. α-Benzoyloxy ketones have been prepared by treatment of their enamines with benzoyl peroxide followed by hydrolysis.[13] Pyrimidines have also been oxidized to their 5-benzoyloxy derivatives.[14]

Peracid oxidation of **2** followed already reported procedures.[10] While peracetic acid gave only the 2-oxide (**4**), *m*-chloroperbenzoic acid (MCPBA) gave a mixture of the 1- and 2-oxides (**3** and **4**). The need for both isomers prompted us to use the latter method where separation of the *N*-oxide mixture was accomplished by column chromatography on silica gel. This method of separation, although it furnished pure isomers, resulted in extensive decomposition of what is believed to be the 1-oxide isomer (**3**) (vide infra). This is evidenced by gas

Scheme I



Scheme II



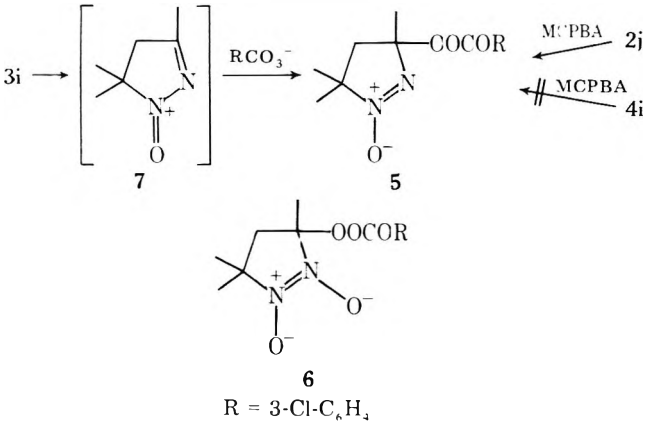
generation and the isolation of the corresponding benzoic acid.

Oxidation of the 4-nitrophenyl compound (**2i**) produced unexpected results. In addition to the 1- and 2-oxides, a minor product was isolated whose mass spectrum suggested the presence of chlorine in the molecule evidenced by pairs of peaks at *m/e* 300, 298; 158, 156; 111, 139; and 113, 111, with intensity ratios of 1:3. The last six fragments are characteristic of chlorobenzoic acids as has been observed in the mass spectra of **3c–3e** and **4c–4e**. That the chlorine is in the meta position is shown by the identity of the aromatic regions in the ^{13}C- and ^{1}H-NMR spectra to those of **3d** and by the absence of the AA′BB′ pattern expected for *p*-nitro benzoic acid. The presence of chlorine was further confirmed by elemental analysis which gave the compound an empirical formula of $C_{13}H_{15}N_2O_4Cl$. Based on the above data the structure of the compound could be either **5** or **6**.[15]

Although ultraviolet data could be used to distinguish between cyclic azoalkane *N*-oxides and *N,N′*-dioxides,[16] this method could not be applied here, since the ultraviolet spectra of **2d**, **3d**, **4d** and the unknown were almost identical.[19] However, the carbonyl absorption of **5** (**6**) was distinctly different

0022-3263/78/1943-2017$01.00/0

Scheme III



from (1786 cm^{-1}) and was shifted to higher frequency than those for **2d**, **3d**, and **4d** (1748 cm^{-1}). Since analogous frequency differences have been observed between esters and peresters,[20] the compound is assigned structure **5**.

The formation of the perester **5** is visualized to arise from protonated **3i** (Scheme III). Elimination of 4-nitrobenzoic acid furnished the intermediate **7** which is trapped with the more nucleophilic *m*-chloroperbenzoate ion to give the product **5**. Support for this mechanism was obtained when **3i** and **4i** were subjected to oxidation with MCPBA. The perester **5** was obtained from the former only thus ruling out the intermediacy of the latter. The oxidation of the 3,5-dinitrophenyl compound **2j** with MCPBA gave increased **5** and the 2-oxide **4j**, while the 1-oxide **4i** was not obtained. This demonstrates further that the stronger the electronegativity of the substituents on the phenyl ring the easier the solvolysis of the 1-oxide.

Determination of the *N*-oxide position was derived from chemical and spectral methods. Freeman reported[10] the base decomposition of **4b** and the isolation of mesityl oxide from the reaction mixture. This result could be duplicated for our compounds resulting in the isolation of the α,β-unsaturated ketone.

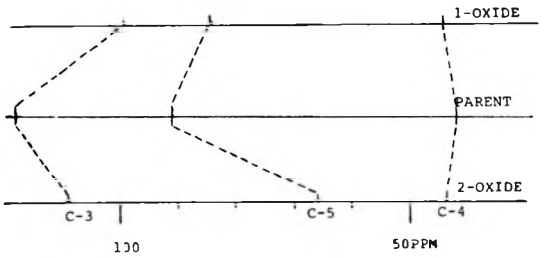


Figure 1.

In addition to the above chemical approach, two spectral methods have been developed for determining the position of the *N*-oxide, namely, ^{13}C-NMR and mass spectral fragmentation studies. The chemical shifts of the carbonyl carbons as well as those of C-3, C-4, and C-5 in compounds **2**, **3**, and **4** are listed in Tables I, II, and III, respectively.

It is noted that *N*-oxidation exerts very little influence on the chemical shifts of >C=O and C-4 while it has a shielding effect on both C-3 and C-5. The shileding magnitude however is not the same for both carbons and is reversed as one goes from a 1-oxide to the isomeric 2-oxide. For example, C-5 is less shielded in **3b** than in **4b** (−6.29 vs. −24.74 ppm) while the reverse is true for C-3 which is more shielded in **3b** than in **4b** (−17.79 vs. −8.86 ppm). A schematic representation of the average of shileding effects on carbons 3, 4, and 5 is shown in Figure 1.

A suggestion for the greater shielding of C-3 in the 1-oxides is offered in Scheme IV. Resonance effects of the *N*-oxide increase electron density at the neighboring nitrogen in **9** and **11**, which results in the observed shielding of the adjacent carbon. Analogous shielding effects have been observed for pyridine oxide[21] and 1,2,4-triazine 1- and 2-oxides.[22]

The observed smaller shielding of C-5 and C-3 in the 1- and 2-oxides, respectively, appears, at first glance, to be an anomaly since one expects the positive charge at the oxygen-bearing nitrogen in **9** and **11** to deshield the adjacent C-3 and C-5, respectively. A reasonable explanation is derived from

Table I. Physical Data and Yields of 1-Pyrazolines (2)

2	Registry no.	^{13}C chemical shift, ppm C_4	C_5	C_3	>C=O	Mp, °C	Yield, %
b	65441-76-1	42.2	90.8	118.1	164.5	68–70 (lit. 70–71)[10]	59
c	65441-77-2	41.8	90.5	118.5	163.4	Oil	20
d	65453-03-4	41.7	90.3	118.1	163.0	37–8	75
e	65441-78-3	42.0	90.6	118.3	163.6	75–6	42
f	65441-79-4	42.0	90.5	118.2	163.7	94–6	55
g	65441-80-7	42.2	90.4	117.9	163.4	70–4	50
h	65441-81-8	41.8	90.5	118.2	163.3	64–7	46
i	65441-82-9	42.1	91.4	119.7	163.4	113–5	42
j	34277-62-8	41.9	91.1	119.4	160.5	159–61	35

[a] Satisfactory analytical data (±0.4 for C, H, and N) were reported for all compounds.

Table II. Physical Data and Yields of 1-Pyrazoline 1-Oxides (3)[a]

3	Registry no.	^{13}C chemical shifts, ppm C_4	C_5	C_3	>C=O	Mp, °C	Yield, %
b	65441-83-0	45.5	84.6	100.3	164.9		*b*
c	65441-84-1	45.1	84.6	100.9	163.7	Oil	27
d	65441-85-2	45.4	84.6	100.6	163.6	52–64	28
e	65441-86-3	45.5	84.8	100.6	164.1	117–19	26
f	65441-87-4	45.6	84.6	100.5	164.1	110–12	37
g	65441-88-5	45.4	84.5	99.9	163.9	110–14	32
h	75441-89-6	45.3	84.7	100.4	163.8	112–14	28
i	65441-90-9	45.5	85.6	101.9	163.8	123	18

[a] Satisfactory analytical data (±0.4 for C, H, and N) were reported for all compounds. [b] Prepared by the method reported in ref 10.

Table III. Physical Data and Yields of 1-Pyrazoline 2-Oxides (4)[a]

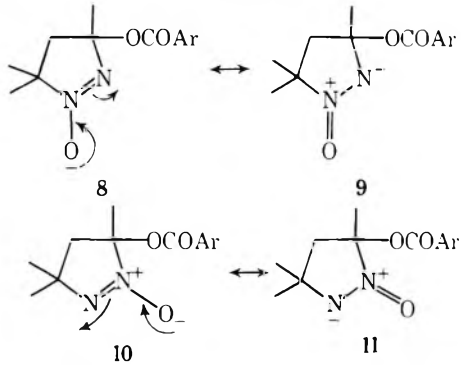
4	Registry no.	^{13}C chemical shifts, ppm C_4	C_5	C_3	>C=O	Mp, °C	Yield, %
b	65441-91-0	43.8	66.1	109.2	163.7		*b*
c	65441-92-1	44.1	66.3	109.6	162.6	92–5	23
d	65441-93-2	43.8	66.2	109.4	162.5	125–7	29
e	65441-94-3	44.1	66.4	109.6	163.1	136–7	21
f	65441-95-4	44.0	66.2	109.4	163.0	137–40	14
g	65441-96-5	44.2	66.1	109.2	163.5	138–40	16
h	65441-97-6	44.1	66.2	109.4	162.8	120–4	18
i	65441-98-7	43.7	66.7	110.7	163.1	187–8	23
j	65441-99-8	43.8	66.5	110.1	160.0	183–5	21

[a] Satisfactory analytical data (± 0.4 for C, H, and N) were reported for all new compounds. [b] Prepared by the method reported in ref 10.

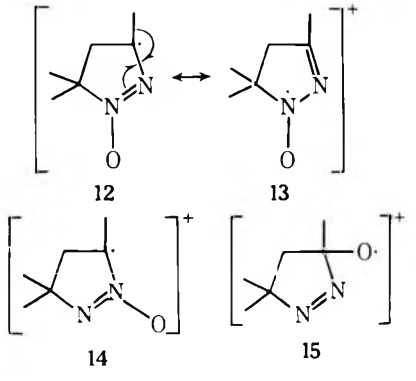
the ^{1}H-NMR data of pyridine and the pyridinium ion.[23] In pyridine, H-2 experiences most the anisotropic effect of the lone electron pair of nitrogen and thus is most deshielded. However, upon protonation, H-3 and H-4 experience a deshielding effect with little change in the chemical shift of H-2. The deshielding effect of the positive charge on nitrogen is largely canceled by the reduction in the anisotropy of the nitrogen atom. Using this argument one can explain the observed shielding of the carbons adjacent to the positive nitrogen in **9** and **11** as a result of incomplete cancellation of two opposite effects. ^{1}H-NMR studies on cis azoxyalkanes have been reported to cause shielding of α protons;[7] however, the authors indicated that similar effects on α carbons were not observed.

Mass spectral data of compounds **2, 3,** and **4** provided an additional method for the location of the N-oxide function. A mass unit *m/e* 127 appeared in the fragmentation pattern of only the 1-oxides, Scheme V. This fragment corresponds to the relatively stable radical cation **12** which can be resonance stabilized by the *N*-oxide function as shown in **13.** This explains the absence of the corresponding species **14** of the 2-oxide which lacks similar resonance stabilization. That the *m/e* 127 peak is not due to species **15** is provided by the absence of this unit in the spectra of the parent pyrazolines (**2**).

Scheme IV



Scheme V



Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{13}C-NMR spectra were recorded on Varian CFT-20 and ^{1}H-NMR data on Varian A-60 or Jeolco C-60HL NMR spectrometers. All NMR spectra were determined in $CDCl_3$, except for the 4-nitro and 3,5-dinitrophenyl derivatives (**i** and **j**) which were obtained in deuterioacetone and are expressed as δ in ppm units downfield from Me_4Si. Mass spectra were obtained on a DuPont 490 mass spectrometer. Elemental analyses were performed by Microanalysis, Inc., Wilmington, Del. Melting points and yields, which were not optimized, for the 1-pyrazolines (**2**) and their 1- and 2-oxides (**3** and **4**) are listed in Tables I, II, and III, respectively.

3-(4-Chlorobenzoyloxy)-3,5,5-trimetyl-1-pyrazoline (2e). The following procedure is representative for all other substituted 3-benzoyloxy-3,5,5-trimethyl-1-pyrazolines.

A mixture of 14.5 g (0.14 mol) of **1,** 46.7 g (0.15 mol) of 4-chlorobenzoyl peroxide, and 550 mL of benzene or chloroform was stirred at room temperature, under nitrogen and illumination by incandescent light, for 12 h. The mixture was filtered and then washed with saturated aqueous sodium bicarbonate solution. The benzene or chloroform layer was dried and filtered through a short column of silica gel. Evaporation of the filtrate and recrystallization of the residue twice from aqueous ethanol or ether–hexane gave **2e.** When crystallization was not possible, column chromatography on silica gel eluting with an ether–hexane mixture was used to purify the products.

3-(4-Chlorobenzoyloxy)-3,5,5-trimethyl-1-pyrazoline 1- and 2-Oxides (3e and 4e). The following procedure is also representative for all other substituted 3-benzoyloxy-3,5,5-trimethyl-1-pyrazoline 1- and 2-oxides.

To a solution of the pyrazoline (**2e,** 3.9 g, 0.015 mol) in 10 mL of chloroform was added a solution of 3-chloroperbenzoic acid (6.1 g, 0.03 mol calcd at 85% purity) in 180 mL of chloroform, and the reaction mixture was stirred at room temperature for 18 h, washed with three 50-mL portions of saturated aqueous sodium bicarbonate solution, dried, and evaporated to give 4.5 g of the crude product which showed two spots on thin layer chromatography (TLC). Column chromatography of the mixture over 120 g of silica gel after elution with benzene–acetone (99:1) gave first 1.45 g of the 1-oxide (**3e**) then 0.7 g of the 2-oxide (**4e**) for a total yield of 51%. After recrystallization from chloroform–hexane, the analytical samples were obtained.

3-(3-Chlorobenzoylperoxy)-3,5,5-trimethyl-1-pyrazoline 1-Oxide (5). To a solution of the pyrazoline (**2i,** 7.5 g, 0.027 mol) in 40 mL of chloroform was added a solution of 3-chloroperbenzoic acid (7.5 g, 0.037 mol calcd at 85% purity) in 220 mL of chloroform and the reaction mixture was stirred at room temperature for 20 h and then another portion of 3-chloroperbenzoic acid (5g, 0.025 mol) in 100 mL of chloroform was added. The reaction mixture was stirred at room temperature for another 20 h, washed with three 100-mL portions of saturated aqueous sodium bicarbonate solution, dried, and evaporated to give 7.9 g of the crude product which showed two spots upon TLC, with the same R_f value as **3i** and **4i.** A first attempt to separate the mixture resulted in the loss of half the amount due to decomposition. The recovered mixture (3.5 g) was washed with aqueous sodium bicarbonate and was rechromatographed on silica gel (100 g), eluting with benzene–acetone (99:1), giving first 0.60 g of a mixture of **3i** and **5,** with **5** as a major component. Further elution yielded the 2-oxide

(4i) for a total yield of 23%. After recrystallization twice from chloroform–hexane, there was obtained pure **5**: mp 91–2 °C; ^{1}H NMR δ 1.58 (s, 3 H), 1.67 (s, 3 H), 1.85 (s, 3 H), 2.39 and 2.61 (AB q, 2 H, J = 14 Hz), 7.23–7.92 (m. 4 H); ^{13}C NMR δ 23.07, 26.52, 27.06 (3 CH_3), 43.70 (C-4), 83.92 (C-5), 103.66 (C-3), 134.41, 133.33, 130.30, 129.55, 128.84, 126.92 (aromatic carbons), 162.11 (C=O); mass spectrum (70 eV) m/e (relative intensity) 300 (M^+), 158 (3-chlorobenzoic acid) (14), 156 (42), 141 (11), 139 (33), 128 (24), 127 (100), 126 (8), 56 (11), 55 (7), 43 (40), 42 (5), 41 (10).

Anal. Calcd for $C_{13}H_{15}N_2O_4Cl$: C, 52.27; H, 5.06; N, 9.38; Cl, 11.87. Found: C, 52.54; H, 4.95; N, 9.43; Cl, 11.85

Acknowledgment. This work was supported by Contract CM-43778 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

Registry No.—**1**, 3975-85-7; **5**, 65442-00-4; 4-chlorobenzoyl peroxide, 94-17-7; benzoyl peroxide, 94-36-0; 2-chlorobenzoyl peroxide, 3033-73-6; 3-chlorobenzoyl peroxide, 845-30-7; 4-bromobenzoyl peroxide, 1712-82-9; 4-fluorobenzoyl peroxide, 582-92-3; 4-methoxybenzoyl peroxide, 849-83-2; 4-nitrobenzoyl peroxide, 1712-84-1; 3,5-dinitrobenzoyl peroxide, 15866-24-7.

References and Notes

(1) Taken in part from the M.S. Thesis of I.I.S., University of Rhode Island, 1977.
(2) B. H. Korsch and N. V. Riggs, *Tetrahedron Lett.*, 523 (1964).
(3) M. Sptaz, *Ann. N.Y. Acad. Sci.*, **163**, 697 (1969).
(4) C. L. Stevens, B. T. Gillis, J. C. French, and T. K. Haskkell, *J. Am. Chem. Soc.*, **80**, 6088 (1958); C. L. Stevens, B. T. Gillis, and T. K. Haskell, *ibid.*, **81**, 1435 (1959).
(5) A. G. Karlson, *Antibiot. Chemother., (Washington, D.C.)*, **12**, 446 (1962).
(6) J. A. Montgomery, R. James, G. S. McCaleb, and T. P. Johnston, *J. Med. Chem.*, **10**, 688 (1967).
(7) (a) J. P. Snyder, V. T. Bandurco F. Darack, and H. Olsen, *J. Am. Chem. Soc.*, **96**, 5158 (1974), and references cited therein; (b) K. G. Taylor, S. R. Isaac, and J. L. Swigert, *J. Org. Chem.*, **41**, 1146 (1976).
(8) K. G. Taylor, M. S. Chi, and M. S. Clark, Jr., *J. Org. Chem.*, **41**, 1131, 1135 (1976).
(9) D. J. Northington and W. M. Jones, *J. Org. Chem.*, **37**, 693 (1972).
(10) J. P. Freeman, *Tetrahedron Lett.*, 749 (1961); J. P. Freeman, *J. Org. Chem.*, **29**, 1379 (1964).
(11) N. A. Maier and Y. A. Ol'dekep, *Vestsi Akad. Navuk B. SSR, Ser. Khim. Navuk*, 74–77 (1971); *Chem. Abstr.*, **75**, 15118 g (1971).
(12) W. Cooper, *J. Chem. Soc.*, 3106 (1951); C. C. Price and E. Krebs in "Organic Syntheses", Collect. Vol. III, E. C. Hornig, Ed., Wiley, London, 1955, p 649.
(13) R. L. Augustine, *J. Org. Chem.*, **28**, 581 (1963); S. O. Lawesson, H. J. Jakobsen, and E. H. Larsen, *Acta Chem. Scand.*, **17**, 1188 (1963).
(14) J. M. McCall and R. E. Ten Brink, *Synthesis*, 443 (1975).
(15) We thank a referee who proposed structure **5** and the use of ultraviolet spectroscopy to distinguish between **5** and **6**.
(16) Cyclic azoalkanes *N*-oxides have ultraviolet absorption maxima at about 230 nm (7900)[17] while the *N,N'*-dioxides absorb in the region of 265–275 nm (6000–9000).[18]
(17) J. Swigert and K. G. Taylor, *J Am. Chem. Soc.*, **93**, 7337 (1971).
(18) J. P. Snyder, M. L. Heyman and E. Suciu, *J. Org. Chem.*, **40**, 1395 (1975).
(19) UV absorption maxima (MeOH): 290 (1000), 285 (1200), 233 nm (13600).
(20) M. Avram and G. H. Matecscu, "Infrared Spectroscopy", Wiley-Interscience, New York, N.Y., 1972, p 438.
(21) R. Cushley, D. Naugler, and C. Ortiz, *Can. J. Chem.*, **53**, 3419 (1975).
(22) R. J. Radel, B. T. Keen, C. Wong, and W. W. Paudler, *J. Org. Chem.*, **42**, 546 (1977).
(23) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1969, p 82.

Synthesis of 3-Substituted 2-Isoxazolines and 5,6-Dihydro-1,2,4*H*-oxazines

Peter A. Wade

Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

Received September 23, 1977

3-Nitro-2-isoxazoline (**1a**) can be prepared by nitrosation of 1-chloro-3-nitropropane followed by in situ tautomerization and cyclization. Similarly, 3-nitro-5,6-dihydro-1,2,4*H*-oxazine (**1b**) can be prepared from 1-chloro-4-nitrobutane. The nitro group of compounds **1a** and **1b** is readily substituted by a wide variety of nucleophiles. The resulting 3-substituted 2-isoxazolines and 5,6-dihydro-1,2,4*H*-oxazines are normally obtained in fair to excellent yield.

Studies directed at the application of 2-oxazolines[1] and 5,6-dihydro-1,3,4*H*-oxazines[2] to organic synthesis have been extensive and have certainly reaped substantial reward. On the other hand, 2-isoxazolines have received relatively little attention toward their utilization in synthetic problems.[3] In furthering the study of 2-isoxazolines, we wish to report a convenient synthetic approach which allows for their preparation with a hefty array of 3 substituents.[4] This approach also provides easy access to the corresponding six-membered heterocycles (5,6-dihydro-1,2,4*H*-oxazines) which have hitherto received scant attention.[5]

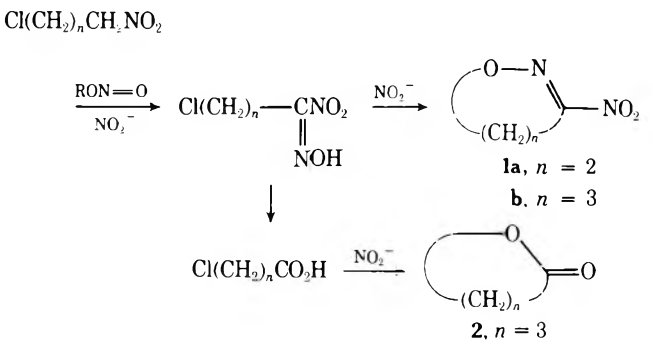
Key intermediates in our approach are 3-nitro-2-isoxazoline (**1a**) and the corresponding six-membered heterocycle **1b**. These can be prepared in yields of 79 and 48%, respectively, by treating 1-chloro-3-nitropropane and 1-chloro-4-nitrobutane with a combination of *n*-propyl nitrite and sodium nitrite in Me_2SO. A convenient alternative preparation[6,7] of **1a** involves treatment of 1-bromo-3-chloropropane with sodium nitrite in DMF; however, the yield of this reaction is only about 50%.[6]

It is proposed that compounds **1a** and **1b** are formed from the nitro compounds[8] by the mechanism of Scheme I. Support for this mechanism rests in the previously reported ability of the combination of *n*-propyl nitrite and sodium nitrite to nitrosate a primary or secondary nitro compound at the α position.[9] For a primary nitro compound, this nitroso derivative would be expected to tautomerize to a nitrolic acid (α-nitrooxime). Normally the nitrolic acid would then be converted to a carboxylic acid.[9b] Here, however, the nitrolic acid preferentially cyclizes via intramolecular substitution (Scheme I). In the preparation of **1b**, a 15% yield of γ-butyrolactone (**2**) is also obtained. This is consistent with the formation and lactonization of 4-chlorobutyric acid as shown in Scheme I. Apparently conversion of the nitrolic acid to carboxylic acid competes with cyclization in this case.

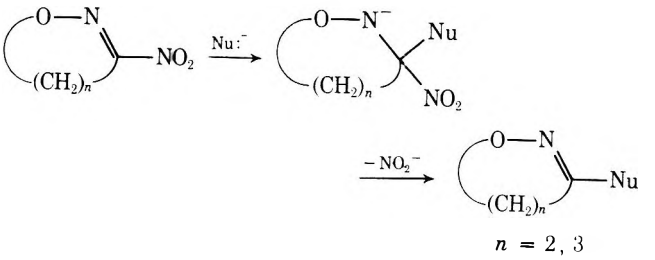
Nucleophilic attack of the carbon–nitrogen double bond of compounds **1a** and **1b** could conceivably occur at either carbon (typical of imines) or at nitrogen (β to the nitro group; compare the reactions of nitroolefins). In fact, we have observed only attack at carbon, the nitro group being expelled in the process. Thus, nitro compounds **1a** and **1b** undergo substitution similar to imidoyl chlorides.[10] Tables I and II

0022-3263/78/1943-2020$01.00/0

Scheme I



Scheme II



show the results obtained for a number of reactions. Nucleophiles ranging from sodium benzenesulfinate to *n*-butylcadmium can be effectively employed.

Concerning the introduction of an alkyl group, we have examined *n*-butyllithium, lithium *n*-butylcuprate, and *n*-butylcadmium. The first two of these lead to complex mixtures containing only traces, at best, of the substitution product. However, the less reactive organocadmium reagent affords substitution in 51% yield.

A logical mechamism for these reactions involves initial attack by the nucleophile to form a tetrahedral intermediate followed, in a second step, by explusion of nitrite ion (Scheme II). The vastly different rates (less than 1 min at room temperature for *n*-butylcadmium to greater than 1 week for sodium benzenesulfinate) of various nucleophiles are consistent with this stepwise mechanism (as well as other mechanisms[11]) assuming a rate-determining transition to the tetrahedral intermediate.

The best solvents for carrying out substitution are, for the most part, protic ones. Thus, sodium thiophenoxide reacts completely with **1b** in methanol solution within 10 min. In Me_2SO the reaction takes 1 h for completion, despite the higher polarity[12] and the greater nucleophilicity of thiophenoxide in this solvent. Azide ion reacts at least as rapidly with **1a** in aqueous alcohol as in Me_2SO, too. On the other hand, reactions of **1a** and **1b** with cyanide are somewhat faster in Me_2SO than in aqueous solution, although the difference is only a factor of 2 to 3. Clearly the rate-determining transition state for these reactions is more easily attained in protic solvents than in aprotic ones. This suggests hydrogen bonding to the ring nitrogen of compounds **1a** and **1b** facilitating transition to the tetrahedral intermediate. Alternatively, **1a** and **1b** may be fully protonated resulting in enhanced substitution.

Experimental Section

Melting points (uncorrected) were determined on a Mel-Temp capillary apparatus. IR spectra were determined on a Perkin-Elmer 457 spectrophotometer. NMR spectra were measured with a Varian A-60A spectrometer; chemical shifts are expressed in ppm downfield from internal Me_4Si. Mass spectra were recorded on a Hitachi RMU-6 spectrometer. VPC analyses were performed on a Varian 1400 gas chromatograph equipped with a 5 ft × 0.125 in. 1.5% OV-101, Chromosorb G column. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz.

Reagents emplcyed were of the finest commercial grade available. Reagent grade solvents were used as received; other solvents were distilled. Methanol was distilled from magnesium methoxide. Ether and THF were distilled from sodium benzophenone ketyl and were stored under nitrogen.

3-Nitro-5,6-dihydro-1,2,4*H*-oxazine (1b). A 34.4-g (0.25 mol) portion of 1-chloro-4-nitrobutane[13] was added to a solution containing 86.3 g (1.25 mol) of sodium nitrite and 45.2 g (0.51 mol) of *n*-propyl nitrite[14] in 800 mL of Me_2SO. The reaction solution was stirred for 18 h with occasional cooling to keep the temperature below 35 °C. The resulting mixture was poured into ice–water and then extracted with ten portions of CH_2Cl_2. The combined extracts were thoroughly washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. Distillation in vacuo of the crude product gave 15.6 g (48% yield) of **1b** as a greenish-yellow oil: bp 89–91 °C (0.17 Torr); IR (neat) 6.17 (C=N), 6.52, and 7.45 μm (NO_2); NMR ($CDCl_3$) δ 4.22 (t, 2 H, J = 5 Hz), 2.87 (t, 2 H, J = 7 Hz), and 2.17 (m, 2 H); mass spectrum *m/e* 130 (M^+). Anal. Calcd for $C_4H_6N_2O_3$: C, 36.93; H, 4.65; N, 21.53. Found: C, 37.16; H, 4.68; N, 21.78.

An additional 1.0 g (3% yield) of 92% pure (VPC) **1b** was obtained: bp 84–9 °C (0.17 Torr). The distillation forecut contained 3.2 g (15% yield) of 91% pure (VPC) lactone **2**, contaminated by Me_2SO.

3-Nitro-2-isoxazoline (1a). Procedure A. The preceding procedure was carried out using 1-chloro-3-nitropropane.[15] Pure **1a** was obtained as a greenish-yellow oil in 79% yield: bp 93–4 °C (1.4 Torr) [lit.[6] bp 105–9 °C (5.5 Torr)]. An additional 2% yield of material which was only 80% pure (VPC) was also obtained.

Table I. Substitution Reactions of 3-Nitro-2-isoxazoline (1a)[a]

No.	Product R =	Registry no.	Nu:	Registry no.	Solvent	% yield[b]
3	R-SC_6H_5	65150-71-2	$NaSC_6H_5$	930-69-8	Methanol	91
4	R-$SO_2C_6H_5$	65150-72-3	$NaO_2SC_6H_5$	873-55-2	Aqueous THF	28[c]
5	R-CN	65150-73-4	NaCN	143-33-9	Me_2SO	85
6	R-C_4H_9	65150-74-5	*n*-Bu_2Cd	3431-67-2	Ether	51
7	R-N_3	65150-75-6	NaN_3	26628-22-8	Aqueous alcohol	69

[a] At room temperature using an excess of the nucleophile. [b] By isolation. [c] After 12 h at 60–65 °C; starting **1a** was recovered in 15% yield.

Table II. Substitution Reactions of 3-Nitro-5,6-dihydro-1,2,4*H*-oxazine (1b)[a]

No.	Product R =	Registry no.	Nu:	Registry no.	Solvent	% yield[b]
8	R-SC_6H_5	65150-76-7	$NaSC_6H_5$		methanol	82
9	R-CN	65150-77-8	NaCN		Me_2SO	81
10	R-$NHCH_3$	65150-78-9	$MeNH_2$	74-89-5	Aqueous $MeNH_2$	70

[a] At room temperature using an excess of the nucleophile. [b] By isolation.

Procedure B.[16] To a solution of 138 g (2.0 mol) of sodium nitrite and 50.3 g (0.50 mol) of *n*-propyl nitrite[14] in 1 L of Me_2SO was added 157.5 g (1.0 mol) of 1-bromo-3-chloropropane. The reaction solution was stirred for 14 h with occasional cooling to keep the temperature below 40 °C. Work-up was as described for **1b**. Distillation gave 52.1 g (45% yield) of pure **1a**.

Similar treatment of 1-bromo-4-chlorobutane gave **1b** but the crude product had to be chromatographed and only a 10% yield of pure product was obtained.

3-Thiophenoxy-5,6-dihydro-1,2,4*H*-oxazine (8). A 0.97-g (0.042 g-atom) portion of cleaned Na^0 was added to 20 mL of anhydrous methanol. After the initial reaction subsided, the mixture was refluxed until complete reaction was attained. To the cooled (10 °C) solution was added 4.98 g (45 mmol) of distilled thiophenol followed, after 10 min, by 2.59 g (20 mmol) of **1b**. The resulting solution was burgundy colored; within 10 min the color faded. After 15 min 100 mL of aqueous 1% NaOH was added and the product was extracted into CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4), and concentrated at reduced pressure. The crude product was chromatographed on silica gel. Elution with cyclohexane/ethyl acetate (90:10) afforded 0.69 g of diphenyl disulfide: mp 57–8.5 °C; mmp (with an authentic sample, mp 58.5–9.5 °C) 57.5–9 °C.

Further elution afforded 3.15 g (82% yield) of **8** as an oil: bp 119–20 °C (0.12 Torr); IR (neat) 3.28, 6.42 (shoulder), 6.78, 13.37, 14.49 (Ph), and 6.32 μm (Ph and C=N); NMR ($CDCl_3$) δ 7.83 (m, 5 H), 3.95 (t, 2 H, J = 5 Hz), and 1.80–2.35 (m, 4 H). Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.13; H, 5.74; N, 7.25; S, 16.60. Found: C, 62.19; H, 5.96; N, 7.32; S, 16.90.

3-Thiophenoxy-2-isoxazoline (3). The preceding procedure was duplicated using **1a**. Chromatography as before gave diphenyl disulfide followed by a 91% yield of **3** as an oil: bp 104–5 °C (0.14 Torr); IR (neat) 3.28, 6.45, 6.78, 13.44, 14.53 (Ph), and 6.37 μm (Ph and C=N); NMR ($CDCl_3$) δ 7.42 (m, 5 H), 4.32 (t with fine structure, 2 H, J = 10 Hz), and 2.92 (t with fine structure, 2 H, J = 10 Hz). Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81; S, 17.89. Found: C, 60.47; H, 5.18; N, 7.98; S, 17.81.

3-Phenylsulfonyl-2-isoxazoline (4). To a solution of 49.20 g (300 mmol) of sodium benzenesulfinate in 90 mL of water and 30 mL of THF was added 3.39 g (29 mmol) of **1a**. The resulting solution was heated under nitrogen at 60–65 °C for 18 h, poured into water, and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4), and concentrated at reduced pressure to a solid, mp 75–84 °C. This crude product was twice recrystallized from ethanol to give 1.25 g (20% yield) of sulfone **4**: mp 98.5–9.5 °C; IR (KBr) 3.28, 6.77, 13.22, 14.70 (Ph), 6.33, 6.29 (Ph and C=N), 7.56, and 8.62 μm (sulfone); NMR ($CDCl_3$) δ 7.5–8.2 (m, 5 H), 4.55 (t with fine structure, 2 H, J = 11 Hz), and 3.30 (t with fine structure, 2 H, J = 11 Hz). Anal. Calcd for $C_9H_9NO_3S$: C, 51,17; H, 4.29; N, 6.63; S, 15.18. Found: C, 50.96; H, 4.39; N, 6.59; S, 14.90.

The combined mother liquors from the recrystallizations were chromatographed on silica gel. Elution with CH_2Cl_2 afforded 0.49 g (15% yield) of starting **1a** followed by 0.48 g (8% yield) of **4**, mp 95–8 °C.

Treatment of sulfide **3** with two equivalents of *m*-CPBA in CH_2Cl_2/ether for 40 h provided an independent synthesis of sulfone **4**. This product was identical to **4** obtained by the substitution reaction: mp 98.5–9.5 °C; mmp 98–9 °C.

3-Cyano-2-isoxazoline (5). To a solution of 2.94 g (60 mmol) of sodium cyanide in 100 mL of Me_2SO was added 5.60 g (48 mmol) of **1a**. After 15 min the reaction was worked up as described for compound **1b**. The crude product was distilled at reduced pressure to give 3.94 g (85% yield) of **5**: bp 117–8 °C (35 Torr); IR (neat) 4.46 (C≡N) and 6.41 μm (C=N); NMR ($CDCl_3$) δ 4.63 (td, 2 H, J = 10 Hz) and 3.23 (td, 2 H, J = 10 Hz). Anal. Calcd for $C_4H_4N_2O$: C, 50.00; H, 4.20; N, 29.15. Found: C, 49.72; H, 4.19; N, 29.10.

3-Cyano-5,6-dihydro-1,2,4*H*-oxazine (9). To a mixture of 4.67 g (95 mmol) of powdered sodium cyanide and 90 mL of Me_2SO was added 3.84 g (29.5 mmol) of **1b**. After 2.5 h the reaction was worked up as described for **1b**. Distillation in vacuo of the crude product gave 2.63 g (81% yield) of 99% (VPC) pure **9**: bp 65–7 °C (0.18 Torr). The analytical sample was prepared by chromatographing this material on silica gel (CH_2Cl_2 elution) and redistilling: IR (neat) 4.70 (C≡N) and 6.41 μm (C=N); NMR ($CDCl_3$) δ 4.18 (t, 2 H, J = 5 Hz), 2.43 (t, 2 H, J = 6 Hz), and 2.03 (m, 2 H). Anal. Calcd for $C_5H_6N_2O$: C, 54.53; H, 5.49; N, 25.44. Found: C, 54.26; H, 5.51; N, 25.63.

3-Butyl-2-isoxazoline (6). Cadmium chloride (79.97 g, 0.44 mol, predried in vacuo over P_2O_5) was flame dried under nitrogen and suspended in 500 mL of anhydrous ether. To the suspension was cautiously added 150 mL of a 2.4 M *n*-butyllithium in hexane solution. The resulting mixture was refluxed with stirring under nitrogen for 15 h[17] and then allowed to stand at room temperature for 3 h. The clear, colorless solution which separated from a black precipitate was transferred under a positive nitrogen pressure to an addition funnel. A 160-mL (ca. 60 mmol as *n*-butylcadmium) portion of this solution was added[18] dropwise over 30 min to a cooled (15 °C) solution of 6.85 g (59 mmol) of **1a** in 50 mL of anhydrous ether. Insoluble cadmium salts were then filtered off and washed with ether. The combined filtrate and washings were washed with saturated aqueous KCl, dried (Na_2SO_4), and concentrated at reduced pressure to an oil. Distillation in vacuo gave 4.55 g of 95% pure (VPC) **6**, contaminated by small amounts of several materials. Pure **6** was obtained by chromatography on silica gel. After elution of 19 mg of unidentified impurities with cyclohexane/ethyl acetate (80:20), 3.84 g (51% yield) of **6** was isolated: bp 46–7 °C (0.25 Torr); IR (neat) 6.20 μm (C=N); NMR ($CDCl_3$) δ 4.27 (t, 2 H, J = 10 Hz), 2.91 (t, 2 H, J = 10 Hz), 2.38 (t, 2 H, J = 7 Hz), 1.2–1.7 (m, 4 H), and 0.92 (distorted t, 3 H). Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.33; H, 10.03; N, 11.29.

3-Azido-2-isoxazoline (7). To a solution containing 8.58 g (132 mmol) of sodium azide in 35 mL of water and 50 mL of ethanol was added 5.75 g (50 mmol) of **1a**. The resulting solution was stirred at room temperature for 40 h and was then poured into water. Extraction with CH_2Cl_2, drying (Na_2SO_4), and concentration at 180 Torr gave an oil. This was cautiously distilled behind a safety shield[19] in vacuo to give 3.86 g (69% yield) of pale yellow **7**: bp 58–60 °C (1.2 Torr); IR (neat) 4.68 (N_3) and 6.26 μm (C=N); NMR ($CDCl_3$) δ 4.50 (t, 2 H, J = 10 Hz) and 2.95 (t, 2 H, J = 10 Hz). Anal. Calcd for $C_3H_4N_4O$: C, 32.15; H, 3.60; N, 49.98. Found: C, 32.50; H, 3.59; N, 49.91.

3-Methylamino-5,6-dihydro-1,2,4*H*-oxazine (10). To 60 mL of aqueous 40% methylamine was added 3.85 g (29.6 mmol) of **1a**. The resulting solution was stirred at 20–25 °C (occasional cooling) for 17 h and then poured into 100 mL of saturated aqueous KCl containing 1% w/v NaOH. Extraction with CH_2Cl_2 followed by washing of the extracts with water, drying (Na_2SO_4), and concentration at reduced pressure gave an oil. This was chromatographed on silica gel. Elution with ethyl acetate afforded 2.36 g (70% yield) of pure **10**. The analytical sample was kugelrohr distilled at 90 °C (0.1 Torr)[20] and dried in vacuo over KOH pellets: IR (neat) 2.85–3.15 (N–H) and 6.23 μm (C=N); NMR ($CDCl_3$) δ 5.05 (broad s, 1 H, shifts with concentration, exchanges with D_2O), 3.78 (t, 2 H, J = 6 Hz), 2.69 (d, 3 H, J = 5 Hz, collapses to an s on D_2O exchange), and 1.8–2.4 (m, 4 H). Anal. Calcd for $C_5H_{10}N_2O$: C, 52.61; H, 8.82; N, 24.54. Found: C, 52.76; H, 8.74; N, 24.58.

Acknowledgment. We wish to thank Drexel University and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—**1a**, 1121-14-8; **1b**, 65150-79-0; 1-chloro-4-nitrobutane, 41168-66-5; propyl nitrite, 543-67-9; 1-chloro-3-nitropropane, 16694-52-3; 1-bromo-3-chloropropane, 109-70-6.

References and Notes

(1) (a) A. I. Meyers and R. Gabel, *J. Org. Chem.*, **42**, 2653 (1977). (b) A. I. Meyers and K. Kamata, *J. Am. Chem. Soc.*, **98**, 2290 (1976). (c) For a general review of oxazoline chemistry, see: J. A. Frump, *Chem. Rev.*, **71**, 483 (1971).
(2) (a) A. I. Meyers and A. C. Kovelesky, *J. Am. Chem. Soc.*, **91**, 5887 (1969); (b) A. I. Meyers and E. M. Smith, *ibid.*, **92**, 1084 (1970).
(3) One example is the use of isoxazolines to prepare aziridines: K. Kotera, Y. Takano, A. Matsura, and K. Kitahanoski, *Tetrahedron Lett.*, 5759 (1968).
(4) For a review of other routes, see: A. Quilico, "The Chemistry of Heterocyclic Compounds", Vol. 7, Wiley-Interscience, New York, N.Y., 1962, p 95.
(5) R. L. McKee, ref 4, p 329.
(6) P. G. Bay, U.S. Patent 3 207 761 (1965).
(7) For another approach, see: V. A. Tartakovskii et al., *Dokl. Akad. Nauk SSSR*, **167**, 844 (1966).
(8) The conversion of 1-bromo-3-chloropropane to **1a** presumably goes by the same route after prior conversion to 1-chloro-3-nitropropane and the corresponding nitrite ester.
(9) (a) N. Kornblum and P. A. Wade, *J. Org. Chem.*, **38**, 1418 (1973); (b) N. Kornblum, R. K. Blackwood, and D. D. Mooberry, *J. Am. Chem. Soc.*, **78**, 1501 (1956).
(10) R. Bonnett, "The Chemistry of the Carbon-Nitrogen Double Bond", Wiley-Interscience, New York, N.Y., 1970, p 597.
(11) Alternatives include S_N2 and S_N1 mechanisms. The wide range in rates as a function of the nucleophile is inconsistent with an S_N1 process.
(12) The dielectric constant of Me_2SO is 47; that of methanol is 33; J. A. Riddick and W. B. Bunger, "Techniques of Chemistry", Vol. 2, Wiley-Interscience, New York, N.Y., 1970.
(13) Prepared in 78% yield by treating 1-chloro-4-iodobutane with one equivalent of silver nitrite.

(14) Preparec analagously to *n*-butyl nitrite: 'W. A. Noyes, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943. p 108.
(15) Prepared in 64% yield from 1-chloro-3-iodopropane.
(16) A convenient modification of the procedure of ref 6.
(17) The reagent obtained employing a shorter reaction time affords a lower yield of **6**. Presumably this is due to *n*-butylcadmium chloride.
(18) Addition of **1a** to an excess of the cadmium reagent gave **6**, too.
(19) A sample of impure **7** detonated during VPC analysis (injector temperature 180 °C) destroying a syringe.
(20) Impure **10** rapicly decomposed at 100 °C on contact with air.

Basic Methanolysis of Benzoylmethylaminopyridines and Their *N*-Oxide and Methyl Quaternary Derivatives

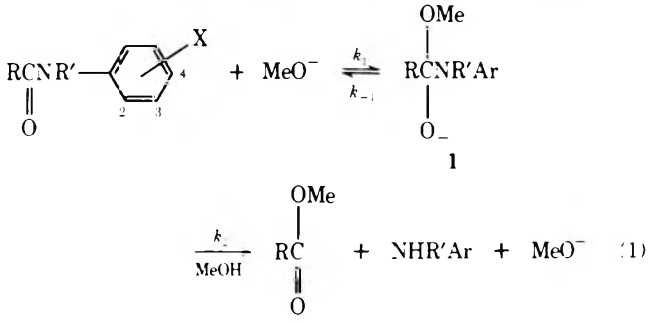
Trevor J. Broxton, Leslie W. Deady,* and Yook-Tau Pang

Organic Chemistry Department, La Trobe University, Bundoora, Victoria 3083 Australia

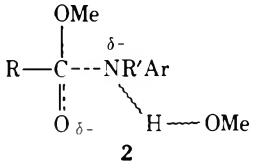
Received October 20, 1977

Rate data for the basic methanolysis of PhCON(Me) derivatives of pyridine pyridine *N*-oxide, and 1-methylpyridinium iodide are reported. Positional reactivities are 4 ≫ 2 > 3 (pyridine), 4 > 3 > 2 (*N*-oxide), and 4 ≫ 3 (methylpyridinium). The heterocycles are also considered as substituted *N*-aryl-*N*-methylbenzamides; when combined with published data, these results yield a linear Hammett plot (ρ = 3.2). Mechanistic implications of this finding are discussed.

The effect of substituents on the rate of basic hydrolysis and methanolysis of anilides (eq 1) is most interesting since



all types of Hammett plots are possible, depending on the particular structure and reaction conditions. Thus linear,[1] curved,[2] and intersecting straight line[3] plots have been obtained, depending on the mechanisms or mechanism change. Of particular interest is the possibility of change from rate-determining breakdown of **1** (mechanism A, solvent assisted C–N cleavage via transition state **2** with Hammett $\rho \approx 3$[1,2]) to

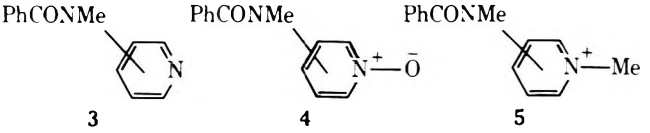


2

rate-determining formation of **1** (mechanism B, $\rho \approx 1.3$[4]) for strongly electron-withdrawing aryl substituents. This mechanism change should be accompanied by a decrease in slope of a Hammett plot.

In the case of *N*-aryl-*N*-methylbenzamides (R = Ph; R′ = Me) the current knowledge seems best fitted by invoking mechanism A for all substituents studied, except 4-nitro where reaction is by mechanism B.[5] The necessity for a strong resonance withdrawing effect for mechanism B is suggested by the observation that the 3,5-dinitro-substituted compound probably reacts by mechanism A, though the total withdrawing effect (σ = 1.42) is greater than that of the 4-nitro (σ^- = 1.26). To probe further into this possible change we decided to extend the range of electron-withdrawing substituents by considering pyridine derivatives with the aza function being regarded as an aromatic substituent.

We have previously noted[6] the similarity in effects of the 4-nitro and 4-aza groups in the methanolysis of *N*-arylacetamides. In this paper we report on the reactivities of the heterocyclic entities **3**, **4**, and **5**.[7] Though the Hammett equation



3 **4** **5**

is not generally applicable to ortho substituents, we have included 2-substituted compounds so as to compare reactivity of a complete series with their behavior in basic ester hydrolysis (BEh) and nucleophilic displacement of ring halogen (S_NAr) reactions. This latter reaction, also powerfully aided by electron-withdrawing substituents, provides the substituent effect data for aza functions[8] with which the correlation of the methanolysis results can be attempted. It is apparent from $\sigma^-_{4N^+Me}$ = 2.32 that we are indeed dealing with strong electron-withdrawing substituents.

Results and Discussion

Reactions were followed spectrophotometrically by either standard UV or stopped flow procedures. The species monitored are indicated in the tables. Pseudo-first-order rate constants were obtained at a series of methoxide concentrations and second-order rate constants, k_e, were obtained from k_ψ/[MeO$^-$] or from a plot of k_ψ vs. [MeO$^-$].

Rate constants at 100 °C were required for comparison with other arylbenzamide results. These were generally obtained by substantial extrapolation from Arrhenius plots.

The 2-methylazonium compound alone showed anomalous behavior in that addition of base produced an immediate UV spectral change, followed by a much slower change. This latter change gave a first-order plot but with nonreproducible results. An NMR investigation showed that more than one organic species was formed in the initial reaction and subsequent spectral changes were complex. The reaction was not investigated further.

Salt effects, generally unimportant in these reactions,[2] were noted in reactions of the other methylazonium isomers. It appeared that both ionic strength and specific salt effects were occurring since a certain minimum concentration of lithium perchlorate was needed before a linear k_ψ vs. [MeO$^-$] plot

0022-3263/78/1943-2023$01.00/0

Table I. Rate Data for the Basic Methanolysis of *N*-Methyl-*N*-Pyridinylbenzamides, 3, at 373 K[a]

Aza position	Registry no.	[MeO⁻], M	Anal. λ, nm	10^2k_e, $M^{-1}s^{-1}$
2	65052-85-9	0.008–0.016	305[b]	6.84
3	65442-07-1	0.02–0.04	315[b]	3.08
4	65052-87-1	0.002–0.004	252[b]	115

[a] No $LiClO_4$ present. [b] Product formation.

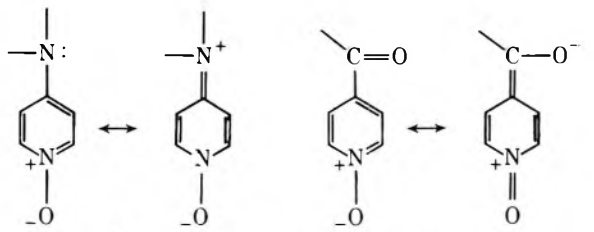
passing through the origin was obtained. Above this concentration (greater for the 3-methylazonium), good k_e values were obtained which decreased as the salt concentration was increased. For comparison with results for other substrates, values of k_e at zero ionic strength were estimated.

Aza 3. The rate constants in Table I show that positional reactivity is in the order 4 ≫ 2 > 3, as for S_NAr[8] and BEh[9] reactions. The substituent exerts its standard combination of resonance and inductive effects.

Aza Oxide 4. For the 3 and 4 isomers $k_\psi/[MeO^-]$ was constant. For the 2 isomer, a plot of k_ψ vs. $[MeO^-]$ was linear with a small positive intercept. This indicates that some reaction with methanol occurs, though the reason for such behavior is not clear.

Rate constants at 100 °C, and activation parameters, are listed in Table II. The amide reactions are characterized by a lower activation enthalpy but less favorable entropy than the corresponding S_NAr reaction. The reactivity order (4 > 3 > 2) may be compared with those for S_NAr[8] (4 > 2 > 3) and BEh[9] (2 ≈ 3 > 4) reactions.

A resonance withdrawing effect of the aza oxide must make a significant contribution to the overall electronic effect to obtain the order 4 > 3. Interaction of the developing charge on the exocyclic nitrogen with the ring determines reactivity and this is enhanced from the 4 position (7). Essentially the same activation occurs in the S_NAr reaction. In the BEh reaction, the reverse reactivity order seems best interpreted in terms of a rate-retarding resonance donation from the 4-aza oxide to the carbonyl group (8). The original interpretation[9]



7 8

was that the reactivity order was determined by the inductive effect, though the resonance donation possibility was recognized.

The low reactivity of the 2-aza oxide requires that an additional effect operates, probably of a steric nature though its origin is not clear. It presumably cannot arise from hindrance to methoxide attack on the carbonyl group as this should be more pronounced in the ester where the carbonyl group is closer to the pyridine ring.

Methylazonium 5. Reactions of the 4 isomer were carried out at various temperatures and three ionic strengths (curvature in a plot of k_ψ vs. $[MeO^-]$ was observed at $\mu \leq 0.05$). A value of 1×10^4 M^{-1} s^{-1} for k_e^{373} at $\mu = 0$ was estimated from the effect of $\mu^{1/2}$ on log k_e^{373} (obtained by temperature extrapolation). Since salt effects obey the Debye–Hückel equation only in dilute solution, this estimate is somewhat imprecise but any likely error does not affect the conclusions drawn below. For the 3 isomer, an ionic strength of 0.4 was

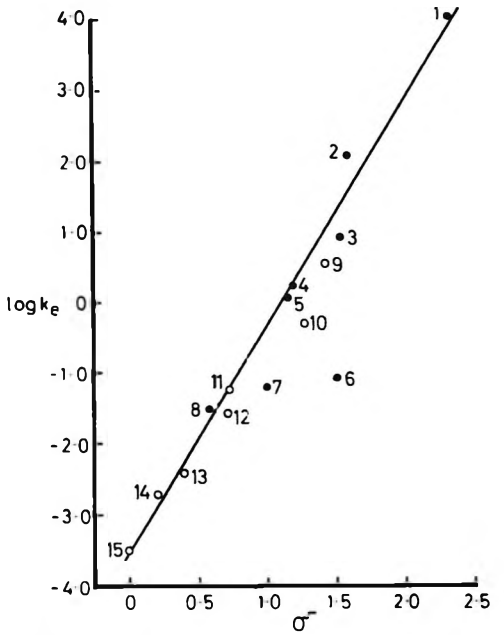


Figure 1. Hammett plot for methanolysis of *N*-aryl-*N*-methylbenzamides: (●), this work, (1) 4-N^+Me, (2) 3-N^+Me, (3) 4-N^+O^-, (4) 3-N^+O^-, (5) 4-N, (6) 2-N^+O^-, (7) 2-N, (8) 3-N; (○) data from ref 5, (9) 3,5-$(NO_2)_2$, (10) 4-NO_2, (11) 3-NO_2, (12) 4-CO_2Me, (13) 3-Br, (14) 4-Br, (15) H.

necessary to obtain a linear k_ψ vs. $[MeO^-]$ plot. Reactions in more concentrated salt solutions were not carried out and the k_e value at $\mu = 0$ (116 M^{-1} s^{-1}) was obtained by assuming that the ionic strength effect on rate was the same for the 3 and 4 isomers. As mentioned earlier, rate data were not obtained for the 2 isomer.

The reactivity order 4 ≫ 3 is also found in the S_NAr[8] and BEh[10] reactions and represents activation by inductive and resonance withdrawing effects.

Hammett Correlation. The rate data obtained in this work, together with published values,[1] make possible correlation of a reactivity range of 10^7 for the basic methanolysis of *N*-aryl-*N*-methylbenzamides. The Hammett plot is shown in Figure 1 (σ values for aza functions are those from S_NAr reactivity[8]). Considering the range of reactivities, uncertainties in some σ values, large temperature extrapolations to get some k_e^{373} values, and salt effects, the correlation is remarkably good. The lower reactivity of the 2-aza oxide has been commented on. The point for the 2-aza compound also lies off the plot. Since proximity effects would be expected to be different in the amide and S_NAr reactions, this deviation is not surprising.

The important point to emerge is that the plot is clearly linear with $\rho = 3.2$. Thus, in spite of an appreciable increase in substituent electron withdrawing power, there is no sign of downward curvature in the plot beyond the point for the 4-nitro substituent. The conclusion is therefore that the mechanism remains the same throughout, i.e., rate-determining breakdown of 1 (mechanism A). This seems entirely reasonable as the basic pK_a of *N*-methyl-4-pyridinimine is ca. 15,[11] i.e., it is only when one gets to the 4-methylazonium substituent that the leaving amine group has a basicity approaching that of methoxide. Thus, with less electron-withdrawing substituents, the amine is a poorer leaving group than methoxide (at least from an electronic viewpoint) and $k_{-1} > k_2$, the requirement for mechanism A.

The 4-nitro-substituted compound remains the anomaly. Though the deviation of the point from the Hammett correlation line is not gross, other evidence suggests that for this compound $k_2 \geq k_{-1}$ and mechanism B operates. We have

Table II. Rate Data for the Basic Methanolysis of *N*-Methyl-*N*-pyridinylbenzamide *N'*-Oxides, 4[a]

Aza oxide position	Registry no.	[MeO⁻], M	Anal. λ, nm	*T*, K	10^2k_e, $M^{-1}\,s^{-1}$	$10^2k_e^{373}$, $M^{-1}\,s^{-1}$
2	65442-08-2	0.004–0.04	328[b]	344	1.16[c,d]	8.67[e]
		0.01–0.04		354	2.43[c,f]	
		0.01–0.04		364	4.81[c,g]	
3	65442-09-3	0.01–0.02	399[b]	288.7	0.70	175[h]
		0.01–0.02		299	1.60	
		0.01–0.02		307	3.00	
4	65442-10-6	0.004–0.02	290[b]	283.7	4.91	829[i]
		0.004–0.02		289	7.20	
		0.004–0.01		295.7	12.7	

[a] No $LiClO_4$ present. [b] Product formation. [c] From plot of k_ψ vs. [MeO⁻]. [d] Intercept at [MeO⁻] = 0, $3 \times 10^{-5}\,s^{-1}$. [e] $\Delta H^{\ddagger}_{298} = 17.1$ kcal; $\Delta S^{\ddagger}_{298} = -18$ cal $mol^{-1}\,K^{-1}$. [f] Intercept = $5 \times 10^{-5}\,s^{-1}$. [g] Intercept = $1.1 \times 10^{-4}\,s^{-1}$. [h] $\Delta H^{\ddagger}_{298} = 13.4$ kcal; $\Delta S^{\ddagger}_{298} = -22$ cal $mol^{-1}\,K^{-1}$. [i] $\Delta H^{\ddagger}_{298} = 11.4$ kcal; $\Delta S^{\ddagger}_{298} = -24$ cal $mol^{-1}\,K^{-1}$.

Table III. Rate Data for the Basic Methanolysis[a] of Benzoylmethylamino-1-methylpyridinium Iodides, 5

Isomer	Registry no.	*T*, K	k_e,[b] $M^{-1}\,s^{-1}$	k_e^{373}, $M^{-1}\,s^{-1}$
4[c]	65442-11-7	285.5	32.6[d]	4590[e]
		297.4	72.7[d]	
		305.2	129[d]	
		286.5	17.2[f]	2220[g]
		298	37.3[f]	
		308	74.6[f]	
		288	14.5[h]	1880[i]
		297.4	28.4[h]	
		309	62.6[h]	
3[j]	65442-12-8	291.6	0.145[h]	21.8[k]
		304	0.369[h]	
		312	0.657[h]	

[a] [MeO⁻] = 0.01–0.07 M. [b] $k_e = k_\psi/[MeO^-]$. [c] Reactant disappearance at λ 305 nm followed. [d] $\mu = 0.1(LiClO_4)$. [e] $\Delta H^{\ddagger}_{298} = 11.4$ kcal; $\Delta S^{\ddagger} = -12$ cal $mol^{-1}\,K^{-1}$. [f] $\mu = 0.25$. [g] $\Delta H^{\ddagger}_{298} = 11.4$ kcal; $\Delta S^{\ddagger}_{298} = -13$ cal $mol^{-1}\,K^{-1}$. [h] $\mu = 0.4$. [i] $\Delta H^{\ddagger}_{298} = 11.6$ kcal; $\Delta S^{\ddagger}_{298} = -13$ cal $mol^{-1}\,K^{-1}$. [j] Product formation at λ 350 nm followed. [k] $\Delta H^{\ddagger}_{298} = 12.7$ kcal; $\Delta S^{\ddagger}_{298} = -19$ cal $mol^{-1}\,K^{-1}$.

previously[5] proposed an explanation involving steric and electronic effects for the apparently enhanced leaving group ability of this amine and can now comment further.

Steric compression exists in the tetrahedral intermediate from an NMe anilide relative to the situation for an NH anilide. While mechanism A is generally followed in both classes of compounds, this steric effect produces a difference in mechanism detail, evidenced by major activation parameter differences,[5] for example, irrespective of the nature of the aryl substituent. The strain in an NMe intermediate is relieved more by loss of amine (k_2) than by loss of methoxide (k_{-1}). Thus, $k_{-1}/k_2(NMe) < k_{-1}/k_2(NH)$, but only for the 4-nitro substituent in the NMe series (in methanol) is the effect sufficient to tip the balance such that $k_{-1} > k_2$ and mechanism B operates. We previously concluded that the reason was that this steric compression was most severe where through conjugation between the exocyclic nitrogen and a para ring substituent is a major factor in the substituent's effect and coplanarity of the NMe group and ring is thereby required.

It seems that the change in substituent effect from aza to quaternized aza (N^+-O^- or N^+-Me) is very much due to an increased inductive effect while the resonance effect is relatively little altered.[12] Thus the planarity requirement for through conjugation is not critical, the steric effect of the methyl is not significantly increased, and, even in these highly reactive compounds, the leaving group ability is not increased sufficiently to produce a mechanism change. It can therefore be deduced that, in this reaction in methanol, a further example of mechanism B requires a substituent with either a total electron-withdrawing effect even greater than that provided by the methylazonium group or a resonance component of σ^- greater than that of the nitro group.

Experimental Section

For product analysis studies, 1-methyl-2-methylaminopyridinium iodide, mp 164–166 °C (lit.[13] mp 159–160 °C), 1-methyl-3-methylaminopyridinium iodide, mp 162–163 °C (Anal. Calcd for $C_7H_{11}IN_2$: C, 33.6; H, 4.4; N, 11.2. Found: C, 33.55; H, 4.5; N, 11.0), were prepared by reaction of the appropriate aminopyridine with methyl iodide in ethanol.

Aza 3. The isomeric *N*-methyl-*N*-pyridinylbenzamides were prepared by benzoylation of the corresponding methylaminopyridines.[14]

Methylazonium 5. Quaternization of the appropriate 3 with methyl iodide in ethanol gave 1-methyl-3-(benzoylmethylamino)pyridiniumiodide, mp 165–166 °C (EtOH) (Anal. Calcd for $C_{14}H_{15}IN_2O$: C, 47.5; H, 4.2; N, 7.9. Found: C, 47.5; H, 4.2; N, 7.6), and 1-methyl-4-(benzoylmethylamino)pyridinium iodide, mp 118–121 °C (EtOH) (Anal. Found: C, 47.2; H, 4.55; N, 7.6). The 2 isomer was initially obtained as a viscous oil. This was washed three times with ethanol in a dry ice–acetone bath. The residue slowly crystallized and gave 1-methyl-2-(benzoylmethylamino)pyridinium iodide, mp 170–173 °C, after recrystallization from ethanol. (Anal Found: C, 47.4; H, 4.35; N, 7.7).

Aza Oxide 4. 2-Methylaminopyridine 1-oxide, mp 102–104 °C (benzene–ether) (lit.[15] mp 103–105 °C), was prepared by reaction of the pyridine with 1 mol of *m*-chloroperbenzoic acid in acetone at room temperature. The 1-oxide crystallized when the solvent was evaporated and ether was added. Benzoylation[16] gave the amide, mp 150–151 °C (lit.[16] mp 152–153 °C).

N-Methyl-*N*-(3-pyridinyl)benzamide *N'*-oxide, mp 178–180 °C (Anal. Calcd for $C_{13}H_{12}N_2O_2$: M, 228.08980. Found: M, 228.09136, by high-resolution mass spectrometry) was prepared by oxidation of the benzamide with *m*-chloroperbenzoic acid in acetone (2 h reflux) as for the amine above. The 4 isomer, mp 149–150 °C (lit. mp[16] 144–145 °C), was prepared similarly.

Kinetics. Rate measurements were carried out in methanol, with varying concentrations of methoxide, under pseudo-first-order conditions.[1] Where applicable, constant salt concentration was maintained with anhydrous lithium perchlorate. Reactions were carried out at least in duplicate and the individual values agreed within 4%.[17] The 3- and 4-methylaminopyridine 1-oxides were not prepared but in all other cases where kinetics were followed, infinity spectra agreed with those of authentic product mixtures.

Stock solutions of the methylazonium compounds, **5**, were made up in acidified methanol (2 drops of 2 M HCl to 50 mL of solvent) and reactions of the 4 isomer were followed by stopped flow kinetics, with k_ψ being calculated from six to nine $t_{1/2}$ measurements. All other reactions were followed by conventional UV monitoring. With the 3 isomer of **5**, where $t_{1/2} \approx 30$ s, it was necessary to preequilibrate separate solutions of amide and methoxide. These were then efficiently mixed within 5 s in the thermostated cell and subsequent reaction was followed.

Registry No.—1-Methyl-3-methylaminopyridinium iodide, 65442-13-9; 1-methyl-4-methylaminopyridinium iodide, 59435-96-0;

1-methyl-2-(benzoylmethylamino)pyridinium iodide, 65442-14-0; 2-methylaminopyridine 1-oxide, 54818-70-1.

References and Notes

(1) T. J. Broxton and L. W. Deady, *J. Org. Chem.*, **39**, 2767 (1974).
(2) R. L. Schowen, C. R. Hopper, and C. M. Bazikian, *J. Am. Chem. Soc.*, **94**, 3095 (1972).
(3) T. J. Broxton, L. W. Deady, and Y-T. Pang, *Tetrahedron Lett.*, 2799 (1975).
(4) G. M. Blackburn and J. D. Plackett, *J. Chem. Soc., Perkin Trans. 2*, 1366 (1972).
(5) T. J. Broxton and L. W. Deady, *J. Org. Chem.*, **40**, 2906 (1975).
(6) T. J. Broxton, L. W. Deady, and P. R. A. Williamson, *Aust. J. Chem.*, **27**, 1053 (1974).
(7) For convenience these compounds will be referred to as *N*-aryl-*N*-methylbenzamides containing "aza", "aza oxide", and "methylazonium" substituents, respectively.
(8) M. Liveris and J. Miller, *J. Chem. Soc.*, 3486 (1963).
(9) P. R. Falkner anc D. Harrison, *J. Chem. Soc.*, 1171 (1960).
(10) L. W. Deady and J. A. Zoltewicz, unpublished observations.
(11) B. D. Batts and E. Spinner, *Aust. J. Chem.*, **22**, 2595 (1969).
(12) P. Tomasik and C. D. Johnson, *Adv. Heterocycl. Chem.*, **20**, 1 (1976).
(13) A. E. Tsitschibabin, R. A. Konawalowa, and A. A. Konawalowa, *Ber.*, **54**, 814 (1921).
(14) R. A. Jones and A. R. Katritzky, *J. Chem. Soc.*, 1317 (1959).
(15) A. R. Katritzky, *J. Chem. Soc.*, 191 (1957).
(16) R. A. Jones and A. R. Katritzky, *J. Chem. Soc.*, 2937 (1960).
(17) The complete results are listed in the Ph.D. Thesis of Y-T. Pang, La Trobe University.

A Novel Intramolecular Homologation of a Phthalimide Group. 1,5,8-Trioxobenz[*f*]indolizidine[1a]

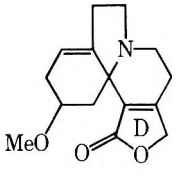
Scott F. Krauser[1b] and Arthur C. Watterson, Jr.*

Organic Chemistry Program, Department of Chemistry, University of Lowell, Lowell, Massachusetts 01854

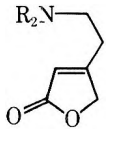
Received October 17, 1977

The Reformatsky reaction between ethyl bromoacetate and 1-acetoxy-4-phthalimido-2-butanone (**4**) produces in modest yield β-acetoxy-β-(2-phthalimidoethyl)butyrolactone (**10**), a product of normal addition to the ketone carbonyl, and in low yield a second compound, which arises from transformation of the phthalimide group. The latter product is shown to be 1,5,8-trioxobenz[*f*]indolizidine (**13**), a material which is of synthetic interest because of its structural relationship to the phenanthroindolizidine and Amaryllidaceae alkaloids. The precursor to ketone **4**, 1-diazo-4-phthalimido-2-butanone (**7**), was found to give **13** directly in preparatively acceptable yield via a novel rearrangement of its derived ketocarbene (**17**).

We are presently investigating a synthetic approach to the ring system of cocculolidine (**1**),[2] a member of the D-ring lactone subgroup of the Erythrina group of alkaloids. This approach requires the as yet unknown amirobutenolide **2**, and our immediate synthetic goal was the amine-protected lactone **3**.

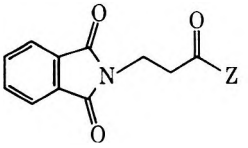


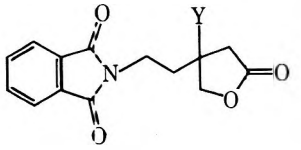
1



2, R = H
3, R = o-phthaloyl

The key step in an initial sequence designed to produce **3** was the Reformatsky reaction between ethyl bromoacetate and 1-acetoxy-4-phthalimido-2-butanone (**4**). This ketone was





4, Z = CH_2OAc **7**, Z = CHN_2 **10**, Y = OAc
5, Z = OH **8**, Z = CH_2OCHO **11**, Y = OCHO
6, Z = Cl **9**, Z = CH_2Cl **12**, Y = OH

readily prepared in four steps from β-alanine (3-aminopropionic acid) via intermediates **5**, **6**, and **7**, respectively.

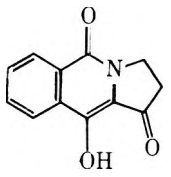
The major product of the Reformatsky reaction was the acetoxylactone **10**, which was formed in modest yield (20%) and presumably arose from normal addition to the ketone followed by transesterification and cyclization. This reaction also produced a second, highly colored, product "A" in lower yield (5%), whose elemental analysis indicated an empirical formula of $C_{12}H_9NO_3$ and whose spectral data indicated that it was not derived from normal addition to the starting ketone. The structure of this product was assigned on the basis of the following.

The ^1H NMR spectrum of the ketone **4** shows a typical A_2X_2 pattern for the adjacent methylene groups: a pair of two-proton triplets at δ 2.9 and 4.1. (J = 8 Hz). The spectrum of A shows these signals unchanged, implying that the NCH_2CH_2CO grouping remains intact in the product. In contrast, the singlets due to the acetate methyl group [δ 2.2 (3 H)] and the 1-methylene group [δ 4.7 (2 H)] in the starting material are absent in the product. In addition, the aromatic protons in **4** show the compact, symmetrical multiplet [δ 7.8 (4 H)] which is typical of N-substituted phthalimides, whereas in A a complex signal [δ 7.6–8.2 (4 H)] appears, suggesting a loss of symmetry in the substitution pattern of the aromatic ring. The only remaining peak in the spectrum of A is a broadened singlet [δ 6.5 (1 H)] which disappears on addition of D_2O.

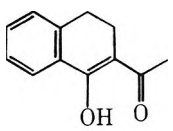
The transformation of the phthalimide group and loss of ester functionality are both immediately evident from the IR spectrum: the peaks of the starting material **4** at 1715 (strong) and 1780 cm^{-1} (moderate), characteristic of phthalimides, and at 1750 cm^{-1} (OAc) are absent in A. Somewhat surprising is that A also lacks the absorption of **4** at 1730 cm^{-1} due to the simple ketone group. Instead, the product exhibits a strong peak at 1685 cm^{-1}, moderately strong peaks at 1700 and 1675 cm^{-1}, and a very strong band at 1630 cm^{-1}. The spectrum of A shows additionally a broad peak at 3240 cm^{-1}, which correlates with the singlet at δ 6.5 in the NMR spectrum.

Consideration of mechanistic possibilities in view of the above data leads to the benzindolizidine **13** as the structure of A.

0022-3263/78/1943-2026$01.00/0



13

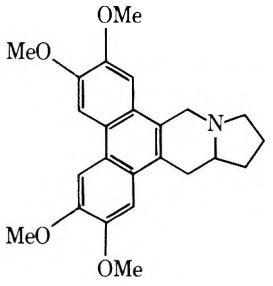


14

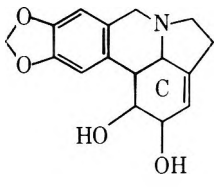
The β-diketone structure is supported both by a positive ferric chloride test and by the IR spectrum. Enol diketones exhibit[3] a very strong principal carbonyl peak in the range 1640–1580 cm^{-1}. Some also show two peaks at somewhat higher frequency. For example, 1-benzoylacetone and 2-acetyl-1-tetralone (14) both show[4] moderately strong peaks at 1715 and 1670 cm^{-1} as well as an intense band at 1605 cm^{-1}. These correlate well with the peaks in A at 1700, 1675, and 1630 cm^{-1}. The remaining adsorption in A at 1685 $^{-1}$ can be reasonably assigned to the δ-lactam carbonyl group. The ^1H NMR spectrum described above is completely consistent with structure **13**, as is the ^{13}C NMR spectrum (see Experimental Section). It should be noted that the absorption of the hydroxyl hydrogen at δ 6.5, an unusually high field for enolic protons, can be explained by assuming a low degree of intramolecular hydrogen bonding[5] and that the relative lack of this bonding is reflected as well in the IR spectrum by the prominence and high frequency of O–H stretch (3240 cm^{-1}).[6]

A plausible pathway for the formation of **13** is shown in Scheme I. Zinc enolates such as B are known[7] to exist in Reformatsky mixtures, and the formation of these species is considered[7] to be responsible for lowered yields of addition product and recovery of starting carbonyl compound, regenerated from the enolate during the hydrolysis. We believe that this factor is particularly important here and that large amounts of B are formed, evidence for which, besides the relatively low yield of **10**, is that considerable amounts (ca. 30%) of starting ketone were found in product mixtures. The unusual ease of conversion of **4** to its enolate would presumably be due to inductive stabilization by the electron-withdrawing group in the 1 position in B.

Beyond its unexpected nature we felt that the formation of **13** is of potential synthetic interest as this compound contains substantial portions of the carbon skeletons of at least two otherwise structurally diverse groups of alkaloids, exemplified by tylophorine (**15**) (phenanthrindolizidine)[8a] and lycorine (**16**) (Amaryllidaceae).[8b] In particular, the synthesis



15

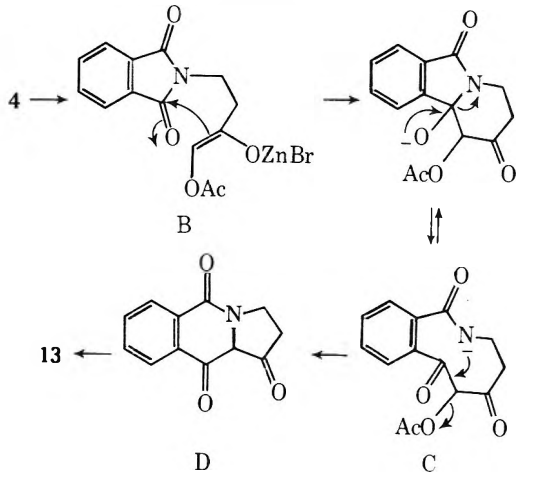


16

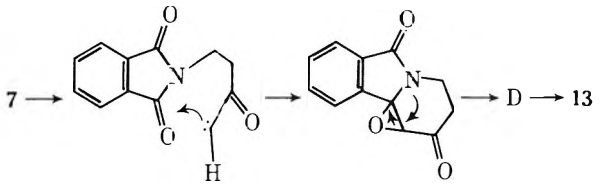
of the Amaryllidaceae ring system could be accomplished by direct elaboration of **13** since the β-diketone functionality is located at the exact points of attachment of the C ring. Consequently, a brief investigation of some possibilities of increasing the yield of **13** to a preparatively useful level seemed justified.

Since our postulated mechanism (Scheme I) implies a key role for the 1-acetoxy group, particularly with respect to its leaving ability, two other 1-substituted 4-phthalimido-2-butanones were prepared and subjected to Reformatsky conditions for comparison. 1-Formyloxy-4-phthalimido-2-

Scheme I



Scheme II



17 18

butanone (**8**) gave a decreased yield of the analogous normal addition product (**11**, 10%) and a somewhat increased yield of **13** (8%). This is qualitatively consistent with the proposed mechanism and the properties of the formyloxy group relative to the acetoxy group, i.e., more electron withdrawing (greater stabilization in B, disfavoring normal addition) and better leaving ability (greater ease of loss in C, favoring **13**). The effect of replacing acetate by chlorine is less predictable, particularly from a steric point of view, and in fact the 1-chloro derivative **9** gave a lower yield of the normal addition product (**12**, 10%) and none of **13**.

It then occurred to us that material already in hand, the diazo ketone **7**, would serve as a ready source of a different type of reactive species that might be used to exploit the susceptibility of the imide carbonyls to attack from the δ position of the *N*-butanone chain. This approach is illustrated in Scheme II.

Thus, it seemed that the carbene derived from **7** (**17**) could undergo rearrangement to **13**, initiated by intramolecular insertion[10] across the imide carbonyl and proceeding via the resulting epoxide **18** through the diketo tautomer D.[9] In the event of $CuSO_4$-catalyzed[10] decomposition of **7** in xylene at 120 °C, **13** was indeed produced directly. The yield was 25%, which, though modest, is acceptable from a practical standpoint in view of the ease of product isolation and the efficiency and simplicity of the sequence leading to **7** (96% overall in three steps from β-alanine). The conditions used were adopted when other experiments indicated that both lower and higher temperatures gave lower yields. For example, at 35 °C the decomposition gave a virtually quantitative yield of a new and apparently polymeric phthalimide (**19**) and only a trace of **13**.

While the use of the intact phthaloyl grouping in an amine-protecting role is well established, the elaboration of phthalimides to more complex heterocyclic systems has received little attention.[11] The results reported here suggest that the sensitivity of the phthalimide carbonyls to intramolecular attack, which in this work provided a facile entry to the benz[f]indolizidine nucleus, could form the basis for a variety of new synthetic approaches to such systems.

Experimental Section

Melting points are uncorrected. IR spectra were determined with a Beckman 4230 instrument on Nujol mulls. ^1H NMR spectra were obtained on a Perkin-Elmer R-24 instrument and ^{13}C spectra on a Jeol PS-100 instrument operating in the FT mode, using Me_4Si as an internal reference. Combustion analyses were performed on a Perkin-Elmer Model 240 automatic elemental analyzer.

β-Phthalimidopropionic Acid (5).[12] Phthalic anhydride (148 g, 1.00 mol) and β-alanine (89.1 g, 1.00 mol) were refluxed together overnight in excess glacial HOAc. The solvent was evaporated and the white solid residue recrystallized from H_2O to give **5**, 213 g (97%), in two crops as pure white crystals, mp 150–151.5 °C (lit.[13] 150–151 °C).

β-Phthalimidopropionyl Chloride (6). β-Phthalimidopropionic acid (**5**; 2.19 g, 0.0100 mol) was heated in excess thionyl chloride until gas was no longer evolved (ca. 0.5 h). The resulting solution was evaporated to an oil from which most of the residual $SOCl_2$ was removed by alternative solution in CH_2Cl_2 and evaporation. The crystalline residue was dried in vacuo to give **6** as a white solid: 2.36 g (99%); mp 104.5–105.5 °C. In a similar run evaporation of a microsample of the original reaction mixture followed by thorough drying in vacuo gave analytically pure material, mp 107.5–108 °C (lit.[14] 107–108 °C).

Anal. Calcd for $C_{11}H_8ClNO_3$: C, 55.60; H, 3.39; N, 5.89. Found: C, 55.50; H, 3.35; N, 5.89.

1-Diazo-4-phthalimido-2-butanone (7). To a solution of an excess of diazomethane (undistilled, from nitrosomethylurea) in Et_2O was added β-phthalimidopropionyl chloride (**6**; 11.9 g, 0.0500 mol) in portions over ca. 0.25 h. The resulting suspension was stirred for an additional 0.5 h and the remaining diazomethane destroyed with HOAc. The mixture was filtered to give, after drying in vacuo, 8.50 g of **7** as fine pale green crystals, mp 125.5–127 °C. Evaporation of the filtrate gave a second crop, mp 125–126.5 °C, of 2.70 g (total yield 12.2 g, 100%). An analytical sample had mp 128–129 °C; IR 2160 (C=N=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.8 (t, J = 7 Hz, 2 H), 4.0 (t, J = 7 Hz, 2 H), 5.3 (s, 1 H), 7.8 (m, 4 H).

Anal. Calcd for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.27; H, 3.70; N, 17.55.

1-Acetoxy-4-phthalimido-2-butanone (4). A solution of 9.14 g (0.0376 mol) of diazo ketone **7** in 150 mL of glacial HOAc was heated to 40–45 °C for 5.5 h and then stirred overnight at room temperature. Evaporating the HOAc and drying the residue in vacuo to a constant weight gave a white solid, mp 122–129 °C, 10.27 g (100% crude yield). An analytical sample had mp 130.5–131 °C; IR 1730 (C=O), 1750 (OAc) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.2 (s, 3 H), 2.9 (t, J = 8 Hz, 2 H), 4.1 (t, J = 8 Hz, 2 H), 4.7 (s, 2 H), 7.8 (m, 4 H).

Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.12; H, 4.72; N, 5.10.

1-Formyloxy-4-phthalimido-2-butanone (8). To 25 mL of 91% HCO_2H was added 2.43 g (0.0100 mol) of **7** in portions, and the resulting mixture was stirred for several minutes until no further gas was evolved. The mixture was diluted with H_2O, made basic with $NaHCO_3$, and extracted with 3 × 100 mL of $CHCl_3$. The combined extracts were dried ($CaSO_4$), evaporated, and dried in vacuo to a constant weight, giving 2.48 g (95% crude yield) of **8** as a pure white solid. An analytical sample had mp 154–154.5 °C; IR 1740 (OCHO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.9 (t, J = 8 Hz, 2 H), 4.1 (t, J = 3 Hz, 2 H), 4.7 (s, 2 H), 7.8 (m, 4 H), 8.0 (s, 1 H).

Anal. Calcd for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.24; N, 5.36. Found: C, 59.64; H, 4.27; N, 5.35.

1-Chloro-4-phthalimido-2-butanone (9). To a stirred solution of 8.56 g (0.0352 mol) of **7** in 150 mL of Me_2CO was added concentrated HCl dropwise until gas was no longer evolved and the initial pale green color was discharged. The solvent was evaporated and the resulting residue dried in vacuo to give a pure white solid, 8.81 g (99% crude yield). An analytical sample had mp 120–120.5 °C; IR 1730 ($COCH_2Cl$) cm^{-1};[15] ^1H NMR ($CDCl_3$) δ 3.0 (t, J = 7 Hz, 2 H), 4.0 (t, J = 7 Hz, 2 H), 4.1 (s, 2 H), 7.8 (m, 4 H).

Anal. Calcd for $C_{12}H_{10}ClNO_3$: C, 57.27; H, 4.01; N, 5.57. Found: C, 57.35; H, 4.05; N, 5.57.

Reformatsky Reaction of 1-Acetoxy-4-phthalimido-2-butanone (4). To a flask containing a stirred solution of 22.90 g (0.0833 mol) of **4** in 200 mL of dry refluxing benzene and 5.45 g (0.0833 g-atom) of granulated zinc was added, under dry nitrogen, a solution of 10 mL (0.090 mol) of ethyl bromoacetate in 100 mL of benzene dropwise over 1.5 h. After 3.5 h (total time) an additional 1 g of zinc and 2 mL of ethyl bromoacetate were added and refluxing was continued for 1 h. To the cooled mixture was added 100 mL of 1 N H_2SO_4 with rapid stirring. The two resulting liquid layers were decanted and separated. After 3 days the crystals that formed in the acid layer[16] were collected on a filter to give 0.881 g (5%) of **13** as orange-yellow[17] needles, mp 219–220 °C. An analytical sample had mp 220–221 °C; IR 3240 (very broad), 1700, 1685, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.9 (t, J = 8 Hz, 2 H, CH_2CO), 4.2 (t, J = 8 Hz, 2 H, NCH_2), 6.5 (s, 1 H, exchangeable with D_2O, OH), 7.6–8.3 (m, 4 H, aromatic); ^{13}C NMR (Me_2SO-d_6; multiplicities in coupled spectrum and relative peak heights indicated) δ 34.8 (t, 0.75), 36.4 (t, 0.90), 122.9 (d, 0.91), 124.6 (d, 0.82), 128.7 (s, 0.56), 130.0 (d, 0.89), 130.0 (s, not distinguishable in decoupled spectrum), 132.2 (d, 1.00), 132.7 (s, 0.60), 133.6 (s, 0.53), 163.9 (s, 0.44), 189.8 (s, 0.55); UV (EtOH) λ_{max} 375 nm (ε 19 000).

Anal. Calcd for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51; mol wt 215. Found: C, 66.74; H, 4.27; N, 6.40; mol wt 238 (Rast); *m/e* 215 (base peak).

Evaporation of the dried ($MgSO_4$) benzene layer gave a dark oily solid; trituration with 65 mL of EtOAc left 5.28 g (20%) of acetoxylactone **10** as light crystals, mp 158–160.5 °C. An analytical sample had mp 161 °C; IR 1735 (OAc), 1770 (γ-lactone C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0 (s, 3 H), 2.4 (t, J = 8 Hz, 1 H), 2.5 (t, J = 8 Hz, 1 H), 2.85 (s, 1 H), 2.95 (s, 1 H), 3.8 (t, J = 3 Hz, 2 H), 4.3 (d, J = 11 Hz, 1 H), 4.7 (d, J = 11 Hz, 1 H), 7.8 (m, 4 H).

Anal. Calcd for $C_{16}H_{15}NO_6$: C, 60.57; H, 4.77; N, 4.41. Found: C, 60.53; H, 4.71; N, 4.34.

Reformatsky Reaction of 1-Formyloxy-4-phthalimido-2-butanone (8). The procedure, using 2.95 g (0.0113 mol) of **8**, was analogous to that described above and the isolation of **13** (0.191 g, 8%) was the same. The formyloxylactone **11** was initially obtained as an oil which crystallized on standing. Recrystallization (EtOAc–cyclohexane) gave 0.345 g (10%) of **11**, mp 140–142 °C. An analytical sample had mp 144–144.5 °C; IR 1780, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.50 (t, J = 8 Hz, 1 H), 2.55 (t, J = 8 Hz, 1 H), 2.9 (s, 1 H), 3.0 (s, 1 H), 3.8 (t, J = 8 Hz, 2 H), 4.4 (d, J = 12 Hz, 1 H), 4.7 (d, J = 12 Hz, 1 H), 7.8 (m, 4 H), 8.0 (s, 1 H).

Anal. Calcd for $C_{15}H_{13}NO_6$: C, 59.41; H, 4.32; N, 4.62. Found: C, 59.56; H, 4.35; N, 4.45.

Reformatsky Reaction of 1-Chloro-4-phthalimido-2-butanone (9). The procedure, using 2.52 g (0.0100 mol) of **9**, was analogous to that described for **4**. No **13** was obtained, and the hydroxylactone **12** was obtained as an oil which crystallized on standing. Recrystallization (EtOH) gave 0.268 g (10%) of **12** as a white solid, mp 160–164 °C. An analytical sample had mp 168–168.5 °C; IR 3480 (OH), 1770 (γ-lactone C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1 (t, J = 7 Hz, 2 H), 2.6 (s, 2 H), 3.9 (t, J = 7 Hz, 2 H), 4.18 (s, 1 H), 4.24 (s, 1 H), 7.8 (m, 4 H).

Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 60.75; H, 4.68; N, 5.13.

Decomposition of Diazo Ketone 7. To a stirred suspension of 0.58 g of anhydrous $CuSO_4$ in 100 mL of dry xylene at 120 °C was added dropwise a solution of 0.565 g (0.00233 mol) of **7** in 50 mL of xylene over 1 h. The solution was filtered hot, the cooled filtrate extracted with 2 N NaOH, and the separated basic layer acidified (H_2SO_4) to pH 1. Extraction of the resulting solution with $CHCl_3$, drying ($MgSO_4$), evaporation, and drying in vacuo gave 0.13 g (25%) of **13** as a yellow-green[17] solid.

The pale yellow solid that had precipitated from the aqueous layers was collected on a filter; this highly insoluble material was purified by refluxing in acetone, and refiltration gave 0.1 g of **19**, mp 210–230 °C dec; IR 1710, 1770 (phthalimide) cm^{-1}.

Anal. Calcd for $(C_{12}H_9NO_4)_n$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.21; H, 4.18; N, 6.07.

Registry No.—**4**, 65465-66-9; **5**, 3339-73-9; **6**, 17137-11-0; **7**, 7504-49-6; **8**, 65465-67-0; **9**, 65495-45-6; **10**, 65465-68-1; **11**, 65465-69-2; **12**, 65465-70-5; **13**, 23428-84-4; phthalic anhydride, 85-44-9; β-alanine, 107-95-9.

References and Notes

(1) (a) This work was presented in part at the 173rd National Meeting of the American Chemical Society, New Orleans, La., March 1977, Abstracts, ORGN 223. (b) Taken from the Ph.D. Thesis of S. F. K.
(2) K. Wada, S. Marumo, and K. Munakata, *Tetrahedron Lett.*, 5179 (1966).
(3) R. T. Conley, "Infrared Spectroscopy", 2nd ed, Allyn and Bacon, Boston, Mass., 1972, p 179.
(4) C. J. Pouchert, Ed., "The Aldrich Library of Infrared Spectra", 2nd ed, Aldrich Chemical Co., Milwaukee, Wis., 1975, p 772.
(5) M. W. Dietrich and R. E. Keller, *Anal. Chem.*, **36**, 258 (1964); R. M. Silverstein, G. C. Bassler, and T. C. Morrill, "Spectrometric Identification of Organic Compounds", 3rd ed, Wiley, New York, N.Y., 1974, p 1977.
(6) R. D. Campbell and H. M. Gilow, *J. Am. Chem. Soc.*, **82**, 5426 (1960).
(7) M. S. Newman, *J. Am. Chem. Soc.*, **64**, 2131 (1942).
(8) (a) T. R. Govindachari, M. V. Lakshmikantham, K. Nagarajan, and B. R. Pai, *Chem. Ind. (London)*, 1484 (1957); (b) W. C. Wildman, *Alkaloids (N.Y.)*, **6**, 289–413 (1960).
(9) Other mechanisms than that shown in Scheme II for the rearrangement

of **17** to **13** are of course possible.

(10) E. Vedejs, W. R. Wilbur, and R. Tweig, *J. Org. Chem.*, **42**, 401 (1977); W. C. Agosta and S. Wolff, *ibid.*, **40**, 1027 (1975); E. Wenkert, B. L. Mylari, and L. L. Davis, *J. Am. Chem. Soc.*, **90**, 3870 (1968); G. Stork and J. Ficini, *ibid.*, **83**, 4678 (1961); W. Kirmse, "Carbene Chemistry", Academic Press, New York, N.Y., 1964, p 120; W. J. Baron, M. R. DeCamp, M. E. Hendrick, M. Jones, Jr., R. H. Levin, and M. B. Sohn, *Carbenes 1973*, **1**, 1–152 (1973).

(11) (a) The general capacity of phthalimides to undergo ring expansion to substituted isoquinolines has, however, long been known; see J. G. M. Hill, *J. Org. Chem.*, **30**, 620 (1965). (b) A different type of homologation of a phthalimide group was recently reported: P. H. Mazzocchi, M. W. Bowen, and N. K. Narain, *J. Am. Chem. Soc.*, **99**, 7063 (1977).

(12) Because of its simplicity this procedure represents an improvement over one recently published: A. K. Bose, "Organic Syntheses", Collect. Vol. 5, Wiley, New York, N.Y., 1973, p 975.

(13) S. Gabriel, *Chem. Ber.*, **38**, 633 (1905).

(14) S. Gabriel, *Chem. Ber.*, **41**, 243 (1908).

(15) On long standing **9** changes its crystalline form; the new polymorph, mp 121–123 °C, shows the ketone carbonyl stretch shifted to 1740 cm^{-1} and the appearance of the fingerprint region substantially altered.

(16) On some runs the same yields could be obtained within 24 h. On much longer standing the product begins to redissolve, eventually giving a clear colorless solution. The same phenomenon was observed in neutral H_2O.

(17) This compound crystallizes in several forms, whose apparent colors range from green through yellow to red-orange; however, when the macrocrystalline structure is destroyed, such as by fine grinding or solution, the same yellow-green material is obtained. Solutions of **13** show a bright blue fluorescence under 365-nm light.

Studies on the Intramolecular Addition of Vinyl Nitrenes to Olefins

Albert Padwa* and Per H. J. Carlsen

Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214

Received November 21, 1977

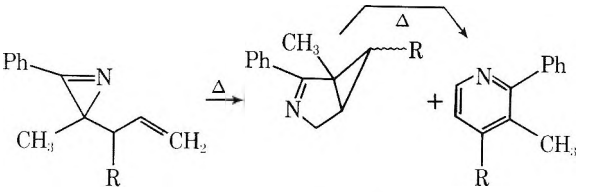
A series of 2-allyl-substituted 2*H*-azirines were found to undergo smooth rearrangement to afford 3-azabicyclo[3.1.0]hex-3-enes in high yield on thermolysis. The reactions can best be rationalized in terms of an equilibration of the 2*H*-azirine ring with a transient vinyl nitrene which subsequently adds to the adjacent π bond. The initially formed bicycloaziridine rearranges to the 3-azabicyclohexene ring system by means of a 1,3-sigmatropic shift. Evidence favoring this pathway is provided by the isolation of 2-phenyl-3-methyl-5-vinyl-Δ^1-pyrroline from the thermolysis of 2-(2-butenyl)-2-methyl-3-phenyl-2*H*-azirine. The formation of the Δ^1-pyrroline ring system can be rationalized as proceeding via a homo[1,5] hydrogen migration from a 6-endo methyl-substituted bicycloaziridine intermediate. Thermolysis of 3-methyl-2-phenyl-2-allyl-substituted 2*H*-azirines affords mixtures of 3-azabicyclohexenes and indoles. The distribution of products with this ring system is controlled by the rates of nitrene attack on the double bond vs. electrocyclization on the adjacent phenyl ring. Finally, the thermolysis of methyl 4-(3-methyl-2-phenyl-2*H*-azirin-2-yl)-2-butenoate results in a novel rearrangement and produces 2-methyl-3-phenyl-5-carbomethoxypyridine as the major product. A tentative but reasonable mechanistic rationale is advanced to rationalize this reaction.

The ready availability of 2*H*-azirines has spurred considerable activity in the chemistry of these strained heterocycles.[1,2] Photochemical and thermal cleavage preferences in 2*H*-azirines appear to be quite distinct.[1,2] Photolysis of 2*H*-azirines leads to irreversible ring opening and the formation of nitrile ylides as intermediates.[3,4] These species may be intercepted by a variety of dipolarophiles to form five-membered heterocyclic rings.[5,6] In certain cases the initially formed 1,3-dipole can be intramolecularly trapped to give novel azabicyclohexenes.[7–10] For example, irradiation of allyl-substituted 2*H*-azirines produces 2-azabicyclo[3.1.0]hex-2-enes via an unusual 1,1-cycloaddition reaction of the 1,3-dipole.[7] Products formed on thermal excitation of the 2*H*-azirine system, on the other hand, appear to involve vinyl nitrenes as intermediates.[11–23] Since examples of the direct addition of vinyl nitrenes to olefins to give aziridines have appeared infrequently in the literature,[24] we decided to investigate the thermal chemistry of a number of allyl-substituted 2*H*-azirines in order to determine whether the initially generated vinyl nitrene would undergo addition to the neighboring double bond. We report here the results of these studies.[25]

Results

The synthesis of the 2-allyl-substituted 2*H*-azirine system was straightforward and involved a modified Neber reaction in which variously substituted 2-methyl-1-phenyl-4-penten-1-ones were allowed to react with dimethylhydrazine. Treatment of the resulting dimethylhydrazone with methyl iodide followed by reaction with base gave the desired 2-allyl-substituted 2*H*-azirines in good yield.

We initially examined the thermal behavior of 2-allyl-2-methyl-3-phenyl-2*H*-azirine (**1**). Thermolysis of **1** in toluene

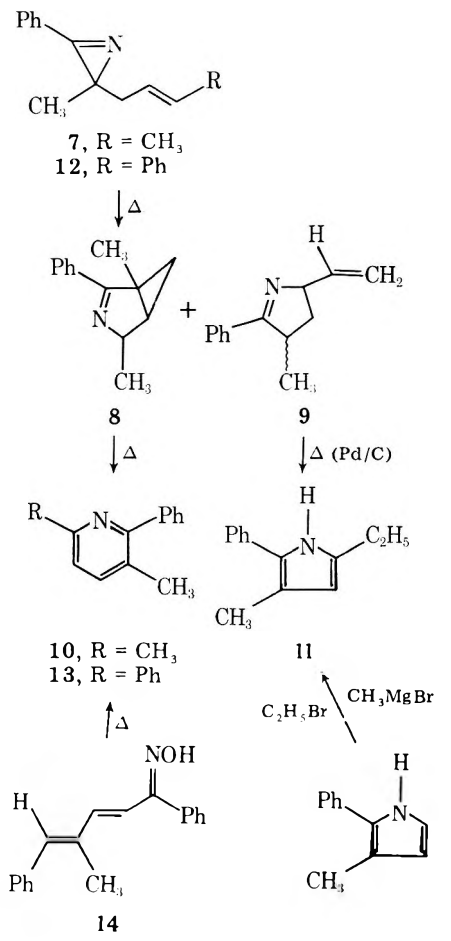


1, R = H; **4**, R = CH_3 — **2**, R = H; **5**, R = CH_3 — **3**, R = H; **6**, R = CH_3

at 195 °C for 180 h or in the absence of solvent at 250 °C for 1.5 h gave 1-methyl-2-phenyl-3-azabicyclo[3.1.0]hex-2-ene (**2**, 90%) and 3-methyl-2-phenylpyridine (**3**, 10%). The identity of **2** was determined by its straightforward spectral characteristics [NMR (100 MHz) τ 9.55 (t, 1 H, J = 4.0 Hz), 9.04 (dd, 1 H, J = 8.0, 4.0 Hz), 8.57 (s, 3 H), 8.36 (m, 1 H), 6.25 (dd, 1 H, J = 17.5, 2.0 Hz), 6.02 (dd, 1 H, J = 17.5, 5.0 Hz), 2.2–2.8 (m, 5 H)] as well as its facile conversion into **3** on further heating. Thermolysis of the closely related 2-(1-methylallyl)-substituted azirine **4** gave 1,6-dimethyl-2-phenyl-3-azabicyclo[3.1.0]hex-2-ene (**5**, 58%) as a 1:1 mixture of endo and exo isomers as well as 3,4-dimethyl-2-phenylpyridine (**6**, 25%). The mixture of exo and endo isomers of **5** was smoothly converted into pyridine **6** on further heating.

Subjection of azirine **7** to similar pyrolysis conditions gave 1,4-dimethyl-2-phenyl-3-azabicyclo[3.1.0]hex-2-ene (**8**, 71%), 2-phenyl-3-methyl-5-vinyl-Δ^1-pyrroline (**9**, 21%) as an inseparable cis–trans mixture, and a trace amount (<5%) of

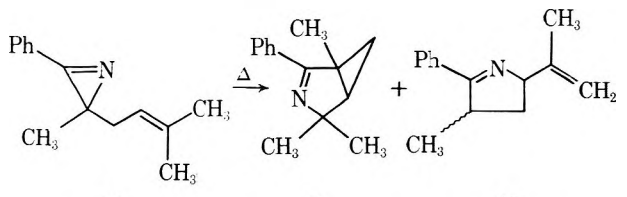
0022-3263/78/1943-2029$01.00/0



2,5-dimethyl-6-phenylpyridine (**10**). The structure of Δ^1-pyrroline **9** was confirmed by refluxing **9** in toluene in the presence of palladium on carbon (5%) for 48 h. This resulted in the quantitative formation of 2-phenyl-3-methyl-5-ethylpyrrole (**11**). The structure of pyrrole **11** was verified by comparison with an authentic sample prepared from the reaction of 2-phenyl-3-methylpyrrole anion with ethyl bromide. That Δ^1-pyrroline **9** did not arise from 3-azabicyclohexene 8 was shown by heating 8 under conditions similar to those used for the pyrolysis of azirine **7**. Under these conditions 8 was converted exclusively into pyridine **10**.

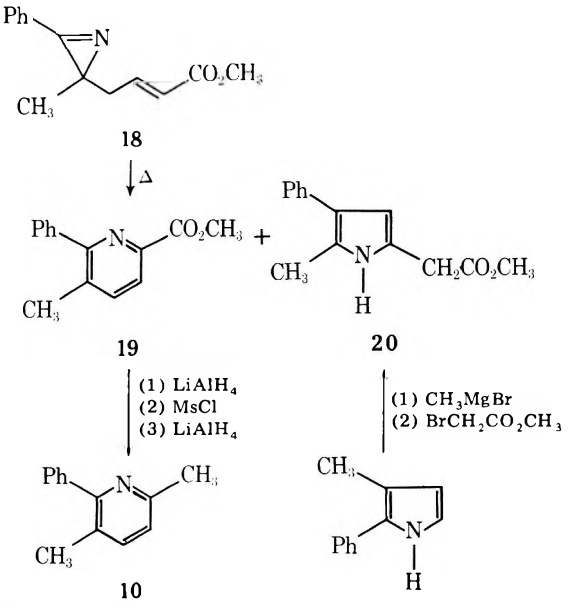
The thermal rearrangement of (*E*)-2-cinnamyl-2-methyl-3-phenyl-2*H*-azirine (**12**) was also studied. Thermolysis of **12** gave 2,6-diphenyl-3-methylpyridine (**13**, 49%) as the only characterizable material. The structure of **13** was verified by comparison with an authentic sample prepared from the thermolysis of oxime **14**. In this case there was no detectable quantities of a 3-aza-substituted bicyclohexene. It would appear as though the initially formed azabicyclohexene is converted into pyridine **13** at a faster specific rate than it is formed.

We also studied the thermal behavior of azirine **15** and found that it was converted to 1,4,4-trimethyl-2-phenyl-3-azabicyclo[3.1.0]hex-2-ene (**16**, 60%) [NMR (100 MHz) τ 9.44 (t, 1 H, J = 4.0 Hz), 9.20 (dd, 1 H, J = 8.0, 4.0 Hz), 8.77 (s, 3 H), 8.67 (s, 3 H), 8.57 (s, 3 H), 8.53 (dd, 1 H, J = 8.0, 4.0 Hz),



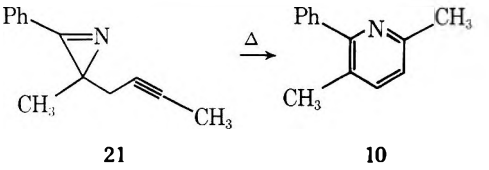
2.2–2.9 (m, 5 H)] and a 1:1 cis–trans mixture of isomeric 2-phenyl-3-methyl-5-(2-propenyl)-Δ^1-pyrrolines (**17**, 30%).

We also decided to investigate the thermal behavior of a 2*H*-azirine which possessed an electron-withdrawing substituent on the double bond. To this end we synthesized methyl 4-(2-methyl-3-phenyl-2*H*-azirin-2-yl)-2-butenoate (**18**). Heating a sample of **18** in toluene at 180 °C gave rise to



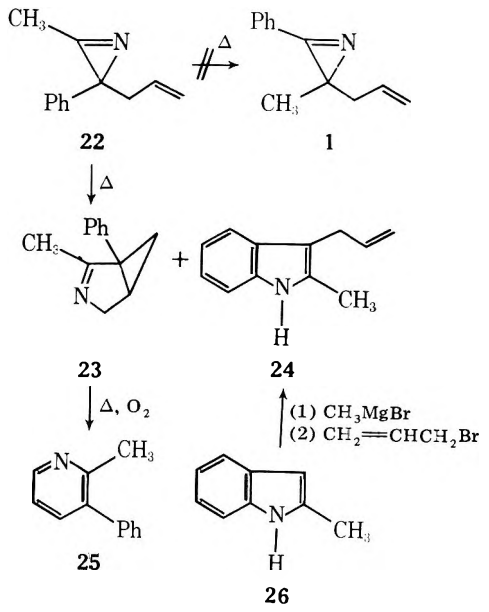
pyridine **19** (47%) and pyrrole **20** (37%). The structure of **19** was confirmed by its straightforward conversion ($LiAlH_4$, MsCl, $LiAlH_4$) to 2,5-dimethyl-6-phenylpyridine (**10**),[26] while the identity of **20** was established by comparison with an independently synthesized sample prepared from the reaction of 2-phenyl-3-methylpyrrole anion with methyl α-bromoacetate.

Further examples which would support the generality of these rearrangements were sought. With this in mind, we decided to prepare an acetylenic 2*H*-azirine with the expectation that this system might undergo some interesting thermal chemistry. Flash vacuum pyrolysis (500 °C at 0.005 mm) of a sample of 2-(2-butynyl)-2-methyl-3-phenyl-2*H*-azirine (**21**) through a quartz tube gave 2,5-dimethyl-6-



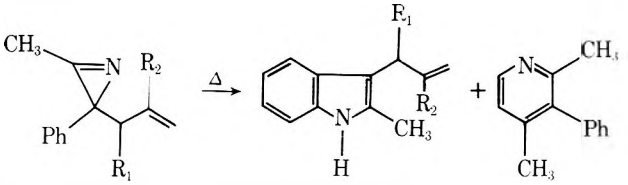
phenylpyridine (**10**) as the only characterizable product in 34% isolated yield.

Attention was next turned to the thermal behavior of the closely related 2-allyl-3-methyl-2-phenyl-2*H*-azirine system. Thermolysis of azirine **22** in toluene at 180 °C for 28 h gave rise to a mixture of 2-methyl-1-phenyl-3-azabicyclo[3.1.0]hex-2-ene (**23**, 31%), 3-allyl-2-methylindole (**24**, 58%), and a trace amount (5%) of 2-methyl-3-phenylpyridine (**25**). The identity of azabicyclohexene **23** was determined by its straightforward spectral characteristics [NMR ($CDCl_3$, 60 MHz) τ 9.48 (t, 1 H, J = 4.0 Hz), 8.56 (dd, 1 H, J = 8.0, 4.0 Hz), 8.13 (t, 3 H, J = 2.0 Hz), 7.98 (m, 1 H), 6.30 (dq, 1 H, J = 17.5, 2.0 Hz), 5.92 (ddq, 1 H, J = 17.5, 5.0, 2.0 Hz), 2.80 (s, 5 H)] as well as its facile conversion into 2-methyl-3-phenylpyridine (**25**) on further heating. The structure of indole **24** was verified by comparison with an authentic sample prepared from the rection of 2-methylindole (**26**) with allyl bromide. Careful monitoring of the reaction showed that **22** was not converted



tc **1** by a Cope rearrangement, as had been encountered with the closely related cyclopropene system.[27]

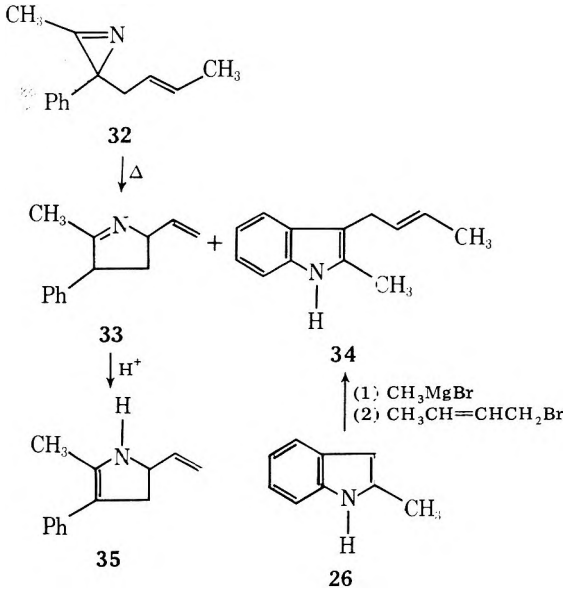
Subjection of azirine **27** to similar pyrolysis conditions gave 2-methyl-3-(1-methylallyl)indole (**28**) and 2,4-dimethyl-3-phenylpyridine (**29**) as the major thermal products. The



27, $R_1 = CH_3$; $R_2 = H$ **28**, $R_1 = CH_3$; $R_2 = H$
30, $R_1 = H$; $R_2 = CH_3$ **31**, $R_1 = H$; $R_2 = CH_3$

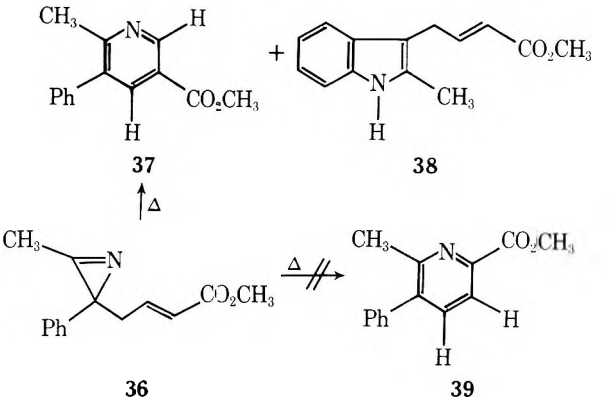
structure of indole **28** was verified by comparison with an authentic sample prepared from the reaction of 2-methylindole (**26**) with 3-chloro-1-butene. In this case there were no detectable quantities of a 3-aza-substituted bicyclohexene. Thermolysis of the closely related 2-(2-methylallyl)-3-methyl-2-phenyl-2*H*-azirine (**30**) gave indole **31** (89%) as the only characterizable material. The structure of this material was verified by comparison with an authentic sample.

When the thermolysis of azirine **32** was carried out in toluene at 180 °C, a mixture of the cis and trans isomers of Δ^1-pyrroline **33** as well as indole **34** were isolated in good yield.



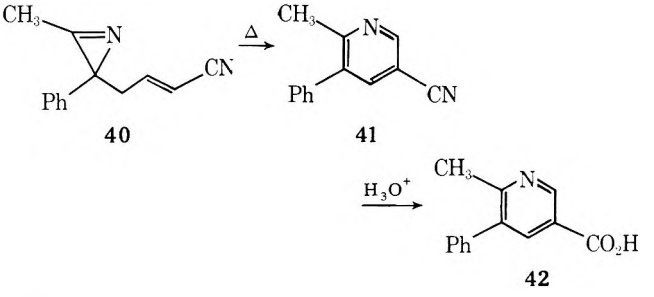
Further evidence supporting the structure of Δ^1-pyrroline was obtained by its ready conversion to **35** on treatment with catalytic quantities of *p*-toluenesulfonic acid. Confirmation of the structure of indole **34** was obtained by comparison with an authentic sample prepared by treating 2-methylindole with 1-bromo-2-butene.

We have also examined the thermolysis of methyl (*E*)-4-(3-methyl-2-phenyl-2*H*-azirin-2-yl)-2-butenoate (**36**) and find



that this compound exhibits substantially different chemical behavior from that encountered with the closely related structural isomer **18**. Heating a sample of azirine **36** in toluene at 185 °C gave 2-methyl-3-phenyl-5-carbomethoxypyridine (**37**, 70%) and methyl (*E*)-4-(2-methylindol-3-yl)-2-butenoate (**38**, 30%) as the only characterizable products. The structure of indole **38** was established by an independent synthesis. Structure **37** could be distinguished from the isomeric 2-methyl-3-phenyl-6-carbomethoxypyridine (**39**) by examination of its unique NMR spectrum, which showed methyl singlets at τ 7.40 (3 H) and 6.04 (3 H), the aromatic protons as a multiplet at τ 2.48–2.72 (5 H), and the pyridine ring protons as doublets at τ 1.86 and 0.90 (J = 2.0 Hz). The magnitude of the coupling constant (J = 2.0 Hz) is consistent with the assigned meta disposition of the ring protons. Pyridine **39** would be expected to exhibit a coupling constant of ca. 8.0 Hz for the ring protons, as was observed with pyridine **19** (see Experimental Section). Unequivocal proof for the structure of pyridine **37** was obtained by comparison with an authentic sample provided by Professor Julia.[28]

A related rearrangement was also encountered when azirine **40** was subjected to thermolysis. The major component iso-

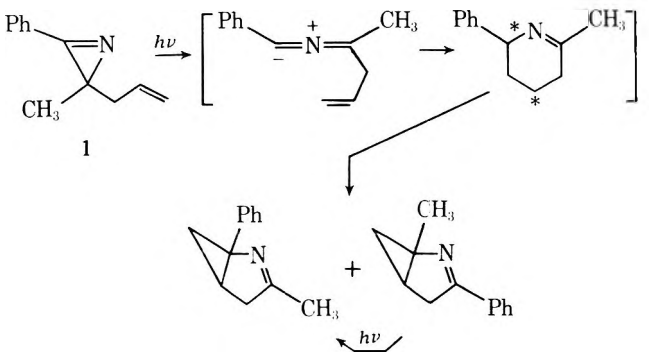


lated (77%) was identified as 2-methyl-3-phenyl-5-cyanopyridine (**41**) on the basis of its spectral properties [NMR (100 MHz) τ 7.48 (s, 3 H), 2.58–2.92 (m, 5 H), 2.35 (d, 1 H, J = 2.0 Hz), 1.38 (d, 1 H, J = 2.0 Hz)] and by hydrolysis to the known 6-methyl-5-phenylnicotinic acid (**42**).[28]

Discussion

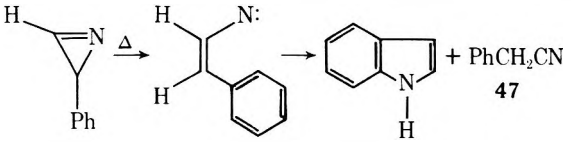
Previous papers from this laboratory have established that the irradiation of allyl-substituted 2*H*-azirines produces 2-azabicyclo[3.1.0]hex-2-enes as primary photoproducts.[7] The photoreaction has been proposed to proceed via C–C bond cleavage and generation of a bent nitrile ylide intermediate

(carbene-like). Attack of the carbene carbon of the dipole onto the terminal position of the neighboring double bond generates a six-membered ring trimethylene intermediate which subsequently collapses to the observed 2-azabicyclohexene ring system.

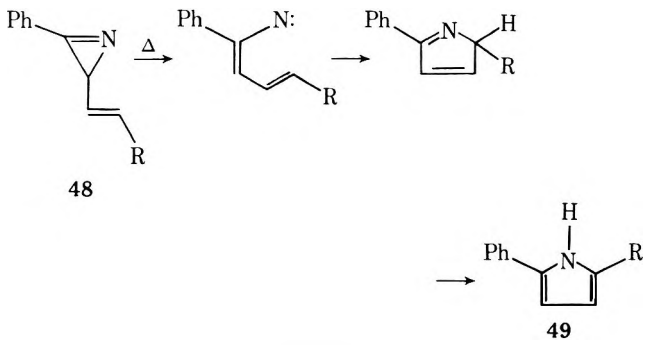


1 43 44

In contrast to the photochemical results, the thermal transformations observed with these systems can best be rationalized in terms of an equilibration of the 2*H*-azirine with a transient vinyl nitrene which subsequently rearranges to the final 3-azabicyclohexene ring system. The products formed on thermal decomposition of 2*H*-azirines generally appear to involve C–N rather than C–C bond cleavage.[11-23] In some cases C–N bond cleavage ultimately leads to fragmentation of the three-membered ring with the subsequent formation of a nitrile and carbene,[11] and in other cases it results in the formation of indoles[14] and pyrroles.[22,29] Thus, Isomura and co-workers report that the thermolysis of 2-phenyl-2*H*-azirine (**45**) produces a 1:1 mixture of indole (**46**) and phenyl acetonitrile (**47**) in 86% isolated yield.[13] The most obvious mechanism for the formation of **46** involves the generation of a vinyl nitrene intermediate followed by electrocyclic closure. Similarly, the thermal rearrangements of a series of vinyl-substituted 2*H*-azirines are best accounted for by C–N bond cleavage, leading to a vinyl nitrene intermediate.[22,29] In fact,



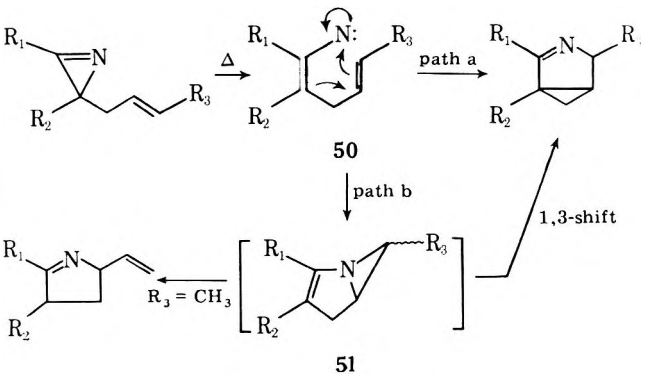
45 46 47



48 49

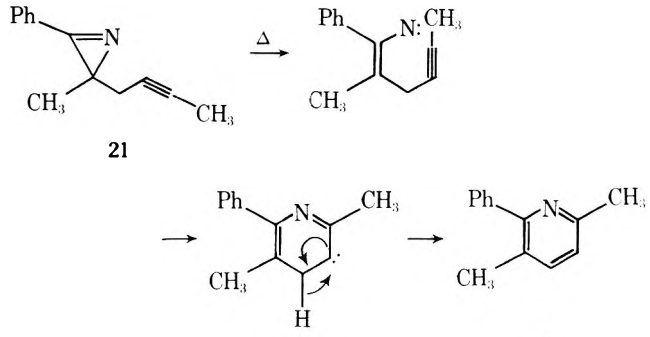
Nishiwaki and co-workers[17,21,30] have shown that the vinyl nitrene intermediate generated from the thermolysis of the 2*H*-azirine ring can actually be trapped with phosphines.

The formation of 3-azabicyclo[3.1.0]hex-2-enes as reaction products with the above systems suggests that the route by which the initially generated vinyl nitrene intermediate rearranges to the final product (path a) involves attack of the neighboring π system on the electrophilic singlet nitrene followed by bond reorganization. An equally plausible mechanism (path b) involves intramolecular addition of the nitrene onto the adjacent π bond to give a bicycloaziridine (**51**) as a transient intermediate. This species can subsequently rearrange to the observed product by a 1,3-sigmatropic shift. The allowed concerted thermal 1,3-shift requires an inversion of the migration center, and this seems sterically prohibited in this system. Although a "forbidden" 1,3-suprafacial concerted process cannot be excluded,[31] the rearrangement of **51** to the observed azabicyclohexene probably involves a diradical intermediate by analogy with the results obtained with the parent carbocycle.[32,33] Several examples of intramolecular addition to nitrenes onto adjacent double bonds are available in the literature[34-36] and provide reasonable chemical analogy for path b. Additional evidence favoring this pathway is provided by the isolation of Δ^1-pyrrolines **9, 17,** and **33** from the thermolysis of azirines **7, 15,** and **32.** The formation of the Δ^1-pyrroline ring system can be rationalized as proceeding via a homo[1,5] hydrogen migration from the endo isomer of bicycloaziridine **51.** This transformation is related to the homo[1,5] sigmatropic reaction which occurs on thermolysis of bicyclo[3.1.0]hex-2-ene-*endo*-6-carboxaldehydes.[37,38]



50 51

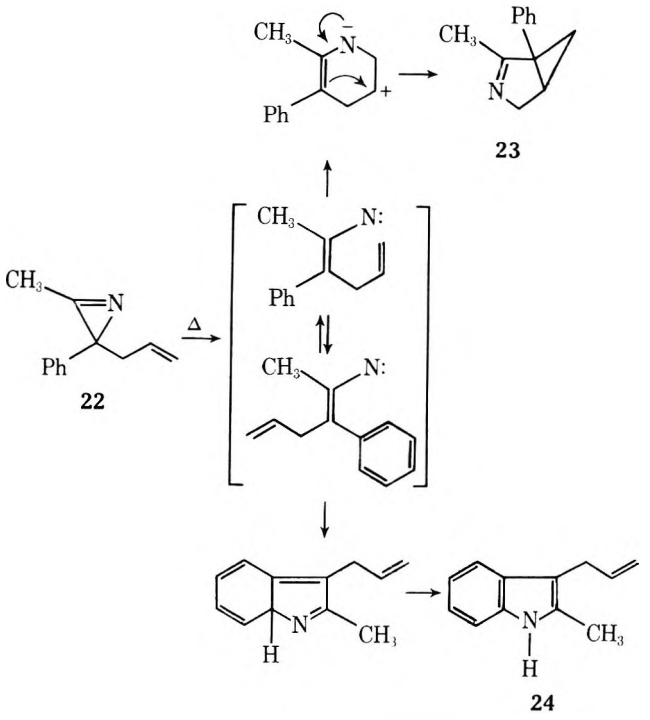
The formation of pyridine **10** from azirine **21** is also compatible with a vinyl nitrene intermediate. In this case, attack by the neighboring acetylenic functionality on the nitrene will lead to carbene **52,** which would be expected to undergo a facile hydrogen migration to produce **10.**



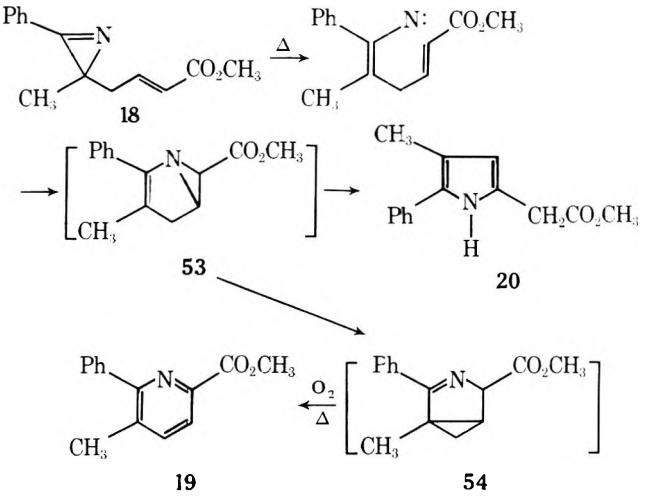
21 52 10

Whereas 3-phenyl-2-methyl-2-allyl-substituted 2*H*-azirines (e.g., **1**) give only 3-azabicyclohexenes on thermolysis, the isomeric 3-methyl-2-phenyl-2-allyl-substituted azirines (e.g., **22**) also produce significant quantities of indoles. The distribution of products with the latter system will be controlled by the rates of nitrene attack on the double bond vs. electrocyclization on the adjacent phenyl ring. It should be noted that there are several examples in the literature which provide good analogy for the cyclization of a butadienyl nitrene to a five-membered ring.[22,29,39]

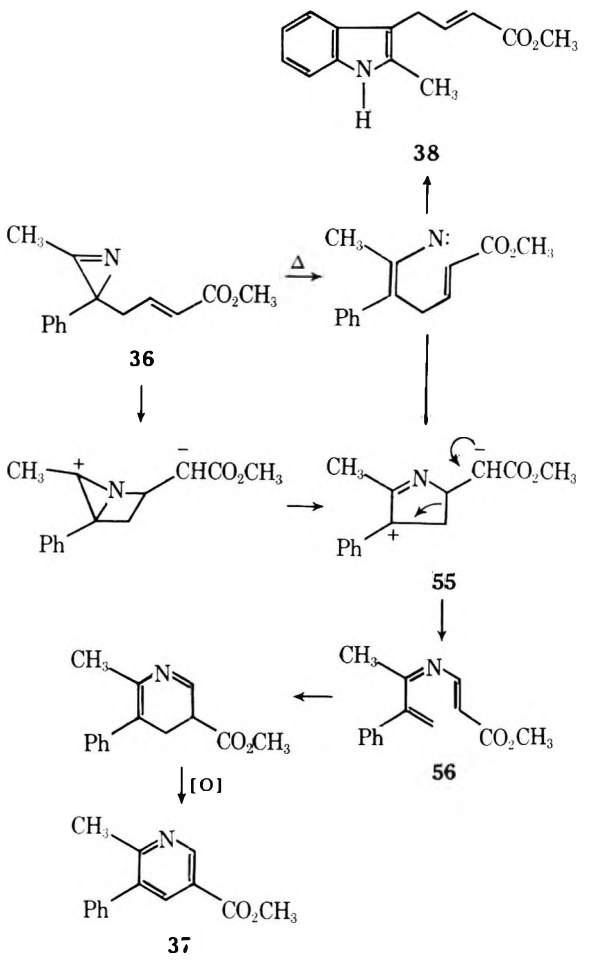
The thermolysis of the carbomethoxy-substituted allyl 2*H*-azirine **18** represents a novel reaction and merits some comment. In simplest valence bond terms, this transformation is explicable in terms of an attack by the vinyl nitrene onto the neighboring double bond to give a short-lived bicycloaziridine



53. Heterolytic cleavage of the C–N bond followed by proton reorganization would furnish pyrrole **20**. The initially produced six-ring zwitterion (or structure **53**) would also be expected to afford the azabicyclohexene ring system **54**, which could in turn give rise to pyridine **19** on further heating.



The conversion of the isomeric carbomethoxy-substituted 2*H*-azirine **36** to pyridine **37**, on the other hand, proceeds by an entirely different pathway. Although information on the mechanistic details of this reaction is minimal, a tentative yet reasonable rationale can be advanced. Thus, the formation of pyridine **37** may be attributed to conjugate addition of the vinyl nitrene onto the electron-deficient double bond. The initially produced five-ring zwitterion **55** can then undergo a subsequent fragmentation to give azatriene **56**. This species would be expected to undergo a ready electrocyclic closure followed by oxidation to ultimately afford pyridine **37**. An alternative path involving nucleophilic attack by the available lone pair of electrons in starting material onto the conjugated double bond also seems possible. A similar mechanism would account for the conversion of azirine **40** to pyridine **41**. The difference in behavior of the isomeric carbomethoxy-substituted azirines (i.e., **18** vs. **37**) can be attributed to the difference in nucleophilicity of the nitrogen atom present in starting material or in the vinyl nitrene intermediate.



Experimental Section

All melting and boiling points are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Ga. The infrared absorption spectra were determined on a Perkin-Elmer Model 137 Infracord spectrophotometer. The ultraviolet absorption spectra were measured with a Cary Model 14 recording spectrophotometer using 1-cm matched cells. The proton magnetic resonance spectra were determined at 100 MHz using a Jeolco ML-100 and a Varian XL-100 spectrometer. Mass spectra were determined with a Perkin-Elmer RMU6 mass spectrometer at an ionizing voltage of 70 eV.

Thermolysis of 2-Allyl-2-methyl-3-phenyl-2*H*-azirine (1). A solution containing 700 mg of azirine **1** in 15 mL of toluene was heated at 195 °C in a sealed tube for 180 h. Removal of the solvent under reduced pressure left a yellow oil which contained two components. Liquid–liquid partition chromatography of the mixture gave 1-methyl-2-phenyl-3-azabicyclo[3.1.0]hex-2-ene (**2**; 637 mg, 92%) as a clear oil: NMR (CCl_4, 100 MHz) τ 9.55 (t, 1 H, J = 4.0 Hz), 9.04 (dd, 1 H, J = 8.0, 4.0 Hz), 8.57 (s, 3 H), 8.36 (m, 1 H), 6.25 (dd, 1 H, J = 17.5, 2.0 Hz), 6.02 (dd, 1 H, J = 17.5, 5.0 Hz), 2.2–2.8 (m, 5 H). When the signals at τ 6.25 and 6.02 were irradiated with an external field, the multiplet at τ 8.36 collapsed to a doublet of doublets with J = 8.0 and 4.0 Hz. IR (neat) 3055, 2950, 2910, 2840, 1593, 1570, 1492, 1445, 1385, 1340, 1000, 775, 698 cm^{-1}; UV (cyclohexane) 239 nm (ϵ 11 000); *m/e* 171 (M^+ and base), 156, 143, 115, 77.

Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.08; H, 7.62; N, 8.04.

The minor component isolated from the column (70 mg, 10%) was identified as 3-methyl-2-phenylpyridine (**3**) by comparison with an authentic sample:[40] picrate mp 164–165 °C (lit.[40] mp 163–164 °C); NMR (CCl_4, 100 MHz) τ 7.68 (s, 3 H), 3.00 (dd, 1 H, J = 8.0, 4.5 Hz); IR (neat) 3030, 2941, 1582, 1570, 1430, 803, 787, 746, 701 cm^{-1}.

Subjection of azabicyclohexene **2** to 195 °C for 85 h resulted in its partial conversion to 3-methyl-2-phenylpyridine (**3**).

Thermolysis of 2-Methyl-2-(1-methylallyl)-3-phenyl-2*H*-azirine (4). A solution containing 200 mg of azirine **4**[7] in 15 mL of toluene was heated at 195 °C in a sealed tube for 182 h. Removal of the solvent under reduced pressure left a yellow oil which was subjected to thick-layer chromatography using a 1:5 ether–cyclohexane mixture as the eluent. The first band consisted of a 1:1 mixture of the endo and exo isomers of 1,6-dimethyl-2-phenyl-3-

azabicyclo[3.1.0]hex-2-ene (**5**, 58%). The two isomers were eventually separated by extensive multielutions on a thick-layer plate. The endo isomer showed the following spectral properties: NMR (CCl_4, 100 MHz) τ 9.25 (d, 3 H, J = 6.0 Hz) 8.78 (dq, 1 H, J = 8.0, 6.0 Hz), 8.58 (s, 3 H), 8.38 (ddd, 1 H, J = 8.0, 7.0, 2.0 Hz), 6.44 (dd, 1 H, J = 18.0, 2.0 Hz), 6.07 (dd, 1 H, J = 18.0, 7.0 Hz), 2.2–2.8 (m, 5 H); IR (neat) 3030, 2955, 2910, 1595, 1570, 1490, 1445, 1380, 1340, 1320, 1000, 781, 758, 697 cm^{-1}; UV (cyclohexane) 237 nm (ϵ 12 000); m/e 185 (M^+), 184 (base), 170, 155, 143, 129, 115.

The exo isomer exhibited the following spectral properties: NMR (CCl_4, 100 MHz) τ 9.30 (p, 1 H, J = 6.0 Hz), 8.81 (d, 3 H, J = 6.0 Hz), 8.75 (ddd, 1 H, J = 6.0, 5.0, 2.0 Hz), 8.62 (s, 3 H), 6.22 (dd, 1 H, J = 17.0, 2.0 Hz), 6.06 (dd, 1 H, J = 17.0, 5.0 Hz), 2.20–2.80 (m, 5 H); IR (neat) 3025, 2950, 2915, 1592, 1565, 1490, 1445, 1388, 1340, 1307, 1000, 780, 740, 695 cm^{-1}; UV (cyclohexane) 236 nm (ϵ 12 000); MS m/e 185 (M^+), 184 (base), 170, 155, 143, 129, 115.

The second band isolated from the thick-layer plate (25%) was identified as 3,4-dimethyl-2-phenylpyridine (**6**) by comparison with an authentic sample:[26] picrate mp 171–172 °C (lit.[26] mp 174–175 °C); NMR (CCl_4, 100 MHz) τ 7.76 (s, 3 H), 7.68 (s, 3 H), 3.04 (d, 1 H, J = 5.0 Hz), 2.62 (m, 5 H), 1.70 (d, 1 H, J = 5.0 Hz); IR (neat) 3050, 2950, 1580, 1444, 1400, 1382, 1183, 1060, 1010, 824, 783, 747, 700 cm^{-1}.

Thermolysis of a sample of either the *exo*- or *endo*-azabicyclohexene **5** in toluene at 195 °C for 72 h gave pyridine **6** as the exclusive product.

Thermolysis of (*E*)-2-(2-Butenyl)-2-methyl-3-phenyl-2*H*-azirine (7). A solution containing 100 mg of azirine **7**[7] in 10 mL of toluene was heated at 195 °C in a sealed tube for 166 h. Removal of the solvent left a yellow oil which was subjected to thick-layer chromatography using a 1:2 mixture of ether–cyclohexane as the eluent. The first fraction (21%) contained an inseparable mixture (1:1) of the cis and trans isomers of 2-phenyl-3-methyl-5-vinyl-Δ^1-pyrroline (**9**): NMR (CCl_4, 100 MHz) τ 8.82 and 8.84 (two doublets, 3 H, J = 7.0 Hz), 8.4–8.7 (m, 1 H), 8.10 (m, 1 H), 6.64 (m, 1 H), 5.40 (m, 1 H), 4.7–5.1 (m, 2 H), 3.8–4.2 (m, 1 H), 2.1–3.0 (m, 5 H); IR (neat) 3080, 3020, 2960, 2925, 2865, 1639, 1605, 1570, 1492, 1445, 1373, 1330, 1267, 1019, 990, 920, 775, 695 cm^{-1}; MS m/e 185 (M^+), 170, 143, 115, 77; UV (methanol) 243 nm (ϵ 13 200).

A 100-mg sample of Δ^1-pyrroline **9** in 50 mL of toluene containing 100 mg of 5% palladium on carbon was heated at reflux for 48 h. Removal of the catalyst followed by evaporation of the solvent left 93 mg of 2-phenyl-3-methyl-5-ethylpyrrole (**11**): NMR (CCl_4, 100 MHz) τ 8.79 (t, 3 H, J = 8.0 Hz), 7.81, (s, 3 H), 7.44 (q, 2 H, J = 8.0 Hz), 4.32 (d, 1 H, J = 3.0 Hz, collapsed to a singlet with D_2O wash), 2.6–3.0 (m, 5 H), 2.0–2.6 (1 H, broad s, exchanged with D_2O); IR (neat) 3420, 3050, 2960, 2920, 2860, 1600, 1510, 1485, 1440, 1375, 1335, 1140, 800, 760, 695, 640 cm^{-1}; MS m/e 185 (M^+), 170, 147, 105, 77.

Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.10; H, 8.05; N, 7.82.

The second band isolated from the thick-layer plate of the crude thermolysis mixture (71%) contained a clear oil whose structure was assigned as *exo*-1, 4-dimethyl-2-phenyl-3-azabicyclo[3.1.0]hex-2-ene (**8**): NMR (CCl_4, 100 MHz) τ 9.52 (t, 1 H, J = 4.0 Hz), 9.04 (dd, 1 H, J = 8.0, 4.0 Hz), 8.75 (d, 3 H, J = 7.0 Hz), 8.54 (dd, 1 H, J = 8.0, 4.0 Hz), 8.04 (s, 3 H), 6.13 (q, 1 H, J = 7.0 Hz), 2.1–2.3 (m, 5 H); IR (neat) 3060, 3025, 2960, 2920, 2855, 1592, 1568, 1490, 1442, 1385, 1340, 1290, 1210, 1170, 1064, 1020, 1000, 990, 775, 700 cm^{-1}; UV (cyclohexane) 238 nm (ϵ 10 200); MS m/e 185 (M^+), 184 (base), 170, 155, 141, 129, 115, 77.

Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.06; H, 8.20; N, 7.40.

The NMR spectrum of the crude reaction mixture showed the presence of small quantities (ca. 5%) of 2,5-dimethyl-6-phenylpyridine (**10**) (singlets at τ 7.72 and 7.52). Thermolysis of a sample of azabicyclohexene **8** at 195 °C for 96 h gave pyridine **10** as the exclusive product,[26] picrate mp 139–140 °C (lit.[26] mp 134–135 °C).

Independent Synthesis of 2-Phenyl-3-methyl-5-ethylpyrrole (11). The structure of the pyrrole obtained from the palladium-induced isomerization of Δ^1-pyrroline **9** was established by comparison with an independently synthesized sample. A solution containing 17.3 g of 2-methyl-1-phenyl-4-penten-1-one in 500 mL of methanol was ozonized at −78 °C. Standard workup conditions afforded 3-methyl-4-phenyl-4-oxybutanal in 92% yield: bp 94–95 °C (0.1 mm); NMR ($CDCl_3$, 60 MHz) τ 8.88 (d, 3 H, J = 7.5 Hz), 7.58 (dd, 1 H, J = 18.0, 6.0 Hz), 6.94 (dd, 1 H, J = 18.0, 8.0 Hz), 6.10 (dp, 1 H, J = 7.5, 6.0 Hz), 2.46–2.80 (m, 3 H), 2.0–2.4 (m, 2 H), 0.3 (s, 1 H); IR (neat) 3010, 2940, 2820, 2700, 1725, 1675 cm^{-1}; MS m/e 176 (M^+), 158, 148, 134, 105 (base), 77.

To a solution containing 3.5 g of the above aldehyde in 40 mL of methanol was added 15 mL of concentrated ammonium chloride and 10 mL of concentrated ammonia. The mixture was heated at reflux for 1 h, cooled, and extracted with ether. The ether layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 2-phenyl-3-methylpyrrole in quantitative yield: NMR (CCl_4, 60 MHz) τ 7.80 (s, 3 H), 4.10 (t, 1 H, J = 3.0 Hz), 3.62 (t, 1 H, J = 3.0 Hz), 2.85 (s, 5 H), 2.4 (broad s, 1 H); IR (neat) 3380, 3030, 2910, 1595, 1495, 1470, 1440, 1400, 1255, 1190, 1110, 1075, 1060, 1010, 897, 842, 765, 725, 699 cm^{-1}; MS m/e 157 (M^+), 156 (base), 129, 128, 105, 77.

To a solution containing 1.57 g of 2-phenyl-3-methylpyrrole in 20 mL of ether at 0 °C was added 3.6 mL of a 2.9 M methylmagnesium bromide solution. After stirring for 30 min, a 2.0-g sample of ethyl bromide was added and the resulting mixture was allowed to stir for 12 h at room temperature. Removal of the solvent followed by thick-layer chromatography gave a pure sample of 2-phenyl-3-methyl-5-ethylpyrrole (31%) which was identical with that obtained from the palladium-induced isomerization of Δ^1-pyrroline **9**.

Preparation and Thermolysis of (*E*)-2-Cinnamyl-2-methyl-3-phenyl-2*H*-azirine. A sample of azirine **12** was prepared by the method previously outlined:[7] bp 132–136 °C (0.2 mm); NMR (CCl_4, 100 MHz) τ 8.58 (s, 3 H), 7.56 (dd, 1 H, J = 14.0, 7.0 Hz), 7.34 (dd, 1 H, J = 14.0, 7.0 Hz), 3.76 (dt, 1 H, J = 16.0, 7.0 Hz), 3.54 (d, 1 H, J = 16.0 Hz), 2.0–3.0 (m, 10 H); IR (neat) 3080, 3060, 3020, 2920, 1724, 1594, 1485, 1450, 1374, 1192, 961, 761, 748, 688 cm^{-1}; UV (cyclohexane) 247 nm; MS m/e 247 (M^+), 246, 245, 121, 119, 117, 105, 91, 77.

Anal. Calcd for $C_{18}H_{17}N$: C, 87.41; H, 6.93; N, 5.66. Found: C, 87.20; H, 6.85; N, 5.62.

Distillation of the above azirine through a 9 in Vigreux column at 200 °C gave a 49% yield of 2,6-diphenyl-3-methylpyridine (**13**): bp 165–168 °C (0.03 mm); picrate mp 172–173 °C; NMR (CCl_4, 100 MHz) τ 7.72 (s, 3 H), 2.4–2.9 (m, 10 H), 1.98 (m, 2 H); IR (neat) 3055, 3025, 2920, 1582, 1560, 1490, 1455, 1430, 1372, 1309, 1264, 1302, 1065, 1015, 830, 784, 760, 749, 692, 633 cm^{-1}; MS m/e 245 (M^+), 244 (base), 77.

An authentic sample of pyridine **13** was independently synthesized according to the procedure of Scholtz[41] and was identical to that obtained from the thermolysis of azirine **12**.

Thermolysis of 2-Methyl-2-(3-methyl-2-butenyl)-3-phenyl-2*H*-azirine (15). A solution containing 400 mg of azirine **15**[7] in 12 mL of toluene was heated at 195 °C in a sealed tube for 58 h. Removal of the solvent left a yellow oil which was subjected to thick-layer chromatography using a 2:5 mixture of ether–cyclohexane as the eluent. The material isolated in the first band contained a 1:1 mixture of isomeric 2-phenyl-3-methyl-5-(2-propenyl)-Δ^1-pyrrolines (**17**). Isomer A: NMR (CCl_4, 100 MHz) τ 8.82 (d, 3 H, J = 7.5 Hz), 8.26 (s, 3 H), 8.12 (t, 1 H, J = 8.0 Hz), 8.08 (t, 1 H, J = 8.0 Hz), 6.55 (m, 1 H), 5.42 (broad t, 1 H, J = 8.0 Hz), 5.22 (broad s, 1 H), 5.05 (broad s, 1 H), 2.0–2.8 (m, 5 H); IR (neat) 3020, 2940, 1650, 1640, 1575, 1515, 1450, 1340, 1240, 1160, 1125, 1075, 1030, 900, 780, 694 cm^{-1}; MS m/e 199 (M^+), 184, 157, 115, 77.

The other isomer (B) showed the following spectral properties: NMR (CCl_4, 100 MHz) τ 8.81 (d, 3 H, J = 7.0 Hz), 8.19 (s, 3 H), 8.07 (m, 1 H), 7.50 (dt, 1 H, J = 12.0, 8.0 Hz), 6.58 (m, 1 H), 5.44 (dd, 1 H, J = 8.0, 7.0 Hz), 5.20 (broad s, 1 H), 5.11 (broad s, 1 H), 2.0–2.8 (m, 5 H); IR (neat) 3020, 2940, 1645, 1630, 1570, 1500, 1450, 1335, 1270, 1130, 1075, 1030, 1000, 901, 775, 697 cm^{-1}; MS m/e 199 (M^+), 184, 157, 104, 77.

The second band from the thick-layer plate contained a clear oil (60%) whose structure was assigned as 1,4,4-trimethyl-2-phenyl-3-azabicyclo[3.1.0]hex-2-ene (**16**) on the basis of its spectral data: NMR (CCl_4, 100 MHz) τ 9.44 (t, 1 H, J = 4.0 Hz), 9.20 (dd, 1 H, J = 8.0, 4.0 Hz), 8.77 (s, 3 H), 8.67 (s, 3 H), 8.57 (s, 3 H), 8.53 (dd, 1 H, J = 8.0, 4.0 Hz), 2.2–2.9 (m, 5 H); IR (neat) 3020, 2940, 1600, 1570, 1493, 1443, 1385, 1355, 1340, 1265, 1235, 1190, 1075, 1030, 1010, 1000, 975, 833, 780, 700 cm^{-1}; MS m/e 199 (M^+), 184, 157, 143, 128, 115, 77.

Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.17; H, 8.45; N, 7.08.

Thermolysis of Methyl 4-(2-Methyl-3-phenyl-2*H*-azirin-2-yl)-2-butenoate (18). A solution containing 75 mg of (*E*)- or (*Z*)-azirinyl-2-butenoate **18**[42] in 10 mL of toluene was heated in a sealed tube at 180 °C for 124 h. Removal of the solvent under reduced pressure left a yellow oil which was subjected to thick-layer chromatography. The minor component (37%) isolated from the thick-layer plate was a colorless oil whose structure was assigned as methyl 4-methyl-5-phenylpyrrol-2-ylacetate (**20**) on the basis of its spectral data: NMR ($CDCl_3$, 100 MHz) τ 7.76 (s, 3 H), 6.34 (s, 2 H), 6.28 (s, 3 H), 4.07 (d, 1 H, J = 1.5 Hz), 2.54–2.90 (m, 5 H), 2.16 (broad s, 1 H, exchanged with D_2O); IR (neat) 3300, 2900, 1720, 1600, 1510, 1430, 1242, 1205, 1156, 1012, 792, 767, 697 cm^{-1}; UV (cyclohexane) 350 nm (ϵ 830), 278 (9700), 236 (7700); MS m/e 229 (M^+), 170, 158, 127, 105, 77.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.30; H, 6.50; N, 6.30.

The structure of this material was verified by comparison with an independently synthesized sample. To a solution containing 15.7 g of 2-phenyl-3-methylpyrrole in 15 mL of benzene at 10 °C was added 3.6 mL of a 2.9 M methylmagnesium bromide solution. After stirring for 30 min, a 2.5-g sample of methyl bromoacetate was added and the resulting mixture was allowed to stir at room temperature for 12 h. After careful hydrolysis, the solution was dried and concentrated under reduced pressure. The crude oil was purified by thick-layer chromatography using a 5% acetone–hexane mixture as the eluent to give a pure sample of methyl 4-methyl-5-phenylpyrrol-2-ylacetate (**20**) which was identical in every detail with the minor component obtained from the thermolysis of azirine **18**.

The major product obtained from the thermolysis of azirine **18** (47%) was identified as 2-phenyl-3-methyl-6-carbomethoxypyridine (**19**): NMR ($CDCl_3$, 100 MHz) τ 7.60 (s, 3 H), 6.01 (s, 3 H), 2.40–2.70 (m, 5 H), 2.0 and 2.32 (AB pattern, 2 H, J = 8.0 Hz); IR (neat) 2900, 1710, 1595, 1430, 1390, 1300, 1235, 1205, 1136, 1110, 1020, 922, 855, 787, 766, 743, 699 cm^{-1}; UV (cyclohexane) 342 nm (ϵ 630), 278 (6400), 238 (10 400); MS m/e 227 (M^+), 226 (base), 212, 170, 169, 168, 167, 166, 115, 105, 77.

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.87; H, 5.68; N, 6.06.

The structure of this material was assigned on the basis of its conversion to 2,5-dimethyl-6-phenylpyridine (**10**).[26] To a slurry containing 25 mg of lithium aluminum hydride in 5 mL of ether was added 8.5 mg of the above pyridine in 1 mL of ether. The reaction mixture was stirred at room temperature for 12 h followed by a basic workup. The resulting oil was identified as 2-phenyl-3-methyl-6-hydroxymethylpyridine on the basis of its spectral properties: NMR ($CDCl_3$, 100 MHz) τ 9.7 (broad s, 1 H), 7.66 (s, 3 H), 5.29 (s, 2 H), 2.96 (d, 1 H, J = 8.0 Hz), 2.58 (m, 5 H), 2.48 (d, 1 H, J = 8.0 Hz); IR (KBr) 3175 (broad), 1590, 1575, 1450, 1430, 1220, 1185, 1073, 1006, 990, 830, 784, 764, 699 cm^{-1}; MS m/e 197, 196, 182, 180, 152, 105 (base), 77.

The above alcohol was dissolved in 1 mL of methylene chloride which contained 4 drops of triethylamine. This mixture was cooled to −15 °C, and then 3 drops of methanesulfonyl chloride was added. The mixture was allowed to stir for 15 min and then was taken up in methylene chloride and washed with a 10% hydrochloric acid solution followed by a saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The resulting mesylate was taken up in 1 mL of ether to which 25 mg of lithium aluminum hydride was added. The resulting mixture was stirred at room temperature for 12 h. The normal basic workup afforded 6.2 mg of 2,5-dimethyl-6-phenylpyridine (**10**), which was identical in every detail with an authentic sample.[26]

Preparation and Thermolysis of 2-(2-Butynyl)-2-methyl-3-phenyl-2*H*-azirine (21). The azirine was prepared in the normal manner[7] from the corresponding trimethylhydrazonium iodide salt: bp 80–81 °C (0.03 mm); NMR ($CDCl_3$, 100 MHz) τ 8.52 (s, 3 H), 8.26 (t, 3 H, J = 2.7 Hz), 7.64 (dq, 1 H, J = 16.5, 2.7 Hz), 7.32 (dq, 1 H, J = 16.5, 2.7 Hz), 2.48–2.68 (m, 3 H), 2.16–2.36 (m, 2 H); IR (neat) 3050, 2940, 2230, 1735, 1600, 1580, 1495, 1450, 1370, 1235, 1195, 1155, 1072, 1010, 976, 926, 875, 763, 687 cm^{-1}; UV (cyclohexane) 242 nm (ϵ 14 000); MS m/e 183 (M^+), 182 (base), 168, 142, 131, 115, 105, 77.

Anal. Calcd for $C_{13}H_{13}N$: C, 85.20; H, 7.15; N, 7.64. Found: C, 85.14; H, 7.03; N, 7.68.

A 100-mg sample of the above azirine was sublimed (0.005 mm) through a 40-cm quartz tube which was held at 500 °C. The products formed were collected on a liquid nitrogen cold finger. The resulting residue was subjected to thick-layer chromatography using a 20% ether–hexane mixture as the eluent. The major component (34%) isolated from the thick-layer plate was identified as 2,5-dimethyl-6-phenylpyridine (**10**) by comparison with an authentic sample:[26] picrate mp 138–139 °C (lit.[26] mp 134–135 °C); NMR (benzene-d_6, 100 MHz) τ 7.97 (s, 3 H), 7.54 (s, 3 H), 3.55 and 2.98 (AB pattern, 2 H, J = 8.0 Hz), 2.70–2.90 (m, 3 H), 2.32–2.44 (m, 2 H); IR (neat) 3030, 2875, 1587, 1563, 1455, 1429, 1370, 1250, 1125, 1062, 1028, 818, 786, 735, 698 cm^{-1}; UV (cyclohexane) 281 nm (ϵ 5000), 238 (7200); MS m/e 183 (M^+), 182 (base), 168.

Thermolysis of 2-Allyl-3-methyl-2-phenyl-2*H*-azirine (22). A solution containing 100 mg of azirine **22**[7] in 20 mL of toluene was heated in a sealed tube at 180 °C for 28 h. Removal of the solvent left a yellow oil which was subjected to thick-layer chromatography using a 15% acetone–hexane mixture as the eluent. The first component isolated from the column (58%) was identified as 3-allyl-2-methylindole (**24**) on the basis of its spectroscopic properties and by comparison with an independently synthesized sample: NMR (CCl_4, 60 MHz) τ 7.87 (s, 3 H), 6.68 (d, 2 H), 4.85–5.30 (m, 2 H), 3.70–4.45 (m, 1 H), 2.5–3.2 (m, 5 H); IR (neat) 3400, 3030, 3020, 2965, 2910, 1630, 1600, 1475, 1455, 1425, 1385, 1292, 1215, 1150, 1070, 985, 910, 740 cm^{-1}; UV (cyclohexane) 290 nm (ϵ 4700), 283 (5950), 274 (6200), 268 (5500), 222 (28 000); MS m/e 171 (M^+), 170, 156, 144, 131 (base), 119, 117, 91, 77.

An authentic sample of 3-allyl-2-methylindole (**24**) was prepared by treating 2-methylindole (**26**) with allyl bromide. To a solution containing 325 mg of 2-methylindole in 5 mL of benzene was added 0.9 mL of a 2.9 M solution of methylmagnesium bromide in ether. The mixture was stirred at 25 °C for 30 min, and then 300 mg of allyl bromide was added. The mixture was allowed to stir at 25 °C for 12 h and was then poured into 100 mL of a 1.0 M hydrochloric acid solution and extracted with ether. The ether layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. Chromatography of the residue on a thick-layer plate gave a 51% yield of 3-allyl-2-methylindole (**24**), which was identical with the major component isolated from the thermolysis of azirine **22**.

The second band obtained from the crude reaction mixture derived from the thermolysis of **22** contained a 5% yield of 2-methyl-3-phenylpyridine (**25**): picrate mp 132–133 °C (lit.[43] mp 135–136 °C); NMR ($CDCl_3$, 60 MHz) τ 7.50 (s, 3 H), 2.40–2.95 (m, 7 H), 1.60 (dd, 1 H, J = 5.0, 2.0 Hz); IR (neat) 3010, 2875, 1695, 1615, 1575, 1490, 1450, 1430, 1370, 1190, 1075, 1010, 810, 763, 738, 702 cm^{-1}; MS m/e 169 (M^+ and base), 168, 154.

The slowest moving band contained a pale oil (31%) whose structure was assigned as 2-methyl-1-phenyl-3-azabicyclo[3.1.0]hex-2-ene (**23**): NMR ($CDCl_3$, 60 MHz) τ 9.48 (t, 1 h, J = 4.0 Hz), 8.56 (dd, 1 H, J = 8.0, 4.0 Hz), 8.13 (s, 3 H, J = 2.0 Hz), 7.98 (m, 1 H), 6.30 (dq, 1 H, J = 17.5, 2.0 Hz), 5.92 (ddq, 1 H, J = 17.5, 5.0, 2.0 Hz), 2.80 (s, 5 H); IR (neat) 3030, 3000, 2920, 2860, 1695, 1630, 1610, 1502, 1460, 1442, 1385, 1310, 1270, 1195, 1160, 1095, 1070, 1026, 935, 830, 757, 700 cm^{-1}; UV (cyclohexane) 250 nm (ϵ 930); MS m/e 171 (M^+ and base), 170, 156, 130, 129, 128, 115, 102, 91, 77.

Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.07; H, 7.62; N, 8.04.

Preparation and Thermolysis of 2-(1-Methylallyl)-2-phenyl-3-methyl-2*H*-azirine (27). The azirine was prepared in the normal manner[7] from the corresponding trimethylhydrazonium iodide salt: bp 54–55 °C (0.05 mm); NMR (CCl_4, 60 MHz) indicated a 7:10 mixture of diastereomers with signals at τ 9.19 and 9.08 (both doublets with J = 7.0 Hz), 7.70 (two singlets with ca. 1.0-Hz spacing), 6.83 and 6.69 (two pentuplets with J = 7.0 Hz), 4.8–5.2 (m, 2 H), 4.0–4.7 (m, 1 H), 2.90 (s, 5 H); IR (neat) 3050, 3020, 2960, 2920, 1755, 1680, 1592, 1489, 1440, 1365, 1265, 995, 915, 772, 730, 695 cm^{-1}; UV (cyclohexane) 272 nm (ϵ 800), 256 (2000), 225 (7000); MS m/e 185 (M^+), 184, 171, 170 (base), 130, 129, 115, 77.

Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.27; H, 8.42; N, 7.39.

A solution containing 280 mg of the above azirine in 10 mL of toluene was heated in a sealed tube at 180 °C for 53 h. Removal of the solvent left a brown oil which was subjected to thick-layer chromatography using a 20% acetone–hexane mixture as the eluent. The fastest moving band contained 35 mg (13%) of 2-methyl-3-(1-methylallyl)indole (**28**). The structure of this material was assigned on the basis of its spectral data and by comparison with an independently synthesized sample: NMR (CCl_4, 100 MHz) τ 8.60 (d, 3 H, J = 7.5 Hz), 7.72 (s, 3 H), 6.14 (m, 1 H), 4.98–5.20 (m, 2 H), 3.80–4.18 (m, 1 H), 3.00–3.30 (m, 2 H), 2.80 (broad s, 1 H, exchanged with D_2O), 2.60–2.76 (m, 1 H); IR (neat) 3330, 3030, 2940, 1625, 1590, 1450, 1415, 1355, 1290, 1240, 1220, 1062, 1010, 995, 935, 787, 765, 743, 699 cm^{-1}; UV (acetonitrile) 290 nm (ϵ 3660), 282 (4200), 223 (23 500); MS m/e 185 (M^+), 170 (base), 158, 146, 130, 115, 77.

Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 83.93; H, 8.31; N, 7.75.

An authentic sample of indole **28** was prepared by treating 2-methylindole (**26**) with 3-chloro-1-butene and was identical in every detail with **28** obtained from the thermolysis of **27**.

The slowest moving component (11%) isolated from the thick-layer plate was identified as 2,4-dimethyl-3-phenylpyridine (**29**) by comparison with the spectral properties reported in the literature:[26] NMR (CCl_4, 100 MHz) τ 8.00 (s, 3 H), 7.82 (s, 3 H), 3.14 (d, 1 H, J = 4.5 Hz), 2.80–3.00 (m, 2 H), 2.56–2.80 (m, 3 H), 1.84 (d, 1 H, J = 4.5 Hz); IR (neat) 3020, 2865, 1613, 1590, 1488, 1445, 1405, 1370, 1237, 1074, 1010, 829, 763, 702 cm^{-1}; MS m/e 183 (M^+), 182 (base), 169, 168, 167, 115, 77.

Thermolysis of 2-(2-Methylallyl)-3-methyl-2-phenyl-2*H*-azirine (30). A solution containing 200 mg of azirine **30**[7] in 10 mL of toluene was heated in a sealed tube at 180 °C for 118 h. Removal of the solvent left a yellow oil which was chromatographed on a thick-layer plate to give 2-methyl-3-(2-methylallyl)indole (**31**) as the ex-

clusive product (89% yield): NMR (CCl_4, 60 MHz) τ 8.33 (s, 3 H), 7.76 (s, 3 H), 6.68 (s, 2 H), 5.35 (m, 1 H), 3.0–3.16 (m, 3 H), 2.5–2.9 (m, 2 H, 1 proton exchanged with D_2O); IR (neat) 3400, 3060, 2960, 2910, 1640, 1616, 1580, 1460, 1430, 1370, 1335, 1300, 1240, 1220, 1150, 1132, 885, 740 cm^{-1}; UV (cyclohexane) 290 nm (ϵ 3950), 282 (5100), 278 (5330), 273 (5400), 222 (25 000); MS *m/e* 185 (M^+), 170, 144 (base).

Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.19; H, 8.45; N, 7.48.

An authentic sample of indole **31** was prepared by treating 2-methylindole (**26**) with 3-chloro-2-methylpropene and was identical with the product obtained from the thermolysis of **30**.

Thermolysis of (*E*)-2-(2-Butenyl)-3-methyl-2-phenyl-2*H*-azirine (32). A solution containing 320 mg of **32** in 10 mL of toluene was heated at 180 °C for 53 h in a sealed tube. The brown residue obtained after removing the solvent under reduced pressure was subjected to preparative thick-layer chromatography using chloroform as the eluent. The slowest moving band contained 43 mg (14%) of a clear oil whose structure was assigned as 2-methyl-3-phenyl-5-vinyl-Δ^2-pyrroline (**35**) on the basis of its spectroscopic properties: NMR (CCl_4, 100 MHz) τ 8.12 (s, 3 H), 6.88 (dd, 1 H, J = 17.6, 6.0 Hz), 6.56 (dd, 1 H, J = 17.6, 4.5 Hz), 5.24 (dd, 1 H, J = 6.0, 4.5 Hz), 4.72–5.00 (m, 2 H), 4.08 (ddd, 1 H, J = 17.6, 11.0, 6.0 Hz), 3.50 (broad s, 1 H, exchanged with D_2O), 2.48–2.80 (m, 3 H), 2.0–2.16 (m, 2 H); IR (neat) 3230, 3030, 2875, 1655, 1590, 1517, 1440, 1361, 1275, 995, 926, 787, 758, 690 cm^{-1}; MS *m/e* 185 (M^+), 158, 129, 115, 105 (base), 77; UV (acetonitrile) 236 nm (ϵ 1530).

Anal. Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.44; H, 8.36; N, 7.94.

When the crude reaction mixture was subjected to preparative vapor-phase chromatography (15% SE-30 column at 170 °C), two additional components were isolated. The faster moving component (76%) consisted of a mixture of isomers of 2-methyl-3-phenyl-5-vinyl-Δ^1-pyrroline (**33**), of which the major component showed the following spectroscopic properties: NMR ($CDCl_3$, 100 MHz) τ 8.16 (d, 3 H, J = 2.0 Hz), 7.90 (dd, 1 H, J = 14.0, 6.5 Hz), 7.40 (dd, 1 H, J = 14.0, 7.0 Hz), 5.39 (m, 2 H), 4.72–5.00 (m, 2 H), 4.08 (ddd, 1 H, J = 16.5, 10.0, 6.0 Hz), 2.76 (s, 5 H); IR (neat) 3175, 1650, 1495, 1450, 1370, 1235, 1064, 985, 926, 766, 702 cm^{-1}; UV (cyclohexane) 245 nm (ϵ 785); MS *m/e* 185 (M^+), 184, 170, 105 (base), 77.

Treatment of the isomeric mixture of Δ^1-pyrrolines with *p*-toluenesulfonic acid in chloroform resulted in isomerization of the double bond and afforded 2-methyl-3-phenyl-5-vinyl-Δ^2-pyrroline (**35**). A similar isomerization also occurred on chromatography over silica gel.

The slower moving component in the gas chromatogram (24%) was identified as (*E*)-3-(2-butenyl)-2-methylindole (**34**) on the basis of its spectral properties and by comparison with an independently synthesized sample: NMR ($CDCl_3$, 100 MHz) τ 8.36 (d, 3 H, J = 4.0 Hz), 7.68 (s, 3 H), 6.64 (m, 2 H), 4.44 (m, 2 H), 2.40–3.0 (m, 4 H), 2.30 (broad s, 1 H); IR (neat) 3390, 3010, 2900, 1680, 1620, 1590, 1490, 1450, 1430, 1285, 1250, 1155, 1140, 1100, 997, 745 cm^{-1}; UV (cyclohexane) 291 nm (ϵ 3200), 283 (4250), 279 (4430), 273 (4560), 223 (21 000); MS *m/e* 185 (M^+), 170, 157, 156, 146 (base), 144, 105, 77.

The structure of this material was unambiguously established by comparison with an authentic sample prepared by treating 2-methylindole (**26**) with 1-bromo-2-butene using the procedure previously described.

Thermolysis of Methyl (*E*)-4-(3-Methyl-2-phenyl-2*H*-azirin-2-yl)-2-butenoate (36). A solution containing 200 mg of the azirine in 10 mL of toluene was heated at 185 °C for 60 h. Removal of the solvent under reduced pressure left a yellow oil which contained two components. Subjection of the crude material to thick-layer chromatography using chloroform as the eluent resulted in a clean separation of the two products. The faster moving band contained 46 mg (23%) of a clear oil whose structure was assigned as methyl (*E*)-4-(2-methylindol-3-yl)-2-butenoate (**38**): NMR ($CDCl_3$, 100 MHz) τ 7.68 (s, 3 H), 4.26 (d, 1 H, J = 16.0 Hz), 2.56–3.04 (m, 5 H); IR (neat) 3400, 3010, 2910, 1695, 1645, 1450, 1430, 1342, 1265, 1198, 1165, 1025, 738 cm^{-1}; MS *m/e* 229, 214, 198, 197, 185, 170, 168, 144 (base), 131, 130, 77.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.20; H, 6.48; N, 6.06.

The structure of this material was verified by comparison with an independently synthesized sample. To a solution containing 1.31 g of 2-methylindole in 20 mL of tetrahydrofuran at −10 °C was added 3.5 mL of a 2.9 M solution of methylmagnesium bromide. The mixture was stirred for 30 min at 25 °C and then cooled to −10 °C. To this solution was added 2.3 g of methyl 4-iodocrotonate[44] in 10 mL of tetrahydrofuran. After stirring for 12 h at 25 °C, the mixture was hydrolyzed and extracted with ether. The organic layer was dried, concentrated under reduced pressure, and purified by vapor-phase chromatography using a 10% SE-30 column at 200 °C. The major product obtained (45%) was identical in every detail with a sample of **38** isolated from the thermolysis of azirine **36**.

The major component (53%) isolated from the thermolysis of azirine **36** was identified as 2-methyl-3-phenyl-5-carbomethoxypyridine (**37**), mp 65–66 °C, on the basis of its spectral data and by comparison with an authentic sample:[28] NMR ($CDCl_3$, 100 MHz) τ 7.40 (s, 3 H), 6.04 (s, 3 H), 2.48–2.72 (m, 5 H), 1.86 (d, 1 H, J = 2.0 Hz), 0.90 (d, 1 H, J = 2.0 Hz); IR (KBr) 3010, 2920, 1710, 1590, 1420, 1400, 1305, 1240, 1117, 1053, 1025, 966, 862, 800, 763, 709 cm^{-1}; MS *m/e* 227 (M^+), 226 (base), 225, 212, 196, 169, 168, 167, 141, 139, 127, 115, 77.

Hydrolysis of the above methyl ester using concentrated hydrochloric acid afforded a quantitative yield of 6-methyl-5-phenylnicotinic acid hydrochloride, mp 205–207 °C (lit.[28] mp 200–203 °C).

Thermolysis of 2-(3-Cyanopropen-2-yl)-2-phenyl-3-methyl-2*H*-azirine (40). A solution containing 35 mg of **40** in 10 mL of toluene was heated at 180 °C for 70 h. Removal of the solvent under reduced pressure left a yellow oil which was purified by thick-layer chromatography. The major component obtained was a clear oil (77%) whose structure was assigned as 2-methyl-3-phenyl-5-cyanopyridine (**41**) on the basis of its spectral data: NMR ($CDCl_3$, 100 MHz) τ 7.48 (s, 3 H), 2.58–2.92 (m, 5 H), 2.35 (d, 1 H, J = 2.0 Hz), 1.38 (d, 1 H, J = 2.0 Hz); IR (neat) 3010, 2900, 2220, 1590, 1540, 1490, 1450, 1425, 1390, 1259, 1227, 1053, 1030, 917, 775, 741, 727, 699 cm^{-1}; UV (cyclohexane) 340 nm (ϵ 570), 321 (890), 274 (6230).

The structure of this material was further verified by hydrolysis with a concentrated hydrochloric acid solution to 6-methyl-5-phenylnicotinic acid hydrochloride: mp 203–204 °C (lit.[28] mp 200–203 °C); NMR (Me_2SO-d_6, 100 MHz) τ 7.28 (s, 3 H), 3.60 (broad s, 1 H, exchanged with D_2O), 2.16 (s, 5 H), 1.28 (d, 1 H, J = 2.0 Hz), 0.56 (d, 1 H, J = 2.0 Hz); IR (KBr) 3500–2300 (broad band), 1725, 1625, 1420, 1380, 1350, 1220, 1135, 1053, 772, 758, 725, 702 cm^{-1}.

The structure of this material was unambiguously established by hydrolysis of an authentic sample of 2-methyl-3-phenyl-5-carbomethoxypyridine (**37**) to the same acid hydrochloride as was obtained from cyanopyridine **40**.

Acknowledgment. We wish to thank the National Cancer Institute, DHEW (CA-12195), and the Hoffmann-La Roche Co. for generous support of this work. Aid in the purchase of the XL-100 NMR spectrometer used in this work was provided by the NSF via an equipment grant.

Registry No.—**1**, 56434-95-8; **2**, 57827-53-9; **3**, 10273-90-2; **4**, 56434-96-9; *endo*-**5**, 57827-54-0; *exo*-**5**, 57885-05-9; **6**, 27063-80-5; **7**, 62736-98-5; **8**, 65530-01-0; *cis*-**9**, 65495-80-9; *trans*-**9**, 65495-81-0; **10**, 27068-69-5; **11**, 65495-82-1; **12**, 65495-83-2; **13**, 28489-52-8; **13** picrate, 65495-84-3; **15**, 62737-00-2; **16**, 65495-87-6; *cis*-**17**, 65495-85-4; *trans*-**17**, 65495-86-5; **18**, 65495-88-7; **19**, 65495-89-8; **20**, 65495-90-1; **21**, 65495-91-2; **22**, 59175-18-7; **23**, 65516-35-0; **24**, 65495-76-3; **25**, 3256-89-1; **26**, 95-20-5; **27** (isomer I), 65495-64-9; **27** (isomer II), 65495-63-8; **28**, 65495-65-0; **29**, 29396-61-0; **30**, 59175-25-6; **31**, 65495-66-1; **32**, 59175-26-7; *cis*-**33**, 65495-68-3; *trans*-**33**, 65495-69-4; **34**, 65495-70-7; **35**, 65495-67-2; **36**, 65495-71-8; **37**, 10176-84-8; **38**, 65504-89-4; **40**, 65495-72-9; **41**, 10176-93-9; **42** (HCl), 65495-75-2; 2-methyl-1-phenyl-4-penten-1-one, 17180-49-3; 3-methyl-4-phenyl-4-oxybutanol, 65495-77-4; 2-phenyl-3-methylpyrrole, 20814-35-1; 2-phenyl-3-methyl-6-hydroxymethylpyridine, 65495-79-6; 2-phenyl-3-methyl-6-hydroxymethylpyridine mesylate, 65495-73-0; 2-(4-hexyn-2-yl)benzaldehydetrimethylhydrazonium iodide, 65495-74-1; 3-phenyl-4-methyl-5-hexen-2-onetrimethylhydrazonium iodide, 62737-09-1; methyl 4-iodocrotonate, 65495-78-5.

References and Notes

(1) F. W. Fowler, *Adv. Heterocycl. Chem.*, **13**, 45 (1971).
(2) D. J. Anderson and A. Hassner, *Synthesis*, 483 (1975).
(3) A. Padwa and J. Smolanoff, *J. Am. Chem. Soc.*, **93**, 548 (1971).
(4) N. Gakis, M. Marky, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **55**, 748 (1972).
(5) A. Padwa, *Acc. Chem. Res.*, 9, 371 (1976).
(6) P. Gilgen, H. Heimgartner, H. Schmid, and H. J. Hansen, *Heterocycles*, **6**, 143 (1977).
(7) A. Padwa and P. H. J. Carlsen, *J. Am. Chem. Soc.*, **97**, 3862 (1975); **98**, 2006 (1976); **99**, 1514 (1977).
(8) A. Padwa, A. Ku, A. Mazzu, and S. I. Wetmore, Jr., *J. Am. Chem. Soc.*, **98**, 1048 (1976).
(9) A. Padwa, P. H. J. Carlsen, and A. Ku, *J. Am. Chem. Soc.*, **97**, 3862 (1975).
(10) A. Padwa and N. Kamigata, *J. Am. Chem. Soc.*, **99**, 1871 (1977).
(11) D. J. Anderson, T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *J. Chem. Soc.*,

Perkin Trans. 1, 550 (1973).
(12) T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 555 (1973).
(13) K. Isomura, S. Kobayashi, and H. Taniguchi, *Tetrahedron Lett.*, 3499 (1968).
(14) K. Isomura, M. Okada, and H. Taniguchi, *Tetrahedron Lett.*, 4073 (1969).
(15) T. Nishiwaki, *J. Chem. Soc., Chem. Commun.*, 565 (1972).
(16) R. Selvarajan and J. H. Boyer, *J. Heterocycl. Chem.*, **9**, 87 (1972).
(17) T. Nishiwaki, A. Nakano, and H. Matsuoka, *J. Chem. Soc. C.*, 1825 (1970).
(18) J. H. Bowier and B. Nussey, *Chem. Commun.*, 1565 (1970).
(19) D. Knittel, H. Hemetsberger, R. Leipert, and H. Weidmann, *Tetrahedron Lett.*, 1459 (1970).
(20) N. S. Narashimhan, H. Heimgartner, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **56**, 1351 (1973).
(21) T. Nishiwaki and F. Fujiyama, *J. Chem. Soc., Perkin Trans. 1*, 1456 (1972).
(22) A. Padwa, J. Smolanoff, and A. I. Tremper, *J. Am. Chem. Soc.*, **96**, 3486 (1974); *J. Org. Chem.*, **41**, 543 (1976).
(23) For current examples where C–C cleavage of a 2*H*-azirine occurs thermally, see L. A. Wendling and R. G. Bergman, *J. Am. Chem. Soc.*, **96**, 309 (1974); *J. Org. Chem.*, **41**, 831 (1976); A. Demoulin, H. Gorissen, A. M. Hesbain-Frisque, and L. Ghosez, *J. Am. Chem. Soc.*, **97**, 4409 (1975).
(24) R. A. Abramovitch, S. R. Challand, and Y. Yamada, *J. Org. Chem.*, **40**, 1541 (1975).
(25) For a preliminary report see A. Padwa and P. H. J. Carlsen, *J. Org. Chem.*, **41**, 180 (1976).
(26) J. M. Bonnier and J. Court, *Bull. Soc. Chim. Fr.*, 142 (1970).
(27) A. Padwa and T. J. Blacklock, *J. Am. Chem. Soc.*, **99**, 2345 (1977).
(28) M. Julia, H. Pinhas, and J. Igolen, *Bull. Soc. Chim. Fr.*, 2387 (1966). We thank Professor Julia for supplying us with a sample of this compound.
(29) K. Isomura, M. Okada, and H. Taniguchi, *Chem. Lett.*, 629 (1972).
(30) T. Nishiwaki, *Tetrahedron Lett.*, 2049 (1969).
(31) J. A. Berson and L. Salem, *J. Am. Chem. Soc.*, **94**, 8917 (1972).
(32) W. von E. Doering and W. R. Roth, *Angew. Chem., Int. Ed. Engl.*, **2**, 115 (1963).
(33) J. S. Swenton, A. R. Crumrine, and T. J. Walker, *J. Am. Chem. Soc.*, **92**, 1406 (1970).
(34) A. L. Logothetis, *J. Am. Chem. Soc.*, **87**, 749 (1965).
(35) R. A. Abramovitch and W. D. Hokomb, *J. Am. Chem. Soc.*, **97**, 676 (1975).
(36) R. N. Carde and G. Jones, *J. Chem. Soc., Perkin Trans. 1*, 2066 (1974).
(37) J. C. Gilbert, K. R. Smith, G. W. Klumpp, and M. Schakel, *Tetrahedron Lett.*, 125 (1972); *J. Org. Chem.*, **41**, 3883 (1976).
(38) A. Padwa and W. Koehn, *J. Org. Chem.*, **38**, 4007 (1973).
(39) P. Germeraad and H. W. Moore, *J. Org. Chem.*, **39**, 774 (1974).
(40) R. A. Abramovitch, G. S. Seng, and A. D. Notation, *Can. J. Chem.*, **38**, 761 (1960).
(41) M. Scholtz, *Ber.*, **32**, 1939 (1899).
(42) P. H. J. Carlsen and A. Padwa, unpublished results.
(43) J. M. Bonnier, J. Court, and T. Fay, *Bull. Soc. Chim. Fr.*, 1204 (1967).
(44) A sample of methyl 4-iodocrotonate was prepared in the following fashion. To a solution containing 20.5 g of methyl crotonate in 110 mL of carbon tetrachloride was added 29.1 g of *N*-bromosuccinimide and 100 mg of dibenzoyl peroxide. The mixture was heated at reflux for 48 h, filtered, and concentrated under reduced pressure. The resulting liquid was distilled at 92–95 °C (10 mm) to give 23 g of methyl 4-bromocrotonate. To a solution containing 9.0 g of this material in 300 mL of dry acetone was added 12 g of sodium iodide. The mixture was stirred at room temperaure for 20 h. A normal workup procedure gave a 93% yield of methyl 4-iodocrotonate.

Intramolecular Cyclization of Nitrile Imines. Synthesis of Indazoles, Fluorenes, and Aza Analogues[1a]

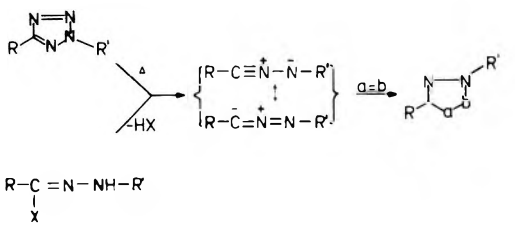
Curt Wentrup,*[1b] Angelika Damerius, and Werner Reichen[1c]

Fachbereich Chemie der Universität, D-3550 Marburg, Federal Republic of Germany, and Institut de Chimie Organique de l'Université, CH-1005 Lausanne, Switzerland

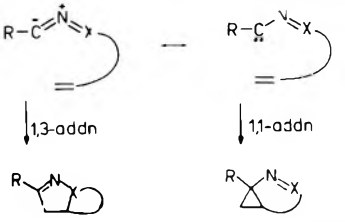
Received November 16, 1977

Flash thermolysis of 2,5-diaryltetrazoles **2** at 400–500 °C (10^{-3} mm) gives 3-arylindazoles **5** in yields of 96–100%. Thus, 2,5-diphenyl-, 2-(*p*-tolyl)-5-phenyl-, 2-phenyl-5-(*p*-tolyl)-, 2,5-di(*p*-tolyl)-, and 2-phenyl-5-(4-pyridyl)tetrazole furnish 3-phenyl-, 3-phenyl-5-methyl-, 3-(*p*-tolyl)-, 3-(*p*-tolyl)-5-methyl-, and 3-(4-pyridyl)indazole, respectively. Indazoles **5** are formed also by heating the tetrazoles **2** in tetralin at 207 °C for 15 min. Flash thermolysis of the same tetrazoles **2** at 800 °C (10^{-3} mm) gives 2,6-disubstituted fluorenes **7** (2,6 substituents = H or CH_3) or 3-azafluorene (**7e**) in yields of 90–100%. The thermolysis of 3-phenylpyrazolo[3,4-*b*]pyridine (**8**) at 770 °C resulted in a 49% conversion to 4-azafluorene (**9**). Thermolysis of 2,4-diphenyl-1,3,4-oxadiazolin-5-one (**16a**) at 500 °C (10^{-2} mm) gave 3-phenylindazole (94%); at 750 °C fluorene was obtained (84%). 2-Methyl-4-phenyl-1,3,4-oxadiazolin-5-one (**16b**) gave at 450 °C 3-methylindazole (89%) and at 650 °C styrene (94%). The results are interpreted in terms of the intermediate formation of nitrile imines by loss of N_2 from **2** and of CO_2 from **16**. The nitrile imines are regarded as a resonance hybrid of bent dipolar and carbene structures (**23**) which cyclize unto the remote aromatic ring.

The cycloaddition of 1,3 dipoles has become an important method for the synthesis of five-membered heterocyclic rings.[2] For example, nitrile imines generated by the thermal decomposition[3a] of 2,5-disubstituted tetrazoles[3c] or by base-induced elimination from hydrazonyl halides[3b] undergo in situ addition to acetylenes, olefins, and nitriles, yielding pyrazole



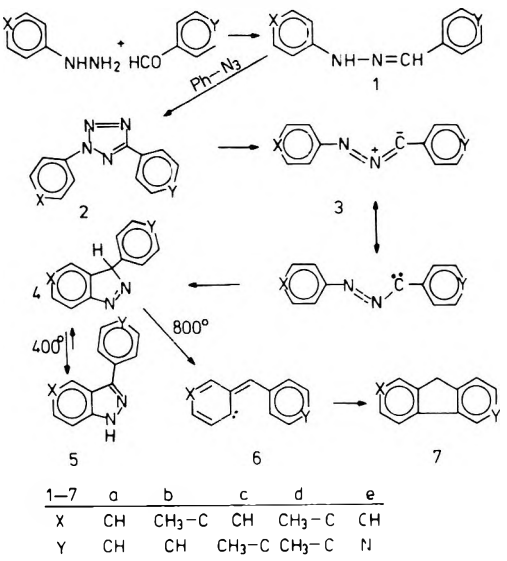
or triazole derivatives.[2] The cycloaddition of 1,3 dipoles can also take place intramolecularly to suitably oriented dipolarophiles.[4] Recently, it has been shown that intramolecular 1,1 addition of nitrile ylides[4,5] as well as nitrile imines[6] can compete with the normal 1,3 addition when certain geometric constraints are imposed. In these cases, the reactions can be formulated in terms of the carbene forms of the dipoles.[4,5]



Huisgen[2] recognized carbene forms as resonance structures of 1,3 dipoles; however, such species may exist in two distinct molecular geometries: a bent carbene-like structure and/or a linear dipolar structure.[7] The ab initio STO-3G and 4–31G

0022-3263/78/1943-2037$01.00/0

Scheme I



1–7	a	b	c	d	e
X	CH	CH_3–C	CH	CH_3–C	CH
Y	CH	CH	CH_3–C	CH_3–C	N

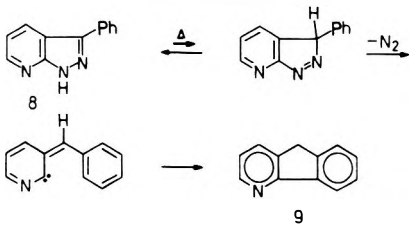
calculations of Houk and Caramella[7b] suggest that the nitrile imine, in particular, is a flexible molecule which can adapt its geometry according to the nature of the reaction; thus, electrophilic reagents would favor a planar structure possessing a relatively high-lying HOMO, whereas nucleophilic reagents would promote the bent carbene-like form, which possesses a low-lying LUMO.

In this paper we wish to report a fundamentally new type of reaction of 1,3 dipoles, namely, intramolecular ring closure of nitrile imines unto aromatic rings. The nitrile imines were generated by thermolysis of 2,5-disubstituted tetrazoles or by a new procedure employing 1,3,4-oxadiazolin-5-ones. The results are of importance with respect to the carbenic nature of 1,3 dipoles.[8]

Results and Discussion

Using the procedure of Dimroth and Merzbacher[9,10] the required 2,5-diaryltetrazoles **2** were prepared by treatment of the hydrazones **1** with phenyl azide (Scheme I). Flash thermolysis of the tetrazoles at 400–500 °C gave near quantitative yields of 3-arylindazoles **5** (Scheme I, Table I). The

Scheme II



substituent pattern in **5** demonstrates that the carbon atom of the nitrile imine **3** becomes bonded to the aromatic ring originating from the arylhydrazine. This would lead initially to the 3*H*-indazoles **4**. When the temperature is high enough (ca. 800 °C) the 3*H*-indazoles may eliminate a further molecule of N_2, leading to the carbenes **6**, which cyclize to 2,6-disubstituted fluorenes **7**, again in near quantitative yields (Table I). The 3*H*-indazoles may also be populated by direct thermal excitation of the 1*H*-indazoles **5**. However, since **4** is an energetically very unfavorable tautomer, yields of fluorene are far from quantitative when starting from **5**. This circumstance in itself supports the assumption of an initial formation of the unfavorable tautomer **4** in the thermolysis of the tetrazoles **2**.

As an example of fluorene formation from indazoles, the known 3-phenylpyrazolo[3.4-*b*]pyridine[11] (**8**) was thermolyzed at 770 °C, resulting in a 49% conversion to 4-azafluorene (**9**) (Scheme II), the remainder of the starting material being recovered. It has been reported[12] that indazoles and pyrazolo[3,4-*b*]pyridines may also yield arylcarbenes by gas-phase thermolysis. This contention has been criticized[13] and can be excluded in the present reaction since it is known[14] that the arylcarbene **10** furnishes a mixture of 1- and 3-azafluorene (**11** and **12**) and not 4-azafluorene (**9**) when generated from the diazo compound **13**.

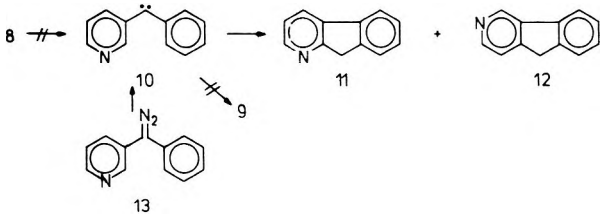
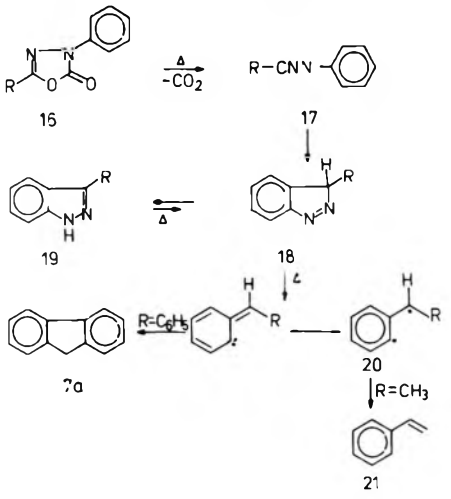


Table I. Thermolysis of 2,5-Diaryltetrazoles 2

			Yield of products, %			
Registry no.	Tetrazole	Conditions[a]	**5**	Registry no.	**7**	Registry no.
18039-45-7	**2a**	420/10^{-3}	100[b]	13097-01-3		
		515/10^{-3}–10^{-2}	92[b]		5[c]	86-73-7
		800/10^{-2}			95[c]	
		Tetralin, reflux 15 min	78[b]			
20433-19-6	**2b**	515/10^{-3}	100[d]	57614-16-1		
		800/10^{-3}			95[e]	1430-97-3
20433-11-8	**2c**	515/10^{-3}	96[f]	65452-73-5		
		800/10^{-3}			100[g]	2523-39-9
59635-32-4	**2d**	500/10^{-3}	98[h]	65452-74-6		
		800/10^{-3}			96[i]	65452-75-7
65452-72-4	**2e**	500/10^{-3}	99[j]	37885-56-6		
		800/10^{-3}			90[k]	244-42-8
		Tetralin, reflux 15 min	64[j]			

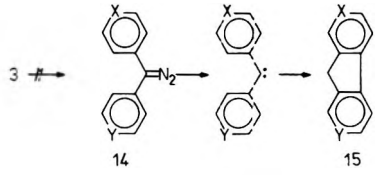
[a] Gas-phase thermolyses used apparatus A (see Experimental Section), and conditions are expressed as temperature (°C)/pressure (mm). [b] 3-Phenylindazole, mp 115–116 °C (from hexane) [lit. mp 115–116 °C: W. Borsche and W. Scriba, *Justus Liebigs Ann. Chem.*, **540**, 83 (1939)]. [c] Fluorene, mp 115–116 °C (identical with an authentic sample). [d] 5-Methyl-3-phenylindazole (see Experimental Section). [e] 2-Methylfluorene, mp 104–105 °C [lit. mp 104–105 °C: *Beilsteins Handbuch der Org. Chem.*, **5**, III, 1991 (1964)]. [f] 3-(*p*-Tolyl)indazole (see Experimental Section). [g] 3-Methylfluorene, mp 88–89 °C [lit. mp 88–90 °C: *Beilsteins Handbuch der Org. Chem.*, **5**, III, 1992 (1964)]. [h] 5-Methyl-3-(*p*-tolyl)indazole (see Experimental Section). [i] 2,6-Dimethylfluorene, mp 65–66 °C (sublimed at 25 °C (0.1 mm)) [lit. mp 66–67 °C: *Beilsteins Handbuch der Org. Chem.*, **5**, III, 2006 (1964)]. [j] 3-(4-Pyridyl)indazole (see Experimental Section). [k] 3-Azafluorene (see Experimental Section).

Scheme II

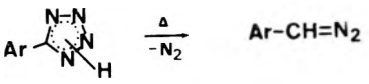


a, $R=C_6H_5$ b, $R=CH_3$

It can also be excluded that the fluorenes **7** (Scheme I) arise via a rearrangement of the nitrile imines **3** to diaryldiazomethanes **14.** The latter are known to give 2,7-disubstituted fluorenes **15** via a double carbene–carbene rearrangement.[15]



The elimination of this pathway was particularly important because 5-aryltetrazoles do decompose thermally to aryldiazomethanes; a hydrogen shift is involved in these reactions.[8c]

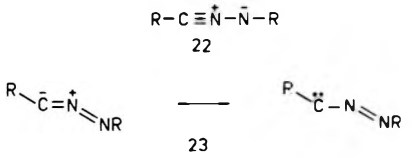


Furthermore, there is some evidence that the parent nitrile imine (isodiazomethane) tautomerizes to diazomethane.[16]

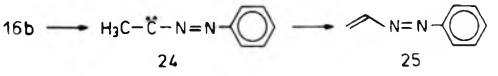
The cyclization of nitrile imines to indazoles is not limited to the gas phase. The tetrazoles **2a** and **2e** were decomposed in the liquid phase, i.e., under conditions where the nitrile imines **3** can be trapped[3] by added dipolarophiles. In the absence of trapping agents, the corresponding indazoles were formed in considerable yields (Table I). Thus, the ability to undergo intramolecular cyclization may be assumed to be a basic property of such 1,3 dipoles.

In order to widen the scope of nitrile imine chemistry, a new precursor was sought. 1,3,4-Oxadiazolin-5-ones **16** are easily accessible from acid hydrazides[17] but have received relatively little attention. The gas-phase thermolyses of oxadiazolinones **16a,b** (Scheme III) are reported in Table II. The reactivity of **16a** is very similar to that of **2a,** leading to high yields of 3-phenylindazole (**19a**) or fluorene (**7a**), depending on the temperature. Similarly, **16b** gives rise to 3-methylindazole (**19b**) in the low temperature range. At higher temperatures, the carbene or diradical **20** isomerizes to styrene (**21**) in near quantitative yield, as has also been observed in the thermolysis of 3-methylindazole itself.[12a,b]

Consider now the mechanism of cyclization of the nitrile imines, **3** → **4** and **17** → **18.** Recent theoretical[7] and experimental[5] work indicates that nitrilium betaines may exist in linear and/or bent forms, of which the latter was found to be the ground state in the case of nitrile ylides.[7b] The related forms of a nitrile imine can be represented in valence bond terms by **22** and **23.**



The requirement of a bent geometry in the transition state leading to **4** and **18** (Schemes I and III) rules out the linear structure **22** but does not, of course, say anything about the ground-state geometry of the species. The bent, carbene-like nitrile imines **23** nicely rationalize the cyclizations as carbene-type reactions. The finer details may involve electrocyclization, electrophilic substitution, or CH insertion by the carbenic carbon. The results obtained with **16b** are particularly important in this respect for they indicate that the reactive intermediate should not be regarded as a pure carbene. Had such a species (**24**) been formed, we would expect a very rapid rearrangement to the azo olefin **25.** Although **25** could



give rise to modest yields of styrene, it cannot account for the virtually quantitative formation of 3-methylindazole.

The 1,2-hydrogen shift in alkylcarbenes is exceedingly fast,[18] competing strongly with all other carbene reactions. However, the bent carbene-like nitrile imine **23** differs from an ordinary singlet carbene in that it is the *second* lowest unoccupied molecular orbital (SLUMO) which possesses a large coefficient at the carbenic carbon atom.[7b] The propensity of **23** toward 1,2-hydrogen shifts may, therefore, be overridden by the interaction with the aromatic ring bonded to N, which can, in principle, overlap simultaneously with the HOMO and the SLUMO of **23.**[14]

The optimized STO-3G geometry of **23** (R = H) resembles a trans azo compound.[7b] In the cyclizations leading to indazoles (**4** and **18**) a geometrical isomerization to the cis azo forms of **23** (R = aryl) is required. The calculated flexibility[7b] of the molecule is expected to facilitate this process.

In conclusion, the hybrid of carbenic and dipolar bent structures (**23**) best describes the nitrile imines involved in the cyclization reactions reported here. These reactions have considerable potential for the synthesis of indazoles and fluorenes since a variety of starting materials **2** and **16** can be prepared from simple chemicals.[17c,19] As an example, 3-azafluorene was prepared previously in 12% overall yield in a lengthy synthesis;[14] it can be obtained in higher yield but as a mixture with 1-azafluorene via a carbene–carbene rearrangement starting with phenyl-3-pyridyldiazomethane

Table II. Thermolysis of 1,3,4-Oxadiazolin-5-ones 16

Registry no.	Oxadiazolone	Conditions[a]	Product, yield	Registry no.
19226-10-9	**16a**	$500/10^{-2}$	3-Phenylindazole (**19a**), 94%	13097-01-3
		$750/10^{-2}$	Fluorene (**7a**), 84%[b]	
28740-63-8	**16b**	$450/10^{-2}$	3-Methylindazole (**19b**), 89%	3176-62-3
		650.10^{-2}	Styrene (**21**), 94%	100-42-5

[a] Apparatus B was used (see Experimental Section), and conditions are expressed as temperature (°C)/pressure (mm). [b] An 8.6% yield of 9,9′-bifluorenyl was also obtained; this is most probably a secondary pyrolysis product of fluorene.

(13).[14] However, 3-azafluorene is a highly unstable compound, rapidly turning blue and later black at room temperature. It is therefore impossible to obtain reasonable yields of this compound unless it is the only reaction product. This requirement is satisfied in the thermolysis of **2e** at 800 °C (Table I).

Experimental Section

General. Two pyrolysis apparatuses were used. Apparatus A employed a 30 × 2 cm quartz tube evacuated with an Edwards "Diffstak," capable of an ultimate vacuum of ca. 10^{-7} mm. Apparatus B consisted of a 40 × 3.5 cm quartz tube, the pump giving an ultimate vacuum of ca. 10^{-3} mm. Further details of the procedure have been published elsewhere.[20] Samples were in all cases sublimed into the pyrolysis tube below their melting points. The products were collected in a trap cooled in liquid N_2 or dry ice–acetone. The pressures recorded during pyrolysis are those of gases escaping the traps. The products were often spectroscopically pure or else they were purified by sublimation or recrystallization. When mixtures of indazoles and fluorenes were obtained, they were readily separable by thin-layer and column chromatography on SiO_2, eluting the fluorene first with $CHCl_3$ and then the indazole with $CHCl_3$–MeOH (9:1).

Mass spectra were recorded on a CEC 21-490 instrument at 70 eV using a direct inlet at a source temperature of 200 °C and are reported as *m/e* values followed by relative abundance (percent of base peak). Melting points are corrected. Microanalyses were performed by Mr. E. Thommen, Universität Basel, Basel, Switz.

2-(*p*-Tolyl)-5-phenyltetrazole (2b). To a solution of 0.545 g (23.7 mmol) of Na in 12 mL of 2-methoxyethanol was added 2.1 g (10 mmol) of benzaldehyde *p*-tolylhydrazone and 1.23 g (10.34 mmol) of phenyl azide. The mixture was stirred magnetically at 100 °C for 14 h, cooled, and diluted with 10 mL of EtOH, after which the product crystallized: 1.37 g (58%) (lit.[10] 19.2%); mp 102–103 °C (lit.[10] mp 103–104 °C).

2,5-Di(*p*-tolyl)tetrazole (2d). To a solution of 0.476 g (20.7 mmol) of Na in 10 mL of 2-methoxyethanol was added 1.97 g (8.79 mmol) of *p*-tolualdehyde *p*-tolylhydrazone and 1.08 g (9.08 mmol) of phenyl azide. The mixture was refluxed (124 °C) for 7 h, cooled, diluted with 10 mL of EtOH, and allowed to crystallize, yielding 1.14 g (52%). Recrystallization from EtOH furnished colorless needles: mp 139 °C (lit.[19a] mp 139–140 °C); mass spectrum, *m/e* 250 (M^+, 12), 222 (40), 118 (4), 117 (3), 116 (3), 105 (100), 104 (23), 78 (20). Anal. Calcd for $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.38. Found: C, 71.70; H, 5.59; N, 22.44.

2-Phenyl-5-(4-pyridyl)tetrazole (2e) was obtained in 81% yield following the above procedure. After recrystallization from ethanol it had mp 141.5–142.5 °C; mass spectrum, *m/e* 223 (M^+, 3), 195 (29), 105 (0.1), 104 (0.1), 91 (100), 77 (0.3), 64 (2), 51 (0.5). Anal. Calcd for $C_{12}H_9N_5$: C, 64.56; H, 4.06; N, 31.37. Found: C, 64.64; H, 3.99; N, 31.40.

Gas-phase pyrolysis of tetrazoles 2 was carried out using apparatus A. Conditions and yields are collected in Table I. Known compounds were identified by TLC and spectral comparison with authentic materials. The following examples are typical.

3-Phenyl-5-methylindazole (5b). 2b (987 mg, 4.22 mmol) was thermolyzed at 515 °C (10^{-3} mm), being sublimed in at 90–100 °C. 3-Phenyl-5-methylindazole (977 mg, 100%) deposited outside the pyrolysis tube. An analytical sample was obtained by recrystallization from ethyl acetate–petroleum ether (bp 40–60 °C): mp 117–118 °C; NMR (CD_3OD) δ 7.8–6.8 (m, 8 H), 2.1 (s, 3 H); IR (KBr) 3150 broad s, 3040 s, 2920 s, 1620 w, 1500 s, 1450 m, 1330 s, 1310 m, 1260 m, 1110 s, 990 s, 940 m, 780 s, 750 s, 700 s cm^{-1}; mass spectrum, *m/e* 208 (M^+, 100), 207 (28), 131 (6), 104 (13), 77 (18). Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.52; H, 5.85; N, 13.40.

3-(*p*-Tolyl)indazole (5c) was prepared in 96% yield from **2c** in a similar manner: mp 95–96 °C (lit.[21] mp 97–98 °C); NMR (CCl_4) δ 7.95 (d, *J* = 8 Hz, 2 H, superimposed on unresolved peaks, 1 H), 7.30 (d, *J* = 8 Hz, 2 H), 7.3–6.6 (m, 3 H), 2.38 (s, 3 H); IR (KBr) 3150–3000 broad s, 2960–2850 broad s, 1630 s, 1485 s, 1545 s, 1260 s, 1110 s, 1010 s, 995 s, 910 s, 825 s, 780 s, 740 s cm^{-1}; mass spectrum, *m/e* 208 (M^+, 100), 104 (M^{2+}, 5), 91 (8).

3-(*p*-Tolyl)-5-methylindazole (5d) was obtained by pyrolysis of **2d** (Table I). An analytical sample was obtained by recrystallization from ethyl acetate–petroleum ether followed by sublimation: mp 120 °C; NMR (CCl_4) δ 8.0 (d, *J* = 8 Hz, 2 H, C-2′ and C-6′), 7.75 (broadened s, 1 H, C-4), 7.35 (d, *J* = 8 Hz, 2 H, C-3′ and C-5′), 6.95 (center, distorted AB pattern, 2 H, C-6 and C-7), 2.45 (s, 6 H, CH_3); IR (KBr) 3130 broad s, 2960 s, 1630 w, 1490 s, 1440 m, 1320 s, 1305 m, 1260 m, 1180 w, 1155 w, 1105 s, 985 s, 940 s, 825 s, 795 s cm^{-1}; mass spectrum, *m/e* 222 (M^+, 100), 111 (6), 110 (5), 91 (6). Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.82; H, 6.39; N, 12.59.

3-(4-Pyridyl)indazole (5e) was prepared by pyrolysis of **2e** (Table I): mp 188 °C (from 2-propanol); NMR (acetone-d_6) δ 8.2 (d, *J* ≅ 6 Hz, 2 H), 7.5 (d, *J* ≅ 6 Hz, 2 H), 7.8–6.6 (m, ~4 H); IR (KBr) 3050 broad s, 2850 broad s, 1600 s, 1470 m, 1410 m, 1360 m, 1345 s, 1310 m, 1255 s, 1220 m, 1110 w, 1060 w, 1010 s, 990 s, 900 m, 825 s, 730 s, 610 s cm^{-1}; mass spectrum, *m/e* 195 (M^+, 100), 168 (5), 118 (6), 97.5 (M^{2+}, 3), 98 (3), 78 (3), 51 (4). Anal. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.58; H, 4.61; N, 21.42.

3-Azafluorene (7e). 2e (400 mg, 1.79 mmol) was pyrolyzed at 800 °C (10^{-3} mm) for 3 h, the sample being sublimed into the apparatus at 100–125 °C. The product, a yellow oil (270 mg, 90%), was taken up in ether and rapidly chromatographed on SiO_2–chloroform, the yellow band being collected under N_2. Concentration afforded a 70% yield of pure **7e**, whose gas chromatographic and NMR, IR, and mass spectral properties were identical with those of an authentic sample.[14] The compound turns blue-green very rapidly and deteriorates even under N_2 and in the cold.

4-Azafluorene (9). 3-Phenylpyrazolo[3,4-*b*]pyridine[11] (8) (500 mg) was pyrolyzed at 770 °C (10^{-3}–10^{-2} mm), being sublimed in at 115–120 °C in the course of 2.5 h. The product was chromatographed on SiO_2, eluting with chloroform to yield 217 mg of starting material (43%) and 210 mg (49%) of 4-azafluorene: mp 93–94 °C; mixture melting point with an authentic sample (Aldrich), 93–95 °C. The compound had spectral properties identical with those of the commercial sample.

Liquid-Phase Thermolysis of Tetrazoles. A solution of 111 mg (0.5 mmol) of 2,5-diphenyltetrazole (**2a**) in 50 mL of tetralin was added dropwise to 50 mL of refluxing tetralin (207 °C). Heating was continued for 15 min longer, after which time the solvent was removed in vacuo. From the residual brown solid 76 mg (78%) of 3-phenylindazole (**5a**) was sublimed at 100 °C (10^{-2} mm). The mixture melting point (115–116 °C) and IR and mass spectra were identical with those of authentic material.

In the same manner, a 64% yield of 3-(4-pyridyl)indazole (**5e**) was obtained from 2-phenyl-5-(4-pyridyl)tetrazole (**2e**). The product was identical with the one prepared by gas-phase thermolysis (vide supra).

Pyrolysis of oxadiazoiinones was carried out using apparatus B. **2,4-Diphenyl-1,3,4-oxadiazolin-5-one**[17a] (**16a**; 500 mg, 2.1 mmol) was pyrolyzed at 500 °C (0.01 mm). The resulting slightly yellow product was recrystallized from petroleum ether to give 384 mg (94%) of 3-phenylindazole, identified by comparison with an authentic sample. The results of pyrolysis at higher temperatures are indicated in Table II.

2-Methyl-4-phenyl-1,3,4-oxadiazolin-5-one[17b] (**16b**; 500 mg, 2.8 mmol) was pyrolyzed at 450 °C (0.01 mm). The resulting slightly colored solid was chromatographed on SiO_2, eluting with ether–hexane (5:1) to give 331 mg (89%) of 3-methylindazole, mp 113 °C (lit.[22] mp 113 °C).

16b (500 mg, 2.8 mmol) was also pyrolyzed at 650 °C (0.01 mm). The liquid product was redistilled under high vacuum and identified as styrene by gas chromatography and NMR and IR spectroscopy, yield 274 mg (94%).

Acknowledgment. We gratefully acknowledge the financial support of this work by the Deutsche Forschungsgemeinschaft and the Schweizerischer Nationalfonds. Some of the early experiments were carried out by Messrs. J.-P. Jubin and J.-P. Hagenbuch (1975).

Registry No.—**1a**, 588-64-7; **1b**, 1858-99-7; **1c**, 2829-25-6; **1d**, 65452-76-8; **1e**, 7757-39-3; **8**, 65452-77-9; **9**, 244-99-5.

References and Notes

(1) (a) This paper is dedicated to Professor K. A. Jensen, University of Copenhagen, on the occasion of his 70th birthday; (b) Universität Marburg; (c) Université de Lausanne.

(2) R. Huisgen, *Angew. Chem.*, **75**, 604, 742 (1963); *Angew. Chem., Int. Ed. Engl.*, **2**, 565, 633 (1963); R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes", S. Patai, Ed., Interscience, New York, N.Y., 1964, p 806ff; R. Huisgen, *J. Org. Chem.*, **41**, 403 (1976).

(3) (a) R. Huisgen, M. Seidel, J. Sauer, J. W. McFarland, and G. Wallbillich, *J. Org. Chem.*, **24**, 892 (1959); R. Huisgen, J. Sauer, and M. Seidel, *Chem. Ber.*, **94**, 2503 (1961); R. Huisgen, R. Grashey, E. Aufderhaar, and R. Kunz, *ibid.*, **98**, 642 (1965); J. S. Clovis, A. Eckell, R. Huisgen, and R. Sustmann, *ibid.*, **100**, 60 (1967); A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, D. Grashey, and E. Spindler, *ibid.*, **100**, 2192 (1967). (b) R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1962). (c) For the photochemical formation of nitrile imine from 2,5-diphenyltetrazole, cf. W. Sieber, P. Gilgen, S. Chaloupka, H.-J. Hansen, and H. Schmid, *Helv.*

Chim. Acta, **56**, 1679 (1973).
(4) A. Padwa, *Angew. Chem.*, **88**, 131 (1976); *Angew. Chem., Int. Ed. Engl.*, **15**, 123 (1976).
(5) A. Padwa and P. H. J. Carlsen, *J. Am. Chem. Soc.*, **99**, 1514 (1977).
(6) L. Garanti, A. Vigevani, and G. Zecchi, *Tetrahedron Lett.*, 1527 (1976).
(7) (a) L. Salem, *J. Am. Chem. Soc.*, **96**, 3486 (1974); (b) P. Caramella and K. N. Houk, *ibid.*, **98**, 6397 (1976).
(8) Preliminary communications: (a) C. Wentrup, Réunion du Groupe Français de Chimie Hétérocyclique, Montpellier, Fr., September 29, 1976, Abstracts, p 12; (b) W. Reichen, *Helv. Chim. Acta*, **59**, 1636 (1976); (c) C. Wentrup, *Chimia*, **31**, 258 (1977).
(9) O. Dimroth and S. Merzbacher, *Ber. Dtsch. Chem. Ges.*, **40**, 2402 (1907).
(10) S.-Y. Hong and J. E. Baldwin, *Tetrahedron*, **24**, 3787 (1968).
(11) I. I. Grandberg, *Zh. Obshch. Khim.*, **31**, 2307 (1961).
(12) (a) W. D. Crow and M. N. Paddon-Row, *Tetrahedron Lett.*, 3207 (1972); (b) *Aust. J. Chem.*, **26**, 1705 (1973); (c) W. D. Crow, A. R. Lea, and M. N. Paddon-Row, *Tetrahedron Lett.*, 2235 (1972).
(13) C. Wentrup, *Tetrahedron*, **30**, 1301 (1974); C. Wentrup in "Reactive Intermediates", Vol. 1, R. A. Abramovitch, Ed., Plenum Press, London, to be published.
(14) C. Mayor and C. Wentrup, *J. Am. Chem. Soc.*, **97**, 7467 (1975).
(15) C. Wentrup, *Top. Curr. Chem.*, **62**, 173 (1976), and references therein.
(16) E. Müller and D. Ludsteck, *Chem. Ber.*, **87**, 1837 (1954); **88**, 921 (1955); J. M. Mills and H. W. Thompson, *Trans. Faraday Soc.*, **50**, 1270 (1954).
(17) (a) M. Freund and B. B. Goldsmith, *Ber. Dtsch. Chem. Ges.*, **21**, 2456 (1888); (b) H. Rupe and H. Gebhardt, *ibid.*, **32**, 10 (1899); (c) A. Hertzheim and K. Mockel, *Adv. Heterocycl. Chem.*, **7**, 183 (1966).
(18) N. Bodor and M. J. S. Dewar, *J. Am. Chem. Soc.*, **94**, 9103 (1972); V. Menéndez and J. M. Figuera, *Chem. Phys. Lett.*, **18**, 426 (1973).
(19) The preparation of a large number of 2,5-diaryltetrazoles carrying very diverse substituents was reported recently: (a) I. Suketaka, T. Yumo, and K. Akikazu, *Bull. Chem. Soc. Jpn.*, **49**, 762 (1976); (b) I. Suketaka, T. Yumo, K. Akikazu, and K. Kendi, *ibid.*, **49**, 1920 (1976).
(20) N. M. Lân and C. Wentrup, *Helv. Chim. Acta*, **59**, 2068 (1976); R. Gleiter, W. Rettig, and C. Wentrup, *ibid.*, **57**, 2111 (1974).
(21) K. v. Auwers and P. Strödter, *Ber. Dtsch. Chem. Ges.*, **59**, 529 (1926).
(22) E. Fischer and J. Tafel, *Justus Liebigs Ann. Chem.*, **227**, 303 (1885).

Annelations of Amidines on Halonitroaromatics. A One-Step Route to Quinoxaline and Imidazoquinoxaline *N*-Oxides and Related Structures

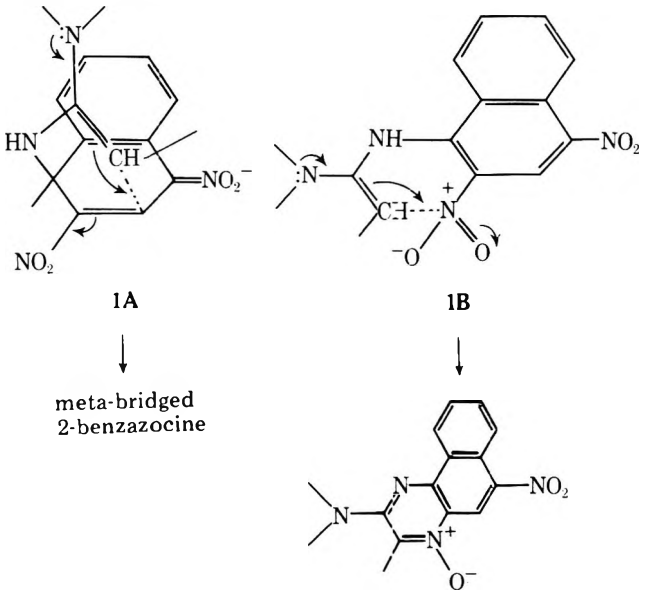
Michael J. Strauss,* David C. Palmer, and Raymond F. Bard

Department of Chemistry, University of Vermont, Burlington, Vermont 05401

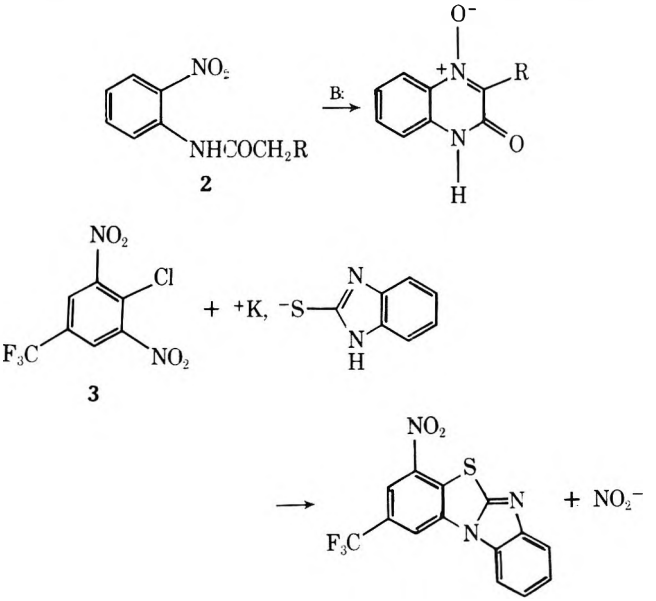
Received November 15, 1977

The reactions of α-phenylacetamidines with *o*-nitrohaloaromatics and related substrates have been shown to yield displacement–addition products in which the amidine is annelated across the ring carbon and nitrogen of an adjacent nitro group in the aromatic. The products are quinoxaline and imidazoquinoxaline *N*-oxides. The reactivity of amidines in meta-bridging reactions vs. ortho substituent annelations is discussed.

We have previously found that the nitrogen and α carbon of α-phenylacetamidines act as nucleophilic centers in meta-bridging reactions[1] (eq 1) of polynitrobenzenes, pyridines, and naphthalenes.[2-4] For example, reaction of α-phenyl-*N,N*-dimethylacetamidine with 1,3-dinitronaphthalene yields products in which a CCN moiety from the amidine is annelated across the 2 and 4 positions of the aromatic substrate.[3] The amidine in this reaction acts as a bifunctional nucleophile. Because of tetrahedral geometry at the C-1 carbon of anionic sigma complexes[5] we have previously proposed that geometrical constraints in the intermediate precursor to benzazocines (the addition complex **1A**) favor nucleophilic attack of amidine carbon at the 3 position in the cyclization step,[1,2] i.e.,



Consideration of geometry in a planar SnAr displacement "intermediate" **1B** (resulting from amidine attack on an aromatic bearing a good leaving group) led us to suppose that attack on an ortho substituent would be favored. This supposition is supported by the observed cyclization of nitroanilides like **2**.[6] o-Nitrite displacement could also occur, however, as observed in the reaction of **3** with 2-mercapto-



benzimidazole.[7] We have carried out reactions of several amidines with various 1-substituted 2-nitroaromatics in order to further explore patterns of amidine reactivity.

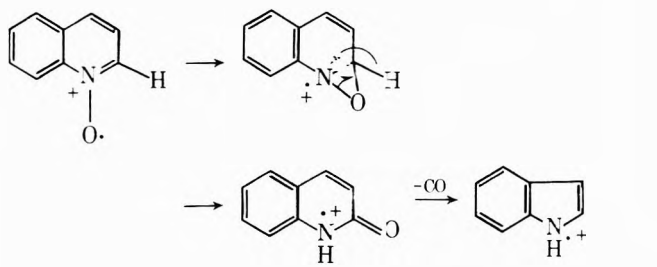
As noted above, while 1,3-dinitronaphthalene yields a 2-benzazocine with α-phenyl-*N,N*-dimethylacetamidine, 1-methoxy-2,4-dinitronaphthalene yields an entirely different

0022-3263/78/1943-2041$01.00/0

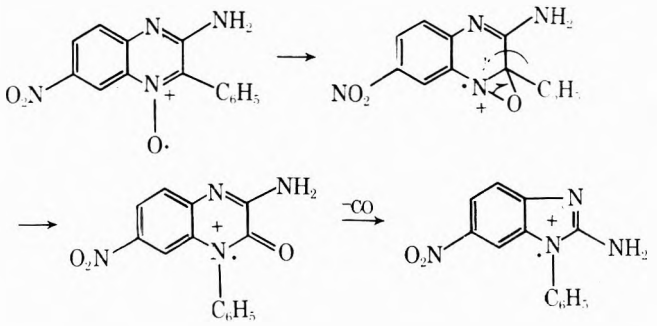
product which is not simply the result of SnAr displacement. The yellow crystalline product obtained from this reaction analyzes correctly for a 1:1 adduct of amidine and aromatic less an equivalent each of methanol and water. No absorptions between δ 3.5 and 7.0 are observed in the ^{1}H NMR spectrum of this material as would be expected if 4 had been formed (H_a, H_b, and H_c).[3] The parent peak in the mass spectrum at *m/e* 360 as well as the M-16 peak at 344 are characteristic of the *N*-oxide **5**.[8] The rest of the spectral data (see Experimental Section) also support this structure. Although the isomeric structure **5a** cannot be ruled out on the basis of spectral and analytical data, mechanistic considerations[9,10] support a structure in which amidine nitrogen attack occurs on carbon bearing methoxy in the aromatic substrate. Formation of **5** is analogous to the previously reported two-step synthesis of 2-amino-6-nitronaphtho[1,2-*e*]triazene 4-oxide **6** from guanidine and 1-chloro-2,4-dinitronaphthalene.[11]

The reaction with 1-methoxy-2,4-dinitronaphthalene was carried out with the intention of clarifying how meta-bridging, **1A**, and ortho substituent cyclization, **1B**, might compete in an aromatic substrate which had structural prerequisites suitable for each type of reaction. It was of interest to carry out the annelation reaction on a substrate which could not be expected to undergo meta bridging. Meta bridging has been shown to occur only on benzenes bearing a minimum of two nitro groups plus one additional electron withdrawing group (not halogen) or a benzofusion.[1] Sangor's reagent (1-fluoro-2,4-dinitrobenzene) reacts after a few minutes in warm ethanol solution with α-phenylacetamidine to yield a yellow insoluble crystalline solid. The elemental analyses, ^{1}H NMR, and mass spectral data are all consistent with **7**. These are summarized in the Experimental Section. A strong parent peak at *m/e* 282 as well as an M − 16 peak characteristic of heterocyclic *N*-oxides (**8**) are present in the mass spectrum. In addition, a strong M − 17 peak is also present which has been reported as characteristic of quinoxaline *N*-oxides,[12a] thus supporting structure **7** rather than the isomeric **7a**. Quinoline *N*-oxide decomposes upon electron impact to yield a major peak at *m/e* 117 which is accounted for by the following rearrangement process followed by loss of CO.[12b] A similar process can occur with **7** which leads to the stable delocalized radical ion **8** which is the largest peak in the mass spectrum of **7** except for M^+ (100%). This lends further support to structure **7** rather than **7a**. The reaction leading to **7** requires a relatively acidic amidine methylene, for the analogous reaction with propionamidine does not occur. This is consistent with the mechanism proposed for the formation of **5** (and presumably **7**). The position of tautomeric equilibrium of the amidine side chain in the initial displacement product (i.e., C ⇌ D) may well determine the rate at which cyclization occurs.

The preparation of the quinoxaline ring system via a one-step annelation with amidines would be useful if it could be adapted to other related heterocyclic compounds of interest. The limited but intriguing patent literature dealing with the imidazo[1,2-*a*]quinoxalines as antiinflammatory,[13-15] antibacterial,[15] and antiviral agents[13] prompted us to attempt a one-step preparation of this interesting ring system using an



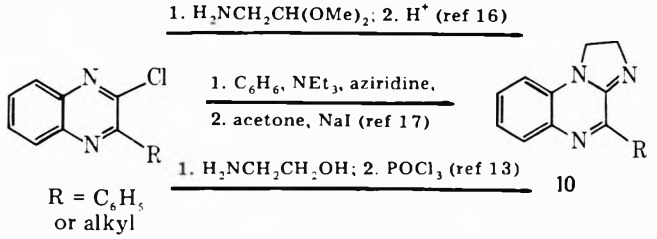
9 (*m/e* 117 (10%))



8 (*m/e* 254 (30%))

amidine annelation. All previously described routes to imidazo[1,2-*a*]quinoxalines involve chloroquinoxalines as precursors in a two-step sequence involving nucleophilic displacement followed by intramolecular cyclization.[13,16,17]

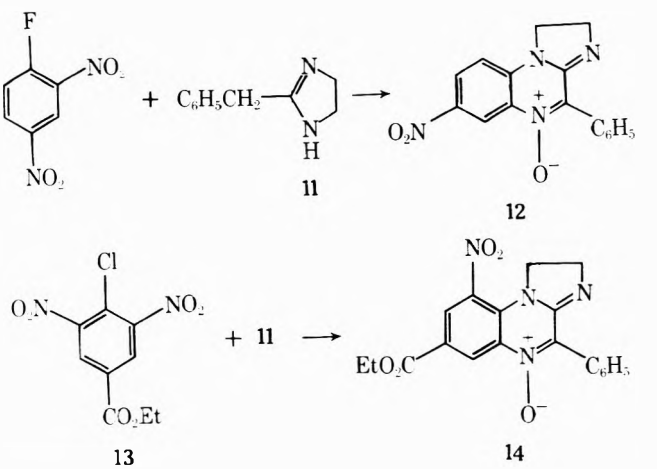
The use of cyclic amidines could provide a potentially useful one-step preparation of imidazo[1,2-*a*]quinoxaline *N*-oxides. These could easily be deoxygenated if desired.[8]



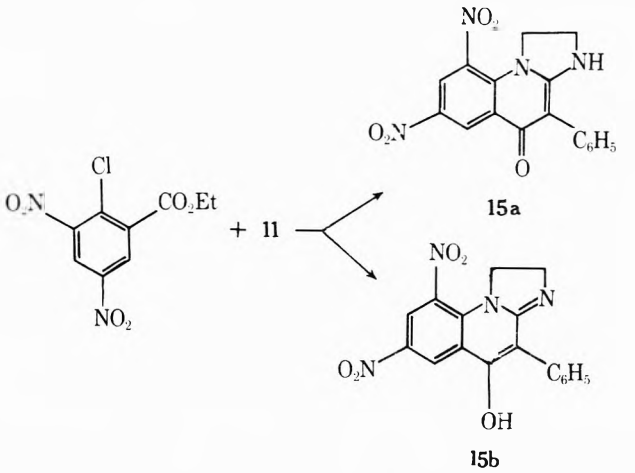
R = C_6H_5 or alkyl

Reaction of 1-fluoro-2,4-dinitrobenzene with the cyclic amidine **11** (Tolazoline) yields a yellow crystalline solid **12** which analyzes correctly for a 1:1 adduct of amidine and aromatic less an equivalent of HF and H_2O (see Experimental Section). The ^1H NMR and mass spectrum are consistent with structure **12**. A similar product, **14**, is formed when 1-chloro-2,6-dinitro-4-carboethoxybenzene (**13**) is the aromatic substrate.

Interestingly, when the carboethoxy group is interchanged with a nitro group ortho to chlorine in **13**, reaction with Tolazoline gives an entirely different product. This material analyzes correctly for an adduct of amidine and aromatic less an equivalent each of HCl and ethanol. The M − 16 peak characteristic of heterocyclic *N*-oxides is not present in the mass spectrum and the ^1H NMR spectrum does not contain a triplet and quartet for the carboethoxy function. All the spectral data are consistent with the imidazoquinoline **15**.



11 **12** **13** **14**



15a **15b**

Annelation has apparently occurred by attack on the ester carbonyl rather than on a nitro group. There is no carbonyl absorption in the IR spectrum of **15** but strong absorption does appear from 3100 to 3500 cm^{-1}, which does not appear in the analogues **12** or **14**. This is consistent with the formation of **15b** rather than the tautomeric **15a**.

These interesting bis nucleophilic reactions further elaborate the utility of amidine annelations in the preparation of heterocyclic ring systems.

Experimental Section

All melting points are uncorrected. ^1H-NMR spectra were run on JEOL C-60 HL and MH-100 spectrometers with Me_4Si as an internal reference. Visible and ultraviolet spectra were recorded on a Perkin-Elmer Model 402 UV-visible spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 237 B infrared spectrophotometer. Mass spectra were obtained on a Perkin-Elmer RMU-6D mass spectrometer. Elemental analyses were cross checked by Galbraith Laboratories, Inc., Knoxville, Tenn., G. I. Robertson Laboratories, Florham Park, N.J., and Integral Microanalytical Laboratories, Inc., Raleigh, N.C.

Preparation of Amidines. α-Phenyl-*N,N*-dimethylacetamidine was prepared as reported previously.[2] α-Phenylacetamidine was prepared by a method similar to that for the preparation of *N*-cyano-*N'*-phenylacetamidine.[18] To 2.0 g of ethyl phenylacetimidate[19] in 5 mL of MeOH was added 15 mL of a saturated solution of ammonia in EtOH. After 3 days the solvent was removed under vacuum at room temperature. The residue was added to 20 mL of a saturated ammonia solution and the mixture was stored for 3 days. Removal of the alcohol gave a residue which was recrystallized from ether–pentane mixtures. The white crystals melted at 62–63 °C. The picrate melted at 224–225 °C (lit.[20] mp 225–226 °C).

Tolazoline hydrochloride was purchased from Aldrich and was converted to the free base as follows. A solution of 14.5 g (0.098 mol) of the hydrochloride in 100 mL of MeOH was added to a solution of 2.28 g (0.099 mol) of Na in 75 mL MeOH at −70 °C. A white precipitate of NaCl formed immediately and the dry ice–acetone bath boiled vigorously indicating an exothermic reaction. The mixture was allowed to stand overnight, the NaCl was filtered off, and the filtrate was stripped on a rotary evaporator to yield a yellow oil. Dry Et_2O was then added. The resulting white solid was filtered off and the filtrate was again stripped on a rotary evaporator to yield 11.2 g of a yellow-white waxy solid, mp 65–68 °C (lit.[21] mp 67 °C). The free base was used without further purification.

Preparation of 5. To a solution of 0.34 g (0.0014 mol) of 1-methoxy-2,4-dinitronaphthalene in 100 mL of MeOH was added 0.53 g (0.003 mol) of α-phenyl-*N,N*-dimethylacetamidine. After 5 days the resulting yellow crystals were filtered off, washed with methanol and ether, and then vacuum dried to give 0.29 g (0.001 mol) of product, mp 277–279 °C. The IR spectrum (KBr) shows absorption bands at

1600, 1750, 1520, 1395, 1370, 1340, 1300, 1245, and 1215 cm^{-1}. The ^1H-NMR spectrum in $CDCl_3$ shows absorptions at δ 3.02 (6 H, s, MNe_2), 7.69 (5 H, m, C_6H_5), 7.92 (2 H, m), 8.78 (1 H, dd, J = 6 and 2 Hz, peri to N), 9.28 (1 H, dd, J = 6 and 2 Hz, peri to NO_2), and 9.35 (1 H, s, peri to N-oxide). The mass spectrum shows a parent peak at m/e 360 as well as peaks at 344 ($M^+ - O$), 343, and 314. Anal. Calcd for $C_{20}H_{16}N_4O_3$: C, 66.66; H, 4.48; N, 15.55. Found: C, 66.77; H, 4.74; N, 15.59.

Preparation of 7. This compound was prepared in a fashion analogous to that for **5.** It was also prepared by generating the amidine from the hydrochloride in situ as follows. To a solution of 1.82 g (0.011 mol) of α-phenylacetamidine hydrochloride in 60 mL of EtOH was added 0.25 g (0.011 mol) of Na. A white precipitate of NaCl formed immediately. The mixture was filtered through a fine frit sintered glass funnel and the filtrate was added directly to 1.0 g (0.005 mol) of 1-fluoro-2,4-dinitrobenzene. The solution was refluxed for about 8 h and after cooling the resulting yellow solid was filtered off and recrystallized from acetonitrile to give 0.2 g of orange crystals, mp 279–282 °C. The crystals changed from orange to yellow at ~265 °C but did not otherwise change at this temperature. The ^1H-NMR spectrum (Me_2SO-d_6) shows absorptions at δ 7.10 (2 H, br, NH), 7.55 (5 H, m, C_6H_5), 7.68 (1 H, d, J = 8 Hz, peri to N), 8.39 (1 H, dd, J = 8 and 3 Hz, para to N-oxide), and 8.92 (1 H, d, J = 3 Hz, ortho to N-oxide). The mass spectrum shows a parent peak at m/e 282 as well as strong peaks at 266, 265, 254, 235, 219, and 207. Anal. Calcd for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.80; H, 3.53; N, 19.71.

An attempt was made to run this reaction under identical conditions using propionamidine hydrochloride instead of phenylacetamidine hydrochloride. No trace of an adduct analogous to **7** could be isolated, however.

Preparation of 12. A solution of 1.28 g (0.008 mol) of Tolazoline in 10 mL absolute ethanol was added to 0.74 g (0.004 mol) of 1-fluoro-2,4-dinitrobenzene in this same solvent. After 5 min an orange solid precipitated. After 24 h the solid was filtered off, washed with a small portion of ethanol, and vacuum dried to yield 1.08 g of **12,** mp 212–213 °C. Recrystallization of a small portion of these crystals from ethanol and then again from acetone yielded crystals melting at 230–231 °C. The ^1H-NMR spectrum (Me_2SO-d_6) shows absorptions at δ 4.07 (4 H, br s, $-CH_2CH_2-$), 7.05 (1 H, d, J = 9 Hz, peri to N), 7.45 (3 H, m, Ar), 7.95 (2 H, m, Ar), 8.32 (1 H, dd, J = 2 and 9 Hz, para to N-oxide), and 8.75 (1 H, d, J = 9 Hz, ortho to N-oxide). The mass spectrum shows a parent peak at m/e 308 as well as strong peaks at 292 and 291 ($M - 16$ and $M - 17$) characteristic of the N-oxide functionality. The IR spectrum shows strong absorptions at 1600 (C=N), 1508 (NO_2), 1425, 1320, 1275, and 1145 cm^{-1}. Anal. Calcd for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.93; N, 18.17. Found: C, 62.24; H, 3.96; N, 18.34.

Preparation of 14. A solution of 2.40 g (0.009 mol) of 1-chloro-2,6-dinitro-4-carboethoxybenzene in 40 mL of hot EtOH was mixed with a solution of 2.79 g (0.018 mol) of Tolazoline in 10 mL of EtOH. The solution was refluxed gently and turned very dark yellow. After 2 more h of refluxing and 2 h at room temperature, the reaction mixture was cooled to 0 °C. The resulting yellow crystals were filtered off and recrystallized twice from ETOH to yield 1.0 g of product, mp 201–202 °C. The ^1H-NMR spectrum (Me_2SO-d_6) shows absorptions at δ 1.50 (3 H, t, J = 7.5 Hz, CH_3CH_2), 4.21 (4 H, m, CH_2CH_2), 4.68 (2 H, q, J = 7.5 Hz, CH_3CH_2), 7.80 (3 H, m, Ar), 8.20 (2 H, m, Ar), 8.77 (1 H, d, J = 3 Hz, para to N-oxide), and 9.17 (1 H, d, J = 3 Hz, ortho to N-oxide). The mass spectrum shows a parent peak at m/e 380 as well as a very strong peak at m/e 364 ($M^+ - O$). These are the most intense peaks in the spectrum. The IR spectrum shows a strong carbonyl absorption at 1700 cm^{-1} as well as strong absorptions at 1600, 1520, 1370, 1310, 1280, 1220, 1190, and 1020 cm^{-1}. Anal. Calcd for $C_{19}H_{16}N_4O_5$: C, 60.00; H, 4.24; N, 14.73. Found: C, 60.15; H, 4.18; N, 15.01.

Preparation of 15b. A solution of 1.72 g (0.006 mol) of 1-chloro-2,4-dinitro-6-carboethoxybenzene in 30 mL of EtOH was added to a solution of 2.0 g (0.012 mol) of Tolazoline in 10 mL of EtOH. The reaction mixture was refluxed for 5 min and a voluminous yellow precipitate formed. This was filtered off and recrystallized from CH_3CN to yield 0.9 g of **15b,** mp 291–293 °C. The ^1H-NMR spectrum (Me_2SO-d_6) shows absorptions at δ 3.80 (2 H, m, CH_2CH_2), 4.28 (2 H, m, CH_2CH_2), 7.65 (5 H, m, Ar), 8.00 (1 H, br s, OH), 9.16 (1 H, d, J = 2 Hz, nitroaromatic ring proton), and 9.28 (1 H, d, J = 2 Hz, nitroaromatic ring proton). The mass spectrum shows a parent peak at m/e 352. No peaks are observed at all in the $M - 16$ or $M - 17$ region confirming the absence of the N-oxide function. The IR spectrum shows broad absorption in the region from 3100 to 3500 cm^{-1} (OH) and no other absorption above 1610 cm^{-1} (absence of C=O). Anal Calcd for $C_{17}H_{12}N_4O_5$: C, 57.95; H, 3.43; N, 15.90. Found: C, 57.83; H, 3.17; N, 16.03.

Acknowledgment. The authors wish to thank the National Institute on Drug Abuse, Grant PHS RO1 00450-02, for support of this research.

Registry No.—5, 65392-15-6; **7,** 65392-16-7; **12,** 65392-17-8; **13,** 19649-81-1; **14,** 65392-18-9; **15b,** 65392-19-0; α-phenylacetamidine, 5504-24-5; ethyl phenylacetimidate, 4971-77-1; 1-methoxy-2,4-dinitronophthalene, 13772-69-5; α-phenyl-N,N-dimethylacetamidine, 56776-16-0; α-phenylacetamidine hydrochloride, 2498-46-6; 1-fluoro-2,4-dinitrobenzene, 70-34-8; tolazoline, 59-98-3; 1-chloro-2,4-dinitro-6-carboethoxybenzene, 7251-28-7.

References and Notes

(1) M. J. Stauss, *Acc. Chem. Res.*, **7,** 181 (1974).
(2) R. R. Bard and M. J. Strauss, *J. Am. Chem. Soc.*, **97,** 3789 (1975).
(3) (a) R. R. Bard and M. J. Strauss, *J. Org. Chem.*, **41,** 2421 (1976); (b) R. Bard, Ph.D. Thesis, University of Vermont, Burlington, Vt.
(4) R. R. Bard, M. J. Strauss, and S. A. Topolosky, *J. Org. Chem.*, **42,** 2589 (1977).
(5) (a) M. J. Strauss, *Chem. Rev.*, **70,** 667 (1970); (b) M. R. Crampton, *Adv. Phys. Org. Chem.*, **7,** 211 (1969); (c) P. Buck, *Angew. Chem., Int. Ed. Engl.*, **8,** 120 (1969).
(6) P. N. Preston and G. Tennant, *Chem. Rev.*, **72,** 627 (1972).
(7) J. J. D'Amico, C. C. Tung, and W. E. Dahl, *J. Org. Chem.*, **42,** 600 (1977).
(8) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides", Academic Press, New York, N.Y., 1971.
(9) G. Biggi, F. Delcima, and F. Pietra, *J. Chem. Soc., Perkin Trans. 2,* 188 (1972).
(10) (a) G. Biggi, F. Delcima, and F. Pietra, *Tetrahedron Lett.*, 2811 (1971); (b) R. H. DeWolfe, "The Chemistry of Amidines and Imidates", S. Patai, Ed., Wiley, New York, N.Y., (1975).
(11) J. K. Horner and D. W. Henry, *J. Med. Chem.*, **11,** 946 (1968).
(12) (a) A. Tatematsu, H. Yoshizumi, E. Hayashi, and N. Nakata, *Tetrahedron Lett.*, 2985 (1967). (b) O. Buchardt, A. M. Duffield, and R. H. Shapiro, *Tetrahedron,* **24,** 3139 (1968).
(13) H. Otsumasu, *Chem. Abstr.*, **81,** P91574b (1974).
(14) H. Otsumasu, *Chem. Abstr.*, **81,** P77967a (1974).
(15) R. E. Rodway and F. F. Cookson, *Chem. Abstr.*, **81,** P13559m (1974).
(16) R. F. Cookson and R. E. Rodway, *J. Chem. Soc.*, **19,** 1854 (1975).
(17) H. W. Heine and A. C. Brooker, *J. Org. Chem.*, **27,** 2944 (1962).
(18) K. R. Hoffman and F. C. Schaeffer, *J. Org. Chem.*, **28,** 1816 (1963).
(19) S. M. McElvain and C. L. Stevens, *J. Am. Chem. Soc.*, **68,** 1917 (1946).
(20) P. Reynaud, R. C. Moreau, and J. C. Tetard, *C. R. Hebd. Seances Acad. Sci., Ser. C,* **262,** 665 (1966).
(21) M. W. Partridge and H. A. Turner, *J. Pharm. Pharmacol.*, **5,** 111 (1953).

Reaction of N-Nitrosodibenzylamine with Phenacyl Bromides

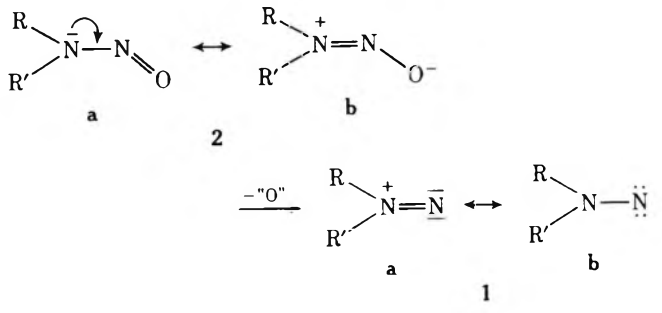
Kozaburo Nishiyama and Jean-Pierre Anselme*

Department of Chemistry, University of Massachusetts at Boston, Harbor Campus, Boston, Massachusetts 02125

Received September 28, 1977

The reaction of *N*-nitrosodibenzylamine (NDBA) with phenacyl bromides in the presence of silver hexafluoroantimonate proceeds via the intermediacy of *N*-dibenzylaminonitrene in ether to give bibenzyl and benzylidenedibenzylhydrazine. In benzene as solvent, diphenylmethane is the major product. In all cases, benzaldehyde was formed, sometimes as the major product of the reaction. Possible mechanisms for these transformations are discussed.

For some time we have been interested in novel methods to generate *N*-nitrenes (**1**). In principle, *N*-nitrosamines (**2**)



could serve as precursors of *N*-nitrenes if they are regarded as *N*-nitrene *N*-oxides, a view supported by the large contribution of mesomeric form **2b** to the structure of *N*-nitrosamines.[1] These considerations coupled with the current interest in the chemistry[2] and biological activity of *N*-nitrosamines[3] prompted the investigation herein described.

The "deoxygenation" of *N*-nitrosamines has been previously accomplished with ethyl diphenylphosphinite,[4] iron pentacarbonyl,[5] and aryl azides.[6] The oxidation of α-halo carbonyl compounds by compounds such as sulfoxides and amine *N*-oxides[7] suggested that *N*-nitrosamines could similarly be "deoxygenated" to *N*-nitrenes. Indeed it was anticipated that phenacyloxy diazenium ions **7** if formed would surrender a proton to an external base to yield the *N*-nitrenes and the α-dicarbonyl compounds.

Results and Discussion

For reasons discussed earlier,[6] *N*-nitrosodibenzylamine (NDBA, **2**, R = R′ = $PhCH_2$) was chosen as the substrate for our investigation. Since *N*-nitrosamines had been reported to be *O*-alkylated by powerful alkylating agents such as trialkyloxonium salts,[8] the reactions of NDBA were carried out with phenacyl bromides **3** and silver hexafluoroantimonate (actually compex **9** is believed to be the reactive species as shown in eq 4).[9]

$$\underset{\mathbf{3}}{ArCOCH_2Br} + AgSbF_6 \rightarrow \underset{\mathbf{4}}{[ArCOCH_2{}^+SbF_6{}^-]} + AgBr \qquad (1)$$

a, Ar = C_6H_5; **b**, Ar = *p*-BrC_6H_4; **c**, Ar = *p*-$NO_2C_6H_4$

The reactions of NDBA with **4** are summarized in Table I. In diethyl ether as solvent (Table I, experiments 7, 11, and 13), bibenzyl (**5**) and benzylidenedibenzylhydrazine (**6**) were isolated and characterized. Their formation can be understood in terms of further reactions of *N*-dibenzylaminonitrene (**1**, R = R′ = $PhCH_2$) as shown in Scheme I.[10]

$$\mathbf{1} \rightarrow \underset{\mathbf{5}}{PhCH_2CH_2Ph} + \underset{\mathbf{6}}{PhCH{=}NN(CH_2Ph)_2} \qquad (2)$$

In most cases, benzaldehyde was a major product of the reaction. Its formation may be rationalized via removal of one of the benzylic hydrogens of **7** as shown in Scheme II.[11]

The results of the reaction of phenacyl bromide with silver hexafluoroantimonate followed by addition of NDBA in wet ether (experiment 7) were informative. The appearance of

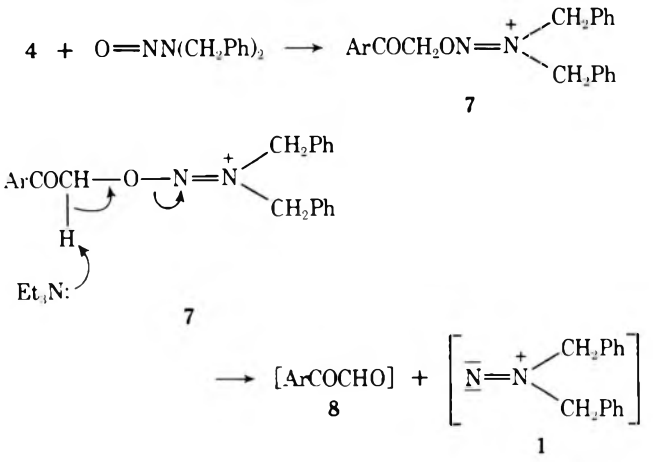
Table I. Reaction of $ArCOCH_2Br$ (3) with NDBA in the Presence of $AgSbF_6$[a]

	$ArCOCH_2Br$ (3) (mmol)	Registry No.	NDBA,[b] mmol	$AgSbF_6$, mmol	Et_3N, mL	Solvent[c] (mL)	Products, %[a] 5	6	10	PhCHO	Others
1	C_6H_5 (7)	70-11-1		7		B (20)					*d*
2			7	7	10	B (20)					*e*
3	C_6H_5 (4)		4			B (10)					*f*
4	C_6H_5 (10)		10	10	10	B (25)	4		42	Traces	*g*
5	C_6H_5 (10)		10	10		B (25)	4		37	19	*h*
6	C_6H_5 (10)[i]		10	10	10	B (25)	5		15		*i*
7	C_6H_5 (10)		10	10	10	E (25)	13	10		10	*j*
8	C_6H_5 (10)		10	10		E (25)	4	4		21	*k*
9	*p*-BrC_6H_4 (8.4)	99-73-0	8.4	8.4	8.4	B (20)	10		45	Traces	*l*
10	*p*-BrC_6H_4 (10)		10	10		B (25)	6		43	16	*m*
11	*p*-BrC_6H_4 (10)		10	10	10	E (25)	11	12		23	*n*
12	*p*-$NO_2C_6H_4$ (10)	99-81-0	10	10	10	B (25)	11		40	Traces	*o*
13	*p*-$NO_2C_6H_4$ (10)		10	10	10	E (20)	10	18		15	*p*

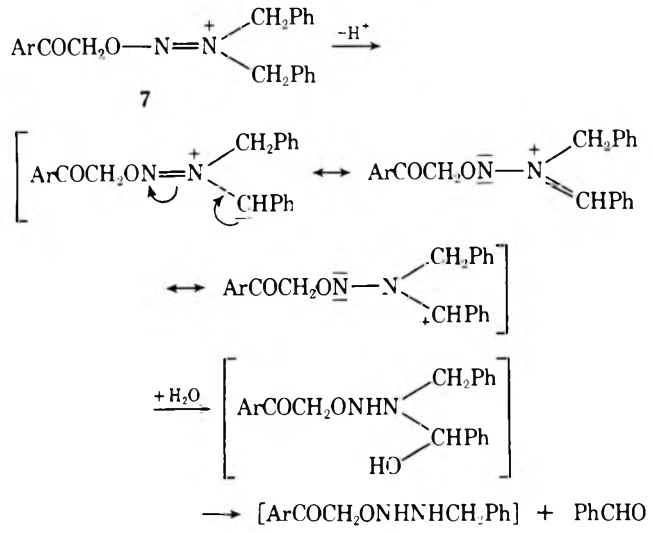
[a] Reactions were carried out at reflux for 24 h; in experiments where Et_3N was used, the reaction mixture was heated for an additional 24 h after the addition. Yields are based on starting material used and were divided by 2 for **10** and multiplied by 2 for **6**. [b] NDBA = *N*-nitrosodibenzylamine (**2**, R = R′ = $PhCH_2$). [c] B = benzene; E = diethyl ether. [d] Phenacyl bromide, 96%. [e] NDBA, 96%. [f] Phenacyl bromide, 95%; and NDBA, 95%. [g] Benzil, 21%. [h] Benzil, traces; benzoic acid, 12%; and phenacyl bromide, 6%. [i] Reaction of phenacyl bromide and $AgSbF_6$ was heated at reflux for only 3 h. [j] NDBA, 10%. [k] Phenacyl alcohol, 94%; NDBA, 23%; and phenacyl bromide 5%. [l] *p*-Bromobenzil, 13%; and NDBA, traces. [m] *p*-Bromobenzoic acid, 5%; *p*-bromophenacyl bromide, 4%; and *p*-Bromobenzil, 12%. [n] NDBA, 24%. [o] *p*-Nitrobenzil, 8.4%. [p] NDBA, 11%.

0022-3263/78/1943-2045$01.00/0

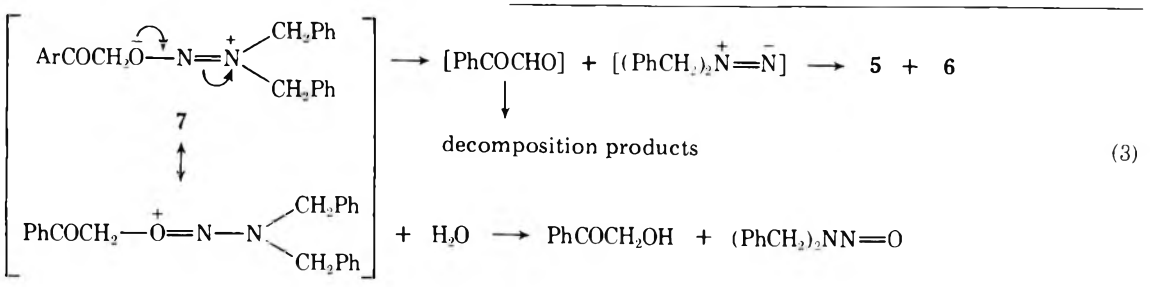
Scheme I



Scheme II

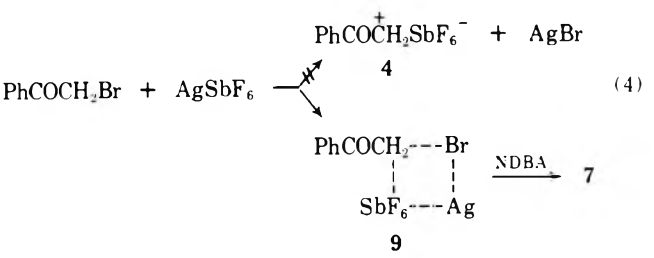


N-nitrene products **5** and **6** coupled with the formation of phenacyl alcohol in 94% yield indicated that intermediate **7**

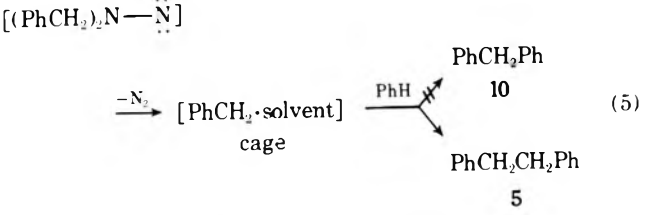


was generated and partially fragmented to **1** thence to **5** and **6** (Scheme I and eq 2). However, the main path was hydrolysis to phenacyl alcohol and NDBA. It was shown in a control experiment that the complex of phenacyl bromide and silver hexafluoroantiomonate, *under the same conditions* (wet ether) but in the *absence* of NDBA, gave phenacyl bromide in nearly quantitative recovery (95%). This suggests that complex **9** and not the phenacyl carbocation is the species that reacts with NDBA and that NDBA must somehow assist in breaking up the complex.

When benzene was used as solvent, the major product (40–45%) was diphenylmethane (**10**). It was initially believed that benzene was acting as an efficient trap for the benzyl radicals. However, oxidation of 1,1-dibenzylhydrazine in *benzene* with manganese dioxide and with lead tetraacetate gave **5** in 34 and 7% and **6** in 48 and 20% yields, respectively.

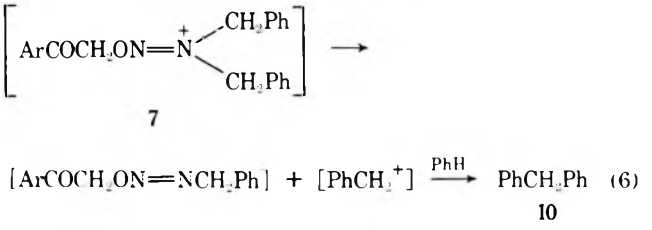


Similarly, reaction of the anion of 1,1-dibenzylhydrazine with tosyl azide[10] afforded **5** and **6** in 26 and 10% yield; in none of

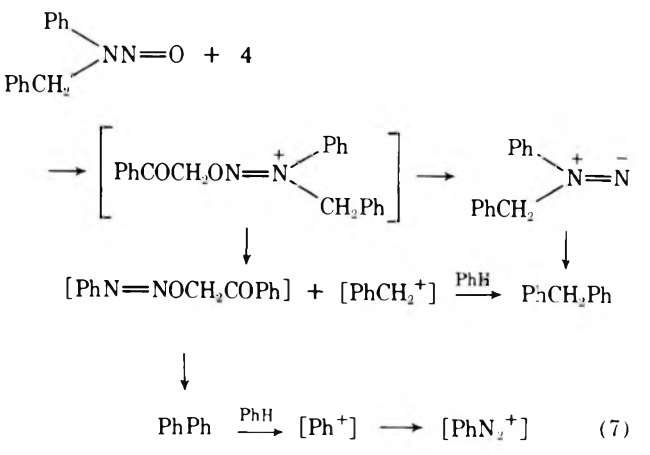


these reactions was diphenylmethane (**10**) detected. The results rule out the reaction of benzyl radical with benzene as the source of diphenylmethane.

The formation of **10** may be understood in terms of a heterolytic breakdown of **7** to give the benzyl carbocation. Indeed



the reaction of benzyl chloride with $AgSbF_6$ in benzene cleanly provided a 95% yield of essentially pure diphenylmethane. Further support for this view came from the reactions of *N*-nitroso-*N*-benzylaniline with phenacyl bromide and $AgSbF_6$ in benzene. Diphenylmethane and biphenyl were obtained in 31 and 10% yields, respectively. The formation of these two compounds must be viewed as arising from heterolytic



breakdown as the corresponding *N*-nitrene does *not* undergo homolytic fragmentation to any major extent.[12] The formation of biphenyl from the reaction of phenyl cation with benzene is well documented.[13] In contrast, the reaction of *N*-nitrosodiphenylamine with phenacyl bromide and silver hexafluoroantimonate in benzene gave *no* biphenyl. In this case, the loss of a relatively stable carbocation (eq 8) is not possible even if intermediate **11** is formed. The formation of **11** might not

$$[PhCOCH_2^+] + Ph_2NN{=}O \xrightarrow{?}$$

$$\left[PhCOCH_2ON{=}\overset{+}{N}(Ph)(Ph)\right] \rightarrow Ph^+ + PhCOCH_2ON{=}NPh \quad (8)$$

$$\mathbf{11} \rightarrow PhCOCHO + [Ph_2N{-}\ddot{N}]$$

be favored since the substituent phenyl groups may render the nitroso oxygen devoid of any nucleophilic power and thus unable to break up complex **9**. The alternate route, namely loss of an α hydrogen, would also be unfavorable since *N*-diphenylaminonitrene would not easily be formed under these conditions. Even if generated this *N*-nitrene is not known to fragment to phenyl radicals.

The absence of the expected arylglyoxals was as puzzling as was the formation of benzils as by-products (experiments 5, 10, and 12). It was surmised that the glyoxals were undergoing further reaction with benzene. This was supported by the report of the formation of benzoins (and their subsequent facile air oxidation to benzils) from the reaction of arylglyoxals with benzene in the presence of aluminum chloride.[14] Indeed the reaction of freshly distilled phenylglyoxal with benzene in the presence of $AgSbF_6$ gave benzil. So far, we are unable to account for the formation of the benzoic acids (experiments 5 and 10). Since *p*-bromobenzoic acid and not benzoic acid was obtained when *p*-bromophenacyl bromide (experiment 10) was used, the benzoic acids evidently arose from the phenacyl component of the reaction.

Experimental Section

All melting points were taken on a Thomas-Hoover Uni-melt apparatus and are uncorrected. Infrared and NMR spectra were recorded on a Perkin-Elmer 137 (Infracord) and Hitachi Perkin-Elmer R-24 spectrometers. VPC analyses were performed on a Perkin-Elmer 154 D fractometer using a stainless steel column packed with silicone grease (20%) on HMDS-CROM W.

Materials. *N*-Nitrosodibenzylamine (NDBA),[15] 1,1-dibenzylhydrazine,[16] and the phenacyl bromides[17] were prepared according to reported procedures. Benzene was purified by a reported method[18] and dried over lithium aluminum hydride. Anhydrous ether, silver hexafluoroantimonate (Alfa Inorganics), and ethyllithium in benzene (Alfa Inorganics) were commercial products and were used as received.

$AgSbF_6$ Induced Reaction of Phenacyl Bromides with NDBA. General Procedure. In Benzene. A mixture of the phenacyl bromide (10 mmol), NDBA (10 mmol), and silver hexafluoroantimonate (10 mmol) in 25 mL of dry benzene was heated to reflux for 24 h with vigorous stirring. Triethylamine (10 mL) was then added to the reaction mixture and heating with stirring was continued for an additional 24 h. The hot reaction mixture was poured into 100 mL of water and the organic layer was washed with water and dilute hydrochloric acid repeatedly. After drying over magnesium sulfate and evaporation of the solvent in vacuo, the resulting dark oil was chromatographed on 50 g of silica gel (60–200 mesh). Rapid elution with *n*-hexane gave diphenylmethane and bibenzyl, identified by comparison with authentic samples. Quantitative analysis of the mixture was performed by NMR and VPC. Further elution with *n*-hexane/benzene and benzene gave benzaldehyde and the more polar fractions. Each product was identified by comparison of its NMR and IR spectra and its VPC retention time with those of authentic samples. Mixture melting points were used also for solid samples.

In the absence of triethylamine, benzoic acid (1.2 mmol) was extracted from the benzene layer with aqueous sodium bicarbonate. Under the same conditions, phenacyl bromides reacted with triethylamine to give the phenacyltriethylammonium bromides. With *p*-bromophenacyl bromide, *p*-bromobenzoic acid (mp 250–252 °C) and 4-bromobenzil (mp 77–80 °C; *m/e* 290, 288) instead of benzoic acid and benzil respectively were obtained in addition to diphenylmethane and bibenzyl. With *p*-nitrophenacyl bromide, 4-nitrobenzil (mp 138–139 °C (lit.[19] mp 140–141 °C); *m/e* 255) was obtained in addition to diphenylmethane and bibenzyl.

In Ether. The procedure was similar to that described above. The reaction mixture was separated and the aqueous layer was extracted with benzene. The combined organic phase was evaporated and the residue was chromatographed. Rapid elution with *n*-hexane gave bibenzyl followed by benzylidenedibenzylhydrazine and benzaldehyde.

Reaction of Phenacyl Bromide, *N*-Nitroso-*N*-benzylaniline, and $AgSbF_6$ in Benzene. The procedure was the same as described for the reaction with NDBA. Chromatography on silica gel gave diphenylmethane (31%), biphenyl (9.7%), benzoic acid (1%), and phenacyl bromide (15%).

Reaction of Phenacyl Bromide, *N*-Nitrosodiphenylamine, and $AgSbF_6$ in Benzene. The procedure described for NDBA was followed. Chromatography of the residue on silica gel gave 65% of the recovered phenacyl bromide but no biphenyl was detected by TLC, IR, or VPC. *N*-Nitrosodiphenylamine when heated to reflux for 24 h gave several compounds (TLC) and diphenylamine in addition to recovered starting nitrosamine.

Oxidation of 1,1-Dibenzylhydrazine in Benzene. With Lead Tetraacetate. To a solution of 1,1-dibenzylhydrazine (10 mmol) in 25 mL of benzene was added portionwise lead tetraacetate (10 mmol) and the mixture was heated to reflux for 20 h with stirring. The precipitated lead diacetate was filtered and the filtrate was washed with water and aqueous sodium bicarbonate repeatedly. The residue obtained from evaporation of the dried benzene solution was chromatographed on silica gel (60–200 mesh, 50 g) and afforded bibenzyl (7%) and benzylidenedibenzylhydrazine (48%) in addition to a liquid (1.03 g) whose IR and NMR spectra indicated it to be mostly benzyl acetate (containing some benzylidenedibenzylhydrazine). There was no substantial difference in the yields of bibenzyl (7.4%) and benzylidenedibenzylhydrazine (41%) and benzyl acetate when 1,1-dibenzylhydrazine was added dropwise to a suspension of lead tetraacetate in benzene at reflux.

With Manganese Dioxide. To a suspension of activated manganese dioxide (1 g) in benzene (25 mL) was added dropwise a solution of 1,1-dibenzylhydrazine (10 mmol) in benzene (25 mL) over a period of 1.5 h and the reaction mixture was then heated to reflux for 20 h with stirring. The precipitated solid was filtered and the filtrate was worked up to give bibenzyl (34%) and benzylidenedibenzylhydrazine (20%).

Reaction of 1,1-Dibenzylhydrazine Anion with Tosyl Azide.[10] Ethyllithium in benzene (10 mL, 1.25 M) was added dropwise to a solution of 1,1-dibenzylhydrazine (10 mmol) in benzene (25 mL) at room temperature over a period of 10 min under a nitrogen atmosphere. Then a solution of tosyl azide (2 g) in benzene (25 mL) was added dropwise at room temperature. After completion of the addition, the reaction mixture was heated to reflux for 2 h, and then quenched by the addition of water. Chromatography of the residue obtained after workup gave bibenzyl (26%) and benzylidenedibenzylhydrazine (10%).

Reaction of Benzyl Chloride with $AgSbF_6$ in Benzene. A mixture of benzyl chloride (10 mmol) and silver hexafluoroantimonate (10 mmol) in 25 mL of benzene was heated to reflux for 24 h with vigorous stirring. The reaction mixture was poured into water and the benzene layer was separated. The aqueous phase was extracted with benzene and the combined organic extract was dried and evaporated to give an oil (1.6 g, 95%) which was characterized as essentially pure diphenylmethane by IR, NMR, VPC, and TLC; no benzyl chloride was present in the oil.

Reaction of Phenacyl Bromide, NDBA, and $AgSbF_6$ in Wet Ether. A mixture of phenacyl bromide (1.92 g, 10 mmol), NDBA (2.26 g, 10 mmol), and silver hexafluoroantimonate (3.5 g, 10 mmol) in wet ether[21] (25 mL) was heated to reflux for 24 h with vigorous stirring. The reaction mixture was poured into water and extracted with benzene. The following compounds were isolated by chromatography of the product with *n*-hexane, varying mixtures of *n*-hexane/benzene and benzene: diphenylmethane (0.39 mmol), benzylidenedibenzylhydrazine (0.21 mmol), benzaldehyde (2.09 mmol), phenacyl bromide (0.48 mmol), NDBA (2.34 mmol) along with unknown products. The fractions eluted with chloroform gave 1.28 g (94%) of phenacyl alcohol, identified by comparison (IR, NMR, TLC) with an authentic sample.[22] Treatment of phenacyl alcohol with *o*-phenylenediamine in methanol gave a 25% yield of 2-phenylquinoxaline, mp 77–78 °C (lit.[23] 77–78 °C).

Reaction of Complex of Phenacyl Bromide and Silver Hexafluoroantimonate with Water. A mixture of phenacyl bromide (1 g, 5 mmol) and silver hexafluoroantimonate (1.8 g, 5 mmol) in anhydrous ether (15 mL) was heated to reflux for 2 h with vigorous stirring. To the reaction mixture was then added water (5 mL) and reflux and stirring were continued for 22 h. The reaction mixture was poured into water and extracted with benzene. The dried benzene extract gave only phenacyl bromide (883 mg, 88.3%).

Reaction of a Complex of Phenacyl Bromide and Silver Hexafluoroantimonate with Benzyl Alcohol. A mixture of phenacyl bromide (1 g, 5 mmol) and silver hexafluoroantimonate (1.8 g, 5 mmol) in anhydrous ether (15 mL) was heated to reflux for 2 h with vigorous stirring. To the reaction mixture was then added benzyl alcohol (5 mL) and reflux and stirring were continued for 22 h. The reaction mixture was poured into water and extracted with benzene. No benzaldehyde was detected on TLC, NMR, and IR.

Reaction of Benzylidenedibenzylhydrazine with $AgSbF_6$ in Wet Ether. A mixture of benzylidenedibenzylhydrazine (1.5 g, 5 mmol) and silver hexafluoroantimonate (1.8 g, 5 mmol) in wet ether[21] (15 mL) was heated to reflux for 24 h with vigorous stirring. The reaction mixture was poured into water and extracted with benzene. Removal of the solvent gave 1.3 g of an oily material which was shown to consist of starting material (89%) and benzaldehyde (11%) by NMR spectral examination.

Reaction of Phenylglyoxal with $AgSbF_6$ in Benzene. A mixture of freshly distilled phenylglyoxal (1.4 g, 10 mmol) and silver hexafluoroantimonate (3.5 g, 10 mmol) in anhydrous benzene was heated to reflux for 24 h with vigorous stirring. The reaction mixture was poured into water and extracted with benzene. The dried benzene extract was evaporated in vacuo and residue was chromatographed on 50 g of silica gel (60–200 mesh). Fractions were eluted rapidly with benzene to give benzil as a thick yellow oil whose IR spectrum and TLC retention time were identical to those of authentic sample; the infrared spectrum of the bis(2,4-dinitrophenylhydrazone), mp 285–290 °C (lit.[24] mp 317–318 °C), was identical to that of an authentic sample.

Acknowledgment. The generous support of this work by NIH under Grant GM 13689 is hereby gratefully acknowledged.

Registry No.—NDBA, 5336-53-8; *p*-bromobenzoic acid, 586-76-5; 4-bromobenzil, 39229-12-4; bibenzyl, 103-29-7; benzylidenedibenzylhydrazine, 21136-32-3; benzaldehyde, 100-52-7; diphenylmethane, 101-81-5; 1,1-dibenzylhydrazine, 5802-60-8; benzyl chloride, 100-44-7; phenylglyoxal, 1074-12-0.

References and Notes

(1) G. J. Karabatsos and R. A. Taller, *J. Am. Chem. Soc.*, **86**, 4373 (1964).
(2) D. Seebach and D. Enders, *Angew. Chem., Int. Ed. Engl.*, **14**, 15 (1975); A. L. Fridman, F. M. Mukhametshir, and S. S. Novikov, *Russ. Chem. Rev. (Engl. Transl.)*, **40**, 34 (1971).
(3) P. P. Roller, D. R. Shimp, and L. K. Keefer, *Tetrahedron Lett.*, 2065 (1975); M. Wiessler, *ibid.*, 2575 (1975); J. E. Baldwin, S. E. Branz, R. F. Gomez, P. L. Kraft, A. J. Sinkey, and S. R. Tannenbaum, *ibid.*, 333 (1976); S. S. Hecht, C. B. Cher, and D. Hoffman, *ibid.*, 593 (1976); C. J. Michejda, S. Koepke, and J. Mahaffy, *ibid.*, 2573 (1976); L. N. Ferguson, *Chem. Soc. Rev.*, **4**, 289 (1975).
(4) J. I. G. Cadogan and J. B. Thomson, *Chem. Commun.*, 770 (1969).
(5) A. Tanaka and J.-P. Anselme, *Tetrahedron Lett.*, 3567 (1971).
(6) K. Nishiyama and J.-P. Anselme, *J. Org. Chem.*, **42**, 2636 (1977).
(7) V. E. Gunn and J.-P. Anselme, *J. Org. Chem.*, **42**, 754 (1977).
(8) S. Hünig, *Rev. Roum. Chim.*, **3**, 935 (1962); A. Schmidpeter, *Tetrahedron Lett.*, 1421 (1963); S. Hünig, L. Geldern, and E. Lücke, *Angew. Chem., Int. Ed. Engl.*, **2**, 327 (1963); K. Hafner and K. Wagner, *ibid.*, **2**, 740 (1963); S. Hünig, G. Büttner, J. Cramer, L. Geldern, H. Hansen, and E. Lücke, *Chem. Ber.*, **102**, 2093 (1969).
(9) D. J. Pasto and J. P. Sevenair, *J. Am. Chem. Soc.*, **93**, 711 (1971); J. P. Begne, M. Charpentier-Morize, and C. Pardo, *Tetrahedron. Lett.*, 4737 (1971); D. Baudry and M. Charpentier-Morize, *ibid.*, 3013 (1973). We are using **4** for the sake of brefity and simplicity since, as is discussed later, it is likely that $ArCOCH_2Br{\cdot}AgSbF_6$ complexes (**9**) are the reactive species in our reactions.
(10) G. Koga and J.-P. Anselme, *J. Org. Chem.*, **35**, 960 (1970).
(11) T. Eicher, S. Hünig, and H. Hansen, *Chem. Ber.*, **102**, 2889 (1969).
(12) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).
(13) M. Kobayashi, H. Minato, E. Yamada, and N. Kobori, *Bull. Chem. Soc. Jpn.*, **43**, 215 (1970); M. Kobayashi, H. Minato, and N. Kobori, *ibid.*, **43**, 225 (1970).
(14) R. C. Fuson, H. H. Weinstock, and G. E. Ullyot, *J. Am. Chem. Soc.*, **57**, 1803 (1935); R. T. Arnold and R. C. Fuson, *ibid.*, **58**, 1295 (1936); W. S. Ide and J. S. Buck, *Org. React.*, **4**, 286 (1948).
(15) C. G. Overberger, B. S. Marks, L. Palmer, and N. Byrd, *J. Am. Chem. Soc.*, **77**, 4100 (1955).
(16) M. Busch and B. Weiss, *Ber.*, **33**, 2703 (1900).
(17) "Organic Syntheses", Collect. Vol. 1, Wiley, New York, N.Y., 1932, p 480.
(18) J. A. Riddick and W. B. Bunger, "Weissberger's Techniques of Chemistry", 3rd ed, Wiley-Interscience, New York, N.Y., 1970, p 606.
(19) T. van Es and O. G. Bacherberg, *J. Chem. Soc.*, 1371 (1963).
(20) A. J. Fatiadi, *Synthesis*, 65 (1970).
(21) Anhydrous ether was shaken with water and used after separation.
(22) T. Tsuji, *Tetrahedron Lett.*, 2413 (1966).
(23) O. Fischer and F. Romer, *Ber.*, **41**, 2350 (1908).
(24) "Heilbron's Dictionary of Organic Compounds", 4th ed. Oxford University Press, New York, N.Y., 1965.

Nitro Displacement by Methanethiol Anion. Synthesis of Bis-, Tris-, Pentakis-, and Hexakis(methylthio)benzenes

James R. Beck* and Joseph A. Yahner

Lilly Research Laboratories, Division of Eli Lilly & Company, Greenfield, Indiana 46140

Received October 4, 1977

Bis- and tris(methylthio)benzenes have been synthesized by a facile process involving nitro displacement. Also prepared were pentakis- and hexakis(methylthio)benzene. The thioethers were readily oxidized to the corresponding sulfones in high yield.

Nucleophilic displacement of nitro groups either ortho of para to an electron pair stabilizing function is well documented. Our previous reports[1] have demonstrated the synthetic utility of nitro displacement ortho to cyano, carboxylic acid ester, and aldehyde functions by a variety of nucleophiles. Other workers[2] have reported nitro displacement involving activation by sulfone, carboxamide, ketone, and phenyl substituents, in addition to the three functions above. Reports also include displacements starting with 3-nitrophthalic anhydride[3] and *N*-substituted 3-nitrophthalimides.[4]

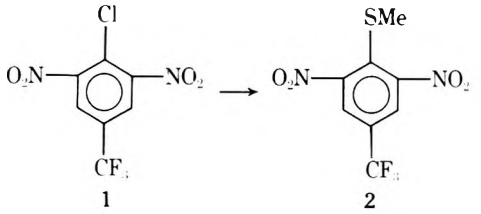
No examples were found for which the stabilization could be attributed to a thioether function. In fact, Miller[5] reported that *p*-methylthio showed only weak activation (similar to the heavier halogens) in rate studies involving methoxide displacement of chlorine activated by an *o*-nitro group. Also, Bordwell and Boutan[6] predicted only slight electron pair stabilization for an aromatic methylthio substituent based on acidity constants and spectral measurements. In contrast to these reports, we wish to describe several examples of facile nitro displacement by methanethiol anion where the activa-

0022-3263/78/1943-2048$01.00/0

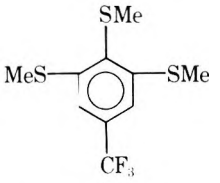
tion is due to an ortho (and in one case a para) methylthio function.

Results

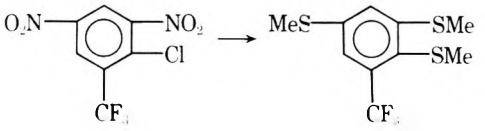
Treatment of 4-chloro-3,5-dinitrobenzotrifluoride (**1**)[7] with methanethiol anion in aqueous alcohol gave the expected



1 **2**

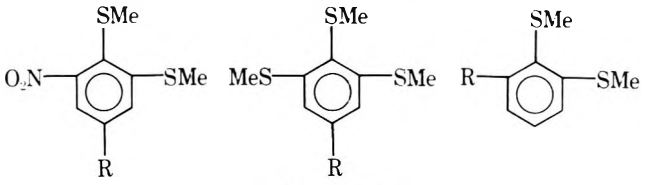


3



4 **5**

thioether **2** (67% yield). When **2** was allowed to react with excess methanethiol anion (lithium salt) in cold DMF (ice bath) for 1 h, the product obtained was 3,4,5-tris(methylthio)benzotrifluoride (**3**, 95%). Similar treatment of **1** yielded **3** directly (74%). The same reaction with 2-chloro-3,5-dinitrobenzotrifluoride (**4**)[8] gave 2,3,5-tris(methylthio)benzotrifluoride (**5**, 70%). The bis thioether **6a** (61%) could be obtained



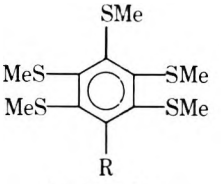
6a, R = CF_3
b, R = H
c, R = Me

7a, R = H
b, R = Me

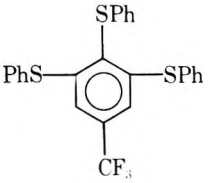
8a, R = Cl
b, R = OMe

from **1** by lowering the reaction temperature to −20 °C, although some **3** was also present in the crude product. When 1-chloro-2,6-dinitrobenzene was subjected to the reaction conditions, the bis(thioether) **6b** was obtained cleanly in 79% yield after only 15 min at ice bath temperature. When the reaction was allowed to continued for 4.5 h at room temperature, the tris(thioether) **7a** (75%) was the isolated product. Similarly, from 4-chloro-3,5-dinitrotoluene[9] was obtained **6c** (78%) and **7b** (60%).

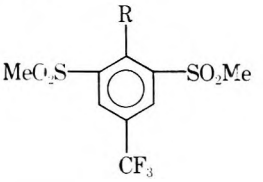
Treatment of 2,3-dichloro-1-nitrobenzene under the usual reaction conditions yielded 1-chloro-2,3-bis(methylthio)-benzene (**8a**, 73%). Similarly, 2-chloro-3-nitroanisole[10] gave 2,3-bis(methylthio)anisole (**8b**, 55%), although the reaction rate was slower (30 h at room temperature). When 1,3,5-trichloro-2,4-dinitrobenzene[11] was utilized as starting material, the product obtained was pentakis(methylthio)benzene (**9a**, 63%). Similar treatment of 1,3,4,5-tetrachloro-2,6-dinitrobenzene[12] yielded hexakis(methylthio)benzene (**9b**, 71%). The same compound was obtained likewise from 1,2,3,4-tetrachloro-5,6-dinitrobenzene[13] (57%), pentachloronitrobenzene (76%), and hexachlorobenzene (75%). The latter result is in contrast to the findings of Kulka,[14] who reported 1,4-bis and 1,2,4,5-tetrakis substitution in the reaction of hexachlorobenzene and ethanethiol anion.



9a, R = H
b, R = SMe



10

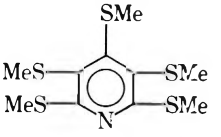


20a, R = OH
b, R = $NHCH_2CH_2NH_2$
c, R = $NHCH(CH_2CH_3)_2$

Displacement products were not obtained with a number of substrates. Although no attempts were made to isolate the desired product in these cases, TLC showed at least five major components, whereas the successful reactions described were essentially one component by TLC. For instance, both *o*- and *p*-chloronitrobenzene underwent chloride displacement at ice bath temperature, but complex mixtures were obtained when the reaction was brought to room temperature, apparently because of competing reactions involving reduction of the nitro group. Similar results were encountered with 2,4-dichloro-1-nitrobenzene, 2,4-dinitro-1-chlorobenzene, 2-chloro-3-nitrotoluene, and 2-chloro-5-nitrobenzotrifluoride. Picryl chloride, even at −60 °C, gave a complex mixture. In the case of compounds **3**, **5**, and **6a** through **8b**, the displaced nitro group (1 position) was always ortho (2 position) to a methylthio function and meta (3 position) to a substituent (nitro, trifluoromethyl, methylthio, chloro, or methoxyl) capable of withdrawing electrons by induction. All cases not meeting this criterion have given complex mixtures, except for the para displacement with compound **5**.

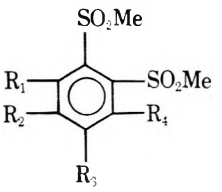
Treatment of **1** with benzenethiol anion at room temperature for 24 h gave 3,4,5-tris(phenylthio)benzotrifluoride (**10**, 50%). The longer reaction time and lower yield is probably due to steric hindrance. Other phenyl thioethers were not investigated. Most of the thioethers were readily oxidized to the corresponding sulfones by treatment with hydrogen peroxide in acetic acid. The yields were in the range of 80–95% and the products are summarized in Table I. Several nucleophilic displacements were examined utilizing the tris sulfonyl derivative **11**. Treatment with dipropylamine in hot Me_2SO produced the phenol **20a** (49%), apparently formed by reaction with water in the solvent. Condensation with the primary amines, ethylenediamine, and 3-aminopentane in alcohol gave the bis(sulfonyl)anilines **20b** (86%) and **20c** (90%), respectively. The NMR spectra of the latter three derivatives all showed singlet methylsulfonyl and aromatic proton signals, thus verifying the assigned symmetrical structures.

The scope of the nitro displacement reaction in heterocyclic systems was investigated for pyridine. Reaction of pentachloropyridine with methanethiol anion at room temperature for 48 h yielded pentakis(methylthio)pyridine (**21**) but only in 10% yield.



21

Table I. Synthesis of Methylsulfonylbenzenes



Compd[a]	Registry no.	Reactant	R_1	R_2	R_3	R_4	Mp, °C	Yield, %
11	65516-86-1	3	SO_2Me	H	CF_3	H	258–260	95
12	65516-87-2	5	CF_3	H	SO_2Me	H	279–281[b]	80
13	65516-88-3	6b	NO_2	H	H	H	237–239	90
14	65516-89-4	6c	NO_2	H	Me	H	256–258	93
15	65516-90-7	7a	SO_2Me	H	H	H	243–245	81
16	65516-91-8	8a	Cl	H	H	H	188–189	85
17	65516-92-9	8b	OMe	H	H	H	199–201	85
18	65516-84-9	9a	SO_2Me	SO_2Me	SO_2Me	H	>300	97
19	65516-25-8	9b	SO_2Me	SO_2Me	SO_2Me	SO_2Me	>300[c]	81

[a] Satisfactory analytical data (±0.4% for C, H, N, or S) were reported for all new compounds listed in the table. [b] Recrystallized from DMF–water. [c] Product triturated with hot DMF.

Discussion

From our observations it appears that the nitro displacement reactions described above occur by means of the classical addition–elimination mechanism of nucleophilic aromatic substitution.[15] The high yields and absence of side reactions, other than those leading to nitro group reduction, support this mechanism, although an alternate route involving radical anion intermediates cannot be ruled out. The reactions appeared to go equally well in the presence or absence of oxygen, but the slower reactions were carried out under nitrogen in order to prevent oxidation of the thiol.

The relative ease of nucleophilic displacement of the aromatic nitro group has been verified by numerous kinetic studies.[16] Also to be taken into consideration is the unusual nucleofuge–nucleophile relationship involving the nitro group and thiol anions. Bartoli and Todesco[17] recently examined the kinetics of the reaction of 1-X-2,4-dinitrobenzenes and benzenethiol anion in methanol at 25 °C. The relative rate of nitro displacement was 2000-times that of chlorine and 50-times that of fluorine. These differences were much larger than those found with other nucleophiles in the earlier kinetic studies. A similar observation was noted by Bunnett and Merritt,[18] who studied the kinetics of the same reaction at 0 °C and reported that nitro displacement was too fast for measurement, although rate constants were readily obtained for both chlorine and fluorine displacement. These authors concluded that the nitro group appears "to have an unusually high replaceability when the reagent is thiophenoxide ion". In our examples this unusual nucleofuge–nucleophile relationship apparently plays a major role, but it is probably not the complete explanation. For example, in the synthesis of compounds **7a–8b**, the only obvious activation of the nitro group must be attributed to an o-methylmercapto function. The requirement for a second electronegative substituent ortho to the methylmercapto group cannot be explained at this time, although effects on the reduction potential of the nitro group should be considered.

Our main interest in the reaction concerns the ease with which a seemingly unactivated nitro group can be converted to a thioether function and applications of the reaction to synthesis. Further examples of this utility are the subject of the following paper.

Experimental Section

All starting materials are commercially available except where literature references are given. Unless otherwise noted, cold solution refers to ice bath conditions. Lithium hydroxide was ground to a fine powder in order to facilitate solution. Addition of the lithium hydroxide was exothermic; in all cases the temperature was not allowed to exceed 15 °C during the addition. Excess reagent was utilized in all cases where molar equivalent is omitted. Alcohol refers to 95% ethanol. NMR spectral data are partial and only signals pertinent to the structural assignment are given. Melting points were determined on a Mel-Temp apparatus and are uncorrected.

α,α,α-Trifluoro-3,4,5-tris(methylthio)toluene (3). To a cold solution (under nitrogen) containing 5.4 g of 4-chloro-3,5-dinitrobenzotrifluoride[7] (20 mmol) and 7 mL of methanethiol in 100 mL of DMF was added portionwise 5 g of lithium hydroxide. The mixture was stirred in the cold for 0.5 h and poured into ice water. The solid was collected and crystallized from alcohol to yield 4.2 g (74%) of product: mp 140–141 °C; NMR ($CDCl_3$) δ 2.33 (s, 3 H), 2.43 (s, 6 H), and 6.99 (s, 2 H). Anal. Calcd for $C_{10}H_{11}F_3S_3$: C, 42.23; H, 3.90; S, 33.82. Found: C, 42.42; H, 4.05; S, 34.10.

α,α,α-Trifluoro-4-(methylthio)-3,5-dinitrotoluene (2). To a cold solution of 5.4 g of 4-chloro-3,5-dinitrobenzotrifluoride[7] (20 mmol) and 2 mL of methanethiol in 75 mL of alcohol was added dropwise a solution of 1.2 g of potassium hydroxide in 15 mL of water. The mixture was stirred in the cold for 1 h and poured into ice water. The solid was collected and crystallized from alcohol to yield 3.8 g (67%) of product, mp 93–96 °C. Anal. Calcd for $C_8H_5F_3N_2O_4S$: C, 34.05; H, 1.79; N, 9.93; S, 11.36. Found: C, 34.20; H, 1.88; N, 9.82; S, 11.37.

Lithium hydroxide (8 g) was added portionwise to a cold mixture containing 11.3 g of **2** (40.1 mmol) and 15 mL of methanethiol in 150 mL of DMF. The solution was stirred in the cold for 1 h and poured into ice water. Crystallization from alcohol yielded 10.8 g (95%) of **3**, mp 140–141 °C.

α,α,α-Trifluoro-2,3,5-tris(methylthio)toluene (5). To a cold solution containing 5.4 g of 2-chloro-3,5-dinitrobenzotrifluoride[8] (20 mmol) and 7 mL of methanethiol in 100 mL of DMF was added portionwise 5 g of lithium hydroxide. The mixture was stirred in the cold for 2 h and at room temperature for 2 h. It was poured into ice water and the crude solid was collected and crystallized from alcohol to yield 4.1 g (70%) of product: mp 61–62 °C; NMR ($CDCl_3$) δ 2.33 (s, 3 H), 2.45 (s, 3 H), 2.52 (s, 3 H), 7.13 (d, 1 H), and 7.32 (d, 1 H). Anal. Calcd for $C_{10}H_{11}F_3S_3$: C, 42.23; H, 3.90; S, 33.82. Found: C, 42.48; H, 3.67; S, 33.90.

α,α,α-Trifluoro-3,4-bis(methylthio)-5-nitrotoluene (6a). A solution (under nitrogen) containing 8.4 g of 4-chloro-3,5-dinitrobenzotrifluoride[7] (31 mmol) and 4 mL of methanethiol in 125 mL of DMF was cooled to −20 °C (dry ice–alcohol). Lithium hydroxide (2 g) was added portionwise at a rate to keep the temperature below −10 °C. The mixture was stirred for 1 h while it slowly warmed to 0 °C and then the mixture was poured into ice water. The solid was collected and crystallized from alcohol to yield 5.3 g (61%) of product: mp 85–87 °C; NMR ($CDCl_3$) δ 2.48 (s, 3 H), 2.58 (s, 3 H), 7.48 (d, 1 H), and 7.60 (d, 1 H). Anal. Calcd for $C_9H_8F_3NO_2S_2$: C, 38.16; H, 2.85; N, 4.94; S, 22.64. Found: C, 38.40; H, 2.76; N, 5.07; S, 22.73.

General Procedure for Preparation of 6b and 6c. Lithium hydroxide (15 g) was added portionwise to a cold solution containing 60

mmol of the appropriate 1-chloro-2,6-dinitrobenzene and 20 mL of methanethiol in 100 mL of DMF. The mixture was stirred in the cold for 15 min and poured into ice water. The following were obtained after collection and crystallization from alcohol: **6b** (79%; mp 102–103 °C) and **6c** (78%; mp 109–110 °C). Anal. Calcd for $C_8H_9NO_2S_2$ (**6b**): C, 44.63; H, 4.21; N, 6.50; S, 29.79. Found: C, 44.77; H, 4.11; N, 6.47; S, 29.42. Calcd for $C_9H_{11}NO_2S_2$ (**6c**): C, 47.14; H, 4.84; N, 6.11; S, 27.96. Found: C, 47.43; H, 4.63; N, 6.13; S, 28.22.

General Procedure for Preparation of 7a and 7b. To a cold solution (under nitrogen) containing 20 mmol of the appropriate 1-chloro-2,6-dinitrobenzene and 10 mL of methanethiol in 80 mL of DMF was added portionwise 5 g of lithium hydroxide. The mixture was stirred in the cold for 15 min and at room temperature for 4.5 h for **7a** and 20 h for **7b**. It was then poured into ice water, and the solid was collected and crystallized from alcohol. The following were obtained: **7a** (75%; mp 111–113 °C; NMR ($CDCl_3$) δ 2.32 (s, 3 H) and 2.39 (s, 6 H)) and **7b** (60%; 156–158 °C). Anal. Calcd for $C_9H_{12}S_3$ (**7a**): C, 49.96; H, 5.59; S, 44.45. Found: C, 50.20; H, 5.37; S, 44.30. Calcd for $C_{10}H_{14}S_3$ (**7b**): C, 52.13; H, 6.12; S, 41.75. Found: C, 52.37; H, 6.22; S, 41.79.

1-Chloro-2,3-bis(methylthio)benzene (8a). To a cold mixture (under nitrogen) of 7.7 g of 2,3-dichloro-1-nitrobenzene (40.1 mmol) and 10 mL of methanethiol in 80 mL of DMF was added portionwise 5 g of lithium hydroxide. The mixture was stirred in the cold for 15 min and at room temperature for 30 min and poured into ice water. The solid was collected and crystallized from alcohol to yield 4.5 g of product, mp 71–72 °C. Concentration of the mother liquor yielded an additional 1.5 g of product: mp 71–72 °C; NMR ($CDCl_3$) δ 2.35 (s, 3 H) and 2.38 (s, 3 H). Anal. Calcd for $C_8H_9ClS_2$: C, 46.93; H, 4.43; Cl, 17.32; S, 31.32. Found: C, 47.11; H, 4.46; Cl, 17.52; S, 31.37.

1-Methoxy-2,3-bis(methylthio)benzene (8b). Lithium hydroxide (5 g) was added portionwise to a cold solution (under nitrogen) containing 3.7 g of 2-chloro-3-nitroanisole[10] (19.7 mmol) and 10 mL of methanethiol in 75 mL of DMF. The mixture was stirred in the cold for 15 min and at room temperature for 36 h. The mixture was then poured into ice water and the solid was collected and crystallized from alcohol–water to yield 2.2 g (55%) of product: mp 102–103 °C; NMR ($CDCl_3$) δ 2.33 (s, 3 H), 2.38 (s, 3 H), and 3.87 (s, 3 H). Anal. Calcd for $C_9H_{12}OS_2$: C, 54.00; H, 6.00; S, 32.00. Found: C, 53.82; H, 5.89; S, 31.70.

Pentakis(methylthio)benzene (9a). Lithium hydroxide (5 g) was added portionwise to a cold solution (under nitrogen) of 5.4 g of 2,4,6-trichloro-1,3-dinitrobenzene[11] (19.9 mmol) and 15 mL of methanethiol in 100 mL of DMF. The mixture was stirred in the cold for 1 h and at room temperature for 44 h. The mixture was then poured into ice water and the solid was collected and crystallized from alcohol to yield 3.9 g (63%) fo product: mp 103–105 °C; NMR ($CDCl_3$) δ 2.38 (s, 6 H), 2.44 (s, 6 H), and 2.53 (s, 3 H). Anal. Calcd for $C_{11}H_{16}S_5$: C, 42.82; H, 5.23; S, 51.96. Found: C, 43.07; H, 4.94; S, 52.26.

Hexakis(methylthio)benzene (9b). To a cold solution (under nitrogen) containing 1.7 g of 2,4,5,6-tetrachloro-1,3-dinitrobenzene[12] (5.6 mmol) and 10 mL of methanethiol in 75 mL of DMF was added portionwise 5 g of lithium hydroxide. The mixture was stirred in the cold for 30 min and at room temperature for 2 h. The mixture was then poured into ice water and the solid was collected and crystallized from alcohol to yield 1.4 g (71%) of product: mp 88–90 °C; NMR ($CDCl_3$) δ 2.52 (s). Anal. Calcd for $C_{12}H_{18}S_6$: C, 40.64; H, 5.12; S, 54.24. Found: C, 40.87; H, 5.27; S, 54.41.

Using the procedure above, 2.6 g of 3,4,5,6-tetrachloro-1,2-dinitrobenzene,[13] 15 mL of methanethiol, and 5 g of lithium hydroxide in 75 mL of DMF stirred in the cold for 30 min and at room temperature for 5 h yielded 1.7 g (57%) of **9b**; 5.9 g of pentachloronitrobenzene, 15 mL of methanethiol, and 5 g of lithium hydroxide in 75 mL of DMF stirred in the cold for 30 min and at room temperature for 5 h yielded 5.4 g (76%) of **9b**; 5.7 g of hexachlorobenzene, 15 mL of methanethiol, and 5 g of lithium hydroxide in 75 mL of DMF stirred in the cold for 1 h and at room temperature for 20 h yielded 5.3 g (75%) of **9b**.

α,α,α,-Trifluoro-3,4,5-tris(phenylthio)toluene (10). To a solution (under nitrogen) containing 4.2 g of 4-chloro-3,5-dinitrobenzotrifluoride[7] (15 mmol) and 5.5 g of thiophenol (50 mmol) in 75 mL of DMF was added portionwise 5 g of lithium hydroxide. The mixture was stirred for 24 h and poured into ice water. The solution was extracted three times with ether and the combined extracts were washed with water. Evaporation of the solvent and crystallization from ether–hexane yielded 3.5 g (50%) of product, mp 72–74 °C. Anal. Calcd for $C_{25}H_{17}F_3S_3$: C, 63.81; H, 3.64; S, 20.44. Found: C, 63.52; H, 3.53; S, 20.64.

General Procedure for Preparation of Methylsulfonylbenzenes (11–19). A solution of the appropriate thioether (Table I) in 1 vol of 30% hydrogen peroxide and 2–3 vol of acetic acid was heated in an open flask at steam-bath temperature for the time shown. In most cases, the product crystallized and was collected and washed with cold alcohol. Otherwise, the mixture was diluted with water until the product crystallized. The following were obtained (reactant, mmol; mL of hydrogen peroxide;[19] reaction time): **11** (**3**, 21.1; 50/10; 2 h); **12** (**5**, 10.6; 25; 3 h); **13** (**6b**, 27.9; 40/20; 2 h); **14** (**6c**, 34.5; 50/25; 2 h); **15** (**7a**, 11.6; 15; 16 h); **16** (**8a**, 12.2; 15/7.5; 2 h); **17** (**8b**, 8.5; 15; 16 h); **18** (**9a**, 3.2; 25; 2 h); **19** (**9b**, 7.0; 20/20; 150 h). Yields and melting points are given in Table I.

α,α,α-Trifluoro-2,6-bis(methylsulfonyl)-*p*-cresol (20a). A solution of 3.8 g of **11** (10 mmol) and 10 mL of dipropylamine in 75 mL of Me_2SO was heated at 80 °C for 2 h. The solution was poured into ice water and then acidified with hydrochloric acid. The solid was collected to yield 1.4 g (49%): mp 226–228 °C; NMR (Me_2SO-d_6) δ 3.37 (s, 6 H) and 8.10 (s, 2 H). Anal. Calcd for $C_9H_9F_3O_5S_2$: C, 33.96; H, 2.85; S, 20.15. Found: C, 34.19; H, 2.84; S, 19.89.

***N*-[α,α,α-Trifluoro-2,6-bis(methylsulfonyl)-*p*-tolyl]ethylenediamine (20b).** A solution containing 3.8 g of **11** (10 mmol) and 10 mL of ethylenediamine in 10 mL of alcohol was stirred for 16 h. The mixture was cooled and the product was collected to yield 3.1 g (86%): mp 188–190 °C; NMR (Me_2SO-d_6) δ 3.38 (s, 6 H) and 8.64 (s, 2 H). Anal. Calcd for $C_{11}H_{15}F_3N_2O_4S_2$: C, 36.66; H, 4.20; N, 7.77; S, 17.79. Found: C, 36.95; H, 4.10; N, 7.79; S, 17.92.

***N*-(1-Ethylpropyl)-α,α,α-trifluoro-2,6-bis(methylsulfonyl)-*p*-toluidine (20c).** A mixture of 1.6 g of **11** (4.2 mmol) and 7 mL of 3-aminopentane in 75 mL of alcohol was heated to reflux for 48 h. The product crystallized from the cooled solution to yield 1.4 g (90%): mp 132–134 °C; NMR ($CDCl_3$) δ 3.12 (s, 6 H) and 8.35 (s, 2 H). Anal. Calcd for $C_{14}H_{20}F_3NO_4S_2$: C, 43.40; H, 5.20; N, 3.62; S, 16.55. Found: C, 43.61; H, 5.30; N, 3.89; S, 16.62.

Pentakis(methylthio)pyridine (21). To a cold solution containing 7.5 g of pentachloropyridine (30 mmol) and 20 mL of methanethiol in 75 mL of DMF was added portionwise 7 g of lithium hydroxide. The mixture was stirred in the cold for 1 h and at room temperature for 48 h. It was poured into ice water and the solid was collected and crystallized from alcohol to yield 0.9 g (10%) of product, mp 78–80 °C. Anal. Calcd for $C_{10}H_{15}NS_5$: C, 38.80; H, 4.88; N, 4.52; S, 51.79. Found: C, 38.57; H, 4.65; N, 4.56; S, 51.59.

Acknowledgment. The authors thank Mr. Paul Unger and associates for spectral measurements and Mr. George Maciak and associates for microanalytical data.

Registry No.—**1**, 393-75-9; **2**, 65516-76-9; **3**, 65516-85-0; **4**, 392-95-0; **5**, 65516-77-0; **6a**, 65516-78-1; **6b**, 65516-79-2; **6c**, 65516-80-5; **7a**, 65516-81-6; **7b**, 65516-82-7; **8a**, 65516-83-8; **8b**, 65516-73-6; **9a**, 65516-74-7; **9b**, 58468-22-7; **10**, 65516-68-9 **20a**, 65516-69-0; **20b**, 65516-70-3; **20c**, 65516-71-4; **21**, 65516-72-5; methanethiol anion, 17302-63-5; 1-chloro-2,6-dintrobenzene, 606-21-3; 4-chloro-3,5-dinitrotoluene, 5264-65-3; 2,3-dichloro-1-nitrobenzene, 3209-22-1; 2-chloro-3-nitroanisole, 3970-39-6; 2,4,5,6-tetrachloro-1,3-dinitrobenzene, 28073-03-2; 3,4,5,6-tetrachloro-1,2-dinitrobenzene, 781-15-7; pentachloronitrobenzene, 82-68-8; hexachlorobenzene, 118-74-1; ethylenediamine, 107-15-3; 3-aminopentane, 616-24-0; pentachloropyridine, 2176-62-7; 2,4,6-trichloro-1,3-dinitrobenzene, 6284-83-9.

References and Notes

(1) J. R. Beck, *J. Org. Chem.*, **37**, 3224 (1972); **38**, 4086 (1973); J. R. Beck and R. G. Suhr, *J. Heterocycl. Chem.*, **11**, 227 (1974); J. R. Beck, R. L. Sobczak, R. G. Suhr, and J. A. Yahner, *J. Org. Chem.*, **39**, 1839 (1974); J. R. Beck and J. A. Yahner, *ibid.*, **39**, 3440 (1974).
(2) C. W. N. Holmes and J. D. Loudon, *J. Chem. Soc.*, 1521 (1940); J. H. Gorvin, *Chem. Ind.*, 1525 (1967); J. H. Gorvin, *Chem. Commun.*, 1120 (1971); R. D. Knudsen and H. R. Snyder, *J. Org. Chem.*, **39**, 3343 (1974); J. B. Baumann, *Synthesis*, 782 (1975); N. Kornblum, L. Cheng, R. C. Kerber, M. M. Kestner, B. N. Newton, H. W. Pinnick, R. G. Smith, and P. A. Wade, *J. Org. Chem.*, **41**, 1560 (1976).
(3) S. Marburg and P. A. Grieco, *Tetrahedron Lett.*, 1305 (1966).
(4) L. R. Caswell and T. L. Kao, *J. Heterocycl. Chem.*, **3**, 333 (1966).
(5) J. Miller, "Aromatic Nucleophilic Substitution", Elsevier, New York, N.Y., 1968, p 87.
(6) F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **78**, 854 (1956).
(7) L. M. Yagupol'skii and V. S. Mospan, *Ukr. Khim. Zh.*, **21**, 81 (1955); *Chem. Abstr.*, **49**, 8866 (1955).
(8) M. E. Friedrich and L. E. Schniepp, U.S. Patent 2 257 093.
(9) W. Meckel and J. Blahak, German Offen., 2 001 570.
(10) F. W. Schlieper, *Ber.*, **26**, 2465 (1893).
(11) H. J. Backer and S. van der Baan, *Recl. Trav. Chim. Pays-Bas*, **56**, 1175 (1937).
(12) C. L. Jackson and H. A. Carlton, *Ber.*, **35**, 3855 (1902).
(13) V. S. F. Berckmans and A. F. Holleman, *Recl. Trav. Chim. Pays-Bas*, **44**, 85 (1925).
(14) M. Kulka, *J. Org. Chem.*, **24**, 235 (1959). Similar results were reported with

hexafluorobenzene and benzenethiol anion: P. Robson, T. A. Smith, R. Stephens, and J. C. Tatlow, J. Chem. Soc., 3692 (1963). See also: K. R. Langille and M. E. Peach, J. Fluorine Chem., 1, 407 (1971).
(15) J. F. Bunnett, Q. Rev., Chem. Soc., 12, 1 (1958).
(16) J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, J. Am. Chem. Soc., 79, 385 (1957); B. A. Bolto and J. Miller, Aust. J. Chem., 9, 74 (1956); R. E. Parker and T. O. Read, J. Chem. Soc., 3149 (1962).
(17) G. Bartoli and P. E. Todesco, Acc. Chem. Res., 10, 125 (1977).
(18) J. F. Bunnett and W. D. Merritt, J. Am. Chem. Soc., 79, 5967 (1957).
(19) Second number indicates volume of hydrogen peroxide added 1 h later.

Nitro Displacement by Methanethiol Anion. Synthesis of Bis-, Tris-, Tetrakis-, and Pentakis(methylthio)benzoic Acids and Related Derivatives

James R. Beck* and Joseph A. Yahner

Lilly Research Laboratories, Division of Eli Lilly & Company, Greenfield, Indiana 46140

Received October 4, 1977

3,4,5-Tris(methylthio)benzamide has been synthesized by a process involving nitro displacement with methanethiol anion. Similarly prepared were various bis-, tris-, and tetrakis(methylthio)benzoic acids and their *S*-methyl thioesters. Several of the thioethers were oxidized to the corresponding sulfones. Also prepared were 3,4,5-tris(methylthio)benzenesulfonamide, 3,4,5-tris(methylthio)phenylacetamide, and pentakis(methylthio)benzamide.

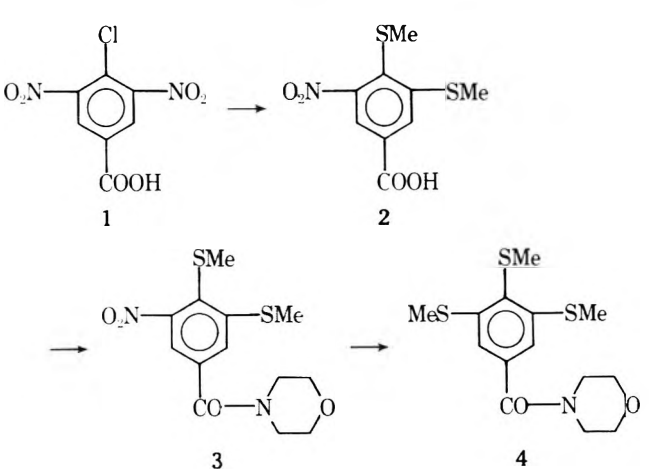
In a previous paper[1] we discussed the nucleophilic displacement of nitro groups, which were activated by *o*- or *p*-methylthio functions, with methanethiol anion. The objective of this work is to demonstrate the utility of this facile reaction for the preparation of bis-, tris-, tetrakis-, and pentakis(methylthio)benzoic acids (and their derivatives) and related benzenesulfonamides and phenylacetamides.

Results

Three general procedures were used for the synthesis of the benzoic acids. The first (Scheme I) involved treatment of 4-chloro-3,5-dinitrobenzoic acid (**1**) with excess methanethiol anion (lithium salt) in cold DMF for 0.5 h to yield 3,4-bis(methylthio)-5-nitrobenzoic acid (**2**, 80%). Attempted displacement of the second nitro group at elevated temperature and longer reaction time was unsuccessful. The benzoic acid **2** was converted to its morpholine amide **3** (81%), which readily underwent nitro displacement to give the tris(thioether) **4** (90%).

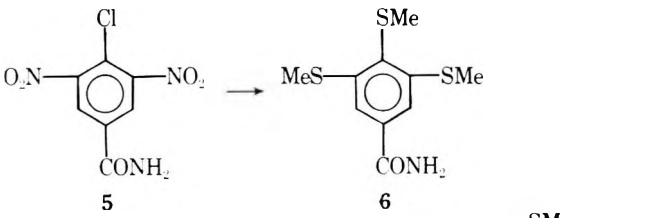
The second approach is illustrated in Scheme II. When 4-chloro-3,5-dinitrobenzamide (**5**) was allowed to react with excess methanethiol anion in DMF at room temperature for 1.5 h, 3,4,5-tris(methylthio)benzamide (**6**, 76%) was formed. This compound was hydrolyzed to yield 3,4,5-tris(methylthio)benzoic acid (**7**, 76%).

Scheme I

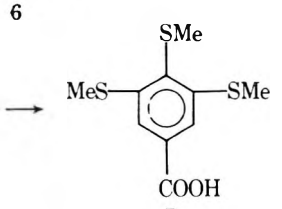


1 2 3 4

Scheme II

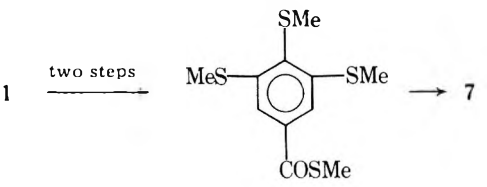


5 6



7

Scheme III



8

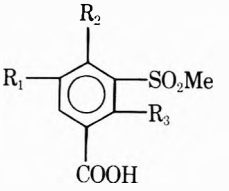
The third procedure is shown in Scheme III. The benzoic acid **1** was first treated with a molar equivalent of 1,1′-carbonyldiimidazole in DMF at room temperature. The reaction mixture was then cooled and the intermediate was allowed to react with excess methanethiol anion. The isolated product was identified as the tris(methylthio) thioester **8** (71%). Hydrolysis of the ester yielded **7** (75%).

When the third procedure was utilized, the following thioesters were synthesized: **9a** (64% from 2-chloro-3-nitrobenzoic acid), **9b** (64% from 2-chloro-3,5-dinitrobenzoic acid), and **9c** (56% from 2,4-dichloro-3,5-dinitrobenzoic acid). Hydrolysis of these thioesters yielded the benzoic acids **10a** (87%), **10b** (93%), and **10c** (93%), respectively. Treatment of pentachlorobenzamide under the usual reaction conditions (Scheme II) for 27 h at room temperature yielded pentakis(methylthio)benzamide (**11**, 41%).

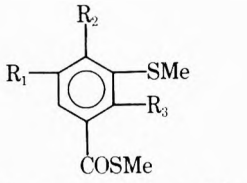
The thioethers were readily oxidized to the corresponding sulfones with hydrogen peroxide in acetic acid and these de-

0022-3263/78/1943-2052$01.00/0

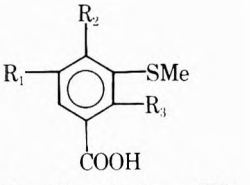
Table I. Synthesis of Methylsulfonylbenzoic Acids



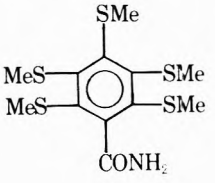
Compd	Reactant	R_1	R_2	R_3	Mp, °C	Yield, %
12a	**7**	SO_2Me	SO_2Me	H	287–293 dec	76
12b	**2**	NO_2	SO_2Me	H	270–280 dec	77
12c	**10a**	H	H	SO_2Me	225–227	26
12d	**10b**	SO_2Me	H	SO_2Me	274–277 dec	95
12e	**10c**	SO_2Me	SO_2Me	SO_2Me	247–250 dec	79



9a, $R_1 = R_2 = H$; $R_3 = SMe$
b, $R_2 = H$; $R_1 = R_3 = SMe$
c, $R_1 = R_2 = R_3 = SMe$

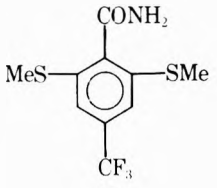


10a, $R_1 = R_2 = H$; $R_3 = SMe$
b, $R_2 = H$; $R_1 = R_3 = SMe$
c, $R_1 = R_2 = R_3 = SMe$

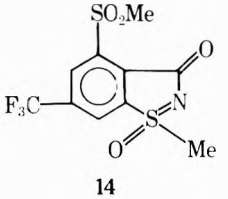


11

rivatives are summarized in Table I. Oxidation of **11** was accompanied by oxidative deamination followed by decarboxylation, and the product obtained was pentakis(methylsulfonyl)benzene (48%).[1] Oxidation of the bis(methylthio) derivative **13**, which was obtained from α,α,α-trifluoro-2,6-



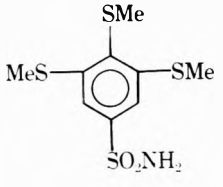
13



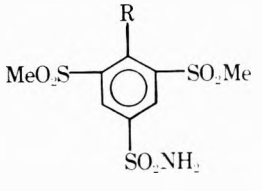
14

dinitro-*p*-toluamide by displacement with methanethiol anion in 80% yield, unexpectedly gave the 1,2-benzisothiazole-3-one 1-oxide **14** (73%). The synthesis of this ring system was first described by Stoss and Satzinger[2] using the reaction of o-(alkylsulfinyl)benzoic acid esters with hydrazoic acid.

4-Chloro-3,5-dinitrobenzenesulfonamide[3] was allowed to react with excess methanethiol anion at room temperature for 2 h, and the product obtained was the tris(methylthio) derivative **15** (71%). Oxidation of **15** with hydrogen peroxide in



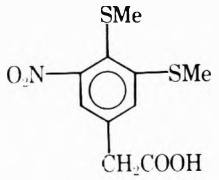
15



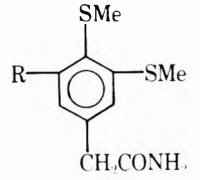
16a, R = SO_2Me
b, R = $NHCH(CH_2CH_3)_2$

acetic acid gave the tris(sulfone) **16a** (91%). Reaction of **16a** with 3-aminopentane in alcohol produced the aniline **16b** (72%). The NMR spectrum of **16b** showed a singlet aromatic proton signal and a singlet methylsulfonyl proton signal.

Still another example of the synthetic utility of the methanethiol anion displacement reaction involved treating 4-chloro-3,5-dinitrophenylacetic acid[4] under the usual reaction conditions (Scheme I). The product obtained was the bis(thioether) **17** (85%). As in the case of the related benzoic



17



18a, R = NO_2
b, R = SMe

acid derivative **2**, conditions could not be found for displacement of the second nitro group. The acid **17** was converted to its carboxamide **18a** (83%), which upon treatment with methanethiol anion gave the tris(thioether) **18b** (57%).

Discussion

The third method for the conversion of nitrobenzoic acids to the corresponding (methylthio)benzoic acid derivatives is probably the most general. It is possible that the use of an acid chloride, instead of the imidazole amide derivative, would yield the same thioester product, although this was not investigated.

The carboxylic acid or its derivative undoubtedly has a positive effect on the rate of displacement but, as was shown in the previous paper,[1] the same type of replacement reactions occurred in the presence of electron-donating substituents and the yields were similar. The same disadvantage noted in the previous examples was encountered with the benzoic acid derivatives. For example, treatment of 4-(methylthio)-3-nitrobenzamide or the corresponding morpholinamide with methanethiol anion under the usual conditions both led to the formation of complex mixtures. Thus, the requirement for an electronegative substituent in the position ortho to the methylthio function and meta to the nitro leaving group appears to be a general requirement for the displacement reaction.

With respect to the choice of the procedure to be used with a given substrate, no standard rules can be applied. For instance, treatment of the morpholinamide of 2-(methylthio)-3-nitrobenzoic acid with methanethiol anion, as in the first procedure, gave a complex mixture of products. However, the reaction of the free acid with methanethiol anion using the third procedure gave a 64% yield of the thioester **9a**.

Experimental Section

All starting materials are commercially available unless literature references are noted. Cold solution refers to ice bath conditions.

Lithium hydroxide was ground to a fine powder in order to facilitate solution. Since the addition of lithium hydroxide was exothermic, the temperature was not allowed to exceed 15 °C during the addition. Excess reagent was utilized in all cases where molar equivalent is omitted. Alcohol refers to 95% ethanol. NMR spectral data are partial and only signals pertinent to structural assignment are given. Melting points were determined on a Mel-Temp apparatus and are uncorrected.

3,4-Bis(methylthio)-5-nitrobenzoic Acid (2). To a cold solution (under nitrogen) containing 7.4 g of 4-chloro-3,5-dinitrobenzoic acid (30 mmol) and 10 mL of methanethiol in 30 mL of DMF was added portionwise 10 g of lithium hydroxide. The mixture was stirred in the cold for 0.5 h and then poured into ice water and acidified with hydrochloric acid. The solid was collected and crystallized from alcohol to yield 6.2 g (80%) of product: mp 210–212 °C; NMR (Me_2SO-d_6) δ 2.44 (s, 3 H), 2.63 (s, 3 H), 7.92 (s, 1 H), and 8.00 (s, 1 H). Anal. Calcd for $C_9H_9NO_4S_2$: C, 41.69; H, 3.50; N, 5.40; S, 24.73. Found C, 41.46; H, 3.49; N, 5.53; S, 24.74.

4-[3,4-Bis(methylthio)-5-nitrobenzoyl]morpholine (3). 1,1′-Carbonyldiimidazole (5.8 g; 35.8 mmol) was added portionwise to a solution of 7.8 g of **2** (34.1 mmol) in 25 mL of DMF. The mixture was stirred at room temperature for 15 min, and then 5 mL of morpholine was added dropwise. The solution was stirred for 15 min and then poured into ice water. The solid was collected and crystallized from alcohol to yield 9.1 g (81%) of product, mp 179–180 °C. Anal. Calcd for $C_{13}H_{16}N_2O_4S_2$: C, 47.55; H, 4.91; N, 8.53; S, 19.53. Found: C, 47.81; H, 4.92; N, 8.50; S, 19.47.

4-[3,4,5-Tris(methylthio)benzoyl]morpholine (4). To a cold solution (under nitrogen) of 4.9 g of **3** (14.9 mmol) and 5 mL of methanethiol in 75 mL of DMF was added portionwise 3 g of lithium hydroxide. The mixture was stirred in the cold for 0.5 h and at room temperature for 1 h. The mixture was poured into ice water, and the solid was collected and crystallized from alcohol to yield 4.4 g (90%) of product: mp 113–114 °C; NMR ($CDCl_3$) δ 2.31 (s, 3 H), 2.38 (s, 6 H), and 6.84 (s, 2 H). Anal. Calcd for $C_{14}H_{19}NO_2S_3$: C, 51.03; H, 5.81; N, 4.25; S, 29.19. Found: C, 51.21; H, 5.95; N, 4.35; S, 28.97.

3,4,5-Tris(methylthio)benzamide (6). Lithium hydroxide (10 g) was added portionwise to a cold solution (under nitrogen) containing 9.8 g of 4-chloro-3,5-dinitrobenzamide (40 mmol) and 20 mL of methanethiol in 150 mL of DMF. The ice bath was removed and stirring was continued for 1.5 h. The mixture was poured into ice water, and the solid was collected and crystallized from alcohol to yield 7.9 g (76%) of product: mp 221–222 °C; NMR (Me_2SO-d_6) δ 2.32 (s, 3 H), 2.50 (s, 6 H), and 7.45 (s, 2 H). Anal. Calcd for $C_{10}H_{13}NOS_3$: C, 46.30; H, 5.05; N, 5.40; S, 37.08. Found: C, 46.13; H, 5.19; N, 5.38; S, 37.25.

3,4,5-Tris(methylthio)benzoic Acid (7). Potassium hydroxide (5 g) and 7.6 g of 6 (29.3 mmol) in 100 mL of alcohol was heated to reflux for 51 h. The mixture was poured into ice water and then acidified with hydrochloric acid. The solid was collected and crystallized from DMF–water to yield 5.8 g (76%) of product: mp 246–248 °C; NMR (Me_2SO-d_6) δ 2.30 (s, 3 H), 2.46 (s, 6 H), and 7.47 (s, 2 H). Anal. Calcd for $C_{10}H_{12}O_2S_3$: C, 46.13; H, 4.65; S, 36.94. Found: C, 46.33; H, 4.58; S, 36.82.

***S*-Methyl 3,4,5-Tris(methylthio)benzenecarbothioate (8).** To a solution containing 25 g of **1** (0.1 mol) in 125 mL of DMF was added portionwise 22.7 g of 1,1′-carbonyldiimidazole (0.14 mol). The mixture was stirred for 0.5 h and then cooled in an ice bath. Methanethiol (30 mL) was added to the solution (under nitrogen), and then 15 g of lithium hydroxide was added portionwise. The mixture was stirred in the cold for 0.5 h and at room temperature for 1 h. The mixture was then poured into ice water and the resulting solid was collected and crystallized from alcohol to yield 20.5 g (71%) of product: mp 121–123 °C; NMR ($CDCl_3$) δ 2.33 (s, 3 H), 2.45 (s, 9 H), and 7.36 (s, 2 H). Anal. Calcd for $C_{11}H_{14}OS_4$: C, 45.48; H, 4.86; S, 44.15. Found: C, 45.78; H, 4.75; S, 44.03.

3,4,5-Tris(methylthio)benzoic Acid (7). Potassium hydroxide (2 g) and 8 g of 8 (27.6 mmol) in 125 mL of alcohol was heated to reflux for 5 h. The solution was poured into ice water and then acidified with hydrochloric acid. The solid was collected and crystallized from alcohol to yield 5.4 g (75%) of product, mp 250–252 °C. The NMR spectrum was identical to that of **7** prepared above.

***S*-Methyl 2,3-Bis(methylthio)benzenecarbothioate (9a).** 1,1′-Carbonyldiimidazole (7.8 g; 48.1 mmol) was added portionwise to a solution of 8.1 g of 2-chloro-3-nitrobenzoic acid (40.2 mmol) in 80 mL of DMF. The mixture was stirred for 15 min and then cooled (under nitrogen) in an ice bath. Methanethiol (12 mL) was added and then 4 g of lithium hydroxide was added portionwise. The solution was stirred in the cold for 1 h and poured into ice water. The solid was collected and crystallized from alcohol–water to yield 6.3 g (64%) of product, mp 92–93 °C. Anal. Calcd for $C_{10}H_{12}OS_3$: C, 49.15; H, 4.95; S, 39.36. Found: C, 49.34; H, 4.91; S, 39.62.

***S*-Methyl 2,3,5-Tris(methylthio)benzenecarbothioate (9b).** To a solution containing 12.3 g of 2-chloro-3,5-dinitrobenzoic acid (49.9 mmol) in 120 mL of DMF was added portionwise 9.7 g of 1,1′-carbonyldiimidazole (59.9 mmol). The mixture was stirred for 15 min and then cooled (under nitrogen) in an ice bath. Methanethiol (12 mL) was added and then 5 g of lithium hydroxide was added portionwise. The mixture was allowed to warm to room temperature with stirring for 1.5 h. The product was isolated as in the case of **9a** to yield 9.3 g (64%), mp 123–124 °C. Anal. Calcd for $C_{11}H_{14}OS_4$: C, 45.48; H, 4.86; S, 44.15. Found: C, 45.67; H, 4.77; S, 44.43.

***S*-Methyl 2,3,4,5-Tetrakis(methylthio)benzenecarbothioate (9c).** 1,1′-Carbonyldiimidazole (13.6 g; 84 mmol) was added portionwise to a solution of 19.7 g of 2,4-dichloro-3,5-dinitrobenzoic acid (70.1 mmol) in 125 mL of DMF. The mixture was stirred for 15 min and then cooled (under nitrogen) in an ice bath. Methanethiol (30 mL) was added and then 15 g of lithium hydroxide was added portionwise. The solution was stirred in the cold for 0.5 h and at room temperature for 0.5 h. The product was isolated as in the case of **9a** to yield 13.2 g (56%); mp 93–94 °C. An analytical sample, mp 94–95 °C, was recrystallized. Anal. Calcd for $C_{12}H_{16}OS_5$: C, 42.82; H, 4.79; S, 47.63. Found: C, 43.11; H, 4.78; S, 47.89.

2,3-Bis(methylthio)benzoic Acid (10a). Potassium hydroxide (1 g) and 3 g of **9a** (12.3 mmol) in 50 mL of alcohol was refluxed for 3 h. The mixture was poured into ice water and then acidified with hydrochloric acid. The solid was collected and crystallized from alcohol–water to yield 2.3 g (87%) of product: mp 145–146 °C; NMR ($CDCl_3$) δ 2.45 (s, 6 H) and 7.40 (m, 3 H). Anal. Calcd for $C_9H_{10}O_2S_2$: C, 50.44; H, 4.70; S, 29.92. Found: C, 50.72; H, 4.84; S, 30.29.

2,3,5-Tris(methylthio)benzoic Acid (10b). Potassium hydroxide (1.5 g) and 6 g of **9b** (20.7 mmol) in 75 mL of alcohol was refluxed for 5.5 h. The product was isolated as in the case of **10a** to yield 5.0 g (93%): mp 146–147 °C; NMR ($CDCl_3$) δ 2.40 (s, 3 H), 2.43 (s, 3 H), 2.50 (s, 3 H), 7.10 (d, 1 H), and 7.43 (d, 1 H). Anal. Calcd for $C_{10}H_{12}O_2S_3$: C, 46.13; H, 4.65; S, 36.94. Found: C, 46.38; H, 4.56; S, 36.85.

2,3,4,5-Tetrakis(methylthio)benzoic Acid (10c). Potassium hydroxide (2 g) and 10 g of **9c** (29.8 mmol) in 125 mL of alcohol was refluxed for 5 h. The product was isolated as in the case of **10a** to yield 8.45 g (93%): mp 173–174 °C; NMR ($CDCl_3$) δ 2.48 (m, 12 H) and 7.50 (s, 1 H). Anal. Calcd for $C_{11}H_{14}O_2S_4$: C, 43.11; H, 4.60; S, 41.85. Found: C, 43.13; H, 4.61; S, 41.75.

2,3,4,5,6-Pentakis(methylthio)benzamide (11). To a cold solution (under nitrogen) containing 11.7 g of pentachlorobenzamide (39.9 mmol) and 20 mL of methanethiol in 120 mL of DMF was added portionwise 10 g of lithium hydroxide. The ice bath was removed and the mixture was stirred for 27 h. It was poured into ice water, and the resulting solid was collected and crystallized from Me_2SO–water to yield 5.7 g (41%) of product: mp 174–176 °C; NMR (Me_2NCHO-d_7) δ 2.46 (s, 6 H) and 2.55 (s, 9 H). Anal. Calcd for $C_{12}H_{17}NOS_5$: C, 40.99; H, 4.87; N, 3.98; S, 45.60. Found: C, 40.69; H, 4.63; N, 3.92; S, 45.75.

3,4,5-Tris(methylsulfonyl)benzoic Acid (12a). A solution of 2.4 g of **7** (9.2 mmol) in 15 mL of 30% hydrogen peroxide and 30 mL of acetic acid was heated in an open flask at steam-bath temperature for 1 h. More hydrogen peroxide (15 mL) was added and the mixture was heated for an additional 18 h. The solid residue was crystallized from DMF–water to yield 2.5 g (76%) of product, mp 287–293 °C dec. Anal. Calcd for $C_{10}H_{12}O_8S_3$: C, 33.70; H, 3.39; S, 26.99. Found: C, 33.50; H, 3.48; S, 27.23.

3,4-Bis(methylsulfonyl)-5-nitrobenzoic Acid (12b). A solution of 5 g of **2** (19.3 mmol) in 30 mL of 30% hydrogen peroxide and 60 mL of acetic acid was heated in an open flask at steam-bath temperature for 1 h. Hydrogen peroxide (15 mL) was added and heating was continued for 19 h. The solution was cooled to yield 4.8 g (77%) of product, mp 270–280 °C dec. Anal. Calcd for $C_9H_9NO_8S_2$: C, 33.44; H, 2.81; N, 4.33; S, 19.84. Found: C, 33.44; H, 2.81; N, 4.52; S, 20.13.

2,3-Bis(methylsulfonyl)benzoic Acid (12c). A solution of 3 g of **10a** (12.3 mmol) in 15 mL of 30% hydrogen peroxide and 30 mL of acetic acid was heated in an open flask at steam-bath temperature for 45 min. Hydrogen peroxide (15 mL) was added and heating was continued for 2 h. The mixture was filtered hot, cooled, and extracted twice with ethyl acetate. The combined organic extracts were washed three times with water, dried, and evaporated. The crude material was crystallized from ethyl acetate–hexane to yield 0.9 g (26%) of product, mp 225–227 °C. Anal. Calcd for $C_9H_{10}O_6S_2$: C, 38.84; H, 3.62; S, 23.04. Found: C, 38.55; H, 3.80; S, 22.83.

2,3,5-Tris(methylsulfonyl)benzoic Acid (12d). A solution containing 2.4 g of **10b** (9.2 mmol) in 10 mL of 30% hydrogen peroxide and 20 mL of acetic acid was heated in an open flask at steam-bath temperature for 1 h. Hydrogen peroxide (10 mL) was added and heating

was continued for 18 h. The solid residue was crystallized from water to yield 3.1 g (95%) of product, mp 274–277 °C dec. Anal. Calcd for $C_{10}H_{12}O_8S_3$: C, 33.70; H, 3.39; S, 26.99. Found: C, 33.91; H, 3.22; S, 27.29.

2,3,4,5-Tetrakis(methylsulfonyl)benzoic Acid (12e). A solution of 2.5 g of **10c** (8.2 mmol) in 15 mL of 30% hydrogen peroxide and 30 mL of acetic acid was heated in an open flask for 1 h. Hydrogen peroxide (15 mL) was added and heating was continued for 18 h. The solid residue was crystallized from water to yield 2.8 g (79%) of product, mp 247–250 °C dec. Anal. Calcd for $C_{11}H_{14}O_{10}S_4$: C, 30.41; H, 3.25; S, 29.52. Found: C, 30.66; H, 3.10; S, 29.72.

Oxidation of Pentakis(methylthio)benzamide. A solution containing 2.5 g of **11** (7.1 mmol) in 15 mL of 30% hydrogen peroxide and 30 mL of acetic acid was heated in an open flask for 1 h. Hydrogen peroxide (15 mL) was added and heating was continued for 1 h. The solution was cooled to yield 1.6 g (48%) of product, mp >350 °C. It was identified by microanalysis and NMR as pentakis(methylsulfonyl)benzene.[1]

α,α,α-Trifluoro-2,6-dinitro-*p*-toluamide. A solution of 5.0 g of α,α,α-trifluoro-2,6-dinitro-*p*-tolunitrile[5] (19.2 mmol) in 10 mL of 80% sulfuric acid was heated at steam-bath temperature for 5 h and then poured into ice water. The product was collected and crystallized from alcohol to yield 3.6 g (68%) of product, mp 256–258 °C. Anal. Calcd for $C_8H_4F_3N_3O_5$: C, 34.42; H, 1.44; N, 15.09. Found: C, 34.65; H, 1.29; N, 14.86.

α,α,α-Trifluoro-2,6-bis(methylthio)-*p*-toluamide (13). To a cold solution (under nitrogen) of 11.1 g of α,α,α-trifluoro-2,6-dinitro-*p*-toluamide (39.8 mmol) and 10 mL of methanethiol in 120 mL of DMF was added portionwise 5 g of lithium hydroxide. The mixture was stirred in the cold for 0.5 h and then poured into ice water. The solid was collected and crystallized from alcohol to yield 9.0 g (80%) of product: mp 249–250 °C; NMR (Me_2SO-d_6) δ 2.50 (s, 6 H) and 7.39 (s, 2 H). Anal. Calcd for $C_{10}H_{10}F_3NOS_2$: C, 42.70; H, 3.58; N, 4.98. Found: C, 42.88; H, 3.73; N, 4.99.

1-Methyl-4-(methylsulfonyl)-6-(trifluoromethyl)-1*H*,3*H*-1,2-benzisothiazol-3-one 1-Oxide (14). A solution of 6.5 g of **13** (23.1 mmol) in 15 mL of 30% hydrogen peroxide and 30 mL of acetic acid was heated in an open flask at steam-bath temperature for 1 h. Hydrogen peroxide (15 mL) was added and heating was continued for 1 h. The mixture was cooled and the product was collected to yield 5.55 g (73%): mp 269–271 °C; NMR (Me_2SO-d_6) δ 3.62 (s, 3 H), 3.97 (s, 3 H), 8.60 (m, 1 H), and 9.35 (m, 1 H); IR (Nujol) 1698 cm^{-1}; MS 327 (M^+). Anal. Calcd for $C_{10}H_8F_3NO_4S_2$: C, 36.70; H, 2.45; N, 4.28; S, 19.57. Found: C, 36.69; H, 2.57; N, 4.31; S, 19.74.

3,4,5-Tris(methylthio)benzenesulfonamide (15). To a cold mixture (under nitrogen) containing 5.6 g of 4-chloro-3,5-dinitrobenzenesulfonamide[3] (19.9 mmol) and 10 mL of methanethiol in 75 mL of DMF was added portionwise 5 g of lithium hydroxide. The mixture was stirred in the cold for 15 min and at room temperature for 2 h. The mixture was poured into ice water which was then acidified with hydrochloric acid. The solid was collected and crystallized from DMF–water to yield 4.2 g (71%) of product: mp 260–262 °C; NMR (Me_2SO-d_6) δ 2.34 (s, 3 H), 2.56 (s, 6 H), and 7.37 (s, 2 H). Anal. Calcd for $C_9H_{13}NO_2S_4$: C, 36.59; H, 4.44; N, 4.74; S, 43.41. Found: C, 36.74; H, 4.69; N, 4.96; S, 43.62.

3,4,5-Tris(methylsulfonyl)benzenesulfonamide (16a). A solution of 6 g of **15** (20.3 mmol) in 50 mL of 30% hydrogen peroxide and 75 mL of acetic acid was heated in an open flask at steam-bath temperature for 3 h. The mixture was cooled and the product was collected to yield 7.1 g (91%) of product, mp 321–325 °C dec. Anal. Calcd for $C_9H_{13}NO_8S_4$: C, 27.61; H, 3.35; N, 3.58; S, 32.76. Found: C, 27.78; H, 3.35; N, 3.66; S, 32.65.

4-[(1-Ethylpropyl)amino]-3,5-bis(methylsulfonyl)benzenesulfonamide (16b). 3-Aminopentane (10 mL) and 2.6 g of **16a** (6.7 mmol) in 100 mL of alcohol was heated at reflux temperature for 18 h. The solution was cooled and the product was collected to yield 1.9 g (72%): mp 192–194 °C; NMR (Me_2SO-d_6) δ 3.38 (s, 6 H) and 8.50 (s, 2 H). Anal. Calcd for $C_{13}H_{22}N_2O_6S_3$: C, 39.18; H, 5.56; N, 7.03; S, 24.14. Found: C, 39.46; H, 5.35; N, 7.17; S, 23.91.

3,4-Bis(methylthio)-5-nitrophenylacetic Acid (17). To a cold solution (under nitrogen) containing 5.2 g of 4-chloro-3,5-dinitrophenylacetic acid[4] (20 mmol) and 10 mL of methanethiol in 80 mL of DMF was added portionwise 5 g of lithium hydroxide. The mixture was stirred in the cold for 15 min and at room temperature for 1 h. It was poured into ice water, which was then acidified with hydrochloric acid. The solid was collected and crystallized from alcohol to yield 4.6 g (85%) of product, mp 165–168 °C. Anal. Calcd for $C_{10}H_{11}NO_4S_2$: C, 43.94; H, 4.06; N, 5.12; S, 23.46. Found: C, 43.97; H, 4.11; N, 5.35; S, 23.19.

3,4-Bis(methylthio)-5-nitrophenylacetamide (18a). 1,1′-Carbonyldiimidazole (3.3 g; 20 mmol) was added portionwise to a solution of 4.3 g of **17** (16 mmol) in 25 mL of DMF. The mixture was stirred for 10 min, and then 10 mL of concentrated ammonium hydroxide was added dropwise. The mixture was then stirred for 1 h and poured into ice water. The solid was collected and crystallized from alcohol to yield 3.6 g (83%) of product, mp 195–197 °C. Anal. Calcd for $C_{10}H_{12}N_2O_3S_2$: C, 44.10; H, 4.44; N, 10.29; S, 23.55. Found: C, 44.32; H, 4.53; N, 10.23; S, 23.80.

3,4,5-Tris(methylthio)phenylacetamide (18b). Lithium hydroxide (5 g) was added portionwise to a cold solution (under nitrogen) containing 7.5 g of **18a** (27 mmol) and 10 mL of methanethiol in 100 mL of DMF. The mixture was stirred in the cold for 15 min and at room temperature for 7 h and then poured into ice water. The solid was collected and crystallized from alcohol to yield 4.2 g (57%) of product: mp 178–180 °C; NMR (Me_2SOd_6) δ 2.26 (s, 3 H), 2.42 (s, 6 H), 3.47 (s, 2 H), and 6.93 (s, 2 H). Anal. Calcd for $C_{11}H_{15}NOS_3$: C, 48.32; H, 5.53; N, 5.12; S, 35.18. Found: C, 48.22; H, 5.31; N, 5.36; S, 35.03.

Acknowledgments. The authors wish to thank Mr. Paul Unger and associates for spectral measurements and Mr. George Maciak and associates for microanalytical data.

Registry No.—**1**, 118-97-8; **2**, 65517-12-6; **3**, 65517-13-7; **4**, 65517-14-8; **5**, 20731-63-9; **6**, 65517-15-9; **7**, 65517-16-0; **8**, 65517-17-1; **9a**, 65517-18-2; **9b**, 65517-19-3; **9c**, 65517-20-6; **10a**, 65517-21-7; **10b**, 65517-22-8; **10c**, 65517-23-9; **11**, 65517-24-0; **12a**, 65517-25-1; **12b**, 65517-26-2; **12c**, 65517-00-2; **12d**, 65517-01-3; **12e**, 65517-02-4; **13**, 65517-03-5; **14**, 65517-04-6; **15**, 65517-05-7; **16a**, 65517-06-8; **16b**, 65517-07-9; **17**, 65517-08-0; **18a**, 65517-09-1; **18b**, 65517-10-4; 2-chloro-3,5-dinitrobenzoic acid, 2497-91-8; 2,4-dichloro-3,5-dinitrobenzoic acid, 52729-03-0; pentachlorobenzamide, 29956-85-2; pentakis(methylsufonyl)benzene, 65516-84-9; α,α,α-trifluoro-2,6-dinitro-*p*-toluamide, 65517-11-5; α,α,α-trifluoro-2,6-dinitro-*p*-tolunitride, 35213-02-6; 4-chloro-3,5-dinitrobenzenesulfonamide, 35168-73-1; 4-chloro-3,5-dinitrophenylacetic acid, 6093-34-1; 2-chloro-3-nitrobenzoic acid, 3970-35-2; methanethiol anion, 17302-63-5.

References and Notes

(1) J. R. Beck and J. A. Yahner, *J. Org. Chem.*, preceding paper in this issue.
(2) P. Stoss and G. Satzinger, *Angew. Chem.*, **83**, 83 (1971).
(3) J. H. Collins, German Offen., 2 120 629; *Chem. Abstr.*, **76**, 45938 (1972).
(4) K. H. Mayer, S. Petersen, H. Scheinpflug, and F. Grewe, German Offen., 1 204 454; *Chem. Abstr.*, **64**, 6570 (1966).
(5) J. R. Beck, *J. Org. Chem.*, **37**, 3224 (1972).

Notes

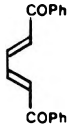
(*E,E*)- and (*E,Z*)-1,4-Dibenzoyl-1,3-butadiene. Synthesis via Wittig Condensation and Solid-State Photochemistry

Howard D. Perlmutter* and Richard B. Trattner

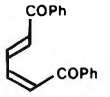
Department of Chemical Engineering and Chemistry, New Jersey Institute of Technology, Newark, New Jersey 07102

Received October 14, 1977

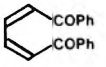
In connection with other studies, we synthesized (*E,E*)-1,4-dibenzoyl-1,3-butadiene (1) according to the method of Bailey and Ross,[1] starting with (*E,E*)-1,3-butadiene-1,4-dicarboxylic acid via Friedel–Crafts phenylation of the acid chloride. Compound 1 was found to be extremely photolabile



1



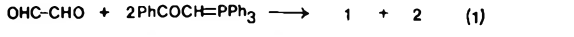
2



3

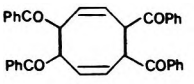
as a solid or in solution, and it could only be handled using special lighting conditions. Inspired by the elegant work of G. M. J. Schmidt and co-workers[2] on the solid-state photochemistry of other 1,3-butadienes, we decided to investigate the photochemistry of solid 1. We wish to report formation of a (2 + 2) dimer from solid 1. In addition, we have succeeded in synthesizing the (*E,Z*) isomer 2 and wish to report preliminary solid-state photochemistry results, the first to be reported on an (*E,Z*)-1,4-disubstituted 1,3-diene.

In our hands, attempts to synthesize the stereoisomers of 1, i.e., 2 and 3, by organometallic or Friedel–Crafts phenylation of the corresponding 1,3-butadiene-1,4-dicarboxylic acid or acid chloride were unsuccessful, resulting in either Michael additions[3] or in isomerization to 1. However, we have succeeded in preparing 2 by the Wittig condensation of glyoxal 4 with 2 mol of phenacyltriphenylphosphorane (5) (reaction 1).

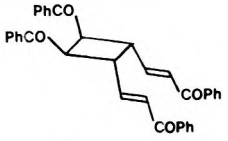


The reaction product was shown to consist of two compounds, chromatographic separation of which gave 1 and a second component, X. This latter compound was shown to be 2. Its IR, ^{1}H NMR, and mass spectra were very similar to those of 1. The IR spectra of 1 and X were extremely similar, both showing strong absorption (KBr) at 1653, 1587, and 1563 cm^{-1}. The ^{1}H NMR spectra of 1 and X were similar, 1 showing multiplets from δ 7.3 to 8.1 and X evincing multiplets from δ 6.0 to 7.0 and from 7.0 to 8.1. The mass spectra of the two compounds both had M$^+$ of 262 plus fragments at *m/e* 197, 157, 128, 105, and 77. A solution of X, when stirred with a crystal of iodine over short periods of time, isomerized to 1. Extended treatment of X or 1 with either iodine or dilute hydrochloric acid resulted in formation of 2-phenacyl-5-phenylfuran.[3] Finally, the number of lines in the proton-decoupled ^{13}C-NMR spectrum of X (i.e., 11, of a maximum of 14) showed it to be the less symmetrical (2). The more symmetrical (*Z,Z*)-3, like 1, could only have shown a maximum of seven lines. Compound 1 indeed gave all seven lines. The number plus the chemical shifts of the resonances support the assignment of structure 2 to compound X, rather than the stereoisomeric 3.

Compounds 1 and 2 were irradiated in the solid state. Compound 1 gave a single photoproduct, whose IR, ^{1}H-NMR, and mass spectra showed it to be either a (4 + 4) dimer (6) or



6



7

a (2 + 2) dimer (e.g., 7). However, the number and chemical shifts of the lines in the proton-decoupled ^{13}C NMR spectrum ruled out the more symmetrical 6 in favor of 7, whose structure is analogous to the dimer obtained from the solid-state photolysis of the stereoisomeric 1,3-butadiene-1,4-dicarboxylic acids.[4] In addition, the UV spectrum of the dimer was almost identical to that of another α,β-unsaturated ketone, 1-phenyl-2-buten-1-one.

Irradiation of 2 resulted in a mixture of two compounds that have proved difficult to separate. However, the mixture did show a M$^+$ of 524, indicating that at least one of the components is a dimer.

Further work, including X-ray crystallographic studies of both monomers and dimers, is in progress.

Experimental Section

(*E,E*)-1,4-Dibenzoyl-1,3-butadiene (1). This compound was prepared using the method of Bailey and Ross,[1] except that special lighting conditions were used to circumvent the photolability of the compound, i.e., Westinghouse lamp No. F 20T 12/GO "Gold-Bug-A-Way" 20W (0% transmittance <500 nm).

(*E,Z*)-1,4-Dibenzoyl-1,3-butadiene (2). A solution of 1.38 g of freshly prepared glyoxal 4[5] and 18.1 g of phenacyltriphenylphosphorane (5)[6] in 300 mL of absolute ethanol was stirred for 24 h at room temperature. The precipitated solid, 4.5 g, was shown by TLC to consist of two compounds of very similar R_f. A 0.4-g portion of this material was dissolved in a minimum amount of methylene chloride and chromatographed on 140 g of neutral silica gel, eluting with benzene. We were able to partially separate the mixture into 0.21 g of pure 1 and 0.10 g of the second component. The IR, ^{1}H-NMR, and mass spectra of the two compounds were extremely similar. A solution of the second component in methylene chloride was stirred with a crystal of iodine. After a short period of time, isomerization to 1 was observed. Extended treatment of either 1 or the second component with either iodine or dilute HCl resulted in formation of a compound that was shown by spectroscopic analysis to be 2-phenacyl-5-phenylfuran.[3] The ^{13}C-proton-decoupled-NMR spectrum of the second compound was, unlike its ^{1}H-NMR spectrum, markedly different from that of 1, evincing 11 lines at 129.0, 129.1, 138.0, and 138.3 (aromatic C), 130.6, 133.3, and 133.7 (aromatic and α-olefinic C), 139.8 and 140.0 (β-olefinic C), and 191.6 and 191.7 ppm (carbonyl C). Compound 1 showed only seven lines in its ^{13}C spectrum, at 128.9, 129.1, 132.9, and 137.8 (aromatic C), 128.9 (α-olefinic C), 141.5 (β-olefinic C), and 190.3 ppm (carbonyl C).

Solid-State Photochemistry of (*E,E*)-1,4-dibenzoyl-1,3-butadiene (1). In a typical experiment either 0.3 g of finely divided 1 was placed in an uncovered Petri dish or a solution of 0.3 g of 1 in methylene chloride was placed in an uncovered Petri dish and allowed to evaporate in the dark. The solid was irradiated with a 275 W sunlamp. After 3 h, thin-layer chromatography showed that the conversion to a single photoproduct was quantitative, with no detectible starting material. This material, a slightly off-white solid, mp 206–7 °C (lit.[1] 207–8 °C), could be recrystallized from either benzene or chloroform to give a white solid that showed no change in melting point.

The IR spectrum (KBr) displayed strong absorption at 1661, 1612, 1600, and 1582 cm^{-1}, consistent with an α,β-unsaturated carbonyl. The UV spectrum (95% EtOH) showed $\lambda\lambda_{max}$ at 250 (log ϵ 4.29) and ca. 330 nm (sh, log ϵ 3.23). The UV spectrum (95% EtOH) of 1-phe-

0022-3263/78/1943-2056$01.00/0

nyl-2-buten-1-one showed $\lambda\lambda_{max}$ at 254 (log ϵ 4.24) and 330 nm (log ϵ 1.77). Its mass spectrum gave a M^+ at 524 plus fragments at *m/e* 506, 488, 419, 401, 299, 262, 157, 105, and 77. The 100-MHz ^{1}H-NMR spectrum evinced multiplets at δ 7.97 and 7.45 (20 H), a multiplet at δ 6.80 (4 H), and a broad singlet at δ 4.48 (4 H). The proton-decoupled ^{13}C-NMR spectrum showed lines at 40.1 and 48.5 (alicyclic C), 128.9, 129.2, 129.4, 133.1, 136.6, and 137.9 (aromatic C), 134.2 and 145.1 (olefinic C), and 190.9 and 198.1 ppm (carbonyl C).

Solid-State Photochemistry of (*E,Z*)-1,4-Dibenzoyl-1,3-butadiene (2). Irradiation of **2** was carried out in a manner similar to that for **1** (vide supra). The product was shown by TLC to consist of two compounds of nearly identical R_f. Thus far the mixture has resisted all attempts at separation.

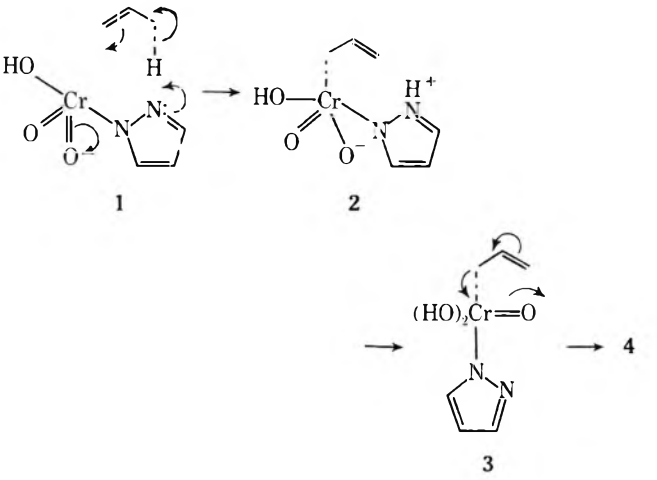
Acknowledgments. We wish to thank Drs. Michael Shapiro and Renate Coombs of Sandoz, Inc. for their help in obtaining ^{13}C-NMR and mass spectra and Mr. Robert Casani for obtaining the UV spectra.

Registry No.—**1**, 65682-02-2; **2**, 65682-03-3; **4**, 107-22-2; **5**, 859-65-4; **7**, 65682-04-4; 2-phenacyl-5-phenylfuran, 54980-24-4; 1-phenyl-2-buten-1-one, 495-41-0.

References and Notes

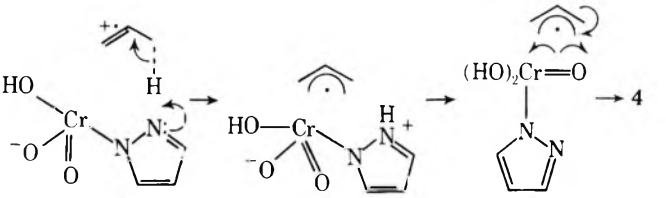
(1) P. S. Bailey and J. H. Ross, *J. Am. Chem. Soc.*, **71**, 2370 (1949).
(2) G. M. J. Schmidt et al., "Solid State Photochemistry", D. Ginsburg, Ed., Verlag Chemie, Weinheim, Germany, 1976, pp 93–144.
(3) P. S. Bailey, W. W. Hakki, and H. W. Bost, *J. Org. Chem.*, **20**, 1034 (1955).
(4) M. Lahav and G. M. J. Schmidt, *J. Chem. Soc. B*, 312 (1967).
(5) C. Harries and F. Temme, *Ber.*, **40**, 165 (1904).
(6) F. Ramirez and S. Dershowitz, *J. Org. Chem.* **22**, 41 (1957).

Scheme I



1 2 3

Scheme II



5 6 7

Allylic Oxidation with 3,5-Dimethylpyrazole. Chromium Trioxide Complex. Steroidal Δ^5-7-Ketones

William G. Salmond,* Mary A. Barta, and Jeffrey L. Havens

The Upjohn Company, Kalamazoo, Michigan 49001

Received November 10, 1977

In our work on syntheses of hydroxylated metabolites of vitamin D[1,2], we have studied various approaches to the introduction of the 5,7-diene system of the provitamins.[3] Bromination at C-7 of a Δ^5-steroid followed by dehydrobromination is a well-known procedure[4] but gives mixtures of $\Delta^{5,7}$- and $\Delta^{4,6}$-dienes, which are often difficult to separate. As an alternative, we recently described the oxidation of a 7β-phenylselenide;[2] this approach does give 5,7-diene uncontaminated by 4,6-diene, but the yield is limited by simultaneous production of a 5β-hydroxy Δ^6-steroid. The thermal decomposition of the lithium salt of a Δ^5-7-tosylhydrazone leads in excellent yield[5] to the corresponding 5,7-diene uncontaminated by 4,6-diene. Accordingly, we set out to study the conversion of Δ^5-steroids to Δ^5-7-ketones.

A number of oxidants based on chromium[6] have been reported to accomplish this transformation. In our work, we chose initially cholesteryl benzoate as a model. The allylic oxidation of cholesteryl benzoate with sodium chromate in acetic acid/acetic anhydride[7] is, in our experience, a poor reaction and our best yield of the Δ^5-7-ketone was 38%. The use of Collins reagent[8,9] produced in situ gave a 68% yield, but the volume of methylene chloride used as solvent and the amount of calcined Celite[11] used to absorb precipitated oily solids is enormous. The time required for complete reaction, in our hands, in the latter case is ca. 50 h and 3–4 days in the former. Pyridinium chlorochromate[12,13] in methylene chloride at room temperature did not bring about any allylic oxidation.

We have found that the allylic oxidation of cholesteryl benzoate with 3,5-dimethylpyrazole chromium trioxide complex[14] (DMP·CrO_3) is remarkably fast.[15] In reactions where the molar ratio of the CrO_3 to steroid is the same (ca. 20:1) as that required for complete reaction with pyridine as ligand, the reaction with DMP as ligand is complete in less than 30 min, representing a rate increase of some 100-fold. The DMP is recoverable in yields ranging from 70–90% and the yield of the Δ^5-7-ketone is routinely 70–75%.

A probable explanation for the rate enhancement of this oxidation lies partly in the much increased solubility of the chromium containing complexes but more importantly in the possibility of intramolecular acceleration due to the pyrazole nucleus. Many of the characteristics of the reaction are consistent with either of the following mechanistic schemes, proposed as reasonable heuristics. They differ only in the details of the manner in which a carbon oxygen bond is first established at C-7. In Scheme I one two-electron transfer is involved; in Scheme II two one-electron transfers take place. The salient feature of both is that the chromium complex attacks first at the double bond and not at the allylic methylene group.[16]

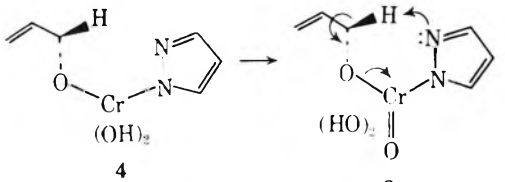
Both schemes assume a one-to-one addition of DMP and CrO_3 to give the complex shown[14,17] (the 3,5-methyl groups are omitted for the sake of clarity), in which one ligand site remains free on the chromium atom allowing facile attack by the π electrons of the double bond. In Scheme I, the complex attacks the 5,6-double bond by means of an "ene" reaction wherein the removal of the axial 7α-hydrogen is hastened by the appositely placed basic nitrogen of the pyrazole ligand. Such an intramolecular course of action is not possible with Py_2-CrO_3 because (a) no ligand sites are available for complexation with π electrons unless pyridine is first displaced and (b) then no basic nitrogen is available to assist in the removal of the 7α-hydrogen except by an intermolecular deprotonation by the displaced pyridine. It is for stereoelectronic reasons[18] that the Cr will attack axially at C-5 and that an axial C-H bond will be severed, since overlap of the interacting orbitals is maximum in this geometrical array.

In passing from **1** to **2**, no reduction of the Cr^{VI} has taken

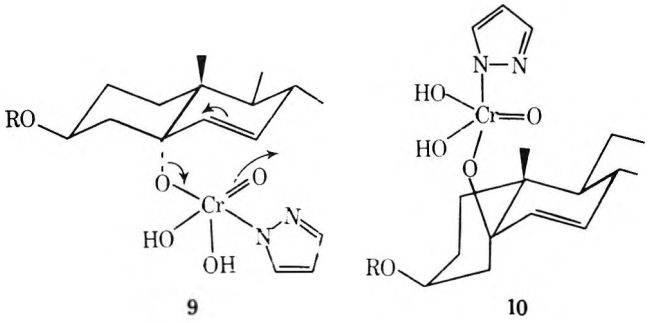
0022-3263/78/1943-2057$01.00/0

place. A proton shift from nitrogen to oxygen gives **3** (this proton shift could occur later). Although we have found no references to the isolation of Cr^{VI} alkyls, Cr^{II} and Cr^{III} alkyls have been described.[19] Complexes such as **2** or **3** containing Cr^{VI}–C σ bonds have been postulated recently by two groups.[20,21] During the 2,3-sigmatropic shift of the chromium alkyl **3** to give the intermediate **4** oxidation of the steroid takes place and reduction of Cr^{VI} to Cr^{IV} occurs.[16]

The same intermediate **4** is reached in Scheme II. In this scheme, Cr^{VI} first removes one electron from the double bond to give the radical cation[22] together with a Cr^{V} species **5**.[20] Removal of a proton from C-7 by the pyrazole ligand leads to the allyl radical **6**, which now does a further one-electron transfer[23] to give the intermediate **4**. Before further collapse



4 **8**



9 **10**

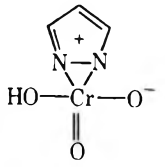
of species **4** to the Δ^5-7-ketone can occur, oxidation of Cr^{IV} to Cr^{VI}, or Cr^{V}, must take place. (Collapse of **4** directly to ketone and a Cr^{II} species is not considered likely.[24]) Again, the decomposition[25] of the resulting chromate ester **8** to the ketone is aided by an intramolecular cyclic mechanism as shown.[14]

In support of the geometrical requirements of this mechanistic scheme is the behavior of cholest-6-ene-3β,5α-diol and cholest-6-ene-3β,5β-diol, 3-benzoates,[2] with the DMP·CrO_3 reagent. At 0 °C, the 5α-hydroxy compound is oxidized very cleanly to the Δ^5-7-ketone in less than 2 min! Primary and secondary alcohols are oxidized to aldehydes and ketones at a comparable rate, indicating that the formation of the chromate ester **9** is fast and that a sigmatropic shift (albeit a 3,3 as opposed to a 2,3 in Scheme I) must ensue rapidly to give the same intermediate as **8** in the schemes above.

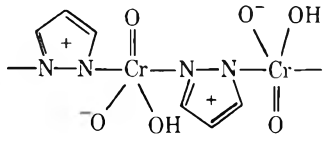
On the other hand, although oxidized in part to the Δ^5-7-ketone, the 5β-hydroxy compound reacts much more slowly and the reaction yields many by-products. The geometry of the chromate ester **10** derived from this AB-cis compound cannot accommodate a 3,3-sigmatropic shift (certainly not at least with the desirable 1,3-diaxial disposition equivalent to that in **9**). Presumably the initially formed chromate ester splits into an ion pair (or radical pair) and it is the resulting allylic carbonium ion (or radical) which is further oxidized in different ways to yield the many observed products. These, and the observations made by Dauben and Michno[13] on the oxidation of tertiary allylic alcohols with pyridinium chlorochromate, support the concerted nature of the 3,3-shift in the 5α-hydroxy case and the necessity for attack from the α face of the steroid with the geometry indicated in the schemes for the oxidation of Δ^5-steroids.

Such mechanisms rationalize some further observations. For example, no attack at C-4 is observed; the 4β-axial hydrogen and approach to the 6β position by Cr are both hindered by 1,3-diaxial interaction with the methyl group on C-10.[9,26] In addition, reaction is hastened at low temperature. This could be due in part to the large negative entropy factor that would be expected in the formation of the highly ordered transition state such as depicted in **1**, which is likely to be the rate-determining step in this sequence.

However, this is probably not the only factor involved in the improved reaction at low temperature. If the complex is allowed to stand at room temperature, it rapidly loses its activity. This may be explained by the possibility of ligand reorganization as in **11**, or more likely by polymerization of



11



12

the oxidant caused by bridging via pyrazole nuclei[17] as in **12**.

Experimentally, the reaction is straightforward. It is important to prepare the oxidant at low temperature (usually −25 to −20 °C) by adding the DMP *as quickly as possible* to the CrO_3 suspended in dry methylene chloride. It is equally important that the CrO_3 be dried over P_2O_5 before use for most efficient oxidation. When the molar ratio of CrO_3 to steroid is ca. 20, the reaction is complete in ca. 30 min; when it is ca. 10, the reaction takes as long as 5 h for completion. A typical reaction is conducted thus: Chromium trioxide (6.0 g, 60.0 mmol) is suspended in dry methylene chloride (50 mL) at −20 °C and the DMP (5.76 g, 60 mmol) is added in one portion. After stirring at −20°C for 15 min, cholesteryl benzoate (2.44 g, 5 mmol) is added and the mixture is stirred for 4 h while maintaining the temperature between −10 and −20 °C. Sodium hydroxide solution (25 mL, 5 N) is then added and the mixture is stirred for 1 h at 0 °C. The phases are then separated. The organic layer is washed with dilute hydrochloric acid to remove the DMP, which can be recovered by subsequent basification of this acidic wash. The methylene chloride phase is now washed with water and saturated sodium chloride solution and evaporated to yield a residue, which is crystallized from cyclohexane to give 7-ketocholesteryl benzoate, 1.86 g, 74%.

A number of Δ^5-steroids have been converted to the Δ^5-7-ketones in a similar manner; for example, 25-hydroxycholesteryl benzoate, stigmasteryl benzoate, 1α,25-hydroxycholesterol, 1,3-diacetate, and 17α-methylandrost-5-ene-3β-17β-diol diacetate.[31]

Registry No.—DMP, 67-51-6; CrO_3, 1333-82-0; DMP·CrO_3, 53143-09-2; cholesteryl benzoate, 604-32-0; 7-ketocholesteryl benzoate, 6997-41-7; cholest-6-ene-3β,5α-diol 3-benzoate, 64746-63-0; cholest-6-ene-3β,5β-diol 3-benzoate, 64746-65-2.

References and Notes

(1) W. G. Salmond and K. D. Maisto, *Tetrahedron Lett.*, 987 (1977); W. G. Salmond, M. C. Sobala, and K. D. Maisto, *ibid.*, 1237 (1977); W. G. Salmond and M. C. Sobala, *ibid.*, 1695 (1977). For a brief review which includes some other work see W. G. Salmond, "Vitamin D, Biochemical Chemical and Clinical Aspects Related to Calcium Metabolism", Walter deGruyter, New York, N.Y., 1977, pp 61–70.

(2) W. G. Salmond, M. A. Barta, A. M. Cain, and M. C. Sobala, *Tetrahedron Lett.*, 1683 (1977).

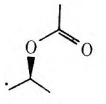
(3) For an excellent review of the vitamin D isomer system, see E. Havinga, *Experientia*, **29**, 1181 (1973).

(4) See, for example, L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, N.Y., 1959, p 158ff.

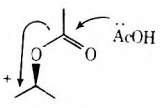
(5) L. Caglioti and P. Casselli, *Chim. Ind. (Milan)*, 559 (1963); W. G. Dauben, M. E. Lorber, N. D. Vietmeyer, R. H. Shapiro, J. H. Duncan, and K. Tomer, *J. Am. Chem. Soc.*, **90**, 4762 (1968); W. G. Dauben and D. S. Fullerton, *J. Org. Chem.*, **36**, 3277 (1971).

(6) For a review of the more classical methods, see ref 7.

(7) C. W. Marshall, R. E. Ray, I. Laos, and B. Riegel, *J. Am. Chem. Soc.*, **79**, 6308 (1957).
(8) J. C. Collins, W. W. Hess, and F. J. Frank, Tetrahedron Lett., 3363 (1968).
(9) W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969).
(10) R. Ratcliffe and R. Rodehurst, *J. Org. Chem.*, **35**, 4000 (1970).
(11) The workup of the reaction is facilitated considerably if dry Celite is added to the reaction mixture.
(12) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(13) W. G. Dauben and D. M. Michno, *J. Org. Chem.*, **42**, 682 (1977).
(14) E. J. Corey and G. W. J. Fleet, *Tetrahedron Lett.*, 4499 (1973).
(15) For an example of benzylic oxidation effected by this reagent, see E. McDonald and A. Suksamrarn, *Tetrahedron Lett.*, 4425 (1975).
(16) It has been suggested that the acid-catalyzed allylic oxidation of olefins by chromic acid in aqueous acetic acid involves direct abstraction of a hydrogen atom by Cr^{IV}: P. Müller and J. Rocek, *J. Am. Chem. Soc.*, **96**, 2836 (1974). See also P. Müller and T. T. Khoi, *Tetrahedron Lett.*, 1939 (1977). It is not at all clear that such a mechanism is relevant in nonaqueous systems involving Cr^{VI} coordinated with basic heterocyclic ligands.
(17) S. Trofimenko, *Chem. Rev.*, **72**, 497 (1972).
(18) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956).
(19) For a leading reference see J. K. Kochi and J. W. Powers, *J. Am. Chem. Soc.*, **92**, 137 (1970). The 2,3-sigmatropic shift of a Cr^{VI} alkyl such as **3** would be expected to be very fast.
(20) Persuasive arguments that the oxidation of allylic alcohols proceeds via Cr^{VI}–olefin π complex → Cr^{VI}–C σ complex have been made: P. Sundararaman and W. Herz, *J. Org. Chem.*, **42**, 813 (1977). These workers also argue against the involvement of charged species such as **5** in Scheme II. However, since the question is still not resolved, Scheme II is included here for completeness.
(21) Oxidation of olefins with CrO_2Cl_2 has also been argued to proceed via the initial formation of a CrO_2Cl_2 olefin π complex, followed by rearrangement to a σ complex: K. B. Sharpless, A. Y. Teranishi, and J-E. Bäckvall, *J. Am. Chem. Soc.*, **99**, 3120 (1977).
(22) The formation of such a radical cation could rationalize the abundant formation of 5β,6β-epoxide with those reagents such as Na_2CrO_4/AcOH/Ac_2O which are accompanied by nuclephilic species. Axial attack[18] by acetate at the 6β position of the radical cation **5** leads to the radical **13**, further



13



14

oxidized by electron transfer to the tertiary carbonium ion **14**, which cyclizes to the oxide with the formation of acetic anhydride. In aqueous systems, of course, water would be the nucleophile.
(23) As in Scheme I the formal proton transfer from N to O designated in 6 → **7** could occur after this second electron transfer.
(24) See, for example, G. Dyrkacz and J. Rocek, *J. Am. Chem. Soc.*, **95**, 4756 (1973); E. J. Corey and L. S. Melvin, *Tetrahedron Lett.*, 929 (1975).
(25) F. Holloway, M. Cohen, and F. H. Westheimer, *J. Am. Chem. Soc.*, **73**, 65 (1951); J. Rocek, F. H. Westheimer, A. Eschenmoser, L. Moldovanyi, and J. Schreiber, *Helv. Chim. Acta*, **45**, 2554 (1962).
(26) It has been clearly established that other eneophiles such as singlet oxygen[27] and diazodimethyl dicarboxylate[28] attack Δ^5-, Δ^6-, and $\Delta^{5,7}$-steroids exclusively from the α face. It is curious that the Sharpless[29] mechanism for allylic oxidation with SeO_2 requires that the initial ene reaction take place from the β side since the SeO_2 oxidation of Δ^5-steroids gives mixtures of 4β-hydroxy-Δ^5-, and 6β-hydroxy-Δ^4-steroids.[30] (Only the former is explicable by the Sharpless mechanism.) Work is in progress in our laboratory toward explaining this dichotomy.
(27) See, for example, G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957); A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, **83**, 1498 (1961).
(28) A. van der Gen, J. Lakeman, M. A. M. P. Gras, and H. O. Huisman, *Tetrahedron* **20**, 2521 (1964).
(29) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **94**, 7154 (1972); D. Arigoni, A. Vasella, K. B. Sharpless, and H. P. Jensen, *ibid.*, **95**, 7917 (1973).
(30) For example, see O. Rosenheim and W. W. Starling, *J. Chem. Soc.*, 377 (1937); A. Butenandt and E. Hausmann, *Ber. Dtsch. Chem. Ges.*, **70**, 1154 (1937); and C. A. Kind and W. Bergmann, *J. Org. Chem.*, **7**, 341 (1942).
(31) For other examples, see W. G. Salmond, U.S. Patent 4 006 172 (February 1, 1977).

Electrocatalytic Hydrogenation of Aromatic Compounds

Larry L. Miller* and Leif Christensen

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

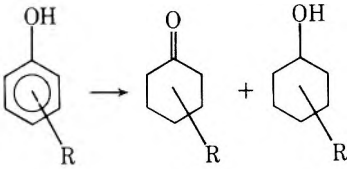
Received November 7, 1977

We are currently interested in exploring electrocatalytic organic reactions and report here some initial results which survey electrohydrogenations of aromatic compounds. This particular aspect of electrocatalysis seems to have obtained only limited attention. The possibility of hydrogenation at the very mild conditions normally employed in electrosynthesis, room temperature, and atmospheric pressure is, however, attractive. Furthermore, the electrochemical production of hydrogen directly at the surface of the catalyst would circumvent the compression, transportation, and storage of hydrogen.

Electrocatalytic hydrogenation of olefins has been the subject of numerous investigations employing both precious metal catalyst electrodes,[1-3] like palladium, platinum, and rhodium, as well as "spongy" nickel. The latter is capable of hydrogenating activated double and triple bonds in very good yields.[4,5]

The reduction of aromatic compounds was discovered long ago. Early workers[6,7] hydrogenated phenol in dilute H_2SO_4 at a platinized platinum (Pt|Pt) cathode to cyclohexanol in fair material yield, but with low current efficiency. Under similar conditions[8] the three isomeric cresols have been hydrogenated, yielding in each case an unseparated mixture of alcohols and ketone. The electrocatalytic hydrogenations of cinnamic acid, phenylacetic acid, and benzoic acid at a Pt|Pt cathode in a pressurized cell have also been reported.[9]

The most widely used electrode in electrocatalytic hydrogenation has been a platinum electrode covered with different kinds of metal "blacks".[2,3] To reduce cost we investigated the use of carbon rods as the conductive base for the catalyst, an approach recently successfully applied in other fields of electrocatalysis.[10] These electrodes were used to hydrogenate several aromatic compounds. As shown in Tables I and II we were able to hydrogenate different phenols, anisole, aniline, benzoic acid, cumene, and *tert*-butylbenzene to the corresponding cyclohexyl compounds in fair to excellent yields. Special attention was given to phenol reduction, in part because we wished to evaluate the competition between hydrogenation and hydrogenolysis of the hydroxy group. The hydrogenation of phenol in dilute H_2SO_4 was initially shown to be much more efficient on a Pt|C electrode than on Pt|Pt. After passage of the theoretical amount of electricity (6 F/mol) at a Pt|C electrode, the isolated mixture contains cyclohexanone (**2**, R = H) and cyclohexanol (**3**, R = H) together with phenol (**1**, R = H).



1 2 3

If a larger amount (12 F/mol) of current is passed the only isolated product is cyclohexanol. The material yield though is still low, suggesting a high degree of hydrogenolysis to benzene and cyclohexane. Cyclohexane could, indeed, be detected by gas chromatography in the catholyte before workup of the reaction mixture.

On a Rh|C electrode the material yield was much higher producing 92% cyclohexanol, with a current efficiency as high as 79%. This is the highest yield reported and it is a quite satisfactory method for the synthesis of cyclohexanols. The observed difference between platinum and rhodium is very similar to the results obtained in normal catalytic hydrogenation where platinum is known to give considerable hydrogenolysis of phenols and phenyl ethers as compared to a rhodium catalyst.[11,12]

It is also clear from the results in Table I that the activity of the catalyst metals follows at least qualitatively the se-

0022-3263/78/1943-2059$01.00/0

Table I. Electrocatalytic Hydrogenation of Phenols[a]

1, R =	Registry no.	Cathode	i, A	F, mol	Yield, % 2	Registry no.	3	Registry no.	1
H	108-95-2	Pt/Pt	0.1	6	7	108-94-1	17	108-93-0	50
H		Pt/C	0.8	6	6		43		11
H		Pt/C	0.8	12			54		
H		Rh/C	0.2	6	8		77		
H		Rh/C	0.8	6	15		74		1
H		Rh/C	0.8	7.2			92		
H		Pd/C	0.2	6	6		2		74
H		Pd/C[b]	0.2	6	15		5		49
2-Methyl	95-48-7	Rh/C	0.2	6	29	583-60-8	45[c]		12
2-Methyl		Rh/C	0.8	6	24		43[d]		9
2-Methyl		Rh/C	1.0	6	30		42[e]		14
2-Methyl		Rh/C	0.8	10.8			83[f]		
2,6-Dimethyl	576-26-1	Rh/C	0.8	6	28	2816-57-1	39	5337-72-4	20
2,6-Dimethyl		Rh/C	0.8	12	1		82		
2,3-Dimethyl[g]	526-75-0	Rh/C	0.8	6	10	13395-76-1	17	1502-24-5	63
2,3-Dimethyl[g]		Rh/C	0.8	12	7		73		9
5,6,7,8-Tetrahydro-1-naphthol[h]	1125-78-6	Rh/C	0.2	20.4	20	4832-17-1	46	825-51-4	6
2-Naphthol[h]	135-19-3	Rh/C	0.2	21	44[i]				5

[a] 0.2 M H_2SO_4 as catholyte. [b] Catholyte heated to 65 °C. [c] 80 cis:20 trans. [d] 83 cis:17 trans. [e] 87 cis:17 trans. [f] 70 cis:30 trans. [g] Catholyte heated to 40 °C. [h] Catholyte heated to 65 °C. [i] 5,6,7,8-Tetrahydro-2-naphthol.

Table II. Electrocatalytic Hydrogenation of Aromatic Compounds[a]

Reactant C_6H_5–X, X =	i, A	F, mol	Yields, % $C_6H_{11}X$	C_6H_5X
NH_2	0.8	12	73	
CO_2H	0.2	10	63	31
$(CH_3)_2CH$	0.2	8.4	56	23
$(CH_3)_3C$	0.2	10	33	51
OCH_3	0.8	6	54[b]	5
OCH_3	0.8	12	50[c]	
1-Methylnaphthalene	0.4	9		95

[a] Using Rh|C in 0.2 M H_2SO_4. [b] Also cyclohexanone (14), cyclohexanol (1). [c] Also cyclohexanol (25).

quence established from "normal" catalytic hydrogenation.[11] Only platinum and rhodium, which are known to hydrogenate aromatic nuclei at atmospheric pressure,[12,13] are effective under the applied electrochemical conditions. Palladium, which requires increased pressure and temperature for normal hydrogenation, gives only low electrocatalytic conversion, and nickel, which normally requires very severe conditions,[11] gives no electrohydrogenation at all; instead hydrogen is evolved and phenol is recovered.

Table I also shows, with hydrogenation of *o*-cresol (**1**, R = 2-methyl) as an example, that variation of the current density from 0.2–1.0 A (approximate geometric area of the electrode, 68 cm^2) only has a small effect on the current efficiency. Therefore, hydrogenations could be performed at a high current density to reduce the time scale of the experiment. It is also clear that the current efficiency is a function of the concentration of substrate as shown by the total depression of the hydrogen evolution in the beginning of the experiment but not at the end.

The electrocatalytic hydrogenation of *o*-cresol produced 2-methylcyclohexanol stereoselectively with a cis:trans ratio of 70:30. This is in accordance with results obtained from catalytic hydrogenation of o-cresol on a Rh catalyst.[14] As reported we also found that the hydrogenation of 2-methylcyclohexanone gave approximately a 50:50 mixture of the cis and trans alcohols, therefore, the hydrogenation of o-cresol cannot all take place through the ketone, and indeed the cis:trans ratio of the alcohol was higher when the hydrogenation was stopped before the total conversion of the ketone to the alcohol. The hydrogenation of 2,6-dimethylphenol also produced one isomer with very high selectivity (82%). From NMR the structure of this isomer was shown to be *cis,cis*-2,6-dimethylcyclohexanol.

Both β-naphthol and 5,6,7,8-tetrahydro-1-naphthol are rather insoluble in water and hydrogenation is not successful on Rh|C at room temperature. We were, however, able to hydrogenate these compounds by heating the catholyte, which allowed sufficient material to dissolve. β-Naphthol gave almost exclusively 5,6,7,8-tetrahydro-2-naphthol which was not further hydrogenated. 5,6,7,8-Tetrahydro-1-naphthol, on the other hand, was hydrogenated (on a fresh catalyst electrode) to a mixture of the decalones and decalols. The current yield, however, was low in both cases and the electrode was somewhat poisoned after each hydrogenation, which probably explains why the hydrogenation of β-naphthol stopped at the tetrahydro stage.

Solvent effects were investigated and a pronounced decrease in catalyst activity due to organic solvents was found. The addition of just 5% methanol to the aqueous catholyte decreases the activity of the Rh|C catalyst electrode toward hydrogenation of phenol. Recovery of 68% **1**, 27% **2**, and only 5% cyclohexanol **3** was observed when 15% methanol in 0.2 M H_2SO_4 was used and 6 F/mol were passed. The same effect was found by addition of ethanol, butanol, dioxane, and acetic acid. The size of the inhibiting effect is dependent on the activity of the particular electrode. Thus, freshly prepared Rh|C electrodes were less sensitive to this cosolvent effect than similar electrodes which had been previously used.

The effect of the organic cosolvent is readily visible since hydrogen evolution at a Pt|C or Rh|C cathode in aqueous H_2SO_4 is totally depressed by addition of phenol to the catholyte. If, however, an organic cosolvent is present, little depression of the hydrogen evolution is observed. The effect of the solvent seems to be the exclusion of the phenol from the catalyst by competitive adsorbtion in such a way that the reduction of protons is still possible. This effect must also be present in catalytic hydrogenations. In that case only the rate, not the yield, is affected because the system is closed. The electrochemical system used here is, however, open and hydrogen gas is lost.

This inhibition by organic cosolvents limits the presently constituted method. Although quite insoluble liquid aromatics like cumene and *tert*-butylbenzene were hydrogenated sat-

isfactorily by using rapid stirring of the suspension, α-methylnaphthalene proved to be inert.

Experimental Section

All hydrogenations were performed in a divided H-type cell with two glass frits of medium porosity as the dividing membrane. The catholyte volume was approximately 100 mL. The electrolyte was 0.2 M H_2SO_4, and the working electrode consisted of six carbon rods (6 mm diameter, 100 mm long), onto which the catalyst metal had been electroplated. The geometric area of the catalyst electrode was approximately 69 cm^2. A piece of Pt sheet was used as the counter electrode. This assured that the anodic reaction was the production of O_2. All experiments were performed at constant current using a H.P. 6266B DC power supply.

The plating solutions used for cathode preparation were either a 2% aqueous H_2PtCl_6 solution, a 2% $RhCl_3$ solution in 0.1 M H_2SO_4, or a 2% $PdCl_2$ solution in 0.1 M H_2SO_4. In one case the H_2PtCl_6 supplied by Alfa Ventron failed to give the expected platinum black plating. Each carbon rod was plated separately centered in a cylindrical Pt-sheet anode using 1 A for 5 min. The Ni|C electrodes were plated from a solution of 10 g of $NiSO_4$ in 50 mL of H_2O + 50 mL of concentrated NH_4OH with a current of 1 A for 5 min.

Most hydrogenations were performed using 2 g of substrate. After the electrolysis was stopped the catholyte was extracted either directly or in the case of hydrogenation of aniline, after basification with $NaHCO_3$, with 5 × 100 mL of CH_2Cl_2, dried over $MgSO_4$, and evaporated.

The products were identified by NMR of the reaction mixture and comparison of the gas liquid chromatography (GC) retention times with these of authentic samples, or after isolation by preparative GC or high-pressure liquid chromatography by their NMR and MS data. Quantitation was performed by GC using internal standards. Current yields were calculated using an assumed stoichiometry of 6 e^-/molecule.

The most abundant isomer of 2,6-dimethylcyclohexanol, produced in 82%, gave a NMR spectrum with a sharp doublet at 1.0 ppm demonstrating equivalency of the two methyls. The methine proton next to the hydroxyl group gave an unresolved singlet at 3.55 ppm with no observable splitting indicating an axial–equatorial or equatorial–equatorial coupling. On this basis the isomer was identified as the *cis,cis*-2,6-dimethylcyclohexanol.

Acknowledgment. This work was generously supported by the National Institutes of Health, GM 24493-01, and in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—*cis*-3 (R = 2-Me), 7443-70-1; *trans*-3 (R = 2-Me), 7443-52-9.

References and Notes

(1) M. Byrne and A. T. Kuhn, *J. Chem. Soc., Faraday Trans. 1*, **68**, 355 (1972).
(2) K. Junghans, U.S. Patent 3 925 173 (1975).
(3) I. V. Kudryashov et al., *Tr. Mosk. Khim. Tekhnol. Inst.*, **68**, 260 (1970).
(4) X. De Hemptinne and J. C. Jungers, *Z. Phys. Chem. (Frankfurt am Main)*, **15**, 137 (1958).
(5) K. N. Campbell and E. E. Young, *J. Am. Chem. Soc.*, **65**, 965 (1943).
(6) F. Fichter and R. Stocker, *Ber.*, **47**, 2015 (1914).
(7) W. D. Bancroft and A. B. George, *Trans. Am. Electrochem. Soc.*, **57**, 399 (1930).
(8) M. V. Sitaraman and V. V. Raman, *Curr. Sci.*, **16**, 23 (1947).
(9) S. Ono and T. Yamauchi, *Bull Chem. Soc. Jpn.* **25**, 404 (1952); S. Ono and T. Hayashi, *ibid.*, **26**, 11 (1953); S. Ono and T. Hayashi, *ibid.*, **26**, 232 (1953).
(10) I. Morcos, *J. Electrochem. Soc.*, **124**, 13 (1977).
(11) R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, New York, N.Y., 1965.
(12) H. A. Smith and R. G. Thompson, *Adv. Catal.*, **9**, 727 (1957).
(13) G. Gilman and G. Cohn, *Adv. Catal.*, 9, 733 (1957).
(14) Y. Takagi et al., *J. Catal.*, **8**, 100 (1967).

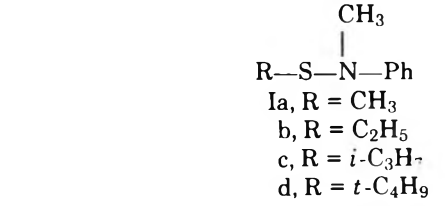
Chemistry of Sulfenamides. 1. Study of the Rearrangements of Sulfenanilides

Parvis Ainpour and Norman E. Heimer*

Department of Chemistry, University of Mississippi, University, Mississippi 38677

Received July 15, 1977

The thermal rearrangement of *N*-arylsulfenamides was first reported by Zincke and Eismayer.[1] Later the rearrangement of various sulfenanilides was studied by Moore and Johnson,[2] and the rearrangement of *N*-thiazolylsulfenamides was reported by Hoggarth.[3] More recently, the rearrangement has been studied by Davis and co-workers.[4] We would like to report here the results of our studies on the rearrangements of *N*-methylalkanesulfenamides Ia–d.



The sulfenamides were prepared by reaction of the appropriate sulfenylchloride with *N*-methylaniline and purified by vacuum distillation. Unless care was taken the methanesulfenanilide (Ia) rearranged to a mixture of *o*- and *p*-methylthio-*N*-methylanilines during distillation; however, the ethane, 1-methylethane- and 1,1-dimethylethanesulfenanilides could be vacuum distilled without decomposition. The structures of the sulfenanilides were confirmed by examination of their spectra and the observation that under acidic conditions in the presence of iodide ion iodine was liberated.[5,6] The NMR spectra of Ia–Id exhibited resonances for the *N*-methyl groups, the *S*-alkyl groups, and 5-aromatic protons and established that the sulfur atom was attached to the nitrogen atom and not to the aromatic ring.

Upon heating Ia neat at 150 °C in an oil bath, it was observed that it was transformed into a mixture of *o*- and *p*-methylthio-*N*-methylanilines. Vacuum distillation of the crude rearrangement products followed by column chromatography of the sulfide-containing fraction over Florisil in hexane gave 2-methylthio-*N*-methylaniline (IIa) and 4-methylthio-*N*-methylaniline (IIIa) as pure liquids. These compounds were identified by their spectroscopic properties. The NMR spectrum of the ortho isomer showed a complex coupling pattern between δ 7.5 and 6.3 that gave an integrated area of four protons, a broad peak for the amino hydrogen at δ 4.75, a three-proton singlet at δ 2.76 for the *N*-methyl group, and a three-proton singlet at δ 2.18 for the *S*-methyl group. The IR spectrum indicated the presence of the N–H group and an absorption band at 750 cm^{-1} which indicated that this was the ortho isomer. The para isomer gave an NMR spectrum that was composed of an aromatic region, δ 7.48 to 6.15, characteristic of the AA′BB′ system of a para-disubsitituted benzene, a broad N–H singlet at δ 4.68, a three-proton singlet for the *N*-methyl group at δ 2.6, and a three-proton singlet for the *S*-methyl group at δ 2.25. The IR spectrum indicated the presence of the N–H group and an absorption band at 820 cm^{-1} which further substantiated the assignment of the para structure. The same products were obtained upon heating Ia at 60 °C in CCl_4, acetonitrile, or CCl_4 with HBr in acetic acid added.

The ethanesulfenanilide (Ib) rearranged as did Ia upon heating in CCl_4 at 60 °C, and the products were separated and identified by the same general procedure just described, the only difference being the presence of an *S*-ethyl group in place of an *S*-methyl group. Under the same conditions, the rearrangement of the *S*-isopropyl, Ic, and *S*-*tert*-butyl, Id, derivatives was not observed, the only products of these attempted rearrangements being *N*-methylaniline and mixtures of dialkyl di- and trisulfides. Heating Ic neat at 150 °C gave a mixture of *N*-methylaniline, isopropyl sulfide, and isopropyl trisulfide. Refluxing Ic in acetonitrile with a trace of *p*-toluenesulfonic acid added gave *N*-methylaniline and isopropyl disulfide as the only identifiable products and heating Ic in benzene with aluminum chloride gave *N*-methylaniline, isopropyl disulfide, and isopropyl trisulfides. Refluxing Ic in

0022-3263/78/1943-2061$01.00/0

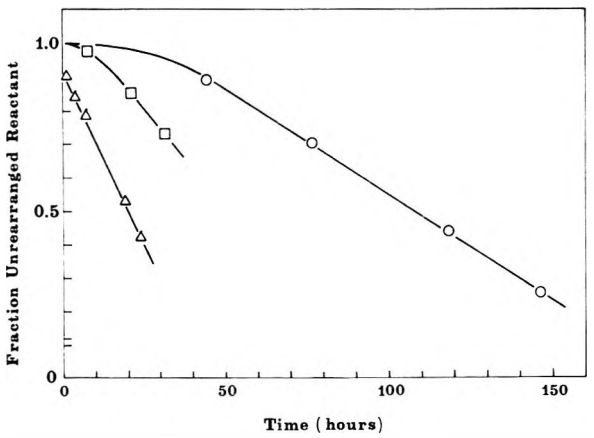


Figure 1. Plot of the fraction of unrearranged Ia vs. time in various solvents (open circles, CD_3CN; squares, CCl_4; triangles, CCl_4 with HBr/HOAc).

ethanol with a molar equivalent of aniline hydrochloride gave *N*-methylaniline, aniline, and isopropyl disulfide as the products. In each of the cases just mentioned, there also were obtained colored materials that were not identified. Similar attempts with Id gave as products disulfides and trisulfides and *N*-methylaniline.

When the rearrangement of Ia in acetonitrile-d_3 was carried out with added *N,N*-dimethylaniline, two new products were observed. Analysis of the product mixture by GC/MS indicated that the new products were methylthio-*N,N*-dimethylanilines based upon the observed molecular ions at *m/e* 167. The *o*- and *p*-methythio-*N,N*-dimethylanilines were prepared by the reaction of methanesulfenyl chloride with dimethylaniline in chloroform. After purification of the products by distillation, they were identified by their NMR spectra and by comparison with the published sepectra.[7] These compounds were shown to be identical with those obtained in the trapping experiment by comparison of the chemical shifts of the sulfur and nitrogen methyl groups, and by comparison, by coinjection onto a gas chromatograph with the material obtained from the rearrangement reaction The yield of the trapped product was approximately four times the yield of the normal rearrangement products.

The above described experiment suggests two interpretations. Either the rearrangement is in part intermolecular or the rearrangement is exclusively intramolecular with rearrangement occurring following sulfenanilide–amine exchange. The latter is known to occur between primary amines and sulfenanilides and has been used to account for the presence of crossover products when arenesulfenanilides are rearranged in the presence of aniline derivatives.[4] Davis has reported that no crossover products were found when arensulfenanilides were rearranged in *N,N*-diethylaniline[4] since tertiary amines cannot undergo sulfenanilide–amine exchange. Since the sulfenanilide–amine exchange reaction can be ruled out as a reaction pathway for the tertiary amines, the transfer of alkylthio groups from the alkanesulfenanilide to *N,N*-dimethylaniline must have been the result of an intramolecular reaction. This is the first unambiguous demonstration of such an intermolecular rearrangement of sulfenanilides.

We have also made a brief study of the kinetics of the rearrangement by monitoring the NMR spectrum of the reaction mixture as a function of time, Figure 1. Fortunately, the *N*-methyl resonance of the reactant (Ia), δ 3.33, is different from that of IIa, δ 2.75, and IIIa, δ 2.65, so that the relative concentrations of reactants and products can be determined by measuring peak heights in the spectrum. Evaluation of concentrations determined this way shows that in CCl_4 and CCl_4 with a trace to HBr/HOAc, the reaction appears to be zero order, that is a plot of concentration vs. time is linear. The rate is enhanced by the addition of acid so that the reaction also appears to be acid catalyzed.[4] When the kinetics of the rearrangement of Ia in acetonitrile-d_3 was followed by NMR, the plot of concentration vs. time is linear after an initial induction period. This evidence also suggests that the reaction is catalyzed by some species generated in the reaction.

The evidence given above suggests that the rearrangement is at least in part intermolecular. If the slow step in the reaction is the displacement of a protonated amine from the conjugate acid of the sulfenamide by either *N*-methylaniline or *N,N*-dimethylaniline giving the sulfide as one product and an aniline, *N*-methylaniline, as the other, then it is also possible to rationalize the linear plot of concentration vs. time since the reactant is regenerated (eq 1).

$$\mathrm{PhNMeR' + RSN(H^+)(Ph)Me \rightarrow NMe_2 - SR + PhN^+H_2Me} \quad (1)$$

R′ = H or Me

It is also possible to rationalize the failure of the *S*-isopropyl and *S*-*tert*-butyl derivatives to react because that reaction corresponds to a nucleophilic displacement in the isobutyl- and neopentylhydrocarbon systems which are known to be slower than displacements in ethyl- and *n*-propylhydrocarbon systems.[8]

The conclusions of the present study are that (1) the rearrangements of sulfenanilides probably provide a convenient route to ortho and para alkythioanilines and (2) the rearrangement is at least in part intermolecular based upon the trapping experiment with *N,N*-dimethylaniline.

Experimental Section

Melting points are corrected. Infrared spectra were run on a Perkin-Elmer 137 spectrophotometer and absorbances are reported in cm^{-1}. Thin-layer chromatograms were run on glass plates coated with a 0.01 in. layer of silica gel PR-254 (Brinkman). GPC analyses were done using a 5 ft by $\frac{1}{8}$ in. copper column packed with 5% SE-30 on 60/80 Chromosorb W. Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer with tetramethylsilane as the internal standard and carbon tetrachloride as the solvent, unless otherwise indicated. Mass spectra were obtained with a DuPont-492 double-focusing high-resolution spectrometer at an ionizing electron energy of 75 eV, an inlet temperature of 200 °C, and using either the direct or gas chromatograph inlet system. The following materials were obtained commercially and used without purification: *N*-methylaniline, *N,N*-dimethylaniline, and methyl, ethyl, and isopropyl disulfide. *tert*-Butyl disulfide was purified from a crude mixture of disulfide and trisulfide by fractional distillation at 0.1 mmHg through a 6 in. column packed with glass helices.

***N*-Methylmethanesulfenanilide.** In a 100-mL round-botton flask, 4.7 g (0.05 mol) of dimethyl disulfide was dissolved in 50 mL of chloroform, and while the solution was stirred, it was cooled to −40 °C. Then 2.26 mL of liquid chlorine, previously condensed into a graduated centrifuge tube and cooled in a dry ice–acetone bath, was allowed to evaporate into the solution of disulfide while the bath temperature was kept between −35 and −40 °C. The contents of the flask were transferred to an addition funnel and added slowly with stirring to a solution of 10.7 g of *N*-methylaniline (0.1 mol), 50 mL of ether, 5 g of NaOH, and 20 mL of water contained in a 200-mL flask which had been placed in an ice bath. After the addition of sulfenyl chloride was complete, the reaction mixture was stirred for 10 min and transferred to a separatory funnel. The organic layer was separated and washed with tap water until the pH of the aqueous phase was about 6. The organic layer was then separated and dried over sodium sulfate and filtered; the filtrate was concentrated under reduced pressure. The resulting oil was then distilled at 0.1 mmHg, and the fraction boiling at 70–80 °C was collected and analyzed as follows: NMR δ 7.3–6.38 (m, 5, aromatic), 3.33 (s, 3, NCH_3), 2.12 (s, 3, SCH_3); MS *m/e* (rel intensity) 155 (3.5), 154 (3.5), 153 (35), 138 (21), 123 (14), 109 (11), 107 (16), 106 (57), 105 (14), 104 (21), 97 (21), 94 (2), 91 (1.4), 79 (29), 78 (23), 77 (100), 76 (3.5), 74 (3.5), 66 (7), 65 (14), 64 (9.3), 63

(14); $n^{25}D$ 1.5760. The yield based on methanesulfenyl chloride was 70%. Anal. Calcd for $C_8H_{11}NS$: C, 62.74; H, 7.19. Found: C, 62.92; H, 7.17.

***N*-Methylethane- and 1-Methylethanesulfenanilide.** The same procedure was followed as outlined for *N*-methylmethanesulfenanilide beginning with the appropriate disulfide. The yields were similar and analytical data are as follows respectively: $n^{25}D$ 1.5653; bp 70 °C (0.1 mm); NMR δ 7.18–6.5 (m, 5, aromatic), 3.2 (s, 3, NCH_3), 2.6 (q, 2, J = 8 Hz, SCH_2CH_3), 1.1 (t, 3, J = 8 Hz, SCH_2CH_3); MS *m/e* (rel intensity) 169 (3.9), 168 (9), 167 (54), 152 (5.4), 140 (3.9), 139 (18), 138 (45), 123 (11.8), 122 (11.8), 109 (27), 108 (4.5), 107 (45), 106 (100), 105 (18), 104 (30), 98 (57), 80 (34), 79 (34), 78 (100), 66 (16), 65 (18), 64 (9), 51 (50). Anal. Calcd for $C_9H_{13}NS$: C, 64.67; H, 7.78; N, 8.35. Found: C, 64.37; H, 7.64; N, 8.37.

***N*-Methyl-1-methylethanesulfenanilide:** $n^{25}D$ 1.5575; NMR δ 7.2–6.5 (m, 5, aromatic), 3.32 (s, 3, NCH_3), 3.28 (septuplet, 1, $SCH(Me)_2$), 8.82 (d, 6, J = 8 Hz, $SCH(CH_3)_2$); MS *m/e* (rel intensity) 181 (100), 139 (15), 117 (5), 116 (5), 106 (10), 105 (11), 99 (13), 97 (90), 76 (15), 75 (20), 74 (80), 64 (33), 60 (20), 59 (15), 58 (55). Anal. Calcd for $C_{10}H_{15}NS$: C, 66.29; H, 8.28; N, 7.73. Found: C, 66.11; H, 8.14; N, 7.56.

***N*-Methyl-1,1-dimethylethanesulfenanilide.** The sulfenyl chloride was prepared by dissolving 10.7 g of *tert*-butyl disulfide in 50 mL of chloroform and chlorinolysis at room temperature with 2.26 mL of liquid chlorine. Titration and NMR indicated an 85% yield of *tert*-butylsulfenyl chloride based on the amount of chlorine. The condensation with 10.7 g of *N*-methylaniline and purification was done as described earlier. The product was distilled at 0.1 mmHg with the head temperature ranging from 80 to 90 °C. The analytical data are as follows: $n^{25}H$ 1.5505; NMR δ 7.18–6.5 (m, 5, aromatic), 3.35 (s, 5, NCH_3), 1.22 (s, 9, $SC(CH_3)_3$); MS *m/e* (rel intensity) 197 (0.7), 196 (1.4), 195 (14), 141 (7), 140 (10), 139 (100), 123 (7), 122 (10), 107 (93), 96 (28), 78 (21), 77 (21), 76 (93), 60 (36), 56 (86), 50 (32). Anal. Calcd for $C_{11}H_{17}NS$: C, 67.69; H, 8.71; N, 7.18. Found: C, 67.45; H, 8.60; N, 7.09.

Rearrangement of *N*-Methylmethanesulfenanilide. Rearrangement was accomplished with either pure or crude sulfenanilide by heating it at 150 °C in an oil bath. The extent of reaction was determined by monitoring the concentration of starting material by GLC. After all of the starting material had vanished, the reaction mixture was distilled under 0.1 mm of pressure and several fractions were collected, ranging from 45 to 90 °C. GLC analysis of the fractions indicated the presence of *N*-methylaniline and two other components. Separation of each component was accomplished by column chromatography. The column was packed with Florisil at a weight ratio of 30/1 and hexane was used as the eluent. Fractions with similar composition as determined by TLC were combined, concentrated under reduced pressure, and then distilled at 0.1 mmHg. The overall yield of rearranged products using *N*-methylaniline as the limiting reagent was 35%.

2-Methylthio-*N*-methylaniline: bp 70 °C (0.1 mm); NMR δ 7.48–6.3 (m, 4, aromatic), 4.7 (s, 1, NH), 7.3 (s, 3, NCH_3), 2.18 (s, 3, SCH_3); IR (neat) 3500 (NH), 750 cm^{-1} (ortho-disubstituted benzene). Anal. Calcd for $C_8H_{11}NS$: C, 62.74; H, 7.10. Found: C, 63.00; H, 7.35.

4-Methylthio-*N*-methlaniline: bp 78 °C (0.1 mm); NMR δ 7.38–6.08 (m, 4, ArH), 3.68 (s, 1, NH), 2.6 (s, 3, NCH_3), 2.25 (s, 3, SCH_3); IR (neat) 3500 cm^{-1} (NH), 820 cm^{-1} (para-disubstituted benzene). Anal. Calcd for $C_8H_{11}NS$: C, 62.74; H, 7.19. Found: C, 63.01; H, 7.17.

Rearrangement of *N*-Methylethanesulfenanilide. The same procedure as was described earlier for *N*-methylmethanesulfenanilide was followed and the rearranged products were separated the same way. The combined yield of rearranged products was 30% based on *N*-methylaniline.

2-Ethylthio-*N*-methylaniline: bp 80 °C (0.1 mm); NMR δ 7.32–6.22 (m, 4, ArH), 4.92 (s, 1, NH), 2.78 (s, 3, NCH_3), 2.58 (q, 2, SCH_2CH_3), 1.16 (t, 3, J = 8 Hz, SCH_2CH_3); IR (neat) 3600 (n-H), 760 cm^{-1} (ortho-disubstituted benzene); MS *m/e* (rel intensity) 169 (5.2), 168 (13), 167 (100), 139 (4.3), 138 (30), 137 (53), 136 (8.6), 135 (22), 134 (13), 110 (6.5), 109 (6.5), 108 (22), 105 (22), 104 (8.6), 103 (8.6), 96 (86), 79 (4.3), 78 (8.6), 77 (22), 65 (17), 58 (17), 43 (22).

4-Ethylthio-*N*-methylaniline: bp 85 °C (0.1 mm); NMR δ 7.2–6.18 (m, 4, 4 ArH), 3.58 (s, 1, N_1H), 7.34 (s, 3, NCH_3), 2.62 (q, 2, J = 8 Hz, SCH_2CH_3), 1.18 (t, 3, J = 8 Hz, SCH_2CH_3); IR (neat) 3550 (NH), 815 (para-disubstituted benzene); MS *m/e* (rel intensity) 169 (3.8), 168 (7.1), 167 (50), 154 (11), 153 (22), 152 (22), 150 (22), 139 (22), 139 (14), 138 (100), 136 (18), 106 (14), 75 (14), 58 (14), 43 (64.5). Anal. Calcd for $C_9H_{13}NS$: C, 64.67; H, 7.78. Found: C, 65.20; H, 7.82.

Rearrangement of Ia in *N,N*-Dimethylaniline. A solution of 100 μL of *N*-methylmethanesulfenanilide and 200 μL of *N,N*-dimethylaniline in 1 mL of CD_3CN was placed in a small test tube closed with a cork stopper and kept at 60 °C. The reaction was followed by observing the intensity of the *N*-methyl protons of Ia in the NMR spectrum of the mixture. After complete disappearance of the starting sulfenanilide, the reaction mixture was analyzed by GC/MS and NMR. The GC/MS indicated the presence of two components with *m/e* 167 for the parent ions corresponding to the molecular weights of the two isomeric crossover products *o*- and *p*-methylthio-*N,N*-dimethylaniline. Coinjection of samples of *o*- and *p*-methylthio-*N,N*-dimethylaniline prepared by the reaction of methanesulfenyl chloride with *N,N*-dimethylaniline in chloroform onto a gas chromatograph with the product mixture obtained from the rearrangement reaction gave enhancement of the peaks that corresponded to the material with molecular weights of 167.

Acknowledgments. We gratefully acknowledge support of this work by the Committee on Faculty Research at The University of Mississippi and the assistance of Dr. S. Billets of the Research Institute of Pharmaceutical Sciences of The University of Mississippi in obtaining the mass spectra.

Registry No.—Ia, 65605-22-3; Ib, 63533-62-0; IC, 63533-63-1; Id, 65605-23-4; *N*-methylaniline, 100-61-8; dimethyl disulfide, 624-92-0; diethyl disulfide, 110-81-6; diisopropyl disulfide, 4253-89-8; methanesulfenyl chloride, 5813-48-9; ethanesulfenyl chloride, 1496-75-9; isopropanesulfenyl chloride, 19760-04-4; *tert*-butyl disulfide, 110-06-5; *tert*-butanesulfenyl chloride, 52322-55-1; 2-methylthio-*N*-methylanine, 13372-62-8; 4-methylthio-*N*-methylaniline, 58259-33-9; 2-ethylthio-*N*-methylanilene, 65605-24-5; 4-ethylthio-*N*-methylanilene, 65606-25-6.

References and Notes

(1) T. Zincke and K. Eismayer, *Ber.*, **51**, 751 (1918).
(2) M. L. Moore and T. B. Johnson, *J. Am. Chem. Soc.*, **57**, 1517 (1935); M. L. Moore and T. B. Johnson, *ibid.*, **57**, 2234 (1935); M. L. Moore and T. B. Johnson, *ibid.*, **58**, 1091 (1936); and M. L. Moore and T. B. Johnson, *ibid.*, **58**, 1960 (1936).
(3) E. Hoggarth, *J. Chem. Soc.*, 110 (1947).
(4) F. A. Davis, E. R. Fretz, and C. J. Horner, *J. Org. Chem.*, **38**, 690 (1973); F. A. Davis, C. J. Horner, E. R. Fretz, and J. F. Stackhouse, *ibid.*, **38**, 695 (1973); F. A. Davis, S. Divald, and A. H. Confer, *Chem. Commun.*, 294 (1971).
(5) O. Foss, *Acta Chem. Scand.*, **1**, 307 (1947).
(6) W. Groebel, *Chem. Ber.*, **92**, 2887 (1959).
(7) A. Zwerg and J. E. Lehnsen, *J. Am. Chem. Soc.*, **87**, 2647 (1965).
(8) A. Streitwieser, "*Solvolytic Displacement Reactions*", McGraw-Hill, New York, N.Y., 1962, p 12.

A Major Improvement in the Osmium Catalyzed Vicinal Hydroxylation of Olefins by *tert*-Butyl Hydroperoxide

Kageyasu Akashi, Robert E. Palermo, and K. Barry Sharpless*[1]

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

Received November 8, 1977

We recently described a new osmium catalyzed procedure for the cis dihydroxylation of olefins.[2] Although generally superior to the existing[3] methods for this transformation, it involves rather alkaline conditions, and thus is successful only with molecules which are not sensitive to base. This limitation has now been removed with the discovery that Et_4NOH can be replaced by Et_4NOAc[4] if at the same time the solvent is changed from *tert*-butyl alcohol to acetone.[5]

As revealed in Table I, this new procedure works well for base-sensitive molecules. Esters are not hydrolyzed (entries 4–7), and ethyl crotonate gave only the *threo*-glycol (entries 4–6) with no sign of the epoxide which would arise if conjugate addition of *tert*-butyl hydroperoxide were a competing process. Furthermore, even for simple olefins such as 4-octene

0022-3263/78/1943-2063$01.00/0

Table I. Vicinal Diols from Olefins[a]

Olefin	Scale in mol	Equiv of[b] Et_4NOAc	% yield[c]
1. (*E*)-4-Octene	0.1	0.25	81
2. (*E*)-4-Octene	1.0	0.25	78
3. (*E*)-4-Octene	0.1	0.25[d]	74
4. Ethyl crotonate	0.1	0.25	71
5. Ethyl crotonate[e]	1.0	0.25	72
6. Ethyl crotonate[f]	0.1	0.25	58
7. Citronellol acetate	0.05	0.25	83
8. Cyclohexene	0.1	0.125	51
9. Cyclohexene[e]	0.1	0.125	52
10. Cyclohexene	0.1	0.125[d]	45
11. 2,3-Dimethyl-2-octene	0.1	0.25	0

[a] In all cases the amount of OsO_4 catalyst was 0.2% (1/500) of the amount of the olefin. [b] Equivalent here is based on the amount of olefin. [c] All yields are for distilled or recrystallized products. [d] In this case Et_4NOAc was generated in situ by stirring $Et_4NCl{\cdot}H_2O$ and anhydrous NaOAc together in acetone. [e] The oxidant here was 70% *tert*-butyl hydroperoxide. [f] In this preparation one-half the usual volume of acetone was used.

(entry 1) the yields were about 10% better than those realized with the Et_4NOH method.[2] Interestingly, the Et_4NOAc method fails with tetrasubstituted olefins (entry 11); it appears that the more vigorous hydrolytic conditions of the Et_4NOH method account for its success with this substitution type.

It is important to emphasize that both these methods (Et_4NOAc and Et_4NOH) still have shortcomings. For example, neither procedure succeeds with cholesterol, and it seems reasonable to anticipate negative results with most hindered tri- and tetrasubstituted olefins. As discussed previously,[2] we feel the problem lies in the inertness of hindered osmate esters to further reaction. Consistent with this hypothesis is the observation that olefins which fail to react in these systems are potent inhibitors of the catalytic process. Thus when the hydroxylation of a normally reactive olefin, such as cyclohexene, is attempted in the presence of cholesterol no reaction occurs. The cholesterol apparently traps the osmium by forming an extremely stable osmate ester. In order to further improve these catalytic hydroxylations we are seeking more effective ways for hydrolyzing such obstinate osmate esters.

These new catalytic procedures (Et_4NOH/TBHP[2] and Et_4NOAc/TBHP) for vicinal cis dihydroxylation of olefins are the most economical methods currently available for this transformation. The only other *effective* catalytic method for this conversion is that employing *N*-methylmorpholine *N*-oxide; this technique was recently reported by chemists at Upjohn.[6a] The *N*-oxide procedure is very impressive especially with disubstituted olefins. It is not yet known how generally applicable it is to trisubstituted olefins (one example was given).[6a] In our hands it failed to react with 2,3-dimethyl-2-octene; this tetrasubstituted olefin is readily converted to the corresponding diol using the Et_4NOH/TBHP procedure.[2] It seems likely that the Et_4NOAc/TBHP procedure and especially the Et_4NOH/TBHP procedure[2] will prove more reliable for tri- and tetrasubstituted olefins than the *N*-oxide method. Another important factor in comparing the TBHP and *N*-oxide methods is cost. A mole of TBHP (Aldrich) is 20 times less expensive than a mole of *N*-methylmorpholine *N*-oxide (E.K.). Since TBHP is available at much lower prices in bulk quantities (55-gal drums and tank cars), this price differential would be even larger for industrial scale applications. A recent patent describes the use of TBHP for the osmium catalyzed oxidation of allyl alcohol to glycerol.[6b]

In conclusion, these new TBHP-based methods are applicable to a wider range of olefin types than are the other catalytic methods.[3,6a] However, it must be pointed out that the most certain means for producing a *cis*-diol from an olefin is still reaction with a stoichiometric amount of osmium tetroxide in pyridine.

Experimental Section

The olefins are available commercially and were used without purification. Reagent grade acetone was employed as the solvent, except in the 1-mol scale oxidation of (*E*)-4-octene (entry 2, Table I) where wash grade acetone was utilized without significant deleterious effect (yield was only 3% lower). $Et_4NOAc{\cdot}4H_2O$ (Eastman Kodak), $Et_4NCl{\cdot}H_2O$ (Aldrich), and anhydrous NaOAc (Aldrich) were used as obtained.

There are three commonly available grades of *tert*-butyl hydroperoxide (TBHP) and all are sold by Lucidol, a division of the Pennwalt Corporation. They differ in the amounts of *tert*-butyl alcohol (TBA), water, and di-*tert*-butyl peroxide (DTBP) present as impurities. There are two 70% grades: one (Lucidol-TBHP-70X) contains TBHP (~70%), water (~30%), and traces (<1%) of aldehydes and TBA; the other (Lucidol-TBHP-70) contains TBHP (~70%), DTBP (~19%), and ~11% of TBA and water. The third grade (Lucidol-TBHP-90) contains ~90%TBHP, ~6%TBA, ~4% H_2O, and <1%DTBP; this 90% grade is also available from Aldrich Chemical Co. We describe here procedures using both the 90% grade (density = 0.90, ~9.0 mmol of TBHP/mL) of TBHP and the 70% grade (density = 0.94, ~7.2 mmol of TBHP/mL) which is free of DTBP (i.e., Lucidol-TBHP-70X). Both work equally well in these oxidations. The only grade to be avoided in this and other catalytic applications of TBHP is that containing ~19% DTBP (i.e., Lucidol-TBHP-70). The presence of DTBP dramatically lowers the thermal stability of TBHP. Although care should always be exercised in handling compounds with O–O bonds, TBHP is one of the most stable commercially available peroxidic substances, and the 70% grade which contains 30% water is sold in 55-gal drums. Detailed information on the use and handling of organic peroxides is contained in various technical bulletins available from Lucidol.

The OsO_4 (Matthey Bishop, Inc.) catalyst solution was prepared as described by Daniels and Fischer with the exception that *tert*-butyl hydroperoxide was used in place of H_2O_2 as the stabilizer and reagent grade *tert*-butyl alcohol was used without further purification. Recipe: 1 g of OsO_4, 199 mL of reagent grade *tert*-butyl alcohol, and 1 mL of 90+% *tert*-butyl hydroperoxide; each milliliter contains 5 mg ($\sim 2 \times 10^{-5}$ mol) of OsO_4.[7]

Two general procedures (A and B) are described below. Although they are very similar, the differences are worth pointing out. Procedure B is intended for cases where water-soluble diols are produced, hence the modification in the workup where the aqueous phase is concentrated before the final extractions. Procedure B also differs from procedure A in that less Et_4NOAc is employed. Less Et_4NOAc is required to obtain good results with olefins (e.g., cyclohexene) which are not prone to over-oxidation than with olefins (e.g. 4-octene) which are. If one is uncertain about how the olefin at hand should be regarded in this context, the higher (25%) level of Et_4NOAc of procedure A should be utilized. Using more Et_4NOAc than the minimum necessary to obtain the optimium yield with a given olefin has no adverse effect. For reasons which are not obvious to us, Et_4NOAc is fairly expensive at present. This provided the incentive for developing a modification (entries 3 and 10, Table I) wherein Et_4NOAc is generated in situ by combining the inexpensive ingredients Et_4NCl and anhydrous NaOAc in acetone (we thank Dr. Irwin Klundt of Aldrich for suggesting this approach).

The reaction in acetone is less vigorous than that in the *tert*-butyl alcohol system,[2] and the amount of heat evolved upon addition of catalyst is dependent upon the olefin. With the volumes used here, the reaction mixtures warm only slightly if at all. The initial cooling serves to slow the reaction at first and this appears to have favorable effects on the yields and helps suppress over-oxidation. If the initial volume of acetone is halved, the pot temperature rises to ca. 40 °C unless cooled with a water bath. While the yield with this reduced solvent volume looked promising by GLC, isolated yields were inferior to those at lower concentrations.

Procedure A. *threo*-4,5-Dihydroxyoctane. A 1-L Erlenmeyer flask, equipped with magnetic stirrer, was charged with 200 mL of acetone, 11.2 g (100 mmol) of (*E*)-4-octene, 6.5 g (25 mmol) of $Et_4NOAc{\cdot}4H_2O$, and 18 mL (ca. 162 mmol) of 90+% *tert*-butyl hydroperoxide. After stirring at room temperature until the Et_4NOAc had dissolved, the resulting solution was cooled in an ice bath and 10 mL (i.e., 50 mg or 0.2 mmol of OsO_4) of the catalyst solution containing OsO_4 in *tert*-butyl alcohol was added in one portion. The solution immediately became brownish purple. After 1 h the ice bath was re-

moved and the reaction mixture was allowed to warm to room temperature, stoppered loosely, and stirred overnight. Ether (400 mL) was added and the resulting mixture was cooled by stirring in an ice bath. Then 50 mL of freshly prepared 10% $NaHSO_3$ solution was added in one portion.[11] The ice bath was removed and stirring was continued for 1 h, at which point the organic layer had become almost colorless. Solid NaCl was added until the aqueous layer was saturated and stirring of the two-phase mixture was continued for several minutes. The organic layer was separated and washed with 50 mL of brine. The combined aqueous layers were extracted twice with 100-mL portions of ether. The combined organic layers were dried (Na_2SO_4), and when concentrated afforded an oil which upon distillation gave 11.8 g (81%) of *threo*-4,5-dihydroxyoctane: bp 87–90 °C (3 mm) [lit.[10a] bp 109.8–110 °C (8 mm)].

1-Mol Scale. The same procedure was also carried out on (*E*)-4-octene on a 1.0-mol scale and afforded 113.9 g (78%) of the distilled *threo*-diol (entry 5, Table I). In this case the amount of all the ingredients was simply increased by a factor of 10 over that employed in the 0.1-mol scale oxidation described in detail above.

Generation of Et_4NOAc in Situ. The Et_4NOAc was generated by combining 4.60 g (25 mmol) of $Et_4NCl{\cdot}H_2O$ and 4.10 g (50 mmol, 2 equiv based on $Et_4NCl{\cdot}H_2O$) of NaOAc in 200 mL of acetone and stirring for ca. 1 h (this use of NaOAc and $Et_4NCl{\cdot}H_2O$ in a molar ratio of 2:1 was found to afford better yields of diol than a 1:1 molar ratio). In the case of (*E*)-4-octene (entry 3, Table I), a somewhat lower yield (74%) was realized with this variation. We have established that chloride ion has a deleterious effect on these catalytic oxidations[8] and the incomplete precipitation of chloride ion (as NaCl) is probably responsible for the slightly poorer yield with this modification. It would be worthwhile to seek a means for causing more complete precipitation of the chloride ion. If chloride ion remains a problem it should be possible to find less expensive routes to tetraalkylammonium acetates ($Et_4NOAc{\cdot}4H_2O$ is presently selling for ca. 80¢/g). In any case, even in its present form this inexpensive method of generating Et_4NOAc should prove useful, especially for large-scale applications.

Procedure A. *threo*-2,3-Dihydroxyethyl Butyrate. Ethyl crotonate (11.4 g, 100 mmol) was transformed (as described in detail for (*E*)-4-octene) into 10.4 g (71%) of the *threo*-diol, bp 102–104 °C (6 mm)[lit.[3h] bp 123–125 °C (18 mm)]. The complete absence of the *erythro*-diol was established by its synthesis and subsequent spectral and chromatographic comparison with the threo reaction product.

Procedure A. 70% TBHP Modification: 1-Mol Scale Oxidation of Ethyl Crotonate. In a 6-L Erlenmeyer flask, equipped with magnetic stirrer, freshly distilled ethyl crotonate (114.14 g, 1 mol), 63.35 g (250 mmol) of $Et_4NOAc{\cdot}4H_2O$, and 240 mL (ca. 1.7 mol) of 70% *tert*-butyl hydroperoxide (Lucidol-70X) were combined in 2 L of acetone and stirred until the salt had dissolved.[9] The solution was cooled in an ice bath and 100 mL of the catalyst stock solution (2 mmol OsO_4) was added in one portion. After stirring for 1 h, the ice bath was removed, the flask was lightly stoppered, and the contents was left to stand overnight at room temperature. The resulting golden solution was divided into two 1250-mL portions and each portion was worked up identically. Two liters of ether was added to each and the mixture cooled by stirring in an ice bath; 250 mL of freshly prepared 10% $NaHSO_3$ solution was added in one portion to each half.[11] The ice bath was then removed from each and stirring continued for 1 h. Sufficient salt was added to saturate the aqueous layer and stirring was continued for several minutes. The phases were partitioned in a 4-L separatory funnel and the organic phase of each half was washed with 250 mL of brine. The aqueous layers of each portion were then extracted with two 500-mL portions of ether. The combined organic layers were dried overnight (Na_2SO_4) and concentrated to afford a residue that still contained considerable amounts of water. This material was diluted with 1500 mL of CH_2Cl_2 and an aqueous layer of ca. 75 mL separated. The two phases were partitioned and the aqueous phase was saturated with solid NaCl. This was then extracted with three 50-mL portions of CH_2Cl_2. The combined organic layers were dried again (Na_2SO_4) and concentrated to afford a clear oil which upon distillation gave 106.3 g (72%) of pure *threo*-2,3-dihydroxyethyl butyrate: bp 106–108 °C (7 mm).

Procedure A. Doubled Concentration. In a 500-mL Erlenmeyer flask, 11.86 g of 96% ethyl crotonate (100 mmol), 6.5 g (25 mmol) of $Et_4NOAc{\cdot}4H_2O$, and 24 mL (ca. 170 mmol) of 70% *tert*-butyl hydroperoxide were combined in 100 mL of acetone. This was chilled by stirring in an ice bath, and 10 mL of OsO_4 stock solution was added in one portion. After 1 h the ice bath was removed and the contents allowed to warm to room temperature. When the pot temperature exceeded 25 °C, it was immersed in a bath of 20 °C tap water, lightly stoppered, and allowed to stand in the bath overnight. The resulting golden solution was diluted with 200 mL of ether and chilled by stirring in an ice bath. Then 25 mL of freshly prepared 20% $NaHSO_3$ solution was added in one portion,[11] the ice bath was removed, and the contents of the flask was stirred for 1 h. The aqueous layer was saturated with NaCl and the two phases were partitioned. The organic layer was washed with 25 mL of brine. The combined aqueous layers were washed with two 50-mL portions of ether. The combined organic layers were dried overnight (Na_2SO_4) and concentrated, and the residue was taken up in 350 mL of CH_2Cl_2 which was then dried again (Na_2SO_4). Concentration of this solution gave a clear oil which upon distillation afforded 8.62 g (58%) of *threo*-2,3-dihydroxyethyl butyrate: bp 102 °C (6 mm).

Procedure A. 1-Acetoxy-6,7-dihydroxy-3,7-dimethyloctane. Citronellol acetate (7.8 g, 50 mmol) was converted to 9.6 g (83%) of the corresponding vicinal diol: bp 141–144 °C (3 mm) [lit.[10b] bp 90–95 °C (0.5 mm)].

Procedure A. Fails with 2,3-Dimethyl-2-octene. Attempted oxidation of 2,3-dimethyl-2-octene (14.0 g, 100 mmol) led to no reaction and the starting olefin was recovered.

Procedure B. *cis*-1,2-Dihydroxycyclohexane. The procedure works well on cyclohexene, with crude yields of crystalline diol approaching 80%. The limitation lies in further purification of this crude material, and recrystallization usually gives less than satisfactory results. Evaporation of mother liquors gives a syrupy residue that cannot be further recrystallized, but is nonetheless predominantly diol as verified by GLC.

Procedure B with cyclohexene (8.20 g, 100 mmol) is the same as A with the following exceptions: (1) Only 3.3 g (12.5 mmol) of $Et_4NOAc{\cdot}4H_2O$ was used (this is half the amount used in procedure A). (2) Before washing the NaCl saturated aqueous layer with ether it was concentrated almost to dryness on a rotary evaporator, then (as in procedure A) it was extracted twice with 100-mL portions of ether. The combined organic layers were dried (Na_2SO_4) and concentrated to give 8.54 g (74%) of white solid: mp 73–83 °C. Recrystallization from ether afforded 5.94 g (51%) of *cis*-1,2-dihydroxycyclohexane, mp 96.5–97 °C [lit.[10c] mp 98 °C]. Evaporation of the mother liquors gave approximately 3 g of yellow oil that was almost exclusively diol by GLC. Procedure B gives identical results when the larger amount of base, 6.5 g of $Et_4NOAc{\cdot}4H_2O$ (25 mmol), is used.

In another experiment, cyclohexene (8.20 g, 100 mmol) was oxidized by the above procedure to afford 8.68 g (75%) of crude solid. This was bulb-to-bulb distilled at reduced pressure to give 6.96 g (60%) of white solid, mp 85–86.5 °C. A single crystallization from chloroform/hexanes afforded 5.56 g (48%) of pure *cis*-1,2-dihydroxycyclohexane, mp 97.5–98 °C.

Procedure B. 70% TBHP Modification. The procedure is identical with that above except that 24 mL of Lucidol-70X TBHP was used as the oxidant. Cyclohexene (8.20 g, 100 mmol) was converted to 6.01 g (52%) of *cis*-1,2-dihydroxycyclohexane, mp 96–96.5 °C.

Procedure B. Generation of Et_4NOAc in Situ. $Et_4NCl{\cdot}H_2O$ (2.30 g, 12.5 mmol) and 2.05 g (25 mmol, 2 equiv based on $Et_4NCl{\cdot}H_2O$) of anhydrous NaOAc were combined in 200 mL of acetone and stirred for 1 h. A white solid remains suspended. Cyclohexene, oxidant, and catalyst stock were added as described above. When the reaction was complete, the golden solution was filtered before beginning the workup as previously described. Cyclohexene (8.20 g, 100 mmol) was converted to 8.49 g (73%) of crude diol. A single recrystallization (EtOAc) afforded 5.15 g (45%) of the cis diol, mp 95–96.5 °C.

Acknowledgment. We thank the National Science Foundation (CHE74-21260), Chevron Research Co., and Asahi Chemical Industry Corporation for financial support. We are grateful to Dr. Chester S. Sheppard of Lucidol for helpful discussions.

Registry No.—TBHP, 75-91-2; OsO_4, 20816-12-0; Et_4NOAc, 1185-59-7; *threo*-4,5-dihydroxyoctane, 53173-74-9; (*E*)-4-octene, 14850-23-8; *threo*-2,3-dihydroxyethyl butyrate, 6982-23-6; ethyl crotonate, 10544-63-5; 1-acetoxy-6,7-dihydroxy-3,7-dimethyloctane, 26759-58-0; citronellol acetate, 150-84-5; *cis*-1,2-dihydroxycyclohexane, 1792-81-0; cyclohexene, 110-83-8.

References and Notes

(1) Address correspondence to this author at the Department of Chemistry, Stanford University, Stanford, Calif. 94305.
(2) K. B. Sharpless and K. Akashi, *J. Am. Chem. Soc.*, **98**, 1986 (1976).
(3) (a) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, **127**, 175 (1925); (b) J. E. Coleman, C. Ricciuti, and D. Swern, *J. Am. Chem. Soc.*, **78**, 5342 (1956); (c) K. A. Hofmann, *Ber. Dtsch. Chem. Ges.*, **45**, 3329 (1912); (d)

R. Criegee, *Justus Liebigs Ann. Chem.*, **522**, 75 (1936); (e) R. Criegee, B. Marchand, and H. Wannowius, *ibid.*, **550**, 99 (1942); (f) N. A. Milas and S. Sussman, *J. Am. Chem. Soc.*, **58**, 1302 (1936); (g) N. A. Milas and S. Sussman, *ibid.*, **59**, 2345 (1937); (h) N. A. Milas, S. Sussman, and H. S. Mason, *ibid.*, **61**, 1844 (1939); (i) N. A. Milas, J. H. Trepagnier, J. T. Nolan, and M. I. Iliopolus, *ibid.*, **81**, 4730 (1959); (j) R. B. Woodward and F. V. Brutcher, Jr., *ibid.*, **80**, 209 (1958); (k) R. Daniels and J. L. Fischer, *J. Org. Chem.*, **28**, 320 (1963).

(4) Et_4NF had a similar effect in acetone. However, neither Et_4NOAc nor Et_4NF had much effect on the reaction in *tert*-butyl alcohol (TBA), whereas the tetraethylammonium salts of chelating diacids such as *o*-phthalic, camphoric, and *cis*-1,2-cyclohexane dicarboxylic acid did substantially improve the reaction even in TBA. $C_6H_5PO_3(Et_4N)_2$ and $(Et_4N)_2CO_3$ also had good effects on the reaction in TBA.

(5) The use of acetone in place of *tert*-butyl alcohol as solvent dramatically increases the beneficial effect of weak bases, such as Et_4NOAc, on these reactions (see also ref 4).

(6) (a) V. Van Rheenen, R. C. Kelly and P. Y. Cha, *Tetrahedron Lett.*, 1973 (1976). (b) We are grateful to a referee for pointing out this patent which describes the use of TBHP in buffered (slightly alkaline) aqueous solution for the osmium catalyzed hydroxylation of allyl alcohol to glycerol [M. N. Sheng and W. A. Mameniskis, U.S. Paten: 4 045 724 (1977)].

(7) A number of other osmium complexes were tried and proved to be equally active as catalysts. For example, in the oxidation of (*E*)-4-octene, OsO_3(pyridine)$_2$, $K_2O_2Os(OCH_3)_4$, and the imido complex OsO_3 (*N*-*tert*-butyl) all gave yields of diol comparable to that realized with OsO_4 as catalyst. These nonvolatile solids can simply be weighed out (0.2% based on olefin) and added to the reactions in place of the portion of OsO_4 stock solution.

(8) (a) K. Akashi and K. B. Sharpless, unpublished results; (b) K. B. Sharpless, A. O. Chong, and K. Oshima, *J. Org. Chem.*, **41**, 177 (1976).

(9) More hydrophobic olefins may oil out of the acetone solution due to the additional water in the 70% *tert*-butyl hydroperoxide. This only slows the initial rate and has no adverse effect on the reaction.

(10) (a) W. G. Young, L. Levanas, and Z. Jasaitis, *J. Am. Chem. Soc.*, **58**, 2275 (1936); (b) L. Lizzani and R. Luft, *Bull. Soc. Chim. Fr.*, **38**, 198 (1971); (c) M. B. Rothstein, *Ann. Chim.*, **13**, 461 (1930).

(11) In the present work we did not encounter any problems in using sodium bisulfite ($NaHSO_3$) as the reagent to reduce the excess *tert*-butyl hydroperoxide (TBHP). However, in other work[12] we have found that use of $NaHSO_3$ can have a celeterious effect on the isolated yields. The problem was especially serious when the product to be isolated contained either epoxide or allylic alcohol moieties. For more detailed discussion of this problem and for alternative means of dealing with the excess TBHP, see ref 12.

(12) (a) T. Hori and K. B. Sharpless, *J. Org. Chem.*, in press; (b) M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, **99**, 5526 (1977); (c) R. C. Michaelson, L. E. Khoo, and K. B. Sharpless, manuscript in preparation.

A Synthesis of α-Azido Nitriles

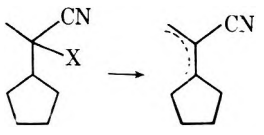
Anthony D. Barone, David L. Snitman, and David S. Watt*

Department of Chemistry, University of Colorado, Boulder, Colorado 80309

Received December 13, 1977

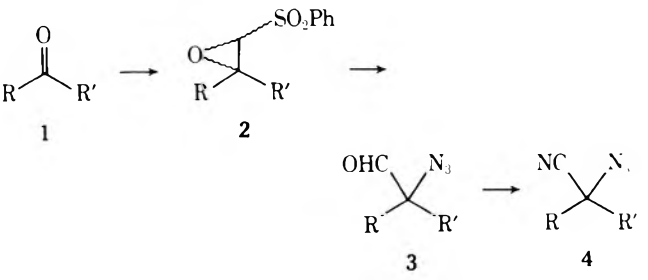
As part of our program to study the chemistry of nitriles bearing photoactive functionality in the α position,[1] we required a general synthesis of α-azidonitriles **4**. This intriguing synthon was first prepared by Moore[2] in the photochemical rearrangement of 2,3-diazido-1,4-quinones. Although the scope of this rearrangement process has not been determined, we were interested in devising other approaches which would utilize ketones **1** as starting materials.

Our initial foray in this area focused on the substitution of α-iodo or α-mesyloxynitriles by azide ion. Although aware of the difficulties which beset such a reaction, we were prodded into exploring this reaction by a report[3] that tertiary α-bromo ketones underwent just such a substitution with azide ion in 82–88% yield. Our efforts to utilize **5** in such a reaction led exclusively to the expected α,β-unsaturated nitriles[4] **6**.



5a, X = I **6**
b, X = OMs

An alternate route involving the ring opening of an epoxide ultimately proved successful in this connection. A modified Darzens condensation of ketones **1** with chloromethyl phenyl sulfone[5] provided the α,β-epoxy sulfones[6] **2**. Contrary to a report by Durst,[7] the ring opening of **2** with sodium azide in dimethylformamide provided the α-azidoaldehydes **3** in good yields. Conversion of **3** to the α-azidonitriles **4** was then accomplished by dehydration of the oximes derived from the aldehydes **3**. We have applied this sequence to the synthesis of α-azidonitriles **4** from aryl alkyl and dialkyl ketones **1** in



overall yields of 23 to 59% as shown in Table I. We have also explored the direct conversion of **3** to **4** using reagents such as hydroxylamine *O*-sulfonic acid but found that this latter procedure offered certain disadvantages. For example, the reaction of 20-azido-6β-methoxy-3α,5α-cyclopregnane-20-carboxyaldehyde (**3g**) with hydroxylamine *O*-sulfonic acid converted not only the aldehyde to the nitrile but also effected the ring opening of the isocyclopropyl ether to give 20-azido-3β-hydroxy-5-pregnene-20-carbonitrile. We are presently engaged in studying the photochemistry of α-azidoaldehydes **3** and α-azidonitriles **4**.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer infracord spectrophotometer. The abbreviation TF denotes thin film. NMR spectra were determined on a Varian EM390 spectrometer. Mass spectra were determined on a Varian MAT CH5 mass spectrometer. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Ga. Samples for elemental analysis were prepared by recrystallization or by chromatography on Merck silica gel F254 preparative layer plates followed by drying under high vacuum at 25 °C for 6–10 h.

The following is a typical experimental procedure.

1,1-Undecamethylene-2-(benzenesulfonyl)-1,2-epoxyethane (2c). The procedure of Tarares[6] was repeated using 1.05 g (5.5 mmol, 1.1 equiv) of chloromethyl phenyl sulfone[5] and 910 mg (5.0 mmol) of cyclododecanone to afford 1.69 g of solid which was recrystallized to furnish 1.15 g (68%) of the α,β-epoxy sulfone **2c**: mp 102–103 °C; IR (KBr) 7.55 and 8.69 μm; NMR ($CDCl_3$) δ 1.17–2.36 (m, 22, CH_2), 3.72 (s, 1, $CHSO_2Ph$), and 7.50–8.02 (m, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 250 (4), 196 (10), 185 (68), 177 (8, $M^+ - (PhSO_2 + H_2O)$), 94 (100), and 77 (31). The loss of *m/e* 159 was characteristic of all α,β-epoxy sulfones.

An analytical sample was prepared from two recrystallizations from dichloromethane–ether. Anal. Calcd for $C_{19}H_{28}O_3S$: C, 67.82; H, 8.39. Found: C, 67.83; H, 8.39.

1-Azidocyclododecane-1-carboxaldehyde (3c). To 890 mg (13.7 mmol, 4 equiv) of sodium azide in 10 mL of anhydrous dimethylformamide under a nitrogen atmosphere was added 1.15 g (3.4 mmol) of α,β-epoxy sulfone **2c** in 10 mL of dimethylformamide. The mixture was stirred for 18 h at 73 °C. This crude product was diluted with 60 mL of 30% dichloromethane–ether and washed with 50 mL of water. The aqueous layer was extracted with 60 mL of 30% dichloromethane–ether. The combined organic layers were washed with 50 mL of water and 50 mL of brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 821 mg (100%) of **3c**: IR (TF) 4.76 and 5.80 μm; NMR ($CDCl_3$) δ 1.26–1.90 (m, 22, CH_2) and 9.48 (s, 1, CHO); mass spectrum (70 eV) *m/e* (rel intensity) 181 (50), 138 (29), 124 (44), 95 (44), 81 (39), and 69 (45).

Anal. Calcd for $C_{13}H_{23}N_3O$: C, 65.78; H, 9.77. Found: C, 65.99; H, 9.82.

1-Azidocyclododecane-1-carbonitrile (4c). To 530 mg (7.68 mmol, 3 equiv) of hydroxylamine hydrochloride and 307 mg (7.68

0022-3263/78/1943-2066$01.00/0

Table I. Synthesis of α-Azidonitriles 4

4	Ketone 1 R	Ketone 1 R′	Registry no.	Base used in condensation 1 → 2 (equiv)	Isolated Yields, % 2	Registry no.	3	Registry no.	4	Registry no.
a	$-(CH_2)_5-$		108-94-1	KO-*t*-Bu (1.1)	97	28937-60-2	52	65516-42-9	67	65545-20-2
b	$-(CH_2)_7-$		502-49-8	KO-*t*-Bu (1.5)	*a*[b]	65516-36-1	63[d]	65516-43-0	66	65516-49-6
c	$-(CH_2)_{11}$		830-13-7	KO-*t*-Bu (1.1)	68	65516-37-2	100	65516-44-1	87	65516-50-9
d	CH_3	Ph	98-86-2	KO-*t*-Bu (1.5)	*a*[b]	65516-38-3	68	65516-45-2	60	65516-51-0
e	CH_2CH_2Ph	CH_2CH_2Ph	5396-91-8	KO-*t*-Bu (1.1)	71	65516-39-4	87	65516-46-3	63	65516-52-1
f	c-C_5H_9	CH_3	6004-60-0	KO-*t*-Bu (1.5)	79[b]	65516-40-7	86[d]	65516-47-4	74	65516-53-2
g	6β-Methoxy-3α,5α-cyclopregnan-20-one		32249-55-1	LiN(*i*-Pr)$_2$ (2)	49	65516-41-8	78	65516-48-5	59[c]	65516-54-3

[a] α,β-Epoxy sulfone **2** was unstable to preparative layer chromatography and crude **2** was converted directly to **3**. [b] Used 1.5 equiv of chloromethyl phenyl sulfone. [c] Used 2 equiv of hydroxylamine hydrochloride and sodium hydroxide. [d] Reaction temperature was 45–50 °C.

mmol, 3 equiv) of sodium hydroxide in 7 mL of water was added 607 mg (2.6 mmol) of the α-azidoaldehyde **3c** in 7 mL of THF. This mixture was stirred at 63 °C for 13 h. The crude product was diluted with 60 mL of 30% dichloromethane–ether and washed with 40 mL of water. The aqueous layer was extracted with 60 mL of 30% dichloromethane–ether. The combined organic layers were washed with 40 mL of water and 40 mL of brine and dried over anhydrous $MgSO_4$. Evaporation of the solvents afforded 666 mg of a light yellow solid. To this crude product and 650 mg (6.40 mmol, 2.5 equiv) of triethylamine in 20 mL of dichloromethane at 0 °C was slowly added 325 mg (2.82 mmol, 1.1 equiv) of methanesulfonyl chloride. This solution was stirred at 25 °C for 1 h. The reaction was poured into 50 mL of cold water and extracted with 50 mL of ether. The aqueous layer was reextracted with 50 mL of 30% dichloromethane–ether. The combined organic layers were washed with 50 mL of saturated sodium bicarbonate solution and 50 mL of brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 598 mg of a yellow solid which was chromatographed on two 20 × 20 cm (2 mm thick) Merck silica gel F254 preparative layer plates in 2:1 dichloromethane–hexane. A band (R_f 0.51) was eluted to afford 521 mg (87%) of **4c**: mp 46–47 °C; IR (KBr) 4.69 and 4.75 μm; NMR ($CDCl_3$) δ 1.20–2.13 (m, 22, CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 192 (50), 163 (25), 149 (34), 135 (41), 121 (33), 80 (50), and 55 (100).

Anal. Calcd for $C_{13}H_{22}N_4$: C, 66.63; H, 9.46. Found: C, 66.63; H, 9.48.

Spectral Data for α,β-Epoxy Sulfones 2. 2a: IR ($CHCl_3$) 7.61 and 8.60 μm; NMR ($CDCl_3$) δ 1.37–2.36 (m, 10, CH_2), 3.74 (s, 1, $CHSO_2Ph$), and 7.39–8.10 (m, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 190 (7), 143 (30), 111 (95), 93 (63), 82 (9), 77 (41), and 76 (100).

Anal. Calcd For $C_{13}H_{16}O_3S$: C, 61.89; H, 6.39. Found: C, 61.84; H, 6.41.

2e: IR(TF) 7.55 and 8.52 μm; NMR ($CDCl_3$) δ 1.80–3.16 (m, 8, CH_2), 3.81 (s, 1, $CHSO_2Ph$), 6.97–7.38 (m, 10, aromatic H), and 7.50–8.03 (m, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 251 (7), 250 (13), 233 (8), 91 (100), and 77 (13).

Anal. Calcd for $C_{24}H_{24}O_3S$: C, 73.45; H, 6.16. Found: C, 73.20; H, 6.21.

2f: IR (TF) 7.61 and 8.60 μm; NMR ($CDCl_3$) δ 1.79 (s, 3, CH_3), 3.78 (s, 1, $CHSO_2Ph$), and 7.40–8.02 (m, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 143 (19), 125 (44), 107 (24), 94 (40), 77 (19), and 67 (77).

Anal. Calcd for $C_{14}H_{18}O_3S$: C, 63.14; H, 6.81. Found: C, 62.91; H, 6.88.

20-Benzenesulfonylmethyl-20,22-epoxy-6β-methoxy-3α,5α-cyclopregnane (2g). To a solution of 101 mg (1.0 mmol, 2 equiv) of diisopropylamine in 0.5 mL of THF under a nitrogen atmosphere at −78 °C was added 0.45 mL of 2.23 M (1 mmol, 2 equiv) *n*-butyllithium. The solution was stirred for 10 min at −78 °C and then warmed to 25 °C. To this diisopropylamide solution, 191 mg (1 mmol, 2 equiv) of chloromethyl phenyl sulfone[5] was added in 0.5 mL of THF. The reaction was stirred for 15 min and 165 mg (0.5 mmol) of 6β-methoxy-3α,5α-cyclopregnan-20-one[9] (**1g**) was added in 0.5 mL of THF. The reaction was stirred at 25 °C for 48 h, diluted with 30 mL of ether, washed two times with 10 mL of water and 10 mL of brine, and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 220 mg of a brown oil. The product was chromatographed on two 20 × 20 cm (2 mm thick) Merck silica gel F254 preparative layer plates in 40:1 benzene–ether. After two developments, a band (R_f 0.44) was eluted to afford 0.12 g (49%) of **2g**: mp 50–67 °C; IR ($CHCl_3$) 7.57 and 8.61 μm; NMR ($CDCl_3$) δ 0.79 and 1.01 (two s, 6, C-18 and C-19 angular CH_3), 1.88 (s, 3, C-21 CH_3), 2.73 (t, J = 3 Hz, 1, C-6α H), 3.30 (s, 3, OCH_3), 3.68 (s, 1, $CHSO_2Ph$), and 7.42–8.01 (m, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 484 (52. M^+), 343 (71), 311 (76), 288 (66), 199 (21), 159 (46), and 90 (100).

Anal. Calcd for $C_{29}H_{40}O_4S$: C, 71.87; H, 8.32. Found: C, 71.64; H, 8.40.

Spectral Data for α-Azidoaldehydes 3. 3a:[8] IR (TF) 4.76 and 6.13 μm; NMR ($CDCl_3$) δ 1.10–2.19 (m, 10, CH_2), and 9.42 (s, 1, CHO); mass spectrum (70 eV) *m/e* (rel intensity) 125 (1), 124 (3), 111 (1), 110 (1), 97 (6), 96 (66), 81 (5), 55 (100), and 54 (20).

3b: IR (TF) 4.75 and 5.78 μm; NMR ($CDCl_3$) 1.43–2.09 (m, 14, CH_2), and 9.44 (s, 1, CHO); mass spectrum (70 eV) *m/e* (rel intensity) 124 (30), 82 (22), 81 (42), 78 (20), and 55 (100).

Anal. Calcd for $C_9H_{15}N_3O$: C, 59.64; H, 8.34. Found: C, 59.75; H, 8.38.

3d: IR (TF) 4.76 and 5.75 μm; NMR ($CDCl_3$) δ 1.77 (s, 3, CH_3), 7.36 (s, 5, aromatic H), and 9.41 (s, 1, CHO); mass spectrum (70 eV) *m/e* (rel intensity) 147 (9), 119 (7), 118 (58), 77 (100), and 51 (25).

Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18. Found: C, 61.76; H, 5.25.

3e: IR (TF) 4.74 and 5.75 μm; NMR ($CDCl_3$) δ 1.84–2.99 (m, 8, CH_2), 7.02–7.41 (m, 10, aromatic H), and 9.58 (s, 1, CHO); mass spectrum (70 eV) *m/e* (rel intensity) 236 (5), 132 (4), 105 (100), and 91 (34).

Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53. Found: C, 73.66; H, 6.56.

3f: IR (TF) 4.75 and 5.78 μm; NMR ($CDCl_3$) δ 1.40 (s, 3, CH_3), 9.49 (s, 1, CHO); mass spectrum (70 eV) *m/e* (rel intensity) 139 (1), 111 (4), 95 (2), 70 (8), and 69 (98).

Anal. Calcd for $C_8H_{13}N_3O$: C, 57.46; H, 7.84. Found: C, 57.28; H, 7.88.

3g: IR (TF) 4.75 and 5.78 μm; NMR ($CDCl_3$) δ 0.84 and 1.01 (two s, 6, C-18 and C-19 angular CH_3), 1.45 (s, 3, C-21 CH_3), 2.74 (t, J = 3 Hz, 1, C-6α H), 3.30 (s, 3, OCH_3), and 9.52 (s, 1, CHO); mass spectrum (70 eV) *m/e* (rel intensity) 385 (10, M^+), 330 (35), 328 (100), 255 (78), and 121 (20).

An analytical sample was prepared from three recrystallizations from hexane, mp 85–86.5 °C.

Anal. Calcd for $C_{23}H_{35}N_3O_2$: C, 71.65; H, 9.15. Found: C, 71.61; H, 9.16.

Spectral Data for α-Azidonitriles 4. 4a:[8] IR (TF) 4.57 and 4.74 μm; NMR ($CDCl_3$) δ 1.09–2.28 (m, 10, CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 150 (9, M^+), 108 (51), 93 (23), 82 (11), 83 (100), 54 (30), and 42 (78).

4b:[8] IR (TF) 4.74 μm; NMR ($CDCl_3$) δ 1.40–2.25 (m, 14, CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 136 (24), 121 (19), 109 (25), 107 (33), and 93 (36).

4d: IR (TF) 4.70 μm; NMR ($CDCl_3$) δ 1.90 (s, 3, CH_3) and 7.32–7.66 (m, 5, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 172 (6, M^+), 131 (11), 130 (100), 103 (41), and 77 (48).

Anal. Calcd for $C_9H_8N_4$: C, 62.77; H, 4.68. Found: C, 62.56; H, 4.71.

4e: IR ($CHCl_3$) 4.69 (sh) and 4.76 μm; NMR ($CDCl_3$) δ 1.93–3.02 (m, 8, CH_2), 7.09–7.50 (m, 10, aromatic H), 9.60 (s, 1, CHO); mass spectrum (70 eV) *m/e* (rel intensity) 262 (9), 248 (1), 171 (15), 158 (52), 105 (49), 91 (100), and 77 (12).

Anal. Calcd for $C_{18}H_{18}N_4$: C, 74.45; H, 6.25. Found: C, 74.29; H, 6.30.

4f: IR (TF) 4.72 (sh) and 4.78 μm; NMR ($CDCl_3$) δ 1.60 (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 122 (13), 94 (16), 69 (100), 67 (71), and 53 (31).

Anal. Calcd for $C_8H_{12}N_4$: C, 58.21; H, 7.37. Found: C, 58.38; H, 7.42.

4g: mp 64–66 °C; IR (TF) 4.76 μm; NMR ($CDCl_3$) δ 0.94 and 1.01 (two s, 6, C-18 and C-19 angular CH_3), 1.69 (s, 3, C-21 CH_3), 2.75 (t, J = 3 Hz, 1, C-6α H), and 3.30 (s, 3, OCH_3); mass spectrum (70 eV) *m/e* (rel intensity) 382 (50, M^+), 368 (52), 351 (81), 328 (100), 159 (19), and 119 (24).

Anal. Calcd for $C_{23}H_{34}N_4O$: C, 72.21; H, 8.96. Found: C, 72.20; H, 8.97.

2-Cyclopentyl-2-iodopropanenitrile (5a). To 486 mg (3.0 mmol, 1.5 equiv) of iodine monochloride at −10 °C under a nitrogen atmosphere was added 474 mg (2.0 mmol) of *N-tert*-butyldimethylsilylcyclopentylmethylketenimine[10] in 2 mL of anhydrous THF. This dark brown solution was stirred for 1 h at 25 °C, diluted with 25 mL of ether, and washed with 25 mL of water. The aqueous layer was reextracted with 25 mL of ether, and the combined organic layers were washed with two 25-mL portions of a saturated sodium thiosulfate solution, with two 25-mL portions of water, and with 25 mL of brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded 542 mg of a brown oil which was chromatographed on a 20 × 20 (2 mm thick) Merck silica gel F254 preparative layer plate in 5:1 hexane–ether. A band (R_f 0.57) was eluted to afford 182 mg (37%) of **5a**:[8] IR (TF) 4.50 μm; NMR ($CDCl_3$) δ 2.25 (s, 3, CH_3); mass spectrum (70 eV) (rel intensity) 127 (3), 122 (93), 105 (11), 95 (63), 80 (21), and 67 (100).

2-Cyclopentyl-2-hydroxypropanenitrile Mesylate (5b). The procedure of Crossland[11] was repeated using 139 mg (1.0 mmol) of 2-cyclopentyl-2-hydroxypropanenitrile, 126 mg (1.1 mmol, 1.1 equiv) of methanesulfonyl chloride, and 111 mg (1.1 mmol, 1.1 equiv) of triethylamine in 3 mL of anhydrous dichloromethane at 0 °C to afford 195 mg (90%) of **5b**: IR ($CHCl_3$) 7.32 and 8.41 μm; NMR ($CDCl_3$) δ 1.94 (s, 3, CH_3) and 3.16 (s, 3, SO_2CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 138 (11), 122 (62), 95 (86), 79 (18), and 69 (100).

Acknowledgment. We wish to thank the National Institutes of Health (GM-22978-02) and the National Science Foundation (CHE76-16788) and G. D. Searle and Co. for their generous financial support. One of us (D.L.S.) wishes to thank the AMC Cancer Research Center, Lakewood, Colo. for a fellowship. We also wish to thank Union Carbide for a gift of peracetic acid and Mr. Richard W. Olsson for technical assistance.

Registry No.—**5a**, 65516-55-4; **5b**, 65516-56-5; chloromethyl phenyl sulfone, 7205-98-3; *N-tert*-butyldimethylsilylcyclopentylmethylketenimine 65516-57-6; 2-cyclopentyl-2-hydroxypropanenitrile, 65516-58-7.

References and Notes

(1) (a) D. S. Watt, *J. Am. Chem. Soc.*, **98**, 271 (1976); and (b) R. W. Freerksen, W. E. Pabst, M. L. Raggio, S. A. Sherman, R. R. Wroble, and D. S. Watt, *ibid.*, **99**, 1536 (1977).
(2) D. S. Pearce, M. J. Locke, and H. W. Moore, *J. Am. Chem. Soc.*, **97**, 6181 (1975).
(3) J. H. Boyer and D. Straw, *J. Am. Chem. Soc.*, **75**, 1642 (1953). For a synthesis of azidodiphenylacetonitrile from bromodiphenylacetonitrile, see R. M. Moriarty and M. Rahman, *Tetrahedron*, **21**, 2877 (1965).
(4) The following experiments afforded the α,β-unsaturated nitrile **6**: (a) **5a** and NaN_3 in Me_2SO; (b) **5b** and NaN_3/dicyclohexyl-18-crown-6 in Me_2SO (25 °C, 16 h); (c) **5b** and KN_3/dicyclohexyl-18-crown-6 in acetone (57 °C, 21 h). In addition, the procedure of Miller using NaN_3 and $ZnCl_3$ in CS_2 which was reported to afford tertiary azides from tertiary chlorides was applied to **5b** but afforded only unreacted starting material: J. A. Miller, *Tetrahedron Lett.*, 2959 (1975).
(5) F. G. Bordwell and G. D. Cooper, *Tetrahedron*, 73 (1951).
(6) P. F. Vogt and D. F. Tarares, *Can. J. Chem.*, **47**, 2875 (1968).
(7) F. Reinach-Hirtzbach and T. Durst, *Tetrahedron Lett.*, 3677 (1976).
(8) Compound was too unstable to obtain a satisfactory elemental analysis.
(9) A. Butenandt and W. Grosse, *Chem. Ber.*, **70B**, 1446 (1937).
(10) D. S. Watt, *Synth. Commun.*, **4**, 127 (1974).
(11) R. K. Crossland K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).

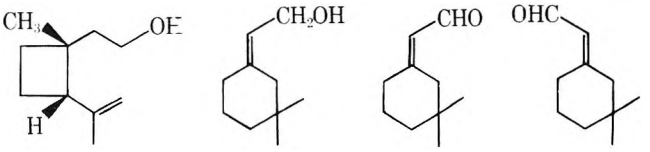
Alternative Route to Three of the Four Terpenoid Components of the Boll Weevil Sex Pheromone

João Pedro de Souza* and Andrea M. R. Gonçalves

Departamento de Química, Universidade de Brasília, 70.000 Brasília DF, Brazil

Received October 25, 1977

The ecological imbalance and environmental pollution due to insectiside residues has stimulated a great interest in the synthesis of pheromones, since they may provide a generally nontoxic method of biological control of insect populations.[1] A pheromone complex emitted by live male boll weevils (*Anthonomus grandis* Boheman) comprising the four terpenoid compounds (+)-*cis*-2-isopropenyl-1-methylcyclobutaneethanol (**1**), (*Z*)-3,3-dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanol (**2**), (*Z*)-3,3-dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde (**3**), and (*E*)-3,3-dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde (**4**) were

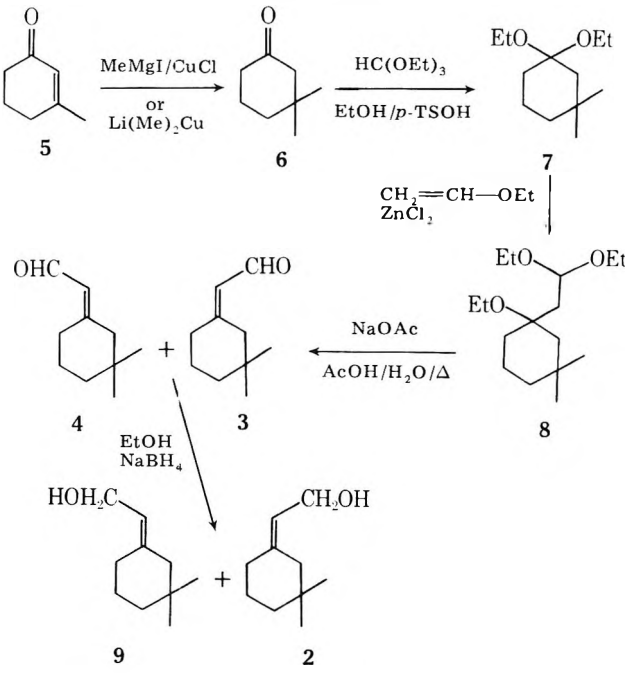


1 2 3 4

identified and first synthesized by Tumlinson et al.[2] We would like to report a simple sequence of reactions which afford the synthesis of alcohol **2** and aldehydes **3** and **4** in high yield from readily available starting materials.

Scheme I shows the synthesis of three cyclohexyl constituents of the boll weevil pheromone. 3,3-Dimethylcyclohexanone (**6**), utilized in previous syntheses,[3-5] was prepared from commercially available 3-methyl-2-cyclohexen-1-one by conjugate addition.[6] Reaction of ketone **6** with triethyl orthoformate in anhydrous ethanol and a catalytic amount of *p*-toluenesulfonic acid afforded 3,3-dimethylcyclohexanone diethyl ketal (**7**) in 87% yield. Treatment of ketal **7** with ethyl vinyl ether in a 10% $ZnCl_2$–ethyl acetate solution[7] gave the acetal **8** in 94% yield. Hydrolysis of compound **8** with glacial acetic acid, sodium acetate, and water afforded the isomeric aldehydes **3** and **4**, in 84% yield.[8] Thus, aldehydes **3** and **4** were prepared in 69% overall yield from starting material **6**. Reduction of a mixture of aldehydes **3** and **4** with $NaBH_4$ in

Scheme I



5 6 7 4 3 8 9 2

0022-3263/78/1943-2068$01.00/0

ethanol gave the corresponding mixture of *Z* alcohol **2** and its *E* isomer **9** in a quantitative yield. Aldehydes **3** and **4** could be separated[9] prior to this step or alcohols **2** and **9** would have to be isolated after reduction.

Experimental Section

All boiling points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 137 spectrometer. NMR spectra were determined in deuteriochloroform solution on Varian Associates spectrometers, Models A-60 or XL-100. Line positions are given in δ scale, with tetramethylsilane as an internal standard. Mass spectra were recorded on an Atlas CH-4B or Associated Electrical Industries MS-902 spectrometer, high resolution measurements being determined with the latter instrument.

3,3-Dimethylcyclohexanone Diethyl Ketal (7). 3,3-Dimethylcyclohexanone (**6**) (6.54 g, 51.0 mmol), triethyl orthoformate (8.98 g, 60.6 mmol), and *p*-toluenesulfonic acid (6 mg) in 38 mL of anhydrous ethanol were stirred at room temperature for 64 h. Enough ethanolic NaOEt was added to neutralize the reaction mixture and the latter was concentrated under vacuum. Fractional distillation through a spinning-band column gave 9 g (87%) of pure 3,3-dimethylcyclohexanone diethyl ketal (**7**): bp 82–83 °C (13 mm); IR (neat) 1385, 1359 ($-C(CH_3)_2$), 1195, 1174, 1119, 1093, 1058 cm^{-1} (COCOC); ^1H NMR ($CDCl_3$) δ 0.95 (s, 6 H, geminal CH_3), 1.14 (t, 6 H, J = 7 Hz, CH_3CH_2-), 1.49 (s, 2 H, $(RO)_2CCH_2C(CH_3)_2$), 3.45 (q, 4 H, J = 7 Hz, CH_3CH_2-); mol wt 200.1777 (calcd for $C_{12}H_{24}O_2$: 200.1776).

2-(1-Ethoxy-3,3-dimethylcyclohexyl)-1,1-diethoxyethane (8). In a three-necked flask equipped with a rubber septum and a dry ice condenser protected with a calcium chloride tube are placed 3,3-dimethylcyclohexanone diethyl ketal (**7**) (7.37 g, 36.9 mmol) and 3 mL of a solution of 10% $ZnCl_2$ in ethyl acetate. The mixture was stirred and maintained at a temperature of 45 °C while 3.8 mL of ethyl vinyl ether (40.5 mmol) was added dropwise with a syringe. After the addition was completed the mixture was stirred for 2 h at 45–50 °C (bath temperature) and then allowed to come to room temperature. The mixture was diluted with ether and washed with a solution of 5% NaOH and the ethereal layer was dried over Na_2CO_3. Filtration and removal of the solvent gave 9.45 g (94%) of 2-(1-ethoxy-3,3-dimethylcyclohexyl)-1,1-diethoxyethane (**8**), which was purified by distillation using a spinning band column: bp 79–80 °C (0.5 mm); IR (neat) 2950, 1389, 1370, 1183, 1124, and 1064 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 and 1.05 (two singlets for geminal methyl group), 1.12 and 1.18 (t, 3 H, CH_3CH_2O), 1.74 (d, 2 H, J = 4 Hz, $EtOCCH_2CH(OEt)_2$), 3.2–38 (m, 6 H, OCH_2CH_3), 4.68 (t, 1 H, J = 4 Hz, $CH(OEt)_2$).

Preparation of (*Z*)-3,3-Dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde(3) and (*E*)-3,3-Dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde (4). To acetal **8** (950 mg, 3.4 mmol) dissolved in 10 mL of glacial acetic acid and 0.77 mL of water was added 1.1 g of sodium acetate. The reaction mixture was stirred and heated for 3 h at 95 °C under an atmosphere of nitrogen. After cooling the resulting mixture was poured into ice, basified by careful addition of solid $NaHCO_3$, and extracted with ether. The combined extracts were washed with water and 5% aqueous $NaHCO_3$ and dried over anhydrous Na_2CO_3. Filtration and removal of the solvent gave 450 mg (84%) of a mixture[7] of aldehydes **3** and **4**, showing properties consistent with those reported by Tumlinson:[2] IR (neat) 1681 and 1639 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (s, 6 H, geminal CH_3), 2.24 (t, 2 H, $-CH_2-$ trans to $-CHO$), 2.50 (s, 2 H, $-CH_2-$ cis to $-CHO$), 5.92 (d, 1 H, J = 8 Hz, $-C=CH-$), and 9.98 (d, 1 H, J = 8 Hz, $-CHO$) were assigned to **3**, while those peaks at 0.93 (s, 6 H geminal CH_3), 2.08 (s, 2 H, $-CH_2-$ trans to $-CHO$), 2.68 (t, 2 H, $-CH_2-$ cis to $-CHO$), 5.78 (d, 2 H, J = 8 Hz, $-C=CH-$), and 10.02 (d, 1 H, J = 8 Hz, $-CHO$) were assigned to **4**. NMR peaks at 1.2–1.9 were common to both isomers: mol wt 152.1206 (calcd for $C_{10}H_{16}O$: 152.1201).

Preparation of the Isomeric Alcohols (*Z*)-3,3-Dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanol (2) and (*E*)-3,3-Dimethyl-($\Delta^{1,\beta}$-cyclohexaneethanol (9). A mixture of 400 mg of aldehydes **3** and **4** (6:4 ratio) in 20 mL of absolute ethanol and 400 mg of $NaBH_4$ was stirred at ambient temperature for 1 h. The reaction mixture was hydrolyzed with water and extracted with CH_2Cl_2. The combined extracts were washed with water and dried over anhydrous $MgSO_4$. Filtration and removal of the solvent gave the isomeric alcohols **2** and **9** in a quantitative yield, showing properties consistent with those reported by Tumlinson:[2] IR (neat) 3400, 1667, 1075, 1031, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 6 H, geminal CH_3), 1.32 (s, 2 H, $-CH_2-$ cis to $-CH_2OH$), 2.07 (t, 2 H, $-CH_2-$ trans to $-CH_2OH$), 4.12 (d, 2 H, J = 7 Hz, $-CH_2OH$), and 5.48 (t, 1 H, J = 7 Hz, $-C=CH-$) were assigned to **2**, while those at 0.87 (s, 6 H, geminal CH_3), 1.89 (s, 2 H, $-CH_2-$ trans to $-CH_2OH$), 2.12 (t, 2 H, $-CH_2-$ cis to $-CH_2OH$), 4.14 (d, 2 H, J = 7 Hz, $-CH_2OH$), and 5.32 (t, 1 H, J = 7 Hz, $-C=CH-$) were assigned to **9**. NMR peaks at 1.2–1.8 were common to both isomers; mol wt 154.1341 (calcd for $C_{10}H_{18}O$: 154.1357).

Acknowledgment. We would like to thank Professor James P. Kutney of the University of British Columbia, Vancouver, Canada and Dr. Paul Baker of CPPN, Rio de Janeiro, Brazil for spectral determinations. The partial support of this work by the National Research Council of Brazil and CAPES is gratefully acknowledged.

Registry No.—**2**, 26532-23-0; **3**, 26532-24-1; **4**, 26532-25-2; **6**, 2979-19-3; **7**, 65392-27-0; **8**, 65392-28-1; **9**, 30346-27-1; triethyl orthoformate, 122-51-0; ethyl vinyl ether, 109-92-2.

References and Notes

(1) M. Jacobson, "Insect Sex Attractants", Interscience, New York, N.Y., 1965.
(2) (a) J. H. Tumlinson, D. D. Hardee, R. C. Gueldner, A. C. Thompson, P. A. Hedin, and J. P. Minyard, *Science*, **166**, 1010 (1969); (b) J. H. Tumlinson, R. C. Gueldner, D. D. Hardee, A. C. Thompson, P. A. Hedin, and J. P. Minyard, *J. Org. Chem.*, **36**, 2616 (1971).
(3) J. H. Babler and T. R. Mortell, *Tetrahedron Lett.*, 669 (1972).
(4) S. W. Pelletier and N. V. Mody, *J. Org. Chem.*, **41**, 1069 (1976).
(5) For a synthesis from geranic acid, see R. H. Bedoukian and J. Wolinsky, *J. Org. Chem.*, **40**, 2154 (1975).
(6) (a) G. Buchi, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **31**, 241 (1948); (b) H. O. House and W. F. Fischer, *J. Org. Chem.*, **33**, 949 (1968).
(7) O. Isler, H. Lindlar, M. Montovan, R. Rüegg, and P. Zeller, *Helv. Chim. Acta*, **39**, 249 (1956).
(8) The ratio 6:4 was determined via integration of the vinyl hydrogen NMR absorption band for each isomer.
(9) For a description to separate aldehydes **3** and **4**, refer to J. H. Tumlinson, R. C. Guelder, D. D. Hardee, A. C. Thompson, P. A. Hedin, and J. P. Minyard, "Chemicals Controlling Insect Behavior", M. Beroza Ed., Academic Press, New York, N.Y., 1970, p 50.

Cobalt-Catalyzed Oxidation of Isotopically Labeled Cyclohexanone

J. D. Druliner

Contribution No. 2512, Central Research and Development Department, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

Received August 15, 1977

A large body of literature exists covering various aspects of metal-catalyzed oxidation of cyclohexanone or cyclohexane to yield predominantly adipic acid.[1-4] We report herein results of studies on cobalt-catalyzed oxidations of isotopically labeled cyclohexanone. Of the numerous by-products formed, glutaric and succinic acids are formed in 10–20% yields. We examined the fate of cyclohexanone labeled at the carbonyl carbon with ^{14}C and with ^{13}C to try to resolve conflicting mechanistic proposals for the formation of glutaric and succinic acids.

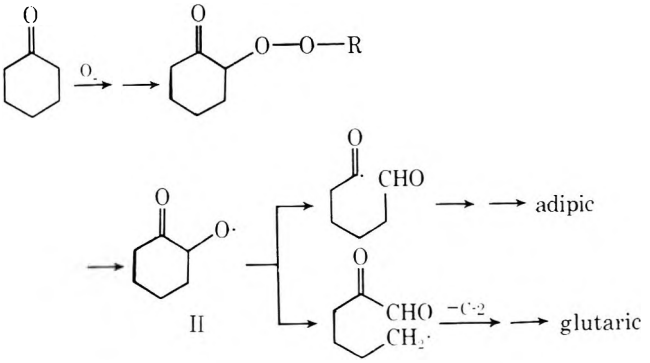
The percentage retention of the carbonyl carbon from labeled cyclohexanone in glutaric and succinic acid products was 91% in glutaric acid and 87% in succinic acid as shown in Table I.

The high retention of C-1 from labeled cyclohexanone is not consistent with a proposal that glutaric acid arises by exclusive

Table I. Oxidation of [1-^{14}C]- and [1-^{13}C]Cyclohexanone (K): Percent Retention of C-1 by Glutaric and Succinic Acids

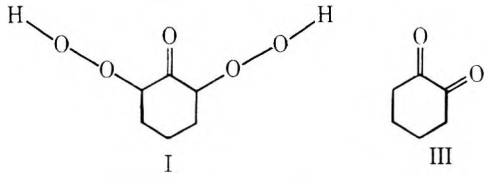
K	% retention of C-1 Glutaric/adipic	% retention of C-1 Succinic/adipic	% K conversion	% yields from K Adipic	Glutaric	Succinic
[1-^{14}C]	88	82	63	18	5	0.4
[1-^{13}C]	96	84	62	23	4	0.5
[1-^{13}C]	88	94	34	37	8	1.1
Average	91	87				

0022-3263/78/1943-2069$01.00/0



loss of C-1 from an intermediate 2,6-dihydroperoxycyclohexanone compound (I).[5] A more recent proposal that glutaric acid is formed by loss of C-2 from an α-ketooxy radical (II) is consistent with the observed high retention of the labeled carbonyl carbon.[3]

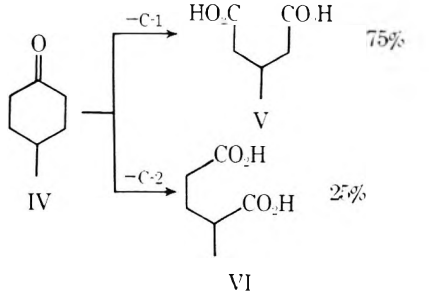
It has been reported that α-ketooxy radicals undergo thermolysis or metal-catalyzed cleavage to generate carboxylic acids in which the carboxyl group is derived from the keto group.[6] It has been proposed that 1,2-cyclohexanedione (III)



is formed during oxidation of cyclohexanone and gives rise to most of the CO and CO_2 evolved.[7] Although 1,2-cyclohexanedione may account for CO and CO_2 generation, it is not a viable intermediate for glutaric or succinic acid formation. Loss of a carbonyl carbon from III would decrease the isotopic enrichment by a factor of 2.

Significant glutaric acid formation from decarboxylation of adipic acid is not consistent with the observed high degree of retention of C-1 from labeled cyclohexanone or with reported carboxylic acid decarboxylation studies.[8,9] The extent to which succinic acid is derived from solvent acetic acid was examined using [1-^{14}C]acetic acid under the oxidation conditions used for labeled cyclohexanone. The conversion of cyclohexanone was 44% with a yield to adipic acid of 27%. Radiometric analysis of isolated succinic acid showed the presence of 0.04 mol of [1-^{14}C]carboxyl groups per mole of succinic acid. Assuming all HO_2C–CH_2· radicals were derived from acetic acid, about 2% of the succinic acid was derived from acetic acid.

The effect of methyl substitution on the extent of loss of C-1 was found to be substantial. Whereas unsubstituted (labeled) cyclohexanone gave glutaric acid with >90% retention of C-1, 4-methylcyclohexanone (IV) gave a 3-methylglutaric (V)/2-methylglutaric (VI) acid ratio of 3:1. The stability of diacid products V and VI to reaction conditions was checked by replacing half of the cyclohexanone in a typical oxidation experiment with equal molar amounts of V and VI. Of the cyclohexanone charged, 34% was converted to adipic acid. The ratio of V/VI in the product was 1.0 within experimental error based on ^{1}H NMR integrals for the methyl resonances for V (δ 1.05) and VI (δ 1.15). The preponderance of loss of C-1 with methyl substitution may be largely a steric effect.



Experimental Section

All oxidation reactions were carried out in 10-cm^3 stainless steel shaker tubes at 100 °C with 200 psi of O_2 for 10–16 h. A typical starting solution consisted of 5.5 g (91.7 mmol) of acetic acid, 1.05 g (10.7 mmol) of [1-^{14}C]cyclohexanone, and 0.10 g (0.42 mmol) of $Co(OAc)_3$. Gas chromatographic analyses for adipic, glutaric, and succinic acids were carried out on a 12 ft × 0.12 in. stainless steel column of OV-1 at 190 °C following treatment with BSTFA to form trimethylsilyl diesters. [1-^{14}C]Cyclohexanone was commercially available.[10] [1-^{13}C]Cyclohexanone was prepared by carbonylation of bisborinane with ^{13}CO.[11] Products containing ^{14}C were analyzed with a Packard liquid scintillation spectrometer using standard dilution techniques. Each sample was crystallized repeatedly to obtain constant specific activity. Products containing ^{13}C were analyzed by gas chromatography/mass spectroscopic techniques.[12]

Acknowledgment. We thank Drs. B. A. Carlson, U. Klabunde, E. J. Lukosius, and J. B. Sieja for helpful discussions.

Registry No.—$Co(OAc)_3$, 917-69-1; cyclohexanone, 108-94-1; glutaric acid, 110-94-1; succinic acid, 110-15-6.

References and Notes

(1) I. V. Berezin, E. T. Denisov, and N. M. Emanuel, "The Oxidation of Cyclohexane", Pergamon Press, London, 1966.
(2) A. Onopchenko and J. G. D. Schulz, *J. Org. Chem.*, **38**, 3729 (1973); **40**, 3338 (1975).
(3) D. G. Hendry, C. W. Gould, D. Schuetzle, M. G. Syz, and F. R. Mayo, *J. Org. Chem.*, **41**, 1 (1976).
(4) K. Tanaka, *Prepr. Div. Pet. Chem. Am. Chem. Soc.*, **19**, 103 (1974).
(5) G. N. Koshel et al., *Neftekhimiya*, **14** (2), 263 (1974).
(6) Y. Sawaki and Y. Ogata, *J. Org. Chem.*, **41**, 2340 (1976).
(7) I. I. Korsak and V. E. Agabekov, *Dokl. Akad. Nauk B. SSR*, **19** (8), 711 (1975).
(8) (a) H. B. Tinker *J. Catal.*, **19**, 237 (1970); (b) S. S. Lande and J. K. Kochi, *J. Am. Chem. Soc.*, **90**, 5196 (1968).
(9) Reaction product vapors contained too little CO and CO_2 for quantitative isotopic measurements. At 100 °C decarboxylation of solvent acetic acid could account for a significant fraction of the total CO and CO_2. It is reported that, at 150 °C, "about 30% of the total carbon oxides results from its (acetic acid) decomposition." [8a]
(10) [1-^{14}C]Cyclohexanone was obtained from Amersham/Searle Corp. That the ^{14}C was contained only in C-1 was shown by oxidizing [1-^{14}C]cyclohexanone to acipic acid and then converting the adipic acid to cyclopentanone by BaC-catalyzed decarboxylation. The specific activity of the cyclopentanone was exactly half that of the starting [1-^{14}C]cyclohexanone.
(11) H. C. Brown, "Organic Syntheses Via Boranes", Wiley, New York, N.Y., 1975, p 158.
(12) GC/MS was done using chemical ionization by T. A. Blazer, Central Research and Development Department.

Synthesis of *N*-(4-Azido-2-nitrophenyl)amino-1-alkyl-β-D-glucopyranosides: Photoaffinity Labeling Derivatives of Glucose

Myrna Hagedorn, Ronald R. Sauers,* and Alexander Eichholz

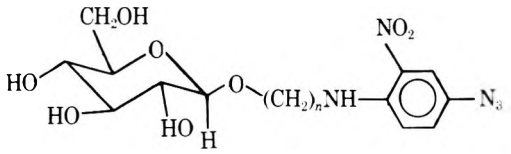
Department of Chemistry, Rutgers—The State University of New Jersey, New Brunswick, New Jersey 08903, and The Department of Physiology, College of Medicine and Dentistry of New Jersey, Rutgers Medical School, Piscataway, New Jersey 08854

Received November 21, 1977

During the course of studies of the mechanism of glucose transport in human erythrocytes, the need arose for derivatives of glucose which could serve as photoaffinity labeling agents.[1,2] Since an integral part of these studies involved the evaluation of reagents in which the distance between the sugar moiety and the photolabile grouping was varied systemati-

*Address correspondence to this author at Rutgers—The State University of New Jersey.

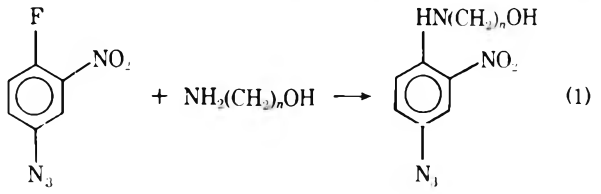
0022-3263/78/1943-2070$01.00/0



1

cally, we designed a synthetic scheme for the preparation of glucosides **1** of ω-(arylazido)alkanols.

The key step in this synthesis involves the highly selective *N*-arylation of an α,ω-amino alcohol by 4-fluoro-3-nitrophenyl azide[1b] (**2**) (eq 1) to form substituted anilines (**3**). The struc-



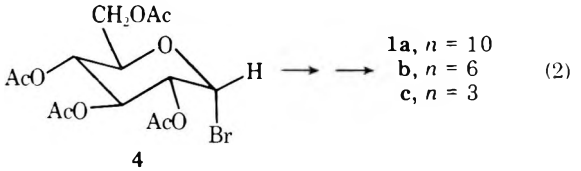
(1)

2 **3**

a, $n = 10$
b, $n = 6$
c, $n = 3$

tural assignments for the anilines are based on the appearance of quartets at ca. δ 3.4 in their NMR spectra.

Glucosylation (eq 2) was accomplished by a modified[3]



(2)

4

Koenigs–Knorr reaction using silver oxide and tetraacetyl-α-D-glucosyl bromide. Deacetylation yielded the free sugar derivatives **1a–c**.

These reactions should be generally applicable to the synthesis of photoaffinity labeling agents of other sugar derivatives provided the glycosylation step is carried out under mild conditions.

Experimental Section

Nuclear magnetic resonance (NMR) data were obtained from a Varian Model T-60 spectrometer in $CDCl_3$ using tetramethylsilane as internal standard. Infrared spectra were determined on a Perkin-Elmer Model 137 spectrometer. The mass spectrum was determined on a Hitachi Perkin-Elmer Model PMU-7 mass spectrometer at 80 eV.

4-Fluoro-3-nitrophenyl Azide (2). This material is commercially available from ICN Pharmaceuticals, Inc., Cleveland, Ohio, or from Pierce Chemicals, Rockford, Ill. Alternatively, it can be synthesized from 4-fluoro-3-nitroaniline by the following procedure.[4] A slurry of 1.561 g (0.010 mol) of 3-nitro-4-fluoraniline in 100 mL of 1.1 M sulfuric acid was cooled to −20 °C. A solution of 1.38 g (0.020 mol) of sodium nitrite in 10 mL of water was added over 5 min to the stirred mixture. The slurry was allowed to warm to −10 °C over 20 min at which time 100 mL of ether was added. Potassium azide (1.622 g, 0.020 mol) in 10 mL of water was added over 5 min at −10 °C. After 10 min of stirring, the layers were separated and the aqueous phase was extracted twice with ether. The extracts were dried ($MgSO_4$) and evaporated to yield 0.896 g of crude product. Recrystallization from petroleum ether (20–40 °C) gave 0.778 g (43%) of orange needles: mp 53–55 °C (lit.[1b] mp 52 °C); NMR δ 7.75 (m, 1 H), 7.35 (m, 2 H); mass spectrum (*m/e*) 182 (molecular ion), 154 ($M^+ - N_2$) and 108 ($M^+ - N_2 - NO_2$, base peak).

10-*N*-(4-Azido-2-nitrophenyl)amino-1-decanol (3a). A solution of 570 mg (2.5 mmol) of **2** and 865 mg (5.0 m mol) of 10-amino-1-decanol in 2.5 mL of dioxane was kept at 25 °C for 2.5 h. The solvent was evaporated at a temperature not exceeding 70 °C.[5] The residue was dissolved in chloroform and chromatographed on a silica gel column (1 × 50 cm) using chloroform as an eluant. The product **3a** was obtained as red crystals: mp 58–59 °C; yield 857 mg (83%); IR (melt) 4.72 μm (N_3); ^1H NMR δ 8.2 (broad, 1 H), 6.7–7.9 (m, 3 H), 3.7 (t, 2 H), 3.3 (q, 2 H, $J = 6$ Hz), 2.3–1.15 (m, 16 H).

Anal. Calcd for $C_{16}H_{25}N_5O_3$: C, 57.29; H, 7.51; N, 20.88. Found: C, 57.53; H, 7.63; N, 20.65.

3-*N*-(4-Azido-2-nitrophenyl)amino-1-propanol (3c). By the above procedure there was obtained a 68% yield[6] of **3c**: mp 86–86.5 °C; IR (Nujol) 4.68 μm (N_3); ^1H NMR δ 8.2 (broad, 1 H), 6.8–7.9 (m, 3 H), 3.84 (t, 2 H), 3.46 (q, 2 H, $J = 6$ Hz), 2.16–1.66 (m, 3 H).

Anal. Calcd for $C_9H_{11}N_5O_3$: C, 45.58; H, 4.63; N, 29.53. Found: C, 45.61; H, 4.56; N, 29.75.

6-*N*-(4-Azido-2-nitrophenyl)amino-1-hexanol (3b). Similarly, compound **3b** was obtained as a red oil in 70% yield; IR (film) 4.78 μm (N_3); NMR δ 8.0 (b 1 H), 7.8–6.7 (m, 3 H), 3.65 (t, 1 H), 3.30 (q, 1 H), 2.0–1.2 (m, 9 H). The oil could not be induced to crystallize.

10-*N*-(4-Azido-2-nitrophenyl)amino-1-decyl-β-D-glucopyranoside (1a). The following mixture was stirred at 25 °C for 22 h: 586 mg (1.75 mmol) of **3a**, 720 mg (1.75 mmol) of tetra-*O*-acetyl-α-D-glucopyranosyl bromide,[7] 410 mg (1.75 mmol) of freshly prepared silver oxide,[8] 270 mg (2.0 mmol) of anhydrous calcium sulfate, and 4.0 mL of benzene. The slurry was filtered and the filtrate was washed thoroughly with a solution of 100 mg of silver nitrate in 25 mL of water, twice with water, and once with brine. The organic phase was dried (Na_2SO_4), filtered through celite, and evaporated. The crude product mixture (1.12 g) was acetylated to aid the chromatographic separation. This was accomplished by treatment with 0.25 mL of acetic anhydride in 1.0 mL of pyridine for 1 h at 25 °C. Benzene (25 mL) was added and the solution was washed once with water, three times with cold HCl, twice with water, and once with brine. The organic layer was dried (Na_2SO_4) and evaporated. Chromatographic separation ($CHCl_3$) on a 3 × 50 cm column of silica gel gave two major fractions: the acetate of **3a** (32%) and the acetate of **1a**[9] which was contaminated with some pentaacetyl glucose. Evaporation of the solvent from the second fraction gave a residue which was dissolved in 40 mL of methanol. This solution was saturated with ammonia gas and kept at 25 °C for 24 h after which the volatile materials were removed by evaporation. The residue was triturated with benzene to remove acetamide and then dissolved in 100 mL of $CHCl_3$. The glucose was removed by washing with water (5×). The dried $CHCl_3$ was evaporated and the residue was crystallized from 2 mL of methanol to give 266 mg of **1a** (46%): mp 105–106.5 °C; IR (Nujol) 4.73 μm (N_3).

Anal. Calcd. for $C_{22}H_{35}N_5O_8$: C, 53.13; H, 7.03; N, 14.08. Found: C, 53.37; H, 7.29; N, 13.85.

Similar results were obtained more conveniently by use of thick layer (5 mm) silica plates in place of the column chromatography.

6-*N*-(4-Azido-2-nitrophenyl)amino-1-hexyl-β-D-glucopyranoside (1b). By a similar procedure to that above **1b** was prepared in 17% yield as a low-melting solid: mp 45°C; IR (Nujol) 4.74 μm (N_3).

Anal. Calcd for $C_{18}H_{27}N_5O_8$: C, 48.97; H, 6.16; N, 15.86. Found: C, 48.69; H, 6.38; N, 15.63.

3-*N*-(4-Azido-2-nitrophenyl)amino-1-propyl-β-D-glucopyranoside (1c). A mixture of 3.78 g (15.5 mmol) of **3c**, 6.15 g (15 mmol) of **4**, 3.46 g (15 mmol) of silver oxide,[8] 2.5 g of anhydrous sodium sulfate, and 65 mL of dry methylene chloride was stirred for 2 days at room temperature. The mixture was filtered and the filtrate was treated with 2.0 mL of pyridine and 2.9 mL (40 mmol) of acetic anhydride. After 5 h at 25 °C the volatiles were removed by rotary evaporation with care being taken not to heat the flask above 65 °C. The residue was chromatographed on a silica column using chloroform as an eluant. The first fraction consisted of the acetate of **3c** (90% recovery). The second band consisted of the acetate of **1c** and a smaller amount of another product. A second purification by preparative TLC (silica, $CHCl_3$) did not separate these two components. The mixture was deacetylated in ammonia–methanol. The solvent was evaporated and the residue was treated with 2 mL of methanol and enough ethyl acetate to precipitate all of the glucose which was formed. The mixture was filtered and the filtrate was evaporated. The residue was stirred with chloroform yielding an orange powder which was filtered and dried in vacuo: yield 480 mg (52%); mp 116–117.5 °C. This material showed a single spot of TLC and azide absorption at 4.72 μm. Anal. Calcd for $C_{15}H_{21}N_5O_8$: C, 45.10; H, 5.30; N, 17.53. Found: C, 44.90; H, 5.30; N, 17.27.

Acknowledgments. We are indebted to the Charles and Johanna Busch Memorial fund and to the National Institutes of Health (AM 17874) for financial support. We also wish to thank J. Chern and J. San Filippo for assistance with the HPLC separation.

Registry No.—**1a**, 65496-00-6; **1b**, 65495-92-3; **1c**, 65495-93-4; **2**, 28166-06-5; **3a**, 65495-94-5; **3b**, 65495-95-6; **3c**, 64309-10-0; 4-fluoro-3-nitroaniline, 364-76-1; 10-amino-1-decanol, 23160-46-5; 3-amino-1-propanol, 156-87-6; 6-amino-1-hexanol, 4048-33-3; tetra-*O*-acetyl-α-D-glucopyranosyl bromide, 572-09-8.

References and Notes

(1) (a) For a general review of the use of photoaffinity labels, see J. R. Knowles, *Acc. Chem. Res.*, **5**, 156 (1972); (b) G. W. J. Fleet, R. R. Porter, and J. R. Knowles, *Nature (London)*, **224**, 511 (1969).
(2) M. B. Perry and L. L. W. Heung, *Can. J. Biochem.*, **50**, 510 (1971), have prepared some other types of glucose derivatives with photolabile groups.
(3) W. Pigman and N. Richtmeyer, *J. Am. Chem. Soc.*, **64**, 369 (1962).
(4) We are deeply indebted to Doreen Lynch for developing this procedure. Only sketchy experimental details are given in ref 1b, and we have found that if conditions are not carefully controlled the major product is 4-hydroxy-3-nitrophenyl azide.
(5) Aryl azides are heat and light sensitive. It is advisable to cover flasks, etc., with aluminum foil during laboratory operations and to store products in refrigerators.
(6) Use of 1 equiv of amino alcohol and a tertiary amine, e.g., triethylamine, led to reduced yields.
(7) Obtained from Sigma Chemical Co., St. Louis, Mo. This material was used directly without purification.
(8) R. Willstätter and A. Pfannenstiel, *Ber.*, **37**, 4744 (1904).
(9) HLPC analysis of this product on a 2 ft × 1/8 in. Corasil column at 150 psi showed one major (>99%) product using benzene as eluent.
(10) The configurations of **1a–c** are assigned by analogy with numerous examples of glycosides prepared by silver salt catalyzed reactions of **4**. See ref 3 and G. Wulff, G. Rohle, and W. Krüger, *Ber.*, **105**, 1097 (1972).

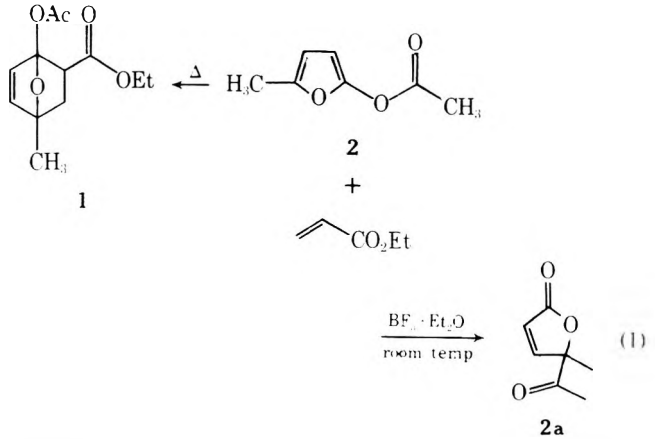
Rearrangements of Acyloxyfurans and Thiophenes

George A. Kraus* and Bruce Roth

Department of Chemistry, Iowa State University, Ames, Iowa 50011

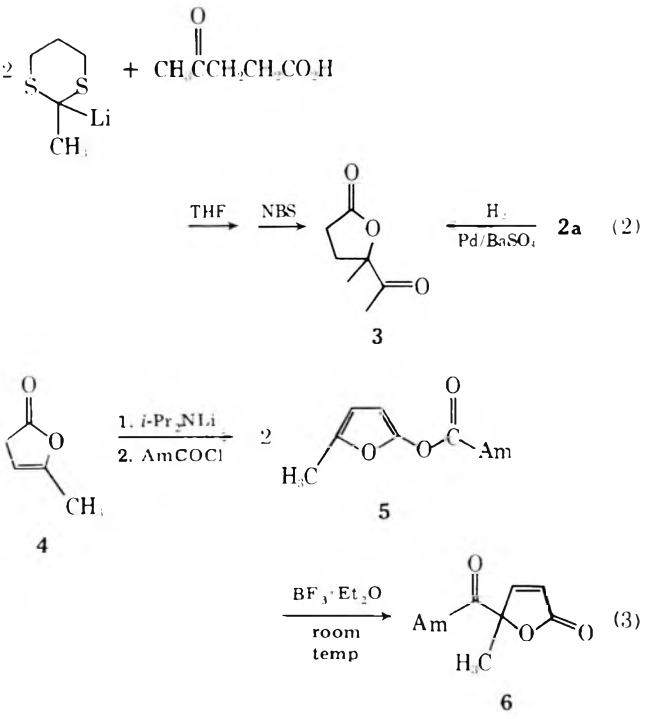
Received June 28, 1977

As part of a program for the synthesis of medium-ring compounds, the preparation of the bicyclic ester **1** became necessary. This could be accomplished in moderate yield by the Diels–Alder reaction shown in eq 1. Attempts to improve



(1)

the yield by the use of Lewis acids such as boron trifluoride etherate provided the unexpected lactone **2a** in good yield. The structure of this novel rearrangement product was proven by hydrogenation[1] to butyrolactone **3** and independent synthesis of **3** by the reaction of levulinic acid with 2 equiv of 2-methyldithiane,[2] followed by oxidative removal of the dithiane moiety using NBS[3] (eq 2). Although the presence of diverse functionality should make this type of compound a versatile synthon, a literature search indicated that the preparation of this class of ketolactones had not been previously reported. Therefore, we sought to probe the extent of this rearrangement with other esters. Compound **5** was readily synthesized by quenching the lithium enolate[4] of angelicalactone **4** with

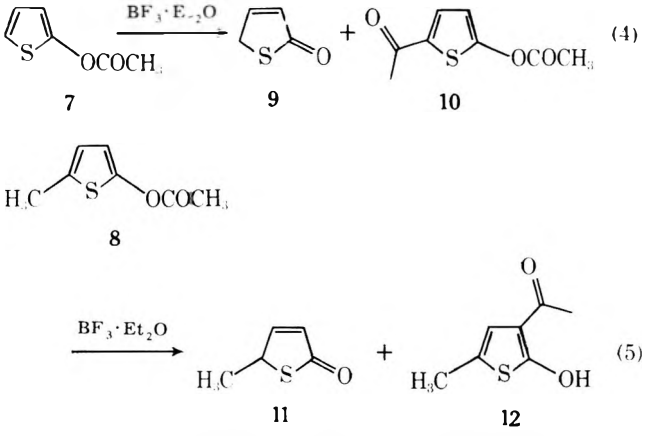


(2)

(3)

hexanoyl chloride (eq 3). Reaction of **5** with boron trifluoride etherate afforded ketolactone **6** in 40% isolated yield. A possible mechanism for this intriguing rearrangement would be one analogous to the Lewis acid catalyzed Fries rearrangement.[5]

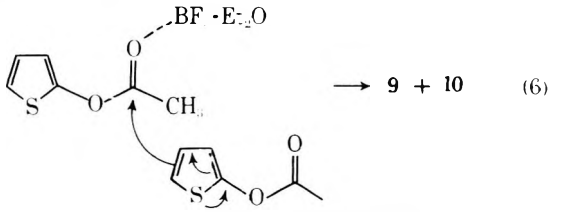
The reactions of thiophene analogues **7** and **8**[6] produced the mixtures shown in eq 4 and 5.



(4)

(5)

Compounds **9** and **10** could arise from intermolecular attack as illustrated in eq 6.



(6)

A similar scheme can account for the formation of compounds **11** and **12** from thiophene **8**.

Experimental Section

NMR spectra were obtained with a Varian (A60) NMR spectrometer. The chemical shifts are reported in δ, using tetramethylsilane as reference. All melting points were taken upon a Fisher-Johns block and are uncorrected. Elemental analyses were determined by Galbraith Laboratories, Knoxville, Tenn. Organic solutions were dried over sodium sulfate.

General Procedure for the Synthesis of 2 and 5. A solution of

0022-3263/78/1943-2072$01.00/0

10 mmol of angelicalactone in 5 mL of tetrahydrofuran (THF) was added over 5 min to a solution of 11 mmol of lithium diisopropylamide in 10 mL of THF at −78 °C. The solution was stirred at −78 °C for 15 min. The appropriate acid chloride (20 mmol) was added rapidly and the resulting suspension was stirred an additional 5 min. The reaction was worked up by the addition of ether and water. The aqueous layer was extracted twice with ether. The organic layer was dried, filtered, and concentrated. Column chromatography (1:10 ether/pentane) on silica gel afforded the acyloxyfurans as oils.

2-Acetoxy-5-methylfuran (2): colorless oil, 40% yield; IR (film) 1785, 1620, 1570, 1175 cm^{-1}; NMR ($CDCl_3$) δ 2.25 (d, J = 1 Hz, 3 H), 2.29 (s, 3 H), 5.82 (d, J = 3 Hz, 1 H), 6.02 (d of t, J = 3 Hz, 1 Hz, 1 H).

2-Hexanoyloxy-5-methylfuran (5): colorless oil, 40% yield; IR (film) 2964, 2940, 2880, 1780 cm^{-1}; NMR ($CDCl_3$) δ 0.7–1.9 (m, 9 H), 2.25 (d, 3 H), 5.75 (d, 1 H), 5.94 (d of t, 1 H).

General Procedure for the Boron Trifluoride Etherate Promoted Rearrangements. To a solution of 1.75 mmol of heterocyclic ester in 4 mL of benzene at 0 °C was added 1.75 mmol of distilled boron trifluoride etherate. The solution was allowed to warm slowly to room temperature and stirred until TLC indicated that reactant had been consumed (4–20 h). The solution was then diluted with ether, washed with sodium bicarbonate and brine, dried, and concentrated. The crude product was filtered through silica gel to afford pure product.

5-Acetyl-5-methyldihydro-2(5*H*)-furanone (2a): 65% yield; bp 65 °C (2 mm); IR (film) 1780, 1725, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.61 (s, 3 H), 2.20 (s, 3 H), 6.20 (d, J = 6 Hz, 1 H), 7.45 (d, J = 6 Hz, 1 H).

Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 59.88; H, 5.80.

5-Hexanoyl-5-methyldihydro-2(5*H*)-furanone (6): 40% yield; bp 77 °C (2 mm); IR (film) 2960, 2935, 2870, 1780, 1725, 1600 cm^{-1}; NMR ($CDCl_3$) δ 0.7–1.7 (m, 9 H), 1.64 (s, 3 H), 2.6 (m, 2 H), 6.23 (d, J = 6 Hz, 1 H), 7.5 (d, J = 6 Hz, 1 H).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 65.70; H, 8.20.

5-Acetylthiophen-2-ol Acetate (10): 45% yield; mp 103–105 °C; IR (mull) 1775, 1660 cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 3 H), 2.55 (s, 3 H), 6.84 (d, J = 4 Hz, 1 H), 7.62 (d, J = 4 Hz, 1 H).

Anal. Calcd for $C_8H_8O_3S$: C, 52.16; H, 4.38. Found: C, 52.19; H, 4.41.

3-Acetyl-5-methylthiophen-2-ol (12): 40% yield, oil; IR (film) 1735, 1630 cm^{-1}; NMR ($CDCl_3$) δ 2.26 (s, 6 H), 6.26 (br s, 1 H); high-resolution mass spectrum, m/e 156.02327 ($C_7H_8O_2S$ requires 156.02451).

4-Hydroxy-4-methyl-5-oxohexanoic Acid γ-Lactone (3). (A) Platinum oxide (10 mol %) and **2a** were stirred at 23 °C in ethanol (0.5 M) under a balloon of hydrogen until TLC indicated that the reaction was complete. The mixture was filtered through Celite and concentrated in vacuo to yield **3**: 97% yield, colorless oil; IR (film) 1790, 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 3 H), 2.32 (s, 3 H), 2.6 (m, 4 H).

(B) An acetone solution of the protected ketolactone (0.86 mmol) was added to a rapidly stirred solution of *N*-bromosuccinimide (5 mmol, 0.3 M in aqueous acetone) at 0 °C. The solution was stirred 15 min at 0 °C, then 5 min at 25 °C. It was then poured into a mixture of hexane/chloroform and saturated sodium bicarbonate. The organic layer was separated, dried, and concentrated. Chromatography on silica gel using 1:4 ether/pentane afforded 0.11 g (90%) of a colorless oil which was identical in all respects (TLC, IR, NMR) with the material prepared in A.

4-Hydroxy-4-methyl-5-oxohexanoic Acid γ-Lactone 1,3-Propylene Dithioketal. Levulinic acid (2.5 mmol) is added dropwise to a solution of 2-lithio-2-methyldithiane (5.0 mmol) at −78 °C. The solution was allowed to warm to −10 °C, then stored in the refrigerator for 20 h. The reaction mixture was then poured into ice and extracted twice with ether/chloroform. The aqueous layer was then acidified to pH 3, extracted with chloroform, dried, and concentrated: 86% yield, colorless liquid; IR (film) 1775, 750 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 3 H), 1.62 (s, 3 H), 1.8–3.6 (m, 10 H).

Anal. Calcd for $C_{10}H_{16}O_2S_2$: C, 51.66; H, 6.94. Found: C, 51.73; H, 7.02.

Acknowledgment. We wish to thank the Department of Health, Education and Welfare for generous financial assistance through Grant No. 5 S05 RR07034 administered by the Iowa State University Research Foundation.

Registry No.—**2,** 65748-93-8; **2a,** 65748-94-9; **3,** 30246-17-4; **4,** 591-12-8; **5,** 65748-95-0; **6,** 65748-96-1; **7,** 36448-58-5; **8,** 65748-97-2; **10,** 65748-98-3; **12,** 65748-99-4; acetyl chloride, 75-36-5; AmCOCl, 142-61-0; 4-hydroxy-4-methyl-5-thioxohexanoic acid γ-lactone 1,3-propylene dithioketal, 65749-00-0; levulinic acid, 123-76-2; 2-lithio-2-methyldithiane, 27969-97-7.

References and Notes

(1) W. A. Jacobs and A. B. Scott, *J. Biol. Chem.*, **87**, 601 (1930).
(2) D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975).
(3) E. J. Corey and B. Erickson, *J. Org. Chem.*, **36**, 3557 (1971).
(4) G. A. Kraus and B. Roth, *Tetrahedron Lett.*, 3129 (1977).
(5) A. Blatt, *Org. React.*, **1**, 342 (1942).
(6) A. B. Hornfeldt and S. Gronowitz, *Ark. Kemi.*, **21**, 250 (1963).

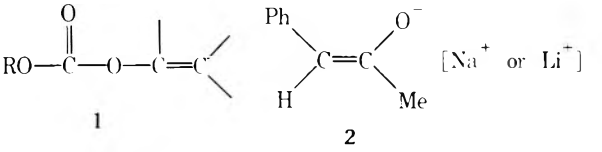
An Efficient Synthesis of Enol Carbonates

R. A. Olofson,* John Cuomo, and Bette A. Bauman

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Received October 28, 1977

Acid of Hg^{2+} catalyzed transesterification provides ready access to most carboxylic acid enol esters. Alternatively, these useful synthetic intermediates and valuable polymer precursors can be made by a second scheme involving acylation of metal enolates with carboxylic acid anhydrides.[1] Because the required starting materials are either unstable or unknown, neither of these complementary routes can be adapted to the preparation of enol carbonates (1). Simple enol esters have been obtained by variations of the second scheme wherein the anhydride has been replaced by the analogous acid halide. However, competitive *C*-acylation of the ambident enolate anion has generally made such processes impractical, a point forcefully demonstrated in the extensive enolate acetylation studies of House.[1] For example, *O*-acetylation of **2** was nearly quantitative with Ac_2O in dimethoxyethane.



1 2

However, with AcCl only 24–50% of the *O*-acetyl product was found and this was contaminated by 14–22% of the *C*-acetyl isomer and unspecified amounts of the *O,C*-diacyl species (from *C*- then *O*-acylation).[2] Even less promising product mixtures were obtained in earlier investigations of the reaction of sodium enolates with ethyl chloroformate.[3]

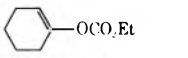
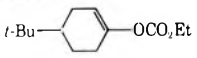
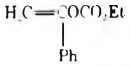
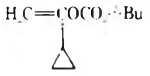
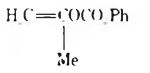
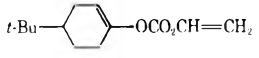
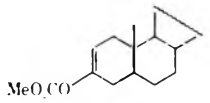
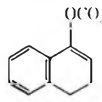
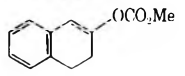
Recent communications from this laboratory have illustrated a few of the unique advantages of enol carbonates (**1**) as synthetic intermediates.[4] These and other results have encouraged us to examine further the acylation of enolates with chloroformates in the hope of developing a broadly useful synthesis of **1**.

Two potential routes to **1** readily extrapolated from the data of House et al. were not explored. These authors reported only *O* attack from treatment of α-mercuri ketones with acetyl chloride.[1] However, the costs and dangers endemic to work with organomercurials led us to discard an approach based on this observation. They also found exclusive *O*-acylation in the reaction of potassium cyclohexanone enolate with ethyl chloroformate (39% yield).[1] Generalization of this scheme was abandoned because of the expense and technical problems inherent in the preparation and use of tritylpotassium, the base required in the best applicable synthesis of potassium enolates.

However, this final result of House did provide an important lead by suggesting that selective *O*-acylation could be accomplished by coercing a lithium enolate to mimic a potassium enolate, an effect sometimes achieved by carrying out

0022-3263/78/1943-2073$01.00/0

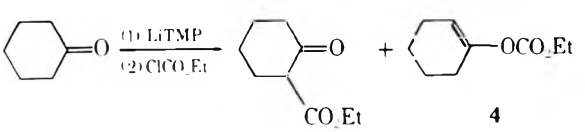
Table I. Enol Carbonates: Synthesis and Properties

Registry no.	Ketone (ROCOCl)	Product	Registry no.	No.	Yield, %	BP (°C) (Torr)	MS parent *m/e* Found (Calcd)	IR stretch (CCl_4), μm C=O	IR stretch (CCl_4), μm C=C	NMR δ ($CDCl_3$) vinyl H[a]
108-94-1 541-41-3	Cyclohexanone (R = ethyl)		65496-21-1	4 76		112–114 (22)	*b*	5.71	5.91	5.3–5.5 (m)
98-53-3	4-*tert*-Butylcyclohexanone (R = ethyl)		65496-22-2	5 78		89–94 (0.1)	226.1582 (226.1568)	5.71	5.89	5.25–5.5 (m)
98-86-2	Acetophenone (R = ethyl)		65496-23-3	6 73		112–115 (3)	*c*	5.68	6.06	5.05 (d, *J* = 2) 5.35 (d, *J* = 2)
765-43-5 543-27-1	c-C_3H_5-COMe (R = isobutyl)		65496-24-4	7 60		89–96 (4)	184.1089 (184.1099)	5.67	6.01	4.55–4.65 (m) 4.68–4.78 (m)
67-64-1 1885-14-9	Acetone (R = phenyl)		65496-25-5	8 49[d]		68–70 (0.2)	178.0632 (178.0629)	5.64	5.96	4.71 (d, *J* = 1.5) 4.89 (d, *J* = 1.5)
5130-24-5	4-*tert*-Butylcyclohexanone (R = vinyl)		65496-26-6	9 47		79–83 (0.2)	224.1428 (224.1412)	5.65	5.89 6.05	4.62 (q, *J* = 2, 6) 4.97 (q, *J* = 2, 14) 5.45–5.65 (m) 7.12 (q, J = 6, 14)
566-88-1 79-22-1	5-α-Cholestan-3-one (R = methyl)		65496-27-7	10 74		107–108 (mp)	444.3594 (444.3603)	5.70	Too weak	5.0–5.5 (m)
529-34-0	α-Tetralone (R = isobutyl)		65496-28-8	11 90		126–129 (0.6)	246.1255 (246.1255)	5.66	6.02	5.80 (t, *J* = 4)
530-93-8	β-Tetralone (R = methyl)		65496-29-9	12 76		115–118 (0.7)	204.0777 (204.0785)	5.65	5.98	6.21 (s)

[a] Coupling constants in Hz, multiplet = m, quartet = q, etc. [b] Known compound, lit. bp 108–110 (20 Torr). [c] Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 69.05; H, 6.22. [d] Corrected yield; see text.

a reaction in a very polar, highly ionizing solvent. Lithium enolates are most conveniently made by deprotonation of ketones with lithium amide bases. For such a process to be useful in the present work, it is crucial that the liberated amine be much less reactive toward chloroformates than the generated enolate.[5] Most amines, including diisopropylamine (the conjugate acid of the most popular amide base), fail this test. Recently lithium 2,2,6,6-tetramethylpiperidide (LiTMP) was introduced by this laboratory as the base of choice in situations with similarly stringent selectivity requirements and its success in a variety of applications[6] invited the prediction that HTMP could not effectively compete with an enolate for chloroformate.

Initial studies were performed on the deprotonation of cyclohexanone with LiTMP followed by acylation with ethyl chloroformate. As anticipated, both the *C*- and *O*-acyl products (**3** and **4**) were isolated with dimethoxyethane (10% **3**, 11% **4**) or THF (−78 °C: 16% **3**, 16% **4**; 25 °C: 16% **3**, 16% **4**) as the solvent. When the THF was diluted with DMF (1:1), the ratio of **4**:**3** improved to 2.5:1 and the yield of **4** increased to 35%.



3 **4**

With the even more polar hexamethylphosphoric triamide (HMPA) as the cosolvent, no *C*-acyl product was found and further increases in the yield of **4** were realized. The best results were obtained when cyclohexanone (1 equiv) was added to LiTMP (1.1 equiv) in THF at −78 °C. The enolate solution was then warmed to room temperature and diluted with an equal volume of HMPA. Addition of ethyl chloroformate (1.1 equiv) was followed by a reaction work-up in which the byproduct, HTMP, and the high-boiling HMPA were removed by extraction from pentane with aqueous pH 4 citrate buffer. The yield of pure, distilled 1-cyclohexenyl ethyl carbonate (**4**) was an excellent 76%.

Other enol carbonates which have been synthesized by this procedure are listed in Table I along with reaction yields, physical properties, and spectral data of structural importance. Yields are generally good to excellent, no *C*-acylation products were found, and all compounds were readily isolated pure except **8** which was contaminated by some diphenyl carbonate. Two products are possible in the reactions of cyclopropyl methyl ketone, β-tetralone, and 5-α-cholestan-3-one but in each case only one isomer was found. The structure (**7**) from the cyclopropyl ketone is in accord with expectations but the isolation of the conjugated product (**12**) from β-tetralone is somewhat surprising since the *C*-formylation, oxalylation, and carboxylation of β-tetralone are reported to give either primarily or exclusively the 3 isomer.[7] Based on analogies with other enolate and enol ester forming reactions of cholestan-3-one,[8] the product **10** should have its C=C bond in the 2

position as pictured. However, a Δ^3-ene structure has not been rigorously excluded. From the products (**8** and **9**), it is evident that in this reaction aryl and vinyl chloroformates[9] behave like simple alkyl chloroformates. To our knowledge, the cyclohexenyl vinyl carbonate (**9**) is the first known example of a mixed bis(enol) carbonate though such species would be of special interest in polymer chemistry.

Efforts to prepare an enol carbonate from cyclohexane carboxaldehyde were unsuccessful. Evidently, the use of LiTMP does not avoid the aldol condensation complications normally encountered in endeavors to make solutions of aldehyde enolates. Attempts to extend the reaction to the synthesis of enol chloroformates by enolate acylation with phosgene also failed. Unlike chloroformates, phosgene reacts rapidly with HMPA at 0 °C.[10]

The HMPA effect carries over to the reaction of LiTMP derived cyclohexanone enolate with acetyl chloride. Using THF as the solvent, the product ratio of 2-acetylcyclohexanone to cyclohexenyl acetate was 2:1. With 1:1 THF–HMPA only the latter was obtained though the yield was a mediocre 25%. Acylation with benzoyl chloride gave 2-benzoylcyclohexanone as the sole product (50% yield) with THF as the reaction solvent but this *C*-acyl product (52% yield) was joined by cyclohexenyl benzoate (13% yield) in 1:1 THF–HMPA. Little practical value of this procedure in the synthesis of simple enol esters is foreseen.

In conclusion, a comment concerning the H^+arpoon base, LiTMP, seems appropriate. In the present synthetic application, unlike most others developed in our laboratory[6] and more recently in other laboratories, the success of LiTMP is not primarily a result of its proton abstracting selectivity. Instead its value derives: first, from the relative inertness of the conjugate acid, HTMP, toward chloroformates and in the longer term toward the activated ester products and, second, from the ease of removal of HTMP by a simple extraction procedure from neutral products. The first advantage is not shared by other often used amide bases and the second is a deficiency in the use of trityl anions. Though both advantages are further optimized with alkali metal hydride bases, solubility problems severely limit their utility in synthesis.

Experimental Section

Melting points were taken in a Thomas-Hoover apparatus equipped with a calibrated thermometer. Infrared spectra were obtained on a Perkin-Elmer 267 spectrophotometer, NMR spectra on a Varian A60-A spectrometer, and mass spectra on an AEI MS-902 spectrometer. Gas chromatographic analyses were performed on a Varian "Aerograph" chromatograph, Model 920, equipped with thermal conductivity detectors and fitted with a 5 ft × 0.25 in. SE-30 on Gas Chrom Q column.

The hexamethylphosphoric triamide (HMPA) was distilled from CaH_2 and the THF from LAH. The distilled chloroformates were stored over $CaCO_3$, the distilled ketones were stored under N_2, and the 2,2,6,6-tetramethylpiperidine (HTMP, Aldrich) was dried over KOH, distilled through a short Vigreaux column, and stored under N_2. The vinyl chloroformate was obtained from D. J. Wancowicz;[9] other reagents were available commercially.

1-Cyclohexenyl Ethyl Carbonate. Glassware was dried at 150 °C, assembled hot in a nitrogen stream, and set up to maintain a slight positive N_2 pressure during the reaction sequence. A three-neck flask was fitted with a stirring magnet, a pressure equalizing dropping funnel, a condenser topped with an N_2 gas inlet, and a septum cap. First, the LiTMP was prepared by dripping MeLi (0.022 mol, Ventron, ca. 1.6 M in ether) into a solution of HTMP (3.10 g, 0.022 mol) in THF (20 mL) slowly enough to accommodate the resulting methane evolution. After another 10 min, the solution was cooled in a dry ice–acetone bath[11] and cyclohexanone (2.08 g, 0.0212 mol) in THF (10 mL) was dripped in (20 min) through the dropping funnel. Stirring at ca. −70 °C was continued for another 15 min and then the clear yellow enolate solution was warmed to 25 °C and diluted with 40 mL of HMPA which caused the color to darken to an orange-brown. Next ethyl chloroformate (2.38 g, 0.022 mol) was rapidly syringed into the reaction vessel (heat generated) again changing the color to a light yellow. The mixture was then poured into 50 mL of aqueous 10% citric acid (buffered to pH 4 with 50% NaOH) and pentane (50 mL) was added.[12] After separation, the aqueous phase was extracted with pentane (2 × 25 mL) and the combined organic layers were washed with 5% $NaHCO_3$ and water and dried (anhydrous Na_2SO_4). Vacuum distillation afforded the product as a colorless liquid: 2.86 g; bp 112–114 °C (22 Torr); NMR (CCl_4) δ 1.28 (3 H, t, J = 7 Hz), 1.5–2.5 (8 H, m), 4.13 (2 H, q, J = 7 Hz), 5.3–5.5 (1 H, m); IR (CCl_4) 5.71, 7.32, 8.0 μm; mass spectrum *m/e* (rel intensity) 170 (p, 15), 98 (100), 83 (63), 70 (98). Analysis (GC) indicated that the product was contaminated by only a trace of cyclohexanone; 76% overall yield.[13]

The other carbonates in Table I were similarly prepared from the appropriate ketones and chloroformates except for the following minor variations. Enolate formation from cyclopropyl methyl ketone was performed at −95 °C (liquid N_2-CH_2Cl_2 bath) to give **7**. The cholestenyl carbonate **10** was isolated by recrystallization from acetone, mp 107–108 °C.

The various control and comparison experiments outlined in the text involving **3**, **4**, cyclohexane carboxaldehyde, phosgene, and acetyl and benzoyl chloride were also carried out by the general procedure above with the modifications discussed in the text. When product mixtures were obtained, these were often analyzed by GC prior to final purification. After 18 h the NMR spectrum of a mixture of ethyl chloroformate and HMPA was still the sum of the spectra of both compounds. In contrast, phosgene rapidly reacted with ethereal HMPA at 0 °C to evolve a gas and precipitate a white solid.

In preliminary tests, **4** was obtained in 20% yield when sodium cyclohexanone enolate was made with $NaNH_2$ in ether, diluted with HMPA, and heated to drive off the NH_3. The main product was the dehydrated aldol condensation dimer of cyclohexanone. With cyclohexanone, NaH (55% in mineral oil), and HMPA, the product mixture was even more complex, and an attempt to use lithium HMPA radical anion[14] in HMPA as the enolate generating base and solvent also failed.

Acknowledgment. We are grateful to the National Institutes of Health for the grant which supported this research.

References and Notes

(1) H. O. House, R. A. Auerbach, M. Gall, and N. P. Peet, *J. Org. Chem.*, **38**, 514 (1973).
(2) The *C*-acyl product is rapidly deprotonated by enolate. For an example of this and a use of *C*-acylation involving chloroformates see: R. G. Salomon and M. F. Salomon, *J. Org. Chem.*, **40**, 1488 (1975).
(3) A. Haller and E. Bauer, *Ann. Chim. (Paris)*, **1**, 275 (1924); for additional studies see the Experimental Section.
(4) R. A. Olofson and R. C. Schnur, *Tetrahedron Lett.*, 1571 (1977); R. A. Olofson, R. C. Schnur, L. Bunes, and J. P. Pepe, *ibid.*, 1567 (1977); R. A. Olofson, Y. S. Yamamoto, and D. J. Wancowicz, *ibid.*, 1563 (1977); R. A. Olofson and J. P. Pepe, *ibid.*, 1575 (1977).
(5) Removal of the amine (even NH_3) prior to chloroformate addition cannot be accomplished completely.
(6) R. A. Olofson and C. M. Dougherty, *J. Am. Chem. Soc.*, **95**, 581, 582 (1973); R. A. Olofson, K. D. Lotts, and G. N. Barber, *Tetrahedron Lett.*, 3381, 3779 (1976); G. N. Barber and R. A. Olofson, *ibid.*, 3783 (1976).
(7) S. W. Pelletier, R. L. Chappell, P. C. Parthasarathy, and N. Lewin, *J. Org. Chem.*, **31**, 1747 (1966), and references therein; K. Wiedhaup, A. J. H. Nollet, J. G. Korsloot, and H. O. Huisman, *Tetrahedron Lett.*, 1599 (1965); P. Grafen and R. B. Turner, *ibid.*, 3935 (1964).
(8) W. G. Dauben, R. A. Micheli, and J. F. Eastham, *J. Am. Chem. Soc.*, **74**, 3852 (1952), and references therein.
(9) Vinyl chloroformate is the only readily available enol chloroformate; made by pyrolysis of $ClCO_2CH_2CH_2OCOCl$.[4] Also see; R. A. Olofson, B. A. Bauman, and D. J. Wancowicz, *J. Org. Chem.*, **43**, 752 (1978).
(10) H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6**, 1046 (1967).
(11) Reaction of HTMP with ethereal MeLi at −70 °C is too slow to be preparatively useful. However, LiTMP rapidly reacts with ketones at this temperature.
(12) If desired, HTMP can be recovered easily from the aqueous phase by basification followed by extraction. For the economical synthesis of large quantities of HTMP, the two-step process from acetone, NH_3, and $CaCl_2$ is recommended: F. Francis, *J. Chem. Soc.*, 2897 (1927); H. K. Hall, *J. Am. Chem. Soc.*, **79**, 5444 (1957).
(13) With lithium diisopropylamide instead of LiTMP as the base, the yield of **4** dropped to ca. 25–30% (even with excess $ClCO_2Et$) and the product distillation fraction contained about an equal amount of $i\text{-}Pr_2NCO_2Et$ (IR, NMR, GC analysis; plus other unidentified impurities).
(14) H. Normant, T. Cuvigny, J. Normant, and B. Angelo, *Bull. Soc. Chim. Fr.*, 3441, 3446 (1965).

Convenient Methods for Deoxygenation of Epoxides to Olefins

Kiyoyuki Yamada,* Shunsuke Goto, Hiroshi Nagase, Yoshinori Kyotani, and Yoshimasa Hirata

Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464, Japan

Received July 29, 1977

Deoxygenation of epoxides to olefins is often required in structural and synthetic work, and various methods for this transformation have been developed.[1,2]

We have found that mono-, di-, and trisubstituted epoxides could readily be converted to olefins on treatment with methyltriphenoxyphosphonium iodide[3] (MTPI, 10 molar equivalents) in the presence of boron trifluoride etherate (1–3 molar equivalents) in acetonitrile[4] under mild conditions (room temperature, 1–2 h) (see Table I). Concerning the stereochemical aspect of this reaction, deoxygenation of trans and cis epoxides [e.g., 3 and 4 in the table] was effected to afford the corresponding trans and cis olefins, respectively, proceeding with retention of stereochemistry.[5] Since in some cases [e.g., 3] an iodohydrin was also formed under conditions using 1 molar equivalent of boron trifluoride etherate, a derivative of the iodohydrin was deduced to be an intermediate of deoxygenation of the epoxide to the olefin; the iodohydrin could be converted to the olefin under conditions employing 3 molar equivalents of boron trifluoride etherate.

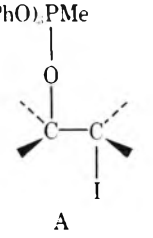
In order to investigate the effect of the reactivity of the iodide ion on the above deoxygenation reaction using MTPI, the following experiments were carried out. When sodium iodide was used instead of MTPI [NaI (10 molar equivalents)–BF_3·OEt_2 (1–3 molar equivalents)–acetone, room temperature, 2 h], epoxides were partly or entirely transformed into iodohydrins without formation of olefins. On the other hand, deoxygenation of epoxides could be effected by potassium iodide complexed with crown ether[6] to an extent less than in the case of MTPI [KI (10 molar equivalents)–dicyclohexyl-18-crown-6 (1 molar equivalent)–BF_3·OEt_2 (1–3 molar equivalents), MeCN or benzene, room temperature–50 °C, 1–5 h][7] (Table I). The above results indicate that the reactivity of the iodide ion is important for deoxygenation of epoxides to olefins. As a reagent for deoxygenation of epoxides to olefins under the present conditions, MTPI is much more effective than the "naked" iodide ion generated from potassium iodide and crown ether.

Table I. Deoxygenation of Epoxides to Olefins by MTPI–BF_3·OEt_2 and by KI–Crown Ether–BF_3·OEt_2

Epoxide	BF_3·OEt_2[a]	Yield[b] of olefin, % MTPI	Yield[b] of olefin, % KI–crown ether
1-Dodecene (1)	3	60[c]	54[c]
5α-Androst-2-en-17-one (2)[d]	1	99	78
Methyl *trans*-9-octadecenoate (3)	3	99[e]	94[e]
Methyl *cis*-9-octadecenoate (4)	3	95[f]	85[f]
Methyl *trans*-13-docosenoate (5)	3	99[e]	71[e]
Methyl *cis*-13-docosenoate (6)	3	86[f]	46[f]
Citronellol methyl ether (7)	3	74	31
Cholest-5-ene (8)[g]	1	91	53
Cholest-4-en-3-one (9)[g]	1	99	44

[a] Molar equivalent. [b] Isolated yields except for 1; the products were purified by preparative TLC and identified by spectral (IR, NMR, and mass) comparison with authentic samples. [c] Yields determined by GLC. [d] 2α,3α-Epoxide. [e] Trans. [f] Cis. [g] A mixture of α- and β-epoxides was employed.

The above findings suggest that a phosphorus-containing intermediate such as A would be involved in the deoxygenation of epoxides using MTPI, which would undergo more readily the β elimination effected by the iodide ion than a corresponding reaction intermediate in the case of the KI–crown ether system. The reaction intermediate similar to the above intermediate A was previously suggested in the conversion of epoxides to *cis*-1,2-dichlorides using the mechanistically related triphenylphosphine–carbon tetrachloride system.[8,9]



A

It should be noted that deoxygenation of epoxides to olefins could be made [e.g., the epoxide of methyl *trans*-13-docosenoate (5), 99%; the epoxide of cholest-4-en-3-one (9), 65%] by methyltriphenylphosphonium iodide [Ph_3MeP·I (10 molar equivalents)–BF_3·OEt_2 (1–3 molar equivalents)–MeCN, room temperature, 1–2 h] to an extent a little less than in the case of MTPI but significantly more than in the case of the KI–crown ether system, suggesting in this case again the important role of a phosphonium ion and that the reaction would proceed through a phosphorus-containing intermediate.[10]

Experimental Section[11]

Methyltriphenoxyphosphonium iodide (MTPI), which was prepared according to the procedure by Verheyden and Moffatt,[3b] was purified prior to use as follows: dry ether was added to a solution of MTPI in dry CH_2Cl_2 to afford precipitates of MTPI, and this procedure of purification was repeated three times, giving almost colorless MTPI, which was filtered and dried in vacuo. Boron trifluoride etherate was distilled from CaH_2 prior to use. Acetonitrile was refluxed over P_2O_5 for 5 h and distilled. Benzene and ether were refluxed over Na and distilled, respectively. Methylene chloride was distilled from $CaCl_2$.

Procedures for Deoxygenation. Similar procedures were used to perform deoxygenation for all the epoxides examined. Representative procedures employing MTPI–BF_3·OEt_2 and KI–crown ether–BF_3·OEt_2 follow.

Deoxygenation of the Epoxides of Cholest-5-ene (8) Using MTPI–BF_3·OEt_2. To a magnetically stirred solution of a mixture of α- and β-epoxides of cholest-5-ene (8) (20.0 mg, 0.052 mmol) and MTPI (234 mg, 0.52 mmol) in 2 mL of MeCN–benzene (v/v, 1:1) was added a solution of BF_3·OEt_2 in MeCN (0.066 mL containing 6.6 μL (0.052 mmol) of BF_3·OEt_2) at room temperature. After 1 h at room temperature the reaction mixture was diluted with saturated $NaHCO_3$ solution and extracted with $CHCl_3$ four times. The combined organic extracts were washed with saturated NaCl solution, dried, and concentrated. The crude product was purified by preparative TLC (silica gel, *n*-hexane) to afford crystals of 8, mp 87–89 °C (17.5 mg, 91%).

Deoxygenation of 2α,3α-Epoxy-5α-androstan-17-one (2) Using KI–Crown Ether–BF_3·OEt_2. A solution of 2α,3α-epoxy-5α-androstan-17-one (2) (23.0 mg, 0.080 mmol) in 2 mL of MeCN was added with stirring to a suspension of KI (133 mg, 0.80 mmol) and dicyclohexyl-18-crown-6 (29.5 mg, 0.080 mmol) in 1 mL of MeCN at room temperature. To this mixture was added a solution of BF_3·OEt_2 in MeCN (0.10 mL containing 0.010 mL (0.080 mmol) of BF_3·OEt_2) at room temperature. After stirring was continued for 3 h at room temperature, the mixture was diluted with saturated $NaHCO_3$ solution (3 mL) and extracted with $CHCl_3$ three times. The organic extracts were washed with saturated NaCl solution, dried, and concentrated. The crude crystalline material was purified by preparative TLC (silica gel, *n*-hexane–EtOAc (v/v, 3:1)), giving crystals of 2, mp 103–106 °C (17.0 mg, 78%).

Registry No.—1, 2855-19-8; 1 corresponding olefin, 112-41-4; 2,

0022-3263/78/1943-2076$01.00/0

965-67-3; **2** corresponding olefin, 963-75-7; **3**, 6084-76-0; **3** corresponding olefin, 1937-62-8; **4**, 2566-91-8; **4** corresponding olefin, 112-62-9; **5**, 6084-74-8; **5** corresponding olefin, 7439-44-3; **6**, 6084-75-9; **6** corresponding olefin, 1120-34-9; **7**, 38595-13-0; **7** corresponding olefin, 55915-70-3; **8** α-epoxide, 20230-22-2; **8** β-epoxide, 24375-46-0; **8** corresponding olefin, 570-74-1; **9** α-epoxide, 2515-12-0; **9** β-epoxide, 1975-34-4; **9** corresponding olefin, 601-57-0.

References and Notes

(1) (a) I. T. Harrison and S. Harrison, "Compendium of Organic Synthetic Methods", Wiley-Interscience, New York, N.Y., 1971, pp 502–504; (b) *ibid.*, Vol. 2, 1974, pp 200 and 201.

(2) (a) P. Dowd and K. Kang, *J. Chem. Soc., Chem. Commun.*, 384 (1974); (b) J. M. Behan, R. A. W. Johnstone, and M. J. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1216 (1975); (c) M. Rosenblum, M. R. Saidi, and M. Madhavararo, *Tetrahedron Lett.*, 4009 (1975); (d) J. E. McMurry and M. P. Flemming, *J. Org. Chem.*, **40**, 2555 (1975); (e) J. Remion, W. Dumont, and A. Krief, *Tetrahedron Lett.*, 1385 (1976); (f) P. B. Dervan and M. A. Shippey, *J. Am. Chem. Soc.*, **98**, 1265 (1976).

(3) (a) S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953); (b) J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2319 (1970). Trivial name for this compound is triphenylphosphite methiodide.

(4) In some cases, benzene was used as a cosolvent to increase the solubilities of materials in the reaction mixture.

(5) Novel methods of converting epoxides to olefins previously reported with retention of stereochemistry: (a) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112, 2539 (1959); (b) K. B. Sharpless, M. A. Umbreit, M. T. Nieh, and T. C. Flood, *J. Am. Chem. Soc.*, **94**, 6540 (1972); (c) D. L. J. Clive and C. V. Denyer, *J. Chem. Soc., Chem. Commun.*, 253 (1973); (d) W. P. Giering, M. Rosenblum, and J. Tancrede, *J. Am. Chem. Soc.*, **94**, 7170 (1972); (e) ref 2b.

(6) For generation and reactions of highly reactive anions using crown ethers, see: (a) C. J. Pedersen and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, **11**, 16 (1972); (b) G. W. Gokel and H. D. Durst, *Synthesis*, 168 (1976).

(7) No deoxygenation of epoxides takes place by tetrabutylammonium iodide under the present conditions.

(8) N. S. Isaacs and D. Kirkpatrick, *Tetrahedron Lett.*, 3869 (1972).

(9) We are indebted to one of the referees for calling our attention to ref 8.

(10) No deoxygenation of epoxides could be made by methyltriphenylphosphonium bromide under the present conditions.

(11) IR spectra were recorded with a JASCO Model IRS spectrophotometer. NMR spectra were obtained using Varian HA-100D (100 MHz) and NV-21 (90 MHz) instruments. Mass spectra were determined on a Hitachi RMU-6C mass spectrometer. For TLC silica gel 60 F_{254} and 60 PF_{254} (E. Merck, A. G., Germany) were used. GLC analysis was performed on a Varian 1820-4 gas chromatograph. The organic solutions were dried over Na_2SO_4 and concentrated by vacuum rotary evaporator.

Allyl Ethers of Ethyl 2-Chloro-2-(2-hydroxyphenylhydrazono)acetate as Intermediates for the Synthesis of 4*H*-1,3,4-Benzoxadiazines

Luisa Garanti* and Gaetano Zecchi

Istituto di Chimica Industriale dell'Università, Centro del C.N.R. per la Sintesi e Stereochimica di Speciali Sistemi Organici, 20133 Milano, Italy

Received July 20, 1977

In a study of 1,3-dipoles bearing an alkenyl substituent, we found[1] that the reaction of 1-chlorohydrazone **1c** with triethylamine gave, in addition to the expected pyrazoline derivative **3c** arising from the intermediate nitrile imine **2c**, minor quantites of the isomeric 4*H*-1,3,4-benzoxadiazines **5c** and **7c**. Since few synthetic methods are available for this ring system,[2-5] further work was done on 1-chlorohydrazones of type **1** as possible precursors of 1,3,4-benzoxadiazines. In view of the fact that 1-chlorohydrozones are well known to follow a general pattern in a basic medium, giving rise to nitrile imines,[6] thermochemical reactions of **1a–c** seemed to be worthy of investigation.

Compounds **1a–c** slowly underwent change in boiling xylene to give a mixture of several products. In all cases, the reaction mixture was worked up before the complete disappearance of the starting substrate; in fact, longer times were not advantageous since formation of tar began to occur. Products, which were isolated by column chromatography, are indicated in Table I along with the corresponding isolation yields.

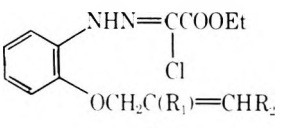
Table I. Reaction of 1-Chlorohydrazones 1 in Boiling Xylene[a]

Compd	Registry no.	Unreacted substrate, %[b]	Products	Registry no.	Mp, °C[c]	Yield, %
1a	61364-10-1	25	**4a**	65465-81-8	103	33
			6a	65465-82-9	129	11
			3a	61364-13-4	*d*	8
			5a	65465-83-0	101[e]	13
1b	65465-79-4	31	**4b**	65465-84-1	91	34
			3b	65495-44-5	132	9
			5b	65465-85-2	97[e]	17
1c	65465-80-7	29	**3c**	65465-86-3	*d*	16
			6c	61364-17-8	*d*	10
			5c	61364-19-0	*d*	20
			7c	61364-18-9	*d*	13

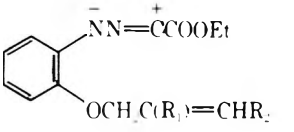
[a] After 42 h. [b] Recovered by column chromatography. [c] From diisopropyl ether. [d] See ref 1. [e] Yellow crystals.

Control experiments showed that compounds **4a,b** and **6a,c** are not stable in boiling xylene but slowly react to afford the corresponding 4*H*-1,3,4-benzoxadiazines **5a,b** and **7a,c**.[7] Some **6a** was detected in the product arising from **4a**.

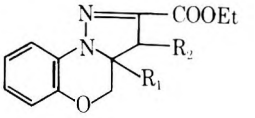
The ring closure of **4a,b** and **6a,c** to **5a,b** and **7a,c** was greatly accelerated in the presence of basic agents. In fact, it was complete within 30 min by treating **4a,b** and **6a,c** with triethylamine (5 mol) in boiling toluene. Under these conditions, the cyclization products **5a,b** and **7a,c** were obtained in quantitative yields.



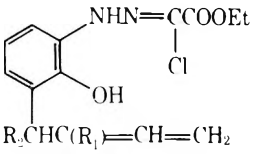
1



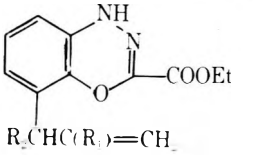
2



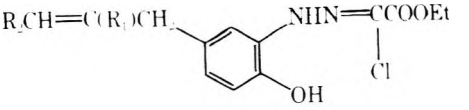
3



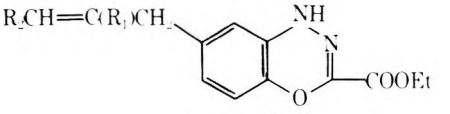
4



5



6



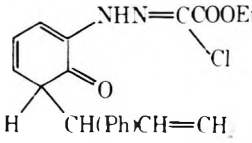
7

a, $R_1 = R_2 = H$
b, $R_1 = Me$; $R_2 = H$
c, $R_1 = H$; $R_2 = Ph$

0022-3263/78/1943-2077$01.00/0

The above results can be accommodated within the frame of the following mechanistic picture. In accord with the known thermochemical behavior of aryl allyl ethers,[8] compounds **1a–c** are capable of undergoing a Claisen rearrangement reaction leading to 2,6-disubstituted phenols **4**. These primary products can then evolve according to one or both of the following pathways: (i) further migration of the allyl-type substituent to give 2,4-disubstituted phenols **6**; (ii) intramolecular nucleophilic displacement of the chlorine atom to afford 8-substituted 4*H*-1,3,4-benzoxadiazines **5**. The latter process, which is very fast in the presence of triethylamine, parallels the intermolecular reaction of 1-chlorohydrazones with phenol under basic catalysis.[9] Of course, a similar ring closure is possible for **6** to give **7**.

Examination of the results given in Table I reveals that the migration of the allyl substituent to the para position, which is lacking in the case of **1b**, proceeds rather easily in the case of **1c**, thus keeping the concentration of phenol **4c** under detectable values (by NMR). The actual formation of the latter compound is demonstrated by the isolation of the corresponding cyclization product **5c**. The observed preference for the para position in the Claisen rearrangement of **1c** could perhaps be the consequence of a steric hindrance by the phenyl group. This effect would be operating in the retroenolization of the primarily formed cyclohexadienone A, thus



A

favoring the alternative pathway, i.e., further migration of the substituent to the para position.

The tricyclic compounds **3** unquestionably arise from **2** via intramolecular 1,3-cycloaddition. In spite of the absence of a basic reagent, the formation of **2** is not surprising since 1-chlorohydrazones have been reported to undergo, although slowly, thermal elimination to give nitrile imines.[6]

Experimental Section

Melting points were taken on a Büchi apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 377 spectrophotometer. NMR spectra were usually obtained on a Varian A-60A instrument with Me_4Si as an internal standard; a Varian HA-100 instrument was used for compound **3b**.

Preparations of **1a, c** have been previously reported.[1]

Ethyl 2-Chloro-2-[2-(2-methylprop-2-enyloxy)phenylhydrazono]acetate (1b). This compound was prepared from 2-(2-methylprop-2-enyloxy)aniline[10] according to the precedure described for **1a,c**:[1] yield 56%; mp 51 °C (*n*-pentane); IR (Nujol) 3350 (NH) and 1740 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.37 (3 H, t, CH_2CH_3), 1.82 (3 H, s, CH_3), 4.30 (2 H, q, CH_2CH_3), 4.42 (2 H, s, CH_2), 4.8–5.2 (2 H, m, CH_2=), 6.7–7.6 (4 H, m, ar), 8.8 (1 H, broad s, NH). Anal. Calcd for $C_{13}H_{17}ClN_2O_3$: C, 56.66; H, 5.78; N, 9.44. Found: C, 56.80; H, 5.48; N, 9.31.

Reaction of 1-Chlorohydrazones 1 in Boiling Xylene. General Procedure. A solution of **1** (40 mmol) in dry xylene (2 L) was heated under reflux for 42 h. The solvent was then removed under reduced pressure and the residue was chromatographed on silica gel column (1 kg) to afford unchanged **1** followed by the products indicated in Table I. Eluents were light petroleum–diethyl ether (3:2) in the case of **1a,b** and benzene–ethyl acetate (4:1) in the case of **1c**.

Reaction of 1-Chlorohydrazones 4 and 6 with Triethylamine. General Procedure. A solution of 1-chlorohydrazone **4** or **6** (5 mmol) and triethylamine (25 mmol) in dry toluene (250 mL) was heated under reflux for 0.5 h. The mixture was then washed with aqueous HCl, dried over $MgSO_4$, and evaporated. The residue gave the cyclization product **5** or **7** in 90–95% yield. Compound **7a**: yellow crystals, mp 139 °C (from diisopropyl ether).

Registry No.—**7a**, 65465-87-4; 2-(2-methylprop-2-enyloxy)aniline, 55000-14-1.

Supplementary Material Available: Spectral (IR and NMR) and analytical data for compounds **3b, 4a,b, 5a,b, 6a,** and **7a** (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) L. Garanti, A. Sala, and G. Zecchi, *J. Org. Chem.*, **42**, 1389 (1977).
(2) R. Huisgen and R. Fleischmann, *Justus Liebigs Ann. Chem.*, **623**, 47 (1959); R. Huisgen, G. Einsch, and H. Koenig, *Chem. Ber.*, **97**, 2834 (1964).
(3) W. Ried and E. Kahr, *Chem. Ber.*, **103**, 331 (1970).
(4) A. J. Elliot and M. S. Gibson, *J. Chem. Soc., Perkin Trans. 1*, 2915 (1972); A. J. Elliot, M. S. Gibson, M. M. Kayser, and G. A. Pawelchak, *Can. J. Chem.*, **51**, 4115 (1973).
(5) P. W. Chow and N. Ishikawa, *Bull. Chem. Soc. Jpn.*, **47**, 2079 (1974).
(6) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).
(7) The product mixture arising from **1a** could have contained a small amount of **7a**, which however was not isolated.
(8) S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1 (1975).
(9) A. F. Hegarty, M. P. Cashman, and F. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, **44** (1972).
(10) R. Fusco, L. Garanti, and G. Zecchi, *J. Org. Chem.*, **40**, 1906 (1975).

Mild Procedure for the Cleavage of α-Hydroxy Ketoximes Using Dichlorocarbene†

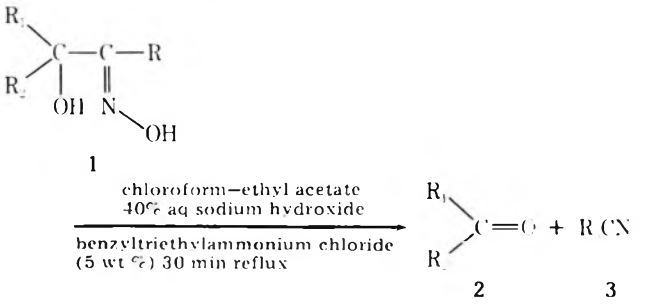
Jayant N. Shah,* Yagnesh P. Mehta, and Girish M. Shah

Research and Development Centre, Indian Petrochemicals Corporation Limited, Baroda 391 346, India

Received September 30, 1977

The fragmentation of *anti*-α-hydroxy ketoximes (**1**) to yield aldehydes or ketones (**2**) and nitriles (**3**) can be effected by a number of reagents such as phosphorus pentachloride,[1] benzenesulfonyl chloride–pyridine,[2] phosphoryl chloride–pyridine,[3] polyphosphoric acid,[4] thionyl chloride,[5] and phosphonitrile dichloride–pyridine.[6]

We now wish to describe a novel Beckmann fragmentation technique for *anti*-α-hydroxy ketoximes using dichlorocarbene as the reagent. The carbene was generated in situ in a two-phase system using a phase-transfer catalyst.[7] The method proceeds under mild conditions to give high yields of the corresponding carbonyl compound and the nitrile:



A wide variety of α-hydroxy ketoximes such as α-benzoin oximes, terpenoid-α-hydroxy ketoximes, and steroid-α-hydroxy ketoximes underwent fragmentation in high yields. The results are summarized in Table I.

A tentative reaction pathway on the lines previously suggested[2b,5,8] for the observed Beckmann fragmentation of *anti*-α-hydroxy ketoximes is shown in Scheme I.

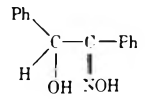
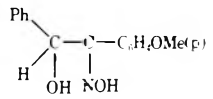
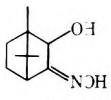
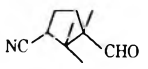
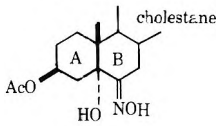
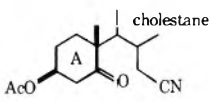
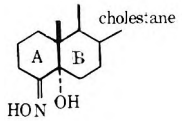
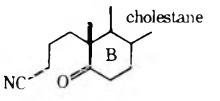
Experimental Section

All melting points are uncorrected. IR spectra were determined on a Perkin-Elmer infracord spectrometer in Nujol and as KBr pellets. All α-hydroxy ketoximes were prepared by previously reported procedures and were fully characterized prior to use. All known products were confirmed by comparison of their IR spectra with authentic samples.

† Dedicated to Professor Bal Dattatrays Tilak on the occasion of his 60th birthday.

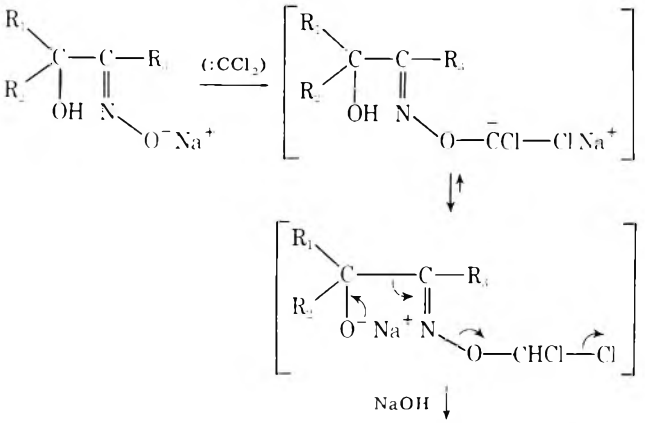
0022-3263/78/1943-2078$01.00/0

Table I. Yields of Products from the Fragmentation of α-Hydroxy Ketoximes

α-Hydroxy ketoximes	Registry no.	Mp, °C	Product	Registry no.	Yield,[a] %	Mp or bp (Torr) °C	Lit. mp or bp (Torr), °C
 1a	574-13-0	150[c]	PhCHO PhCN	100-52-7 100-47-0	80[b] 76	236 191 (760)	236[c] 191[c] (760)
 1b	65414-48-4	136[d]	PhCHO p-OMeC$_6$H$_4$CN	874-90-8	74[b] 65	236 62	236 62[c]
 1c	3221-98-4	157–58[e]		65414-49-5	85[b]	195–96	
 1d	65451-08-3	179[f]		27270-59-3	85	96	96–7[g]
 1e	65452-44-0	190 and 212[h]		65414-50-8	86	66	66–68[h]

[a] Isolated yields of products purified by chromatography or distillation. [b] Isolated as 2,4-dinitrophenylhydrazone. [c] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", Wiley, New York, N.Y., 1965. [d] M. Tiffeneau and J. Levy, *Bull. Soc. Chim. Fr.*, **49**, 725 (1931). [e] R. A. Chittenden and G. H. Cooper, *J. Chem. Soc. C*, **49**, (1970). [f] L. F. Fieser and S. Rajagopalan, *J. Am. Chem. Soc.*, **71**, 3938 (1949). [g] L. Knof, *Justus Liebigs Ann. Chem.*, **642**, 194 (1961). [h] Reference 5.

Scheme I



2 + 3 + NaCl + HCOONa

General Procedure for the Reaction of the Dichlorocarbene with the α-Hydroxy Ketoximes. Cleavage of 2-exo-Hydroxy-3-hydroxyiminobornane (1c). To a solution of **1c** (9.15 g, 50 mmol) in chloroform–ethyl acetate (200 mL, 1:1 v/v) was added 40% sodium hydroxide (50 mL, 0.7 mol) followed by benzyltriethylammonium chloride (2.2 mmol) with stirring. Upon addition of 40% sodium hydroxide, the formation of a white precipitate was observed. The reactants were refluxed for 30 min, during which time the precipitate slowly went into complete solution. The progress of the reaction was followed by TLC (silica gel; benzene–ethyl acetate (5:1) as eluent). The organic layer was then separated, washed with 2 N HCl (5 mL) and water, and dried. IR (CCl_4) of product showed 2240 (CN) and 1723 cm^{-1} (CO). The crude product was converted into its 2,4-dinitrophenylhydrazone and recrystallized from ethanol as yellow needles (14.6 g, 85%): mp 195–96 °C; IR (KBr) ν_{max} 3280 and 2220 cm^{-1}. Anal. Calcd for $C_{16}H_{19}N_5O_4$: C, 55.65; H, 5.50; N, 20.29. Found: C, 55.80; H, 5.62; N, 20.13.

Registry No.—**1c** DNP, 65414-47-3; dichlorocarbene, 1605-72-7.

References and Notes

(1) (a) A. Werner and A. Piguet, *Ber.*, **37**, 4295 (1904); (b) A. Werner and T. Detscheff, *ibid.*, **38**, 69 (1905).
(2) (a) J. S. Buck and W. S. Ide, *J. Am. Chem. Soc.*, **53**, 1912 (1931); (b) A. H. Blatt and R. P. Barnes, *ibid.*, **56**, 1148 (1934).
(3) (a) J. Schmidt-Thome, *Justus Liebigs Ann. Chem.*, **603**, 43 (1957); (b) T. Komeno, *Chem. Pharm. Bull.*, **8**, 680 (1960).
(4) R. T. Conley and F. A. Mikulski, *J. Org. Chem.*, **24**, 97 (1959).
(5) C. W. Shoppee and S. K. Roy, *J. Chem. Soc.*, 3774 (1963).
(6) G. Rosini, A. Medici, and S. Cacchi, *Synthesis*, **10**, 665 (1975).
(7) E. V. Dehmlow, *Angew. Chem., Int. Ed. Engl.*, **13**, 170 (1974), and references cited therein.
(8) H. P. Fischer, C. A. Grob, and E. Renk, *Helv. Chim. Acta*, **45**, 2539 (1962).

Synthesis of Methylaryloxypropanolamines[1]

Thomas L. Lemke,* Robert L. Bohlitt, George A. Capiton, Lindley A. Cates, and Gary E. Martin

Department of Medicinal Chemistry and Pharmacognosy, University of Houston, College of Pharmacy, Houston, Texas 77004

Received October 21, 1977

Several years ago we initiated a project directed toward developing a general synthesis of α-methylaryloxypropanolamines. These compounds were of interest because of their reported selective β-adrenergic blocking action.[2-5] The route proposed for the synthesis of these compounds consisted of

0022-3263/78/1943-2079$01.00/0

Table I. α-Methylaryloxypropanolamines (4) and γ-Methylaryloxypropanolamines (5)

Compd	Registry no.	R_1	R_2	R_3	^{1}H NMR[a] CH_3[b]	^{1}H NMR[a] $NC(CH_3)_3$	MS Ion A	MS Ion C[c]	Mp, °C	Yield, %[f]	Formula[g]
4a	65701-89-5	3-CH_3	4-CH_3	$C(CH_3)_3$	1.12	1.07	100	221 (47)		8.1	
4a HCl	65701-90-8	3-CH_3	4-CH_3	$C(CH_3)_3$	1.32	1.37			159–161[d]		$C_{16}H_{27}NO_2HCl$
4b	65701-91-9	3-H	4-C_2H_5	$C(CH_3)_3$	1.10	1.02	100	221 (9)		8.4	
4b HCl	65701-92-0	3-H	4-C_2H_5	$C(CH_3)_3$	1.31	1.37			174–176[d]		$C_{16}H_{27}NO_2HCl$
4c	65701-93-1	H	H	$C(CH_3)_3$	1.18	1.13	100	193 (3)		7.0	
4c HCl	65701-94-2	H	H	$C(CH_3)_3$	1.30	1.30			135–139[d]		$C_{14}H_{23}NO_2HCl$
5a	65701-95-3	3-CH_3	4-CH_3	$C(CH_3)_3$	1.18	1.03	86	207 (66)		14.4	
5a HCl	65701-96-4	3-CH_3	4-CH_3	$C(CH_3)_3$	1.20	1.33			169–171[d]		$C_{16}H_{27}NO_2HCl$
5b	65701-97-5	3-H	4-C_2H_5	$C(CH_3)_3$	1.21	1.03	86	207 (11)		21.0	
5b HCl	65701-98-6	3-H	4-C_2H_5	$C(CH_3)_3$	1.22	1.33			150–152[e]		$C_{16}H_{27}NO_2$ HCl
5c	65701-99-7	H	H	$C(CH_3)_3$	1.33	1.12	86	179 (47)		41.0	
5c HCl	65702-00-3	H	H	$C(CH_3)_3$	1.30	1.40			132–135[d]		$C_{14}H_{23}NO_2HCl$

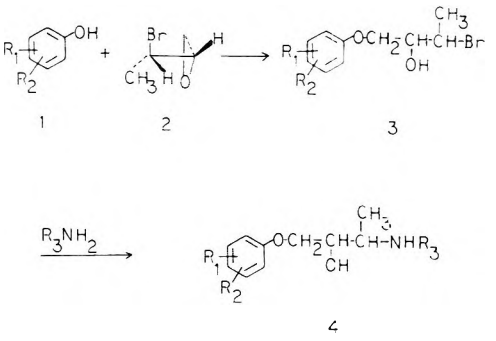
[a] All spectra were run in Me_2SO-d_6 and chemical shifts are reported in parts per million downfield from Me_4Si. The Me_2SO-d_6 peak was used as the internal standard. [b] The methyl existed as a doublet centered at the location indicated. [c] Figure in parentheses is relative intensity (%) with ion A the base peak. [d] From EtOAc. [e] From EtOAc-c-C_6H_{12}. [f] Yields based on the two-step reaction starting with **2** and are isolated yields. [g] All compounds were analyzed for C, H, N, and Cl where present and the results were within ±0.4% theory.

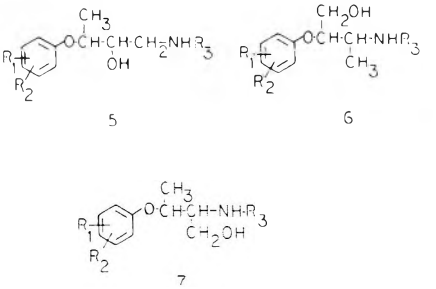
addition of substituted phenols (**1**) to *threo*-3-bromo-1,2-epoxybutane (**2**) using boron trifluoride etherate as a catalyst (Scheme I). It was expected that this would give rise to bromohydrins (**3**) which upon treatment with a primary amine should result in formation of the desired α-methylaryloxypropanolamines (**4**). Upon attempting the first step in this sequence it was noted that the reaction led to a mixture of bromohydrins. Attempts to separate the resulting bromohydrins proved fruitless and therefore the mixture was treated with a primary amine to give the alkyl-substituted aryloxypropanolamines. At this point separation was possible and resulted in isolation of two products, a minor product **4** and the major product γ-methylaryloxypropanolamine (**5**). This paper reports the identification of these compounds.

Results and Discussion

The addition of nucleophiles to haloepoxides under neutral or basic conditions has been reported to lead to a stereoselective addition to the epoxides.[6,7] When electron-withdrawing substituents, such as a methyl halide, are attached to the epoxide ring, opening of the epoxide usually is inhibited at the carbon which bears the electronegative substituent. In the case of **2** this should result in addition to the 1 position. A similar trend has been noted for acid-catalyzed addition to epoxides.[6,8] Although addition to **2** under acidic conditions should lead to **3** and finally on to **4**, one cannot rule out the possible addition to the 2 position which would ultimately lead to minor quantities of **6**. In addition, with opening of the epoxide followed by migration of the bromide and addition of phenol a compound with structure **7** might be expected. The identity of the products as **4** and **5** and the absence of **6** and **7** was confirmed by ^{1}H NMR, ^{13}C NMR, and MS.

Scheme I





The α-methyl group in **4** and **6** should show a characteristic downfield shift if the ^{1}H NMR of the hydrochloride is compared with that of the free base. On the other hand, the chemical shift of the γ-methyl or β-methyl of the free base and the hydrochloride of **5** and **7**, respectively, should not significantly change. As an internal standard, the shift of the methyl protons of the *tert*-butyl group was used for comparison. The base to salt shift [$\Delta = \delta$(salt) − δ(base)] of the *tert*-butyl protons is 0.3 (Table I). The γ-methyl group in **5a–c** does not experience a change between the free base and salt. This proves that the major product does not contain an α-methyl group. The minor product does show a base to salt shift of 0.2 ppm when **4a–c** are compared with their respective salts. These results suggest an α-methyl group but do not differentiate between **4** and **6**. The MS does differentiate between **4** and **6** and between **5** and **7**. Two important fragmentations and the lack of another in the methylarloxypropanolamines were of considerable value in the structure proof. The base peak results from fragmentation between C-2 and C-3 to give ion A, Figure 1. The expulsion of neutral aldehydes, D, and ion C have been noted with compounds **4** and **5**. This is similar to results reported by Rix and Webster.[9] The base peak for **4a–c was** *m/e* 100. This corresponds to ion A, $R_5 = CH_3$ and R_3 = *tert*-butyl. The same base peak would result from **6**, but **6** would be expected to also undergo α cleavage of the primary alcohol to give a M − 30 peak.[10] No such ion was found. The additional cleavage of **4** should result in elimination of acetaldehyde, D (R_4 = H), and formation of ion C ($R_5 = CH_3$). This is found to occur as shown in Table I. In a similar manner **5** ionized to give a base peak of *m/e* 86 where R_5 = H and **5** expells propionaldehyde along with ion C, *m/e* 207. Compound **7** would be expected to ionize to give a base peak of *m/e* 116. This was not seen with any of the compounds isolated.

Perhaps the most convincing evidence for **4** and **5**, which in addition allows the differentiation between **4** and **6**, is the

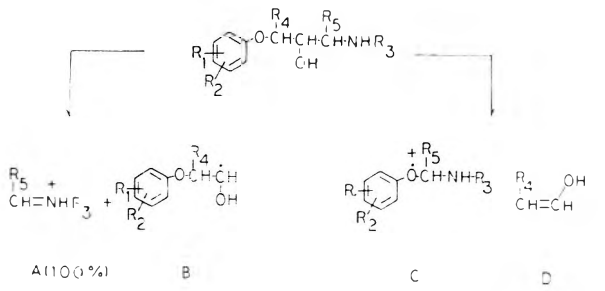
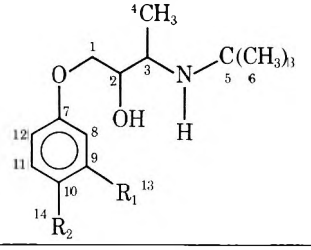


Figure 1.

Table II. Observed 25.2-MHz ^{13}C-NMR Chemical Shifts of 3-*tert*-Butylamino-2-hydroxy-1-aryloxybutanes (4)



	4a, $R_1 = R_2 = CH_3$	4b, $R_1 = H$; $R_2 = CH_2CH_3$	4c, $R_1 = R_2 = H$
1	69.6	69.8	69.5
2	72.3	72.7	72.7
3	49.4	48.9	48.6
4	20.3	21.2	21.3
5	52.3	51.3	51.0
6	29.4	30.0	30.0
7	156.9	156.9	158.8
8	116.2	114.5	114.5
9	137.4	128.5	129.2
10	128.6	136.4	120.6
11	130.1	128.5	129.2
12	111.4	114.5	114.5
13	18.6[a]		
14	19.8[a]	(CH_2) 27.9	
		(CH_3) 15.7	

[a] Could not be unambiguously assigned.

^{13}C-NMR spectra of the compounds. Calculated chemical shifts may be obtained for the aromatic portion of the molecule through the use of additivity parameters.[11,12] For the aliphatic portion of the molecule, approximate chemical shifts were obtained on the basis of polar group replacements of the appropriate methyl groups of 2,3-dimethylpentane with the value for the phenyl substituent obtained from 2-phenoxybutane. As is shown in Figure 2, the calculated chemical shifts of **8**, **9**, and **10** have an inherent pattern which allows the differentiation of both the α-methyl from the γ-methyl isomers, **8** and **9**, respectively, as well as from **10**. One of the characteristics which permits the discrimination between α- and γ-methyl isomers is the position of the methyl group itself. In the case of the α-methyl isomers, **4**, the observed, average chemical shift of the methyl group is δ 20.9 which agrees reasonably well with the predicted value of δ 19.4. It should also be noted that this observation does not facilitate the differentation of **4** from **6**, as the calculated methyl shifts for both of these structural possibilities are identical. In the case of the γ-methyl isomer, **5**, the observed average shift of the methyl group at δ 15.9 also agrees reasonably well with the predicted value from the model of δ 14.4 (Table III).

A second factor contributing to the differentiation between the α- and γ-methyl isomers is the relative behavior of the α and γ carbons themselves. As expected, the α and γ carbons

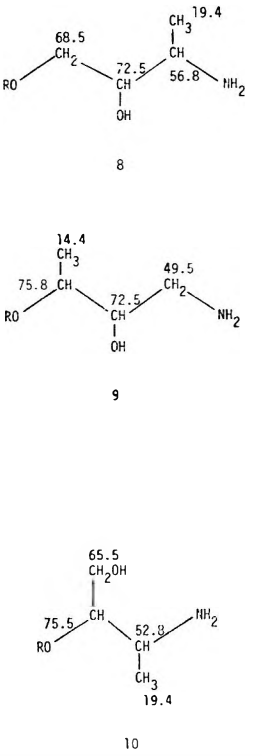
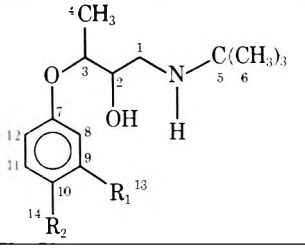


Figure 2. Calculated ^{13}C-NMR chemical shifts for models of the aminobutanol portion of the methylaryloxypropanolamines.

Table III. Observed 25.2-MHz ^{13}C-NMR Chemical Shifts of 1-*tert*-Butylamino-2-hydroxy-3-aryloxybutanes (5)



	5a, $R_1 = R_2 = CH_3$	5b, $R_1 = H$; $R_2 = CH_2CH_3$	5c, $R_1 = R_2 = H$
1	41.8	43.8	43.8
2	71.8	72.5	72.4
3	76.2	76.4	76.1
4	15.3	16.7[a]	15.8
5	51.8	50.2	50.2
6	28.1	29.3	29.0
7	154.7	155.8	157.7
8	117.7	116.0	115.9
9	137.6	128.6	129.3
10	128.9	136.4	120.8
11	130.2	128.6	129.3
12	111.2	116.0	115.9
13	17.9[a]		
14	19.3[a]	(CH_2) 27.9	
		(CH_3) 16.8[a]	

are both shifted downfield when they carry the methyl group, relative to the position when they carry hydrogen. Although the values observed for the carbons (Table II and III) do not agree precisely with the predicted values (Figure 2), this may be accounted for by the relative accuracy of the model itself. The models represent a system containing a primary amino group as opposed to the secondary amine of the observed system. It will be noted that the observed shifts of the methyl groups agree reasonable well with the predicted values as does the chemical shift of the β carbons which carries the hydroxyl group common to **4** and **5**. There is also excellent agreement

observed for the carbon in **4** and **5** with the appropriate carbon in **8** and **9**. It should be noted that these correlations provide the basis for discrimination between **4** and **6**. Thus, on the basis of ^{13}C NMR, in conjunction with the observed mass spectra behavior, **6** can be ruled out in favor of **4** as the product actually formed.

The formation of **5**, which is thought to proceed through 1-bromo-3-aryloxy-2-propanol, is under investigation both as to the nature of the mechanism of the rearrangement and also from the stereochemical standpoint. It is not known whether **4** and **5** are diastereomeric mixtures or pure isomers.

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. Satisfactory IR and ^1H-NMR spectra were obtained for all compounds reported. ^1H-NMR spectra were recorded on Varian T-60 and EM-360 spectrometers in Me_2SO-d_6. MS spectra were obtained on a Hitachi Perkin-Elmer RMU-6H spectrometer. Chromatography was performed using Brinkmann silica gel whereas TLC was done on silica G with 254 fluorescent indicator (Analtech uniplates). ^{13}C-NMR spectra were run on a Varian XL-100 spectrometer operating in the pulsed fourier transform mode and equipped with a Nicolet TT-100 data system and NT-440 frequency synthesizer at ambient temperature in $CDCl_3$. All resonance lines are relative to the central line of $CDCl_3$ at δ 76.9. Typical fixed instrument parameters were: pulse width 10 μs; pulse delay 10 s; sweep width 5 kHz; acquisition time 1.638 s. Aliphatic signal assignments were confirmed by the use of off-resonence decoupling techniques.

Bromohydrin Mixture. To a stirred solution of freshly recrystallized 3,4-dimethylphenol (32.4 g, 0.28 mol) and freshly distilled BF_3-Et_2O (0.7 g) in dry C_6H_6 (240 mL) maintained at 0–5 °C was added 2[13,14] (10.0 g, 0.071 mol). The addition took 0.75 h and the reaction was maintained at 0 °C for an additional 0.5 h and then allowed to warm to 25 °C. A few drops of H_2O were added and the mixture was dried ($MgSO_4$). Removal of the solvent and crystallization of the residue from hexanes led to recovery of 21 g of 3,4-dimethylphenol. The filtrate was concentrated and the residue was taken up in Et_2O, washed with three 50-mL portions of cold 5% NaOH and H_2O, and dried ($MgSO_4$). Removal of the solvent resulted in recovery of 13.7 g of crude product which was used without further purification for the next step. Partial purification of the bromohydrin mixture resulted in recovery of an oil. Anal. Calcd for $C_{12}H_{17}BrO_2$: C, 52.76; H, 6.27; Br, 29.25. Found: C, 51.72; H, 6.16; Br, 28.74. A similar procedure was used to prepare the bromohydrin mixture when 4-ethylphenol and phenol were used as reactants.

3-*tert*-Butylamino-1-(3,4-dimethylphenoxy)butan-2-ol (4a) and 1-*tert*-butylamino-3-(3,4-dimethylphenoxy)butan-2-ol (5a). A solution of bromohydrins (13.5 g, 0.05 mol), freshly distilled *tert*-butylamine (10.9 g, 0.15 mol), and EtOH (25 mL) was heated under reflux for 48 h. Concentration of the reaction mixture gave a residue which was taken up in 10% HCl and washed with three 25-mL portions of Et_2O. The H_2O layer was cooled, made alkaline with 30% KOH, and extracted with $CHCl_3$. The combined $CHCl_3$ was dried ($MgSO_4$) and evaporated to give 10 g of **4a** and **5a**. This oil was chromatographed on silica gel (1 kg) eluting with EtOAc–MeOH–Et_3N (95:2:3). Compound **4a**, 2.1g, was the first product off the column. The second product **5a**, 4.0 g, was collected and showed a single product by TLC. Each compound was individually converted to their respective HCl salt. The recrystallization solvent, yield, and physical constants for these products and the other compounds **4** and **5** which were prepared by a similar procedure are given in Table I.

Acknowledgment. The authors wish to thank the Institute for Cardiovascular Studies (University of Houston) and Eli Lilly and Co. (Indianapolis, Ind.) for financial support. The authors would also like to express their appreciation to Dr. M. R. Wilcott, III and Mrs. Ruth Inners for assistance with the acquisition of the FT-^{13}C-NMR data and to Mrs. Deborah Jones for preparation of this manuscript.

Registry No.—**1a**, 95-65-8; **1b**, 123-07-9; **1c**, 108-95-2; **2**, 65702-01-4; *erythro*-**3a**, 65702-02-5; *threo*-**3a**, 65702-03-6; *erythro*-**3b**, 65702-04-7; *threo*-**3b**, 65702-05-8; *erythro*-**3c**, 65702-06-9; *threo*-**3c**, 65702-07-0.

References and Notes

(1) Presented in part at the 30th Southwestern Regional Meeting of the American Chemical Society, Houston, Texas, Dec. 9–11, 1974, MEDI 256.
(2) B. Levy, *J. Pharmacol. Exp. Ther.*, **151**, 413 (1966).
(3) B. Levy, *Br. J. Pharmacol. Chemother.*, **37**, 277 (1966).
(4) B. Levy, *J. Pharmacol. Exp. Ther.*, **156**, 452 (1967).
(5) B. Levy, *Br. J. Pharmacol.*, **49**, 514 (1973).
(6) R. E. Parker and N. S. Issaacs, *Chem. Rev.*, **59**, 737 (1957).
(7) A. A. Akhrem, A. M. Moiseenkov, and V. N. Dobrynin, *Russ. Chem. Rev. (Engl. Transl.)*, **37**, 448 (1968).
(8) R. A. Wohl, *Chimia*, **28**, 1 (1974).
(9) M. J. Rix and B. R. Webster, *J. Chem. Soc. B*, 254 (1968).
(10) L. M. Weinstock, D. M. Mulvey, and R. Tull, *J. Org. Chem.*, **41**, 3121 (1976). Personal communication from L. M. W. reported a characteristic M − 30 peak for a compound similar to **6**.
(11) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, pp 79–108.
(12) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, p 196.
(13) A. A. Petrov, *J. Gen. Chem. USSR (Engl. Transl.)*, **11**, 713 (1941); *Chem. Abstr.*, **36**, 404 (1942).
(14) C. F. Hiskey, H. L. Slates, and N. L. Wendler, *J. Org. Chem.*, **21**, 429 (1956).

Communications

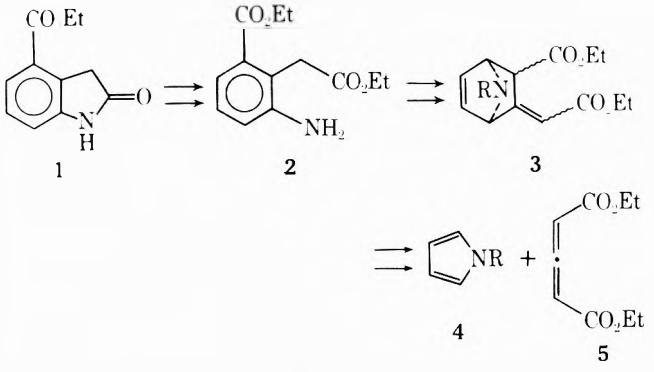
A Novel Potassium Hydride Induced Reorganization Reaction. Synthesis of Condensed Heterocycles

Summary: The potassium hydride induced β elimination of the heteroatom bridge of specifically substituted 7-heterobicyclo[2.2.1]heptenes has been examined as a new route to condensed heterocycles.

Sir: The Diels–Alder reaction is one of the most powerful tools available for the construction of complex organic molecules.[1] We now report an efficient method for the preparation of fused-ring heterocycles by base-induced heterolysis of the 7-heterobicyclo[2.2.1]heptenes available from the Diels–Alder reaction of furans and pyrroles with 1,3-dicarboethoxyallene.[4]

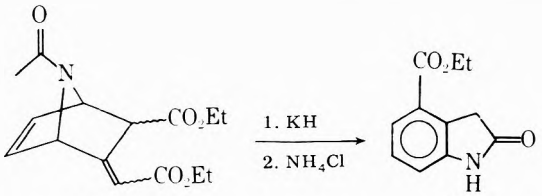
The primary objective of this investigation was the development of a direct process for the preparation of 4-carboethoxyoxindole (1). This product was deemed a valuable precursor for the synthesis of various ergot alkaloids.[2] These compounds have aroused renewed interest because of their possible use as prolactin inhibitors and anti-Parkinsonian drugs.[3]

Structural analysis of the target **1** suggested its derivation from the aminohomophthalate **2**, which in turn could be generated from an intermediate of structure **3**, the cycloadduct of a pyrrole **4** and 1,3-dicarboethoxyallene (**5**).

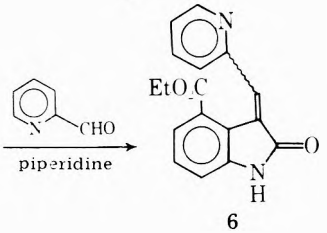


1 2 3 4 5

That cycloadduct **3** does indeed possess all the structural features required for conversion to oxindole **1** was readily demonstrated. The azabicyclo[2.2.1]heptene **3** (R = $COCH_3$), available in 70% yield from the Diels–Alder reaction of *N*-acetylpyrrole and 1,3-dicarboethoxyallene (**5**),[4] was treated with a large excess of potassium hydride (4–5 equiv) in tetrahydrofuran for 1 h at room temperature. The reaction mixture was then quenched with aqueous ammonium chloride and extracted with chloroform. The solid residue obtained after concentration was recrystallized from methanol to afford 4-carboethoxyoxindole (1) (mp 184–185 °C) in 60–75% yield.



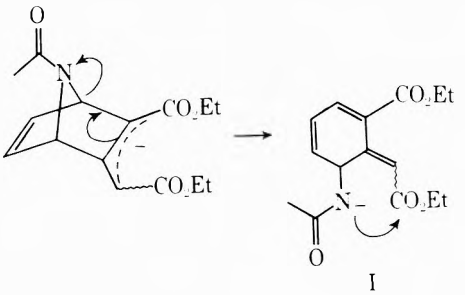
3 1



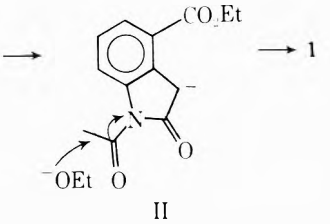
6

The structure of this product was confirmed by spectral analysis [IR ($CHCl_3$) 3450, 3200, 1705 (overlapping C=O groups) cm^{-1}; NMR ($CDCl_3$) δ 9.33 (br s, 1 H), 7.00–7.90 (m, 3 H), 4.43 (q, J = 7 Hz, 2 H), 3.90 (s, 2 H), 1.40 (t, J = 7 Hz, 3 H); M^+ *m/e* 205.07390] and by its facile base-catalyzed condensation with pyridine-2-carboxaldehyde to give the crystalline derivative **6**.[5]

A possible mechanism for this novel molecular reorganization is shown below. The first two steps of this process are



I



II

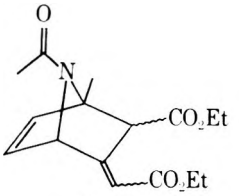
envisioned to involve carbanion formation followed by carbon–nitrogen bond cleavage to yield intermediate I. An analogous base-induced β elimination of a heteroatom bridge has previously been recorded by Stork and co-workers in some of their initial attempts to synthesize cantharidin.[6]

Intermediate I is now transformed by lactamization and aromatization (the timing of these steps is uncertain and, of course, will depend on the olefin geometry of I) to intermediate II.[7] Subsequent deacetylation of II by the ethoxide ejected during the course of this reaction affords **1** on acidic workup.

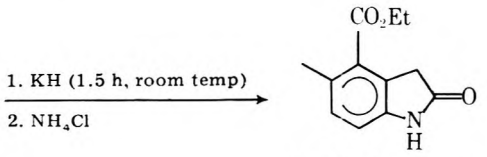
This methodology was also shown to be applicable to the synthesis of 5-methyl-4-carboethoxyoxindole (**8**) [IR ($CHCl_3$) 3450, 3200, 1720, 1710 cm^{-1}; NMR ($CDCl_3$) δ 8.45 (br s, 1 H), 6.93 (ABq, 2 H, J = 8 Hz, ν_{AB} = 13.86), 4.33 (q, J = 7 Hz, 2 H), 3.70 (s, 2 H), 2.48 (s, 3 H), 1.40 (t, J = 7 Hz, 3 H); M^+ *m/e* 219.08879] and 4-carboethoxy-2-oxo-2,3-dihydrobenzofuran (**10**) [IR ($CHCl_3$) 1810, 1720 cm^{-1}; NMR ($CDCl_3$) δ 7.07–7.83 (m, 3 H), 4.33 (q, J = 7 Hz, 2 H), 4.00 (s, 2 H), 1.40 (t, J = 7 Hz, 3 H); M^+ *m/e* 206.05580] from the precursor cycloadducts **7**[8] and **9**,[4] respectively.

The potassium hydride induced β elimination of a heteroatom bridge was also examined with cycloadduct **11** as substrate. Subjection of this oxabicycloheptene, prepared from the Diels–Alder reaction of 4-methyl-2,3-pentadienenitrile and furan, to excess potassium hydride in tetrahydro-

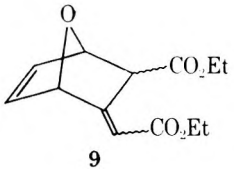
0022-3263/78/1943-2083$01.00/0



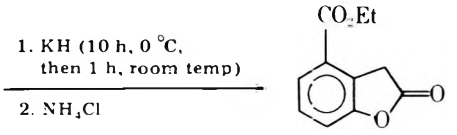
7



8 (55% isolated yield)

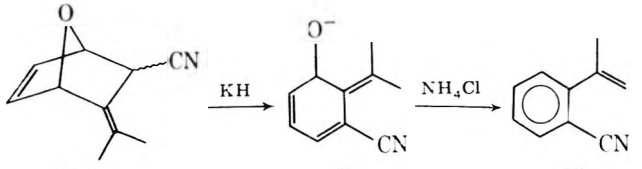


9



10 (45% isolated yield)

furan afforded isopropenylbenzonitrile (12) on ammonium chloride workup.



11 III 12

This product results from the acid-catalyzed dehydration of III, an intermediate which cannot aromatize in the basic milieu.

The heterolytic scission reaction reported herein thus provides a convenient method for the synthesis of fused heterocycles. This method is, however, limited to the use of allenes bearing specific electron-withdrawing groups in both the 1 and 3 positions.

Acknowledgments. The authors are indebted to the Health Research and Services Foundation (HRSF) of Pittsburgh, Pa., and the National Institutes of Health (Grant No. R01 HL2059-01) for support of these investigations. We also thank Anthony Ames, William C. Floyd, and Glen Herman for obtaining spectral data.

References and Notes

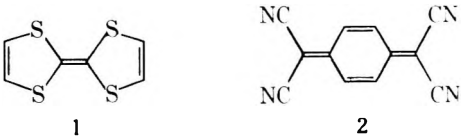
(1) A. S. Onishchenko, "Diene Synthesis", Daniel Davey and Co., New York, N.Y., 1964; W. Oppolzer, *Angew. Chem., Int. Ed., Engl.*, **16**, 10 (1977), and references cited therein.
(2) A. Hofmann, "Die Mutterkornalkaloide", Ferdinand Enke Verlag, Stuttgart, Germany, 1964; H. G. Floss, *Tetrahedron*, **32**, 873 (1976).
(3) H. G. Floss, J. M. Cassady, and J. E. Robbers, *J. Pharm. Sci.*, **62**, 699 (1973); J. M. Cassady, G. S. Li, E. B. Spitzner, H. G. Floss, and J. A. Clemens, *J. Med. Chem.*, **17**, 300 (1974).
(4) A. P. Kozikowski, W. C. Floyd, and M. P. Kuniak, *J. Chem. Soc., Chem. Commun.*, 582 (1977). *N*-Acetylpyrrole, prepared by the method of G. S. Reddy, *Chem. Ind.*, 1426 (1965), was reacted with 1,3-dicarboethoxyallene in refluxing benzene for 84 h to afford cycloadduct **3**.
(5) G. N. Walker, R. T. Smith, and B. N. Weaver, *J. Med. Chem.*, **8**, 626 (1965).
(6) G. Stork, E. E. van Tamelen, L. J. Friedman, and A. W. Burgstahler, *J. Am. Chem. Soc.*, **75**, 384 (1953), footnote 10.
(7) TLC analysis of cycloadduct **3** reveals three separable components (two are major). Although definitive assignments of stereochemistry to these products have not been made, NMR analysis of the isomers indicates that the major components probably have the same stereochemical features as found for the cycloadducts of pentadienedioic acid and cyclopentadiene: W. C. Agosta, *J. Am. Chem. Soc.*, **86**, 2638 (1964). Also see H. Hauth, D. Stauffacher, P. Niklaus, and A. Melera, *Helv. Chim. Acta*, **48**, 1087 (1965) for the effect of the olefin geometry of an α,β-unsaturatec acid on the chemical shift of neighboring protons. Since isomerization is likely to occur under these reaction conditions, the olefinic geometry of the starting materials is apparently not crucial to the success of this process.
(8) *N*-Acetyl-2-methylpyrrole, prepared from the potassium salt of 2-methylpyrrole [J. L. Rainey and H. Adkins, *J. Am. Chem. Soc.*, **61**, 1104 (1939)] and acetyl chloride, was transformed to cycloadduct **7** by refluxing with 1,3-dicarboethoxyallene in benzene for 3 days.
(9) The 4-methyl-2,3-pentadienenitrile was prepared by the method of P. M. Greaves, S. R. Landor, and D. R. J. Laws, *Chem. Commun.*, 321 (1965), and reacted with furan at 120 °C for 30 h to afford **11**. Attempts to prepare the cycloadduct of diethyl 3-methyl-1,2-butadienylphosphonate [V. Mark, *Tetrahedron Lett.*, 281 (1962)] and furan were unsuccessful.

Alan P. Kozikowski,* Michael P. Kuniak
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260
Received February 8, 1978

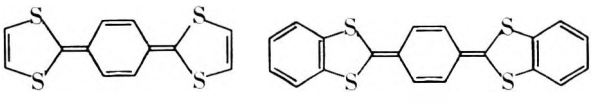
p-Quinobis(benzo-1,3-dithiole)

Summary: The synthesis and characterization of *p*-quinobis(benzo-1,3-dithiole) (**4**) is described. Compound **4** represents the first isolable *p*-quinodimethane derivative substituted by electron-donating groups at the *exo*-methylene groups.

Sir: The unusually high solid-state electrical conductivity of the charge-transfer complex of tetrathiafulvalene (TTF, **1**) with tetracyanoquinodimethane (TCNQ, **2**)[1] has provided the impetus for the synthesis of a variety of derivatives of TTF.[2] One of our recent goals has been the synthesis of derivatives of the unknown *p*-quinodimethane analogue of TTF, *p*-quinobis(1,3-dithiole) (**3**).[3] We now report the synthesis in pure crystalline form of the dibenzo derivative of **3**, namely *p*-quinobis(benzo-1,3-dithiole) (**4**), which also represents the first isolable *p*-quinodimethane substituted by electron-donating groups at C_7 and C_8.

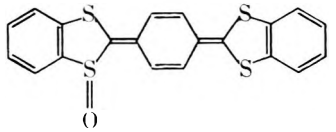


1 2

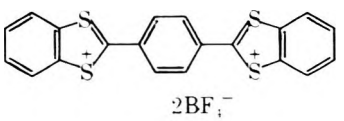


3 4

The recently described push–pull stabilized sulfoxide **5**,[4] as well as the stable bis(dithiolium)fluoborate **6**[4] should be convertible to **4** by chemical reduction; however, our attempts



5

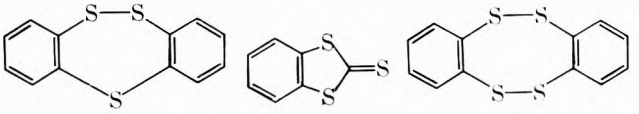


6

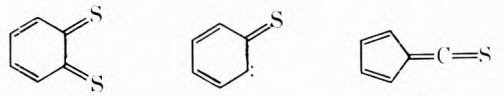
0022-3263/78/1943-2084$01.00/0

to effect such reductions using a variety of reagents (e.g., dithionite, silanes, thiols, phosphines, and phosphites) were unsuccessful, affording only ill-defined products.

The mass spectrum of sulfoxide **5** shows no molecular ion (*m/e* 396), but the appearance of a strong M − 16 peak (*m/e* 380) led us to investigate the pyrolysis of **5**. When **5** was heated to 300 °C under 0.01-mm pressure, three distinct zones of sublimate (A, B, and C) were collected. Chromatography of the yellow zone A on silica afforded colorless needles of trisulfide **7** (10%) [mp 149–153 °C;[5] *m/e* 248 (M^-, 17%), 216 (M − 32, 100%) and 184 (M − 64, 87%)]; a minor constituent of zone A (5%) was benzo-1,3-dithiole-2-thione (**8**), mp 165–167 °C, identical with an authentic sample. Silica chromatography of the orange zone B gave the known tetrasulfide **9** (14%) [mp 215–230 °C (lit.[6] mp 215–230 °C); *m/e* 280 (M^+, 100%)]. Products **7**, **8**, and **9** may all be considered to be derived from dithio-o-benzoquinone (**10**), which corresponds to the base peak (*m/e* 140) in the mass spectrum of **5**, and from the partially desulfurized intermediates **11** and **12** which can form from **10**.



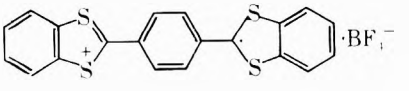
7 **8** **9**



10 **11** **12**

The red zone C consisted of almost pure quinodimethane **4** (38%). Recrystallization without decomposition could be achieved only from a large volume of carbon disulfide under argon, giving small crimson plates: mp 280 °C dec; *m/e* 380 (100%); IR (KBr) 3003 (w), 1527 (m), 1443 (s), 1427 (m), 1307 (m), 1285 (m), 1121 (m), 966 (m), 793 (s), 735 (s) cm^{-1}; visible λ_{max} (CS_2) (log ϵ) 478 (4.81), 503 nm (4.96). Anal. Calcd for $C_{20}H_{12}S_4$: C, 63.12; H, 3.18; S, 33.70. Found: C, 63.38; H, 2.90; S, 33.59. Proof that **4** has the unrearranged skeleton of **5** was easily obtained by treating **4** with HBF_4 in acetic anhydride, followed by crystallization from acetonitrile–HBF_4 (air present) to give an almost quantitative yield of fluoborate **6**.

Attempts to obtain a pure crystalline TCNQ complex of **4** have not yet succeeded, due to a combination of the great insolubility of **4** in organic solvents and by its ready decomposition in dilute solution in all solvents except carbon disulfide. Differential pulse polarography measurements of **6** in acetonitrile showed two reductions at $\epsilon_{1/2}^1 = 0.330$ and $\epsilon_{1/2}^2 = +0.057$ V, corresponding to the monothiolium radical cation **13** and the neutral compound **4**. As evidenced by the irreversibility for polarographic reduction, both **13** and **4** appear highly unstable with respect to **6**. Corresponding polarographic oxidation measurements of **4** were severely hampered by the presence of oxygen even though common precautionary procedures were followed. A single, irreversible oxidation was observed for **3** at approximately −0.142 V.



13

Acknowledgment. This work was supported by grants from the National Science Foundation MRL program, DMR 76-00678 and CHE 76-83417.

References and Notes

(1) (a) A. F. Garito and A. J. Heeger, *Acc. Chem. Res.*, **7**, 218 (1974), and references cited therein; (b) H. Perlstein, *Angew Chem., Int. Ed. Engl.*, **16**, 519 (1977).
(2) (a) M. Narita and C. U. Pittman, Jr., *Synthesis*, 489 (1976); (b) N. C. Gonnella and M. P. Cava, *J. Org. Chem.*, **43**, 369 (1978).
(3) The generation of a diphenyl derivative of **3** was reported recently: Y. Ueno, M. Bahry, and M. Okawara, *Tetrahedron Lett.*, 4607 (1977).
(4) M. V. Lakshmikantham and M. P. Cava, *J. Org. Chem.*, **43**, 82 (1978).
(5) Structure **7** is proposed on the basis of elemental composition and spectroscopic data alone. Confirmation of this structure has to await a separate synthetic study.
(6) L. Field, W. D. Stephens, and E. L. Lippert, Jr., *J. Org. Chem.*, **26**, 4782 (1961).
(7) Department of Physics.

Masaru Sato, M. V. Lakshmikantham
Michael P. Cava,* Anthony F. Garito*[7]
Departments of Chemistry and Physics
University of Pennsylvania
Philadelphia, Pennsylvania 19104

Received January 13, 1978

Deamination of 1-Methylcytosine by the Carcinogen *N*-Acetoxy-4-acetamidostilbene: Implications for Hydrocarbon Carcinogenesis[1]

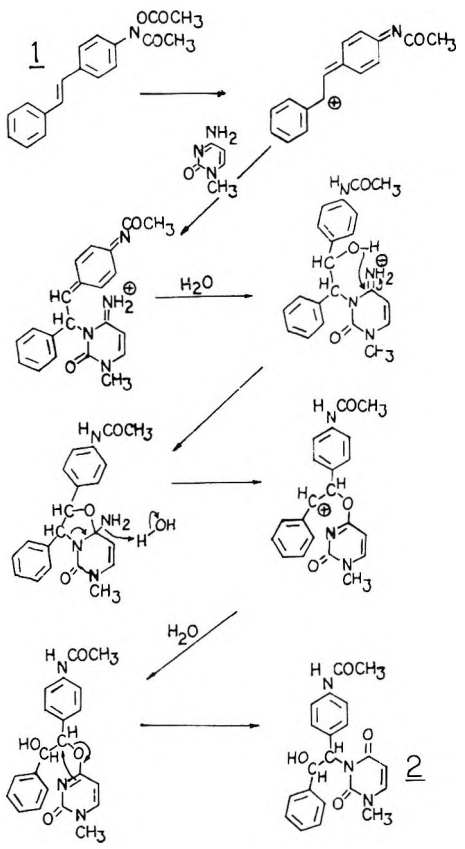
Summary: Reaction of the carcinogen *N*-acetoxy-4-acetamidostilbene with 1-methylcytosine in water and acetone results in a uracil derivative, apparently 1-(4-acetamidophenyl)-1-[3-(1-methyluracilyl)]-2-hydroxy-2-phenylethane.

Sir: Upon solvolysis in water and acetone, the potent local carcinogen *N*-acetoxy-4-acetamidostilbene (*N,O*-diacetyl-*N*-(4-stilbenyl)hydroxylamine, **1**) yields α,β-dihydroxy-4-acetamidobibenzyl, while in aqueous methanol dimethoxyacetamidobibenzyl and hydroxymethoxyacetamidobibenzyl are formed.[2] Comparable products were expected in the reactions of this compound with nucleosides. In the case of 1-methylcytosine and cytidine, it appears that initial alkylation of N-3 in the pyrimidine ring is followed by neighboring group attack on the adjacent exocyclic amino group (N^4) to yield a uracil derivative (Scheme I). This appears to be the first demonstration of alteration of the CNO content of a nucleic acid base by an alkylating agent, and presents the possibility of induction of base pair transitions in DNA.

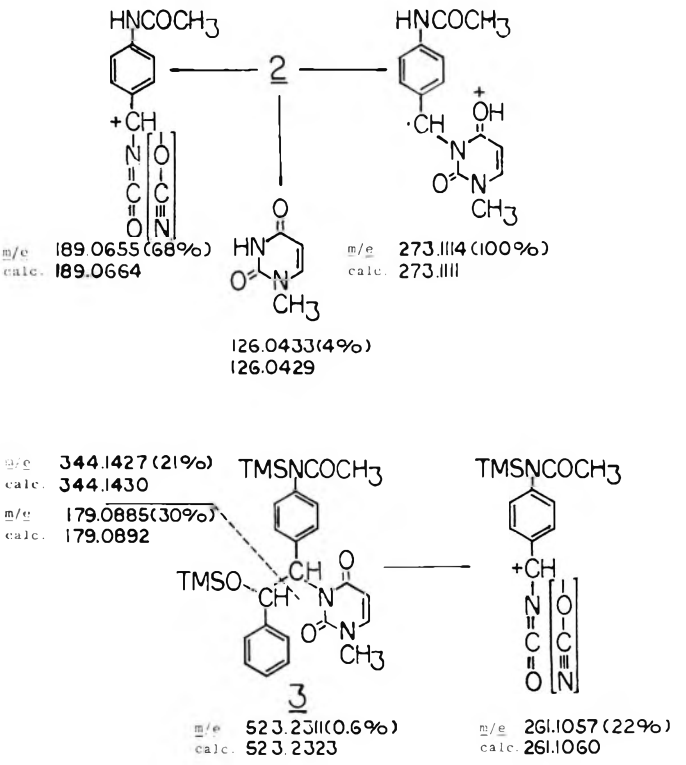
1-Methylcytosine (1 g) in water (50 mL) was treated with 1 N H_2SO_4 to reduce the pH to 7.3. **1** (300 mg) in 33 mL of acetone was added and the mixture incubated at 37 °C overnight. Acetone was evaporated under reduced pressure, the remaining mixture was extracted with four 50-mL portions of ethyl acetate, and the combined extracts were dried over sodium sulfate and evaporated. The residue was taken up in a minimal amount of 95% ethanol and applied to a dry column of silica gel (1 × 15 cm). Dihydroxyacetamidobibenzyl was eluted with CH_2Cl_2, and then adduct and some unreacted 1-methylcytosine were eluted with methanol. The residue from the methanol eluate was then applied to a 20 × 20 cm silica thin-layer plate, which was developed four times with ethyl acetate. Some residual dihydroxyacetamidobibenzyl ran close to the front, and the next major band was eluted with large volumes of methanol and evaporated and the isolated solid (31 mg) redissolved in methanol and precipitated with ether. After centrifugation and washing with ether, the product (**2**) was homogeneous on silica gel TLC: mp 252–253 °C (corr); UV absorption max at 253 nm (95% ethanol, log ϵ 4.16). Anal. Calcd for $C_{21}H_{21}N_3O_4$-CH_3OH: C, 64.23; H, 6.08; N, 10.21. Found: C, 64.30; H, 5.62; N, 10.23. Acetylation with

0022-3263/78/1943-2085$01.00/0

Scheme I



Scheme II



acetic anhydride and pyridine at room temperature gave a product of mp 258–260 °C (ethyl acetate/petroleum ether), with strong IR absorption at 1750, 1708, 1690, 1652, and 1230 cm^{-1}. A 270-MHz NMR spectrum in dimethyl-d_6 sulfoxide (70 °C) revealed only three CH_3 groups in the acetate at 1.86, 1.97, and 3.29 ppm (Me_2SO-d_5 reference at 2.49 ppm). Doublets corresponding to single protons were found at 5.69, 6.40, 6.98, and 7.63 ppm. In methanol, the doublets at 5.69 and 6.40 ppm appeared to have been replaced by a broad singlet at 4.65 ppm, while the remaining downfield peaks were all located between 7.08 and 7.69 ppm. 6-H of the pyrimidine ring thus seems to be little shifted from its position in cytidine or uridine,[3] while 5-H, normally found near 5.8 ppm, is now buried among the aromatic protons of the bibenzyl group.

Identification of the base in **2** as uracil was made by rigorous establishment of molecular weight and elemental composition by mass spectrometry[4] of **2** and its bis(trimethylsilyl) derivative **3**, using field desorption (**2**, M^+ 379, MNa^+ 402), field ionization (**3**, M^+ 523), and electron impact (**3**, M^+ 523) methods. Further data showing uracil and placement of substituents on the ethylene carbons were provided by exact mass measurements on fragment ions from **2**[5] and **3** (Scheme II). In particular, the two major fragments (masses 344 and 179) of the Me_3Si derivative of **2** (shown as structure **3** in Scheme II) can only be obtained by attachment of methyluracil to the "toluidine" carbon and of –OH to the benzyl carbon. The alternative substitution would yield different fragments which were not found.

The mass spectra do not permit unambiguous assignment of the position of attachment at the pyrimidine ring, as shown by the structurally plausible alternate forms of *m/e* 261 and 189 (Scheme II). The apparent change in chemical shift (NMR) of 5-H in the pyrimidine from near 6 ppm to greater than 7 ppm suggests an alteration of O^4 rather than at N-3. On the other hand, both 5-H and 6-H were found to be shifted in O^4-ethyluridine,[6] the latter to 8.32 ppm. Thus, the NMR data cannot be meaningfully compared with earlier results.

Kuśmierek and Singer[6] noted that O^4-methyluridine is 90% converted to uridine in 0.01 N HCl after 21 h at room temperature, and that O^4-ethyluridine is converted to cytidine after 2 days in methanolic ammonia at 37 °C. **2** shows no change in its UV spectrum between pH 12 and 2, and is stable toward both mild acid and methanolic ammonia. This chemical evidence thus speaks for alkylation of N-3, and is supported by several C=O peaks in the IR spectrum of the acetate of **2** (acetate, amide, O^2 and O^4 of uracil).

Treatment of cytidine with **1** under the same conditions, or with *trans*-4-acetamidostilbene α,β-epoxide,[7] results in a major adduct with the same UV properties as **2**. RNA was prepared with ^{14}C in cytosine, treated with **1** in acetone and water, isolated, degraded enzymatically, and the enzyme digest chromatographed on Sephadex LH-20. About one-third of the carcinogen-modified cytidine appeared at the same retention volume as the major nucleoside adduct. Details of the cytidine and RNA studies will be published in the near future, together with studies on other nucleosides and polynucleotides.

While conjectural, the mechanism in Scheme I has certain features which make it consistent with previous observations of reactions of both **1** and cytosine derivatives. A referee has suggested that the deamination could occur simply by hydrolysis of the intermediate immonium ion. This suggests, however, that any alkylation of N-3 of a 1-alkylcytosine would largely lead to a uridine product. However, this has never been observed with monofunctional alkylating agents, such as benzyl bromide or dimethyl sulfate. Thus, it seems essential that a neighboring group in the alkylating agent be involved. One could also well ask why the initial site of reaction between cytosine and nitrenium ion is proposed to be the benzyl carbon, rather than the toluidine carbon of the nitrenium ion. Reaction of **1** with methionine at pH 7.5 leads to β-methylmercapto-4-acetamidostilbene as the major product (76% of all methionine adducts),[8] while HMO calculations for the *N*-acetyl-*N*-(4-stilbenyl)nitrenium ion show that the molecular orbital coefficient for the β carbon is higher tha that for the α carbon in the two lowest unoccupied orbitals, and that

there is a higher positive charge on the 3 carbon.[9] These data suggest that the reactions with nucleosides should also begin at the β carbon. An alternative mechanism would have initial attack by water, with the nucleoside attacking the intermediate quinone imide methide. Further pursuit of this mechanism, however, leads to structures which appear less likely than those proposed in Scheme I.

It is clear that the mechanism shown in Scheme I, or one of the alternatives suggested above, could apply equally well to any reaction which would result in an initial adduct bearing a hydroxyl group vicinal to N-3. Such a reaction could well take place between cytidine or a nucleic acid and a hydrocarbon epoxide. Reaction of benzo[*a*]pyrene-7,8-dihydrodiol 9,10-oxide with poly(C) in vitro[10] and with cytosine in RNA in tissue explants[11] has already been demonstrated. However, it has not been established that the products are actually cytosine compounds. In light of our finding, it appears worthwhile to undertake structural studies on the putative benzpyrene–cytidine adducts.

References and Notes

(1) This is part 6 of the series "*N*-Arylnitrenium Ions in Aromatic Amine Carcinogenesis". This work was supported by Grants CA 18632 (J. D. S.) and CA 18024 (J. A. M.) from the National Cancer Institute. We thank N. C. Yang, University of Chicago, for obtaining NMR spectra.
(2) J. D. Scribner, *J. Org. Chem.*, **41**, 3820–3824 (1976).
(3) N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "NMR Spectra Catalog", Varian Associates, Palo Alto, Calif., 1963.
(4) Determined with a Varian MAT 731 instrument.
(5) Obtained by James Nielsen, Eppley Institute for Research in Cancer, using an AEI MS-902 instrument.
(6) J. T. Kusmierek and B. Singer, *Nucleic Acids Res.*, **3**, 989–1000 (1976).
(7) M. Metzler and H.-G. Neumann, *Xenobiotica*, **7**, 117–132 (1977).
(8) E. C. Miller, B. W. Butler, T. L. Fletcher, and J. A. Miller, *Cancer Res.*, **34**, 2232–2239 (1974).
(9) J. D. Scribner, Doctoral Dissertation, University of Wisconsin, Madison, 1967.
(10) K. W. Jennette, A. M. Jeffrey, S. H. Blobstein, F. A. Beland, R. G. Harvey, and I. B. Weinstein, *Biochemistry*, **16**, 932–938 (1977).
(11) A. M. Jeffrey, I. B. Weinstein, K. W. Jennette, K. Grzeskowiak, K. Nakanishi, R. G. Harvey, H. Autrup, and C. Harris, *Nature (London)*, **269**, 348–350 (1977).

John D. Scribner*
Pacific Northwest Research Foundation
Seattle, Washington 98104

David L. Smith, James A. McCloskey
Departments of Biopharmaceutical Sciences and Biochemistry, University of Utah
Salt Lake City, Utah 84112

Received February 10, 1978

Meldrum's Acid in Organic Synthesis. 2. A General and Versatile Synthesis of β-Keto Esters

Summary: On acylation with various acyl chlorides Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione, gave the corresponding acyl Meldrum's acids, which readily underwent alcholysis with methanol, ethanol, *tert*-butyl alcohol, benzyl alcohol, and trichloroethanol to give various β-keto esters; the acyl Meldrum's acids can be regarded as a synthetic equivalent of mixed diketenes.

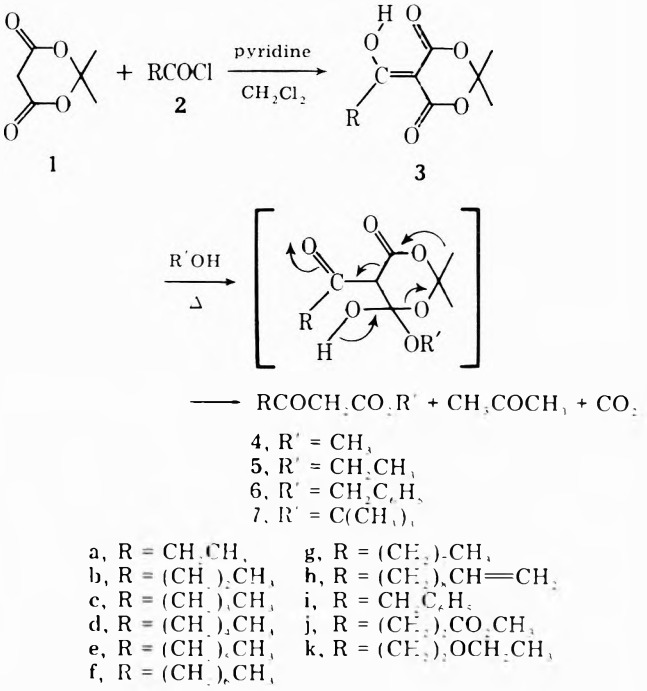
Sir: Since the first example of the Claisen condensation was discovered more than a century ago, β-keto esters have been one of the most important intermediates in organic synthesis.[1] However, it is still required to establish a general and practical method for the preparation of arbitrary β-keto esters of the type $RCOCH_2CO_2R'$.[2] Among the many methods for synthesizing β-keto esters of the type $RCOCH_2CO_2C_2H_5$, two classical syntheses via acetoacetic esters[4] and via mixed malonic esters[5] rather than some modern methods[6] are practically useful, though not always satisfactory in yield, and none is capable of modifying the ester group. We wish to report here a general and versatile method for the synthesis of β-keto esters based on the noteworthy reactivity of Meldrum's acid (**1**), 2,2-dimethyl-1,3-dioxane-4,6-dione,[7] as outlined in Scheme I.

Table I. Yields of Various β-Keto Esters (4–7)[a]

Starting chloride	Yield, %			
	4	5	6	7
2a	82	74	74	86
2b	79	70	77	75
2c	75	74	80	78
2d	84	80	80	82
2e	86	78	71	75
2f	90	77	73	74
2g	92	85	79	80
2h	85	82	60	74
2i	79	84	74	82
2j	81	78	78	73
2k	69	73	73	71

[a] See footnote 19.

Scheme I



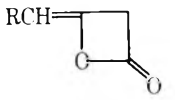
In marked contrast with acetoacetic esters (pK_a 10.7)[8] and acyclic malonic esters (pK_a 13.7),[8] **1** readily reacts with electrophiles such as aldehydes even in the absence of a strong base[9] because of its great acidity (pK_a 4.97).[10] Therefore, acylation of **1** is also expected to occur under similar conditions. When a dichloromethane solution of **1** was treated with 1.1 equiv of propionyl chloride (**2a**) in the presence of pyridine (2 equiv) at 0 °C for 1 h and then at room temperature for 1 h under nitrogen, an acyl Meldrum's acid (**3a**) [mp 55 °C; δ (CCl_4) 1.26 (3 H, t, J = 7 Hz), 1.70 (6 H, s), 3.08 (2 H, q, J = 7 Hz), 15.0 (1 H, s)] was isolated in almost quantitative yield.[11] Similarly, **1** was acylated with various chlorides (**2b–k**) to give the corresponding acyl Meldrum's acids (**3b–k**) almost quantitatively.[12]

Although ethanolysis of **1** and its monoalkyl derivatives

0022-3263/78/1943-2087$01.00/0

proceeds quite slowly without acid catalyst,[9] its acyl derivatives (3) are expected to undergo easily the ethanolysis because of enolization of the acyl group.[11] When the crude 3a[13] was heated in methanol under reflux, the methanolysis took place smoothly with the evolution of carbon dioxide. After 2 h, the solvent was evaporated and the residue was distilled under reduced pressure to give methyl propionylacetate (4a)[5a] in 82% yield from 1. Various methyl acylacetates (4b–k) were similarly synthesized. In the same manner, the ethanolysis of 3 also proceeded readily to give the corresponding ethyl esters (5a–k) in good yield. The results are summarized in Table I.

The reactivity of 3 in alcoholysis is comparable to that of diketene,[14] which is known to be susceptible to attack by various nucleophiles such as alcohols[15] and amines[16] to give acetoacetic acid derivatives. Therefore, 3 can be regarded as a synthetic equivalent of mixed diketene 8, which is usually not available.



8

This alcoholysis of 3 was extended to the synthesis of acylacetic acid benzyl and *tert*-butyl esters without any difficulty. A benzene solution of 3 containing 3 equiv of benzyl alcohol or *tert*-butyl alcohol was refluxed for 3 h. After evaporation of the solvent, the residue was distilled to give 6 or 7 in good yield. The results are also summarized in Table I.

Finally, some trichloroethyl esters,[17] which can be hydrolyzed by zinc in acetic acid,[18] were synthesized in fair yield.[19]

$$RCOCH_2CO_2CH_2CCl_3$$

9a, R = $CH(CH_3)_2$; 67%

b, R = $(CH_2)_2CO_2CH_3$; 70%

c, R = $(CH_2)_2OCH_2CH_3$; 67%

Further applications of this simple and versatile synthesis of β-keto esters to some developments of the Carroll reaction,[20] indole synthesis,[21] etc., are currently in progress.

References and Notes

(1) A. Genther, *Arch. Pharm.*, **106**, 97 (1863); L. Claisen and O. Lowman, *Ber. Dtsch. Chem. Ges.*, **20**, 651 (1887); C. R. Hauser and B. E. Hudson, *Org. React.*, **1**, 266 (1942).

(2) These compounds can be easily converted into β-keto esters of the more general type RCOCHR″CO_2R′ by the alkylation with appropriate alkyl halides.[3]

(3) H. D. Durst and L. Liebeskind, *J. Org. Chem.*, **39**, 3271 (1974); A. Brändström and U. Junggren, *Acta Chem. Scand.*, **23**, 2204 (1969).

(4) R. L. Shriner, A. G. Schmidt, and L. J. Roll, "Organic Syntheses", Collect. Vol. 2, Wiley, New York, N.Y., 1943, p 266; M. Guha and D. Nasipuri, *ibid.*, Collect. Vol. 5, 1973, p 384; M. Viscontini and N. Merckling, *Helv. Chim. Acta*, **35**, 2280 (1952).

(5) (a) D. S. Breslow, E. Baumgarten, and C. R. Hauser, *J. Am. Chem. Soc.*, **66**, 1286 (1944); (b) E. C. Taylor and A. McKillop, *Tetrahedron*, **23**, 897 (1967); (c) R. E. Bowman and W. D. Fordham, *J. Chem. Soc.*, 2758 (1951); (d) L. Pichat and J.-P. Beaucout, *Synthesis*, 537 (1973).

(6) H. H. Wasserman and S. H. Wentland, *Chem. Commun.*, 1 (1970); H. J. Bestmann, G. Graf, H. Hartung, S. Kolewa, and E. Vilsmaier, *Chem. Ber.*, **103**, 2794 (1970); L. Weiler, *J. Am. Chem. Soc.*, **92**, 6702 (1970); R. M. Carlson and J. L. Isidor, *Tetrahedron Lett.*, 4819 (1973); M. W. Rathke and D. F. Sullivan, *ibid.*, 1297 (1973); R. A. Olofson and C. M. Dougherty, *J. Am. Chem. Soc.*, **95**, 582 (1973); J. Nokami, N. Kunieda, and M. Kinoshita, *Tetrahedron Lett.*, 3997 (1974).

(7) A. N. Meldrum, *J. Chem. Soc.*, **93**, 598 (1908); D. Davidson and S. A. Bernhardt, *J. Am. Chem. Soc.*, **70**, 3426 (1948).

(8) R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, **75**, 2439 (1953).

(9) Y. Oikawa, H. Hirasawa, and O. Yonemitsu, *Tetrahedron Lett.*, in press, and references cited therein.

(10) K. Pihlaja and M. Seilo, *Acta Chem. Scand.*, **23**, 3003 (1969).

(11) The NMR spectrum shows clearly that 3a is present completely in its enol form.

(12) These compounds are oily substances except 3l (mp 96–97 °C dec) and 3j (mp 77–78 °C).

(13) After the acylation was complete, the dichloromethane solution was washed with dilute HCl and water, dried, and evaporated to leave almost pure 3, which can be used for the alcoholysis without further purification.

(14) T. Kato, *Acc. Chem. Res.*, **7**, 265 (1974).

(15) S. O. Lawesson, S. Gronwall, and R. Sandberg, "Organic Synthesis", Collect. Vol. 5, Wiley, New York, N.Y., 1973, p 155.

(16) J. W. Williams and J. A. Krynitsky, "Organic Syntheses", Collect. Vol. 3, Wiley, New York, N.Y., 1955, p 10.

(17) Recently, esters of type 9 were applied to the regiospecific aldol condensation: T. Mukaiyama, T. Sato, S. Suzuki, and T. Inoue, *Chem. Lett.*, 95 (1976).

(18) R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbruggen, *J. Am. Chem. Soc.*, **88**, 852 (1966).

(19) Boiling points of new β-keto esters, °C (Torr): **6c**, 130 (0.15); **6d**, 134 (0.1); **6e**, 142 (0.2); **6f**, 153 (0.3); **6g**, 165 (0.25); **6h**, 176 (0.3); **6i**, 169 (0.25); **6k**, 134 (0.3); **7c**, 66 (0.1); **7d**, 79 (0.15); **7e**, 88 (0.15); **7f**, 96 (0.2); **7g**, 117 (0.2); **7h**, 133 (0.3); **7l**, 112 (0.25) (mp 36 °C); **7j**, 101 (0.2); **7k**, 79 (0.2); **9a**, 88 (0.3); **9b**, 141 (0.35); **9c**, 121 (0.35).

(20) M. F. Carroll, *J. Chem. Soc.*, 704 (1940); 507 (1941); F. E. Ziegler, *Acc. Chem. Res.*, **10**, 227 (1977).

(21) T. Kato, K. Tabei, and E. Kawashima, *Chem. Pharm. Bull.*, **24**, 1544 (1976).

Yuji Oikawa, Kiyoshi Sugano, Osamu Yonemitsu*

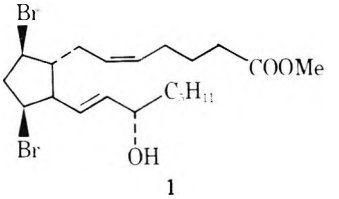
Faculty of Pharmaceutical Sciences
Hokkaido University, Sapporo 060, Japan

Received March 2, 1978

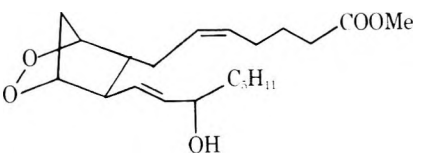
Prostaglandin H_2 Methyl Ester

Summary: Prostaglandin H_2 methyl ester has been prepared in 20–25% yield from 9β,11β-dibromo-9,11-dideoxyprostaglandin $F_{2\alpha}$ with silver trifluoroacetate and hydrogen peroxide.

Sir: The prostaglandin endoperoxides PGH_2 and PGG_2 have attracted considerable attention in recent years. These intermediates in prostaglandin biosynthesis play an important role in diverse physiological functions such as blood platelet aggregation,[1-3] and an understanding of the chemistry and pharmacology of these species may well provide new insights into the chemical mechanism of heart attack and stroke.[4] Several different synthetic approaches to the 2,3-dioxabicyclo[2.2.1]heptane system have been reported[5,6] and recently the Upjohn group of Johnson, Nidy, Baczynskyj, and Gorman[7] have reported a synthesis of PGH_2 methyl ester (2) in 3% yield from 9β,11β-dibromo-9,11-dideoxyprostaglandin $F_{2\alpha}$ methyl ester (1). The method reported by Johnson et al.[7] involves reaction of 1 with potassium superoxide[8,9,10] in an S_N2 displacement reaction. Inasmuch as the yields of 2 formed by the



1



2

superoxide method are low, and prospects for yield improvement are limited,[7] we have sought to develop other methods for carrying out the conversion 1 → 2. In particular, the potential conversion of 1 to 2 by silver salts and hydrogen

0022-3263/78/1943-2088$01.00/0

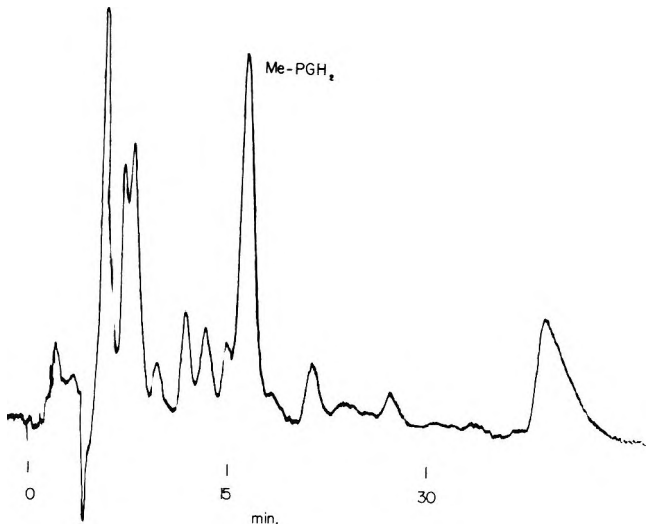


Figure 1. LC trace from reaction mixture of 3.9 mg of **1**, 59 mg of silver trifluoroacetate, and 68 μL of H_2O_2 in 0.5 mL of ether (conditions of chromatography as stated in General Procedure).

peroxide seemed promising, since this method had been used successfully to prepare the model PGH endoperoxide 2,3-dioxabicyclo[2.2.1]heptane from *cis*-1,3-cyclopentane dibromide.[1] We report here the preparation of **2** from **1** by the Ag^+/H_2O_2 method.[11,12] The yields of **2** formed by this method (20–25%) are superior to the superoxide method[7] and this advantage makes the chemical synthesis of **2** or its analogues (including the free acid, PGH_2) synthetically reasonable.

The reaction of **1**[13] with Ag^+/H_2O_2 was carried out under a variety of experimental conditions. Of primary importance in determining the course of reaction of **1** with Ag^+/H_2O_2 was: (1) the silver salt used; (2) the reaction time; and (3) the concentration of Ag^+ and H_2O_2 employed. Preliminary screening reactions (3 mg) were carried out using silver acetate, silver trifluoroacetate, or silver stearate reagents in several organic solvents. Although some **2** may have been produced from the stearate and acetate, by far the best reagent proved to be silver trifluoroacetate/H_2O_2 in diethyl ether. Further, side products appeared to be minimized by using relatively concentrated solutions of silver trifluoroacetate/H_2O_2 and short reaction times. For example, when **1** (7.9 mg/mL) was reacted with silver trifluoroacetate (54 mg/mL) and H_2O_2 (110 μL/mL) in diethyl ether, reaction times of >0.5 h were required for consumption of **1**, and nonpolar compounds were the major products. An increase of the silver reagent to 118 mg/mL and H_2O_2 to 136 μL/mL led to rapid consumption of **1** and, if reaction was terminated after 15 min, a product mixture of which **2** was a significant component.[15]

A major problem encountered in the preparation of PGH_2 methyl ester by the superoxide[7] or silver trifluoroacetate/H_2O_2 methods is the separation of **2** from the complex product mixture. The Upjohn group used preparative TLC, but noted that considerable decomposition of **2** could occur if chromatography was not carried out immediately after application of **2** to the TLC plates.

High-pressure liquid chromatography (LC) is an important separations method, but no reports of PGH_2 purification by LC have appeared. We have been able to greatly simplify the isolation of **2** from the Ag^+/H_2O_2 reaction mixture by LC. A typical LC trace of a crude reaction mixture chromatographed at −11 °C on microporasil (solvent 70:20:10 hexane/EtOAc/THF; refractive index detection) is presented in Figure 1. PGH_2 methyl ester can be readily detected in product mixtures resulting from reaction of as little as 1 mg of dibromide **1**. Thus, quantities of **2** as low as 150 μg can be detected. Although most of our chromatography has been carried out in jacketed columns at −10 °C or colder, we have no evidence that suggests that this low temperature precaution is entirely necessary. In fact, we have carried out LC of pure **2** at room temperature with no apparent decomposition.

The product, **2**, purified by LC was peroxide positive to ferrous thiocyanate reagent,[7] it chromatographed under several different solvent conditions identically with authentic PGH_2 methyl ester,[13] and it was reduced to $PGF_{2\alpha}$ methyl ester with triphenylphosphine.[16]

The sevenfold improvement in the yield of **2** for the Ag^+/H_2O_2 method as compared to the superoxide approach and the easy isolation of PG endoperoxides by LC opens the way for the synthesis of a variety of endoperoxide analogues[17] and makes the parent free acid, PGH_2, potentially available by chemical synthesis.

Silver Trifluoroacetate/H_2O_2 (General Procedure). To 12.4 mg (2.51×10^{-5} mol) of **1** in 1.6 mL of anhydrous ether was added 212 μL of 98% H_2O_2[14] (8.8×10^{-3} mol, 350 equiv) followed by addition of 183 mg of silver trifluoroacetate[18] (8.4×10^{-4} mol, 33 equiv) in one batch to the dibromide–H_2O_2 solution. The mixture was stirred for 15 min at room temperature, during which time a light yellow solid precipitated from solution. The reaction mixture was diluted to 25 mL and washed with 30-mL portions of cold water, cold bicarbonate, and cold water. The ether layer was dried over sodium sulfate at 0 °C and the solvent then removed. LC on a Waters microporasil column (−11 °C) with 70:20:10 hexane (distilled from sodium)/EtOAc (distilled form P_2O_5)/THF (distilled from $LiAlH_4$) with a Waters refractive index detector resulted in a LC trace similar to that shown in Figure 1. Removal of the solvent, first by rotary evaporator at aspirator pressure followed by vacuum pump solvent removal (<0.1 mm for 45 min), resulted in 1.9 mg of **2** (21%), pure by TLC and LC.

Acknowledgments. We gratefully acknowledge financial support from the National Institutes of Health and the Army Research Office. We also thank Dr. R. A. Johnson for helpful discussions and the Upjohn Co. for generous gifts of **1** and **2**.

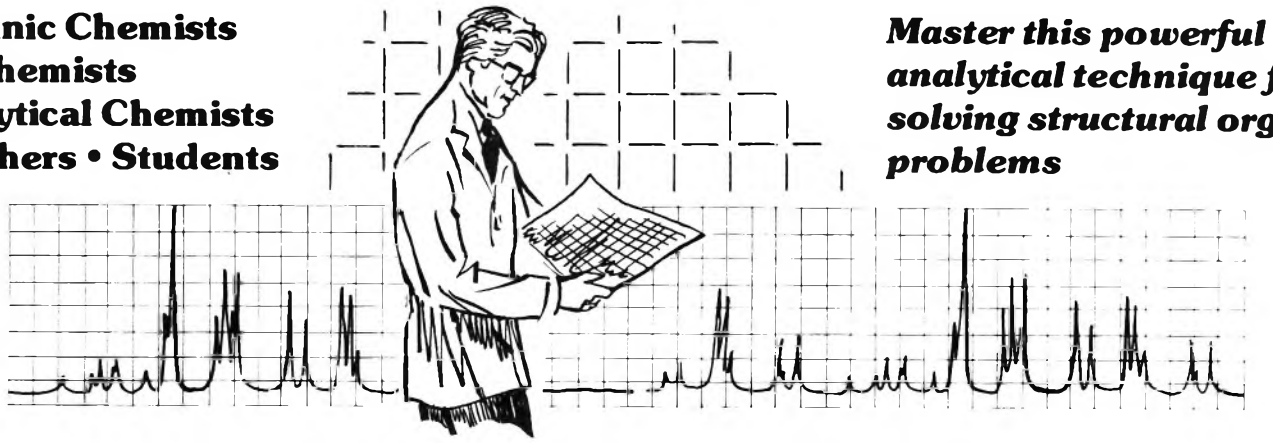
References and Notes

(1) M. Hamberg and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 899 (1973).
(2) D. H. Nugteren and E. Hazelhof, *Biochem. Biophys. Acta*, **326**, 448 (1973).
(3) B. Samuelsson, E. Granstrom, K. Green, M. Hamberg, and S. Hammarström, *Annu. Rev. Biochem.*, **44**, 669 (1975).
(4) S. Moncada and J. R. Vane, "Biochemical Aspects of Prostaglandins and Thromboxanes", N. Kharasch and J. Fried, Ed., Academic Press, New York, N.Y., 1977.
(5) R. G. Salomon and M. F. Salomon, *J. Am. Chem. Soc.*, **99**, 3501 (1977).
(6) W. Adam and H. J. Eggelte, *J. Org. Chem.*, **42**, 3987 (1977).
(7) R. A. Johnson, E. G. Nidy, L. Baczynskyj, and R. R. Gorman, *J. Am. Chem. Soc.*, **99**, 7738 (1977).
(8) R. A. Johnson and E. G. Nidy, *J. Org. Chem.*, **40**, 1680 (1975).
(9) E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Lett.*, 3183 (1975).
(10) J. San Filippo, C. . Chern, and J. S. Valentine, *J. Org. Chem.*, **40**, 1678 (1975).
(11) N. A. Porter and D. W. Gilmore, *J. Am. Chem. Soc.*, **99**, 3503 (1977).
(12) P. G. Cookson, A. G. Davies, and B. P. Roberts, *J. Chem. Soc., Chem. Commun.*, 1022 (1976).
(13) We thank Dr. R. A. Johnson and The Upjohn Co. for generous gifts of **1** and PGH_2 methyl ester.
(14) 98% H_2O_2 is no longer available from F.M.C., but anhydrous hydrogen peroxide (*caution*) may be prepared from 90% H_2O_2 by crystallization (P. Miller, Duke University Thesis, 1964) or by drying ethereal H_2O_2 solutions.
(15) The two major products observed were found at R_f 0.46 and 0.36 (**2**). Minor products were observed at R_f 0.56, 0.38, and 0.25. The R_f of **1** and **2** were 0.50 and 0.36 under these conditions (65:35 EtOAc/hexane; 5 cm × 20 cm × 0.25 mm E. Merck Silica Gel 60F-254 plates).
(16) The tris(trimethylsilyl) ether of $PGF_{2\alpha}$ methyl ester was analyzed by GC-MS and compared to authentic material. Unsilylated $PGF_{2\alpha}$ methyl ester was

also compared to authentic material by TLC (see ref 7).
(17) N. A. Porter and R. C. Mebane, submitted for publication.
(18) Commercial silver trifluoroacetate was not satisfactory and its addition to the reaction mixture resulted in slow or no reaction and a vigorous gas evolution. The salt was prepared by the method reported: D. E. Janssen and C. V. Wilson, "Organic Synthesis", Collect. Vol. 4, Wiley, New York, N.Y., 1963, p 547.
(19) NIH Career Development Awardee (1977–1982).

N. A. Porter,*[19] J. D. Byers, R. C. Mebane
D. W. Gilmore, J. R. Nixon
Paul M. Gross Chemical Laboratory
Duke University, Durham, North Carolina 27706
Received January 24, 1978

Organic Chemists
Biochemists
Analytical Chemists
Teachers • Students



Master this powerful analytical technique for solving structural organic problems

Brand New! ACS Audio Course

Interpretation of NMR Spectra

Vitally important to beginners as well as experienced organic chemists, an understanding of the interpretation of NMR spectra is essential for elucidating the structure of organic molecules.

Emphasizing practical applications, the course provides an in-depth introduction to the theory and methodology of interpreting spectra. Real spectra and clear, concise diagrams are used to illustrate the principles of interpretation. The discussions move logically from simple spectra illustrating basic principles through those of increasing complexity.

The course involves you in numerous problems designed to demonstrate the application of the principles set forth in the lectures. Each problem is discussed in detail by the instructors. Moving through the sessions at your own pace, you can check your understanding of the concepts by working on the problems, referring to the instructor's explanations at will.

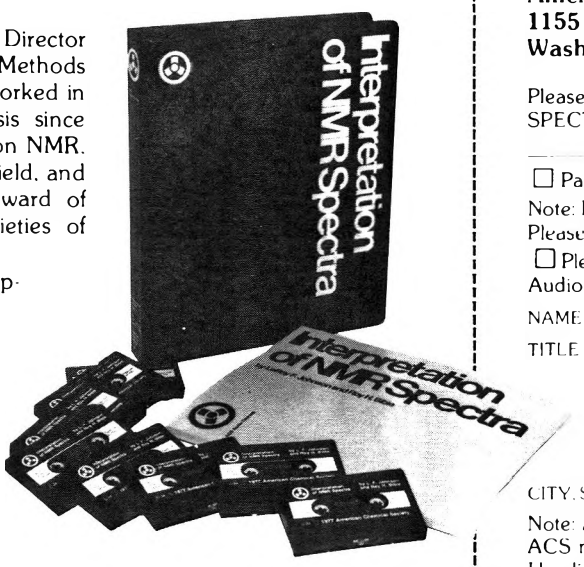
Topics covered include basic NMR theory, the integration curve and its use, chemical shifts and the factors determining them, spin-spin coupling and its causes and importance in the interpretation of spectra, the interpretation of first- and second-order spectra, line broadening effects, and much more.

INSTRUCTORS

LeRoy F. Johnson, currently Vice President-Research at Nicolet Technology Corp., previously served as NMR Applications Laboratory Manager at Varian Associates. He is the co-author, with William C. Jankowski, of *Carbon-13 NMR Spectra*, and has written more than 60 papers dealing with a wide variety of NMR applications.

Dr. Roy H. Bible, Assistant Director of Analytical Resources and Methods at G. D. Searle & Co., has worked in the field of organic synthesis since 1951. Author of two books on NMR, he has taught widely in the field, and received the 1972 Merit Award of the Chicago Technical Societies of Chemists.

The instructors are exceptionally well qualified through their years of experience teaching the ACS Short Course on the subject throughout the U.S.



FOR INDIVIDUAL OR GROUP USE

Excellent for individual use, this ACS Audio Course will be a valuable tool for industrial organic chemists, undergraduate and graduate students, and faculty members. Since extra manuals can be ordered for each participant, the course is ideal for group use by laboratories, libraries, universities, corporations, etc.

UNIT

The complete unit includes eight audiotape cassettes (5.9 hours playing time) and a 117-page manual . . . $175.00. Additional manuals, 1-9 copies . . . $9.50 each; 10-49 . . . $7.50 each; 50 or more . . . $7.00 each.

ACS Triple-Impact Audio Courses

Combine the ease of **listening**
The reinforcement of **reading**
The challenge of **doing**

Learn from the leaders—renowned authorities—teaching the subjects they know best in their own words and voices.

NO RISK – 10-DAY FREE TRIAL

Order now . . . if you are not satisfied, just return the course within ten days for full credit or refund.

Department of Educational Activities
American Chemical Society
1155 Sixteenth Street, N.W.
Washington, D.C. 20036

Please send_____copy(ies) of INTERPRETATION OF NMR SPECTRA at $175.00 each.

_____Additional manuals at $_____each.

☐ Payment enclosed ☐ Please send invoice

Note: Payment must accompany orders of $25.00 or less.
Please allow up to five weeks for delivery.

☐ Please send additional information on this and other ACS Audio Courses.

NAME _____

TITLE _____

ORGANIZATION _____

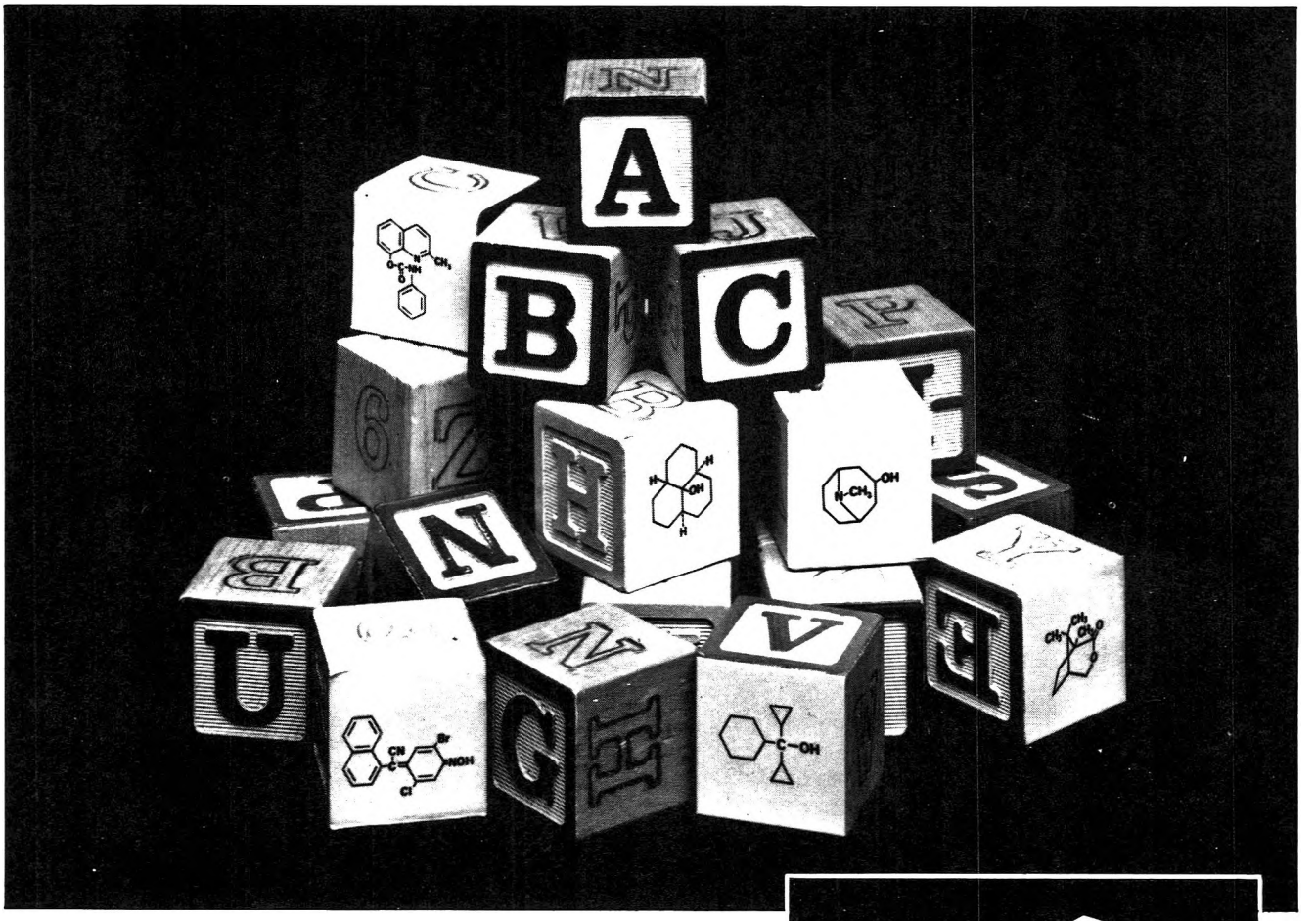
ADDRESS _____

_____

CITY, STATE, ZIP _____

Note: All customers outside the U.S.A. and Canada who are not ACS members should address their orders to Pergamon Press, Headington Hill Hall, Oxford OX3 OBW, England.

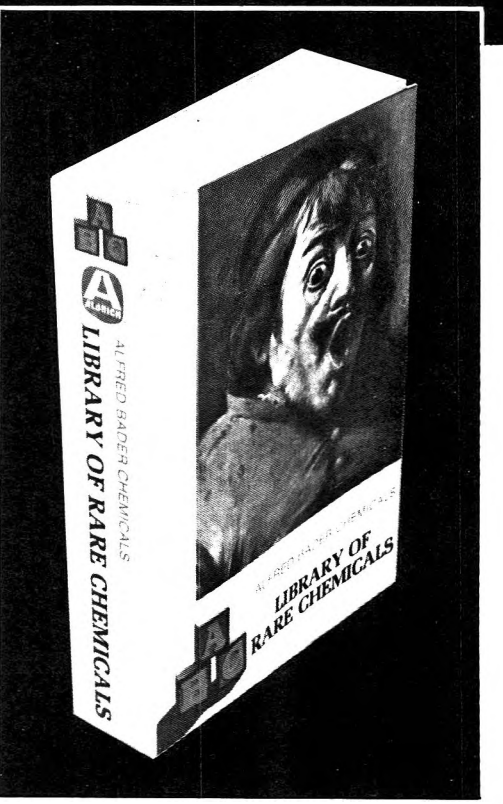
This Valuable New Catalog Contains Over 17,000 Computer-Coded Building Blocks for Research.



First, we pioneered the ***usable*** catalog. Remember what catalogs were like before Aldrich — no structures, no molecular formulas, no classes of compounds, just compilations of names where you might or might not have found what you were looking for? Our ***usable*** catalog has grown like Topsy, from **one** page in 1951 to **999** pages this year. There are thousands of other chemicals we could offer, many of these right on our shelves — compounds which we think are out-of-the-way, but which may help someone: be it for screening, for testing a new reaction, or for comparison with unknown compounds. So we decided to offer some 17,000 of these investigational tools in a simple catalog — with structures, names, and molecular formulas only. We offer these on a first-come-first-served basis, and we will make every effort to obtain more if any real interest develops in a given compound.

A complete listing of any group or class of the library chemicals is available through our computer-searching service. The searches are designed to meet your specific request. If you would like a list, say, of all our adamantanes, isocyanates or phenethylamines, just write us and we'll send you the complete list at no charge.

If you really need out-of-the-way chemicals, write or call us for a copy of the new 4th edition of the *Library of Rare Chemicals*.



chemists helping chemists in research & industry

940 W. Saint Paul Ave., Milwaukee, Wisconsin 53233 • (414)273-3850

11.