VOLUME 41 FEBRUARY 6, 1976 NUMBER 3 JOCEAH

# THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

# THE JOURNAL OF Organic Chemistry



**EDITOR-IN-CHIEF:** FREDERICK D. GREENE

*Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139*

**SENIOR EDITORS**

**Werner Herz**
*Florida State University*
*Tallahassee, Florida*

**James A. Moore**
*University of Delaware*
*Newark, Delaware*

**Martin A. Schwartz**
*Florida State University*
*Tallahassee, Florida*

**ASSISTANT EDITOR:** Theodora W. Greene

**ADVISORY BOARD**

Robert A. Benkeser
John I. Brauman
Orville L. Chapman
Stanton Ehrenson
David A. Evans
Neville Finch
Paul G. Gassman
Ralph Hirschmann
Donald M. Jerina
Carl R. Johnson
William M. Jones
Jay K. Kochi
James A. Marshall
James C. Martin
Albert I. Meyers
John G. Moffatt
Roy A. Olofson
Leo A. Paquette
Marvin L. Poutsma
Henry Rapoport
William Sheppard
Robert V. Stevens
Barry M. Trost
Nicholas J. Turro

**EX-OFFICIO MEMBERS:** George H. Coleman, *Sanibel Island, Florida*
Edward M. Burgess, *Georgia Institute of Technology (Secretary-Treasurer of the Division of Organic Chemistry of the American Chemical Society)*



*Published by the*
**AMERICAN CHEMICAL SOCIETY**

**BOOKS AND JOURNALS DIVISION**

D. H. Michael Bowen, *Director*

Editorial Department: Charles R. Bertsch, Head; Marianne C. Brogan, Associate Head; Eileen B. Segal, Production Editor; Fern S. Jackson, Assistant Editor; Andrew J. D'Amelio, Editorial Assistant; Jane U. Lutick, Production Assistant.
Graphics and Production Department: Bacil Guiley, Head
Research and Development Department: Seldon W. Terrant, Head

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



© Copyright, 1976. by the American Chemical Society. No part of this publication may be reproduced in any form without permission in writing from the American Chemical Society.



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


### Editorial Information

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

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

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

**Page charges** of $70.00 per page are assessed for papers published in this journal. Ability to pay does not affect acceptance or scheduling of papers.

**Bulk reprints or photocopies** of individual articles are available. For information write to Business Operations, Books and Journals Division, at the ACS Washington address. Requests for **permission to reprint** should be directed to Permissions, Books and Journals Division, at the ACS Washington address.

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

### Subscription and Business Information

1976 subscription rates—including surface postage:

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

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

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

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

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

**Supplementary material** must be ordered directly from Business Operations, Books and Journals Division, at the ACS Washington address. Orders over 20 pages are available only on microfiche, 4 × 6 in., 24×, negative, silver halide. Orders must state photocopy or microfiche if both are available Full bibliographic citation including names of all authors and prepayment are required. Prices are subject to change.

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


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

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

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


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

JOCEAH 41(3) 403–588 (1976)
ISSN 0022-3263

# THE JOURNAL OF Organic Chemistry®

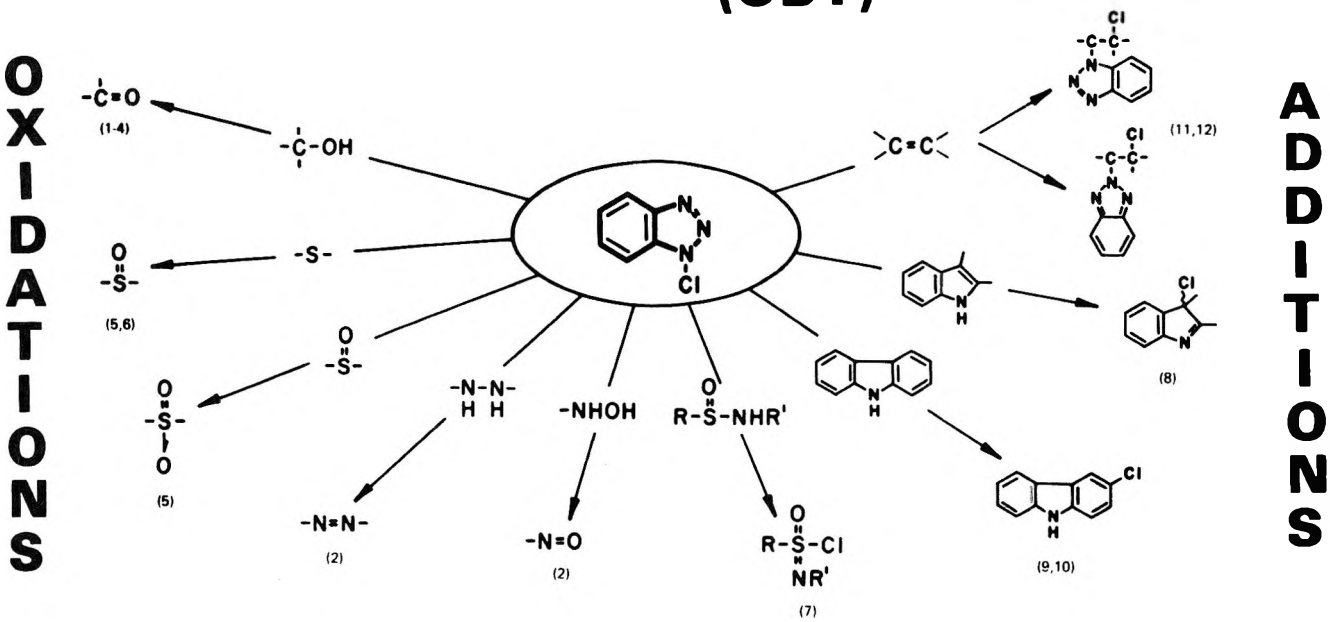
VOLUME 41, NUMBER 3 FEBRUARY 6, 1976





ห้องสมุด กรมวิทยาศาสตร์
15 มิ.ย. 2519

# High Yields
# Mild Conditions
# 1 - CHLOROBENZOTRIAZOLE
# (CBT)




## CHLORINATIONS

**1-Chlorobenzotriazole (CBT) is a superior oxidizing agent.** Reactions proceed rapidly and selectively under mild conditions to give high yields of pure products. Primary alcohols are oxidized to the corresponding aldehydes without further oxidation to the acid, while secondary alcohols are oxidized to the corresponding ketones.[1-4] **CBT** oxidation of cyclobutanol, for example, gives cyclobutanone in 72% yield with no rearrangement, whereas N-chlorosuccinimide oxidation fails to give any of the desired product.[4] **CBT** oxidation of cetyl alcohol in the presence of pyridine gives palmitaldehyde in 90% yield.[3]

Sulfides are selectively oxidized to sulfoxides with no sulfone contamination.[5,6] For example, methylphenylsulfide is oxidized to the corresponding sulfoxide in nearly quantitative yield in less than 45 minutes. Further oxidation of the isolated methylphenylsulfoxide with **CBT** gives the sulfone in nearly quantitative yield.[5]

Hydroxylamines are oxidized to nitroso compounds without any nitro formation, whereas hydrazo compounds are oxidized to the corresponding azo compounds.[2] For example, ethyl quinoline-2-hydrozocarboxylate is oxidized to the corresponding azo compound in 96% yield.[2]

**CBT** also serves as a versatile and selective chlorinating agent.[7-10] For example, **CBT** is the preferred reagent in the conversion of sulfinamides to sulfonimicoylchlorides[7] and indoles to chloroindolenines.[8] **CBT** also chlorinates various aromatic rings with or without a Lewis acid present.[9,10]

**CBT** also undergoes sterospecific *trans* addition to carbon-carbon double bonds to give products with Markovnikov orientation.[11,12]

**CBT** is a must for researchers conducting oxidations, chlorinations or electrophilic additions. **We invite you to put CBT on YOUR shelf, where it belongs!**


(1) C. W. Rees and R. C. Storr, *Chem. Commun.*, 1305 (1968).
(2) C. W. Rees and R. C. Storr, *J. Chem. Soc. C*, 1474 (1969).
(3) W. J. Ferrell and K. Yao, *J. Lipid Res.*, **13**, 23 (1972).
(4) J. B. Sieja, *J. Chem. Eng. Data*, **17**, 108 (1972).
(5) W. D. Kingsbury and C. R. Johnson, *Chem. Commun.*, 365 (1969).
(6) P. R. Heaton, J. M. Midgley, and W. B. Whalley, *Chem. Commun.*, 750 (1971).
(7) E. U. Jonsson, C. C. Bacon and C. R. Johnson, *J. Amer. Chem. Soc.*, **93**, 5306 (1969).
(8) K. V. Lichman, *J. Chem. Soc. C*, 2539 (1971).
(9) P. M. Bowyer, D. H. Iles, and A. Ledwith, *J. Chem. Soc. C*, 2775 (1971).
(10) H. Oelschlaeger and E. Ehlers, *Pharm. Acta Helv.*, **47**, 1 (1972).
(11) G. Garcia-Munoz, R. Madronero, M. C. Saldana, and M. Stud, *J. Heterocycl. Chem.*, **8**, 1031 (1971).
(12) C. W. Rees and R. C. Storr, *J. Chem. Soc. C*, 1478 (1969).


1099 1-Chlorobenzotriazole 100g $28.50

You never pay more than the price we list in our catalog.

PARISH CHEMICAL COMPANY

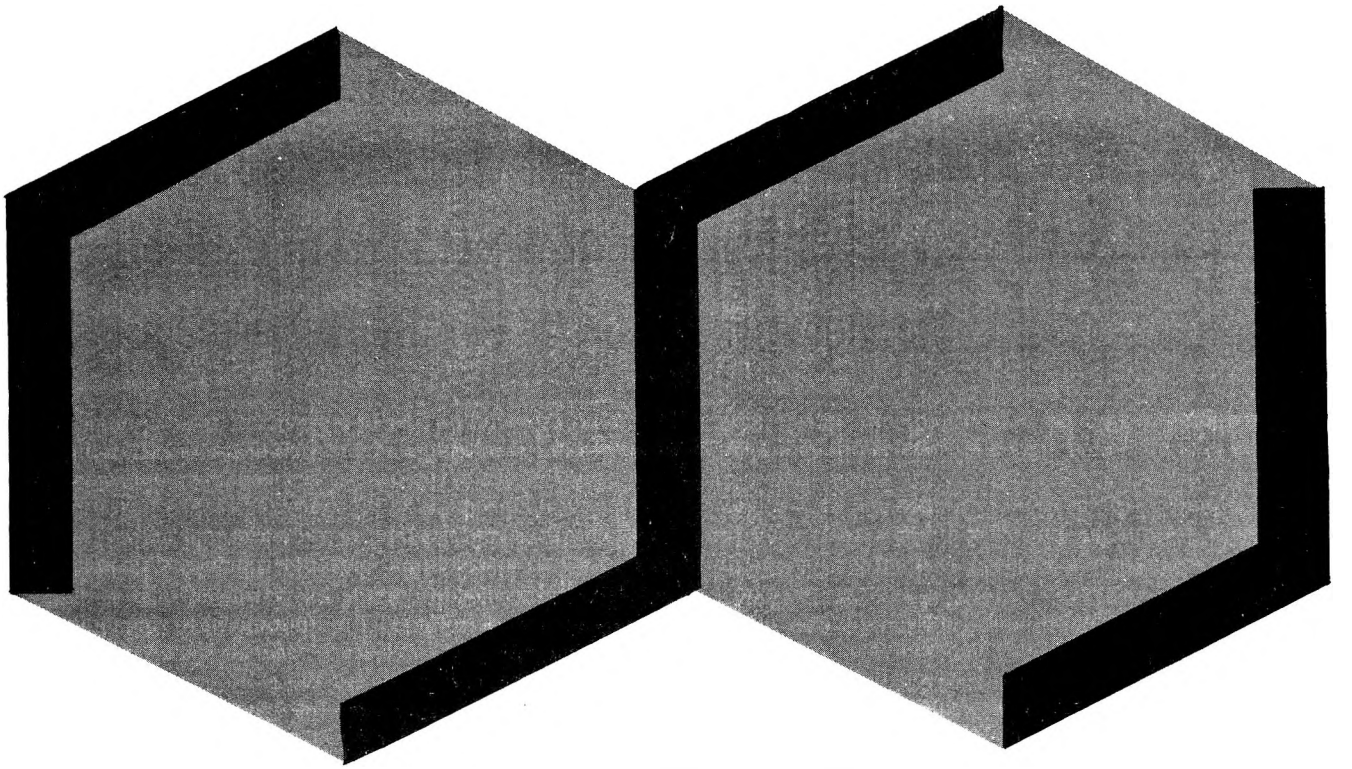
815 WEST COLUMBIA LANE, PROVO, UTAH 84601

## NOTES



## COMMUNICATIONS

# The leading American journal devoted to general organic chemistry:



# The Journal of Organic Chemistry

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

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

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

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

Send your order today.

. . . another ACS service

**The Journal of Organic Chemistry**
**American Chemical Society** **1976**
1155 Sixteenth Street, N.W.
Washington, D.C. 20036

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

| | *U.S.* | *Canada*** | *Latin America*** | *Other Nations*** |
|---|---|---|---|---|
| ACS Member One-Year Rate* | ☐ $26.00 | ☐ $34.25 | ☐ $33.25 | ☐ $34.25 |
| Nonmember | ☐ $104.00 | ☐ $112.25 | ☐ $111.25 | ☐ $112.25 |

Bill me ☐ Bill company ☐ Payment enclosed ☐

*Air freight rates available on request.*

Name _____

Street _____ Home ☐ Business ☐

City _____ State _____ Zip _____

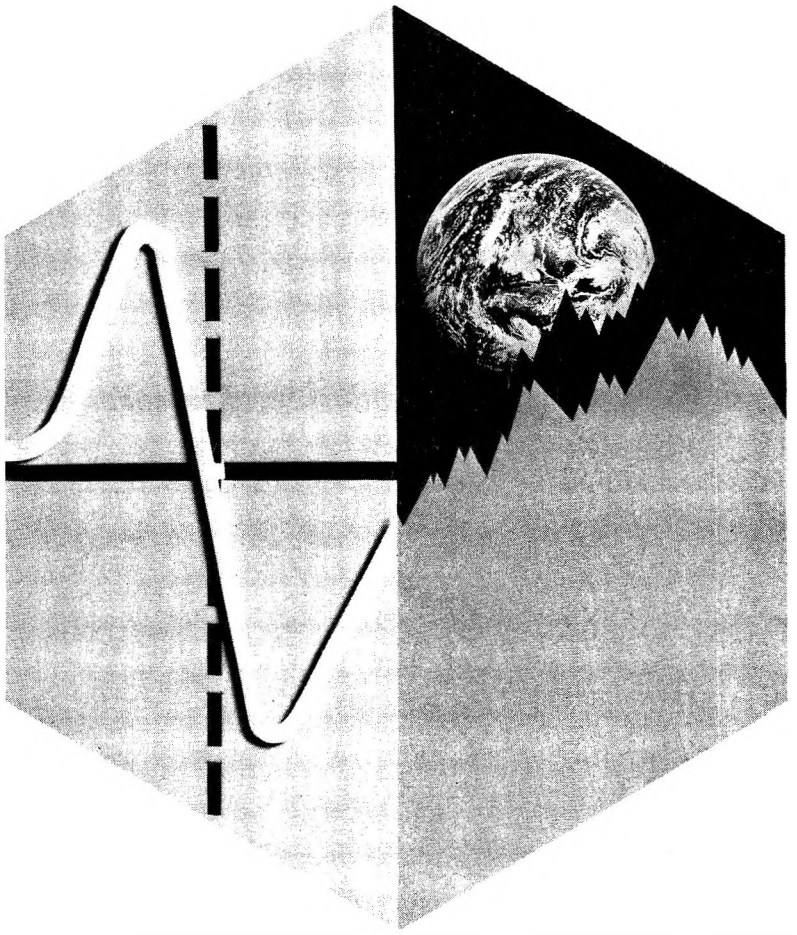
**Journal subscriptions start January '76**

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

■ 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 frontiers of chemical research

*short, critical, informative articles by active, prominent investigators in*

# ACCOUNTS OF CHEMICAL RESEARCH

First-hand accounts of work done in the authors' own laboratories and relevant contributions by other investigators—that is what makes ACCOUNTS OF CHEMICAL RESEARCH one of the timeliest, most informative journals in the field . . . and, equally important, the accounts are concise, critical, current. If chemical research is important to you, the monthly issues of ACCOUNTS OF CHEMICAL RESEARCH are vital in keeping you current on the latest developments. Complete the form below and mail it back to us today!

**Accounts of Chemical Research**
**American Chemical Society** **1976**
1155 Sixteenth Street, N.W.
Washington, D.C. 20036

Yes, I would like to subscribe to ACCOUNTS OF CHEMICAL RESEARCH at the rate checked below:

| | U.S. | **Canada, PUAS | **Other Nations |
|---|---|---|---|
| *ACS member: | ☐ $10.00 | ☐ $13.50 | ☐ $13.50 |
| Nonmember: | ☐ $40.00 | ☐ $43.50 | ☐ $43.50 |

☐ Payment enclosed. ☐ Bill me ☐ Bill company. *Air freight rates available on request.*

Name _____ Position _____

Your Employer _____

Address ☐ Home
☐ Business _____

City _____ State _____ Zip _____

Employer's Business: ☐ Manufacturing ☐ Government ☐ Academic ☐ Other _____

If Manufacturer, Type of Products Produced _____

**Journal subscriptions start January '76**

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

THE JOURNAL OF Organic Chemistry

VOLUME 41, NUMBER 3
© Copyright 1976
by the American Chemical Society
FEBRUARY 6, 1976

# The Concerted Nature of 1,3-Dipolar Cycloadditions and the Question of Diradical Intermediates[1]

Rolf Huisgen

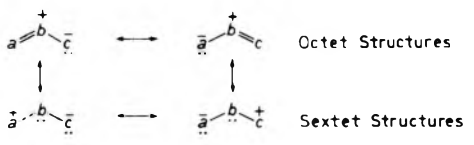
*Institut für Organische Chemie der Universität, 8 München 2, Germany*

*Received February 18, 1975*

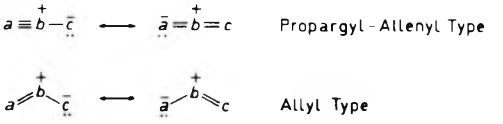
The concerted mechanism of 1,3-dipolar cycloadditions was challenged recently by Firestone, who proposed a diradical alternative on thermochemical and regiochemical grounds. His arguments are critically disproved here. The retention of configuration of 1,3-dipole and dipolarophile in the cycloaddition is incompatible with a diradical intermediate. 1,3-Dipoles are "heteroallyl anions" which lose the allylic resonance energy in forming a diradical intermediate; taking this into consideration, the energies of diradical formation exceed the experimental activation energies of cycloadditions. Following the symmetry-allowed scheme $[{}_{\pi}4_s + {}_{\pi}2_s]$, 1,3-dipoles undergo only cycloadditions of the ring size classification 3 + 2 → 5 while allyl cations are only amenable to 1,4 additions of the type 3 + 4 → 7. The activity sequences of dipolarophiles are 1,3-dipole specific; the diradical hypothesis fails to explain this phenomenon while recent MO perturbation treatments provide elegant interpretations for dipolarophile activities as well as for directions of addition. The frequently found "bidirectionality", i.e., different orientations of dipolarophiles with electron-releasing and electron-attracting substituents, is at variance with diradical intermediates. The regioselectivity is connected with the ambident nucleophilic and electrophilic properties of 1,3-dipoles. An independently synthesized 1,5-diradical does not show the reactivity postulated by Firestone.

**Definitions and Classification.** A general principle for the synthesis of five-membered heterocycles, introduced in 1960 as "1,3-dipolar cycloaddition",[2] has turned out to be valuable, as the increasing number of applications testifies. The "1,3-dipole" is defined as a species which is represented by zwitterionic resonance structures and which undergoes 1,3 cycloadditions to a multiple bond system, the "dipolarophile".[3]

In 1963 it was deduced from experimental models that the allyl anion type orbital (four electrons in three parallel $\pi$ orbitals) is responsible for the cycloaddition reaction.[4] While the terminal centers of the allyl anion are only nucleophilic, the termini of the "heteroallyl anion" systems of 1,3-dipoles are both *nucleophilic and electrophilic* (ambivalent) as the resonance structures with a terminal electron sextet suggest.

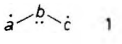



An element of variation of 1,3-dipoles is provided by the incorporation of an additional $\pi$ bond in the plane perpendicular to the allyl anion MO. This additional $\pi$ bond makes 1,3-dipoles of the propargyl–allenyl type[5] linear while those of the allyl type are bent.




If one restricts the atoms a, b, and c to carbon, nitrogen, and oxygen, the 1,3-dipoles shown in Table I result.[3] Representatives of all but two of these classes, many of them as short lived in situ intermediates, have been shown to undergo 1,3 cycloaddition. Inclusion of phosphorus and sulfur atoms as centers increases the variety of 1,3-dipoles manyfold; examples have been described. Also numerous "anionic 1,3 cycloadditions"[6] and the "criss-cross additions" to species free of formal charges[7] follow the same mechanistic pattern.

The formal analogy between ring-opened cyclopropanes and 1,3-dipoles was emphasized recently by ascribing a varying contribution of the diradical structure 1 to the

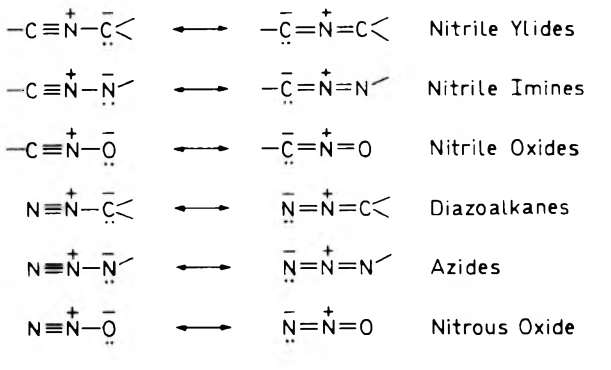


1

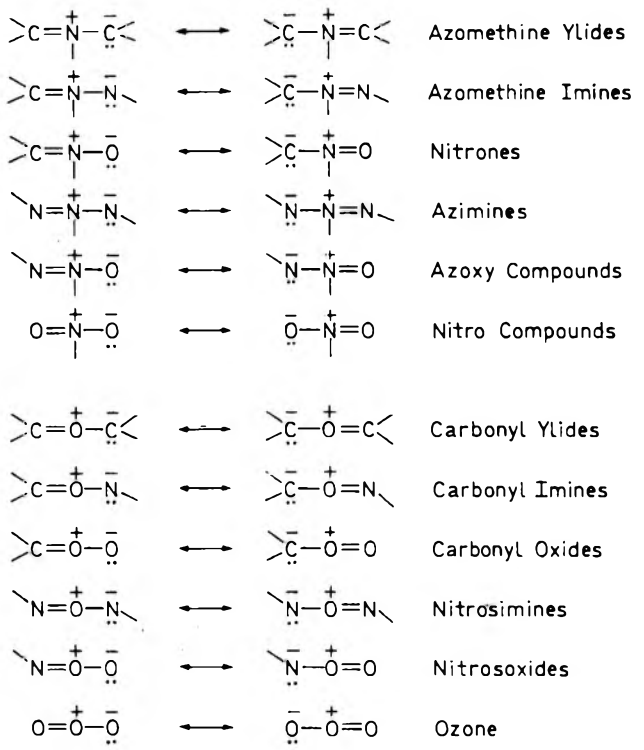
ground state of the 1,3-dipole.[8] As in trimethylene[9] one deals with a spin-paired diradical which still allows a weak bond of $\sigma$ or $\pi$ type to exist between the terminal centers.[10] The dramatic rate ratio of $\geq 10^{29}$ between the reactions 2 → 3 (concerted cycloreversion 5 → 3 + 2) and 4 → 5 (formation of a trimethylene) at −197° illustrates the energetic

Table I
Classification of 1,3-Dipoles Consisting of Carbon, Nitrogen, and Oxygen Centers

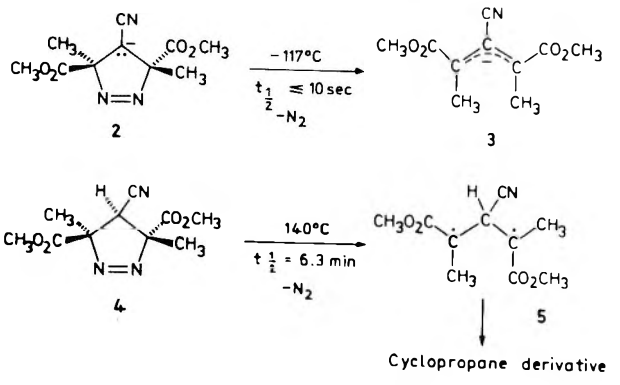
A. Propargyl-Allenyl Type




B. Allyl Type



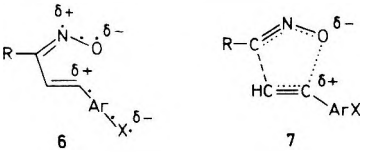

advantage of the allyl anion bond system over the long-bond trimethylene species.[11] However, with increasing




electronegativity of the middle atom of a 1,3-dipole some ground state participation of the diradical structure **1** is conceivable.[12]

**Mechanistic Proposals.** The concerted mechanism of 1,3-dipolar cycloaddition, first discussed in 1960,[2] was supported by many experimental tests[4,13] and is generally accepted.[14,15] It is an orbital symmetry-allowed $[\pi 4_s + \pi 2_s]$ cycloaddition wherein the 1,3-dipole with its allyl anion type MO functions as $\pi 4$ reactant and the dipolarophile as $\pi 2$ reactant.[15] The MO symmetry correlation diagram of 1,3-dipolar cycloaddition[16] bears a more than superficial resemblance to that of the Diels–Alder reaction. Another description attributes the concertedness to a Hückel aromatic type MO of the transition state.[17-19]

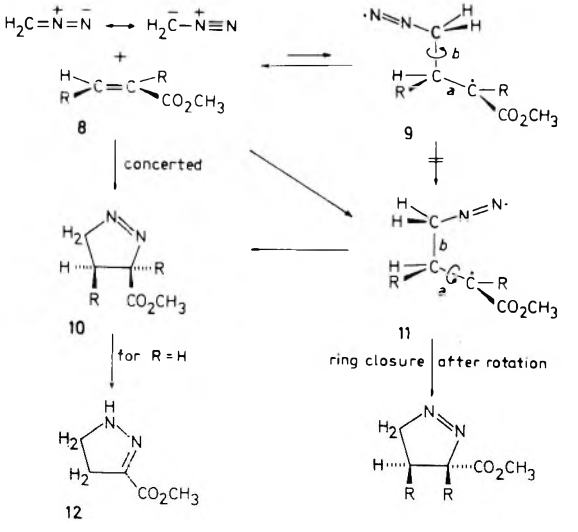
As an alternative, Firestone[20] proposed a mechanism with a *diradical intermediate* in 1968. Although the original arguments were refuted,[13] the diradical hypothesis of 1,3-dipolar cycloaddition (and of the related Diels–Alder reaction) was recently refurbished on the basis of bond energy considerations[21] and orientation phenomena.[22]




Firestone[22] recently equipped the formulae of the diradical intermediates with partial charges which are a consequence of Linnett notation[23] and which suggest electrostatic attraction. The diradical **6**, the assumed intermediate in the addition of a nitrile oxide to a substituted phenylacetylene,[22] is very similar to formula **7** which we have been using to illustrate the transition state of the concerted addition for 12 years.[4] The strength of the new CC $\sigma$ bond in **7** is developed to a higher extent than that of the CO $\sigma$ bond, thus creating partial charges. This depiction **7** of the transition state was recently modernized in a MO perturbational treatment which will be discussed below.

Though it is hard to discern a difference in the meaning of **6** and **7** except of notation, one has to pay a high price for designating **6** a diradical intermediate, as the following discussion will reveal. Duplication of earlier arguments[13] will be held to a minimum. Not all readers may be sufficiently familiar with the Linnett notation;[23] therefore, throughout this paper conventional structural formulae are used unless the Linnett notation is specifically required.

**The Diradical Hypothesis and the Stereochemical Criterion.** The addition of diazomethane to methyl acrylate (**8**, R = H), which gives a quantitative yield of **12**[24] via the 1-pyrazoline **10**, R = H,[25] serves as a model. The activation parameters are $\Delta H^{\ddagger} = 7.5$ kcal/mol and $\Delta S^{\ddagger} = -33$ eu in DMF.[26] On replacing the acrylic ester by the cis–trans isomeric $\alpha,\beta$-dimethylacrylic esters (**8**, R = $CH_3$, is angelic ester), diastereomeric 1-pyrazolines are formed; Van Auken



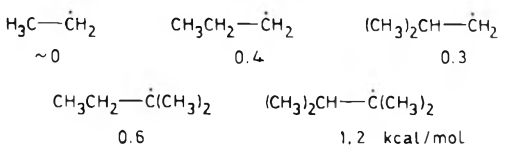
and Rinehart found the stereospecificity to be ≥98%.[27] A recent reinvestigation of the addition to methyl angelate by capillary GC demonstrated a stereospecificity greater than 99.8%.[28] Retention of 1,3-dipole[29,30] and dipolarophile[4,13] configurations is a characteristic of 1,3-dipolar cycloadditions; *no exceptions* have been observed.

While stereospecificity is an obvious requirement for the concerted process, it is an insurmountable obstacle to an advocate of the diradical mechanism, as illustrated by the following five points.

(1) If the diradical is formed in conformation **11** with all centers lined up for ring closure ("cyclo diradical"),[22] the cyclization to give **10** must be faster than rotation around *a*, the former double bond of the dipolarophile, otherwise the rule of stereospecificity would be violated. Allowing for <0.2% nonstereospecific reaction as the analytical limit, *the free energy of cyclization must be smaller than the barrier to rotation by >3.4 kcal/mol.*

(2) How large a rotational barrier is to be expected for bond *a* in diradical **11**? Alkanes possess barriers of 2.9–4.2 kcal/mol,[31] but these do not provide the best comparison. Carbon radicals like the one in **11** are known to be "$\pi$ radicals" with $sp^2$-hybridized bond system.[32,33] The sixfold barriers to rotation between $sp^3$- and $sp^2$-hybridized carbon atoms are lower, e.g., $V_6$ = 0.014 and 0.006 kcal/mol for toluene and nitromethane, respectively. If such symmetrical substitution is lacking, the $sp^3$–$sp^2$ bond assumes again a threefold barrier but with lower heights than the $sp^3$–$sp^3$ bond; 0.78 and 2.1 kcal/mol were measured for $V_3$ of acetone and isobutene.[31]

Rotational barriers of alkyl radicals have recently been evaluated from ESR hfs line shape analysis. These barriers were found in the range of 0–1.2 kcal/mol[34] depending on the nature and the number of substituents.

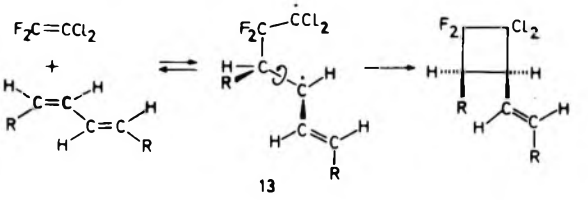



Should one expect a higher rotational barrier for bond *a* in the diradical **11**, R = $CH_3$, than 1.2 kcal/mol (tetramethylethyl radical)? Probably not. The barrier of the methylmalonic acid radical, $CH_3$–$\dot{C}(CO_2H)_2$, is immeasurably small.[35] For $CH_3$–$CH_2CO_2H$ $V_3$ is 2.4 kcal/mol, i.e., an even smaller value than $V_3$ = 3.4 kcal/mol for $CH_3$–$CH_2CH_3$.[31] Thus, a carboxy group does not give rise to higher barriers than a methyl in $sp^3$–$sp^3$ bonds. Moreover, in cases of unsymmetrically substituted bonds *the energetically easier* of the two possible 180° rotations about the former double bond of the olefinic dipolarophile is sufficient to effect nonstereospecific addition.

Thus, it is safe to conclude: *the cyclization barrier of the diradical* **11** *should be nil if it has to be lower by 3.4 kcal/mol than that of rotation about bond a,* i.e., the cycloaddition must be concerted. The energy profile cannot contain the diradical as a discrete intermediate as postulated.[20,21]

(3) What happens to "extended diradicals" like **9**, i.e., those which are formed in other conformations than the "cyclo diradical" **11**? Conversion to **10** should be preceded by rotation about the axis *b* ($sp^3$–$sp^3$) in formula **9**. However, this rotation should require more energy than rotation about the former acrylic ester double bond a, which in turn would cause a drop in stereospecificity. To save the diradical hypothesis, one is forced to assume[20] that dissociation of the bond *b*, i.e., reversal of **9** to the reactants, takes place much faster than rotation around a. Taking into account the deep-seated structural changes accompanying the rehybridization during the dissociation of **9**, an activation barrier of ≪1.2 kcal/mol reveals the artificiality of the diradical concept.

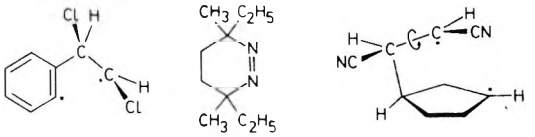
(4) The behavior of relatives of the alleged 1,5-diradicals of type **9** and **11** is known. According to Bartlett's classic investigation, 1,4-diradicals occur as intermediates in the addition of 1,1-dichloro-2,2-difluoroethylene to the cis,-trans isomers of hexa-2,4-diene or 1,4-dichlorobutadiene; these [2 + 2] cycloadditions are forbidden as concerted processes. For the diradical **13**, R = $CH_3$, rotation around the marked bond takes place ten times faster than cyclization at 80°.[36] A temperature of 120° is needed for dissociation of **13**, R = $CH_3$, to become noticeable and to compete with ring closure.[37] For **13**, R = Cl, at 150° rotational equilibrium is nearly attained, and cyclization is still four times faster than cleavage to reactants.[38]




13

One might argue that cyclization of the diradical **11** is faster than that of **13** because **11** gives rise to a more favored ring size. It is noteworthy that **13** still undergoes cyclobutane ring closure much faster than dissociation.

In the nonstereospecific 2 + 2 → 4 addition of *cis*- and *trans*-1,2-dichloroethylene to benzyne the 1,4-diradical **14** is a putative intermediate. The ratio of ring closure to rotation was found to be 1.3 and 2.3 for *cis*- and *trans*-dichloroethylene.[39] The [2 + 2] additions of *cis*- and *trans*-propenyl alkyl ether to benzyne proceed likewise nonstereospecifically without reaching conformational equilibrium of the 1,4-diradical.[40] On the other hand, *meso*-**15** and *dl*-**15** produce at 145° the tetrasubstituted cyclobutanes with >98% retention of configuration, probably via the 1,4-diradical;[41] it is possible that the nitrogen elimination produces the substituted tetramethylene diradical in a state permitting some 1,4 bonding. Nearly half of the azo compound **15** is converted to 2-methyl-1-butene.[41]




14 15 16

Tetramethylene diradicals have been suggested as intermediates in the pyrolysis of cyclobutanes. The homolysis of one $\sigma$ bond creates the tetramethylene in a conformation suitable for splitting into two molecules of olefin.[42] While the diradical from *cis*-1,2-dimethylcyclobutane undergoes dissociation to propylene four times faster (430°) than rotation and reclosure of the four-membered ring,[43] the corresponding ratio for the diradical from 1,1,2,2-tetramethylcyclobutane-$d_6$ is ≥22 at 401°.[44]

A 1,5-diradical is the intermediate **16** which Gassman et al. proposed for the cycloaddition of maleonitrile to bicyclo[2.1.0]pentane.[45] The analysis of the stereoisomeric 2,3-dicyanonorbornanes revealed that **16** undergoes cyclization ca. four times (ca. nine times in the case of fumaronitrile) faster than rotation. That the plethora of alleged 1,5-diradicals[20–22] from all tested combinations of 1,3-dipoles and dipolarophiles would suffer cyclization ≥50 times (>500 in the example of **11**, R = $CH_3$) faster than rotation (≥98% or

>99.8% stereospecificity, respectively), seems improbable.

An independently synthesized 1,5-diradical of the Firestone type whose reactivity differs from that postulated will be described in the last section.

(5) The assumption of the CC bond dissociation in the process **9** → **8** via a barrier of ≪1.2 kcal/mol, already highly artificial, becomes even more doubtful on scrutinizing the structure of the diazo diradical **9**. Diazo radicals RN=N· are hypothetical intermediates in the reaction of diazoalkanes with radicals.[46] It has also been suggested, though not generally accepted,[47] that the thermolysis and photolysis of certain azo compounds is initiated by rupture of *one* CN bond producing RN=N·; the evidence rests on kinetics,[48] steric course,[49] and rearrangement.[50] The chemistry of the highly elusive diazo radicals is rather monotonous: except for some recombinations in caged radical pairs in the liquid phase, the radicals RN=N· only lose nitrogen. The species $C_6H_5N{=}N\cdot$ expels $N_2$ so fast that it cannot combine with triphenylmethyl in solution.[51] On the other hand, not a trace of $N_2$ is liberated during the cycloaddition of diazomethane to methyl acrylate. *The hypothesis that the conformation* **9** *exclusively suffers dissociation of the CC bond while the C–$N_2$· remains intact*[20,22] *is unreasonable.*

**Potential Hypersurface of the Firestone Diradical.** The cyclization of the postulated 1,3-diradical to the five-membered ring, e.g., **11** → **10**, would be a radical combination.

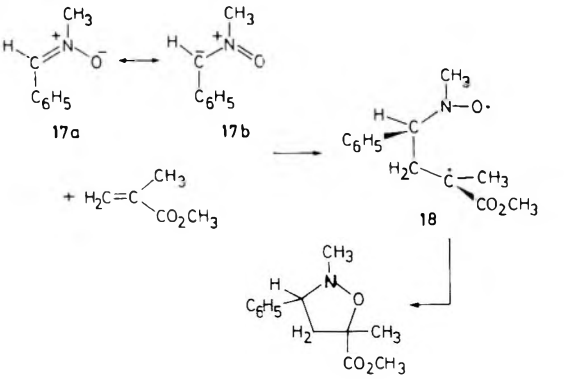
Although combination of methyl radicals is believed to take place without activation, the variation of the ESR measured termination (combination + disproportionation) rates of cumyl and related radicals[52] by a factor of 20 demonstrates that zero barriers cannot be the rule. Substantially lower termination rates for branched-chain alkyls have been reported recently.[53] The rate ratio of radical combination and disproportionation ($k_c/k_d$), originally regarded as purely entropy controlled, showed a temperature dependence which suggested finite barriers for both processes.[54] If $\Delta H_c^{\ddagger} - \Delta H_d^{\ddagger}$ equals 2.6 kcal/mol for the β,β-dimethyl-α-phenethyl radical,[55] the combination barrier must even be larger. *Barriers appear to occur if substantial structural changes accompany the rehybridization.* For the combination of triphenylmethyl radicals $E_a$ = 7 kcal/mol,[56] and for the termination of di-*tert*-butylmethyl $E_a$ = 19 kcal/mol[57] have been measured.

*Intramolecular* radical combination should be faster than structurally corresponding intermolecular processes. If one or both of the radical centers are well stabilized (see next section), a barrier to combination should be expected for the Firestone diradical.

What consequences would the assumption of a zero barrier have for the cyclization of the hypothetical 1,5-diradical? There could no longer be an intermediate, i.e., a dip in the energy profile; the *two-step* process becomes at best a *two-stage* process. Rather flat potential hypersurfaces have been described for the trimethylene[9,58] and the tetramethylene diradicals.[42] However, *rotation still can take place on such flat surfaces,* the amount of rotation being dependent on substitution.[42,58] This suppression of rotation in favor of cyclization in Firestone's diradical would build discrete mountains into the energy surface with the effect that radical combination becomes the unequivocal minimum energy pathway. The one-step cycloaddition which must result is indistinguishable from the *concerted mechanism,* particularly since the transition state—only the diradical with the proper conformation will cyclize[20]—is inconceivable without partial bond between the radical centers. The signs of the orbitals allow a bonding overlap from the start.

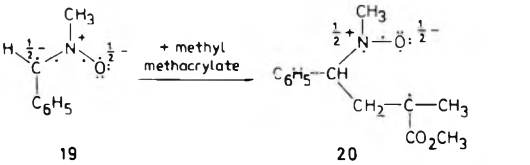
This conclusion is independent of the model used for the description of the diradical, e.g., valence bond structure, HMO, or Linnett formulae. On theoretical grounds, based on Linnett structures, Harcourt recently rejected 1,5-diradicals as *intermediates* in 1,3-dipolar cycloadditions.[10]

**Energies of Formation of the Diradical Intermediates.** In our earlier paper[13] we estimated the energy which should be required to convert a 1,3-dipole and a dipolarophile to the alleged 1,5-diradical. The lack of thermochemical data for bond energies in onium ions and for some radical stabilizations renders the estimates rather imprecise. Our approximation for the loss of bond energy in the formation of the diradical **18** from *N*-methyl-*C*-phenylnitrone (**17**) and methyl methacrylate, an arbitrarily chosen example, amounted to 54 kcal/mol while the measured activation enthalpy of the cycloaddition was only 15.7 kcal/mol.[59]




*Huisgen's estimate*[61]

| | | |
|---|---|---|
| Freezing of the allyl resonance by converting the nitrone to the fictitious resonance structure **17b** | | 34 kcal/mol |
| Conversion of N=O into N–O[62] | | 77 |
| Loss of conjugation $C_6H_5$–C⁻ | | 6 |
| Conversion C=C → C–C of dipolarophile | | 63 |
| Loss of conjugation C=C($CH_3$)$CO_2CH_3$ | | 6 |
| | Loss | 186 kcal/mol |
| Formation of a new C–C | | 83 kcal/mol |
| Stabilization energy of –Ċ($CH_3$)$CO_2CH_3$ | | 11 |
| Stabilization energy of –N($CH_3$)–O· | | 35 |
| | Gain | 129 kcal/mol |



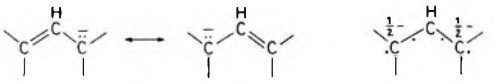

*Firestone's estimate*[21]

| | | |
|---|---|---|
| Conversion of the three-electron bond C–N into the two-electron bond C–N | | 34 kcal/mol |
| Electron correlation (see below) | | 4 |
| Loss of substituent conjugation in both reactants | | 8 |
| Conversion C=C → C–C of dipolarophile | | 63 |
| *L* strain[21] | | 5 |
| | Loss | 114 kcal/mol |
| Formation of a new C–C | | 83 kcal/mol |
| Stabilization energy of –Ċ($CH_3$)$CO_2CH_3$ | | 11 |
| *L* strain[21] | | 5 |
| | Gain | 99 kcal/mol |

Corresponding data for the addition of diphenyldiazomethane to methyl acrylate were ≈65 kcal/mol calculated for diradical formation vs. $\Delta H^{\ddagger}$ = 8.0 kcal/mol found for the cycloaddition.[60] In contrast, Firestone's calculations of the formation enthalpies of the two 1,5-diradicals[21] were in astonishing agreement with the experimental activation enthalpies. How is this feasible? The two estimates may be contrasted.

The main differences between the formation enthalpies of the 1,5-diradical **18** (or **20**), 57 vs. 15 kcal/mol, rests in Firestone's overestimation of the nitroxide radical stabilization.

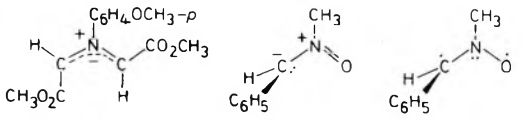
(1) How large is the *resonance energy of the allyl anion and of 1,3-dipoles?* Neither the p$K_a$ value of propane nor that of propylene have been measured with sufficient precision nor are the p$K_a$'s of protonated 1,3-dipoles and their saturated analogs known. An approximate figure of the allyl anion resonance is based on the rotational barrier.



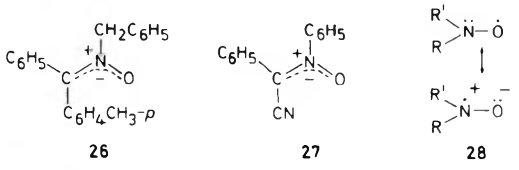
**21** **22**

The bond system corresponding to one resonance structure of **21** is found in an allyl anion with 90° rotation about the formal single bond.[63] The rotational barrier of 1-phenylallylpotassium in THF amounts to >20 kcal/mol.[64] A recent ab initio calculation afforded 28 kcal/mol for the rotational barrier of the allyl anion.[65]

The allyl anion resonance energy of a 1,3-dipole should be influenced by the zwitterionic character—1,3-dipoles possess quadrupole moments—and by the exchange of carbon by heteroatoms. The rotational barrier of the substituted azomethine ylide **23** was measured to be 22 kcal/mol,[66] while an ab initio calculation provided 29 kcal/mol for the parent azomethine ylide.[65]



**23** **24** **25**

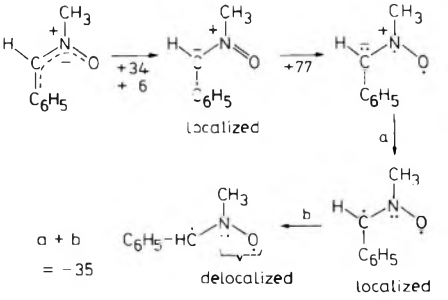


**26** **27** **28**

The two "frozen" resonance structures of methylphenylnitrone (**17**) are nonequivalent; the CN and NO bond energies calculated by additivity favor **17b** somewhat,[62] while the anionic charge is better accommodated by **17a**. Rotation about the nitrones CN bond converts the ground state to a 90° twist conformation **24** with the approximate bond energy of the fictitious resonance structure **17b**. Only a couple of rotational barriers for the cis,trans isomerization of nitrones have been measured; that of *N*-benzyl-*C*-phenyl-C-*p*-tolylnitrone (**26**) amounts to 33.6 kcal/mol.[67] The barrier to rotation should be higher for methylphenylnitrone (**17**),[68] because the aryl substituents on carbon—two in **26**, only one in **17**—contribute more to the stabilization of the carbanion in the twist form **24** than in the delocalized ground state. Thus, the energy loss in converting the ground state of **17** into **17b** is at least 34 kcal/mol.

It is a priori conceivable that the 90° twist conformation is the diradical **25**[69] instead of the zwitterion **24**. However, this is ruled out by a rotational barrier of 24.6 kcal/mol for *C*-cyano-C,*N*-diphenylnitrone (**27**).[70] The superior stabilization of the carbanion by the cyano group—acetonitrile is by 10–16 p$K$ units more acidic than toluene[71]—lowers the energy of the 90° twist conformation and reduces the barrier height of **27** by 9 kcal/mol compared with **26**. One would expect no or even an opposite substituent influence on a diradical twist conformation of the type **25**. Phenyl stabilizes a carbon radical slightly better than cyano.[72]

(2) Nevertheless, it is the nitrone diradical like **25** (but planar) which combines in our thermochemical consideration with methyl methacrylate to give **18**. One electron has to be transferred from the nonbonding carbanion orbital of **17b** into an antibonding orbital of the nitroso group producing the nitroxide radical of **18**. The formal charges of **17b** are converted to those typical of the nitroxide resonance **28**. We account for the process on the debit side with the conversion of N=O to N–O and on the credit side with 35 kcal/mol for electron transfer and nitroxide resonance. The following scheme comprises the energetic changes (in kcal/mol).




(3) The Linnett structure **19** of methylphenylnitrone contains *two three-electron bonds* of which one is *retained* in the 1,4-diradical **20**.[21] Correspondingly, the 1,3-dipoles of the propargyl–allenyl type (nitrilium and diazonium betaines in Table I) are described by formulae with three- and five-electron bonds. The unknown *bond energies of three- and five-electron bonds* are assessed by Firestone in an ingenious way:[21] linear interpolation from experimental bond energies of single, double, and triple bonds! This standardization neglects major differences in the bond systems. While 1,3-dipoles like **17** accommodate the valence electrons in bonding orbitals ($\Psi_2$ weakly bonding), the diradicals of type **18** possess, like nitric oxide, in the MO description one electron in an *antibonding* MO.

For the allyl anion itself two three-electron bonds in **22** total 232 kcal/mol while the sum of C=C and C–C bond energies is 229 kcal/mol. Thus, the calculated[21] bond energy sum of the allyl anion comes very close to that of *one resonance contributor*. Though allylic stabilization was not mentioned,[21] it is taken care of[69] by "electron correlations", defined as stabilization energy for a distant pair of electrons relative to a close pair. The allyl anion possesses four such pairs corresponding to an increase of the bond energy by 4 × 4 = 16 kcal/mol, and the nitrone **19** contains six pairs amounting to 24 kcal/mol.[21]

(4) *What happens to the allylic stabilization of the 1,3-dipole in the 1,5-diradical formation?* In the resonance and MO description the allylic stabilization terminates with the destruction of the allylic system, and a new stabilization is introduced for the nitroxide radical. In the Linnett description, for the process **19** → **20** the nonbonding electron on the carbon of the nitrone group bonds to C-3 of methyl methacrylate, the three-electron CN bond changes to a two-electron CN bond with the third electron becoming a nonbonding electron on nitrogen, and the three-electron NO bond remains unchanged. For this overall process, Firestone also cancels one "distant pair"[21] electron correlation (4 kcal/mol). Thus, one finds the nitroxide group in **20** endowed with 119 kcal/mol for the three-electron bond.

| | |
|---|---|
| Bond energy N–O[21] | 99 kcal/mol |
| Five-electron correlations in the nitroxide group | 20 |
| | 119 kcal/mol |

Such a high bond energy for the nitroxide system in **18/20** can be foreseen neither by the resonance description **28** nor by the MO model with an electron in an antibonding orbital.

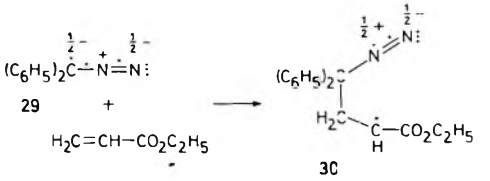
(5) While no thermochemical data are known about nitroxide radicals, one is better off with the related hydrazyl radicals, of which many representatives are known. The standard heats of formation (in kcal/mol)[73] listed below the formulae allow evaluation of the NN bond energy of $N_2H_3^+$ and the hydrazyl radical $N_2H_3$·.

$$\underset{237}{H_2\overset{+}{N}{=}NH} \longrightarrow \underset{304}{\overset{+}{N}H_2} + \underset{79}{NH} \qquad (+146)$$

$$\underset{87}{H_2\dot{N}{-}\dot{N}H} \longrightarrow \underset{41}{NH_2} + \underset{79}{NH} \qquad (+33)$$

Provided that the appearance potential measurements for the two $N_2H_3$ species[74] are correct, the electron in the antibonding orbital of $N_2H_3$· would reduce the NN bond strength by 113 kcal/mol to a value (33 kcal/mol) which is even somewhat below the N–N bond energy (39 kcal/mol). According to Firestone's interpolation, $N_2H_3$· should have a NN bond energy of 73 kcal/mol (N–N 66 kcal/mol + 3 electron correlations, minus $L$ strain 5 kcal/mol).

(6) Firestone estimated $\Delta H_a$ = 16 kcal/mol for the formation of the diradical **30** from **29** and ethyl acrylate;[21] this may serve as a second example. Diphenyldiazomethane possesses according to the Firestone thermochemistry a $CN_2$ bond energy of 257 kcal/mol (C–N 109, N=N 148

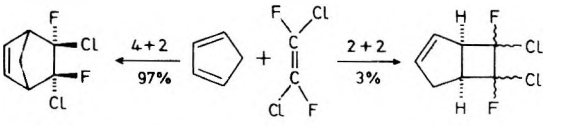



kcal/mol)[21] plus an electron correlation of 24 kcal/mol for six distant pairs, corresponding to the allylic resonance. On the debit side for diradical formation is included for the 1,3-dipole moiety: the conversion of C–N into C–N with 34 kcal/mol, one electron correlation of 4 kcal/mol for the loss of one distant pair, and 4 kcal/mol for the blocking of the phenyl conjugation. Thus, the bond energy of the diazo radical, R–$N_2$·, in **30** would total 239 kcal/mol (281 − 42 kcal/mol). *The very fast decomposition of the notoriously labile diazo radical* (vide supra), R–$N_2$· → R· + $N_2$ (N≡N 226 kcal/mol), *would become endothermic* by 13 kcal/mol, diminished by whatever stabilization of R· is present. Thermochemical calculations based on improved $\Delta H_f$ values of azoalkanes have made accessible enthalpies for the *exothermic* decompositions of alkyl diazo radicals recently,[75] e.g.

$$H_3C{-}N{=}N\cdot \rightarrow H_3C\cdot + N{\equiv}N \quad -16.1 \text{ kcal/mol}$$

The $\Delta H_f$ for higher alkyls is greater by the stabilization energy of the alkyl radical. Thus, the energy level of the diazo radicals is ~29 kcal/mol (13 + 16 kcal/mol) higher than assumed by Firestone.[21] On correcting his estimate for the formation enthalpy of **30** from the reactants by this amount, one reaches $\Delta H \approx +45$ kcal/mol, which is far above the experimental activation enthalpy of 8 kcal/mol[60] for the cycloaddition of **29** to ethyl acrylate. Firestone's erroneous assessment of diradical bond energies becomes obvious here.

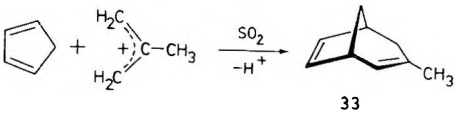
**The Criterion of Ring Size and Electronic Demand in Cycloadditions.** Diels–Alder reactions and 1,3-dipolar cycloadditions owe their wide scope and synthetic potential to the very fact that they are concerted, i.e., that high-energy intermediates (diradicals, zwitterions) are avoided. In contrast to these [$_\pi4_s$ + $_\pi2_s$] processes, [$_\pi2_s$ + $_\pi2_s$] additions are not allowed to be concerted by orbital symmetry.[15] Unlike the cycloadditions 3 + 2 → 5 and 4 + 2 → 6,[76] the processes 2 + 2 → 4 are limited in application. Polyhaloethylene[36–38] and conjugated dienes[77] can enter into [2 + 2] cycloadditions owing to the stabilization of carbon radicals by adjacent halogen or vinyl groups, respectively. The combination of electron-rich and electron-deficient multiple bonds constitutes an alternative with 1,4-zwitterions as intermediates.[78–80]



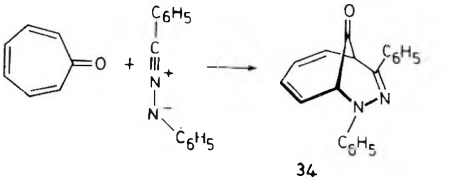

An experiment of Wheland and Bartlett[81] sheds light upon the relationship of rate, concertedness, and stereospecificity. *trans*-1,2-Dichloro-1,2-difluoroethylene reacts with cyclopentadiene to form the six-membered ring of **31** with retention of dienophile configuration, while the closure of the four-membered ring in a side reaction produces all the four conceivable diastereomers of **32.** If one would postulate diradical intermediates for the Diels–Alder reaction,[22] it should be *one and the same diradical intermediate which closes the six-membered ring stereospecifically and the four-membered ring nonstereospecifically.*

The cycloadditions of benzyne bring the diradical hypothesis into the same dilemma. The nonstereospecific four-membered ring formation with 1,2-dichloroethylene is contrasted by a stereospecific Diels–Alder reaction with *trans,trans*-2,4-hexadiene or *trans,trans*-muconic ester.[39]

1,3-Dipoles as zwitterionic heteroallyl anions add even to cis-fixed 1,3-dienes only in the 1,2 manner, furnishing five-membered rings; a 1,4 addition to produce a seven-membered ring would be the forbidden process [$_\pi4_s$ + $_\pi4_s$]. Though allyl anions, the all-carbon system, do not share the propensity of 1,3-dipoles for the closure to five-membered rings, a few examples of [3 + 2] cycloadditions were described recently.[82]

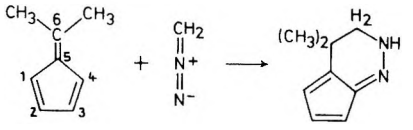



By way of contrast, allyl cations add to 1,4-dienes exclusively to produce seven-membered rings, as the formation of **33** from methallyl iodide and silver trichloroacetate in the presence of cyclopentadiene testifies.[83] This 4 + 3 → 7 addition is a new variant of the symmetry-allowed electronic type [$_\pi4_s$ + $_\pi2_s$]. The formation of five-membered rings from allyl cations and alkenes, both as $_\pi2$ reactants, is not known.



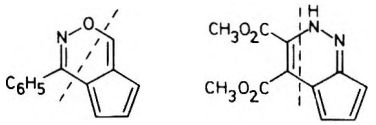

Spectacular cases of symmetry-allowed concerted cycloadditions in which larger numbers of π electrons cooperate were reported recently. Tropone combines as a triene

with cyclopentadiene in a [$_{\pi}6_s$ + $_{\pi}4_s$] reaction giving a polycyclic adduct with ten-membered perimeter.[84] The synthesis of **34** from tropone and diphenylnitrilimine, along with [2 + 3] adduct,[85] illustrates the addition of a 1,3-dipole to the terminal positions of a triene system; electronically, this reaction is of the [$_{\pi}6_s$ + $_{\pi}4_s$] type, the ring size classification being 6 + 3 → 9.



35 36

Fulvenes also possess a triene system. Houk and Luskus[86] have observed that 6,6-dimethylfulvene (**35**) accepts diazomethane at the 1,6, rather than 1,2 or 1,4 positions to give **36**. While the addition of benzonitrile oxide to **35** takes place at the 1,2 positions, 6-dimethylaminofulvene combines 1,6 with the same 1,3-dipole producing **37** after subsequent elimination of dimethylamine.[87] Both the [$_{\pi}6_s$ + $_{\pi}4_s$] and [$_{\pi}4_s$ + $_{\pi}2_s$] cycloadditions are symmetry-allowed concerted processes, while the forbidden [$_{\pi}4_s$ + $_{\pi}4_s$] reaction, though easily acceptable from the standpoint of ring strain, has not been observed. The addition of dimethyl acetylenedicarboxylate to diazocyclopentadiene to yield **38**[88] follows another symmetry-allowed path, [$_{\pi}8_s$ + $_{\pi}2_s$].



37 38

This selectivity of cycloadditions with respect to the total number of $\pi$ electrons involved overrides effects of ring size and must be more than a coincidence. Why does the dimerization of azepine-*N*-carboxylic ester choose a pathway[89] in which one molecule acts as a 1,3-diene and the second as a 1,3,5-triene system? No reason can be seen why in stepwise processes via diradicals or zwitterions such a discrimination should be obeyed. After the first $\sigma$ bond has been established, the termini of the intermediate would no longer be conjugated and, therefore, would not influence one another; all conceivable encounters of the reactive centers should take place as long as not prevented by ring strain. The reason for the selectivity, however, has been found: the conservation of orbital symmetry[15] or the "aromatic" number of (4*q* + 2) $\pi$ electrons in the transition state[17-19] of *concerted cycloadditions!*

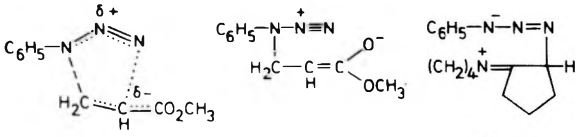
**Reactivity Scale of Dipolarophiles.** The dipolarophilic activities of the CC double or triple bond and heteromultiple bonds depends highly on substituents. The addition rate constants usually range over many powers of ten. A peculiar phenomenon frequently observed: common alkenes and alkynes add to the 1,3-dipoles rather slowly, whereas electron attraction as well as electron release by substituents increase the dipolarophilic activity of the multiple bond. U-Shaped curves result from plotting addition constants of dipolarophiles vs. the electron density of their multiple bond systems.[4,13] Such behavior has been found for the 1,3-dipolar cycloadditions of nitrile imines,[16] nitrile oxides,[90] azides,[91] azomethine imines,[92] azomethine oxides (nitrones),[59] and carbonyl ylides,[93] with curves specific for each class of 1,3-dipoles and, to a minor extent, even for each individual 1,3-dipole. The U-shapes can vary considerably and sometimes degenerate to the extent that only half of the U is preserved. The additions of nitrile ylides[94] and diazoalkanes[26,60,95] are accelerated only by electron-attracting substituents in the dipolarophile whereas ozone[96] and nitrous oxide[97] show a strong preference for electron-rich multiple bonds.

We ascribed earlier the large spread of dipolarophile activity to three effects.[4,16]

(a) The high activity of conjugated systems was attributed to increased polarizability.

(b) Unequal bond formation in the transition state creates partial charges which are stabilized by the moieties stemming from 1,3-dipole and dipolarophile.

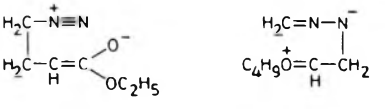
(c) Steric hindrance increase with the degree of substitution of ethylene or acetylene; the large negative entropies of activation, observed for all concerted cycloadditions, emphasize steric requirements.



39 40 41

Two examples may illustrate the strengths and shortcomings of argument b. The addition of phenyl azide to ethyl acrylate yielding ethyl 1-phenyl-1,2,3-triazoline-4-carboxylate[98] is 40 times faster than the addition to 1-heptene.[91] This was interpreted by the stabilization of partial charges in the transition state **39** in which one of the two new $\sigma$ bonds is developed to a greater extent than the other. The participation of **40** as a hyperconjugated contributor to the concerted transition state would be an alternative way of symbolizing the same idea. Analogously, the zwitterion **41** as a hyperconjugated structure contributes to the resonance hybrid of the transition state of the phenyl azide addition to 1-pyrrolidinocyclopentene, which is 480,000 times faster than the one to 1-heptene[91] and furnishes the 5-amino-substituted triazoline.[99,100] The structures **40** and **41** symbolize the capability of 1,3-dipoles to stabilize charges of either sign which is in accordance with the U-shaped activity sequence.

The hyperconjugated contributors **40** and **41** correspond to the adducts of an electrophilic and a nucleophilic reagent, respectively, with the azide system. The cycloaddition of phenyl azide to 1-pyrrolidinocyclopentene is only ten times faster in DMF than in cyclohexane;[91] thus the contribution of the zwitterionic structure **41** to the transition state cannot be very high. Why then is the rate constant for addition to enamines so large?



42 43

Correspondingly, **42** and **43** contribute to the transition state of the concerted additions of diazomethane to ethyl acrylate and to vinyl butyl ether. Formulae **42** and **43** do not disclose why diazomethane adds to ethyl acrylate 2700 times *faster* and to vinyl butyl ether 4500 times *slower* than to ethylene.[26] However, the basic and nucleophilic qualities of diazomethane are more pronounced than its electrophilicity. The correlation between the cycloaddition rates and the nucleophilicity of diazomethane finds its converse in the cycloadditions of ozone and of nitrous oxide, which act as electrophilic reagents. Thus, the various deviations from the U shape of dipolarophile activity scale can be rationalized.

The advantage of the concerted mechanism of cycloaddition lies in the partial compensation of the energy required for bond breaking by that of making two new $\sigma$ bonds. Is it

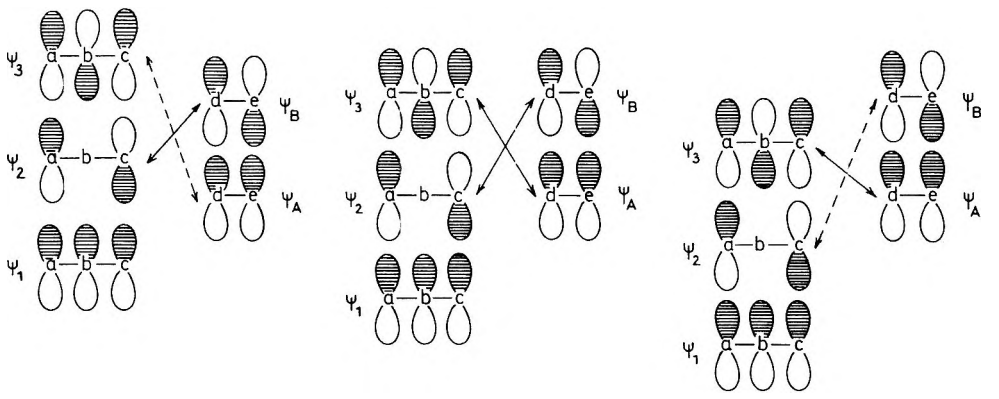



**Figure 1.** The HOMO–LUMO interaction between 1,3-dipole and dipolarophile depends on the orbital energies of the 1,3-dipole: ——, strong; - - - -, weak interaction.

reasonable to ascribe the large rate accelerations of 1,3-dipolar cycloadditions by substituents to small contributions of zwitterionic structures in which *only one σ bond* connects the reactants?

One welcomes recent successful attempts of MO perturbation theory to cope with nucleophilicity scales[101] as well as with dienophile[102] and dipolarophile activity sequences. The reactions of nucleophilic with electrophilic reagents—cycloadditions provide specific examples—are controlled by the HOMO–LUMO interplay which depends on orbital energies and size of the eigenvector coefficients. *The rate of a cycloaddition is not simply a function of the nucleophilicity and electrophilicity of the reactants, but rather all these phenomena have common underlying reasons.*

As 1,3-dipole and dipolarophile approach each other, their frontier orbitals begin to interact and new MO's of $C_s$ symmetry are formed in the transition state. According to perturbation theory, the interaction energy of the two HO–LU combinations is expressed by eq 1.[103] $E_I$ and $E_{II}$

$$\Delta E = \frac{(c_a c'_d \beta_{ad} + c_c c'_e \beta_{ce})^2}{E_I} + \frac{(c'_a c_d \beta_{ad} + c'_c c_e \beta_{ce})^2}{E_{II}} \quad (1)$$

$E_I = E_{\Psi_2} - E_{\Psi_B}$ = HO(1,3-Dipole) – LU(Dipolarophile)

$E_{II} = E_{\Psi_A} - E_{\Psi_3}$ = HO(Dipolarophile) – LU(1,3-Dipole)

are the orbital energy differences; $c$ and $c'$ the coefficients of the atomic orbitals of HO and LU, respectively. The subscripts are defined in Figure 1. The larger the number of heteroatoms (increased Coulomb integral) in a 1,3-dipole, the lower are its orbital energies compared with those of the parent allyl anion ($\Psi_2$ nonbonding in HMO). $\Psi_2$ is the HO, $\Psi_2$ the LU of 1,3-dipoles. The $\sigma$ resonance integrals $\beta$ in eq 1 depend not only on the distance of the atoms, but also on their nature ($\beta_{C-C} > \beta_{C-N} > \beta_{C-O}$).

If the dipolarophile d=e is part of a conjugated system, then $\Psi_A$ will be destabilized and $\Psi_B$ stabilized. The decreased HO–LU distance leads via smaller values of $E_I$ and $E_{II}$ in eq 1 to a larger $\Delta E$ which effects rate acceleration.[104] Our earlier concept[4,16] of the increased polarizability of conjugated systems has thus achieved a more authoritative meaning.

Sustmann[104] deduced qualitatively the various U-shape dipolarophile activity scales from the three types of HO–LU interactions sketched in Figure 1. For 1,3-dipoles of type II the interactions $\Psi_2$–$\Psi_B$ and $\Psi_A$–$\Psi_3$ are of comparable importance. Electron-attracting conjugated substituents like $CO_2R$, COR, and $NO_2$ will lower the orbital energies of ethylene. The increase of the first term in eq 1 due to a reduced $E_I$ (energy difference $\Psi_2 - \Psi_B$) exceeds the loss in the second term caused by an increased $E_{II}$; rate acceleration will be the result. Electron-releasing substituents (OR, $NR_2$) raise the dipolarophile orbital energies. In this case the second term of eq 1 gains more than the first one loses; once more an increase of rate will result. Azides, nitrile imines, nitrile oxides, etc., belong to this type II.

For 1,3-dipoles of type I essentially the interaction $\Psi_2$–$\Psi_B$ is important; owing to the larger energetic distance $\Psi_A$–$\Psi_3$, the second term in eq 1 becomes small. Electron-attracting substituents will lower, i.e., stabilize, $\Psi_B$ and accelerate the reaction by reducing $E_I$; electron-donating substituents, however, deactivate the dipolarophile by raising $\Psi_B$. Nitrile ylides and diazoalkanes belong to type I. Correspondingly, for 1,3-dipoles of type III the dominating interaction $\Psi_A - \Psi_3$ (energy difference $E_{II}$) profits from lifting $\Psi_A$ by electron-releasing substituents, but is weakened by electron-attracting groups. Cycloadditions of nitrous oxide and ozone follow this pattern.

$$\Delta E = A\beta^2 \left[ \frac{1}{E_I + X} + \frac{1}{E_{II} - X} \right] \quad (2)$$

A semiquantitative correlation can be achieved by drastic approximation. After setting equal the numerators of the two terms in eq 1 and assuming that the substituent changes the energy of $\Psi_A$ and $\Psi_B$ by the same amount, $x$, Sustmann and Trill[105] derived eq 2. On plotting log $k_2$ for cycloadditions of phenyl azide to 20 dipolarophiles[91] vs. the ionization potentials of the highest occupied $\pi$ molecular orbitals of these dipolarophiles—the ionization potentials represent an experimental measure of $\Psi_A$ energies—the data fit fairly well the paraboloid function (superposition of two hyperbolae) of eq 2. Similar curves were obtained for benzonitrile oxide and diphenylnitrilimine cycloadditions[90] (type II of Figure 1). In contrast, log $k_2$ values of diazomethane cycloadditions (type I) to ten monosubstituted

Table II
Substituent Influence Expected for the Formation of Firestone's Diradical from Dipolarophiles $H_2C{=}CHR$ and Relative Rate Constants of 1,3-Dipolar Cycloaddition

| | R=H | Alkyl | $CO_2R$ | OR | $CH{=}CH_2$ | $C_6H_5$ |
|---|---|---|---|---|---|---|
| A. Thermochemical Data (kcal/mol) for Diradical Formation from Monosubstituted Ethylenes | | | | | | |
| Ground state conjugation free energy (ref 107) | =0 | 3.2 | 3.2 | 5.2[a] | 4.9 | 4.9 |
| Stabilization enthalpy of $H_2\dot{C}$–R (ref 108) | 0 | 6 | 8[b] | 11 | 16 | 19 |
| Stabilization free energy of $H_2\dot{C}$–R (25°, ref 108) | 0 | 7 | 9[b] | 11 | 15 | 18 |
| Gain of stabilization free energy[c] | 0 | 4 | 6 | 6 | 10 | 13 |
| B. Relative Rate Constants of 1,3-Dipolar Cycloadditions | | | | | | |
| $C_6H_5C{=}\overset{+}{N}{-}\overset{-}{O}$, 0° (ref 90) | 3.2 | =1.0 | 27 | 6.8 | | 3.9 |
| $C_6H_5C{=}\overset{+}{N}{-}\overset{-}{N}{-}C_6H_5$, 80° (ref 16) | | 1.0 | 350 | 2.2 | 10.2 | 8.5 |
| $H_2C{=}\overset{+}{N}{=}\overset{-}{N}$, 25° (ref 26) | 103 | 1.0 | 280,000 | 0.02 | 49 | 101 |
| $(C_6H_5)_2C{=}\overset{+}{N}{=}\overset{-}{N}$, 40° (ref 26, 60) | | 1.0 | 14,000 | | 13 | 21 |
| $C_6H_5N{=}\overset{+}{N}{=}\overset{-}{N}$, 25° (ref 91) | | 1.0 | 41 | 1.7 | 0.6 | 1.7 |
| $C_6H_5CH{=}\overset{+}{N}(CH_3){-}\overset{-}{O}$, 80° (ref 59) | | 1.0 | 150 | 2.8 | | 4.4 |

[a] Values for $OCH_3$. [b] 70% of the stabilization energy of $H_2\dot{C}COCH_3$; see H. E. O'Neal and S. W. Benson, *J. Phys. Chem.*, 72, 1866, 1882 (1968). [c] Difference of third and first line.

ethylenes fit a good linear relation with $1/E_I$, i.e., the energy difference of HO(diazomethane) and LU(dipolarophile).[26]

Can the diradical hypothesis rationalize these specific dipolarophile activity sequences? No. Firestone deduces the regioselectivity from energy differences—sometimes quite small—of isomeric diradicals in which the dipolarophile has become attached to either terminus of the 1,3-dipole.[22] If the same kind of reasoning is applied to the variation of the dipolarophiles, these consequences follow.

(1) In combining with a 1,3-dipole to give a diradical, the dipolarophile loses its ground state conjugation energy, but contributes through its radical moiety to the stabilization energy of the diradical (Table IIA). Both these energies depend on the dipolarophile alone. The endothermicity of diradical formation (near zero activation energy of the reverse reaction) demands that the transition state is structurally very close to the diradical. Thus, *the dipolarophile activity scale should be uniform and independent of the nature of the 1,3-dipole.* The whole wondrous diversity of dipolarophile scales would be exterminated by assuming diradical intermediates.

(2) *The uniform sequence of dipolarophile activity* expected on the basis of rate-determining diradical formation *bears no resemblance to the experimental activity scales* observed for various 1,3-dipoles (Table IIB). The log $k_2$ of the cycloadditions should be proportional to the difference between the stabilization free energy of the dipolarophile moiety in the diradical and the conjugation free energy of the olefinic bond in the ground state.[106] While the latter is fairly well known,[107] the free energies of radical stabilization are less reliable and only available for monosubstituted methyls.[108] Therefore, the values for the gain of stabilization free energy, as given on the fourth line of Table IIA, provide an approximation.

Neither conjugation energies nor radical stabilization energies are strictly additive in polysubstituted structures. We had to be content with using the stabilization energies for $R–\dot{C}H_2$, because those of $R–\dot{C}H(CH_3)$, though a better model, are not available. The data of the fourth line of Table IIA may thus be somewhat too large, but their trend is expected to be correct.

Nevertheless, the discrepancy with the rate constants of Table IIB is obvious. In contrast to the expectation for radical stabilization, ethylene reacts faster than 1-alkenes. Styrene should exceed acrylic ester in dipolarophilic activity by $\sim 10^5$; the rate constants show acrylic ester to be faster than styrene by factors of 7–2800. The vinyl ether column of Table II is symptomatic. The diradicals from 1,3-dipoles and vinyl ethers should be formed $\sim 10^4$ times faster than the ones from ethylene. However, diazomethane (1,3-dipole of type I) reacts with vinyl butyl ether 4500 times slower than with ethylene. All the other 1,3-dipoles of Table II are of type II; they also respond to the ether function in the dipolarophile with a small rate increase.

(3) Only one of the two substituents in 1,2-disubstituted ethylenes or acetylenes can contribute to the stabilization of the Firestone diradical and assist in its formation. The second substituent loses its conjugation with the double bond and could even retard diradical formation. Nevertheless, for dimethyl fumarate–methyl acrylate the following addition rate ratios have been measured: *C*-methyl-*N*-phenylsydnone, 7; diphenylnitrilimine, 6; 3,4-dihydroisoquinoline *N*-phenylimine, 4; diphenyldiazomethane, 3.

The diradical hypothesis of the Diels–Alder reaction[22] encounters the same difficulties. 9,10-Dimethylanthracene reacts with tetracyanoethylene $10^5$ times faster than with 1,1-dicyanoethylene;[109] diradical formation with tetracyanoethylene should be slower than with the 1,1-dicyano compound, because the conjugation energy of two cyano groups has to be sacrificed. However, the lower LU energy of tetracyanoethylene together with an early transition state of the concerted cycloaddition offers a satisfactory explanation.[102]

**Regioselectivity.** "The orientation phenomena in 1,3-dipolar as well as Diels–Alder addition offer perhaps the biggest *unsolved* problem in the field."[13] This was my opinion 7 years ago, and it was only recently that in this cloud of uncertainty a silver lining became visible. As the substituent effects offered by classic resonance theory are inadequate to interpret the regiochemistry of concerted cycloadditions, we were often tempted to overemphasize presumed steric effects.

While the range of dipolarophile activity corresponds to differences in activation free energies of 10 kcal/mol and more, the competition of the two addition directions of a 1,3-dipole to a dipolarophile is energetically more subtle. A free energy difference of 3 kcal/mol suffices to make the minor isomer disappear below the 1% analytical limit. Regiochemistry is a phenomenon of kinetic competition and cannot be detached from the question of dipolarophile activity.

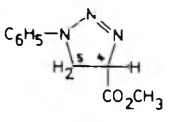
"The diradical mechanism predicts that the regiospecificity observed with both electron-poor and electron-rich

olefins should be the same toward any given 1,3-dipole",[22] because relative to hydrogen all substituents stabilize a radical center. Thus, Firestone regards "unidirectionality" as normal, but admits that the "bidirectionality" of the additions of azides to monosubstituted ethylenes and acetylenes does not conform to this rule. The alleged superiority of the diradical concept was illustrated with 147 examples including six "exceptions".[22]

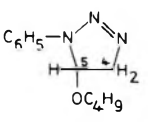
"The strong tendency for each 1,3-dipole to add in the same direction to both electron-rich and electron-poor olefins" [22] is basically erroneous. In fact, only the cycloadditions of nitrile imines and nitrile oxides are unidirectional and even these to a limited extent. Bidirectional are the cycloadditions to nitrile ylides,[94,110] diazoalkanes, azides, azomethine imines,[111] and nitrones. If the dipolarophiles are ordered by the electron density of their double or triple bonds, one finds that the point of switching from one orientation to the other is 1,3-dipole specific. As shown below, there is no sharp borderline between unidirectional and bidirectional behavior, but a mechanistically enlightening continuous transition. Even "unidirectionality" is not in conflict with the concerted mechanism as argued.[22]

The stabilization of partial charges in the transition state can make the concerted addition nonsynchronous. One would expect an orientational pattern in which the more nucleophilic end of the 1,3-dipole controls the addition to ethylenes and acetylenes with electron-withdrawing substituents, while the more electrophilic terminus would become attached to the $\beta$ position of a dipolarophile bearing an electron-releasing substituent. The ambivalence of the termini of the 1,3-dipole (see above) occasionally complicates the assignment of the nucleophilic and electrophilic end. Nevertheless, it is tempting to see if there is an analogy between the directional behavior of 1,3-dipoles in their concerted cycloadditions and their nucleophilic and electrophilic properties in additions leading to acyclic products. By the way, an inherent polarity is not a requirement; ozone or azomethine ylides are not less reactive in concerted cycloadditions because their ends are identical.

**A. Azides.** Phenyl azide accepts acrylic ester and vinyl ethers (and enamines) in different addition directions as illustrated by the adduct structures **44**[98] and **45**[100] in accordance with the resonance contributors of the type **40** and **41** to the transition state. The allegation[22] that this regioselectivity both for electron-poor and for electron-rich olefins is incorrect for the concerted mechanism rests on the assumption that "azides are polarized with the outer nitrogen negative". This misunderstanding stems from the direction of the net dipole moment of phenyl azide; the azido group as a whole attracts electrons from the benzene ring. Firestone[22] invokes a dipole interaction between the two reactants as a potent orientational factor,[112] although the formation of his "cyclo diradical" requires virtually the same relative orientation of 1,3-dipole and dipolarophile in the activation process. This mentioned dipole interaction appears to be of minor importance for the orientation.[113,114]

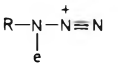


44

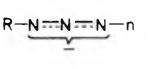


45

The acid-catalyzed decomposition of aryl azides is initiated by protonation at the inner nitrogen atom (**46**, e = H)[115] and the protonated hydrogen azide bears both hydrogens at the same nitrogen.[116] The azidium complexes of silyl, chloroantimonyl, and fluoroboryl azide[117] also correspond to type **46**. Thus, it is the inner nitrogen which is more basic and nucleophilic. The hyperconjugated contributor **40** to the transition state of the acrylic ester addition is likewise of the general type **46** and explains straightaway the formation of adduct **44**.



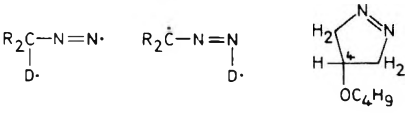
46



47

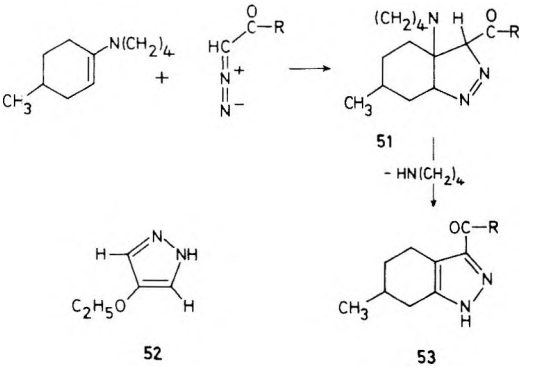
All additions of nucleophilic reagents n (cyanide, phosphines, carbanions, phosphorus and sulfur ylides, etc.) to organic azides take place via structures like **47** at the outer nitrogen atom,[118] thus marking the preferred electrophilic center. Likewise the $\beta$ position of vinyl ethers and enamines in cycloadditions become bonded to the outer nitrogen; e.g., the resonance contributor **41** is of type **47**. Thus, the regioselective additions to electron-deficient and electron-rich olefins do not fit the unidirectionality expected for a diradical intermediate.

**B. Diazoalkanes.** Firestone[22] compared the formation energies of the two conceivable diradicals **48** and **49**, formed from a diazoalkane and a dipolarophile D, and estimated a preference for **48** as high as 17 kcal/mol. Therefore, all cycloadditions of diazoalkanes to monosubstituted ethylenes or acetylenes should take place unidirectionally via the diradical **48** to produce 3-substituted pyrazolines or pyrazoles.



48 49 50

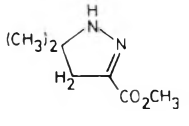
While the formation of **10** from diazomethane and methyl acrylate obeys this rule, the additions to electron-rich dipolarophiles are decidedly at variance. Butyl vinyl ether and diazomethane yield 4-butoxypyrazoline (**50**).[119] Diazoacetic ester and diazoketones combine with 1-pyrrolidine-4-methylcyclohexene to give the structurally secure tetrahydroindazoles **53**[120] via the primary adducts **51**. It is the nucleophilic enamine $\beta$ position which becomes attached to the diazoalkane nitrogen. Finally, diazomethane and ethoxyacetylene produce solely 4-ethoxypyrazole (**52**) of established structure.[121]



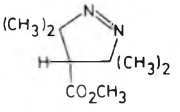
51 52 53

The regioselectivity toward electron-deficient and electron-rich dipolarophiles is thus symbolized by the zwitterionic contributors **42** and **43** to the transition state and these, again, would fit the anticipation for additions which are controlled by nucleophilicity and electrophilicity. Protonation on carbon induces the nitrogen loss from diazoalkanes; acylation, alkylation, and azo coupling (with aryldiazonium ions) of diazomethane also take place on carbon.[122] On the other hand, Grignard reagents add to the outer nitrogen of diazomethane[123] as does triphenylphosphine in the formation of triphenylphosphazine.[124] The more electron-depleted diazoalkane system in $\alpha$-diazocarbonyl and

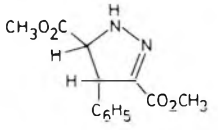
-dicarbonyl compounds easily reacts with thiolates, amines, and other nucleophiles, always at the terminal nitrogen atom.[122] Dicyanodiazomethane even undergoes azo coupling with dimethylaniline.[125] According to the diradical hypothesis, however, the opposite direction of cycloaddition to electron-rich multiple bonds should be favored by a rate factor of $10^{12}$ ($\Delta\Delta G^{\ddagger} = 17$ kcal/mol).[22]



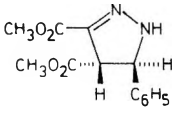
54



55



56

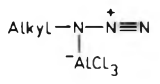


57

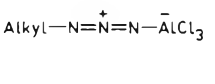
A revealing feature: the orientation rules of diazoalkane cycloadditions to electron-deficient multiple bonds (electron-attracting substituent ending up in pyrazoline 3 position) are not very strict. The normal addition direction to $\alpha,\beta$-unsaturated nitro compounds and sulfones can be reversed by encumbering $\beta$ substitution.[126,127] While dimethyldiazomethane combines with methyl acrylate to give the "normal" adduct **54** (analogous to **12**), $\beta,\beta$-dimethylacrylic ester adds dimethyldiazomethane in the opposite direction to give **55** and only a trace of the "normal" adduct.[128] Cinnamic ester accepts diazomethane with quantitative formation of the pyrazoline 3-carboxylate.[129] Diazoacetic ester, however, produces the "normal" adduct **56** and the "anomalous" adduct **57** in a 8:1 ratio.[130] The 2-pyrazolines **54, 56,** and **57** are results of subsequent tautomerization of 1-pyrazolines.

A similar reversal of the "normal" orientation has been observed in diazoalkane cycloadditions to the CC triple bond of tetrolic and arylpropiolic esters.[131] The anomalous adducts have been interpreted as the result of switching from electronic to steric control.[128] In our opinion the change in regioselectivity is strong evidence for the *ambident nucleophilicity* of diazoalkanes.

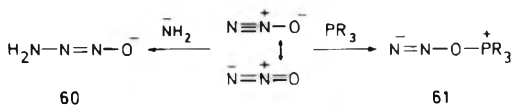
**C. 1,3-Dipoles as Ambident Nucleophiles and Electrophiles.** The attack of numerous electrophilic reagents on the diazoalkane carbon is followed by fast subsequent reactions, usually loss of $N_2$.[122] The fast nitrogen evolution on treatment with acids prevents clarification of the possibility that protonation might take place on carbon *and* nitrogen competitively. N-Protonation is suggested by the formation of aminoisonitrile, $H_2N$–N=C, from diazomethyllithium with acid.[132] There is some evidence that alkyl azides are ambident nucleophiles. The intermediates **58** and **59** have been postulated as being responsible for the simultaneous loss of $N_2$ and azide ion in the reaction with aluminum chloride.[133]



58



59



60 61

The sextet formulae suggest that 1,3-dipoles are ambident *electrophiles* as well. The conversion of nitrous oxide to alkali azide by alkali amide involves attack at the terminal nitrogen with **60** as intermediate.[134] On the other hand, the deoxygenation by triethylphosphine[135] probably takes place via **61**.

While nitrile oxides add nucleophiles HB on carbon to given hydroximoyl derivatives,[136] triphenylphosphine attacks on oxygen to effect reduction to nitriles.[137] Benzonitrile oxide reacts with benzyl mercaptan both at the carbon and oxygen atom forming the thiobenzhydroximic ester and benzonitrile, respectively.[138] Nitrones show a similar dual behavior toward nucleophilic reagents.[139]

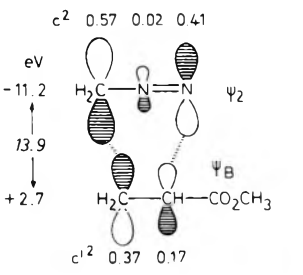
**D. The Silver Lining.** According to Fukui,[140] reactions take place in the direction of maximal HO–LU overlap. In concerted cycloadditions that orientation should be favored in which the centers with the largest atomic orbital coefficients interact. This principle allows the interpretation of most of the heretofore problematic orientation phenomena in Diels–Alder reactions.[141] Equation 1 contains in the numerator of the two terms the square of the sum of the products of orbital coefficients.

Bastide et al. used the perturbation approach, based on CNDO/2 calculations, to correlate the regioselectivity in cycloadditions of diazomethane[114] and substituted diazomethanes[142] to numerous olefinic and acetylenic dipolarophiles with the first interaction energy term of eq 1 for the two addition directions. These diazoalkanes belong to the 1,3-dipoles of Sustmann's type I[104] where only the interaction HO(diazoalkane) – LU(dipolarophile) is important. The treatment was refined by including all interactions between occupied and vacant orbitals of the reactants.[143,144] Also for fulminic acid, benzonitrile oxide, diphenylnitrilimine, and phenyl azide a satisfactory agreement between calculated and experimental orientations has been achieved; the addition directions of these 1,3-dipoles of type II are governed by both HO–LU interactions.

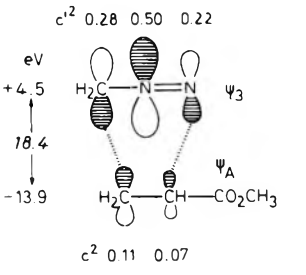
Independently, Houk calculated by CNDO/2 the orbital energies and atomic orbital coefficients of the three diazonium betaines and deduced the bidirectionality of the additions to dipolarophiles with donor and with acceptor substituents.[145] A similar procedure for all other classes of 1,3-dipoles led to rationalizations of addition directions.[146,147] The calculated orbital energies were adjusted with the help of known ionization potentials and $\pi \rightarrow \pi^*$ transitions.

Introduction of a conjugating substituent ($C_6H_5$, CH=$CH_2$) or an electron-attracting group ($CO_2R$, CN) into ethylene will influence the atomic orbital coefficients of the $\alpha$ and $\beta$ carbon in the sense of $c_\alpha < c_\beta$ in both HO and LU, according to CNDO/2.[143,146] Electron-releasing substituents (OR, $NR_2$) also lead to $c_\alpha < c_\beta$ in HO, but to $c_\alpha > c_\beta$ in LU.

The HO of diazomethane possesses the largest atomic orbital coefficient on carbon; hence carbon has the greatest nucleophilicity. The size of the orbitals in the orientation complex formulae **62–65** reflect the squares of the atomic orbital coefficients.[114,148] The carbon orbital of diazomethane overlaps in the important $\Psi_2$–$\Psi_B$ interaction preferably with that dipolarophilic carbon which possesses the

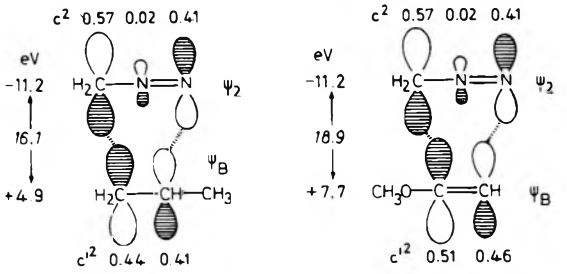


62



63

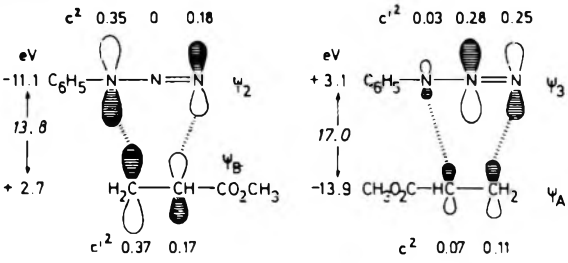
ห้องสมุด กรมวิทยาศาสตร์



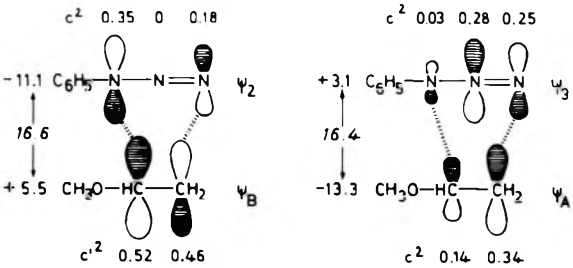

64 65

higher $c'^2$ values. The smaller energy distance $\Psi_2$–$\Psi_B$ makes the contribution of **62** larger than **63** in the reaction with methyl acrylate though both result in the same orientation. The increasing $\Psi_2$–$\Psi_B$ distance (nonadjusted CNDO/2 figures)[148] in **62, 64,** and **65** indicates decreasing rate, and the squares of $c'$ illustrate why diazomethane produces 3-substituted pyrazolines with acrylic ester and 1-alkenes, but the 4-alkoxypyrazole with ethoxyacetylene. Vinyl ethers and alkoxyacetylenes are borderline cases, because the two HO–LU interactions favor different orientations.

The "anomalous" orientation in the formation of **55** from dimethyldiazomethane and $\beta,\beta$-dimethylacrylic ester is also easily explained. The difference in the size of the terminal atomic orbital coefficients is diminished in both of the reactants[142] compared with diazomethane and acrylic ester. The less stringent electronic orientation is now overcome by steric control. The squares of $c_\alpha'$ and $c_\beta'$ of phenylpropiolic ester are less different than in cinnamic ester;[142] therefore, only the triple-bonded ester accepts diazomethane in the two addition directions.[131]




66 67

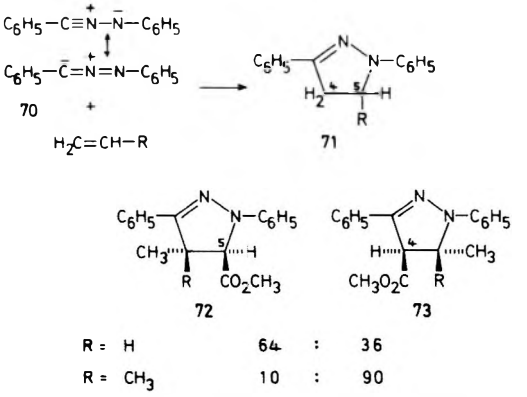



68 69

Replacement of the diazomethane carbon by nitrogen functions to give organic azides causes a lowering of $\Psi_3$. The dominant interaction of phenyl azide, a 1,3-dipole of type II,[104] in the reaction with acrylic ester is still $\Psi_2$–$\Psi_B$, i.e., **66** ≫ **67**. The contributions of $\Psi_2$–$\Psi_B$ (**68**) and $\Psi_A$–$\Psi_3$ (**69**) to the transition state of the vinyl ether addition are nearly equal, while $\Psi_A$–$\Psi_3$ preponderates for enamines. Both the interactions **68** and **69** direct the donor substituent to the 5 position of the triazoline, while **66** and **67** influence the orientation in opposite directions

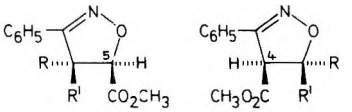
The opposite orientations obeyed in the cycloadditions of diazonium betaines to electron-deficient and electron-rich dipolarophiles, which can hardly be reconciled with the diradical hypothesis, are accounted for elegantly.

**E. The Unidirectionality.** Some 1,3-dipoles combine "unidirectionally" with both electron-rich and electron-poor monosubstituted ethylenes, i.e., the donor as well as the acceptor substituent ends up at the same position of the heterocyclic ring. This behavior is the heart of the diradical hypothesis.[20,22] On closer inspection one sees that the orientation rules are not strict; the argument loses its strength.




| | | | |
|---|---|---|---|
| R = H | 64 | : | 36 |
| R = $CH_3$ | 10 | : | 90 |

*Diphenylnitrilimine* (**70**) reacts with methyl acrylate,[149] styrene,[150] 1-hexene,[151] and vinyl butyl ether[150] to produce the 5-substituted pyrazolines **71** exclusively. While in all adducts of enol ethers and enamines the donor substituent is directed to the 5 position, the orientation in the cycloaddition to $\alpha,\beta$-unsaturated esters can easily be reversed. Methyl crotonate and methyl $\beta,\beta$-dimethylacrylate produce **72** *and* **73** with increasing amounts of the 4 ester **73.**[149] The orientations with acetylenic dipolarophiles are even less strict: methyl propiolate, the monosubstituted acetylene, gives the methyl 1,3-diphenylpyrazole-5- and -4-carboxylates in a 78:22 ratio.[149]

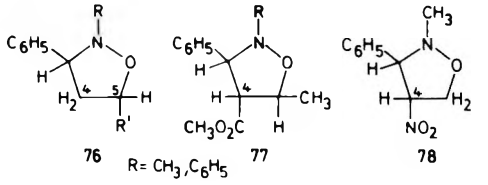



| R | R' | | | |
|---|---|---|---|---|
| H | H | 96 | : | 4 |
| $CH_3$ | H | 34 | : | 66 |
| $CH_3$ | $CH_3$ | 0 | : | 100 |
| $C_6H_5$ | H | 30 | : | 70 |

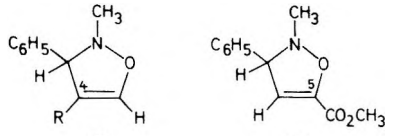
*Benzonitrile oxide* cycloadditions show a related pattern of regioselectivity. Additions to 1-alkenes, styrene, vinyl ethers, and enamines give 2-isoxazolines bearing alkyl, phenyl, ether, or amino groups, respectively, in position 5.[152–154] The predominance of the 5-carboxylic ester in the addition to methyl acrylate (96% **74** and 4% **75**) is reversed in the adducts of $\beta$-substituted acrylic esters; $\beta,\beta$-dimethylacrylic ester affords the 4 ester **75** only.[155] Methyl propiolate, likewise, gives rise to isoxazole-5- and -4-carboxylic esters; ratios from 91:9 to 22:78 have been observed for 16 nitrile oxides.[156] In contrast, dipolarophiles with donor substituents produce 5-substituted products exclusively.

*Nitrile imines, nitrile oxides,* and *nitrones* belong to type II (Figure 1) where both frontier orbital interactions contribute. While the terminal nitrogen or oxygen possesses a larger atomic orbital coefficient than carbon in $\Psi_2$, it is the other way around in $\Psi_3$.[146,148] Both the interactions $\Psi_2$–$\Psi_B$ and $\Psi_A$–$\Psi_3$ enforce one and the same addition direction for donor-substituted ethylenes or acetylenes. On the other hand, orientational forces on the acrylic ester

type dipolarophile are *opposite* for the interactions $\Psi_2$–$\Psi_B$ and $\Psi_A$–$\Psi_3$, as in the case of phenyl azide (**65** vs. **66**). In contrast to phenyl azide, the two HO–LU pairs are closer in energetic distance. The final outcome depends on a delicate balance, i.e., small structural changes can cause marked differences in the addition directions of unsaturated esters and nitriles. Occasionally the energetically greater interaction loses orientational control because the orbital coefficients of one reactant are not sufficiently different. PMO rationalizations of "unidirectional" behavior have been published recently.[143,144,147]



**76** R= $CH_3$, $C_6H_5$ **77** **78**



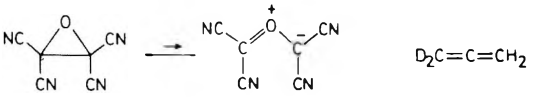
**79** **80**

*N*-Methyl-*C*-phenylnitrone or *C,N*-diphenylnitrone combines with 1-alkenes,[157] styrene, vinyl ethers,[158] enamines,[159] acrylic ester, and acrylonitrile[160] to yield the 5-substituted isoxazolidines **76.** Both HO–LU interactions appear to direct alkyl, phenyl, and alkoxy to the 5 position. In the reaction with electron-deficient dipolarophiles the $\Psi_2$–$\Psi_B$ interaction seems to dominate somewhat in energy,[147] but $\Psi_A$–$\Psi_3$ exerts stronger orientational control owing to a larger difference between $c_O\beta_{C-O}$ and $c_C\beta_{C-C}$. The reversal of the addition direction of methyl crotonate is noteworthy: the 4-carboxylic ester **77** is formed.[160] With $c_\alpha$ slightly larger than $c_\beta$ in $\Psi_A$ of methyl crotonate,[148] both HO–LU interactions now favor the 4-carboxylic ester.

The reversal can also be effected by another trick: lowering of the orbital energies in going from acrylic ester to nitroethylene results in an accretion of the $\Psi_2$–$\Psi_B$ interaction which directs the ethylenic substituent into position 4. According to Sims and Houk,[161] *N*-methyl-*C*-phenylnitrone and nitroethylene produce the 4-nitroisoxazolidine **78.** Methyl propiolate, a borderline case, no longer accepts the nitrone unidirectionally, but gives the isoxazole-4-carboxylate **79,** R = $CO_2CH_3$, and the 5 isomer **80** in a 58:42 ratio;[162] cyanoacetylene affords only **79,** R = CN,[161] as an outcome of further lowering of orbital energies.

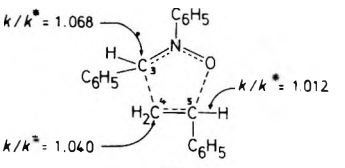
These satisfying results of PMO foster the hope that the vexing orientation problem in 1,3-dipolar cycloadditions will be completely solved in the near future. Urgently needed are additional data on HO energies from ionization potentials, on LU energies from electron affinities and more reliable quantum-chemical values for eigenvectors and orbital energies. CNDO/2 exaggerates the energy distance of HO and LU.

**Kinetic Isotope Effects.** Dolbier et al.[163] studied the 1,3-dipolar cycloaddition of the carbonyl ylide **82,** which is in thermal equilibrium with tetracyanoethylene oxide (**81**),[164] to 1,1-dideuterioallene (**83**). The result, $k_H/k_D$ = 0.93, agrees with the secondary kinetic isotope effect found in the Diels–Alder reaction of **83** with hexachlorocyclopentadiene. The cycloadditions of acrylonitrile and tetrafluoroethylene to **83** as well as the dimerization of **83** show $k_H/k_D$ = 1.14–1.21; these reactions probably include diradical intermediates.



**81** **82** **83**

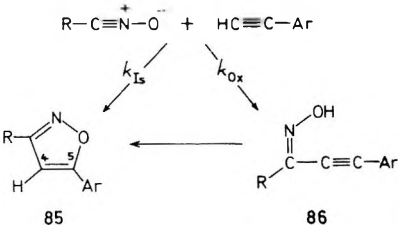
Bayne and Snyder[165] investigated the cycloaddition of **82** to the three isomeric monodeuterated styrenes specifically labeled at the olefinic positions. The identical secondary isotope effects observed, $k_H/k_D$ = 0.96–0.97, render it highly probable that both olefinic centers are equally involved in bond reorganization in the transition state of the concerted process.



**84.**

Benjamin and Collins[166] recently labeled the $\alpha$-carbon atom of *C,N*-diphenylnitrone and the $\alpha$- or $\beta$-carbon atom of styrene with $^{14}C$ and found the primary kinetic isotope effects (see **84**) in the formation of 2,3,5-triphenylisoxazolidine to be compatible only with the concerted mechanism. The diradical hypothesis would suggest that one of the isotope effects should be *secondary.* However, the observed $k/k^*$ values in **84** are larger than known secondary $^{14}C/^{12}C$ isotope effects, which, moreover, are generally <1.

**Crucial Tests. A. Oxime Formation from Nitrile Oxides and Arylacetylenes.** Alkyl radicals not only recombine, but also disproportionate to give alkane + alkene. The alleged diradical intermediates of 1,3-dipolar cycloadditions might be expected to undergo at least some hydrogen transfer reaction to form open-chain compounds along with cyclization and dissociation.

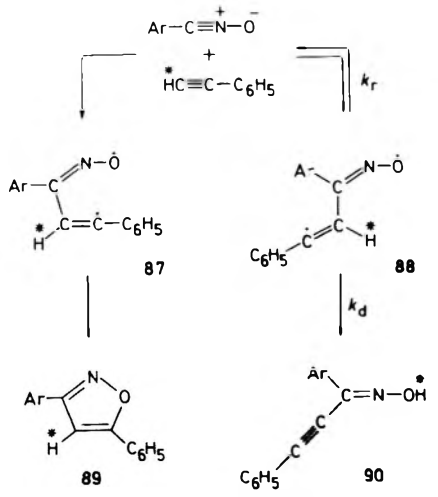


**85** **86**

Grünanger et al.[167] noticed that the synthesis of isoxazoles **85** from nitrile oxides and arylacetylenes is accompanied by the formation of acetylenic oximes **86** which cyclize to **85** on heating or under base catalysis. When the reaction was run in THF–$D_2O$, the cyclization **86** → **85,** but not the cycloaddition ($k_{Is}$), is accompanied by deuterium incorporation into the 4 position of **85.**[168] Therefore, the Italian authors proposed the scheme above with simultaneous reactions leading to **85** and **86.**[167–169] Analogously, diarylnitrilimines and arylacetylenes produce pyrazoles and acetylenic hydrazones in concurrent reactions.[170]

Investigating the reaction of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide with phenylacetylene, Beltrame et al.[171] found that a deuterium label in the starred position neither affected the overall rate constant *nor the ratio* **89:90,** 0.18. A careful reinvestigation by Dondoni et al.,[172] who used *p*-chloro- and *p*-methylbenzonitrile oxide, confirmed the absence of an isotope effect.

Beltrame et al.[171] considered a common (diradical or zwitterionic) intermediate, but later dismissed that idea.[173] Firestone[22] ascribes the oxime formation to the "extended diradical" **88** which is postulated to be in a highly mobile



equilibrium with the reactants, while **89** is conjectured to be produced via the "cyclo diradical" **87.**

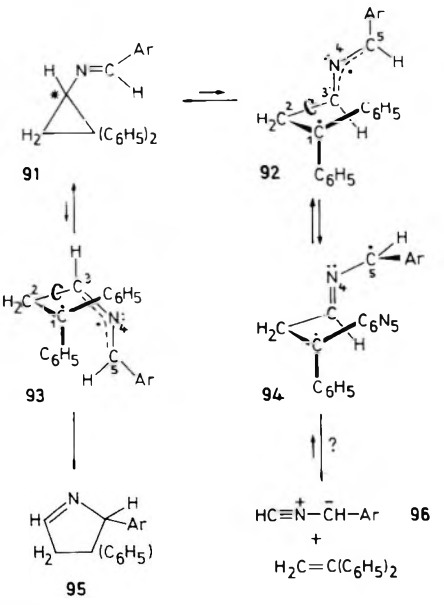
Only the hydrogen transfer in **88** → **90,** but not the conversion **87** → **89,** should be subject to a primary kinetic isotope effect. The process **88** → **90** would be comparable to a radical disproportionation which has an early transition state. Therefore, one should perhaps not expect the sizable isotope effects known for hydrogen abstractions by oxygen radicals,[174] but a smaller magnitude; e.g., $k_H/k_D = 1.87$ has been measured for the disproportionation of the $\alpha$-phenethyl radical.[55] The replacement of H* by D should result in an increase of the isoxazole yield at the expense of oxime formation. The nonoccurrence of this effect makes it improbable that the C–H* bond-breaking step is connected by mobile reversible reactions with the product-determining step leading to **89.** The diradical scheme above would be compatible with the facts only under the stringent condition that the step **88** → **90** ($k_d$) is much faster than the dissociation of **88** to reactants ($k_r$) for which we deduced a very small barrier above ($E_a \ll 1.2$ kcal for **9**). For example, if $k_H/k_D = 1.6$, a ratio $k_d/k_r = 1$, 5, or 10 would increase the product ratio **89:90** by 30, 10, or 5%, respectively.

I agree with the Italian authors[167-173] that the concomitant formation of isoxazoles and acetylenic oximes does not "establish the correctness of the diradical mechanism beyond a reasonable doubt." [22] No objections can be raised against an *irreversibly* formed diradical **87** or a zwitterion[171] as precursor of the acetylenic oxime. The recently proposed 1,1-cycloadduct as intermediate[172] constitutes an interesting alternative.

**B. Independent Synthesis of 1,5-Diradicals.** Close relatives of Firestone-type diradicals have recently become accessible; they do not show the asserted behavior.

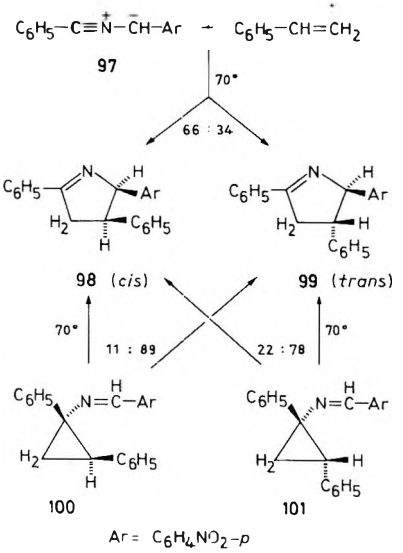
The rate constants of racemization of the optically active *N*-cyclopropylazomethines **91** and the $k$ values of their ring expansion to the pyrrolines **95** display a linear relation on the log scale for 12 different Ar's. The log $k$ values also correlate linearly with the logarithms of the partial rate factors of radical aromatic phenylation and methylation as well as with atom localization energies.[175] This corroborates the widespread assumption that the vinylcyclopropane rearrangement proceeds via diradical intermediates[176] as does the racemization (or cis–trans isomerization) of substituted cyclopropanes.[9] The racemization of **91** may take place by ring opening to **92** or **93,** rotation about the 2,3 bond, and reclosure of the three-membered ring; **92** contains an exo,exo and **93** an endo,exo disubstituted azaallyl radical. Only **93** can undergo 1,5 combination to give the pyrroline **95.**

According to the diradical hypothesis,[22] the allyl anion type orbital of the (unknown) nitrile ylide **96** should inter-



act with diphenylethylene to produce reversibly the "extended diradical" **94** and a related "cyclo diradical" which closes the ring to **95.** The diradical **94** differs from **92** only by a 90° rotation about the 4,5 bond and this also differentiates the "cyclo diradical" from **93.** It is hard to predict whether the allylic resonance in **92** or the three-electron bond in **94** will provide greater stabilization. Is it conceivable that diradical manifolds of the types **92** and **94** are separated by substantial energy barriers?[69] A smooth conversion to the more stable conformation is expected because the rotational barrier between **92** and **94** should be wiped out owing to the $\cos^2 \alpha$ relation for the interaction energy of twisted $\pi$ systems.

According to Firestone,[22] the "extended diradical" **94** should dissociate very rapidly to 1,3-dipole and dipolarophile. However, even at 165° the conversion **91** → **95** is quantitative. The racemization of **91,** Ar = $C_6H_4OCH_3$-*p*, is 110 times faster than its ring enlargement to **95** at 101°,[175] i.e., the diradical intermediates are often created from **91** before the pyrroline **95** is irreversibly formed. The lack of any dissociation of the 1,5-diradical intermediates is at variance with their alleged behavior.[22]



Benzonitrile *p*-nitrobenzylide (**97**) combines with styrene to produce the pyrrolines **98** and **99** in 79% yield (at 20°).[177] The cis,trans isomeric *N*-cyclopropylazomethines **100** and **101** yield the same pyrrolines **98** and **99** quantitatively at 70°. Three arguments allow one to reject a com-

mon manifold of diradical intermediates in the two processes.

(1) The diradicals from **100** and **101** rotate and reclose the three-membered ring with a similar rate as they suffer ring expansion at 65°.[178] Though the azomethines **100** and **101** are stable at 20°, they do not occur as products in the cycloaddition of **97** + styrene at room temperature.

(2) The azomethine **100** (**101**) yields via rotameric diradicals the pyrrolines **98** and **99** in a 11:89 (22:78) ratio at 70°.[177,179] With a ratio of 66:34 of **98** and **99** at 70°,[180] however, the concerted cycloaddition of **97** to styrene shows a well-understood preference for the *cis isomer*.

(3) The conversion of the azomethines **100** and **101** into **98** + **99** is quantitative, even in methyl acrylate as solvent. That rules out any dissociation of diradical intermediates into **97** + styrene because methyl acrylate exceeds styrene ≥20-fold in dipolarophilic activity toward **97**.[180]

**Calculation of the Transition State.** Polanski and Schuster[181] used HMO to calculate the transition state energy for the concerted addition of diazomethane to ethylene. In a more refined study Fukui et al.[182] applied a semiempirical SCF including CI to the same reaction. They found the formation of the new $\sigma$ bonds concerted, but nonsynchronous in the sense of CC < CN distance in the transition state due to the predominant HO(1,3-dipole)–LU(dipolarophile) interaction.

Recently Leroy and Sana[183] calculated the hypersurface of the reaction diazomethane + ethylene by an ab initio method. The transition state of the concerted cycloaddition was found at the following distances: CC 2.27 Å and CN 2.24 Å; the results excluded a secondary energy minimum. In agreement with PMO, there is a net flow of charge (6% of an electron charge) from diazomethane to ethylene in the transition state.

## Conclusion

All mechanistic criteria underline the superiority of the concerted mechanism over the diradical hypothesis. My main concern, however, was not just to refute the arguments for diradical intermediates, but rather to point out how well the large bulk of data on 1,3-dipolar cycloadditions complies with the expectations for the concerted process $[{}_{\pi}4_{s} + {}_{\pi}2_{s}]$. The MO perturbational treatment provides a deeper insight and promises a solution of remaining problems in the near future.

**Acknowledgment.** I express my gratitude to Professors Paul D. Bartlett, Albert T. Bottini, Clair J. Collins, Paolo Grünanger, Kendall N. Houk, Paul v. R. Schleyer, and Reiner Sustmann for critical comments and illuminating discussions. I am especially grateful to A. T. Bottini and P. v. R. Schleyer for their help in preparing the English manuscript.

## References and Notes

(1) 1,3-Dipolar Cycloadditions. 77. Part 76: R. Huisgen, A. Ohta, and J. Geittner, *Chem. Pharm. Bull. (Tokyo)*, **23** (1975), in press.
(2) R. Huisgen, "10 Jahre Fonds der Chemischen Industrie", Düsseldorf, 1960, p 73; *Proc. Chem. Soc.*, 357 (1961).
(3) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).
(4) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 633 (1963).
(5) We have replaced the cumbersome nomenclature of "1,3-dipoles with or without double bond in the sextet structure" [3] by the more descriptive "propargyl" and "allyl type".
(6) Review: T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, **13**, 627 (1974).
(7) J. R. Bailey and N. H. Moore, *J. Am. Chem. Soc.*, **39**, 279 (1917); J. R. Bailey and A. T. McPherson, *ibid.*, **39**, 1322 (1917); T. Wagner-Jauregg, *Ber. Dtsch. Chem. Ges.*, **63**, 3213 (1930); T. Wagner-Jauregg and L. Zirngibl, *Chimia*, **19**, 393 (1965).
(8) E. F. Hayes and A. K. Q. Siu, *J. Am. Chem. Soc.*, **93**, 2090 (1971).
(9) Review: R. A. Bergman in "Free Radicals", Vol. I, J. K. Kochi, Ed., Wiley, New York, N.Y., 1973, p 191.
(10) R. D. Harcourt, *J. Mol. Struct.*, **12**, 351 (1972).
(11) R. Huisgen and J. Nishimura, unpublished experiments, 1974. See also P. Eberhard and R. Huisgen, *J. Am. Chem. Soc.*, **94**, 1345 (1972).
(12) Our earlier assumption[13] that "the MO description of a 1,3-dipole leaves no room for a spin-paired diradical structure" was incorrect; one can combine wave equations for the zwitterion and the spin-paired diradical.[8]
(13) R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968).
(14) E.g., R. Hoffmann and R. B. Woodward, *Acc. Chem. Res.*, **1**, 17 (1968); A. Ledwith, *Annu. Rep. Prog. Chem., Sect. B*, **65**, 141, 153 (1968); G. W. Cowell and A. Ledwith, *Q. Rev., Chem. Soc.*, **24**, 119 (1970); G. L'abbé, *Chem. Rev.*, **69**, 345 (1969); C. Grundmann and P. Grünanger, "The Nitrile Oxides", Springer-Verlag, West Berlin, 1971, p 7, 85; T. L. Gilchrist and R. C. Storr, "Organic Reactions and Orbital Symmetry", Cambridge University Press, New York, N.Y., 1972, p 111, 117; R. Sustmann, "Thermische Cycloadditionen Neutraler Moleküle, Methodicum Chimicum", in press.
(15) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781, 817 (1969).
(16) A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, D. Grashey, and E. Spindler, *Chem. Ber.*, **100**, 2192, 2212 (1967).
(17) M. G. Evans and E. Warhurst, *Trans. Faraday Soc.*, **34**, 614 (1938); M. G. Evans, *ibid.*, **35**, 824 (1939).
(18) H. E. Zimmerman, *Acc. Chem. Res.*, **4**, 272 (1971).
(19) M. J. S. Dewar, *Angew. Chem., Int. Ed. Engl.*, **10**, 761 (1971).
(20) R. A. Firestone, *J. Org. Chem.*, **33**, 2285 (1968).
(21) R. A. Firestone, *J. Chem. Soc. A*, 1570 (1970).
(22) R. A. Firestone, *J. Org. Chem.*, **37**, 2181 (1972).
(23) J. W. Linnett, *J. Am. Chem. Soc.*, **83**, 2643 (1961); "The Electronic Structure of Molecules", Methuen, London, 1964.
(24) H. v. Pechmann and R. Burkard, *Ber. Dtsch. Chem. Ges.*, **33**, 3594 (1900).
(25) D. S. Matteson, *J. Org. Chem.*, **27**, 4293 (1962).
(26) R. Huisgen and J. Geittner, unpublished; J. Geittner, Ph.D. Thesis, University of Munich, 1974.
(27) T. V. Van Auken and K. L. Rinehart, *J. Am. Chem. Soc.*, **84**, 3736 (1962).
(28) R. Huisgen and W. Bihlmaier, unpublished experiments, 1974.
(29) R. Huisgen, W. Scheer, and H. Huber, *J. Am. Chem. Soc.*, **89**, 1753 (1967).
(30) J. H. Hall and R. Huisgen, *Chem. Commun.*, **1187** (1971); J. H. Hall, R. Huisgen, C. H. Ross, and W. Scheer, *ibid.*, **1188** (1971).
(31) Review: J. P. Lowe, *Prog. Phys. Org. Chem.*, **6**, 1 (1968).
(32) R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963); R. W. Fessenden, *J. Phys. Chem.*, **71**, 74 (1967); M. C. R. Symons, *Tetrahedron Lett.*, 207 (1973).
(33) It is only with increasing electronegativity difference between C and X that radicals $CX_3$ become pyramidal: R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **43**, 2704 (1965); L. Pauling, *ibid.*, **51**, 2767 (1969); J. Cooper, A. Hudson, and R. A. Jackson, *Mol. Phys.*, **23**, 209 (1972); K. S. Chen and J. K. Kochi, *J. Am. Chem. Soc.*, **96**, 794 (1974).
(34) R. W. Fessenden, *J. Chim. Phys. Physicochim. Biol.*, **61**, 1570 (1964); P. Krusic, P. Meakin, and J. Jesson, *J. Phys. Chem.*, **75**, 3438 (1971).
(35) From ESR data in solid methylmalonic acid: C. Heller, *J. Chem. Phys.*, **36**, 175 (1962).
(36) L. K. Montgomery, K. Schueller, and P. D. Bartlett, *J. Am. Chem. Soc.*, **86**, 622 (1964).
(37) P. D. Bartlett, C. J. Dempster, L. K. Montgomery, K. E. Schueller, and G. E. H. Wallbillich, *J. Am. Chem. Soc.*, **91**, 405 (1969).
(38) P. D. Bartlett and G. E. H. Wallbillich, *J. Am. Chem. Soc.*, **91**, 409 (1969).
(39) M. Jones and R. H. Levin, *J. Am. Chem. Soc.*, **91**, 6411 (1969).
(40) I. Tabushi, R. Oda, and K. Okazaki, *Tetrahedron Lett.*, 3743 (1968); H. H. Wasserman, A. J. Solodar, and L. S. Keller, *ibid.*, 5597 (1968); L. Friedman, R. J. Osiewicz, and P. W. Rabideau, *ibid.*, 5735 (1968).
(41) P. D. Bartlett and N. A. Porter, *J. Am. Chem. Soc.*, **90**, 5317 (1968).
(42) R. Hoffmann, S. Swaminathan, B. G. Odell, and R. Gleiter, *J. Am. Chem. Soc.*, **92**, 7091 (1970); R. Gleiter, *Angew. Chem., Int. Ed. Engl.*, **13**, 696 (1974).
(43) H. R. Gerberich and D. W. Walters, *J. Am. Chem. Soc.*, **83**, 4884 (1961).
(44) J. A. Berson, D. C. Tompkins, and G. Jones, *J. Am. Chem. Soc.*, **92**, 5799 (1970).
(45) P. G. Gassman, K. T. Mansfield, and T. J. Murphy, *J. Am. Chem. Soc.*, **90**, 4746 (1968).
(46) See ref 24–29 in ref 13.
(47) J. Hinz, A. Oberlinner, and C. Rüchardt, *Tetrahedron Lett.*, 1975 (1973).
(48) S. Seltzer and P/ T. Dunne, *J Am. Chem. Soc.*, 87, 2628 (1965); H. van Zwet and E. C. Kooyman, *Recl. Trav. Chim. Pays-Bas*, **86**, 1143 (1967); W. A. Pryor and K. Smith, *J. Am. Chem. Soc.*, **92**, 5403 (1970); K. Takagi and R. J. Crawford, *ibid.*, **93**, 5910 (1971).
(49) N. A. Porter, M. E. Landis, and L. J. Marnett, *J. Am. Chem. Soc.*, **93**, 795 (1971).
(50) J. Hollaender and W. P. Neumann, *Angew. Chem., Int. Ed. Engl.*, **9**, 804 (1970); N. A. Porter and P. M. Iloff, *Chem. Commun.*, 1575 (1971).
(51) J. F. Garst and G. S. Hammond, *J. Org. Chem.*, **23**, 98 (1958).
(52) S. A. Weiner and G. S. Hammond, *J. Am. Chem. Soc.*, **91**, 986 (1969).
(53) D. F. McMillen, D. M. Golden, and S. W. Benson, *J. Am. Chem. Soc.*, **94**, 4403 (1972); R. Hiatt and S. W. Benson, *Int. J. Chem. Kinet.*, **5**, 375 (1973).
(54) L. E. Reid and D. J. Le Roy, *Can. J. Chem.*, **46**, 3275 (1968); R. S. Konar, *Int. J. Chem. Kinet.*, **2**, 419 (1970); J. H. Georgakakos, B. S. Rabinovitch, and C. W. Larson, *ibid.*, **3**, 535 (1971). Review: M. J. Gibian and R. C. Corley, *Chem. Rev.*, **73**, 441 (1973).
(55) M. J. Gibian and R. C. Corley, *J. Am. Chem. Soc.*, **94**, 4178 (1972).
(56) K. Ziegler, P. Orth, and K. Weber, *Justus Liebigs Ann. Chem.*, **504**, 131 (1933); F. S. D'iachkovskii, N. N. Bubnov, and A. E. Shilov, *Dokl. Akad. Nauk SSSR*, **122**, 629 (1958).

(57) G. D. Mendenhall and K. U. Ingold, *J. Am. Chem. Soc.*, **95**, 3422 (1973).
(58) L. Salem, *Int. Congr. Pure Appl. Chem., XXIIIrd, Suppl.*, **1**, 197 (1971); L. Salem and C. Rowland, *Angew. Chem., Int. Ed. Engl.*, **11**, 92 (1972).
(59) R. Huisgen, H. Seidl, and I. Brüning, *Chem. Ber.*, **102**, 1102 (1969).
(60) R. Huisgen, H. Stangl, H. J. Sturm, and H. Wagenhofer, *Angew. Chem.*, **73**, 170 (1961).
(61) Improved recent data lead to some changes of the earlier values.[13] I used the same set of bond energies for single and double bonds as Firestone did.[21]
(62) For reasons which are explained below, we consider the bond energy of the resonance structure **17b** (and not **17a** as earlier)[13] and, therefore, convert N=O into N–O. The bond energy of 145 kcal/mol for N=O[21] is based on nitrites, which are resonance stabilized. We estimate the lower value of 130 kcal/mol for N=O; otherwise the discrepancy between Firestone's and our calculation would become even larger.
(63) The planar allyl system possesses the substituents in eclipsed conformations. During the 90° rotation the ground-state strain (ca. 2 kcal/mol) is relieved and only partially used up by pyramidalization of the carbanion. In the examples of the nitrone and azomethine ylide series (see below) the carbanion remains planar during rotation because of resonance interaction with substituents. Thus, allyl resonance energies evaluated from rotational barriers will not come out too high.
(64) V. R. Sandel, S. V. McKinley, and H. H. Freedman, *J. Am. Chem. Soc.*, **90**, 495 (1968). The lower value of 17.1 kcal/mol, measured for 1-phenylallyl*lithium* in THF, is probably due to rotation in a small equilibrium concentration of the covalent species; see R. B. Bates, D. W. Gosselink, and J. A. Kaczynski, *Tetrahedron Lett.*, 205 (1967); D. Seyferth and T. F. Jula, *J. Organomet. Chem.*, **8**, P 13 (1967).
(65) W. J. Hehre, University of California, Irvine, private communication. For the 4-31G method see W. J. Hehre, R. Ditchfield, L. Radom, and J. A. Pople, *J. Am. Chem. Soc.*, **92**, 4796 (1970).
(66) H. Hermann, R. Huisgen, and H. Mäder, *J. Am. Chem. Soc.*, **93**, 1779 (1971).
(67) T. S. Dobashi, M. H. Goodrow, and E. J. Grubbs, *J. Org. Chem.*, **38**, 4440 (1973).
(68) L. W. Boyle, M. J. Peagram, and G. H. Whitham, *J. Chem. Soc. B*, 1728 (1971), conjectured that the cycloaddition of **17** to norbornene at 85° is preceded by a trans → cis isomerization. The configurations of the cycloadducts were not assigned; there is also no necessity to assume *cis*-**17** as a reactant.
(69) R. A. Firestone, private communication. I am grateful to Dr. Firestone for an extended correspondence.
(70) K. Koyano and I. Tanaka, *J. Phys. Chem.*, **69**, 2545 (1965).
(71) R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, **75**, 2439 (1953); K. P. Butin, I. P. Beletskaya, A. N. Kashnin, and O. A. Reutov, *J. Organomet. Chem.*, **10**, 197 (1967); A. Streitwieser, M. R. Granger, F. Mares, and R. A. Wolf, *J. Am. Chem. Soc.*, **95**, 4257 (1973).
(72) Bond dissociation energies: $CH_3$–H 104, $C_6H_5CH_2$–H 85, $NCCH_2$–H 86 kcal/mol; J. A. Kerr, *Chem. Rev.*, **66**, 465 (1966). Our argument would gain weight by accepting the recently proposed value of 7 kcal/mol for the radical stabilization by cyano: D. Bellus and G. Rist, *Helv. Chim. Acta*, **57**, 194 (1974).
(73) J. L. Franklin, J. G. Dillard, H. M Rosenstock, J. T. Herron, K. Draxl, and F. H. Field, *Natl. Stand. Ref. Data Ser., Natl. Bur. Stand.*, 26 (1969).
(74) V. H. Dibeler, J. L. Franklin, and R. M. Reese *J. Am. Chem. Soc.*, **81**, 68 (1959).
(75) P. S. Engel, J. L. Wood, J. A. Sweet, and J. L. Margrave, *J. Am. Chem. Soc.*, **96**, 2381 (1974).
(76) Ring size classification of cycloadditions: R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **7**, 321 (1968).
(77) J. D. Roberts and C. M. Sharts, *Org. React.*, **12**, 1 (1962); D. Seebach in Houben-Weyl, "Methoden der Organischen Chemie", Vol. IV/4, Georg Thieme Verlag, Stuttgart, 1971, pp 267–270, 277–292.
(78) L. L. Muller and J. Hamer, "1,2-Cycloaddition Reactions", Interscience, New York, N.Y., 1967.
(79) F. Effenberger, *Angew. Chem., Int. Ed. Engl.*, **8**, 295 (1969); R. Gompper, *ibid.*, **8**, 312 (1969).
(80) R. Huisgen and G. Steiner, *J. Am. Chem. Soc.*, **95**, 5054, 5055 (1973); G. Steiner and R. Huisgen, *ibid.*, **95**, 5056 (1973); R. Huisgen, R. Schug, and G. Steiner, *Angew. Chem., Int. Ed. Engl.*, **13**, 80, 81 (1974).
(81) R. Wheland and P. D. Bartlett, *J. Am. Chem. Soc.*, **92**, 3822 (1970). See also B. M. Jacobson and P. D. Bartlett, *J. Org. Chem.*, **38**, 1030 (1973). General discussion of four- vs. six-membered ring formation from diradicals: P. D. Bartlett, *Int. Congr. Pure Appl. Chem., XXIIIrd* **4**, 281 (1971).
(82) R. Eidenschink and T. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, **11**, 292 (1972); G. Boche and D. Martens, *ibid.*, **11**, 724 (1972).
(83) H. M. R. Hoffmann, D. R. Joy, and A. K. Suter, *J. Chem. Soc. B*, 57 (1968). 1,4-Addition of the 2-methoxyallyl cation to benzene and toluene: A. E. Hill and H. M. R. Hoffmann, *J. Am. Chem. Soc.*, **96**, 4597 (1974).
(84) R. C. Cookson, B. V. Drake, J. Hudec, and A. Morrison, *Chem. Commun.*, 15 (1966); Y. Fujise, T. Okuda, and Y. Inone, *Bull. Chem. Soc. Jpn.*, **39**, 1351 (1966).
(85) K. N. Houk and C. R. Watts, *Tetrahedron Lett.*, 4025 (1970).
(86) K. N. Houk and L. J. Luskus, *Tetrahedron Lett.*, 4029 (1970).
(87) P. Caramella, P. Frattini, and P. Grünanger, *Tetrahedron Lett.*, 3817 (1971).
(88) D. J. Cram and R. D. Partos, *J. Am. Chem. Soc.*, **85**, 1273 (1963).
(89) L. A. Paquette and J. H. Barrett, *J. Am. Chem. Soc.*, **88**, 2590 (1966).
(90) K. Bast, M. Christl, R. Huisgen, and W. Mack, *Chem. Ber.*, **106**, 3312 (1973).
(91) R. Huisgen, G. Szeimies, and L. Möbius, *Chem. Ber.*, **100**, 2494 (1967).
(92) R. Huisgen and A. Eckell, *Tetrahedron Lett.*, **12**, 5 (1960); R. Huisgen, R. Grashey, A. Eckell, and H. Leitermann, *Angew. Chem.*, **72**, 416 (1960). Kinetic investigations: A. Eckell, M. V. George, R. Huisgen, and A. S. Kende, unpublished; R. Schiffer, Ph.D. Thesis, University of München, 1966.
(93) H. Hamberger and R. Huisgen, *Chem. Commun.*, 1190 (1971); V. Markowski, Ph.D. Thesis, University of Munich, 1974.
(94) R. Huisgen, H. Stangl, H. J. Sturm, R. Raab, and K. Bunge, *Chem. Ber.*, **105**, 1258 (1972).
(95) A. Ledwith and D. Parry, *J. Chem. Soc. C*, 1408 (1966); A. Ledwith and Y. Shih-Lin, *J. Chem. Soc. B*, 83 (1967).
(96) T. Vrbaski and R. Cvetanović, *Can. J. Chem.*, **38**, 1053 (1960); T. W. Nakagawa, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **82**, 269 (1960); Y. K. Wei and R. J. Cvetanović, *Can. J. Chem.*, **41**, 913 (1963); D. G. Williams and R. J. Cvetanović, *J. Am. Chem. Soc.*, **90**, 3668, 4248 (1968).
(97) F. S. Bridson-Jones, G. D. Buckley, L. H. Cross, and A. Driver, *J. Chem. Soc.*, 2999 (1951); F. S. Bridson-Jones and G. D. Buckley, *ibid.*, 3009 (1951).
(98) R. Huisgen, G. Szeimies, and L. Möbius, *Chem. Ber.*, **99**, 475 (1966).
(99) R. Fusco, G. Bianchetti, and D. Pocar, *Gazz. Chim. Ital.*, **91**, 849 (1961).
(100) R. Huisgen, L. Möbius, and G. Szeimies, *Chem. Ber.*, **98**, 1138 (1965); R. Huisgen and G. Szeimies, *ibid.*, **98**, 1153 (1965).
(101) G. Klopman, *J. Am. Chem. Soc.*, **90**, 223 (1968); "Chemical Reactivity and Reaction Paths", G. Klopman, Ed., Wiley-Interscience, New York, N.Y., 1974, p 55.
(102) O. Eisenstein and N. T. Anh, *Tetrahedron Lett.*, 1191 (1971); R. Sustmann, *ibid.*, 2721 (1971); R. Sustmann and R. Schubert, *Angew. Chem., Int. Ed. Engl.*, **11**, 840 (1972).
(103) For leading references: W. C. Herndon, *Chem. Rev.*, **72**, 152 (1972); R. F. Hudson, *Angew. Chem., Int. Ed. Engl.*, **12**, 36 (1973).
(104) R. Sustmann, *Tetrahedron Lett.*, 2717 (1971).
(105) R. Sustmann and H. Trill, *Angew. Chem., Int. Ed. Engl.*, **11**, 838 (1972).
(106) In the exothermic additions of radicals to olefins the activity sequences of olefins depend on the nature of the radical. The transition states of addition are closer to reactants than to products; polar and steric factors influence the transit on state energy as shown by F. R. Mayo and C. Walling, *Chem. Rev.*, **46**, 191, 234 (1950). A fundamentally different situation is expected for the diradical formation from 1,3-dipole and dipolarophile; here the transition state is closely related to the diradical.
(107) The conjugation free energies of Table II are based on three-carbon tautomerism equilibria: J. Hine and N. W. Flachskam, *J. Am. Chem. Soc.*, **95**, 1179 (1973). The value for butadiene (4.9 kcal/mol) is the difference between the first hydrogenation free energy of butadiene (to give 1-butene) and the one of ethylene. Standard enthalpies and entropies were taken from S. W. Benson, R. F. Cruickshank, D. M. Golden, G. R. Hangen, H. E. O'Neal, A. S. Rodgers, R. Shaw, and R. Walsh, *Chem. Rev.*, **69**, 279 (1969).
(108) Bond dissociation energies: S. W. Benson, "Thermochemical Kinetics", Wiley, New York, N.Y., 1968, p 215; K. W. Egger and A. T. Cocks, *Helv. Chim. Acta*, **56**, 1537 (1973). The free bond dissociation energies of methane and substituted methanes were calculated from standard enthalpies and entropies: S. W. Benson, "Thermochemical Kinetics", pp 42, 204; H. E. O'Neal and S. W. Benson, *Int. J. Chem. Kinet.*, **1**, 221 (1969); "Free Radicals", Vol. II, J. K. Kochi, Ed., Wiley, New York, N.Y., 1973, p 275.
(109) J. Sauer, H. Wiest, and J. Mielert, *Chem. Ber.*, **97**, 3183 (1964); J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967).
(110) K. Bunge, R. Huisgen, R. Raab, and H. Stangl, *Chem. Ber.*, **105**, 1279 (1972); K. Bunge, R. Huisgen, R. Raab, and H. J. Sturm, *ibid.*, **105**, 1307 (1972); K. Burger, K. Einhellig, W.-D. Roth, and L. Hatzelmann, *Tetrahedron Lett.*, 2701 (1974).
(111) *C*-Biphenylene-$N^{\beta}$-*p*-chlorophenyl-$N^{\beta}$-cyanoazomethine imine[92] adds to acrylic ester and acrylonitrile with an orientation opposite to that of styrene, butyl vinyl ether, and allyl alcohol: R. Huisgen and A. Eckell, unpublished experiments, 1963–1964.
(112) Firestone[22] calculates Coulomb c repulsions even at 2 and 3 Å with an equation which applies only at arger distances. Moreover, the dielectric constant of the medium reduces the in vacuo interaction energy.
(113) Small effect of solvent polarity on the ratio of regioisomeric adducts from trimethylbenzonitrile oxide and methyl propiolate: M. Christl and R. Huisgen, *Chem. Ber.*, **106**, 3345 (1973).
(114) Diazomethane + alkenes and alkynes: J. Bastide, N. El Ghandour, and O. Henri-Rousseau, *Tetrahedron Lett.*, 4225 (1972).
(115) P. A. S. Smith and B. B. Brown, *J. Am. Chem. Soc.*, **73**, 2438 (1951).
(116) A. Schmidt, *Chem. Ber.*, **99**, 2976 (1966).
(117) P. I. Paetzold, *Z. Anorg. Allg. Chem.*, **326**, 47 (1963); P. I. Paetzold, M. Gayoso, and K. Dehnicke, *Chem. Ber.*, **98**, 1173 (1965); N. Wiberg and K. H. Schmid, *ibid.*, **100**, 741 (1967); *Angew. Chem., Int. Ed. Engl.*, **6**, 1002 (1967).
(118) Review: G. L'abbé, *Ind. Chim. Belge*, **34**, 519 (1969).
(119) I. A. D'yakonov, *J. Gen. Chem. USSR (Engl. Transl.)*, **17**, 67 (1947); *Chem. Abstr.*, **42**, 902*h* (1948).
(120) F. Piozzi, A. Umani-Ronchi, and L. Merlini, *Gazz. Chim. Ital.*, **95**, 814 (1965).
(121) S. H. Groen and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **80**, 879 (1961).
(122) Review: R. Huisgen, *Angew. Chem.*, **67**, 439, 453 (1955).
(123) G. H. Coleman, H. Gilman, C. E. Acams, and P. E. Pratt, *J. Org. Chem.*, **3**, 102 (1938).
(124) G. Wittig and W. Haag, *Chem. Ber.*, **88**, 1654 (1955).
(125) E. Ciganek, *J. Org. Chem.*, **30**, 4198 (1965).

(126) W. E. Parham, C. Serres, and P. R. O'Connor, *J. Am. Chem. Soc.*, **80,** 588 (1958); W. E. Parham, H. G. Braxton, and P. R. O'Connor, *J. Org. Chem.*, **26,** 1805 (1961).
(127) W. E. Parham, F. D. Blake, and D. R. Theissen, *J. Org. Chem.*, **27,** 2415 (1962); D. C. Dittmer and R. Glassmann, *ibid.*, **35,** 999 (1970).
(128) S. D. Andrews, A. C. Day, and A. N. McDonald, *J. Chem. Soc. C,* 787 (1969). β-*tert*-Butylacrylic ester produces only the anomalous adduct.
(129) K. v. Auwers and W. Cauer, *Justus Liebigs Ann. Chem.*, **470,** 284, 302 (1929); E. v. Auwers and O. Ungemach, *Ber. Dtsch. Chem. Ges.*, **66,** 1198 (1933).
(130) P. Eberhard and R. Huisgen, *Tetrahedron Lett.*, 4337 (1971). Methyl *cis*-cinnamate produces **56** and **57** in a 7:3 ratio.
(131) E. Buchner and M. Fritsch, *Ber. Dtsch. Chem. Ges.*, **26,** 256 (1893); E. Buchner and W. Behaghel, *ibid.*, **27,** 869, 3247 (1894); K. v. Auwers and O. Ungemach, *ibid.*, **66,** 1205 (1933); R. Hüttel, J. Riedl, H. Martin, and K. Franke, *Chem. Ber.*, **93,** 1425 (1960); A. C. Day and R. N. Inwood, *J. Chem. Soc. C,* 1065 (1969); J. Bastide and L. Lematre, *Bull. Soc. Chim. Fr.*, 3543 (1970); L. Aspart-Pascot and J. Bastide, *C. R. Acad. Sci.*, 1772 (1971).
(132) E. Müller, P. Kästner, R. Beutler, W. Rundel, H. Suhr, and B. Zech, *Justus Liebigs Ann. Chem.*, **713,** 87 (1968); E. Müller, R. Beutler, and B. Zeeh, *ibid.*, **719,** 72 (1968).
(133) R. Kreher and G. Jäger, *Z. Naturforsch. B,* **19,** 657 (1964).
(134) W. Wislicenus, *Ber. Dtsch. Chem. Ges.*, **25,** 2084 (1892). Evidence by $^{15}N$ labeling techniques: K. Clusius and H. Schuhmacher, *Helv. Chim. Acta,* **41,** 792 (1958).
(135) H. Staudinger and E. Hauser, *Helv. Chim. Acta,* **4,** 861 (1931).
(136) Review: C. Grundmann and P. Grünanger, "The Nitrile Oxides", Springer-Verlag, West Berlin, 1971, pp 143–169, 159, 176.
(137) P. Grünanger and M. R. Langella, *Atti. Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.*, **36,** 387 (1964); C. Grundmann and H.-D. Frommeld, *J. Org. Chem.*, **30,** 2077 (1965).
(138) T. Bacchetti and A. Alemagna, *Rend. Ist. Lomb. Sci. Lett. Cl. Sci. Mat. Nat.*, **91,** 574 (1957).
(139) Review: J. Hamer and A. Macaluso, *Chem. Rev.*, **64,** 473 (1964).
(140) K. Fukui, T. Yonezawa, C. Nagata, and H. Shingu, *J. Chem. Phys.*, **22,** 1433 (1964). Review: K. Fukui, *Fortschr. Chem. Forsch.*, **15,** 1 (1970).
(141) J. Feuer, W. C. Herndon, and L. H. Hall, *Tetrahedron,* **24,** 2475 (1968); O. Eisenstein, J. M. Lefour, and N. T. Anh, *Chem. Commun.*, 969 (1971); T. Inukai, H. Sato, and T. Kojima, *Bull. Chem. Soc. Jpn.*, **45,** 891 (1972); K. N. Houk, *J. Am. Chem. Soc.*, **95,** 4092 (1973).
(142) J. Bastide, O. Henri-Rousseau, and L. Aspart-Pascot, *Tetrahedron,* **30,** 3355 (1974).
(143) J. Bastide, N. El Ghandour, and O. Henri-Rousseau, *Bull. Soc. Chim. Fr.*, 2290 (1973).
(144) J. Bastide and O. Henri-Rousseau, *Bull. Soc. Chim. Fr.*, 2294 (1973).
(145) K. N. Houk, *J. Am. Chem. Soc.*, **94,** 8953 (1972).
(146) K. N. Houk, J. Sims, R. E. Duke, R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, **95,** 7287 (1973).
(147) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Am. Chem. Soc.*, **95,** 7301 (1973).
(148) O. Henri-Rousseau, Ph.D. Thesis, Université du Languedoc, 1974. I wish to express my thanks to Dr. J. Bastide, Perpignan, France, for discussions.
(149) R. Huisgen, R. Sustmann, and G. Wallbiilich, *Chem. Ber.*, **100,** 1786 (1967).
(150) J. S. Clovis, A. Eckell, R. Huisgen, R. Sustmann, G. Wallbiilich, and V. Weberndörfer, *Chem. Ber.*, **100,** 1593 (1967).
(151) R. Huisgen, H. Knupfer, R. Sustmann, G. Wallbillich, and V. Weberndörfer, *Chem. Ber.*, **100,** 1580 (1967).
(152) G. Stagno d'Alcontres and P. Grünanger, *Gazz. Chim. Ital.*, **80,** 831 (1950); G. Stagno d'Alcontres, *ibid.*, **82,** 627 (1952).
(153) G. Bianchetti, D. Pocar, and P. Dalla Croce, *Gazz. Chim. Ital.*, **93,** 1714, 1726 (1963); M. E. Kuehne, S. J. Weaver, and P. Franz, *J. Org. Chem.*, **29,** 1582 (1964).
(154) K. Bast, M. Christl, R. Huisgen, W. Mack, and R. Sustmann, *Chem. Ber.*, **106,** 3258 (1973).
(155) M. Christl and R. Huisgen, *Tetrahedron Lett.*, 5209 (1968); M. Christl, R. Huisgen, and R. Sustmann, *Chem. Ber.*, **106,** 3275 (1973).
(156) M. Christl and R. Huisgen, *Chem. Ber.*, **106,** 3345 (1973).
(157) R. Huisgen, R. Grashey, H. Hauck, and H. Seidl, *Chem. Ber.*, **101,** 2043, 2548 (1968).
(158) R. Huisgen, R. Grashey, H. Seidl, and H. Hauck, *Chem. Ber.*, **101,** 2559 (1968).
(159) O. Tsuge, M. Tashiro, and Y. Nishihara, *Tetrahedron Lett.*, 3769 (1967); *J. Chem. Soc. Jpn.*, **92,** 72 (1971).
(160) R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *Chem. Ber.*, **101,** 2568 (1968). The same orientation was observed in the additions of methylated pyrroline *N*-oxides to ethyl acrylate: G. R. Delpierre and M. Lamchen, *J. Chem. Soc.*, 4693 (1963).
(161) J. Sims and K. N. Houk, *J. Am. Chem. Soc.*, **95,** 5798 (1973).
(162) H. Seidl, R. Huisgen, and R. Knorr, *Chem. Ber.*, **102,** 904 (1969).
(163) W. R. Dolbier and S. Hong Dai, *Tetrahedron Lett.*, 4645 (1970).
(164) W. J. Linn and R. E. Benson, *J. Am. Chem. Soc.*, **87,** 3657 (1965).
(165) W. F. Baine and R. I. Snyder, *Tetrahedron Lett.*, 2263 (1970).
(166) B. M. Benjamin and C. J. Collins, *J. Am. Chem. Soc.*, **95,** 6145 (1973).
(167) S. Morrocchi, A. Ricca, A. Zanarotti, G. Bianchi, R. Gandolfi, and P. Grünanger, *Tetrahedron Lett.*, 3329 (1969).
(168) S. Morrocchi, A. Ricca, A. Selva, and A. Zanarotti, *Rend. Accad. Naz. Lincei,* **48,** 231 (1970); *Chem. Abstr.*, **73,** 98158 (1970).
(169) A. Battaglia and A. Dondoni, *Tetrahedron Lett.*, 1211 (1970).
(170) S. Morrocchi, A. Ricca, and A. Zanarotti, *Tetrahedron Lett.*, 3215 (1970).
(171) P. Beltrame, P. Sartirana, and C. Vintani, *J. Chem. Soc. B,* 814 (1971).
(172) A. Dondoni and G. Barbaro, *J. Chem. Soc., Perkin Trans. 2,* 1591 (1974).
(173) Professor P. Beltrame, Università di Cagliari, private communication.
(174) $k_H/k_D$ = 9.9, 5.1, and 6.7 have been reported for reactions of the acetoxy radical with toluene, ethylbenzene, and diphenylmethane: K. B. Wiberg, *Chem. Rev.*, **55,** 713 (1955). The reaction of cumene with the cumylperoxy or the *tert*-butylperoxy radical showed $k_H/k_D$ = 8.0 and 20, respectively: J. A. Howard, K. U. Ingold, and M. Symonds, *Can. J. Chem.*, **46,** 1017 (1968).
(175) P. Caramella, R. Huisgen, and B. Schmolke, *J. Am. Chem. Soc.*, **96,** 2997, 2999 (1973).
(176) H. M. Frey, *Adv. Phys. Org. Chem.*, **4,** 147 (1966); M. R. Willcott and V. H. Cargle, *J. Am. Chem. Soc.*, **89,** 723 (1967); P. H. Mazzocchi and Tamburin, *ibid.*, **92,** 7220 (1970).
(177) R. Huisgen, R. Sustmann, and K. Bunge, *Chem. Ber.*, **105,** 1324 (1972).
(178) B. Schmolke, Ph.D. Thesis, University of Munich, 1973, p 78; experiments of J. Mulzer, 1974.
(179) The somewhat larger share of **98** from **101** than from **100** stems from the participation of a mechanism with double rotation of the trimethylene intermediates.[180]
(180) Experiments of K. H. Schröder, University of Munich, 1974.
(181) O. E. Polansky and P. Schuster, *Tetrahedron Lett.*, 2019 (1964).
(182) T. Minato, S. Yamabe, S. Inagaki, H. Fujimoto, and K. Fukui, *Bull. Chem. Soc. Jpn.*, **47,** 1619 (1974).
(183) G. Leroy and M. Sana, *Tetrahedron,* **31,** 2091 (1975).

# Halocyclopropanes

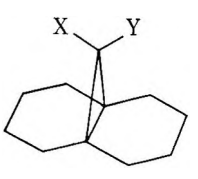
D. B. Ledlie,*[1] T. Swan, J. Pile, and L. Bowers

*Department of Chemistry, Middlebury College, Middlebury, Vermont 05753*

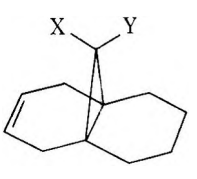
*Received June 27, 1975*

The chemistry of the tricyclic monobromides **4, 5, 6,** and **7** has been examined. Evidence is presented which implicates a partially opened cyclopropyl cation as a reaction intermediate.

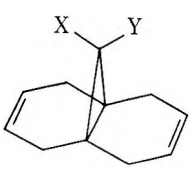
The chemical properties of various tricyclic cyclopropyl halides have been of interest to us and several others for some time now.[2] We recently reported on the silver ion assisted solvolysis of the *gem*-dibromides **1, 2,** and **3**.[3] A continued interest in this area led us to examine the corresponding monobromo compounds **4, 5, 6,** and **7**. The chemistry of these monobromo derivatives differed significantly from that observed for the aforementioned dibromo systems. We now wish to report on these differences, and we attempt to offer reasonable explanations as to their origins.




1, X = Y = Br
4, X = H; Y = Br

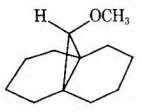
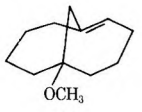
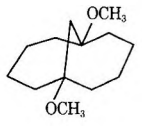
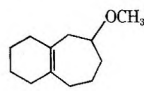
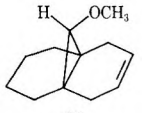
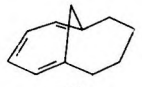
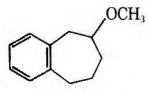
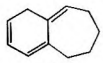
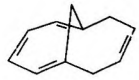
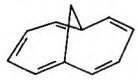



2, X = Y = Br
5, X = H; Y = Br
6, X = Br; Y = H




3, X = Y = Br
7, X = H; Y = Br

Table I
Products Obtained in the Silver Ion Assisted Solvolysis of 4, 5, 6, and 7

| Compd | Products[a] | | | |
|---|---|---|---|---|
| 4[b] |  8 (18, 18) |  9 (10, 24) |  10 (2, 20) |  11 (41, 8) |
| 5 |  12 (12) |  13 (46) |  14 (19) | |
| 6 |  15 (12) | 13 (73) | 14 (2–3) | |
| 7[c] |  16 (3–4) |  17 (2–4) |  18 (2–3) | |

[a] Absolute yields reprinted in parentheses. Reactions were carried out at reflux unless noted otherwise. [b] Yields reported are for reflux and room temperature runs, respectively. [c] Reaction carried out at 100°C. The remaining nonvolatile material consists of intractable substances.[2]

## Results

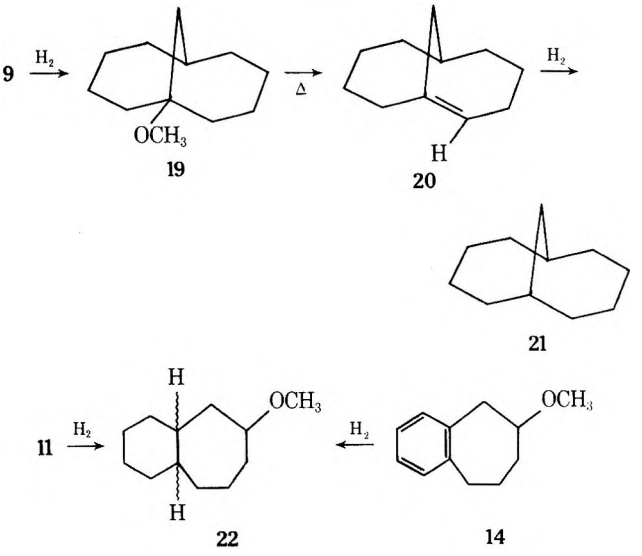
Synthesis of the requisite monobromides was readily accomplished by treating the corresponding dibromides with tri-*n*-butyltin hydride. Yields in all cases were between 50 and 60%. The structure of **4** was assigned based on a correct elemental analysis and an NMR spectrum which exhibits a sharp singlet at 2.94 ppm (1 proton). Monobromides **5, 6,** and **7** were identical in every respect with those reported by Paquette et al.[4] Isomers **5** and **6** were separated via column chromatography. Product studies were carried out using the same techniques reported previously.[3] Our results are contained in Table I.

The structures of **8** and **10** were assigned on the basis of elemental analysis and spectral data (see Experimental Section). It should be noted that the $^{13}C$ NMR spectrum of **10** has five lines. This is consistent with the symmetry of the assigned structure and unambiguously rules out several mechanistically feasible isomers as possible structures.

The NMR spectrum of **9** exhibits absorption at 5.28 (triplet, $J$ = 6 Hz, 1 proton), 3.03 (singlet, 3 protons), 2.66 (doublet, $J$ = 12 Hz, 1 proton), and 0.80–2.35 ppm (complex, 15 protons). This is certainly consistent with the structure assigned; the doublet at 2.66 ppm is characteristic of bicyclic systems of this type and can be assigned to the proton on the methylene bridge which is anti to the olefinic linkage.[2,5a] Unambiguous proof of structure, however, was based on the synthetic sequence outlined in Scheme I.

A few comments concerning this sequence are perhaps necessary. The saturated bicyclic ether **19** had an NMR spectrum very similar to that of **10**. A sample of the material assumed to be **19** was collected via gas chromatography for elemental analysis. Surprisingly, it analyzed correctly for $C_{11}H_{18}$. The NMR absorption of the collected material shows absorption at 5.48 (triplet, $J$ = 6 Hz, 1 proton), 2.73 (doublet, $J$ = 12 Hz, 1 proton), and 2.53–1.06 ppm (complex, 16 protons). The triplet at 5.48 ppm and the doublet at 2.73 pm lend credence to the assigned structure **20**. Reduction of **20** afforded **21**, which was identical in every respect with authentic material. These facts we feel adequately support the structure assigned to **9**.

Scheme I




Scheme I also outlines the structure proof of **11**. Catalytic reduction of **11** afforded a mixture of four isomeric saturated ethers which were identical in every respect with those obtained from the reduction of **14**.[5b] Both structures **13** and **14** had infrared and NMR spectra identical with those of authentic material. The identity of **12** was confirmed by its reduction to **8**. The stereochemistry of the methoxyl group has been tentatively assigned. Comments as to this point will be made later.

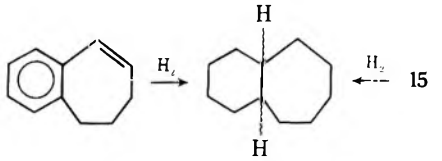
The nature of the bicyclic carbon skeleton of **15** was ascertained as outlined below.

Reduction of **23** afforded two isomeric hydrocarbons **24** which were identical in every respect with those obtained from the reduction of **15**.[7] The placement of the double

Table II
Rate Constants and Activation Parameters for the Silver Ion Assisted Solvolysis of 4, 5, 6, and 7

| Compd | Temp, °C[a] | $k$, l. mol$^{-1}$ sec$^{-1}$ | $\Delta H^{\ddagger}$, kcal mol$^{-1}$ | $\Delta S^{\ddagger}$, eu | $k^{25}_{rel}$ |
|---|---|---|---|---|---|
| 4 | 24.4 | $5.86 \times 10^{-4}$ (±0.07) | 21.6 | −0.8 | $2 \times 10^{5}$ |
| | 39.6 | $3.63 \times 10^{-3}$ (±0.03) | | | |
| | 25.0 | $6.32 \times 10^{-4}$ [b] | | | |
| | 100.0 | 1.20 [b] | | | |
| 5 | 76.0 | $5.41 \times 10^{-4}$ (±0.08) | 20.4 | −15.3 | $1 \times 10^{3}$ |
| | 89.5 | $1.68 \times 10^{-3}$ (±0.02) | | | |
| | 25.0 | $3.01 \times 10^{-6}$ [b] | | | |
| | 100.0 | $3.83 \times 10^{-3}$ [b] | | | |
| 6 | 48.2 | $1.34 \times 10^{-4}$ (±0.02) | 21.4 | −9.8 | $3 \times 10^{3}$ |
| | 65.4 | $7.76 \times 10^{-4}$ (±0.12) | | | |
| | 25.0 | $9.14 \times 10^{-6}$ [b] | | | |
| | 100.0 | $1.64 \times 10^{-2}$ [b] | | | |
| 7 | 124.8 | $5.03 \times 10^{-4}$ (±0.06) | 27.6 | −4.7 | 1 |
| | 140.0 | $1.89 \times 10^{-3}$ (±0.02) | | | |
| | 25.0 | $3.12 \times 10^{-9}$ [b] | | | |
| | 100.0 | $4.62 \times 10^{-5}$ [b] | | | |

[a] At least two runs were made at each temperature. [b] This is an extrapolated value.




23 24

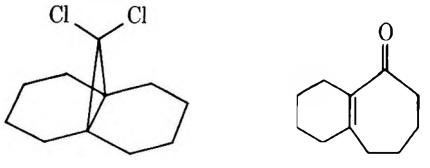
bonds within **15** was based on its NMR spectrum.[8] Complex absorption was observed between 1.40 and 1.75 (4 protons) and 1.75–2.50 ppm (6 protons). Absorption in the olefinic region (complex, 5.05–6.35 ppm) accounted for four protons. The structures of **16**, **17**, and **18** have been previously assigned.[2]

Rate studies were carried out as previously described.[3] Rate data as well as activation parameters for both mono- and dibromides are contained in Tables II and III. We have also solvolyzed the bicyclic dibromides **27** and **28** (see Table IV).


27 28

## Discussion

We observe that the products of solvolyses of the monobromo derivatives **4**, **5**, **6**, and **7** are strikingly different from those obtained in the silver ion assisted solvolyses of **1**, **2**, and **3**. Warner has recently performed a labeling experiment with the *gem*-dihalide **29**.[9] His results indicate




29 30

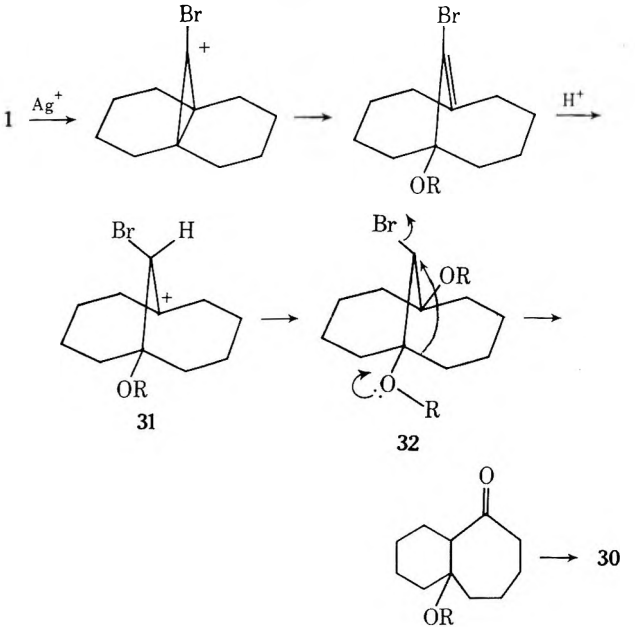
that the bicyclic enone **30** does not arise via the alkyl shift mechanism postulated initially by us and other workers.[2,3] Rather it is derived from the intermediate **31**, which after capture by solvent then undergoes an alkyl shift (Scheme II). This mechanistic scheme clearly explains the lack of bicyclic product of the general type **33** or **34** in the solvolysis of the monobromides **4–7**. According to our earlier mechanistic suggestions, products of this type would have been expected; however, they cannot form if a mechanism as outlined in Scheme II is in operation. One would thus expect "cyclopropyl" trapping products and bicyclic products derived directly from a bridgehead double bond species. This is exactly what we have observed.

Table III
Rate Constants at 25° for the Silver Ion Assisted Solvolysis of 1, 2, and 3[a]

| Compd | $k$, l. mol$^{-1}$ sec$^{-1}$ | $k^{25}_{rel}$ |
|---|---|---|
| 1 | $1.87 \times 10^{-2}$ | $3 \times 10^{6}$ |
| 2 | $4.83 \times 10^{-4}$ | $7 \times 10^{4}$ |
| 3 | $6.97 \times 10^{-9}$ | 1 |

[a] These are extrapolated values.

Scheme II





33 34

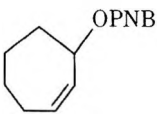
Whether or not a full-fledged cyclopropyl cation is an intermediate in the solvolysis of these tricyclic cyclopropyl systems has been briefly discussed.[3] We offer here evidence which seems to point toward a partially opened species.[10]

Table IV
Rate Constants and Activation Parameters for the Silver Ion Assisted Solvolysis of 27 and 28

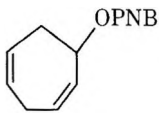
| Compd | Temp, °C[a] | $k$, l. mol$^{-1}$ sec$^{-1}$ | $\Delta H^{\ddagger}$, kcal mol$^{-1}$ | $\Delta S^{\ddagger}$, eu | $k^{25}_{rel}$ |
|---|---|---|---|---|---|
| 27 | 86.7 | $8.34 \times 10^{-4}$ (±0.10) | 24.3 | −5.5 | 24 |
| | 100.5 | $3.04 \times 10^{-3}$ (±0.12) | | | |
| | 25.0 | $6.11 \times 10^{-7}$[b] | | | |
| | 100.0 | $2.90 \times 10^{-3}$[b] | | | |
| 28 | 120.0 | $3.12 \times 10^{-4}$ (±0.15) | 22.4 | −18.26 | 1 |
| | 136.0 | $1.03 \times 10^{-3}$ (±0.08) | | | |
| | 25.0 | $2.55 \times 10^{-8}$[b] | | | |
| | 100.0 | $6.29 \times 10^{-5}$[b] | | | |

[a] At least two runs were made at each temperature. [b] This is an extrapolated value.

If one compares the relative rates of solvolysis of the bicyclic dibromides **27** and **28** at 25° a rate ratio ($k_{27}/k_{28}$) of approximately 24 is observed, while the tricyclic dibromides **1** and **2** give a ratio ($k_1/k_2$) of 39. The difference in free energy of activation between the members of each pair is for all practical purposes identical. Now, the mechanism of solvolysis of the bicyclic system **27** is well documented, i.e., concerted ionization to a cis allyl cation and subsequent capture by solvent.[12] The mechanism of solvolysis of **28** is not well documented, however. It could be argued that rather than form an antiaromatic allyl cation, **28** would ionize to form a cyclopropyl cation.[13] However, Gassman has demonstrated that the allyl *p*-nitrobenzoates **35** and **36** sol-




35




36

volyze at essentially the same rates ($k_{35}/k_{36}$ = 1.9 at 120°).[14] The additional double bond in **36** apparently does not interact sufficiently with the allyl ribbon to impart any degree of antiaromaticity. The effect observed is probably purely an inductive one (slightly destabilizing). It would seem reasonable then that both **27** and **28** solvolyze via similar mechanisms and that the difference in relative rates between the two pairs can be attributed for the most part to the electron-withdrawing effect of silver ion which can complex with the double bond in **28**.[3]

If one assumes that both **1** and **2** ionize initially to form a cyclopropyl cation, then one would expect that the difference in energy of activation between **1** and **2** would be less than the difference observed between **27** and **28** since the site of positive charge in the ion formed from **2** is further removed from the complexed silver ion than in the allyl ion formed from **28**.[15] The fact that the observed relative rates are nearly identical then implies that there is some degree of ring opening (i.e., some allyl character) at the transition state in the solvolysis of **1** and **2**. An increase in strain energy might well accompany this partial opening and be of a greater magnitude for **2** than **1**.

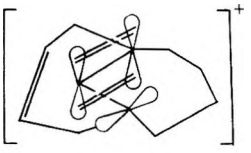
That a true cyclopropyl cation is probably not a viable intermediate in the solvolysis of the tricyclic monobromides is exemplified by the behavior of the unsaturated isomeric monobromides **5** and **6**. Molecular mechanics were carried out on the systems in question (see Table V).[16]

These calculations indicate that there is a difference in ground state energy between **5** and **6** of about 3.5 kcal/mol (**6** being more stable than **5**). The method of calculation in all probability exaggerates this difference.[17] Our rate data (25°) put an upper limit on this value of approximately 2.5 kcal/mol (compare **1** vs. **2**, **4** vs. **6**, and **27** vs. **28**). This does

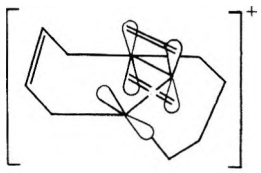
Table V
Calculated Strain Energies for Tricyclic Bromocyclopropanes

| Compd | Strain, kcal mol$^{-1}$ | Compd | Strain, kcal mol$^{-1}$ |
|---|---|---|---|
| 1 | 120.30 | 5 | 113.18 |
| 2 | 117.26 | 6 | 109.71 |
| 3 | 108.50 | 7 | 104.72 |
| 4 | 112.32 | | |

not take into consideration the destabilization of the transition state afforded the unsaturated ions by the complexed silver ion. A more reasonable estimate (which takes the effect of the silver ion into consideration) of the difference in ground state strain between **5** and **6** would be on the order of 1.0–1.5 kcal/mol. Thus, one would expect that isomer **5** would solvolyze some ten times faster than **6** if the reaction proceeded via a common intermediate, namely, a cyclopropyl cation. In fact the observed reactivity is reversed, i.e., **6** solvolyzes approximately three times faster than **5**. The kinetic evidence thus seems to eliminate a common intermediate for the two reactions. The product data (Table I) are also consistent with this hypothesis. We would like to propose that both **5** and **6** begin to open in a disrotatory fashion, the direction of which depends on the stereochemistry of the leaving groups and thus should be different for each isomer. Thus, if taken to the limit, **5** would afford **37** while **6** should yield **38**. We stress that these are limiting cases

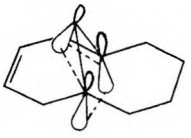


37



38

and that ion **37** has a greater amount of inherent strain owing to the presence of the double bond in the same ring as the trans allyl ion. We suggest, then, that **5** on solvolysis yields an ion having less allyl character than either **37** or **38**, i.e., it has more cyclopropyl character and is represented by structure **39**. This would nicely explain the lack of



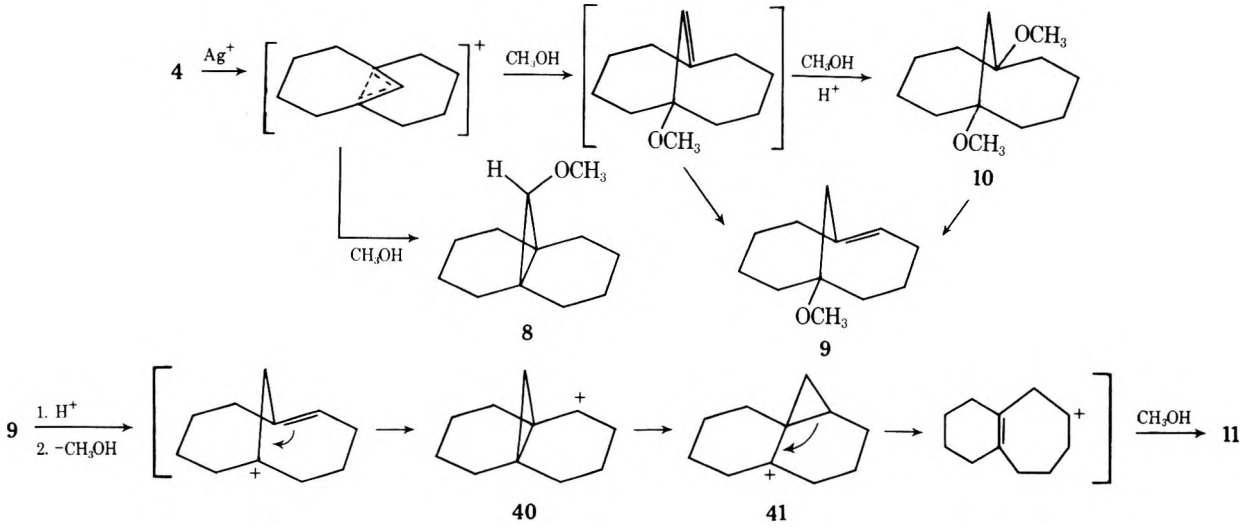
39

any cyclopropyl trapping product observed in the solvolysis of **6**.

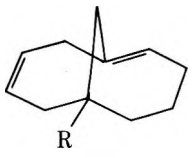
The product ratios obtained in the solvolysis of **4** are temperature dependent (see Table I). While the absolute yield of **8** remains unchanged, at the higher temperature **11** is formed at the expense of both **9** and **10**. We have demonstrated that both **9** and **10** are converted quantitatively into **11** when refluxed in methanol containing a trace of nitric acid. It is postulated, then, that **9** and **10** are initially formed from a partially opened ion and then rearrange to **11** under the condition of the reaction (see Scheme III).[18]

The major product obtained in the solvolysis of both **5** and **6** is the bicyclic conjugated triene **13**. However, the yield of the material obtained from **6** is almost 30% higher than that obtained from **5** (Table I). We have stated previously that the ion formed from **6**, namely **38**, in all probability has a greater degree of allyl character than the ion (**39**) formed from **5**. It would seem that the conformation of **38** is well suited such that either elimination of a proton or rearrangement of the bridgehead double bond will prefer-

Scheme III

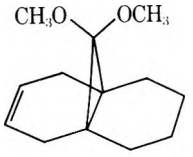



entially place a double bond in the ring already containing unsaturation. We emphasize that we are not sure as to the timing of these steps. Monobromide **5** tends to open in the opposite sense and not to as great an extent. The conformation of **39** would favor the formation of **42** which would account for the higher yield of **14** obtained from **5**, for **42** is an intermediate in the formation of **14**.[20]




42

The stereochemistry of the tricyclic ether **12** has been tentatively assigned. The location of the methoxyl absorption in its NMR spectrum indicates that the methoxyl is syn to the double bond. The methoxyl absorbtions in **44**




44

occur at 3.17 and 3.24 ppm, while in **8** and **12** methoxyl absorbs at 3.15 and 3.25 ppm, respectively. If the stereochemical assignment is correct, the behavior of ion **39** is quite different from that of the bicyclic ion reported by Schleyer, Schollkopf, et al.[11]

The products **17** and **18** isolated in the solvolysis of **7** can also be rationalized in terms of a partially opened species similar to **39**. The origin of the naphthalene has been discussed previously.[3]

## Experimental Section[22]

**11-Bromotricyclo[4.4.1.0$^{1,6}$]undecane (4).** To a refluxing solution of 4.7 g (0.015 mol) of 11,11-dibromotricyclo[4.4.1.0$^{1,6}$]undecane and a trace of AIBN was added with stirring and under a nitrogen atmosphere 4.4 g (0.015 mol) of tri-*n*-butyltin hydride dissolved in an equal volume of ether. After addition of the hydride the reaction mixture was refluxed for 5 hr and then stirred at room temperature for 18 hr. Distillation of the crude reaction mixture followed by elution chromatography and redistillation afforded 1.7 g (50%) of the desired material. The NMR of **4** exhibited absorption at 2.97 (singlet, 1 proton) and 0.97–2.18 ppm (complex absorption, 16 protons).

Anal. Calcd for $C_{11}H_{17}Br$: C, 57.65; H, 7.48; Br, 34.87. Found: C, 57.78; H, 7.54; Br, 34.67.

***anti*- and *syn*-11-Bromotricyclo[4.4.1.0$^{1,6}$]undec-3-ene (5 and 6).** The procedure described for the synthesis of **4** was employed. A mixture of the two isomers was obtained which was separated via elution chromatography (silica gel eluted with ligroin). A yield of 3.24 g (20%) of the anti isomer **5** [bp 74–75° (0.6 mm)] and 1.69 g (10%) of the syn isomer **6** [bp 77–78° (0.5 mm)] was obtained. Spectral properties of the above isomers were in complete agreement with those reported by Paquette et al.[4]

**11-Bromotricyclo[4.4.1.0$^{1,6}$]undeca-3-diene (7).** The material was prepared according to the procedure previously reported.[2]

**Silver Ion Assisted Solvolysis of 4. A. At Reflux.** Silver nitrate (0.738 g, 4.36 mmol) and **4** (0.060 g, 0.218 mmol) dissolved in 25 ml of methanol were refluxed for 20 hr. After the usual work-up the crude reaction mixture was subjected to gas chromatographic analysis on a 3 ft × 0.25 in. 10% Carbowax 20M column.[3] Four major components were shown to be present and all were collected. The NMR spectrum of **8** exhibited absorption at 3.15 (singlet, 3 protons), 2.50 (singlet, 1 proton), and 2.05–0.68 ppm (complex absorption, 16 protons).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.11; H, 11.28.

Compound **11** exhibited absorption in the NMR at 0.95–2.47 (complex absorption, 16 protons), 2.70 ppm (complex multiplet, 1 proton), and 3.12 ppm (singlet, 3 protons).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.75; H, 11.02.

The third component **10** absorbs in the NMR at 1.55 (broad singlet, 16 protons), 1.90 (singlet, 2 protons), and 2.97 ppm (singlet, 6 protons).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.27; H, 11.18.

In addition a $^{13}C$ NMR spectrum of **10** exhibits the expected five-line spectrum: 41.5, 52.3, 61.6, 61.9, and 88.2 ppm relative to $Me_4Si$.

The NMR of the fourth component (**9**) is reported in the text.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.77; H, 11.27.

In runs in which yields were determined an internal standard (β-methylnaphthalene) was added directly to the reaction mixture after all starting material had been consumed. The reaction mixture was then analyzed via VPC without further work-up. For a tabulation of yields see text.

**B. At Room Temperature.** The same procedures were followed as described in A. The reaction mixture was stirred for 20 hr at room temperature and then analyzed.

**Reduction of 9.** A mixture of 50 mg of **9** and approximately 0.1 g of 5% Rh on alumina in ethanol was stirred under a hydrogen atmosphere until thin layer chromatography indicated that all the starting material had been consumed. The reaction mixture was analyzed via gas chromatography on a 3 ft × 0.25 in. 10% Carbowax 20M column. Only one volatile component was shown to be present. The material was collected and its NMR measured. The compound absorbed at 0.28–2.22 (complex absorption with a broad singlet at 1.53 ppm and a smaller one at 1.88 ppm, 19 protons) and 3.02 ppm (singlet, 3 protons).

**Treatment of 9 with Acid.** Compound **9** (40 mg, 0.22 mmol)

and 2 drops of concentrated nitric acid in 25 ml of methanol were refluxed for 12 hr. After the usual work-up the crude product was analyzed via VPC. One volatile product was in evidence. It was collected and its infrared spectrum was measured. It was identical with that of **11**.

**Treatment of 10 with Acid.** Compound **10** (60 mg, 0.33 mmol) and 2 drops of concentrated nitric acid in 25 ml of methanol were refluxed for 12 hr. After the usual work-up the crude product was analyzed via VPC. A single volatile product was shown to be present. Its infrared spectrum was identical with that of **11**.

**Reduction of 11.** Compound **11** (50 mg, 0.27 mmol) was reduced in a manner identical with that described for the reduction of **9**. Gas chromatographic analysis of the crude product showed four major components. These were collected and their infrared spectra were measured. These were identical with the products obtained in the reduction of **14**. An NMR of the mixture showed no olefinic absorption.

**Synthesis of Benzocyclohepten-2-ol.** The compound was synthesized according to the method of Huisgen et al.[7] It was identical in all respects with the reported material.

**Synthesis of 14.** 1,2-Benzocyclohepten-4-ol (0.1 g, 0.617 mmol) in 5 ml of anhydrous ether was added dropwise with stirring and under a nitrogen atmosphere to a suspension of 0.044 g (1.8 mmol) of sodium hydride. The resulting mixture was stirred at room temperature for 1.5 hr. Methyl iodide (2.5 g, 6.0 mmol) was then added and the reaction mixture was stirred for 48 hr. After the usual work-up the product was subjected to VPC analysis. One major component was in evidence. It was collected and its NMR spectrum exhibited absorption at 1.07–1.90 (complex absorption with a broad multiplet centered at 1.70 ppm and complex absorption between 2.47 and 3.17 ppm, 9 protons), 3.23 (singlet, 3 protons), and 6.93 ppm (singlet, 4 protons).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.02. Found: C, 81.54; H, 9.02.

**Silver Ion Assisted Solvolysis of 5.** The reaction was carried out in exactly the same manner as described for the solvolysis of **4**. Three major volatile products were isolated: **12**, **13**, and **14**. The NMR spectrum of **12** exhibited absorption at 1.08–2.42 (complex, 12 protons), 2.83 (singlet, 1 proton), 3.25 (singlet, 3 protons), and 5.40 ppm (broad singlet, 2 protons). The infrared and NMR spectra of **13** were identical with those of authentic material.[5] The infrared spectrum of **14** was identical with that of authentic material. Yields were determined as described previously. Biphenyl was employed as the internal standard. See text for yield tabulations.

**Silver Ion Assisted Solvolysis of 6.** The reaction was carried out in the same manner as reported for the solvolysis of **5**. Yields were determined via gas chromatography and are listed in the text. The proof of structure for **15** is discussed in the text.

**Reduction of 15.** Compound **15** was reduced at atmospheric pressure ($H_2$, $PtO_2$, EtOH). The usual work-up yielded **24** which was identical with material obtained in the catalytic reduction of **23**.

**Silver Ion Assisted Solvolysis of 7.** Details concerning the solvolysis of **7** are contained in a previous publication.[2]

**Kinetic Procedures.** Rate constants and activation parameters were determined as previously described.[2]

**Catalytic Hydrogenation of 12.** Compound **12** was reduced at atmospheric pressure ($H_2$, 5% Rh/alumina, EtOH). The usual work-up afforded material whose infrared spectrum was identical with that of **8**.

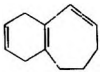
**Synthesis of 27 and 28.** Both **27** and **28** were synthesized in a manner analogous to that employed for **1**, **2**, and **3**.[3] The properties of the materials obtained were identical with those reported earlier.[23,24]

**Acknowledgment.** We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

**Registry No.**—**1**, 20564-71-0; **2**, 38760-88-2; **3**, 4578-96-5; **4**, 57379-33-6; **5**, 52910-32-4; **6**, 52949-67-4; **7**, 4622-37-1; **8**, 57346-27-7; **9**, 57346-28-8; **10**, 57346-29-9; **11**, 57346-30-2; **12**, 57346-31-3; **14**, 57346-32-4; **15**, 57346-33-5; **27**, 2415-79-4; **28**, 6802-78-4; tri-*n*-butyltin hydride, 688-73-3; silver nitrate, 7761-88-8; 1,2-benzocyclohepten-4-ol, 13249-77-9.

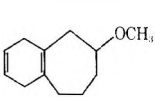
## References and Notes

(1) Address correspondence to Department of Chemistry, University of Vermont, Burlington, Vt. 05401.
(2) D. B. Ledlie and L. Bowers, *J. Org. Chem.*, **40**, 792 (1975), and references cited therein.
(3) D. B. Ledlie, J. Knetzer, and A. Gitterman, *J. Org. Chem.*, **39**, 708 (1974).
(4) L. A. Paquette, W. E. Heyd, and G. L. Thompson, *J. Am. Chem. Soc.*, **96**, 3177 (1974).
(5) (a) E. Vogel, W. Wiedemann, H. D. Roth, J. Eimer, and H. Gunther, *Justus Liebigs Ann. Chem.*, **759**, 1 (1972). (b) Compound **14** was synthesized via a modified Williamson ether synthesis from the corresponding alcohol.[6] The alcohol was synthesized according to the procedure of Huisgen et al.[7]
(6) W. G. Dauben and G. H. Berzin, *J. Am. Chem. Soc.*, **85**, 468 (1963).
(7) R. Huisgen, E. Ravenbusch, G. Seidl, and I. Wimmer, *Justus Liebigs Ann. Chem.*, **671**, 41 (1964).
(8) Another reasonable structure would be the isomeric triene **26**; however,



26

the ratio of allylic to nonallylic protons would be 4:1. We feel that structure **15** is the only one which fits the data at hand. It is, however, puzzling as to why **15** does not aromatize under the conditions of the reaction.
(9) P. Warner and S. Lu, *J. Am. Chem. Soc.*, **97**, 2536 (1975).
(10) A partially opened cyclopropyl cation has been postulated by Schöllkopf and Schleyer for a bicyclic cyclopropyl tosylate.[11]
(11) U. Schöllkopf, P. V. R. Schleyer, K. Fellenberger, M. Patsch, T. Su, and G. W. Van Dine, *Tetrahedron Lett.*, 3639 (1967).
(12) See D. B. Ledlie, *J. Org. Chem.*, **37**, 1439 (1972), and references cited therein.
(13) R. Hoffmann and M. J. Goldstein, *J. Am. Chem. Soc.*, **93**, 6193 (1972).
(14) P. G. Gassman and X. Creary, *J. Am. Chem. Soc.*, **95**, 6852 (1973).
(15) We assume here that the differences in ground state energy between the members of the two pairs are essentially the same.
(16) We are deeply indebted to Diane Khoury of Professor Schleyer's group for performing these calculations for us.
(17) For a critical review of molecular mechanics see P. v. R. Schleyer, J. D. Andose, and E. M. Engler, *J. Am. Chem. Soc.*, **95**, 8005 (1973).
(18) Formation of **41** from **40** may occur either as shown or through a cyclobutyl cation.[19]
(19) For a discussion of cyclopropylcarbinyl and cyclobutyl cations see K. B. Wiberg et al. in "Carbonium Ions", Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience New York, N.Y., 1972.
(20) We envision that **14** arises via a mechanism similar to that postulated for **11** (Scheme III). Oxidation of the diene **43** by silver ion yields **14**.[3]




43

(21) We are rather perplexed as to the origin of **15**. The NMR data are certainly consistent with the assigned structure, and we are certain that the carbon skeleton is correct. However, if **15** arose from the immediate precursor to **43** (and this would negate our arguments above), then **26** would be a likely structural candidate. As pointed out earlier the NMR is not in agreement with this structure.
(22) Infrared spectra were determined with a Perkin-Elmer 457 recording spectrohotometer. The NMR spectra were measured at 60 MHz with an Hitachi Perkin-Elmer R20 spectrometer using tetramethylsilane as the internal reference. All spectra were measured in $CCl_4$ unless otherwise stated. A Hewlett-Packard 5750B gas chromatograph was used for all VPC analyses. All peak areas were integrated with a planimeter. Magnesium sulfate was employed as the drying agent. All reactions involving air- or moisture-sensitive compounds were carried out under a nitrogen atmosphere.
(23) W. V. E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **76**, 6162 (1954).
(24) K. Hofmann, S. F. Orochena and C. W. Yoho, *J. Am. Chem. Soc.*, **79**, 3608 (1957).

# Electrophilic Addition Reactions of Alkenylidenecyclopropanes. Formation of Highly Substituted, Nonplanar Butadienes[1]

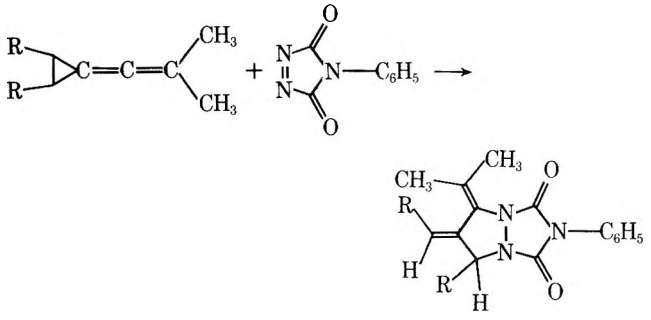
Daniel J. Pasto* and Michael F. Miles

*Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556*

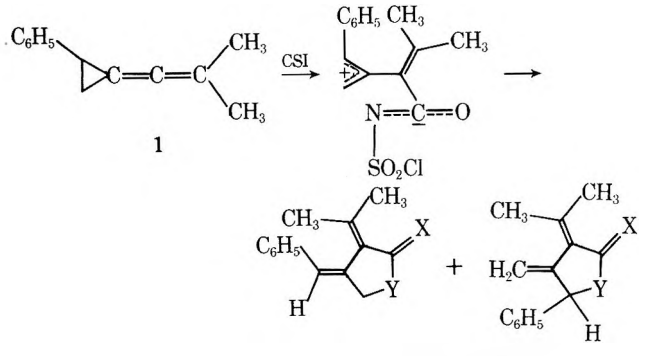
*Received July 8, 1975*

The reactions of 2-phenyl- (1) and 2,2,3,3-tetramethylisobutenylidenecyclopropane (2) with selected electrophilic reagents has been investigated. Electrophilic attack by proton, acetoxymercuri cation, and benzenesulfenyl cation occurs by highly selective attack on the $C_1$–$C_4$ (exocyclic) double bond leading to ring-opened products. Some attack on the three-membered ring of 1 occurs during acetoxymercuration, while benzenesulfenyl chloride undergoes some attack on the $C_4$–$C_5$ double bond. The ring-opened products derived from 1 are highly substituted 1,3-butadienes which must exist in nonplanar conformations separated by high energy barriers as evidenced by the appearance of the diastereotopic methylene hydrogens of **21** as AX doublets at 30°. The nature of the group interactions in **21** and the isomeric **20** in the transition state for enantiomerization of the diene is discussed. The acid-catalyzed and possible thermal rearrangements and isomerizations of these 1,3-butadienes have also been investigated. In contrast to the preference for electrophilic attack on the $C_1$–$C_4$ double bond of 1, electrophilic attack by proton and benzenesulfenyl cation occurs exclusively on the $C_4$–$C_5$ double bond of 2, while acetoxymercuration results in attack only on the $C_1$–$C_4$ double bond and the three-membered ring. The difference in position of electrophilic attack between 1 and 2 is discussed in terms of functional group interactions in transition states and intermediates, and of the nature of the electrophilic species.

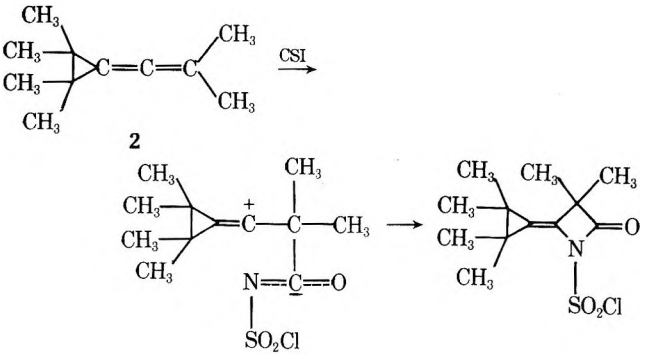
Previous studies in our laboratories on the chemical properties of alkenylidenecyclopropanes have been focused in the area of cycloaddition reactions. Although alkenylidenecyclopropanes undergo cycloaddition with 4-phenyl-1,2,4-triazoline-3,5-dione only across the methylenecyclopropane system[2] with increased reactivity with increasing methyl substitution on the ring,[3] cycloaddition reactions



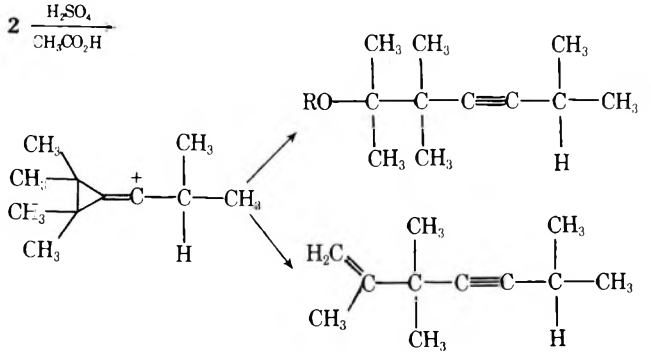
with chlorosulfonyl isocyanate (CSI) do not always display the same selectivity.[4] 2-Phenylisobutenylidenecyclopropane (1) reacts with CSI via electrophilic attack at the p orbital on $C_4$ of the $C_1$–$C_4$ double bond to produce a dipolar intermediate which collapses to products having structures similar to those derived with PTAD.[4] In contrast, 2,2,3,3-tetramethylisobutenylidenecyclopropane (2) undergoes attack at $C_5$ ultimately leading to the formation of a β-lactam derivative.[4a]



X = O; Y = $NSO_2Cl$
X = $NSO_2Cl$; Y = O



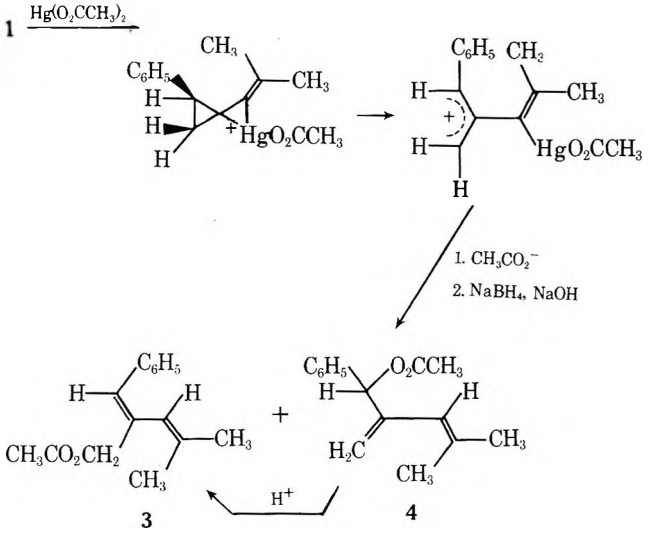
The dramatic difference in mode of reaction of 1 and 2 with CSI has prompted an investigation of the reactions of alkenylidenecyclopropanes with a variety of electrophilic species. The only previous reports of reactions of alkenylidenecyclopropanes with electrophilic reagents involve epoxidation[5] and protonation[5,6] of 2; reactions which involve electrophilic attack on the $C_4$–$C_5$ double bond, for example[5]



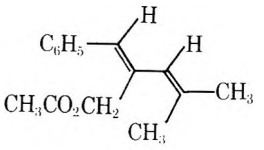
## Results and Discussion

**Solvomercuration. Acetoxymercuration of 1.** Acetoxymercuration of 1 followed by reductive demercuration using a great excess of sodium borohydride[7] produces a complex mixture of the monomeric acetates **3** and **4** (60:40 ratio), dimeric diacetates, and bis(acetoxyalkyl)mercury compounds.[7] Acetates **3** and **4** were isolated in a pure state by chromatographic techniques and their structures were readily assigned from ir, NMR, and mass spectral data.

The stereochemistry of **3** has been assigned on the basis of mechanistic arguments. Disrotatory ring opening of an intermediate spiromercurinium ion (or possible cyclopropyl cation as a transition state) is expected to occur with outward rotation of the phenyl group, i.e., in the least sterically congested manner, to produce an allylic cation which then reacts with acetate to produce **3** and **4**. Efforts to more




rigorously define the stereochemistry of **3** have met with failure. Attempted cycloaddition of **3** with maleic anhydride at 100° for 14 days resulted in no reaction. Various efforts to isomerize **3** to stereoisomer **5** for comparison of differences in chemical shifts of the isopropylidene methyls in **3** and **5** (arising from long-range shielding effects of the

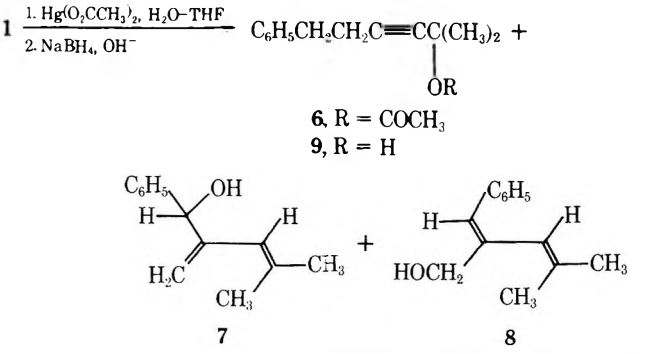


5

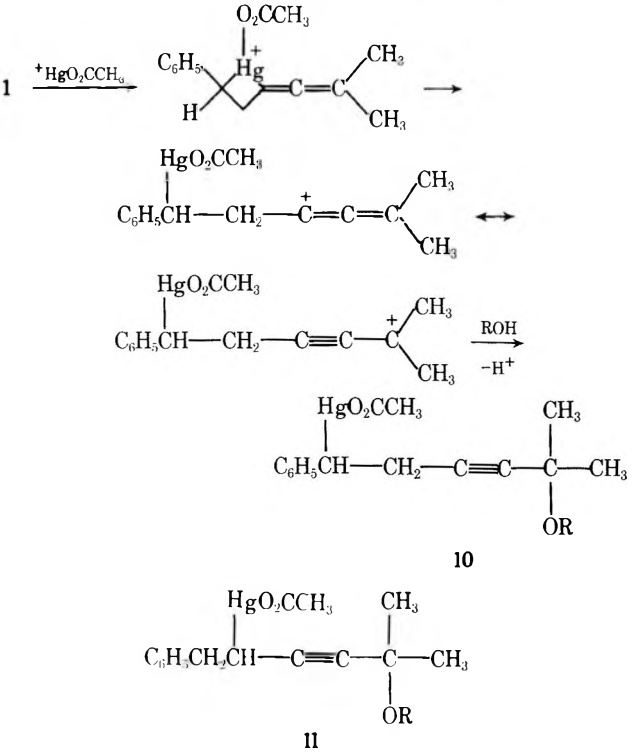
aromatic ring)[8] have failed. Attempted iodine-catalyzed thermal isomerization at 100° failed. Heating a benzene solution of **3** in a sealed tube at 300° for 5 days in an attempt to effect a reversible [3,3] sigmatropic rearrangement equilibrium[9] between **3** and **4** and hopefully **5** resulted only in partial polymerization. In the presence of strong protic acids, however, **4** cleanly rearranges to **3** (vide ante); no peaks are present in the NMR spectrum of the rearranged product which would suggest any formation of **5**. The inability to thermally or chemically isomerize **3** to **5** and the acid-catalyzed rearrangement of **4** to **3** suggest that **3** is considerably more thermodynamically stable than **5**. Inspection of models of various conformations of **3** and **5** suggests that **3** can in fact exist in a twisted conformation which possesses less steric strain than does any conformation of **5**.

The three dimeric diacetates isolated from the acetoxymercuration of **1** (see Experimental Section for characterization and proposed structures) are formed by combination of the free radicals formed during the reductive demercuration.[9] NMR and mass spectral data indicate that the bis(acetoxyalkyl)mercury compounds contain acetoxyalkyl groups corresponding to **3** and **4** (see Experimental Section for characterization and partial structures).

**Hydroxymercuration of 1.** In addition to the formation of alcohols **7** and **8**, which correspond to the acetates **3** and **4** formed in acetoxymercuration of **1**, hydroxymercuration of **1** in 50% aqueous tetrahydrofuran also results in the formation of the acetylenic alcohol **9** (small amounts of ace-




tates **3**, **4**, and **6** are also formed). The acetate **6** and alcohol **9** must be formed by initial attack by acetoxymercuri cation on one of the ring bonds, either as shown to produce **10** or alternatively on the $-CH_2-C=$ bond to give **11**, both of which would be reduced to **6** and **9**. Attack by a mercuri

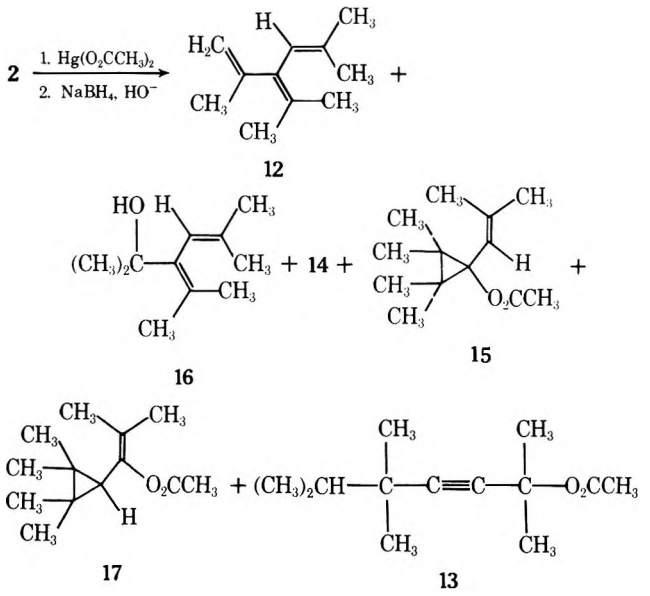



cation on a ring bond of a substituted cyclopropane has been observed previously by DePuy and co-workers[11] and in our laboratories with a bisalkylidenecyclopropane.[12] In aqueous THF electrophilic attack on the ring bond(s) of **1** accounts for 25% of the reactivity of **1**, whereas in acetic acid no attack on the ring bonds is observed. We feel that this change in mode of reaction is primarily due to differences in the dielectric constants of the two solvent systems which affects the stabilization afforded transition states and/or intermediates, and not to changes in the nature of the electrophilic species.

**Acetoxymercuration of 2.** Acetoxymercuration–demercuration of **2** produces a complex mixture from which the five most abundant components were separated by preparative GLC. Identification of the two major components (**12** and **16**) has been achieved from ir, NMR, and mass spectral data, while the structures proposed for the minor components (**13**, **15**, and **17**) are based solely on proton Fourier transform NMR spectra. The fraction containing **13** also contained ~30% of another compound (**14**) which we have not been able to identify. The ratio of the products **12:16:13:14:15:17** is approximately 26:100:15:10:5:5.

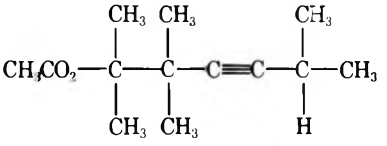
The triene **12** was easily identifiable by its characteristic NMR spectrum, which contains three vinyl hydrogen mul-

tiplets and five long-range coupled methyl resonances. Alcohol **16**, which is structurally identical with triene **12**, was similarly identified by its NMR spectrum, which showed one vinyl proton, four long-range coupled methyl doublets, a six-proton singlet, and an exchangeable OH resonance. The acetate of **16** must have been the primary product formed in the acetoxymercuration of **2** and must have undergone hydrolysis, or reduction, under the basic reductive demercuration conditions.



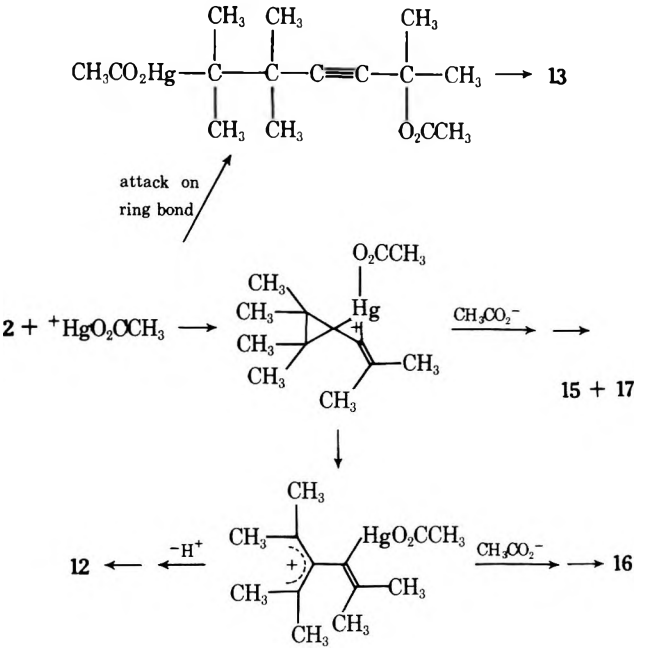

The structures of the cyclopropane ring containing products **15** and **17** are based solely on their FT spectra. The spectrum of acetate **15** contains a single vinyl proton resonance at $\delta$ 5.46 and two long-range coupled methyl doublets characteristic of a $-CH{=}C(CH_3)_2$ group. The methyl groups attached to the three-membered ring appear at high field as sharp singlets at $\delta$ 0.90 and 0.98, with the acetate methyl appearing at $\delta$ 1.91. In the NMR spectrum of acetate **17**, the low-field vinyl methyl groups appear as sharp singlets along with a single proton singlet. Also present are sharp, high-field methyl singlets at $\delta$ 1.04 and 1.21 for the ring methyls.

The structure of **13** is assigned on the basis of its NMR spectrum and by comparison of its spectral characteristics with those of **19**, which is the product formed in the acid-




catalyzed acetolysis of **2** (vide infra).[5] The isopropyl hydrogen of **13** appears as a multiplet at $\delta$ 1.40 characteristic of an isopropyl group attached to a saturated carbon atom. In contrast, the isopropyl hydrogen of **19** is deshielded by the triple bond and appears at $\delta$ 2.48. The isopropyl methyl doublet of **13** similarly appears at higher field than the isopropyl doublet of **19**.

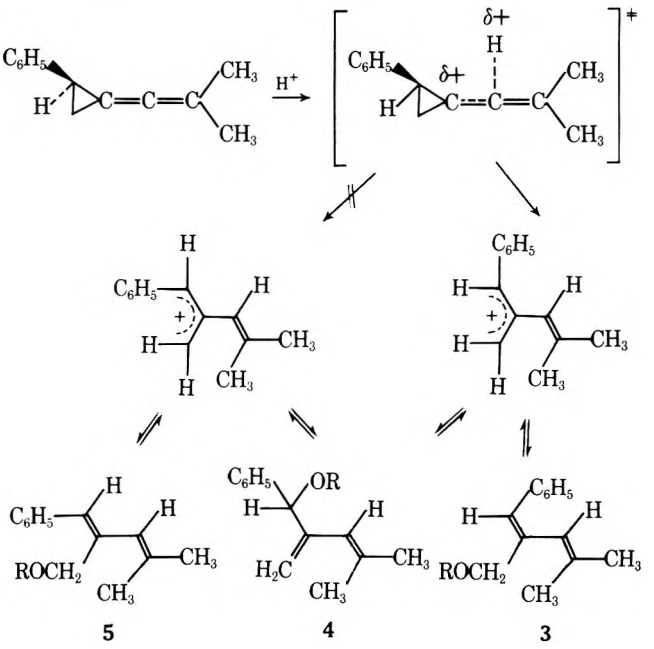
The formation of **12**, **16**, **15**, and **17** occurs via initial electrophilic attack on the $C_1$–$C_4$ double bond as illustrated in the following scheme. The formation of **13** must occur by attack on the three-membered ring as illustrated for the hydroxymercuration of **1**. No structures were isolated and characterized which would be formed via electropholic attack on the $C_4$–$C_5$ double bond (e.g., **18** and **19**).[13] This behavior is in contrast to that observed in the acid-catalyzed




acetolysis of **2**, which proceeds exclusively by attack of proton at $C_5$ (vide infra).

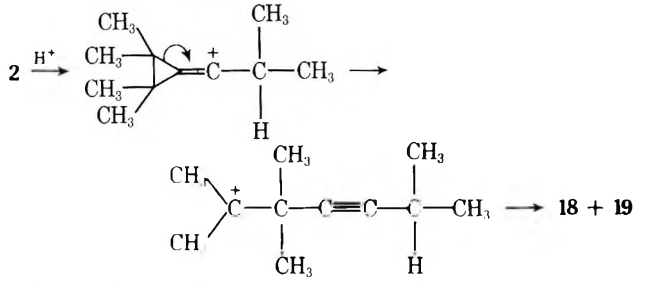
**Acetolysis. Acetolysis of 1.** **1** reacts very slowly with acetic acid at 115° to produce a 35:65 mixture of **3** and **4**. In order to avoid complications arising from thermal rearrangement of **1** at temperatures >100°, as well as polymerization, catalysis of the acetolysis by *p*-toluenesulfonic (pTS) acid was investigated. In the presence of catalytic quantities of pTS **1** reacts slowly at 70° to produce *only* **3**! Heating a sample of pure **4** in acetic acid in the presence of pTS at 105° results in quantitative rearrangement to **3**. Thus, **4** appears to be the kinetically favored product in the acetolysis of **1**, but **3** is the thermodynamically favored product.[14]

The exclusive rearrangement of **4** to **3**, and not to any extent to the stereoisomer **5**, at first appeared unusual. Although the stereochemistry in **3** is that expected in the product directly derived in the acetolysis of **1**, such stereochemical constraints are not present in the acid-catalyzed rearrangement; i.e., different rotomers of **4** can give rise to allylic cations of differing stereochemistry which should then react to give **3** and **5**, respectively. Inspection of mo-



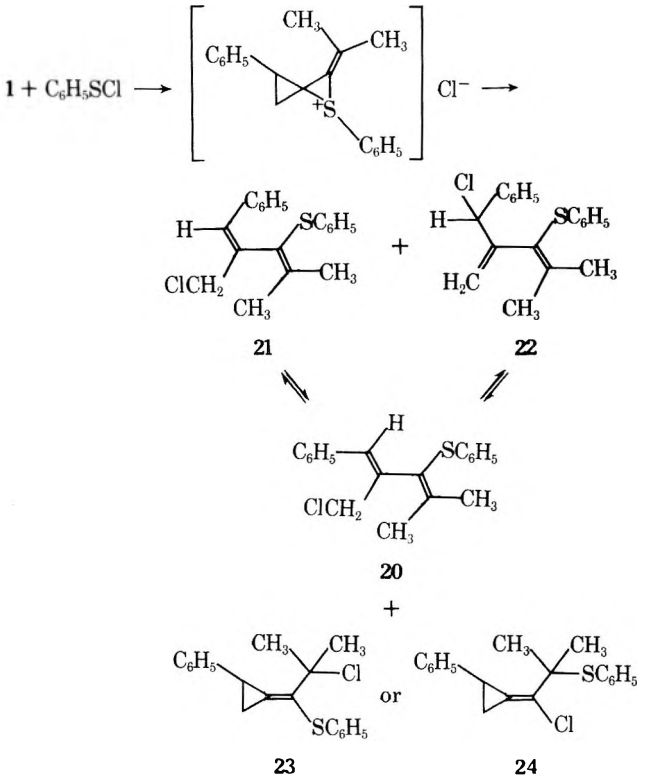
lecular models of **3** and **5** indicate that **5** is more sterically conjested than is **3** and, thus, should be less thermodynamically stable. As the rearrangements of **4** to **3** and **5** are reversible, the only observable rearrangement is to the most thermodynamically stable product **3**.

**Acetolysis of 2.** pTS-catalyzed acetolysis of **2** produces a 40:60 mixture of **18** and **19**[5] which were separated by column chromatography. The formation of **18** and **19** occurs via protonation at $C_5$ followed by ring opening as illustrated in the following scheme. No products were detected



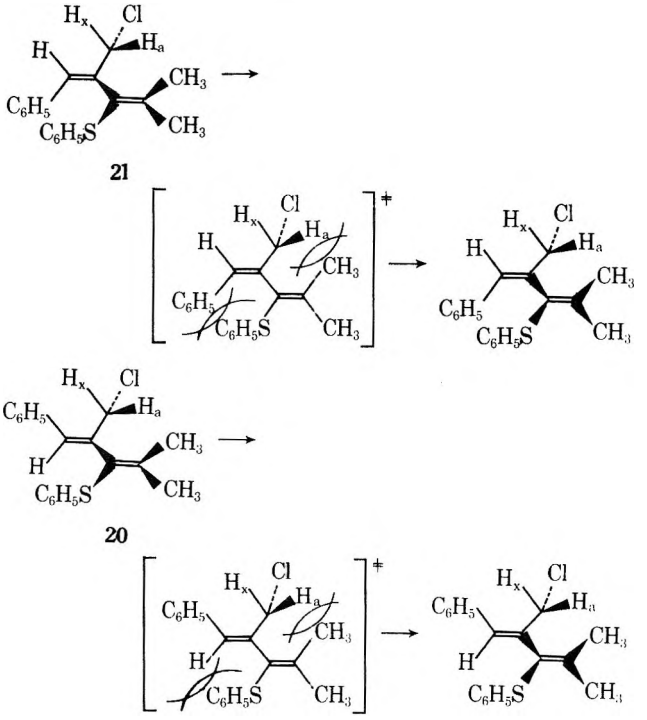

which would have been formed by electrophilic attack on the $C_1$–$C_4$ double bond (i.e., **12** or the acetate of **16**) or the three-membered ring (i.e., **13** or an enyne derived thereof). Qualitatively, **2** undergoes pTS-catalyzed acetolysis considerably more rapidly than does **1**.

**Benzenesulfenyl Chloride. Reaction with 1.** Benzenesulfenyl chloride reacts with **1** to produce a complex mixture of products which can be partially separated; extensive decomposition during chromatography, however, has precluded characterization of at least two minor products. Chromatography on silica gel resulted in the isolation of adducts **20, 21,** and **22,** and a mixture of **21, 22,** and a reactive adduct believed to possess structure **23.** Comparison of




the NMR spectrum of **20** with that of the original reaction mixture indicates that **20** is not a primary reaction product, but is an artifact of the chromatographic separation procedure. Integration of the NMR spectrum of the original reaction mixture indicates that **21, 22,** and **23** are formed in a 29:57:14 ratio.

The structures of the adducts are assigned on the basis of NMR and mass spectral data. In the mass spectrometer the molecular ions of **20, 21,** and **22** all undergo dominant fragmentation by loss of chlorine atom and hydrogen chloride characteristic of an allylic chloride, and not by dominant loss of phenylthio radical as observed with isomeric adducts in which the positions of the chlorine and phenylthio groups are interchanged.[15] The NMR spectrum of **22** is straightforward, displaying two broadened terminal methylene doublets and a broadened methine singlet. The NMR spectra of **20** and **21** at 30° are dramatically different and merit detailed discussion. The NMR spectrum of **20** shows a singlet for the $-CH_2Cl$ protons while the spectrum of **21** contains AX doublets with a geminal coupling constant of 12.7 Hz. The diastereotopicity of the $-CH_2Cl$ protons of **21** arises from slowed rotation about the central C–C bond of the butadiene chromophore which becomes a chiral diene on the NMR time scale.[16,17] On raising the temperature the AX doublets reversibly coalesce to produce a sharp singlet at 142°. (Coalesence occurs at approximately 95° resulting in a crude estimate for $\Delta G_{368}$ of ~18 kcal/mol.)[19] The assignments of the stereochemistry of **20** and **21** is based on mechanistic arguements (vide supra) and their NMR spectral behavior. Inspection of molecular models of **20** and **21** reveals that the barrier to rotation about the central C–C bond of **21,** via the lower energy transoid transition state,[20] must be higher than for **20.** In the transoid transition state for enantiomerization of the skewed diene system in **21** two severe "1,3-diaxial-type" interactions are present: one between phenyl and phenylthio, the other between chloromethyl and methyl. In the transition state for enantiomerization of **20** only one severe 1,3 interaction is present, that being between chloromethyl and methyl. Thus, the barrier

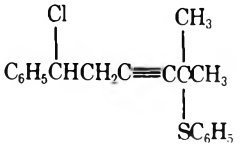



to rotation in **21** must be higher than that in **20** and is consistent with the stereochemistry of **21** assigned on the basis of mechanistic reasoning.

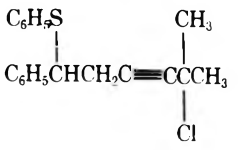
During the chromatographic separation **20** is formed by isomerization of **21** and/or rearrangement of **22.** That double bond isomerization is apparent in this system but does not occur in the acid-catalyzed isomerization of **4** to **3** is due to different substitution patterns on the butadiene frameworks. In the more stable twisted transoid conforma-

tion of **3** a 1,3 interaction exists between phenyl and hydrogen whereas in **21** a 1,3 interaction exists between phenyl and phenylthio. In both **5** and **20** substantial cis 1,2 interactions are present, in **5** between phenyl and acetoxymethyl and in **20** between phenyl and chloromethyl. Thus, the energy of **21** is higher relative to **20** than is the energy of **3** relative to **5**, and in a thermodynamically controlled situation **21** is more prone to isomerize to **20** than is **3** to **5**.

NMR evidence indicates that a ring-retained adduct is also formed. This adduct was isolated only as a mixture with **21** and **22**, and appears to undergo decomposition during chromatography. The NMR spectrum of this adduct shows distinct A and X resonance patterns of an AMX spin system (the M resonances are obscured by the methyl resonances of **21** and **22**). That the adduct is a methylenecyclopropane derivative and not a cyclopropane derivative is indicated by the chemical shift of the ring benzyl hydrogen ($\delta$ 2.76) while in **1** the benzyl hydrogen appears at $\delta$ 2.80. In addition, the methyl protons of the adduct appear as a singlet at $\delta$ 1.67 whereas in an isobutenylcyclopropane the two methyl groups would be expected to appear as two singlets at lower field. The positions of the chloro and phenylthio groups on the isobutylidenecyclopropane framework cannot be unambiguously specified. Both possible structures **23** and **24** are anticipated to be quite reactive; **23** being a tertiary halide and **24** being a halomethylenecyclopropane.[21] As no adducts were apparently formed that would be derived by electrophilic attack on the $C_4$–$C_5$ double bond followed by ring opening (e.g., **25** or its dehydrochlorination product), we believe that the structure of the ring-retained adduct is **23** which would be derived via the same episulfonium ion intermediate that would ultimately give rise to **21** and **22**. No adducts were observed that would be formed by electrophilic attack on the three-membered ring (e.g., **26**).

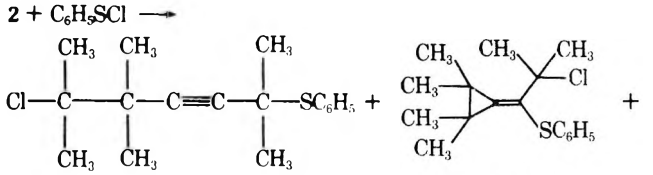


**25**

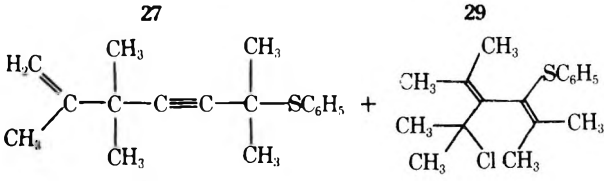


**26**

**Reaction of Benzenesulfenyl Chloride with 2.** Benzenesulfenyl chloride reacts with **2** to produce a mixture of apparently two major, very reactive adducts along with a dehydrochlorination product of one adduct and smaller amounts of unidentified products. The NMR spectrum of the product mixture shows only two low-field methyl resonances, a vinyl methyl double doublet belonging to **28** and a low-field singlet believed to belong to **29**. All other methyl resonances appear as singlets and fall in the $\delta$ 1.61–0.97 region characteristic of methyl groups attached to quaternary carbon atoms. The lack of low-field methyl resonances precludes the presence of structures related to **30** which would be formed by attack on the $C_1$–$C_4$ double bond as is observed with **1**. The products characterized are formed by electrophilic attack on the $C_4$–$C_5$ double bond.



**27** **29**

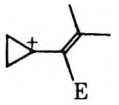


**28** **30**

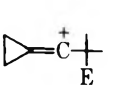
Storing the reaction mixture at 5° for short periods of time resulted in extensive change. Attempted chromatographic separation on silica gel resulted in extensive decomposition, although a substantial fraction was obtained which we believe contained **28** along with an unidentified compound. The structure of **28** is assigned by comparison of peak intensities and chemical shifts with those of **18**, the correspondence for the $H_2C{=}C(CH_3)C(CH_3)_2$– portions of **18** and **28** being within 0.03 ppm. The peaks of **28** are present in the NMR spectrum of the original sample and account for approximately 10% of the mixture. The formation of **28** during attempted chromatographic separation occurs by dehydrochlorination of **27**, whose NMR peaks in the original mixture are assigned by comparison of chemical shifts of **27** and **28** with **18** and **19**. **27** accounts for approximately 35% of the original product mixture. The presence of **29** is indicated by intense methyl singlets in the NMR spectrum of the original mixture at $\delta$ 0.97, 1.15, and 1.78. No decomposition products of **29** could be identified.

**Discussion of Factors Affecting Selectivity of Electrophilic Attack.** The results outlined in the forgoing portion show that the selectivity of attack by an electrophile on the alkenylidenecyclopropane system is greatly dependent on the nature of the substituents attached to the three-membered ring and, to some extent, the nature of the electrophilic species. Attack by proton occurs on the p orbital on $C_4$ of the $C_1$–$C_4$ double bond of the phenyl substituted system **1**, while with the tetramethyl substituted compound **2** attack occurs only at $C_5$. The benzenesulfenyl cation, which like the proton may be considered a "hard", irreversible, but bridging, electrophile, undergoes exclusive attack on the $C_1$–$C_4$ double bond of **1** while with **2** attack occurs on the $C_4$–$C_5$ double bond to form intermediate episulfonium ions. To gain an understanding of the difference in mode of reaction of **1** and **2** one must consider the nature of the bonding interactions in the cationic intermediates, or contributing structures to the episulfonium ion intermediates, formed in both processes and the interaction of groups attached to the three-membered ring with the molecular orbitals of the ring system.

Electrophilic attack on the p orbital of $C_4$ of the $C_1$–$C_4$ double bond produces a cyclopropyl cation (**31**) which derives little stabilization from groups attached to the three-membered ring. Although the $p_z$ orbital on $C_1$ interacts strongly with the $p_z$ orbitals on $C_2$ and $C_3$ to generate a set of bonding, degenerate group orbitals, the latter do not overlap strongly with the orbitals of carbon atoms attached to $C_2$ and $C_3$[22] and thus little stabilization is afforded carbonium ion formation at $C_1$ by alkyl groups attached to $C_2$ and $C_3$. Development of charge at $C_1$ does result in ultimate ring opening and release of ring strain but from the above reasoning this process should be little affected by groups attached to $C_2$ and $C_3$. Electrophilic attack at $C_5$ results in the formation of cation **32** in which the in-plane,



**31**



**32**

vacant p orbital on $C_4$ interacts strongly with the Walsh-type orbitals[23] of the three-membered ring.[22] Although un-

saturated groups attached to the three-membered ring do not interact strongly with the Walsh orbitals of the three-membered ring owing to the small coefficients on the requisite p orbital on the atom attached to the ring,[24,25] alkyl groups interact to a much greater degree owing to the substantial coefficients of the appropriate atomic orbitals on both $C_2$ (or $C_3$) and the attached carbon atom.[22,25] Therefore, alkyl groups attached to the three-membered ring stabilize positive charge formation at $C_4$ to a greater degree than at $C_1$, and unsaturated groups (e.g., phenyl) do not lead to stabilization of charge formation at either center.[26]

The selectivity of attack by the acetoxymercuri cation on **2**, and in part on **1** in aqueous tetrahydrofuran differs from that observed in protonation and in attack by benzenesulfenyl cation. In contrast to the proton and the benzenesulfenyl cation, the acetoxymercuri ion is a soft electrophile and reacts reversibly with $\pi$ bonds to form mercurinium ions.[27] The acetoxymercuri cation apparently is not as strong an electrophile and on attack on the $\pi$ system does not polarize the $C_1$–$C_4$ or the $C_4$–$C_5$ double bonds sufficiently to induce ring opening or attack by a nucleophile, and by default undergoes electrophilic attack on a strained ring bond.

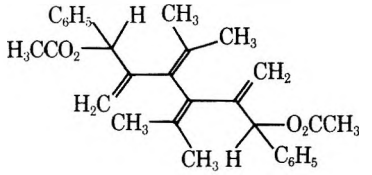
## Experimental Section

**Acetoxymercuration of 1.** To a stirred solution of 3.18 g (10 mmol) of mercuric acetate in 10 ml of acetic acid at 25° was slowly added 1.70 g (10 mmol) of **1**. After stirring for 30 min the reaction mixture was cooled to 0° in an ice bath and a 12-fold excess of sodium borohydride[7] (4.96 g) in 60 ml of 10% sodium hydroxide was added as rapidly as possible, maintaining the temperature of the reaction mixture below 20°. Saturated aqueous sodium chloride (25 ml) was added and the mixture was extracted with two 40-ml portions of ether. The ether extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure, leaving 2.43 g of a colorless liquid of which approximately one-half was soluble in hexane.

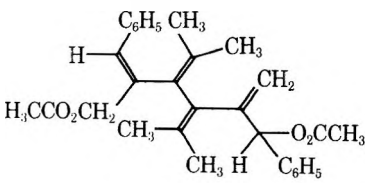
The hexane-soluble portion of the above product was chromatographed on a 2 × 25 cm column of silica gel. Elution with 20–25% benzene in hexane produced 96 mg of pure **4**: bp ~40° (0.08 mm in a microstill); ir (cap film) 1735 ($\nu_{C=O}$) and 905 $cm^{-1}$ ($\nu_{=CH_2}$); NMR ($CDCl_3$) $\delta$ 1.68 (bs, 3 H), 1.70 (bs, 3 H), 2.08 (s, 3 H), 5.03 (bs, 1 H), 5.34 (bs, 1 H), 5.47 (bs, 1 H), 6.18 (bs, 1 H), 7.31 (s, 5 H); mass spectrum $M^{\cdot+}$ 230.129 (calcd for $C_{15}H_{18}O_2$, 230.131), major peaks at *m/e* 215, 188, 173, 170, 155 (base peak), 143, 141, 129, 115, and 91.

Elution with 30% benzene in hexane produced pure **3**: bp ~40° (0.08 mm in a microstill); ir (cap film) 1742 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.43 (d, $J$ = 0.9 Hz, 3 H), 1.76 (d, $J$ = 1.6 Hz, 3 H), 2.06 (s, 3 H), 4.66 (m, 2 H), 5.75 (bm, 1 H), 6.46 (bm, 1 H), and 7.25 (m, 5 H); mass spectrum $M^{\cdot+}$ 230.129 (calcd for $C_{15}H_{18}O_2$, 230.131) (the mass spectrum of **3** was identical in all respects with that of **4**).

Elution with 45–50% benzene in hexane produced fractions containing a mixture of dimers [40 mg, mp (from hexane) 118–125°, $M^{\cdot+}$ *m/e* 458] i and ii: ir ($CCl_4$) 1744 and 1731 $cm^{-1}$; NMR of i



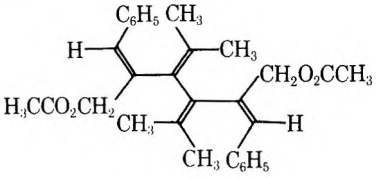
i



ii

($CDCl_3$) $\delta$ 1.69 (bs, 3 H), 1.92 (bs, 3 H), 2.11 (s, 3 H), 4.86 (m, 1 H), 5.38 (m, 1 H), 6.14 (bs, 1 H), 7.33 (s, 5 H); NMR of ii ($CDCl_3$) $\delta$ 1.69 (s, 3 H), 1.70 (s, 3 H), 1.93 (s, 3 H), 2.01 (s, 3 H), 2.02 (s, 3 H), 2.04 (s, 3 H), 5.08 (bs, 1 H), 5.31 (bs, 1 H), 6.18 (bs, 1 H), 6.75 (bs, 1 H), 7.25 (m, 10 H).

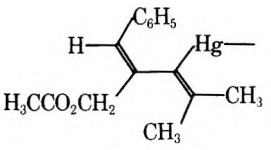
Further elution with 50% benzene in hexane gave 35 mg of unidentified material. Elution with 55% benzene in hexane gave iii as



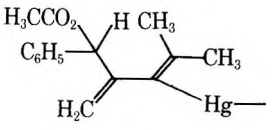
iii

a viscous liquid: ir ($CCl_4$) 1733 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.70 (s, 6 H), 2.04 (s, 6 H), 2.12 (s, 6 H), 4.66 (bs, 4 H), 6.46 (bs, 2 H), and 7.33 (m, 10 H).

The NMR and mass spectra ($M^{\cdot+}$ series of peaks at *m/e* 656–662) of the hexane insoluble fraction indicate the presence of a mixture of bis(acetoxyalkyl)mercury compounds with partial structures iv and v: NMR ($CDCl_3$) of iv $\delta$ 1.70 (s), 2.02 (s), 2.07 (s),



iv



v

4.64 (m), 6.40 (bs), and ~7.2 (m); NMR of v $\delta$ 1.62 (s), 1.72 (s), 2.10 (s), 4.87 (m), 5.36 (m), 6.15 (m), and 7.31 (s).

**Hydroxymercuration of 1.** To a bright yellow solution of 3.5 g (11.4 mmol) of mercuric acetate in 22 ml of 50% aqueous tetrahydrofuran was added 1.87 g (11.1 mmol) of **1**. The yellow color was rapidly discharged. After stirring for 30 min at 25° a solution of 0.5 *M* sodium borohydride in 10% sodium hydroxide (22 ml) was rapidly added with stirring. The reaction mixture was added to 100 ml of water and was extracted with two 40-ml portions of ether. The combined extract was washed with water and dried ($MgSO_4$), and the solvent was removed under reduced pressure, giving 2.79 g (135% based on 1 plus $H_2O$) of residue. The residue was chromatographed on a 2 × 25 cm column of silica gel. Elution with benzene gave 0.15 g of a mixture of **3** and **4**. Further elution with benzene gave 50 mg of a mixture containing some **3** and **4** along with mostly a compound assigned structure **6** (structure is assigned by comparison of NMR spectral properties with those of alcohol **9** below): NMR ($CDCl_3$) $\delta$ 1.44 (s), $A_2X_2$ multiplets at 2.52 and 2.74 ($J$ = 5.8 Hz), and ~7.3 (s).

Still further elution with benzene gave 150 mg of pure **7** (purified by molecular distillation at 40°, 1.0 mm): ir (cap film) $\nu_{OH}$ 3430, $\nu_{=CH_2}$ 904 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.72 (overlapping doublets, $J \simeq 1$ Hz, 6 H), 5.02 (m, 1 H), 5.15 (bs, 1 H), 5.41 (m, 1 H), 5.47 (very broad m, 1 H), and 7.33 (s, 5 H); mass spectrum $M^{\cdot+}$ 188.119 (calcd for $C_{13}H_{16}O$, 188.120), major peaks at *m/e* 170 ($M^{\cdot+} - H_2O$), 107 ($C_6H_5CHOH^+$, base peak), 105 ($C_6H_5CO^+$).

Elution with 50% chloroform in benzene gave 350 mg of pure **8** (purified by molecular distillation at 40–43°, ~0.07 mm): ir $\nu_{OH}$ 3390 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.43 (d, $J$ = 1.1 Hz, 3 H), 1.74 (d, $J$ = 1.3 Hz, 3 H), 3.60 (bs, 1 H), 4.16 (d, $J$ = 1.2 Hz, 2 H), 5.77 (bm, 1 H), 6.54 (t, $J$ = 1.2 Hz, 1 H), 7.28 (m, 5 H); mass spectrum $M^{\cdot+}$ 188.119 (calcd for $C_{13}H_{16}O$, 188.120), major peaks at *m/e* 173 ($M^{\cdot+} - CH_3$), 170 ($M^{\cdot+} - H_2O$), 157 ($M^{\cdot+} - CH_2OH$), 155, 143, 115, and 91 (base peak).

Following the elution of **8**, fractions containing **8** and **9** (0.47 g, ~50:50 ratio of **8**:**9**) were eluted and rechromatographed on a similar column to give pure **9**: ir (5% in $CCl_4$) $\nu_{OH}$ 3608 and $\nu_{C\equiv C}$ 2258 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.45 (s, 6 H), 1.79 (s, 1 H, $\delta$ is concentration dependent), 2.44 ($X_2$ portion of an $A_2X_2$ system, $J$ = 5.7 Hz, 2 H), 2.79 ($A_2$ portion of an $A_2X_2$ system, $J$ = 5.7 Hz, 2 H), and 7.25 (s, 5 H); mass spectrum $M^{\cdot+}$ 188.119 (calcd for $C_{13}H_{16}O$, 188.120), major peaks at *m/e* 173 ($M^{\cdot+} - CH_3$), 170 ($M^{\cdot+} - H_2O$), and 91 (base peak).

**Acetoxymercuration of 2.** To a solution of 1.21 g (3.8 mmol) of mercuric acetate in 20 ml of acetic acid at 0° was added 0.57 g (3.8 mmol) of **2**. The reaction mixture was stirred for 15 min at 0° and was then allowed to warm to 25° for 1.75 hr. Sodium borohydride (10 ml of 0.5 *M* in 10% sodium hydroxide) was added and the resulting reaction mixture was stirred for 2 hr. The reaction mixture

was transferred to a separatory funnel and 15 ml of saturated sodium chloride was added followed by extraction with three 15-ml portions of ether. The ether extract was washed with aqueous sodium bicarbonate and was dried ($MgSO_4$). The solvent was carefully removed by distillation, leaving 0.49 g of a colorless, viscous oil containing some white solid material: ir ($CHCl_3$) 3680, 3470 (broad), 1737, 1725 (shoulder), 1665, 1635, and 914 $cm^{-1}$; NMR ($CDCl_3$) indicated a complex mixture. Analysis by GLC on an 8-ft Carbowax 20M column programmed from 85 to 145° at 2°/min indicated the presence of up to 12 components. Preparative GLC using the above conditions yielded sufficient sample for identification of the five major (total >85%) components (in order of elution).

**12:** colorless oil; NMR ($CDCl_3$) $\delta$ 1.56 (d, $J$ = 1.2 Hz, 3 H), 1.59 (d, $J$ = 0.9 Hz, 3 H), 1.73, 1.75, 1.77 (overlapping broad singlets, 9 H total), 4.62 (m, 1 H), 4.90 (m, 1 H), and 5.59 (m, 1 H).

**13** (also contains ~30% of an unknown structure 14): colorless oil; NMR ($CDCl_3$, $^1H$ FT) $\delta$ 0.94 (d, $J$ = 6.7 Hz), 1.33 (s), 1.40 (m), 1.63 (s), 1.99 (s). **14:** NMR ($CDCl_3$) $\delta$ 1.10, 1.12, 1.17, 1.25 (s).

**15:** NMR ($CDCl_3$, $^1H$ FT) $\delta$ 0.90 (s), 0.98 (s), 1.60 (d, $J$ = 0.9 Hz), 1.66 (d, $J$ = 1.2 Hz), 1.91 (s), 5.46 (m); mass spectrum $M^{\cdot+}$ 210.1620 (calcd for $C_{13}H_{22}O_2$, 210.1620).

**16:** colorless crystals from hexane (colorless plates), mp 67.5–69°; ir ($CHCl_3$) $\nu_{OH}$ 3660 and $\nu_{=CH_2}$ 907 or 917 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.35 (s, 6 H), 1.51 (d, $J$ = 1.2 Hz, 3 H), 1.58 (d, $J$ = 1.3 Hz, 3 H), 1.64 (s, peak disappears on addition of deuterium oxide, 1 H), 1.76 (d, $J$ = 1.4 Hz, 3 H), 1.96 (d, $J$ = 1.8 Hz, 3 H), 5.67 (m, 1 H); mass spectrum $M^{\cdot+}$ 168.1514 (calcd for $C_{11}H_{20}O$, 168.1514), major peaks at $m/e$ 153, 150, 135 (base peak), 119, 110, 107, 95, and 59. **16** could be isolated from the original reaction mixture by precipitation with hexane.

**17:** NMR ($CDCl_3$, $^1H$ FT) $\delta$ 1.04, 1.21, 1.26, 1.69, 1.72, and 2.11 (all singlets with approximate relative intensities of 6:6:1:3:3:3); mass spectrum $M^{\cdot+}$ 210.1620 (calcd for $C_{13}H_{22}O_2$, 210.1620).

The GLC analysis and the NMR spectrum of the original reaction mixture indicate that the relative ratio of the products **12:13:14:15:16:17** is 26:15:10:5:100:5. Insufficient quantities of the other fractions prevented obtaining good NMR spectra for identification purposes. No significant dialkylmercury formation was indicated or observed with **2**.

***p*-Toluenesulfonic Acid Catalyzed Acetolysis of 1.** A solution of 65 mg of **1** in 1 ml of acetic acid containing one small crystal of *p*-toluenesulfonic acid was sealed in an NMR tube and heated in a sand bath at 70°. After 2 hr analysis by NMR indicated that no **1** remained and that **3** was formed as the only product. The tube was opened and its contents were poured into 15 ml of water. The mixture was extracted twice with 15-ml portions of ether. The combined ether extract was washed with 5% sodium bicarbonate until free from acetic acid. The extract was dried ($MgSO_4$) and the solvent was removed, giving 50 mg of pure **3** (by NMR).

**Acetolysis of 1.** A solution of 65 mg of **1** in 1 ml of glacial acetic acid was sealed in an NMR tube and was heated in a sand bath at 115°. The reaction was periodically monitored by NMR. After 20 hr at 115° peaks corresponding to **3** and **4** were observed (~25% reaction producing a ~35:65 ratio of **3** to **4** along with some apparent polymerization and/or isomerization of **1** also occurring).

**Acid-Catalyzed Isomerization of 4 to 3.** A solution of 37 mg of **4** in 1 ml of acetic acid containing one small crystal of *p*-toluenesulfonic acid was sealed in an NMR tube and was heated at 105° in a sand bath. Analysis by NMR indicated that **4** was essentially completely rearranged to **3** within 45 min.

**Acetolysis of 2.** In an NMR tube was sealed 126 mg of **2** in 1 ml of acetic acid with one small crystal of *p*-toluenesulfonic acid. After standing at 25° for 24 hr NMR analysis indicated that **2** had completely reacted. The contents of the tube were dissolved in 20 ml of ether and the ether solution was washed repeatedly with saturated sodium bicarbonate until free of acetic acid. The solution was dried ($MgSO_4$) and the solvent was carefully removed under reduced pressure, leaving 143 mg of a 40:60 mixture of **18** and **19**[5] which were separated by chromatography on a 1 × 45 cm column of silica gel. Elution with hexane gave **18:** NMR ($CDCl_3$) $\delta$ 1.13 (d, $J$ = 6.4 Hz, 6 H), 1.30 (s, 6 H), 1.84 (m, 3 H), 2.48 (septet, $J$ = 6.4 Hz, 1 H), 4.74 and 5.00 (m's, 1 H each). Elution with 30% benzene–hexane gave **19:** NMR ($CDCl_3$) $\delta$ 1.12 (d, $J$ = 6.4 Hz, 6 H), 1.21 (s, 6 H), 1.61 (s, 6 H), 1.97 (s, 3 H), and 2.48 (septet, $J$ = 6.4 Hz, 1 H).

**Reaction of 1 with Benzenesulfenyl Chloride.** To 365 mg (2.1 mmol) of **1** in 3 ml of dichloromethane containing 50 mg of calcium carbonate was slowly added 295 mg (2.0 mmol) of benzenesulfenyl chloride dissolved in 2 ml of dichloromethane at 0° under a nitrogen atmosphere, the red color of the benzenesulfenyl chloride being discharged immediately. The reaction mixture was allowed to warm to room temperature and was stirred for 20 min. The reaction mixture was dried over magnesium sulfate and filtered, and the solvent was removed under reduced pressure, leaving a pale yellow oil. The residue was dissolved in hexane and was applied to a 2 × 27.5 cm column of silica gel. Extensive decomposition occurred at the top of the column. Elution with 5% benzene–hexane gave 42 mg of **1**. Elution with 10% benzene–hexane produced 14 mg of **20:** NMR ($CDCl_3$) $\delta$ 2.10 (s, 3 H), 2.17 (s, 3 H), 4.41 (s, 2 H), 6.39 (s, 1 H), and 7.3 (m, 10 H); mass spectrum $M^{\cdot+}$ 314.0892 (calcd for $C_{19}H_{19}S^{35}Cl$, 314.0896), major peaks at $m/e$ 316, 314, 278 (base peak, $M^{\cdot+}$ − HCl), 263, 248, 219, 205 (rel intensity 11.5), 201, and 185.

Further elution with 10% benzene–hexane gave 110 mg of a mixture of **21, 22,** and **23** or **24** from which pure fractions of **21** and **22** were obtained by careful rechromatography on a 2 × 25 cm column of silica gel using pure hexane as eluent. **21:** NMR ($CDCl_3$) $\delta$ 1.72 (s, 3 H), 2.00 (s, 3 H), 4.14 (d, $J$ = 12.7 Hz, 1 H), 4.50 (d, $J$ = 12.7 Hz, 1 H), 6.47 (bs, 1 H), and 7.3 (m, 10 H); mass spectrum $M^{\cdot+}$ 314.0889 (calcd for $C_{19}H_{19}S^{35}Cl$, 314.0896), spectrum essentially identical with that of **20. 22:** NMR ($CDCl_3$) $\delta$ 1.73 (s, 3 H), 1.75 (s, 3 H), 4.78 (bs, 1 H), 4.97 (broadened d, $J$ = 1.7 Hz, 1 H), 5.43 (broadened d, $J$ = 1.7 Hz, 1 H), and 7.2 (m, 10 H); mass spectrum $M^{\cdot+}$ 314.0876 (calcd for $C_{19}H_{19}S^{35}Cl$, 314.0896), spectrum essentially identical with that of **20** and **21.** Unknown structure **23** or **24:** NMR (from $CDCl_3$ solution of mixture with **21** and **22**) $\delta$ 0.72 (dd, $J$ = 5.2 and 10.2 Hz, 1 H), 1.67 (s, 6 H), ~1.7 (dd, $J$ = 5.2 and 7.9 Hz, 1 H), 2.76 (dd, $J$ = 7.9 and 10.2 Hz, 1 H), ~7.2 (m, 10 H).

Further elution with more polar solvent systems produced continuous fractions, the NMR spectra of which did not correspond to peaks appearing in the NMR spectrum of the crude reaction mixture. These fractions represent decomposition products formed on the silica gel column. As no clean separation of these decomposition products could be achieved, further characterization was not attempted.

Careful inspection of the NMR spectrum of the crude reaction mixture does not show the presence of peaks corresponding to **20.** Integration of the peaks corresponding to **21, 22,** and **23** or **24** indicate they were formed in a ratio of 29:57:14 and account for at least 75% of the product. Peaks appearing in the NMR spectrum which were not identified with an isolable product appear at $\delta$ 1.85 (bs), 3.21 (an apparent triplet), and weak multiplets at 4.65 and 5.85.

**Reaction of 2 with Benzenesulfenyl Chloride.** Benzenesulfenyl chloride (283 mg, 2.0 mmol) and 300 mg (2.0 mmol) of **2** were allowed to react following the procedure outlined above for the reaction with **1**. Peaks in the NMR spectrum of the reaction mixture assigned to **27, 28,** and **29** are as follows. **27:** NMR ($CDCl_3$) $\delta$ 1.21, 1.47, and 1.61 (all singlets of equal intensity). **28:** $\delta$ 1.28 (s, 6 H), 1.53 (s, 6 H), 1.86 (dd, $J$ = 1.4 and 0.7 Hz, 3 H), 4.75 and 4.97 (m's, 1 H each) (the relative intensities are assigned from the NMR spectrum of a chromatography fraction rich in **28. 29:** $\delta$ 0.97 (s, 6 H), 1.15 (s, 6 H), and 1.78 (s, 6 H). Attempted chromatographic separation of the mixture on a 2 × 16 cm column of silica gel resulted in extensive decomposition. Elution with benzene gave one fraction rich in **28.**

**Registry No.**—i, 57443-31-9; ii, 57443-32-0; iii, 57443-33-1; **1,** 4544-23-4; **2,** 13303-30-5; **3,** 57443-34-2; **4,** 57443-35-3; **6,** 57443-36-4; **7,** 57443-37-5; **8,** 57443-38-6; **9,** 57443-39-7; **12,** 25914-11-8; **13,** 57443-40-0; **15,** 57443-41-1; **16,** 30762-44-8; **17,** 57484-05-6; **18,** 21860-12-8; **19,** 21860-14-0; **20,** 57443-42-2; **21,** 57443-43-3; **22,** 57443-44-4; **23,** 57443-45-5; **27,** 57443-46-6; **28,** 57443-47-7; **29,** 57443-48-8; mercuric acetate, 1600-27-7; benzenesulfenyl chloride, 931-59-9.

## References and Notes

(1) Research supported in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society.
(2) D. J. Pasto, A. F.-T. Chen, and G. Binsch, *J. Am. Chem. Soc.*, **95,** 1553 (1973); D. J. Pasto and A. F.-T. Chen, *ibid.*, **93,** 2526 (1971).
(3) D. J. Pasto, J. K. Borchardt, T. P. Fehlner, H. F. Baney, and M. E. Schwartz, *J. Am. Chem. Soc.*, **98,** 526 (1976).
(4) D. J. Pasto, A. F.-T. Chen, G. Ciurdaru, and L. A. Paquette, *J. Org. Chem.*, **38,** 1015 (1973); D. J. Pasto and J. K. Borchardt, *J. Am. Chem. Soc.*, **96,** 6937 (1974).
(5) J. K. Crandall, D. R. Paulson, and C. A. Bunnell, *Tetrahedron Lett.*, 5063 (1968).
(6) M. L. Poutsma and P. A. Ibarbia, *J. Am. Chem. Soc.*, **93,** 404 (1971).
(7) We have observed that reduction with lesser amounts of sodium borohydride results in the formation of greater amounts of dialkylmercury compounds. We have not been successful in fully depressing dialkyl-

mercury formation even when using large quantities of reducing agent.
(8) As an example see D. J. Pasto, R. L. Smorada, B. L. Turini, and D. J. Wampfler, *J. Org. Chem.*, following paper in this issue.
(9) See D. J. Pasto and J. Gontarz, *J. Am. Chem. Soc.*, **91**, 719 (1969); G. A. Gray and W. R. Jackson, *ibid.*, **91**, 6205 (1969); G. M. Whitesides and J. San Filippo, Jr., *ibid.*, **92**, 6611 (1970).
(10) The mass spectra of **3** and **4** were completely identical, suggesting that the radical cations derived from the two structures were identical. This further suggested the possibility that under thermal activation **3** and **4** could be interconverted.
(11) C. H. DePuy and R. J. Van Lanen, *J. Org. Chem.*, **39**, 3360 (1974).
(12) See references in ref 8.
(13) Comparison of GLC retention times of **18** and **19** with those of the components in the crude acetoxymercuration reaction mixture indicated possible identity with two of the very minor components.
(14) Similar behavior has been observed in preliminary kinetic studies of the trichloroacetolysis of **1** in carbon tetrachloride (D. J. Pasto, unpublished observations).
(15) See references in ref 8.
(16) Similar behavior with other highly substituted acyclic butadienes has been reported: A. Mannschreck, V. Jonas, H.-O. Bödecker, H.-L. Elbe, and G. Köbrich, *Tetrahedron Lett.*, 2153 (1974), and references cited therein; Professor E. F. Kiefer, University of Hawaii, private communication.
(17) The ease of synthesis of chiral alkenylidenecyclopropanes[18] presents the possibility of the direct formation of optically active acyclic, substituted butadienes. Efforts are underway along such lines.
(18) D. J. Pasto and J. K. Borchardt, *Tetrahedron Lett.*, 2517 (1973).
(19) Insufficient material has prevented obtaining high quality spectra of necessary for accurate determination of $T_c$ or for full line-shape analyses for either **20** or **21** (see ref 15).
(20) Enantiomerization via the planar transoid transition state is of lower energy than via the planar cisoid conformation (see references by Mannschreck in ref 16).
(21) M. Hanack, T. Bassler, W. Eymann, W. E. Heyd, and R. Kopp, *J. Am. Chem. Soc.*, **96**, 6686 (1974).
(22) D. J. Pasto, T. P. Fehlner, M. E. Schwartz, and H. F. Baney, *J. Am. Chem. Soc.*, **98**, 530 (1976).
(23) A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949); *Nature (London)*, **159**, 167, 712 (1947).
(24) C. F. Wilcox, L. M. Loew, and R. Hoffmann, *J. Am. Chem. Soc.*, **95**, 8193 (1975).
(25) See also discussion in ref 3.
(26) Other factors which might also contribute to preferential attack at $C_5$ of **2** relative to $C_4$ in **1** would be reduced steric inhibition to attack at the perpendicular p orbital at $C_4$ of the $C_1$–$C_4$ double bond, and steric inhibition to disrotatory ring opening in the cyclopropyl cation derived from **2**.
(27) D. J. Pasto and J. A. Gontarz, *J. Am. Chem. Soc.*, **93**, 6902, 6909 (1971).

# Electrophilic and Radical Addition Reactions of a Bisalkylidenecyclopropane[1]

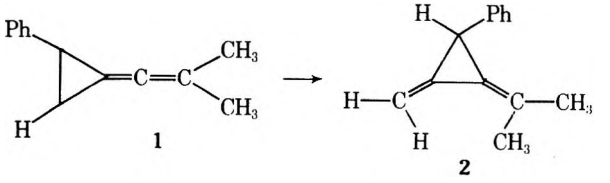
Daniel J. Pasto,* Ronald L. Smorada, Barry L. Turini, and David J. Wampfler

*Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556*

*Received July 8, 1975*

The reactions of 2-isopropylidene-3-phenylmethylenecyclopropane (**2**) with the electrophilic reagents acetic acid, mercuric acetate in acetic acid, benzenesulfenyl chloride (BSC), chlorosulfonyl isocyanate (CSI), and borane in tetrahydrofuran, and thiophenol have been investigated. The acetolysis of **2** and reactions with BSC and CSI occur by electrophilic attack on the methylene double bond giving ring-opened, butadiene-type products. The acetoxymercuration of **2** appears to occur by attack on the isopropylidene double bond. In the hydroboration of **2** attack occurs on both double bonds ultimately giving both ring-retained and ring-opened products. The addition of thiophenol to **2** occurs solely by attack of the thiophenoxy radical on the methylene group giving a ring-retained product of cis stereochemistry.

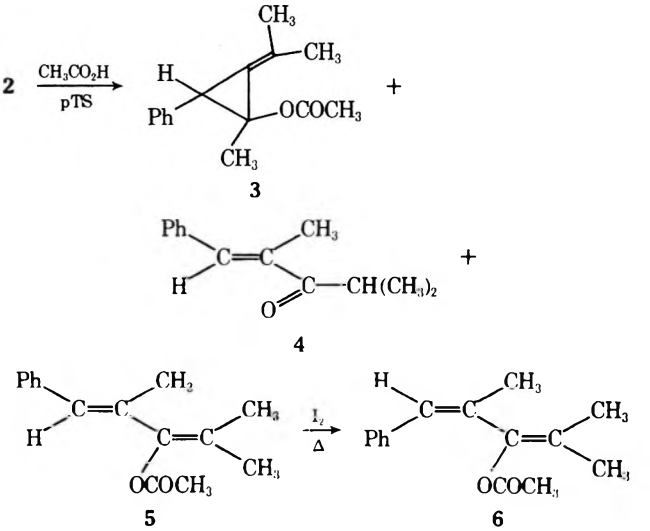
In conjunction with other chemical and physical studies of alkenylidenecyclopropanes carried out in our laboratories we initiated a stereochemical study of the thermal rearrangement of alkenylidenecyclopropanes to bisalkylidenecyclopropanes;[2] for example, the rearrangement of **1** to **2**. However, the high reactivity of **1** and **2** and the similarities in their physical properties have made separation of the mixtures of **1** and **2** very difficult. In an attempt to circumvent these problems we have investigated various reactions of **1** and **2** which could conceivably prove useful for converting **1** and **2** to more tractable and easily separated compounds still containing the chiral center present in **1** and **2**. In the foregoing article we have described some of the more interesting reactions of **1**;[3] in the present article we wish to report the results of similar studies with **2**.



**1** **2**

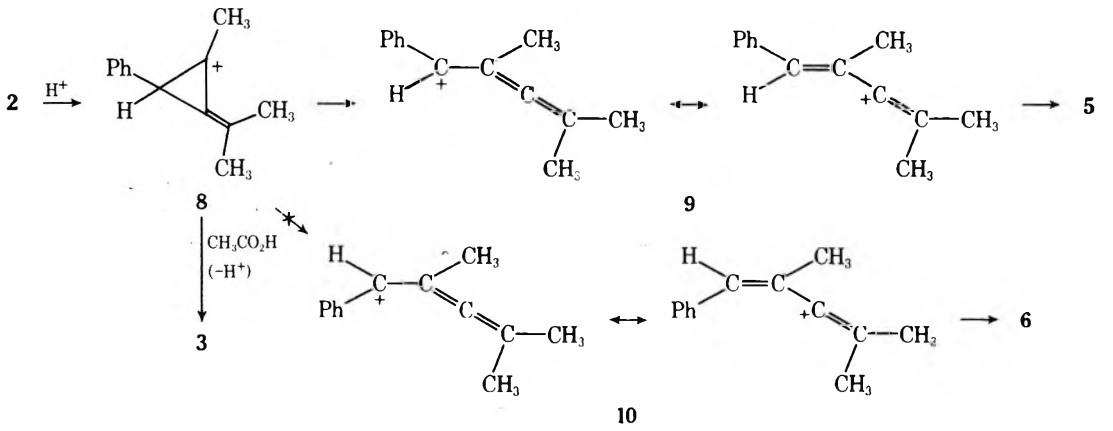
## Results and Discussion

**Acetolysis of 2.** Heating **2** in acetic acid at 115°C for prolonged periods of time did not result in acetolysis. The addition of a catalytic amount of *p*-toluenesulfonic acid, however, resulted in complete reaction at 115°C in 23 hr. Chromatographic separation on silica gel resulted in the isolation of small amounts of **3**[4] and **4**, with the major product being **5**. The structures of the products were identified



**3** **4** **5** **6**

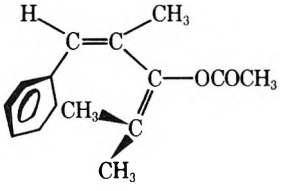
by their ir and NMR spectral properties. The ir spectrum of **3** shows a typical alkyl acetate band at 1736 $cm^{-1}$. In the NMR spectrum of **3** the isolated methyl appears as a singlet at $\delta$ 1.56 while the isopropylidene methyls appear as doublets at $\delta$ 1.96 and 2.06 ($J \simeq 1.1$ Hz). The cyclopropyl hydrogen appears as a multiplet at $\delta$ 2.17. The phenyl hy-



10

drogens appear as a singlet at δ 7.24 typical of a phenyl group attached to a saturated center. The unsaturated ketone **4** ($\nu_{C=O}$ 1665 $cm^{-1}$) appears to be a true reaction product and not an artifact of the work-up or separation procedures (by NMR analysis of the acetic acid reaction solution). The NMR spectrum of **4** shows a doublet at δ 1.31 ($J$ = 7.3 Hz) for the isopropyl methyls, a doublet for the vinyl methyl at δ 2.05 ($J$ = 1.3 Hz), a multiplet for the vinyl hydrogen at δ 6.36, and a multiplet for the aromatic hydrogens at ~δ 7.3.

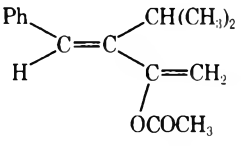
The acetate carbonyl of the major product **5** absorbs at 1755 $cm^{-1}$, typical of vinyl acetates. The isopropylidene methyls appear as singlets at δ 1.67 and 1.87, while the acetate methyl appears at δ 2.15 and the remaining vinyl methyl as a doublet at δ 1.94 ($J$ = 1.7 Hz). The vinyl hydrogen appears as a quartet at δ 6.58 with the aromatic hydrogens appearing as a broad singlet at δ 7.29. The stereochemistry of **5** is assigned on the basis of mechanistic reasoning, and by NMR spectral comparisons with **6** which is formed from **5** by thermal isomerization in the presence of iodine. Heating a deuteriochloroform solution of **5** in the presence of a trace of iodine resulted in the isomerization of **5** to **6** which possesses an NMR spectrum substantially different from that of **5**. The isopropylidene methyls of **6** are appreciably shielded in **6** (δ 1.06 and 1.17) relative to those in **5** (δ 1.67 and 1.87). In addition, the vinyl hydrogen of **6** is substantially deshielded (δ 7.56) relative to that in **5** (δ 6.58), and the β-styryl methyl group has shifted from δ 1.94 to 2.08. Inspection of molecular models of **5** and **6** indicate that the various groups experience substantially different long-range shielding effects by the phenyl and carbonyl groups in the two structures. It appears that an important conformation of **6** is that in which the isopropylidene group resides in a highly diamagnetic shielding region above the face of the aromatic ring.[5] There is no conformation of **5**



which places the isopropylidene group in such a shielding region.

From a mechanistic point of view, protonation of the methylene double bond of **2** produces the cyclopropyl cation **8**, which undergoes ring opening in a disrotatory manner. Rotation of the phenyl in an outward manner away from the isopropylidene group produces **9**, while inward rotation toward the isopropylidene group produces **10**. As the outward rotation is sterically more feasible, the formation of **9** dominates, ultimately producing **5**.[6] (It should be noted that **9** reacts to produce only **5**; no evidence was found for the formation of an allenyl acetate.) Whether **8** is a distinct intermediate capable of giving rise to **3** and **9**, or a transition state capable only of going to **9**, cannot be defined. The cyclopropyl acetate **3** could also be formed by a different mechanism, for example, via an AdE3 process.[7] The fact that ring opening of **8** involves cleavage of a vinyl C–C bond should be manifest in a slower rate of ring opening relative to cyclopropyl cations, the ring opening of which is calculated to have an energy barrier of only a few kilocalories.[8] If this change in structure results in a significant activation barrier for the ring-opening process, **8** could be an intermediate.

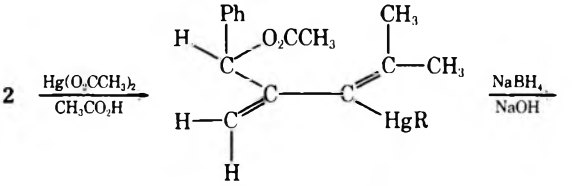
It is important to note that although **2** contains two double bonds, one a methylene and one an isopropylidene type, protonation occurs >98% at the methylene group. The NMR spectrum of the crude reaction product does not contain resonances typical of a terminal methylene in the alternative product **11**. One might have anticipated that pro-



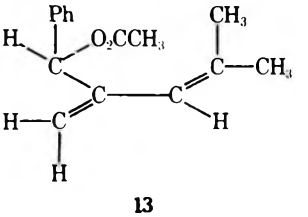
**11**

tonation on the more highly alkyl substituted double bond would have occurred in keeping with the known effect of alkyl substitution on the reactivity of double bonds toward electrophilic reagents.

**Acetoxymercuration of 2.** Acetoxymercuration of **2** followed by reductive demercuration with sodium borohydride followed by chromatographic separation produced low, variable yields of acetate **13** along with considerable quantities of bis(acetoxyalkyl)mercury **12b**[9] (see Experimental Section). The structure of **13** is clearly evident from

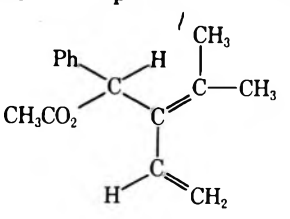


**12a**, R = $O_2CCH_3$
**b**, R = $C_{15}H_{17}O_2$



**13**

its ir and NMR spectra. Characteristic bands for an alkyl acetate and terminal methylene appear at 1739 and 909 $cm^{-1}$, respectively. The NMR spectrum displays three vinyl hydrogen resonances at $\delta$ 5.02, 5.35, and 5.47 which are broadened by long-range coupling. The resonance pattern is definitely not the expected AMX pattern for a $-CH{=}CH_2$ as would be present in the alternative structure **14**. In addition, the NMR spectrum of 13 contains overlap-

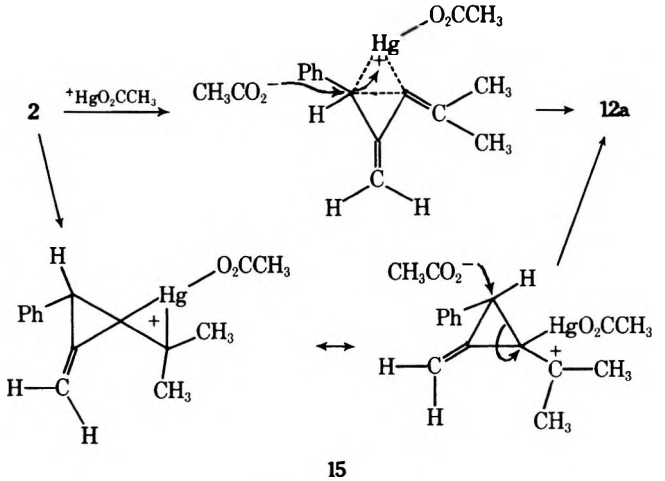


**14**

ping methyl doublets at $\delta$ 1.72 ($J$ = 1.1 Hz), a broadened singlet at $\delta$ 6.18 for the benzylic hydrogen, an acetate methyl singlet at $\delta$ 2.10, and an aromatic hydrogen singlet at $\delta$ 7.27.

The structure of the bis(alkoxyalkyl)mercury compound **12b** is indicated by its mass and NMR spectra. The mass spectrum of **12b** shows a series of parent ion peaks in the *m/e* 655–660 region with relative intensities comparable to the natural abundance ratio of the isotopes of mercury. The NMR spectrum contains two broad vinyl hydrogen resonances at $\delta$ 5.08 and 5.30.

Two mechanisms can be written for the formation of **12a**, one involving electrophilic attack on one of the bonds of the three-membered ring, the other involving attack on the isopropylidene double bond. Direct attack on a ring bond has been observed by DePuy and Van Lanen[10] in the solvomercuration of cyclopropanes. Attack on the isopropylidene double bond to produce the intermediate mercurinium ion **15** followed by conjugate attack by acetate ion on the three-membered ring[11] can also produce **12a**. Because of the vinylic nature of the bonds of the three-membered ring in **2** we favor the latter mechanism.



**15**

The apparent difference in the positions of electrophilic attack on **2** by proton and acetoxymercuri ion can be understood if one considers the mechanism of solvomercuration in greater detail. In prior studies we have shown that formation of the mercurinium ion intermediate occurs in a fast and reversible manner.[12] Attack by acetoxymercuri ion probably is also occurring at the methylene double bond of **2**, but owing to the lesser stabilization afforded the mercurinium ion by the hydrogens in the mercurinium ion formed by attack at the methylene double bond this ion reverts to reactants, while the ion formed by attack on the isopropylidene double bond leads to product formation. Apparently, the acetoxymercuri ion is not a sufficiently strong electrophile to cause sufficient cyclopropyl cation character to be developed which would result in ring opening as do the other electrophiles described in this article.

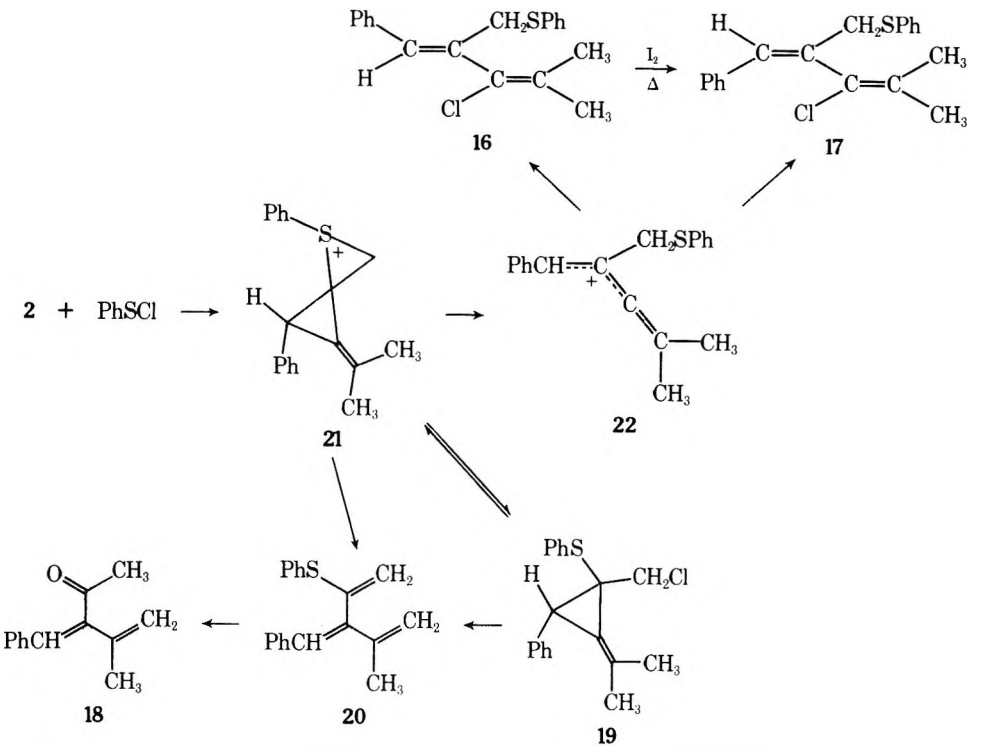
**Reaction of 2 with Benzenesulfenyl Chloride.** The NMR spectrum of the crude reaction mixture was very complex, indicating the formation of several products. Attempted chromatographic separation on silica gel resulted in the destruction of two of the original products with formation of a ketone whose structure was readily assigned. From the structure of the ketone and the NMR spectrum of the original product mixture structures can be assigned to all of the primary products.

Early fractions from the column contained pure **16** whose structure was readily assigned from its NMR and mass spectra. The NMR spectrum shows two methyl singlets ($\delta$ 1.86 and 1.90), a methylene singlet ($\delta$ 4.02), a vinyl hydrogen singlet ($\delta$ 6.62), and two five-proton aromatic singlets ($\delta$ 7.27 and 7.36). The presence of the $-CH_2SPh$ group, instead of a $-CH_2Cl$ group, is indicated by the mass spectrum, in which the molecular ion undergoes fragmentation by loss of thiophenoxy radical to give a chlorine-containing daughter ion, but does not show a substantial peak for loss of only a chlorine atom. The loss of the group from an allylic position occurs much more readily than from a vinylic position, thus placing the thiophenoxy group at the allylic position.

Later fractions contained a mixture of **16** and its stereoisomer **17**. Compound **17** was formed from **16** by heating with iodine in chloroform solution. Substantial differences exist between the chemical shifts of the isopropylidene methyl groups in **16** and **17**. In **17** these methyls are shielded ($\delta$ 1.34 and 1.79) relative to those in **16** ($\delta$ 1.86 and 1.90). Compound **17** is a true product of the reaction and is not formed by isomerization during chromatography as indicated by the presence of peaks of **17** in the NMR spectrum of the reaction product mixture.

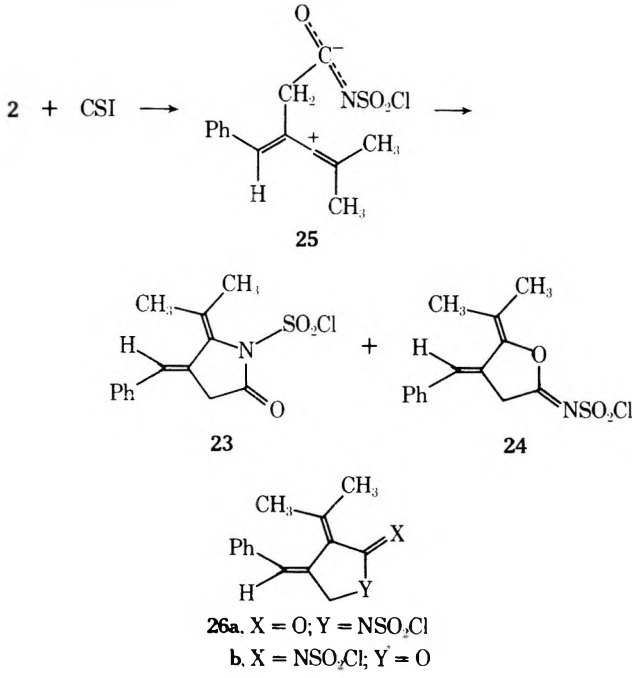
Late fractions from the column contained ketone **18**. The structure of **18** was indicated by its ir ($\nu_{C=O}$ 1663 $cm^{-1}$ and $\nu_{=CH_2}$ 913 $cm^{-1}$) and NMR spectra [vinyl methyl double doublet ($\delta$ 1.96, $J$ = 1.5, 1.0 Hz), ketone methyl singlet ($\delta$ 2.39), vinyl methylene multiplets ($\delta$ 4.97 and 5.32), and 6 H multiplet ($\delta$ 7.30)]. The presence of the benzylidene group was further demonstrated by the formation of benzaldehyde on ozonolysis of **18**. The presence of a methyl ketone was also indicated by the mass spectrum of **18**, in which the only dominant mode of fragmentation of the molecular ion was by loss of methyl radical.

Comparison of the NMR spectrum of **18** with that of the original product mixture clearly showed that **18** was not a primary product, and that it must have been formed by decomposition of one, or more, of the primary reaction products on the silica gel column. Peaks present in the NMR spectrum of the reaction mixture, but not present in the products eluted from the column, include vinyl methyl singlets at $\delta$ 1.91 and 1.94, an AB double doublet ($\delta$ 3.35 and 3.46, $J$ = 12.0 Hz), terminal methylene hydrogen multiplets ($\delta$ 4.88 and 4.98), and a benzylic vinyl hydrogen multiplet ($\delta$ 6.09). The presence of an AB system suggests the presence of a $-CH_2X$ group in a structure containing a chiral carbon. The only possible type of structure fulfilling these requirements is one in which the cyclopropane ring is retained. We believe that structure **19** fulfills these requirements, having two vinyl methyls and the diastereotopic methylene hydrogens. The formation of **19** can be visualized as involving chloride ion attack on the intermediate episulfonium ion **21**, instead of **21** undergoing ring opening to **22** which then results in the formation of **16** and **17**. On the surface of the silica gel **19** can give **20** directly, or it can revert to the epi-

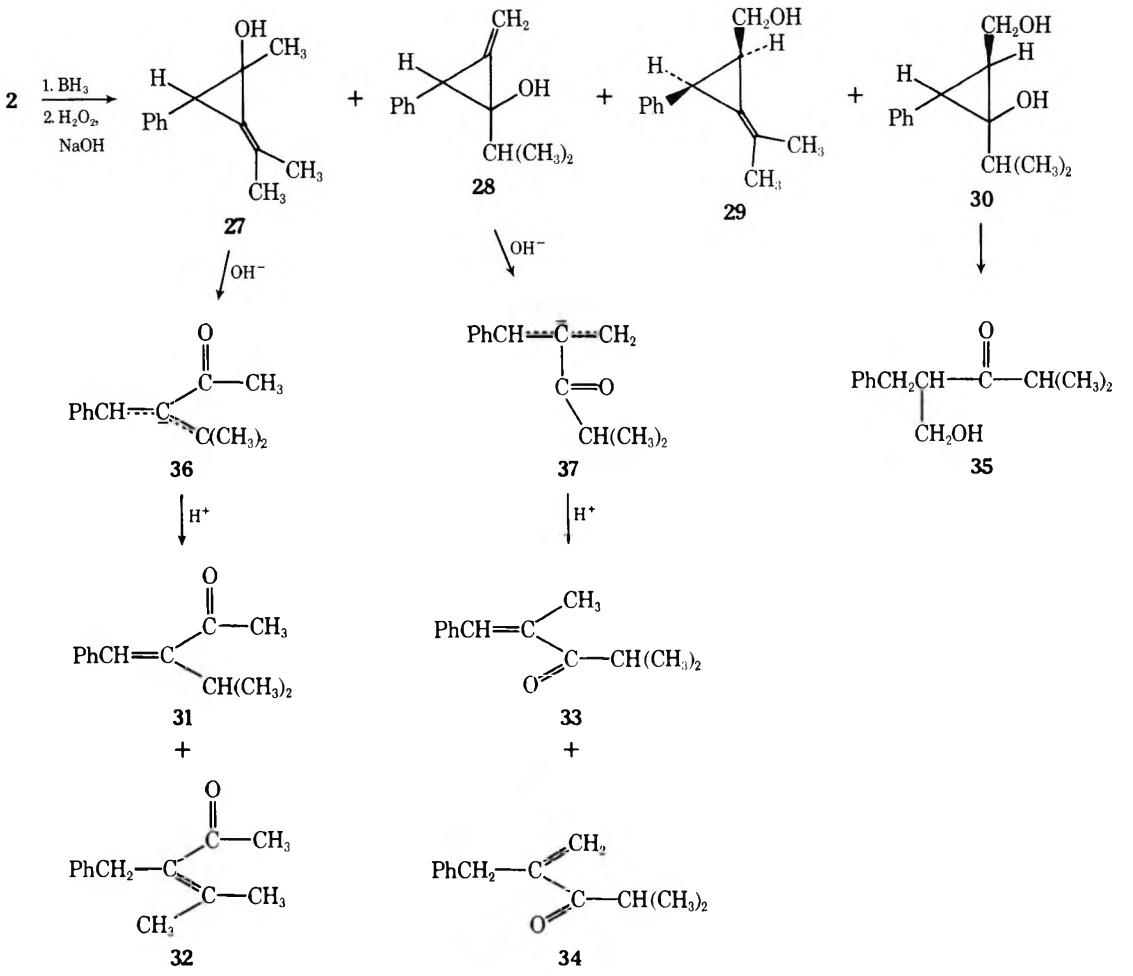


sulfonium ion **21**, which then rearranges to **20** and then hydrolyzes to the ketone **18**. The other product indicated to be present in the original reaction mixture is believed to be **20**, formed in the original reaction as indicated and hydrolyzed during chromatography.

**Reaction of 2 with Chlorosulfonyl Isocyanate.** The reaction of chlorosulfonyl isocyanate (CSI) with **2** in methylene chloride solution resulted in the clean formation of two products in a 78:22 ratio (by NMR). Attempted separation and purification by chromatography on Florisil (oven dried at 110° for 48 hr) resulted in complete decomposition. Attempted separation by low-temperature crystallization also met with failure. Attempted hydrolysis followed by isolation of the hydrolysis products also was not successful. (The extreme reactivity and sensitivity of the adducts must be due to the presence of the vinyl ester and amide functions. This is in contrast to the stability of the isomeric adducts **26a** and **26b** formed in the reaction of **1** with CSI which can be successfully chromatographed and hydrolyzed.)[13] Although neither product could be isolated in pure form, nor could any derivative thereof, the structures of the two adducts could be easily assigned from the NMR and ir spectra of the mixture. The major product is characterized by a peak in the ir at 1740 $cm^{-1}$ typical for the five membered ring *N*-chlorosulfonyllactam in **23**. The NMR spectrum of **23** shows methyl singlets at $\delta$ 2.02 and 2.16, a methylene doublet at $\delta$ 3.59 ($J$ = 2.3 Hz), a vinyl hydrogen triplet at $\delta$ 6.81 ($J$ = 2.3 Hz), and a multiplet at $\delta$ 7.33. The minor adduct **24** ($\nu_{C=N}$ 1595 $cm^{-1}$) shows methyl singlets at $\delta$ 2.06 and 2.22, a methylene doublet at $\delta$ 4.20 ($J$ = 2.6 Hz), a triplet at $\delta$ 6.50, and a multiplet at $\delta$ 7.33. The stereochemistry about the benzylidene group in **23** and **24** is assigned on the basis of mechanistic arguments and the NMR chemical shifts of the isopropylidene methyl groups. The "inside" methyl groups of **26**[13] and similar adducts[13,14] are highly shielded ($\delta$ 1.54 and 1.47, respectively, in **26a**) by the "inside" phenyl group. In the isomeric adducts with "outside" phenyl groups, the shielding effect of the phenyl group is absent and both methyls appear in the $\delta$ 2.0–2.3 region.[13,14] The absence of a highly shielded methyl group in **23** and **24** is consistent with the indicated stereochemistry. From a mechanistic point of view, in the opening of the three-membered ring during electrophilic attack on the $=CH_2$, the phenyl group moves toward the $-CH_2-$ group instead of toward the more sterically bulky isopropylidene group to produce the dipolar intermediate **25**, which then collapses to **23** and **24**. No evidence was obtained regarding the possible intermediate formation of a $\beta$-lactam derivative which would then undergo ring opening to the dipolar intermediate **25**.



**Hydroboration of 2.** The hydroboration of **2** (3:1 mole ratio of 2:$BH_3$) resulted in the formation of a complex mixture of compounds which was partially separated by chromatography on Florisil. Early fractions contained a mixture of the unsaturated ketones **32**, **33**, and **34** in a 35:27:38 ratio (by NMR). The infrared spectrum of the mixture showed characteristic bands for an $\alpha,\beta$-unsaturated ketone (1677 $cm^{-1}$), terminal methylene (923 $cm^{-1}$), and trisubstituted double bond (870 $cm^{-1}$). The mass spectrum showed

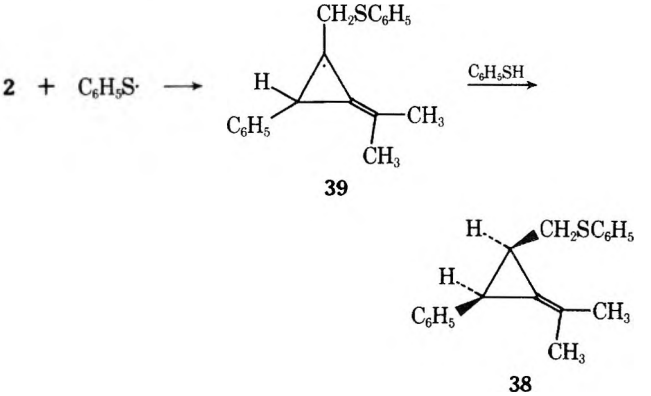


major peaks for loss of methyl and isopropyl radicals from the molecular ions. The NMR spectrum of the mixture was complex, but could be interpreted in terms of specific structures on the basis of relative intensities and peak positions (see Experimental Section for the NMR data). Compound 31 does not appear to have been formed in any substantial amount (i.e., <5%). The unsaturated ketones are formed from the cyclopropanols **27** and **28** which undergo base-catalyzed ring opening[15] to the anions **36** and **37** during the basic oxidation of the intermediate organoboranes.

Intermediate fractions contained the major product **29.** The NMR spectrum of **29** displayed two broadened vinyl methyl singlets at $\delta$ 1.88 and 1.92 (long-range coupled to the two cyclopropyl ring hydrogens), a broad multiplet at $\delta$ ~2.15, a highly broadened doublet at $\delta$ 2.90 with $J$ = 9.2 Hz (the benzylic hydrogen), an AB portion of an ABX system with $\delta_A$ 3.52, $\delta_B$ 3.19, $J_{AB}$ = 11.6, $J_{AX}$ = 5.6, and $J_{BX}$ = 8.0 Hz, and a singlet at $\delta$ 7.13. That structure **29** has the cis stereochemistry is indicated by the large coupling constant (9.2 Hz) between the cyclopropyl hydrogens.[16] This is consistent with the approach of the borane from the least hindered side of the ring opposite the phenyl group as is observed in other hydroboration reactions.[17]

The final fraction isolated possessed both hydroxyl (3430 $cm^{-1}$) and saturated ketone (1705 $cm^{-1}$) bands in the infrared spectrum. The structure is assigned as **35** based on its very characteristic NMR spectrum. The diastereotopically related methyls appear as doublets at $\delta$ 0.87 and 1.02 with the isopropyl methine hydrogen appearing as a septet at $\delta$ 2.47 ($J$ = 6.7 Hz). The diastereotopic benzyl hydrogens appear as two double doublets at $\delta$ 2.76 ($J$ = 10.7 and 4.9 Hz) and 2.84 ($J$ = 10.7 and 3.9 Hz). The carbinol methylene hydrogens appear as a tightly coupled AB portion ($\delta$ ~3.7) of an ABX system ($\delta_X$ ~3.13). Compound **35** is derived from the cyclopropanol **30,** a dihydroboration product, under the basic conditions of the oxidation of the intermediate organoborane.

**Addition of Thiophenol to 2.** Thiophenol undergoes rapid addition to **2** in the absence of solvent or in benzene solution at room temperature via what we believe to be a radical-chain addition to produce a single product **38.** The



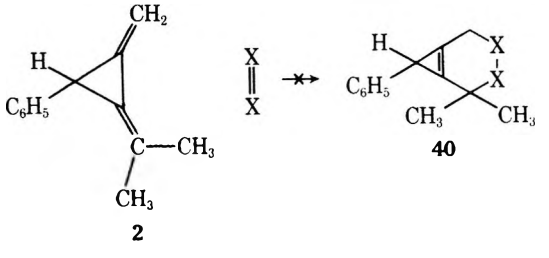
NMR spectrum of the product shows a one-hydrogen doublet ($\delta$ 3.11) with $J$ = 6.7 Hz. The chemical shift and the coupling constant indicate a cis relationship between the cyclopropyl hydrogens.[16] No vinyl or saturated methyl resonances (<5%) were present in the NMR spectrum which would be characteristic of an addition product formed by addition to the isopropylidene double bond.

The cis stereochemistry in **38** must be due to steric effects present in the transition state for abstraction of the

hydrogen atom from thiophenol by the intermediate radical **39**, thiophenol approaching **39** from the least hindered side of the three-membered ring opposite the phenyl group. The structure of the intermediate radical **39**, however, is not indicated by the overall stereochemical outcome of the reaction. A planar radical center would benefit from resonance interaction with the isopropylidene group but suffers from ring bond-angle strain. For a nonplanar radical center it would be the opposite. Should the radical center be nonplanar, inversion between nonplanar forms must be reasonably facile in that as initially formed the nonplanar radical should have the phenyl and phenylthiomethyl functions trans, whereas in the final product the two groups are cis.

**General Chemical Properties of 2.** The foregoing sections indicate that the diene chromophore of **2** undergoes electrophilic and radical attack only at the exocyclic methylene function to produce both ring-opened and ring-retained products. The greater tendency to form ring-retained products with **2** relative to **1** apparently is due to the more difficult cleavage of a vinyl ring bond in the cation derived from **2** relative to the allylic bond in the cation derived from **1**.[3] The reactivity of **2** and **1** are comparable as indicated by the consumption of approximately equal quantities of **2** and **1** when a mixture is treated with a limited quantity of CSI.

Although **2** contains a conjugated diene chromophore, **2** does not react with dienophiles such as maleic anhydride even under prolonged forcing conditions. Treatment with the very reactive dienophile 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) results in reaction; however, we have not been successful in purifying or characterizing the adduct.[18] In competition experiments **2** and **1** exhibit comparable reactivities with PTAD. The reactivity of **1**, however, is ~320 times less than that of *trans*-1,3-pentadiene,[19] which, in turn, is much less reactive than 1,3-dienes which are permanently constrained in a cisoid conformation (e.g., cyclopentadiene). The lack of reactivity of **2** toward cycloaddition can be attributed to any, or all, of three factors. (1) The diene chromophore of **2** is undoubtedly twisted, which decreases the overlap between the double bonds, which thus lowers the energy of the highest occupied molecular orbital. (2) Because of the geometry of the three-membered ring the termini of the diene chromophore are separated by a greater distance than in the normal cisoid dienes and thus the dieneophile has more difficulty in spanning that distance in the transition state. (3) The product is a $\Delta^{1,6}$-bicyclo[4.1.0]heptene system (**40**), a highly strained system.




**2** **40**

## Experimental Section

**Acetolysis of 2.** A solution of 0.7118 g of **2** in 1 ml of acetic acid containing 10 mg of *p*-toluenesulfonic acid was heated in a sealed NMR tube at 115° for 23 hr, at which time NMR analysis indicated complete consumption of **2** with formation of only **3**, **4**, and **5** in a ratio of 3:6:91. The reaction mixture was poured into 10 ml of cold water and was immediately extracted with ether. The extract was washed with 5% sodium bicarbonate until free of acid and dried ($MgSO_4$). The solvent was removed and the residue was chromatographed on a 2 × 36 cm Florisil column.

Elution with 25% dichloromethane–hexane gave ~70 mg of a mixture of **3** and **4**: ir 1736 and 1665 $cm^{-1}$; NMR of **3** ($CDCl_3$) δ 1.56 (s, 3 H), 1.96 and 2.06 (d's, $J$ = 1.1 Hz, 3 H each), 2.18 (s, 3 H), and 7.24 (s, 5 H); NMR of **4** δ 1.31 (d, $J$ = 7.3 Hz, 6 H), 2.05 (d, $J$ = 1.3, 3 H), 2.27 (m, 1 H), 6.36 (m, 1 H), and 7.3 (m, 5 H).

Further elution with 25% dichloromethane–hexane gave fractions containing **4** and **5** followed by fractions containing pure **5**: ir 1755 $cm^{-1}$; NMR ($CDCl_3$) δ 1.67 and 1.87 (s's, 3 H each), 1.94 (d, $J$ = 1.7 Hz, 3 H), 2.15 (s, 3 H), 6.58 (m, 1 H), and 7.29 (m, 5 H); mass spectrum $M^{\cdot+}$ 230.1330 (calcd for $C_{15}H_{18}O_2$, 230.1306).

**Iodine-Catalyzed Isomerization of 5.** A solution of 37 mg of **5** in 0.5 ml of deuteriochloroform containing one small crystal of iodine was sealed in an NMR tube and was heated at 95°. The NMR spectrum was recorded periodically. After heating for 168 hr conversion of **5** to **6** had progressed to ~80% completion: NMR of **6** δ 1.06 and 1.17 (s's, 3 H each), 2.00 (d, $J$ = 1.9 Hz, 3 H), 2.18 (s, 3 H), 7.3 (m, 5 H), and 7.56 (m, 1 H).

**Acetoxymercuration–Demercuration of 2.** To a stirred solution of 0.0949 g (0.56 mmol) of **2** in 10 ml of acetic acid and 10 ml of tetrahydrofuran was added 0.1842 g (0.58 mmol) of mercuric acetate at 0°. The reaction mixture was stirred at 0° for 75 min and then at 25° for 20 min. A fine, white precipitate formed during the reaction. A solution of 0.0874 g (2.3 mmol) sodium borohydride in 10 ml of 10% sodium hydroxide was slowly added. The reaction mixture was stirred for 45 min and the liquid layer was decanted from the mercury into 20 ml of water. The resulting mixture was extracted twice with ether. The ether extract was washed with water and 5% sodium bicarbonate and dried ($MgSO_4$). Removal of the ether under reduced pressure gave 0.1207 g of material.

Chromatography on silica gel produced two fractions. Elution with 50% dichloromethane–hexane gave 32.5 mg of **13** as a colorless, viscous oil: ir 1739 and 909 $cm^{-1}$; NMR ($CDCl_3$) δ 1.71 (overlapping d's, $J$ = 1.3 Hz, 6 H), 2.10 (s, 3 H), 5.02, 5.35, 5.47, and 6.20 (bs, 1 H each), and 7.28 (s, 5 H); mass spectrum $M^{\cdot+}$ 230.1316 (calcd for $C_{15}H_{18}O_2$, 230.1306), major peaks at $m/e$ 215 ($M^{\cdot+}$ – $CH_3\cdot$), 188 ($M^{\cdot+}$ – $H_2C{=}C{=}O$), 160, 145, 135, 133, 131, 97.

Elution with 50–75% dichloromethane–hexane gave 91.0 mg of a white solid identified as a bis(acetoxyalkyl)mercury: mass spectrum $M^{\cdot+}$ series of peaks $m/e$ 655–660 of relative intensities corresponding to the isotopic distribution of mercury (calcd for $C_{30}H_{34}O_4{}^{200}Hg$, 658); NMR ($CDCl_3$) δ 1.6 and 1.9 (bs's), 2.18 (s), 5.09, 5.32, and 6.62 (bs's), and 7.27 (m).

**Reaction of 2 with Benzenesulfenyl Chloride.** To a stirred solution of 0.1661 g (0.98 mmol) of **2** in 10 ml of dichloromethane containing ~50 mg of calcium carbonate at −70° was added 0.1401 g (0.97 mmol) of benzenesulfenyl chloride in 10 ml of dichloromethane. The reaction mixture was stirred at −60° for 30 min and was then allowed to come to room temperature and stirred for 25 min, producing a yellow solution. The reaction mixture was filtered and the solvent was removed under reduced pressure. The NMR of the reaction product was very complex, showing peaks in the vinyl methyl region at δ 1.34, 1.79, 1.86, 1.88, 1.90, 1.91, and 1.94. Characteristic lower field peaks were at δ 3.35 (d, $J$ = 12.0 Hz), 3.46 (d, $J$ = 12.0 Hz), 4.02 (s), 4.88 (m), 4.98 (m), 6.09 (bs), 6.62 (bs), and 7.3 (m).

Chromatography (78% total recovery based on **2**) on a 1 × 36 cm column of heat-treated silica gel (110° for 48 hr) resulted in immediate blackening of the top of the column upon adding the reaction mixture. Elution with hexane gave 10.5 mg of diphenyl disulfide (mp 55–56°) followed by 45.8 mg of **16** as a pale-yellow, viscous liquid: NMR ($CDCl_3$) δ 1.86 and 1.90 (s, 3 H each), 4.02 (s, 2 H), 6.62 (s, 1 H), 7.27 and 7.36 (s, 5 H each); mass spectrum $M^{\cdot+}$ 314.0880 (calcd for $C_{19}H_{19}ClS$, 314.0896), major peaks at $m/e$ 316 ($^{37}Cl$ containing $M^{\cdot+}$), 314 ($^{35}Cl$ containing $M^{\cdot+}$), 278 ($M^{\cdot+}$ – HCl, low intensity), 207 ($^{37}Cl$ containing $M^{\cdot+}$ – $C_6H_5S\cdot$), 205 ($^{35}Cl$ containing $M^{\cdot+}$ – $C_6H_5S\cdot$).

Further elution with hexane gave 12 mg of a 1:1 mixture of **16** and **17**, the latter identified by NMR spectral comparison with **17** prepared by isomerization of **16** (vide ante).

Elution with 50–100% chloroform–hexane gave 109 mg of **18** as a dark yellow, viscous material: ir (neat) 1663 and 913 $cm^{-1}$; NMR ($CDCl_3$) δ 1.96 (dd, $J$ = 1.5, 1.0 Hz, 3 H), 2.39 (s, 3 H), 4.97 and 5.32 (m's, 1 H each) and 7.3 (m, 6 H); mass spectrum $M^{\cdot+}$ 186.1042 (calcd for $C_{13}H_{14}O$, 186.1045), major peaks at $m/e$ 186, 171, 143, 128, 115.

**Iodine-Catalyzed Isomerization of 16.** A solution of 8 mg of **16** in 1 ml of deuteriochloroform containing two small crystals of iodine in a sealed NMR tube was heated in a sand bath at 95–100°. The NMR spectrum was recorded periodically. After about 30 hr an equilibrium mixture of **16** and **17** containing ~77% of the latter was obtained. The NMR spectrum of **17** showed peaks at δ 1.33 and 1.78 (s, 3 H each), 3.91 (s, 2 H), 6.94 (s, 1 H), and 7.27 (m, 5 H).

**Reaction of 2 with Chlorosulfonyl Isocyanate.** To a stirred

solution of 0.1259 g (0.74 mmol) of **2** in 15 ml of dichloromethane at 0° was added 0.1056 g (0.74 mmol) of chlorosulfonyl isocyanate in 15 ml of dichloromethane. The reaction mixture was stirred at 0° for 15 min and then allowed to come to 25° for an additional 35 min, resulting in a medium-red solution. The solvent was removed under reduced pressure, giving a red, viscous liquid containing **22** and **23** in an 87:13 ratio: ir 1740 and 1595 $cm^{-1}$; NMR ($CDCl_3$) of **22** $\delta$ 2.02 and 2.16 (s, relative intensities 3 H), 3.59 (d, $J$ = 2.3 Hz, 2 H), 6.81 (t, $J$ = 2.3 Hz, 1 H), and 7.33 (m, 5 H); **23** $\delta$ 2.06 and 2.22 (s, 3 H each), 4.20 (d, $J$ = 2.6 Hz, 2 H), 6.50 (t, $J$ = 2.6 Hz, 1 H), and 7.33 (m, 5 H).

Attempted chromatographic separation of **22** and **23** on dried Florisil resulted in decomposition of the compounds. Small amounts of several materials were eluted from the column; however, the NMR spectra of all of the fractions contained peaks *not present* in the original reaction mixture. The fractions eluted from the column were not further characterized.

Attempted hydrolysis in pH 5–7 buffer did not yield characterizable products.

**Hydroboration of 2.** To 1.3 ml of 0.7 $M$ borane in tetrahydrofuran (0.9 mmol) at 0° was added 0.471 g (2.8 mmol) of **2**. The reaction mixture was stirred for 20 min whereupon the mixture was allowed to come to 25° and was stirred for an additional 15 min. The reaction mixture was cooled to 0° and 10 ml of water was added followed by 2.5 ml of 3 $N$ sodium hydroxide and 2.5 ml of 30% hydrogen peroxide. After stirring for 30 min the mixture was extracted twice with ether. The extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was chromatographed on a 2 × 45 cm Florisil column set in benzene. Elution with benzene gave 99 mg of unreacted **2**.

Further elution with benzene gave 76 mg of a mixture of **32, 33,** and **34** as a yellow liquid: ir 1677, 923, and 870 $cm^{-1}$; mass spectrum $M^{\cdot+}$ 188.1198 (calcd for $C_{13}H_{16}O$, 188.1201), major peaks $m/e$ 173 ($M^{\cdot+} - CH_3\cdot$) and 145 [$M^{\cdot+} - \cdot CH(CH_3)_2$]. The peaks in the NMR spectrum ($CDCl_3$) could be assigned to the individual components by their relative intensities and positions: **32,** $=C(CH_3)$ singlets at $\delta$ 1.97 and 2.06, $-COCH_3$ singlet at 2.37, $C_6H_5CH_2-$ singlet at 3.67, and $C_6H_5-$ at ~7.25; **33,** $-CH(CH_3)_2$ doublet at $\delta$ 1.14, $=CCH_3$ broad singlet at 2.03, $-CH(CH_3)_2$ septet at 3.34 ($J$ = 6.7 Hz), $=CH-$ broad singlet at 6.54, and $C_6H_5-$ multiplet at ~7.3; **34,** $-CH(CH_3)_2$ doublet at $\delta$ 1.15, $-CH(CH_3)_2$ septet at 2.84 ($J$ = 6.7 Hz), $C_6H_5CH_2-$ broad singlet at 3.57, $=CH_2$ broad singlets at 5.57 and 5.97, and $C_6H_5-$ at ~7.30.

Elution with 10% ether–benzene gave 210 mg of **29** as a viscous, pale yellow liquid: ir $\nu_{OH}$ 3670 and 3510 $cm^{-1}$ (nonbonded and bonded O–H); mass spectrum $M^{\cdot+}$ 188.1197 (calcd for $C_{13}H_{16}O$, 188.1201), major peaks $m/e$ 170 ($M^{\cdot+} - H_2O$), 157 ($M^{\cdot+} - \cdot CH_2OH$), 155, 145, 143, 142, 141, 129, *128,* 127, 117, 115; NMR ($CCl_4$) $=C(CH_3)_2$ broad singlets at $\delta$ 1.88 and 1.92, $>CHCH_2OH$ broad multiplet at 2.15 ($J$ = 9.2 Hz), $C_6H_5CH<$ very broad doublet at 2.90 ($J$ = 9.2 Hz), $-CH_AH_BOH$ double doublet at 3.19 ($J$ = 11.6 and 8.0 Hz), $-CH_AH_BOH$ double doublet at 3.52 ($J$ = 11.6 and 5.6 Hz), and $C_6H_5-$ at 7.13.

Elution with 25% ether–benzene gave 57 mg of **35** as a low-melting solid: ir ($CHCl_3$) $\nu_{OH}$ 3430 and $\nu_{C=O}$ 1705 $cm^{-1}$; mass spectrum $M^{\cdot+}$ 206.1310 (calcd for $C_{13}H_{18}O_2$, 206.1307), major peaks $m/e$ 188 ($M^{\cdot+} - H_2O$), 176 ($M^{\cdot+} - CH_2OH$ by a McLafferty-type rearrangement), 175 ($M^{\cdot+} - \cdot CH_2OH$), 145, 133, 117, 105, *91,* and 77; NMR ($CDCl_3$) $-CH(CH_3)(CH_3)$ doublets at $\delta$ 0.87 and 1.02 ($J$ = 6.7 Hz), $-CH(CH_3)_2$ septet at 2.47 ($J$ = 6.7 Hz), $-CH_AH_BC_6H_5$ doublets at 2.76 ($J$ = 10.7 and 4.9 Hz) and 2.84 ($J$ = 10.7 and 3.9 Hz), $>CH-$ multiplet at 3.13, $HOCH_AH_BCH<$ multiplet at ~3.7, and $C_6H_5-$ multiplet at 7.3.

**Reaction of 2 with Thiophenol.** The addition of an equimolar quantity of **2** to thiophenol, either neat or dissolved in benzene (~1 $M$), open to the laboratory light and atmosphere results in rapid reaction (~30 min) to give a viscous, pale-yellow liquid (after removal of the benzene if carried out in benzene solution). The NMR spectrum of the crude product ($CDCl_3$) showed broad singlets at $\delta$ 1.79 and 1.94 (3 H each), a very broad multiplet at 2.39 (1 H), a multiplet at ~2.86 (2 H), a doublet at 3.11 ($J$ = 6.7 Hz, 1 H), and a multiplet at 7.23 (10 H). Chromatography on silica gel (elution with 20% benzene–hexane) gave a single fraction with an NMR spectrum identical with that of the crude product. Mass spectrum $M^{\cdot+}$ 280.1286 (calcd for $C_{19}H_{20}S$, 280.1286), only major fragmentation peak at $m/e$ 171 ($M^{\cdot+} - C_6H_5S\cdot$).

**Registry No.**—**2,** 30896-86-7; **3,** 57443-49-9; **4,** 57443-50-2; **5,** 57443-51-3; **6,** 57443-52-4; **13,** 57553-35-3; **16,** 57443-53-5; **17,** 57443-54-6; **18,** 57443-55-7; **22,** 57443-56-8; **23,** 57443-57-9; **29,** 57443-58-0; **32,** 14771-80-3; **33,** 57443-59-1; **34,** 57443-60-4; **35,** 57443-62-6; **38,** 57443-61-5; acetic acid, 64-19-7; mercuric acetate, 1600-27-7; e benzenesulfenyl chloride, 931-59-9; diphenyl disulfide, 882-33-7; chlorosulfonyl isocyanate, 1189-71-5; thiophenol, 108-98-5.

## References and Notes


(1) Research supported in part by the donors of the Petroleum Research Fund, administered by the American Chemical Society.
(2) D. J. Pasto, unpublished results.
(3) D. J. Pasto and M. F. Miles, *J. Org. Chem.*, preceding paper in this issue.
(4) The formation of three membered ring retained products has also been observed in reactions with **1** (ref 3).
(5) L. Pauling, *J. Chem. Phys.*, **4,** 673 (1936).
(6) A similar preference for rotation of the plane of the H–C–$C_6H_5$ group in the sterically least hindered manner has been observed in reactions of **1** with electrophiles (ref 3) and cycloaddition reagents [see D. J. Pasto and J. K. Borchardt, *J. Am. Chem. Soc.*, **96,** 6937, 6944 (1974), and references cited therein].
(7) See R. C. Fahey, *Top. Stereochem.*, **3,** 237 (1968).
(8) P. Merlet, S. D. Peyerimhoff, R. J. Buenker, and S. Shih, *J. Am. Chem. Soc.*, **96,** 959 (1974), and references cited therein.
(9) It is our experience that the reductive demercuration of vinylmercurials produces extensive amounts of bisvinylmercurials (see also ref 3). Increasing the amount of excess sodium borohydride reduces the amount of bisvinylmercurial, but we have not been successful in completely suppressing its formation.
(10) C. H. DePuy and R. J. Van Lanen, *J. Org. Chem.*, **39,** 3360 (1974).
(11) S. Danishefsky, S. J. Etheredge, J. Dynak, and P. McCurry, *J. Org. Chem.*, **39,** 2658 (1974).
(12) D. J. Pasto and J. A. Gontarz, *J. Am. Chem. Soc.*, **93,** 6902, 6909 (1971).
(13) D. J. Pasto, A. F.-T. Chen, G. Cuirdaru, and L. A. Paquette, *J. Org. Chem.*, **38,** 1015 (1973).
(14) D. J. Pasto, A. F.-T. Chen, and G. Binsch, *J. Am. Chem. Soc.*, **95,** 1553 (1973); D. J. Pasto and A. F.-T. Chen, *ibid.*, **93,** 2562 (1971).
(15) C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, *J. Am. Chem. Soc.*, **88,** 3347 (1966).
(16) R. M. Silverstein, G. C. Bassler, and T. C. Morrill, "Spectrometric Identification of Organic Compounds", 3rd ed, Wiley, New York, N.Y., 1974, p 226.
(17) D. J. Pasto and F. M. Klein, *J. Org. Chem.*, **33,** 1468 (1968).
(18) The NMR spectrum of the product indicates the presence of vinyl hydrogen and methyl groups indicating that an "ene" reaction had possibly occurred (in part).
(19) D. J. Pasto, J. K. Borchardt, T. P. Fehlner, H. F. Baney, and M. E. Schwartz, *J. Am. Chem. Soc.*, **98,** 526 (1976).

# Reaction of Dilithium Derivatives of Oximes with Electrophiles. Regiospecific Substitution of Ketones

William G. Kofron* and Ming-Kuo Yeh

*Chemistry Department, The University of Akron, Akron, Ohio 44325*

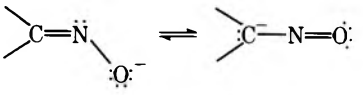
*Received September 15, 1975*

Dilithium derivatives of ketoximes react with alkyl halides and carbonyl compounds to give α-substituted oximes. The position of substitution is governed by the configuration of the oxime. The intermediate monolithio oximes are configurationally stable, allowing successive substitution on the same carbon. Since no oxime exchange is observed with carbonyl compounds, directed aldol condensation is possible.

Many methods have been developed for the introduction of a carbon chain onto the α carbon of a ketone, an important one being alkylation of an enolate or equivalent species. For example, potassium enolates, formed from the ketone with potassium hydride,[1] enamines, from the ketone and a secondary amine,[2] metalloenamines, from ketone and primary amine (via an imine) and an organometallic reagent,[3] all have been developed as a means of introduction of the alkyl group into a ketone. A serious problem which arises in these routes is the lack of control over the position of alkylation if the ketone has two different activated carbons. We now find that the dilithium derivatives of ketoximes, formed from the oxime and 2 equiv of alkyllithium reagent, react with electrophilic reagents (alkyl halides and carbonyl compounds), and that the reaction is regiospecific, the position of substitution being controlled by the stereochemistry of the oxime.

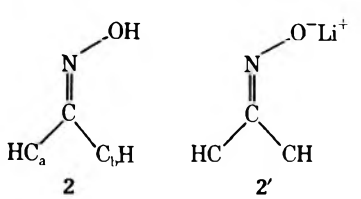
Dilithiation of oximes has previously been demonstrated.[4,5] The oxime of acetophenone was alkylated with benzyl chloride, and oximes of several substituted acetophenones and α-tetralone, cyclopentanone, and cyclohexanone were acylated and cyclized to isoxazoles.[5] Apparently the stereochemical features of the reactions were not examined.

Of all the azomethine ketone derivatives, oximes have been the most thoroughly studied. Generally oximes are configurationally stable, and configuration may be fairly reliably assigned.[6] An anion of an oxime would be expected to have less configurational stability than the oxime itself, since one contributing structure (1) has lost its stereochem-



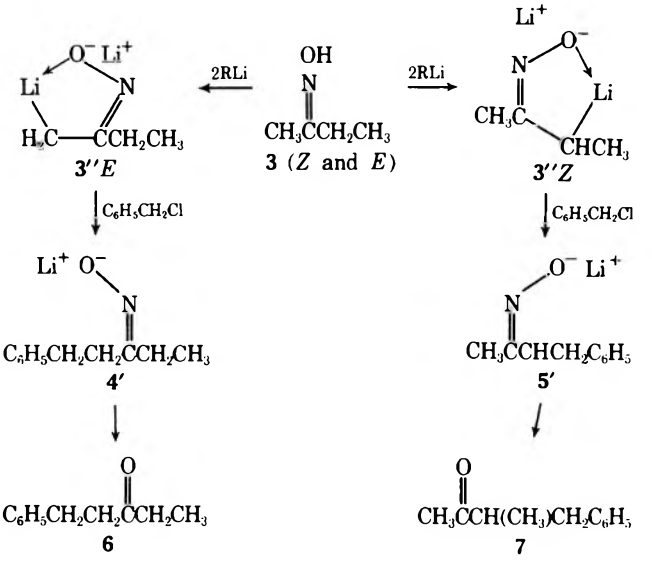
1

ical identity. However, in none of our studies at −78° or at room temperature (with the possible exception of mesityl oxide oxime) have we observed loss of stereochemical integrity. The configuration would be expected to be maintained in the dianion (2″), since chelation would be expected to play an important role.[4,7] It is this chelation, we believe, that directs the metalation onto that α carbon cis to the oxime hydroxyl group, and which is responsible for the regioselectivity of the reactions reported here. It is interesting to note that although azines, imines, and phenylhydrazones also can show stereoisomerism of the type shown by oximes, and chelation is apparently important in their metal derivatives, no directive effect of geometry has been observed.[3-5]



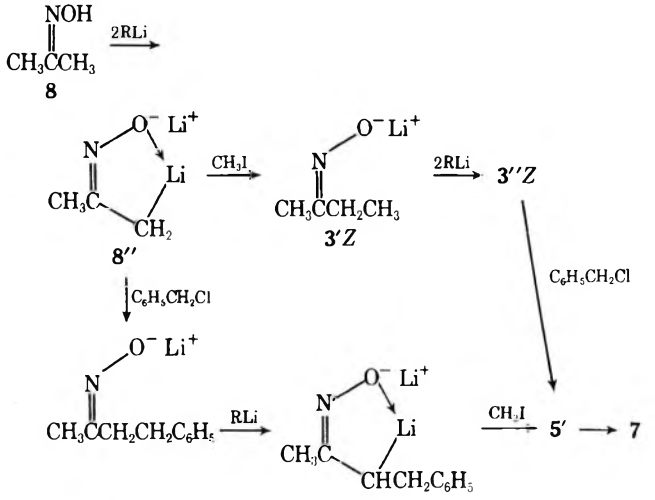
2 2′ 2″

The oxime prepared from 2-butanone consists of 72% of the *E* and 28% of the *Z* isomer.[8] When a solution of this oxime mixture in tetrahydrofuran was treated with 2 molar equiv of butyllithium, a two-step reaction could be observed. The first half of the butyllithium caused the solution to become white (milky), but the mixture finally became clear and yellow when the second half had been added. The lithium salt (2′) is apparently not completely soluble in the THF–hexane medium, but is converted by the second equivalent of butyllithium to the soluble dilithio derivative (2″). When the yellow solution was treated with 1 mol of benzyl chloride, the yellow color was discharged and the milky appearance noted. After aqueous work-up of the reaction and hydrolysis of the resulting oximes, gas chromatography showed two products in 73:27 ratio, identified (separately) by NMR as, respectively, 1-phenyl-3-pentanone (**6**) and 3-methyl-4-phenyl-2-butanone (**7**). This experiment was interpreted as a conversion of the mixture of oximes (**3**), each stereoselectively, to the corresponding dilithio derivative (**3″*E*** and **3″*Z***), benzylation without change in configuration to the two lithium salts (**4′** and **5′**), and hydrolysis to the two isomeric ketones (**6** and **7**).



That the formation of the dilithio derivative from each oxime is truly stereoselective, and the agreement of product isomer distribution with oxime stereoisomer distribution is not simply a coincidence, was demonstrated by sequential methylation and benzylation of acetone oxime. When acetone oxime (**8**) was converted to its dilithio derivative (**8″**) and treated with 1 equiv of methyl iodide, only the lithium salt of the *Z* oxime (**3′*Z***) was produced; **3′*Z*** was

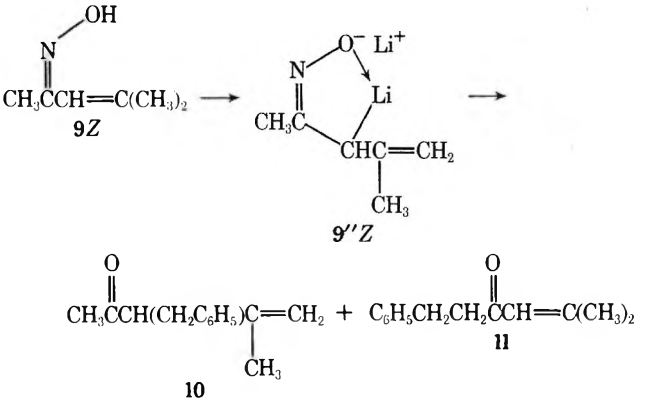
converted to a single dilithio derivative (3″Z) by reaction with a third mole of butyllithium. Reaction of this dilithio derivative with benzyl chloride gave, after hydrolysis, exclusively ketone 7 (67% yield from acetone oxime). Similarly, benzylation of 8″ followed by lithiation and methylation again gave isomer 7 (64% yield from acetone oxime; 1% of isomer 6 was indicated by gas chromatography).



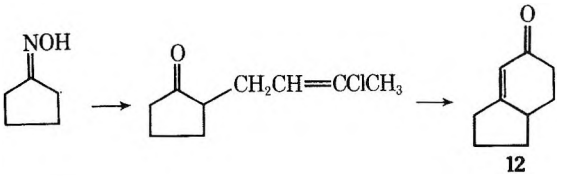
It would be gratifying to report that this method of alkylation is completely successful, but candor compels us to state that attempts to introduce a third alkyl group onto the same carbon atom of acetone failed completely, and in no case have we been successful in alkylating a tertiary carbon atom. Apparently the metalation step fails, since either treatment of the reaction mixture containing 5′ (from either sequence) with a fourth mole of butyllithium, treatment of a *Z* oxime (such as 5) from a secondary alkyl ketone, or a dialkylation series on a ketoxime such as cyclohexanone oxime did not give the expected yellow solution indicating formation of a dilithio derivative (2″), but generally gave brownish solutions, reaction of which with alkyl halides did not give the desired product. The oxime of 3-methyl-2-butanone was reported to consist of 14% of the *Z* and 86% of the *E* isomer.[8] When this mixture of oximes was benzylated via the dilithio derivative the product consisted of 71% of 2-methyl-5-phenyl-3-pentanone, 17% of 1,2-diphenylethane, and 12% of unidentified material which was not 3,3-dimethyl-4-phenyl-2-butanone. Thus it appears that only the *E* isomer of the oxime undergoes metalation and alkylation.

The oxime obtained directly from an unsymmetrical ketone is usually either mainly or completely that isomer with the hydroxyl trans to the larger group. Thus 2-methylcyclohexanone yields an oily oxime which shows two spots on TLC, but from which the crystalline *E* isomer, mp 42.5–43.5°, can be obtained. Beckmann rearrangement of the crystalline oxime produces in 69% yield a single lactam, 6-heptanolactam. When cyclohexanone oxime was methylated via its dilithio derivative, none of the *E* oxime was detected in the product by TLC (a small amount of cyclohexanone oxime was indicated), and Beckmann rearrangement gave 2-methylhexanolactam and 6-heptanolactam in a ratio of 9:1.[9] Similarly, 2-benzylcyclohexanone yields a crystalline (*E*) oxime, mp 125.5–126°. From the benzylation of cyclohexanone oxime we obtained the crystalline *Z* oxime, mp 103.6–104.4°, which was converted to the *E* oxime (mp 125°) when held at 130° for 3 min. Thus this alkylation is an excellent method for stereospecific synthesis of thermodynamically less favored oxime isomers.

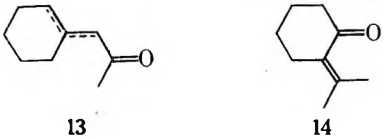
Mesityl oxide forms a mixture of oximes (65% *E*, 35% *Z* by NMR), from which the hydrochloride of the *Z* oxime can be crystallized, and pure crystalline *Z* oxime (9*Z*) obtained. When the dilithio *Z* oxime (9″*Z*) was benzylated, hydrolysis afforded a mixture consisting of 62% of 3-benzyl-4-methyl-4-penten-2-one (10) and 21% of 1-phenyl-5-methyl-4-hexen-3-one (11). Benzylation of the mixture of oximes (65% *E*) afforded a mixture containing 71% of 11 and 11% of 10. The oxime of mesityl oxide is more labile than those discussed previously, and formation of 11 from 9*Z* does not indicate that the reaction is not stereoselective.[10]



Alkylation of cyclopentanone, difficult by other methods owing to the tendency of the ketone to undergo aldol condensation in the presence of basic reagents, was accomplished via the oxime in fair yield. From cyclopentanone oxime 2-butylcyclopentanone was obtained in 59% yield (from butyl iodide), 2-allylcyclopentanone in 64% yield (from allyl bromide), and 2-benzylcyclopentanone in 64% yield. Also, cyclopentanone oxime was converted to 5,6,7,8-tetrahydroindan-5-one (12) by alkylation with 1,3-dichloro-2-butene, hydrolysis to the ketone, and cyclization with sulfuric acid.



**Aldol Condensation.** The problems associated with directing the aldol condensation between two carbonyl compounds toward one of the four products have been discussed elsewhere.[11] The most successful method has been the reaction of a lithio imine with a ketone.[12] We have found that dilithio oximes react with carbonyl compounds to give aldols, and do not observe exchange or other side reactions which plague the previous methods. Thus from dilithio acetone oxime and cyclohexanone were obtained cyclohexylideneacetone and cyclohexenylacetone (13), while from dilithio cyclohexanone oxime and acetone was obtained isopropylidenecyclohexanone (14).



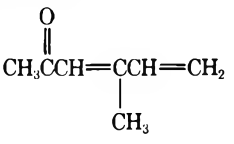
**Conjugate Addition Reactions.** It is interesting that when conjugate addition reactions were attempted between dilithio oximes and Michael acceptors none of the 1,4 adduct was produced. When dilithio acetone oxime was treated with 3-buten-2-one, none of the expected[13] conjugate addition product was obtained, but the dienone 15 was obtained in 17% yield. Acrolein with 8″ also gave dienone 16

Table I
Alkylation and Aldol Condensation of Dilithio Oximes

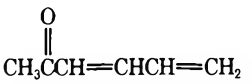
| Oxime | Alkylating agent | Registry no. | Oxime cleavage[a] | Product | Yield, % |
|---|---|---|---|---|---|
| $CH_3CCH_3$ (8) | $C_6H_5CH_2Cl$ | 100-44-7 | A | $C_6H_5CH_2CH_2CCH_3$ | 72 |
| 8 | $C_4H_9I$ | 542-69-8 | B | $C_5H_{11}COCH_3$ | 63[b] |
| (20) | $C_6H_5CH_2Cl$ | | B | 2-$C_6H_5CH_2C_6H_9O$ | 77 |
| 20 | $CH_2$=$CHCH_2Br$ | 106-95-6 | B | 2-$CH_2$=$CHCH_2C_6H_9O$ | 65 |
| 20 | $C_4H_9I$ | | A | 2-$C_4H_9C_6H_9O$ | 59 |
| 20 | $C_4H_9Br$ | 109-65-9 | A | 2-$C_4H_9C_6H_9O$ | 35 |
| 20 | $C_4H_9Cl$ | 109-69-3 | A | 2-$C_4H_9C_6H_9O$ | 24 |
| 20 | $C_4H_9I$ | | C | 2-$C_4H_9C_6H_9O$ | 58 |
| (21) | $C_6H_5CH_2Cl$ | | D | 2-$C_6H_5CH_2C_5H_7O$ | 64 |
| 21 | $C_4H_9I$ | | A | 2-$C_4H_9C_5H_7O$ | 59 |
| 21 | $CH_2$=$CHCH_2Br$ | | B | 2-$CH_2$=$CHCH_2C_5H_7O$ | 64 |
| 8 | 1. $CH_3I$ 2. $C_6H_5CH_2Cl$ | 74-88-4 | A | $CH_3COCH(CH_3)CH_2C_6H_5$ | 67 |
| 8 | 1. $C_6H_5CH_2Cl$ 2. $CH_3I$ | | D | $CH_3COCH(CH_3)CH_2C_6H_5$ | 64 |
| 8 | $(C_6H_5)_2C$=$O$ | 119-61-9 | A[c] | $(C_6H_5)_2C$=$CHCOCH_3$ | 55 |
| 8 |  | 108-94-1 | A | 13 | 51 |
| 20 | $CH_3COCH_3$ | 67-64-1 | B[c] | 14 | 48 |
| 20 | $CH_3CHO$ | 75-07-0 | A | 2-$CH_3CH$=$C_6H_8O$ | 45 |
| 8 | $CH_3CCH$=$CH_2$ | 78-94-4 | B | $CH_3CCH$=$C(CH_3)CH$=$CH_2$ | 17 |
| 8 | $CH_2$=$CHCHO$ | 107-02-8 | B | $CH_3CCH$=$CHCH$=$CH_2$ | 15 |
| $CH_3CH_2CH$=$NOH$ | $C_6H_5CH_2Cl$ | | B | $C_6H_5CH_2CH(CH_3)CH$=$O$ | 37 |
| 21 | $ClCH_2CH$=$CClCH_3$ | 926-57-8 | B | $CH_3CCl$=$CHCH_2C_5H_7O$ | 54[d] |

[a] Yields are based on ketone isolated after hydrolysis of the oxime. Method A employed $Cr(OAc)_2$ with the oxime acetate; see ref 15. Method B employed $TiCl_3$; see ref 16. Method C employed $Na_2S_2O_5$; see ref 17. Method D employed $Ce(NH_4)_2(NO_3)_6$; see ref 18. [b] 2-Heptanone oxime was isolated in 84% yield. We believe that the yields of the oximes in these reactions are substantially higher than the yields of ketones indicated. [c] Hydroxy ketones were obtained from hydrolysis of the oximes; dehydration was effected by steam distillation from a solution containing oxalic acid. [d] After distillation the oxime was obtained in 71% yield. The ketone was cyclized to 5,6,7,8-tetrahydroindan-5-one; see Experimental Section.

in 15% yield, and acrylonitrile or ethyl acrylate with 8″ gave only resinous material.

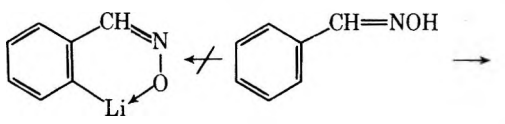


15



16

**Aldoximes.** The alkylation of dilithio aldoximes was not successful. From propionaldehyde oxime the benzylated material was obtained in 33% yield, but attempts to alkylate acetaldehyde oxime gave no identifiable product. Benzaldoxime was of interest because of the possibility of a six-membered chelate to give ortho metalation (17), but reaction of benzaldehyde oxime with 2 mol of butyllithium



17

$$[C_6H_5C{\equiv}N] \longrightarrow C_6H_5COC_4H_9 + C_6H_5COCHC_3H_7$$

18 19

followed by methyl iodide gave 1-phenylpentanone (18) and 2-methyl-1-phenylpentanone (19), presumably via benzonitrile. Examination of the product mixture from acetaldoxime by infrared spectrometry revealed absorption at 2460 $cm^{-1}$, suggestive of a nitrile.

Finally, since $\alpha$-oximino ketones are readily made by nitrosation of ketones, it was of interest to examine such an oxime, which would allow $\beta$-alkylation of a ketone. However, 2,3-butanedione monoxime reacted with butyllithium to give the carbonyl adduct, and hydrolysis gave 3-hydroxy-3-methyl-2-heptanone. Butylmagnesium bromide has similarly been reported to add to the carbonyl group of this oxime.[14]

The results of these experiments are summarized in Table I.

## Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus; the thermometer was calibrated with the standards provided. Infrared spectra were determined on a Perkin-Elmer Model 337 spectrometer; NMR spectra on a Varian A-60 spectrometer.

**Preparation of Oximes.** Generally oximes were prepared in aqueous ethanol from the ketone, hydroxylamine hydrochloride, and sodium hydroxide. Crystalline oximes were recrystallized from hexane or from ethanol. Oximes of 2-butanone, 3-methyl-2-buta-

none, mesityl oxide, benzaldehyde, acetaldehyde, and propionaldehyde were distilled before recrystallization.

**Alkylation of Oximes.** Since the procedures for the reactions were so similar, a few representative experiments are described in detail. In general the oxime was hydrolyzed without purification. Yields in Table I are yields of distilled ketone. Methods of cleavage of oximes are reported in ref 15–18. Reactions with ketones gave aldol oximes, which were cleaved to aldols in a separate step and dehydrated.

**Alkylation of Cyclopentanone Oxime. 5,6,7,8-Tetrahydro-5-indanone.** To a stirred solution of 5 g (0.05 mol) of cyclopentanone oxime in 70 ml of tetrahydrofuran at room temperature was added during 5 min 60 ml (0.1 mol) of 1.66 M butyllithium in hexane. After 30 min a solution of 6.3 g (0.05 mol) of 1,3-dichloro-2-butene was added to the yellow-brown lithium derivative during 15 min. The resulting light brown solution was stirred for 1 hr, and 40 ml of water was added. The organic layer was separated, combined with an ether extract of the aqueous layer, dried over magnesium sulfate, and evaporated. Distillation of the residue gave 7.7 g (71%) of 2-(3′-chloro-2′-butenyl)cyclopentanone oxime: bp 131–135° (1.3 mm); ir (film) 3240, 1660, 1656 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 9.76 (s, 1 H, OH), 5.50 (t, 1 H, vinyl), 2.42 (m, 5 H, $\alpha$-CH, $\alpha$-$CH_2$, allylic $CH_2$), 2.10 (s, 3 H, $CH_3$), 1.75 (m, 4 H, $CH_2$). The oxime was hydrolyzed by the method of Timms[16] to 6.39 g (54% overall) of 2-(3′-chloro-2′-butenyl)cyclopentanone: bp 93–95° (1.2 mm); ir (film) 1736, 1665 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 5.48 (t, 1 H, vinyl), 2.70–1.30 (overlapping peaks, 12 H).

A portion of the chloro ketone was cyclized. A mixture of 4.3 g (0.025 mol) of ketone and 6 ml of 90% sulfuric acid was stirred at room temperature overnight, poured into 50 g of ice, and extracted with ether. The ethereal solution was dried over magnesium sulfate and concentrated. The residue, 3.4 g, was shown by gas chromatography to consist of 1.6 g of 5,6,7,8-tetrahydroindan-5-one (33% from cyclopentanone oxime) [ir (film) 1660, 1620 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 5.74 (m, 1 H, vinyl), 2.8–1.1 (overlapping peaks, 11 H); 2,4-dinitrophenylhydrazone mp 196.5–197.5° (lit.[19] 199.5°)] and 1.8 g of 2-hydroxy-2-methylbicyclo[3.2.1]octan-8-one [ir (film) 3400, 1750 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 2.67 (s, 1 H, OH), 1.84 (overlapping peaks, 10 H), 1.33 (s, 3 H, $CH_3$)]. The samples for spectra were collected from the gas chromatograph.

**Twofold Alkylation of Acetone Oxime. 3-Methyl-4-phenyl-2-butanone.** To a solution of 1.46 g (0.05 mol) of acetone oxime in 70 ml of THF was added during 5 min 60 ml (0.1 mol) of 1.66 M butyllithium in hexane. The yellow solution was stirred for 30 min in an ice bath. A solution of 7.46 g (0.053 mol) of methyl iodide in 30 ml of THF was added slowly. The resulting milky white suspension was allowed to warm to room temperature and 34 ml (0.056 mol) of butyllithium was added. The yellow solution was stirred for 30 min and a solution of 6.33 g (0.05 mol) of benzyl chloride in 30 ml of THF was added. The resulting yellow solution was stirred for 1 hr, 50 ml of water was added, and the aqueous solution was separated and extracted with ether. The combined organic solution was dried over magnesium sulfate and evaporated. An aliquot (two-fifths) of the crude oxime was converted to the ketone by the method of Corey.[15] Distillation gave 2.16 g (67%) of 3-methyl-4-phenyl-2-butanone: bp 53–57° (0.05 mm) [lit.[20] 72–73.5° (0.5 mm)]; NMR ($CCl_4$) $\delta$ 7.10 (s, 5 H, Ar), 2.70 (m, 1 H, $\alpha$-CH), 1.94 (s, 3 H, $CH_3$), 1.02 (d, 3 H, $CH_3$); 2,4-dinitrophenylhydrazone mp 75–77° (lit.[21] 76–77°). Gas chromatography indicated the ketone to be homogeneous (the isomers **6** and **7** were separated by GC).

**Aldol Condensation. 2-Ethylidenecyclohexanone.** Dilithio cyclohexanone oxime was prepared from 5.65 g (0.05 mol) of cyclohexanone oxime in 70 ml of THF and 0.1 mol of butyllithium (60 ml of 1.66 M solution). The yellow solution was stirred in a dry ice–acetone bath for 15 min, and a solution of 2.64 g (0.05 mol) of acetaldehyde in 40 ml of THF was added. The solution was allowed to warm to room temperature and 40 ml of saturated brine was added. The aqueous layer was extracted with 80 ml of a 2:1 mixture of ether and acetone. The organic solutions were combined, dried over magnesium sulfate, and evaporated. The crude oxime was hydrolyzed by the method of Corey[15] to give 2-(1′-hydroxyethyl)cyclohexanone. The crude aldol was combined with 45 g (0.5 mol) of oxalic acid and 300 ml of water and distilled. The distillate was saturated with sodium chloride and extracted with ether. The ethereal solution was dried over magnesium sulfate and distilled to give 2.88 g (46%) of 2-ethylidenecyclohexanone: bp 88–91° (12 mm) [lit.[22] 68–70° (7 mm)]; ir (film) 1695, 1622 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 6.58 (quartet of triplets, 1 H, vinyl, $J_q$ = 7, $J_t$ = 2 Hz), 2.67–1.17 (overlapping t and m, 4 H, $\alpha$-$CH_2$, allylic $CH_2$), 1.70 (doublet of triplets, 3 H, $CH_3$, $J_d$ = 7, $J_t$ = 1 Hz), 1.82 (m, 4 H, $CH_2$); 2,4-dinitrophenylhydrazone mp 216.5–218° (lit.[22] 219–220°).

**Isolation of a Less Stable Oxime. 2-Benzylcyclohexanone (*Z*)-Oxime.** To a yellow solution of dilithio cyclohexanone oxime, prepared from 5.65 g (0.05 mol) of cyclohexanone oxime in 70 ml of THF and 60 ml of 1.66 M butyllithium (0.1 mol), was added a solution of 6.33 g (0.05 mol) of benzyl chloride in 30 ml of THF. The yellow solution was stirred for 1 hr and 50 ml of water was added. The aqueous layer was extracted with ether and the combined organic solution was dried over magnesium sulfate and evaporated. The residue was recrystallized from methanol to give 8.63 g (85%) of 2-benzylcyclohexanone (*Z*)-oxime: mp 103.6–104.4°; ir (KBr) 3240, 1664 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 9.76 (s, 1 H, OH), 7.18 (s, 5 H, Ar), 3.74 (m, 1 H, $\alpha$-CH), 2.78 (d, 2 H, $ArCH_2$), 2.26 (m, 2 H, $\alpha$-$CH_2$), 1.50 (m, 6 H, $CH_2$); 2,4-dinitrophenylhydrazone mp 162.5–164° (lit.[23] 163–165°). A portion (1 g) of the *Z* oxime was heated in an oil bath to 130° for 3 min and cooled, and the solid recrystallized from methanol to give 0.85 g of 2-benzylcyclohexanone (*E*)-oxime: mp 125° (lit.[24] 125.5–126.5°); ir (KBr) 3230, 1675 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 8.13 (s, 1 H, OH), 7.22 (s, 5 H, Ar), 2.72 (m, 5 H, CH, $CH_2$), 1.62 (m, 6 H, $CH_2$).

**Registry No.**—**7**, 2550-27-8; **8**, 127-06-0; **8″**, 57428-27-0; **12**, 1489-28-7; **20**, 100-64-1; **20** dilithio derivative, 57428-28-1; **21**, 1192-28-5; **21** dilithio derivative, 57428-29-2; 2-(3′-chloro-2′-butenyl)cyclopentanone oxime, 57428-30-5; 2-(3′-chloro-2′-butenyl)cyclopentanone, 57428-31-6; 2-hydroxy-2-methylbicyclo[3.2.1]octan-8-one, 57428-32-7; 2-ethylidenecyclohexanone, 1122-25-4; 2-benzylcyclohexanone (*Z*)-oxime, 57428-33-8; 2-benzylcyclohexanone (*E*)-oxime, 57428-34-9; 2-methylcyclohexanone, 583-60-8; 2-methylcyclohexanone (*E*)-oxime, 32179-89-8.

## References and Notes


(1) C. A. Brown, *J. Org. Chem.*, **39**, 3913 (1974).
(2) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954).
(3) G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).
(4) F. E. Henoch, K. G. Hampton, and C. R. Hauser, *J. Am. Chem. Soc.*, **91**, 676 (1969).
(5) C. F. Beam, M. C. D. Dyer, R. A. Schwarz, and C. R. Hauser, *J. Org. Chem.*, **35**, 1806 (1970).
(6) C. G. McCarty in "The Chemistry of the Carbon-Nitrogen Double Bond", S. Patai, Ed., Interscience, New York, N.Y., 1970.
(7) F. N. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 701 (1962).
(8) K. D. Berlin and S. Rengaraju, *J. Org. Chem.*, 36, 2912 (1971).
(9) Thin layer chromatography and NMR spectra show slow interconversion of oximes in solution or the liquid state at room temperature. See also ref 6, p 384.
(10) See P. A. S. Smith and E. P. Antoniades, *Tetrahedron*, **9**, 210 (1960).
(11) G. Wittig, *Angew. Chem., Int. Ed. Engl.*, **7**, 7 (1968).
(12) G. Wittig, *Angew. Chem., Int. Ed. Engl.*, **2**, 683 (1963).
(13) F. Lewis, Thesis, The University of Akron, 1971.
(14) P. Freon, *Ann. Chim. (Paris)*, **11**, 470 (1939).
(15) E. J. Corey and J. C. Richman, *J. Am. Chem. Soc.*, **92**, 5276 (1970).
(16) G. H. Timms and E. Wildsmith, *Tetrahedron Lett.*, 195 (1971).
(17) S. H. Pines, J. M. Chemerda, and M. A. Kozlowski, *J. Org. Chem.*, **31**, 3446 (1966).
(18) J. W. Bird and D. G. M. Diaper, *Can. J. Chem.*, **47**, 145 (1969).
(19) V. Prelog and M. Zimmerman, *Helv. Chim. Acta*, **32**, 2360 (1949).
(20) C. L. Arcus, L. A. Cort, T. J. Howard, and L. B. Loc, *J. Chem. Soc.*, 1195 (1960).
(21) R. Jacquier, M. Mousseron and S. Boyer, *Bull. Soc. Chim. Fr.*, 1653 (1956).
(22) A. S. Dreiding and S. N. Nickel, *J. Am. Chem. Soc.*, **76**, 3967 (1954).
(23) R. Fusco, F. Tenconi, C. Pirola, and M. Riva, *Farmaco, Ed. Sci.*, **20**, 393 (1965); *Chem. Abstr.*, **63**, 8246*b* (1965).
(24) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

# Electrochemistry of Natural Products. VI. Oxidative Decarboxylation of Some Tetrahydroisoquinoline-1-carboxylic Acids[1]

J. M. Bobbitt* and Theresa Y. Cheng

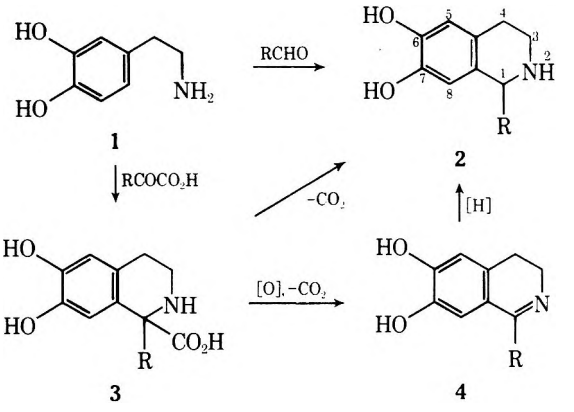
*Department of Chemistry, The University of Connecticut, Storrs, Connecticut 06268*

*Received July 29, 1975*

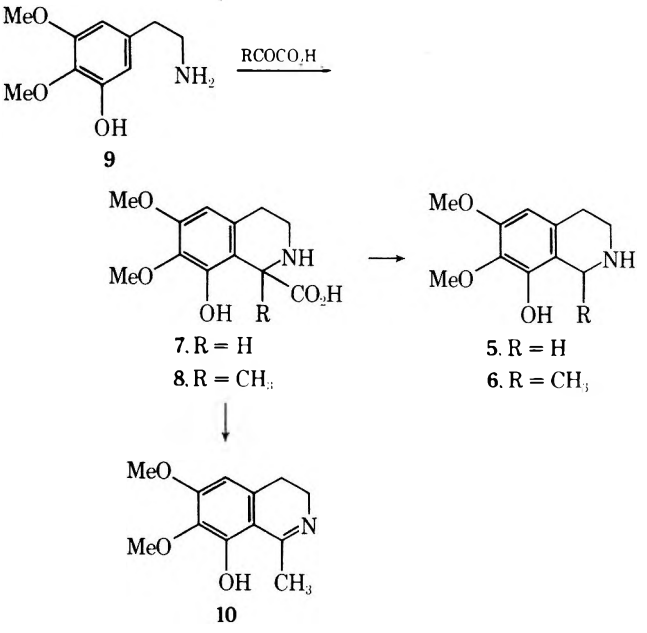
A series of oxygenated 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids has been electrochemically oxidatively decarboxylated to yield 3,4-dihydroisoquinolines. The 3,4-dihydro derivatives were reduced chemically to tetrahydro derivatives for isolation. Overall yields were 50–90% in simple cases. The ease of decarboxylation was correlated with the electron density of the aromatic ring, and the decarboxylation is thought to be triggered by removal of electrons through the ring, making it an example of the pseudo-Kolbe reaction. The effect of various functional groups was studied, and a concerted two-electron mechanism is proposed. The reaction tends to support Hahn's theory of the biosynthesis of isoquinoline alkaloids by providing a laboratory analogy for the crucial decarboxylation step. The possible impact of this observation on classical ideas of oxidative phenol coupling reactions is discussed.

The nitrogen atom, carbons 3 and 4, and the aromatic ring of the isoquinoline portion of the isoquinoline alkaloids are derived biosynthetically from tyrosine, probably by way of 3,4-dihydroxyphenylalanine (Dopa) and β-(3,4-dihydroxyphenyl)ethylamine (dopamine, **1**).[2] The source of carbon 1, the various groups attached to it, and the mode of ring closure have not been clearly established. Two major theories have emerged as shown in Scheme I.[3] According to one theory, carbon 1 is an aldehyde carbon; the ring closure is a classical Pictet–Spengler reaction; and the tetrahydroisoquinoline is formed directly (**1** → **2**). According to the second theory, generally attributed to Hahn,[4a] and recently considered by others,[4b,c] carbon 1 is derived from the ketone carbonyl of an α-keto acid (**1** → **3**) and a decarboxylation is needed to yield the final product (**3** → **2**). Both ring closures have been shown to take place readily under "physiological conditions" when a free phenol group is ortho or para to the point of closure. Since α-keto acids are more stable metabolites than aldehydes and are readily available by transamination reactions from amino acids, the Hahn route is the more plausible of the two possibilities. The problem with the Hahn theory is that no methods have been found for decarboxylating the tetrahydroisoquinoline-1-carboxylic acids (**3**) under any conditions that could be termed "physiological". In this paper, we would like to describe a decarboxylation reaction which may well suit this purpose.

Scheme I




Scheme II

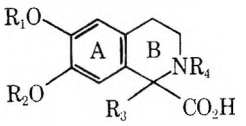



Kapadia, Leete, Fales, and their co-workers[3] have recently shown that the cactus alkaloids, anhalamine (**5**) and anhalonidine (**6**), are definitely synthesized in the plant by the Hahn route (Scheme II). The intermediate carboxylic acids, **7** and **8**, were isolated from the cactus and shown by radioactive tagging experiments to be intermediates. The interesting point to us was that when acid **8** was incubated with fresh cactus slices, the product of the decarboxylation reaction was not the alkaloid **6**, but the 3,4-dihydroisoquinoline **10**. Thus, it appeared that the crucial decarboxylation may be an *oxidative decarboxylation* (**3** → **4**) and that a reduction step (**4** → **2**) may be necessary to yield the alkaloid. Since the logical site for any oxidation of the carboxylic acids would be the phenol groups present in the aromatic ring, or even the ring itself, it appeared that our experience in the electrochemical oxidation of phenols[1b] might be applicable. Thus, a series of substituted isoquinoline derivatives, **11**–**20** (Table I), was prepared for study.

**Preparation of Starting Materials.** Compounds **11**, **12**, and **13** were prepared from the appropriate phenylethylamines and pyruvic acids by a classical Pictet–Spengler synthesis[5] (**1** → **3**) and suitably modified by methylation[6] and/or acetylation[7] to give **15**, **17**, and **18**. Compounds **14** and **16** were prepared through a Bischler–Napieralski reaction[8] to yield 3,4-dihydroisoquinolines which were substituted at the 1 position by the Reissert sequence worked out by Shamma and Jones.[9] Compounds **19**[10] and **20**[4a] are known and were prepared by a Pictet–Spengler synthesis.

The NMR spectra of compounds **12**–**18** are summarized in Table II as far as they were interpretable. In addition to the peaks noted, the compounds showed entirely predict-

Table I
Tetrahydroisoquinoline-1-carboxylic Acids



| Compd | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| 11 | H | H | $C_6H_5CH_2$ | H |
| 12 | H | $CH_3$ | $p$-$CH_3OC_6H_4CH_2$ | H |
| 13 | H | $CH_3$ | $p$-$HOC_6H_4CH_2$ | H |
| 14 | $CH_3$ | H | $C_6H_5CH_2$ | H |
| 15 | H | $CH_3$ | $p$-$CH_3OC_6H_4CH_2$ | $CH_3CO$ |
| 16 | $CH_3$ | $CH_3$ | $p$-$HOC_6H_4CH_2$ | H |
| 17 | $CH_3$ | $CH_3$ | $p$-$CH_3OC_6H_4CH_2$ | H |
| 18 | $CH_3$ | $CH_3$ | $p$-$CH_3OC_6H_4CH_2$ | $CH_3CO$ |
| 19 | H | H | $CH_3$ | H |
| 20 | H | $CH_3$ | $CH_3$ | H |

A. Those containing two phenol groups (**11** and **19**) are oxidized at potentials 0.2–0.3 V lower than those containing one phenol group (**20**, **12–15**), and those containing no phenol groups (**17** and **18**) are relatively difficult to oxidize. Second, it makes little difference whether the free phenol group is meta (**14** and *m*-hydroxyphenylacetic acid) or para (**12** and *p*-hydroxyphenylacetic acid) to the phenylacetic acid part of the molecule. This is of interest because a para phenol group is necessary to promote a facile isoquinoline ring closure (**1** → **3**). It is interesting, however, that a phenol group in ring A is not necessary for decarboxylation since **17** and **18** are decarboxylated, albeit with complicating secondary reactions.

As will be shown subsequently, the initial products of the preparative oxidations of compounds **11–15** and **17** at potentials similar to the values of the lowest half-wave potential are, indeed, the predicted 3,4-dihydroisoquinolines

Table II
NMR Spectral Data on Starting Materials and Products

| Compd | Solvent[a] | NMR Shift, $\delta$[b] $C_5$ H | $C_8$ H | 6-$OCH_3$ | 7-$OCH_3$ | $C_\alpha$ H | Other |
|---|---|---|---|---|---|---|---|
| 12 | $CD_3CN$–NaOD | 6.28 | 7.16 | | 3.80 | 3.25 AB, ics = 8 Hz $J_{AB}$ = 13 Hz | |
| 13 | $CD_3CN$–NaOD | 6.34 | 7.23 | | 3.81 | 3.14 AB, ics = 19 Hz $J_{AB}$ = 13 Hz | |
| 14 | $Me_2SO$–NaOD | 6.49 | 7.13 | 3.66 | | 3.12 AB, ics = 12 Hz $J_{AB}$ = 13 Hz | |
| 15 | Acetone-$d_6$ | 6.38 | 7.00 | | 3.75 | | 2.02, $CH_3CO$ |
| 16 | $Me_2SO$–NaOD | 6.48 | 7.24 | 3.74 | 3.67 | | |
| 17 | $CF_3CO_2H$ | 6.99 | 7.59 | 4.1 | 4.03 | | 3.99, $OCH_3$ |
| 18 | Acetone-$d_6$ | 6.51 | 7.11 | 3.82 | 3.76 | | 3.63, $OCH_3$ 3.0, $CH_3CO$ |
| 22 | $Me_2SO$–$CCl_4$–$CF_3CO_2H$ | 6.86 | 7.56 | | 3.86 | 4.47 | |
| 25 | $CDCl_3$ | 6.66 | 6.66 | | 3.83 | 4.15 | 3.83 4-$OCH_3$ |
| 26 | $CDCl_3$–NaOD | 6.81 | 6.57 | 3.83 | | 4.15 | 7.32, benzyl |
| 27 | $CDCl_3$–$Me_2SO$ | 6.81 | 6.81 | | 3.70 | | 3.80, 4-$OCH_3$, 7.53, AB, ics = 50 Hz, $J_{AB}$ = 8 Hz |
| 28 | $CDCl_3$ | 6.49 | 6.49 | 3.77 | 3.70 | | 7.16, benzyl |
| 29 | $Me_2SO$–HCl | 6.67 | 6.25 | | 3.57 | | 3.33 $C_\alpha$ $OCH_3$ |
| 30 | $Me_2SO$–HCl | 6.63 | 6.24 | | 3.56 | | 3.3, 3.2 two $C_\alpha$ $OCH_3$ |
| 32 | $CDCl_3$ | 6.80 | 7.00 | 3.80 | 3.88 | | 7.53, AB, ics = 58 |
| 33 | $CCl_4$–$CDCl_3$–NaOD | 6.52 | 6.40 | 3.75 | 3.67 | 4.15 | Hz, $J_{AB}$ = 9 Hz |
| 34 | $CDCl_3$ | 6.74 | 6.74, 7.30 | | 3.75, 3.80 | 4.92, 5.05 | 1.80 $COCH_3$ 4.1, 4-$OCH_3$ |
| 35 | $CDCl_3$ | 7.29 | 6.92 | | 3.90 | 4.17 | 1.9 $COCH_3$ |

[a] $Me_2SO$ is dimethyl sulfoxide; NaOD and DCl imply that the solvent was just basified or acidified with NaOD–$D_2O$ or DCl–$D_2O$, respectively. [b] The term ics refers to the distance between the inner peaks of a pattern.

able aromatic peaks for the protons on the benzyl ring and poorly resolved multiplets in the region of $\delta$ 2.5–3.5 corresponding to four protons on carbons 3 and 4. The most interesting feature is the presence of the $C_8$ H at exceptionally low fields (over $\delta$ 7), probably due to the conformation of the molecule dictated by the carboxyl group at $C_1$.

**Voltammetry.** Compounds **11–20**, *m*- and *p*-hydroxyphenylacetic acids, and the reaction products **22** and **27** were studied by cyclic voltammetry in two solvent systems, 0.1 *M* $NaHCO_3$ in MeOH–$H_2O$, 6:4, and 0.1 *M* NaOMe in MeOH. The cyclic voltammograms (Figure 1 for **12** is representative) seem to indicate an irreversible EC process.[11] The half-peak potentials are given in Table III.

Several conclusions may be drawn from the data in Table III. First, the ease of oxidation can be directly correlated with the number of free phenol groups present in ring shown in Schemes I (**4**) and II (**10**). Since such a decarboxylation requires the loss of two electrons and a coulometric experiment on **12** indicated a two-electron reaction, it is reasonable to believe that the lowest half-wave potential is that of a two-electron oxidation. The second half-wave potential at about +0.3–0.4 V observed for most of the compounds and the products, **22** and **27** (Scheme II), is apparently associated with the 3,4-dihydroisoquinoline moiety in some as yet unknown way. It is of interest to note that the half-wave potential of the decarboxylated product (of **12**, for example) is about 0.2 V higher than that of the starting carboxylic acid. Thus, the oxidation has a convenient "stopping place" which will be referred to in the Discussion.

It appears from the data that the oxidative decarboxylation depends upon the relative electron density in the aro-

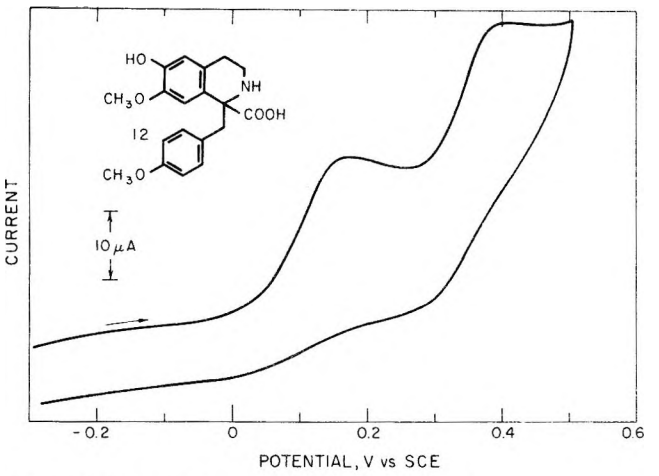



**Figure 1.** Cyclic voltammogram of compound 12.

matic ring and, further, that the electrons are probably withdrawn through the aromatic ring. Two recent papers in electrochemistry clearly point to the same conclusion. Coleman, Utley, and Weedon[12] studied the decarboxylation of a series of substituted phenylacetic acids (some are in Table III), and concluded that electron-rich ring systems tended to promote a two-electron, oxidative reaction leading to carbonium ion formation at the carbon containing the original carboxyl group.[13] Furthermore, the oxidations of some anthracene-10-acetic acids and their salts have supported this conclusion.[14] Eberson has called this type of reaction a "pseudo-Kolbe reaction".

**Preparative Oxidations and Products.** Preparative oxidations of compounds **11–18** were carried out in two solvent systems, 0.1 *M* NaOMe in MeOH and 0.1 *M* $NaHCO_3$ in MeOH–$H_2O$ (2:1). The anode was graphite felt; the cathode was platinum; the potential was controlled by a potentiostat against a standard calomel electrode; and the reactions were carried out under nitrogen in a two-compartment cell.[15] The two solvent systems each had advantages and disadvantages. Oxidations in the NaOMe system took place at lower potentials and showed less electrode coating than those in the $NaHCO_3$ system. Frequently, however, overoxidation to 1-benzoyl-3,4-dihydroisoquinolines (such as **27, 31** and **32**) or to $\alpha$-methoxy derivatives (such as **29** and **30**) was unavoidable in the NaOMe system. The $NaHCO_3$ system allowed cleaner reactions for some of the substrates, but frequently led to serious electrode coating. Furthermore, some of the substrates were not very soluble in the $NaHCO_3$ system.

The products of the various reactions are shown in Scheme III, and their NMR spectra are summarized in Table II. Under optimized conditions for each substrate, compounds **11, 12,** and **14** were decarboxylated to the dihydroisoquinolines **21, 22,** and **23,** and reduced in the electrolytic cell with $NaBH_4$ to give the tetrahydroisoquinolines **24, 25,** and **26.** Compounds **11** and **14** were decarboxylated in the NaOMe system whereas **12** was oxidized in the $NaHCO_3$ system. The diphenol **24** was methylated to the known compound **28**[16] in an overall yield of 66%. Compound **25** was obtained in a yield of 88%. It gave the correct analysis and had the NMR pattern expected. Compound **26** is known[17] and was obtained in 52% yield.

In the oxidations of **11, 12,** and **14,** the immediate products of electrooxidation, **21, 22,** and **23,** were observed by TLC to be the sole or major products. The TLC spots on silica gel GF254 had a characteristic blue fluorescence when viewed at 254 and at 360 nm. In the oxidation of **12,** the intermediate dihydro compound, **22,** was isolated and partially characterized. This oxidation, carried out in the

**Table III**
**Half-Wave Potentials of Some Tetrahydroisoquinoline-1-carboxylic Acids and Reference Compounds**

| Compd | Hydroxyl groups in ring A | Half-wave potentials: 0.1 *M* $NaOCH_3$ in MeOH, 1st wave | 0.1 *M* $NaOCH_3$ in MeOH, 2nd wave | 0.1 *M* $NaHCO_3$ in MeOH–$H_2O$ (2:1), 1st wave | 0.1 *M* $NaHCO_3$ in MeOH–$H_2O$ (2:1), 2nd wave |
|---|---|---|---|---|---|
| | | Isoquinoline Acids | | | |
| **11** | 2 | −0.17 | 0.32 | 0.00 | |
| **19** | 2 | −0.17 | 0.31 | 0.03 | |
| **20** | 1 | 0.08 | 0.30 | 0.18 | 0.38 |
| **12** | 1 | 0.08 | 0.30 | 0.13 | 0.36 |
| **13** | 1 | 0.05 | 0.30 | 0.13 | 0.36 |
| **14** | 1 | 0.10 | 0.27 | 0.22 | |
| **15** | 1 | 0.14 | 0.30 | 0.21 | 0.35 |
| **16** | 0 | 0.28 | 0.40 | 0.37 | |
| **17** | 0 | >0.60 | | >0.80 | |
| **18** | 0 | >0.60 | | >0.80 | |
| | | Reference Compounds | | | |
| *p*-Hydroxyphenylacetic acid | | 0.29 | | 0.38 | |
| *m*-Hydroxyphenylacetic acid | | 0.34 | | 0.43 | |
| *p*-Methoxyphenylacetic acid | | 1.39[a] | | | |
| Phenylacetic acid | | 2.5[a] | | | |
| | | Representative Products | | | |
| **22** | | 0.30 | | 0.34 | |
| **27** | | 0.36 | | 0.36 | |

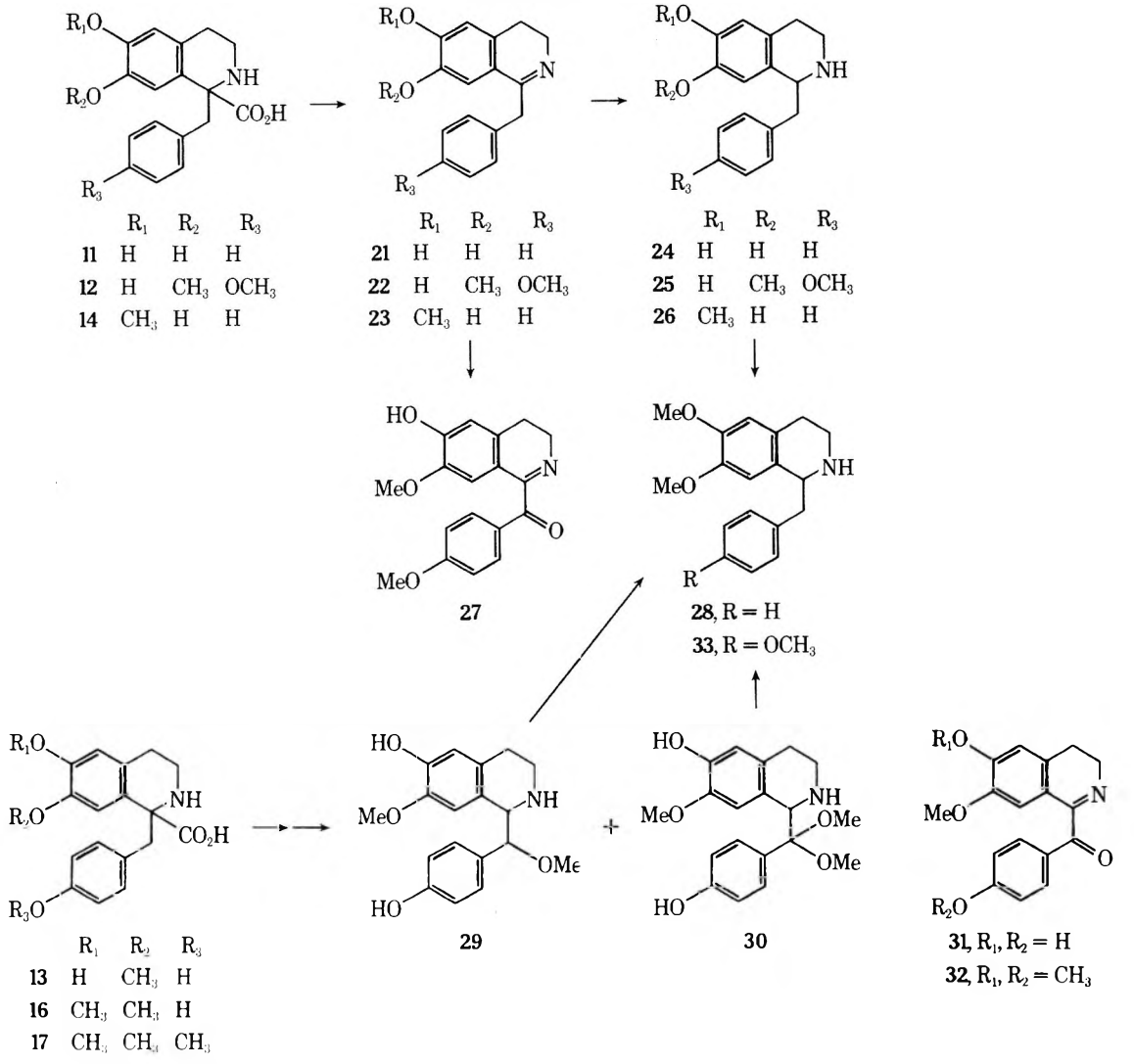
[a] These values were taken from ref 12 and may not be directly comparable with others.

NaOMe system, yielded a separable mixture of **22** and the product of the overoxidation, the 1-benzoyl derivative, **27.** Compound **22** had a typical C=N ir absorption at 1600 $cm^{-1}$ and an NMR peak attributable to the $C_\alpha H$ which varied from $\delta$ 4.05 in phosphate pH 7.5 buffer to 4.5 in $CF_3CO_2H$–$CDCl_3$ to 4.7 in DCl–$CDCl_3$. This striking behavior is presumably due to the difference in degree of nitrogen protonation in the various media. On recrystallization, **22** was partially converted to **27** by air oxidation.[18] The ketone **27** was characterized by its NMR spectrum, which showed an unusually large spacing between the two halves of the AB pattern due to the aromatic protons of the benzyl ring (50 Hz). This is due to the strongly electron-withdrawing effect of the keto group. Compound **27** was methylated to give the known compound **32.**[18] The overoxidation to the 1-benzoyl derivatives was not noticed when no oxygen was present in the benzyl group.

When free phenol groups were present in the para position[19] of the benzyl group and in the isoquinoline ring, oxidation at the $\alpha$ carbon of the benzyl group is unavoidable. Thus, **13** on oxidation in the NaOMe system followed by $NaBH_4$ reduction led to the methoxylated products, **29** and **30.** Compounds **29** and **30** had clear methoxyl peaks in their NMR spectra which were neither aromatic methoxy groups nor MeOH/ These peaks disappeared when **29** and **30** were hydrogenolyzed over Pd on carbon to give the known compound **33.**[20] The methoxylation reactions are charateristic anodic substitution reactions.[21,22]

When a free phenol was present in the benzyl ring and none was present in the isoquinoline ring (as in **16**), exten-

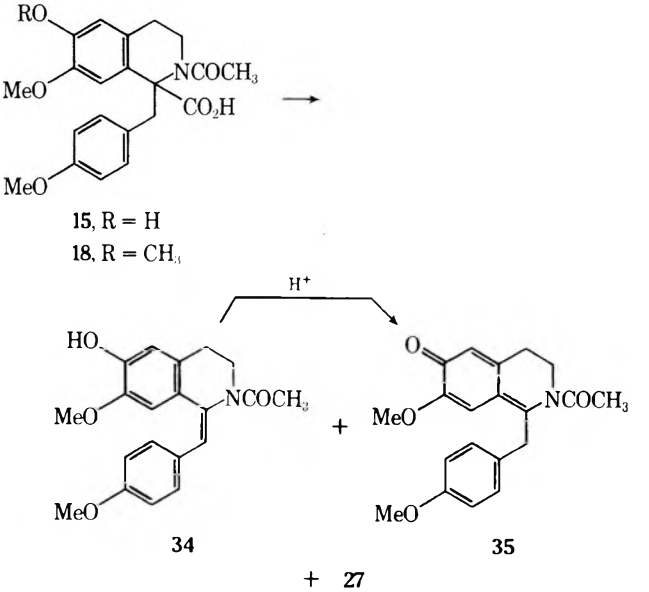
Scheme III




sive fragmentation resulted and no products were isolated. Such fragmentations have been previously noted.[23,24] When no phenol groups are present, as in **17**, decarboxylation did take place at a high potential in the NaOMe system to give 29% of the known 1-benzoyl derivative **32**[18] and 5% of the compound methyl anisate.[25] Compound **32**, like **27**, showed a large spacing (58 Hz) between the halves of the AB pattern in its NMR spectrum, due to the ketone.

The role, if any, of the isoquinoline nitrogen in the decarboxylation is not clear, although it certainly furnishes an electron pair for the formation of the 3,4-dihydroisoquinolines. It is known that N-acylated alanines can be decarboxylated electrochemically in MeOH to give methyl ethers,[26] and quinuclidene-2-carboxylic acid has been decarboxylated to yield 2-methoxyquinuclidine.[27] In our experiments, acetylation of the nitrogen has little effect on the ease of oxidation in one case (compare **12** and **15** in Table III), but seemed to block the reaction entirely in another case (compound **17** vs. **18**). The major product from the preparative oxidation of **15** in the $NaHCO_3$ system was the ketone **27** (Scheme IV) in 26% yield. Compound **27** is the product of decarboxylation, a remarkably easy deacetylation, and overoxidation at the $\alpha$ carbon. The more interesting products, however, are **34** and **35**, which were obtained in yields of 9 and 15%, respectively. When treated with acid, **34** is rearranged to **35**. Compound **34** showed essentially a double NMR spectrum, probably due to a cis–trans mixture around the double bond. Compound **35** was completely

Scheme IV




+ **27**

characterized by its NMR spectrum, especially the large shifts for $C_5H$ and $C_8H$ and the $C_\alpha H$ at $\delta$ 4.17 (Table II). Both **34** and **35** had carbonyl absorptions at 1650–1660 $cm^{-1}$ in their ir spectra. The isolation of **34** and **35** show how the decarboxylation reaction can lead to quinone methides and unsaturated compounds which may be of in-

terest in the "oxidative coupling" of phenolic isoquinolines (see Discussion).

When the nitrogen was acylated and no phenol groups were present as in **18**, no decarboxylation took place up to about 1.0 V and starting material was recovered.

All of the products mentioned gave calculated mass spectral molecular ions and fairly predictable fragmentation patterns.[1d]

## Discussion

It appears that the oxidative decarboxylation involves the removal of electrons through the aromatic ring and is of the "pseudo-Kolbe" type.[14] Since it makes little difference whether the free phenol is in the 6 or 7 position, any mechanism must be a fairly general carbonium type.[12-14] The reaction could take place by two paths. In the first path the electrons might be removed one at a time in a conventional ECE process similar to that proposed by Coleman and Eberson for the "pseudo-Kolbe" reaction.[14] The second path might then be a concerted reaction in which two electrons "flow" out through the aromatic ring at the same time that $CO_2$ is lost. It is impossible to state whether either or neither of the paths is valid. However, it does appear from the voltammetry that a single two-electron wave is present at which, on preparative reaction, the appropriate products are obtained. This is supported by a crude coulometric study on **12** which indicated that about two electrons per mole of **12** were transferred during the reaction. Since the decarboxylations do take place at the same potentials as phenol oxidations and phenol oxidations certainly take place in natural environments,[28,29] these decarboxylations would appear to be plausible model reactions supporting Hahn's hypothesis for insoquinoline alkaloid biosynthesis.

The most interesting redox systems in isoquinoline biosynthesis are, however, surely the phenol coupling reactions which lead from the simple 1-benzyltetrahydroisoquinolines to a large number of complex alkaloids.[30] Most, but not all, of these coupled products involve the loss of two electrons per isoquinoline residue. Thus, coupling tends to be intramolecular (two electrons per molecule) or to involve the formation of a double coupled intermolecular dimer (four electrons, two per isoquinoline). If Hahn's hypothesis is correct, and if the decarboxylation is oxidative as we suggest, the 3,4-dihydroisoquinoline products have the correct oxidation state for the majority of the coupled isoquinoline alkaloids. The various coupled products would then be formed by some type of quinone addition[31] and *without further oxidation*. This would then be an example of what Hamilton[29] has called a NOC or nonoxidative coupling. A few examples of reactions which may involve such quinone additions in the isoquinoline series have been observed by Hoshino, Toshioka, and Umezawa[32] and by Kupchan and Liepa.[33]

Such an hypothesis has considerable appeal in that the decarboxylation could serve as a driving force for the oxidation. Furthermore, the oxidation would be expected to stop after the loss of two electrons due to the relative deactivation of the aromatic ring by the 1,2 double bond (see Table III, **22** and **27** vs. others). Much of the difficulty encountered in laboratory oxidations of phenols has been caused by overoxidation. It is quite likely that coupling reactions could be triggered by pH changes or by quaternization of the nitrogen in the 3,4-dihydro compounds. Experiments to check this hypothesis are in course.

It remains to be seen whether electrochemical decarboxylations can be made to serve an even wider role in biomimetic alkaloid synthesis. Van Tamelen and his co-workers[34] have made a case for the involvement of some oxidative decarboxylations of amino acids in biosynthesis. Some of these intermediates were 3-carboxy-1,2,3,4-tetrahydroisoquinolines and 2,3,4,5-tetrahydro-β-carboline-4-carboxylic acids. The oxidant used to test the hypothesis was hypochlorite, and the results were inconclusive. In that case, the point of oxidation was the nitrogen rather than, as in our case, the aromatic ring. The ring was also separated from the carboxylic acid by one additional saturated carbon atom.

## Experimental Section[35]

**Preparation of 11, 12, and 13.** Phenylpyruvic acid (2.3 g, 13.9 mmol) was added to 2.4 g (13.1 mmol) of β-(3,4-dihydroxyphenyl)ethylamine hydrochloride in 40 ml of $H_2O$, and the pH was adjusted to 4.5–5.0 with $NH_4OH$. The product crystallized during 5 days and was collected by filtration, washed (cold $H_2O$, then EtOH, then acetone), and dried to give 3.3 g (87%) of **11**. Compound **11** was crystallized from concentrated HCl–MeOH (1:2) to give **11** hydrochloride, mp 243–246° dec (lit.[10] 240° dec).

In a similar manner, **12** was prepared in 88% yield from *p*-methoxyphenylpyruvic acid and β-(3-hydroxy-4-methoxyphenyl)ethylamine hydrochloride. The hydrochloride of **12**, prepared from concentrated HCl–MeOH (1:1), melted at 258–261° dec, mass spectrum $M^+$ *m/e* 343, calcd 343 ($C_{19}H_{21}NO_5$).

Anal. Calcd for $C_{19}H_{21}NO_5$·HCl: C, 60.02; H, 5.84; N, 3.68. Found: C, 59.79; H, 6.11; N, 3.54.

In a similar manner, **13** was prepared in 68% yield from *p*-hydroxyphenylpyruvic acid and β-(3-hydroxy-4-methoxyphenyl)ethylamine hydrochloride. Compound **13**, as the free base, was crystallized from MeOH, and melted at 270° dec.

Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.65; H, 5.77; N, 4.25. Found: C, 65.23; H, 6.07; N, 4.14.

**Preparation of 14 and 16.** Benzoyl chloride (16 ml, 135 mmol) was added dropwise to a vigorously cooled (10°), stirred solution of 7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline[36] (13 g, 49 mmol) in a two-phase system of 100 ml of $CH_2Cl_2$ and 40 ml of $H_2O$ containing 14 g of KCN.[37] The mixture was stirred for an additional 2 hr at room temperature. The $CH_2Cl_2$ layer was separated, washed ($H_2O$, 10% HCl, 5% NaOH, and saturated NaCl, successively), dried ($Na_2SO_4$), and evaporated to a gum. Trituration of the gum with MeOH gave 7.5 g (39%) of crystalline *N*-benzoyl-7-benzyloxy-6-methoxy-1-cyano-1,2,3,4-tetrahydroisoquinoline, mp 178–180°.

Anal. Calcd for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.11; H, 5.73; N, 7.10.

Benzyl chloride (3.23 g, 25.6 mmol) was added to a cooled (0–10°) suspension of the above nitrile (6.8 g, 17.1 mmol) in 30 ml of dried (molecular sieve 3 A) dimethylformamide. Sodium hydride (850 mg, 17 mmol in a 48% oil dispersion) was added slowly.[9] The cooling bath was removed, and the mixture was stirred for 15 hr during which time the suspension became a clear, light yellow solution. The reaction mixture was poured over crushed ice to give a white gum. The gum was collected by filtration and triturated with warm MeOH to give crude *N*-benzoyl-7-benzyloxy-1-benzyl-1-cyano-6-methoxy-1,2,3,4-tetrahydroisoquinoline.

The above crude benzylisoquinoline nitrile (1.5 g, 3.06 mmol) was hydrolyzed by heating it to 100° in 10 ml of 85% $H_3PO_4$ for 15 min. The mixture was cooled, diluted with 10 ml of ice water, and filtered. The filtrate was carefully neutralized with $NH_4OH$. After standing overnight at 0–5°, the product precipitated to give, after collection by filtration, 0.9 g (66%) of **14**. Crystallization from concentrated HCl–MeOH (1:1) yielded the hydrochloride of **14**, mp 245–248° dec.

Anal. Calcd for $C_{18}H_{19}NO_4$·HCl: C, 61.80; H, 5.76; N, 4.00. Found: C, 61.88; H, 5.49; N, 3.82.

In a similar sequence, the known compound, *N*-benzoyl-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline,[9] was converted in 61% yield to *N*-benzoyl-1-(*p*-benzyloxybenzyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, mp 152–153° from MeOH.

Anal. Calcd for $C_{33}H_{30}N_2O_4$: C, 76.42; H, 5.83; N, 5.40. Found: C, 76.61; H, 6.00; N, 5.53.

Again, in a similar manner, the benzyloxybenzyl isoquinoline nitrile was hydrolyzed to give, in 66% yield, **16**. Recrystallization from concentrated HCl–MeOH (1:1) gave white microcrystals, mp 244–247° dec.

Anal. Calcd for $C_{19}H_{21}NO_5$·HCl: C, 60.08; H, 5.84; N, 3.69. Found: C, 60.45; H, 6.11; N, 3.42.

**Preparation of the *N*-Acetyl Derivatives, 15 and 18.**[7] Acetyl

chloride (1.1 g, 14 mmol) was added dropwise to a stirred mixture of 1 g (3 mmol) of 12 and 1.65 g of $K_2CO_3$ in 75 ml of acetone. The mixture was heated to reflux for 20 hr. The inorganic salts were removed by filtration, and the filtrate was evaporated to near dryness, taken up in $CHCl_3$, washed (10% HCl, $H_2O$, and saturated NaCl, successively), dried ($Na_2SO_4$), and evaporated to give 0.42 g (26%) of crystalline **15**. Recrystallization from $CCl_4$ yielded pure **15** as white needles, mp 143–145°.

Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.01; N, 3.64. Found: C, 65.28; H, 6.07; N, 3.57.

In a similar manner, acetylation of **17** yielded **18** in 24% yield. Compound **18** melted at 124–126° and had an NMR spectrum similar to that of **15** except that three $OCH_3$ peaks were present.

Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.43; H, 5.95; N, 3.89.

**Preparation of 17.** A large excess of $CH_2N_2$ (from 7.5 g of *N,N'*-dimethyl-*N,N'*-dinitrosoterephthalamide)[6] in 200 ml of ether was added to 3.0 g of **12** in 50 ml of MeOH. After being stirred overnight at about 10°, the solvents were evaporated and the $CH_2N_2$ treatment was repeated. Evaporation of the solvents and partition of the residue between $CHCl_3$ and phosphate buffer (pH 7.5) afforded a $CHCl_3$ extract which, after evaporation, gave 3.2 g of the methyl ester of **17** as a light yellow oil. The oil was dissolved in $CHCl_3$–hexane (1:1) and purified by passing it over a short column of silica gel GF (2 × 1 in.). Evaporation of the solvents gave pure ester. This ester (3 g) was saponified by heating it to reflux with 1 g of KOH in 10% aqueous EtOH for 2 hr. Upon cooling the mixture in ice, the potassium salt of **17** precipitated and was collected by filtration. The salt was dissolved in 100 ml of alcoholic NaOH [10% in EtOH–$H_2O$ (1:1)] and acidified with HCl. The hydrochloride of **17** precipitated (2.8 g, 90%) and was recrystallized from concentrated HCl–MeOH (1:1) to give white needles, mp 278–281°.

Anal. Calcd for $C_{20}H_{23}NO_5 \cdot HCl \cdot H_2O$: C, 58.32; H, 6.36; N, 3.40. Found: C, 58.49; H, 6.33; N, 3.72.

**Oxidative Decarboxylations. General Procedure.** The oxidations were conducted on a graphite felt anode (6.2 × 16 cm) separated from a Pt cathode by a medium porosity glass frit.[15] The reactions were carried out under nitrogen at 15–25°. A standard calomel electrode was connected by a salt bridge to a point as close as possible to the anode, and the potential was electronically controlled. In general, about 1.5 mmol of substrate was added to a stirred, preequilibrated, preelectrolyzed, deoxygenated cell containing about 250 ml of electrolyte. The anode potential was adjusted so that 20–50 mA of current passed and the reaction was continued until the current dropped back to the residual of 5 mA or so or until TLC showed that no starting material remained. The reaction mixture, along with the anode, were blended in a Waring blender, and the suspension was filtered. The particles of anode were washed several times with MeOH, and the combined filtrate and washings were evaporated to a residue and processed for specific compounds.

**Oxidation of 11.** Compound **11** (500 mg) was oxidized at −0.28 V in 250 ml of 0.1 *N* NaOMe in MeOH. The initial current of 43 mA fell to a residual in 3 hr; the oxidation was stopped; and the reaction mixture was processed as described above. The residue so obtained was extracted twice with MeOH, and the MeOH extracts were treated with $CH_2N_2$ (from 7.5 g of *N,N'*-dimethyl-*N,N'*-dinitrosoterephthalamide). After about 15 hr, the solvents were evaporated, and the methylated compound was dissolved in 15 ml of MeOH, cooled in ice, and stirred while 0.5 g of $NaBH_4$ was added. The pH was maintained between 6 and 7 by periodic additions of 6 *N* HCl. After 2.5 hr, the MeOH was evaporated, and the residue was partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$. The layers were separated; the aqueous portion was washed once more ($CHCl_3$); and the combined $CHCl_3$ extracts were washed (twice with saturated NaCl), dried ($Na_2SO_4$), and evaporated to yield 524 mg of crude product. Purification by preparative TLC yielded 310 mg (66%) of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**28**), the NMR spectrum of which checked exactly with the literature.[16]

**Oxidation of 12.** Compound **12** (515 mg) was oxidized at +0.01 V in 250 ml of 0.1 *N* NaOMe in MeOH. The initial current was 48 mA, and the reaction was continued until starting material was gone (TLC, $CH_3CN$–$H_2O$, 85:15), in about 3.7 hr. The mixture was processed as described above, and the residue was partitioned between $CHCl_3$ and aqueous, pH 7.5, phosphate buffer. The $CHCl_3$ layer was washed (saturated NaCl), dried ($Na_2SO_4$), and evaporated to give 485 mg of products (**22** and **27**) which was separated on a short column of silica gel G using $CHCl_3$ as an eluent. Compound **22** (130 mg, 29%) showed the expected C=N peak in its ir spectrum and has a predictable NMR and mass spectrum. Since it decomposed on attempted crystallization to give **27**, it was characterized by $NaBH_4$ reduction to give **25** as characterized below. Compound **27** (235 mg, 50%) melted at 186–188°: mass spectrum, $M^+$ *m/e* 311, calcd 311; ir ($CHCl_3$) 1645 $cm^{-1}$ (C=O). Compound **27** was methylated as described above to yield **32**, mp 103–106° (lit.[16] 105°).

Compound **12** (515 mg) was also oxidized at 0.28 V in 250 ml of 0.1 *M* $NaHCO_3$ in MeOH–$H_2O$, 6:4. The initial current of 34 mA dropped rapidly to about 12 mA, and the reaction was continued for 6.5 hr. The electrolyte solution, still in the cell, was made slightly acidic (pH about 6.5) with HCl and treated with 1 g of $NaBH_4$. The solution was kept acidic by periodic acid additions. The mixture was processed as described above, and the residue was acidified with HCl. Crystallization from MeOH gave 445 mg (88%) of **25** as its hydrochloride, mp 233–234°.

Anal. Calcd for $C_{18}H_{22}NO_3Cl$: C, 64.37; H, 6.55; N, 4.17. Found: C, 64.62; H, 6.61; N, 4.11.

**Oxidation of 14.** Compound **14** (300 mg) was oxidized in the methoxide system for 5.5 hr. The potential was slowly raised from 0.0 to +0.2 V to maintain a current of 37 mA during the reaction. The reaction mixture was acidified, reduced with $NaBH_4$, and processed as described above for **12**. The residue was dissolved in 5 ml of MeOH–HCl (1:1) and precipitated with 10 ml of acetone to yield 153 mg (52%) of the hydrochloride of **26**, mp 115–119°, which was identical with a known sample.[17]

**Oxidation of 13.** Compound **13** (500 mg) was oxidized in the methoxide system at −0.12 V for 4.5 hr. Preliminary attempts to isolate the two observed products, probably the 3,4-dihydroisoquinolines corresponding to **29** and **30**, were unsuccessful owing to their instability. The reaction mixture was then reduced with $NaBH_4$ as described for **12**. Compounds **29** and **30** were isolated by preparative TLC ($CHCl_3$–MeOH–$NH_4OH$, 100:25:0.1) in yields of 77 (16%) and 16 mg (3%), respectively. These compounds showed methoxyl groups in their NMR spectra at $\delta$ 3.33 for **29** and at $\delta$ 3.2 and 3.3 for **30** along with the presence of one and no protons on $C_\alpha$, respectively. The remainder of the spectra were as predicted. Further characterization was not possible, and both compounds were methylated with $CH_2N_2$ and hydrogenolyzed over Pd/C in EtOH to give **33**. Compound **33** was found to be identical with a sample prepared from **25** which had the properties recorded.[18]

**Oxidation of 15.** Compound **15** (423 mg) was oxidized in the bicarbonate system for 3.5 hr at +0.15 V. The contents of the cell were processed as described in the general procedure, and the residue was separated by preparative TLC ($CHCl_3$–EtOH, 9:1) to give 0.088 g (26%) of **27**, identified previously, and a pair of tautomers, **34** and **35**, in amounts of 35 (9%) and 55 mg (15%), respectively. Neither compound gave a satisfactory analysis owing to instability. Compound **34** melted at 224–226° as crystallized from MeOH and had the following spectral properties: NMR in Table II; mass spectrum $M^+$ *m/e* 339, calcd 339.

Compound **35** was not crystalline and had the following spectral properties: NMR in Table II; mass spectrum $M^+$ *m/e* 339.1468, calcd 339.1470.

Compound **34**, when allowed to stand overnight in $CHCl_3$–MeOH–HCl, 2:1:1, was converted to **35** (by TLC) with a small amount of decomposition. In an experiment 7.3 mg of **35** (46%) was obtained from 16 mg of **34**.

**Oxidation of 16 and 18.** Compound **16** was oxidized in the methoxide system at +0.2 V. Extensive decomposition resulted, and no products could be isolated. When **18** was oxidized in the methoxide system at +0.6–0.8 V, no current flowed, and starting material was recovered.

**Acknowledgment.** In addition to the financial assistance previously acknowledged, we would like to thank Dr. I. G. C. Coutts of Trent Polytechnic, Nottingham, England, for help in the Reissert synthesis.

**Registry No.**—**11**, 57256-22-1; **12**, 57256-23-2; **12** HCl, 57256-24-3; **13**, 57256-25-4; **14**, 57256-26-5; **14** HCl, 57256-27-6; **15**, 57256-28-7; **16**, 57256-29-8; **16** HCl, 57256-30-1; **17**, 57256-31-2; **17** HCl, 57256-32-3; **18**, 57256-33-4; **19**, 57256-34-5; **20**, 31758-50-6; **22**, 57256-35-6; **25**, 31804-74-7; **25** HCl, 31804-73-6; **26**, 57256-36-7; **26** HCl, 57256-37-8; **27**, 57256-38-9; **28**, 3423-37-8; **29**, 57256-39-0; **30**, 57256-40-3; **32**, 17052-80-1; **33**, 41498-37-7; **34**, 57256-41-4; **35**, 57256-42-5; phenylpyruvic acid, 156-06-9; β-(3,4-dihydroxyphenyl)ethylamine hydrochloride, 62-31-7; *p*-methoxyphenylpyruvic acid, 28030-16-2; β-(3-hydroxy-4-methoxyphenyl)ethylamine hy-

drochloride, 645-33-0; *p*-hydroxyphenylpyruvic acid, 156-39-8; benzoyl chloride, 98-88-4; 7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline, 15357-92-3; *N*-benzoyl-7-benzyloxy-6-methoxy-1-cyano-1,2,3,4-tetrahydroisoquinoline, 57256-43-6; benzyl chloride, 100-44-7; *N*-benzoyl-7-benzyloxy-1-benzyl-1-cyano-6-methoxy-1,2,3,4-tetrahydroisoquinoline, 57256-44-7; *N*-benzoyl-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 10174-83-1; *N*-benzoyl-1-(*p*-benzyloxylbenzyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, 57256-45-8; acetyl chloride, 75-36-5; diazomethane, 334-88-3.

## References and Notes


(1) (a) Presented at the 166th National Meeting of the American Chemical Society, Chicago, Ill., August 1973. (b) Part V: J. M. Bobbitt, I. Noguchi, R. S. Ware, K. N. Chiong, and S. J. Huang, *J. Org. Chem.*, **40**, 2924 (1975). (c) This work was supported by a Research Fellowship given to T. Y. Cheng by Merck and Co., Inc., Rahway, N.J., and by Research Grant CA-10494 from the Cancer Institute of the National Institutes of Health. (d) Taken in part from the Ph.D. Dissertation of T. Y. Cheng, University of Connecticut, 1974. (e) Discussed briefly by J. M. Bobbitt, *Heterocycles*, **1**, 181 (1973).

(2) (a) M. Shamma, "The Isoquinoline Alkaloids, Chemistry and Pharmacology", Academic Press, New York, N.Y., 1972, pp 32, 75, 505; (b) T. Kametani, "The Isoquinoline Alkaloids", Hirokawa Publishing Co., Tokyo, 1968, p 13.

(3) The historical background and pertinent references are given in the elegant paper of G. J. Kapadia, G. S. Rao. E. Leete, M. B. E. Fayez, Y. N. Vaishav, and H. M. Fales, *J. Am. Chem. Soc.*, **92**, 6943 (1970).

(4) (a) G. Hahn and F. Rumpf, *Ber.*, **71**, 2141 (1938); (b) I. J. McFarlane and M. Slaytor, *Phytochemistry*, **11**, 235 (1972); (c) M. L. Wilson and C. J. Coscia, *J. Am. Chem. Soc.*, **97**, 431 (1975); (d) A. R. Battersby, R. C. F. Jones, and R. Kazlauskas, *Tetrahedron Lett.*, 1873 (1975); (e) S. Tewari, D. S. Bhakuni, and R. S. Kapil, *J. Chem. Soc., Chem. Commun.*, 554 (1975).

(5) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 151 (1951).

(6) J. A. Moore and D. E. Reed, *Org. Synth.*, **41**, 16 (1961).

(7) W. Dilthey and H. Passing, *J. Prakt. Chem.*, **153**, 26 (1939); *Chem. Abstr.*, **33**, 6288 (1939).

(8) W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 74 (1951).

(9) M. Shamma and C. D. Jones, *J. Org. Chem.*, **35**, 3119 (1970).

(10) G. Hahn and K. Stiehl, *Ber.*, **69**, 2627 (1936).

(11) A. J. Fry, "Synthetic Organic Electrochemistry", Harper and Row, New York, N.Y., 1972, Chapter 3.

(12) J. P. Coleman, J. H. P. Utley, and B. C. L. Weedon, *Chem. Commun.*, 438 (1971).

(13) A one-electron decarboxylation forming radical intermediates which dimerize is the traditional Kolbe reaction. The two-electron decarboxylation yielding carbonium ions is generally called the Hofer–Moest reaction. See L. Eberson in "Chemistry of the Carboxylic Acids and Esters", S. Patai, Ed., Wiley, New York, N.Y., 1969, Chapter 2, and ref 11, p 283.

(14) J. P. Coleman and L. Eberson, *Chem. Commun.*, 1300 (1971).

(15) J. M. Bobbitt, H. Yagi, S. Shibuya, and J. T. Stock, *J. Org. Chem.*, **36**, 3006 (1971).

(16) G. Fraenkel, M. P. Cava, and D. R. Dalton, *J. Am. Chem. Soc.*, **89**, 329 (1967).

(17) R. C. Hallcher, Ph.D. Dissertation, University of Connecticut, 1972, p 91.

(18) J. A. Weisbach, J. L. Kirkpatrick, E. Macko, and B. Douglas, *J. Med. Chem.*, **11**, 752 (1968).

(19) Recent work by C. L. Kulkarni in our laboratory has shown that a compound with a meta phenol in the benzyl ring, specifically 1-(3-hydroxy-4-methoxybenzyl)-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid, can be cleanly decarboxylated to the 3,4-dihydroisoquinoline with little or no overoxidation.

(20) M. Tomita and F. Kusuda, *J. Pharm. Soc. Jpn.*, **72**, 793 (1952).

(21) Reference 11, p 295.

(22) A. Ronlán and V. D. Parker, *J. Chem. Soc. C*, 3214 (1971).

(23) J. M. Bobbitt and R. C. Hallcher, *Chem. Commun.*, 543 (1971).

(24) J. R. Falck, L. L. Miller, and F. R. Stermitz, *Tetrahedron*, **30**, 931 (1974).

(25) L. G. Radcliffe and W. H. Brindley, *Perfum. Essent. Oil Rec.*, **13**, 414 (1922).

(26) R. P. Linstead, B. R. Shephard, and B. C. L. Weedon, *J. Chem. Soc.*, 2854 (1951).

(27) P. G. Gassman and B. L. Fox, *J. Org. Chem.*, **32**, 480 (1967).

(28) B. R. Brown in "Oxidative Coupling of Phenols", W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N.Y., 1967, p 167.

(29) P. D. McDonald and G. A. Hamilton in "Oxidation in Organic Chemistry", W. S. Trahanovsky, Ed., Academic Press, New York, N.Y., 1973, p 97.

(30) A. R. Battersby in ref 28, p 119.

(31) H. Musso in ref 28, p 78.

(32) O. Hoshino, T. Toshioka, and B. Umezawa, *Chem. Commun.*, 1533 (1971); 740 (1972).

(33) S. M. Kupchan and A. J. Liepa, *J. Am. Chem. Soc.*, **95**, 4062 (1973).

(34) E. E. van Tamelen, V. B. Haarstad, and R. L. Orvis, *Tetrahedron*, **24**, 687 (1968).

(35) Melting points were taken on a Kofler hot stage apparatus and are corrected. Elemental analyses were carried out by Baron Consulting Co., Orange, Conn. The NMR spectra were measured on a Varian A-60 instrument, and the mass spectra were recorded on a AEI MS-9 instrument using a direct inlet system at 70 eV. TLC was carried out on silica gel GF layers. Cyclic voltammetry was carried out on a P. A. R. Electrochemistry System (Model 170), and preparative electrolyses were carried at potentials controlled against a standard calomel electrode by a Wenking potentiostat (Model 61TR). All evaporations were carried on a rotary vacuum evaporator.

(36) This known compound [M. Tomita and H. Watanabe, *J. Pharm. Soc. Jpn.*, **58**, 783 (1938)] was prepared in 25% yield by the $POCl_3$ cyclization of the appropriate *N*-alkylformamide in $CHCl_3$ at room temperature in a similar manner to that used by M. P. Cava and K. T. Buck, *Tetrahedron*, **25**, 2795 (1969). The formamide was prepared from ethyl formate and β-(4-benzyloxy-3-methoxyphenyl)ethylamine by a procedure detailed in a footnote to I. Ugi, R. Meyr, M. Lipinski, F. Bodesheim, and F. Rosendahl, *Org. Synth.*, **41**, 13 (1961).

(37) F. D. Popp and W. Blount, *J. Org. Chem.* **27**, 297 (1962).


# The Polyphenolic Acids of *Lithospermum ruderale*. II. Carbon-13 Nuclear Magnetic Resonance of Lithospermic and Rosmarinic Acids


Charles J. Kelley, Richard C. Harruff, and Marvin Carmack*

*Contribution No. 2739 from the Department of Chemistry*
*Indiana University, Bloomington, Indiana 47401*


*Received May 7, 1975*


The $^{13}C$ NMR spectra of caffeic acid (**3a**) and 3-(3,4-dihydroxyphenyl)lactic acid (**4a**) and a series of their O-alkylated derivatives in neutral aqueous solutions are fully assigned. These chemical shifts are used to assign the carbons of rosmarinic (**2**) and chlorogenic (**5**) acids. The foregoing compounds serve as models to interpret the $^{13}C$ NMR spectrum of lithospermic acid (**1**), $C_{27}H_{22}O_{12}$. Also discussed are the $^{13}C$ NMR spectra of quinic acid (**6**) and two morphinane derivatives, oxymorphone (**10**), and oxycodone (**11**), containing aromatic rings structurally similar to **1**.

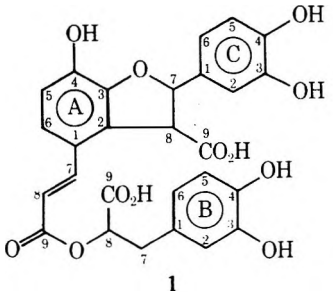

In recent work on the constituents of the roots of *Lithospermum ruderale* (Dougl. ex Lehm.), we postulated structure **1** for lithospermic acid, the principal polyphenolic acid in the plant.[1] Rosmarinic acid (**2**) was also identified as a minor plant constituent. Evidence for structure **1** and for the presence of **2** in *L. ruderale* rested largely on $^1H$ NMR and mass spectral data from derivatives of **1** and **2**. To obtain further confirmation for structure **1** and to develop an analytical method for the assay of fractionated aqueous extracts from the plant, we undertook a study of the $^{13}C$ NMR spectra of **1**, **2**, and a series of model compounds.

Compounds **1** and **2** are composed of phenylpropanoid subunits. For convenience in comparing chemical shift data, each subunit (the aromatic ring and the attached

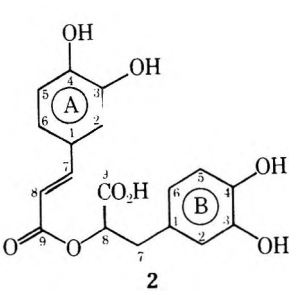
Table I
Carbon-13 Chemical Shift Assignments of Catechol-Containing Acids[a]

| Acid | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | C-7 | C-8 | C-9 | Cation | pH | M |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (1) Lithospermic acid[c] | | | | | | | | | | K, etc. | 5.5[b] | 0.3 |
| Unit A | 123.5 | 128.6 | 146.8 | 144.2 | 117.6 | 121.4 | 142.4 | 115.6 | 168.3 | | | |
| Unit B | 130.3 | 116.9 | 144.0 | 142.7 | 116.3 | 121.6 | 37.2 | 76.6 | 176.9 | | | |
| Unit C | 133.3 | 113.4 | 144.2 | 142.4 | 116.3 | 118.1 | 88.9 | 59.0 | 178.8 | | | |
| (2) Rosmarinic acid | | | | | | | | | | Na | 7.5[b] | 0.6 |
| Unit A | 126.5 | 113.6 | 143.7 | 146.7 | 115.9 | 122.4 | 145.8 | 115.0 | 168.6 | | | |
| Unit B | 129.9 | 117.1 | 143.7 | 142.4 | 115.9 | 121.8 | 36.8 | 76.2 | 177.2 | | | |
| (3a) Caffeic acid | 127.8 | 114.5 | 144.1 | 145.9 | 116.1 | 121.4 | 141.0 | 121.2 | 176.0 | Li | 7.4 | 1.0 |
| (4a) 3-(3,4-Dihydroxyphenyl)lactic acid | 130.8 | 117.2 | 143.7 | 142.4 | 116.1 | 121.7 | 39.7 | 73.5 | 180.5 | Na | 6.2 | 1.0 |
| | 129.3 | 117.2 | 143.7 | 142.8 | 116.2 | 121.8 | 38.9 | 71.3 | 177.1 | (HCl) | 0.3 | 1.0 |
| (5) Chlorogenic acid | | | | | | | | | | Na | 4.5 | 0.5 |
| Unit A | 126.6 | 114.1 | 144.2 | 147.0 | 116.0 | 122.6 | 145.9 | 115.2 | 168.9 | | | |
| Unit B | 76.6 | 38.3 | 70.6 | 72.8 | 71.0 | 37.3 | 180.1 | | | | | |
| (6) Quinic acid | 77.0 | 40.7 | 67.1 | 75.2 | 70.5 | 37.4 | 181.2 | | | Li | 4.6 | 1.2 |
| | 74.9 | 40.3 | 66.5 | 75.7 | 70.1 | 36.9 | 177.7 | | | (HCl) | 0.7 | 1.1 |
| (7) Dopa [3-(3,4-Dihydroxyphenyl)alanine] | 126.4 | 117.1 | 144.3 | 143.7 | 116.6 | 121.9 | 35.1 | 54.5 | 171.7 | (HCl) | 1.0 | 0.8 |
| (8) 3,4-Dihydroxyphenylacetic acid | 129.7 | 117.2 | 143.9 | 142.5 | 116.4 | 121.6 | 43.4 | 181.0 | | Li | 5.2 | 1.0 |

[a] Spectra were obtained at 15.1 MHz (1 at 25.2 MHz) in $H_2O$ (1 and 2 in $D_2O$). [b] These values are pD's, i.e., glass electrode measured pH + 0.4. [c] Most of the carbon resonances of 1 fall in groups where alternate assignments are possible. Many of our reasons for assigning the carbons as they appear in this table are discussed in the last section of the paper.

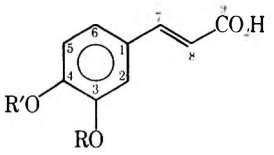


1

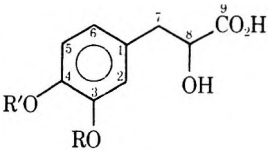


2

three-carbon side chain) has been labeled with a letter, A, B, or C. Within each subunit, the carbon atoms are numbered from C-1 to C-9. The model compounds, caffeic acid (**3a**) and 3-(3,4-dihydroxyphenyl)lactic acid (**4a**), are numbered by the same system.



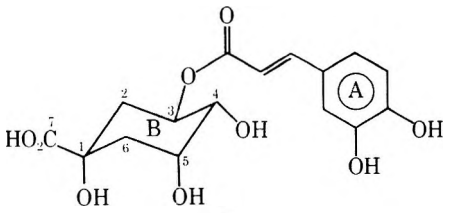
**3a**, R = R′ = H
**b**, R = Me; R′ = H
**c**, R = H; R′ = Me
**d**, R = R′ = Me
**e**, R-R′ = -$CH_2$-
**f**, R-R′ = -$CMe_2$-



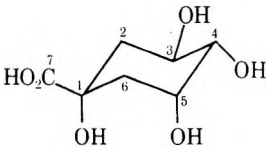
**4a**, R = R′ = H
**b**, R = Me; R′ = H
**c**, R = H; R′ = Me
**d**, R = R′ = Me
**e**, R-R′ = -$CH_2$-
**f**, R-R′ = -$CMe_2$-

Table I contains assignments of the $^{13}C$ NMR chemical shifts observed for compounds 1 and 2, the assignments for model compounds **3a**, **4a**, chlorogenic acid (**5**), quinic acid (**6**), and 3,4-dihydroxyphenylacetic acid (**8**)—all in neutral solution as alkali metal salts—and for comparison the chemical shifts of **4a**, **6**, and Dopa (**7**) in acidic solution.

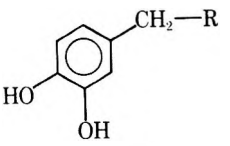
**Chemical Shift Assignments for Monomeric Phenylpropanoids.** Since both natural products 1 and 2 contain units like model compounds **3a** and **4a**, we put a special effort into correctly assigning the individual carbon resonances in these two models. Using chemical shift theory[2] and residually coupled $^{13}C$ NMR spectra obtained by the off-resonance decoupling technique, we assigned carbons 1, 7, and 9 of **3a** and 1 and 6–9 of **4a**. Pairs of similar carbons



5



6



7, R = $CHCO_2H$ | $NH_2$
8, R = $CO_2H$

2, 5 and 3, 4 in **3a** and **4a** and 6, 8 of **3a** were not distinguishable.

Another way to establish carbon assignments is by analysis of the fine structure of fully coupled $^{13}C$ NMR spectra. Coupled spectra can be obtained with NOE enhancement by alternatively pulsing carbon and proton frequencies, a technique called gated decoupling.[2b,3] The 1,3,4-trisubstituted benzene derivatives studied here are easily analyzed by this technique because of the pattern of long-range coupling constants generally observed in benzene rings.[4] The magnitude of the three-bond coupling constant ($^3J$) is so much greater than either $^2J$ or $^4J$ that it will be the dominant factor in determining the fine structure of the carbon resonances. Spectral parameters for **3a** and **4a** obtained by gated decoupling are presented in Table II. By inspection, C-2 will have two $^3J$'s in **3a** and three $^3J$'s in **4a**, while C-5 will experience no $^3J$'s in either compound. Thus in the undecoupled spectra of **3a** and **4a**, C-5 appears as a pair ($^1J$ = 160 Hz) of very sharp lines, while C-2 is a pair of triplets in **3a** and a pair of quartets in **4a**.

A similar analysis can be used to distinguish the pair of carbons 3, 4 in both models. C-3 should have only a single $^3J$ while C-4 should have two $^3J$'s. C-4 appears as a clean triplet with no discernible $^2J$ in both **3a** and **4a**. Unfortunately the fine structure of C-3 in **3a** is obscured by acci-

Table II
Fully Coupled $^{13}C$ NMR Spectra of 3a and 4a

| | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | C-7 | C-8 | C-9 |
|---|---|---|---|---|---|---|---|---|---|
| 3a multiplicity, $^1J_{CH}$, Hz | s | d, 157 | s | s | d, 160 | d, 160 | a | d, 155 | s |
| Fine structure, $^2J_{CCH}$, $^3J_{CCCH}$, Hz | m | t, 5.4 | a | t, 7.0 | s | dd, 6,7 | m | s | dd, 3, 7 |
| 4a multiplicity, $^1J_{CH}$, Hz | s | d, 162 | s | s | d, 164 | d, 164 | t, 132 | d, 151 | s |
| Fine structure, $^2J_{CCH}$, $^3J_{CCCH}$, Hz | tt, 2+ 7 | q, 6 | dd, 3 7 | t, 7+ | s | q, 6 | t 4 | t, 4 | b |

[a] Not analyzable owing to accidental overlap of C-3 resonance with the low-field leg of C-7 resonance. [b] Not measured.

Table III
Carbon-13 Chemical Shifts of Alkylated Catechol Acids[a]

| Acid | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | C-7 | C-8 | C-9 | C–O | C–C–O | Cat-ion | pH |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (3b) Ferulic acid[b,c] | 127.7 | 110.5 | 147.1 | 146.4 | 115.3 | 121.9 | 141.3 | 121.1 | 175.8 | 55.6 | | Li | 6.6 |
| (3c) Isoferulic acid | 128.0 | 113.5 | 144.7 | 148.5 | 111.6 | 121.5 | 140.8 | 121.3 | 175.7 | 55.5 | | Li | 7.0 |
| (3d) 3,4-Dimethoxycinnamic acid | 127.8 | 109.2 | 147.5 | 148.8 | 110.7 | 121.6 | 140.9 | 121.6 | 175.7 | 55.1 | | Na | 11.0 |
| (3e) 3,4-Methylenedioxy-cinnamic acid[d] | 129.6 | 106.3 | 147.4 | 148.1 | 108.3 | 123.6 | 140.7 | 122.1 | 175.7 | 101.4 | | Li | 7.4 |
| (3f) 3,4-Isopropylidene-dioxycinnamic acid[e] | 129.1 | 106.3 | 147.0 | 147.7 | 108.3 | 123.2 | 140.8 | 122.1 | 175.3 | 118.8 | 25.0 | Li | 7.3 |
| (4b) Vanillactic acid | 130.7 | 113.6 | 147.1 | 143.4 | 115.4 | 122.1 | 40.0 | 73.5 | 180.6 | 56.0 | | Na | 8.2 |
| (4c) Isovanillactic acid[e,f] | 131.4 | 116.5 | 144.5 | 145.9 | 112.6 | 121.4 | 39.7 | 73.4 | 180.4 | 56.1 | | Na | 7.2 |
| (4d) 3-(3,4-Dimethoxy-phenyl)lactic acid | 131.3 | 113.0 | 147.6 | 146.5 | 111.6 | 121.9 | 40.1 | 73.5 | 180.6 | 55.7 | | Na | 5.6 |
| (4e) 3-(3,4-Methylene-dioxyphenyl)lactic acid | 132.0 | 109.7 | 146.8 | 145.3 | 108.2 | 122.5 | 40.1 | 73.4 | 180.5 | 100.8 | | Li | 6.8 |
| (4f) 3-(3,4-Isopropyli-denedioxyphenyl)-lactic acid[e] | 131.8 | 109.7 | 146.4 | 145.1 | 108.2 | 122.2 | 40.2 | 73.5 | 180.5 | 118.3 | 24.8 | Li | 6.6 |

[a] Spectra obtained at 15.1 MHz on 0.8–1.0 *M* solutions in $H_2O$. [b] $^{13}C$ NMR reported in acetone-$d_6$–$D_2O$ (9:1) with shifts of carbons 3, 4 reversed.[8] [c] Assignments of carbons 3, 4 verified by pH change 7.5 → 8.6; $\Delta\delta_{C-4}$ = +2.0 ppm; $\Delta\delta_{C-3}$ = +0.6 ppm with that 1.1-unit pH change; $\delta_{C-3} = \delta_{C-4}$ = 147.4 ppm at pH 8.2. [d] $^{13}C$ NMR of amide reported.[6] [e] Assignments of carbons 2, 5 confirmed by gated decoupling. [f] Change of pH from 7.2 to 8.6 results in a downfield shift of C-3 (0.3 ppm) but no change in any other resonance.

dental overlap with the downfield leg of the C-7 resonance. In **4a**, however, the fine structure of C-3 is a doublet of doublets. The doublet with $J$ = 7 Hz is clearly the $^3J$ coupling with H-5, while the second doublet with $J$ = 3 Hz most likely arises from an unusually large $^2J$ to H-2.

In compound **3a**, C-8 is easily distinguished from C-6 since the resonance of the former is a pair ($^1J$ = 155 Hz) of sharp peaks with no three- (or large two-) bond couplings, while the latter is a pair ($^1J$ = 160 Hz) of doubled doublets due to slightly unequal $^3J$'s to H-2 and H-7. The carboxylate carbon (C-9) in **3a** appears as a doublet of doublets, $^3J > {}^2J$, in the $^{13}C$ NMR spectrum as expected from the observed $^1H$ NMR spectrum of $^{13}C$-labeled *trans*-crotonic acid.[5]

The distinguishing features of the $^{13}C$ NMR spectra of the 3,4-dihydroxybenzene rings of **3a** and **4a** then are the reversals observed in the relative chemical shifts of carbons 2, 5 and 3, 4 on going from the unsaturated to the saturated side chains. This effect may be produced by the shielding of C-2 and a deshielding of C-4 by the unsaturated side chain in **3a**. Carbons 3, 5, and 6 remain relatively unaffected by the nature of the C-1 side chain. The selective shielding of C-2 but not C-6 in **3a** apparently reflects a conformational preference in solution. For example, preferred rotamers have been postulated to explain selective shieldings in the $^{13}C$ NMR spectrum of the alkaloid piperine.[6]

Although assignments of carbon resonances by gated decoupling are sufficiently unambiguous, we sought to confirm these assignments in a series of compounds in which the phenolic groups are alkylated. Compilations of these data would be useful in assigning alkylation patterns for related series of compounds from their $^{13}C$ NMR spectra. Previous additivity schemes for these types of aromatic rings have given admittedly ambiguous predictions for vanil and isovanil rings.[7]

Table III contains the $^{13}C$ NMR data for similar series of cinnamate (**3b–f**) and phenyllactate (**4b–f**) derivatives. The shifts observed in these series are in agreement with chemical shift theory if one makes the reasonable assumption that for the caffeate derivatives the shielding of C-2 and the deshielding of C-4 by the unsaturated side chain at C-1 in **3a** are maintained throughout the series.

Independent assignments of carbons 3, 4 in **3b** were obtained by varying the pH of the solution. Since even partial ionization of a phenolic hydroxyl group results in a strong deshielding of the phenolic carbon resonance, titration over only a small pH range serves to identify the individual carbons. Comparison of the $\Delta\delta$ values for **3b** on titration to pH 8.6 (see Table III, footnote c) with the published $^{13}C$ NMR titration of a tyrosine dipeptide[9] indicates that the phenolic function of **3b**, which has an unsaturated group para to it, is somewhat more acidic than the phenolic group of tyrosine. The $^{13}C$ NMR spectrum of **4b** at pH 8.2 (Table III) by analogy to the tyrosine titration curve[9] should not show any effects of phenolic ionization.

Independent confirmation of the assignments of carbons 2, 5 in **3f**, **4c**, and **4f** were obtained by gated decoupling. The same technique confirmed the assignment of carbons 3, 4 in **4c**, but the resolution of the fine structure of the resonances of these carbons in **3f** and **4f** was so poor, possibly through four-bond coupling to the methyl protons, that

Table IV
$^{13}$C NMR Chemical Shifts in Morphinane Aromatic Rings

| | C-① | C-② | C-③ | C-④ | C-⑤ | C-⑥ |
|---|---|---|---|---|---|---|
| Oxymorphone (10) | 121.7 | 127.1 | 143.0 | 138.9 | 118.6 | 121.0 |
| Oxycodone (11) | 122.6 | 127.1 | 144.0 | 142.6 | 115.4 | 121.0 |

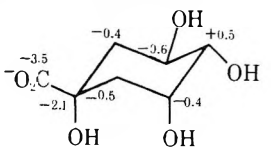
these assignments could not be confirmed by this method.

**Chemical Shift Assignments for Natural Products. A. Caffeate Esters.** To help in assigning the natural products 1 and 2, we desired a model ester of caffeic acid to complement the data obtained for the caffeate salt **3a.** Such a model was found in chlorogenic acid (**5**), a caffeate ester of quinic acid (**6**). The deshielding of carbons 1, 8, and 9 and the shielding of C-7 in the salt **3a** as compared with the ester **5** are completely consonant with the observation[10] that the introduction of a charge into an $\alpha,\beta$-unsaturated carboxylate system imposes strong shifts of alternating polarity along the unsaturated chain.

A detailed analysis of the $^1$H NMR spectra of chlorogenic and quinic acids left no doubt that in solution the cyclohexane rings are in those chair conformations depicted in structures **5** and **6**.[11] The $^{13}$C NMR spectra of chlorogenic and quinic acids (Table I) are in full agreement with this picture.

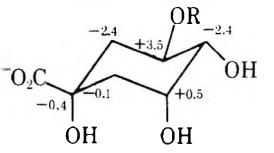
In quinic acid (**6**), the axial proton H-3 is 1,3-diaxially disposed to two OH groups (at C-1 and C-5). This relationship causes a strong deshielding[12] of the resonance of C-3 and allows its unambiguous assignment in **6**. The oxygenated carbon at 75.2 ppm in the quinate salt was identified as C-4 since the intensity of this resonance was least affected by the addition of 1 mol % of Mn(II) acetate to the quinate solution.[13] The paramagnetic Mn(II) ion, which would coordinate with the carboxylate anion in **6**, broadens the resonances of carbons 1 and 7 so that they are not observable, while the resonances of carbons 2, 3, 5, and 6 are truncated with intensities about one-third that observed for the 75.2-ppm resonance. The remaining oxygenated methine, C-5, must resonate at 70.5 ppm in the quinate salt. The two methylene carbons (2, 6) in **6** differ only in that C-2 experiences a $\beta$ effect from an equatorial OH and C-6 experiences a $\beta$ effect of an axial OH. Chemical shift theory thus places C-2 at lower field than C-6.[14] Carbon 1 was identified by off-resonance decoupling. These assignments of the resonances of quinate anion are completely consistent with the change in the chemical shifts ($\Delta\delta$) observed on passing from the anion to the fully protonated acid (cf. Chart I). The chemical shift changes observed upon protonation of quinate anion are analogous to those occurring with the protonation of the $\alpha$-hydroxy acid **4a** [compare carbons 7–9 in **4a** at pH 6.2 and at pH 0.3 (Table I)].

Chart I
$\Delta\delta$ Values (ppm) for Quinate Anion on Protonation




The assignments of carbon resonances for chlorogenic acid (**5**) are based on similar arguments, and are supported by specific proton–carbon decoupling experiments employing known $^1$H NMR chemical shifts for H-3, H-4, and H-5 of **5**.[10] Moreover, a comparison of the changes ($\Delta\delta$) in the carbon resonances of the quinate anion on replacing the C-3 hydroxyl with a caffeyloxy group (see Chart II) shows a strong deshielding of the acylated carbon and symmetrically disposed shieldings for the $\beta$ carbons. The dissymmetry

Chart II
$\Delta\delta$ Values (ppm) for Quinate Anion on Acylation at C-3

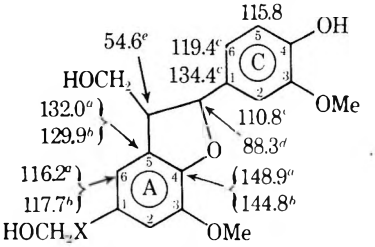



of the $\gamma$ effect may indicate a preferred orientation for the caffeyl group in **5** with respect to the quinate ring.

Having assigned the carbons of the quinic acid ester of caffeic acid, it then becomes a simple matter to assign the caffeate (unit A) carbons of rosmarinic acid (**2**) by comparison. The phenyllactate portion of rosmarinic acid (unit B) can be assigned by comparison to the chemical shifts of the corresponding carbons of **4a.** The significant differences which exist between carbons C-1 and C-7–C-9 of **2** and of **4a** correspond in magnitude to the differences observed in the quinate anion on acylation as shown in Chart II.

**B. Lignan and Morphinane Models.** The distinctive structural features of **1**, the 1,2,3,4-tetrasubstituted ring A and the dihydrobenzofuran (coumaran) ring, are not duplicated in any of the compounds heretofore mentioned. $^{13}$C NMR spectra of several lignan model compounds containing a dihydrobenzo[*b*]furan ring system have been reported, but these differ significantly from **1** in that the point of attachment of the three-carbon side chain is not ortho to the fused dihydrofuran ring.[8] To aid in the discussion of the assignments of the carbon resonances of **1**, the literature assignments for the two lignan models, **9a** and **9b,** are included in Chart III. The rings are labeled A and C to correspond with **1**, but it should be noted that the numbering system within ring A does not correspond to that employed in **1**.

Chart III
Selected $^{13}$C NMR Chemical Shifts for Dihydrobenzo[*b*]furans in Acetone-$d_6$–$D_2O$ (9:1)[a]



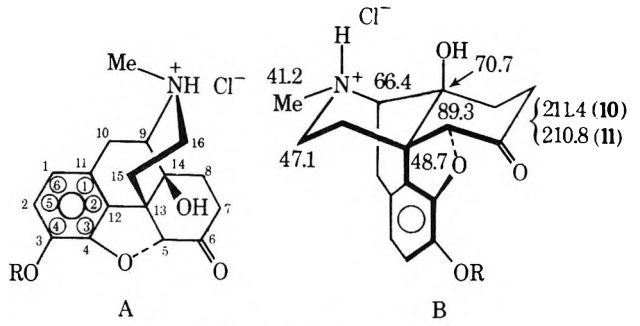

**9a**, X = CH=CH
**b**, X = $CH_2CH_2$

[a] for 9a. [b] for 9b. [c] ±0.1 ppm. [d] ±0.2 ppm. [e] ±0.3 ppm.

Somewhat surprisingly, a more closely congruent model for the A ring of **1** is present in an important alkaloidal family, the morphinanes. The model compounds which we have chosen, oxymorphone (**10**) and oxycodone (**11**), contain both a 1,2,3,4-tetrasubstituted benzene ring with 1,2-carbon substitution and 3,4-oxygen substitution; the 2,3 positions are the carbon and oxygen, respectively, of a dihydrofuran ring.

$^{13}$C NMR spectra of **10** and **11** in the form of their hydrochloride salts were recorded at 25.2 MHz in aqueous solu-

tions, and a gated decoupled spectrum of **10** was obtained. Assignments for the chemical shifts of the aromatic carbons are listed in Table IV, while the shifts of those aliphatic carbons assignable on the basis of multiplicity and chemical shift theory appear in formula B.[15] The numbering system for the morphinane skeleton appears on formula A, but in addition another set of circled numbers *within* the aromatic ring is added to designate those carbon atoms equivalent to the same-numbered aromatic carbon atoms in ring A of **1**. This latter set of numbers enclosed in circles is used exclusively in Table IV and in the following discussion.




10, R = H, oxymorphone
11, R = Me, oxycodone

Three pairs of aromatic carbons, quaternary, C-(1,2), oxygenated, C-(3,4), and protonated, C-(5,6), are easily distinguished from the spectra in Table IV and the gated decoupled spectrum of **10**. Individual carbons within the pairs 1,2 and 5,6 are identified by recourse to empirical shielding parameters[7] which predict that on O-methylation of a phenol, ortho and para carbons experience changes in chemical shift while carbons meta to the phenolic center remain invariant. An analogy which allows one to distinguish C-(3) from C-(4) was derived from examination of spectra in Tables I and II. As is exemplified by many pairs of compounds, e.g., **3a → 3b, 3a → 3c, 3b → 3d,** etc., O-methylation of one oxygen function of a catechol ring causes *both* oxygenated carbons to be deshielded. In going from **10** to **11**, then, deshielding of both oxygenated carbons would be expected. This happens only if C-(3) and C-(4) in **11** are as assigned in Table IV.[16]

**C. Lithospermic Acid.** $^{13}$C NMR spectra of lithospermic acid salts were obtained at 15.1 MHz in water and 25.2 MHz in $D_2O$. Resolution of 26 of the 27 carbons present was obtained in the latter measurement. The only unresolved resonance (at 116.3 ppm) is clearly due to two carbons on the basis of its intensity. In discussing the assignments of the resonances of **1**, we have found it convenient to break up the 27 carbons into six groups of resonances based on chemical shift, and thus to a large extent functional type. In some cases chemical shift theory and model compounds are sufficient to provide unambiguous assignment of individual carbons. In many cases, however, the similarity of chemical environment of several carbons precluded their definitive assignment. The following six paragraphs contain a discussion of the assignments of the resonances within the various groups of resonances of lithospermic acid.

The three carboxylate carbons (two anions and an ester) were assigned on the basis of the close correspondence of two of these chemical shifts to those of the two carboxylates in **2**.

Six oxygenated aromatic carbons and one protonated vinyl carbon, C-7(A), resonate between 142 and 147 ppm. The latter carbon was easily assigned by off-resonance decoupling. The oxygenated aromatics include five phenolic carbons and one alkylated ether. The most deshielded of these resonances, 146.8 ppm, is assigned to the aromatic ether carbon, C-3(A), in agreement with the assignments of **3b** (Table III), and the morphinanes, **10** and **11** (Table IV). Carbon 4(A) in **1**, which might be expected to resonate at lower field like C-4(A) in **2** and **5**, is assigned in agreement with the observed shieldings for carbons ortho to fused carbocyclic[2a] and fused heterocyclic five-membered rings (compare carbons 2, 5 of model compounds **3e/3f** and **4e/4f** with **3d** and **4d** in Table III).

The four quaternary aromatic carbons in **1** resonate between 123 and 134 ppm. The most deshielded of these is assigned as C-1(C) on the basis of the chemical shift of carbon C-1(C) in models **9a** and **9b**. The resonance of C-1(B) is little changed from the corresponding resonance in **2**. In fact, in the 15.1-MHz $^{13}$C NMR spectrum of mixtures of **1** and **2** from *L. ruderale*,[1] the resonances of C-1(B) for both compounds appear as a broadened singlet. The remaining two quaternary carbons, C-1(A) and C-2(A), are assigned by comparison with the corresponding carbons in the morphinane aromatic rings of **10** and **11**.[19]

Lithospermic acid (**1**) contains three carbons of the C-6 type. Two of these carbons resonate in the normal range, i.e., between 121 and 122 ppm. The third C-6 carbon, which resonates at 118.1 ppm, is shielded by a full 3 ppm. Two possibilities exist for the assignment of this shielded carbon. On the basis of the chemical shifts observed for carbons C-6(C) in models **9a** and **9b** and also the shift of C-6 in epinephrine,[21] carbon C-6(C) in **1** should be shielded by 1–2 ppm owing to the presence of the $\alpha$ oxygen atom on C-7(C). This shielding is somewhat less than that required to fully explain the 118.1-ppm resonance. Alternatively, the shielding by about 3 ppm of C-2 in caffeic acids and their esters, which we explained by a preferred orientation of the unsaturated side chain, might in **1** be felt by C-6(A) because the bulky substituents at C-2(A) would cause a reorientation of the unsaturated group toward C-6(A). Such a reorientation would also be felt by C-7(A) in **1** which in fact is found to be shielded by more than 3 ppm relative to C-7(A) in **2** and **5**. If this latter explanation were accepted, however, the lack of any enhanced shielding for C-6(C) would remain to be explained.

The remaining protonated, unsaturated carbons in **1**, which include five aromatic carbons with ortho oxygen substituents and the vinyl carbon C-8(A), resonate between 113.4 and 117.6 ppm. Gated decoupling experiments with **1** did not provide sufficient evidence to allow unambiguous assignments within this group of resonances. These resonances are tentatively assigned in Table I, however, by reference to model compounds. A purer sample of **1** and additional model compounds will be required to make definitive assignments.

The assignments of the four aliphatic carbons, three methine and one methylene groups, are in **1** unambiguous with **2** and **9a,b** as models.

In solving the structure of lithospermic acid, we synthesized a variety of fully methylated esters of model compounds.[1] $^{13}$C NMR spectra, measured in $CHCl_3$ at 15.1 MHz, of a selected set of these compounds are reported in Table V. Chemical shift assignments in Table V are internally consistent and are in complete agreement with the assignments made for the sets of phenolic model compounds recorded in aqueous solution.

## Experimental Section

$^{13}$C NMR spectra were measured at 15.1 MHz in a Varian spectrometer operating in the pulsed Fourier mode. Samples of 2-ml volume were measured in spinning 13-mm tubes at an operating

Table V
$^{13}$C NMR Chemical Shifts for Fully Methylated Derivatives[a]

| Registry no. | | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | C-7 | C-8 | C-9 | OMe (ether) | OMe (ester) | Other |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5396-64-5 | Methyl 3,4-dimethoxycinnamate[b] | 127.2 | 109.7 | 149.1 | 151.1 | 111.0 | 122.4 | 144.6 | 115.4 | 167.5 | 55.8 | 51.4 | |
| 57362-39-7 | Pentamethyl rosmarinate | | | | | | | | | | | | |
| | Unit A | 127.1 | 109.8 | 149.2 | 151.3 | 111.0 | 122.9 | 145.9 | 114.6 | 166.2 | 55.9 | | |
| | Unit B | 128.3 | 112.6 | 148.7 | 148.1 | 111.3 | 121.4 | 37.2 | 72.9 | 170.2 | 55.9 | 52.3 | |
| 54640-00-5 | Methyl 3-(3,4-dimethoxyphenyl)lactate | 128.8 [130.0 | 112.8 113.6 | 148.7 149.1 | 147.9 148.2 | 111.3 111.9 | 121.4 121.7 | 40.1 40.2 | 71.3 71.9 | 174.7 174.1 | 56.0 55.4 | 52.3 51.5][b-d] | |
| 57362-40-0 | Methyl 2-acetoxy-3-(3,4-dimethoxyphenyl)-propanoate | 128.3 | 112.5 | 148.7 | 148.0 | 111.3 | 121.4 | 36.9 | 73.0 | 170.1 | 55.8 | 52.2 | 170.1 (C=O), 17.6 (Me) |

[a] Recorded at 15.1 MHz in $CHCl_3$; $\delta(CHCl_3) = 77.2$ ppm. [b] Assignments of carbons 2, 5 confirmed by gated decoupling; fine structure of carbons 3, 4 obscured by $^3J$ to Me protons. [c] Spectrum recorded in acetone-$d_6$ at 25.2 MHz; $\delta(CD_3$ of solvent) = 29.2 ppm.[2b] [d] Downfield shifts for aromatic carbons in acetone-$d_6$ with respect to $CHCl_3$ have been noted before.[8]

probe temperature of 36 ± 3°. Chemical shifts were recorded from spectra with a digital resolution of 0.13 ppm. All chemical shifts in aqueous solutions were measured with respect to an internal standard of 1% dioxane: $\delta$(dioxane) = 66.5 ppm in water with respect to external $Me_4Si$ in $CHCl_3$ (1:4 by volume); $\delta(Me_4Si)$ = 0.0 and $\delta$ ($CHCl_3$) = 77.2 ppm.

The experiments with gated decoupling were performed in a Varian XL-100 spectrometer operating at 25.2 MHz. Carbon frequencies were pulsed every 5 sec and the proton decoupler was gated on for 3.73 sec prior to the $^{13}$C observation pulse. Samples of 2-ml volume were measured in spinning 12-mm tubes at 34 ± 1°. An average of 400 pulses was used to accumulate data for the noise-decoupled spectra of the phenylpropanoid monomers and **10** and **11**. From 1500 to 4000 pulses were used to obtain decoupled spectra of **1**. From 1000 to 1500 pulses were required for the gated decoupling experiments.

The sample of **1** used in this study was obtained by fractionation of water-soluble portion of the roots of *L. ruderale* and was designated F3 in our earlier publication.[1] The organic material was at least 85% pure, in the form of metallic salts (mostly potassium). In our initial $^{13}$C NMR spectrum of this plant fraction, the resonances of the carboxylate anions, C-9(B) and C-9(C), were very broad, as were, to a lesser extent, those of the neighboring carbons C-8(B) and C-8(C). Since traces of paramagnetic ions, e.g., Mn(II), Fe(III), and Cu(II), would cause this effect, we added 20 $\mu$l of 0.25 *M* disodium EDTA to our 2-ml samples to chelate any interfering ions. This treatment dramatically increased the peak heights of the anionic carboxylate resonances. Subsequently, EDTA was added to all solutions of natural plant materials before their $^{13}$C NMR spectra were measured.

The synthetic carboxylic acids were measured as their sodium or lithium salts. At the concentrations employed (0.8–1.2 *M*) the sodium salts were not always soluble, e.g., **3a** and **3c**, so we used lithium salts routinely in later work. No specific effects for either cation were noted in the $^{13}$C NMR spectra.

**Registry No.**—**1**, 28831-65-4; **2**, 20283-92-5; **3a**, 331-39-5; **3b**, 1135-24-6; **3c**, 537-73-5; **3d**, 2316-26-9; **3e**, 2373-80-0; **3f**, 57362-37-5; **4a**, 23028-17-3; **4b**, 2475-56-1; **4c**, 52262-43-8; **4d**, 32255-79-1; **4e**, 949-14-4; **4f**, 57362-38-6; **5**, 327-97-9; **6**, 36413-60-2; **7**, 59-92-7; **8**, 102-32-9; **10**, 76-41-5; **11**, 76-42-6.

## References and Notes


(1) C. J. Kelley, J. R. Mahajan, L. C. Brooks, L. A. Neubert, W. R. Breneman, and M. Carmack, *J. Org. Chem.*, **40**, 1804 (1975).
(2) (a) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972; (b) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972.
(3) (a) O. A. Gansow and W. Schittenhelm, *J. Am. Chem. Soc.*, **93**, 4294 (1971). (b) R. Freeman and H. D. W. Hill, *J. Magn. Reson.*, **5**, 278 (1971).
(4) F. J. Weigert and J. D. Roberts, *J. Am. Chem. Soc.*, **89**, 2967 (1967), reported that in benzene $^2J_{CCH}$ = 1.0, $^3J_{CCCH}$ = 7.4, and $^4J_{CCCCH}$ = 1.1 Hz.
(5) J. L. Marshall, D. E. Miller, S. A. Conn, R. Seiwell, and A. M. Ihrig, *Acc. Chem. Res.*, **7**, 333 (1974).
(6) E. Wenkert, D. W. Cochran, E. W. Hagaman, R. B. Lewis, and F. M. Schell, *J. Am. Chem. Soc.*, **93**, 6271 (1971).
(7) K. N. Scott, *J. Am. Chem. Soc.*, **94**, 8564 (1972).
(8) H. D. Lüdemann and H. Nimz, *Makromol. Chem.*, **175**, 2393 (1974).
(9) R. S. Norton and J. H. Bradbury, *J. Chem. Soc., Chem. Commun.*, 870 (1974).
(10) E. Wenkert, B. L. Buckwalter, I. R. Burfitt, M. J. Gasić, H. E. Gottlieb, E. W. Hagaman, F. M. Schell, and P. M. Wovkulich, "Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances", in G. C. Levy, "Topics in Carbon-13 NMR Spectroscopy", Vol. 2, Wiley, New York, N.Y., 1976.
(11) J. Corse, R. E. Lundin, E. Sondheimer and A. C. Waiss, Jr., *Phytochemistry*, **5**, 767 (1966).
(12) D. E. Dorman, S. J. Angyal, and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 1351 (1970).
(13) Broadening of specific resonances in adenine nucleotides has been observed after addition of 0.02–0.2 mol % of Mn(II): G. Kotowycz and K. Hayamizu, *Biochemistry*, **12**, 517 (1973).
(14) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *J. Am. Chem. Soc.*, **92**, 1338 (1970).
(15) Chemical shifts for the corresponding aliphatic carbons of **10** and **11** are within 0.15 ppm. Shifts for the carbonyl carbons differ as noted on formula B. The four methylene carbons in **10** and **11** which were not unambiguously assignable resonate at 23.3, 27.3, 30.7, and 34.7 ppm. The OMe carbon in **11** resonates at 56.7 ppm.
(16) Additionally, the assignments of the quaternary and the oxygenated aromatic carbons in the morphinanes **10** and **11** are in agreement with the relative shieldings of the corresponding ring carbons in codeine as deduced from spin-lattice relaxation data[17] and other considerations.[18]
(17) F. W. Wehrli, *Chem. Commun.*, 379 (1973).

(18) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley-Interscience, New York, N.Y., 1972, cf. spectrum no. 479.
(19) Since the chemical shift differences ($\delta\Delta$) between C-(1) and C-(2) in **10** and **11** is $\simeq$ 4–5 ppm and the $\delta\Delta$ between C-1(A) and C-2(A) in **1** is 5.1 ppm, a reversal of the relative chemical shifts between the morphinanes and lithospermic acid would involve a shielding of C-2 by $\simeq$ 5 ppm and a simultaneous deshielding of C-1 by the same amount. The principal structural differences between **1** and **10/11**, i.e., the tertiary vs. quaternary center $\alpha$ to C-2 and the unsaturated side chain vs. the $\beta$-ammonium-substituted fused [C-(1) to C-(2)] cyclohexane ring, are in all probability insufficient to cause so large a chemical shift change.[20]
(20) In simple models, e.g., isopropylbenzene vs. *tert*-butylbenzene, the additional $\beta$ effect of the third methyl group is $<1$ ppm, and similarly, the $\delta\Delta$ of C-1 between *o*-xylene and tetralin is also $<1$ ppm.[2a] Interestingly, in models lacking all substitution at C-2, i.e., Dopa (**8**), with a saturated side chain bearing a $\beta$-ammonium ion, vs. caffeate esters **2** and **5**, the resonances of C-1 and C-1(A) are virtually identical (see Table I). This observation further supports our use of morphinanes as models for ring A of **1**.
(21) Cf. ref 18, spectrum no. 356.

# The 1-Hetera-4-cyclohexanone System. Proton and Carbon-13 Magnetic Resonance, Transannular Effects, and Conformational Analysis

Jerry A. Hirsch*[1] and E. Havinga

*Department of Chemistry, Seton Hall University, South Orange, New Jersey 07079, and the Gorlaeus Laboratories, Department of Organic Chemistry, University of Leiden, The Netherlands*

*Received October 30, 1975*

Proton ($^1$H NMR) and carbon-13 ($^{13}$C NMR) magnetic resonance have been applied to a series of 1-hetera-4-cyclohexanones in order to acquire information about ring conformations. The $^1$H NMR results require evaluation of long-range couplings through the carbonyl groups prior to *R*-value analysis. Comparison of the $^{13}$C NMR data with that from a series of 1-heteracyclohexanes and from acyclic analogues indicates (a) that the effects $\alpha$ and $\beta$ to the heteroatom groups in the 1-hetera-4-cyclohexanones are proportional to the effects in the same positions in the 1-heteracyclohexanes except for cyclohexane-1,4-dione, and, therefore, indicate chair conformations; (b) that additivity relationships from the 1-heteracyclohexanes may be used as indications of chair or twist conformations in 1,4-diheteracyclohexanes and 1-hetera-4-cyclohexanones; and (c) that upfield carbonyl shifts in 1-hetera-4-cyclohexanones and related systems do not contain transannular electron-transfer components. Previous suggestions that upfield carbonyl shifts of approximately 10 ppm or less may be used to indicate transannular electron donation are refuted. An ordering of heteroatom group effects is presented based on $^{13}$C NMR $\alpha$ shifts in these cyclic systems.

Cyclohexane and its derivatives have been subjected to extensive conformational analyses.[2] Numerous examples have been reported of both chair[2] and nonchair[2,3] preferences. In view of the predominantly twist nature of cyclohexane-1,4-dione[4,5] (**1a**) and its derivatives[4,6] and the predominantly chair nature of 1,4-dimethylenecyclohexane[4,7] and its analogues,[7,8] the question may be raised as to the extent to which $sp^2$-like hybridizations and electronic interactions cause this conformational dichotomy. A useful type of compound to help answer this question is the 1-hetera-4-cyclohexanone system (**1b–n**).

Various representative 1-hetera-4-cyclohexanones have been readily available for some time. Allinger and Jindal[9] investigated 1-acetyl-4-piperidone (**1b**) and 1-methyl-4-piperidone (**1c**) using *Z* values with n $\rightarrow \pi^*$ transitions, dipole moments, and infrared spectroscopy, and concluded that both compounds were predominantly in chair conformations. In particular, the *N*-acetyl system **1b** was not believed[9] to exhibit a transannular charge-transfer electrostatic interaction between the carbonyl groups in a boat conformation. However, no *Z*-value correlation was observed for this compound.

A series of papers by Katritzky and co-workers[10] has reported the cis–trans equilibrations of 3,5-dimethyl-1-hetera-4-cyclohexanones. These workers assumed that only chair conformations were significant; e.g., "... it is generally accepted that these compounds exist in a chair form".[10] Their base-catalyzed equilibrations were accomplished simultaneously with deuteration at the position $\alpha$ to the carbonyl group to simplify the proton magnetic resonance ($^1$H NMR) spectra, thereby eliminating the possibility of a concurrent *R*-value[4] type of conformational analysis.

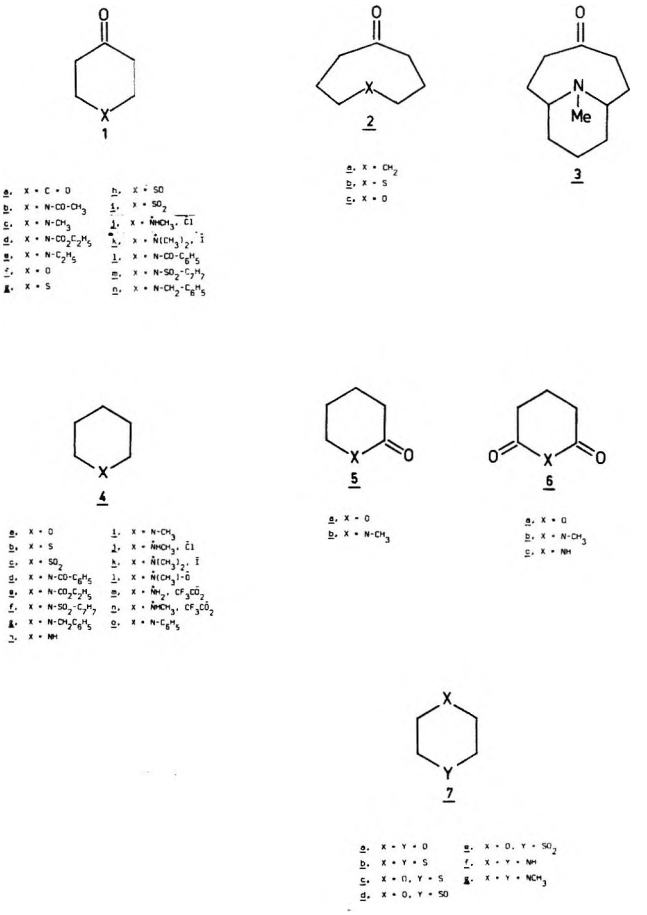


Table I
Results of Dahn, Schlunke, and Temler[13]

| Compd | $^{17}O$ NMR signal[a] | Rate of hydration[b] |
|---|---|---|
| Cyclohexanone | −564, −561 | 6 |
| 1e (X = $NC_2H_5$) | −561 | 19 |
| 1f (X = O) | −568 | 14 |
| 1g (X = S) | −569 | 20 |

[a] In parts per million relative to water. Measured on dioxane solutions at 28 ± 2°. [b] Determined by $^{17}O$ NMR on 8:1 dioxane–water solutions at 28 ± 2° in pH 5 acetate buffer.

Reported $^1H$ NMR analyses of 4-piperidones[11] indicate "the near-symmetrical pattern of an AA'BB' system" for the ring protons in 1-methyl-4-piperidone (**1c**). This suggests that an *R*-value approach[4] might be useful in a related heterocyclic system, but raises the question of the cause of the lack of symmetry in the spectrum. A conclusion drawn[11] on the basis of first-order coupling constants that 1-*tert*-butyl-*trans*-3,5-dimethyl-4-piperidone is nonchair must be viewed with some skepticism.[3] A subsequent report[12] of the $^1H$ NMR spectrum of 1-carboethoxy-4-piperidone (**1d**) provided little useful conformational information.

Other spectrometric and kinetic techniques have been applied to members of this series to probe interactions between the heteroatom and the carbonyl group. Dahn and co-workers[13] have examined the *N*-ethyl (**1e**), O (**1f**), and S (**1g**) systems using $^{17}O$-labeled ketones, and report that neither $^{17}O$ NMR spectra nor rates of hydration of the carbonyl groups provide any evidence for transannular interactions (Table I). Nevertheless, their results do indicate the presence of some type of heteroatom effect whose nature is not discussed. Changing the heteroatom must introduce some effect[14] related to the electronegativity of the heteroatom (and its substituents), and this electronegativity effect, whether through bonds or through space,[14] must be evaluated before any additional transannular interaction can be postulated or dismissed.

Some sulfur-containing members of this series (**1g–i**) have been subjected to mass spectrometric investigation.[15,16] Changing the nature of the heteroatom or its substituents influences the fragmentation pattern primarily by affecting the relative amounts of charge localization at the various possible sites on ionization. No definitive functional group interactions as such[17] were encountered. However, in a more extensive study[18] of the analogous 1-hetera-3-cyclohexanones, Djerassi and co-workers concluded that few fragmentations occur in such difunctional compounds which directly reflect the fragmentation patterns of the individual monofunctional systems (the heterocycle and the cyclohexanone).

Another technique which might be a useful probe for conformational analysis and/or transannular interactions is carbon-13 nuclear magnetic resonance spectroscopy[19,20] ($^{13}C$ NMR). Jones and Hassan[21] have reported $^{13}C$ NMR data for 1-methyl-4-piperidone (**1c**), a series of ring-methylated analogues, and their hydrochloride and methiodide salts (including hydrochloride **1j** and methiodide **1k**). The observed $^{13}C$ NMR chemical shifts were analyzed in terms of the equatorial and axial positions of the methyl groups and of the nitrogen substituents in chair conformations (based on previous[11] $^1H$ NMR studies). Additivity substituent parameters were derived and compared to the corresponding cyclohexane, cyclohexanone, and piperidine substituent parameters. The *N*-methyl, $N^+$, and C=O centers were considered as electronegative substituents in the cyclohexane system in order to rationalize smaller substituent parameters in the piperidone series. Since the observed effects of protonation and methiodation were small, Jones and Hassan[21] concluded that, by analogy with the piperidines[22] and the cyclohexanones, the major effect of the nitrogen and carbonyl groups on the carbons to which they are bonded is an inductive[19] (through-bond[14]) one, but that the effects of the tertiary and quaternary nitrogens on C-4, the carbonyl carbon in the piperidones, require postulation of an electric field effect.[19,22]

Table II
$^{13}C$ NMR of Carbonyl Carbons in 5-Heteracyclooctanones[23]

| Compd | $\delta^a$ ($C_6H_{12}$) | $\Delta\delta^b$ | $\delta^a$ (1:9 $C_6H_{12}$–$CHCl_3$) | $\Delta\delta^b$ |
|---|---|---|---|---|
| **2a** | 212.4 | | 218.2 | |
| **2b** | 210.9 | −1.5 | 215.8 | −2.4 |
| **2c** | 208.7 | −3.7 | 214.3 | −3.9 |
| **3** | 199.6 | −12.8 | 129.7 | −88.5 |

[a] In parts per million relative to $Me_4Si$ as reported by ref 24. [b] In parts per million relative to **2a**.

The sensitivity of $^{13}C$ NMR to transannular electron donation to carbonyl groups has been suggested by Nakashima and Maciel[23] using 5-heteracyclooctanones (**2a–c, 3**). Results in cyclohexane and 1:9 cyclohexane–chloroform (Table II[24]) are reported to provide evidence for transannular electron donation from the heteroatom to the carbonyl group in the upfield shifts of the $^{13}C$ NMR signals of the carbonyl carbons, thereby extending conclusions based primarily on the behavior of **3** in other investigations.[13,23] Nevertheless, Nakashima and Maciel[23] point out that it is possible that the observed effects for **2b** and **2c** may be partly inductive, but suggest that such an inductive effect through four $\sigma$ bonds would probably not have such a magnitude. Only two possible interactions are considered—a through-bond effect and an electron-transfer bonding transannular effect. The possibility of a dipolar through-space ("field") effect[14] is not differentiated from the bonding type of transannular effect, as it must be. It would be useful to be able to compare the cyclooctanone series with the corresponding heteracyclooctane compounds so as to treat the data[19,20] as ($\delta_{ketone} - \delta_{hydrocarbon}$) and better evaluate the inductive and field effects.

It is the intent of this work to investigate the $^1H$ NMR and $^{13}C$ NMR characteristics of representative 1-hetera-4-cyclohexanones (**1**) in the hope of being able to draw definite conclusions with respect to ring conformation[68] and with respect to the types of interactions existing between the heteroatom and the carbonyl group. The $^{13}C$ NMR of related 1-heteracyclohexanes (**4**), 1-hetera-2-cyclohexanones (**5**), and 1-hetera-2,6-cyclohexanediones (**6**) were determined for comparison purposes.

## Experimental Section

All $^{13}C$ NMR spectra were recorded on a JEOL PS-100 NMR spectrometer equipped with a JEOL-JNM-PFT-100 pulse unit and a JEOL-JEC-6 computer. Field-frequency stabilization was established by the deuterium signal of the solvent utilized [$CDCl_3$ or $(CD_3)_2SO$]. The chemical shifts are expressed in parts per million relative to internal $Me_4Si$ at 26 ± 2°C (unless otherwise indicated) and are believed to be accurate to 0.2 ppm.[25] The spectra were obtained under conditions of proton-noise decoupling, with off-resonance decoupling used to verify peak assignments where needed. All $^1H$ NMR spectra were recorded on the above JEOL spectrometer or on a Varian A-60A spectrometer, and are expressed in parts per million relative to internal $Me_4Si$.

All samples exhibited properties corresponding to literature data and were donated, purchased, or prepared as indicated: cyclohexane-1,4-dione[26] (**1a**), tetrahydropyran[27] (**4a**), tetrahydropyran-4-one[28] (**1f**), δ-valerolactone[26] (**5a**), pentamethylene sulfide[27] (**4b**), tetrahydrothiopyran-4-one[29] (**1g**), pentamethylene sulfone[30] (**4c**), tetrahydrothiopyran-4-one 1,1-dioxide[31] (**1i**), 1-methyl-2-piperi-

Table III
$^{13}$C NMR Data[a] for 1-Hetera-4-Cyclohexanones (1)

| Compd | X | Solvent | α to X | α to C=O | C=O | Other |
|---|---|---|---|---|---|---|
| 1a | C=O | $CDCl_3$ | 36.5 | 36.5 | 208.8 | |
| 1c | $NCH_3$ | Neat[b] | 55.4 | 40.9 | 206.2 | $NCH_3$, 45.1 |
| | | $CDCl_3$[c] | 54.7 | 40.9 | | $NCH_3$, 44.6 |
| | | $CDCl_3$ | 55.3 | 41.0 | 207.1 | $NCH_3$, 45.4 |
| | | $(CD_3)_2SO$ | 55.1 | 40.8 | 207.4 | $NCH_3$, 45.1 |
| 1d | $NCO_2C_2H_5$ | $CDCl_3$ | 43.0 | 40.9 | 207.2 | NCO, 155.3; $OCH_2$, 61.6; $CH_3$, 14.7 |
| | | $(CD_3)_2SO$ | 42.5 | 40.6 | 207.1 | NCO, 155.0; $OCH_2$, 61.3; $CH_3$, 14.7 |
| 1f | O | $CDCl_3$ | 67.7 | 42.8 | 206.2 | |
| 1g | S | $CDCl_3$ | 30.0 | 44.0 | 208.0 | |
| | | $(CD_3)_2SO$ | 28.8 | 43.4 | 207.7 | |
| 1i | $SO_2$ | $(CD_3)_2SO$ | 48.2 | 37.7 | 203.1 | |
| 1j | $^+NHCH_3,Cl^-$ | $CDCl_3$[b] | 52.0 | 38.4 | 203.1 | $NCH_3$, 42.2 |
| 1k | $^+N(CH_3)_2,I^-$ | $(CD_3)_2SO$[b] | 60.6 | 35.9 | 201.7 | $NCH_3$, 51.8 |
| 1l | $NCOC_6H_5$ | $CDCl_3$[d] | 43.9 | 41.0 | 206.0 | NCO, 170.6; Ar, 135.5, 130.0, 128.5, 126.9 |
| 1m | $NSO_2C_7H_7$ | $CDCl_3$ | 45.7 | 40.4 | 205.6 | $CH_3$, 21.4; Ar, 144.0, 133.2, 129.8, 127.5 |
| | | $(CD_3)_2SO$ | 45.1 | 39.8 | 205.3 | $CH_3$, 21.0; Ar, 144.7, 133.1, 130.0, 127.4 |
| 1n | $NCH_2C_6H_5$ | $CDCl_3$ | 52.8 | 41.0 | 207.7 | $ArCH_2$, 61.8; Ar, 138.1, 128.6, 128.3, 127.2 |

[a] Chemical shifts in parts per million relative to internal $Me_4Si$. [b] Reference 21. [c] Reference 45b. [d] At 60°C, ref 38.

done[26] (**5b**), 1-methyl-4-piperidone[26] (**1c**), *N*-methylglutarimide[27] (**6b**), 1-benzoylpiperidine[32] (**4d**), 1-benzoyl-4-piperidone[32] (**11**), 1-carboethoxypiperidine[33] (**4e**), 1-carboethoxy-4-piperidone[26] (**1d**), 1-tosylpiperidine[34] (**4f**), 1-tosyl-4-piperidone[35] (**1m**), 1-benzylpiperidine[36] (**4g**), and 1-benzyl-4-piperidone[32] (**1n**). A sample of tetrahydrothiopyran-4-one 1-oxide (**1h**) was prepared,[37] but is not included because of solubility difficulties and facile hydration and decomposition reactions.

## Results and Discussion

**$^1$H NMR Results.** Spectra were obtained for compounds **1c, 1d, 1g, 1i,** and **1m,** and were compared with available spectra for **1c,**[11] **1d,**[12] and **11.**[32] Only spectra exhibiting a first-order appearance were obtained at 60 and 100 MHz over a range of temperatures (−50 to 70°C) except for compounds **1g** and **11.**[38] The spectrum of tetrahydrothiopyran-4-one (**1g**) appeared as an unsymmetrical AA′BB′ system. Analysis with the aid of the iterative computer program LAME[27] (LAOCOON with magnetic equivalence) using estimated $J_{gem}$ values[4,39] suggested that the lack of symmetry resulted from long-range couplings[40] through the carbonyl group and that a complete analysis[4] was not reasonable because of insufficient spectral resolution. After completion of these experiments, $^1$H NMR data for *N*-alkyl-3,5-diphenyl-4-piperidones were reported[41] and analyzed in detail. The results[41] indicate chair conformations and both equatorial–equatorial and equatorial–axial long-range couplings through the carbonyl group.

**$^{13}$C NMR Results.** Spectra were obtained for cyclohexane-1,4-dione (**1a**) and 1-hetera-4-cyclohexanones **1c,d,f,g,i,l,m,n** (Table III), 1-heteracyclohexanes **4a–g** (Table IV), 1-hetera-2-cyclohexanones **5a** and **5b** (Table V), and 1-hetera-2,6-cyclohexandiones **6a–c** (Table V) and were compared with literature values for these[19–22,42–51] and analogous[47,49,52] systems. Spectra were obtained in $CDCl_3$ as a primary solvent. Since some compounds were not sufficiently soluble in this solvent, $(CD_3)_2SO$ was also used. Sufficient compounds were determined in both solvents to indicate the presence of small but reasonable consistent solvent effects.[19,20,23,53] In order to minimize such solvent effects, a given signal in a 1-hetera-4-cyclohexanone (**1**) is considered only relative to the analogous signal in the corresponding 1-heteracyclohexane (**4**) in the same solvent (except where literature values are used and not redetermined). Data for the *N*-benzoyl compounds **11** and **4d** are reported at temperatures sufficiently high[38] to ensure conditions of rapid exchange. An attempt to consider the 1-hetera-4-cyclohexanones (**1**) as analogues of 1,2-disubstituted ethanes[54] and to thereby compare the cyclic and acyclic cases[55] was prevented by lack of data on common substituents in the two systems.

Before attempting to evaluate the $^{13}$C NMR resonances in the 1-hetera-4-cyclohexanones (**1**), some reference point must be established for the electrostatic effects of the heteroatoms (and their substituents) in the absence of transannular interactions and/or conformational distortions. Since all of the carbon-unsubstituted 1-heteracyclohexanes (**4**) analyzed to date are believed to prefer chair conformations, chemical shifts in the 1-heteracyclohexanes (relative to cyclohexane as a standard[56]) should reflect primarily the heteroatom group electrostatic effects. Plots (Figure 1) of the chemical shifts (Table IV) of the carbon resonances α to X ($\delta^{\alpha}_{C_5H_{10}X} - \delta_{C_6H_{12}}$) against the methyl chemical shifts[57] of the corresponding acyclic $CH_3XCH_3$ and against the methylene chemical shifts[58] of the corresponding acyclic $CH_3CH_2XCH_2CH_3$ appear to be linear[60] within the limitation of the available data. The results in Figure 1, therefore, support the assumption of consistent (chair) conformations in these heterocyclic systems.

These data indicate an α substituent effect in the order O > $^+N(CH_3)_2$ ≫ $NCH_3$ > $^+NHCH_3$ > $NCH_2C_6H_5$ > $NC_6H_5$ > $SO_2$ > NH > $NSO_2C_7H_7$ > $NCOC_6H_5$ > C=O ≫ S. It is not resonable to consider the effects of the charged species on the same basis as the uncharged species because of monopole-induced effects. In addition, the charged species and the sulfone group contain both equatorial and axial substituents on the heteroatom, requiring consideration of conformationally dependent substituent effects,[19,20] while the nitrogen species will also have different steric components. Because of the observed correlation with acyclic $^{13}$C NMR chemical shifts, it seems consistent with current terminology[19] to describe the order of the observed substituent effects of the uncharged species as indicating relative electron-withdrawing abilities.[70] However, the order within the uncharged nitrogen species is itself, at first glance, somewhat surprising. The usual approach[14,61] is to consider an alkyl group on nitrogen as electron donating and an amide or sulfonamide group as electron withdrawing, suggesting a relative electron-withdrawing order of NCO, $NSO_2$ > *N*-alkyl. The opposite order observed here may be discussed in several ways. The benzoyl, sulfonyl, and ethoxycarbonyl groups delocalize the lone pair on nitrogen, effecting a rehybridization with diminished electron density at the nitrogen. The nitrogen has less tendency to withdraw electrons from the adjacent carbon (and hy-

Table IV
$^{13}$C NMR Data[a] for 1-Heteracyclohexanes (4)

| Compd | X | Solvent | α to X | β to X | γ to X | Other | Ref |
|---|---|---|---|---|---|---|---|
| 4a | O | Neat | 69.5 | 27.7 | 24.9 | | 20, 42 |
| | | Neat | 69.7 | 27.9 | 25.1 | | 19, 42 |
| | | $(CD_3)_2CO$ | 69.8 | 27.4 | 24.3 | | 43 |
| | | $CDCl_3$ | 68.7 | 26.9 | 23.8 | | Here |
| 4b | S | Neat | all 30 ± 2.5 | | | | 19, 20, 42 |
| | | $CDCl_3$ | 29.1 | 27.9 | 26.6 | | Here |
| 4c | $SO_2$ | $(CD_3)_2SO$ | 51.2 | 24.1 | 22.8 | | Here |
| 4d | $NCOC_6H_5$ | $CDCl_3$[b] | 45.8 | 26.1 | 24.5 | NCO, 170.0; Ar, 136.8, 129.2, 128.2, 126.8 | Here |
| | | $(CD_3)_2SO$[b] | 45.2 | 25.7 | 24.3 | NCO, 168.9; Ar, 136.8, 129.2, 128.4, 126.7 | Here |
| 4e | $NCO_2C_2H_5$ | $CDCl_3$ | 44.8 | 25.8 | 24.6 | NCO, 155.4; $OCH_2$, 60.9; $CH_3$, 14.8 | Here |
| | | $(CD_3)_2SO$ | 44.5 | 25.7 | 24.4 | NCO, 154.8; $OCH_2$, 60.7; $CH_3$, 14.8 | Here |
| 4f | $NSO_2C_7H_7$ | $CDCl_3$ | 47.0 | 25.1 | 23.4 | $CH_3$, 21.5; Ar, 143.3, 133.1, 129.6, 127.7 | Here |
| | | $(CD_3)_2SO$ | 46.6 | 24.8 | 22.9 | $CH_3$, 21.0; Ar, 143.3, 133.2, 129.7, 127.4 | Here |
| 4g | $NCH_2C_6H_5$ | $CDCl_3$ | 54.6 | 26.0 | 24.5 | $ArCH_2$, 64.0; Ar, 138.6, 129.1, 128.0, 126.8 | Here |
| 4h | NH | Dioxane | 47.9 | 27.8 | 25.9 | | 44 |
| | | Neat | 47.7 | 27.5 | 26.1 | | 19, 22 |
| | | Neat (?) | 48.2 | 28.0 | 26.0 | | 19, 45a |
| | | c | 47.1 | 27.0 | 24.5 | | 46 |
| | | Neat[d] | 47.9 | 27.9 | 25.9 | | 47a |
| | | Neat | 50.2 | 28.6 | 26.8 | | 48a |
| | | $CDCl_3$ | 47.9 | 27.9 | 26.2 | | 48b |
| | | $C_6D_6$ | 47.9 | 27.7 | 25.9 | | 47b |
| 4i | $NCH_3$ | Neat | 57.4 | 26.6 | 26.6 | $NCH_3$, 47.9 | 19, 20, 42 |
| | | Neat | 56.7 | 26.2 | 24.3 | $NCH_3$, 46.9 | 19, 22 |
| | | Neat | 57.9 | 27.3 | 25.3 | $NCH_3$, 48.0 | 48a |
| | | Neat[d] | 57.0 | 26.6 | 24.6 | $NCH_3$, 47.1 | 47a |
| | | c | 56.7 | 26.0 | 24.1 | $NCH_3$, 46.6 | 46 |
| | | $CDCl_3$ | 57.4 | 26.7 | 22.7 | $NCH_3$, 47.7 | 48b |
| 4j | $^+NHCH_3$, $Cl^-$ | e | 55.2 | 23.7 | 21.8 | $NCH_3$, 44.3 | 19, 22 |
| | | c | 55.7 | 23.9 | 21.7 | $NCH_3$, 44.3 | 46 |
| 4k | $^+N(CH_3)_2$, $I^-$ | e | 63.3 | 20.6 | 21.0 | $NCH_3$, 52.7 | 19, 22 |
| | | c | 63.8 | 20.8 | 21.3 | $NCH_3$, 52.8 | 46 |
| 4l | $^+N(CH_3)O^-$ | $C_6H_6$ | 66.1 | 21.1 | 21.7 | $NCH_3$, 59.6 | 19, 22 |
| 4m | $^+NH_2$, $CF_3CO_2^-$ | $CF_3CO_2H$[f] | 47.4 | 23.8 | 22.9 | | 48a |
| 4n | $^+NHCH_3$, $CF_3CO_2^-$ | $CF_3CO_2H$[f] | 57.8 | 24.5 | 22.0 | $NCH_3$, 45.3 | 48a |
| 4o | $NC_6H_5$ | Neat | 52.4 | | | | 19, 45a |

[a] Chemical shifts in parts per million relative to internal $Me_4Si$ or converted to this basis. [b] At 56°C.[38] [c] 50% aqueous dioxane. [d] With 10% cyclohexane. [e] Water or dioxane; not clearly specified. [f] Results vary with mole fraction $CF_3CO_2H$; see ref 48a.

Table V
$^{13}$C NMR Data[a] for Other Relevant Systems

| Compd | X (Y) | Solvent | C-2 | C-3 | C-4 | C-5 | C-6 | Other | Ref |
|---|---|---|---|---|---|---|---|---|---|
| Cyclohexanone | | Neat | 40.7 | 26.8 | 24.1 | 26.8 | 40.7 | CO, 208.8 | 19, 20, 49 |
| | | $CDCl_3$ | 41.9 | 27.1 | 25.1 | 27.1 | 41.9 | CO, 211.3 | 44 |
| | | $CDCl_3$ | 41.9 | 27.1 | 25.0 | 27.1 | 41.9 | CO, 211.5 | 50 |
| 5a | O | | 167.5 | | | | | | 19 |
| | | | 175.2 | | | | | | 20 |
| | | $CDCl_3$ | 171.2 | 29.9 | 19.1 | 22.3 | 69.3 | | Here |
| 5b | $NCH_3$ | | 170 ± 3 | | | | | | 21 |
| | | $CDCl_3$ | 169.2 | 32.4 | 21.8 | 23.3 | 49.9 | $NCH_3$, 34.3 | Here |
| 6a | O | | 168.2 | | | | | | 20 |
| | | $CDCl_3$ | 167.8 | 29.6 | 16.1 | 29.6 | 167.8 | | 51 |
| | | $(CD_3)_2CO$ | 168.5 | 30.1 | 16.7 | 30.1 | 168.5 | | 51 |
| 6b | $NCH_3$ | $CDCl_3$ | 172.8 | 32.6 | 17.2 | 32.6 | 172.8 | $NCH_3$, 26.0 | Here |
| 6c | NH | $(CD_3)_2CO$ | 173.8 | 32.2 | 18.7 | 32.2 | 173.8 | | 51 |
| 7a | O, O | $CDCl_3$ | 67.8 | 67.8 | | 67.8 | 67.8 | | 52 |
| 7b | S, S | $CDCl_3$ | 29.1 | 29.1 | | 29.1 | 29.1 | | 52 |
| 7c | O, S[c] | $CDCl_3$ | 68.5 | 27.0 | | 27.0 | 68.5 | | 52 |
| 7d | O, SO[c] | $CDCl_3$ | 59.0 | 46.2 | | 46.2 | 59.0 | | 52 |
| 7e | O, $SO_2$[c] | $CDCl_3$ | 66.0 | 52.8 | | 52.8 | 66.0 | | 52 |
| 7f | NH, NH | Neat[b] | 47.9 | 47.9 | | 47.9 | 47.9 | | 47a |
| 7g | $NCH_3$, $NCH_3$ | Neat[b] | 55.7 | 55.7 | | 55.7 | 55.7 | | 47a |

[a] Chemical shifts in parts per million relative to internal $Me_4Si$. [b] With 10% cyclohexane. [c] Oxygen at position 1.

drogen) atoms than the NH or *N*-alkyl groups. The validity of this type of reasoning is supported by the position of $NC_6H_5$ relative to *N*-alkyl in the sequence. In a sense, this behavior of the various nitrogen groups[48a] is another manifestation of the Pople–Gordon suggestion[14,62] that through-bond inductive effects exhibit an alternation in magnitude of polarity in saturated systems.

An additional (or alternative) qualitative electron-density argument may be developed from considerations of dipole-induced σ polarizations. The different orientations

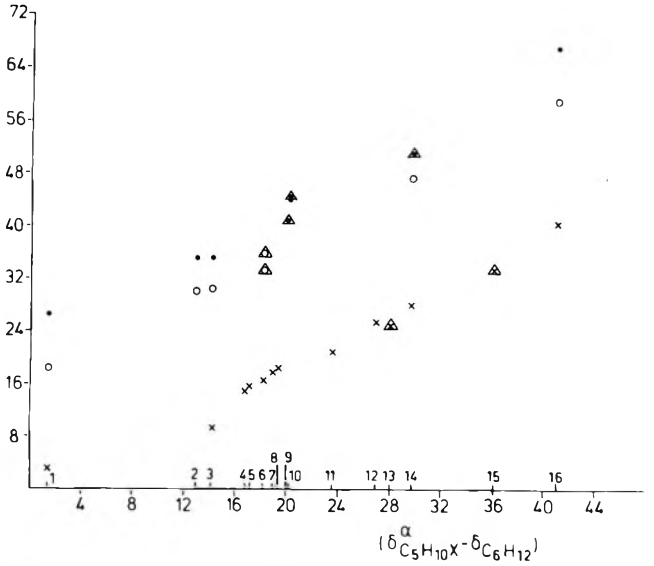



**Figure 1.** Comparison of the chemical shifts of the carbons $\alpha$ to the heteroatom in **4** (relative to cyclohexane) with (a) the chemical shifts $\alpha$ to the heteroatom in $(CH_3CH_2)_2X$ (●), (b) in $(CH_3)_2X$ (○), and (c) in **1** (relative to the position $\beta$ to the carbonyl in cyclohexanone) (×). Points involving comparisons in different solvents are indicated by Δ. Heteroatomic group and number assigned: S, 1; C=O (neat), 2; C=O, 3; $NCO_2C_2H_5(Me_2SO)$, 4; $NCO_2C_2H_5$, 5; $NCOC_6H_5$, 6; $NSO_2C_7H_7(Me_2SO)$, 7; $NSO_2C_7H_7$, 8; $NCH_3$, 9; NH, 10; $SO_2$, 11; $NCH_2C_6H_5$, 12; $NHCH_3$, 13; $NCH_3$, 14; $^+N(CH_3)_2$, 15; O, 16.

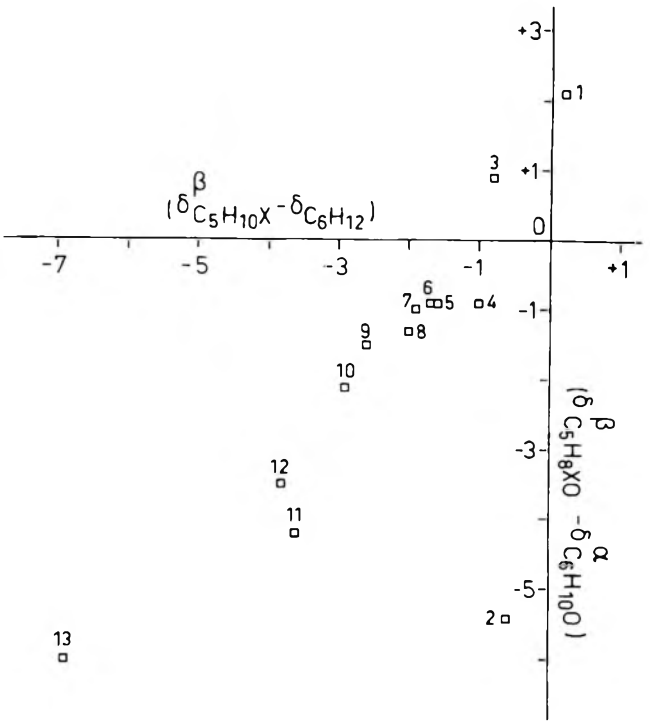



**Figure 2.** Comparison of the chemical shifts of the carbons $\beta$ to the heteroatom in **4** (relative to cyclohexane) with the chemical shifts of the carbons $\beta$ to the heteroatom in **1** (relative to the position $\alpha$ to the carbonyl in cyclohexanone): X = S, 1; C=O, 2; O, 3; $NCH_3$, 4; $NCOC_6H_5$, 5; $NCH_2C_6H_5$, 6; $NCO_2C_2H_5$, 7; $NCO_2C_2H_2(Me_2SO)$, 8; $NSO_2C_7H_7$, 9; $NSO_2C_7H_7(Me_2SO)$, 10; $SO_2$, 11; $^+NHCH_3$, 12; $^+N(CH_3)_2$, 13.

and magnitudes of the group dipole moments in the *N*-alkyl and benzamide–urethane–sulfonamide systems would induce different charge densities at the $\alpha$ and $\beta$ carbons in these two types of structures. Combination of such a dipole-induced dipole interpretation with nitrogen hybridization effects may best explain the order of both the $\alpha$ and $\beta$ chemical shifts. The fact that the $\alpha$ shifts are downfield and the $\beta$ shifts are upfield illustrates the complexity of these phenomena.

Having established the electrostatic nature of the heteroatom group effects on the $\alpha$ carbons in the 1-heteracyclohexanes (**4**), comparison of the heteroatom effects in the 1-hetera-4-cyclohexanones (**1**) to those in **4** is required. A plot (Figure 1) of the chemical shifts (Table III) of the carbons $\alpha$ to the heteroatom in **1** relative to the chemical shift of the corresponding position ($\beta$ to the carbonyl) in cyclohexanone (Table V, from ref 44) ($\delta^{\alpha}_{C_5H_8XO} - \delta^{\beta}_{C_6H_{10}O}$) against the chemical shifts of the $\alpha$ carbons in **4** relative to cyclohexane ($\delta^{\alpha}_{C_5H_{10}X} - \delta_{C_6H_{12}}$) gives a good linear relationship except for cyclohexane-1,4-dione (**1a**). Since the latter compound is believed[4,5] to exist predominantly in a twist conformation in solution, the linear relationship observed in Figure 1 for all of the other 1-hetera-4-cyclohexanones suggests that they all possess similar chairlike conformations.[68]

A similar plot of ($\delta^{\beta}_{C_5H_{10}X} - \delta_{C_6H_{12}}$) against the methyl chemical shifts[58] of the $CH_3CH_2XCH_2CH_3$ series indicates no obvious relationship. The order of these $\beta$ shifts in the 1-heteracyclohexanes (**4**) is different from that of the $\alpha$ shifts. Explanations based on conformational influences in the acyclic compounds[55] and conformational effects[48a] in the heterocyclic compounds related to positions of monopoles, lone pairs, and dipoles on the heteroatomic groups are reasonable.

Reasonably strong evidence for chair conformations of **1** is provided in Figure 2, where ($\delta^{\beta}_{C_5H_8XO} - \delta^{\alpha}_{C_6H_{10}O}$) is found to be proportional to ($\delta^{\beta}_{C_5H_{10}X} - \delta_{C_6H_{12}}$) except for cyclohexane-1,4-dione. Any conformational dependence of the $\sigma$ inductive effect[48a] in **1** is cancelled by the analogous conformational effect in **4** if each series of compounds exists in similar (chair) conformations. The dramatically divergent behavior of **1a** suggests that such $\beta$ shifts may be the most useful $^{13}C$ NMR probe of ring conformational preference.[70]

It may be argued that the "abnormal" behavior of cyclohexane-1,4-dione (**1a**) in both Figure 1 and Figure 2 is not the result of a conformational difference, but arises from the symmetry of this compound, where all of the methylene carbons are equivalent. If this were true, discrepancies would be observed whenever symmetrical structures (e.g., **7**) were compared with similar unsymmetrical ones. As shown in Figure 3, comparison of observed $^{13}C$ NMR chemical shifts (Tables III and V) and chemical shifts calculated from monosubstituted systems (Table IV) by assuming additivity relationships illustrates the validity of the additivity relationships (within ±2.5 ppm) for all of the compounds listed other than cyclohexane-1,4-dione. An explanation of these results on other than conformational grounds does not seem reasonable.

Further support for the validity of the conclusion that the $^{13}C$ NMR results of Figures 1 and 2 require chair conformations for the 1-hetera-4-cyclohexanones (**1**) (other than **1a**) may be found in a comparison (Figure 4) of the 1-hetera-4-cyclohexanones with the 1-hetera-2-cyclohexanones (**5**) and the 1-hetera-2,6-cyclohexanediones (**6**) (Table V[63]), neither of which exists in a normal chair conformation.[39,51] Additivity relationships do not hold, which should be expected since **5** and **6** might better be considered as containing single new functional groups. Any possible correlation similar to Figures 1 and 2 would have significantly different slopes. Treatment of **5** and **6** as containing a new functional group set and comparison with the corresponding acyclic esters, amides, anhydrides, and imides

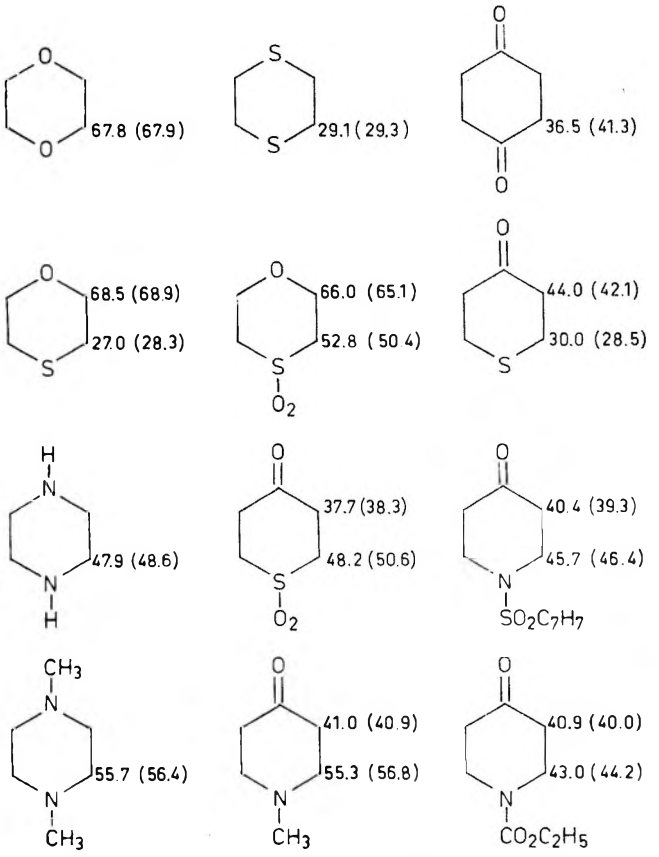



**Figure 3.** Comparison of observed $^{13}C$ NMR chemical shifts with those calculated (in parentheses) assuming additivity of effects from monosubstituted compounds.

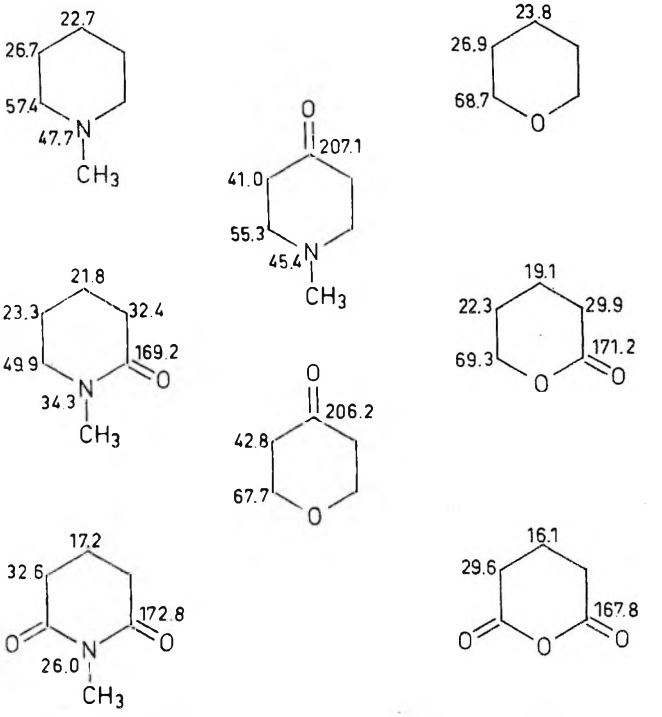



**Figure 4.** $^{13}C$ NMR comparison of 1-oxa- and 1-azamethylcyclohexanes, -2-cyclohexanones, -4-cyclohexanones, and -2,6-cyclohexanediones.

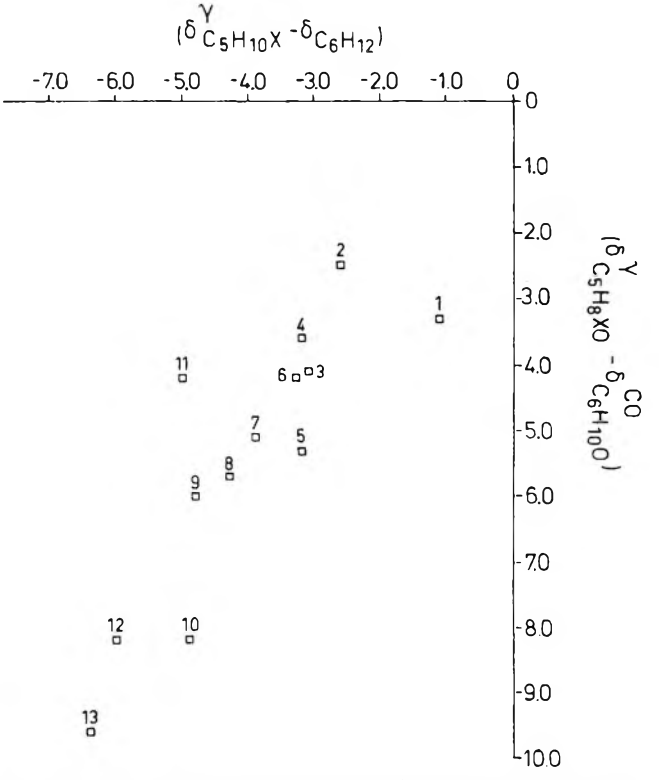



**Figure 5.** Comparison of the chemical shifts of the carbons $\gamma$ to the heteroatom in **4** (relative to cyclohexane) with the chemical shifts of the carbonyl carbons in **1** (relative to the carbonyl carbon in cyclohexanone): X = S, 1; C=O, 2; $NCO_2C_2H_5$, 3; $NCH_2C_6H_5$, 4; $NCOC_6H_5$, 5; $NCO_2C_2H_5(Me_2SO)$, 6; O, 7; $NSO_2C_7H_7$, 8; $NSO_2C_7H_7(Me_2SO)$, 9; $SO_2$, 10; $NCH_3$, 11; $NHCH_3$, 12; $^+N(CH_3)_2$, 13.

(where available[64]) gives a more or less parallel correlation to those in Figure 1 (although solvent corrections must be introduced for meaningful correlation). Conformational changes in going from **4** to **5** and to **6** are consistent in the two heteroatom series, but correlation with **1** does not occur.

The final question is the extent to which a field effect or an electron transfer occurs in the 1-hetera-4-cyclohexanones. As suggested by the calculations of Jones and Hassan[21] and Duch,[19,22] an electric field effect is probably the major interaction between the heteroatom group and the $\gamma$ position in these systems. In all members of compound sets **1** and **4**, the $\gamma$ carbon is shifted upfield (relative to cyclohexane in **4** and relative to the cyclohexanone carbonyl in **1**) (Tables III and IV). As shown in Figure 5, a plot of the $\gamma$ chemical shifts in **1** against those in **4** appears as clustering about a possible linear relationship. The $\gamma$ upfield shifts in **1** are larger than in **4** [except for cyclohexane-1,4-dione (**1a**)], an effect ascribable to the greater sensitivity of the carbonyl group to electrostatic effects through polarization of the $\pi$ electrons. Since the largest shifts are for quaternary nitrogen heterocycles, which cannot donate electrons to carbonyl groups, any transannular electron donation must be minimal in the 1-hetera-4-cyclohexanones (**1**).[65]

A recent publication by Eliel et al.[66] provides greater insight into heteroatom effects on both gauche and anti $\gamma$ carbons. Incremental $\gamma$ upfield shifts on anti positions are greater than on gauche positions and are most pronounced for second-row heteroatoms. These authors propose a hyperconjugative-type interaction of free-electron pairs centered on second-row heteroatoms with the $C_\alpha$–$C_\beta$ bond accompanied by a subsequent alternation of the electron density at the $\gamma$ anti-periplanar carbon. Electrostatic through-space field effects are discounted because of observed dependence on heteroatom row and not on heteroatom electronegativity. Enhanced $\gamma$ anti effects in positively charged systems require an additional monopole-induced $\sigma$-inductive effect or electrostatic field effect. Simple steric arguments[19,20] may still be important in $\gamma$ gauche relationships

and may not be discarded. While these new data[66] are extremely significant, they do not appear to materially affect the conclusions reached herein.

According to Nakashima and Maciel,[23] an upfield shift in the carbonyl carbon resonance provides evidence for transannular electron donation. While the heteroatom is fewer $\sigma$ bonds distant from the carbonyl group in **1** than in **2** and **3**, the upfield shifts of the carbonyl carbons in **1** and the $\gamma$ carbons in **4** are larger than the upfield shifts reported for **2b** and **2c**, requiring the conclusion that Nakashima and Maciel only observed transannular electron donation in **3**. The observed upfield shifts in **2b** and **2c** relative to **2a** must be ascribed to the normal effects of the heteroatoms in these molecules.

The $^{13}C$ NMR results reported herein indicate unambiguously that the hybridization at nitrogen does affect the electron density at each ring carbon in a six-membered nitrogen heterocycle. Assumptions[67] that hybridization at nitrogen is of little significance and that rotational barriers in *N*-acetylpiperidines and *N*-nitrosopiperidines provide an indirect method to evaluate conformational equilibria (such as $\Delta G°$ for 2-methyl substituents) in the corresponding piperidines must be accepted with caution.

**Acknowledgments.** We wish to thank Mr. C. Erkelens for operating the JEOL spectrometer, Professor A. K. Bose for $^{13}C$ NMR spectra in the early stages of this work, and Dr. F. J. Koer and Dr. C. Altona for use of their program for $^1H$ NMR simulation. We are grateful to Dr. F. J. Koer, Dr. C. Altona, Dr. H. J. C. Jacobs, and Professor R. L. Augustine for helpful discussions, and to all those persons indicated who supplied valuable compounds. Dr. H. M. Seip, Dr. H. M. R. Hoffmann, and Professor J. Reisse also kindly provided unpublished material or preprints of manuscripts. J. A. H. is especially grateful to Seton Hall University for a sabbatical leave, and to Professor Havinga for his generous hospitality in Leiden.

**Registry No.**—**1a,** 637-88-7; **1c,** 1445-73-4; **1d,** 29976-53-2; **1f,** 29943-42-8; **1g,** 1072-72-6; **1i,** 17396-35-9; **1j,** 34737-83-2; **1k,** 26822-37-7; **1l,** 24686-78-0; **1m,** 33439-27-9; **1n,** 3612-20-2; **4b,** 1613-51-0; **4c,** 4988-33-4; **4d,** 776-75-0; **4e,** 5325-94-0; **4f,** 4703-22-4; **4g,** 2905-56-8; **5a,** 542-28-9; **5b,** 931-20-4; **6b,** 25077-25-2.

## References and Notes

(1) Address correspondence to Seton Hall University. On sabbatical leave from Seton Hall University at University of Leiden, 1974–1975.
(2) J. A. Hirsch, "Concepts in Theoretical Organic Chemistry", Allyn and Bacon, Boston, Mass., 1974, Chapter 12, and references cited therein.
(3) G. M. Kellie and F. G. Riddell, *Top. Stereochem.*, **8**, 225 (1974); D. L. Robinson and D. W. Theobald, *Q. Rev., Chem. Soc.*, **21**, 314 (1967).
(4) J. B. Lambert, *Acc. Chem. Res.*, **4**, 87 (1971).
(5) P. Dowd, T. Dyke, and W. Klemperer, *J. Am. Chem. Soc.*, **92**, 6327 (1970), and references cited therein; A. Mossel, C. Romers, and E. Havinga, *Tetrahedron Lett.*, 1247 (1963).
(6) P. Groth, *Acta Chem. Scand.*, **22**, 128 (1968); H. Saito and K. Nukada, *J. Mol. Spectrosc.*, **8**, 355 (1965).
(7) M. St. Jacques and M. Bernard, *Can. J. Chem.*, **47**, 2911 (1969); N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Am. Chem. Soc.*, **90**, 5773 (1968); D. S. Bailey and J. B. Lambert, *J. Org. Chem.*, **38**, 134 (1973).
(8) A. Aihara, C. Kitazawa, and F. Iwasaki, *Bull. Chem. Soc. Jpn.*, **41**, 1034 (1968); B. Rickborn and M. J. Wuesthoff, *J. Am. Chem. Soc.*, **92**, 6894 (1970); J. B. Lambert, J. L. Gosnell, Jr., and D. S. Bailey, *J. Org. Chem.*, **37**, 2814 (1972).
(9) N. L. Allinger and S. P. Jindal, *J. Org. Chem.*, **37**, 1042 (1972).
(10) M. D. Brown, M. J. Cook, and A. R. Katritzky, *J. Chem. Soc. B*, 2358 (1971), and references cited therein.
(11) M. M. A. Hassan and A. F. Casy, *Tetrahedron*, **26**, 4517 (1970); *Org. Magn. Reson.*, **2**, 197 (1970); **1**, 389 (1969).
(12) G. R. Krow and D. M. Fan, *J. Org. Chem.*, **39**, 2674 (1974).
(13) H. Dahn, H.-P. Schlunke, and J. Temler, *Helv. Chim. Acta*, **55**, 907 (1972).
(14) Reference 2, Chapters 4 and 6.
(15) A. A. Kutz and S. J. Weininger, *J. Org. Chem.*, **33**, 4070 (1968).
(16) R. Herzschuh and H. Remane, *Org. Mass Spectrom.*, **9**, 665 (1974).
(17) M. M. Green, D. S. Weinberg, and C. Djerassi, *J. Am. Chem. Soc.*, **88**, 3883 (1966); J. R. Dias and C. Djerassi, *Org. Mass Spectrom.*, **6**, 385 (1972).
(18) J. H. Block, D. H. Smith, and C. Djerassi, *J. Org. Chem.*, **39**, 279 (1974).
(19) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(20) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Interscience, New York, N.Y., 1972.
(21) A. J. Jones and M. M. A. Hassan, *J. Org. Chem.*, **37**, 2332 (1972).
(22) M. W. Duch, Dissertation, University of Utah, 1970; *Diss. Abstr. B*, **31**, 1200 (1970).
(23) T. T. Nakashima and G. E. Maciel, *Org. Magn. Reson.*, **4**, 321 (1972).
(24) N. K. Wilson and J. B. Stothers, *Top. Stereochem.*, **8**, 1 (1974).
(25) From dilution studies on cyclooctanone,[23] it has been concluded that the $^{13}C$ NMR carbonyl resonance has a total range of about 2 ppm between 0.05 and 0.6 *M*. In our work, all solutions were prepared as 10–15%, so some small dilution effects might be present. Other evidence[19,20] indicates that $sp^3$-carbon $^{13}C$ NMR resonances are much less sensitive to concentration than are carbonyl resonances.
(26) Aldrich Chemical Co.
(27) Kindly provided by Dr. F. J. Koer and Dr. C. Altona.
(28) Kindly provided by Professors L. A. Paquette and H. Dahn.[13]
(29) Prepared by R. W. Kosley, Jr., by method of P. Johnson and G. A. Berchtold, *J. Org. Chem.*, **35**, 584 (1970), or by sublimation of material purchased from Aldrich Chemical Co.
(30) Method of E. V. Whitehead, R. A. Dean, and F. A. Fidler, *J. Am. Chem. Soc.*, **73**, 3632 (1951), as modified by ref 15.
(31) Prepared by R. W. Kosley, Jr., from **1g** by method of E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **70**, 1813 (1948).
(32) Kindly provided by Professor R. L. Augustine.
(33) Prepared by modification of C. Schotten, *Ber.*, **15**, 425 (1882).
(34) Prepared using the procedure of A. I. Vogel, "A Textbook of Practical Organic Chemistry", 3rd ed, Longmans, London, 1956, p 653.
(35) Kindly provided by Dr. W. N. Speckamp.
(36) Prepared by J. Brussee by method of Y. Kikukawa, S. Ikegami, and S. Yamada, *Chem. Pharm. Bull.*, **17**, 98 (1969).
(37) Prepared by R. W. Kosley, Jr., from **1g** by method of C. R. Johnson and N. J. Leonard, *J. Org. Chem.*, **27**, 282 (1962). Product was obtained only when freshly opened bottles of sodium metaperiodate were used.
(38) A detailed analysis of the $^1H$ NMR and $^{13}C$ NMR behavior of 1-benzoyl-4-piperidone (**11**) and related *N*-benzoyl systems will be found in J. A. Hirsch, R. L. Augustine, G. Koletar, and H. G. Wolf, *J. Org. Chem.*, **40**, 3547 (1975).
(39) F. J. Koer, T. M. W. van Asbeck, and C. Altona, *Recl. Trav. Chim. Pays-Bas*, **92**, 1003 (1973); M. Anteunis, G. Swalens, and J. Gelan, *Tetrahedron*, **27**, 1917 (1971).
(40) C. Cuvelier, R. Ottinger, and J. Reisse, *Tetrahedron Lett.*, 277 (1972); M. Barfield and B. Chakrabati, *Chem. Rev.*, **69**, 757 (1969).
(41) R. Andrisano, A. S. Angeloni, and G. Gottarelli, *Tetrahedron*, **30**, 3827 (1974).
(42) G. E. Maciel and G. B. Savitsky, *J. Phys. Chem.*, **69**, 3925 (1965).
(43) A. J. de Hoog, *Org. Magn. Reson.*, **6**, 233 (1974).
(44) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley, New York, N.Y., 1972.
(45) (a) T. Pehk and E. Lippmaa, *Eesti NSV Tead. Akad. Toim. Keem. Geol.*, **17**, 291 (1968); (b) Y. Takeuchi, *J. Chem. Soc., Perkin Trans. 2*, 1927 (1974).
(46) W. O. Crain, Jr., W. C. Wildman, and J. D. Roberts, *J. Am. Chem. Soc.*, **93**, 990 (1971). Corrected from original $CS_2$ scale to $Me_4Si$ scale using 193.7 ppm.
(47) (a) G. Ellis and R. G. Jones, *J. Chem. Soc., Perkin Trans. 2*, 437 (1972); (b) H. Booth and D. V. Griffiths, *ibid.*, 842 (1973).
(48) (a) I. Morishima, K. Yoshikawa, K. Okada, T. Uonezawa, and K. Goto, *J. Am. Chem. Soc.*, **95**, 165 (1973); (b) I. Morishima, K. Okada, T. Yonezawa, and K. Goto, *ibid.*, **93**, 3922 (1971); (c) converted from original $CS_2$ scale to $Me_4Si$ scale using 193.7 ppm.
(49) F. J. Weigert and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 1347 (1970).
(50) J. B. Stothers and C. T. Tan, *Can. J. Chem.*, **52**, 308 (1974).
(51) F. J. Koer, A. J. de Hoog, and C. Altona, *Recl. Trav. Chim. Pays-Bas*, **94**, 75 (1975).
(52) W. A. Szarek, D. M. Vyas, A. M. Sepulchre, S. D. Gero, and G. Lukacs, *Can. J. Chem.*, **52**, 2041 (1974).
(53) G. E. Maciel and J. J. Natterstad, *J. Chem. Phys.*, **42**, 2752 (1965), and references cited therein.
(54) L. Simeral and G. E. Maciel, *J. Phys. Chem.*, **77**, 1590 (1973), and previous paper in series.
(55) It is hoped that additional examples of the 1,2-disubstituted ethanes will be studied since this type of comparison with the 1-hetera-4-cyclohexanones might permit evaluation of conformational effects on the ethane $^{13}C$ NMR resonances.
(56) A value of $\delta$ 27.7 was used for neat cyclohexane.[19,20]
(57) Reference 19: $(CH_3)_2O$ $\delta$ 59.4 (neat); $(CH_3)_3N$ $\delta$ 47.5 (neat); $(CH_3)_2S$ $\delta$ 19.5 (neat); $(CH_3)_2CO$ $\delta$ 30.2 (neat). Reference 44: $(CH_3)_2CO$ $\delta$ 30.6 ($CDCl_3$); $(CH_3)_2NCHO$ $\delta$ 31.1 and $\delta$ 36.2 ($CDCl_3$) for average of $\delta$ 33.6; $(CH_3)_2NCOCH_3$ $\delta$ 34.5 and $\delta$ 37.5 (dioxane) for average of $\delta$ 36.0.
(58) Reference 19: $(CH_3CH_2)_2O$ $\alpha$ $\delta$ 67.4, $\beta$ $\delta$ 17.1 (neat); $(CH_3CH_2)_2S$ $\alpha$ $\delta$ 26.5, $\beta$ $\delta$ 15.8 (neat); $(CH_3CH_2)_2NH$ $\alpha$ $\delta$ 44.1, $\beta$ $\delta$ 15.4 (neat); $(CH_3CH_2)_2CO$ $\alpha$ $\delta$ 35.3, $\beta$ $\delta$ 7.3 (neat). Reference 44: $(CH_3CH_2)_2CO$ $\alpha$ $\delta$ 35.4, $\beta$ $\delta$ 7.9 ($CDCl_3$). Reference 59: $(CH_3CH_2)_2NH$ $\alpha$ $\delta$ 44.4, $\beta$ $\delta$ 15.7 ($C_6D_6$); $(CH_3CH_2)_2NCH_3$ $\alpha$ $\delta$ 51.4, $\beta$ $\delta$ 12.8, $NCH_3$ $\delta$ 41.0 ($C_6D_6$).
(59) H. Eggert and C. Djerassi, *J. Am. Chem. Soc.*, **95**, 3710 (1973).
(60) The isolated carbonyl group is treated as a heteroatom in all correlations since the only effect it should exert is an electrostatic electron withdrawal similar to that of a heteroatomic group.
(61) For a $^1H$ NMR study of the effects of N substitution on lone pair interaction with polyene systems, see A. G. Anastassiou, R. L. Elliott, and E. Reichmanis, *J. Am. Chem. Soc.*, **96**, 7823 (1974), and references cited therein.

(62) J. A. Pople and M. Gordon, *J. Am. Chem. Soc.*, **89**, 4253 (1967).
(63) The resonances resulting from the various carbons in *N*-methylglutarimide (**6b**) were assigned using off-resonance decoupling and by analogy with those in glutarimide[51] (**6c**) and those reported for more highly substituted analogues by C. Dorlet and G. Van Binst, *Anal. Lett.*, **6**, 785 (1973).
(64) Reference 19: $CH_3OC(=O)CH_3$ acid $CH_3$ $\delta$ 19.6, alcohol $CH_3$ $\delta$ 51.0 (neat). Reference 44: $(CH_3)_2NCHO$, ref 57; $(CH_3)_2NCOCH_3$ amine $CH_3$ ref 57, acid $CH_3$ $\delta$ 21.3 (dioxane). Reference 51: $CH_3OC(=O)CH_3$ acid $CH_3$ $\delta$ 20.4 $[(CD_3)_2CO]$; $(CH_3CO)_2O$ $\delta$ 22.0 $[(CD_3)_2CO]$.
(65) Future plans include studying the 1-hetera-3-cyclohexanone system in a manner similar to that used in this work.
(66) E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Am. Chem. Soc.*, **97**, 322 (1975).
(67) R. M. Fraser and T. B. Grindley, *Tetrahedron Lett.*, 4169 (1974); Y. L. Chow, C. J. Colon, and J. N. S. Tam, *Can. J. Chem.*, **46**, 2821 (1968).
(68) An electron diffraction study of gaseous 4-thiacyclohexanone (**1g**) has recently provided evidence that the chair conformation is favored in this system: R. Seip, H. M. Seip, and Z. Smith, to be published.
(69) Values of 36.7 and 208.4 ppm have been obtained for **1a** in $CDCl_3$ by another group: B. K. Carpenter, D. I. Rawson, and H. M. R. Hoffmann, *Chem. Ind. (London)*, 866 (1975).
(70) Similar conclusions are reached (based on unpublished results) in a recent review article: J. B. Lambert and S. I. Featherman, *Chem. Rev.*, **75**, 611 (1975).

# Carbon-13 Nuclear Magnetic Resonance Spectra of Chlorinated Pentacyclo[5.3.0.0$^{2,6}$.0$^{3,9}$.0$^{4,8}$]decanes

Earl G. Alley,[1a] Bobby R. Layton,*[1a] and James P. Minyard, Jr.[1a]

*Mississippi State Chemical Laboratory, Mississippi State, Mississippi 39762*

C. E. Westerman[1b]

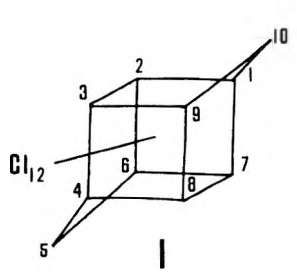
*University of Florida, Department of Radiology, Gainesville, Florida 32610*

*Received September 16, 1975*

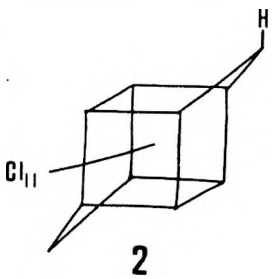
The $^{13}C$ NMR spectra of dodecachloropentacyclo[5.3.0.0$^{2,6}$.0$^{3,9}$.0$^{4,8}$]decane and four of its hydrogen-substituted derivatives have been obtained. The assignment of the $^{13}C$ resonances was based on chemical shifts, coupling constants, and Overhauser enhancements of the signals. Good correlation was found between the observed chemical shifts and those predicted from substituent parameters and between $^{1}H$ chemical shifts and $^{13}C$ chemical shifts. Some unusual variations in the two- and three-bond coupling constants were observed.

Proton-coupled $^{13}C$ NMR studies have generally been limited to simple molecules because of the complexity of the spectra and the low sensitivity associated with this technique. The availability of dodecachloropentacyclo[5.3.0.0$^{2,6}$.0$^{3,9}$.0$^{4,8}$]decane (compound **1**) and some of its hydrogen derivatives provided an excellent opportunity to investigate the $^{1}H$–$^{13}C$ coupling and the inductive effects in a set of closely related and relatively large molecules. These compounds have a rigid carbon skeleton, and on account of its symmetry, **1** contains only three sets of magnetically different carbons. Four hydrogen derivatives of **1** were available from photochemical reactions[2-4] and other synthetic routes.[5]

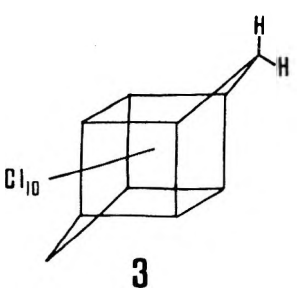
Compound **1** was first synthesized in 1945 by Prins.[6] Its structure was deduced from infrared,[7] x-ray,[8] and mass spectral[9] data. This compound has been used commercially as a pesticide (Mirex)® and a fire retardant (Dechlorane)® and has been the subject of pyrolysis,[10] chemical,[5,8] and photochemical[2-4] investigations. The structures of compounds **2**, **3**, and **5** were assigned from NMR, infrared, and mass spectral data.[2-4] The geometry of compound **4** was deduced in this study.



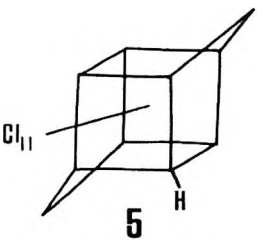

**1**




**2**




**3**




**5**

## Experimental Section

The $^{13}C$ NMR spectra were obtained at 22.6 MHz with a Bruker HX-90 spectrometer, operated in the single coil configuration with a heteronuclear $^{19}F$ lock and equipped for fast Fourier transformation with a Nicolet 1083 data system. $^{1}H$ NMR spectra were obtained at 90 MHz in the continuous wave mode with a homonuclear lock.

Chemical shifts were measured while employing noise-modulated $^{1}H$ decoupling[11] at ambient probe temperature (approximately 25°C). Saturated solutions in carbon disulfide containing 5% (v/v) hexafluorobenzene and 10% (v/v) tetramethylsilane were used for the lock and chemical shift reference, respectively. Approximately 1.3 ml of sample solution was contained in 10-mm o.d. sample tubes fitted with vortex plugs. Chemical shift data encompassing a 5000-Hz spectral region were collected into 8K data points, yielding a computer resolution of 1.2 Hz (0.04 ppm). Typically, 20 000 scans with a delay time of 2 sec between scans were necessary to obtain a good spectrum.

Gated, noise-modulated $^{1}H$ decoupling was applied in order to observe long-range $^{13}C$–$^{1}H$ coupling.[12,13] The BSV-2 decoupler was on for 1.8 sec and off 0.2 sec prior to the data acquisition, using circuitry similar to that of Dorn et al.[14]

Compound **1** (98%), obtained from Allied Chemical Corp., was recrystallized from benzene. Two hydrogen-substituted derivatives of compound **1** were prepared by the methods of Dilling.[5] Two other derivatives were prepared by the photolysis of compound **1** as described elsewhere.[2,3]

## Discussion

The $^{13}C$ spectrum for compound **1** (Table I) consisted of three singlets at 91.6, 82.4, and 76.5 ppm downfield from $Me_4Si$ with relative areas of 1:3:2. The peak at the lowest field and with the smallest intensity was assigned to the di-

Table I

| Compd | Decoupled spectra: Chemical shifts, ppm from $Me_4Si$ | Decoupled spectra: Relative area | Coupled spectra: Multiplicity | Coupled spectra: Coupling constant, Hz | Coupled spectra: Relative area | Assignment |
|---|---|---|---|---|---|---|
| 1 | 91.6 | | 1 | 0 | 1.0 | 5 and 10 |
| | 82.4 | | 1 | 0 | 3.0 | 1, 4, 6, and 9 |
| | 76.5 | | 1 | 0 | 2.0 | 2, 3, 7, and 8 |
| 2 | 92.0 | 1.0 | 1 | 0 | 1.0 | 5 |
| | 83.1 | 2.9 | 1 | 0 | 2.6 | 4 and 6 |
| | 78.2 | 9.3 | 2 | 3.9 ± 1 | 5.1 | 2 and 3 |
| | 77.1 | 2.3 | 2 | 8.7 ± 1 | 1.7 | 7 and 8 |
| | 75.4 | 3.7 | 1 | 0 | 2.4 | 1 and 9 |
| | 67.4 | 30 | 2 | 164 ± 1 | 25 | 10 |
| 3 | 92.7 | | 1 | 0 | 1.0 | 5 |
| | 83.2 | | 1 | 0 | 3.1 | 4 and 6 |
| | 77.0 | | 3 | 5.4 ± 1 | 10 | 2, 3, 7, and 8 |
| | 75.1 | | 3 | 5.4 ± 1 | 24 | 1 and 9 |
| | 45.9 | | 3 | 141 ± 1 | 120 | 10 |
| 4 | 93.5 | 1.0 | 1 | 0 | 1.0 | 5 and 10 |
| | 76.8 | 3.0 | 1 | 0 | 1.8 | 1, 4, 6, and 9 |
| | 71.8 | 1.1 | 2 | 17 ± 1 | 1.0 | 3 and 7 |
| | 61.0 | 9.6 | 2 | 176 ± 1 | 4.8 | 2 and 8 |
| 5 | 92.6 | 2.2 | 1 | | 2.2 | 5 and 10 |
| | 82.8 | 1.8 | 1 | | 1.8 | 1 and 6 |
| | 78.6 | 1.0 | 2 | 12.2 ± 1 | 1.0 | 2 or 3 |
| | 76.2 | 4.5 | 1 | 0 | 3.8 | 3 or 2 |
| | 76.2 | ... | 1 | 0 | ... | 4 and 9 |
| | 69.6 | 1.6 | 2 | 4.9 ± 1 | 1.6 | 7 |
| | 60.9 | 9.4 | 2 | 176 ± 1 | 5.2 | 8 |

chloromethylene bridge carbons (C-5 and C-10). The bridgehead carbons (C-1, C-4, C-6, and C-9) are bonded to one dichloro carbon and two monochloro carbon atoms. Thus, they have one more $\beta$-chlorine substituent than carbons C-2, C-3, C-7, and C-8 and would be expected to appear at approximately 6 ppm lower field strength.[15] Therefore, the resonance at 82.4 ppm was assigned to C-1, C-4, C-6, and C-9, and the one at 76.5 ppm was assigned to C-2, C-3, C-7, and C-8. The discrepancy in the relative intensity of the resonance lines was attributed, in part, to the experimental conditions employed.[16]

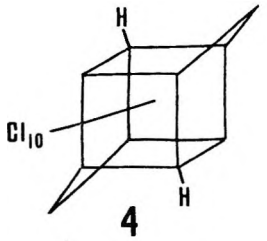
For the hydrogen derivatives, the resonances for carbon atoms bonded to hydrogen were differentiated from those for carbons not bonded to a hydrogen by the higher field chemical shift values, the larger coupling constants and, in the proton-decoupled spectra, the nuclear Overhauser effect. The chemical shifts of other resonances were compared to predicted values[15] for carbons in various positions. In a study of perchlorinated compounds, it was observed that replacement of a chlorine substituent by a hydrogen produced a high-field shift of 25 and 6 ppm at the $\alpha$ and $\beta$ carbons, respectively, and a low-field shift of 1 ppm at the $\gamma$ carbons.[15] Except for the $\beta$ parameters, these substituent increments are in good agreement with those reported for one group of aliphatic compounds[17] but are somewhat smaller than those reported for polychloromethanes[18], 1-chloroalkanes,[19] chlorocyclohexane, and chloroadamantane.[20]

Compound 2 (1,2,3,4,5,5,6,7,8,9,10-undecachloropentacyclo[5.3.0.$0^{2,6}$.$0^{3,9}$.$0^{4,8}$]decane) has fewer symmetry planes than compound 1 and thus has six magnetically different carbon atoms. The spectrum of 2 (Table I) consisted of six resonances at 92.0 (s), 83.1 (s), 78.2 (d, $J$ = 3.9 Hz), 77.1 (d, $J$ = 8.7 Hz), 75.4 (s), and 67.4 ppm (d, $J$ = 164 Hz). The large, one-bond $^{13}C$–$^{1}H$ coupling and the high-field shift readily identified the 67.4-ppm absorption as that due to the monochloromethylene bridge carbon, C-10. The resonances at 83.1 and 92.0 ppm were assigned to carbons C-4 and C-6 and carbon C-5, respectively, using arguments analogous to those made for the assignments of the resonances in 1. The resonance at 75.4 ppm was assigned to carbons C-1 and C-9 which is in good agreement with the predicted value[15] (Table II) for these carbon atoms. The inductive effect associated with the replacement of a chlorine on C-10 with a hydrogen will be transmitted through bonds equally to carbons C-2 and C-3 and to carbons C-7 and C-8. However, the interaction exerted on carbons C-7 and C-8 by the chlorine atom on C-10 will be absent for carbons C-2 and C-3, which have a hydrogen situated syn to them. This leads to the expectation that C-7 and C-8 will resonate at a higher field (77.1 ppm) than carbons C-2 and C-3 (78.2 ppm).[17,21-24] Similar 1,4-nonbonded interactions in aliphatic hydrocarbons produce approximately a 2.5-ppm high-field shift,[21] while the steric compression exerted on C-6 of *endo*-2-chloro and *endo*-2-hydroxy derivatives of bornane causes approximately a 9-ppm high-field shift.[17]

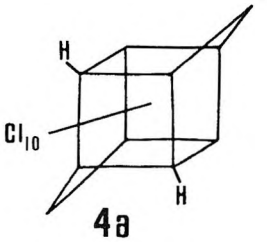
Table II

| Compd | Carbon atom | $\delta$ observed | $\delta$ predicted | $\Delta$ |
|---|---|---|---|---|
| 1 | 5, 10 | 91.6 | | |
| | 1, 4, 6, 9 | 82.4 | | |
| | 2, 3, 7, 8 | 76.5 | | |
| 2 | 5 | 92.0 | 91.6 | +0.4 |
| | 4, 6 | 83.1 | 82.4 | +0.7 |
| | 2, 3 | 78.2 | 77.5 | +0.7 |
| | 7, 8 | 77.1 | 77.5 | −0.4 |
| | 1, 9 | 75.4 | 76.4 | −0.1 |
| | 10 | 67.4 | 66.6 | +0.8 |
| 3 | 5 | 92.7 | 91.6 | +1.1 |
| | 4, 6 | 83.2 | 82.4 | +0.8 |
| | 2, 3, 7, 8 | 77.0 | 78.0 | −1.0 |
| | 1, 9 | 75.1 | 71.4 | +3.7 |
| | 10 | 45.9 | 45.6 | +0.3 |
| 4 | 5, 10 | 93.5 | 93.6 | −0.1 |
| | 1, 4, 6, 9 | 76.8 | 77.4 | −0.6 |
| | 3, 7 | 71.8 | 71.5 | +0.3 |
| | 2, 8 | 61.0 | 51.5 | +9.5 |
| 5 | 5, 10 | 92.6 | 92.6 | 0.0 |
| | 1, 6 | 82.8 | 83.4 | −0.6 |
| | 2 | 78.6 or 76.2 | 76.5 | +2.1 or −0.3 |
| | 3 | 76.2 or 78.6 | 77.5 | −1.3 or +1.1 |
| | 4, 9 | 76.2 | 76.5 | −0.3 |
| | 7 | 69.6 | 70.5 | −0.9 |
| | 8 | 60.9 | 51.5 | +9.4 |

The $^{13}C$ NMR spectrum for 1,2,3,4,5,5,6,7,8,9-decachloropentacyclo[5.3.0.0$^{2,6}$.0$^{3,9}$.0$^{4,8}$]decane (compound **3**, Table I) consisted of five resonances at 92.7 (s), 83.2 (s), 77.0 (t, $J$ = 5.4 Hz), 75.1 (t, $J$ = 5.4 Hz), and 45.9 ppm (t, $J$ = 141 Hz). The high-field shift and the large coupling constant of the resonance at 45.9 ppm dictated that it be assigned to the methylene bridge, C-10. The assignment of the triplets at 75.1 and 77.0 ppm was made to carbons C-1 and C-9 and to carbons C-2, C-3, C-7, and C-8, respectively. This assignment minimized the deviations between the observed and the predicted chemical shifts. The enhancement of the 75.1-ppm resonance supported its assignment to C-1 and C-9. By analogy with the resonances of compound **1**, the peaks at 83.2 and 92.7 ppm were assigned to carbons C-4 and C-6 and carbon C-5, respectively.




**4**




**4a**

The structure of a second dihydro derivative of compound **1** is either **4** or **4a**.[2] Compound **4** has four magnetically different carbons, and **4a** has five because the molecules have different symmetry properties. The observed four-peak spectrum is consistent with structure **4** (1,3,4,5,5,6,7,9,10,10-decachloropentacyclo[5.3.0.0$^{2,6}$.0$^{3,9}$.0$^{4,8}$]decane). The observed resonances were at 93.5 (s), 76.8 (s), 71.8 (d, $J$ = 17 Hz), and 61.0 ppm (d, $J$ = 176 Hz). The absence of a signal near 82 ppm excluded from consideration structure **4a** (the 3,8-dihydro isomer). The resonance at 61.0 ppm can be assigned unequivocally to the carbons bonded directly to the hydrogens (C-2 and C-8) by reason of the large splitting of this peak (176 Hz). The peak at 93.5 ppm was assigned to the dichloromethylene bridges (C-5 and C-10), utilizing arguments analogous to those employed for compounds **1**, **2**, and **3**. The methylene bridgeheads (C-1, C-4, C-6, and C-9) are each bonded to a dichloro carbon atom and a monochloro carbon atom, whereas carbons C-3 and C-7 have only two chlorines in the $\beta$ positions. The predicted values[15] for the methylene bridgeheads (C-1, C-4, C-6, and C-9) and carbons C-3 and C-7 are 77.4 and 71.5 ppm, respectively. The predicted values deviated from the observed ones by an average of only 0.5 ppm if the 76.8-ppm resonance was assigned to carbons C-1, C-4, C-6, and C-9, and the 71.8-ppm resonance was assigned to carbons C-3 and C-7. The normalized intensity ratios revealed a slight Overhauser enhancement for the 76.8-ppm resonance, supporting its assignment to C-1, C-4, C-6, and C-9.

The $^{13}C$ NMR spectrum of 1,2,3,4,5,5,6,7,9,10,10-undecachloropentacyclo[5.3.0.0$^{2,6}$.0$^{3,9}$.0$^{4,8}$]decane (compound **5**, Table I) consisted of six resonances at 92.6 (s), 82.8 (s), 78.6 (d, $J$ = 12.2 Hz), 76.2 (s), 69.6 (d, $J$ = 4.9 Hz), and 60.9 ppm (d, $J$ = 176 Hz) from $Me_4Si$. The line width and relative integrated intensity of the 76.2-ppm resonance indicated that it was a pair of overlapping resonances. The resonances at 92.6 and 82.8 ppm were assigned to the dichloromethylene bridges (C-5 and C-10) and their bridgeheads (C-1 and C-6), respectively. The large splitting of the resonance at 60.9 ppm (176 Hz) dictated that it be assigned to carbon C-8. The doublet at 69.6 ppm was assigned to carbon C-7, since it is bonded to the most shielded carbon (C-8) and to only two monochloro carbon atoms (C-4 and C-9). The chemical shift of this resonance compared favorably with a value of 70.5 ppm predicted from literature parameters.[15] The resonance at 76.2 ppm was assigned to carbons C-4 and C-9 because the closely related carbons (C-1, C-4, C-6, and C-9) in **4** resonate at 76.8 ppm. The two remaining resonances at 76.2 and 78.6 ppm could not be assigned unequivocally. The predicted chemical shift[15] for carbon C-3 is 77.5 ppm, and the 12-Hz coupling constant is not unreasonable for a three-bond coupling. However, all the carbon atoms which are three bonds from the hydrogen atom were not coupled with it; and in compound **4**, C-3 and C-7 were coupled to only one hydrogen atom. In both the coupled and decoupled spectra, the 78.6-ppm resonance had the smallest signal intensity. Therefore, these couplings and the nuclear Overhauser enhancement indicated that the resonances at 76.2 and 78.6 ppm were from C-3 and C-2, respectively. This assignment requires that carbon C-2 be coupled to the hydrogen through four bonds (12 Hz). Although the assignment of the 78.6-ppm resonance to C-2 was not certain, the unusually large four-bond coupling could find its basis in the overlapping back lobes[25,26] of bonding orbitals of the two carbon atoms (C-2 and C-8).

Table II contains the observed resonances, a set of predicted chemical shifts, and the deviations between the predicted and observed values. The predicted shifts were obtained by adding the appropriate substituent parameters[15,17] to the resonances of compound **1**. The influence of a substituent on a given carbon was counted once for each equivalent path.[27] The range of observed chemical shifts was 48 ppm. Agreement of predicted and observed values was good except for the hydrogen-substituted carbons of compounds **4** and **5**, for which the largest deviations were 20% of the range. The next largest deviation is 8% for C-1 and C-9 of compound **3**. The range of the deviations for the remaining nineteen shifts was only 0–4.4%.

A comparison of the chemical shift of each carbon atom bonded to a hydrogen and the chemical shift of that hydrogen[2,5] revealed that the two shifts were related linearly. These data yielded the empirical equation

$$\delta_c = 12.5\,\delta H + 13.8$$

The correlation coefficient for the regression analysis of the data was 0.999. Spiesecke and Schneider[28,29] also have observed linear relationships between chemical shifts of hydrogen and carbons for groups of similar compounds but found that these relationships broke down where steric hindrance was important.

There were some anomalies in the $^1H$–$^{13}C$ coupling of these molecules. For compounds with a hydrogen on the 2 or 8 position (compounds **4** and **5**), the hydrogen coupled with only one of the three $\beta$ carbons. Variations in the two- and three-bond coupling constants were assumed to be related to the hybridization of the carbons,[30–33] the dihedral angles,[34,35] and the substituent effects.[30,33] The magnitude of the two- and three-bond coupling constants for compound **3** were identical, and for compound **2** the hydrogen was coupled with the $\gamma$ carbons but not with the $\beta$ carbons. Although this seemed unusual, similar results have been obtained for other compounds.[31,32] In compound **2**, the three-bond, $^1H$–$^{13}C$ coupling constant for carbons C-7 and C-8 was different than the one for carbons C-2 and C-3. These differences could be the result of a sensitive dependence on the dihedral angle[34] or of coupling by a back lope overlap mechanism.[24,25,36] These results indicate that caution should be employed when long-range $^1H$–$^{13}C$ coupling constants are used as criteria for structure assignments. Preparation of additional compounds related to those in this study has been initiated. These compounds will be used to investigate variations in the $^1H$–$^{13}C$ coupling constants.

**Registry No.**—1, 2385-85-5; 2, 845-66-9; 3, 15443-23-9; 4, 57096-48-7; 5, 39801-14-4.

## References and Notes


(1) (a) Mississippi State Chemical Laboratory; (b) Department of Radiology, University of Florida.
(2) E. G. Alley, B. R. Layton, and J. P. Minyard, Jr., *J. Agric. Food Chem.*, **22**, 442–445 (1974).
(3) E. G. Alley, D. A. Dollar, B. R. Layton, and J. P. Minyard, Jr., *J. Agric. Food Chem.*, **21**, 138–139 (1973).
(4) E. G. Alley, B. R. Layton, and J. P. Minyard, Jr., *J. Agric. Food Chem.*, **22**, 727–729 (1974).
(5) W. L. Dilling, H. P. Braendlin, and E. T. McBee, *Tetrahedron*, **23**, 1211–1224 (1967).
(6) H. J. Prins, *Recl. Trav. Chim. Pays-Bas*, **65**, 455–467 (1946).
(7) D. H. Zijp and H. Gerding, *Recl. Trav. Chim. Pays-Bas*, **77**, 682–691 (1958).
(8) Y. Okaya and A. Bednowitz, *Acta Crystallogr.*, **22**, 111 (1967).
(9) W. L. Dilling and M. L. Dilling, *Tetrahedron*, **23**, 1225–1233 (1967).
(10) P. Eaton, E. Carlson, P. Lombardo, and P. Yates, *J. Org. Chem.*, **25**, 1225–1226 (1960).
(11) R. E. Ernst, *J. Chem. Phys.*, **45**, 3845–3861 (1966).
(12) J. Feeney, D. Shaw, and P. J. S. Pauwels, *Chem. Commun.*, 554–555 (1970).
(13) O. A. Gansow and W. Schittenhelm, *J. Am. Chem. Soc.*, **93**, 4294–4295 (1971).
(14) H. C. Dorn, S. J. Uurtamo, and G. E. Maciel, *Rev. Sci. Instrum.*, **44**, 128–132 (1973).
(15) G. E. Hawkes, R. A. Smith, and J. D. Roberts, *J. Org. Chem.*, **39**, 1276–1290 (1974).
(16) R. Ernst and W. A. Anderson, *Rev. Sci. Instrum.*, **36**, 1696–1706 (1965).
(17) E. Lippmaa, T. Pehk, J. Paasivirta, N. Belikova, and A. Plate, *Org. Magn. Reson.*, **2**, 581–604 (1970).
(18) W. M. Litchman and D. M. Grant, *J. Am. Chem. Soc.*, **90**, 1400–1407 (1968).
(19) J. B. Strothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, pp 134–138.
(20) T. Pehk, E. Lippmaa, V. V. Sevostyanova, M. M. Kraguschkin, and A. I. Tarasova, *Org. Magn. Reson.*, **3**, 783–790 (1971).
(21) D. M. Grant and B. V. Cheney, *J. Am. Chem. Soc.*, **89**, 5315–5318 (1967).
(22) D. M. Grant and E. G. Paul, *J. Am. Chem. Soc.*, **86**, 2984–2990 (1964).
(23) W. R. Woolfenden and D. M. Grant, *J. Am. Chem. Soc.*, **88**, 1496–1502 (1966).
(24) D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **89**, 6612–6622 (1967).
(25) J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 7107–7120 (1970).
(26) M. Barfield, *J. Chem. Phys.*, **41**, 3825–3832 (1964).
(27) D. E. Dorman, M. Jautelat, and J. D. Roberts, *J. Org. Chem.*, **36**, 2757–2766 (1971).
(28) H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 731–738 (1961).
(29) H. Spiesecke and W. G. Schneider, *Tetrahedron Lett.*, 468–472 (1961).
(30) O. Yamamoto, K. Hayamiza, S. Satoh, and K. Kushida, *J. Magn. Reson.*, **5**, 429–434 (1971).
(31) G. J. Karabatsos, *J. Am. Chem. Soc.*, **83**, 1230–1232 (1961).
(32) G. J. Karabatsos, J. D. Graham, and F. M. Vane, *J. Am. Chem. Soc.*, **84**, 37–40 (1962).
(33) G. Miyazima, Y. Utsumi, and K. Takahashi, *J. Phys. Chem.*, **73**, 1370–1373 (1969).
(34) J. A. Schwarcz and A. S. Perlin, *Can. J. Chem.*, **50**, 3667–3676 (1972).
(35) R. Wasylishen and T. Schaffer, *Can. J. Chem.*, **50**, 2710–2712 (1972).
(36) J. Meinwald and A. Lewis, *J. Am. Chem. Soc.*, **83**, 2769–2770 (1969).


# Carbon-13 Chemical Shifts in Bicyclo[2.2.2]octanes


Peter J. Garratt* and Ricardo Riguera

*Department of Chemistry, University College London, London WC1H OAJ, United Kingdom*

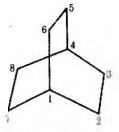
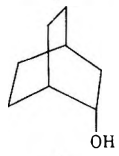
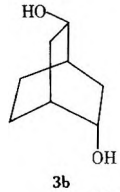
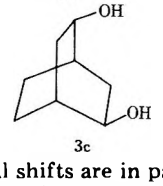

*Received August 1, 1975*


The $^{13}C$ chemical shifts for a number of bicyclo[2.2.2]octanes substituted in the 2 and 2,5 positions have been obtained in natural abundance. Substitution parameters have been derived from the 2-substituted compounds and these parameters can be used to determine the relative stereochemistry of groups at C-2 and C-5. A comparison of the presently derived parameters with the known parameters for the norbornyl system has been made.


The value of $^{13}C$ NMR spectroscopy for the study of the stereochemistry of relative rigid molecules, such as norbornyl derivatives, has been demonstrated by Grutzner et al.[1] and Schneider and Bremser.[2] In the course of synthetic studies we have had occasion to prepare a number of bicyclo[2.2.2]octane derivatives, largely with substituent at positions 2 and 5,[3] and we have examined the $^{13}C$ NMR spectra of these compounds as an aid to the assignment of the relative stereochemistry of these substituents. Following the earlier studies,[1,2,4] we have classified the substituent perturbations in terms of $\alpha$, $\beta$, $\gamma$, and $\delta$ effects, the substituent being introduced at the $\alpha$-carbon atom. The special $\gamma$ effect which is operative in the norbornyl series[1] is operative in the bicyclo[2.2.2]octanes. The parameters obtained in the present work have been compared with those obtained for the norbornyl system, and substantial agreement both in the size and magnitude of the shifts is observed. Differences can probably be accounted for in the greater flexibility of the bicyclo[2.2.2]octane framework.

**Assignments.** Our initial studies were carried out on bicyclo[2.2.2]octane (**1**), bicyclo[2.2.2]octan-2-ol (**2**), and the three epimeric bicyclo[2.2.2]octan-2,5-diols (**3a–c**). The structure and assignment are shown in Table I. The epimeric diols **3b** and **3c** were extremely valuable in establishing these assignments, since each contain only four carbon atoms with different chemical environments due to the symmetry of the system. In **3b**, C-2 and C-5, the carbons substituted by the hydroxyl groups, were shown to be doublets by an off-resonance experiment, and show the largest downfield shift compared to the corresponding carbons in bicyclo[2.2.2]octane, and this is readily correlated with a similar $\alpha$ shift in alcohols. The tertiary carbons C-1 and C-4 are also doublets in the off-resonance experiment, and are shifted downfield, mainly due to the $\beta$ effect. The remaining carbons to be assigned are the equivalent pairs C-3, C-6 and C-7, C-8. Based on the shielding and deshielding effect of the $\gamma$ effect in norbornanes, we assign the carbons shifted downfield as C-3, C-6 and those upfield as C-7, C-8. In **3c**, C-2 and C-5 were again doublets in the off-resonance experiment, and are again shifted downfield, and the tertiary atoms C-1 and C-4 are also doublets and show a downfield shift. With the remaining two pairs of carbon atoms, C-3, C-6 and C-7, C-8, the assignments are again based on the expected direction of shift from the norbornanes. Further, the gross magnitude of the shifts are as expected, C-7, C-8 less affected in **3c** than in **3b** because of the smaller interaction, and the C-3, C-6 shift in **3c** smaller than in **3b** because of the opposed direction of the two effects. The assignments receive further strong support from the spectrum of the unsymmetrical isomer, **3a**. Here C-1,

Table I
$^{13}C$ Chemical Shifts of Bicyclo[2.2.2]octan-2-ols[a]

| Registry no. | Compd | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | C-7 | C-8 |
|---|---|---|---|---|---|---|---|---|---|
| 280-33-1 |  1 | 24.14 | 26.16 | | | | | | |
| 18684-63-4 |  2 | 31.64 | 69.41 | 37.47 | 24.87 | 24.59* | 23.82 | 18.70 | 25.70* |
| 57346-04-0 |  3a | 32.50** | 68.55* | 30.51 | 32.43** | 68.20* | 35.64 | 17.29 | 23.45 |
| 57378-52-6 |  3b | 32.73 | 68.40 | 34.60 | 32.73 | 68.40 | 34.60 | 18.35 | 18.35 |
| 57378-53-7 |  3c | 32.52 | 69.08 | 30.37 | 32.52 | 69.08 | 30.37 | 22.78 | 22.78 |

[a] The chemical shifts are in parts per million downfield from internal $Me_4Si$; the asterisks designate pairs of shifts which have been assigned for consistency of parameter values but which could be reversed.

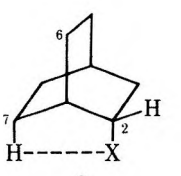
C-4, C-2, and C-5 can be identified as before. The remaining four carbon atoms are now of four types, C-7 is very similar to C-7 in **3b**, C-8 similar to C-8 in **3c**, C-3 is similar to C-3 in **3c**, and C-6 is similar to C-6 in **3b**, and the four carbon atoms do indeed show these expected shifts. In the mono-ol **2**, C-1 and C-2 are doublets in the off-resonance experiment and the remaining assignments are made by a comparison of the gross chemical shifts with those in the diols. The value for C-5 and C-8 may be interchanged, but the assignments given provide the best fit with the data obtained from the diols.

The carbon-13 shifts for a number of 2-substituted and 2,5-disubstituted bicyclo[2.2.2]octanes are collected in Table II. The symmetry of bicyclo[2.2.2]octane-2,5-dione was again useful in assignment; atoms C-1 and C-4 were identified as doublets in an off-resonance experiment, the other carbons being assigned on the basis of the expected gross chemical shifts from bicyclo[2.2.2]octane. The assignments to bicyclo[2.2.2]octan-2-one followed from off-resonance experiments and a comparison with the dione. The assignments to the remaining compounds in this table are more tentative, double resonance experiments identifying certain carbons but the remaining assignments being based on the expected chemical shifts and the consistency of related data. In certain cases, as indicated in Table II, the assignment could be interchanged, but such an interchange would not affect the general discussion.

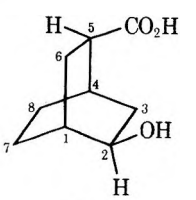
In Table III, the carbon-13 spectra of four bicyclo[2.2.2]octanes which were geminally substituted at position 2 by methyl and carboxyl are collected. Atom C-2 was identified in all cases by its lower intensity, C-1 in **4** and C-5 in **5a,b** by off-resonance experiments, and the other atoms by the expected gross chemical shifts caused by the substituents.

## Discussion

The introduction of a substituent on the bicyclo[2.2.2]octane framework causes the now expected[1-4] change in the $\alpha$, $\beta$, and $\gamma$ carbons, together with the smaller effects at the $\delta$ carbons.[6] Because of the symmetry of bicyclo[2.2.2]octane, there is no endo, exo distinction of substituents, as there is in the case of the norbornyl system, and consequently there is only one parameter value for the $\alpha$ and $\beta$ carbons in the bicyclo[2.2.2]octanes. The $\alpha$ and $\beta$ effects do depend on the degree of substitution of the $\alpha$ and $\beta$ carbon atoms, and in the present work this largely involves the difference between the bridgehead C-1 and the C-3 parameters. A marked difference is found in the $\gamma$ effects depending on whether the substituent is syn or anti to the carbon



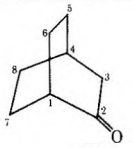
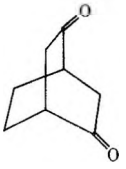
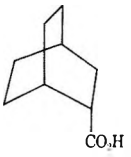
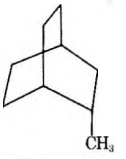
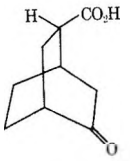
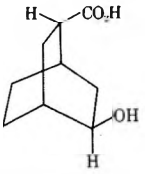
6



7

in question. Thus in **6**, the substituent at C-2 is syn to C-7 and anti to C-6. The effect on C-7 is clearly steric in origin,

Table II
$^{13}C$ Chemical Shifts of 2-Substituted Bicyclo[2.2.2]octanes[a]

| Registry no. | Compd | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | C-7 | C-8 | Others |
|---|---|---|---|---|---|---|---|---|---|---|
| 2716-23-6 |  | 42.42 | 216.87 | 44.80 | 28.09 | 24.88 | 23.48 | 23.48 | 24.88 | |
| 57346-05-1 |  | 45.10 | 211.41 | 40.30 | 45.10 | 211.41 | 40.30 | 22.19 | 22.19 | |
| 29221-25-8 |  | 27.51 | 41.92 | 28.08 | 23.78 | 25.09* | 25.31* | 21.94 | 26.37 | $CO_2H$ 183.03 $CO_2CH_3$ [b] 176.28 51.39 |
| 766-53-0 |  | 30.22 | 30.22 | 35.64 | 25.03 | 26.15 | 25.03 | 21.30 | 27.45 | $CH_3$ 20.31 |
| 49826-60-0 |  | 41.92* | 216.41 | 40.16* | 31.25 | 40.94* | 25.81 | 22.63** | 25.28** | $CO_2H$ 180.08 $CO_2CH_3$ [b] 174.98 51.88 |
| 41977-18-8 |  | 31.16 | 68.46 | 33.68 | 28.55 | 41.47 | 21.28 | 22.80 | 25.01 | $CO_2H$ 180.04 $CO_2CH_3$ [b] 177.84 52.00 |

[a] See footnote *a*, Table I. [b] The values for chemical shifts of the C-1–C-8 carbons of the methyl esters of the acids are virtually identical with those of the acids.

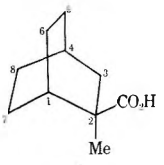
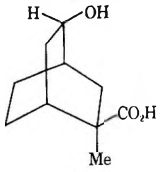
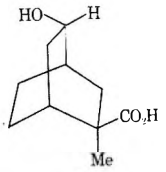
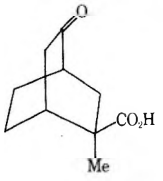
and is similar, both in size and magnitude, to that observed in the norbornyl series.[1,6] The series of parameters obtained by comparing the chemical shifts in the 2-monosubstituted bicyclo[2.2.2]octane with those in the parent hydrocarbon are shown in Table IV. These parameters can be readily transferred to the other members of the series, as may be illustrated for compound **7**. C-3 in **7** experienced a $\beta$ effect from the 2-OH and a $\gamma$-syn effect from the $CO_2H$, which gives a predictive shift to 33.46 ppm, compared to the observed 33.68 ppm. Similarly, C-6 experiences a $\beta$ effect from the $CO_2H$ and a $\gamma$-syn effect from the OH, resulting in a predictive shift to 20.96 ppm, compared to the observed 21.28 ppm. A plot of the calculated against the experimental chemical shifts for atoms C-1, C-2, and C-7 of seven substituted bicyclo[2.2.2]octan-2-ols had a slope of 1.00 and a standard deviation of 0.46, showing that the correlation is satisfactory. These atoms were chosen since the assignments of C-1 and C-2 are secure, and the effect on C-7 large.

With the geminal 2,2-disubstituted derivatives, the parameter values for each of the individual C-2 substituents cannot be used to predict the shifts on the other carbons compared with bicyclo[2.2.2]octane, a situation which was also observed in the norbornyl system.[1] However, when the effect of introducing substituents at the C-5 position into the 2,2-geminally substituted compound **4** is examined, it is found that the shifts produced by the substituent compared with the shifts in **4** can be accurately predicted using the substituent parameters found for the mono-2-substituted bicyclo[2.2.2]octanes.

Comparison of the parameters derived in the present study with those found in the norbornyl system showed that both the magnitudes and signs of the $\alpha$ and $\beta$ shifts are very similar.[7] Small trends are observed, the shifts for OH and =O appearing slightly larger, and those for Me and $CO_2H$ slightly smaller for the bicyclo[2.2.2]octanes. However, the norbornyl shifts are averages for the substituent in the exo and endo positions, and the overall trends are probably not significant. The $\gamma$-syn effects are smaller in the bicyclo[2.2.2]octanes, and this most probably reflects the greater rigidity of the norbornyl system which can less readily distort to remove steric strain. The $\delta$ effects are small, but it is of interest to note that the methyl group causes a downfield shift, whereas the other substituents cause upfield shifts, of the $\delta$-carbon atom. This again parallels the situation in the norbornyl system.

Using the parameters listed in Table IV it is now comparatively easy to assign the relative stereochemistry of the two groups at positions 2 and 5 by inspection of the chemical shifts of C-3, C-6, C-7, and C-8. The major factor involved in the difference in the spectra is the larger perturbation caused by a $\gamma$-syn as compared to a $\gamma$-anti substituent, and the differences are readily illustrated in the spectra of the alcohols **3a–c** and the acids **5a,b**. Thus C-3 in **5a**

Table III
$^{13}$C Chemical Shifts of 2-Geminally Substituted Bicyclo[2.2.2]octanes[a]

| Registry no. | Compd | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | C-7 | C-8 | Others |
|---|---|---|---|---|---|---|---|---|---|---|
| 57346-06-2 |  4 | 32.07 | 44.01 | 36.55 | 25.17* | 24.31 | 24.31 | 21.57 | 25.31* | $CO_2H$ 186.18 $CO_2CH_3$ [b] 179.04 51.57 Me 26.63 |
| 38347-91-0 |  5a | 33.43* | 43.44 | 30.01 | 32.53* | 68.29 | 35.80 | 20.07 | 22.76 | $CO_2H$ 182.78 $CO_2CH_3$ [b] 178.03 52.19 Me 26.63 |
| 57378-54-8 |  5b | 33.11* | 42.76 | 34.31 | 32.78* | 68.00 | 35.53 | 20.91 | 17.61 | $CO_2H$ 181.80 Me 26.28 |
| 57346-07-3 |  | 35.84 | 43.23 | 33.60 | 42.66* | 214.33 | 42.94* | 20.75 | 22.15 | $CO_2H$ 182.27 Me 26.13 $CO_2CH_3$ [b] 177.42 52.05 |

[a, b] See footnotes to Tables I and II.

Table IV
$^{13}$C Substituent Effects for 2-Substituted Bicyclo[2.2.2]octanes[a]

| Effect | Substituent | | | |
|---|---|---|---|---|
| | −OH | =O | −Me | $-CO_2R$ |
| α | 43.25 (43.35)[b] | 190.7 (185.2) | 4.1 (5.6) | 15.8 (16.5) |
| α (gem) | | | 1.5 | 13.8 |
| β (C-3) | 11.3 (10.9) | 18.0 (15.1) | 9.5 (10.35) | 2.3 (3.25) |
| β (C-1) | 7.5 (7.0) | 18.3 (13.3) | 6.1 (6.0) | 3.5 (4.4) |
| γ-syn | −7.5 (−9.7)[c] | −2.7 (−5.8) | −4.9 (−7.7)[c] | −4.0 (−4.8)[c] |
| γ-anti | −2.3 (−5.2)[d] | | −1.1 (−1.1)[d] | −1.1 (−1.0)[d] |
| δ [e] | −0.5 (−0.5) | −1.3 (−2.4) | 0.8 (0.35) | −0.5 (−0.45) |

[a] Values obtained by comparison of shifts in the 2-substituted derivative with those in bicyclo[2.2.2]octane. [b] Values in parentheses for the norbornyl derivatives and were obtained from ref 1. For the α and β effect an average value has been taken from the exo and endo shifts. [c] Value for the *endo*-norbornyl parameter. [d] Value for the *exo*-norbornyl parameter. [e] Values for the δ effect are much less reliable than the other parameters owing to problems of assignment.

shows a much larger upfield shift than C-3 in **5b**, whereas C-8 shows a larger upfield shift in **5b** than in **5a**.

## Experimental Section

The $^{13}$C NMR spectra were recorded on a Varian CFT-20 spectrometer at 20 MHz. Spectra were normally taken with broad-band proton decoupling as 10% w/v solutions in $CDCl_3$ and chemical shifts were measured with reference to internal $Me_4Si$ and are reported in parts per million.

Most of the compounds were prepared by known literature methods.[8] Bicyclo[2.2.2]octan-2-ol was prepared in 90% yield by treatment of bicyclo[2.2.2]octane with mercuric acetate,[9] and was identical with a sample prepared by a reported method.[10] 2-Methylbicyclo[2.2.2]octane was obtained from bicyclo[2.2.2]octan-2-one by reaction with methyltriphenylphosphonium bromide, and subsequent hydrogenation ($PtO_2$) of the product. The sample was identical in all observed properties with those reported.[11] Bicyclo[2.2.2]octane-2,5-dione was prepared by a modification of the method of Guha and Krishnamurthy.[12] The bicyclo[2.2.2]octane-2,5-diols were prepared by reduction of the diketone.[5] Bicyclo[2.2.2]octane-2-carboxylic acid and 2-methylbicyclo[2.2.2]octane-2-carboxylic acid were prepared by catalytic reduction of the Diels–Alder adduct formed by reaction of 1,3-cyclohexadiene with acrylic[13] and methacrylic acid,[14] respectively. 5-Oxobicyclo[2.2.2]octane-2-*endo*-carboxylic acid and 2-*exo*-methyl-5-oxobicyclo[2.2.2]octane-2-*endo*-carboxylic acid were prepared by the method of Lee.[15] The corresponding alcohols were prepared by reduction.[5]

**Acknowledgments.** We thank the Science Research Council (U.K.) for support, and Dr. R. A. Lee (Du Pont) for providing unpublished experimental details.

## References and Notes

(1) J. B. Grutzner, M. Jautelar, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 7107 (1970).
(2) H. J. Schneider and W. Bremser, *Tetrahedron Lett.*, 5197 (1970).
(3) For $^{13}$C studies on 1-substituted bicyclo[2.2.2]octanes see G. E. Maciel and M. C. Dorn, *J. Am. Chem. Soc.*, **93**, 1268 (1971).
(4) See D. M. Grant and B. V. Cheney, *J. Am. Chem. Soc.*, **89**, 5315, 5319 (1967).
(5) D. Davalian, P. J. Garratt, and R. Riguera, in preparation.
(6) S. H. Grover and J. B. Stothers, *Can. J. Chem.*, **52**, 870 (1974).
(7) We have adopted the opposite sign convention to that of Grutzner et al.[1] for these parameters, since these workers used $CS_2$ as the stan-

dard rather than $Me_4Si$. With $Me_4Si$ taken as zero, a downfield shift is then added if given a positive sign and an upfield shift added if it is given a negative sign.
(8) H. M. Walborsky and D. F. Loncrini, *J. Am. Chem. Soc.*, **76**, 5396 (1954).
(9) See H. C. Brown and J. H. Kavakami, *J. Am. Chem. Soc.*, **95**, 8665 (1973).
(10) K. Alder, H. Krieger, and M. Weiss, *Chem. Ber.*, **88**, 144 (1955).
(11) B. A. Kasamsky and A. F. Plate, *Chem. Ber.*, **68**, 1259 (1935).
(12) P. C. Guha and C. Krishnamurthy, *Chem. Ber.*, **72**, 1374 (1939).
(13) R. Seka and O. Tramposch, *Chem. Ber.*, **75**, 1379 (1942).
(14) W. R. Boehme, E. Schipper, W. G. Sharpf, and J. Nichols, *J. Am. Chem. Soc.*, **80**, 5488 (1958).
(15) R. A. Lee, *Tetrahedron Lett.*, 3333 (1973).

# Elucidation of the Conformational Equilibria for the *cis*-8-Oxabicyclo[4.3.0]non-3-ene Series

Donna J. Bennett, Arnold C. Craig,* Bradford P. Mundy,* Gary W. Dirks, and Kenneth B. Lipkowitz

*Department of Chemistry, Montana State University, Bozeman, Montana 59715*

*Received June 24, 1975*

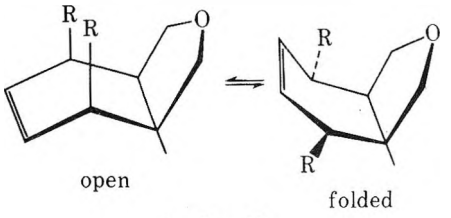
A method for quantitatively determining the solution equilibrium for conformers in a conformationally mobile system by computer analysis of LIS spectra is developed. The relative population of the two major conformations of *cis*-8-oxabicyclo[4.3.0]non-3-ene and *cis*-2,5-dimethyl-*cis*-8-oxabicyclo[4.3.0]non-3-ene have been determined. A second, independent conformational analysis of these molecules supports the use of this method. Some limitations of shift reagents, as applied to conformational analysis, are examined.

There has been considerable interest in utilizing lanthanide shift reagents to deduce conformations of molecules in solution. Until recently, however, very little quantitative work has been attempted owing to the uncertain and tedious nature of the calculations involved. We became interested in lanthanide induced shift (LIS) studies as a tool to probe the subtle effects of a heteroatom on conformation, and, as a result, have taken an active interest in the development of LIS techniques. As part of this effort, we report on the conformational equilibria of the *cis*-8-oxabicyclo[4.3.0]non-3-ene series.

## Results and Discussion

Dreiding models clearly demonstrate that there are two major conformations for members of the *cis*-8-oxabicyclo-[4.3.0]non-3-ene series, *"open"* and *"folded"* (Chart I).

Chart I
Major Conformations of the 8-Oxabicyclo[4.3.0]non-3-enes




**1a**, R = H
**b**, R = Me

Based on NMR spectral analysis, we have previously suggested that the preferred conformation of *cis*-8-oxabicyclo-[4.3.0]non-3-ene (**1a**) is *"open"*.[1] At that time we had no quantitative data on this preference, and we undertook a systematic analysis of LIS data.

In all cases the necessary LIS data were obtained by adding aliquots of a carbon tetrachloride solution of $Eu(fod)_3$ to a precisely weighed amount of substrate, also in carbon tetrachloride.[2] For each proton the induced shift was plotted against the ratio of $Eu(fod)_3$ to substrate and the slope determined (Table I). These slopes are the necessary input data for PDIGM, a program designed by Davis and Wilcott.[3]

For a given set of molecular coordinates, PDIGM systematically varies the lanthanide position over a series of spheres of increasing radius. The coordinates for the heteroatom are taken as the center of the sphere and a theoretical shift for each proton, as given by the McConnell–Robertson equation, is calculated and compared with the experimentally determined values. The position of best fit for each radial increment, accompanied by an agreement factor, is given by means of two defining angles, $\rho$ and $\phi$. The agreement factor is expressed as a standard deviation

$$R = \left[\frac{\sum \omega_j(\text{obsd}_j - \text{calcd}_j)^2}{\sum \omega_j(\text{obsd}_j)}\right]^{1/2}$$

where $\omega_j$ is the weight associated with $j$th observation. For a given conformation, the lanthanide position is taken to be that at which the best agreement factor occurs.

PDIGM may be used for a qualitative analysis of conformational equilibria by comparing the $R$ values obtained for the various stable conformations and choosing the lowest value among them. That PDIGM may also be used for quantitative work can be inferred from magnetic resonance theory. Specifically, a proton signal appearing in the NMR spectrum will be a time average of the signal for this proton in its various environments, providing that the interconversion of the conformers is fast relative to the NMR time scale.[4] It follows that the signal appearing on the NMR spectrum is representative of a molecule of "intermediate conformation". It is also known that the observed shift in the presence of a lanthanide shift reagent is a linear combination of the induced shifts of the extremes[5]

$$\delta_{\text{obsd}} = n\delta_1 + (1 - n)\delta_2$$

where $\delta_1$ = shift for proton in conformation 1 and $\delta_2$ = shift for proton in conformation 2. From the McConnell–Robertson equation

$$\delta_1 = f(r_1, \theta_1)$$

$$\delta_2 = f(r_2, \theta_2)$$

and hence

$$\delta_{\text{obsd}} = nf(r_1, \theta_1) + (1 - n)f(r_2, \theta_2).$$

Table I
Slopes for the Plots $\Delta\delta$ vs. Eu(fod)$_3$/Sub

| | 1a | 1b | 2 | 3 |
|---|---|---|---|---|
| Slope A | 0.514 | 0.820 | 0.198 | 3.695 |
| B | 0.988 | 0.900 | 0.454 | 3.002 |
| C | 1.371 | 2.200 | 0.745 | 5.273 |
| D | 3.425 | 4.08 | Me: 0.694 | 12.663 |
| E | 4.00 | 4.48 | | 12.663 |
| | | Me: 0.739 | | |

The question, then, becomes whether $\delta_{obsd}$ can be expressed as eq 1. This can be restated in another form: does the average value of the pseudocontact shifts for the stable conformers equal the pseudocontact shift for the average values of $r$ and $\theta$?

$$\delta_{obsd} = f[n(r_1, \theta_1) + (1 - n)(r_2, \theta_2)] = f(r_{obsd}, \theta_{obsd}) \quad (1)$$

A rigorous proof of this relationship has been attempted,[6] but difficulties in integrating the expressions

$$\langle \cos^2 \theta - 1/r^3 \rangle$$

and

$$\cos^2 \langle \theta \rangle - 1/\langle r^3 \rangle$$

caused inconclusive, although favorable, results.

Lacking concrete mathematical proof, we attempted to establish the relationship by direct comparison of the two methods of averaging. If $(\cos^2 \phi - 1)/r^3$ (del) is calculated for all protons in a molecule and then plotted against the observed shift for these protons, a straight line results. Further, if

$$(\cos^2 \phi - 1)/r^3 = (\cos^2 \langle \phi \rangle^{-1})/\langle r \rangle^3$$

the slope of the line obtained by averaging the del values for the two conformers should be identical with the slope of the line obtained by averaging the coordinates of the two conformers and then calculating the del values. Compound **1b** was examined in this manner at a conformational weighting of 1:1 using the program BODEL.[7] The least-squares slope for the average of the del values is found to be 0.533, with a standard deviation of 0.048; while that for the del values of the averaged coordinates is 0.519, with a standard deviation of 0.052. Variances obtained are 0.963 and 0.960, respectively. Although this does not constitute a rigorous proof of eq 1, the results are strongly supportive of its use.

Despite the lack of solid theory, the relationships above are exceedingly useful and have been utilized to good advantage.[8] If then we can accept eq 1, it follows that the set of theoretical calculations which will most closely approximate the experimentally obtained values will be found at the weighted average of the coordinates for the stable conformations which represent the "intermediate conformation". If the sum of the conformers present is unity, the weights placed on the coordinates of the stable conformations at the point of best fit will be identical with the amount of that conformer in solution.

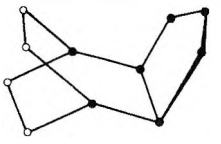
Consequently, a program for averaging the coordinates for the two stable conformers was developed and merged into the existing PDIGM system. It should be noted at this point that the atom positions for the various conformations should overlap in every possible respect, and in the system 1 requires superimposing the furan rings before the averaging process.[9] Neglect of this factor would cause identical atom positions to be averaged (Chart II).

The data obtained are presented in Table II and Figure 1. The result for **1a**, a 94:6 preference for the *open* conformation, substantiates our earlier views of its preferred conformation. It may be argued that the difference in agreement factors is small in the immediate vicinity of the minimum and that a range rather than an absolute number should be specified. Although the method of reporting the data is immaterial for our purposes, the symmetry of the curve encourages our belief in its accuracy.[10]

Table II
Agreement Factors for Weighted Averages of Conformation

| % open conformation | $R$ values, %, at 2.2 Å (1b) | $R$ values, %, at 2.9 Å (1a) |
|---|---|---|
| 100 | 10.1 (3.81 at 2.9 Å) | 1.98 |
| 95 | | 1.91 |
| 94 | | 1.90 |
| 93 | | 1.91 |
| 92 | | 1.92 |
| 90 | 3.93 (3.55 at 2.3 Å) | 1.96 |
| 85 | | 2.17 |
| 80 | | 2.50 |
| 75 | 2.37 | 2.93 |
| 70 | 2.16 | |
| 65 | 2.03 | |
| 63 | 2.01 | |
| 62 | 2.00 | |
| 61 | 1.99 | |
| 60 | 1.99 | |
| 55 | 2.05 | |
| 50 | | 5.66 |
| 35 | 3.36 (3.29 at 2.3 Å) | 7.19 |
| 20 | 3.59 | 8.16 |
| 0 | 5.94 (5.23 at 2.9 Å) | 5.75 (4.74 at 3.3 Å) |

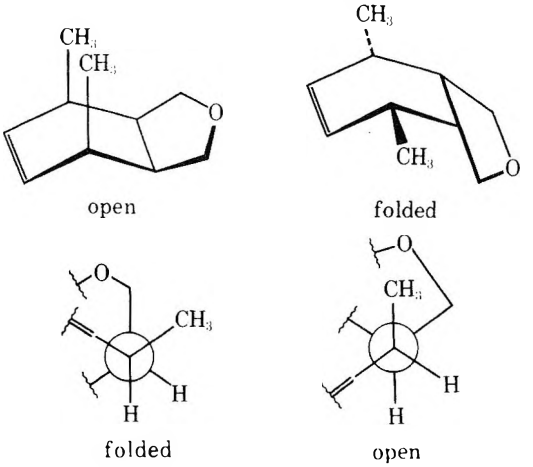
Chart II
Relationships of Folded to Open Coordinates



• equivalent positions
○ nonequivalent positions

The analysis of one other system, *cis*-2,5-dimethylbicyclo[4.3.0]non-3-ene (**1b**), seemed potentially fruitful since, a priori, it could be assumed to exist largely in the folded form. This assumed preference for the folded form is attributed to the 1,4-dimethyl interaction which exists in the open conformer. However, allylic strain[13] in the folded form, plus increased gauche interactions,[14] might tend to counteract the dimethyl interaction so that the exact extent of folding is obscure (Chart III).

Chart III
Steric Interactions of
*cis*-2,5-Dimethylbicyclo[4.3.0]non-3-ene



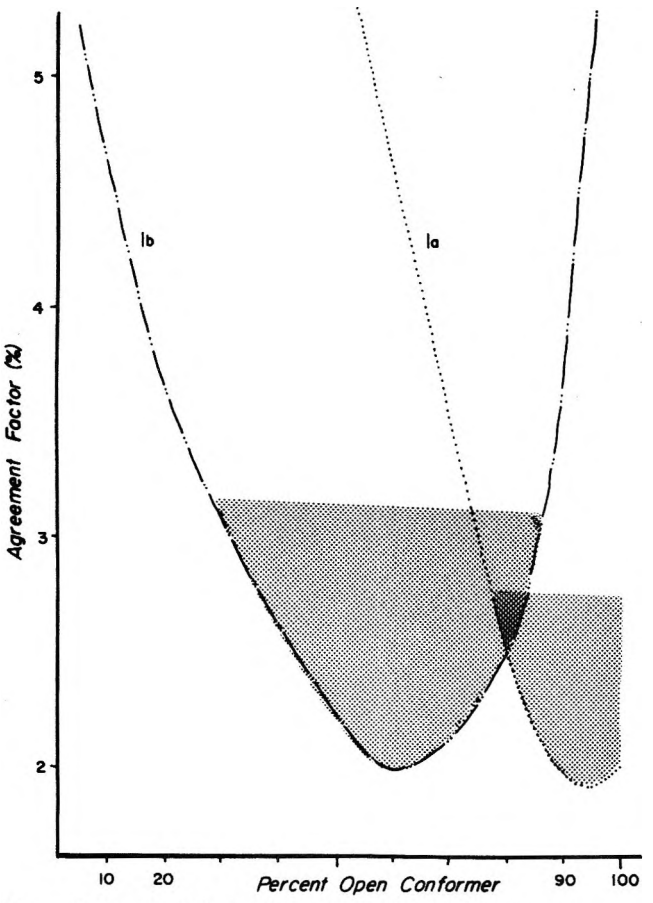



**Figure 1.** Graph of $R$ value vs. percent *open* conformer.

The results obtained from PDIGM for the various weighted averages are displayed in Table II and Figure 1 with the best agreement of theory to experiment ($R$ = 1.99) found at 60% *open* conformer and 40% *folded*.[15]

Several interesting artifacts of PDIGM may be noted. One is the observation that the lanthanide–substrate bond distance changes for the two conformations, the minimum for the open form being found at 2.9 Å, while the partially closed exists at 2.2 Å. At present we have no reasonable rationalization for this; however, differences in lanthanide–substrate distances for rigid exo/endo isomers has been previously observed.[16]

Another notable observation is the deviation, at extreme conformations, of the lanthanide–substrate bond distance at which the best agreement (minimum $R$) is found. These "numeric" $R$ minima are very erratic in their positioning of the lanthanide and often place the lanthanide in physically improbable environments. A numeric minimum is a minimum only once. For example, if there is a numeric minimum at 3.0 Å in a 90:10 *open/closed* equilibrium calculation, a minimum will not exist at 3.0 Å in the 80:20 calculation. Consequently, it may be asserted that these numeric minima are fortuitous, the result of forcing a fit of theoretical and experimental data to a conformation that, for NMR, does not exist.

Recently, Servis and co-workers examined the conformational equilibria of some 2-alkylcyclohexanones using lanthanide shift reagents.[17] An extension of this work provides a convenient check on our calculations. Basically, Servis has assumed that the observed shift for any proton in the presence of a shift reagent ($\delta_{obsd}{}^{H_a}$) will be the sum of the shift for the uncomplexed molecule ($\delta_0{}^{H_a}$) and the induced shift for the complexed form ($\Delta^{H_a}$) multiplied by the fraction of molecules complexed ($F$).

$$\delta_{obsd}{}^{H_a} = \delta_0{}^{H_a} + F\Delta^{H_a}$$

If two conformations exist for the molecule (i.e., if the proton occupies two different regions of space) then the observed shift can be expressed as the weighted averages of the shifts for the two conformations (eq 2)

$$\delta_{obsd}{}^{H_a} = n_1\delta_0{}^{H_{1a}} + n_2\delta_0{}^{H_{2a}} + F(n'_1\Delta^{H_{1a}} + n'_2\Delta^{H_{2a}}) \quad (2)$$

where $\Delta^{H_{1a}}$ is the bound shift of proton $H_a$ in environment 1 and $\Delta^{H_{2a}}$ is the bound shift of proton $H_a$ in environment 2. Similarly, for any other proton in the molecule, $H_b$,

$$\delta_{obsd}{}^{H_b} = n_1\delta_0{}^{H_{1b}} + n_2\delta_0{}^{H_{2b}} + F(n'_1\Delta^{H_{1b}} + n'_2\Delta^{H_{2b}}) \quad (3)$$

Simultaneous solution of these two equations (2 and 3) and subsequent simplifications yields eq 4

$$\frac{\Delta^{H_a}}{\Delta^{H_a} + \Delta^{H_b}} = n'_1\frac{\Delta^{H_{1a}}}{\Delta^{H_{1a}} + \Delta^{H_{2b}}} + n'_2\frac{\Delta^{H_{2b}}}{\Delta^{H_{1a}} + \Delta^{H_{2b}}} \quad (4)$$

where $\Delta^{H_a}/\Delta^{H_a} + \Delta^{H_b}$, the relative induced shift, may be shown to equal the slope of the plot of $\delta_{obsd}{}^{H_a}$ vs. $\delta_{obsd}{}^{H_a} + \delta_{obsd}{}^{H_b}$.[12]

A characteristic relative induced shift is obtained from a rigid model system and the conformational equilibria of its nonrigid cousins ascertained by comparison of the relative induced chemical shifts with the characteristic relative induced shift of the model system. Owing to the unique relationship of axial and equatorial protons in cyclohexanes, only one model is needed for complete analysis of the system. However, for any system in which proton $H_a$ in conformation 1 does not occupy the same space as proton $H_b$ in conformation 2, a two-model system is needed.

The mathematical relationships for the two-model system may be derived in exactly the same manner as done by Servis and Bowler with the end result displayed in eq 5.

relative induced shift =

$n_0$ (characteristic relative induced shift 1) +

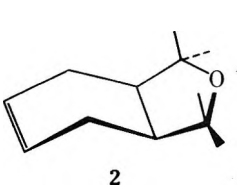
$(1 - n_0)$ (characteristic relative induced shift 2)

or

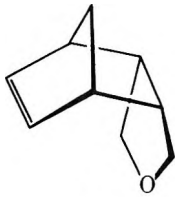
obsd slope ($\delta_{obsd}{}^{H_a}$ vs. $\delta_{obsd}{}^{H_a} + \delta_{obsd}{}^{H_b}$) =

$n_0$ (standard slope 1) + $(1 - n_0)$ (standard slope 2) (5)

We chose for our open model *cis*-7,7,9,9-tetramethylbicyclo[4.3.0]non-3-ene (**2**)[18] and for our folded model *endo*-4-oxatricyclo[5.2.1.$0^{2,6}$]dec-8-ene (**3**).[19] Examination of Drieding models revealed that **2** should exist entirely in the *open* form owing to the prohibitive bulk of the four methyl groups. Nevertheless, **2** was examined using PDIGM and found to have an agreement ($R$) factor of 1.43% for the *open* conformer while the corresponding factor for the *folded* conformer was 6.32%. Since this difference is significant to the 99.5% level, we feel justified in stating that **2** exists exclusively in the *open* form.[20] For **3**, rigid covalent bonds, not assumptions, hold it in the *folded* form!




**2**




**3**

For convenience in the analysis, we needed two protons whose signals in the NMR were free of interference, at least one of which changed significantly with a conformation change. The vinyl protons ($H_v$) and the ring juncture protons ($H_j$) satisfied these specifications. The shift data ob-

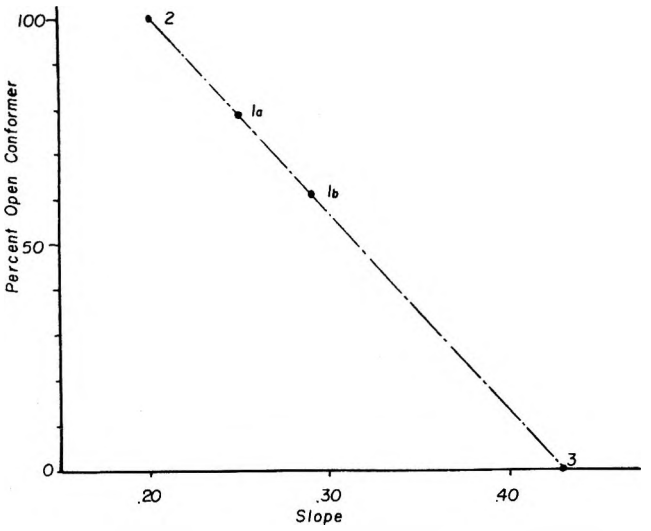



**Figure 2.** Graphical determination of conformational equilibria of *cis*-8-oxabicyclo[4.3.0]non-3-enes.

tained at various concentrations of $Eu(fod)_3$ with the slopes of the graphs ($\delta^{H_v}$ vs. $\delta^{H_v} + \delta^{H_j}$) are displayed in Table III. Figure 2 represents the graphical interpretation of the linear combination, eq 5, and gives a value of 78% *open* for **1a** and 60% *open* for **1b**.

In view of the assumptions and simplifications involved these figures are in good agreement with those obtained from the computer analysis.

If one considers the McConnell–Robertson equation

$$\Psi\text{-contact shift} = K\left[\frac{3\cos^2\theta - 1}{r^3}\right]$$

a direct comparison of the induced shifts for one molecule with those for another may be made only if the distance from the lanthanide to any specific proton, $r$, and $\theta$, the angle generated by $r$, and the lanthanide–substrate bond axis, are constant. This is rarely, if ever, the case. A method is needed whereby differences in $r$ and $\theta$ "factor out". The procedure of Servis and Bowler is such a method.

Given $r$ and $r'$, the lanthanide–proton distances for two conformers, a relationship may always be derived whereby

$$r = kr'$$

and it follows that

$$r^3 = k^3 r'^3$$

or, redefining the constant,

$$r^3 = kr'^3$$

It is this constant, $K$, which prevents direct comparison of the shift data. However, when $\delta_{obsd}{}^{H_a}$, which is a function of $Kr'^3$, is plotted against another value also designed to vary as $Kr'^3$ ($\delta_{obsd}{}^{H_a} + \delta_{obsd}{}^{H_b}$) the deviation is constant along both the absicca and the ordinate. The slope of the plot $\delta_{obsd}{}^{H_a}$ vs. ($\delta_{obsd}{}^{H_a} + \delta_{obsd}{}^{H_b}$) is, therefore, independent of the constant. Unfortunately, this simple relationship does not hold for the ($\cos^2\theta - 1$) term, since it may not be deduced from an equation of the form

$$a = kb$$

that

$$a - 1 = k(b - 1)$$

If the change in $\theta$ is less than 20° the change in the $\Psi$-contact shift is not large and the errors introduced by assuming $\cos^2\theta$ constant are acceptable. It must be noted, however, that preferential binding of the lanthanide to one orbital over another, a consideration of much import in heterocyclic chemistry,[21] would be manifest in this term and may result in larger errors than expected.

Table III
Shift of Vinyl and Juncture Protons with $Eu(fod)_3$

| Compd | $\delta_{H_v}$ | $Eu(fod)_3$/substrate | $\delta_{H_v} + \delta_{H_j}$ | $\delta_{H_j}$ | Slope[a] |
|---|---|---|---|---|---|
| 1a | 5.64 | | 8.02 | 2.38 | |
| | 5.73 | 0.176 | 8.28 | 2.55 | |
| | 5.82 | 0.352 | 8.63 | 2.81 | |
| | 5.92 | 0.528 | 9.05 | 3.13 | |
| | 5.99 | 0.704 | 9.40 | 3.41 | 0.25 |
| 3 | 6.01 | | 8.77 | 2.76 | |
| | 6.18 | 0.203 | 9.19 | 3.01 | |
| | 6.36 | 0.407 | 9.59 | 3.23 | |
| | 6.62 | 0.815 | 10.19 | 3.57 | |
| | 7.05 | 1.22 | 11.18 | 4.13 | 0.43 |
| 2 | 5.67 | | 7.76 | 2.09 | |
| | 5.72 | 0.373 | 7.95 | 2.23 | |
| | 5.81 | 0.747 | 8.44 | 2.63 | |
| | 5.89 | 1.12 | 8.82 | 2.93 | |
| | 5.94 | 1.49 | 9.11 | 3.17 | 0.20 |
| 1b | 5.58 | | 8.13 | 2.55 | |
| | 5.76 | 0.216 | 8.76 | 3.00 | |
| | 5.93 | 0.431 | 9.36 | 3.43 | |
| | 6.11 | 0.647 | 9.96 | 3.85 | |
| | 6.29 | 0.863 | 10.57 | 4.28 | 0.29 |

[a] $r^2$ for each of these values exceeds 0.99.

A further source of error in this method lies in the suitability of the model compounds. It is essential to choose the model systems carefully and, for the case in hand, to keep in mind that the protons of the models, particularly the folded model, will not have the same chemical shifts as the protons of the molecules of interest, and that considerable error may result from this.

In this paper we have demonstrated the utility of lanthanide shift reagents for conformational analysis, in solution, of mobile systems and have provided a convenient method for quantifying the results. This method, although used to examine the equilibrium between only two conformers, may be applied to any number of species in equilibrium.

## Experimental Section[22]

The NMR spectra were recorded on a Varian A-60 instrument using tetramethylsilane as the internal standard. Chemical shifts were measured from $Me_4Si$.

**Typical Procedure.** A solution of **1a** (0.140 g, $1.117 \times 10^{-3}$ mol) and reagent grade carbon tetrachloride with 1% $Me_4Si$ to bring the total volume to 250 μl was placed in an NMR tube and the spectrum was recorded. To this sample tube were then added 100-μl aliquots of a 0.198 *M* $Eu(fod)_3$ solution in carbon tetrachloride. The spectrum was again recorded. This procedure was repeated from five to ten times. The shift data were collected and analyzed.

**Acknowledgments.** Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this work. The assistance of Clarence Whitworth in unraveling some of the computer problems has been greatly appreciated.

**Registry No.**—**1a**, 50305-98-1; **1b**, 57346-34-6; **2**, 57346-35-7; **3**, 43187-61-7; $Eu(fod)_3$, 17631-68-4.

## References and Notes

(1) B. P. Mundy, K. R. Sun, and R. D. Otzenberger, *J. Org. Chem.*, **37**, 2793 (1972).
(2) J. J. Cawley and D. V. Petrocine, *Org. Magn. Reson.*, **6**, 544 (1974).
(3) R. E. Davis and M. R. Willcott, III, in "Nuclear Magnetic Resonance Shift

Reagents", R. E. Sievers, Ed., Academic Press, New York, N.Y., 1973, pp 143–158.
(4) J. D. Roberts, "Nuclear Magnetic Resonance", McGraw-Hill, New York, N.Y., 1959, p 63.
(5) T. P. Forrest, D. L. Hooper, and S. Ray, *J. Am. Chem. Soc.*, **96**, 4286 (1974).
(6) I. M. Armitage, L. D. Hall, A. G. Marshall, and L. G. Werbelow in ref 3, pp 322–323.
(7) Program written by G. D. Smith, Montana State University.
(8) M. R. Willcott, III, and R. E. Davis in ref 3, pp 159–169.
(9) For all PDIGM calculations, coordinates of all conformations were taken so that the oxygen atom and the four carbon atoms of the tetrahydrofuran ring were superposed in all conformations. Comparison of any two *R* factors is a comparison of the goodness of fit for two different positions for the substituents on the four nonfused carbon atoms of the six-membered ring.
(10) We applied the Hamilton *R*-ratio tests[11] to observed *R* factors in the following way. The conformation or mix of conformations with the lowest *R* factor was deemed the "best fit conformation". Any other conformation or mix of conformations was considered a "restrained conformation" with the number of protons unable to assume the "best fit conformation" defining the number of restrained parameters (*b*). Further, the number of experimental observations (*n*) was taken as the number of observed NMR peaks used in the calculation of slopes and the number of parameters (*p*) was taken as the number of protons in the molecule. The observed *R*-ratio, $R_{rest}/R_{best\ fit}$, was compared to the calculated *R*-ratio values, $R_{b,n-p,\alpha}$, which have to be exceeded to reject the hypothesis that the two conformations are indistinguishable. The confidence level at which the hypothesis is rejected is $(1 - \alpha) \times 100\%$. Values of $R_{b,n-p,\alpha}$, were taken from Hamilton[12] or calculated by the relation

$$R_{b,n-p,\alpha} = [(b/n - p)F_\alpha + 1]^{1/2}$$

as given by Hamilton.[11]
For **1a**, $n = 25$, $p = 12$, $b = 6$. The conformational mix of 94% *open*, 16% *folded* with the lowest *R* factor is not significantly different from the totally *open* conformation but is significantly different from any conformational mix of 75% or less *open* form at the 90% confidence level. The stipled area in Figure 1 shows the limits of the 90% level.
(11) W. C. Hamilton, "Statistics in Physical Science", Ronald Press, New York, N.Y., 1964, pp 157–162.
(12) Reference 11, pp 216–222.
(13) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).
(14) D. H. Wertz and N. L. Allinger, *Tetrahedron*, **30**, 1579 (1974).
(15) For **1b** $n = 30$, $p = 16$, $b = 10$. The 60%:40% conformational mix is significantly different from conformational mixes of 90% *open* or greater and 35% *open* and less at the 90% confidence level. The stipled area of Figure 1 shows the limits of the 90% level.
(16) R. E. R. Craig, A. C. Craig, and G. D. Smith, *Tetrahedron Lett.*, 1189 (1975).
(17) (a) K. L. Servis, D. J. Bowler, and C. Ishii, *J. Am. Chem. Soc.*, **97**, 73 (1975); (b) K. L. Servis and D. J. Bowler, *ibid.*, **97**, 81 (1975).
(18) J. Wolinsky and M. Senyek, *J. Org. Chem.*, **33**, 3950 (1968).
(19) P. Wilder, Jr., and C. V. A. Drinnan, *ibid.*, **39**, 414 (1974).
(20) For **2** $n = 25$, $p = 20$, $b = 6$.
(21) I. D. Blackburne, A. R. Katritzky, and Y. Takeuchi, *J. Am. Chem. Soc.*, **96**, 682 (1974).
(22) The compounds used in this study were prepared by established literature procedures, with physical and spectral data in agreement: **1a**, ref 1; **1b**, A. P. Krapcho and B. P. Mundy, *J. Heterocycl. Chem.*, **2**, 355 (1965); **2**, ref 13; **3**, B. P. Mundy, *Org. Prep. Proced. Int.*, **7**, 21 (1975).

# Crystal and Molecular Structure of a Spirobicyclic Pentaoxyphosphorane, $(PO_5)(C_6H_4)_2(C_6H_5)$

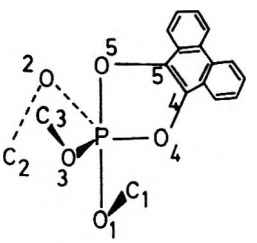
Raghupathy Sarma,*[1a] Fausto Ramirez,*[1b] and James F. Marecek[1b]

*Biochemistry and Chemistry Departments of the State University of New York at Stony Brook, Stony Brook, New York 11794*

*Received July 15, 1975*

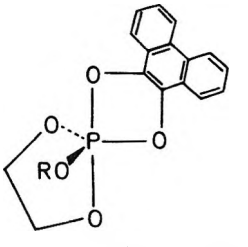
The crystal and molecular structure of a monoclinic form of spirodicatecholphenoxyphosphorane was determined by single-crystal x-ray diffraction techniques. The space group is $P2_{1/c}$ with four molecules in a unit cell of dimensions $a = 6.910$ Å, $b = 15.305$ Å, $c = 14.779$ Å, $\beta = 88.5°$. The final *R* factor for 2840 independent reflections is 8.7%. The molecular structure does not correspond to an ideal or a "slightly distorted" trigonal bipyramid or tetragonal (square) pyramid. It is suggested that the phosphorus and its five oxygen ligands have the skeletal geometry of a 15°-turnstile rotation configuration.

Compounds with five oxygen ligands covalently bonded to phosphorus, e.g., the trimethyl phosphite–phenanthrenequinone adduct **1**, have been extensively studied from structural[2] and synthetic[3] points of view. The geometry around the phosphorus in the analogous pentaoxyphosphorane **2** is TBP,[4] as established by x-ray crystallography,[5] which revealed also the existence of severe crowding around the central atom. It was suggested[5] that the relatively planar ring minimizes the crowding and contributes to the stability of this type of compound.



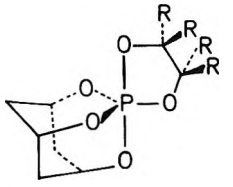

**1** $C_1,C_2C_3{\equiv}CH_3$; $\delta^{31}P = +44.7$ ppm
**2** $C_1,C_2,C_3{\equiv}$ iso-$C_3H_7$; $\delta^{31}P = +48.6$ ppm
**3** $C_1,C_2,C_3 \equiv C_6H_5$; $\delta^{31}P = +58.6$ ppm

Spirobicyclic pentaoxyphosphoranes, e.g., **4** and **5**, are also known, and are relatively stable.[6] The introduction of an additional five-membered ring into the monocyclic pentaoxyphosphoranes is accompanied by a significant displacement of the $^{31}P$ NMR chemical shift toward lower magnetic field, i.e., by a decrease in the shielding of the P nucleus by electrons, cf. **4** vs. **1** and **5** vs. **3**. This effect could reflect significant differences in molecular structure between spirobicyclic and monocyclic pentaoxyphosphoranes, but there are no x-ray data on the molecular structure of **4** and **5**. Six-membered rings do not cause this effect.[6,7]

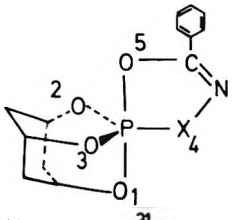



**4** $R = CH_3$; $\delta^{31}P = +23.0$ ppm
**5** $R = C_6H_5$; $\delta^{31}P = +27.0$ ppm

There seems to be a tendency toward the TBP geometry in five-coordinate phosphorus, as there is in five-coordinate antimony.[8] Although there are as yet no x-ray crystallographic data for the caged polycyclic pentaoxyphosphorane[9,10] **6**, the molecular structures of the two analogous compounds **7** and **8** are known.[11,12] The skeletal geometry about the P atom is close to TBP in **7** and **8**, but there are significant distortions in them from ideal $D_3h$ symmetry, e.g., O(2)–P–O(3) = 106° and O(5)–P–X(4) = 84° in **7** and **8**, while O(1)–P–O(5) = 170° in **7** and 168° in **8**. It was suggested[11,12] that the molecules of phosphoranes **7** and **8**, in their ground state in the crystal, have geometries which begin to resemble those of TR configurations.[4,13] If so, when those molecules are placed in solution, they are able to undergo relatively rapid intramolecular permutational isomerization, since they require relatively little energy to reach the barrier configuration of the TR mechanism.[13]



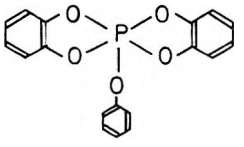
**6** R = $CF_3$; $\delta^{31}P$ = +42.4 ppm



**7** X = $NC_6H_5$; $\delta^{31}P$ = +56.8 ppm

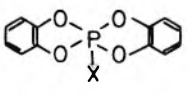
**8** X = $C(CF_3)_2$; $\delta^{31}P$ = +17.9 ppm

The purpose of this investigation was to ascertain the effect exerted on the *static stereochemistry of a pentaoxyphosphorane* by the presence of two five-membered rings in the spiro configuration. The molecule chosen was the spirodicatecholphenoxyphosphorane,[6b] **9**.



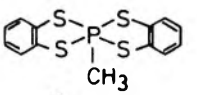
**9** $\delta^{31}P$ = +30.2 ppm

The results of x-ray crystallographic analysis of a number of spirobicyclic phosphoranes having combinations of P–O and P–C[14] (**10**), P–O and P–F[14] (**11**), P–S and P–C[15] (**12**), and P–O, P–S, and P–C[16] bonds have been interpreted in terms of more or less distorted TP[4] skeletal geometries.[17a]



**10** X = $CH_3$

**11** X = F



**12**

The TP geometry has also been suggested from x-ray data for certain spirodioxatricarbophosphoranes with four- and five-membered rings;[18] in contrast, some monocyclic dioxatricarbophosphoranes with a four-membered ring have slightly distorted TBP configuration.[19] Unfortunately, the effect of the spirobicyclic feature on the skeletal geometry of phosphoranes is obscured in these examples[14–16,18] by the circumstance that they have quite different "ligand subset symmetry",[13,20] i.e., the equatorial and the apical subsets of ligands cannot be made up of the same element, and electronic, as well as steric, factors may contribute to the striking differences in molecular geometry in these cases.

Several examples of phosphoranes with P–C bonds, and with certain combinations of P–C and P–O bonds, are known to have slightly distorted TBP geometries according to x-ray crystallography.[21–28]

## Experimental Section

**Preparation of Spirodicatecholphenoxyphosphorane (9).** This substance was prepared as described.[6b] The crystals for x-ray analysis were obtained from a mixture of benzene and hexane at 20°; they had mp 108–110° and $\delta^{31}P$ +30.0 ppm vs. $H_3PO_4$ ($CH_2Cl_2$ solution).

**Crystal Data.** Compound **9**: $C_{18}H_{13}O_5P$; monoclinic; $P2_{1/c}$; $a$ = 6.910 ± 0.01 Å, $b$ = 15.305 ± 0.01 Å, $c$ = 14.779 ± 0.01 Å, $\beta$ = 88.5°; $Z$ = 4; $d$ calcd = 1.445 g/cm$^3$; $d$ meas = 1.437 g/cm$^3$.

**Data Collection and Structure Determination.** The crystals were extremely sensitive to atmospheric moisture and dissolved readily during exposure. This was prevented by sealing the crystal in a capillary tube filled with a small amount of $P_2O_5$ at one end of the tube. The crystal used for data collection had dimensions 0.7 × 0.4 × 0.4 mm.

Intensity data were collected using a computer controlled CAD4 automatic diffractometer using Cu K$\alpha$ (1.542 Å) radiation. Nearly 3000 reflections were collected using $\theta$–$2\theta$ scan with a scan width of 1.2°. Four reflections were measured periodically to monitor any crystal deterioration. No such effects were observed during the entire data collection. Ninety-six separate measurements were made for each scan; the first 16 and the last 16 measurements were summed to provide the background measurements for each reflection. There were approximately 2840 reflections with $|F_0|^2 > 2\sigma(|F_0|^2)$ with $\sigma$ estimated from counting statistics.

Since the crystal was sealed inside a capillary tube, an empirical absorption correction was applied;[29] this correction was determined by performing an azimuth scan for a reflection occurring at a $\chi$ value of approximately 90°. The variation in intensity of such a reflection for the different azimuth angles is dependent on the thickness of the crystal traversed by the incident and the reflected beams and this variation is used to calculate the transmission factor for the crystal for all the other reflections. The transmission factor varied from a value of 1.00 to approximately 1.30 during the azimuth scan.

Structure amplitudes derived in the usual way were used in calculating a sharpened Patterson map, which was used in deducing the position of the phosphorus atom. Remaining atoms were located from a series of structure factors followed by weighted Fourier syntheses calculated using $w|F_N|\exp\alpha$ as coefficients, where the weighting factor $w$ = tanh ($|F_N||F_P|/\Sigma f_{Qj}^2$);[30] $|F_N|$ is the observed structure amplitude, $|F_P|$ is the contribution from the known atoms, and $Qj$ corresponds to the unknown atoms. The structure was refined by full matrix least squares, minimizing the function $\Sigma w(\Delta F)^2$. The weighting scheme used was of the form $w = 1/(a + |F_0| + c|F_0|^2)$ where $a$ and $c$ were of the order of $2F_{min}$ and $2/F_{max}$, respectively.[31] The atomic scattering factors for all the nonhydrogen atoms were taken from a standard source. The final least-squares cycle was performed with anisotropic temperature parameters for all the nonhydrogen atoms. No attempt was made to locate the positions of the hydrogen atoms. Refinement was stopped with an $R$ value of 8.7% for 2840 reflections. A final difference Fourier synthesis $\rho_{obsd} - \rho_{calcd}$ was calculated. The maximum electron density in this synthesis was 0.383 e/A$^3$, indicating that no atoms other than hydrogen remain to be located. The final positional and thermal parameters are given in Table I. The observed and calculated structure factors are given in Table II.

## Discussion

**Molecular Structure of 9.** The interatomic distances[32] and bond angles and their standard deviations are listed in Table III. Some intramolecular distances between nonbonded atoms are collected in Table IV. Equations of least-squares planes, and deviations of certain atoms from these

Table I
A. Atomic Coordinates and Their Standard Deviations (in Parentheses)

| Atom | X | Y | Z |
|---|---|---|---|
| P | 0.0817 (2) | 0.3153 (0) | 0.4739 (0) |
| O1 | −0.1440 (7) | 0.3530 (3) | 0.4841 (2) |
| O2 | 0.1522 (7) | 0.4036 (3) | 0.4159 (3) |
| O3 | 0.0619 (7) | 0.2426 (3) | 0.3972 (3) |
| O4 | 0.0236 (7) | 0.2650 (3) | 0.5708 (2) |
| O5 | 0.3157 (7) | 0.3046 (3) | 0.4904 (2) |
| Cl | −0.1759 (11) | 0.4233 (4) | 0.4254 (4) |
| C2 | −0.0010 (11) | 0.4507 (4) | 0.3878 (4) |
| C3 | −0.1027 (12) | 0.1896 (4) | 0.3906 (4) |
| C4 | 0.1828 (11) | 0.2262 (4) | 0.6065 (4) |
| C5 | 0.3540 (11) | 0.2470 (4) | 0.5617 (4) |
| C6 | 0.0078 (13) | 0.5217 (5) | 0.3267 (5) |
| C7 | −0.1708 (14) | 0.5596 (5) | 0.3071 (5) |
| C8 | −0.3497 (14) | 0.5309 (5) | 0.3469 (5) |
| C9 | −0.3548 (12) | 0.4582 (5) | 0.4092 (5) |
| C10 | −0.0976 (16) | 0.1061 (5) | 0.4297 (6) |
| C11 | −0.2661 (18) | 0.0542 (6) | 0.4212 (7) |
| C12 | −0.4275 (17) | 0.0804 (6) | 0.3770 (6) |
| C13 | −0.4252 (16) | 0.1634 (6) | 0.3384 (6) |
| C14 | −0.2603 (14) | 0.2183 (5) | 0.3447 (6) |
| C15 | 0.5321 (12) | 0.2183 (5) | 0.5854 (5) |
| C16 | 0.5336 (13) | 0.1609 (5) | 0.6623 (5) |
| C17 | 0.3594 (14) | 0.1404 (5) | 0.7095 (5) |
| C18 | 0.1783 (13) | 0.1718 (5) | 0.6846 (4) |

B. Thermal Parameters

| Atom | B11 | B22 | B33 | B23 | B13 | B12 |
|---|---|---|---|---|---|---|
| P | 0.0194 | 0.0038 | 0.0030 | −0.0020 | 0.0041 | 0.0002 |
| O1 | 0.0213 | 0.0051 | 0.0035 | −0.0002 | 0.0035 | 0.0018 |
| O2 | 0.0219 | 0.0041 | 0.0041 | −0.0014 | 0.0040 | 0.0016 |
| O3 | 0.0259 | 0.0050 | 0.0035 | −0.0023 | 0.0052 | −0.0017 |
| O4 | 0.0233 | 0.0043 | 0.0033 | −0.0008 | 0.0051 | 0.0009 |
| O5 | 0.0219 | 0.0050 | 0.0036 | −0.0022 | 0.0024 | 0.0023 |
| C1 | 0.0258 | 0.0037 | 0.0031 | −0.0006 | 0.0013 | −0.0010 |
| C2 | 0.0237 | 0.0037 | 0.0037 | −0.0016 | 0.0030 | −0.0003 |
| C3 | 0.0285 | 0.0042 | 0.0032 | −0.0005 | 0.0033 | −0.0014 |
| C4 | 0.0240 | 0.0035 | 0.0033 | −0.0010 | 0.0026 | −0.0003 |
| C5 | 0.0250 | 0.0036 | 0.0033 | −0.0021 | 0.0029 | 0.0003 |
| C6 | 0.0298 | 0.0040 | 0.0047 | −0.0002 | 0.0019 | 0.0005 |
| C7 | 0.0329 | 0.0042 | 0.0053 | 0.0002 | 0.0002 | −0.0008 |
| C8 | 0.0329 | 0.0042 | 0.0054 | 0.0012 | −0.0028 | −0.0015 |
| C9 | 0.0274 | 0.0045 | 0.0042 | 0.0015 | 0.0001 | −0.0012 |
| C10 | 0.0422 | 0.0038 | 0.0063 | 0.0021 | −0.0043 | 0.0002 |
| C11 | 0.0528 | 0.0038 | 0.0074 | −0.0047 | −0.0053 | 0.0003 |
| C12 | 0.0446 | 0.0047 | 0.0069 | −0.0045 | −0.0034 | −0.0016 |
| C13 | 0.0394 | 0.0051 | 0.0071 | −0.0029 | −0.0069 | −0.0021 |
| C14 | 0.0341 | 0.0043 | 0.0058 | −0.0019 | −0.0079 | −0.0006 |
| C15 | 0.0240 | 0.0050 | 0.0043 | −0.0012 | 0.0003 | 0.0002 |
| C16 | 0.0305 | 0.0044 | 0.0044 | −0.0020 | −0.0004 | −0.0002 |
| C17 | 0.0344 | 0.0043 | 0.0041 | 0.0010 | 0.0006 | 0.0001 |
| C18 | 0.0330 | 0.0046 | 0.0034 | 0.0008 | 0.0035 | 0.0008 |

planes, are given in Table V. The dihedral angles formed by pairs of these planes are shown in Table VI.

The data in Tables III–VI demonstrate that the skeletal geometry about the phosphorus atom in the spiropentaoxyphosphorane **9** does not resemble a regular TBP, or even a reasonably distorted TBP. This is brought out by Figure 1, which is a drawing of the molecule of **9** generated by computer from the experimental data, and by formula I, Figure 2, which is the hypothetical ideal TBP arrangement of the P05 group. In formula I, the five-membered rings formed by the phosphorus atom and the two catechol bidentate ligands, A and C, are placed in apical-equatorial skeletal positions in accordance with previous observations[5] in the related system 2.

A superficial examination of the data suggests, at first, the skeletal geometry of a regular TP for compound **9**. However, a more detailed analysis reveals significant deviations from ideal TP symmetry. This is shown in Figure 3

Table III
Bond Distances and Angles in Spirodicatecholphenoxyphosphorane (9)

A. In $PO_5$ Group

| Bond angles, deg | | Bond distances, Å | |
|---|---|---|---|
| O(1)–P–O(5) | 160.02 (2.3) | P–O(1) | 1.666 (10) |
| O(2)–P–O(4) | 151.36 (2.1) | P–O(2) | 1.666 (10) |
| O(3)–P–O(4) | 105.37 (1.0) | P–O(4) | 1.666 (10) |
| O(2)–P–O(3) | 103.26 (1.0) | P–O(5) | 1.650 (10) |
| O(1)–P–O(3) | 101.99 (1.0) | P–O(3) | 1.597 (10) |
| O(3)–P–O(5) | 97.98 (0.9) | | |
| O(4)–P–O(5) | 92.38 (0.8) | | |
| O(1)–P–O(2) | 91.47 (0.8) | | |
| O(2)–P–O(5) | 83.25 (0.8) | | |
| O(1)–P–O(4) | 83.04 (0.8) | | |

B. In the Phenoxy Ligand (Ring B)

| Bond angles, deg | | Bond distances, Å | |
|---|---|---|---|
| P–O(3)–C(3) | 122.51 (1.8) | O(3)–C(3) | 1.403 (17) |
| O(3)–C(3)–C(14) | 120.37 (2.6) | | |
| O(3)–C(3)–C(10) | 117.95 (2.5) | | |

| X | Y | Z | <XYZ, deg | D(X–Y), Å | D(Y–Z), Å |
|---|---|---|---|---|---|
| C(3) | C(10) | C(11) | 116.35 (3.0) | 1.403 (23) | 1.418 (28) |
| C(10) | C(11) | C(12) | 124.07 (3.8) | 1.418 (28) | 1.368 (28) |
| C(11) | C(12) | C(13) | 117.56 (3.5) | 1.368 (28) | 1.392 |
| C(12) | C(13) | C(14) | 120.86 (3.4) | 1.392 (27) | 1.421 (26) |
| C(13) | C(14) | C(3) | 119.48 (3.1) | 1.421 (26) | 1.371 (22) |
| C(14) | C(3) | C(10) | 121.65 (3.1) | 1.371 (22) | 1.403 (23) |

C. In Five-Membered Ring Fused to Ring A

| Bond angles, deg | | Bond distances, Å | |
|---|---|---|---|
| O(1)–P–O(2) | 91.47 (0.8) | | |
| P–O(2)–C(2) | 111.66 (1.4) | O(2)–C(2) | 1.355 (17) |
| O(2)–C(2)–C(1) | 113.41 (2.1) | O(1)–C(1) | 1.403 (16) |
| C(2)–C(1)–O(1) | 109.34 (1.8) | C(1)–C(2) | 1.382 (19) |
| C(1)–O(1)–P | 111.83 (1.4) | | |
| O(1)–C(1)–C(9) | 124.24 (2.0) | | |
| O(2)–C(2)–C(6) | 125.74 (1.8) | | |

D. In Ring A

| X | Y | Z | <XYZ, deg | D(X–Y), Å | D(Y–Z), Å |
|---|---|---|---|---|---|
| C(1) | C(2) | C(6) | 120.83 (2.7) | 1.382 (19) | 1.413 (21) |
| C(2) | C(6) | C(7) | 115.31 (2.6) | 1.413 (21) | 1.401 (21) |
| C(6) | C(7) | C(8) | 123.13 (3.1) | 1.401 (21) | 1.424 (23) |
| C(7) | C(8) | C(9) | 120.47 (2.9) | 1.424 (23) | 1.444 (23) |
| C(8) | C(9) | C(1) | 113.84 (2.5) | 1.444 (23) | 1.374 (21) |
| C(9) | C(1) | C(2) | 126.40 (2.9) | 1.374 (21) | 1.382 (19) |

E. In Five-Membered Ring Fused to Ring C

| Bond angles, deg | | Bond distances, Å | |
|---|---|---|---|
| O(4)–P–O(5) | 92.38 (0.8) | O(4)–C(4) | 1.368 (17) |
| P–O(4)–C(4) | 110.76 (1.4) | O(5)–C(5) | 1.405 (17) |
| O(4)–C(4)–C(5) | 113.78 (2.0) | C(4)–C(5) | 1.377 (19) |
| C(4)–C(5)–O(5) | 109.21 (1.8) | | |
| C(5)–O(5)–P | 112.23 (1.4) | | |
| O(4)–C(4)–C(18) | 124.48 (2.1) | | |
| O(5)–C(5)–C(15) | 125.81 (1.8) | | |

F. In Ring C

| X | Y | Z | <XYZ, deg | D(X–Y), Å | D(Y–Z), Å |
|---|---|---|---|---|---|
| C(4) | C(5) | C(15) | 124.92 (2.9) | 1.377 (19) | 1.361 (21) |
| C(5) | C(15) | C(16) | 115.25 (2.5) | 1.361 (21) | 1.437 (23) |
| C(15) | C(16) | C(17) | 120.21 (2.9) | 1.437 (23) | 1.410 (23) |
| C(16) | C(17) | C(18) | 123.44 (3.1) | 1.410 (23) | 1.399 (23) |
| C(17) | C(18) | C(4) | 114.47 (2.5) | 1.399 (23) | 1.423 (21) |
| C(18) | C(4) | C(5) | 121.67 (2.6) | 1.423 (21) | 1.377 (19) |

and in the hypothetical ideal TP arrangement of the P05 group, namely, formula II,[33,34] Figure 2. This question will be discussed in the next sections.

Table IV
Intramolecular Nonbonded Distances
≤3.5 Å in Compound 9

| | | | |
|---|---|---|---|
| O(2)–O(5) | 2.203 (14) | O(1)–O(3) | 2.536 (14) |
| O(1)–O(4) | 2.208 (13) | O(2)–O(3) | 2.559 (14) |
| O(1)–O(2) | 2.386 (14) | O(3)–O(4) | 2.595 (14) |
| O(4)–O(5) | 2.392 (13) | O(2)–O(4) | 3.228 (13) |
| O(3)–O(5) | 2.450 (14) | O(1)–O(5) | 3.265 (13) |
| C(3)–O(1) | 2.868 (17) | C(1)–O(3) | 3.238 (17) |
| C(3)–O(4) | 3.051 (17) | C(4)–O(3) | 3.236 (17) |
| C(5)–O(3) | 3.202 (17) | C(2)–O(5) | 3.502 (17) |
| C(2)–O(3) | 3.218 (17) | C(4)–O(1) | 3.515 (17) |
| C(14)–O(3) | 2.406 (20) | C(14)–O(1) | 3.038 (20) |
| C(10)–O(3) | 2.404 (21) | | |
| P–C(4) | 2.502 (14) | P–C(3) | 2.632 (14) |
| P–C(2) | 2.506 (14) | P–C(14) | 3.417 (17) |
| P–C(5) | 2.539 (14) | P–C(10) | 3.501 (19) |
| P–C(1) | 2.546 (14) | | |

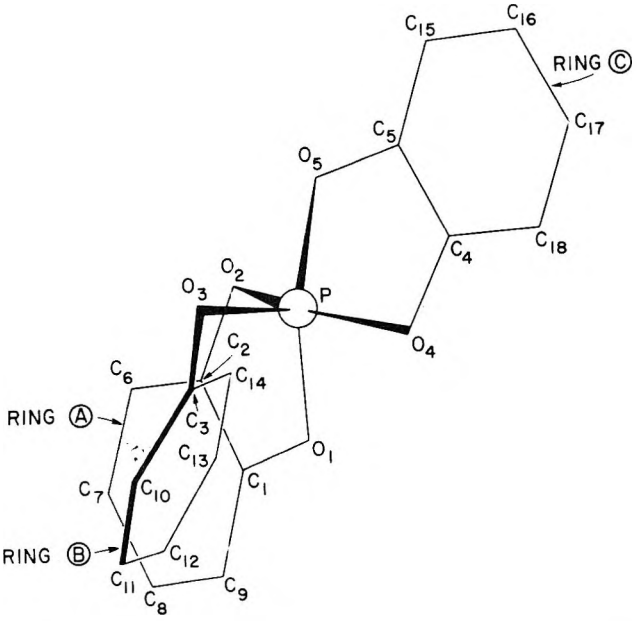



**Figure 1.** Computer-generated drawing of one molecule of spirodicatecholphenoxyphosphorane (**9**), emphasizing the deviations from the ideal skeletal TBP geometry. Best least-squares plane is P, O(2), O(3), O(4).

It is suggested that the skeletal geometry of the molecules of **9** in the crystal resembles that of a *15°-TR configuration.*[13,20,38] The TR mechanism was advanced as a dynamic concept (see Figure 4), but it appears that in certain phosphoranes, including a "homophosphorane" such as **9**, the TR configuration represents the best compromise between the tendency of the phosphorus to become TBP, the strain present in both rings, and the various steric requirements associated with the bond angles, the interatomic distances, and the intramolecular nonbonded distances.

In TR, the five ligands of I ≡ a move as a pair, which is made up of the ligands of catechol C, O(4), O(5), and as a trio, which consists of the exocyclic ligand O(3) plus the ligands of catechol A, O(1), O(2).[35] The diequatorial angle of the trio, O(2)–P–O(3), contracts from 120° to 90° to give b. The pair tilts 9° in the plane P, O(1), O(4), O(5), toward the apical ligand of the trio, O(1), to give c, which is conveniently represented by the Newman projection d. The pair rotates (or twists) against the trio in opposite directions, with the pair-equatorial O(4) moving toward the trio-equatorial O(3) that will remain equatorial in the newly formed TBP.[36] *The ideal 15°-TR configuration is depicted in formula e.* Further rotation leads to the 30°-TR, f, and the

Table V
Least-Squares Planes[a]

A. Deviations from the Planes of All Atoms Included in the Plane Calculation

1. P, O(2), O(3), O(4)
   $0.9601X - 0.2578Y + 0.1080Z = 0.2382$; P, −0.003; O(2), 0.001; O(3), 0.001; O(4), 0.001
2. P, O(1), O(3), O(5)
   $-0.1803X - 0.6852Y + 0.7057Z = 1.4922$; P, 0.006; O(1), −0.003; O(3), −0.001; O(5), −0.003
3. P, O(1), O(2), O(5)
   $0.1164X + 0.5978Y + 0.7931Z = 8.7139$; P, −0.188; O(1), 0.095; O(2), −0.006; O(5), 0.096
4. P, O(1), O(4), O(5)
   $0.1653X + 0.7838Y + 0.5986Z = 8.2901$; P, −0.192; O(1), 0.093; O(4), 0.002; O(5), 0.094
5. O(1), O(2), O(4), O(5)
   $0.1425X + 0.6996Y + 0.7002Z = 8.7355$; O(1), −0.062; O(2), 0.062; O(4), 0.062; O(5), −0.062
6. P, O(1), O(2), C(1), C(2)
   $0.1792X + 0.5700Y + 0.8019Z = 8.5871$; P, −0.087; O(1), 0.084; O(2), 0.079; C(1), −0.042; C(2), 0.035
7. C(1), C(2), C(6), C(7), C(8), C(9)
   $0.1287X + 0.6352Y + 0.7616Z = 8.7661$; C(1), 0.001; C(2), −0.002; C(6), 0.005; C(7), −0.007; C(8), 0.005; C(9), −0.002
8. P, O(4), O(5), C(4), C(5)
   $0.0879X + 0.8220Y + 0.5627Z = 8.0472$; P, −0.075; O(4), 0.066; O(5), 0.071; C(4), −0.027; C(5), −0.036
9. C(4), C(5), C(15), C(16), C(17), C(18)
   $0.1255X + 0.7968Y + 0.5911Z = 8.2530$; C(4), −0.010; C(5), −0.001; C(15), 0.012; C(16), −0.012; C(17), 0.002; C(18), 0.009
10. C(3), C(10), C(11), C(12), C(13), C(14)
    $-0.3570X + 0.3822Y + 0.8523Z = 6.2170$; C(3), 0.009; C(10), −0.006; C(11), 0.006; C(12), 0.002; C(13), 0.001; C(14), 0.006
11. O(3), C(3), C(10), C(14)
    $-0.3573X + 0.3822Y + 0.8522Z = 6.2143$; O(3), 0.011; C(3), 0.011; C(10), −0.004; C(14), −0.004

B. Deviations from the Planes of the Phosphorus Atom That Is Not Included in the Plane Calculation

12. O(2), O(3), O(4)
    Same as plane 1
    P, −0.004
13. O(1), O(3), O(5)
    Same as plane 2
    P, 0.008
14. O(1), O(2), O(5)
    $0.1283X + 0.6453Y + 0.7531Z = 8.769$; P, −0.286
15. O(1), O(4), O(5)
    $0.1559X + 0.7497Y + 0.6432Z = 8.5252$; P, 0.287
16. O(2), O(4), O(5)
    $0.2150X + 0.6763Y + 0.7046Z = 8.768$; P, 0.410
17. O(1), O(2), O(4)
    $0.0693X + 0.7190Y + 0.6915Z = 8.775$; P, −0.411
18. O(1), O(2), O(3)
    $0.5022X - 0.2224Y + 0.8357Z = 4.372$; P, 0.784
19. O(3), O(4), O(5)
    $-0.3699X + 0.9168Y - 0.1508Z = 2.303$; P, 0.787
20. O(1), O(3), O(4)
    $0.7617X + 0.6474Y = 0.0284Z = 2.783$; P, 0.816
21. O(2), O(3), O(5)
    $-0.6327X + 0.0757Y + 0.7707Z = 4.433$; P, 0.852
5. O(1), O(2), O(4), O(5)
   $0.1425X + 0.6996Y + 0.7002Z = 8.7355$: P, −0.350

C. Three-Atom Planes for Calculation of Dihedral Angles

22. P, O(3), C(3)
    $0.4292X - 0.6753Y + 0.5998Z = 1.2637$
23. P, O(1), O(2)
    $0.2516X + 0.4551Y + 0.8541Z = 8.3659$
24. P, O(1), O(4)
    $0.3421X + 0.7887Y + 0.5108Z = 7.6400$
25. P, O(2), O(5)
    $-0.0693X + 0.5511Y + 0.8316Z = 8.4295$
26. P, O(4), O(5)
    $0.0170X + 0.8788Y + 0.4769Z = 7.5925$

[a] $X$, $Y$, and $Z$ are in orthogonal coordinates with deviations of the individual atoms from the planes given in Å.

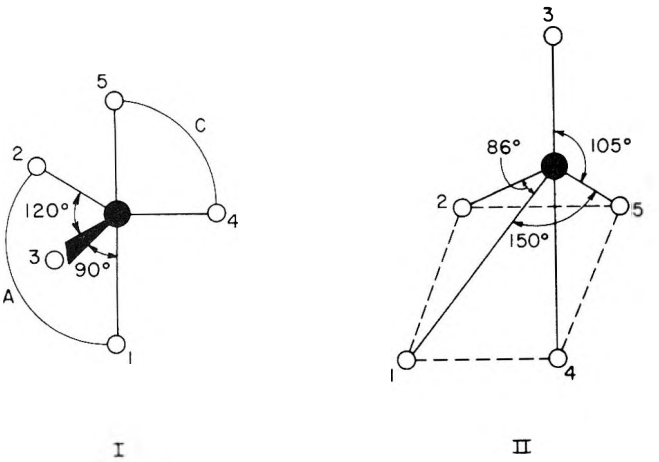
Table VI
Some Dihedral Angles Between Planes[a]

| Plane a | Plane b | Angle, deg | Plane a | Plane b | Angle, deg |
|---|---|---|---|---|---|
| 1 | 2 | 85 | 19 | 1 | 53 |
| 1 | 3 | 88 | 18 | 5 | 60 |
| 1 | 4 | 89 | 21 | 5 | 60 |
| 2 | 3 | 83 | 19 | 5 | 61 |
| 2 | 4 | 82 | 20 | 5 | 57 |
| 3 | 4 | 16 | 18 | 17 | 63 |
| 2 | 5 | 88 | 18 | 20 | 78 |
| 1 | 5 | 89 | 17 | 20 | 60 |
| 6 | 8 | 21 | 21 | 16 | 63 |
| 8 | 24 | 15 | 21 | 19 | 79 |
| 6 | 25 | 14 | 16 | 19 | 64 |
| 11 | 22 | 84 | 18 | 21 | 72 |
| 1 | 22 | 49 | 18 | 19 | 59 |
| 2 | 22 | 36 | 18 | 20 | 78 |
| 6 | 7 | 5 | 20 | 19 | 72 |
| 8 | 9 | 3 | 17 | 16 | 9 |
| 7 | 17 | 7 | 21 | 19 | 79 |
| 9 | 17 | 8 | 21 | 20 | 63 |
| 7 | 8 | 3 | 19 | 20 | 72 |
| 9 | 4 | 2 | 14 | 15 | 9 |
| 7 | 1 | 88 | 23 | 26 | 36 |
| 9 | 1 | 89 | 24 | 25 | 33 |
| 18 | 1 | 51 | 23 | 5 | 18 |
| 17 | 1 | 87 | 23 | 5 | 17 |
| 20 | 1 | 56 | 26 | 5 | 18 |
| 21 | 1 | 57 | 24 | 5 | 17 |
| 16 | 1 | 84 | | | |

[a] The planes are defined in Table V. The dihedral angles, $\theta$, are expressed as $\leq 90°$. To visualize these angles in terms of Figures 1–5, use $\theta$ or $180° - \theta$.

60°-TR, g ≡ h, configurations. From i a tilt of the pair, O(5), O(4), away from O(2), and an expansion of angle O(1)–P–O(3) from 90° to 120° generates the new TBP isomer (j). It is recognized that the configuration of the molecules of **9** in solution need not be like that in the crystal, but the absence of strongly polar groups suggests that the differences may not be very significant. If so, compound **9** in solution can undergo facile permutational isomerization from a 15°-TR to a 45°-TR simply by going over a barrier that resembles the 30°-TR (f in Figure 4) and is not much higher in energy than the ground state configuration.

**Molecular Parameters of Compound 9 in Relation to the TBP, TP, and TR Skeletal Geometries. A. Bond Distances.** The virtual identity of the four endocyclic P–O bond lengths in **9** contrasts with the difference between the




I II

**Figure 2.** The five oxygen ligands of compound **9** with hypothetical ideal skeletal geometries: I = TBP; II = TP.

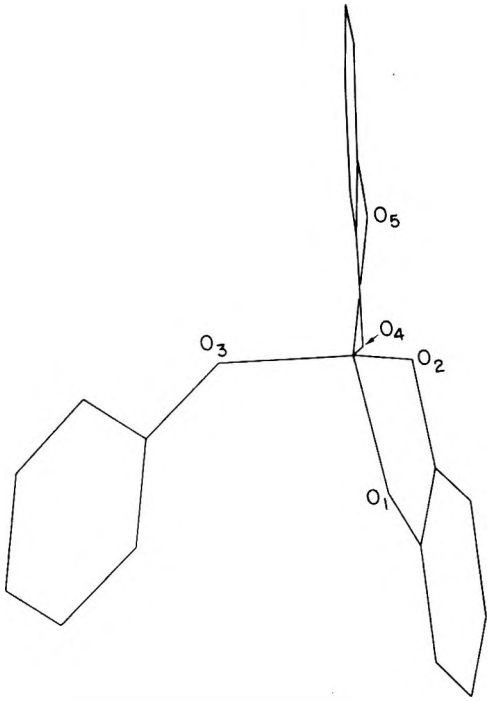



**Figure 3.** Computer-generated drawing of the molecule of **9** emphasizing the deviations from the ideal skeletal TP geometry. Note the twisted spirobicyclic system.

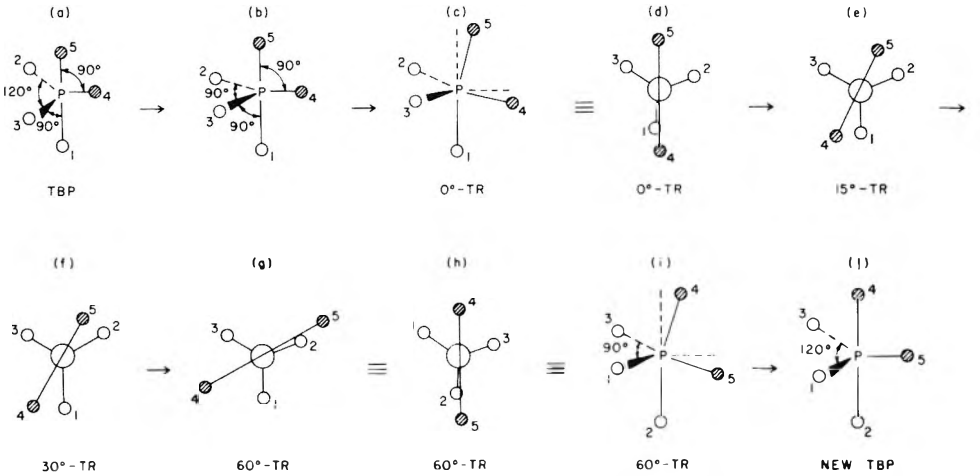



**Figure 4.** Permutational isomerization of an oxyphosphorane with ideal TBP skeletal symmetry by the turnstile rotation (TR). Ligand pair = O(4), O(5). Ligand trio = O(1), O(2), O(3).

Table VII
Deviations from Ideal Skeletal Symmetries in Compound 9
A. From Trigonal Bipyramid (TBP)

| Bond angle | Deviation from TBP | Bond angle | Deviation from TBP |
|---|---|---|---|
| O(2)–P–O(3) | −16.7° (from 120°) | O(2)–P–O(4) | +31.4° (from 120°) |
| O(1)–P–O(5) | −20.0° (from 180°) | O(1)–P–O(3) | +12.0° (from 90°) |
| O(4)–P–O(5) | +2.4° (from 90°) | O(3)–P–O(5) | +8.0° (from 90°) |
| O(1)–P–O(4) | −7.0° (from 90°) | O(2)–P–O(5) | −6.7° (from 90°) |
| O(3)–P–O(4) | −14.6° (from 120°) | O(1)–P–O(2) | +1.5° (from 90°) |

B. From Tetragonal Pyramid (TP)

| Bond angle | Deviation from TP | Bond angle | Deviation from TP |
|---|---|---|---|
| O(1)–P–O(5) | +10° (from 150°) | O(3)–P–O(4) | +0.4° (from 105°) |
| O(2)–P–O(4) | +1.5° (from 150°) | O(1)–P–O(4) | −3.0° (from 86°) |
| O(3)–P–O(5) | −7.0° (from 105°) | O(2)–P–O(5) | −2.8° (from 86°) |
| O(1)–P–O(3) | −3.0° (from 105°) | O(1)–P–O(2) | +5.5° (from 86°) |
| O(2)–P–O(3) | −1.7° (from 105°) | O(4)–P–O(5) | +6.4° (from 86°) |

apical and equatorial endocyclic P–O bond lengths in 2.[5] The exocyclic P–O(3) bond in **9** is relatively short; this suggests that the catechol rings are competitors for the electrons of the oxygen atoms which can contribute to p–d $\pi$ bonding in the P–O bonds. On the other hand, the corresponding oxygen electrons of the phenoxy ligand are more available for $\pi$ bonding to phosphorus, which causes the relative shortening of that P–O bond.

**B. Bond Angles.** The O–P–O angles fall in three categories: two angles are relatively large, four are intermediate in value, and four are relatively small. The data are consistent with the TR or TP geometries, but not with the TBP configuration; see Table VII. Angle O(2)–P–O(3) is the "diequatorial angle of the trio" in the TR mechanism (Figure 4). In this interpretation angle O(2)–P–O(4) has expanded +31° from the TBP 120° as a result of the motion of O(4) toward O(3). Among the deviations from TP note the expansion of O((1)–P–O(5) and the contraction of O(3)–P–O(5).

The two endocyclic angles, O(1)–P–O(2) and O(4)–P–O(5), are quite small and suggestive of the overall ring strain associated with the spiropentaoxyphosphorane system.

**C. Intramolecular Nonbonded Distances.** As shown in Table IV, the O–O distances are consistent with TR or TP configurations, but not with TBP geometry.

The O–O and C–O distances disclose considerable intramolecular crowding. The placement of the phenoxy ring may be related to this feature. The estimated[37] half-thickness of the aromatic ring is 1.85 Å, and the maximum separations between O(3) and other oxygens are O(2)–O(3) = 2.56 Å and O(3)–O(4) = 2.59 Å. Models show that, in fact, ring B occupies the most favorable position to avoid interferences between ring B and the catechol rings A and C. Note also the relatively short distances C(3)–O(1) and C(14)–O(1) (the latter compared to C(10)–O(1) = 3.87 Å).

**D. Least-Squares Planes and Dihedral Angles Between Them.** The planarity of the catechol ring systems, A and C, is evident in planes 6–9 (Table V). Ring B is planar (plane 10) and O(3) is on that plane (plane 11). The dihedral angles formed by planes 11 and 22, and by planes 1 and 22, reveal the position of ring B.

In the regular TBP the phosphorus should be in these planes: O(2), O(3), O(4); O(1), O(2), O(5); O(1), O(3), O(5); O(1), O(4), O(5). In compound **9** this is true only for the first two planes (1 and 2 in Table V). Both TR and TP geometries can accommodate these observations. Planes 1 and 2 are nearly, but not exactly, orthogonal (Table VI).

Four oxygens define a fairly good plane (5 in Table V) as would be expected of a TP (II, Figure 2). However, note that O(1), O(5) are on one side of the plane, while O(2), O(4), are on the opposite side; these pairs would be transdibasal in the regular TP. The P is 0.350 Å from plane 5 and on the same side as O(1), O(5). These deviations from regular TP can, in fact, be seen in Figure 3. One can imagine that O(1) and O(5) have been lifted from the basal plane of the TP, toward the phosphorus. The net effect is a twist of one catechol A against the other, C.

The dihedral angle between planes 8 and 24 (Table V) is 15° (Table VI). This angles is the basis for assigning the 15°-TR configuration to the skeletal geometry of compound **9**.

Other deviations from ideal TBP and TP geometry are revealed by the positions of the phosphorus atom with respect to several three-oxygen planes (Table V), and by a number of dihedral angles given in Table VI.

It seems clear that spirobicyclic phosphoranes, not only those which have different kinds of ligands bonded to the phosphorus,[14–18] such as **10**, **11**, **12**, and **13**, but also those of the pentaoxyphosphorane type, **9**, depart drastically from the skeletal geometry of the TBP. However, whether these departures should be described in terms of "hybrids" between TP and TBP[17] or in terms of TR configurations is debatable. The fact is that a number of known phosphoranes are ideal or nearly ideal TBP, while none is an ideal or nearly ideal TP. Hence, the simplest thing is to express the deviations from ideal TBP in terms of the same type of skeletal geometry, such as the TR configuration,[38] which can accommodate all the data. With this approach, the x-ray data for a new structure can be easily sorted out. First, the ligands are placed on an ideal TBP skeleton according to the assumptions and rules of the oxyphosphorane concept, e.g., apicophilicities, placement of four-, five- and six-membered rings in appropriate skeletal positions of the ideal TBP, etc.[7,13,20] Then, the motions of the atoms on the TR mechanism are applied to the ideal TBP molecule as defined in Figure 4. Finally, the actual molecular parameters are compared with the expectations based on this treatment and the soundness of the original choice of pair–trio combination is assessed by the correspondence between the expected and the observed parameters.

**Acknowledgment.** We are grateful to Drs. H. J. Bernstein and L. Andrews of Brookhaven National Laboratories, Upton, N.Y., for their advice in the production of Figures 1, 3. The TR concept which guided us in the interpretation of the experimental data stems from an extended collaboration between one of us (F.R.) and Professor I. Ugi and Dr. D. Marquarding of Technische Universität, München.

**Registry No.**—**9**, 19579-02-3.

**Supplementary Material Available.** Table II (26 pages). Ordering information is given on any current masthead page.

## References and Notes


(1) (a) Send correspondence to this author at the Department of Biochemistry, State University of New York at Stony Brook. (b) Department of Chemistry, State University of New York. The support of this research by the National Science Foundation Grant GP-40523 is gratefully acknowledged.
(2) F. Ramirez, *Acc. Chem. Res.*, **1**, 168 (1968).
(3) F. Ramirez, *Synthesis*, 90 (1974).
(4) The following abbreviations will be used: TBP = trigonal bipyramid or trigonal bipyramidal; TP = tetragonal pyramid or tetragonal pyramidal; TR = turnstile rotation.
(5) (a) W. C. Hamilton, S. J. LaPlaca, and F. Ramirez, *J. Am. Chem. Soc.*, **87**, 127 (1965); (b) W. C. Hamilton, S. J. LaPlaca, F. Ramirez, and C. P. Smith, *ibid.*, **89**, 2268 (1967).
(6) (a) F. Ramirez, M. Nagabhushanam, and C. P. Smith, *Tetrahedron*, **24**, 1785 (1968); (b) F. Ramirez, A. J. Bigler, and C. P. Smith, *ibid.*, **24**, 5041 (1968).
(7) F. Ramirez, *Bull. Soc. Chim. Fr.*, 3491 (1970).
(8) K. W. Shen, W. E. McEwen, S. J. LaPlaca, W. C. Hamilton, and A. P. Wolf, *J. Am. Chem. Soc.*, **90**, 1718 (1968).
(9) F. Ramirez, I. Ugi, S. Pfohl, E. A. Tsolis, J. F. Pilot, C. P. Smith, P. Gillespie, P. Hoffmann, and D. Marquarding, *Phosphorus*, **1**, 1 (1971).
(10) F. Ramirez, I. Ugi, F. Lin, S. Pfohl, P. Hoffmann, and D. Marquarding, *Tetrahedron*, **30**, 371 (1974).
(11) W. C. Hamilton, J. S. Ricci, Jr., F. Ramirez, L. Kramer, and P. Stern, *J. Am. Chem. Soc.*, **95**, 6335 (1973).
(12) H. L. Carrell, H. M. Berman, J. S. Ricci, Jr., W. C. Hamilton, F. Ramirez, J. F. Marecek, L. Kramer, and I. Ugi, *J. Am. Chem. Soc.*, **97**, 38 (1975).
(13) (a) P. Gillespie, P. Hoffmann, H. Klusacek, D. Marquarding, S. Pfohl, F. Ramirez, E. A. Tsolis, and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, **10**, 687 (1971); (b) F. Ramirez and I. Ugi, *Adv. Phys. Org. Chem.*, **9**, 256 (1971).
(14) (a) H. Wunderlich, D. Mootz, R. Schmutzler, and M. Wieber, *Z. Naturforsch. B*, **29**, 32 (1974); (b) H. Wunderlich and D. Mootz, *Acta Crystallogr., Sect. B*, **30**, 935 (1974); (c) H. Wunderlich, *ibid.*, **30**, 939 (1974).
(15) M. Eisenhut, R. Schmutzler, and W. S. Sheldrick, *J. Chem. Soc., Chem. Commun.*, 144 (1973).
(16) E. Duff, D. R. Russell, and S. Trippett, *Phosphorus*, **4**, 203 (1974).
(17) (a) R. R. Holmes, *J. Am. Chem. Soc.*, **96**, 4143 (1974); (b) *Acc. Chem. Res.*, **5**, 296 (1972).
(18) J. A. Howard, D. R. Russell, and S. Trippett, *J. Chem. Soc., Chem. Commun.*, 856 (1973).
(19) M. Ul-Haque, C. N. Caughlan, F. Ramirez, J. F. Pilot, and C. P. Smith, *J. Am. Chem. Soc.*, **93**, 5229 (1971).
(20) F. Ramirez and I. Ugi, *Bull. Soc. Chim. Fr.*, 453 (1974).
(21) P. J. Wheatley, *J. Chem. Soc.*, 2206 (1964).
(22) H. Hess and D. Frost, *Z. Anorg. Allg. Chem.*, **342**, 240 (1966).
(23) L. G. Hoard and R. A. Jacobson, *J. Chem. Soc. A*, 1203 (1966).
(24) J. W. Cox and E. R. Corey, *Chem. Commun.*, 123 (1967).
(25) G. Chioccola and J. J. Daly, *J. Chem. Soc. A*, 568 (1968).
(26) A. Almenningen, B. Anderson, and E. E. Artrup, *Acta Chem. Scand.*, **23**, 2179 (1969).
(27) D. D. Swank, C. N. Caughlan, F. Ramirez, and J. F. Pilot, *J. Am. Chem. Soc.*, **93**, 5236 (1971).
(28) M. J. C. Hewson, R. Schmutzler, and W. S. Sheldrick, *J. Chem. Soc., Chem. Commun.*, 190 (1973).
(29) A. C. T. North, D. C. Phillips, and F. S. Mathews, *Acta Crystallogr., Sect. A*, **24**, 351 (1968).
(30) G. A. Sim, *Acta Crystallogr.*, **13**, 511 (1960).
(31) D. E. Pilling, D. W. J. Cruickshank, A. Bujosa, F. M. Lovell, and M. R. Truter in "Computing Methods and the Phase Problem in X-Ray Crystal Analysis", Pergamon Press, Oxford, 1961, p 32.
(32) The value of 1.76 Å has been given for the pure single P–O bond: D. W. Cruickshank, *J. Chem. Soc.*, 5486 (1961).
(33) TBP formula I (Figure 2) becomes TP formula II as a result of a 30° contraction of angle O(1)–P–O(5) *in the plane P, O(1), O(3), O(5)*, and a 30° expansion of angle O(2)–P–O(4) *in the plane P, O(2), O(3), O(4)*; these two planes are orthogonal at all stages of the motions. These motions form part of the Berry pseudorotation mechanism to explain the permutational isomerization of phosphoranes having regular or slightly distorted TBP geometry (cf. ref 34).
(34) R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960).
(35) The choice of ligands O(1), O(2) of catechol A as the pair, and of ligand O(3) plus ligands O(4), O(5) of catechol C as the trio, provides an alternate and nearly equivalent TR mechanism for compound **9**. To visualize this alternative rotate formula a, Figure 4, 180° about bond P–O(3), and carry out a set of motions analogous to those depicted in Figure 4, using the appropriate ligands. The TR mechanisms of **9** using O(1), O(2) or O(4), O(5) as the pair generate configurations which are indistinguishable within the uncertainty in the data of Tables III–VII.
(36) To retain the apical-equatorial placement of the five-membered rings in the ideal TBP, O(4) must move toward O(3).
(37) L. Pauling, "The Nature of the Chemical Bond", 2nd ed, Cornell University Press, Ithaca, N.Y., 1948, p 189.
(38) NOTE ADDED IN PROOF. The term "static TR configuration" is a convenient designation for those phosphoranes which clearly do not resemble a TBP about the phosphorus atom. As originally conceived (ref 13), "TR configuration" had the dynamic connotation defined in Figure 4; however, this concept now seems more general and capable of providing an adequate description of the molecular geometry of certain complex phosphoranes. X-Ray analyses carried out since the submisssion of this paper have uncovered other examples of 5,5-spirobicyclic homophosphoranes (five oxygen ligands), and 5-monocyclic heterophosphoranes (two oxygen and three carbon ligands) whose geometry conform to the definition of static TR configuration.


# Structural Effects on Excited State Production by Dioxetanes. 3,4-Dimethyl-3,4-diphenyldioxetane and 3-Methyl-3-phenyldioxetane

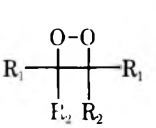

Martha A. Umbreit and Emil H. White*

*Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218*

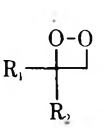

*Received August 12, 1975*


The preparation of 3,4-dimethyl-3,4-diphenyldioxetane (**1c**) is reported. Its activation energy for decomposition is 25 ± 1 kcal/mol, and its activation entropy is −3 ± 3 eu. The efficiency of excited triplet ketone production of **1c** is equal to that of tetramethyldioxetane (**1a**) as determined by direct comparison of dioxetane-induced dibromoanthracene emission. The efficiency of 3-methyl-3-phenyldioxetane (**2c**), determined by the same method, is less than one-third that of **1a**.


Excited triplet carbonyl products are efficiently generated in the thermal cleavage of 1,2-dioxetanes in apparent violation of spin-conservation rules.[1,2] Large differences have been observed in the yields of triplet products (in effect, the percentage of carbonyl products formed in the triplet state) from various dioxetanes,[1,3] although no explanations for this have been advanced. The efficiencies range from 30–50% for tetramethyldioxetane (**1a**) (100% corresponds to one triplet carbonyl per dioxetane[4])[1b] to 2–4% for 3,4-dimethyl-3,4-di-*n*-butyldioxetane (**1b**)[3a,5] and 3,3-dibenzyl- and 3,3-diphenyldioxetanes (**2a**[3b] and **2b**).[3c] In an effort to identify some of the basic structural factors affecting the efficiency of triplet production, we wish to report the efficiences of excited state formation of the dioxetanes **1c** and **2c** relative to **1a**.



**1a**, $R_1 = R_2 = Me$
**b**, $R_1 = Me$; $R_2 = n\text{-Bu}$
**c**, $R_1 = Me$; $R_2 = Ph$
**d**, $R_1 = H$; $R_2 = OEt$



**2a**, $R_1 = R_2 = CH_2Ph$
**b**, $R_1 = R_2 = Ph$
**c**, $R_1 = Me$; $R_2 = Ph$

We have prepared the new dioxetane, 3,4-dimethyl-3,4-diphenyldioxetane (**1c**), via the bromohydroperoxide, by a

Table I
Triplet Yields of 1c and 2c Relative to 1a[a]

| | Temp,[b] °C | $10^4 k$, $sec^{-1}$ [c] | $k(1a)/k$[d] | $I/I(1a)$[e] | $^3\Phi/^3\Phi$ (1a)[f] |
|---|---|---|---|---|---|
| 1c[g] | 71 | 1.76 ± 0.10 | 2.6 ± 0.2 | 0.34 ± 0.02 | 0.98 ± 0.10 |
| | 55 | 0.30 ± 0.04 | 2.6 ± 0.4 | 0.32 ± 0.02 | 0.92 ± 0.15 |
| 2c[h] | 48.5 | 4.49 ± 0.10 | 0.080 ± 0.009 | 4.8 ± 0.3 | 0.29 ± 0.04 |
| | 37 | 1.22 ± 0.05 | 0.070 ± 0.013 | 5.1 ± 0.3 | 0.27 ± 0.06 |

[a] Solvent, xylenes. [b] Corrected internal temperature, ±0.5°. [c] Calculated from the Arrhenius equation, using $E_a$ = 25 ± 1 kcal/mol for 1c and 22.6 ± 0.3 kcal/mol for 2c. Errors show range. [d] Using $k$(1a) calculated from the Arrhenius equation, $E_a$ = 25 ± 1 kcal/mol. Errors propagated as variance, treating ranges as standard deviations. [e] Errors estimated graphically. [f] Errors propagated as variance. [g] c(1c) $2.9 \times 10^{-3}$ M, c(1a) $3.2 \times 10^{-3}$ M, c(DBA) $2 \times 10^{-3}$ to $2 \times 10^{-2}$ M. [h] c(2c) $5.4 \pm 0.3 \times 10^{-3}$ M, c(1a) $4.1 \times 10^{-3}$ M, c(DBA) $1.5 \times 10^{-3}$ to $1.5 \times 10^{-2}$ M.

modification of the procedure developed by Kopecky et al.[6] Both geometric isomers of the dioxetane were observed in solution by NMR, but only the major isomer was obtained crystalline, and was the material studied.[7] Thermolysis of 1c produced only acetophenone by NMR and ir analysis. Its decomposition in toluene or xylenes, followed by the fluorescence decay of added dibromoanthracene (DBA), was first order, with $E_a$ = 25 ± 1 kcal/mol and $\Delta S^{\ddagger}$ = −3 ± 3 eu. (For 1a we observed $E_a$ = 25 ± 1 kcal/mol and $\Delta S^{\ddagger}$ = −1 ± 3 eu; lit.[6a] $E_a$ = 25.8 ± 0.5 kcal/mol, $\Delta S^{\ddagger}$ = −2 ± 2 eu.) Dioxetane 2c was prepared according to literature procedures,[1a,8] and was not isolated from solution. Its decomposition in xylenes was first order, with $E_a$ = 22.6 ± 0.3 kcal/mol and $\Delta S^{\ddagger}$ = −3.4 ± 1 eu (lit.[8] $E_a$ = 22.9 kcal/mol, $\Delta s^{\ddagger}$ = −5.3 ± 0.9 eu).

The efficiency of triplet production by 1c and 2c relative to 1a was obtained by comparing the emission intensity from solutions of the dioxetane and DBA.[9] It has been shown that the fluorescence of DBA in the presence of decomposing dioxetanes is due essentially only to energy transfer from triplet carbonyl species.[9] The intensity is thus described by eq 1

$$I = k[\text{dioxetane}]\,{}^3\Phi\,\Phi_{ET}\,\Phi_F \qquad (1)$$

where $k$ is the rate constant for dioxetane decomposition, $^3\Phi$ is the efficiency of triplet formation, $\Phi_{ET}$ is the efficiency of triplet–singlet energy transfer from the excited carbonyl to DBA, and $\Phi_F$ is the fluorescence quantum yield of DBA. At sufficiently high DBA concentrations, $\Phi_{ET}$ reaches a limiting value of 0.25, which is determined by the competition between triplet–triplet and triplet–singlet energy transfer to DBA, and is assumed to be general for carbonyl compounds.[9] The ratio of intensities from two dioxetane solutions, when extrapolated to infinitely high DBA concentration, is expressed in eq 2.

$$\frac{I_A}{I_B} = \frac{{}^3\Phi_A\, k_A\, [A]}{{}^3\Phi_B\, k_B\, [B]} \qquad (2)$$

The ratio of intensities from dilute xylene solutions of 1c or 2c to 1a were obtained, under identical conditions, over a tenfold range of DBA concentrations and extrapolated graphically to infinite acceptor concentration (intercept of the plot of the intensity ratio vs. the reciprocal of the DBA concentration). Rate constants at the temperatures of the intensity measurements were calculated from the Arrhenius equation, using conveniently measured rate constants and the average $E_a$ determined for each dioxetane. Values of $E_a$ obtained by rapid temperature change experiments[1c,10] agreed with the Arrhenius values within our experimental error, indicating the absence of significant dark decomposition pathways.[11]

The results, which are summarized in Table I, show that 1c was as efficient in triplet formation as 1a [$^3\Phi$(1c)/$^3\Phi$(1a) = 0.98 ± 0.1], while 2c was significantly less efficient [$^3\Phi$(2c)/$^3\Phi$(1a) = 0.29 ± 0.04].[12] The reproducibility of the ratios at different temperatures is consistent with the finding that $^3\Phi$ (for 1a) is temperature independent.[10]

The cleavage products from these dioxetanes, acetone, acetophenone, and formaldehyde, all have lowest energy triplet n,$\pi^*$ states.[13] In aromatic ketones such as acetophenone, however, a small degree of mixing of this state with a higher energy triplet $\pi,\pi^*$ state is believed to occur.[14] The equality of triplet yields from 1c and 1a shows that such perturbations caused by a neighboring phenyl ring do not affect the energy surface crossing in dioxetane decompositions. The greatly reduced efficiency of 2c, which produces acetophenone and formaldehyde, suggests that the large dissymmetry in the dioxetane structure significantly affects excited state production.[15] Consistent with this possibility are the low triplet yields of the geminally disubstituted dioxetanes 2a and 2b.[3b,c] The symmetrical disubstituted *cis*-diethoxydioxetane 1d, in contrast, is almost as efficient as 1a in excited triplet production.[16] Evidently, other factors are also involved in determining the yield of excited states. The symmetrical 1b, for example, is relatively inefficient in triplet formation,[3a] while trimethyldioxetane is as efficient as 1a,[9] Clearly, more experimental studies are needed for a full understanding of this unique reaction.

## Experimental Section

*Caution!* Hydroperoxides and dioxetanes are potentially explosive.[6]

Melting points are uncorrected. NMR spectra were recorded on a Varian A-60 or on a JEOL MH-100 spectrometer, with $Me_4Si$ as the internal standard. Reactions in tetrahydrofuran were conducted under nitrogen and the solvent was freshly distilled from sodium benzophenone ketyl. All water which came into contact with dioxetane solutions had stood for several hours over $Na_2EDTA$. Anhydrous $H_2O_2$ solutions were prepared by slowly pouring 84% $H_2O_2$ (FMC Corp.) into ice-cold anhydrous ether or glyme and stirring with $MgSO_4$ at 0° for 8–10 hr.[17] Molarity was determined by iodometric titration. Authentic samples of *dl*- and *meso*-2,3-dibromo-2,3-diphenylbutane[18] and 3,3-diphenyl-2-butanone[19] were prepared by established routes for spectral comparison with side products formed in the reactions leading to 1c.

**Dimethylstilbene (2,3-Diphenyl-2-butene).** Dimethylstilbene was prepared by reductive coupling of acetophenone using either a reduced tungsten[20] or a reduced titanium reagent.[21] To 300 ml of THF cooled to −70° was added 45.4 g (0.114 mol) of $WCl_6$ (Pressure Chemical Co.), followed by 116 ml (0.232 mol) of 1.97 *M* *n*-BuLi (Alfa). The vigorously stirred mixture was allowed to reach room temperature and 9 g (0.075 mol) of acetophenone (Amend, distilled) was added. The reaction mixture was stirred at reflux for 4 days, then cooled and poured into an aqueous alkaline tartrate solution and extracted with hexanes. The dried ($MgSO_4$) organic phase was concentrated and the oily product chromatographed on silica gel to give 6 g (78%) of a mixture of roughly equal amounts of *cis*- and *trans*-dimethylstilbene. Fractional recrystallization from methanol gave samples of, first, *trans*-dimethylstilbene, white needles or prisms, mp 94–100° (lit.[22] 105°), NMR ($CCl_4$) δ 1.88 (s, 6 H), 7.22 (s, 10 H), and then of *cis*-dimethylstilbene, white granular crystals, mp 53–63° (lit.[22] 66°), NMR ($CCl_4$) δ 2.16 (s, 6 H), 6.96 (m, 9.4 H). Alternatively, to 200 ml of THF at −70° was added 20 g (0.13 mol) of $TiCl_3$ (Alfa) and 2.6 g (0.068 mol) of $LiAlH_4$ (Alfa). The stirred mixture was allowed to warm to room temperature, and 7.4 g (0.062 mol) of acetophenone was added. The reaction mixture was stirred at reflux for 5.5 hr, and then at ambient temperature for ≈12 hr. Work-up as above gave 7 g of products, which was found by NMR to consist of 45% dimethylstilbene diol ($CCl_4$ δ

1.42, $CH_3$), 20% *trans*-, and 35% *cis*-dimethylstilbene. The olefins were separated from the diol by recrystallization from methanol.

**3-Bromo-2,3-diphenyl-2-butyl Hydroperoxide.** Modifications of solvent, reaction time at low temperature, and $H_2O_2$ concentration were introduced into the literature procedure for bromohydroperoxidation.[6b] A mixture of dimethylstilbene isomers (1.08 g, 5.2 mmol; cis:trans ≈ 3:1) was dissolved in 12 ml of THF under nitrogen. The solution was cooled to −40° and 7 ml of a 7.8 *M* solution of $H_2O_2$ in anhydrous glyme (55 mmol) was added by pipet. While the solution was stirred at −40°, 0.8 g (2.8 mmol) of 1,3-dibromo-5,5-dimethylhydantoin (Matheson Coleman and Bell) was added in small portions over 1.5–2 hr. The solution, now pale yellow, was allowed to reach −20°, and stirred at that temperature for 5 hr. The reaction flask was stoppered and placed in a freezer (−20°) for ≈12 hr. The mixture was poured into 50 ml of ice-cold water and extracted with ether. The aqueous phase was extracted again with ether, and the combined organic phases were washed with two 50-ml portions of cold water, followed by cold saturated brine, and dried over $Na_2SO_4$. An NMR of the reaction mixture in benzene showed the isomeric bromohydroperoxides[23] (δ 1.81, 2.11, threo, 44%; 1.88, 2.05, erythro, 6%), the isomeric dibromides (δ 2.45, *dl*, 22%; δ 2.29, meso, 2%), a product believed to be the allylic bromide (δ 1.79, 4.03, 13%), and *trans*-dimethylstilbene (δ 1.92, 14%). The concentrated reaction mixture was applied to a 2.5 × 10 cm silica gel column prepared in hexanes (room temperature). Elution with hexanes removed the unreacted olefin. Ten percent ether in hexanes eluted the bromohydroperoxides, NMR (benzene) δ 1.82 (s), 2.12 (s), threo, 79%; 1.86 (s), 2.05 (s), erythro, 10%. Small amounts of acetophenone (δ 2.1) and of 3,3-diphenyl-2-butanone (δ 1.71, 1.82) were present. A similar product mixture resulted when pure *cis*-dimethylstilbene was used, including the formation of *trans*-dimethylstilbene. Pure *trans*-dimethylstilbene gave analogous yields, but the erythro bromohydroperoxide predominated over the threo 4:1.

**3,4-Dimethyl-3,4-diphenyldioxetane (1c).** A solution of approximately 0.8 mmol of 3-bromo-2,3-diphenyl-2-butyl hydroperoxide (erythro:threo 4:1) in 6 ml of benzene was cooled to 7°. To the stirred solution was added 35 mg (0.21 mmol) of silver acetate (J. T. Baker, purified powder). After 6 min the suspension was filtered. The orange filtrate was washed with ice-cold water, extracted with ether, and dried ($Na_2SO_4$). The NMR spectrum ($CCl_4$) showed 3,3-diphenyl-2-butanone (δ 1.79, 2.02, 7.25, 60%), **1c** (δ 1.98, 7.06, 16%), acetophenone (δ 2.50, 7.4, 7.9, 13%), and six signals due to minor impurities (10%). The reaction mixture in a small volume of benzene was applied to a silica gel column (12 g of Grace silica gel mixed with 200 mg of $Na_2EDTA$) made up in hexanes and chilled to 5° with an ice–water jacket. Rapid elution with 10% $CH_2Cl_2$ in hexanes recovered the dioxetane in the second 100 ml of eluent, NMR ($CCl_4$) δ 1.99 (s, 6.0 H), 7.07 (broad s, 9.5 H), major isomer, 84%; 1.45 (s, 6.0 H), 7.42 (broad s, 10.0 H), minor isomer, 16%. The estimated total yield of pure dioxetanes, based on the NMR signal intensity, was 10%. Starting with a solution of 8:1 threo:erythro bromohydroperoxide resulted in analogous yields, except that the dioxetane isomer ratio was 2:1, with the same isomer predominating. Crystallization from 2–3 ml of cold pentane in either case gave tiny off-white needles of the isomer, mp 85–91° (oil bath preheated to 70°), NMR ($CCl_4$) δ 1.99 (s, 6 H), 7.06 (s, 10 H). No other signals were present in the NMR spectrum. Refluxing either this isomer or the isomer mixture in $CCl_4$ for several hours produced only acetophenone by NMR and ir analysis.

**1-Bromo-2-phenyl-2-propyl Hydroperoxide.**[1a,8] To 2.4 g (20 mmol) of α-methylstyrene (City Chemical Corp.) in 40 ml of anhydrous ether, chilled to −40°, was added 20 ml (130 mmol) of a solution of 6.5 *M* $H_2O_2$ in anhydrous ether, followed by 3.0 g (10 mmol) of 1,3-dibromo-5,5-dimethylhydantoin (added slowly over 1 hr). The stirred solution was allowed to warm to room temperature over 1 hr, and then was poured into 75 ml of cold saturated $NaHCO_3$ solution. The ether phase was washed with three more portions of cold water and dried over $Na_2SO_4$ in a freezer. The NMR spectrum ($CCl_4$) showed 65% of the desired product, and at least 15% of unreacted olefin. The reaction mixture was chromatographed, at room temperature, on a silica gel column prepared in cyclohexane. Cyclohexane elution removed the olefin, and 1:1 ether–cyclohexane recovered the bromohydroperoxide, NMR ($CCl_4$) δ 1.6 (s, 3.1 H), 3.7 (s, 1.9 H), 7.24 (m, 5.0 H), 7.6 (s, 1.0 H, –OOH) [lit.[1a] δ 1.64 (s, 3 H), 3.76 (s, 2 H), 7.35 (m, 5 H)].

**3-Methyl-3-phenyldioxetane (2c).**[1a,8] To 10 ml of a methanol solution containing 1 g of NaOH and 20 mg of $Na_2EDTA$ and cooled to −20° was added, dropwise, a methanol–ether suspension of 1-bromo-2-phenyl-2-propyl hydroperoxide (≈3 mmol). The mixture was stirred at −20 to −10° for 50 min, and then poured into 50 ml of cold water and extracted with 50 ml of $CCl_4$ in several portions. The combined organic phases were washed with several portions of cold water and dried over $Na_2SO_4$ in a freezer. The NMR ($CCl_4$) showed 65–70% of **2c**, δ 1.96 (s, 3 H), 5.1 (s, 2 H), 7.3 (m, 5 H) [lit.[8] δ 1.83 (s, 3.0 H), 5.00 (s, 2.0 H), external $Me_4Si$]. The mixture also contained acetophenone (14%) and unreacted bromohydroperoxide (20%). Efforts to purify the dioxetane by chromatography on silica gel at room temperature resulted in almost complete decomposition. The impure solution of **2c** was used in the studies described, and its concentration was determined by adding toluene as an internal standard and averaging the relative NMR integrations.

**Tetramethyldioxetane (1a).** Tetramethyldioxetane was prepared closely following the literature procedure.[6a] The long yellow needles used in these studies were recrystallized twice from pentane and gave only a sharp singlet at δ 1.43 in $CCl_4$ (lit.[6a] 1.51).

**Relative Intensity and Kinetic Measurements.** Stock solutions of dioxetanes and of DBA were prepared in xylenes (Baker). For each intensity measurement 0.20 ml of a dioxetane solution and 0.20 ml of a DBA solution were pipetted into a cylindrical glass vial (solutions were not degassed). This was placed in a brass sleeve and attached to an IP-21 photomultiplier photometer. A stirred oil bath (temperature constant within ±0.5°) was raised to a standard level around the brass sleeve. The recorded intensity leveled in 7–10 min. At the higher temperatures the less stable dioxetanes showed a measurable decay; in these cases the decay curve was linearly extrapolated to initial time. Kinetic measurements were made on identically prepared solutions. The externally measured temperature was correlated with the internal temperature of the solution using a copper–constantan thermocouple coiled in a standard vial containing xylenes and mounted on the photometer apparatus. A plot of the internal vs. the oil bath temperature was used to convert the measured temperatures to the actual temperatures of the dioxetane–DBA solutions.

**Acknowledgment.** We thank the U.S. Public Health Service (Grant GM 19488) for its financial support.

**Registry No.**—*cis*-**1c**, 57274-08-5; *trans*-**1c**, 57274-09-6; **2c**, 35322-45-3; acetophenone, 98-86-2; *trans*-dimethylstilbene, 782-06-9; *cis*-dimethylstilbene, 782-05-8; 1,3-dibromo-5,5-dimethylhydantoin, 77-48-5; *threo*-3-bromo-2,3-diphenyl-2-butyl hydroperoxide, 57274-10-9; *erythro*-3-bromo-2,3-diphenyl-2-butyl hydroperoxide, 57288-84-3; 3,3-diphenyl-2-butanone, 2575-20-4; 1-bromo-2-phenyl-2-propyl hydroperoxide, 35295-64-8; α-methylstyrene, 98-83-9.

## References and Notes

(1) (a) E. H. White, P. D. Wildes, J. Wiecko, H. Doshan, and C. C. Wei, *J. Am. Chem. Soc.*, **95**, 7050 (1973); (b) N. J. Turro and P. Lechtken, *ibid.*, **94**, 2886 (1972); (c) T. Wilson and A. P. Schaap, *ibid.*, **93**, 4126 (1971).

(2) (a) N. J. Turro and P. Lechtken, *J. Am. Chem. Soc.*, **95**, 264 (1973); (b) N. J. Turro and A. Devaquet, *ibid.*, **97**, 3859 (1975); (c) W. H. Richardson, F. C. Montgomery, M. B. Yelvington, and H. E. O'Neal, *ibid.*, **96**, 7525 (1974); (d) M. J. S. Dewar and S. Kirschner, *ibid.*, **96**, 7578 (1974); (e) D. R. Kearns, *ibid.*, **91**, 6554 (1969).

(3) (a) C. S. Foote and T. R. Darling, *J. Am. Chem. Soc.*, **96**, 1625 (1974). (b) W. H. Richardson, M. B. Yelvington, and H. E. O'Neal, *ibid.*, **94**, 9277 (1972). The yield of triplet dibenzylketone was found to be about 3%. No experimental information on the state of formaldehyde was given. (c) W. H. Richardson, F. C. Montgomery, M. B. Yelvington, and C. Ranney, *ibid.*, **96**, 4045 (1974). (d) H. E. Zimmerman and G. E. Keck, *ibid.*, **97**, 3527 (1975).

(4) H. E. O'Neal and W. H. Richardson, *J. Am. Chem. Soc.*, **92**, 6553 (1970).

(5) **1b** produced a 5% yield of excited singlet ketone, in marked contrast to the low excited singlet yield (ca. 0.1%) of **1a** (ref 1b).

(6) (a) K. R. Kopecky, J. E. Filby, C. Mumford, P. A. Lockwood, and J. Y. Ding, *Can. J. Chem.*, **53**, 1103 (1975); (b) K. R. Kopecky, J. H. van de Sande, and C. Mumford, *ibid.*, **46**, 25 (1968).

(7) The major isomer of **1c** exhibited a downfield methyl proton shift and an upfield aryl proton shift relative to the minor isomer in the NMR spectrum ($CCl_4$). The *cis*-dimethylstilbene epoxide (prepared by the reaction of the olefin with *m*-chloroperbenzoic acid) showed similar shifts relative to the trans epoxide, suggesting that the cis dioxetane was isolated.

(8) W. H. Richardson, M. B. Yelvington, and H. E. O'Neal, *J. Am. Chem. Soc.*, **94**, 1619 (1972).

(9) N. J. Turro, P. Lechtken, G. Schuster, J. Orell, H. C. Steinmetzer, and W. Adam, *J. Am. Chem. Soc.*, 96, 1627 (1974). A footnote in Table I of this communication indicated the use of "direct comparison" to the emission of **1a** to obtain $^3\Phi$ for several dioxetanes. As in our work, comparable rate constants for acceptor quenching of all triplet carbonyl species was assumed.

(10) N. J. Turro, H. C. Steinmetzer, and A. Yekta, *J. Am. Chem. Soc.*, **96**, 282 (1974).
(11) T. Wilson, M. Landis, A. Baumstark, and P. D. Bartlett, *J. Am. Chem. Soc.*, **95**, 4765 (1973).
(12) We are not able, by this method, to distinguish triplet states produced directly from those produced by rapid intersystem crossing from the excited singlet state.
(13) J. G. Calvert and J. N. Pitts, "Photochemistry", Wiley, New York, N.Y., 1966.
(14) G. S. Hammond and P. J. Wagner, *J. Am. Chem. Soc.*, **88**, 1245 (1966).
(15) It has been postulated (ref 3b) that the energy partitioning in an unsymmetrical dioxetane follows a Boltzmann distribution, perferentially populating the lower triplet energy carbonyl. Available estimates place the triplet energies of both formaldehyde (gas phase, ref 24) and acetophenone (solution, ref 25) at 72.5 kcal/mol. We have not attempted to distinguish between excited acetophenone and excited formaldehyde from **2c**; our method should trap both species, if formed.
(16) T. Wilson, presented at the 19th Annual Meeting of the Biophysical Society, Philadelphia, Pa., Feb 1975.
(17) F. D. Greene and J. Kazan, *J. Org. Chem.*, **28**, 2168 (1963).
(18) Prepared by the reaction of the olefin with pyridinium hydrobromide perbromide: L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 967.
(19) K. Sisido and H. Nozaki, *J. Am. Chem. Soc.*, **70**, 776 (1948).
(20) K. B. Sharpless, M. A. Umbreit, M. T. Nieh, and T. C. Flood, *J. Am. Chem. Soc.*, **94**, 6538 (1972).
(21) J. E. Mc Murry and M. P. Fleming, *J. Am. Chem. Soc.*, **96**, 4708 (1974).
(22) P. S. Skell, W. R. Brasen, S. W. Kantor, and C. R. Hauser, *J. Am. Chem. Soc.*, **79**, 397 (1957).
(23) Stereochemical assignments are made assuming anti addition to the double bond.
(24) G. W. Robinson and V. E. DiGiorgio, *Can. J. Chem.*, **36**, 31 (1958).
(25) P. J. Wagner, I. Kochevar, and A. E. Kemppainen, *J. Am. Chem. Soc.*, **94**, 7489 (1972).

# Organic Reactions of Sulfur Dioxide. II. Reaction with Ortho Esters

Milorad M. Rogić,* Karl P. Klein, James M. Balquist, and Bryce C. Oxenrider

*Chemical Research Center, Allied Chemical Corporation, Morristown, New Jersey 07960*

*Received September 5, 1975*

Ortho esters react with an excess of sulfur dioxide to produce the corresponding esters and dialkyl sulfites. Thus, triethyl orthoacetate gave ethyl acetate and diethyl sulfite, triethyl orthopropionate, and triethyl orthobenzoate produced ethyl propionate, ethyl benzoate, and diethyl sulfite. On the other hand, triethyl orthoformate was less reactive and in addition to ethyl formate and diethyl sulfite also afforded diethyl carbonate. The reaction evidently involves formation of the corresponding dialkoxy carbonium ions and the alkyl sulfite anions, followed by a nucleophilic attack of the latter at the alkyl group of the dialkoxy carbonium ion to give the ester and the dialkyl sulfite.

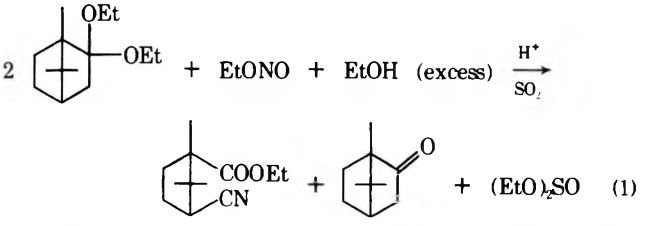
Recently we described the nitrosolysis reaction, a novel single step carbon–carbon bond cleavage of various ketones[1] and ketone acetals[2] effected through nitrosation. In the discussion of the mechanism of the nitrosolysis of cyclohexanone diethyl acetal, it was suggested that the initial cleavage affords the triethyl 6-oximinoorthohexanoate which in the presence of acid underwent dehydration to the ethyl 5-cyanopentanoate. The experimental evidence that this kind of dehydration of aldoximes with ortho esters to the corresponding nitrile is indeed a facile and general reaction was presented earlier.[3]

We wish now to describe a different transformation of an ortho ester intermediate in a particular nitrosolysis reaction, which led to a recognition of a novel and general reaction of ortho esters with sulfur dioxide.

Cyclohexanone enol ethers undergo facile reaction with sulfur dioxide,[4] and there is evidence that sulfur dioxide readily cleaves an alcohol from various ketone acetals.[5] It was recently reported that a reaction of photoexcited sulfur dioxide with trialkyl formates led to the formation of the corresponding "carbenium" ions,[6] but to our knowledge no reaction of ortho esters with unexcited sulfur dioxide was previously described.

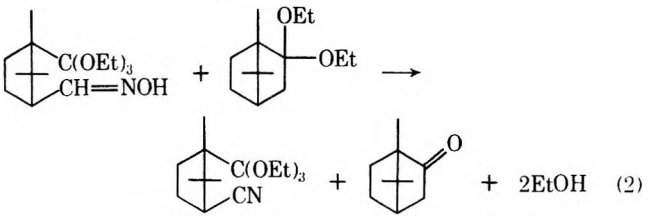
## Results and Discussion

A reaction of camphor diethyl acetal with ethyl nitrite in sulfur dioxide solution containing excess ethanol and a catalytic amount of an acid gave about a 50% yield of the expected 1-carbethoxy-1,2,2-trimethyl-3-cyanocyclopentane. A preliminary experiment indicated that the reaction was unusually slow. Consequently, a Fisher pressure bottle, equipped with a pressure gauge and magnetic stirring bar, was charged with sulfur dioxide, camphor diethyl acetal, a solution of ethyl nitrite in ethanol, and ethanol containing a catalytic amount of dry hydrogen chloride. After the dry ice–acetone bath was removed, the reaction mixture was stirred at room temperature overnight. Unexpectedly, a GLC analysis of an aliquot revealed that in addition to approximately 50% of the expected 1-carbethoxy-1,2,2-trimethyl-3-cyanocyclopentane about 50% of camphor and diethyl sulfite were also present (eq 1).

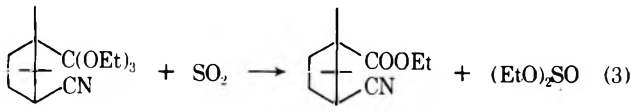



(1)

While camphor diethyl acetal is extremely easily hydrolyzed by water,[7] it was demonstrated that the presence of camphor in the reaction mixture was not a consequence of the hydrolysis of unreacted camphor acetal during the analysis. Neither camphor diethyl acetal–ethanol in sulfur dioxide nor ethyl nitrite–ethanol solution in sulfur dioxide produced any diethyl sulfite. Consequently, it follows that both camphor and diethyl sulfite must be by-products in the nitrosolysis reaction of the camphor acetal itself. Hence, it was postulated that in the nitrosolysis of the acetal, the initially produced ortho ester oxime underwent a fast dehydration reaction with still unreacted camphor diethyl acetal to give the corresponding ortho ester nitrile (eq 2), which in turn reacted with sulfur dioxide to give the




(2)



ester nitrile and diethyl sulfite (eq 3). Indeed, camphor diethyl acetal is a very efficient dehydrating reagent for conversion of aldoximes to nitriles[3] as indicated by almost instantaneous transformations of *n*-heptaldehyde oxime and *n*-butyraldehyde oxime to the corresponding nitriles in sulfur dioxide–ethanol solutions.

We have now established that trialkyl ortho esters do react with sulfur dioxide to give the esters and dialkyl sulfites (eq 4).

$$RC(OR')_3 + SO_2 \longrightarrow RCOOR' + (R'O)_2SO \quad (4)$$

Thus, NMR analysis of a solution of triethyl orthoacetate in liquid sulfur dioxide (sealed in an NMR tube at −70°), after 24 hr at room temperature, indicated practically complete conversion of the ortho ester to a mixture of ethyl acetate and diethyl sulfite. The GLC analysis confirmed this finding and showed that these were the only products in the reaction mixture.

The reaction appeared to be of a general nature as indicated by the similar transformation of triethyl orthopropionate, tri-*n*-propyl orthoacetate, triethyl orthobenzoate, and triethyl orthoformate. However, while the alkyl and aryl ortho esters reacted at room temperature, the triethyl orthoformate, under the same reaction conditions, appeared essentially unchanged. The relative reactivities of these ortho esters after 24 hr at 0° follow: triethyl orthoacetate, 1; triethyl orthopropionate, 1.16; triethyl orthobenzoate, 0.35; and triethyl orthoformate, ~0 (Table I).

The reaction of triethyl orthoformate with sulfur dioxide required more drastic conditions. After heating at 85–90° for *2 weeks*, a 60-MHz NMR analysis of a solution of triethyl orthoformate in an excess of sulfur dioxide indicated that only 45–50% of the orthoformate reacted. However, besides ethyl formate and diethyl sulfite, diethyl carbonate was also formed.[8]

When an equimolar mixture of tri-*n*-propyl orthoacetate and triethyl orthopropionate was treated with a catalytic amount of sulfur dioxide, a 60-MHz spectrum taken immediately after mixing suggested that a very fast alkoxy exchange had taken place. The GLC analysis indicated that in addition to the two starting ortho esters, tri-*n*-propyl orthopropionate, triethyl orthoacetate, *n*-propyldiethyl orthopropionate, di-*n*-propylethyl orthopropionate, *n*-propyldiethyl orthoacetate, and di-*n*-propylethyl orthoacetate were also present in the reaction mixture.[9] A reaction of the *trans*-4-*tert*-butylcyclohexyldiethyl orthoacetate with excess sulfur dioxide afforded a mixture of the *trans*-4-*tert*-butylcyclohexylethyl sulfite and *trans*-4-*tert*-butylcyclohexyl acetate with the configuration at the $C_1$ of the cyclohexane ring unchanged.

The following known facts are pertinent to the mechanism of reaction of sulfur dioxide with ortho esters. It is well established that sulfur dioxide readily enters in an equilibrium with alcohols[10] (eq 5), and causes racemization

$$ROH + SO_2 \rightleftharpoons ROSO_2H \quad (5)$$

of optically active α-phenylethyl alcohol[11] and 1-phenylethyl chloride.[12] The latter reaction apparently does not involve intermediate formation of styrene.[13] On the other hand, sulfur dioxide readily eliminates an alcohol from certain ketone acetals.[5] From the racemization studies with α-phenylethyl alcohol, Tokura and Akigama concluded that the reaction with sulfur dioxide probably involved

Table I
Reaction of Various Ortho Esters with Sulfur Dioxide[a]

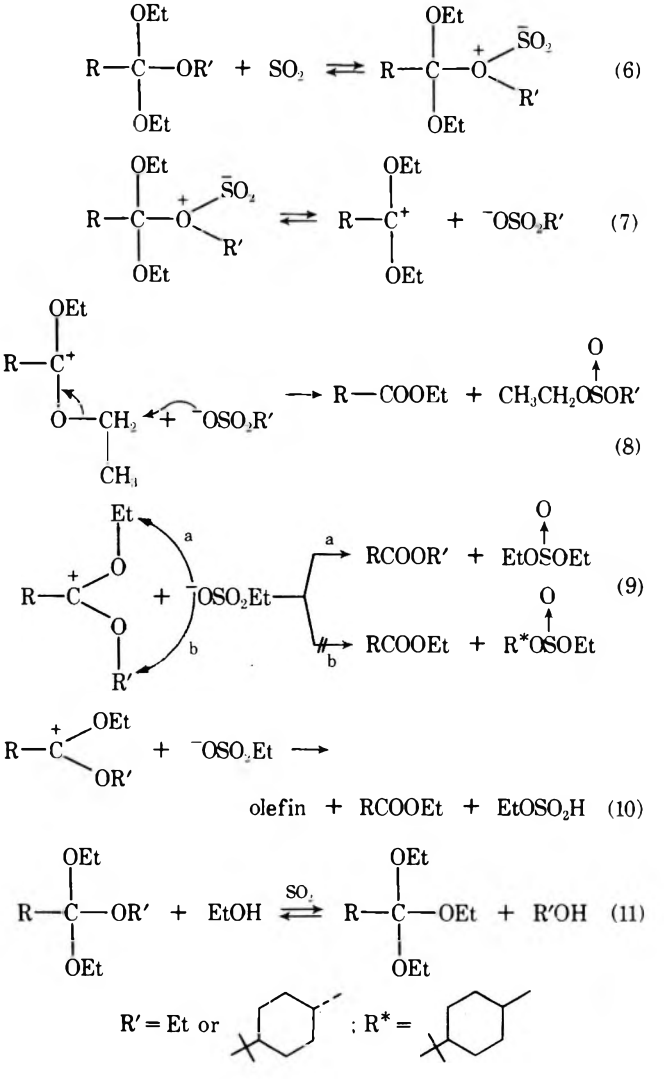
| Ortho ester | Products[b] | Relative reactivity[c] |
|---|---|---|
| $CH_3C(OEt)_3$ | $CH_3COOEt$, $(EtO)_2SO$ | 1.0[d] |
| $CH_3CH_2C(OEt)_3$ | $CH_3CH_2COOEt$, $(EtO)_2SO$ | 1.3 |
| $C_6H_5C(OEt)_3$ | $C_6H_5COOEt$, $(EtO)_2SO$ | 0.36 |
| $HC(OEt)_3$ | $HCOOEt$, $OC(OEt)_2$, $(EtO)_2SO$ | ~0[e] |

[a] Reaction carried out in an NMR tube at an appropriate temperature using approximately 20% (by volume) solutions in sulfur dioxide; see Experimental Section for details. [b] The extent of the reaction was followed by NMR and when starting ortho ester disappeared, the NMR tube was cooled, opened, and analyzed by GLC. [c] From incomplete conversions at 0° for 24 hr. [d] Approximately 35% conconversion. [e] The reaction was very slow and no attempt was made to determine time required to achieve complete conversion; see Experimental Section.

slow, rate-determining formation of an intermediate (probably as an ion pair) which then underwent fast dissociative racemization.[11]

The mechanism of the reaction of ortho esters with sulfur dioxide very likely involves the following transformation (Scheme I). Initially, sulfur dioxide forms an interme-

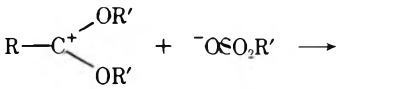
Scheme I



diate via a fast and reversible coordination with a free electron pair at the oxygen (eq 6), which undergoes the oxygen-acyl bond cleavage (eq 7) followed either by the recombination to provide the exchanged ortho ester, or by a nucleophilic substitution by the just generated sulfite anion on the primary center of the dialkoxy carbonium ion,[14] to produce the ester and the dialkyl sulfite (eq 8). Since a nucleophilic substitution with sulfinate ions $RSO_2^-$ at the positive oxygen provides sulfinic esters rather than sulfones,[15] it is perhaps not surprising that the sulfite anions generated in eq 7 also act as an oxygen rather than a sulfur nucleophile in eq 8.

In the above discussed experiment with the *trans*-4-*tert*-butylcyclohexyldiethyl orthoacetate, in addition to the *trans*-4-*tert*-butylcyclohexyl acetate and the *trans*-4-*tert*-butylcyclohexylethyl sulfite, a substantial quantity of 4-*tert*-butylcyclohexene (about 20–30% of maximum possible) and *trans*-4-*tert*-butylcyclohexanol were also formed.[16] The formation of the *trans*-4-*tert*-butylcyclohexylethyl sulfite can be viewed as a consequence of nucleophilic substitution with *trans*-4-*tert*-butylcyclohexyl sulfite anion (R′ = *trans*-4-*tert*-butylcyclohexyl) at the primary center (eq 8), while the formation of the *trans*-4-*tert*-butylcyclohexyl acetate is probably a result of the nucleophilic substitution with the ethyl sulfite anion at the primary (eq 9a) rather than at the secondary center (eq 9b) of the dialkoxy carbonium ion (R′ = *trans*-4-*tert*-butylcyclohexyl, R* = *cis*-4-*tert*-butylcyclohexyl). The absence of the *cis*-4-*tert*-butylcyclohexylethyl sulfite, which might be expected from the nucleophilic attack by the ethyl sulfite anion at the $C_1$ carbon of the *trans*-4-*tert*-butylcyclohexyl group in the corresponding dialkoxy carbonium ion (eq 9b, R* = *cis*-4-*tert*-butylcyclohexyl), is not surprising in view of the propensity of secondary systems to undergo the elimination rather than substitution reactions.[17,18] Indeed, a substantial quantity of the olefin (4-*tert*-butylcyclohexene) formed in this reaction (eq 10) further supports this view. Since the half ester of sulfurous acid formed in eq 10 exists in an equilibrium with the alcohol[10] (eq 5), it also follows that the ethanol should replace *trans*-4-*tert*-butylcyclohexanol from the "mixed" ortho ester to provide the thermodynamically more stable triethyl orthoacetate (eq 11), as indeed has been observed.[19]

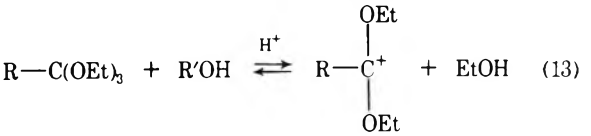
In the reaction of an all-secondary trialkyl orthoformate with sulfur dioxide, nucleophilic substitution by the secondary alkyl sulfite anion on the secondary carbon atom of the corresponding dialkoxy carbonium ion should be very ineffective. Instead, formation of the corresponding olefin, secondary alkyl formate, and the alcohol in equimolar quantities should be expected (eq 12). A reaction of the tri-



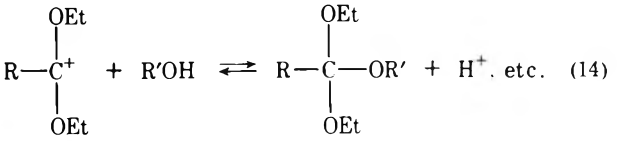
olefin + HCOOR′ + R′OSO₂H (12)

*trans*-4-*tert*-butylcyclohexyl orthoformate (eq 12, R′ = *trans*-4-*tert*-butylcyclohexyl) with excess of sulfur dioxide at room temperature was complete in less than 1 hr. The fact that 4-*tert*-butylcyclohexene, *trans*-4-*tert*-butylcyclohexanol, and *trans*-4-*tert*-butylcyclohexyl formate were formed in equimolar amounts, and that di-4-*tert*-butylcyclohexyl sulfite was not found among the reaction products, further supports the above mechanism.

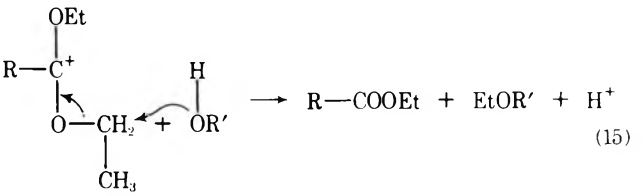
It is of interest to recall that the accepted mechanism for acid-catalyzed hydrolysis of ortho esters calls for a fast and reversible protonation of the ortho ester, followed by a slow, rate-determining formation of the corresponding dialkoxy carbonium ion, and the fast and irreversible reaction of the latter with water to produce the ester and the alcohol.[20] If, however, an ortho ester is subjected to a reaction with an alcohol in the presence of an acid catalyst, it may be expected that the alkoxy exchange would also proceed through a slow, rate-determining formation of the dialkoxy carbonium ion (eq 13), followed by reaction of the latter with the alcohol to regenerate the original or the exchanged ortho ester (eq 14). Contrary to the hydrolysis mechanism,



(13)



(14)



(15)

in which the dialkoxy carbonium ion reacts irreversibly with water as the nucleophile,[20] the reaction of the dialkoxy carbonium ion with the available alcohol nucleophile is a reversible one. Hence, it is conceivable that under these reaction conditions a competing, higher energy but irreversible reaction path, a nucleophilic attack of the alcohol at the alkoxy carbon atom of the dialkoxy carbonium ion to produce the corresponding ester and ether (eq 15), may become operational. Alternatively, in the case of an ortho ester containing a secondary alkoxy group, by analogy with the reaction with sulfur dioxide, elimination rather than substitution may be expected. Indeed, both of these reactions were observed. Thus, when triethyl orthopropionate was heated under reflux with an excess of ethanol, the ortho ester gradually disappeared and the reaction solution contained the ethyl propionate and diethyl ether. On the other hand, heating the tri-*trans*-4-*tert*-butylcyclohexyl orthoformate with a catalytic amount of methanesulfonic acid led to the formation of the *trans*-4-*tert*-butylcyclohexyl formate, 4-*tert*-butylcyclohexene, and *trans*-4-*tert*-butylcyclohexanol, as expected.

## Experimental Section

Most of the ortho esters used in this work were commercial products purified when necessary by distillation. The sulfur dioxide was MCB anhydrous grade and was passed through Linde AW-300 molecular sieves prior to use. *trans*-4-*tert*-Butylcyclohexanol was prepared by a reduction of the ketone with "mixed hydride", according to Eliel's procedure.[21] Boiling and melting points reported are uncorrected. GLC analyses were carried out generally on Hewlett-Packard 5700A instrument 3- or 6-ft columns of either 10% SE-30 on Chromosorb W or the corresponding 10% Carbowax 20M columns. Proton NMR spectra were recorded on either Varian A-60 MHz or HA-100 MHz instruments.

**Camphor Diethyl Acetal.** Camphor diethyl acetal was prepared from camphor, triethyl orthoformate, and ethanol, according to the published procedure.[21]

**Reaction of Camphor Diethyl Acetal with Ethyl Nitrite–Ethanol in Sulfur Dioxide.** A 100-ml Fisher pressure bottle, equipped with a magnetic stirring bar and a pressure gauge, protected with a nitrogen bubbler, was placed in a dry ice–acetone bath and charged with sulfur dioxide (25 ml), camphor diethyl acetal (3.61 g, 16 mmol) in 5 ml of ethanol, a solution of ethyl nitrite in ethanol (3.5 ml, 20 mmol), and 0.5 ml of 1*N* solution of dry hydrogen chloride in absolute ethanol. The dry ice–acetone bath was removed and the reaction solution stirred overnight at room tem-

perature. The reaction vessel was cooled in a dry ice–acetone bath, opened, and the contents poured into an excess of precooled chloroform containing an internal standard. The excess of sulfur dioxide was allowed to evaporate and GLC analysis of the residue indicated about 40–50% yield of diethyl sulfite, 40–50% yield of camphor, and 40–50% yield of 1-carbethoxy-1,2,2-trimethyl-3-cyanocyclopentane. A distillation afforded 1.16 g of the cyano ester, bp 80–84° (0.4 mm). Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.78; H, 9.02; N, 7.0. Ir 2252, 1738 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 4.15 (q, 2 H), 3.0–1.5 (m, 5 H), 1.3–1.05 (1 t + 3 S, 12 H).

**Dehydration of *n*-Heptaldehyde Oxime and *n*-Butylaldehyde Oxime with Camphor Diethyl Acetal.** To a solution of the oxime (10 mmol) in sulfur dioxide–ethanol (7 + 3 ml), a few drops of a 1 *N* solution of dry hydrogen chloride in ethanol were added. An exothermic reaction occurred and GLC analysis indicated that the oxime was essentially quantitatively converted to the corresponding nitrile, while the camphor diethyl acetal was converted into camphor.

***trans*-4-*tert*-Butylcyclohexyldiethyl Orthoacetate.** A mixture of *trans*-4-*tert*-butylcyclohexanol (15.6 g, 100 mmol) and triethyl orthoacetate (32.5 g, 200 mmol) was placed in a distilling flask attached to a short distilling column and a few drops of methanesulfonic acid were added. The flask was slowly heated until approximately 100 mmol of ethanol distilled off. The acid was neutralized with a slight excess of sodium methoxide and the residue distilled in vacuo. There was obtained 20.3 g of *trans*-4-*tert*-butylcyclohexyldiethyl orthoacetate, bp 100–104° (0.5–0.6 mm). Anal. Calcd for $C_{16}H_{32}O_3$: C, 71.28; H, 11.54. Found: C, 71.35; H, 11.42. NMR ($CDCl_3$) $\delta$ 3.6 (q + broad s, 5 H), 1.48 (s, 3 H), 1.19 (t, 6 H), 0.88 (s, 9 H), and remaining cyclohexyl hydrogens appearing as several broad signals between $\delta$ 2.2 and 0.8.

**Tri-*trans*-4-*tert*-butylcyclohexyl Orthoformate.** A mixture of *trans*-4-*tert*-butylcyclohexanol (15.6 g, 100 mmol), triethyl orthoformate (3.3 ml, 20 mmol), and a drop of methanesulfonic acid was placed in a distilling flask and heated at 50° under slight vacuum until approximately 60 mmol of alcohol distilled off. The reaction mixture was made alkaline with sodium methoxide and the residue distilled in vacuo to give tri-*trans*-4-butylcyclohexyl orthoformate, bp 132–136° (0.1 mm), 5.3 g. Anal. Calcd for $C_{31}H_{58}O_3$: C, 77.77; H, 12, 21. Found: C, 78.01; H, 12.18. NMR ($CDCl_3$) $\delta$ 5.4 (s, 1 H), 3.6 (broad s, 3 H), 2.2–0.8 (broad multiplet, 27 H), 0.8 (s, 27 H).

**Typical Procedure for a Reaction of Ortho Esters with Sulfur Dioxide.** A heavy-wall glass NMR tube containing triethyl orthoacetate and a drop of tetramethylsilane was attached via convenient adapter to a small dry ice condenser and flushed with dry nitrogen. The condenser was filled with dry ice–acetone and the NMR tube placed in a small dry ice–acetone bath. Sulfur dioxide was passed through a Linde AW-300 molecular sieve column and condensed directly into the NMR tube to obtain a solution approximately 20% by volume. The sulfur dioxide line was closed, the NMR tube sealed under slight vacuum at −70°, and brought to the desired temperature,[24] and the reaction progress followed up by NMR analysis. After 24 hr at room temperature a 60-MHz NMR spectrum revealed that about 80% of the ortho ester was converted to a mixture of equal amounts of ethyl acetate and diethyl sulfite: $\delta$ 4.1 (2 q, 6 H), 2.0 (s, 3 H), 1.2 (t, 9 H). The gas chromatographic analysis after complete reaction confirmed the above finding and, in addition, showed that these were the only reaction products. The results are summarized in Table I.

**Reaction of Triethyl Orthoformate with Sulfur Dioxide.** A mixture of triethyl orthoformate with excess sulfur dioxide was sealed in a NMR tube as above.[24] After 24 hr at 0°, NMR analysis indicated that no appreciable reaction took place. The NMR tube was placed in a bath and heated at 85–90° and periodically analyzed by NMR. After heating for 2 weeks, only 45–50% of the orthoformate was consumed. In addition to ethyl formate and diethyl sulfite, diethyl carbonate was also formed: $\delta$ 8.1 (s, HCOO–), 4.1–4.2 (3 q, $CH_3CH_2O$). GLC analysis confirmed the above finding and also showed that several other unidentified compounds were present in small quantities. While the ratio of the ethyl formate to diethyl sulfite was approximately the same, the ratio of the ester to the diethyl carbonate was approximately 4:1.

**Reaction of a Mixture of Tri-*n*-propyl Orthoacetate and Triethyl Orthopropionate with Excess Sulfur Dioxide.** A mixture of equal parts of tri-*n*-propyl orthoacetate and triethyl orthopropionate with 4–5 parts of sulfur dioxide was sealed in a NMR tube as above.[24] After 3 days at room temperature the NMR tube was cooled and opened, and the contents were poured into a precooled chloroform. A GLC analysis indicated the presence of ethyl acetate, ethyl propionate, *n*-propyl acetate, *n*-propyl propionate, diethyl sulfite, di-*n*-propyl sulfite, and *n*-propylethyl sulfite. A control experiment showed that neither dialkyl and di-*n*-propyl sulfite nor the corresponding acetates and propionates exchanged under the reaction conditions.

**Reaction of a Mixture of Tri-*n*-propyl Orthoacetate and Triethyl Orthopropionate with an Insufficient Amount of Sulfur Dioxide.** A mixture of equal parts of tri-*n*-propyl orthoacetate and triethyl orthopropionate was mixed with sulfur dioxide (about 5% by volume) in a NMR tube and sealed at −70° as above.[24] The NMR tube was warmed up to room temperature and immediately analyzed by NMR. A complex NMR spectrum suggested that a fast alkoxy exchange had taken place. GLC analysis (as above) showed eight peaks. No appreciable quantity of the products observed in the preceding experiment were present in the reaction mixture. Tri-*n*-propyl orthoacetate, tri-*n*-propyl orthopropionate, triethyl orthopropionate, and triethyl orthoacetate were identified by peak enhancement with the authentic samples, and the remaining four peaks were assumed to be *n*-propyldiethyl orthopropionate, di-*n*-propylethyl orthopropionate, *n*-propyldiethyl orthoacetate, and di-*n*-propylethyl orthoacetate.[25]

**Reaction of *trans*-4-*tert*-Butylcyclohexyldiethyl Orthoacetate with Sulfur Dioxide.** A solution of *trans*-4-*tert*-butylcyclohexyldiethyl orthoacetate containing a drop of tetramethylsilane in liquid sulfur dioxide (about 20% by volume) was sealed in a NMR tube.[24] After standing at room temperature for 3 days, NMR analysis suggested the presence of 4-*tert*-butylcyclohexene, ethyl acetate, diethyl sulfite, ethanol, etc. After removal of excess sulfur dioxide, GLC analysis showed the presence of ethyl acetate (65–70%), 4-*tert*-butylcyclohexene (~25–30%), diethyl sulfite (~50–55%), *trans*-4-*tert*-butylcyclohexanol (~20%), *trans*-4-*tert*-butylcyclohexyl acetate (30–35%), and *trans*-4-*tert*-butylcyclohexylethyl sulfite (~20%). All compounds, except the mixed sulfite, were identified by peak enhancement with the authentic samples. Upon hydrolysis the mixed sulfite afforded *trans*-4-*tert*-butylcyclohexanol, thus showing that the stereochemistry of the $C_1$ cyclohexane carbon was not changed in the course of the reaction.

**Reaction of Tri-*trans*-4-*tert*-butylcyclohexyl Orthoformate with Sulfur Dioxide.** A solution of tri-*trans*-4-*tert*-butylcyclohexyl orthoformate containing a drop of tetramethylsilane in liquid sulfur dioxide (about 20% by volume) was sealed in a NMR tube.[24] After standing at room temperature for 1 hr, NMR analysis suggested complete reaction. GLC analysis of the solution showed that 4-*tert*-butylcyclohexene, *trans*-4-*tert*-butylcyclohexanol, and *trans*-4-*tert*-butylcyclohexyl formate were formed in approximately the same quantities.

**Acid-Catalyzed Reaction of Triethyl Orthopropionate and Ethanol.** A solution of triethyl orthopropionate (8.8 g, 50 mmol) and ethanol (46 g, 1 mol) containing a few drops of methanesulfonic acid was heated under reflux and periodically analyzed by GLC. The ortho ester gradually disappeared and diethyl ether and ethyl propionate were formed.

**Acid-Catalyzed Reaction of Tri-*trans*-4-*tert*-Butylcyclohexyl Orthoformate.** The tri-*trans*-4-*tert*-butylcyclohexyl orthoformate (5 g), in the presence of a few drops of methanesulfonic acid, was heated at 100° under vacuum and the decomposition products collected in a trap cooled with liquid nitrogen. A GLC analysis indicated the presence of *tert*-butylcyclohexene, *trans*-4-*tert*-butylcyclohexyl formate, and *trans*-4-*tert*-butylcyclohexanol in equal amounts.

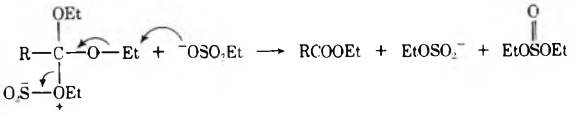
**Registry No.**—Camphor diethyl acetal, 52162-25-1; ethyl nitrite, 109-95-5; ethanol, 64-17-5; 1-carbethoxy-1,2,2-trimethyl-3-cyanocyclopentane, 57346-54-0; *n*-heptaldehyde oxime, 5314-31-8; *n*-butyraldehyde oxime, 110-69-0; *trans*-4-*tert*-butylcyclohexyldiethyl orthoacetate, 57346-55-1; *trans*-4-*tert*-butylcyclohexanol, 21862-63-5; triethyl orthoacetate, 78-39-7; tri-*trans*-4-*tert*-butylcyclohexyl orthoformate, 57346-56-2; triethyl orthoformate, 122-51-0; tri-*n*-propyl orthoacetate, 55844-54-7; triethyl orthopropionate, 115-80-0; triethyl orthobenzoate, 1663-61-2; sulfur dioxide, 7446-09-5.

## References and Notes


(1) M. M. Rogić, J. Vitrone, and M. D. Swerdloff, *J. Am. Chem. Soc.*, **97**, 3848 (1975).
(2) M. M. Rogić and J. Vitrone, to be published.
(3) M. M. Rogić, J. F. Van Peppen, K. P. Klein, and T. R. Demmin, *J. Org. Chem.*, **39**, 3424 (1974).
(4) M. M. Rogić and J. Vitrone, *J. Am. Chem. Soc.*, **94**, 8642 (1972).
(5) Reference 4 and unpublished observations.
(6) J. R. Nooi, P. C. Van der Hoeven, and W. P. Haslinghuis, *Recl. Trav. Chim. Pays-Bas*, **91**, 161 (1972).
(7) The formation of camphor diethyl acetal under usual reaction condi-

tions[22] is a slow process. This is very likely a consequence of the pronounced steric hindrance imposed by the geminal methyl group. For the same reasons one would expect the acetal to be very reactive. Indeed, camphor diethyl acetal is hydrolyzed in the presence of a catalytic amount of acid, or sulfur dioxide, to camphor and ethanol with extreme ease.

(8) We did not investigate this particular reaction in any detail.
(9) A similar mixture of these eight ortho esters was also found when a drop of methanesulfonic acid was added to a mixture of the same two ortho esters.
(10) G. Hesse and S. Majmudar, *Chem. Ber.*, **93**, 1129 (1960).
(11) N. Tokura and F. Akigama, *Bull. Chem. Soc. Jpn.*, **39**, 838 (1966).
(12) E. D. Hughes, C. K. Ingold, and A. D. Scott, *J. Chem. Soc.*, 1271 (1937).
(13) H. Hart and G. Levitt, *J. Org. Chem.*, **21**, 921 (1956).
(14) This may be an oversimplification and certainly there are alternative possibilities. For example, the reaction between the ethyl sulfite anion and the ortho ester coordinated with sulfur dioxide may provide the same products.



(15) M. Kobayashi, *Bull. Chem. Soc. Jpn.*, **39**, 1296 (1966).
(16) The relative amounts varied from experiment to experiment.
(17) See, for example, E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, p 227.
(18) For the same reason one would not expect that the corresponding dicyclohexyl sulfite would be formed in the reaction, and indeed it was not observed among the reaction products.
(19) Clearly, the extent of the exchange reaction, i.e., the formation of the *trans*-4-*tert*-butylcyclohexanol (eq 11), will be a function of the relative rates of the respective processes. The relative amounts of the products varied from experiment to experiment and the ratio of ethanol/*trans*-4-*tert*-butylcyclohexanol was not constant.
(20) See, for example, E. H. Cordes in "The Chemistry of Carboxylic Acids and Esters", S. Patai, Ed., Interscience, New York, N.Y., 1967, pp 632–656.
(21) E. L. Eliel, R. J. L. Martin, and D. Nasipuri, *Org. Synth.*, **47**, 16 (1967).
(22) A. Arbuzow, *Chem. Zentralbl.*, **79**, 1340 (1908).
(23) Ethyl nitrite was prepared from sodium nitrite and ethanol according to the procedure of W. L. Semon and V. R. Damerell, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 204.
(24) *Caution:* excessive pressure!
(25) The same eight peaks were also present in the reaction mixture of the same two ortho esters a short time after a catalytic amount of methanesulfonic acid was added.

---

# Cyclobutylcarbinyl *p*-Bromobenzenesulfonate Solvolysis. 1-Aryl Substituent Effect upon Product Distribution

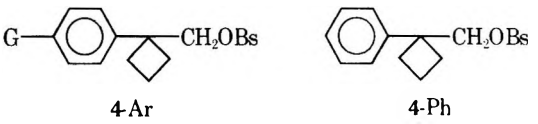
Donald D. Roberts

*Department of Chemistry, Louisiana Tech University, Ruston, Louisiana 71270*

*Received April 23, 1975*

The acetolysis products of 1-phenylcyclobutylcarbinyl (4-Ph), 1-*p*-nitrophenylcyclobutylcarbinyl (4-NPh), and 1-*p*-methoxyphenylcyclobutylcarbinyl (4-MPh) brosylates have been determined in the presence of urea. All of the substrates give 1,2-phenyl rearranged products. The products of the reactions along with previously determined kinetic data[1] suggest that ionization occurs prior to rearrangement. In turn, the phenonium ion intermediate (II) partitions itself among the various product pathways. The mechanistic details are discussed in terms of the Winstein solvolysis scheme.

In a previous[1] solvolytic investigation, it was reported that the transition state for the acetolysis of 4-Ar has little phenonium ion character. Support for this postulate was afforded by the Hammett behavior of 4-Ar ($\rho = -1$), which reveals little direct conjugation between the para substituent and the developing cationic center. For example, the Hammett behavior of a series[2] of para-substituted neophyl tosylates and related systems, solvolyzing with aryl participation, is characterized by $\rho$ values of about $-3$; while other related systems, solvolyzing without aryl participation, are characterized[2] by $\rho$ values of about $-1$.



4-Ar 4-Ph

On the other hand, the fact that only 1,2-phenyl rearranged products were isolated[1a] from the acetolysis of 4-Ph provides strong evidence for phenyl bridging in the transition state leading to the intermediate which reacts with solvent.

These findings were rationalized[1b] in terms of Scheme I,

**Scheme I**

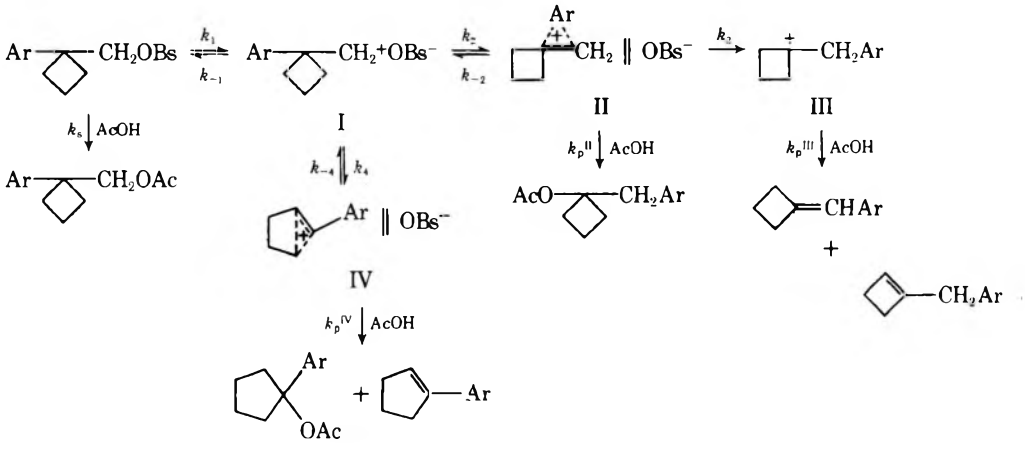


Table I
Acetolysis Products of Selected Tertiary-Carbinyl Systems

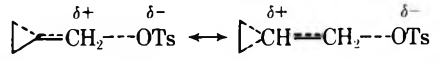
| Substrate | % Ester | % Alkene | Ref |
|---|---|---|---|
| $CH_3CH_2C(CH_3)CH_3$ \| Cl | *a* | 85 | 11a |
| $CH_3C(C_6H_5)CH_2CH_3$ \| Cl | | 95 | 11b |
| $CH_3CH_2C(CH_3)C(CH_3)CH_2CH_3$ \| Ph \| OBBZ | | 100 | 11c |

[a] Did not report substitution product. [b] p-Bromobenzoate.

which has been expanded to include ion-pair partitioning pathways.[3] Based upon the substrate's Hammett behavior, generation of the intimate ion pair (I) is considered rate determining, while aryl assistance controls ion-pair partitioning between the two bridging pathways: neighboring group participation (or internal displacement) by the cyclobutyl ($k_4$) or aryl ($k_2$) group. In turn, the phenonium ion intermediate (II) partitions itself among the product forming pathways $k_p^{II}$ (solvent attack on the bridged ion) and $k_p^{III}$ (rearrangment to open ion followed by solvent attack).

Basically, Scheme I rests on the mechanistic speculation of Sneen,[4] Shiner,[5] and Brown[3a] that solvolysis proceeds through a first-formed tight ion pair which partitions itself among the various product pathways. Furthermore, such a mechanistic scheme has been generally accepted[6] for solvolysis of the related substrate, the cyclopropylcarbinyl system.

The recent proposal of Traylor[7] that strained $\sigma$ bonds, such as those in cyclopropylcarbinyl substrates, can afford stabilization of neighboring cationic centers via $\sigma$–$\pi$ conjugation affords an interesting possibility for the structure of I. Thus it is speculated that I is stabilized by $\sigma$–$\pi$ conjuga-



tion between the cyclobutyl group and the neighboring cationic center where little movement of the cyclobutyl group toward the developing cationic center occurs, i.e., vertical stabilization takes place in which the $\sigma$ bond is delocalized without changing its bond length or angle significantly.

Delineation of all the mechanistic possibilities for product formation is assisted considerably by assessment of the various product distributions resulting from solvent interaction with each intermediate listed in Scheme I. Thus solvent attack on covalent substrate ($k_s$ pathway) is eliminated from consideration by the absence of nonrearranged ester in the product. Furthermore, the absence of ring-expanded ester and/or alkene in the product mixture is evidence against reorganization of I to IV ($k_p^{IV}$pathway) or a ring-expanded open ion.

The assessment that solvent interaction with II leads to exclusively aryl rearranged esters and that interaction with III leads to predominantly aryl rearranged alkenes is based upon less compelling arguments than the above owing to the paucity[8] of product distribution data in acetolysis studies, but nevertheless, the data collected in Table I make such an assessment attractive. Not only are high percentages of alkene products obtained from the acetolysis of the listed tertiary-carbinyl compounds, but also there is a growing body of evidence[11] that in the solvolysis of tertiary-carbinyl substrates a more reactive leaving group produces a higher percentage of alkene. This evidence suggests

Table II
Acetolysis Products for 1-p-X-Phenylcyclobutylcarbinyl Brosylates[a]

| X | p-XPhCH= | p-XPhCH$_2$– | p-XPH– | p-XPhCH$_2$–OAc |
|---|---|---|---|---|
| MeO | 0 | 0 | 10[b] | 90 |
| H | 92 | 8 | 0 | 0 |
| $NO_2$ | 100 | 0 | 0 | 0 |

[a] All product studies carried out at 65°C in the presence of urea. [b] See ref 17.

that greater progress along the traditional Winstein solvolysis scheme,[12] as would be the case[13] for a brosylate ion pair compared to a chloride ion pair, leads to an increasing percentage of alkene in the product distribution.

Furthermore, examination of the structure of II reveals that it is stereoelectronically unfavorable[14] for an E1 elimination, that is, the relevant $\sigma$ bonds are not in the colinear relationship necessary for $\pi$-bond formation. This expectation was confirmed recently by the observed[15] solvolytic behavior of the parent compound, cyclobutylcarbinyl brosylate, which produced no cyclopentene while cyclopentyl brosylate, under the same reaction conditions, yielded 20% cyclopentene.

To further test Scheme I, the acetolysis products of 1-p-nitrophenylcyclobutylcarbinyl brosylate (4-NPh) and 1-p-methoxyphenylcyclobutylcarbinyl brosylate (4-MPh) have been determined in the presence of urea. Also, as a control experiment, the acetolysis products of 1-phenylcyclobutylcarbinyl brosylate (4-Ph) were redetermined in the presence of urea.

Based upon the known[1] product partitioning behavior of 4-Ph in acetic acid (without buffer) and the normal para-substituent effect behavior,[16] it was anticipated that acetolysis of 4-NPh would produce some ring-expanded ester while acetolysis of 4-MPh would yield some phenyl-rearranged ester.

As seen by the product data listed in Table II, the latter expectation was fulfilled but not the former. Thus the acetolysis of 4-MPh yielded 1-p-methoxybenzylcyclobutyl acetate (5) and a small amount[17] of 1-p-methoxyphenylcyclopentene, while acetolysis of 4-NPh yielded a single product, identified as 1-p-nitrobenzalcyclobutane (6).[18] The previously reported[1] products for the acetolysis of 4-Ph, in the absence of buffer, were replicated in the presence of urea.

The structures of the alkene products were identified by comparison of their GLC, ir, and NMR data with that of authentic reference samples. The structure of 1-p-nitrobenzalcyclobutane was established by oxidative cleavage of the 1,2-diol derivative to p-nitrobenzoic acid, and confirmed by mass spectral evidence (see Experimental Section for details); while the structure of 1-p-methoxybenzylcyclobutyl acetate was confirmed by GLC, ir, and NMR analysis (see Experimental Section for detail).

On the basis that cyclobutyl participation is more effective than methyl participation (cyclobutylcarbinyl brosylate solvolyzes some 200 times faster than isobutyl brosylate via a nearly exclusive $k_\Delta$ pathway in formic acid[15,19]), and the demonstrated[20] ability of a neighboring methyl group to compete with a neighboring p-nitrophenyl group in anchimerically assisting the solvolysis of p-nitroneophyl brosylate, it is intriguing that solvolysis of 4-NPh yields no detectable amount of ring-expanded product. Despite the p-nitro group's deactivation of the benzene ring in 4-NPh, aryl participation ($k_2$) dominates completely over cyclobutyl participation ($k_4$) in the partitioning of the first formed intimate ion-pair species.

This finding suggests that the relief of ring strain that normally[15,21] would accompany reorganization of I to IV is

reduced by the presence of the 1-*p*-nitrophenyl group, or more specifically the 1-*p*-nitrophenyl group introduces steric factors into the transition state leading to IV which reduce the magnitude of the expected steric strain relief associated with bridging. The present level of understanding[3c] of steric factors in intimate ion pairs is insufficient to permit productive speculation. Whatever the details as to the steric factors, the presence of the 1-*p*-nitrophenyl group in I unexpectedly inhibits ring expansion.

## Experimental Section

Infrared spectra were obtained on a Bausch and Lomb IR-270 spectrophotometer, and the nuclear magnetic resonance spectra were taken on a Hitachi Perkin-Elmer R-24 instrument with tetramethylsilane as internal standard. A Beckman GC-4 chromatographic instrument equipped with a thermal conductivity detector, a Disc automatic integrator–printer, and a 6 ft × 0.125 in. column of 20% Carbowax 20M on Chromosorb W (80–100 mesh) was used for analytical GC work. The mass spectral analysis was carried out at Rockefeller University and the microanalysis was performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

**1-*p*-Methoxyphenylcyclobutylcarbinyl (4-MPh), 1-*p*-nitrophenylcyclobutylcarbinyl (4-NPh), and 1-*p*-phenylcyclobutylcarbinyl (4-Ph) brosylate** were the same materials as previously described.[1]

**Preparation of Reference Olefins and Esters.** 1-Phenylcyclopentene was prepared via acid-catalyzed dehydration of 1-phenylcyclopentanol and the structure assignment was confirmed by NMR. 1-*p*-Anisylcyclopentene was prepared via acid-catalyzed dehydration of 1-*p*-anisylcyclopentanol, mp 86–86.5° (lit.[23] 87–90°). Analysis by GLC revealed the presence of a single compound and the NMR spectrum confirmed the structure assignment. 1-Phenylcyclobutylcarbinyl acetate, 1-*p*-methoxyphenylcyclobutylcarbinyl acetate, 1-*p*-nitrophenylcyclobutylcarbinyl acetate, and 1-phenylcyclopentyl acetate were prepared from their respective carbinols[1] with acetyl chloride in pyridine. Their purity and structure assignments were confirmed by GLC and NMR data.

**Solvent.** Acetic acid solvent was prepared from 994.9 ml of glacial acetic acid (Matheson Scientific, 99.8%) and 5.1 ml of acetic anhydride.

**Acetolysis Product Studies. A. 1-Phenylcyclobutylcarbinyl Brosylate (4-Ph).** A solution (50 ml, 0.25 *M*) of 1-phenylcyclobutylcarbinyl brosylate in acetic acid (0.3 *M* in urea) was sealed in ampoules under $N_2$ and immersed in a constant-temperature bath at 65 ± 0.1°. After 7 half-lives (ca. 22 hr) the solution was diluted with 200 ml of water and continuously extracted with ether for 48 hr. The ether extract was neutralized with cold saturated $NaHCO_3$ solution, washed four times with 60-ml portions of water, and dried ($MgSO_4$), and the solvent was removed by controlled distillation with a Nester-Faust NFA-200 annular still. The residue was further distilled to yield 1.75 g (97% yield) of distillate (boiling range 42–45°, 0.1 mm). The distillate on analysis by gas chromatography (175°, 35 ml/min He flow rate) gave rise to two peaks, A (4.2 min retention time) and B (7.1 min retention time), with 11.5:1 relative peak areas, in addition to the air peak. Under the same conditions 1-phenylcyclopentene gave rise to a peak with a 1.9-min retention time. Peak A was identified as 1-benzalcyclobutane and peak B as 1-benzylcyclobutene from the following facts: catalytic hydrogenation of the distillate over platinum oxide (Englehard Industries, 82.3%) in methanol (40 psi) yielded a product whose NMR spectrum agreed with that of benzylcyclobutane;[24] and 1-benzylcyclobutene was differentiated from 1-benzalcyclobutane by presence of benzylic protons (a sharp singlet a δ 3.12) in the NMR spectrum of peak B.

**B. 1-*p*-Methoxyphenylcyclobutylcarbinyl Brosylate (4-MPh).** 1-*p*-Methoxyphenylcyclobutylcarbinyl brosylate was solvolyzed and worked up as in section A with the exception that 25 ml of a 0.10 *M* solution of 4-MPh (0.12 *M* in urea) was used and the residue (0.7 g) was not distilled. The residue on analysis by gas chromatography (150°, 35 ml/min He flow rate) gave rise to two major peaks,[25] A (4.3-min retention time) and B (8.5-min retention time), with 1.0:11.2 relative peak areas.[26] The retention time for peak A is identical with that of authentic 1-*p*-methoxyphenylcyclopentene, and analysis by NMR revealed the presence of a multiplet at δ 6.0, typical of vinylic protons. Peak B was identified as 1-*p*-methoxybenzylcyclobutyl acetate from the following facts. Analysis by ir revealed the presence of a strong carbonyl stretching absorption at 1740 $cm^{-1}$ and analysis by NMR gave the following spectrum: δ 7.0 (q, 4 H, aromatic), 3.7 (s, 3 H, typical *p*-MeO aryl protons), 1.6–2.6 (broad, 6 H, typical cyclobutane ring pattern), and 1.9 (s, 3 H, $CH_3COO$).

**C. 1-*p*-Nitrophenylcyclobutylcarbinyl Brosylate (4-NPh).** 1-*p*-Nitrophenylcyclobutylcarbinyl brosylate was solvolyzed as in section A with the exception that 50 ml of a 0.15 *M* solution of 4-NPh (0.18 *M* in urea) was used. After 7 half-lives (ca. 7 days), the solution was diluted with 200 ml of water and extracted six times with 50-ml portions of ether. The combined ether extracts were neutralized with cold saturated $NaHCO_3$, washed three times with 50-ml portions of water, and dried ($MgSO_4$) and most of the solvent was removed via rotovaporization to yield a dark orange oil. The oil was dissolved in 95% ethanol, treated with Norite A, and upon cooling to −10° the alcohol solution gave 1.37 g (7.25 mmol, 96.5% yield) of 1-*p*-nitrobenzalcyclobutane (**6**), light yellow crystals, mp 95.5–95.6°. Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.90; H, 5.82; N, 7.40. Found: C, 69.79; H, 5.73; N, 7.21. NMR ($CCl_4$) δ 8.06 (d, 2 H, aromatic), 7.45 (d, 2 H, aromatic), 6.32 (s, 1 H, vinylic,[27] 2.9–2.3 (broad, 4 H, cyclobutyl), 2.3–2.1 (m, 2 H, cyclobutyl). The mass spectrum of **6** showed *m/e* 91 (tropylum cation)[28] in addition to the molecular ion peak at *m/e* 189 and many other peaks. Additional definitive evidence for the assigned product structure of **6** was provided by the isolation of *p*-nitrobenzoic acid (mp 240–241°, lit.[29] mp 240–242°)[30] from the reaction of **6** with a mixture of potassium permanganate and potassium periodate in aqueous solution at pH 7.7.[31]

**Registry No.**—4-Ph, 50978-05-7; 4-MPh, 50978-03-5; 4-NPh, 50978-07-9; **5**, 57573-61-2; **6**, 57573-62-3.

## References and Notes


(1) (a) J. W. Wilt and D. D. Roberts, *J. Org. Chem.*, **27**, 3434 (1962); (b) D. D. Roberts, *ibid.*, **39**, 1265 (1974).
(2) C. J. Lancelot, D. J. Cram, and P. v. R. Schleyer in "Carbonium Ions", Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley, New York, N.Y., 1972, p 1394.
(3) (a) H. C. Brown and C. J. Kim, *J. Am. Chem. Soc.*, **93**, 5765 (1971); (b) D. J. Raber and J. M. Harris, *J. Chem. Educ.*, **49**, 60 (1972); (c) R. A. Sneen, *Acc. Chem. Res.*, **6**, 46 (1973); (d) K. Humski, V. Sendijarevic, and V. J. Shiner, Jr., *J. Am. Chem. Soc.*, **95**, 7722 (1973).
(4) R. A. Sneen and J. W. Larsen, *J. Am. Chem. Soc.*, **91**, 362 (1969).
(5) V. J. Shiner, Jr., and R. D. Fisher, *J. Am. Chem. Soc.*, **93**, 2553 (1971).
(6) (a) K. B. Wiberg and G. Szeimies, *J. Am. Chem. Soc.*, **92**, 571 (1970); (b) Z. Majerski and P. v. R. Schleyer, *ibid.*, **93**, 665 (1971).
(7) W. Hanstein, H. J. Berwin, and T. G. Traylor, *J. Am. Chem. Soc.*, **92**, 829 (1970).
(8) Although solvolytic investigations have been reported[9] for para-substituted benzyldimethylcarbinyl chlorides, no product data were obtained. Also, in our hands, 1-benzylcyclobutanol failed to yield a significant amount of 1-benzylcyclobutyl chloride upon treatment with HCl for 3 hr in a Brown[10] hydrochlorination apparatus.
(9) (a) A. Landis and C. A. Vander Werf, *J. Am. Chem. Soc.*, **80**, 5277 (1958); (b) M. M. Tassler and C. A. Vander Werf, *J. Org. Chem.*, **30**, 405 (1965); (c) H. C. Brown and C. J. Kim, *J. Am. Chem. Soc.*, **90**, 2082 (1968).
(10) H. C. Brown and M. H. Rei, *J. Org. Chem.*, **31**, 1090 (1966).
(11) (a) M. Cocivera and S. Winstein, *J. Am. Chem. Soc.*, **85**, 1702 (1963); (b) D. J. Cram and M. R. Sahyun, *ibid.*, **85**, 1257 (1963); (c) D. J. Cram and J. D. Knight, *ibid.*, **74**, 5839 (1952); (d) S. G. Smith and D. J. W. Goon, *J. Org. Chem.*, **34**, 3127 (1969); (e) H. L. Goering and J. V. Clevenger, *J. Am. Chem. Soc.*, **94**, 1010 (1972).
(12) S. Winstein, B. Appel, R. Baker, and A. Diaz, *Chem. Soc., Spec. Publ.*, **No. 19**, 109 (1965).
(13) S. Winstein, A. H. Fainberg, and E. Grunwald, *J. Am. Chem. Soc.*, **79**, 4146 (1957).
(14) (a) D. J. Cram, *J. Am. Chem. Soc.*, **74**, 2137 (1952); (b) P. D. Bartlett, W. D. Closson, and T. J. Cogdell, *ibid.*, **87**, 1308 (1965).
(15) D. D. Roberts and C. Wu, *J. Org. Chem.*, **39**, 1570 (1974).
(16) For a recent discussion see C. D. Johnson, "The Hammett Equation", Cambridge University Press, New York, N.Y., 1973.
(17) Stability experiments revealed that under product run conditions (cf. Experimental Section), 1-*p*-methoxyphenylcyclobutyl acetate is converted into 1-*p*-methoxyphenylcyclopentene.
(18) The acetolysis of 1-*p*-nitrophenylcyclobutylcarbinyl brosylate thus provides a convenient synthesis of this new four-membered ring compound.
(19) In formic acid at 35° ($sec^{-1}$), *k* (isobutyl brosylate) = 0.82 × $10^{-6}$; at 45°, 2.4 × $10^{-6}$; at 55°, 7.9 × $10^{-6}$ (D. D. Roberts, unreported data).
(20) H. Tanida, T. Tsuji, H. Ishitobi, and T. Irie, *J. Org. Chem.*, **34**, 1086 (1969).
(21) (a) K. B. Wiberg and B. A. Hess, Jr., *J. Am. Chem. Soc.*, **88**, 4433 (1966); (b) W. G. Dauben, J. L. Chitwood, and D. V. Scherer, Jr., *ibid.*, **90**, 1014 (1968).
(22) W. H. Tallent, *J. Org. Chem.*, **21**, 862 (1956).
(23) J. Paseual and R. Crespo, *An. R. Soc. Esp. Fis. Quim., Ser. B*, **48**, 273–280 (1952).
(24) J. W. Wilt, J. M. Kosturik, and R. C. Orlowski, *J. Org. Chem.*, **30**, 1052 (1965).
(25) The sample was not stable on the gas chromatograph and with increas-

ing temperature and prolonged retention time tended to pyrolyze, yielding additional unidentified peaks.
(26) As the sample aged, the ratio of the relative peak areas A:B increased; therefore, we assign production of 1-phenylcyclopentene to an isomerization reaction of 1-*p*-methoxybenzylcyclobutyl acetate. Such ready conversion of tertiary esters to alkenes has been previously observed.[15]
(27) The $\delta$ 6.32 value is consistent with that observed[20] for vinylic protons in $\beta,\beta$-dimethyl-*p*-nitrostyrene (a model for 1-*p*-nitrobenzalcyclobutane) and contrasts with the $\delta$ 5.97 value observed[20] for the vinylic protons in $\alpha,\beta$-dimethyl-*p*-nitrostyrene (a model for 1-*p*-nitrophenylcyclopentene).
(28) The presence of the tropylium cation is consistent with a 1-*p*-nitrobenzalcyclobutane fragmentation reaction.
(29) O. Kamm and A. O. Matthews, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1932, p 385.
(30) The NMR spectrum was consistent with that of authentic *p*-nitrobenzoic acid.
(31) R. V. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701, 1710 (1955).

# 1-Alkyl- (or aryl-) amino-2-methylpropane-2-thiols. Some Bi- and Tetradentate Nitrogen–Sulfur Ligands from Schiff's Base Disulfides

James L. Corbin* and Dale E. Work

*Contribution No. 547 from the Charles F. Kettering Research Laboratory, Yellow Springs, Ohio 45387*

*Received September 9, 1975*

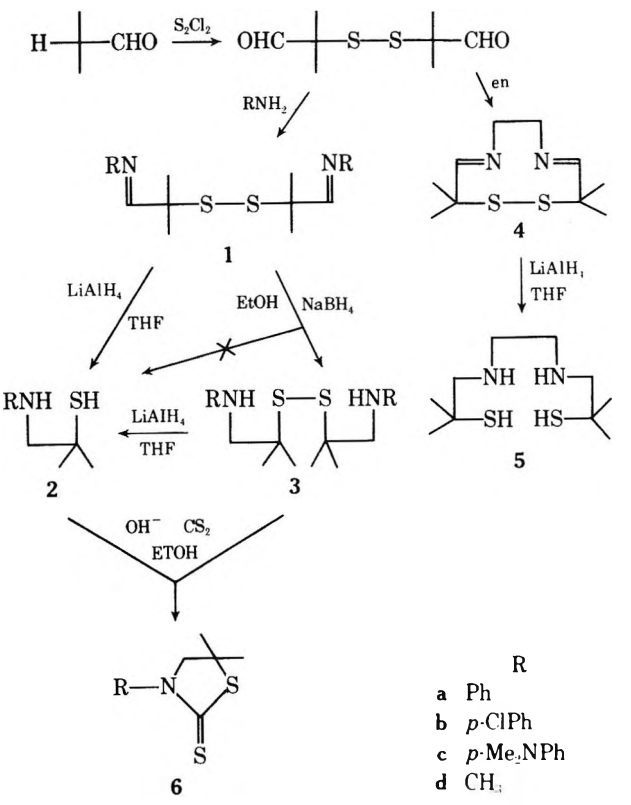
Repetition of a published procedure for the preparation of several N-substituted 1-amino-2-methylpropane-2-thiols (**2a–d**) for use as bidentate ligands indicated that the products characterized therein were not thiols, but the corresponding disulfides (**3a–d**). Preparation of the authentic thiols was accomplished by reduction of the intermediate Schiff's bases (**1a–d**) with $LiAlH_4$ in refluxing tetrahydrofuran. The novel tetradentate **5** was also synthesized from **4** using the same procedure. The chelating ability of **5** was demonstrated by formation of a neutral Ni(II) complex. It was also shown that the 3-arylamino-5,5-dimethylthiazolidine-2-thiones (**6**) were obtained from both the thiols and disulfides, indicating that formation of this derivative does not prove the presence of a thiol function.

Nitrogen- and sulfur-donor ligand systems[1] are of continuing interest in coordination chemistry, and at our laboratory we are especially interested in complexes of molybdenum[2] and iron.[3] Recently, interesting properties have been found for complexes with tertiary thiol groups such as 3-mercaptovaline (penicillamine).[2c,4] We sought to synthesize a variety of such tertiary thiols (**2a–d**), and a straightforward route for these compounds had recently appeared in this journal.[5] This involved Schiff's base formation using $\alpha,\alpha'$-dithiodiisobutyraldehyde followed by reduction with $NaBH_4$ (Scheme I), and no difficulty was anticipated. This same route also appeared suitable for the novel tetradentate **5**, because the cyclic Schiff's base **4** was a known compound.[6] However, our attempts to repeat this synthetic sequence failed, and the preparation and characterization of these compounds by a revised procedure is the subject of this paper.

Attempts to make **2a** gave the viscous, pale yellow, nondistillable liquid previously described.[5] However, only 1–2% thiol was found ($I_2$ titration), and ir and NMR showed NH, but no SH. Molecular weight data were consistent with a dimer, which we assign as the disulfide **3a**. This is a surprising result because the reaction and subsequent work-up were conducted under argon. Neither diselenide-catalyzed hypophosphorous acid reduction[7] nor more vigorous $NaBH_4$ treatment (2 hr in refluxing acetonitrile) would cleave **3a**. The literature reveals tertiary disulfides to be fairly resistant to reduction; e.g., di-*tert*-butyl disulfide is resistant to $LiAlH_4$ in refluxing ether, but is reduced in refluxing tetrahydrofuran (THF),[8] and while penicillamine disulfide is little affected by $NaBH_4$ (50°),[9] it can be cleaved by $Na–NH_3$.[10] Treatment of either **3a** or its precursor **1a** with $LiAlH_4$ in THF gave the desired thiol as a distillable, mobile liquid (Table I), which exhibited an SH peak (NMR, ir) and the correct molecular weight, and consumed 2 equiv of iodine, a characteristic of some tertiary thiols (sulfenyl iodide formation).[11]

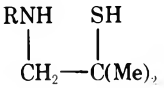
It was apparent that the previous report[5] of **2a** was in error, and that the others (**2b–d**) of interest to us were

Scheme I




probably disulfides (**3b–d**) also. In order to test this, we repeated the synthesis of "**2b**", "**2c**", and "**2d**", reported to be a viscous, nondistillable liquid, a crystalline solid (mp 82–83°), and a volatile liquid [bp 113–114° (0.75 Torr)], respectively. Again the $NaBH_4$ reduction gave products with these same properties. These compounds were shown to be the disulfides **3b–d** by an analogous process. When these Schiff's bases (**1b–d**) were reduced with $LiAlH_4$ in THF,

Table I
Properties of the 1-Amino-2-methylpropane-2-thiols[a]



| R | Bp, °C (Torr) | % yield | Mol wt (theory) | NMR, ppm (Me)$_2$ | CH$_2$ | NH/SH[b] | ArH | Other |
|---|---|---|---|---|---|---|---|---|
| Ph | 90–92 (0.7)[c] | 64 | 180[d] | 1.38 | 3.08 | 3.88 (b) | 6.4–7.3 | |
| (2a) | | | (181) | | | 1.71 | (m) | |
| *p*-ClPh | 111–114 (0.1)[c] | 63 | 216[d] | 1.42 | 3.10 | 4.07 (b) | 6.4–7.3 | |
| (2b) | | | (216) | | | 1.72 | (m) | |
| *p*-Me$_2$NPh | 135–137 (0.15) | 67 | 224[d] | 1.40 | 3.09 | 3.60 (b) | 6.7 (m) | 2.80 |
| (2c) | (mp 50–51.5)[e] | | (224) | | | 1.79 | | (Me$_2$N) |
| Me | 47 (20)[f] | 20 | 117[g] | 1.37 | 2.54 | 1.56 | | 2.47 |
| (2d) | | | (119) | | | 1.56 | | (MeN) |
| Ethylene | 101–103 (0.07)[c] | 50 | 230[g] | 1.37 | 2.62 | 1.76 | | 2.78 |
| (5) | | | (236) | | | 1.76 | | (CH$_2$CH$_2$) |

[a] Satisfactory C, H, N analyses were obtained for the new compounds 2a–c and 5. [b] Both protons exchangeable with $D_2O$. [c] Mobile liquid, solidifying in the freezer. [d] VPO in 1,2-dichloroethane. [e] Recrystallized from hexane. [f] Hydrochloride mp 229.5–230° dec (lit.[12] 222–224° dec). [g] Cryoscopy in benzene.

the authentic thiols summarized in Table I were obtained. The *N*-methyl compound (**2d**) has been isolated before as the hydrochloride,[12] but this is the first report of the free base. In view of the low yield we obtained (20%), this compound is probably better prepared (79%) by the route described in ref 12.

The cyclic Schiff's base **4** was prepared and reduced ($LiAlH_4$) to give the new tetradentate **5** in reasonable yield. Its properties are described in Table I and its chelating ability demonstrated by formation of a neutral Ni(II) complex. Further studies of the coordination chemistry of **5** and **2a–d** are currently in progress.

The mass spectral evidence given previously[5] to support the formulation of "**2a**" can be attributed to the presence of a few percent of the authentic, more volatile thiol in the disulfide. The NMR evidence given[5] for thiol must be rejected. The SH was supposedly under the *gem*-dimethyl resonance for "**2a–c**", and our NMR data clearly show only six protons in this peak before and after $D_2O$ exchange. Only one NH or SH proton was even listed for "**2d**", and this was no doubt the NH, as we see a sharp two-proton peak for these in **2d**. The formation of a crystalline thiazolidine-2-thione (**6c**) from **3c** remains to be explained, as this was used as further evidence of an SH. Upon examination, *both* the free thiol **2c** and the disulfide **3c** yielded this derivative on treatment with $CS_2$ and NaOH in ethanol. **2a** and **3a** behaved similarly, and thus, while providing crystalline derivatives (**6a–c**), their formation cannot be used as evidence of a thiol function. The differing yields of these derivatives (*p*-$Me_2N$ > *p*-H > *p*-Cl) appears to reflect the varying basicity of the nitrogen atom.

The mechanism of formation of **6** from the disulfide is not clear, but may arise from small, equilibrium amounts of thiol formed by reaction with the xanthate or sulfide which must be present (from the $CS_2$, NaOH, and ethanol present). The lability of the S–S bond in the presence of $RS^-$ types is well known.[13]

$$RSSR + R'S^- \rightleftarrows RSSR' + RS^-$$

Although it is beyond the scope of our interest to reexamine the remaining compounds reported as thiols in ref 5, it is reasonable to assume that they are also disulfides (**3**). Nevertheless, the general synthetic sequence reported there is still of value as long as $LiAlH_4$–THF is used in the reduction step and reductant-compatible substituents are present.

## Experimental Section

NMR spectra were obtained with a Varian A-60 instrument (35°) with tetramethylsilane as the internal standard. Either a Hewlett-Packard 302B vapor pressure osmometer (37°) or an anaerobic cryoscopy cell[14] were used for molecular weight determinations. The H-P Model 185 CHN Analyzer was used for the elemental microanalyses, and infrared spectra were obtained on a Beckman IR20-A as KBr disks or as smears between salt plates. All evaporations were done at or near ambient temperature with a Swissco rotary vacuum evaporator. Thiol titrations with 0.05 *N* ethanolic $I_2$–KI (dead stop end point) were adapted from the literature.[15] Melting points were determined with a hot stage microscope and are corrected. $\alpha,\alpha'$-Dithioisobutyraldehyde was prepared according to the literature[6] [70%, bp 92–93° (0.3 Torr)], as was the cyclic Schiff's base 4,[6] except that MeOH was used as a solvent (93%, mp 163–166°).

**Bis[1-(N-substituted)imino-2-methyl-2-propyl] Disulfides (1a–d).** Instead of the more complex published procedure,[5] the imines **1a–c** were more expeditiously prepared by refluxing the amine with $\alpha,\alpha'$-dithiodiisobutyraldehyde (30–60 min) in isopropyl alcohol (followed by $H_2O$ washing and recrystallization from *i*-PrOH). The NMe compound **1d** was obtained[5] in 84% yield with a reaction period of 4 hr instead of the 4 days prescribed.

**Bis[1-(N-substituted)amino-2-methyl-2-propyl] Disulfides (3a–d).** The $NaBH_4$ reductions were performed as described,[5] but under argon, and the reactions worked up in the same way. Products with the reported physical appearance (**3a,b**), melting point (**3c**), or boiling point (**3d**) were obtained, but no thiol beyond 1–2% was found (titration). No SH could be found under the *gem*-dimethyl peak by NMR, the integration showing only six protons before or after $D_2O$ exchange (see text). NH (ca. 3340–3420 $cm^{-1}$) was seen in the ir, but SH was absent. Molecular weight data (VPO, 1,2-dichloroethane) were consistent with the disulfide **3**: **3a**, 346 (theory 360); **3b**, 440 (theory 429); **3c**, 439 (theory 446); **3d**, 250 (theory 236).

**1-Alkyl- (or aryl-) amino-2-methylpropane-2-thiols (2a–d) and Ethane-1,2-bis(*N*-1-amino-2-methylpropane-2-thiol) (5).**[16] The appropriate Schiff's base, **1a–d** or **4** (0.10 mol), or disulfide (**3a**) was dissolved in dry THF (100–300 ml) and added with stirring (argon atmosphere) to $LiAlH_4$ (0.12 mol; 0.16 mol for **4**) in dry THF (100 ml) over 30–40 min. The reaction mixture was refluxed for 2 hr and hydrolyzed by the cautious addition of saturated NaK–tartrate solution (50–75 ml), and then ether (300 ml) added. The sludge was separated by decanting or filtration (Celite) and washed well with ether. The solvent was removed (a Vigreux column was used for **2d** because of its volatility), and the residual liquid subjected to simple distillation (in vacuo) to give the thiols described in Table I. The ir showed SH as a medium-weak to weak band at 2530–2550 $cm^{-1}$, and the NH as a medium to medium-strong band at 3340–3420 $cm^{-1}$. A separate SH was seen in the NMR for **2a–c**, but was pooled with the NH in **2d** and **5**. Titration with $I_2$ gave 97–100% of 2 equiv/thiol for **2a,b** and 1 equiv/thiol for **2d** and **5**.[17] A colored complex was formed between $I_2$ and **2c** and

the end point was not distinct. The products were stored (frozen) in serum bottles under argon.

**Preparation of 3-Aryl-5,5-dimethylthiazolidine-2-thiones (6a–c).** The general method[5] was to reflux a mixture of the thiol (3.0 mmol) or disulfide (1.5 mmol), 10 *N* NaOH (0.30 ml), $CS_2$ (7 mmol), and ethanol (10 ml) for 24 hr (argon), add water (3–4 ml), and chill. The crystalline derivative was filtered, washed (cold MeOH, then $H_2O$), and recrystallized from the same ethanol–water mixture prior to analysis. The yields listed are for the crude products. Use of the disulfides **3a** and **3c** led to similar (or higher) yields of the identical **6** (melting point and mixture melting point).

**3-Phenyl-5,5-dimethylthiazolidine-2-thione (6a):** colorless plates (45%), mp 114–115°. Anal. Calcd for $C_{11}H_{13}NS_2$: C, 59.15; H, 5.86; N, 6.27. Found: C, 58.80; H, 5.87; N, 6.17.

**3-(*p*-Chlorophenyl)-5,5-dimethylthiazolidine-2-thione (6b):** colorless needles (34%), mp 111–111.5°. Anal. Calcd for $C_{11}H_{12}ClNS_2$: C, 51.25; H, 4.69; N, 5.43. Found: C, 51.34; H, 4.81; N, 5.81.

**3-(*p*-Dimethylaminophenyl)-5,5-dimethylthiazolidine-2-thione (6c):** pale yellow needles (79%), mp 156–157° (lit.[5] 157–158°).

**Nickel(II) Complex of 5.** A solution of **5** (1 mmol) in MeOH (4 ml) was added to a warm solution of $Ni(OAc)_2 \cdot 4H_2O$ (1 mmol) in MeOH (8 ml). The solid, which separated immediately, was filtered, washed (MeOH), and vacuum dried (1 hr at 50°) to give 188 mg (61.4%) of the tan-pink crystalline complex. Its ir spectrum exhibited bands at 3220 and 3270 $cm^{-1}$ (sh) (coordinated NH). Anal. Calcd for $C_{10}H_{22}N_2S_2Ni \cdot \frac{1}{2}H_2O$: C, 39.75; H, 7.67; N, 9.27. Found: C, 39.67; H, 7.85; N, 9.59.

**Registry No.**—**1a,** 54410-19-4; **1b,** 54410-20-7; **1c,** 54410-23-0; **1d,** 57443-08-0; **2a,** 54410-26-3; **2b,** 54410-28-5; **2c,** 54410-33-2; **2d,** 54410-35-4; **3a,** 57443-09-1; **3b,** 57443-10-4; **3c,** 57443-11-5; **3d,** 57443-12-6; **4,** 57443-13-7; **5,** 57443-14-8; **5** Ni(II) complex, 57443-07-9; **6a,** 57443-15-9; **6b,** 57443-16-0; **6c,** 54410-36-5; α,α′-dithiodiisobutyraldehyde, 15581-80-3; aniline, 62-53-3; *p*-chloroaniline, 106-47-8; *N,N*-dimethyl-*p*-phenylenediamine, 99-98-5; methylamine, 74-89-5; $Ni(OAc)_2$, 373-02-4.

## References and Notes


(1) (a) J. L. Corbin and D. E. Work, *Can. J. Chem.*, **52,** 1054 (1974); (b) J. L. Corbin, *Synth. React. Inorg. Met.-Org. Chem.*, **4,** 347 (1974).
(2) (a) J. W. McDonald, W. E. Newton, C. T. C. Creedy, and J. L. Corbin, *J. Organomet. Chem.*, **92,** C25 (1975); (b) J. W. McDonald, J. L. Corbin, and W. E. Newton, *J. Am. Chem. Soc.*, **97,** 1970 (1975), and references cited therein; (c) E. I. Stiefel, J. L. Corbin, and N. Pariyadath, to be published.
(3) W. E. Newton, J. L. Corbin, P. W. Schneider, and W. A. Bulen, *J. Am. Chem. Soc.*, **93,** 268 (1971).
(4) J. A. Thich, D. Mastropaolo, J. Potenza, and H. J. Schugar, *J. Am. Chem. Soc.*, **96,** 726 (1974).
(5) J. J. D'Amico and W. E. Dahl, *J. Org. Chem.*, **40,** 1224 (1975).
(6) K. W. Merz and M. Specker, *Arch. Pharm. (Weinheim, Ger.)*, **296,** 427 (1963).
(7) W. H. H. Günther, *J. Org. Chem.*, **31,** 1202 (1966).
(8) R. C. Arnold, A. P. Lien, and R. M. Alm, *J. Am. Chem. Soc.*, **72,** 731 (1950).
(9) K. Bir, J. C. Crawhill, and D. Maudlin, *Clin. Chim. Acta*, **30,** 183 (1970).
(10) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids", Wiley, New York, N.Y., 1961, p 2647.
(11) L. Field, J. L. Vanhorne, and L. W. Cunningham, *J. Org. Chem.*, **35,** 3267 (1970); ref 15, p 190.
(12) R. Luhowy and F. Meneghini, *J. Org. Chem.*, **38,** 2405 (1973).
(13) E. E. Reid, "Organic Chemistry of Bivalent Sulfur", Vol. 3, Chemical Publishing Co., New York, N.Y., 1960, pp 372–373.
(14) This apparatus will be described elsewhere.
(15) K. G. Stone, "Determination of Organic Compounds", McGraw-Hill, New York, N.Y., 1956, pp 7–8, 190–192.
(16) No attempt was made to optimize yields.
(17) We have no explanation as yet for the uptake of less $I_2$ by those thiols containing aliphatic amino groups.


# Ferrocene-1,1′-disulfonyl Azide and 2,4,6-Trimethylpyridinium Ferrocenesulfonyl Ylide. Synthesis and Decomposition

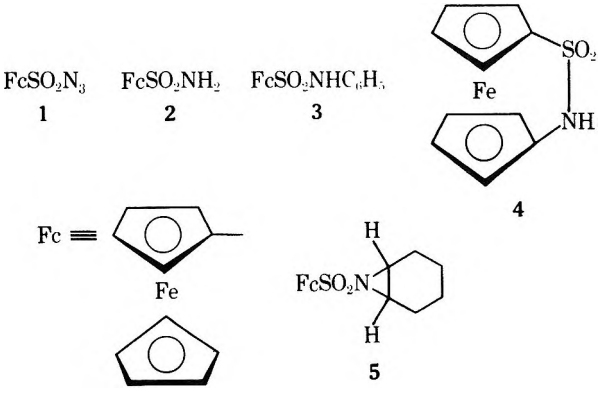

Rudolph A. Abramovitch* and William D. Holcomb

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


*Received August 15, 1975*

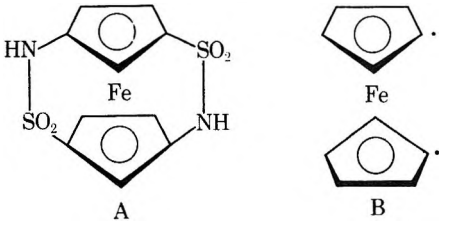

Photolysis of ferrocene-1,1′-disulfonyl azide in various solvents and at different wavelengths gave 1′-sulfamylferrocenesulfonyl azide and ferrocene-1,1′-disulfonamide. The thermolysis products depended on the solvent used. In cyclohexane, 1′-sulfamylferrocenesulfonyl azide, ferrocene-1,1′-disulfonyl azide, *N,N′*-dicyclohexylferrocene-1,1′-disulfonamide, 1′-(*N*-cyclohexylsulfamyl)ferrocenesulfonyl azide, and 1′-(*N*-cyclohexylsulfamyl)ferrocenesulfonamide were obtained. In benzene, products both of kinetic (azepine) and thermodynamic control (anilide) were formed but disubstitution did not occur. In mesitylene, the dimesitylamide was obtained. No intramolecular cyclization products were ever detected. 2,4,6-Trimethylpyridinium ferrocenesulfonyl ylide did not undergo photolysis but did thermolyze to ferrocenesulfonamide and *sym*-collidine. Again no ferrocenophane was formed.


The thermal and photochemical decomposition of ferrocenylsulfonyl azide (**1**) has led to some very interesting results.[1,2] Thermolysis in benzene led to a unusually high yield (for such reactions[3]) of hydrogen-abstraction product, ferrocenesulfonamide (**2**), and to a low yield of "substitution"[4] into the aromatic nucleus (**3**).[2] More solvent insertion and less hydrogen abstraction were observed in cyclohexane, but the yield of **2** was very high in cyclohexene. Photolysis of **1** led to quite different results. Thus, the main product formed in benzene was the novel bridged derivative **4**, [2]ferrocenophanethiazine 1,1-dioxide,[1] together with much smaller amounts of **2**. The same products were formed in cyclohexene, but now, for the first time, was observed what is probably the addition of a singlet sulfonyl

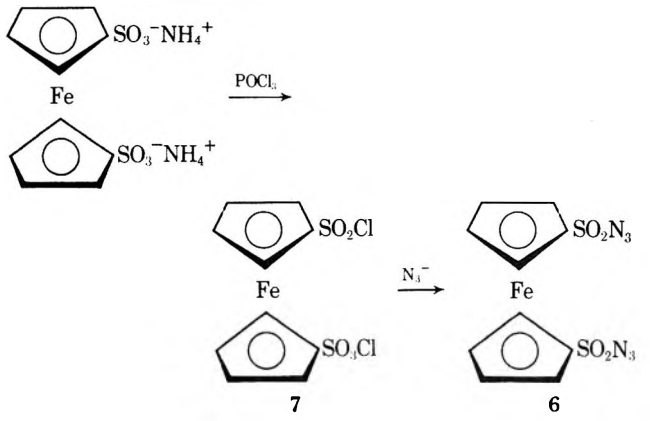


nitrene to an olefinic double bond, namely the aziridine derivative 5.[2]

In a subsequent study, the decomposition of *o*- and *p*-benzenedisulfonyl azides in various solvents was examined.[5] A number of interesting reactions were observed, particularly with the ortho derivative, decomposition of which led, among others, to the generation of benzyne, as well as to the loss of one of the sulfonyl azide moieties. It was, therefore, decided to study the behavior of ferrocene-1,1′-disulfonyl azide (**6**). Among the possibilities were that a ferrocenophane derivative related to **4** would be formed and that the second sulfonyl azide group would react with solvent [formation of a dibridged species such as A was considered unlikely since models showed (and x-ray analysis has since confirmed[6]) that the two cyclopentadienyl rings were certainly not parallel in **4**]. As well, the formation of a "ferrocyne" (B) was a possibility. Certainly, it was felt that interaction between the two sulfonyl azides functions was possible and that this would result in some interesting behavior, and this is what has been observed. No evidence for the formation of A or B has been found.




Ferrocene-1,1′-disulfonyl azide (**6**) was prepared from diammonium ferrocene-1,1′-disulfonate (**9**)[7] with phosphorus oxychloride (no product was obtained with phosphorus trichloride), followed by treatment of **9** with sodium azide in aqueous acetone. It was found necessary to protect the azide from light during the reaction and after isolation, since the compound darkened noticeably on exposure to ordinary light. The structure of the diazide was confirmed by its spectroscopic properties: $\nu_{max}$ 2155 ($N_3$), 1355 and 1150 $cm^{-1}$ ($SO_2$), two triplets of equal intensity centered at $\delta$ 4.83 ($\beta$-H) and 5.00 ($\alpha$-H) ($A_2B_2$), and $M^{\cdot+}$ *m/e* 396.

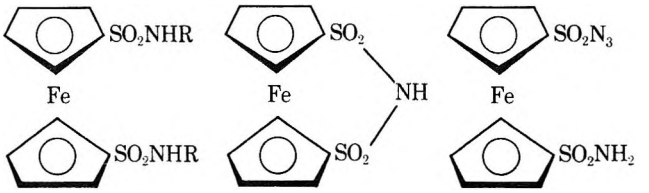



An authentic sample of *N,N′*-dicyclohexylferrocene-1,1′-disulfonamide (**8**) (an expected product from one of the reactions) was readily prepared from **7** and cyclohexylamine, but ferrocene-1,1′-disulfonamide (**9**) could not be obtained from **7** and ammonia under a large variety of conditions and solvents, e.g., aqueous or dry ammonia in benzene, ethyl acetate, or acetone. Since only small amounts of **7** were recovered we suspect that a bridged imide such as **10** may form which decomposes readily to give dark, intractable products. Amides **9** and **11** obtained as described below appear to be stable. Similar results were obtained on attempted preparation of **11** from **7** and aniline.

Table I
Photolysis of Ferrocene-1,1′-disulfonyl Azide (6) at 35°

| Solvent | Wavelength, Å | Time, hr | Recovered 6, % | % 9 | % 12 |
|---|---|---|---|---|---|
| $C_6H_6$ | 2537 | 1 | 62.3 | | 17 |
| $C_6H_6$ | 3000 | 1 | 14.2 | | 25 |
| $C_6H_6$ | 3500 | 1 | 50.0 | | 11 |
| $C_6H_6$ | 3500 | 8 | 5.3 | 3.6 | 5.1 |
| $C_6H_6$[a] | 3000 | 1 | 70.6 | | 22 |
| $C_6H_{12}$ | 2537 | 1 | 54.7 | | 9 |
| $C_6H_{12}$ | 3000 | 1 | 78.4 | | 17 |
| $C_6H_{12}$ | 3500 | 1 | 56.5 | | 16 |
| $C_6H_{10}$ | 3000 | 1 | 76 | | 21 |

[a] Ferrocene added as sensitizer; 92% was recovered.




8, R = $C_6H_{11}$
9, R = H
11, R = Ph

Photolysis of **6** in benzene, cyclohexane, or cyclohexene at various wavelengths and for varying periods of time gave only two identifiable products and a lot of insoluble tarry material. The results are summarized in Table I. The first of these products was identified as 1′-sulfamylferrocenesulfonyl azide (**12**) on the basis of its spectral properties: $\nu_{max}$ 3280, 3210 ($NH_2$), 2120 ($N_3$), 1375, 1320, and 1135 $cm^{-1}$ (two different $SO_2$); two $A_2B_2$ systems, $\delta$ 4.95 ($H_2$, $H_5$), 4.81 ($H_3$, $H_4$), 4.95 ($H_2'$, $H_5'$, overlapping with $H_2$ and $H_5$), 4.68 ($H_3'$, $H_5'$). The base peak in the mass spectrum of **12** was at *m/e* 344, which corresponds to $M^{\cdot+} - 26$. This could either be due to loss of $N_2$ followed by hydrogen abstraction to give the **9** ion (indeed, with the exception of a small peak corresponding to $M^{\cdot+} - 28$, the rest of the spectrum was the same as that of **9**), or to the loss of $C_2H_2$ as has been found to be the case with some aryl azides.[8] If **9** was indeed formed it would probably have to be in the inlet of the mass spectrometer by thermolysis and intramolecular hydrogen abstraction prior to volatilization. This remains to be resolved by accurate mass measurements. Continued photolysis of **12** did not lead to any ferrocenophane formation.

The second product formed in the photolyses on longer irradiation was ferrocene-1,1′-disulfonamide (**9**). It exhibited bands at 3330, 3255 ($NH_2$), 1345, and 1145 $cm^{-1}$ ($SO_2$), an $A_2B_2$ system [$\delta$ 4.85 (4, $\alpha$-H), 4.65 (4, $\beta$-H), 7.15 (4, exchangeable $NH_2$)], and a parent ion (also the base peak) at *m/e* 344. It is likely that **9** is formed from **12** on longer exposures (Table I).

Thermolysis of **6** in cyclohexane at 135° for 16 hr gave **9** (7.8%), **8** (8.7%), 1′-(cyclohexylsulfamyl)ferrocenesulfonyl azide (**13**, 0.6%), and 1′-(*N*-cyclohexylsulfamyl)ferrocenesulfonamide (**14**, 10.7%). When the thermolysis was carried out for only 4 hr, only **13** (26.2%) and **12** (4.7%) were

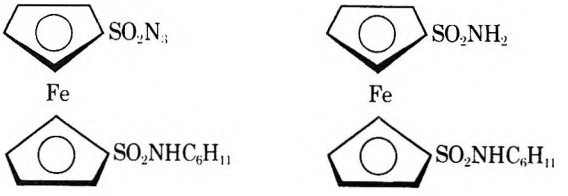
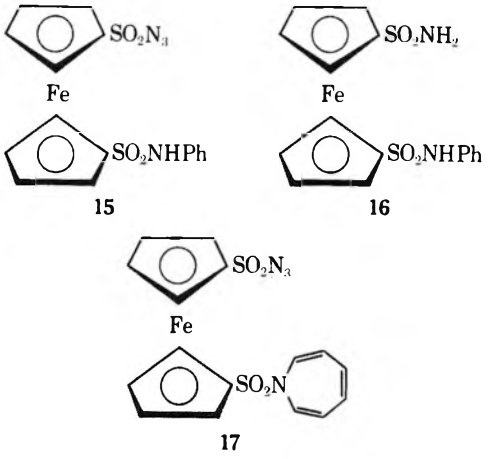


Table II
Thermolysis of 6 in Benzene

| Temp, °C | Time, hr | Additives | Products, % Recovered 6 | 9 | 12 | 15 | 17 | Other |
|---|---|---|---|---|---|---|---|---|
| 135 | 4 | | 23 | trace | 8.2 | 12.5 | | |
| 135 | 16 | | | 5.4 | | | | Aniline (trace) |
| 135 | 3 | Ferrocene | 14 | | 16.2 | 15.1 | | Ferrocene (94.5) |
| 135 | 3 | Tetracyclone | 16.1 | 14.4 | 12.3 | 8.5 | | Tetracyclone (88.6) |
| 135 | 4 | TCNE | 8 | 3.1 | 6.4 | 2.4 | | |
| 100 | 63 | | 54 | 1.4 | 8.2 | 6.3 | 9.4 | |
| 100 | 116 | | 18.5 | 2.4 | 5.2 | 2.8 | 2.5 | |
| 100 | 188 | | 13.9 | 6.8 | 4.6 | 3.9 | 0.5 | |
| 100 | 53 | TCNE | 71 | 2.8 | 5.0 | 3.0 | | |

obtained, and much azide (43%) was recovered. The structural assignments of **13** and **14** are based on the spectroscopic properties of the compounds (see Experimental Section). It seems likely, therefore, that **9** arises from **12** in this reaction on prolonged heating, while **14** arises from **13** by hydrogen abstraction by the sulfonyl nitrene from the solvent. When the thermolysis was carried out at 100° for 53 hr, **13** (9%), **12** (2.7%), and **9** (7.2%) were obtained, together with much recovered azide (34.4%).

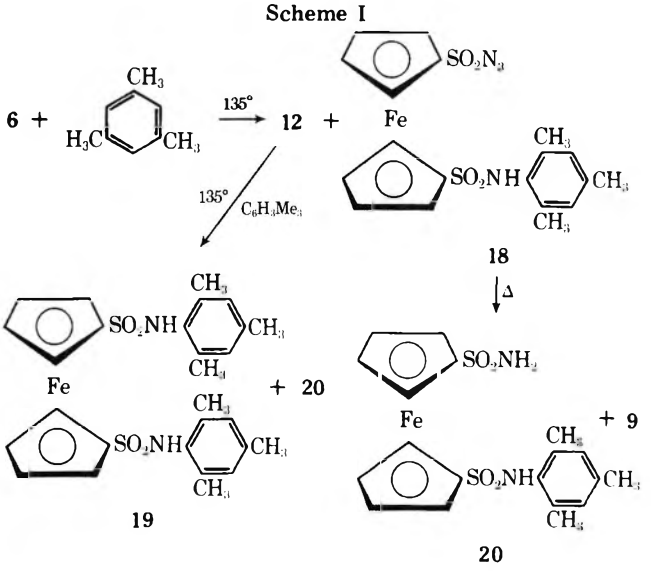
The results of the decomposition of **6** in benzene are given in Table II. At 135°, 1′-(*N*-phenylsulfamyl)ferrocenesulfonyl azide (**15**) was obtained. Interestingly neither the disulfonanilide (**11**) nor 1′-(*N*-phenylsulfamyl)ferrocenesulfonamide (**16**) could be detected, though a careful



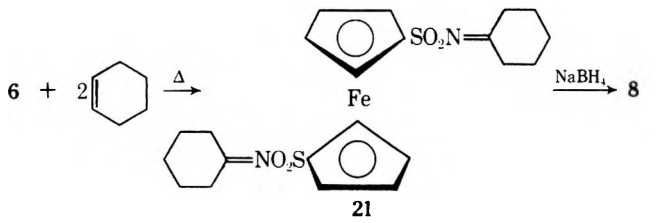

search was made for them. This contrasts (as do most of the above results) with the behavior of *o*-benzenedisulfonyl azide, which, on thermolysis in benzene, gives both *o*-benzenedisulfonylanilide and benzenesulfonylanilide-2-sulfonamide.[5] The addition of ferrocene to the solution before thermolysis had a slight beneficial effect upon the yields of products but no change in their nature was observed. When the temperature at which the thermolysis was carried out was lowered a new product was obtained which proved to be the *N*-sulfonylazepine **17**. Evidence of its structure is based mainly on the infrared, NMR, and mass spectra of **17**, since, unlike simpler *N*-acylazepines,[9,10] no [4 + 2]π adduct was formed with tetracyanoethylene (TCNE) nor could the azepine be trapped with tetracyclone (which gives [4 + 2]π and [6 + 4]π adducts with *N*-mesylazepine[11]). It exhibited bands at 2130 ($N_3$), 1640, 1620 (C=C in azepine[12]), 1360, and 1145 $cm^{-1}$ ($SO_2$), the usual 1,1′-disubstituted ferrocene $A_2B_2$–$A_2'B_2'$ patterns in the NMR, as well as a complex multiplet (6 H) at δ 5.96 and 5.67 (azepine vinyl protons[12]). The base peak in the mass spectrum was at *m/e* 92 corresponding to $C_6H_6N^+$, the azatropylium ion, behavior characteristic of N-substituted azepines.[12] *N*-Mesylazepine has previously been isolated from the decomposition of $MeSO_2N_3$ in benzene at 80–100° and is the product of kinetic control.[9] At higher temperatures, the *N*-sulfonylanilide is formed (in the present case, **15**) as the product of thermodynamic control.

In the hope of achieving attack by *both* sulfonylnitrene groups upon the solvent aromatic nucleus, the latter was made more nucleophilic and the thermolysis of **6** in mesitylene was examined. At 135° for 3 hr the only products formed were **12** (13.5%) and 1′-(*N*-2,4,6-trimethylphenylsulfamyl)ferrocenylsulfonyl azide (**18**, 26.2%). Starting azide was recovered. When heating was prolonged for 16 hr, however, *N,N′*-di-(2,4,6-trimethylphenyl)ferrocene-1,1′-disulfonamide (**19**, 11.6%) *was* obtained, together with 1′-(*N*-2,4,6-trimethylphenylsulfamyl)ferrocenesulfonamide (**20**, 17.2%) and **9** (14.2%). These products probably arise as shown in Scheme I.

Scheme I




Decomposition of **6** in boiling cyclohexene give the diimine **21** (no NH absorption; strong band due to C=N at 1610 $cm^{-1}$) which was very unstable and hydrolyzed very readily in moist air to give cyclohexanone and **9** (65%). Reduction of the reaction product with $NaBH_4$ without isolation gave **8** (42.6%), together with some **9** (24.3%) undoubtedly due to hydrolysis of **21** before addition of borohydride. The reaction of sulfonyl azides with unstrained olefins has been reported[13,14] to give imines, probably by 1,3-dipolar addition of the azide to the olefin followed by thermal elim-



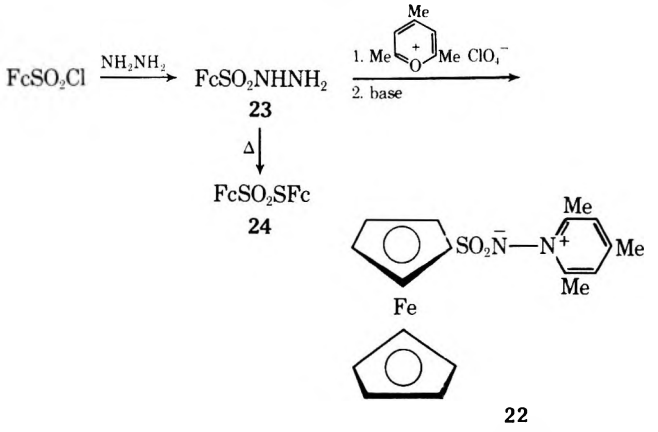

21

ination of $N_2$, and the in situ reduction of the imines to sulfonamides with $NaBH_4$ has been described.[14]

Even when an "inert" solvent not containing hydrogen was used, hydrogen abstraction products were the only ones that could be isolated in low yield: no intramolecular cyclization was achieved with the disulfonyl azide. Thus, thermolysis of **6** in Freon 113 gave only **9** (3.5%) and **12** (2.8%), so that intermolecular hydrogen abstraction, or hydrolysis of more complex materials during work-up, must be occurring.

It was of interest to see whether the ferrocenophane **4** could be obtained from a source other than the sulfonyl azide. To that end, 2,4,6-trimethylpyridinium ferrocenesulfonyl ylide (**22**) was prepared by the sequence in Scheme II.

Scheme II




22

Ylide **22** appears to fragment in a number of ways upon electron impact. The most important pathway seems to be fragmentation to the collidinium radical cation *m/e* 121 (100) and ferrocenesulfonylnitrene, the latter undergoing a Curtius-type rearrangement with loss of $SO_2$ to give ferrocenylnitrene [*m/e* 199 (12)].[15] Other important fragments are $Me_3C_5H_2N^+$–N [*m/e* 135 (21%)][15] and $FcSO_2NH_2^+$ [*m/e* 265 (36)]. Contrary to the behavior of *N*-methanesulfonylimino-2,4,6-pyridinium ylide, which gives a diazepine on photolysis,[15] irradiation of **22** with 2500-, 3000-, or 3500-Å light led only to the recovery of the ylide. Thermolysis of **22** in benzene at 175° gave $FcSO_2NH_2$ (54%) and 2,4,6-collidine (71%). No intramolecular cyclization to **4** was observed in accord with the fact that no singlet sulfonylnitrenes have been observed in the photolysis of *N*-sulfonyliminopyridinium ylides[15] and the suggestion that thermal decomposition of ferrocenesulfonyl azide leads to a nitrene metal complex which hydrogen abstracts rather than cyclizes.[2]

It was noted that ferrocensulfonyl hydrazide (**23**) melted with evolution of a gas and then resolidified. This sequence was carried out on a preparative scale at 150–160°. A basic gas was evolved and the yellow residue was shown to be ferrocenyl ferrocenethiolsulfonate (**24**). Small amounts of ferrocene were also formed in this reaction.

## Experimental Section

Melting points are uncorrected. Ir spectra were determined on Perkin-Elmer 257, 357, or Beckman Acculab 3 instruments, and NMR spectra on a Varian Associates HA-100 or a Hitachi Perkin-Elmer R20B spectrometer using tetramethylsilane as internal standard. The mass spectra were determined on a CEC 21-104 or Hitachi Perkin-Elmer RMU-6M spectrometer and uv spectra on a Cary 14 spectrophotometer.

Reagents and solvents were usually reagent grade and were fractionally distilled or recrystallized before use. Drying of organic extracts was effected with calcium chloride, magnesium sulfate, or molecular sieves (Davidson, type 4A, grade 514, 8–12 mesh). Light petroleum refers to the fraction of bp 30–60° unless otherwise stated. Basic alumina for chromatography was Alcoa (F-20) and neutral alumina was prepared from this basic alumina.

**Ferrocene-1,1′-disulfonyl Azide (6).** A stirred mixture of phosphorus oxychloride (50 ml) and diammonium ferrocene-1,1′-disulfonate (16.5 g) was heated under reflux on a steam bath for 6 hr. The yellow salt had turned to a white solid. The slurry was cooled, ice water (50 ml) was added carefully, and the solution was poured onto ice (400 g). A dark precipitate was collected, dried in vacuo, dissolved in chloroform (400 ml), and filtered to remove a rust-colored insoluble material. Light petroleum (400 ml) was added, and the solution was treated with charcoal and cooled in a dry ice–acetone bath. Yellow-orange crystals were collected, washed with light petroleum (2 × 20 ml), and dried in vacuo to give ferrocene-1,1′-disulfonyl chloride (10.6 g, 62%) which had no clear melting point but darkened noticeably at 160° and was black by 180°: ir (KBr) 1360 (s), 1205 $cm^{-1}$ (s); NMR ($CDCl_3$) $\delta$ 4.80 (t, 2 H), 5.02 (t, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 386 ($M^{\cdot+}$ $^{37}Cl_2$, 4), 384 (16), 382 (23).

The chloride (10.5 g) in acetone (300 ml) was treated dropwise with sodium azide (4.1 g) in water (50 ml) with vigorous stirring at room temperature for 24 hr in the absence of light, evaporated to about 40 ml in vacuo, and poured into water. The yellow precipitate was collected, washed with water (3 × 30 ml), and dried under vacuum. It was recrystallized from absolute ethanol to give yellow prisms of **ferrocene-1,1′-disulfonyl azide** (6.1 g, 58%): mp 128–129° dec; $\lambda_{max}$ (EtOH) 207, 247, and 307 nm ($\epsilon$ 34 200, 10 810, and 2250).

Anal. Calcd for $C_{10}H_8FeN_6O_4S_2$: C, 30.32; H, 2.04. Found: C, 30.56; H, 2.16.

***N,N′*-Dicyclohexylferrocene-1,1′-disulfonamide (8).** Ferrocene-1,1′-disulfonyl chloride (3.76 g) was dissolved in benzene (50 ml) and cyclohexylamine (6.2 g) was added dropwise. The solution was boiled under reflux for 12 hr in the absence of light. It was then evaporated under vacuum, the dark, oily material was poured into 3 *N* HCl (100 ml), and the dark precipitate was collected and dried in vacuo (3.62 g). Recrystallization from light petroleum (bp 60–110°)–ethyl acetate gave ***N,N′*-dicyclohexylferrocene-1,1′-disulfonamide (8,** 1.88 g, 36%): mp 203–204° dec; ir (KBr) 3310 and 3270 (s, br), 1320 (s), 1190 (s), 1135 $cm^{-1}$ (s); NMR ($CDCl_3$) $\delta$ 4.81 (t, 4 H), 4.61 (t, 4 H), 4.49 (s, exchanges with $D_2O$), 3.12 (s, br, 2 H), and 1.0–0.9 (br, 20 H); mass spectrum (70 eV) *m/e* (rel intensity) 510 (14), 509 (30), 508 ($M^{\cdot+}$, 100).

Anal. Calcd for $C_{22}H_{32}FeN_2O_4S_2$: C, 51.97; H, 6.34. Found: C, 52.23; H, 6.54.

**Attempted Preparation of Ferrocene-1,1′-disulfonamide.** Ferrocene-1,1′-disulfonyl chloride (2.15 g) was dissolved in acetone (40 ml) and 15 *M* aqueous ammonia (30 ml) was added. The solution was boiled under reflux for 1 hr on a steam bath and cooled, a second portion of aqueous ammonia (20 ml) was added, and the solution was boiled under reflux for another 1 hr. It was evaporated under vacuum to ca. one-third of its volume and poured into water (200 ml). A dark solid was collected, dried, and dissolved in ethyl acetate, dried ($CaCl_2$), and evaporated onto neutral alumina (ca. 20 g). Chromatography on a column of neutral alumina (2.3 × 35 cm) yielded only starting disulfonyl chloride (0.12 g, 6%) which eluted with benzene–ethyl acetate (1:1 v/v).

Similar reactions using benzene as solvent and 15 *M* aqueous ammonia gave only small quantities of starting disulfonyl chloride.

Ferrocene-1,1′-disulfonyl chloride (1.50 g) was dissolved in benzene (80 ml, Na dried) and ammonia gas (KOH dried) was bubbled through the solution for 2 hr at room temperature. A dark precipitate formed continuously during the addition. This solution, including the precipitate, was evaporated in vacuo onto neutral alumina (ca. 20 g) and chromatographed as above. Only ferrocene-1,1′-disulfonyl chloride (0.025 g, 17%) was obtained. Similar reactions carried out in acetone, ethyl acetate, and chloroform gave only small amounts of recovered disulfonyl chloride.

**Attempted Preparation of *N,N′*-Diphenylferrocene-1,1′-disulfonamide.** Ferrocene-1,1′-disulfonyl chloride (1.82 g) was dissolved in acetone (30 ml) and aniline (8.0 g) was added. The solution was boiled under reflux for 12 hr in the absence of light. It

was cooled and concentrated under vacuum, the dark, oily residue was poured into 3 *N* HCl (100 ml), and the acid solution was extracted with ether (3 × 50 ml). The ether solution was dried ($CaCl_2$) and evaporated under vacuum into neutral alumina (ca. 20 g). Chromatography on a column of neutral alumina (2.3 × 40 cm) yielded only starting disulfonyl chloride (0.35 g, 19%).

Reaction of 1,1′-ferrocenedisulfonyl chloride with aniline in benzene in the presence of an excess of triethylamine at room temperature for 14 days yielded only a small amount of starting disulfonyl chloride.

**Photolysis of Ferrocene-1,1′-disulfonyl Azide in Benzene Using 2537-Å Radiation for 1 Hr.** The azide (0.74 g) was dissolved in benzene (100 ml, Na dried) and nitrogen (dry, $O_2$ free) was bubbled through the solution for 30 min. It was then irradiated in a Vicor vessel fitted with a Pyrex glass wool stirrer to clean the sides of the vessel in a Rayonet reactor equipped with 2537-Å lamps for 1 hr at 35° under dry, oxygen-free nitrogen. After irradiation the solution was pale yellow with a brown solid material adhering to the glass wool. The solution was removed, the apparatus washed with ethyl acetate (3 × 20 ml), the glass wool extracted with ethyl acetate (3 × 40 ml) until colorless, and the combined solutions evaporated in vacuo onto neutral alumina (10 g). Chromatography on a column of neutral alumina (2.3 × 25 cm) and elution with benzene–ethanol (99.5:0.5 v/v) and benzene–ethanol (98:2 v/v) gave starting azide (0.46 g, 62.3%) (infrared spectrum identical with that of authentic azide). Elution with benzene–ethanol (96:4 v/v) gave **1′-sulfamylferrocenesulfonyl azide (12,** 0.045 g, 17%) (from ethyl acetate–light petroleum), mp 154–156° dec.

Anal. Calcd for $C_{10}H_{10}FeN_4O_4S_2$: C, 32.45; H, 2.72. Found: C, 32.73; H, 2.81. No other compounds were eluted.

The azide **6** was photolyzed under identical conditions but using 3000 Å and 3500 Å. The results are given in Table I.

**Photolysis of 6 in Benzene for 8 Hr.** The azide (1.47 g) in benzene (100 ml, Na dried) in a Pyrex vessel was irradiated using 3500-Å lamps for 8 hr at ca. 35°. The photolysis mixture was chromatographed as above. Elution with benzene–ethyl acetate (99:1 v/v) gave starting azide (0.079 g, 5.3%). Elution with ethyl acetate–ethanol (99:1 v/v) gave 1′-sulfamylferrocenesulfonyl azide (0.067 g, 5.1%) (ir spectrum identical with that of compound obtained above). Elution with ethyl acetate–ethanol (99:1 and 95:5 v/v) gave yellow, granular crystals of **ferrocene-1,1′-disulfonamide (9,** 0.045 g, 3.6%), darkens at 180°, mp 198–202° dec (from ethyl acetate–light petroleum).

Anal. Calcd for $C_{10}H_{12}FeN_2O_4S_2$: C, 34.90; H, 3.55. Found: C, 35.12; H, 3.40.

No other compounds were eluted.

**Photolysis at 3000 Å of 6 in Benzene in the Presence of Ferrocene.** The azide (0.84 g) and ferrocene (4.88 g) were dissolved in benzene (100 ml, Na dried) and the solution was photolyzed using 3000-Å lamps for 1 hr at 30°. The photolysis mixture was chromatographed as above. Elution with benzene gave ferrocene (4.52 g, 92%). Further elution with benzene gave starting azide (0.59 g, 70.6%). Elution with benzene–ethanol (9:1 v/v) gave 1′-sulfamylferrocenesulfonyl azide (0.049 g, 22%) (ir spectrum identical with that of product obtained above).

**Photolysis of 6 in Cyclohexane Using 2537-Å Radiation.** The azide (0.69 g) was added to cyclohexane (100 ml, Na dried) and the solution flushed with nitrogen (dry, $O_2$ free) for 30 min. Not all of the azide was dissolved at this time. The suspension was irradiated for 1 hr at ca. 30° using 2537-Å lamps. The product was isolated and chromatographed as above. Elution with benzene–ethyl acetate (99:1 v/v) gave starting azide (0.38 g, 54.7%). Elution with benzene–ethanol (98:2 v/v) gave 1′-sulfamylferrocenesulfonyl azide (0.026 g, 9%).

The results of related reactions at other wavelengths and in cyclohexene are collected in Table I.

**General Procedure for the Thermal Decompositions.** The azide was added to the solvent in a thick-walled glass vessel containing a small glass rod. Nitrogen (dry, $O_2$ free) was flushed through the solution for 30 min and the vessel sealed with a solid ground glass stopper secured by copper wire. The glass vessel was placed in a metal bomb, solvent (ca. 20 ml) added to the bomb, and the bomb sealed with a screw-on top. The bomb was placed in an oven maintained at the desired temperature and rotated at a slight angle for the desired length of time. After thermolysis, the bomb was removed and cooled, and the glass vessel was carefully taken out. The solution was removed, the vessel rinsed with ethyl acetate (2 × 20 ml), and the solutions combined and evaporated in vacuo onto neutral alumina (ca. 10 g).

**Thermolysis of Ferrocene-1,1′-disulfonyl Azide in Cyclohexane at 135°. A. For 4 Hr.** The azide (0.84 g) in cyclohexane (30 ml, Na dried) was heated for 4 hr at 135°. After the thermolysis the solution was pale yellow and contained a moderate amount of black solid. The decomposition products were chromatographed on a column of neutral alumina (2.3 × 25 cm). Elution with benzene–ethyl acetate (98:2 v/v) gave starting azide (0.37 g, 43%). Elution with benzene–ethyl acetate (3:1 v/v) gave a yellow solid which, on recrystallization from light petroleum (bp 60–110°)–ethyl acetate, gave **1′-(*N*-cyclohexylsulfamyl)ferrocenesulfonyl azide (13,** 0.14 g, 26.2%): mp 115–116°; ir (KBr) 3235 (s), 2125 (s), 1370 (s), 1325 (s), 1195 (s), 1140 $cm^{-1}$ (s); NMR ($CDCl_3$) δ 5.00–4.80 (m, 6 H), 4.71 (t, 2 H), 4.38 (d, 1 H, exchanges with $D_2O$), 3.15 (s, br, 1 H), and 2.0–0.9 (m, 1 OH); mass spectrum (70 eV) *m/e* (rel intensity) 453 (11), 452 ($M^{\cdot+}$, 45) 426 (100).

Anal. Calcd for $C_{16}H_{20}FeN_4O_4S_2$: C, 42.49; H, 4.46. Found: C, 42.55; H, 4.61.

Elution with ethyl acetate–ethanol (99:1 v/v) gave a yellow solid identified by its infrared spectrum as 1′-sulfamylferrocenesulfonyl azide (**12,** 4.7%).

No other compounds were eluted.

**B. For 16 Hr.** Elution with benzene–ethyl acetate (3:1 v/v) gave 1′-(cyclohexylsulfamyl)ferrocenesulfonyl azide (**13,** 0.066 g, 0.6%) (ir identical with that above).

Elution with benzene–ethyl acetate (1:1 v/v) gave *N,N′*-dicyclohexylferrocene-1,1′-disulfonamide (8, 0.094 g, 8.7%), mp 203–204°, identical with an authentic sample prepared above. Further elution with this solvent gave **1′-(*N*-cyclohexylsulfamyl)ferrocenesulfonamide (14,** 0.098 g, 10.7%) [from light petroleum (bp 60–110°)–ethyl acetate]: mp 136–137°; ir (KBr) 3340 (w), 3260 (m), 3220 (w), 1320 (s), 1150 (s), 1140 $cm^{-1}$ (s); NMR ($CDCl_3$) δ 5.58 (s, 2 H, exchanges with $D_2O$), 4.92 (t, 2 H), 4.81 (t, 2 H), 4.65–4.60 (m, 4 H), 4.05 (s, 1 H, exchanges with $D_2O$), 3.10 (s, 1 H), and 2.0–0.8 (m, 1 OH); mass spectrum (70 eV) *m/e* (rel intensity) 428 (13), 427 (23), 426 ($M^{\cdot+}$, 100), 344 (40).

Anal. Calcd for $C_{16}H_{22}FeN_2O_4S_2$: C, 45.08; H, 5.20. Found: C, 45.37; H, 5.38.

Elution with ethyl acetate–ethanol (99:1 and 95:5 v/v) gave ferrocene-1,1′-disulfonamide (0.058 g, 7.8%) (ir spectrum identical with that of sample above). No other compounds were eluted.

Thermolysis of **6** in cyclohexane at 100° for 53 hr and work-up as above gave **9** (7.2%), **12** (2.7%), and **13** (9%), together with recovered **6** (34.4%).

**Thermolysis of 6 in Benzene at 135°. A. For 4 Hr.** The azide (0.68 g) was dissolved in benzene (30 ml, Na dried) and the solution heated for 4 hr at 135°. After thermolysis the solution was dark yellow and contained some black solid. The decomposition products were chromatographed on a column of neutral alumina (2.3 × 25 cm). Elution with benzene–ethyl acetate (98:2 v/v) gave starting azide (0.16 g, 23%). Elution with benzene–ethyl acetate (1:1 v/v) gave **1′-(*N*-phenylsulfamyl)ferrocenesulfonyl azide (15,** 0.081 g, 8.2%): mp 135–137° dec (from benzene–light petroleum); ir (KBr) 3240 (s), 2130 (s), 1365 (s), 1200 (s, broad), 1140 $cm^{-1}$ (s); NMR ($CDCl_3$) δ 7.29–7.16 (m, 5 H), 6.70 (s, 1 H, exchanges with $D_2O$), 4.92 (t, 2 H), 4.86–4.75 (m, 4 H), and 4.67 (t, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 446 ($M^{\cdot+}$, 9), 420 (30), 104 (44), 77 (100).

Anal. Calcd for $C_{16}H_{14}FeN_4O_4S_2$: C, 43.06; H, 3.16. Found: C, 43.34; H, 3.34.

Elution with ethyl acetate–ethanol (99:1 v/v) gave 1′-sulfamylferrocenesulfonyl azide (**12,** 0.044 g, 8.2%) identical with the compound obtained above. Elution with ethyl acetate–ethanol (9:1 v/v) gave ferrocene-1,1′-disulfonamide (**9,** 0.002 g, trace) (ir).

No other compounds were eluted.

**B. For 16 Hr.** The azide (1.33 g) in benzene (30 ml, Na dried) was heated at 135° for 16 hr. The solution after thermolysis was very light yellow and contained a large amount of black solid in suspension. A small quantity (ca. 1 ml) of solution was removed and concentrated in a stream of nitrogen. Gas chromatographic analysis [OV-17 (20%) on Gas-Chrom Q, 6 ft × 3/16 in., He flow 80 ml/min; temperature program isothermal 400 sec at 70° then 6°/min] showed only one very small peak (retention time 1010 sec). Collection of this peak using capillary technique and mass spectroscopic analysis showed this to be aniline (*m/e* 93, fragmentation pattern identical with that of authentic sample of aniline), and its retention time was identical with that of aniline under these analysis conditions. No quantitative analysis was performed but the amount of aniline in the solution was very small. The remaining solution was chromatographed on a column of neutral alumina (2.3 × 25 cm). Elution with ethyl acetate–ethanol (9:1 v/v) gave ferrocene-1,1′-disulfonamide (0.062 g, 5.4%) (ir).

No other compounds were eluted.

**C. In the Presence of Ferrocene for 3 Hr.** The azide (0.88 g) was dissolved in benzene (40 ml, Na dried) and ferrocene (7.05 g) was added. The solution was heated at 135° for 3 hr and the products were chromatographed on a column of neutral alumina (2.3 × 45 cm). Elution with light petroleum–benzene (3:1 v/v) gave ferrocene (6.66 g, 94.5%). Elution with benzene–ethanol (99:1 v/v) gave starting azide (0.13 g, 14%). Elution with benzene–ethanol (98:2 v/v) gave 1′-(*N*-phenylsulfamyl)ferrocenesulfonyl azide (**15**, 0.13 g, 15.1%), identical with the sample previously characterized. Elution with benzene–ethanol (95:5 v/v) gave 1′-sulfamylferrocenesulfonyl azide (**12**, 0.11 g, 16.2%) (ir).

No other compounds were eluted.

The results of other reactions carried out at 135° in the presence of tetracyclone and tetracyanoethylene are given in Table II.

**Thermolysis of Ferrocene-1,1′-disulfonyl Azide in Benzene at 100°.** The azide (1.51 g) in benzene (35 ml, Na dried) was heated at 100° for 63 hr. After thermolysis the solution was dark yellow orange and contained a large amount of black solid. The decomposition products were chromatographed on a column of neutral alumina (2.3 × 25 cm). Elution with benzene and benzene–ethyl acetate (95:5 v/v) gave starting azide (0.81 g, 54%). Further elution with benzene–ethyl acetate (95:5 v/v) gave a yellow solid which, on recrystallization from light petroleum (bp 60–110°), gave light yellow crystals of ***N*-(1′-sulfonylazidoferrocenesulfonyl)-azepine** (**17**, 0.074 g, 9.4%): mp 109–110° dec; mass spectrum (70 eV) *m/e* (rel intensity) 446 ($M^{\cdot+}$, 2), 92 (100), 65 (24).

Anal. Calcd for $C_{16}H_{14}FeN_4O_4S_2$: C, 43.06; H, 3.16. Found: C, 43.12; H, 3.31.

Elution with benzene–ethyl acetate (85:15 v/v) gave a brown gum (0.007 g) which could not be identified. Elution with benzene–ethyl acetate (1:1 v/v) gave a yellow-brown gum (0.011 g) which could not be identified. Elution with ethyl acetate gave 1′-(*N*-phenylsulfamyl)ferrocenesulfonyl azide (**15**, 0.049 g, 6.3%) (ir). Elution with ethyl acetate–ethanol (98:2 v/v) gave 1′-sulfamylferrocenesulfonyl azide (0.054 g, 8.2%) (ir). Elution with ethyl acetate–ethanol (9:1 v/v) gave ferrocene-1,1′-disulfonamide (0.008 g, 1.4%) (ir).

No other compounds were eluted.

The reaction was repeated but heating was prolonged to 116 and 188 hr. The results are summarized in Table II, as are those of the reaction carried out in the presence of tetracyanoethylene.

**Thermolysis of Ferrocene-1,1′-disulfonyl Azide in Mesitylene at 135°. A. For 3 Hr.** The azide (0.74 g, 0.00188 mol) in mesitylene (30 ml, dried over molecular sieves) was heated at 135° for 3 hr. Chromatography on a column of neutral alumina (2.3 × 25 cm) and elution with benzene–ethyl acetate (95:5 v/v) gave starting azide (0.15 g, 20.4%). Elution with benzene–ethyl acetate (1:1 v/v) gave a light powder of **1′-(*N*-2,4,6-trimethylphenylsulfamyl)ferrocenesulfonyl azide** (**18**, 0.191 g, 26.2%): mp 136–139° dec [from light petroleum (bp 60–110°)]; ir (KBr) 3250 (m, br), 2120 (s), 1365 (s), 1325 (m), 1195 (s), 1135 $cm^{-1}$ (s); NMR ($CDCl_3$) $\delta$ 6.79 (s, 2 H), 5.97 (s, 1 H, exchanges with $D_2O$), 4.90 (t, 2 H), 4.77–4.67 (m, 6 H), 2.22 (s, 3 H), and 2.05 (s, 6 H); *m/e* (rel intensity) 488 ($M^{\cdot+}$, 5).

Anal. Calcd for $C_{19}H_{20}FeN_4O_4S_2$: C, 46.73; H, 4.13. Found: C, 46.87; H, 4.22.

Elution with benzene–ethanol (95:5 v/v) gave 1′-sulfamylferrocenesulfonyl azide (0.075 g, 13.5%) (ir).

No other compounds were eluted.

**B. For 16 Hr.** The decomposition products were chromatographed on a column of neutral alumina (2.3 × 25 cm) and eluted with benzene–ethyl acetate (1:1 v/v) to give ***N,N′*-di(2,4,6-trimethylphenyl)ferrocene-1,1′-disulfonamide** (**19**, 0.15 g, 11.6%): mp >280° (darkened rapidly above 200°) [from light petroleum (bp 60–160°)–ethyl acetate]; ir (KBr) 3310 (m, sh), 3295 (m), 3265 (m, sh), 1325 (s), 1135 $cm^{-1}$ (s); NMR ($CDCl_3$) $\delta$ 6.84 (s, 4 H), 5.80 (s, 2 H, exchanges with $D_2O$), 4.66 (s, 8 H), 2.24 (s, 6 H), and 2.07 (s, 12 H); mass spectrum (70 eV) *m/e* (rel intensity) 582 (11), 581 (25), 580 ($M^{\cdot+}$, 65), 318 (32), 134 (100).

Anal. Calcd for $C_{28}H_{32}FeN_2O_4S_2$: C, 57.93; H, 5.56. Found: C, 57.90; H, 5.62.

Elution with ethyl acetate–ethanol (98:2 v/v) gave **1′-(*N*-2,4,6-trimethylphenylsulfamyl)ferrocenedisulfonamide** (**20**, 0.18 g, 17.2%): mp 195–196° dec [from light petroleum (bp 60–110°)–ethyl acetate]; ir (KBr) 3350 (m), 3270 (m), 1315 (s), 1195 (s), 1135 $cm^{-1}$ (s); NMR (acetone-$d_6$) $\delta$ 7.9 (s, 1 H, exchanges with $D_2O$), 6.88 (s, 2 H), 6.46 (s, br, 2 H, exchanges with $D_2O$), 4.83 (t, 2 H), 4.67 (m, 6 H), 2.22 (s, 3 H), and 2.10 (s, 6 H); mass spectrum (70 eV) *m/e* (rel intensity) 464 (3), 463 (5), 462 ($M^{\cdot+}$, 19), 134 (43), 58 (27), 43 (100).

Anal. Calcd for $C_{19}H_{22}FeN_2O_4S_2$: C, 49.36; H, 4.80. Found: C, 49.56; H, 4.88.

Elution with ethyl acetate–ethanol (9:1 v/v) gave a ferrocene-1,1′-disulfonamide (0.101 g, 14.2%) (ir).

**Thermolysis of 6 in Cyclohexene.** The azide (0.85 g, 0.00215 mol) was added to cyclohexene (30 ml, freshly distilled, dried over molecular sieves) and the solution boiled under reflux under nitrogen (dry, $O_2$ free). After 11 hr a small quantity of orange needles was seen at the surface. On cooling, the yellow solution, which contained no dark solid, yielded a further small quantity of orange needles. A few crystals were removed from the solution, washed with light petroleum (2 × 10 ml), and dried in a stream of nitrogen for 2 min: ir (KBr) 1610 (s), 1310 (s), 1125 $cm^{-1}$ (s). Gas chromatography of the solution [OV-17 (20%) on Gas-Chrom Q, 6 ft × 3/16 in., isothermal at 130°, He flow 80 ml/min] showed the presence of a small peak with retention time 171 sec, identified as cyclohexanone (vide infra). Addition of moist alimina to the reaction solution caused a marked (tenfold) increase in the area of the peak (relative to solvent peak area). Collection of this peak by capillary technique gave a colorless liquid, identical with an authentic sample of cyclohexanone (ir, MS, retention time). The decomposition products were chromatographed on a column of neutral alumina. Elution with ethyl acetate–ethanol (99:1 v/v) gave 1′-sulfamylferrocenesulfonyl azide (0.16 g, 20.2%) (ir). Elution with ethyl acetate–ethanol (9:1 v/v) gave ferrocene-1,1′-disulfonamide (0.211 g, 29.4%).

**Thermolysis of 6 in Cyclohexene and Sodium Borohydride Reduction.** The azide (1.49 g, 0.00377 mol) was dissolved in cyclohexene (35 ml, freshly distilled, dried over molecular sieves), molecular sieves (1 g) was added, and the solution was heated at 135° for 4 hr. The solution was orange and contained some orange needles mixed with a small amount of black solid. The thermolysis vessel was opened under a cone of nitrogen, a small magnetic stirring bar was introduced, and then sodium borohydride (0.45 g) in acetonitrile (20 ml, dried over molecular sieves) was added and a drying tube ($CaCl_2$) was placed on the vessel. The solution was stirred at room temperature for 3 hr in the absence of light and a second portion of sodium borohydride (0.25 g) was added. The solution was stirred overnight in the absence of light at room temperature and then aqueous acetic acid (5% v/v, 10 ml) was added dropwise. The aqueous layer was made basic to litmus with sodium carbonate, ethyl acetate (300 ml) was added, and the solution was dried ($CaCl_2$). The products were chromatographed on a column of neutral alumina (2.3 × 25 cm). Elution with benzene–ethyl acetate (1:1 v/v) gave *N,N′*-dicyclohexylferrocene-1,1′-disulfonamide (8, 0.82 g, 42.6%), identical with an authentic sample. Elution with ethyl acetate–ethanol (98:2 v/v) gave ferrocene-1,1′-disulfonamide (0.32 g, 24.3%) (ir).

**Thermolysis of 6 in Freon 113.** The azide (0.88 g, 0.00222 mol) was dissolved in Freon 113 and the solution was heated at 135° for 3 hr. The products were chromatographed on a column of neutral alumina (2.3 × 25 cm). Elution with benzene–ethanol (98:2 v/v) gave starting azide (0.11 g, 12.1%). Elution with benzene–ethanol (95:5 v/v) gave 1′-sulfamylferrocenesulfonyl azide (0.020 g, 2.8%) (ir). Elution with benzene–ethanol (9:1 v/v) gave ferrocene-1,1′-disulfonamide (0.023 g, 3.5%) (ir).

**Ferrocenesulfonyl Hydrazide (23).** To a stirred solution of ferrocenesulfonyl chloride (2.83 g, 0.01 mol) in benzene (12 ml) was added 50% hydrazine hydrate (1.60 g, 0.025 mol) dropwise over a 30-min period at 5–10°. The solution was kept at 50° for 6 hr, cooled, and evaporated in vacuo to give a yellow residue. This was recrystallized from absolute ethanol to give **ferrocenesulfonyl hydrazide** (**23**, 1.71 g, 61%): mp 135–140° dec; ir (KBr) 3400 (m), 3275–3270 (m, br), 1325 (s), 1130 $cm^{-1}$ (s); NMR ($CDCl_3$) $\delta$ 5.65 (s, br 1 H, exchanges with $D_2O$, NH), 4.75 (t, $J_{2,3}$ = 1.7 Hz, 2 H, $H_2$ and $H_5$), 4.49 (t partially under 4.47, 1 H, $H_3$ and $H_4$), 4.47 (s, 5 H, $H_1'$–$H_5'$), and 3.48 (s, br, 2 H, exchanges with $D_2O$, $NH_2$); mass spectrum (70 eV) *m/e* (rel intensity) 281 (4), 280 ($M^{\cdot+}$, 31), 250 (60), 202 (33), 186 (90), 185 (44), 138 (100), 129 (67), 121 (68), 56 (79).

Anal. Calcd for $C_{10}H_{12}FeN_2O_2S$: C, 42.88; H, 4.32. Found: C, 43.14; H, 4.44.

**Ferrocenyl Ferrocenethiolsulfonate (24).** Ferrocenosulfonyl hydrazide (20 mg) was heated in an open test tube in an oil bath at 150–160° for about 25 min (until no further evolution of gas was noted). The gas evolved was basic. A small amount of yellow material solidified on the sides of the test tube above the level of the oil bath. This was shown to be ferrocene by comparison of its ir and MS with that of an authentic sample.

The yellow residue which remained at the bottom of the test

tube was recrystallized from benzene–light petroleum (bp 60–110°) to give golden yellow plates of **ferrocenyl ferrocenethiolsulfonate,** begins to darken at 180° and melts at 194–195° (dec): ir (KBr) 1320 (s), 1120 $cm^{-1}$ (s); NMR ($CDCl_3$) $\delta$ 4.40 (m, 9 H), 4.32 (m, 2 H), 4.21 (s, 5 H), and 4.18 (m, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 467 (2), 466 ($M^{\cdot+}$, 7), 402 (52), 306 (22), 304 (24), 272 (24), 233 (21), 218 (36), 217 (100), 186 (29), 153 (39), 121 (40), 56 (31).

Anal. Calcd for $C_{20}H_{18}Fe_2O_2S_2$: C, 51.53; H, 3.89. Found: C, 51.66; H, 3.95.

**2,4,6-Trimethylpyridinium Ferrocenesulfonylimino Ylide (22).** Ferrocenesulfonyl hydrazide (7.00 g) and 2,4,6-trimethylpyrylium perchlorate[16] (5.68 g) in 95% ethanol (300 ml) were boiled under reflux for 24 hr under nitrogen. The solution was cooled and evaporated in vacuo to ca. 30 ml at 50°. A solution of potassium hydroxide (1.41 g) in water (9 ml) was added dropwise at 0° to the stirred solution. After 30 min at 0° the mixture was filtered cold and the filtrate evaporated onto basic alumina (10 g). The ylide was chromatographed on a column of basic alumina (2 × 45 cm) prepared in benzene. It was eluted with ethyl acetate–ethanol (95:5 v/v) and recrystallized from methanol–ether at −78° to give yellow-orange plates of **2,4,6-trimethylpyridinium ferrocenesulfonylimino ylide** (4.96 g, 52%): mp 180–182° dec; ir (KBr) 1290 (s), 1120 $cm^{-1}$ (s); $\lambda_{max}$ (EtOH) 212 nm ($\epsilon$ 37 000), 249 (13 360), 350 (730), and 426 nm (206); NMR ($CDCl_3$) $\delta$ 7.15 (s, 2 H, $H_3$ and $H_5$ of pyr), 4.44 (t, $J_{2,3}$ = 3.3 Hz, 2 H, $H_2$ and $H_5$), 4.35 (s, 5 H, $H_1'$–$H_5'$), 4.21 (t, $J_{2,3}$ = 3.3 Hz, 2 H, $H_3$ and $H_4$), 2.59 (s, 6 H, 2-$CH_3$ and 6-$CH_3$), and 2.39 (s, 3 H, 4-$CH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 385 (7), 384 ($M^{\cdot+}$, 33), 265 (36), 199 (12), 177 (29), 135 (21), 121 (100).

Anal. Calcd for $C_{28}H_{20}FeN_2O_2S$: C, 56.26; H, 5.24. Found: C, 56.58; H, 5.39.

**Decomposition of the Ylide 22. A. Thermolysis.** The ylide (0.34 g) in benzene (25 ml, Na dried) was heated at 175° for 10 hr. After cooling, the yellow solution and dark precipitate were removed, the liner was rinsed with benzene (3 × 10 ml), and the product mixture was evaporated onto neutral alumina (3 g). The mixture was chromatographed on a column of neutral alumina (1 × 20 cm). Elution with benzene–ethyl acetate (95:5 and 1:1 v/v) gave 2,4,6-trimethylpyridine (0.068 g, 71%), identical (ir, NMR, and MS) with an authentic sample. Further elution with benzene–ethyl acetate (1:1 v/v) gave ferrocenesulfonamide (0.11 g, 54%), identical (ir and NMR) with an authentic sample. Elution with ethyl acetate–ethanol (95:5 v/v) gave unchanged 2,4,6-trimethylpyridiniumferrocenesulfonylimino ylide (0.038 g, 11%).

**B. Photolysis.** The ylide (1.00 g) was dissolved in benzene (100 ml, Na dried) in a quartz photolysis vessel equipped with a nitrogen bubbler and drying tube ($MgSO_4$). The solution was purged with nitrogen (dry, $O_2$ free) for 30 min and then irradiated with 2537-Å lamps in a Rayonet reactor at a temperature of about 40°. Nitrogen was bubbled slowly through the solution during the irradiation. The progress of the photolysis was followed by removing an aliquot at regular intervals, evaporating to dryness under a cone of nitrogen, and observing the ir. After 72 hr no detectable change had occurred in the infrared spectrum. The solution was then removed, the vessel rinsed with benzene (2 × 20 ml), and the combined solutions chromatographed on a column of neutral alumina. Elution with ethyl acetate–ethanol (95:5 v/v) gave only starting ylide (0.72 g, 72%).

Experiments using 3000- and 3500-Å lamps gave similar results.

**Acknowledgments.** This work was supported by Grant GP-33361X2 from the National Science Foundation, for which we are grateful.

**Registry No.**—**6,** 57362-98-8; **7,** 41686-87-7; **8,** 57363-01-6; **9,** 57363-02-7; **12,** 57363-08-3; **13,** 57363-07-2; **14,** 57363-00-5; **15,** 57363-03-8; **17,** 57363-06-1; **18,** 57363-05-0; **19,** 57363-04-9; **20,** 57362-99-9; **22,** 57395-85-4; **23,** 57395-86-5; **24,** 57395-90-1; phosphorus oxychloride, 10025-87-3; diammonium ferrocene-1,1′-disulfonate, 12184-14-4; sodium azide, 26628-22-8; cyclohexylamine, 108-91-8; cyclohexane, 110-82-7; mesitylene, 108-67-8; 2,4,6-trimethylpyrylium perchlorate, 940-93-2.

## References and Notes

(1) R. A. Abramovitch, C. I. Azogu, and R. G. Sutherland, *Chem. Commun.*, 1439 (1969).
(2) R. A. Abramovitch, C. I. Azogu, and R. G. Sutherland, *Tetrahedron Lett.*, 1637 (1971).
(3) D. S. Breslow in "Nitrenes", W. Lwowski, Ed., Interscience, New York, N.Y., 1970, p 245.
(4) R. A. Abramovitch and R. G. Sutherland, *Fortschr. Chem. Forsch.*, **16,** 1 (1970).
(5) R. A. Abramovitch and G. N. Knaus, *J. Org. Chem.*, **40,** 883 (1975).
(6) R. A. Abramovitch, J. L. Atwood, M. L. Good, and B. A. Lampert, *Inorg. Chem.*, in press.
(7) G. R. Knox and P. L. Pauson, *J. Chem. Soc.*, 692 (1958).
(8) R. A. Abramovitch, E. P. Kyba, and E. F. V. Scriven, *J. Org. Chem.*, **36,** 3796 (1971).
(9) R. A. Abramovitch, T. D. Bailey, T. Takaya, and V. Uma, *J. Org. Chem.*, **39,** 340 (1974); R. A. Abramovitch and V. Uma, *Chem. Commun.*, 797 (1968).
(10) J. E. Baldwin and R. A. Smith, *J. Am. Chem. Soc.*, **87,** 4819 (1965).
(11) R. A. Abramovitch and G. N. Knaus, *J. Chem. Soc., Chem. Commun.*, 238 (1974).
(12) L. A. Paquette, D. E. Kuhla, J. H. Barrett, and R. J. Haluska, *J. Org. Chem.*, **34,** 2866 (1969).
(13) R. A. Wohl, *J. Org. Chem.*, **38,** 3862 (1973).
(14) R. A. Abramovitch, G. N. Knaus, M. Pavlin, and W. D. Holcomb, *J. Chem. Soc., Perkin Trans. 1,* 2169 (1974).
(15) R. A. Abramovitch and T. Takaya, *J. Org. Chem.*, **38,** 3311 (1973).
(16) D. Diels and K. Alder, *Ber.*, **60,** 716 (1927).

# Interaction of Alkali Metals with Unsaturated Heterocyclic Compounds. II. 2,4-Diphenylquinazoline

James G. Smith,* John M. Sheepy, and Earl M. Levi

*Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada*

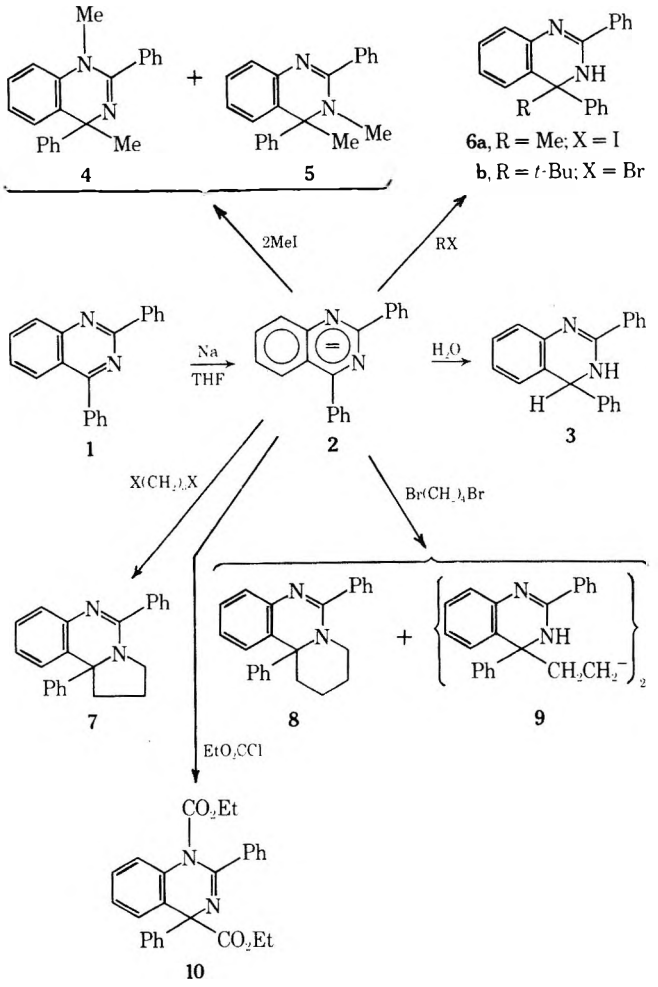
*Received August 14, 1975*

2,4-Diphenylquinazoline (1) is reduced by sodium in tetrahydrofuran to a dianion 2. Alkylation of this dianion with methyl iodide, *tert*-butyl bromide, 1,3-dihalopropanes, and 1,4-dibromobutane is described as well as acylation with ethyl chloroformate. Generally the alkylation products are 3,4-dihydroquinazoline derivatives but 1,4-dihydro derivatives are isolated in the case of methyl iodide and dimeric products formed by intermolecular alkylation are observed with 1,4-dibromobutane. The products formed by alkylation with *tert*-butyl bromide also contain compounds containing the alkyl group in the benzo ring. These products were also formed by the reaction of 1 with *tert*-butyllithium. In the case of acylation only 1,4-dihydroquinazoline derivatives were detected.

The reduction of conjugated bisimines by alkali metals in aprotic solvents has been examined in earlier studies.[1,2] In this report the combination of two imine groups conjugated through a carbon–nitrogen bond is studied by the reductive metalation of 2,4-diphenylquinazoline (1). This compound was selected since it both contained the desired conjugative arrangement and is similar to a compound examined in an earlier report,[2b] 2,3-diphenylquinoxaline.

Only the reduction of 1 in tetrahydrofuran (THF) by sodium was examined in detail, since under these conditions

Scheme I
Reactions of the Dianion from 2,4-Diphenylquinazoline




the dianion **2** (Scheme I) was produced smoothly. In diethyl ether the reduction was very slow and with lithium in THF excessive reduction was obtained.

Protonation of the dianion, **2**, produced 3,4-dihydro-2,4-diphenylquinazoline (**3**). The 3,4-dihydro structure was assigned since the same product was obtained from the lithium aluminum hydride reduction[3] of 2,4-diphenylquinazoline and from the addition of phenylmagnesium bromide to 2-phenylquinazoline.[4]

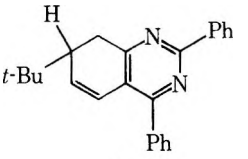
Alkylation of the dianion, **2**, with methyl iodide produced an isomeric mixture of 1,4-dimethyl-1,4-dihydro- and 3,4-dimethyl-3,4-dihydroquinazolines (**4** and **5**), respectively, in the ratio of 2.2:1. Separation was effected by chromatography on alumina and the compounds proved identical with those prepared earlier[5] by a different route and characterized by spectroscopic correlations.

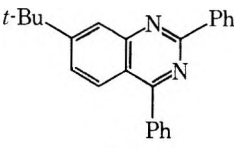
The stepwise nature of the alkylation was indicated by the formation of the monoalkylation product 4-methyl-3,4-dihydro-2,4-diphenylquinazoline (**6a**) when only 1 equiv of the alkylating agent was employed.

An extension of the fused ring system was effected by alkylating **2** with dihaloalkanes. Attachment of a five-membered ring to the 3,4 position (i.e., **7**) was successful with 1,3-dichloro- and 1,3-dibromopropane: the reaction was less efficient with iodide as the leaving group since appreciable amounts of **1** were regenerated. Attempts to fuse a six-membered ring to the quinazoline framework to give **8** by using 1,4-dibromobutane were less satisfactory. While **8** was obtained, competitive intermolecular alkylation occurred giving dimeric product **9** and apparently oligomeric material.

Alkylation of dianion **2** with *tert*-butyl bromide proceeded smoothly to give a reaction mixture containing approximately 75% alkylation product, the remainder being 2,4-diphenylquinazoline (**1**). The main product was 4-*tert*-butyl-2,4-diphenyl-3,4-dihydroquinazoline (**6b**), and an authentic sample was synthesized by treating **1** with *tert*-butyllithium. Like the known 4-*tert*-butyl-3,4-dihydroquinazoline,[4] **6b** was oxidatively dealkylated by alkaline potassium ferricyanide to 2,4-diphenylquinazoline.

Two additional products, **11** and **12**, were isolated in lower yields from both the alkylation reaction and from the reaction of **1** with *tert*-butyllithium.

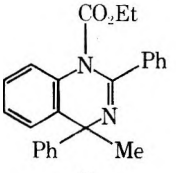


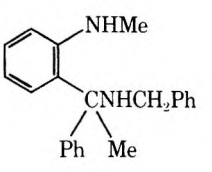



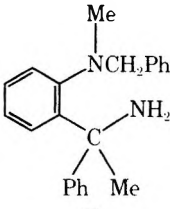

Structure **11** was deduced from spectral data. The presence of a pyrimidine ring was indicated by the characteristic[6] downfield chemical shift of the ortho protons of the 2-phenyl substituent and by the presence of a strong absorption band at 1550 $cm^{-1}$ in the infrared spectrum characteristic[7] of the pyrimidine ring. A much more complex pattern exists[5] in the 1500–1650-$cm^{-1}$ region in the case of quinazolines or their 1,4- and 3,4-dihydro derivatives. Integration of the NMR spectrum of **11** showed that the benzo ring of **1** had been alkylated, since, aside from the *tert*-butyl protons, two vinyl, three aliphatic, and ten aromatic protons were present. Substitution in the 4-phenyl (or 2-phenyl) rings would produce quite different ratios. Decoupling of the signals showed that the methylene group was coupled only to the tertiary proton while the latter was coupled to both vinyl protons. This plus the substantial difference in chemical shift of the two vinyl protons ruled out a 5,8-dihydroquinazoline derivative and narrowed the choice to a 5,6- or 7,8-dihydro compound. The 7,8-dihydro structure was selected because of the pronounced downfield position of the methylene resonance and because this chemical shift remained essentially unchanged when the solvent was changed from carbon tetrachloride to benzene-$d_6$. By analogy with alkyl-substituted pyridine derivatives,[8] these observations indicated that the methylene group was attached to the heterocyclic ring at a carbon $\alpha$ to the nitrogen. If it were attached $\beta$ to the heteroatom, a marked change in the chemical shift would accompany the change of solvent.

Dehydrogenation of **11** produced 7-*tert*-butyl-2,4-diphenylquinazoline (**12**), thus relating the position of the alkyl group in the two minor products.

Acylation of **2** with ethyl chloroformate produced the single product 1,4-di(ethoxycarbonyl)-2,4-diphenyl-1,4-dihydroquinazoline (**10**). This structure was assigned on the basis of the similarity of its spectroscopic properties[5] to those of **13**. Confirmation of the 1,4-dihydro structure of **13** was obtained by the lithium aluminum hydride reduction[9] of both **13** and **4** to the same product **14**. In the case of the



reduction of 13, the yield of 14 was 30%; the major product 6a arose by loss of *N*-ethoxycarbonyl group during reduction. Presumably this involved elimination of formaldehyde from the intermediate *N*-hydroxymethyl derivative.

Structure 14 is compatable with the reported[3] direction of cleavage of the quinazoline ring during metal hydride reduction and with the NMR spectra of model compounds. Thus the N–Me resonance of 14 was observed at δ 2.68 in closer agreement with that of *N*-methylaniline (δ 2.80) than that of *N*-benzyl-*N*-methylaniline (δ 3.00, cf. 15). The methylene protons of the *N*-benzyl group were observed as an AB quartet centered at δ 3.53 which closely agreed with the chemical shift of the methylene protons of dibenzylamine (δ 3.67) and benzylmethylamine (δ 3.77) but differed markedly from the shift of the corresponding protons of *N*-benzyl-*N*-methylaniline (δ 4.50, cf. 15). The nonequivalency of the benzylic methylene protons also suggests a proximity of the group to the chiral center as in 14. Furthermore the mass spectrum of 14 showed the base peak at *m/e* 194 corresponding to $[PhC{\equiv}NCH_2Ph]^+$, essentially the main side chain of 14.

The mass spectra of the various dihydroquinazolines prepared here showed a simple pattern. Unlike the parent 2,4-diphenylquinazoline (1) (or its derivative 12), the parent ion was relatively small. The major fragmentation resulted from loss of one or the other of the two substituents at the 4 position to give the base peak and a second major fragment. Loss of the 4-phenyl substituent dominated when the second substituent was hydrogen (i.e., 3) or when the other substituent was part of a ring (i.e., 7 and 8). When the second substituent was an alkyl group, the $M^+ - R$ fragment formed the base peak and $M^+ - Ph$ a peak of no more than half its intensity.

The presence of ethoxycarbonyl groups introduced additional major fragmentation pathways and differences were observed between a 1- and a 4-ethoxycarbonyl group. The 4-ethoxycarbonyl group was lost in a single step while the 1-ethoxycarbonyl group fragmented stepwise with loss of $CO_2$ and $C_2H_4$.

## Discussion

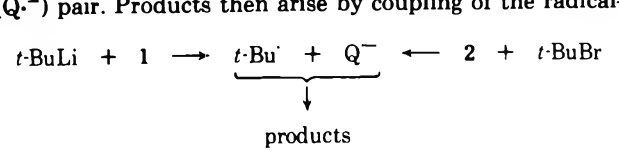
The efficient alkylation of dianion 2 with *tert*-butyl bromide is unexpected and indicates that the reaction cannot be regarded simply as a nucleophilic substitution. The similarity between this reaction and that of *tert*-butyllithium with 2,4-diphenylquinazoline suggests that the alkylation proceeds through a halogen–metal exchange with 2 acting as a source of "dissolved" sodium. Thus,

$$2 + t\text{-BuBr} \rightarrow 1 + t\text{-BuNa} + \text{NaBr}$$

$$1 + t\text{-BuNa} \rightarrow \mathbf{6b} + 11 + 12$$

Such exchange reactions with lithium dihydronaphthylide have been described[10] by Screttas. The main product is **6b** formed by nucleophilic addition to the reactive 3,4 bond of 1 and the minor products arise by a "1,6 addition" facilitated by the steric bulk of the attacking nucleophile followed either by protonation to give 11 or by loss of metal hydride to give 12.

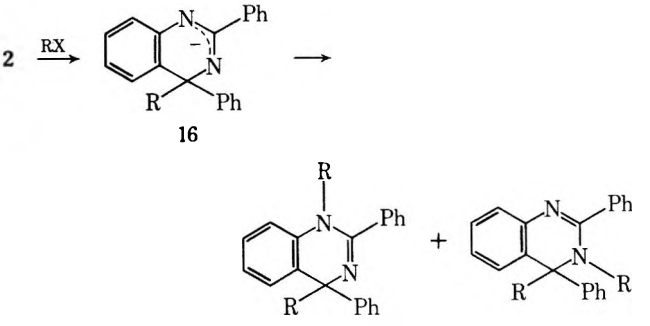
However, an alternative view is that the reaction of 1 with *tert*-butyllithium and 2 with *tert*-butyl bromide are similar since both proceed by one-electron transfer to form a *tert*-butyl radical–diphenylquinazoline radical anion ($Q\cdot^-$) pair. Products then arise by coupling of the radical–radical anion pair with delocalization of the spin density in the radical anion leading to significant amounts of alkylation in the benzo ring. Both reactions are organic redox reactions with the reducing agent being the alkyllithium compound in one case and the dianion 2 in the other.




Insofar as the organolithium compound is concerned, radical intermediates have been detected in the reaction of these organometallic compounds with alkyl halides[11] and with polycyclic aromatic substrates[12]. One-electron transfer mechanisms have been considered for many reactions[13] including that between diaryl ketones and *tert*-butylmagnesium halides[14] and metalation of aromatic compounds by organolithium reagents.[12b]

In the case of the reaction between radical anions and alkyl halides, one-electron reduction is well established[15] as is the facile transfer of electrons from dianions such as 2 to a receptive substrate.[15c]

In any case, the stepwise nature of the alkylation of 2 is evident and similar to that noted earlier.[2b] The marked difference in reactivity between the original dianion 2 and its monoalkylated product is no doubt due to the effective delocalization of the residual charge over the amidine portion of the molecule (i.e., 16) which leads also to the two dialk-




ylation products observed in those cases where rapid dehydrohalogenation of the alkylating agent does not occur.

In the case of 1,3-dihalopropanes and 1,4-dihalobutanes, the monomeric products are necessarily 3,4-dihydro derivatives. The much higher yield of 7 compared to 8 can be the result of several factors. One of these, as has been suggested in a related case,[16] may be unfavorable nonbonded interactions of the substituents attached to the forming six-membered ring which slows its rate of formation sufficiently that competitive intermolecular alkylation occurs leading to **9**.

## Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Analyses are by M-H-W Laboratories, Garden City, Mich. Spectra were recorded on Beckman IR-10 (ir), Unicam SP-800 (uv), and Varian T-60 (NMR) instruments. The NMR spectra were determined in $CDCl_3$ and are reported in parts per million downfield from $Me_4Si$ as the internal standard (δ scale). Mass spectra were obtained on an AEI-MS-30 double beam, double focusing mass spectrometer at 70 eV. Samples were inserted via the direct probe and perfluorokerosene was used in the reference beam. In column chromatography, silica gel (70–325 mesh) or neutral aluminum oxide from E. Merck AG was used. Preparative thin layer chromatography was performed with PF-254 aluminium oxide also from E. Merck.

2,4-Diphenylquinazoline (1) was prepared by a published procedure.[17] It was purified by distillation [bp 227° (2 mm)] followed be recrystallization from ethanol, white needles, mp 121–122°.

The procedure used to reduce 1 with alkali metals has been described.[18] Titration of aliquot samples showed that the reaction between 1 and sodium in tetrahydrofuran (THF) was complete in 8 hr forming a deep blue solution of the dianion 2. Generally, complete reaction was ensured by a 12–16-hr reaction time. When diethyl ether (DEE) was used as a reaction solvent, the reduction was inordinately slow. With lithium and THF, the reduction ap-

peared to exceed the requirement of 2 g-atom of Li per mole of **1**. Consequently, only the sodium–THF system was employed in subsequent reactions.

**Preparation of 3,4-Dihydro-2,4-diphenylquinazoline (3).** The dianion **2** (4.3 mmol) in 100 ml of THF was treated at −78° with 3 ml of water. Decolorization was rapid and after 15 min the reaction product (1.2 g) was isolated by diluting the mixture with water and extracting with ether. Chromatography on silica gel with benzene as eluent gave 0.11 g (9%) of **1** and 1.08 g (88%) of **3**, mp 149–152°. Recrystallization from benzene–petroleum ether gave 0.83 g (70%) of **3**, mp 153–155°, identical with a sample previously prepared[5] by the reaction between phenylmagnesium bromide and 2-phenylquinazoline: mass spectrum *m/e* (rel intensity) 284 ($M^+$, 19), 283 (11), 208 (18), 207 (100), 180 (15), 129 (19), 77 (38).

In an alternative reduction procedure, a mixture of 0.42 g (1.5 mmol) of **1**, 0.3 g (7.9 mmol) of lithium aluminum hydride, and 125 ml of ether was stirred for 3 days at 20°. Water was added to destroy excess hydride, the mixture was filtered and evaporated, and the residue was recrystallized from pentane giving 0.34 g (80%) of **3**, mp 150–153°.

**Alkylation of the Dianion 2 with Methyl Iodide. Preparation of 4, 5, and 6a.** A solution of the dianion **2** (0.015 mol) in 250 ml of THF was treated at −78° with 5.2 g (0.037 mol) of methyl iodide. After 1 hr at −78°, the solution was allowed to warm to 20° and stand for 12 hr. Dilution with water and extraction with ether provided the crude product, which was chromatographed on 120 g of silica gel using 2:3 diethyl ether–30–60° petroleum ether. In order of elution, there were obtained 0.6 g (14% recovery) of starting material **1**, 2.83 (60% yield) of crude 1,4-dimethyl-1,4-dihydro-2,4-diphenylquinazoline (**4**), and 1.28 g (27% yield) of crude 3,4-dimethyl-3,4-dihydro-2,4-diphenylquinazoline (**5**).

The crude **4** was recrystallized from cyclohexane–pentane to give 2.28 g (49%), mp 94–95°. A mixture melting point with an authentic sample[5] was undepressed and spectral properties were identical: mass spectrum *m/e* (rel intensity) 312 ($M^+$, 2), 298 (24), 297 (100), 236 (12), 235 (50), 194 (10), 42 (11).

The crude **5** was purified by several recrystallizations from cyclohexane–pentane, mp 114–115°, undepressed on admixture with an authentic sample,[5] and having identical spectral properties: mass spectrum *m/e* (rel intensity) 312 ($M^+$, 8), 298 (24), 297 (100), 236 (10), 235 (48), 118 (15), 42 (13).

The dianion **2** (0.005 mol) when treated under the same reaction conditions with 0.70 g (0.005 mol) of methyl iodide changed color from dark blue to red. After 20 min, 8 ml of ethanol was added and the solution became colorless. Addition of water, ether extraction, and evaporation of the extract gave the crude product (1.5 g). Recrystallization from benzene–petroleum ether gave 1.1 g (74%) of 4-methyl-2,4-diphenyl-3,4-dihydroquinazoline (**6a**), as a pale yellow solid, mp 168–170.5°, undepressed on admixture with an authentic[5] sample and having identical spectral properties: mass spectrum *m/e* (rel intensity) 298 ($M^+$, 5), 284 (22), 283 (100), 222 (9), 221 (53), 77 (12).

**With 1,3-Dihalopropane. Preparation of 7.** The dianion (3.65 mmol) in 100 ml of THF was cooled to −78° and treated with 0.42 g (3.72 mmol) of 1,3-dichloropropane. The solution slowly became dark green and, after 1 hr, the solution was allowed to warm to 20°. Water was added and the crude product (1.20 g) isolated by extraction with chloroform. Recrystallization from 50 ml of ether–30–60° petroleum ether gave 0.47 g of **7**, mp 136–138°. The mother liquors were concentrated and chromatographed on 30 g of alumina (activity grade III) using petroleum ether containing 20% ether to give an additional 0.52 g of **7**, mp 135–137° (combined yield 84%).

An analytical sample was obtained by recrystallization from diethyl ether, mp 137.5–138°. Spectral properties have been reported[5] except for the mass spectrum: *m/e* (rel intensity) 324 ($M^+$, 4), 248 (20), 247 (100).

Anal. Calcd for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.63. Found: C, 85.08; H, 6.23; N, 8.39.

Using 1,3-dibromopropane in the above experiment gave an 83% yield of **7** and a 3% recovery of **1** while alkylating the dianion **2** at 20° with 1,3-diodopropane gave a 60% yield of **7** with 40% of **1** being regenerated.

**With 1,4-Dibromobutane. Preparation of 8 and 9.** The preceding reaction was repeated with 5.1 mmol of **2** in 100 ml of THF and 1.14 g (5.2 mmol) of 1,4-dibromobutane. The crude reaction product, 1.85 g, was chromatographed on 100 g of alumina (activity III) using petroleum ether containing 25% DEE to give in order of elution 0.09 g (6%) of **1**, 0.665 g (39%) of **8**, mp 176–177°, 0.485 g of oligomeric material as a gum, and 0.357 g of an oil identified as **9**.

Recrystallization of **8** from methanol or from petroleum ether–ether gave an allotropic modification with mp 162–163°; mixture melting point with the higher melting form was 176–177°; ir ($CCl_4$) showed the 3,4-dihydroquinazoline pattern[5] at 1560 (s), 1590 (w), 1615 (w) as well as bands at 1490, 1460, 1400 (C–N), 700 $cm^{-1}$; NMR $\delta$ 1.3–3.7 (methylene envelope, 8), 6.7–7.9 (m, 14, aromatic H); uv (EtOH) $\lambda_{max}$ (log $\epsilon$) 235 nm (4.31), 305–320 (3.84); mass spectrum *m/e* (rel intensity) 338 ($M^+$, 7), 282 (13), 262 (18), 261 (100).

Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.27. Found: C, 84.96; H, 6.63; N, 8.07.

The crude **9** was "recrystallized" from benzene to give 0.20 g of an amorphous solid which melted to a viscous gum at 110–113°: ir ($CHCl_3$) 3440 (NH), 2930 (CH), 3,4-dihydroquinazoline pattern[5] at 1560 (s), 1590 (w), 1615 (w) as well as 1490, 690 $cm^{-1}$; NMR $\delta$ 1.3–1.7 (broad s, 4) and 2.0–2.5 (broad s, 4) (methylene H), 6.9–8.1 (m, 28, aromatic H); uv (EtOH) $\lambda_{max}$ (log $\epsilon$) 234 nm (4.64), 310–320 (4.05); mass spectrum *m/e* (rel intensity) 622 ($M^+$, 0.3), 341 (12), 340 (38), 284 (41), 283 (100), 282 (9), 281 (11), 221 (8), 77 (41).

Anal. Calcd for $C_{44}H_{38}N_4$: C, 84.85; H, 6.15; N, 9.00. Found: C, 84.61; H, 6.18; N, 8.89.

The crude oligomer was recrystallized from cyclohexane: mp 287–289° dec; ir ($CHCl_3$) 2940, 1,4-dihydroquinazoline pattern 1620 (s), 1600 (w), 1580 (w), and 1480, 1460, 1380, 700 $cm^{-1}$; NMR $\delta$ 1.1–2.4 (methylene envelope, 6), 3.4–3.9 (broad s, 2, $CH_2N$), 6.3–7.7 (m, 14, aromatic H); the sample was too nonvolatile for a mass spectrum.

**With *tert*-Butyl Bromide. Preparation of 6b, 11, and 12.** The dianion **2** (0.005 mol) in 125 ml of THF was treated at room temperature with 1.5 g (0.011 mol) of *tert*-butyl bromide. An immediate color change to a dark reddish brown occurred. After 12 hr, water was added and the reaction products (1.88 g) isolated by extraction with ether. Chromatography on 225 g of neutral alumina (activity grade II) using petroleum ether graded to 1:1 petroleum ether–diethyl ether gave, in order of elution, 0.19 g (11%) of **11**, 0.11 g of a mixture (see below), 0.21 g (15%) of regenerated **1**, and 1.02 g (61%) of 4-*tert*-butyl-3,4-dihydro-2,4-diphenylquinazoline (**6b**). Two recrystallizations of the crude **6b** gave 0.61 g of an analytical sample: mp 136–137°; NMR $\delta$ 1.30 [s, 9, $C(CH_3)_3$], 5.77 (s, 1, NH), 6.9–8.1 (m, 14, aromatic H); ir ($CHCl_3$) 3440 (NH), 1620, 1590, 1560, 1510, 1490, 1460, 1400, 1370, 930, 840, 690 $cm^{-1}$; uv (EtOH) $\lambda$ (log $\epsilon$) 236 (4.30), 265 (3.85), 320 (3.75); mass spectrum *m/e* (rel intensity) 340 ($M^+$, 0.1), 284 (22), 283 (100), 282 (12), 281 (15), 97 (16), 57 (17).

Anal. Calcd for $C_{24}H_{24}N_2$: C, 84.67; H, 7.10; N, 8.23. Found: C, 84.49; H, 6.94; N, 8.08.

Treatment of **6b** with hot alkaline potassium ferricyanide[21] led to the loss of the *tert*-butyl group with formation of 2,4-diphenylquinazoline (**1**) in 71% yield.

The crude **11** was purified by recrystallization from methanol to give 0.08 g of an analytical sample: mp 114–115°; NMR[19] $\delta$ 1.00 [s, 9, $C(CH_3)_3$], 2.52 [m, 1, CH ($H_7$), $J_{7,8}$ = 10, $J_{7,8'}$ = 9.5, $J_{6,7}$ = 3.7, $J_{5,7}$ = 2.2 Hz), 3.08 and 3.23 [AB portion of ABX, 2, $CH_2$ ($H_8$ and $H_{8'}$), $J_{8,8'}$ = 16.5 Hz], 6.09 [double d, 1, vinyl H ($H_6$), $J_{5,6}$ = 10 Hz], 6.69 [double d, 1, vinyl H ($H_5$)], 7.3–7.9 (m, 8, aromatic H), 8.4–8.7 (m, 2, ortho H of 2-Ph) [Spectra were also recorded with solutions of **11** in $CCl_4$ and $C_6D_6$ to determine the solvent shift. The chemical shifts of the nonaromatic protons are reported in $CCl_4$ ($C_6D_6$): $C(CH_3)_3$ 0.97 (0.78); CH ($H_7$) 2.33 (2.10); $CH_2$ ($H_8$, $H_{8'}$) 2.93, 3.07 (2.90, 3.05); vinyl $H_6$ 6.03 (5.80); vinyl $H_5$ 6.72 (6.65).]; ir ($CHCl_3$) 2970, 1545, 1540, 1420, 1370, 690 $cm^{-1}$; uv (EtOH) $\lambda$ (log $\epsilon$) 239 (4.23), 253 (4.30), 301 (4.39); mass spectrum *m/e* (rel intensity) 340 ($M^+$, 4), 284 (26), 283 (41), 181 (14), 180 (100), 77 (37), 57 (13).

Anal. Calcd for $C_{24}H_{24}N_2$: C, 84.67; H, 7.10; N, 8.23. Found: C, 84.66; H, 7.17; N, 8.25.

The mixture (0.11 g) obtained as the second fraction was chromatographed on a silica gel preparative thin layer plate using 1:1 benzene–petroleum ether. The center cut of the largest band was isolated and rechromatographed on a second plate. The purified material was triturated with pentane to give 30 mg of **12**: mp 100–101.5°; NMR $\delta$ 1.43 [s, 9, $C(CH_3)_3$], 7.4–8.2 (m, 11, aromatic H), 8.67–8.87 (m, 2, ortho H of 2-Ph); ir ($CHCl_3$) 2960, 1620, 1560, 1535, 1490, 1400, 1345, 690 $cm^{-1}$; uv (EtOH) $\lambda$ (log $\epsilon$) 267 (4.75), 306 (sh, 3.88), 329 (3.79); mass spectrum *m/e* (rel intensity) 339 (13), 338 ($M^+$, 67), 337 (19), 323 (18), 282 (20), 281 (100), 220 (15), 58 (10).

Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.00; H, 6.60; N, 8.25.

**Dehydrogenation of 11 to 12.** A mixture of 80 mg of **11**, 4 ml of dry decalin, and 200 mg of 5% palladium on carbon was refluxed

for 40 hr.[20] The cooled mixture was diluted with chloroform, filtered free of the catalyst, and steam distilled to remove the solvents. Extraction of the aqueous residue with chloroform provided the crude product which was purified by preparative TLC on silica gel with trichloroethylene as the developing solvent. The third band from the origin was isolated and gave 45 mg (57% yield) of **12**, identical in its spectral properties with the previously isolated material. Recrystallization from pentane gave 23 mg of **12**, mp 104–106°, mmp 102–104°.

Attempts to oxidize **11** with alkaline ferricyanide[21] were unsuccessful.

**Acylation of 2 with Ethyl Chloroformate. Preparation of 10.** A solution of the dianion (0.005 mol) in 100 ml of THF at −78° was treated with 1.25 g (0.011 mol) of ethyl chloroformate. An immediate color change from blue to purple was observed. The solution was allowed to warm to 20° during which time the color faded to yellow. Addition of water, ether extraction, and evaporation of the extracts gave 1.83 g (85%) of crude **10**, mp 139–141°. Two recrystallisations from ethanol gave an analytical sample, mp 141–142°. Spectral properties have been reported[5] except for the mass spectrum: *m/e* (rel intensity) 356 (25), 355 (100), 312 (19), 311 (75), 284 (17), 283 (75), 281 (19), 205 (10), 180 (10), 77 (9).

Anal. Calcd for $C_{26}H_{24}N_2O_4$: C, 72.88; H, 5.64; N, 6.54. Found: C, 72.91; H, 5.56; N, 6.42.

**Reaction of 2,4-Diphenylquinazoline with *tert*-Butyllithium.** A solution of 1.0 g (3.4 mmol) of **1** in 200 ml of anhydrous diethyl ether was cooled under nitrogen in a dry ice–2-propanol bath and treated with 6 ml (6 mmol) of a solution of *tert*-butyllithium in *n*-pentane. An immediate dark red-brown color developed. After 1 hr the solution was warmed to 20°, water was added, and the product (1.25 g) was isolated by ether extraction.

The reaction product was chromatographed on silica gel using 2:1 petroleum ether–benzene as eluent and the following products, in order of elution, were isolated and identified by their NMR and ir spectra: 0.27 g (24%) of **11**, mp 113–116°, 57 mg of a 1:1 mixture of **11** and **12**, followed by 25 mg of a mixture of **12** and some unidentified material. Further elution of the column with methylene chloride gave 0.65 g (55%) of **6b** as an oil. Recrystallization from hexane gave 0.39 g of **6b**, mp 134–136°.

The fractions containing **12** were rechromatographed on silica gel (preparative TLC) using trichloroethylene as eluent to give 29 mg of **12**.

The above reaction was repeated using 100 ml of THF as the solvent for **1**. Reaction products were separated by chromatography on silica gel with benzene as eluent. All products except **6b** elute rapidly and **6b**, was later removed from the column with methylene chloride. This separation gave an 80% crude yield of **6b** while the remaining products were not isolated but assessed by the integration of the appropriate *tert*-butyl peaks in the NMR spectrum of the fast-moving products. This indicated a 2% yield of **11** and a 7% yield of **12**.

**Reduction of 1,4-Dimethyl-1,4-dihydro-2,4-diphenylquinazoline (4).** A solution of 0.16 g (0.5 mmol) of **4** in 50 ml of THF was added to 0.3 g (8 mmol) of lithium aluminum hydride in 10 ml of THF. After 8 hr of reflux, the mixture was cooled and the excess hydride was destroyed with water, pentane was added, and the organic layer was decanted from the inorganic precipitate. Removal of the solvent gave the crude product, which was purified by preparative thin layer chromatography on silica gel using 1:1 benzene–petroleum ether as developing solvent. In order of increasing $R_f$, there were isolated 53 mg (33% recovery) of **4**, 13 mg of unidentified material, and 87 mg (55% yield) of **14** as an oil. The material was purified by recrystallization of the hydrochloride (decomposed above 138°) from benzene. The purified **14**, an oil, had NMR $\delta$ 1.75 (broad s, 1, NH, exchanges with $D_2O$), 1.90 (s, 3, $CCH_3$), 2.67 (s, 3, $NCH_3$), 3.32 and 3.55 (AB q, $J$ = 12 Hz, 2, $CH_2Ph$), 6.67 (broad t, 2, aromatic H), 7.00 (s, 12, aromatic H); ir ($CHCl_3$) 3300 (NH), 1600, 1580, 1520, 1500, 1460, 1320, 1300, 700 $cm^{-1}$; mass spectrum *m/e* (rel intensity) 316 ($M^+$, 0.4), 301 (1), 239 (3), 211 (29), 210 (11), 209 (22), 208 (29), 194 (100), 165 (11), 106 (50), 91 (57), 77 (27).

Anal. Calcd for $C_{22}H_{24}N_2$: C, 83.50; H, 7.65; N, 8.85. Found: C, 83.24; H, 7.82; N, 8.66.

**Reduction of 1-Ethoxycarbonyl-4-methyl-2,4-diphenyl-1,4-dihydroquinazoline (13).** The **13** was prepared by a modification of our earlier procedure.[5] After the reaction of methyllithium with **1**, the lithium salt was directly treated with ethyl chloroformate. This increased the yield of **13** to 79%. Spectral properties have been reported except for the mass spectrum: *m/e* (rel intensity) 370 ($M^+$, 2), 356 (28), 355 (100), 312 (11), 311 (45), 293 (20), 284 (10), 283 (46), 249 (19), 221 (22), 195 (10), 194 (65), 193 (10), 58 (11).

A solution of 0.75 g (2 mmol) of **13** in 25 ml of diethyl ether was added dropwise to a suspension of 0.3 g of lithium aluminum hydride in 100 ml of ether. After stirring at 20° for 18 hr and refluxing for 6 hr, the mixture was hydrolyzed with water and the ether layer decanted and evaporated. The residue (0.57 g) was treated with 20 ml of diethyl ether to give 0.23 g of **6**, mp 167–170°. The soluble portion was separated by preparative TLC on silica gel using 1:1 benzene–petroleum ether as developing solvent, giving as a fast-moving band 0.17 g (26% yield) of **14** and an additional 0.17 g of **6** (total yield 67%).

Repetition of the reduction in THF at 20° produced only **6**.

**Acknowledgment.** This research was financially supported by the National Research Council of Canada. One of us (J.M.S.) is grateful to the University of Waterloo for a bursary.

**Registry No.**—**1**, 31730-65-1; **3**, 56844-90-7; **4**, 57256-03-8; **5**, 56844-85-0; **6a**, 56844-86-1; **6b**, 57256-04-9; **7**, 56844-91-8; **8**, 57256-05-0; **9**, 57256-06-1; **10**, 56869-71-7; **11**, 57256-07-2; **12**, 57256-08-3; **13**, 56844-89-4; **14**, 57256-09-4; lithium aluminum hydride, 16853-85-3; methyl iodide, 74-88-4; 1,3-dichloropropane, 142-28-9; 1,3-dibromopropane, 109-64-8; 1,3-diiodopropane, 627-31-6; 1,4-dibromobutane, 110-52-1; *tert*-butyl bromide, 507-19-7; ethyl chloroformate, 541-41-3; *tert*-butyllithium, 594-19-4.

## References and Notes

(1) E. J. MacPherson and J. G. Smith, *Can. J. Chem.*, **48**, 1904, 1915 (1970).
(2) (a) E. J. MacPherson and J. G. Smith, *J. Org. Chem.*, **36**, 2516 (1971); *Tetrahedron*, **27**, 2645 (1971); (b) J. G. Smith and E. M. Levi, *J. Organomet. Chem.*, **36**, 215 (1972).
(3) R. F. Smith, P. C. Briggs, R. A. Kent, J. A. Albright, and E. J. Walsh, *J. Heterocycl. Chem.*, **2**, 157 (1965).
(4) W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc.*, 5360 (1965).
(5) J. G. Smith and J. M. Sheepy, *J. Heterocycl. Chem.*, **12**, 231 (1975).
(6) (a) J. M. Murrell, V. M. S. Gil, and F. B. van Duijneveldt, *Recl. Trav. Chim. Pays-Bas*, **84**, 1399 (1965). (b) This downfield shift is absent in the 1,4-dihydro- and 3,4-dihydro-2-phenylquinazolines prepared during this study.
(7) P. Lardenois, M. Selim, and M. Selim, *Bull. Soc. Chim. Fr.*, 1858 (1971).
(8) F. R. McDonald, A. W. Decora, and G. L. Cook, *Appl. Spectrosc.*, **22**, 329 (1968).
(9) R. L. Dannley, M. Lukin, and J. Shapiro, *J. Org. Chem.*, **20**, 92 (1955).
(10) C. G. Screttas, *J. Chem. Soc., Chem. Commun.*, 752 (1972).
(11) (a) G. A. Russell and D. W. Lamson, *J. Am. Chem. Soc.*, **91**, 3967 (1969); (b) H. R. Ward and R. G. Lawler, *ibid.*, **91**, 4928 (1969).
(12) D. A. Shirley, T. E. Harmon, and C. F. Ching, *J. Organomet. Chem.*, **69**, 327 (1974), and references cited therein.
(13) K. A. Bilevitch and O. Yu. Okhlobystin, *Russ. Chem. Rev.*, **37**, 954 (1968).
(14) (a) T. Holm and I. Crossland, *Acta Chem. Scand.*, **25**, 59 (1971); (b) E. C. Ashby, I. G. Lopp, and J. D. Buhler, *J. Am. Chem. Soc.*, **97**, 1965 (1975).
(15) (a) J. F. Garst, *Acc. Chem. Res.*, **4**, 400 (1971); (b) H. E. Zieger, I. Angres, and L. Maresca, *J. Am. Chem. Soc.*, **95**, 8201 (1973); (c) N. L. Holy, *Chem. Rev.*, **74**, 243 (1974).
(16) J. G. Smith, J. R. Talvitie, and A. R. E. Eix, *J. Chem. Soc., Perkin Trans. 1*, 1474 (1975).
(17) H. Meerwein, German Patent 1,074, 047 (Jan 28, 1960); *Chem. Abstr.*, **55**, 21152b (1960).
(18) (a) J. G. Smith, *Can. J. Chem.*, **44**, 59 (1966); (b) J. G. Smith and C. D. Veach, *ibid.*, **44**, 2245, 2497 (1966).
(19) Recorded on a Bruker 90-MHz spectrometer with decoupling used to determine the coupling constants.
(20) Dehydrogenation of 5,6,7,8-tetrahydroquinazoline was reported using this procedure: J. P. Burnett, Jr., and C. Ainsworth, *J. Org. Chem.*, **23**, 1382 (1958).
(21) K. Schofield, *J. Chem. Soc.*, 1927 (1952).

# Mechanistic Studies of Iron Catalysis in the Cross Coupling of Alkenyl Halides and Grignard Reagents

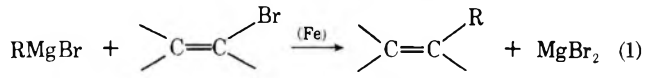
R. Scott Smith and Jay K. Kochi*

*Department of Chemistry, Indiana University, Bloomington, Indiana 47401*

*Received August 26, 1975*

The cross coupling of 1-bromopropene with a variety of primary, secondary, and tertiary alkylmagnesium bromides can be effected with an iron(I) catalyst derived from tris(dibenzoylmethido)iron(III). A detailed study with ethylmagnesium bromide reveals the presence of ethane, ethylene, propylene, propenylmagnesium bromide, and 2,4-hexadiene as side products formed in addition to 2-pentene. The quantities of these products are shown to be in agreement with those expected for a complete material balance and electron balance in the catalytic process. 2-Pentene is formed stereospecifically from either (*Z*)- or (*E*)-1-bromopropene, as is the 2,4-hexadiene side product. Isotopic labeling of the ethyl group shows that ethane, ethylene, and propylene are formed by disproportionation of ethylmagnesium bromide and 1-bromopropene. A mechanism which accommodates all the products as well as the stereochemical and labeling results is proposed, in which the oxidative addition of 1-bromopropene to iron(I) is rate limiting and stereospecific. The propenyliron(III) intermediate subsequently undergoes metathetical exchange with the Grignard reagent and finally reductive elimination of the cross coupled product to regenerate the iron(I) species. Side reactions are considered to proceed from organoiron(III) intermediates by multiple exchanges and reductive disproportionations.

Grignard reagents are cross coupled stereospecifically with alkenyl halides such as 1-bromopropene in the presence of catalytic amounts of iron complexes.[1]



$$RMgBr + \text{>C=C(Br)} \xrightarrow{(Fe)} \text{>C=C(R)} + MgBr_2 \quad (1)$$

Iron(III) complexes are employed, but they are rapidly reduced by Grignard reagent in situ to generate a catalytically active reduced iron species, presumably iron(I). Among various iron complexes examined, tris(dibenzoylmethido)iron(III), $Fe(DBM)_3$, was found to be the most effective, particularly with respect to deactivation of the catalyst.[2] The yields of olefins obtainable by this catalytic process vary according to the structure of the alkyl moiety in the Grignard reagent. Thus, high yields of cross coupled products are obtainable with methylmagnesium bromide. Under the same conditions, ethylmagnesium bromide afforded ethane and ethylene as side products in addition to the expected cross coupled product. The difference can be attributed to the availability of $\beta$ hydrogens in the latter, a factor which is also important in a variety of other organometallic reactions.[3]

In this study we have carried out a thorough analysis of the products formed during the reaction of ethylmagnesium bromide with (*Z*)- and (*E*)-1-bromopropene in the presence of tris(dibenzoylmethido)iron(III). A complete accounting of the material balance as well as the electron balance has been achieved. Together with stereochemical and isotopic labeling studies, they provide substantial mechanistic information about this interesting catalytic process.

## Results

**Cross Coupling of EtMgBr and 1-Bromopropene with $Fe(DBM)_3$.** The iron-catalyzed reaction of ethylmagnesium bromide and 1-bromopropene was examined in detail initially because the yields of cross coupled product were the lowest and significant amounts of side products were generated with this combination. Furthermore, the gaseous hydrocarbon products could be examined directly and quantitatively by gas chromatography without recourse to prior hydrolysis of the reaction mixture.

**A. Products and Stoichiometry.** 1-Bromopropene was added to a solution of the iron catalyst and ethylmagnesium bromide in tetrahydrofuran (THF). The catalyst was prepared beforehand by adding an aliquot of the Grignard solution to a known amount of tris(dibenzoylmethido)iron(III) in the absence of oxygen. The small amount of ethane and ethylene formed during the preparation of the catalyst solution[4] was determined by gas chromatography using the internal standard method.

The cross coupled product, 2-pentene, is formed in approximately 40–50% yields according to the stoichiometry in eq 2. The remainder of the material balance is made up of ethane and ethylene (in excess of that formed during the catalyst preparation), together with propylene and 2,4-hexadiene as shown in Table I. Only traces (<0.01 mmol) of *n*-butane were observed. Control experiments showed that no reaction occurred in the absence of $Fe(DBM)_3$.

$$CH_3CH_2MgBr + BrCH{=}CHCH_3 \xrightarrow{(Fe)} CH_3CH_2CH{=}CHCH_3 + MgBr_2 \quad (2)$$

Ethane and ethylene formally represent the oxidation of ethylmagnesium bromide according to eq 3. The resultant electron deficit can be balanced by the formation of an equivalent amount of 2,4-hexadiene by the reduction given in eq 4. A comparison of the yields of ethane and hexadiene in Table I is in accord with this expectation.

$$2CH_3CH_2MgBr \xrightarrow{-2e} CH_3CH_3 + CH_2{=}CH_2 + 2MgBr^+ \quad (3)$$

$$2CH_3CH{=}CHBr \xrightarrow{+2e} CH_3CH{=}CHCH{=}CHCH_3 + 2Br^- \quad (4)$$

Stoichiometrically, the formation of propylene can be offset by an equivalent amount of ethylene according to the iron-catalyzed disproportionation represented in eq 5.

$$CH_3CH{=}CHBr + CH_3CH_2MgBr \xrightarrow{(Fe)} CH_3CH{=}CH_2 + CH_2{=}CH_2 + MgBr \quad (5)$$

Indeed, the combined yield of propylene and ethane in Table I is close to that of ethylene as given by the sum of eq 3 and 5.

The side reactions represented in eq 3–5 were deduced largely on the basis of material balance and electron balance. Mechanistic information for such processes was obtained by isotopic labeling and stereochemical studies described in the following sections.

Table I
Products and Stoichiometry of the Iron-Catalyzed Reaction of Ethylmagnesium Bromide and 1-Bromopropene[a]

| $C_2H_5MgBr$, mmol | $BrC_3H_5$,[b] mmol | Products, mmol | | | | | Mat. bal,[c] % |
|---|---|---|---|---|---|---|---|
| | | $C_2H_4$ | $C_2H_6$ | Propene | 2-Pentene | 2,4-Hexadiene | |
| 1.02 | 2.96[d] | 0.23 | 0.18 | 0.10 | 0.41 | 0.18 | 92 |
| 2.04 | 1.2 | 0.30 | 0.27 | 0.10 | 0.35 | nd | 105[e] |
| 0.96 | 1.0 | 0.24 | 0.14 | 0.14 | 0.32 | nd | 102[f] |
| 0.96 | 9.4 | 0.33 | 0.14 | 0.15 | 0.45 | nd | 105 |
| 0.96 | 25.8 | 0.34 | 0.12 | 0.19 | 0.53 | nd | 108 |

[a] In reactions containing $3.6 \times 10^{-3}$ mmol of $Fe(DBM)_3$ in 9 ml of THF at 25° for 1 hr. [b] Mixture of 95% (*Z*)- and 5% (*E*)-1-bromopropene. [c] Based on EtMgBr as limiting reagent. [d] 24% *E* and 76% *Z* isomers. Includes [e] 0.28 and [f] 0.31 mmol of EtMgBr unreacted. nd = not determined.

Table II
Stereochemistry of 2-Pentene and 2,4-Hexadiene Formation during the Reaction of Ethylmagnesium Bromide and (*Z*)- or (*E*)-1-Bromopropene[a]

| 1-$BrC_3H_5$, mmol | Convn,[b] % | Products, mmol | | | | | | Mat. Bal,[d] % |
|---|---|---|---|---|---|---|---|---|
| | | $C_2H_4$ | $C_2H_6$ | $C_3H_6$ | 2-$C_5H_{10}$ | 2,4-$C_6H_{10}$ | $C_3H_5MgBr$[c] | |
| 1.16 *Z* | 84 | 0.33 | 0.28 | 0.12 | 0.35 (*Z*) | 0.21[e] (*Z*,*Z*) | 0.08 | 103 |
| 1.16 *E* | 22 | 0.16 | 0.15 | 0.03 | 0.06 (*E*) | 0.07[d] (*E*,*E*) | 0.09 | 97 |

[a] In reactions containing 2.04 mmol of EtMgBr and $3.6 \times 10^{-3}$ mmol of $Fe(DBM)_3$ in 9 ml of THF at 25° for 1 hr. [b] Based on $C_2H_6$ formed on hydrolysis. [c] Based on extra $C_3H_6$ formed after hydrolysis. [d] Based on EtMgBr consumed, including 0.08 mmol in the catalyst preparation. [e] < 0.01 mmol of other isomers.

**B. Examination of the Effect of Various Iron(III) Compounds on the Cross Coupling Reaction.** Ferric chloride ($FeCl_3$), ferric pivalate [$Fe(Pv)_3$], and tris(acetylacetonato)iron(III) [$Fe(acac)_3$] were also used to catalyze the reactions of ethylmagnesium bromide and 1-bromopropene in order to investigate the effect of different types of ligands on the cross coupling reaction. The mixture containing ethylmagnesium bromide and the iron(III) complex was cooled to −46°C after formation of the reduced iron intermediate, in order to inhibit deactivation of this intermediate.[2] Upon addition of 1-bromopropene, the reactions were allowed to warm to room temperature for 1 hr. The results for all four iron(III) complexes showed no significant differences among the products formed in the reaction.

**C. Concentration of Reactants and Temperature.** Ethane, ethylene, and propylene are undesired side products in the cross coupling of ethylmagnesium bromide and 1-bromopropene to 2-pentene. Figure 1 shows that all of these products are formed concurrently, albeit at different rates. An accurate kinetic study of the reaction was not carried out because of the multiplicity of products. However, the rate of production of 2-pentene responded roughly in proportion to the variation in the bromopropene concentration, but it was relatively unaffected by changes in the concentration of ethylmagnesium bromide. This result is in agreement with an earlier more detailed kinetic study of the ferric chloride promoted cross coupling of methylmagnesium bromide and 1-bromopropene, in which side reactions are relatively minor.[1,2]

The amounts of side products are somewhat dependent on the relative concentrations of ethylmagnesium bromide and 1-bromopropene as shown in Table I. Thus, the yield of 2-pentene rises slightly with increasing concentrations of 1-bromopropene; ethylene and propylene change more slowly with variations in concentrations.

The production of propylene can be eliminated by reducing the temperature of the reaction to −40°C, but cross coupling to 2-pentene proceeds much more slowly under these conditions. The production of ethane and ethylene parallels that of 2-pentene and could not be avoided by temperature variations. Interestingly, the addition of catalytic amounts of molecular oxygen into a reaction carried out at −46°C appeared to increase the rates of formation of products. It was also noted that the addition of oxygen caused a change of the blue color[2] to yellow, but no effect on the yields of products was apparent.

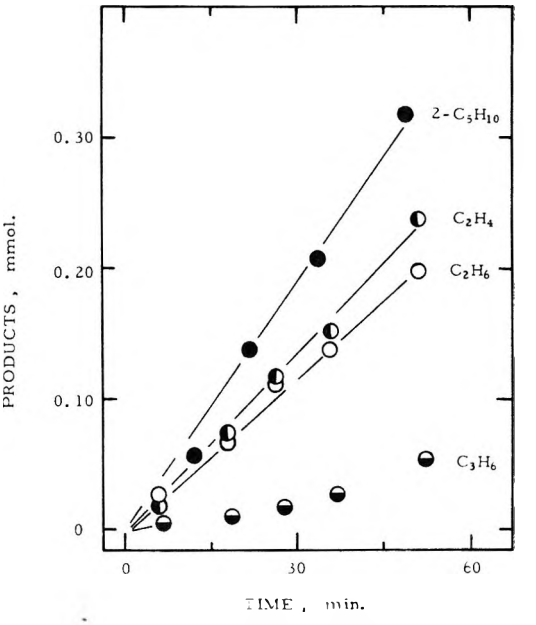


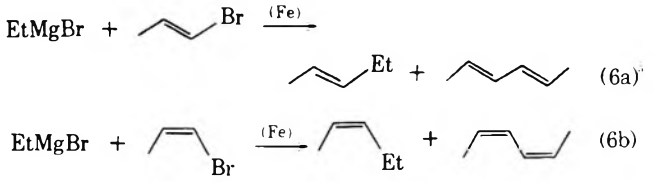

**Figure 1.** Catalyzed reaction of 0.11 *M* ethylmagnesium bromide and 0.35 *M* 1-bromopropene with $4.2 \times 10^{-4}$ *M* $Fe(DBM)_3$ in tetrahydrofuran at 5°C (initial portion only).

**D. Formation of 2-Pentene and 2,4-Hexadiene. Stereochemistry.** The stereochemistry of the coupling reaction in the presence of $Fe(DBM)_3$ was examined using isomerically pure (*Z*)- and (*E*)-1 bromopropenes. The results in Table II show that the cross coupled product, 2-pentene, is formed stereospecifically. Furthermore, the homo coupled side product, 2,4-hexadiene, is also formed stereospecifically since only (*Z*,*Z*)-2,4-hexadiene was found starting with (*Z*)-1-bromopropene. Likewise, only (*E*,*E*)-2,4-hexadiene was formed from (*E*)-1-bromopropene.

Table III
Iron-Catalyzed Coupling of 1-Propenylmagnesium Bromide and 1-Bromopropene[a]

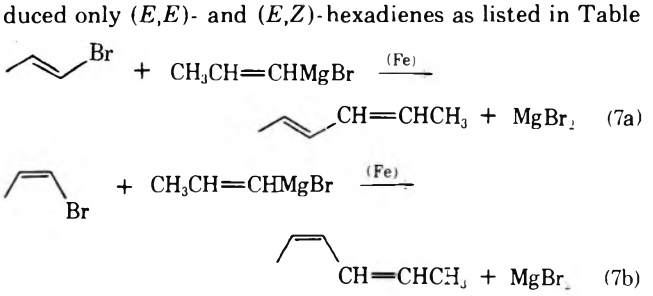
| 1-$C_3H_5MgBr$,[b] mmol | 1-$BrC_3H_5$, mmol | Convn,[c] % | Products, mmol: 2,4-$C_6H_{10}$ | Products, mmol: $C_3H_6$ | Mat. bal,[d] % |
|---|---|---|---|---|---|
| 0.94 *Z*[f] | 1.16 *Z* | 26 | 0.16 (*Z*,*Z*)<br>0.075 (*Z*,*E*)<br><0.01 (*E*,*E*) | 0.02 | 107 (*e*) |
| 1.00 *E*[f] | 1.16 *E* | 30 | 0.25 (*E*,*E*)<br>0.07 (*E*,*Z*)<br><0.01 (*Z*,*Z*) | 0.02 | 108 (105) |

[a] In THF solutions at 25° for 1.5 hr. [b] Isomer employed in Grignard preparation. [c] Based on extra propylene liberated on aqueous quench after 1 hr (includes that consumed in catalyst preparation). [d] Material balance based on RMgX ($BrC_3H_5$). [e] Not determined. [f] Grignard reagent contains 20–25% of the other isomer.




The isomeric 2,4-hexadienes were analyzed by gas–liquid chromatography using either 1,2,3-tris(cyanoethoxy)propene, Apiezon L, or β,β-oxydipropionitrile in the liquid phase as previously established.[6] A mixture of all three isomers, (*E*,*E*)-, (*E*,*Z*)-, and (*Z*,*Z*)-2,4-hexadienes, was prepared by thermolysis of the mixture of propenylsilver complexes derived from (*Z*)- and (*E*)-propenylmagnesium bromide and silver(I).[7]

The stereochemistry of hexadiene formation was also examined in the cross coupling reaction of 1-propenylmagnesium bromide and 1-bromopropene in the presence of $Fe(DBM)_3$. Propenylmagnesium bromide prepared from either pure (*Z*)- or (*E*)-1-bromopropene and magnesium consisted of a mixture of *Z* and *E* isomers, as shown by carboxylation followed by GLC analysis of the methyl esters. Reaction of propenylmagnesium bromide [prepared from (*Z*)-1-bromopropene] with (*Z*)-1-bromopropene afforded a mixture of (*Z*,*Z*)- and (*Z*,*E*)-2,4-hexadienes, but no *E*,*E* isomer. Analogously, propenylmagnesium bromide [derived from (*E*)-1-bromopropene] and (*E*)-1-bromopropene produced only (*E*,*E*)- and (*E*,*Z*)-hexadienes as listed in Table III. These results strongly suggest that homo coupling of propenyl groups is stereospecific, similar to the cross coupling of alkyl and propenyl groups described in eq 1. Unfortunately, the partial isomerization of the propenyl moiety during the preparation of the Grignard reagent[8] prevented us from establishing this point unequivocally. Moreover, the iron-catalyzed cross coupling of vinylmagnesium bromide and either (*Z*)- or (*E*)-1-bromopropene (designed to eliminate stereochemistry at the vinylic center in the Grignard reagent) was unsuccessful. The latter could not be attributed to inhibition of the cross coupling reaction by 1,3-pentadiene or its destruction under reaction conditions; addition of 1,3-pentadiene had little effect on the iron-catalyzed reaction of ethylmagnesium bromide and 1-bromopropene from which it could be recovered.




**Iron-Catalyzed Exchange and Disproportionation of Ethylmagnesium Bromide and 1-Bromopropene.** *Exchange* of halogens between ethylmagnesium bromide and 1-bromopropene would afford propenylmagnesium bromide according to eq 8.

$$CH_3CH_2MgBr + CH_3CH{=}CHBr \xrightarrow{(Fe)} CH_3CH{=}CHMgBr + CH_3CH_2Br \quad (8)$$

The propenyl moiety converted in this manner does not generate propylene during the reaction, but only after subsequent hydrolysis. Indeed, at the end of the reaction the results in Table II (column 8) show that about 7% of the propenyl bromide is converted to an "anionic" form (which affords propylene on hydrolysis). The exchange is most noticeable when ethylmagnesium bromide is present in amounts in excess of that of 1-bromopropene. In order to verify this source of propylene, the iron-catalyzed reaction of EtMgBr (in excess) and 1-bromopropene was run to completion and the volatile components ($C_2$–$C_3$ hydrocarbons) removed in vacuo. The addition of $D_2O$ to the mixture afforded propylene-$d_1$ (>80% isotopic enrichment), determined by comparison of the mass spectral cracking pattern with authentic 1-deuteriopropylene (see Experimental Section). Equivalent results were obtained when the Grignard component was substituted with β,β,β-trideuterioethylmagnesium bromide; and acidolysis with acetic acid afforded propylene-$d_0$ (<10% isotopic enrichment).

$$C_2H_5MgBr + CH_3CH{=}CHBr \xrightarrow{(Fe)} C_2H_5Br + CH_3CH{=}CHMgBr \xrightarrow{D_2O} CH_3CH{=}CHD \quad (9)$$

If the metathetical exchange in eq 8 were the sole source of propenylmagnesium bromide, an equimolar amount of ethyl bromide should also be produced. However, analysis of the reaction mixtures indicated the presence of less than 0.01 mmol of ethyl bromide. Part of the deficiency arises from its subsequent catalytic reaction with either ethylmagnesium bromide according to eq 10[4]

$$CH_3CH_2Br + CH_3CH_2MgBr \xrightarrow{(Fe)} CH_3CH_3 + CH_2{=}CH_2 + MgBr_2 \quad (10)$$

or propenylmagnesium bromide as described in Table IV. Alternatively, it is possible to obviate ethyl bromide as an intermediate, i.e., halogen exchange as described in eq 8, since its replacement with reaction 11

$$CH_3CH{=}CHBr + 2CH_3CH_2MgBr \xrightarrow{(Fe)} CH_3CH{=}CHMgBr + C_2H_6 + C_2H_4 + MgBr_2 \quad (11)$$

is tantamount to summing eq 8 and eq 10.

*Disproportionation* of 1-bromopropene with ethylmag-

Table IV
Iron-Catalyzed Reaction of Propenylmagnesium Bromide and Ethyl Bromide[a]

| $C_2H_5Br$, mmol | $C_3H_5MgBr$,[b] mmol | Time,[c] min | Convn,[c] % | Products, mmol[d] | | | | Mat. bal,[c] % |
|---|---|---|---|---|---|---|---|---|
| | | | | $C_2H_6$ | $C_3H_6$ | 2-$C_5H_{10}$[e] | $C_2H_5MgBr$[f] | |
| 1.34 | 1.66 | 90 | 17 | 0.08 | 0.10 | 0.15 | 0.01 | 79 |
| 1.34 | 2.07 | 500 | 38 | 0.19 | 0.14 | 0.25 | 0 | 74 |
| 3.00 | 0.82 | 90 | 60 | 0.13 | 0.09 | 0.22 | 0 | 70 |
| 3.00 | 0.97 | 500 | 71 | 0.27 | 0.14 | 0.32 | 0.03 | 58 |

[a] In the presence of $3.6 \times 10^{-3}$ mmol of $Fe(DBM)_3$ in 9 ml of THF at 25°. [b] Mixture of *Z* and *E* isomers. [c] Based on $C_3H_6$ formed on hydrolysis after time indicated. [d] In addition to traces of ethylene, 2,4-hexadiene, and propyne. [e] Mixture of *Z* and *E* isomers. [f] Determined by extra ethane formed on hydrolysis.

nesium bromide according to eq 12 could account for the propylene which is observed *during* the catalytic reaction.

$$CH_3CH{=}CHBr + CH_3CH_2MgBr \xrightarrow{(Fe)} CH_3CH{=}CH_2 + CH_2{=}CH_2 + MgBr_2 \quad (12)$$

This type of disproportionation would result in the transfer of a $\beta$ hydrogen of the ethyl group onto the propenyl moiety. Thus, labeled Grignard reagent, $D_3CCH_2MgBr$, was treated with 1-bromopropene and the resultant mixture of $C_2$–$C_3$ hydrocarbons transferred directly from the reaction mixture in vacuo without an aqueous quench. Analysis of the hydrocarbon mixture with the aid of a tandem gas chromatograph–mass spectrometer combination (see Experimental Section) showed that the ethylene fraction consisted exclusively of $C_2H_2D_2$ and the propylene fraction was roughly 90% $C_3H_5D$.

$$CH_3CH{=}CHBr + D_3CCH_2MgBr \xrightarrow{(Fe)} CH_3CH{=}CHD + D_2C{=}CH_2 + MgBr_2 \quad (13)$$

Moreover, the ethane fraction was enriched with $C_2H_2D_4$ to an extent of 82%, suggesting that ethane is also produced by a disproportionation process such as that in eq 10 or 11.

**Structural Effects of the Grignard Reagent in the Cross Coupling with 1-Bromopropene.** The foregoing studies of the iron-catalyzed reaction between ethylmagnesium bromide and 1-bromopropene indicate that disproportionation of the ethyl moiety occurs by transfer of a $\beta$ hydrogen, and it is a major side reaction. Various alkylmagnesium bromides, differing in the number and availability of $\beta$ hydrogens, were treated with 1-bromopropene under a standard set of reaction conditions given in Table V.

Among the primary, secondary, and tertiary alkylmagnesium bromides examined, ethylmagnesium bromide affords the lowest yields of cross coupled product with 1-bromopropene. Otherwise, yields of the cross coupled products in the range of 60–80% were obtainable by GLC analysis. The formation of alkene [R(–H) in Table V] and propylene, which are diagnostic of $\beta$-elimination from the Grignard component, is actually less important in secondary alkyl groups such as isopropyl, *sec*-butyl, and 2-pentyl compared to the primary alkyl analogues. We also deduce from the relative yields of *Z* and *E* alkenes formed from reactions containing an excess of (*Z*)- and (*E*)-bromopropenes that primary alkylmagnesium halides react preferentially with (*Z*)-1-bromopropene (Table V). If the same mixture of 1-bromopropenes is used, secondary alkylmagnesium bromides and *tert*-butylmagnesium bromide produce substantially increased yields of *E* alkenes. The same trend, although on a decreased scale, appears to apply to the formation of 2,4-hexadienes.

## Discussion

The iron-catalyzed reaction of various alkylmagnesium bromides, RMgX, with 1-bromopropene affords cross coupled products, $RCH{=}CHCH_3$, in relatively good yields with excellent stereospecificity.

$$RMgBr + BrCH{=}CHCH_3 \xrightarrow{(Fe)} RCH{=}CHCH_3 + MgBr_2 \quad (14)$$

Five major types of side products are produced during the catalytic process, in greater or lower yields depending on the relative concentrations of the reactants, the temperature of the reaction, and the structure of the alkylmagnesium bromide. Thus, alkene R(–H) and alkane RH from the Grignard component as well as propylene, propenylmagnesium bromide, and 2,4-hexadiene from 1-bromopropene are always formed. No simple relationship could be found for the formation of these side products in relationship to the predominant cross coupled product. The latter suggests that the side products are intimately connected with the principal reaction, and that both processes involve common reactive intermediates. Alternatively, the side products could arise via concurrent but largely independent reactions from the cross coupling process.[9] The rigorous delineation between these basic mechanistic categories is extremely difficult to make in a catalytic system in which the isolation of intermediates is impractical.

Any mechanistic formulation of the catalytic process must take into account the diversity of side products, as well as the isotopic labeling and stereochemical results. In the following discussion we wish to present a reaction scheme which is consistent with the available data, while at the same time keeping the number of intermediates to a minimum.

*The catalyst* is best described as an iron(I) species formed by the facile reduction of the iron(III) precursor by the Grignard reagent.[1,2,4,10] It is a metastable species subject to deactivation on standing, probably by aggregation. Formally, iron(I) species consist of a $d^7$ electron configuration, isoelectronic with manganese(0) and cobalt(II). Only a few complexes of iron(I) have been isolated, but a particularly relevant one is the paramagnetic hydrido complex, $HFe(dppe)_2$, which is stabilized by the bisphosphine ligand, dppe[$Ph_2PCH_2CH_2PPh_2$]. A toluene solution shows a strong ESR signal centered at $\langle g \rangle = 2.085$ with poorly resolved fine structure.[11]

An intense ESR spectrum is also obtained if $Fe(DBM)_3$ is treated with excess ethylmagnesium bromide in THF solutions at −40°C. The ESR spectrum centered at $\langle g \rangle = 2.08$ is broad ($\Delta H \simeq 200G$) and shows no hyperfine structure. A similar broad resonance is observed when $FeCl_3$[$\langle g \rangle = 2.07$] or $Fe(acac)_3$[$\langle g \rangle = 2.08$] are employed. In addition to the broad absorption, ethylmagnesium bromide and $Fe(DBM)_3$ afford an additional spectrum in Figure 2 showing hyperfine splittings. This spectrum at $(g) = 2.00$ retains the same general features when *n*-pentyl- or *sec*-butylmagnesium bromide are employed as reducing agents. It is destroyed immediately by molecular oxygen and has

Table V
Cross Coupling of Primary, Secondary, and Tertiary Alkyl Grignard Reagents with 1-Bromopropene[a]

| Registry no. | RMgBr, mmol | Products, mmol R(−H)[b] | RH | $C_3H_6$ | $C_3H_5R$ (%)[c] | $C_6H_{10}$ | $R_2$ | Mat. bal,[d] % |
|---|---|---|---|---|---|---|---|---|
| 107-26-6 | 1.02 $CH_3CH_2$ | 0.32 | 0.12 | 0.19 | 0.41 *Z*<br>0.05 *E* (49) | nd[e] | Tr[f] | 96 |
| 927-77-5 | 1.04 $CH_3CH_2CH_2$ | 0.45 | 0.03 | | 0.65 *Z*<br>0.02 *E* (73) | 0.02 (*Z*,*Z*) | Tr | 101 |
| 693-25-4 | 1.13 $CH_3(CH_2)_4$ | 0.38 | nd | 0.29 | 0.64 *Z* (60) | 0.08 (*Z*,*Z*) | nd | 96 |
| 926-62-5 | 1.09 $(CH_3)_2CHCH_2$ | 0.12 | 0.0[illegible] | 0.11 | 0.79 *Z* (79) | nd | Tr | 97 |
| 920-39-8 | 1.04 $(CH_3)_2CH$ | 0.07 | 0.02 | | 0.79 (82)[g] | 0.05[h] | 0.05 | 98 |
| 922-66-7 | 1.01 $CH_3CH_2(CH_3)CH$ | 0.04 | 0.03 | 0.02 | 0.5 *Z*<br>0.2 *E* (77)[i] | 0.05[h] | 0.01 | 94[i] |
| 57325-22-1 | 1.00 $CH_3CH_2CH_2(CH_3)CH$ | 0.13 | nd | 0.02 | 0.5 *Z*<br>0.2 *E* (75)[i] | nd | nd | 102[i] |
| 931-50-0 | 1.01 c-$C_6H_{11}$ | 0.04 | nd | Tr | 0.56 *Z*<br>0.15 *E* (76) | nd | nd | 85 |
| 2259-30-5 | 0.95 $(CH_3)_3C$ | 0.1 | nd | 0.08 | 0.37 *Z*<br>0.15 *E* (60) | nd | 0 | 86 |

[a] In reactions containing 2.96 mmol of 1-bromopropene (95% *Z* and 5% *E*) and 3.6 × $10^{-3}$ mmol of $Fe(DBM)_3$ in 9 ml of THF at 25° for 1 hr. [b] Alkene by loss of β hydrogen. [c] Cross coupled product (*Z* is cis and *E* is trans isomer); yields based on RMgX consumed including 0.08 mmol in catalyst preparation. [d] Based on RMgX consumed (determined by hydrolysis). [e] Not determined (nd). [f] Tr, ~0.01 mmol detected. [g] Mixture of *E* and *Z* isomers. [h] 0.04 (*Z*,*Z*) and 0.01 (*Z*,*E*). [i] Value approximate owing to unavailability of authentic product (see Experimental Section).

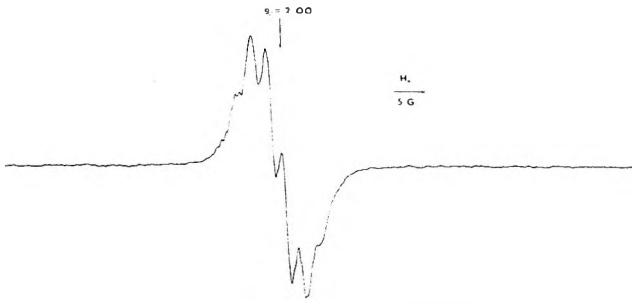
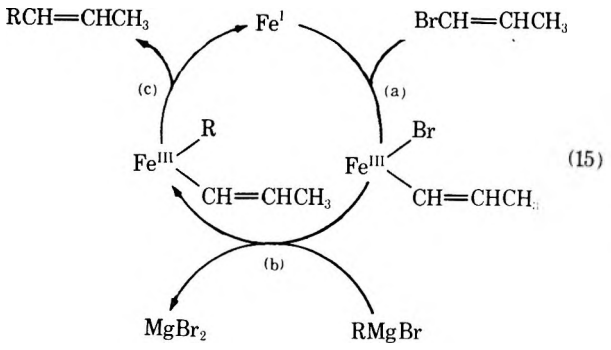


**Figure 2.** ESR spectrum at ⟨*g*⟩ = 2.00 obtained from the reaction of $Fe(DBM)_3$ and ethylmagnesium bromide in THF solution.

been assigned to the reduced ligand, dibenzoylmethide dianion radical.[12]

*The mechanism* of the cross coupling reaction can be accommodated by an oxidative addition of 1-bromopropene to iron(I) followed by exchange with ethylmagnesium bromide and reductive elimination. Scheme I is intended to

**Scheme I**



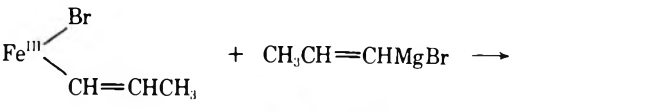

(15)

form a basis for discussion and further study of the catalytic mechanism.[13] In order to maintain the stereospecificity, the oxidative addition of bromopropene in step a should occur with retention. Similar stereochemistry has been observed in oxidative additions of platinum(0) and nickel(0) complexes.[14,15] The methathesis of the iron(III) intermediate in step b is expected to be rapid in analogy with other alkylations.[16] The formation of a new carbon–carbon bond by the reductive elimination of a pair of carbon-centered ligands in step c has been demonstrated to occur with organogold(III), organonickel(II), organoplatinum(IV), and organorhodium(III) complexes.[17]

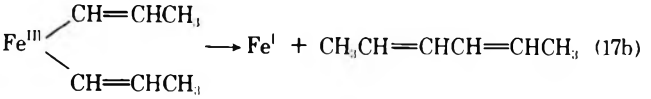
The iron(III) intermediates in Scheme I serve as focal points for the formation of the side products. For example, metathetical exchange of propenyliron(III) with Grignard reagent would afford propenylmagnesium bromide in eq 16.[13,18]

$$Fe^{III}CH{=}CHCH_3 + RMgBr \rightleftharpoons Fe^{III}R + CH_3CH{=}CHMgBr \quad (16)$$

Further exchange in eq 17 would produce bis(1-propenyl)iron(III) species which reductively eliminate to produce the 2,4-hexadienes stereospecifically.[19,20]

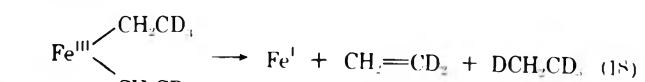



(17a)

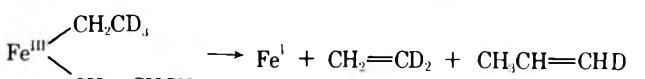



(17b)

Disproportionation products are postulated to arise from alkyliron(III) and/or dialkyliron(III) species formed by an analogous metathesis between iron(III) species and alkylmagnesium bromide. Thus, the disproportionation processes previously represented in eq 10 and 12 may proceed as follows.[21,22]




(18)




(19)

These disproportionations could proceed directly or by a two-step mechanism involving prior transfer of a $\beta$ hydrogen to iron followed by reductive elimination. Similar disproportionation processes have been described with organocopper(I), organomanganese(II), and organoplatinum(II) complexes.[23]

The mechanism in Scheme I accommodates much of the extant data on the iron-catalyzed cross coupling reaction of Grignard reagents and alkenyl halides. The side products derive naturally from organoiron(III) intermediates by reasonably well-established pathways. However, there are a number of interesting observations which merit further scrutiny in the light of this mechanism. For example, it is commonly held that organometallic compounds such as the alkyl- and propenyliron(III) species in Scheme I undergo elimination of $\beta$ hydrogens in the order tertiary R > secondary R > primary R. However, the results presented in Table V run counter to this expectation. Furthermore, if the oxidative addition of 1-bromopropene to iron(I) is rate limiting, the reactivities of the *Z* and *E* isomers should be relatively independent of the Grignard reagent. It is found, however, that the (*Z*)-bromopropene is more reactive than the *E* isomer with primary alkylmagnesium bromide, but the converse is true of methyl,[1,2] secondary, and tertiary alkylmagnesium bromides.[24] The degree of association and complex formation[25] of the latter no doubt affect a quantitative evaluation, but even a qualitative rationalization of this result remains obscure. Changes in the concentration of the reactants as well as the temperature of the reaction could affect the rates and equilibria of the various reactions outlined in Scheme I and eq 16–19, in a manner to change the product distribution (cf. Table I). Nonetheless, the apparent anomalies presented above ultimately must be resolved before this mechanistic formulation can be accepted with more confidence.

Finally, the mechanism in Scheme I bears a resemblance to that previously presented for the nickel-catalyzed reaction of methylmagnesium bromide and aryl bromides.[17c] However, there are outstanding differences between iron and nickel in their abilities to effect cross coupling reactions. Iron is a catalyst which is effective at lower concentrations and temperatures than used with nickel. Even more importantly, cross coupling can be effected completely stereospecifically with an iron catalyst and no alkyl isomerization of the Grignard component has been observed, in contrast to the nickel-catalyzed reactions.[15c,26]

## Experimental Section

**Materials. 1-Bromo-1-propene** obtained from Aldrich Chemical Co. (technical grade) was purified by shaking with aqueous sodium carbonate solution, washing with water several times, and drying over anhydrous calcium chloride. Distillation under nitrogen through a 60-cm Teflon-coated spinning band column afforded material boiling at 60–64°C. GLC analysis on a 40-ft column of oxydipropionitrile on Chromosorb P at 55°C indicated a mixture consisting of 76% (*Z*)- and 24% (*E*)-1-bromopropene (retention time relative to *n*-octane: $r_Z$ 2.77, $r_E$ 2.96). Enriched samples of (*Z*)-1-bromopropene (95%) and (*E*)-1-bromopropene (92%) obtained from Chemical Samples Co. were purified further by preparative GLC on a 10 ft × 0.25 in. column of ODPN on Chromosorb P to afford isomerically pure (>99%) samples of each isomer. All samples were stored in Schlenk tubes under an argon atmosphere in the dark.

**Alkyl bromides** were commercial samples repurified by washing and then redistilled through a spinning band column under nitrogen.[27]

**2-Pentene** was obtained as a mixture of *Z* and *E* isomers (Baker Chemical Co.). **2-Hexene,** 4-methyl-2-pentene, 5-methyl-2-hexene, and 4,4-dimethylpentene-2 (Chemical Samples Co.) and **2-octene** (Phillips Petroleum Co.) were also obtained as mixtures of *Z* and *E* isomers. Propenylcyclohexane was prepared previously.[2] 2,4-Hexadiene as a mixture of *Z,Z* (7%), *E,E* (20%), and *E,Z* (73%) isomers (Aldrich Chemical Co.) was analyzed by GLC on a 3-m 15% TCEP column on Chromosorb W at 45° (retention time relative to the *Z,Z* isomer: $r_{E,E}$ 0.76, $r_{Z,E}$ 0.91). 2,5-Dimethylhexane, 2,3-dimethylbutane (Aldrich Chemical Co.), 3,4-dimethylhexane (Chemical Samples Co.), and cyclohexene (Mallinckrodt) were used without further purification.

**Magnesium** (triply sublimed) in the form of small boules was kindly supplied by the Dow Chemical Co. and used in this form without further preparation. **Tetrahydrofuran** (THF) generously supplied by E. I. du Pont de Nemours and Co. was further purified by vacuum transfer from a dark blue (purple) solution of potassium benzophenone ketyl (with excess potassium) to a dry flask. It was then partially retransferred to a Schlenk tube in vacuo to remove traces of benzophenone, and the flask filled with argon.

**Ethyl-2,2,2-$d_3$ bromide** was prepared from ethyl-2,2,2-$d_3$ alcohol,[28] the deuterium content of which was determined earlier to be >98.5%.[29] The deuterium content of ethyl-2,2,2-$d_3$ bromide (bp 38–40°) was checked by its mass spectrum showing important peaks at *m/e* 113 (63%) and 111 (67%).

**Iron(II) tris complexes** of dibenzoylmethido, acetylacetonato, pivalato, and chloro described earlier were redried in a vacuum oven and used without further purification.[2]

**Grignard reagents** were prepared under an argon atmosphere by slowly adding a THF solution (~1 *M*) of the alkyl halide to excess magnesium with stirring. The colorless mixture was heated to reflux for 30–60 min to assure complete reaction. An aliquot was quenched with acetic acid and the solution analyzed for any unreacted alkyl halide by GLC (40-ft column of ODPN/Chromosorb P at 55°). The liberated alkane was also determined quantitatively by GLC using the internal standard method. Finally, the solution was analyzed by quenching in water and titrating with standard acid (yields 80–95%). The more reactive bromides, *sec*-butyl (50%), 2-pentyl, and cyclohexyl derivatives (40–80%) yield) were treated at 0°, then stirred at room temperature for an additional period. The low yield (30–40%) of *tert*-butylmagnesium bromide necessitated large corrections for isobutane and isobutylene and may have contributed to some uncertainty in the yields.

**General Considerations.** All glassware was cleaned in chromic acid–sulfuric acid solutions, rinsed thoroughly, and soaked in concentrated nitric acid for 30 min. It was thoroughly rewashed and dried in an oven at 110°. The flask was then flame dried on a vacuum line, cooled, and filled with argon. Reagents were introduced with a hypodermic syringe via a silicon rubber septum held by a screw-on top. Reagents were stored in Schlenk tubes under an argon atmosphere and dispensed by drawing them into hypodermic syringes with argon pressure. A standard solution ($3.6 \times 10^{-3}$ *M*) of $Fe(DBM)_3$ in THF was stored under argon and used as needed. Retention times reported hereafter as *r* are relative to the internal standard.

**Ethylmagnesium Bromide and 1-Bromopropene. Standard Procedure.** A solution of ethylmagnesium bromide was added to a solution of $Fe(DBM)_3$ at room temperature, whereupon the solution immediately turned dark blue. Methane was added as internal standard, and the amount of ethane and ethylene measured by GLC (2 ft Porapak Q, $r_{C_2H_6}$ 12.8, $r_{C_2H_4}$ 8.5) immediately. Bromopropene was added after 15 min and the reaction allowed to go to completion for 1 hr, the color of the reaction mixture changing to green and finally yellow. Ethanes and ethylene (Porapak Q) and propylene (*n*-butane internal standard, 15 ft Dowtherm on Chromosorb P, $r_{C_3H_6}$ 0.35) were reanalyzed by GLC. The reaction was quenched with acetic acid and the 2-pentene (*n*-hexane internal standard, 10 ft 15% Carbowax 20M–Chromosorb P at 25°, $r_{(Z)\text{-}2\text{-}C_5H_{10}}$ 0.74, $r_{(E)\text{-}2\text{-}C_5H_{10}}$ 0.59) and 2,4-hexadienes (either *n*-octane internal standard, 40 ft ODPN–Chromosorb P at 55°, $r_{E,E}$ 1.96, or tetramethylbutane internal standard, 15 ft 15% Apiezon L–Chromosorb P at 75°, $r_{Z,Z}$ 0.64, $r_{E,Z}$ 0.59, $r_{E,E}$ 0.56) analyzed, together with additional ethane (to determine conversion) and propylene formed in the acidolysis.

***n*-Propylmagnesium bromide and 1-bromopropene** were examined in an analogous manner. Propene and propane were analyzed on a 20-ft column consisting of 3 *N* silver nitrate–benzyl cyanide on Chromosorb P with ethane as internal standard ($r_{C_3H_6}$ 5.6, $r_{C_3H_8}$ 3.0). 2-Hexene and hexane were analyzed on a 40-ft ODPN column at 60° with *n*-pentane as internal standard ($r_{(Z)\text{-}C_6H_{12}}$ 4.3, $r_{(E)\text{-}C_6H_{12}}$ 3.6, $r_{C_6H_{14}}$ 1.4).

**Isopropylmagnesium bromide and 1-bromopropene** reacted as above to produce propane and propylene, which were analyzed in a similar manner. 4-Methyl-2-pentene and 2,3-dimethylbutane were analyzed on the 40-ft ODPN column at 60° with *n*-pentane as internal standard ($r_{(Z)\text{-}C_6H_{12}}$ 3.30, $r_{(E)\text{-}C_6H_{12}}$ 3.13, $r_{C_6H_{14}}$ 2.15).

***sec*-Butylmagnesium bromide and 1-bromopropene** produced *n*-butane, 1-butene, (*Z*)- and (*E*)-2-butene, and propylene, which were analyzed on the 15-ft Dowtherm column at 25° with isobutane as internal standard ($r_{1\text{-}C_4H_8}$ 2.00, $r_{C_4H_{10}}$ 1.82, $r_{(Z)\text{-}C_4H_8}$ 3.18, $r_{(E)\text{-}C_4H_8}$ 2.64, $r_{C_3H_6}$ 0.64). The 4-methyl-2-hexenes were analyzed on the 40-ft ODPN column at 60° by comparing the areas of the peaks with (*Z*)-2-hexene as internal standard ($r_{(Z)\text{-}C_7H_{14}}$ 1.33, $r_{(E)\text{-}C_7H_{14}}$ 1.45), assuming the same calibration factor. The methylhexenes were not otherwise identified. 3,4-Dimethylhexane was analyzed on the 40-ft ODPN column at 60° with *n*-octane as internal standard ($r_{C_8H_{18}}$ 0.94).

**Isobutylmagnesium bromide and 1-bromopropene** afforded propylene, isobutane, and isobutylene, which were analyzed on the 15-ft Downtherm column with (*Z*)-2-butene as internal standard ($r_{C_4H_{10}}$ 0.31, $r_{C_4H_8}$ 0.74, $r_{C_3H_6}$ 0.20). 5-Methyl-2-hexene was analyzed on the 10-ft 15% Carbowax column at 25° with *n*-hexane as internal standard ($r_{(Z)\text{-}C_7H_{16}}$ 2.23, $r_{(E)\text{-}C_7H_{16}}$ 1.82) and 2,5-dimethylhexane analyzed on the 15-ft Apiezon L column at 75° with tetramethylbutane as internal standard ($r_{C_7H_{16}}$ 0.94).

***n*-Pentylmagnesium Bromide and 1-Bromopropene.** Before the addition of bromopropene a small aliquot of the reaction mixture was quenched with acetic acid. Accurate analysis of the $C_5$ hydrocarbons was complicated by their relatively high boiling points. *n*-Pentane, 1-pentene, and 2-pentene were analyzed on the 40-ft ODPN column at 60° with *n*-heptane as internal standard ($r_{C_5H_{12}}$ 0.25, $r_{1\text{-}C_5H_{10}}$ 0.46, $r_{(Z)\text{-}C_5H_{10}}$ 0.60, $r_{(E)\text{-}C_5H_{10}}$ 0.52). 2-Octenes were analyzed on the same column with *n*-octane was internal standard ($r_{(Z)\text{-}C_8H_{16}}$ 2.03, $r_{(E)\text{-}C_8H_{16}}$ 1.76).

**2-Pentylmagnesium bromide and bromopropene** gave *n*-pentane, 1-pentene, and *Z* and *E* pentenes which were analyzed as described above. 4-Methyl-2-heptene was analyzed on the 40-ft ODPN column at 60° using (*Z*)-2-octene as internal standard ($r_{(Z)\text{-}C_8H_{16}}$ 0.550, $r_{(E)\text{-}C_8H_{16}}$ 0.597).

***tert*-Butylmagnesium bromide and 1-bromopropene** afforded propene, isobutylene, and isobutane, which were analyzed in the manner described above. Relatively large amounts of $C_4$ hydrocarbons produced during the preparation of the Grignard reagent necessitated sizable corrections of the amounts of these gases produced in the reaction and limit their reliability. 4,4-Dimethyl-2-pentene and tetramethylbutane were analyzed on the 40-ft ODPN column at 60° with *n*-octane as an internal standard ($r_{(Z)\text{-}C_7H_{14}}$ 0.43, $r_{(E)\text{-}C_7H_{14}}$ 0.65, $r_{C_8H_{18}}$ 0.78). No 5-methyl-2-hexenes were found.

**Cyclohexylmagnesium bromide and 1-bromopropene** produced cyclohexene and cyclohexane, which were analyzed on the 40-ft ODPN column at 60° with *n*-octane as internal standard ($r_{C_6H_{12}}$ 0.67, $r_{C_6H_{10}}$ 1.64). Propenylcyclohexane was analyzed on the 15-ft Apiezon L column at 150° with styrene as an internal standard ($r_{(Z)\text{-}C_9H_{16}}$ 1.10, $r_{(E)\text{-}C_9H_{16}}$ 1.18).

**1-Propenylmagnesium Bromide and Bromoethane.** 1-Propenylmagnesium bromide was prepared from a mixture of 76% (*Z*)- and 24% (*E*)-1-bromopropenes. Approximately 2–3% of 2,4-hexadienes are formed during the preparation of the Grignard reagent. The analyses were carried out in the same manner as described above. In addition, propyne was analyzed on the 40-ft ODPN column.

Propenylmagnesium bromide was also treated with 1-bromopropene by the standard procedure, and the 2,4-hexadienes analyzed by GLC as decribed above.

**Reactions Utilizing $FeCl_3$, $Fe(Pv)_3$, and $Fe(acac)_3$ as Catalysts.** THF solutions of known molarity of the iron compounds were prepared [$FeCl_3$, $6.17 \times 10^{-3}$ *M*; $Fe(Pv)_3$, $3.6 \times 10^{-3}$ *M*; $Fe(acac)_3$, $3.6 \times 10^{-3}$ *M*]. One milliliter of iron solution was added to ethylmagnesium bromide in approximately 7 ml of THF and a −46°C cold bath (liquid nitrogen–acetonitrile) was placed under the reaction flask. 1-Bromo-1-propene was added after 15 min while the reaction mixture was at −46°C. In a like manner $Fe(DBM)_3$ and ethylmagnesium bromide solutions remained active for at least 3 hr at −46°C (1-bromo-1-propene was added at this point). The analytical procedures were the same as used for the ethylmagnesium bromide reaction (vide supra).

**Rate studies** were carried out on reactions prepared using the standard procedure by removing small samples of the head gas to analyze the volatile components. A 0.1-ml aliquot of the reaction mixture was also removed periodically with a hypodermic syringe and quenched with acetic acid. Internal standard (methane, ethane, and *n*-hexane) was added before the commencement of the reaction.

**ESR experiments** were carried out with 0.1 ml of $3.6 \times 10^{-3}$ $Fe(DBM)_3$ solution and 1 ml of THF in an ESR tube flushed with argon and capped with a rubber septum. The Grignard reagent (ethyl, *sec*-butyl, or *n*-pentyl) was added (0.1 ml of 1 *M*) at various temperatures and the spectrum measured immediately on a Varian E4 spectrometer, using a solution of sodium [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadizole anion radical in THF solution as an external standard [$\langle g \rangle = 2.00648$].

Mass spectral analysis was carried out on a Varian CH7 spectrometer interfaced with a specially designed gas chromatograph which was adapted with a $H_2$/Pd splitter operated at 260° and a 3-m 0.04 in. column packed with graphitized carbon black. We are indebted to Professor J. M. Hayes for the use of this facility. The chromatography using hydrogen as carrier gas was capable of separating ethane (4.20 min, −46°), ethylene (2.7 min, −46°), propylene (20 min, −40°; 5.9 min, 0°), and *n*-butane (45 min, 0°). The details of the mass spectral analysis are described elsewhere.[30]

**Acknowledgment.** We wish to thank the National Science Foundation for partial financial support, the Ira E. Lee Fund of Indiana University for a scholarship to R. Scott Smith, Dr. Dwight Matthews and Dr. John Hayes for invaluable assistance with the mass spectral analysis, and Dr. C. Kwan for recording the ESR spectra.

**Registry No.**—(*E*)-1-Bromopropene, 590-15-8; (*Z*)-1-bromopropene, 590-13-6; (*E*)-1-propenylmagnesium bromide, 13154-15-9; (*Z*)-1-propenylmagnesium bromide, 13154-14-8; bromoethane, 74-96-4.

## References and Notes

(1) M. Tamura and J. K. Kochi, *J. Am. Chem. Soc.*, **93**, 1487 (1971).
(2) S. M. Neumann and J. K. Kochi, *J. Org. Chem.*, **40**, 599 (1975).
(3) P. S. Braterman and R. J. Cross, *Chem. Soc. Rev.*, **2**, 271 (1973).
(4) M. Tamura and J. K. Kochi, *J. Organomet. Chem.*, **31**, 289 (1971). M. Tamura and J. K. Kochi, Bull. Chem. Soc. Japan, *44*, 3063 (1971).
(5) Stereochemistry intended only, reaction is not balanced.
(6) L. K. Montgomery, K. Schueller, and P. D. Bartlett, *J. Am. Chem. Soc.*, **86**, 622 (1964).
(7) Cf. G. M. Whitesides and C. P. Casey, *J. Am. Chem. Soc.*, **88**, 4541 (19666).
(8) G. J. Martin, B. Mechin, and M. L. Martin, *C. R. Acad. Sci., Ser. C*, **267**, 986 (1968).
(9) See ref 1, 2, and 30 for additional possibilities.
(10) Iron(0) species cannot be ruled out unequivocally, but replacement of iron(I) with iron(0) does not change the following discussion materially.
(11) M. Gargano, P. Giannocaro, M. Rossi, G. Vasapollo, and A. Sacco, *J. Chem. Soc., Dalton Trans.*, 9 (1975).
(12) C. L. Kwan and J. K. Kochi, to be published.
(13) (a) Coordination around iron will be largely unspecified hereafter, unless required for the discussion. (b) Oxidation numbers are included only as a device for electron accounting and are not necessarily intended to denote actual changes in oxidation states.
(14) (a) J. A. Osborn in "Prospects in Organotransition Metal Chemistry", M. Tsutsui, Ed., Plenum Press, New York, N.Y., in press, citing unpublished results of A. V. Kramer; (b) J. Rajaram, R. G. Pearson, and J. A. Ibers, *J. Am. Chem. Soc.*, **96**, 2103 (1974).
(15) (a) K. Tamao, M. Zembayashi, Y. Kiso, and M. Kumada, *J. Organomet. Chem.*, **55**, C91 (1973); (b) M. F. Semmelhack, P. M. Helquist, and J. D. Gorzynski, *J. Am. Chem. Soc.*, **94**, 9234 (1972); but see (c) M. Zembayashi, K. Tamao, and M. Kumada, *Tetrahedron Lett.*, 1719 (1975); (d) L. S. Hegedus and L. L. Miller, *J. Am. Chem. Soc.*, **97**, 459 (1975).
(16) J. Chatt and B. L. Shaw, *J. Chem. Soc.*, 1718 (1960); J. R. Moss and B. L. Shaw, *ibid.*, 1794 (1966); G. Calvin and G. E. Coates, *ibid.*, 2008 (1960).
(17) (a) A. Tamaki, S. A. Magennis, and J. K. Kochi, *J. Am. Chem. Soc.*, **96**, 6140 (1974); (b) G. W. Parshall, *ibid.*, **96**, 2360 (1974); (c) D. M. Morrell and J. K. Kochi, *ibid.*, **97**, 7262 (1975); (d) M. P. Brown, R. J. Puddephatt, and C. E. E. Upton, *J. Chem. Soc., Dalton Trans.*, 2457 (1974); (e) M. F. Semmelhack and L. Ryono, *Tetrahedron Lett.*, 2967 (1973).
(18) Propenylmagnesium bromide formed in this manner should retain the stereochemistry of the reactant bromopropene in contrast to that formed with magnesium metal. Cf. H. M. Walborsky and M. S. Aronoff, *J. Organomet. Chem.*, **51**, 31 (1973); H. L. Goering and F. H. McCarron, *J. Am. Chem. Soc.*, **80**, 2287 (1958); R. J. Rogers, H. L. Mitchell, Y. Fujiwara, and G. M. Whitesides, *J. Org. Chem.*, **39**, 857 (1974); cf. also ref 8.
(19) Retention of stereochemistry in the reductive elimination of the propenyl moiety is inferred from studies of oxidative addition and cross coupling reactions, but it remains to be proven.
(20) Cf. G. M. Whitesides, C. P. Casey, and J. K. Krieger, *J. Am. Chem. Soc.*, **93**, 1379 (1971).
(21) (a) There are numerous examples of exchanges between Grignard reagents and alkyl halides catalyzed by transition metal species and leading to disproportionation and coupling. For leading references see M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances", Prentice-Hall, Englewood Cliffs, N.J., 1954; L. H. Slaugh, *J. Am. Chem. Soc.*, **83**, 2734 (1961). (b) The presence or absence of alkyl bromide resulting from exchange in this system is uncertain, but it is not crucial to the discussion as presented earlier in eq 8, 10, and 11. (c) Cf. G. Vavon and P. Mottez, *Bull. Soc. Chim. Fr.*, [53] 11 (1944).

(22) Disproportionation of organic ligands as presented in eq 18 and 19 may also proceed between two iron nuclei and is not required by the data to be intramolecular.
(23) G. M. Whitesides, E. R. Stedronsky, C. P. Casey, and J. San Filippo, Jr., *J. Am. Chem. Soc.*, **92**, 1426 (1970); G. M. Whitesides, E. J. Panek, and E. R. Stedronsky, *ibid.*, **94**, 232 (1972); M. Tamura and J. K. Kochi, *ibid.*, **93**, 1483 (1971); *J. Organomet. Chem.*, **42**, 205 (1972); **29**, 111 (1971); G. M. Whitesides, J. F. Gaasch, and E. R. Stedronsky, *J. Am. Chem. Soc.*, **94**, 5251 (1972).
(24) The absence of crossover products reported earlier[1,2] when a pair of different organic bromides are employed also poses some difficult questions for the mechanism in Scheme I.
(25) For example, it is possible that three or more organic ligands are present on the iron(III) intermediates to form ferrate(III) complexes.
(26) K. Tamao, Y. Kiso, K. Sumitani, and M. Kumada, *J. Am. Chem. Soc.*, **94**, 9269 (1972).
(27) D. D. Perrin, W. L. Armaego, and D. R. Perrin, "Purification of Laboratory Chemicals", Pergamon Press, Elmsford, N.Y., 1966.
(28) O. Kamm and C. S. Marvel, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1932, p 25.
(29) A. Tsolis, P. P. Hunt, J. K. Kochi, and S. Seltzer, *J. Am. Chem. Soc.*, in press.
(30) Taken in part from the B.S. Thesis of R. Scott Smith submitted to Indiana University, 1975.

# A Study of the Chemistry of Lithiotriphenylphosphineacetylmethylene[1]

Emre A. Sancaktar, Jack D. Taylor, James V. Hay, and James F. Wolfe*

*Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061*

*Received July 29, 1975*

Treatment of triphenylphosphineacetylmethylene (**3**) with 1.2 equiv of *n*-butyllithium in THF–hexane at −78° resulted in abstraction of a methyl proton to form the ylide anion, lithiotriphenylphosphineacetylmethylene (**4**, M = Li). Reactions of **4** with several alkyl halides, aldehydes, saturated and α,β-unsaturated ketones, and benzoate esters occurred at the terminal carbanion site to afford β-ketophosphonium ylides **9**, δ-hydroxy-β-keto ylides **14**, and the β,δ-diketo ylide **17**, respectively. Sequential treatment of **4** with *n*-butyl iodide and benzaldehyde or with allyl bromide and 3,4-dichlorobenzaldehyde gave 1-phenyl-1-octen-3-one (**13a**) and 1-(3,4-dichlorophenyl)-1,6-heptadien-3-one (**13b**), respectively. Reaction of **4** with o-phthaldehyde afforded 4,5-benzotropone (**16**). Triphenylphosphine(3-phenylpropanoyl)methylene (**9a**) was converted into ylide anion **10** by means of *n*-butyllithium as shown by alkylation with benzyl chloride and allyl bromide to give triphenylphosphine(2-benzyl-3-phenylpropanoyl)methylene (**11a**) and triphenylphosphine(2-allyl-3-phenylpropanoyl)methylene (**11b**). Attempted formation of **4** (M = K) by means of potassium amide in liquid ammonia lead to cleavage of **3** with formation of diphenylacetonylphosphine oxide (**5**) and diphenylphosphinic amide (**6**).

The synthetic utility of 1,3-dicarbanions[2] of type **1** where A may be a ketone,[3a–c] aldehyde,[4a–c] or ester[5a–f] group, and A′ is a ketone function, was discovered and exploited by Hauser and his co-workers.[2,6] The major preparative value of these intermediates lies in the fact that they undergo regiospecific reactions with electrophilic reagents at the more nucleophilic carbanion site to form compounds of type **2**, where R corresponds to the moiety furnished by the electrophile. When we began the present study, dianions of type **1** had been used primarily to elaborate the structure of their precursors, e.g., in the synthesis of new β-diketones from various β-diketone dianions.[3–c] It occurred to us that the synthetic utility of intermediates of type **1** might be expanded in an interesting new direction if activating group A could be easily removed or altered in several ways after introduction of appropriate R groups adjacent to A′. Thus, A would act as a control element[7] and its subsequent replacement could give rise to compounds differing significantly from the original dianion precursor.[8]

$$\underset{\mathbf{1}}{A{-}\overset{-}{C}H{-}A'{-}\overset{-}{C}H_2} \xrightarrow{\text{electrophiles}} \underset{\mathbf{2}}{A{-}CH_2{-}A'{-}CH_2R}$$

The ability of the triphenylphosphonium function to stabilize an adjacent carbanion center, its propensity toward cleavage[9] and participation in carbonyl olefination reactions,[9,10] and the fact that no compounds possessing a phosphorus containing activating function had been converted to 1,3-dianions, prompted us to test the above hypothesis with triphenylphosphineacetylmethylene[11] (**3**) as the precursor to ylide anion **4**. The present paper represents an expanded account of our preliminary findings[12] concerning the chemistry of lithiotriphenylphosphineacetylmethylene (**4**, M = Li). Following our communication, Cooke[13] reported on the alkylation of **4** and hydrolysis of the resulting β-keto phosphonium ylides to afford methyl ketones in good yields. Cooke and Goswami[14] also used an ylide dianion related to **4** in the synthesis of an eight-membered-ring diketo ylide. Grieco and Pogonowski have recently made elegant use of dianions containing an expendable activating-control unit in cases involving 1,3-dianions of β-keto phosphonates[15a–b] and β-keto sulfoxides.[16a–b] Kuwajima and Iwasawa[17] have also investigated the chemistry of dianions derived from β-keto sulfoxides.

$$\underset{\mathbf{3}}{(C_6H_5)_3\overset{+}{P}\overset{-}{C}HCOCH_3} \longrightarrow \underset{\mathbf{4}}{[(C_6H_5)_3\overset{+}{P}\overset{-}{C}HCOCH_2]M^+}$$

## Results and Discussion

Initially, formation of ylide anion **4** (M = K) from **3** was attempted using potassium amide in liquid ammonia. However, we were unable to obtain evidence for the desired proton abstraction. Instead, reaction of **3** with 2 equiv of potassium amide in liquid ammonia followed by benzyl chloride afforded a 57% yield of acetonyldiphenylphosphine oxide (**5**) and none of the expected benzyl derivative **9a**.

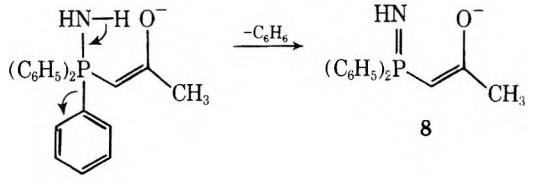
$$3 \xrightarrow{KNH_2} \underset{\mathbf{5}}{(C_6H_5)_2PCH_2COCH_3} + \underset{\mathbf{6}}{(C_6H_5)_2PNH_2}$$

This reaction was repeated several times using potassium amide, but no benzyl chloride. In each case **5** was again produced, along with varying amounts of diphenylphosphinic amide (**6**). Apparently amide ion preferentially attacks the electrophilic phosphorus of **3** to form a pentavalent intermediate such as **7**, which then decomposes with loss of benzene to form iminophosphorane anion **8**. This series of

Table I
Reactions of Lithiotriphenylphosphineacetylmethylene (4)

| Electrophile | Registry no. | Product (no.) | Mp, °C | % yield |
|---|---|---|---|---|
| $C_6H_5CH_2Cl$ | 100-44-7 | $(C_6H_5)_3\overset{+-}{P}CHCOCH_2CH_2C_6H_5$ (9a) | 147.5–149.5[a,b] | 47 |
| $C_6H_5CH_2Br$ | 100-39-0 | $(C_6H_5)_3\overset{+-}{P}CHCOCH_2CH_2C_6H_5$ (9a) | 149–151[a,b] | 44 |
| $CH_2$=$CHCH_2Br$ | 106-96-7 | $(C_6H_5)_3\overset{+-}{P}CHCOCH_2CH_2CH$=$CH_2$ (9b) | 94–96.5[c] | 52 |
| $C_6H_5CH_2Cl$, $C_6H_5CH_2Cl$ | | $(C_6H_5)_3\overset{+-}{P}CHCOCH(CH_2C_6H_5)_2$ (11a) | 177–177.5[d] | 37 |
| $C_6H_5CH_2Cl$, $CH_2$=$CHCH_2Br$ | | $(C_6H_5)_3\overset{+-}{P}CHCOCH(CH_2CH$=$CH_2)(CH_2C_6H_5)$ (11b) | 127.5–130[e] | 50 |
| $Br(CH_2)_3Br$ | 109-64-8 | $(C_6H_5)_3\overset{+-}{P}CHCO(CH_2)_5\overset{-}{C}O\overset{+}{C}HP(C_6H_5)_3$ (12) | 200–207[d] | 59 |
| $CH_3CHO$ | 75-07-0 | $(C_6H_5)_3\overset{+-}{P}CHCOCH_2CH(OH)CH_3$ (14a) | 160–161[d] | 43 |
| $C_6H_5CHO$ | 100-52-7 | $(C_6H_5)_3\overset{+-}{P}CHCOCH_2CH(OH)C_6H_5$ (14b) | 163[d] | 50 |
| $(C_6H_5)_2CO$ | 119-61-9 | $(C_6H_5)_3\overset{+-}{P}CHCOCH_2C(OH)(C_6H_5)_2$ (14c) | 180–182[f] | 81 |
| $C_6H_5COCH_3$ | 98-86-2 | $(C_6H_5)_3\overset{+-}{P}CHCOCH_2C(OH)(CH_3)C_6H_5$ (14d) | 187–187.5[d] | 66 |
| $CH_3COCH_3$ | 67-64-1 | $(C_6H_5)_3\overset{+-}{P}CHCOCH_2C(OH)(CH_3)_2$ (14e) | 185–187[d] | 63 |
|  | 120-92-3 | $(C_6H_5)_3\overset{+-}{P}CHCOCH_2$  (14f) | 154–155[d] | 59 |
|  | 930-68-7 | $(C_6H_5)_3\overset{+-}{P}CHCOCH_2$  (14g) | 124–126[d] | 52 |
| $C_6H_5CH$=$CHCOC_6H_5$ | 94-41-7 | $(C_6H_5)_3\overset{+-}{P}CHCOCH_2C(OH)(C_6H_5)CH$=$CHC_6H_5$ (14h) | 148–150[d] | 63 |
| $C_6H_5COOC_6H_5$ | 93-99-2 | $(C_6H_5)_3\overset{+-}{P}CHCOCH_2COC_6H_5$ (17) | 158–160[a] | 58 |
| $C_6H_5COOCH_3$ | 93-58-3 | $(C_6H_5)_3\overset{+-}{P}CHCOCH_2COC_6H_5$ (17) | 158–160[a] | 60 |

[a] Recrystallized from ethyl acetate–hexane. [b] Lit.[9] mp 148–150°. [c] Recrystallized from hexane. [d] Recrystallized from ethyl acetate. [e] Recrystallized from benzene–petroleum ether. [f] Recrystallized from acetone.



7 8

steps is analogous to the mechanisms for decomposition of phosphonium salts by organolithium reagents[18] and hydrolysis of phosphonium salts and ylides.[19] In the case of basic hydrolysis of β-keto phosphonium ylides, the leaving group is normally the relatively stable enolate ion derived from the carbonyl portion of the ylide.[11,13] Under the present conditions, loss of phenyl anion from **7** may be favored since expulsion of the acetonyl moiety would require its departure as a dianion. Formation of **5** and/or **6** could then arise from protonation and hydrolysis of **8** during work-up.[20] Thus, hydrolytic loss of ammonia from protonated 8 would give phosphine oxide **5**, while competitive loss of acetone from the same intermediate could yield amide **6**. Attempts to isolate an intermediate corresponding to 8 by omitting the final hydrolysis step were unsuccessful. However, benzene was shown to be formed in these experiments, thereby lending support to the proposed mechanism for formation of **5** and **6**.

Formation of ylide anion **4** (M = Li) proceeded smoothly and without appreciable nucleophilic attack at phosphorus when **3** was treated with 1.2 equiv of *n*-butyllithium in THF–hexane at −78°.[21] Initial evidence for the formation of **4** was obtained by quenching with deuterium oxide followed by $^1H$ NMR analysis, which revealed incorporation of 0.9 deuterium atom at the methyl group of recovered **3**.

Alkylation of **4** with benzyl chloride, benzyl bromide, and allyl bromide afforded β-keto ylides **9a,b** (Table I). Surprisingly, **4** failed to undergo C-alkylation with trimethylchlorosilane, and methyl iodide functioned poorly as an alkylating agent. In our preliminary account of this work we reported that alkylations of **4** were best carried out at −68°. Subsequent examinations of these reactions by us and others[13] have revealed that alkylations occur satisfactorily at temperatures from −78 to 0° depending on the reactivity of the halide. Since Cooke[13] had thoroughly investigated the alkylations of **4** with primary and secondary halides, we did not attempt to extend this line of investigation or optimize our yields of **9a,b.** However, we found that **9a** could be converted into secondary ylide anion **10** by means of *n*-butyllithium, and that **10** underwent alkylation with benzyl chloride and allyl bromide to give disubstituted ylides **11a** and **11b** in yields of 37 and 50%, respectively. This procedure could presumably be carried through

$$[(C_6H_5)_3\overset{+-}{P}CHCO\overset{-}{C}HCH_2C_6H_5]Li^+ \xrightarrow{RX}$$

**10**

$$(C_6H_5)_3\overset{+-}{P}CHCOCH(R)CH_2C_6H_5$$

**11**

a hydrolysis step[13] to yield various methyl secondary alkyl ketones. Attempts to alkylate **11a** via its ylide anion were unsuccessful.

Reaction of **4** (2 equiv) with 1 equiv of 1,3-dibromopropane gave bis ylide **12** in 59% yield. Alkylations of **4** could also be followed by Wittig-type reactions without extensively purifying the initial alkylation products. Thus, treatment of **4** with butyl iodide followed by benzaldehyde gave **13a** (63%). Similarly, the combination of allyl bromide and

$$(C_6H_5)_3\overset{+-}{P}CHCO(CH_2)_5\overset{-}{C}O\overset{+}{C}HP(C_6H_5)_3$$

**12**

$$ArCH{=}CHCOCH_2R$$

**13a**, Ar = $C_6H_5$; R = $nC_4H_9$
**b**, Ar = 3,4-$Cl_2C_6H_3$; R = $CH_2$=$CHCH_2$

3,4-dichlorobenzaldehyde afforded **13b** (59%). This reaction sequence provides a convenient method for the synthesis of $\alpha,\beta$-unsaturated ketones of type **13** within the limitations associated with alkylations of **4**.[13]

Next, we examined the reactions of **4** (M = Li) with a series of aldehydes and ketones. In all instances involving both aliphatic and aromatic aldehydes and ketones, condensations occurred exclusively at the terminal carbanion site of **4** to form **14a–h**. No evidence for Wittig products

$$4 + R_1R_2C{=}O \longrightarrow (C_6H_5)_3\overset{+}{P}\overset{-}{C}HCOCH_2\underset{|}{\overset{OH}{C}}R_1R_2$$

**14**

was obtained in any of the cases examined. The results of these experiments are presented in Table I. Structural assignments were verified by analytical and $^1$H NMR data (Table II). In particular the methyl signal of **3**, which appeared at 2.06 ppm, was replaced by a resonance for the methylene protons adjacent to the carbonyl group of **14a–h**. The diastereotopic methylene and the methinyl protons of **14a** and **14b** appeared as ABX patterns while the methylene protons of **14d, 14g,** and **14h** gave rise to AB patterns (Table II).

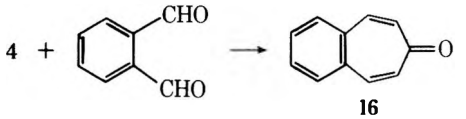
Reaction of ylide anion **4** with the $\alpha,\beta$-unsaturated ketones, 2-cyclohexenone and chalcone, gave predominantly 1,2-addition products, **14g** and **14h.** Several attempts were made to increase the amount of conjugate addition with 2-cyclohexenone by converting **4** into the cuprate derivative **15**[22] using cuprous iodide,[23] cuprous *tert*-butoxide,[24a,b] and

$$[(C_6H_5)_3\overset{+}{P}\overset{-}{C}HCOCH_2]_2CuLi$$

**15**

cuprous cyanide.[25] In each instance 1,2 addition still predominated. At this point we cannot be certain whether **15** was actually formed and added to the carbonyl of the unsaturated ketone, or if the cuprous reagents employed failed to satisfactorily convert **4** into **15.**

Reaction of **4** with *o*-phthalaldehyde afforded directly 4,5-benzotropone (**16**) in 49% yield. This one-step procedure compares favorably with more complex previous methods[26] for the preparation of **16,** and could conceivably be used for the synthesis of 2-alkyl-4,5-benzotropones from ylide anions such as **10.**



**16**

Acylation of **4** was accomplished with methyl benzoate and phenyl benzoate to give diketo ylide **17** (Table I). The $^1$H NMR spectrum of this compound, which was consistent with the assigned structure, revealed that **17** existed as ca. 50% of one or more $\beta$-dicarbonyl enol tautomers in $CDCl_3$.

In summary, ylide anion **4** has been found to react satisfactorily with a representative series of electrophilic compounds including alkyl halides, aldehydes, ketones, and benzoate esters. Among the electrophiles examined we found that cyclohexene oxide and styrene oxide failed to react with **4**, even after 24 hr at 25°.

## Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed in this department, by T. E. Glass, using a Perkin-Elmer 24 Elemental Analyzer. Infrared (ir) spectra were taken on a Beckman IR 20A-X infrared spectrophotometer using 10% chloroform solutions or liquid films. Proton magnetic resonance ($^1$H NMR) spectra were recorded on a JEOL JHM-PS-100 spectrometer, using deuteriochloroform ($CDCl_3$) or deuteriodimethyl sulfoxide ($Me_2SO$-$d_6$) as solvents. Tetramethylsilane ($Me_4Si$) was used as internal standard. Chemical shifts were measured to the center of a singlet or multiplet and are given in $\delta$ units, parts per million (ppm). In all $^1$H NMR descriptions, s = singlet, d = doublet, t = triplet, and m = multiplet. Mass spectra were taken by F. Battrel using a Hitachi Perkin-Elmer RMU-7 spectrometer. Thin layer chromatography (TLC) was carried out using Eastman Chromatogram sheets (silica gel) type 6060 with fluorescent indicator. Acetone–benzene (1:1) was generally used as the developing solvent. Spots were visualized with ultraviolet light. The yield of 4,5-benzotropone (**16**) was determined on a Varian Aerograph Model 90-P gas chromatograph, equipped with a 6-ft column, packed with 6.3% Carbowax 20M on a Gas-Chrom Z 30/60, at a column temperature of 200°. *n*-Butyllithium, as a 2.04 *M* solution in hexane, was purchased from Ventron Co., Alfa Products, Beverly, Mass. Liquid ammonia, obtained from the Matheson Co., E. Rutherford, N.J., was dried prior to use by distillation from potassium metal. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride immediately prior to use. Triphenylphosphineacetylmethylene (**3**) was prepared as described previously.[11]

**Attempted Formation and Benzylation of Potassiotriphenylphosphineacetylmethylene (4, M = K).** In a 500-ml three-necked round-bottomed flask equipped with a mechanical stirrer and a dry ice condenser was prepared 0.032 mol of potassium amide from 0.032 g-atom of potassium metal and a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$ in 250 ml of anhydrous liquid ammonia. To this amide suspension was added 5.0 g (0.016 mol) of solid triphenylphosphineacetylmethylene (**3**) and the reaction mixture was stirred for 1 hr to ensure complete dissolution of **3** and its conversion into the anticipated ylide anion. Then 5.13 g (0.045 mol) of benzyl chloride in 30 ml of anhydrous ether was added. The purple color associated with stilbene formation[27] was observed, indicating the presence of excess potassium amide. The reaction mixture was

Table II
$^1$H NMR Absorptions of Products Obtained from Lithiotriphenylphosphineacetylmethylene (4)[p]

| Product no. | Types of hydrogen and chemical shifts, $\delta$ | | | |
|---|---|---|---|---|
| | Aromatic | $-\overset{+}{P}\overset{-}{C}H-$ | $-CH_2-$ | Other |
| 9a | 7.44 (m) | 3.64 (d, broad) | 2.84 (m) | |
| 9b | 7.52 (m) | 3.80 (s, broad) | 2.44 (m) | 5.96 (m)[a] |
| | | | | 5.04 (t)[b] |
| 11a | 7.16 (s)[c] | 3.36 (s, broad) | 2.86 (m) | 2.86 (m)[d] |
| | 7.44 (m) | | | |
| 11b | 7.2 (s)[c] | 3.52 (d, broad) | 2.6 (m) | 5.92 (m)[a] |
| | 7.48 (m) | | | 5.02 (t)[b] |
| | | | | 2.6 (m)[d] |
| 12 | 7.52 (m) | 3.6 (s, broad) | 2.36 (t)[e] | |
| | | | 1.68 (m)[f] | |
| 14a | 7.7 (m) | 3.8 (broad) | 2.59 (m)[g] | 4.2 (m) |
| | | | 2.32 (m)[g] | 1.2 (d)[h] |
| 14b | 7.56 (m) | 3.68 (d, broad) | 2.79 (m)[i] | 5.1 (m) |
| | | | 2.65 (m)[i] | |
| 14c | 7.52 (m) | 3.72 (d, broad) | 3.28 (s) | |
| 14d | 7.44 (m) | 3.6 (s, broad) | 2.99[j] | 1.48 (s)[h] |
| | | | 2.71[j] | |
| 14e | 7.52 (m) | 3.78 (d, broad) | 2.46 (s) | 1.24 (s)[h] |
| 14f | 7.56 (m) | 3.8 (s, broad) | 2.6 (s) | 1.74 (m)[k] |
| 14g | 7.64 (m) | 3.82 (d, broad) | 2.57[l] | 1.92 (m)[m] |
| | | | 2.49[l] | 5.78 (s)[n] |
| 14h | 7.46 (m) | 3.74 (d) | 3.06[o] | 6.72 (q)[n] |
| | | | 2.98[o] | |
| 17 | 7.8 (m) | 4.00 (d, broad) | 4.14 (d) | 6.11 (s)[a] |
| | 8.52 (q) | | | |

[a] CH=C. [b] $CH_2$=C. [c] $CH_2C_6H_5$. [d] Methine proton. [e] $-COCH_2-$. [f] $-(CH_2)_3-$. [g] Calculated values for AB protons of an ABX system with $J_{AB}$ = 15, $J_{AX}$ = 9.43, and $J_{BX}$ = 2.57 Hz. [h] $-CH_3$. [i] Calculated values for AB protons of an ABX system with $J_{AB}$ = 15, $J_{AX}$ = 11.57, and $J_{BX}$ = 3.43 Hz. [j] Calculated values for an AB system with $J_{AB}$ = 14 Hz. [k] Cyclopentyl group. [l] Calculated chemical shift values for an AB system with $J_{AB}$ = 14 Hz. [m] Methylene protons of the cyclohexenyl group. [n] CH=CH. [o] Calculated chemical shift values for an AB system with $J_{AB}$ = 14.5 Hz. [p] Satisfactory analytical data (±0.4% for C, H) for all compounds were submitted for review.

stirred for 1 hr before neutralization with excess solid ammonium chloride. The liquid ammonia was evaporated and replaced with 250 ml of anhydrous ether. The resulting suspension was poured over a slurry of 15 ml of 12 *N* HCl and 150 g of ice and stirred until dissolution was complete. The ethereal layer was separated and the acidic aqueous solution was extracted twice with 150-ml aliquots of ether. The combined ethereal fractions were dried ($MgSO_4$) and concentrated to leave 4.1 g of recovered benzyl chloride. The acidic aqueous solution was then adjusted to pH 11 with 10% aqueous potassium hydroxide and extracted three times with 150-ml portions of chloroform. The combined chloroform extracts were dried ($MgSO_4$) and concentrated to give 2.4 g (57%) of acetonyldiphenylphosphine oxide (**5**). The analytical sample, recrystallized from benzene–heptane, had mp 127.5–129° (lit.[28] 127–129°); $^1H$ NMR ($CDCl_3$) $\delta$ 7.76 (m, 10, phenyl) 3.64 (d, 2, $CH_2$), and 2.32 (s, 3, $CH_3$); ir ($CHCl_3$) 5.84 (C=O) and 8.25 $\mu$ (P=O).

A reaction similar to that described above was repeated except that benzyl chloride was omitted. The reaction mixture was processed in the same manner to afford a 42% yield of **5**.

**Attempted Isolation of an Iminophosphorane Intermediate.** Treatment of **3** (0.008 mol) with 0.016 mol of potassium amide in 150 ml of liquid ammonia for 1 hr was followed by replacement of the liquid ammonia with 150 ml of anhydrous ether. This ethereal suspension was filtered, and the ether evaporated. The $^1H$ NMR spectrum of the resulting ether-soluble solid showed the presence of acetonyldiphenylphosphine oxide (**5**) along with diphenylphosphinic amide (**6**). Recrystallization of this solid from benzene afforded 0.31 g of amide **6**. The solid remaining after filtering the ethereal suspension was digested in chloroform. The chloroform solution was concentrated and the resulting crude solid was recrystallized from benzene to give an additional 0.47 g of **6**, bringing the total yield of **6** to 0.78 g (44%): mp 163.5–164.5° (lit.[29a–e] values vary between 160 and 168°); $^1H$ NMR ($CDCl_3$) $\delta$ 7.76 (m, 10, phenyl) and 3.84 (s, 2, $NH_2$).

Anal. Calcd for $C_{12}H_{12}NOP$: C, 66.36; H, 5.57; N, 6.45. Found: C, 66.41; H, 5.66; N, 6.56.

**General Procedure for Formation of Ylide Anion 4 (M = Li) and Reactions with Various Electrophiles.** A 5.00-g (0.016 mol) sample of **3** was dissolved in 300 ml of anhydrous THF under a nitrogen atmosphere. The solution was cooled by means of a dry ice–acetone bath and then 9.23 ml (0.019 mol) of *n*-butyllithium in hexane was added. The red-brown ylide anion solution was stirred for 20 min before addition of 0.019 mol of the appropriate electrophile as a solution in anhydrous THF. The reaction mixture was stirred for 1 hr at −78° and then allowed to warm to room temperature. The dark ylide anion color was discharged either at −78° or during the warm-up period. The resulting orange-yellow solution was poured into 300 ml of water–ether (2:1) and stirred for 5 min. The ethereal layer was separated and the basic aqueous solution was extracted three times with 150-ml portions of chloroform. All the ethereal and chloroform extracts were combined, washed with 10% aqueous sodium chloride, dried ($MgSO_4$), and concentrated to give usually an oil, which solidified upon standing or when triturated with ether or ether–hexane. The crude products were recrystallized from appropriate solvents (Table I).

Reaction of **4** (0.019 mol) with 0.02 mol of methyl iodide produced 6.71 g of light yellow solid, mp 165–209°. Several recrystallizations afforded 6.0 g of solid consisting of starting ylide **3**, the desired C-methylated ylide, and O-methylated phosphonium iodide as evidenced by $^1H$ NMR spectroscopy.

Treatment of **4** (0.019 mol) with 0.02–0.04 mol of trimethylchlorosilane failed to discharge the ylide anion color after 2 hr at 25°. When the reaction employing the lesser amount of silyl halide was processed, ylide **3** was recovered in 64% yield. When 0.04 mol of halide was used, there was isolated 48% of acetonyltriphenylphosphonium chloride, mp 234–237° (lit.[11] 237–238°). The $^1H$ NMR spectrum of this material was identical with that of an authentic sample.

Formation and alkylation of ylide anion **10** was carried out in a manner essentially identical with that described for **4**.

In the reactions of **4** with 2-cyclohexenone and chalcone, $^1H$ NMR analysis of the crude product mixtures indicated that only minor amounts (<10%) of conjugate addition products may have been present.

Attempts to convert **4** into cuprate derivative **15** were carried out by first preparing 7 mmol of **4** in 150 ml of THF and then adding 7 mmol of cuprous iodide, cuprous *tert*-butoxide,[24a,b] or cuprous cyanide at −78°. After 2–4 hr a 7-mmol sample of 2-cyclohexone was added via syringe and the reaction allowed to warm to 25° and stir for 2 hr. The reaction mixtures were processed as above and the crude products analyzed by TLC and $^1H$ NMR. In each case the major product was the 1,2 adduct **14g**.

Elemental analyses and $^1H$ NMR spectra of all products (Table II) were consistent with the assigned structures.

**1-Phenyl-1-octen-3-one (13a) and 1-(3,4-Dichlorophenyl)-1,6-heptadien-3-one (13b).** Ylide anion **4** (0.016 mol) was alkylated as described above with 3.88 g (0.021 mol) of *n*-butyl iodide to give, after concentration of the organic extracts, 6.0 g (98%) of crude triphenylphosphinehexanoylmethylene as an oil: $^1H$ NMR ($CDCl_3$) $\delta$ 7.60 (m, 15, phenyl), 3.80 (d, 1, $-P^+C^-H-$) and 1.60 (m, 11, $n$-$C_5H_{11}$). A 3.8-g (0.010 mol) sample of this crude product and 1.06 g (0.010 mol) of benzaldehyde in 30 ml of $Me_2SO$ was stirred at 50–55° (oil bath) for 19 hr under a nitrogen atmosphere. After cooling, the reaction mixture was poured into 150 ml of cold water and a white solid separated. To this suspension was added 100 ml of hexane, the mixture was stirred for 10 min, and undissolved solid was collected by suction filtration. Recrystallization of this solid from acetone–heptane gave 1.42 g of triphenylphosphine oxide. The hexane layer was separated and the aqueous solution extracted once with 100 ml of hexane. The combined hexane extracts were dried ($MgSO_4$) and concentrated to give a red oil which was vacuum distilled at 145–150° (0.55 mm) to give a yellow distillate which partially crystallized. This semisolid was recrystallized from methanol–water to give 1.28 g (63% based on **4**) of predominantly *trans*-1-phenyl-1-octen-3-one (**13a**): mp 44.5–46.5° (lit.[30] 47°); $^1H$ NMR ($CDCl_3$) $\delta$ 7.45 (m, 6, $=CHC_6H_5$), 6.70 (d, 1, =CHCO, $J_{trans}$ = 16 Hz), 2.64 (t, 2, $COCH_2$), 1.45 [m, 6, $-(CH_2)_3-$], and 0.91 (t, 3, $CH_3$); ir ($CHCl_3$) 5.93 (s-cis C=O), 6.05 (s-trans C=O), and 6.19 $\mu$ (conjugated C=C).

Alkylation of **4** (0.032 mol) with 0.036 mol of allyl bromide produced, after concentration of the organic extracts, a quantitative yield of crude triphenylphosphine(4-pentenoyl)methylene (**9b**) as a light brown oil. A solution of 7.38 g (0.020 mol) of this crude product and 3.50 g (0.020 mol) of 3,4-dichlorobenzaldehyde in 35 ml of $Me_2SO$ was stirred at 55° for 18 hr under a nitrogen atmosphere. Following the same procedure as described above, 2.79 g of triphenylphosphine oxide was isolated. The original hexane layer was separated, and the aqueous solution was then extracted four times with 100-ml aliquots of ether. The combined organic extracts were dried ($MgSO_4$) and concentrated to give 5.34 g of yellow oil, which was vacuum distilled at 145–150° (0.15 mm) to give 3.03 g (59% based on **4**) of predominantly *trans*-1-(3,4-dichlorophenyl)-1,6-heptadien-3-one (**13b**). The $^1H$ NMR spectra of this material indicated the presence of ca. 10% of triphenylphosphine oxide as a contaminant: $^1H$ NMR ($CDCl_3$) $\delta$ 7.50 (m, 6.55, $=CHC_6H_5$), 6.70 (d, 1, C=CHCO, $J_{trans}$ = 16 Hz), 5.90 (m, 1, =CH), 5.10 (m, 2, $C=CH_2$), and 2.6 (m, 4, $-CH_2CH_2-$); ir (neat), 5.90 (s-cis C=O), 6.00 (s-trans C=O), and 6.19 $\mu$ (conjugated C=C).

**4,5-Benzotropone (16).** A solution of 0.008 mol of **4** was prepared as described above and a solution of 1.23 g (0.009 mol) of *o*-phthalaldehyde in THF was added. The reaction mixture was stirred for 1 hr at −78°, then allowed to warm to room temperature. The resulting dark orange solution was poured into 150 ml of water–ether (2:1) and stirred. The organic phase was separated and the aqueous solution was extracted twice with 75-ml portions of chloroform. The organic extracts were combined, washed with 10% aqueous sodium chloride, dried ($MgSO_4$), and concentrated to give a dark yellow oil. TLC analysis [acetone–benzene (1:1)] of the reaction mixture indicated the presence of four products. The presence of triphenylphosphine oxide, *o*-phthalaldehyde, and phthalic acid was detected by comparison of their $R_f$ values with those of authentic samples. The reaction mixture was chromatographed on silica gel to afford 0.12 g of pure 4,5-benzotropone: mp 66–67° (lit.[31] 65–66°); $^1H$ NMR ($CDCl_3$) $\delta$ 7.66 (m, 4, phenyl), 7.44 (d, 2, $H_2$ and $H_7$), and 6.7 (d, 2, $H_3$ and $H_6$).

Anal. Calcd for $C_{11}H_8O$: C, 84.59; H, 5.16. Found: C, 84.63; H, 5.15.

The above reaction was repeated and the yield of 4,5-benzotropone in the resulting crude product mixture was shown to be 49% by VPC using chalcone as the internal standard.

**Registry No.**—**3** charged form, 29942-64-1; **3** uncharged form, 1439-36-7; **4** (M = Li) charged form, 38938-34-0; **4** (M = Li) uncharged form, 38938-46-4; **5**, 1733-52-4; **6**, 5994-87-6; **9a** charged form, 57362-41-1; **9a** uncharged form, 16640-69-0; **9b** charged form, 38938-47-5; **9b** uncharged form, 38938-35-1; **11a** charged form, 57362-42-2; **11a** uncharged form, 57362-43-3; **11b** charged form, 57362-44-4; **11b** uncharged form, 57362-45-5; **12** charged form, 57362-46-6; **12** uncharged form, 57362-47-7; **13a**, 29478-39-5; **13b**, 57362-48-8; **14a** charged form, 57362-49-9; **14a** uncharged

form, 57362-50-2; **14b** charged form, 57362-51-3; **14b** uncharged form, 57362-52-4; **14c** charged form, 38938-48-6; **14c** uncharged form, 38938-36-2; **14d** charged form, 57362-53-5; **14d** uncharged form, 57362-54-6; **14e** charged form, 57362-55-7; **14e** uncharged form, 57362-56-8; **14f** charged form, 57362-57-9; **14f** uncharged form, 57362-58-0; **14g** charged form, 57362-59-1; **14g** uncharged form, 57362-60-4; **14h** charged form, 57362-61-5; **14h** uncharged form, 57362-62-6; **16**, 4443-91-8; **17** charged form, 57362-63-7; **17** uncharged form, 57362-64-8; potassium amide, 17242-52-3; *n*-butyllithium, 109-72-8; methyl iodide, 74-88-4; trimethylchlorosilane, 75-77-4; *n*-butyl iodide, 542-69-8; trihhenylphosphinehexanoylmethylene charged form, 57362-65-9; triphenylphosphinehexanoylmethylene uncharged form, 33803-58-6; *o*-phthalaldehyde, 643-79-8.

## References and Notes


(1) (a) Taken in part from the M.S. Thesis of E. A. Sancaktar, Virginia Polytechnic Institute and State University, Dec 1974, and the Ph.D. Dissertation of J. D. Taylor, Virginia Polytechnic Institute and State University, June 1971. (b) Supported by NIH Grants GM 14340 and NS 10197 and NASA Grant NSG 1064.

(2) The term dicarbanion was first coined by C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958). Although the negative charges are certainly delocalized into groups A and A′, reactions with electrophiles occur predominantly at carbon. This designation is also useful for indicating that both acidic hydrogens are removed from carbon.

(3) (a) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **25**, 158 (1960); (b) R. J. Light and C. R. Hauser, *ibid.*, **25**, 538 (1960); (c) R. O. Pendarvis and K. G. Hampton, *ibid.*, **39**, 2289 (1974).

(4) (a) T. M. Harris, S. Boatman, and C. R. Hauser, *J. Am. Chem. Soc.*, **85**, 3273 (1963); (b) T. M. Harris, S. Boatman, and C. R. Hauser, *ibid.*, **87**, 82 (1965); (c) T. M. Harris, S. Boatman, and C. R. Hauser, *ibid.*, **87**, 3186 (1965).

(5) (a) J. F. Wolfe, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **29**, 3249 (1964); (b) L. Weiler, *J. Am. Chem. Soc.*, **92**, 6702 (1970); (c) S. N. Huckin and L. Weiler, *Tetrahedron Lett.*, 4835 (1971); (d) *ibid.*, 2405 (1972); (e) *J. Am. Chem. Soc.*, **96**, 1082 (1974); (f) *Can. J. Chem.*, **52**, 1343 (1974).

(6) T. M. Harris and C. M. Harris, *Org. React.*, **17**, 155 (1969).

(7) S. Turner, *Chem. Br.*, **7**, 191 (1971).

(8) When we initiated this study, the only reported example of removal of an activating group following formation and reaction of a 1,3-dianion involved alkylation of several α-formyl cycloalkanone dianions and subsequent hydrolytic cleavage of the formyl function to give α-alkyl cycloalkanones in moderate yields.[4b]

(9) H. J. Bestmann and B. Arnason, *Chem. Ber.*, **95**, 1513 (1962).

(10) A. Maercker, *Org. React.*, **14**, 270 (1965).

(11) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957). The nomenclature used in the present paper is based on the system suggested by these authors.

(12) J. D. Taylor and J. F. Wolfe, *J. Chem. Soc., Chem. Commun.*, 876 (1972).

(13) M. P. Cooke, *J. Org. Chem.*, **38**, 4082 (1973).

(14) M. P. Cooke and R. Goswami, *J. Am. Chem. Soc.*, **95**, 7891 (1973).

(15) (a) P. A. Grieco and C. S. Pogonowski, *J. Am. Chem. Soc.*, **95**, 3011 (1973); (b) *Synthesis*, 425 (1973).

(16) (a) P. A. Grieco and C. S. Pogonowski, *J. Org. Chem.*, **39**, 732 (1974); (b) *J. Chem. Soc., Chem. Commun.*, **72** (1975).

(17) I. Kuwajima and H. Iwasawa, *Tetrahedron Lett.*, 107 (1974).

(18) D. Seyferth, *J. Am. Chem. Soc.*, **84**, 1764 (1962).

(19) A. Schnell and J. C. Tebby, *J. Chem. Soc., Chem. Commun.*, 134 (1975).

(20) L. Horner and H. Winkler, *Tetrahedron Lett.*, 175 (1964).

(21) Lithium diisopropylamide in THF–hexane at −78° was also suitable for generation of **4** (M = Li) as shown by benzylation to form **9a**.

(22) G. H. Posner, *Org. React.*, **19**, 1 (1972).

(23) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).

(24) (a) G. H. Posner and J. J. Sterling, *J. Am. Chem. Soc.*, **95**, 3076 (1973); (b) G. H. Posner and C. E. Whitten, *Tetrahedron Lett.*, 1815 (1973).

(25) J. P. Gorlier, L. Hamon, J. Levisalles, and J. Wagnon, *J. Chem. Soc., Chem. Commun.*, **88** (1973).

(26) F. Pietra, *Chem. Rev.*, **73**, 293 (1973).

(27) C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 (1956).

(28) M. Saunders and G. Burchman, *Tetrahedron Lett.*, 8 (1959).

(29) (a) I. N. Zhmurova, I. Yu. Voitsekhovskarya, and A. V. Kirsanov, *Zh. Obshch. Khim.*, **29**, 2083 (1959); *Chem. Abstr.*, **54**, 8681*h* (1960); (b) I. C. Popoff and B. I. D'Ilorio, *U.S. Dep. Commer., Off. Tech. Serv., AD*, 264, 773 (1961); *Chem. Abstr.*, **59**, 3947*h* (1963); (c) N. Kreutzkamp and H. Schindler, *Arch. Pharm. (Weinheim, Ger.)*, **293**, 269 (1960); *Chem. Abstr.*, **60**, 4179*g* (1964); (d) D. L. Herring and C. M. Douglas, U.S. Patent 3,249,560 (1966); *Chem. Abstr.*, **65**, 2297*c* (1966); (e) S. E. Frazier and H. H. Sisler, *Inorg. Chem.*, 5, 925 (1966).

(30) N. Metayer, *Recl. Trav. Chim. Pays-Bas*, **71**, 153 (1952).

(31) J. Thiele and E. Weitz, *Justus Liebigs Ann. Chem.*, **377**, 1 (1910).


# Atomic Oxygen. V. Reactions of Enol Ethers with Oxygen ($^3$P) Atoms[1]


James J. Havel* and Kam H. Chan

*Department of Chemistry, Rice University, Houston, Texas 77001*


*Received June 27, 1975*


The products of the gas-phase reactions of ground state ($^3$P) oxygen atoms with methyl vinyl ether, ethyl vinyl ether, 2-methoxypropene, 1-methoxy-2-methylpropene, 2,3-dihydrofuran, and dihydropyran are reported. The oxygen atoms were generated by the mercury photosensitized decomposition of nitrous oxide. The reactions produced alkoxyoxiranes, α-alkoxycarbonyl compounds, esters, and fragmentation products. Novel alkoxy radical rearrangements and a reinvestigation of the acid-catalyzed reaction between 3-hydroxy-3-methyl-2-butanone and methanol are reported.


The reactions of atomic oxygen are of continuing interest because of their application to mechanisms of photochemical air pollution,[2] upper atmosphere chemistry,[3] and combustion. Oxygen atom reactions have also been applied to the synthesis of new or labile organic compounds. For example, 3-butenal is produced by reaction of 1,3-butadiene with oxygen ($^3$P) atoms.[4]

Ground state ($^3$P) oxygen atoms react with olefins of formula $C_nH_{2n}$ to produce epoxides, aldehydes, and ketones of formula $C_nH_{2n}O$. Cvetanovic[5] has proposed that O($^3$P) atoms add to olefins to form short-lived carbon–oxygen 1,3-biradicals. These biradicals can either close to epoxides or rearrange to aldehyde and ketones. The 1,2 migration of a hydrogen atom is intramolecular, but alkyl groups become at least partially detached during rearrangement. The rearrangement of hydrogen atoms and alkyl radicals in 1,3-biradicals is significant, because these groups do not commonly migrate in monoradical systems.

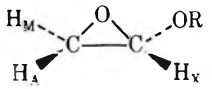
It was expected that reaction of atomic oxygen with enol ethers would produce enol ether epoxides (or alkoxyoxiranes). Four methods have been applied to the synthesis of simple enol ether epoxides: (a) reaction of diazomethane with esters,[6] (b) epoxidation of enol ethers with peracids,[7,8] (c) reaction of α-halocarbonyl compounds with sodium methoxide,[9] and (d) base-induced ring closure of alkoxy-substituted chlorohydrins.[10] Each of these alkoxyoxirane syntheses has disadvantages.

**Reaction Conditions.** In this study, conditions for the gas-phase production and reaction of atomic oxygen were derived from the pioneering work of Cvetanovic and coworkers.[5] Ground state ($^3$P) oxygen atoms were produced by the mercury photosensitized decomposition of nitrous

oxide.[11] The reaction apparatus and conditions have been described previously.[12] The total pressure before photolysis was 0.9 atm, and the reaction temperature was 25–30°.

Product yields reported below are based on the quantity of nitrogen produced. Two experimental conditions were used to limit the reactions to primary processes. First, a high ratio of nitrous oxide to substrate (>15) was maintained in order to minimize mercury photosensitized reactions of substrate or products. Second, conversion of organic substrate was limited to <30% to minimize secondary oxidations and reactions of products.

**Enol Ether Reactions. Methyl Vinyl Ether.** Oxygen atoms react with methyl vinyl ether to produce methoxyoxirane (**1**, 45% yield), methoxyacetaldehyde (26%), methyl acetate (2%), and carbon monoxide (13%). The total yield of oxygenated product is 86%.



1, R = $CH_3$
2, R = $C_2H_5$

Methoxyoxirane (1) has been prepared previously by reaction of diazomethane with methyl formate, but no spectra of this material were given.[6] The NMR spectrum of **1** shows a well-resolved AMX system and a singlet at $\delta$ 3.45.

Positions and coupling constants of the AMX system follow: $H_A$ $\delta$ 2.56, $H_M$ $\delta$ 2.74, and $H_X$ $\delta$ 4.50; $J_{AM}$ = 3.9, $J_{AX}$ = 2.3, and $J_{MX}$ = 1.2 Hz. These assignments are consistent with epoxide spectral parameters reported by Lehn and Riehl.[13]

Epoxide **1** is stable in $CDCl_3$ solution for several hours at room temperature. However, an attempt to isolate **1** by short-path distillation (atmospheric pressure) of the combined product mixtures of several reactions led to decomposition of the epoxide. A purified sample of **1** did not survive gas chromatography under mild conditions. The sample apparently polymerized in the instrument, since no $C_3H_6O_2$ products (other than the methyl acetate impurity known to be present by NMR) eluted from the GC.

**Ethyl Vinyl Ether.** The reaction of atomic oxygen with ethyl vinyl ether produced ethoxyoxirane (**2**, 50% yield); ethoxyacetaldehyde (18%); ethyl acetate (3%); and carbon monoxide (9%). The total product yield was 80%.

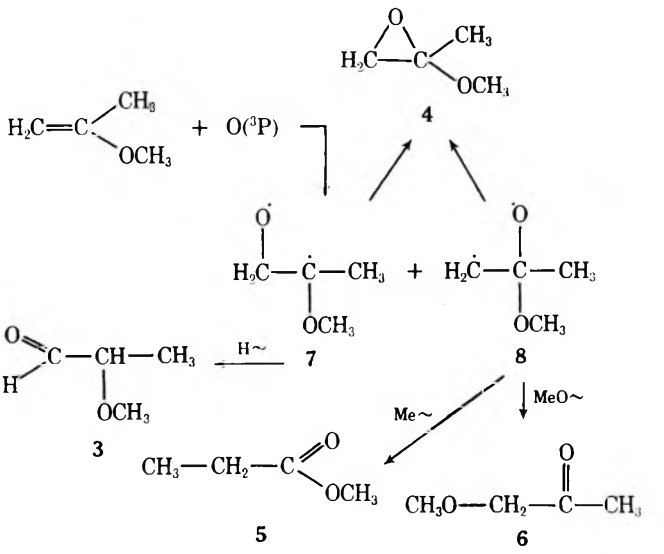
Epoxide **2** is also thermally labile. The NMR spectrum of its AMX system is quite similar to that of compound **1**.

**2-Methoxypropene.** The products of the reaction of 2-methoxypropene with oxygen ($^3P$) atoms were 2-methoxypropanal (**3**, 49% yield); 2-methoxy-2-methyloxirane (**4**, 21%); methyl propionate (**5**, 2.4%); methoxyacetone (**6**, 1.3%); and carbon monoxide (10%). The total yield of product was 84%.

The reaction of 2-methoxypropene with atomic oxygen is of mechanistic interest, because it provides information on both orientation of atom addition and migratory aptitudes in 1,3-biradical systems (Scheme I).

The addition of an oxygen atom to carbon 1 of the olefin would yield 1,3-biradical **7**, with a tertiary carbon radical site, while addition to carbon 2 produces biradical **8**, containing a primary carbon radical. As would be expected from conventional radical stabilities, formation of **7** is preferred over formation of **8**. If one assumes that biradicals **7** and **8** produce epoxide **4** at equal rates, then the ratio of addition to carbon 1 vs. carbon 2 is 13 [as indicated by the product ratio 3/(5 + 6)]. This ratio is similar to the addition ratio observed in the reaction of atomic oxygen with 2-methylpropene,[5] where addition to carbon 1 vs. carbon 2 is 14.

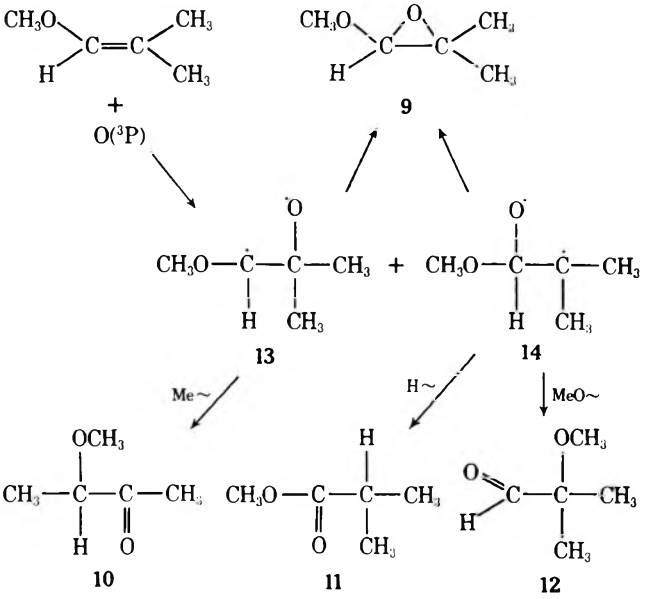
Scheme I



Products **5** and **6** are formed from the minor biradical intermediate **8** by 1,2 migration of a methyl radical and a methoxy radical, respectively. The ratio of these products indicates the relative migratory aptitudes of the two groups: Me~/MeO~ = 5/6 = 1.8. There is no apparent literature precedent for the 1,2 rearrangement of an alkoxy group in a monoradical or biradical system.

**1-Methoxy-2-methylpropene.** Atomic oxygen reacts with 1-methoxy-2-methylpropene to produce 3,3-dimethyl-2-methoxyoxirane (**9**, 46% yield); 3-methoxy-2-butanone (**10**, 15%); methyl isobutyrate (**11**, 10%); 2-methoxy-2-methylpropanal (**12**, 5%); and carbon monoxide (1%). The total product yield is 77%. A scheme for the formation of these products is shown in Scheme II.

Scheme II



If one assumes that biradicals **13** and **14** close to epoxide **9** at equal rates, then the ratio of the carbonyl products [10/(11 + 12) = 1.0] indicates the orientation of addition. This product ratio means that one methoxy substituent directs the orientation of addition (to form biradical **13**) as well as two methyl groups (to form biradical **14**).

Products **11** and **12** are formed from 1,3-biradical **14** by competing 1,2 rearrangements of a hydrogen atom and a methoxy radical, respectively. The ratio of these two prod-

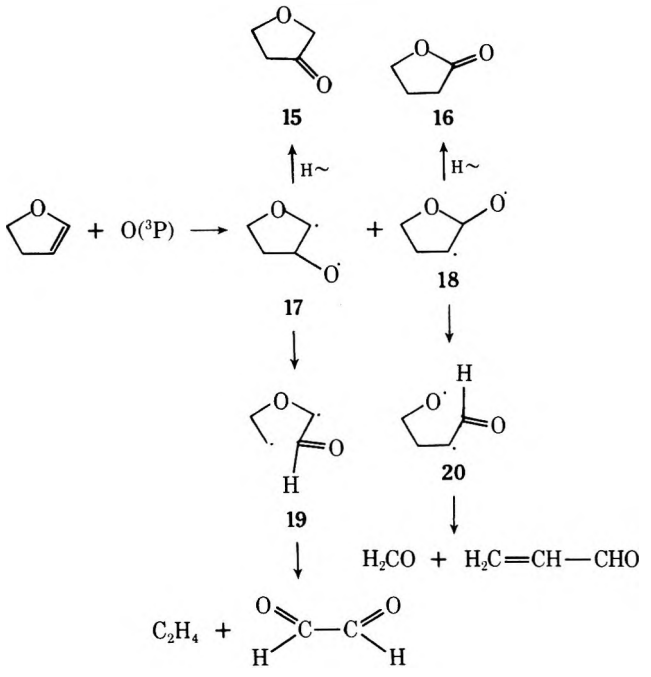
ucts indicates that hydrogen migrates twice as fast as methoxy.

The low yield of carbon monoxide from this reaction (1%) is consistent with previous results.[5] Simple alkenes show decreased fragmentation with increased substitution of the olefin.

**2,3-Dihydrofuran.** The reaction of 2,3-dihydrofuran with oxygen atoms produced carbon monoxide (45%); dihydro-3(2*H*)-furanone (**15**, 20%); ethylene (17%); acrolein (1.9%); and dihydro-2(3*H*)-furanone (**16**, 1.4%). The NMR spectrum of the product mixture showed no peaks that could be attributed to the epoxide, 2,6-dioxabicyclo-[3.1.0]hexane. Other possible products, formaldehyde, glyoxal, and hydrogen, would not have been detected under the reaction and analysis conditions used.

The reaction of 2,3-dihydrofuran with O($^3P$) should proceed in a manner similar to the reaction of cyclopentene, which has been studied extensively by Cvetanovic and coworkers.[14] A mechanism for the formation of the observed products is proposed in Scheme III.

Scheme III

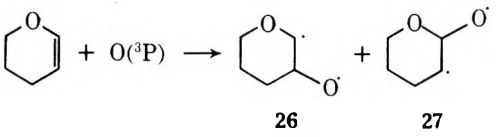



The ambiguous origin of the carbon monoxide formed in this reaction makes an exact calculation of the orientation of addition somewhat doubtful. However, it is apparent from the high ratio of products attributable to biradical **17** (ketone **15** and ethylene) vs. products derived from biradical **18** (lactone **16** and acrolein) that formation of biradical **17** is preferred.

Precedence for the extensive ring opening of 1,3-biradicals **17** and **18** to form 1,4-biradicals **19** and **20** is seen in the reaction of cyclopentene with atomic oxygen.[14] 1,4-Biradicals formed in other atomic oxygen systems consistently show $\beta$-cleavage as their major reaction.[1,4,14] The large yield of carbon monoxide from the dihydrofuran reaction may arise by decomposition of excited glyoxal and formaldehyde.

**Dihydropyran.** The reaction of dihydropyran with atomic oxygen differed markedly from the 2,3-dihydrofuran reaction in that the dihydropyran reaction produced no detectable carbon monoxide (detection limit $\cong$0.5% yield). The products of the dihydropyran reaction follow: 2,7-dioxabicyclo[4.1.0]heptane (**21**, 48% yield); dihydro-2*H*-pyran-3(4*H*)-one (**22**, 32%); tetrahydrofurfural (**23**, 0.4%); pentanedial (**24**, 0.4%); and tetrahydro-2*H*-pyran-2-one (**25**, 0.1%). In addition, three minor peaks with a total yield of 2% appeared in the GC of the product mixture. Two of these minor peaks may have been 5-hydroxy-2-pentenal and 3-oxa-5-hexenal. The formation of these two products is predicted by analogy with the reaction between cyclohexene and oxygen ($^3P$) atoms.[1]

The initial biradical intermediates formed by addition of O($^3P$) to dihydropyran are shown below.




The distribution of carbonyl products shows that there is a large preference for formation of the oxygen-substituted biradical **26** over the carbon-substituted biradical **27**.

**Reinvestigation of the Reaction of 3-Hydroxy-3-methyl-2-butanone with Methanol.** Thorne[15] has reported that the acid-catalyzed reaction of 3-hydroxy-3-methyl-2-butanone (**28**) with anhydrous methanol produces 2-methoxy-2,3,3-trimethyloxirane (**29**). This result is surprising in light of the observations of Stevens[8] concerning the facile ring opening of alkoxyoxiranes under these conditions.

Upon reinvestigation of the reaction reported by Thorne, it was found that the material boiling at the point reported for epoxide **29** was really the hydroxy ketone reactant, **28**. In addition, the NMR spectrum of the crude reaction mixture shows no absorptions other than those due to starting materials. Thus, no acid-catalyzed reaction takes place between **28** and methanol under the conditions reported by Thorne.

## Conclusions

With the exception of 2,3-dihydrofuran, the gas-phase reactions of enol ethers with atomic oxygen produce good yields of alkoxyoxiranes, $\alpha$-alkoxycarbonyl compounds, and smaller amounts of esters and other products. The mild and neutral reaction and work-up conditions allow for the isolation of alkoxyoxiranes which either are not available or are difficultly prepared by other methods.

In order that the reactions described herein and other reactions can be scaled up to make larger amounts of oxygenated material, we are currently investigating convenient solution phase precursors of atomic oxygen. Research is also underway to elucidate the nature of the fragmentation processes observed in atomic oxygen reactions.

## Experimental Section

**Reactants.** Commercial reactants were distilled or trap-to-trap distilled before reaction. 2-Methoxypropene was made by the method of Newman and Vander Zwan.[16] 1-Methoxy-2-methylpropene was prepared by the method of Wenkert et al.[17]

2,3-Dihydrofuran was prepared by the method of Hubert et al.[18] A stirred mixture of 50 g of 2,5-dihydrofuran and 2 g of iron pentacarbonyl was irradiated with a sun lamp for 3 days. The reaction mixture was filtered and distilled to give 2,3-dihydrofuran (bp 55–57°) in 85% yield. The NMR spectrum of this material matched a reported spectrum.[19]

**Reaction Procedures.** The apparatus and techniques for atomic oxygen reactions have been described previously.[12] A typical product analysis is discussed below.

**Methyl Vinyl Ether.** The crude mixture of organic products was isolated by trap-to-trap distillation into a −107° trap (isooctane slush). Integration of the NMR spectrum of this fraction (with benzene added as an internal integration standard) allowed calculation of the yields of the methoxyoxirane and methoxyacetaldehyde products.

In another reaction, a sample of methoxyoxirane (**1**) which was contaminated with 3% methyl acetate (as determined by NMR)

was obtained by distillation through a −96° trap (acetone slush) into a −106° trap. Gas chromatography of this sample (NMR reported in the results section) showed elution of only the methyl acetate impurity. This demonstrated lack of rearrangement of **1** under GC conditions allowed for determination of the methyl acetate to methoxyacetaldehyde product ratio by GC of the crude product mixture.

Other spectra of the purified methoxyoxirane (**1**) follow: high-resolution MS of parent peak, obsd, 74.0355 (calcd for $C_3H_6O_2$, 74.0367); low-resolution MS (70 eV) *m/e* (rel intensity) 74 (9), 73 (5), 59 (100), 57 (42), 43 (93), 41 (35), 31 (67); ir (vapor phase), 3020, 2960, 2860, 1470, 1382, 1297, 1288, 1280, 1217, 1130, 1160, 910, 828, and 745 $cm^{-1}$.

**Products.** For comparison of GC retention times and spectra, samples of products **5, 6, 11, 16, 24, 25,** methyl acetate, ethyl acetate, ethylene, and acrolein were obtained commercially. Tetrahydrofurfural (**23**) was prepared by the oxidation of tetrahydrofurfuryl alcohol with chromium trioxide–pyridine.[20] Spectra of GC-purified products **15** and **22** matched literature spectra of these compounds.[21-23] Spectra of other α-alkoxycarbonyl products, **3, 10, 12,** methoxyacetaldehyde, and ethoxyacetaldehyde, were simple and unambiguous.

An authentic sample of 3,3-dimethyl-2-methoxyoxirane (**9**) was prepared by the reaction of 2-chloro-2-methylpropanal with sodium methoxide.[9] It should be noted that freshly prepared sodium methoxide was needed for this reaction. Three attempts to prepare **9** with commercial sodium methoxide, which had been vacuum dried, were unsuccessful. The NMR spectrum of **9** showed absorptions at δ 1.21 (s, 3 H), 1.31 (s, 3 H), 3.44 (s, 3 H), and 4.22 (s, 1 H).

Epoxides of enol ethers, other than **1**, were not separated from other reaction products, but their yields were calculated by NMR integration vs. other major reaction products and internal integration standards. Ethoxyoxirane (**2**) was determined by its AMX system at δ 4.45–4.60 and 2.45–2.85; 2-methoxy-2-methyloxirane (**4**) by singlets at δ 2.58 and 2.64; 3,3-dimethyl-2-methoxyoxirane (**9**) by its singlet at δ 4.23; and 2,7-dioxabicyclo[4.1.0]heptane (**21**) by its doublet at δ 4.61 and its multiplet at δ 2.98.[10]

**Attempted Reaction of 3-Hydroxy-3-methyl-2-butanone (28) with Methanol.** Following the procedure of Thorne,[15] a mixture of 14 g of distilled **28**, 50 ml of anhydrous methanol, and 0.012 mol of anhydrous hydrogen chloride was stirred for 4 hr. The NMR spectrum of the mixture showed only starting materials. The reaction mixture was neutralized with $Ag_2CO_3$, filtered, and vacuum distilled. The fraction boiling at 83–85° (100 mm) contained only **28** by NMR, ir, and mass spectrometry (85% recovery).

This reaction was repeated several times using halved and doubled HCl concentrations, $K_2CO_3$ neutralization, and reaction times up to 48 hr. In each case, only starting materials were recovered.

**Acknowledgments.** Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. The support of the Robert A. Welch Foundation is acknowledged.

**Registry No.**—**1,** 57346-02-8; **2,** 53332-61-9; **4,** 57346-03-9; **9,** 26196-04-3; **21,** 286-26-0; **28,** 115-22-0; methyl vinyl ether, 107-25-5; ethyl vinyl ether, 109-92-2; 2-methoxypropene, 116-11-0; 1-methoxy-2-methylpropene, 17574-84-4; 2,3-dihydrofuran, 1191-99-7; dihydropyran, 110-87-2; atomic oxygen, 17778-80-2; methanol, 67-56-1.

## References

(1) Part IV: J. J. Havel and K. H. Chan, *J. Am. Chem. Soc.*, **97,** 5800 (1975).
(2) J. N. Pitts, Jr., and B. J. Finlayson, *Angew. Chem., Int. Ed. Engl.*, **14,** 1 (1975).
(3) The proceedings of a symposium on this subject have been published: *Can. J. Chem.*, **52,** 1381–1634 (1974).
(4) J. J. Havel and K. H. Chan, *J. Org. Chem.*, **39,** 2439 (1974).
(5) R. J. Cvetanovic, *Adv. Photochem.*, *1,* 115 (1963).
(6) H. Meenwein, H. Disselnkötter, F. Rappen, H. v. Rintelen, and H. van de Vloed, *Justus Liebigs Ann. Chem.*, **604,** 151 (1957).
(7) C. L. Stevens and J. Tazuma, *J. Am. Chem. Soc.*, **76,** 715 (1954).
(8) C. L. Stevens and S. J. Dykstra, *J. Am. Chem. Soc.*, **75,** 5975 (1953).
(9) C. L. Stevens and B. T. Gillis, *J. Am. Chem. Soc.*, **79,** 3448 (1957), and references therein.
(10) C. Wakselman and L. Wartski, *Bull. Soc. Chim. Fr.*, 2242 (1967).
(11) R. J. Cvetanovic, *J. Chem. Phys.*, **23,** 1203 (1955).
(12) J. J. Havel, *J. Am. Chem. Soc.*, **96,** 530 (1974).
(13) J. M. Lehn and J. J. Riehl, *Mol. Phys.*, **8,** 33 (1964).
(14) R. J. Cvetanovic, D. F. Ring, and L. C. Doyle, *J. Phys. Chem.*, **75,** 3056 (1971).
(15) N. Thorne, *J. Chem. Soc.*, 2587 (1956).
(16) M. S. Newman and M. C. VanderZwan, *J. Org. Chem.*, **38,** 2910 (1973).
(17) E. Wenkert, R. A. Mueller, E. J. Reardon, Jr., S. S. Sathe, D. J. Scharf, and G. Tosi, *J. Am. Chem. Soc.*, **92,** 7428 (1970).
(18) A. J. Hubert, A. George, R. Warin, and P. Teyssie, *J. Chem. Soc., Perkin Trans. 2,* 366 (1972).
(19) P. K. Korver, P. J. van der Haak, H. Steinberg, and T. J. dePoer, *Recl. Trav. Chim. Pays-Bas,* **84,** 129 (1965).
(20) J. R. Holum, *J. Org. Chem.*, **26,** 4814 (1961).
(21) J. H. Sperna Weiland, H. Dijkstra, and A. B. Pik, *Recl. Trav. Chim. Pays-Bas,* **82,** 653 (1963).
(22) S. Wolff, W. L. Schreiber, A. B. Smith, and W. C. Agosta, *J. Am. Chem. Soc.*, **94,** 7797 (1972).
(23) H. Budzikiewicz and L. Grotjahn, *Tetrahedron,* **28,** 1881 (1972).

# Reactions of Cation Radicals of EE Systems. III. Chlorination of 9,10-Diphenylanthracene[1]

John F. Evans and Henry N. Blount*

*Brown Chemical Laboratory, The University of Delaware, Newark, Delaware 19711*

*Received September 2, 1975*

Stopped-flow kinetic studies of the reaction of 9,10-diphenylanthracene (DPA) cation radical ($DPA^{\cdot+}$) with chloride ion in acetonitrile gives rise to a rate law which is second order in $DPA^{\cdot+}$, first order in $Cl^-$, and independent of DPA. The product of the reaction of electrogenerated $DPA^{\cdot+}$ with $Cl^-$ was shown to be 9,10-dichloro-9,10-diphenyl-9,10-dihydroanthracene (**1**), which undergoes both surface catalyzed and thermally induced rearrangement to 2-chloro-DPA (**2**) via loss of HCl. The mechanism proposed for the addition of $Cl^-$ to $DPA^{\cdot+}$ to form **1** involves an associative equilibrium and is of a form which accounts for the observed kinetics as well as those previously reported for the hydroxylation and pyridination of $DPA^{\cdot+}$, which followed a different rate law.

Investigators in several laboratories have examined the reactions of various nucleophiles with the cation radicals derived from aromatic hydrocarbon and heterocyclic fused ring systems such as 9,10-diphenylanthracene (DPA),[1-8] thianthrene,[9-17] dibenzodioxin,[9,18,19] and phenoxathiin.[9,20] Each of these substrates exhibits EE electrochemistry in that one observes two successive monoelectronic oxidation steps, initially to the cation radical and subsequently to the corresponding dication at increasingly anodic potentials. While these aforementioned substrates exhibit strikingly similar electrochemical behavior, the mechanisms postulated for various nucleophilic additions to the cation radi-

cals of these systems have invoked participation by both cation radical and dication.[21] In this report, we show mechanistic findings which are germane to a unifying overview of these apparently divergent reaction pathways.

## Results and Discussion

While conducting a series of experiments designed to establish the relative nucleophilicities of various reagents toward the carbon-centered cation radical DPA·+,[22] it was noted that the rate of reaction of DPA·+ with chloride ion showed unusual dependence on DPA and DPA·+ concentrations. These data are shown in Table I. It is evident that a rate law appropriately describing these data assumes the form

$$-\frac{d[DPA\cdot^+]}{dt} = k_{app}[DPA\cdot^+]^2[Cl^-] \quad (1)$$

The stoichiometry observed for this reaction was consistent with that reported previously:[2]

$$2DPA\cdot^+ + 2Cl^- \rightarrow DPA(Cl)_2 + DPA \quad (2)$$

The chlorinated product $DPA(Cl)_2$ was confirmed to be 9,10-dichloro-9,10-diphenyl-9,10-dihydroanthracene. In combination, these observations are consistent with a mechanism of the form

$$DPA\cdot^+ + Cl^- \overset{K}{\rightleftarrows} DPA(Cl)\cdot \quad (3)$$

$$DPA(Cl)\cdot + DPA\cdot^+ \overset{k_2}{\rightarrow} DPA(Cl)^+ + DPA \quad (4)$$

$$DPA(Cl)^+ + Cl^- \xrightarrow{\text{fast}} DPA(Cl)_2 \quad (5)$$

where the electron transfer step (eq 4) is rate determining. In addition, the process described by eq 3 must indeed be an equilibrium condition to ensure an overall second-order dependence of the rate of reaction on the concentration of DPA·+.

The intermediate DPA(Cl)· has been proposed as a participant in the electrochemiluminescence observed in the $DPA(Cl)_2$–DPA·− [23,24] and trihalide–DPA·− [25] systems. The analogous intermediate DPA(F)· has been suggested to participate in the anodic fluorination of DPA.[6] The results presented here lend support to the participation of such free radicals in the halide–DPA redox systems.

It should be noted that the mechanism proposed here is not unlike that demonstrated for the anodic hydroxylation[4] of DPA. The significant fact is that the present system, the second step of the mechanism (eq 4), is rate determining while in the case of the hydroxylation, the initial encounter of DPA·+ with nucleophile (eq 6) is rate determining.[4]

$$DPA\cdot^+ + H_2O \overset{k}{\rightarrow} DPA(OH_2)\cdot^+ \quad (6)$$

$$DPA(OH_2)\cdot^+ + H_2O \overset{K}{\rightleftarrows} DPA(OH)\cdot + H_3O^+ \quad (7)$$

$$DPA(OH)\cdot + DPA\cdot^+ \xrightarrow{\text{fast}} DPA(OH)^+ + DPA \quad (8)$$

$$DPA(OH)^+ + 2H_2O \xrightarrow{\text{fast}} DPA(OH)_2 + H_3O^+ \quad (9)$$

In the hydroxylation mechanism (eq 6–9), this difference in kinetic control is tenable in view of the equilibrium deprotonation of the product of the rate-determining step, $DPA(OH_2)\cdot^+$. It is quite reasonable to expect the acid–base equilibrium embodied in eq 7 to lie far to the right and preclude any significant back reaction to $DPA(OH_2)\cdot^+$. Consequently, application of steady-state kinetics to DPA-

Table I
Stopped-Flow Kinetic Data for Reaction of DPA·+ with Cl−[a]

| $[DPA]_0 \times 10^4$ | $[DPA\cdot^+]_0 \times 10^5$ | $[Cl^-]_0 \times 10^4$ | Replicates | $k_2K$,[b] $M^{-2}$ $sec^{-1} \times 10^{-9}$ |
|---|---|---|---|---|
| 4.64 | 2.73 | 47.3 | 5 | 4.75 (± 0.13)[c] |
| 4.69 | 2.46 | 4.73 | 9 | 4.56 (± 0.13) |
| 4.61 | 1.03 | 0.473 | 5 | 4.18 (± 0.07) |
| 0.233 | 2.59 | 4.73 | 6 | 5.00 (± 0.11) |

[a] Chloride as tetra-*n*-butylammonium salt; all concentrations in moles/liter; $T$ = 25.0 (± 0.1)°. [b] $k_2K = k_{app}/2$ (eq 1). Data fitted for 75% reaction (minimum) via method of least squares, giving rise to a coefficient of correlation of at least 0.995 for all cases. [c] Standard deviation.

$(OH_2)\cdot^+$ and DPA(OH)· results in a rate expression identical with that reported previously,[4] namely[26]

$$-\frac{d[DPA\cdot^+]}{dt} = 2k[DPA\cdot^+][H_2O] \quad (10)$$

The anodic pyridination of DPA as studied by single potential step spectroelectrochemical techniques in these laboratories[1a] gave rise to data which were shown to fit a mechanism similar to that proposed for the corresponding hydroxylation reaction. The proposed mechanism yielded a rate law reflecting first-order dependence on the concentration of DPA·+ and first-order dependence on the concentration of pyridine (Py). This mechanism is restated here for the sake of the ensuing argument.

$$DPA\cdot^+ + Py \overset{k}{\rightarrow} DPA(Py)\cdot^+ \quad (11)$$

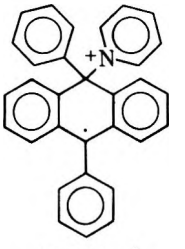
$$DPA(Py)\cdot^+ + DPA\cdot^+ \xrightarrow{\text{fast}} DPA(Py)^{2+} + DPA \quad (12)$$

$$DPA(Py)^{2+} + Py \xrightarrow{\text{fast}} DPA(Py)_2{}^{2+} \quad (13)$$

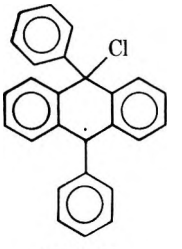
In this case, the initial encounter of nucleophile with cation radical was also proposed to be the rate-determining step (eq 11) followed by fast electron transfer with DPA·+ (eq 12). The intermediate DPA(Py)·+ which is involved in this *fast electron transfer step* is analogous to the DPA(Cl)· intermediate proposed to participate in the *rate-determining electron transfer step* (eq 4) of the mechanism for the reaction of DPA·+ with Cl− advanced in this present work.

The reactivity of these radicals is essentially the same[27] owing to the inability of the pyridinium and chloro substituents to participate in resonance stabilization of the respective radicals.[28] One might then conclude the reactivity of the DPA(Py)·+ and DPA(Cl)· radicals toward DPA·+ to be very similar.[29] Consequently, the rate constants for the two processes (eq 4 and 12) would be comparable.

The foregoing, then, presents an incongruity between the results of the previous kinetic study of the anodic pyridination[1a] of DPA and the results presented here. Pyridine, the stronger[30] nucleophile, follows a mechanism wherein formation of the radical species, DPA(Py)·+ (eq 11), is rate de-



DPA(Py)·+



DPA(Cl)·

termining whereas chloride, the weaker[30] nucleophile, follows a mechanism in which the electron-transfer step (eq 4) is rate determining. Why should this be the case if the rate constants for the corresponding electron transfer reactions of the two systems (eq 4 and 12) are expected to be of comparable magnitudes?

In the previous study[1a] employing electrogeneration of $DPA^{\cdot+}$, a pertinent consideration is that the concentrations of cation radical, nucleophile, intermediates, and products are inhomogeneously distributed in solution as a function of distance from the electrode surface.[31] Thus, for the Py/DPA concentration ratios employed, there existed excesses of cation radical in that portion of the reaction zone close to the electrode surface, and this effect was augmented by the regenerative nature of the reaction (eq 12). In view of this it is tenable that although the rate constants for the electron-transfer reactions of $DPA(Py)^{\cdot+}$ and $DPA(Cl)^{\cdot}$ with $DPA^{\cdot+}$ are most likely of similar magnitudes, the relative rates of these two reactions (eq 4 and 12) compared to the respective preceding steps (eq 3 and 11) may be quite different. This is attributable to the different relative concentrations of $DPA^{\cdot+}$ and nucleophile arising as a consequence of the different experimental conditions *and* techniques employed in the previous[1a] and present study. A reexamination of the *homogeneous* reaction of $DPA^{\cdot+}$ with Py under conditions similar to those reported here for the chloride reaction is presently in progress.[22]

The pathway for the reaction of $DPA^{\cdot+}$ with water, pyridine, and chloride is seen to be essentially the same with definition of the rate-determining step depending upon (1) the type of nucleophile (containing active hydrogen or not), (2) the intrinsic nucleophilicity of the nucleophile in question, and (3) the experimental conditions under which the kinetic parameters are measured. Moreover, the mechanism proposed here is compatible with that recently advanced for the anisylation of the cation radical of thianthrene.[17]

It is clear that the reversible nature of all steps in such mechanisms must be considered en route to a comprehensive understanding of nucleophilic additions to EE systems.[32]

## Experimental Section

**Materials.** DPA (Aldrich Gold Label) was doubly recrystallized from ethanol, mp 251–252°. Authentic 9,10-dichloro-9,10-diphenyl-9,10-dihydroanthracene [$DPA(Cl)_2$] was prepared after the manner of Chandross and Sonntag,[23] mp 187–189° dec. All tetraalkylammonium salts were obtained from Eastman Organic Chemicals. Tetra-*n*-butylammonium perchlorate (TBAP) was twice recrystallized from acetone–water (15:85) and vacuum dried at 60° for 6 hr prior to use, mp 211.5–212.5°. Tetraethylammonium perchlorate (TEAP) was doubly recrystallized from water and vacuum dried at 70° for 12 hr. After preliminary drying in a vacuum desiccator, tetra-*n*-butylammonium chloride (TBAC) was three times precipitated from acetone with anhydrous ether and vacuum dried at 56° for 18 hr, mp 76–77.5°. Acetonitrile (Burdick and Jackson Laboratories, uv grade) was purified in the manner previously described.[33] Water content of this purified material was determined by vapor phase chromatography to be ca. 1 m*M*. All other chemicals were reagent grade or equivalent. All solutions were prepared in an inert, anhydrous atmosphere.

**Apparatus.** The electrochemical cell used for large-scale reactions has been previously described.[1b] The potentiostat used was similar to that reported by Pilla.[34] Electrode potentials are quoted relative to the aqueous saturated calomel electrode. Kinetic runs were made using a Durrum Model D-110B stopped-flow spectrophotometer interfaced to a dedicated minicomputer for acquisition and reduction of data. The cation radical of DPA was generated by partial electrolysis of acetonitrile solutions containing 0.10 *M* TBAP and the appropriate concentration of DPA. This oxidation was carried out at a platinum gauze working electrode potentiostatted at +1.40 V. The solution so generated was then delivered via a closed system to one drive syringe of the stopped-flow spectrophotometer, the other drive syringe containing the desired concentration of TBAC in a solution of 0.10 *M* TBAP in acetonitrile.[35] The analytical wavelength used was the $\lambda_{max}$ of $DPA^{\cdot+}$, 653.0 nm, and the molar absorptivity of this species[3] was taken as $8.70 \times 10^3$ l./(mol cm).

Stoichiometry experiments were carried out in the stopped-flow spectrophotometer by monitoring the DPA regenerated[36] upon reaction of solutions of partially electrolyzed DPA with solution of TBAC in anhydrous acetonitrile.[37] The DPA regenerated was found to be 53.1 (±2.8)% of $DPA^{\cdot+}$ initially present for 17 experiments conducted at 25.0 (± 0.1)°.

**Macroscale Reaction of $DPA^{\cdot+}$ with TBAC.** DPA (75.6 mg, 0.229 mmol) was added to 150 ml of 0.10 *M* TEAP in acetonitrile in the anode chamber of a two-compartment electrolysis cell.[1b] This vessel was fitted with a buret containing 0.050 *M* TBAC in acetonitrile. The platinum gauze working electrode was potentiostatted at +1.40 V and as the characteristic blue color of $DPA^{\cdot+}$ appeared, it was discharged nearly to completion by the addition of the TBAC solution. At no time was excess TBAC added. The use of numerous such "titration" steps ensured against the buildup of cation radical concentration and thus minimized the likelihood of appreciable side reactions of $DPA^{\cdot+}$ with residual water in the solvent. After 5 hr the blue fluorescence of DPA was absent in the anolyte and the oxidative current had diminished to essentially zero. The acetonitrile was removed by rotary evaporation and the resulting yellow residue was vacuum dried at room temperature. A 25-ml volume of nitromethane was then added with stirring, giving rise to a yellow solution and a suspension of fine white crystals. The latter were filtered, crushed, and washed with several portions of cold nitromethane. After drying, the material was recrystallized from methylene chloride–hexane to give colorless crystals of 9,10-dichloro-9,10-diphenyl-9,10-dihydroanthracene (**1**, 78.2 mg, 0.195 mmol), mp 189–190° dec (lit. 187–189° dec), mmp (with authentic[23]) 187–189° dec.

Alternatively, removal of the acetonitrile from the reaction mixture and introduction of the benzene-soluble portion of the resulting yellow solids onto a silica gel chromatographic column and subsequent elution with benzene and methanol resulted in degradation of **1** (nonfluorescent) to a material exhibiting blue fluorescence. This fluorescence was manifest both on the column and in the eluent. Removal of solvent from the major fraction of this material gave rise to yellow needles, **2**, from methylene chloride, mp 185–187°. Anal. Calcd for $C_{26}H_{17}Cl$: C, 85.59; H, 4.70; Cl, 9.72. Found: C 85.77; H, 4.29; Cl, 9.94. It is concluded that **2** is 2-chloro-9,10-diphenylanthracene, mp 185°.[38] Authentic **1** was prepared as described earlier.[23] Chromatography of this material in the manner described above also gave rise to the surface-catalyzed loss of HCl and yielded a mixture of **2** (80%) and DPA (20%).

Mass spectral analysis of the electrolysis product[39] and authentic **1** showed a parent ion of *m/e* 364 (DPA + Cl − H) rather than the expected *m/e* 400 [$DPA(Cl)_2$] under electron impact ionization. Most probably, the heated glass sample probe induced degradative rearrangement[38] of **1** to **2** prior to volatilization from the probe, since a high relative abundance of HCl was noted in the mass spectra of both compounds as the probe temperature was increased.

The decomposition of **1** to **2** was examined by thermogravimetric analysis (TGA) of both the electrolysis product[39] and authentic **1**. In both cases, a well-defined weight loss was observed between 160 and 205°, followed by a plateau in the thermogram up to 230°. For **1**, calcd weight loss to give **2** (**1** − HCl): 9.08%. Observed weight loss: authentic **1**, 9.36%; electrolysis product, 9.20%.

**Registry No.**—**1**, 6486-01-7; **2**, 43217-28-3; DPA, 1499-10-1; TBAP, 1923-70-2; TBAC, 1112-67-0; TEAP, 2567-83-1.

## References and Notes

(1) "EE" systems are those species capable of undergoing two monoelectronic oxidation (or reduction) processes $E_1$ and $E_2$, where $E_2 > E_1$. For

$$A \rightarrow A^{\cdot+} + e^- \quad (E_1)$$

$$A^{\cdot+} \rightarrow A^{2+} + e^- \quad (E_2)$$

previous papers in this series, see (a) H. N. Blount, *J. Electroanal. Chem.*, **42**, 271 (1973); (b) D. T. Shang and H. N. Blount, *ibid.*, **54**, 305 (1974).
(2) R. E. Sioda, *J. Phys. Chem.*, **72**, 2322 (1968).
(3) G. C. Grant and T. Kuwana, *J. Electroanal. Chem.*, **24**, 11 (1970).
(4) H. N. Blount and T. Kuwana, *J. Electroanal. Chem.*, **27**, 464 (1970).
(5) G. Mengoli and G. Vidotto, *Makromol. Chem.*, **150**, 277 (1971).
(6) C. J. Ludman, E. M. McCarron, and R. F. O'Malley, *J. Electrochem. Soc.*, **119**, 874 (1972).

(7) O. Hammerich and V. D. Parker, *J. Electroanal. Chem.*, **38**, App. 9 (1972).
(8) U. Svanholm and V. D. Parker, *Acta Chem. Scand.*, **27**, 1454 (1973).
(9) C. Barry, G. Cauquis, and M. Maurey, *Bull. Soc. Chim. Fr.*, 2510 (1966).
(10) H. J. Shine and Y. Murata, *J. Am. Chem. Soc.*, **91**, 1872 (1969).
(11) Y. Murata and H. J. Shine, *J. Org. Chem.*, **34**, 3368 (1969).
(12) V. D. Parker and L. Eberson, *J. Am. Chem. Soc.*, **92**, 7488 (1970).
(13) J. J. Silber and H. J. Shine, *J. Org. Chem.*, **36**, 2923 (1971).
(14) H. J. Shine and J. J. Silber, *J. Am. Chem. Soc.*, **94**, 1026 (1972).
(15) H. J. Shine, J. J. Silber, R. J. Bussey, and T. Okuyama, *J. Org. Chem.*, **37**, 2691 (1972).
(16) O. Hammerich and V. D. Parker, *J. Electroanal. Chem.*, **36**, App. 11 (1972).
(17) U. Svanholm, O. Hammerich, and V. D. Parker, *J. Am. Chem. Soc.*, **97**, 101 (1975).
(18) G. Cauquis and M. Maurey-Mey, *Bull. Soc. Chim. Fr.*, 3588 (1972).
(19) H. J. Shine and L. R. Shade, *J. Heterocycl. Chem.*, **11**, 139 (1974).
(20) H. J. Shine and R. J. Small, *J. Org. Chem.*, **30**, 2140 (1965).
(21) See ref 1a for a synopsis of mechanisms.
(22) J. F. Evans and H. N. Blount, to be published.
(23) E. A. Chandross and F. I. Sonntag, *J. Am. Chem. Soc.*, **88**, 1089 (1966).
(24) T. M. Siegel and H. B. Mark, Jr., *J. Am. Chem. Soc.*, **94**, 9020 (1972).
(25) T. Kihara, M. Sukigara, and K. Honda, *Electrochim. Acta*, **18**, 639 (1973).
(26) Previous experiments[4] were conducted at relatively high water concentrations (2.5–4.0 *M*. Recent stopped-flow experiments conducted in these laboratories over the range of water concentrations $5.0 \times 10^{-3}$–1.50 *M* yielded data exhibiting first-order kinetic dependence on $[DPA\cdot^+]$ and $[H_2O]$; $k = 5.78 (\pm 0.31) \times 10^{-2}\ M^{-1}\ sec^{-1}$ for fit to eq 10. The concentration of DPA· in these experiments was on the order of $3.0 \times 10^{-5}$ *M*. The rate of decay of $DPA\cdot^+$ was found tc be independent of DPA concentration, thereby ruling out cation radical disproportionation.
(27) On the basis of HMO calculations.
(28) Through-space interactions of these substituents with the ring system would be unlikely, although such cannot be dismissed a priori.
(29) Differences being primarily attributable to steric consideration which might affect the juxtaposition of the respective radicals and $DPA\cdot^+$ necessary for electron transfer.
(30) R. G. Pearson, H. Sobel, and J. Songstad, *J. Am. Chem. Soc.*, **90**, 319 (1968), report pyridine to be nearly 1.5 orders of magnitude more reactive than chloride in the SN2 displacement of iodide from methyl iodide in methanol.
(31) R. F. Broman, W. R. Heineman, and T. Kuwana, *Discuss. Faraday Soc.*, **56**, 16 (1973).
(32) J. F. Evans and H. N. Blount, Abstracts, 169th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1975, No. ANAL-106.
(33) T. Osa and T. Kuwana, *J. Electroanal. Chem.*, **22**, 389 (1969).
(34) A. A. Pilla, *J. Electrochem. Soc.*, **118**, 702 (1971).
(35) Inclusion of TBAP in this solution is essential to prevent thermal effects and changes in refractive index upon mixing.
(36) The DPA absorbance at 392.5 nm is free from interference by $DPA\cdot^+$ and all reaction products.
(37) See ref 2 for details.
(38) E. Bergmann and O. Blum-Bergmann, *J. Am. Chem. Soc.*, **59**, 1439 (1937).
(39) "Electrolysis product" refers to the material isolated and purified from the macroscale electrolysis.

# Racemization and Bromide-Exchange Studies on 1-Phenylbromoethane and the Question of the Ion-Pair Mechanism for Bimolecular Nucleophilic Substitutions at Saturated Carbon

Allan R. Stein

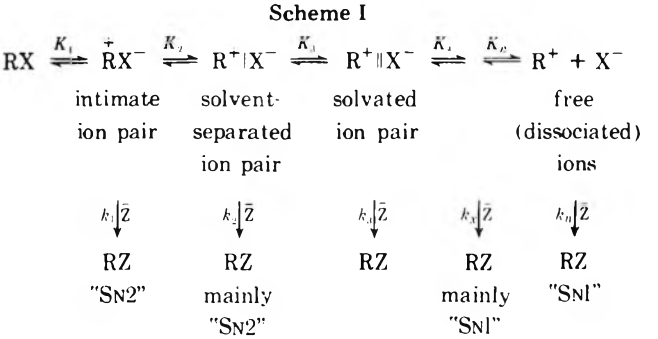
*Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland, Canada,* and Avdelningen för Fysikalisk Kemi, Umeå Universitet, Umeå, Sweden*

*Received August 27, 1975*

In an effort to determine whether the ion-pair mechanism for nucleophilic substitution at saturated carbon operates in bimolecular reactions, the racemization and bromide–radiobromide exchange of 1-phenylbromoethane were examined in anhydrous acetone containing lithium bromide. Within experimental error, the rate constants and Arrhenius and thermodynamic activation parameters are identical for the racemizations and exchanges. There is no evidence for inversion without exchange or exchange without inversion. Consequently, for the ion-pair mechanism to be operating, all of the ion pairs formed by the substrate and leaving group must be intercepted (or collapse to starting material) before the ions separate sufficiently to allow the alkyl group to turn over and give, on the collapse of the ion pair, inversion without halide exchange. On the other hand, the results are completely consistent with the classical Hughes–Ingold SN2 mechanism.

The observation that the rates of halide–radiohalide exchange and racemization of optically active 1-phenylbromoethane[1] and those of 2-iodooctane[2] were the same within experimental error was the basis for the postulation of the SN2 mechanism for the bimolecular nucleophilic displacement at saturated carbon by Gleave, Hughes, and Ingold.[3] It was the carbonium ion route, the SN1 or unimolecular mechanism of the mechanistic pair, which was the more difficult to establish;[4,5] chemists, on the other hand, readily accepted the concerted nucleophilic attack–leaving group departure of the SN2 mechanism. As Sneen and Larsen point out, however, it is the traditional SN2 reaction pathway which is the less likely.[6] They have proposed an elaboration of the ion-pair scheme of Winstein and his colleagues[7] as a single unified mechanism to replace the SN1–SN2 dichotomy. In their ion-pair mechanism, which is summarized in Scheme I, it is proposed that the initial step is the formation of a contact or intimate ion pair by the substrate with its leaving group. The reaction could show the characteristics of SN2, mixed, or SN1 mechanisms depending upon where in the series of solvation equilibria from intimate ion pair to the free, independently solvated ions nucleophilic attack occurs.

Scheme I




Should such a mechanistic scheme be proven correct, it has wide ramifications not only for all nucleophilic substi-

* Address to which correspondence should be sent.

Table I
Second-Order Rate Constants for the Racemization of (+)- or (−)-1-Phenylbromoethane in Anhydrous Acetone at Various Temperatures and Lithium Bromide Concentrations

| Temp, | Rate constants[a] × $10^3$ mol sec/l. at [LiBr] given | | | | |
|---|---|---|---|---|---|
| K | 0.0100 *M* | 0.00500 *M* | 0.00200 *M* | 0.00100 *M* | 0.000500 *M* |
| 298.15 | 1.334 ± 0.014 | 1.678 ± 0.004 | 2.349 ± 0.024 | 3.005 ± 0.029 | 3.712 ± 0.024 |
| 303.15 | 2.092 ± 0.010[b] | 2.630 ± 0.007[b] | 3.645 ± 0.012[b] | 4.601 ± 0.057[b] | 5.783 ± 0.065[c] |
| 308.15 | 3.273 ± 0.009[b] | 4.091 ± 0.011[b] | 5.597 ± 0.019 | 7.117 ± 0.050[b] | 9.229 ± 0.084[c] |
| 313.15 | 4.929 ± 0.010 | 6.274 ± 0.039[b] | 8.449 ± 0.024 | 11.116 ± 0.099[b] | 14.329 ± 0.110 |
| 318.15 | 7.328 ± 0.056 | 9.395 ± 0.032 | 12.705 ± 0.035 | 16.360 ± 0.070 | 18.305 ± 0.084 |

[a] Least-squares values. [b] Average of two runs. [c] Average of three runs.

tution reactions but also for other substitutions, and for elimination and addition reactions among others.[8] The importance of ion pairs in nucleophilic substitutions at saturated carbon is quite well established at or near the unimolecular or dissociated ion extreme of the mechanistic range[9] but not for bimolecular displacements. Hughes et al.[1] reported that both the halide exchange and the racemization of 1-phenylbromoethane in anhydrous acetone with lithium bromide were bimolecular. Since in that system the leaving group and the nucleophile are identical, some of the variables are eliminated. Also as a bulwark of the SN2 mechanism, what system could be more appropriate for a detailed examination to determine whether ion pairs play a role in bimolecular nucleophilic substitutions at saturated carbon?

## Results

The racemization of optically active alkyl halide by halide ion can be represented by the equations

$$(+)\mathrm{RX} + \mathrm{X}^- \xrightarrow{k} (-)\mathrm{RX} + \mathrm{X}^-$$

$$(+)\mathrm{RX} + (-)\mathrm{RX} \xrightarrow[\text{or concurrent}]{\text{instantaneous}} (\pm)\mathrm{RX}$$

Note that the inversion of one molecule of, say, the (+) isomer to the (−) isomer not only removes the rotational contribution of one (+) species but cancels that of another, giving two molecules of racemic (±) mixture. The rate expression, eq 1, applies

$$\ln \frac{[\mathrm{RX}]_0}{[\mathrm{RX}]_t} = 2k[\mathrm{X}]t \qquad (1)$$

where $[\mathrm{RX}]_0$ and $[\mathrm{RX}]_t$ are the concentrations of the optically active alkyl halide initially and at time $t$, $k$ is the rate constant, and [X] the concentration of the halide ion.[10] In practice, the alkyl halide concentration terms were replaced with the angle of rotation of plane polarized light or, more precisely, the recorder output of the recording polarimeter. Good linearity was obtained for 3–6 half-lives, depending upon when the instrument instability became a significant fraction of the rotational value.

For the halide exchange studies, the electrodeposition method developed by Beronius[11] was used. In this method, the solution of inorganic halide (e.g., LiBr) in the solvent (e.g., acetone) containing radiohalide (e.g., $^{82}\mathrm{Br}^-$) is placed in the thermostatted electrolysis cell and a very small portion of the halide electrodeposited on a silver disk as AgX. The activity of that disk is a measure of the $t = 0$ halide activity. A known amount of RX is then added and, at various time intervals, AgX is deposited on fresh silver disks at the same current for the same time as was used for the $t = 0$ electrode. The decreasing activity of subsequent electrodes is then a measure of the amount of radiohalide incorporated into the RX and no longer available for electrodeposition.

The halide exchange reaction can be represented as

$$\mathrm{RX} + \mathrm{X}^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{RX} + \mathrm{X}^-$$

where $k_1$ and $k_{-1}$ are the rate constants for the forward and reverse reactions. They are identical and equal to $k$. Assuming that any isotope effects are negligible, the rate constants for the incorporation of the radiohalide, X*, the process actually studied, will be the same or

$$\mathrm{RX} + \mathrm{X}^{*-} \underset{k}{\overset{k}{\rightleftharpoons}} \mathrm{RX}^* + \mathrm{X}^-$$

and

$$\frac{-\mathrm{d}[\mathrm{X}^*]}{\mathrm{d}t} = k[\mathrm{RX}][\mathrm{X}^*] - k[\mathrm{RX}^*][\mathrm{X}]$$

$$= k([\mathrm{RX}][\mathrm{X}^*] - [\mathrm{RX}^*][\mathrm{X}])$$

Since the total amount of X* is constant,

$$[\mathrm{RX}^*] = [\mathrm{X}^*]_0 - [\mathrm{X}^*]$$

where $[\mathrm{X}^*]_0$ is the initial, or $t = 0$ concentration, of radiohalide as measured by the activity of the first electrode. Substituting and rearranging gives

$$\frac{\mathrm{d}[\mathrm{X}^*]}{-[\mathrm{X}][\mathrm{X}^*]_0 + ([\mathrm{RX}] + [\mathrm{X}])[\mathrm{X}^*]} = -k\,\mathrm{d}t$$

Noting that

$$\int \frac{1}{nx + a}\,\mathrm{d}x = \frac{1}{n}\ln(nx + a) + c$$

allows integration of the expression to

$$\frac{1}{[\mathrm{RX}] + [\mathrm{X}]} \ln\{([\mathrm{RX}] + [\mathrm{X}])[\mathrm{X}^*] - [\mathrm{X}][\mathrm{X}^*]_0\} = -kt + c$$

Rearranging and adding the constant $\ln[1/([\mathrm{RX}] + [\mathrm{X}])]$ to both sides gives

$$\ln\left|[\mathrm{X}^*] - \frac{[\mathrm{X}][\mathrm{X}^*]_0}{[\mathrm{RX}] + [\mathrm{X}]}\right| = -([\mathrm{RX}] + [\mathrm{X}])kt + c'$$

Again ignoring isotope effects, at infinite time the radiohalide will be statistically distributed between inorganic and organic halide so that the $t = \infty$ activity will be given by

$$[\mathrm{X}^*]_\infty = \frac{[\mathrm{X}^*]_0[\mathrm{X}]}{[\mathrm{RX}] + [\mathrm{X}]} \qquad (2)$$

Thus the rate expression becomes

$$\ln\{[\mathrm{X}^*] - [\mathrm{X}^*]_\infty\} = -([\mathrm{RX}] + [\mathrm{X}])kt + c' \qquad (3)$$

Equation 3 can be converted to the form used by other workers[12]

$$\ln\left|\frac{[\mathrm{X}^*]}{[\mathrm{X}^*]_\infty} - 1\right| = -([\mathrm{RX}] + [\mathrm{X}])kt + C \qquad (4)$$

Slopes of the plot of the ln term of eq 3 or 4 (with $[\mathrm{X}^*]_\infty$

Table II
Second-Order Rate Constants for the Bromide–Radiobromide Exchange of 1-Phenylbromoethane in Anhydrous Acetone at Various Temperatures and Lithium Bromide Concentrations

| Temp, K | Rate constant[a] × $10^3$ mol sec/l. at [LiBr] given | | | |
|---|---|---|---|---|
| | 0.0100 *M* | 0.00500 *M* | 0.00200 *M* | 0.000500 *M* |
| 298.15 | 1.313 | | 2.370 ± 0.026[b] | 3.613 ± 0.003[b] |
| 303.15 | 2.1500 ± 0.0003[c] | 2.679 ± 0.020[d] | 3.803 ± 0.018[e] | 6.321 ± 0.026[e] |
| 308.15 | 3.3113 ± 0.0001 | | 6.2085 ± 0.0001[b] | 9.46 ± 0.23[d] |
| 313.15 | 5.033 | | 8.330 | 12.6 ± 2.1[b] |

[a] Rate constants were determined graphically. Where least-squares determinations were also done, agreement was within ±0.2%. [b] Average of two runs. [c] Average of three runs. [d] Average of four runs. [e] Average of five runs.

Table III
Activation Parameters at 303.15 K for the Reaction of 1-Phenylbromoethane and Bromide Ion in Anhydrous Acetone[a]

| | Arrhenius parameters | | Thermodynamic parameters | | |
|---|---|---|---|---|---|
| | ln *A* | $E_a$, kJ/mol | $\Delta H^\ddagger$, kJ/mol | $-\Delta S^\ddagger$, J/deg mol | $\Delta G^\ddagger$, kJ/mol |
| Racemization | 20.94 ± 0.14 | 67.0 ± 0.2 | 64.199 ± 0.087 | 79.88 ± 0.67 | 88.41 ± 0.29 |
| Exchange | 20.93 ± 0.15 | 66.9 ± 0.5 | 64.083 ± 0.516 | 80.38 ± 1.06 | 88.45 ± 0.84 |

[a] Values given are averages of those obtained at each concentration of lithium bromide reported in Tables I and II. At individual concentrations of lithium bromide, agreement between the parameters of racemization and exchange was normally within the sum of the standard deviations of the two values.

calculated by eq 2) vs. *t* were used to evaluate the rate constants for the exchange reaction. In some runs good linearity was obtained for over 7 half-lives. Nor was the calculated rate constant dependent upon the concentration of the alkyl bromide, since changing the concentration by as much as a factor of 20 left the rate constant unchanged within experimental error.

The rate constants for both the exchanges and the racemizations at the lower concentrations of lithium bromide were quite sensitive to moisture. The maximum rate was found for freshly prepared solutions; a rate that fell off as the acetone–lithium bromide solutions picked up moisture even in tightly stoppered flasks stored in a nitrogen-flushed drybox. Consequently, the rate constants for the lowest concentration of lithium bromide are the least secure of those reported in Tables I and II.

## Discussion

From Tables I and II it is apparent that the rate constants for both the exchange and the racemization of 1-phenylbromoethane in anhydrous acetone containing lithium bromide decrease with increasing concentration of lithium bromide. Hughes et al.[1] reported a similar observation. This fall-off has been assigned to ion pairing or association of the lithium bromide.[10] Such association would reduce the activity coefficient of the bromide ion. Because concentrations, not activities, were used in determining the rate constants via eq 1 and 3 or 4, the apparent rate constant decreases as the lithium bromide concentration increases. Normally, to avoid such problems, high constant ionic strengths and concentrations of the cation are used to keep the activity coefficient of the nucleophile constant as its concentration is varied.[10,13] Concentration and activity are then linearly related and the rate constants are independent of the concentration of the ionic reactant. Unfortunately, all of the lithium salts, nitrate, chlorate, perchlorate, picrate, etc., which were tried as inert electrolytes were either not sufficiently soluble in the acetone, were too nucleophilic, or else interfered with the electrodeposition of the silver bromide in the exchange studies.

Other halide salts for which association would be much less, salts like the tetraalkylammonium bromides, do indeed give a much smaller drop-off of rate constant with increasing bromide salt concentration. Thus with tetrabutylammonium bromide at 303.15 K the racemization rate constants at 0.001 and 0.01 *M* were 9.70 and 8.42 × $10^{-13}$ l./mol sec, respectively.[14] While such salts could have been used in the racemization studies, they would have added the complication of ion exchange treatment to the exchange experiments because the radiobromide was most conveniently made by neutron bombardment of inactive lithium bromide.

Despite the decrease in the apparent rate constant with increasing lithium bromide concentration,[14] the reaction is obviously second order, first order in each of alkyl halide and halide ion. Thus increasing the lithium bromide concentration fivefold from 0.002 to 0.01 *M* increases the rate of the racemization and the exchange reactions by an average factor of 2.86 while the rate constant decreases, on average, to 57% of its former value. A 20-fold concentration change from 0.0005 to 0.01 *M* led to an average rate increase by a factor of 7.28 with an average decrease in second-order rate constant to 36.4% of its former value.

In Table III Arrhenius activation parameters and thermodynamic data are reported. Like the rate constants in Tables I and II, which are apparent values uncorrected for the activity of the bromide ion, the parameters in Table III include contributions due to changes in salt effects and activity coefficients on the temperature dependence of the rates. However, as with the rate constants, comparisons between racemization and exchange reactions which were done under the same reaction conditions are valid.

Comparison of the rate data for racemization in Table I with that for exchange in Table II shows that, as Hughes et al. reported, the rate constants for the two processes are the same within experimental error. The one-to-one nature of the two processes is confirmed by the activation and thermodynamic parameters, the values of which were generally within one standard deviation for racemization and exchange at the same concentration of lithium bromide and, indeed, were independent of the concentration of inorganic halide. These results are consistent with the classical Hughes–Ingold mechanism for the bimolecular nucleophilic displacement at saturated carbon. They are compatible with the Sneen ion-pair mechanism of Scheme I only if nucleophilic attack occurs early in the ionization sequence. It must occur before the separation of the alkyl group and the leaving group is sufficient for the alkyl group to turn over and so give detectable racemization with internal return.

If the ion-pair mechanism is operating, stabilizing the carbonium ion species by the introduction of appropriate substituents on the phenyl group should shift the average point of nucleophilic attack toward the right of Scheme I, perhaps sufficiently so that significant amounts of racemization with internal return can occur. Racemization then should be faster than halide exchange. This possibility is currently under investigation. Some preliminary results for the bromide–radiobromide exchange have already been reported.[15] However, with 1-phenylbromoethane itself, no evidence confirming that the Sneen ion-pair mechanism applies to bimolecular nucleophilic displacements at saturated carbon has been obtained to date.

## Experimental Section

**Solvent.** Just before preparation of the solutions, reagent grade acetone was dried and purified as previously described.[10]

**Lithium Bromide.** Reagent grade, "Certified" (Fisher) or "Suprapur" (Merck), $LiBr \cdot x H_2O$ was oven dried at 250°C for at least 24 hr and cooled in a desiccator immediately before weighing and preparation of the 0.05000 ± 0.0002 *M* stock solution which, with appropriate dilutions, was used to make the acetone solutions for this study.

**(±)-, (+)- and (−)-1-Phenylbromoethane** were made from the corresponding 1-phenylethanol as previously described.[10,16] The alkyl bromides showed no detectable hydroxylic absorptions in infrared spectra neat or at high concentration in $CCl_4$, nor were anomalous signals present in the proton nuclear magnetic resonance spectra or the vapor phase chromatograms of the halides so examined. Spectra (NMR, ir, mass spectrum) and physical properties were consistent with the structure. The 1-phenylbromoethanes were stored under nitrogen in glass ampules in a freezer until needed but even under these conditions the optically active halides very slowly racemized. Fresh material was made every few weeks. Configurational purity was not established but since the racemizations were first order in alkyl bromide, it is of no consequence to this study.

**Racemization Studies.** The procedure was analogous to that described earlier[10] except that a Perkin-Elmer Model 141 MC polarimeter equipped with a retransmitting potentiometer and a Honeywell Electronik 194 potentiometric recorder was used. All manipulations of solvent and solution were done in a dry nitrogen-filled glove bag. Concentrations of (+)- or (−)-1-phenylbromoethane (i.e., 0.07–0.14 *M*) that gave near full-scale initial recorder pen deflections were used. Results are reported in Table I.

Reactions using $R_4N^+Br^-$, especially tetrabutylammonium bromide, were run analogously. (See paragraph at end of paper regarding supplementary material.)

**Exchange Studies.** The radiobromide ($^{82}Br^-$) was made by Aktiebolaget Atomenergi, Isotopservice, 611 01 Nykoping 1, Sweden, by irradiating at high neutron flux 0.87 mg of LiBr in a quartz vial. With adequate lead shielding throughout, the vial was opened and its contents extracted with several portions of hot distilled deionized water. The solution was evaporated to dryness, the 15-ml Erlenmeyer flask was then heated to 300°C for several hours and cooled, and the lithium radiobromide taken up in 5 ml of anhydrous acetone. An aliquot (0.1–0.4 ml) of this solution was added to the 50-ml stirrer-equipped Teflon-lined jacketed aluminum electrolysis cell containing the lithium bromide–acetone solution already equilibrated to the desired temperature. After electrodeposition of AgBr (for the initial, or $t = 0$, activity) on two or three electrodes, a weighed amount of (±)-1-phenylbromoethane (to give a solution of 0.35–7.5 × $10^{-2}$ *M*) was added and the reaction timer started. Electrolysis was with silver electrode disks 0.4 cm in diameter at a carefully controlled and reproduced constant current of 200–2000 μA for 20–60 sec depending upon the LiBr concentration. Six to ten electrodepositions spread over about 3 half-lives were used.

Individual electrodes were counted for 3–20 min; the time interval was chosen so that the $t = 0$ electrode would give 30000–1000000 counts. The counts were corrected for background (invariably less then 1% of the $t = 0$ values), for variations in electrodeposition time (rarely more than ±0.1 sec), and for radioactive decay of the $^{82}Br$ between the time of counting the first and the current electrode of the run. The infinity values were calculated using corrected counts in eq 2. In those runs in which the infinity values were approached, the empirical and calculated values were in good agreement. For example, in one run where the corrected $t = 0$ count (average of two electrodes) was 37229, the calculated infinity value was 3597 while the last electrode (at $t = 66615$ sec) gave 3844 counts, a value only 107% of the calculated infinity value. The last point deviates little from the best line of the $\ln\{[X^*] - [X^*]_\infty\}$ vs. $t$ plot and represents over 7 half-lives of the exchange reaction. The rate constants reported in Table II were generally determined graphically using eq 3 or 4. In those cases where standard least-squares treatment of data was also done, the calculated rate constants were normally within ±0.2% and eq 3, not unexpectedly, gave the smaller standard deviation.

Details of the procedure, electrode preparation, electrolysis cell design, and current source are well presented by Beronius.[11] Results are summarized in Table II. (See paragraph at end of paper regarding supplementary material.)

**Control Experiments.** To establish that the elimination of hydrogen bromide is much slower than the racemization–exchange reaction, the disappearance of 1-phenylbromoethane ($7 \times 10^{-2}$ *M*) in acetone 0.00, 0.0005, and 0.01 *M* in lithium bromide was followed at 303.15 K by vapor phase chromatography (all-glass system, 4-ft Ucon HB 1500 column, FID, 100°C). In 24 hr there was no detectable change in the concentration nor did any peaks other than acetone and the alkyl halide appear in the chromatograms. The first order or pseudo-first-order rate constants for elimination are considerably less than $1 \times 10^{-9}$ $sec^{-1}$ under these conditions.[17]

**Acknowledgment.** The author wishes to thank the Swedish Natural Science Research Council for financial assistance and Dr. P. Beronius and A. Holmgren at Umeå Universitet for their assistance and for the use of their laboratories and equipment for the exchange studies. The assistance of Memorial University throughout made this study possible and is gratefully acknowledged.

**Registry No.**—(±)-1-phenylbromoethane, 38661-81-3; (+)-1-phenylbromoethane, 1459-14-9; (−)-1-phenylbromoethane, 3756-40-9; lithium bromide, 7550-35-8; lithium radiobromide, 57256-21-0; tetrabutylammonium bromide, 1643-19-2.

**Supplementary Material Available.** Typical data for a racemization and a bromide–radiobromide exchange (1-phenylbromoethane at 303.15 K and [LiBr] = 0.0002000 *M* in acetone) (4 pages). Ordering information is given on any current masthead page.

## References and Notes

(1) E. D. Hughes, F. Juliusburger, A. D. Scott, B. Topley, and J. Weiss, *J. Chem. Soc.*, 1173 (1936).
(2) E. D. Hughes, F. Juliusburger, S. Masterman, B. Topley, and J. Weiss, *J. Chem. Soc.*, 1525 (1935).
(3) J. L. Gleave, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 236 (1935).
(4) E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 244 (1935).
(5) A general discussion of the establishment of the SN1 mechanism can be found, for example, in J. Hine, "Physical Organic Chemistry", 2nd ed, McGraw-Hill, New York, N.Y., 1962, pp 128–137.
(6) R. A. Sneen and J. W. Larsen, *J. Am. Chem. Soc.*, **91**, 362, 6031 (1969).
(7) For a summary see S. Winstein, B. Appel, R. Baker, and A. Diaz in "Organic Reaction Mechanisms", *Chem. Soc., Spec. Publ.*, **No. 19**, 109–130 (1965).
(8) See, for example, (a) R. J. Muller, C. Winsternitz, and B. L. Murr, *J. Org. Chem.*, **40**, 412 (1975); D. D. Roberts and C.-H. Wu, *ibid.*, **39**, 3937 (1974); R. D. Fisher et al., *J. Am. Chem. Soc.*, **97**, 2408 (1975); V. P. Vitullo and F. P. Wilgis, *ibid.*, **97**, 458 (1975); (b) R. A. Sneen, *Acc. Chem. Res.*, **6**, 46 (1973); F. G. Bordwell, *ibid.*, **5**, 374 (1972); (c) V. L. Heasley and C. N. Griffiths, *J. Org. Chem.*, **40**, 1358 (1975); (d) W. T. Ford and D. J. J. Pietsek, *J. Am. Chem. Soc.*, **97**, 2194 (1975).
(9) (a) H. L. Goering and K. Humski, *J. Org. Chem.*, **40**, 920 (1975), and references cited therein; (b) H. L. Peeters and M. Anteunis, *ibid.*, **40**, 307, 312 (1975); (c) F. G. Bordwell, P. F. Wiley, and T. G. Mecca, *J. Am. Chem. Soc.*, **97**, 132 (1975), and references cited therein; (d) V. F. Raaen, T. Juhlke, F. J. Brown, and C. J. Collins, *ibid.*, **96**, 5928 (1974), and references cited therein; (e) V. J. Shiner, Jr., and R. D. Fisher, *ibid.*, **93**, 2553 (1971); (f) J. M. W. Scott, *Can. J. Chem.*, **48**, 3807 (1970); (g) J. M. W. Scott and R. E. Robertson, *ibid.*, **50**, 167 (1972).
(10) A. R. Stein, *J. Org. Chem.*, **38**, 4022 (1973).
(11) P. Beronius, *Trans. R. Inst. Technol., Stockholm*, **No. 213** (1963).
(12) H. A. C. McKay, *J. Am. Chem. Soc.*, **65**, 702 (1943); P. Beronius, *Z. Phys. Chem. (Frankfurt am Main)*, **40**, 33 (1964); A. Holmgren and P. Beronius, *Acta Chem. Scand.*, **26**, 3881 (1972).
(13) See for example, A. Ceccon, I. Papa, and A. Fava, *J. Am. Chem. Soc.*, **88**, 4643 (1966).

(14) P. Beronius, A.-M. Nilsson, and G. Wikander, *Acta Chem. Scand.*, **24**, 2826 (1970), have recently shown that the association constant for LiBr is some 14 times that of $Bu_4NBr$ in acetone at 298.15 K, i.e. $K_a = 4680$ vs. 334. In this study a value of $K_a \simeq 1950$ for LiBr gives a racemization rate constant at 298.15 K of $5.9613 \pm 0.0008 \times 10^{-3}$ l./mol sec for the lowest three concentrations.

(15) A. R. Stein, *Tetrahedron Lett.*, 4145 (1974).
(16) E. Downer and J. Kenyon, *J. Chem. Soc.*, 1156 (1939).
(17) Ford and Pietsek (ref 8d) report $k = 5.8 \times 10^{-4}\ M^{-1}\ sec^{-1}$ at 347.8 K for the *n*-$Bu_4NBr$-catalyzed elimination with 1-phenylbromopropane in acetone, a reaction that would presumably be more facile than that of the ethane derivative in question.

# Bimolecular Homolytic Substitution at Carbon. A Stereochemical Investigation[1]

Charles J. Upton*[2] and Joseph H. Incremona

*Department of Chemistry, Duquesne University, Pittsburgh, Pennsylvania 15219*

*Received August 20, 1975*

Photochlorination of 1,1-dichlorocyclopropane (**1**) at 0–5°C in carbon tetrachloride yields 1,1,1,3-tetrachloropropane (**2**) and 1,1,1,3,3-pentachloropropane (**3**) as major products, with lesser amounts of 1,1,1,2,3-pentachloropropane (**4**). Photobromination of **1** yields 1,3-dibromo-1,1-dichloropropane (**5**) as the only product. Both the chlorination and bromination were shown to be radical processes, accelerated by benzoyl peroxide and azobisisobutyronitrile and inhibited by benzoquinone or darkness. The stereochemistry of the ring opening of **1** was determined from a $^1H$ NMR analysis of the 1,1,1,3-tetrahalopropane-2,3-$d_2$ isomers produced upon photochlorination and photobromination of 1,1-dichloro-2,3-*trans*-dideuteriocyclopropane (**7**) and its cis isomer **8**. In each case, **7** yielded >96% erythro isomer, and **8** >96% threo isomer. The results clearly demonstrate that attack of both chlorine and bromine atoms on the cyclopropane ring, occurs with essentially complete inversion of configuration. The proposed mechanism involves ring opening via an SN2-like transition state; attack of the halogen atom is postulated to occur at a minor lobe of the $C_1$–$C_2$ hybrid orbital, with concomitant cleavage of the $C_1$–$C_2$ bond. Evidence favoring the proposed mechanism over one proceeding via a bridged intermediate or transition state is presented.

Bimolecular homolytic substitution (SH2) reactions represent one of the most common reaction pathways available to free radicals.[3] Examples of SH2 displacements at multivalent atoms are well documented, and have been recently reviewed.[4] Unfortunately, few studies have examined the particular case of an SH2 displacement at saturated carbon, leaving the mechanism and stereochemistry the subject of speculation.

Theoretical and experimental approaches to this problem[5–15] have not predicted a favored stereochemical path. A simple Hückel MO approach predicted that the reaction might have a low degree of stereospecificity.[6] Initial experimental attempts to detect an SH2 displacement on carbon by iodine atoms, by observing racemization of optically active *sec*-butyl iodide in either liquid or vapor phase, were unsuccessful.[7,8] Displacement occurred instead on iodine,[9,10] yielding the *sec*-butyl radical and molecular iodine which on recombination gave racemic products. A similar result has recently been reported for methyl iodide,[11] as well as for bromine exchange in bromotrichloromethane.[12] Several attempts to detect an intramolecular SH2 (SHi) reaction have also been unsuccessful,[13,14] although Kaplan[15] has proposed an SHi reaction to explain the formation of cyclopropane and cyclopentane from decomposition of 1,3-diiodopropane and 1,5-diiodopentane.

It has become increasingly apparent that the only unambiguous examples of SH2 displacements on carbon are radical induced cleavages of the strained carbon–carbon bonds of cyclopropanes. Examples of cyclopropane ring openings under free-radical chlorination,[16] bromination,[17] and iodination[18] are well known. Ring opening of perfluorocyclobutane by fluorine atoms has recently been reported.[19]

The stereochemistry of the radical induced cyclopropane ring opening would be of interest since both nucleophilic[20] and electrophilic[21] ring openings have been studied in some detail. Only a few studies, however, have examined the stereochemistry of the radical induced ring opening, and all have been subject to varying degrees of steric and electronic bias. Applequist and Searle demonstrated that radical attack with inversion is possible. Bromination of 9,10-dehydrodianthracene occurs with inversion at both centers.[22] Attack with retention, however, is sterically restricted. Chlorination of nortricyclene gives *exo,exo*-2,6-dichloronorborane,[23] presumed to arise by initial attack with inversion followed by exo chain transfer. Reaction of bromotrichloromethane with dibenzotricyclo[3.3.0.$0^{2,8}$]-3,6-octadiene occurs with inversion of configuration by the trichloromethyl radical.[24] More recently, Shea and Skell[25] have shown that photobromination of 2,4-dehydroadamantane occurs with inversion at one center and randomly at the other, yielding a mixture of (a,e)- and (e,e)-2,4-dibromoadamantane. In all of the above examples the cyclopropane ring is part of a structurally more complex polycyclic system, and thus may not be stereochemically indicative of a monocyclic system.

We have previously reported[1] the first example where the stereochemistry of the ring opening of a monocyclic cyclopropane was determined; reaction of chlorine atoms with 1,1-dichlorocyclopropane (**1**) proceeds with >96% inversion of configuration. Our complete results on the photochlorination and photobromination of **1** are presented herein. As our work in this area was being completed, Maynes and Applequist[26] described the ring opening of *cis*- and *trans*-1,2,3-trimethylcyclopropane upon photobromination, the only other monocyclic systems examined to date. Photobromination of the cis isomer gave equal amounts of (*S*)-*meso*- and *dl*-3-methyl-2,4-dibromopentane, while the trans isomer gave the (*R*)-meso, (*S*)-meso, and *dl* products. The results demonstrate that attack at one carbon occurs with inversion of configuration, while bromination at the second carbon occurs nonstereospecifically.

Somewhat more recently, several examples of SH2 displacements by inorganic radicals have been described.[27] Results in these studies appear to indicate that in alicyclic systems, attack with inversion may also be favored.

## Results and Discussion

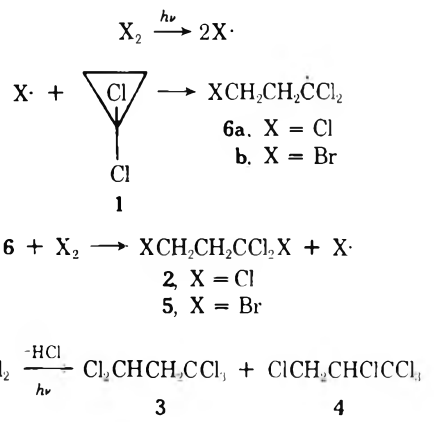
When a carbon tetrachloride solution, 3.14 *M* in 1 and 0.5 *M* in molecular chlorine, is irradiated at 0–5°, the chlorine color fades within 0.5 hr. Analysis by GLC indicated four products: 1,1,1,3-tetrachloropropane (**2**), 1,1,1,3,3-pentachloropropane (**3**), and 1,1,1,2,3-pentachloropropane (**4**), in addition to unreacted **1**, and a trace of what was believed to be 1,1,2-trichlorocyclopropane. The identities of **2**–**4** are based upon a comparison of their physical[16c,28] and spectral[29] properties with those reported, as well as by comparison to authentic samples. Both **2** and **3** were previously reported for the chlorination of **1** with sulfuryl chloride.[16c]

Yields of **2** and **3** determined by analytical GLC and $^1$H NMR were 32–36 and 41–45%, respectively, based on chlorine consumed. That **3** and **4** arise from subsequent chlorination of initially formed **2** and not via ring opening of 1,1,2-trichlorocyclopropane is based on the report[16c] that chlorination of the latter yields 1,1,2,2-tetrachlorocyclopropane. Analogously chlorination of cyclopropyl chloride[16b] gives mostly **1**. In addition, photochlorination of **2** has been reported[30] to yield **3** and **4** in mole ratios of ca 7:1; and we have confirmed this report.

Photobromination of **1** also occurs smoothly. Irradiation of a 1.1 *M* solution of bromine in neat **1** at 35 ± 2° results in a total loss of bromine color within 1–2 hr. Analysis by GLC indicated three unidentified minor products (<5% total GLC peak areas) and one major product shown to be 1,3-dibromo-1,1-dichloropropane (**5**) by its physical and spectral properties and elemental analysis. The yield of **5** was as high as 94% as determined by analytical GLC, with no evidence (GLC or $^1$H NMR) of more highly brominated products.

A radical chain mechanism that accounts for the observed products in each case is shown in Scheme I, and is analogous to those proposed previously for other cyclopropane halogenations.[16–18]

**Scheme I**

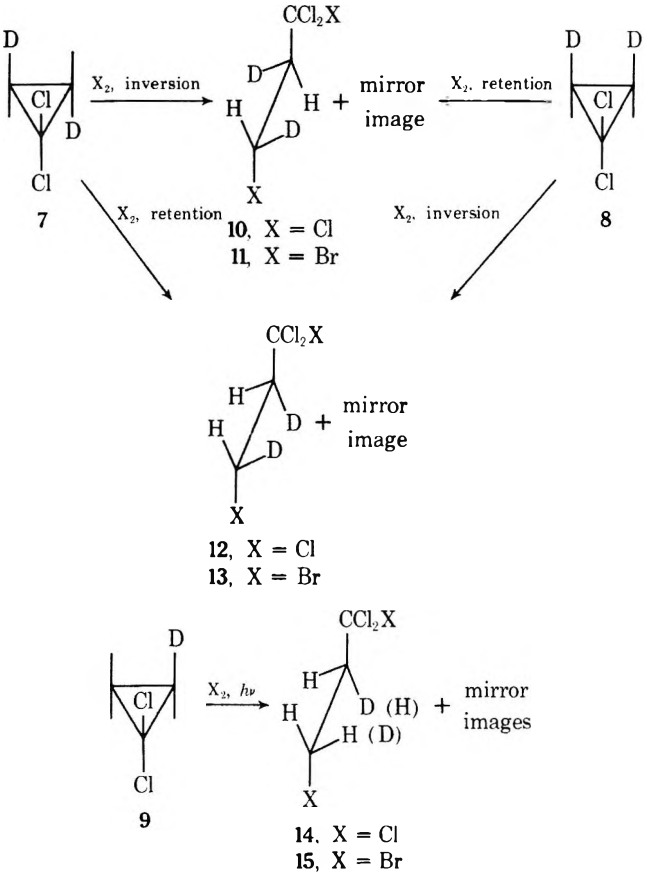



The known stability of **1** to ionic conditions[16c,31] strongly implied that the reactions with chlorine and bromine were radical in nature. This was conclusively proven by observing the relative amounts of products formed in the presence of known radical accelerators and inhibitors. Benzoyl peroxide and azobisisobutyronitrile (AIBN) were effective as accelerators, while benzoquinone, molecular oxygen, and darkness were examined for their inhibitory effects. The results of these studies are presented in Tables I and II.

Chlorination of **1** is markedly accelerated by peroxide or AIBN and is severely inhibited by quinone, oxygen, and darkness. Additionally a sample of **1** in carbon tetrachloride saturated with hydrogen chloride gave no evidence of reaction after 24 hr. Material balances are high indicating the absence of any appreciable side reactions. Similarly bromination of **1** is accelerated by peroxide and to a lesser degree by AIBN. The latter effect may be the result of increased cage recombination of AIBN in the more polar **1**.[32] The acceleration of photobrominations by molecular oxygen is well known,[33] although the nature of the effect is not well understood. Material balances are excellent, again indicating no appreciable side reactions.

In order to elucidate the stereochemistry of attack of both chlorine and bromine atoms on **1**, 1,1-dichloro-*trans*-2,3-dideuteriocyclopropane (**7**) and its cis isomer **8** as well as monodeuterated **9** were synthesized, photochlorinated, and photobrominated. The stereochemical possibilities are presented in Scheme II.

**Scheme II**




An effective synthetic approach to **7**–**9** would be addition of dichlorocarbene to (*E*)- and (*Z*)-ethylene-$d_2$ and ethylene-$d_1$, respectively. Although addition of dichlorocarbene to ethylene proceeds poorly,[34] two recent reports giving good yields have appeared.[35,36] The most promising route appeared to be that of Fields, Haszeldine, and Peters,[36] where pyrolysis of trichloromethyltrifluorosilane (**16**) at 140° in excess olefin gave excellent yields of the corresponding 1,1-dichlorocyclopropanes. Nearly complete ste-

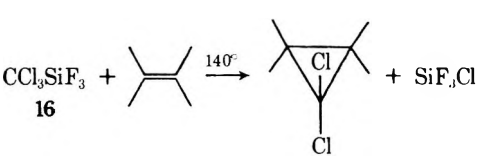


Table I
Effect of Added Modifiers on the Chlorination of 1,1-Dichlorocyclopropane (1) at 0–5°

| Modifier added[a,b] | Light (±) | Time, min | % 2[c] | % 3[c] | % $Cl_2$ consumed[c] | Material balance of 1[c] |
|---|---|---|---|---|---|---|
| $N_2$ | + | 5 | 15.1 | 10.8[d] | 25.9 | 93.9 |
| $N_2$ | + | 10 | 31.0 | 44.3 | 75.3 | 93.5 |
| $N_2$ | + | 30 | 32.6 | 47.7 | 80.3 | 97.1 |
| $N_2$ | − | 1440 | <1.5 | <1.9 | <1.5 | 98.1 |
| $O_2$ | + | 10 | 2.2 | <1.9 | 2.2 | 97.1 |
| A | + | 5 | 25.0 | 28.0 | 51.0 | 92.2 |
| B | + | 5 | 27.1 | 29.5 | 56.6 | 96.9 |
| Q | + | 5 | 4.7 | <1.9 | 4.7 | 99.9 |
| HCl | − | 1440 | <1.5 | <1.9 | <1.5 | |

[a] A = AIBN; B = benzoyl peroxide; Q = benzoquinone. [b] Modifiers A, B, and Q added 2–3 mol % based on chlorine. [c] All values are the average of at least two separate determinations. [d] A referee has pointed out that the change in 3/2 with the extent of chlorination is further evidence for formation of 3 and 4 from 2 (vide supra).

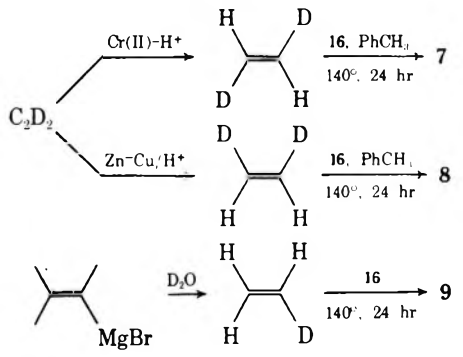
Table II
Effect of Added Modifiers on the Bromination of 1 at 35 ± 2°

| Modifier added[a,b] | Light (±) | Time, hr | % 5[d] | Material balance of 1[d] |
|---|---|---|---|---|
| $N_2$ | + | 1 | 10.4 | 98.0 |
| $N_2$ | −[c] | 22 | 2.8 | 93.4 |
| $O_2$ | + | 1 | 82.7 | 96.0 |
| $O_2$ | −[c] | 22 | 1.6 | 95.4 |
| $N_2$ | + | 3 | 94.5 | 98.0 |
| A | + | 1 | 15.3 | 99.8 |
| B | + | 1 | 92.8 | 97.5 |
| Q | + | 1 | 5.2 | 100.4 |

[a] A = AIBN, B = benzoyl peroxide, Q = benzoquinone. [b] Modifiers A, B, and Q used at 2–3 mol % of bromine. [c] Reaction at 45°. [d] All values are the average of two separate determinations.

reospecific addition was observed for isomerizable olefins if 0.5–1.0 equiv of toluene was added to the reaction.[37] Reaction with ethylene gave 1 in 86% yield.

The appropriately deuterated ethylenes were prepared by previously described procedures[38] (see Experimental Section). The ir spectra of all acetylenes and ethylenes were in excellent agreement with those reported.[39,40] Pyrolysis of 16 in the presence of excess deuterated ethylene, and where necessary toluene, gave 7–9 in good yields. Although the reaction mixtures were frequently dark colored and contained some polymeric material, the only volatile products (GLC) were chloroform, 7–9, and, if added, toluene. Purification was accomplished by distillation and preparative GLC, yielding 7–9 as clear, colorless liquids, with GLC behavior identical with that of 1. The overall synthetic route is summarized below.




Stereospecificity of the carbene addition was assumed from previous work,[36,37] and qualitative confirmation achieved spectroscopically. Spectroscopic differences between 7 and 8 are more apparent in the Raman than in the infrared. The Raman spectrum of 7 exhibits a medium-intensity band at 835 $cm^{-1}$, a peak present, but extremely weak, in the spectrum of 8. Similarly 8 has a medium-intensity band at 865 $cm^{-1}$, present, but extremely weak, in the spectrum of 7. The relative peak intensities indicate ca. 5% stereoisomeric impurity in each case.[41]

Distinction between erythro tetrahalopropanes 10–11 and threo isomers 12–13 obtained on halogenation of 7 or 8 should be provided by their $^1H$ NMR coupling constants.[42] The $^1H$ NMR of 2 has been reported[29b] as an AA'BB' spin system with $J_{AB}$ = 10.9 and $J_{AB}$ = 4.8 Hz. Deuterium substitution for $H_{A'}$ and $H_{B'}$ should reduce the spectra of 10–13 to AB spin systems with similar couplings. The erythro isomers 10–11 would be expected to exhibit the larger coupling.

Chlorination of 7 and 8 was carried out in carbon tetrachloride similar to chlorination of 1 (see Experimental Section). The 1,1,1,3-tetrachloropropane-2,3-$d_2$ obtained from chlorination of 7 gave the 60-MHz $^1H$ NMR spectrum shown in Figure 1a. The AB pattern is clearly evident, $J_{AB} \simeq 11$ Hz, and clearly is predominantly the erythro isomer, 10. Similarly chlorination of 8 gave threo isomer 12, $J_{AB} \simeq 5$ Hz. The $^1H$ NMR of 12 (Figure 1b) collapses to two broad multiplets as a result of the smaller coupling. Also isolated from both 7 and 8 was 1,1,1,3,3-pentachloropropane (17), presumed to be a mixture of 2,3-$d_2$ and 2-$d_1$. Chlorination of 9 gave 14 and pentachloropropane 18. The $^1H$ NMR of 14 indicated no appreciable isotope effect introduced by the single CHD functionality.

$CCl_3CHDCHCl_2$ (D) — 17

$CCl_3CH_2CHCl_2$ (HD) (D) — 18

Bromination of 7–9 was carried out exactly as described for 1. Both products 11, 13, and 15 as well as unreacted 7–9 were collected by preparative GLC. A Raman spectrum of recovered 8 gave no evidence of any isomerization. The $^1H$ NMR spectra of the 1,3-dibromo-1,1-dichloropropane-2,3-$d_2$ products from 7 and 8 were strikingly similar to those of 10 and 12, clearly indicating predominant inversion of configuration by the bromine atom.

Vicinal and geminal hydrogen–deuterium coupling in the 60-MHz $^1H$ NMR spectra made accurate determination of $J_{AB}$ impossible, and more importantly eliminated any quantitative estimation of the amount of stereoisomeric impurity (e.g., a retention pathway). Spectral clarification of 10–13 was achieved using a 250-MHz spectrometer and deuterium decoupling. The decoupling frequency was chosen to optimize both the A and B portions simultaneously. The decoupled spectra of both 10 and 12 are shown in Fig-

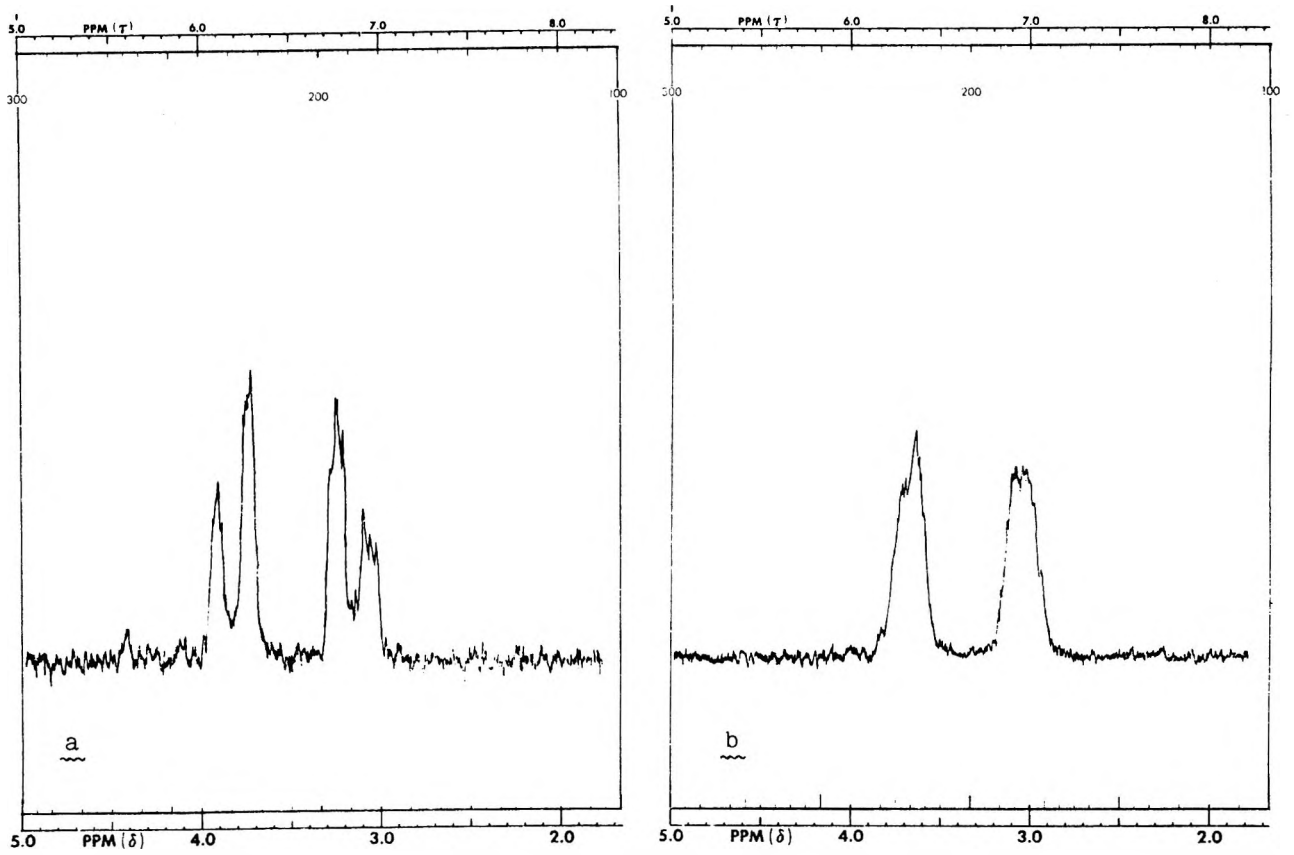



**Figure 1.** 60-MHz $^1$H NMR spectra of (a) *erythro*-1,1,1,3-tetrachloropropane-2,3-$d_2$ (**10**); (b) *threo*-1,1,1,3-tetrachloropropane-2,3-$d_2$ (**12**).

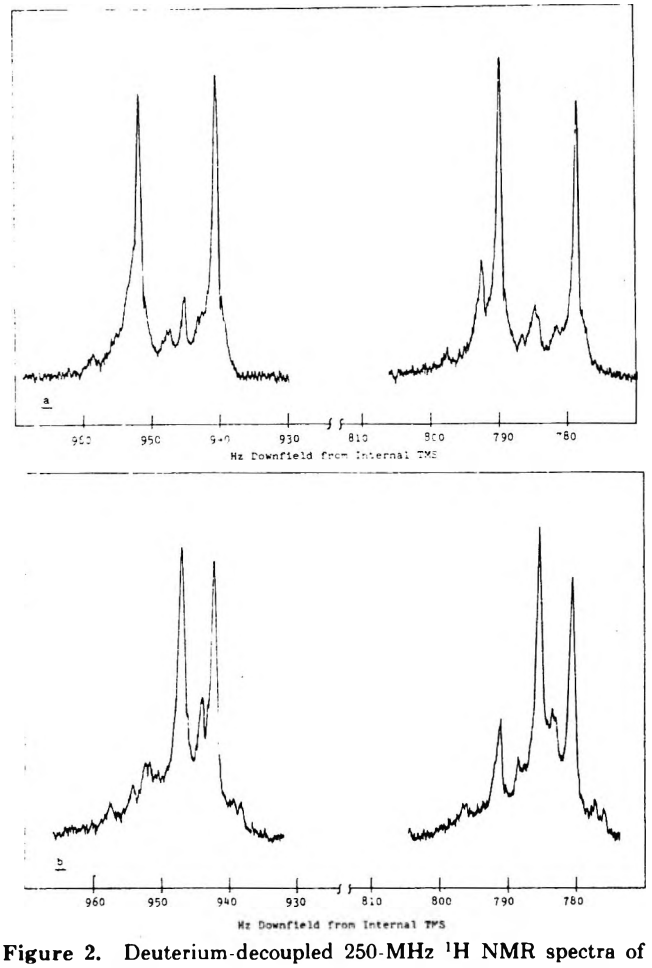
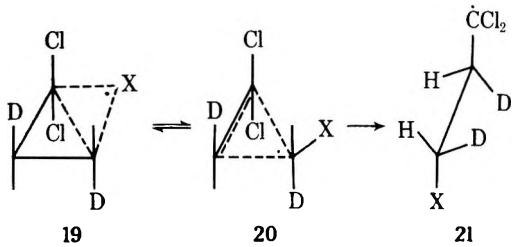



**Figure 2.** Deuterium-decoupled 250-MHz $^1$H NMR spectra of (a) **10** and (b) **12**.

ure 2; isomer assignments, coupling constants (measured directly from the spectra), decoupling frequencies, and peak positions from internal $Me_4Si$ are summarized in Table III.

The decoupled spectra of **10–13** are sufficiently distinct to observe traces of stereoisomeric impurity as well as monodeuterated **14** or **15**. Planimetry integration of each spectrum allowed calculation of the stereoisomeric ratios: **10/12**, and **12/10** for chlorination of **7–8** and **11/13** and **13/11** for bromination. These ratios were all found to be 0.96 ± 0.04, while the amount of **14** and **15** was 9.5 ± 2.0% in all cases. The observation of identical stereoisomeric ratios, within experimental error, for two radicals of considerably different energies, as well as the Raman evidence that **7** and **8** were not stereoisomerically pure, suggests that product stereoisomeric impurities arise by stereospecific reactions of **7** and **8** and not via a retention pathway.

Observation of essentially complete inversion by both chlorine and bromine atoms eliminates mechanisms resulting in retention of configuration. Thus formation of an edge-attached or corner-attached species, **19** and **20**, as intermediates or transition states does not occur to a detectable extent. Both would be expected to lead to ring-opened



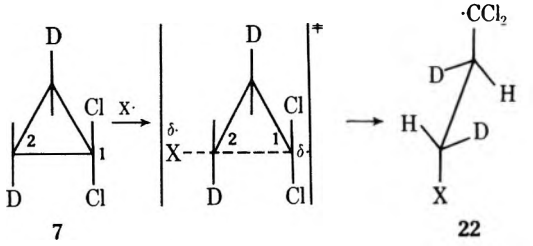

radical **21** resulting in retention of configuration, contrary to our experimental results.

Table III
$^1$H NMR Data (250 MHz) and Product Assignments for Chlorination and Bromination of 7–9

| Reactant | Halogen | Product | $J_{AB}$, Hz | $^2$H decoupling frequency, Hz | Peak positions, Hz from internal $Me_4Si$ | |
|---|---|---|---|---|---|---|
| 7 | $Cl_2$ | 10 | 11.2 | 38, 376, 652 | 940.5, 951.8 | 778.5, 789.7 |
| 8 | $Cl_2$ | 12 | 4.7 | 38, 376, 650 | 942.2, 946.9 | 780.5, 785.3 |
| 9 | $Cl_2$ | 14 | | 38, 376, 650 | 938.6, 944.5 | 776.5, 783.9 |
| | | | | | 946.7, 952.4 | 791.7 |
| | | | | | 954.5 | |
| 7 | $Br_2$ | 11 | 12.0 | 38, 376, 651 | 904.6, 892.6 | 820.4, 808.4 |
| 8 | $Br_2$ | 13 | 4.6 | 38, 376, 650 | 901.3, 896.8 | 818.2, 813.6 |
| 9 | $Br_2$ | 15 | | 38, 376, 651 | 907.6, 905.7 | 806.7, 814.7 |
| | | | | | 904.4, 899.9 | 822.5 |
| | | | | | 896.7, 891.1 | |

Nonclassical radicals **19** and **20** would not be expected to lead to significantly increased radical stability.[43] Furthermore, neither leads to any significant release of ring strain, the obvious driving force of the reaction. Additionally **20** could suffer attack by halogen at $C_3$ resulting in formation of some 1,2,2,3-tetrahalopropane, none of which was detected in any experiment.

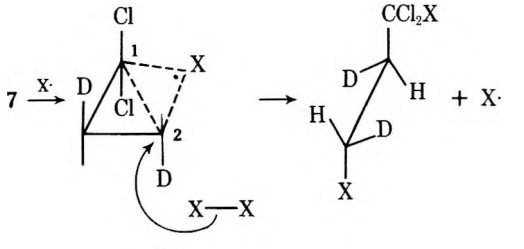
Inversion could occur via two pathways. The most likely in our opinion would be a one-step displacement process, proceeding via a transition state geometrically similar to that of an SN2 displacement. Attack of X· occurs at a minor lobe of the $C_1$–$C_2$ hybrid orbital, with concomitant cleavage of the $C_1$–$C_2$ bond. This would lead directly to ring-opened radical **22**, provides direct relief of ring strain,




7 22

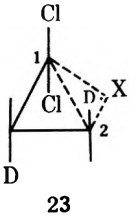
would not be expected to yield any 1,2,2,3-tetrahalopropane, and most importantly predicts the observed stereochemistry. Attack of halogen on **22** would be expected to occur nonstereospecifically.

A second mechanism also leading to inversion involves initial formation of edge-attached **19** which is then inverted at $C_2$ by halogen.




19

This latter mechanism appears unlikely, particularly based on the questionable existence of **19** (vide supra). If initial formation of **19** does occur, it would most likely exist as unsymmetrical **23**;[44] unpaired electron density in both




23

**19** and **23** should be greatest at $C_1$. Reaction with halogen should be favored there, and lead to retention.

Nonetheless, attack by symmetrical reagents, chlorine and bromine, fails to distinguish between the partial or exclusive operation of either mechanism. A distinction could be effected, however, by reaction of **1** and, by analogy, **7–8**, with a generalized unsymmetrical addend AB. If B· serves as the chain carrier, then reaction of **1** by an SN2-like path (a) would give **24**, while a mechanism involving **19** or **23** (b) would yield **25**.

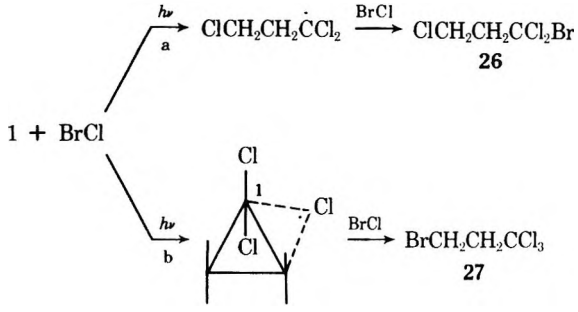
$ACl_2CH_2CH_2B$ **24** $BCl_2CH_2CH_2A$ **25**

Reactions of **1** with bromotrichloromethane (A = Br, B = $CCl_3$) or trichloromethanesulfonyl chloride (A = Cl, B = $CCl_3$) under a variety of conditions (see Experimental Section) were unsuccessful. Formation of hexachloroethane in each case implied formation of the trichloromethyl radical, but no ring opening appears to occur.[45]

The use of bromine chloride to effect difficult brominations is well known,[33,46] and the mechanism is established to be initial hydrogen abstraction by chlorine atoms, followed by reaction of the generated radical with BrCl.

$$RH + Cl\cdot \xrightarrow{-HCl} R\cdot \xrightarrow{BrCl} RBr + Cl\cdot$$

The analogous reaction of **1** should yield 1-bromo-1,1,3-trichloropropane (**26**) via path a, or 3-bromo-1,1,1-trichloropropane (**27**) via path b.




Photolysis of a solution of **1**, bromine, and chlorine in mole ratios of 23.5:1:3 leads to a rapid reaction and formation of at least ten products (Experimental Section). The tetrahalopropanes isolated from the reaction were found to be **2**, **5**, and *only* **26**. An excess of chlorine served to divert bromine to BrCl, eliminating the possibility of bromine bridging (**19** or **23**, X = Br). Evidence supporting this conclusion is that **5**, while formed, possibly from **23**, more likely from **6b**, is formed as <1% of the total product peak areas in the GLC. There was no evidence by GLC for the presence of any **27** and 1% should have been detectable. We conclude, therefore, that attack of chlorine and bromine

atoms on 1 and 7–9 occurs with complete inversion of configuration, and that the mechanism of inversion does not involve a bridged radical species to any detectable degree. Our results appear to be in close agreement with those of Maynes and Applequist.[26]

## Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are corrected. Boiling points are uncorrected. Infrared spectra were recorded on a Beckman IR-20 spectrophotometer using 10% (v/v) solutions in carbon tetrachloride and carbon disulfide. Peak positions were calibrated with the 1601.8-$cm^{-1}$ band of polystyrene. Vapor phase ir spectra were obtained with a standard 10-cm cell with sodium chloride windows. Laser Raman spectra were recorded using neat samples, on a Cary Model 81 spectrophotometer using a Spectra Physics Model $Ar^+$ laser at 4880 Å.

Proton magnetic resonance ($^1H$ NMR) spectra were recorded on a Varian A-60 using 10% (v/v) solutions in carbon tetrachloride. Chemical shifts are reported in parts per million ($\delta$) from internal tetramethylsilane. Spectra at 250 MHz and deuterium decoupling experiments were performed at the NMR Biomedical Facility, Carnegie Mellon University Pittsburgh, Pa.

Analytical and preparative GLC were performed using a Varian Aerograph A-90-P3 chromatograph. Columns all prepared on 60/80 mesh Chromosorb P as support were: A, 6 ft × 0.25 in. 20% SE-30; B, 12 ft × 0.25 in. 20% SE-30; C, 15 ft × 0.25 in. 10% Ucon 50-lb 550X; and D, 5 ft × 0.25 in. stainless steel, 20% SE-30.

Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Elbach, West Germany.

Antimony trifluoride (Alpha), methyltrichlorosilane (Dow Corning), and cyclopropane (National Cylinder Gas) were all used as received.

Carbon tetrachloride, THF, and bis(2-ethoxyethyl) ether (DEC) were distilled from and stored over calcium hydride. Commercial 1,1,1,3-tetrachloropropane (**2**) (Peninsular Chemresearch) and 1,1,1,3,3-pentachloropropane (**3**) (K and K Laboratories) were purified by preparative GLC using column B at 165 and 180°, respectively. Benzoyl peroxide[47a] and AIBN[47b] were purified by several recrystallizations.

1,1-Dichlorocyclopropane (**1**) was prepared by vapor phase chlorination of cyclopropane following the procedure described by Stevens.[16c] Purification by distillation and then preparative GLC on column A at 88° gave pure **1** with physical[16b,c] and spectral[48] properties identical with those reported.

Acetylene-$d_2$ and (*E*)- and (*Z*)-ethylene-$d_2$ were prepared following the general procedure described by Nicholas and Carroll.[38] The only modification: in the case of (*Z*)-ethylene-$d_2$, the partially reduced mixture was shaken for an additional 24 hr to effect complete reduction, not isolated and treated with fresh catalyst as described.[38] Any traces of unreduced acetylene-$d_2$ did not interfere in subsequent reactions. Ethylene-$d_1$ was prepared by addition of deuterium oxide to freshly prepared vinylmagnesium bromide.[49] Trichloromethyltrichlorosilane,[50] prepared by photochlorination of methyltrichlorosilane, was purified by short-path distillation.

Trichloromethyltrifluorosilane (**16**) was prepared by a modification of the procedure described by Meuller, Reichel, and Dathe.[51–53] Trichloromethyltrichlorosilane (0.25 mol) in xylene (50 ml) was added at −20° to an equimolar suspension of antimony trifluoride in xylene (50 ml) under a dry nitrogen atmosphere over a 2-hr period. After stirring at −20° for an additional 1 hr, a stream of dry nitrogen was used to sweep **16** into two dry ice–2-propanol traps as the mixture warmed over 2 hr to 25°. After 2 hr at 25° the mixture was warmed to 50° and maintained at 50° for 2 hr. The contents of both traps were combined and distilled through an 8-in. vacuum-jacketed Vigreux column into a dry ice cooled receiver, giving **16** in 75% yield, bp 44–45° (lit.[36,51] 43.5–45°). Purified **16** was stored in a tightly stoppered flask at −78° and was stable for at least 1 month. The liquid reacts vigorously with moist air and should be handled with considerable care.

**Synthesis of Deuterated 1,1-Dichlorocyclopropanes 7–9.** Reaction of deuterated ethylenes with **16** was carried out in a 3-l. flask, the top of which was sealed and two high-vacuum stopcocks fused into the neck. The ethylenes were dried by passage through a calcium sulfate drying tower and introduced into the reaction flask by vacuum transfer. Then 5.5–6.0 g (27–29 mmol) of **16** and toluene (1.0–1.2 g, 11–13 mmol), where necessary, were introduced by chilled syringe. The ratio of ethylene:**16** is thus ca. 4.8:1 assuming ideality. The stopcocks were securely fastened and the flask heated at 140° for 22–24 hr, removed, and cooled to −20°. The liquid that condensed was drawn off and the flask washed with two 15-ml portions of DEC.

In the case of (*E*)- and (*Z*)-ethylene-$d_2$, the above procedure was repeated and the initially collected liquid and DEC washings were combined with those of the first run. Both the washings and crude liquid were then separately distilled, and material boiling to 100° collected. Isolation of **7** and **8** was then accomplished by preparative GLC of each distillate using column C at 110°. With ethylene-$d_1$ only the DEC washings were distilled, the distillate and initially isolated liquid then subjected to preparative GLC as described above to give **9**.

From two runs with (*E*)-ethylene-$d_2$ using a total of 58 mmol of **16** and 26 mmol of toluene was obtained after preparative GLC 2.44 g (21.6 mmol, 37%) of **7**: bp 75–76°; $d^{25}{}_4$ 1.235; $n^{25}D$ 1.4362; ir 1280, 1208, 1082, 970, 950, 920, 818, 700, 682, and 490 $cm^{-1}$; Raman 3060, 3020, 2285, 1208, 927, 872, 834, 490, and 272 $cm^{-1}$; $^1H$ NMR $\delta$ 1.43 ppm (s).

Similarly from (*Z*)-ethylene-$d_2$, 57 mmol of **16**, and 27 mmol of toluene was obtained 2.33 g (20.6 mmol, 36%) of **8**: bp 75–76°; $d^{25}{}_4$ 1.231; $n^{25}D$ 1.4358; ir 1288, 1210, 1122, 1090, 1072, 960, 950, 920, 815, 708, 682, and 492 $cm^{-1}$; Raman 3060, 3020, 2285, 865, 492, and 272 $cm^{-1}$; $^1H$ NMR $\delta$ 1.45 ppm (s).

Reaction of ethylene-$d_1$ and **16** (30 mmol) gave 1.4 g (13 mmol, 41%) of **9**: bp 75–76°; $d^{25}{}_4$ 1.241; $n^{25}D$ 1.4382; ir 1432, 1320, 1220, 1120, 1090, 1052, 960, 952, 820, 705, 656, and 490 $cm^{-1}$; Raman 3062, 3020, 2285, 1222, 872, 496, and 272 $cm^{-1}$; $^1H$ NMR $\delta$ 1.44 (s).

**Chlorination of 1.** A solution of **1** (11.0 mmol) in carbon tetrachloride (1.5 ml) was added to 1.0 ml of chlorine-saturated carbon tetrachloride, 1.72 mmol of chlorine.[54] The solution was placed in a small ampoule, sealed, cooled to 0–5°, and irradiated with a 150-W GE "reflector spot" incandescent lamp placed 6 in. from the sample until colorless (10–35 min). Analysis of the reaction mixture by GLC using column A at 150° or B at 170° indicated four components in addition to unreacted **1**. In order of increasing retention time these were shown to be a minor product, 2–3% of total product peak area, believed to be 1,1,2-trichlorocyclopropane, **2**, **3**, and **4**. Yields of **2** and **3** varied from run to run, ranging between 32–36% **2** and 41–45% **3**. Preparative GLC using column A at 150° gave pure **2** (18%), **3** (20%), and **4** (ca. 3%), identified by their physical[28] and spectral[29] properties and comparison to authentic samples.

**Chlorination of 7–9.** Owing to more limited quantities of **7–9**, the following general procedure was employed. The dichlorocyclopropane (0.4 ml, 4.4 mmol) in 0.6 ml of carbon tetrachloride was treated with 0.6 ml of chlorine–carbon tetrachloride and chlorinated as described for **1**. The reaction mixture was transferred to a small flask, carbon tetrachloride and unreacted **7–9** were carefully distilled off, and the mixture was then rechlorinated with 0.45 ml of chlorine solution. Redistilling, chlorinating a third time with 0.30 ml of chlorine solution (total chlorine 2.3 mmol), and redistilling left a high-boiling residue that was separated by preparative GLC on column A at 150°. Only 1,1,1,3-tetrachloropropanes **10**, **12**, and **14** and 1,1,1,3,3-pentachloropropanes **17** and **18** were collected.

Reaction of **7** as described yielded after preparative GLC 0.36 mmol (16%) of *erythro*-1,1,1,3-tetrachloropropane-2,3-$d_2$ (**10**): ir 1288, 1260, 1211, 1123, 1078, 1040, 950, 888, 800, 728, and 700 $cm^{-1}$; Raman 2960, 2225, 388, 242, and 227 $cm^{-1}$; $^1H$ NMR $\delta$ 2.98–3.32 (m, $CCl_3$–CHD) and 3.62–3.98 ppm (m, CHDCl). See Figure 1a.

Also isolated was 0.46 mmol (38%) of 1,1,1,3,3-pentachloropropane **17**, its $^1H$ NMR indicating it to be a mixture of 2,3-$d_2$ and 2-$d_1$ isomers: ir 1257, 1211, 1108, 1027, 947, 930, 911, 899, 828, 790, 699, 654, and 562 $cm^{-1}$; Raman 2970, 2240, 705, 564, 388, 318, 277, 208, and 190 $cm^{-1}$; $^1H$ NMR $\delta$ 3.50–3.65 (m, $CCl_3CH$–) and 5.82–6.00 ppm (m, $CHCl_2$).

Chlorination of **8** was repeated a fourth time with 0.30 ml of chlorine solution (vide supra) to yield after preparative GLC 0.51 mmol (17%) of *threo*-1,1,1,3-tetrachloropropane-2,3-$d_2$ (**12**): ir 1315, 1285, 1092, 1012, 992, 940, 885, 800, 712, and 522 $cm^{-1}$; Raman 2995, 2960, 712, 558, 462, 388, 350, 242, and 224 $cm^{-1}$; $^1H$ NMR $\delta$ 2.88–3.23 (m, $CCl_3CHD$) and 3.53–3.88 ppm (m, CHDCl), see Figure 1b.

In addition 0.53 mmol (35%) of **17** was also isolated, and was identical in ir, Raman, and $^1H$ NMR with that obtained from **7**.

Chlorination of **9** as described for **7** gave after preparative GLC 0.30 mmol (13%) of 1,1,1,3-tetrachloropropane-2- and -3-$d_1$ (**14**): ir 1455, 1435, 1312, 1292, 1263, 1215, 1081, 1050, 1031, 1015, 945, 900, 830, 800, 741, 712, 680, 660, 570, and 540 $cm^{-1}$; Raman 2980, 2945, 2225, 716, 572, 560, 390, 250, and 228 $cm^{-1}$; $^1H$ NMR $\delta$ 3.00–3.30 (m, $CCl_3CHD$) and 3.67–4.00 ppm (m, CHDCl).

In addition 0.45 mmol (36%) of 1,1,1,3,3-pentachloropropane **18** was isolated, presumed to be a mixture of *2*- and *3*-$d_1$ and $d_0$: ir 1418, 1218, 1090, 1022, 978, 935, 917, 900, 830, 792, 710, 660, and 565 $cm^{-1}$; Raman 2950, 2245, 830, 722, 708, 580, 566, 381, 318, 278, 208, and 190 $cm^{-1}$; $^1H$ NMR $\delta$ 3.47–3.40 (m, $CCl_3CH$) and 5.85–6.05 ppm (m, $CHCl_2$).

In all cases, the GLC behavior of 1,1,1,3-tetrachloropropanes **10, 12,** and **14** and 1,1,1,3,3-pentachloropropanes **17** and **18** was identical with that of their undeuterated analogues **2** and **3** on all columns tested.

**Bromination of 1.** When a solution of bromine (0.64 mmol) in **1** (6.0 mmol) was irradiated at 35°, the color faded within 1–2 hr. Analysis of the reaction mixture by GLC, column D, 170° (copper columns caused extensive decomposition) indicated three minor products totaling ca. 5% of total product peak areas and a major product shown to be **5**. Two of the minor components are likely due to thermal decomposition of **5** as purified samples of **6** also show two minor peaks and **5** on reinjection. Yields of **5** (GLC) were shown (Table II) to be as high as 94%. Preparative GLC of the reaction mixture gave **5** in 65% isolated yield, as a clear, colorless liquid with an odor similar to that of **2**: $n^{25}D$ 1.5422 (lit.[55] $n^{20}D$ 1.5450); ir 1217, 1153, 800, 785, 679, and 647 $cm^{-1}$; Raman 2985, 2940, 650, 579, 369, 339, 290, 228, and 169 $cm^{-1}$; $^1H$ NMR $\delta$ 3.00–3.33 (m, $CCl_2BrCH_2$) and 3.40–3.73 (m, $CH_2Br$).

Anal. Calcd for $C_3H_4Br_2Cl_2$: C, 13.29; H, 1.49; Br 59.03; Cl, 26.19. Found: C, 13.25; H, 1.39; Br, 58.97; Cl, 26.19.

Bromination of **7–9** was accomplished similarly using 5.5 mmol of cyclopropane and 0.58 mmol of bromine. Both unreacted **7–9** and products **11, 13,** and **15** were isolated by preparative GLC on column D at 170°.

Thus **7** gave 0.39 mmol (67%) of *erythro*-1,3-dibromo-1,1-dichloropropane-*2,3*-$d_2$ (**11**) after preparative GLC: ir 1283, 1180, 1028, 945, 850, 781, 742, 712, 690, and 630 $cm^{-1}$; Raman 632, 364, 338, 289, 275, 225, and 169 $cm^{-1}$; $^1H$ NMR $\delta$ 2.97–3.35 (m, $CCl_2BrCHD$) and 3.40–3.73 ppm (m, CHDBr).

Bromination of **8** followed by preparative GLC yielded 0.32 mol (55%) of *threo*-1,3-dibromo-1,1-dichloropropane-*2,3*-$d_2$ (**13**): ir 1200, 1085, 1008, 988, 940, 850, 782, 740, 708, 688, and 631 $cm^{-1}$; Raman 634, 364, 338, 290, 276, 225, and 168 $cm^{-}$; $^1H$ NMR $\delta$ 3.07–3.38 (m, $CCl_2BrCHD$) and 3.40–3.68 ppm (m, CHDBr).

Finally, bromination of **9** gave 0.35 mmol (59%) of **15** as a mixture of *2*- and *3*-$d_1$, isomers: ir 1284, 1230, 1180, 1072, 1005, 937, 863, 805, 785, 740, 725, 710, and 632 $cm^{-1}$; Raman 2985, 632, 368, 339, 292, 228, and 169 $cm^{-1}$; $^1H$ NMR $\delta$ 3.00–3.38 (m, $CCl_2BrCHD$) and 3.41–3.70 ppm (m, CHBr).

**Reaction of 1 with Bromine–Chlorine Mixtures.** Photolysis of **1** (5.5 mmol) in a solution of bromine (0.23 mmol) in 0.40 ml of chlorine-saturated carbon tetrachloride (0.70 mmol of $Cl_2$) at 20° resulted in a complete loss of color within 20 min. Analysis of the reaction mixture by GLC on column D at 145° indicated at least ten components. In order of increasing retention time they were two trace products not identified but likely 1,1,2-trichloro- and 1,1-dichloro-2-bromocyclopropane; **2**, 1-bromo-1,1,3-trichloropropane (**26**), **3, 4, 5,** and three higher boiling components. Identification of **2–5** was initially confirmed by coinjection with authentic samples. After unreacted **1** and carbon tetrachloride were carefully distilled off, preparative GLC allowed spectroscopic (ir) verification. The three highest boiling components were not specifically identified but the ir and $^1H$ NMR of two of them strongly indicated that they were 1,1,1,3,3-pentahalopropanes. The other had ir very similar to that of **4** and is likely a 1,1,1,2,3-pentahalopropane.

The identity of **26,** isolated in ca. 20% yield, is based upon its ir, Raman, and $^1H$ NMR spectra and elemental analysis: $n^{20}D$ 1.5147; ir 1446, 1425, 1240, 1254, 1173, 1070, 1025, 970, 822, 795, 720, 703, 560, and 530 $cm^{-1}$; Raman 2979, 2943, 1434, 1068, 1025, 825, 799, 721, 677, 534, 376, 345, 303, 289, 232, and 211 $cm^{-1}$; $^1H$ NMR $\delta$ 2.92–3.27 (m, $CCl_2BrCH_2$) and 3.61–3.80 ppm (m, $CH_2Cl$). The refractive index of **27** is reported[56] to be $n^{20}D$ 1.5127.

Anal. Calcd for $C_3H_4BrCl_3$: C, 15.90, H, 1.76; Br, 35.30; Cl, 47.02. Found: C, 15.88; H, 1.67; Br, 35.16; Cl, 46.80.

**Attempted Reactions of 1 with Trichloromethyl Radicals. A. Bromotrichloromethane.** Heating a solution of **1** (5.5 mmol) and bromotrichloromethane (42 mmol) with 50 mg of benzoyl peroxide at 105° for either 2 or 8 hr yielded no products. Only starting materials and a trace of bromobenzene were observed (GLC, $^1H$ NMR).

In a second experiment, four solutions of **1** and bromotrichloromethane were prepared providing mole ratios of **1**:bromotrichloromethane of 1:1, 1:1, 1:2, and 1:0.5. Benzoyl peroxide (50 mg) was added to the latter three solutions and all were irradiated at 95° for 22 hr, cooled, and analyzed by GLC, column D at 145°. The only observable products in samples with added peroxide were bromobenzene and hexachloroethane and in one case (1:2) a trace of **5**.[45] The sample without peroxide gave an extremely weak peak with retention time identical with that of **5**.[45]

**B. Trichloromethanesulfonyl Chloride.** A solution of **1** (6.6 mmol) and trichloromethanesulfonyl chloride (5.6 mmol) and 50 mg of benzoyl peroxide were heated at reflux for 8 hr. Analysis by GLC, column D, 145°, indicated only starting materials, chlorobenzene, and hexachloroethane. Extending the reaction time to 16 hr gave identical results.

**Chlorination and Bromination of 1 in Presence of Added Modifiers.** A solution of **1** (11.0 mmol) in carbon tetrachloride (1.5 ml) was added to a small flask and deoxygenated with nitrogen, bubbled into the solution via a small capillary. Then, in a darkened room, 1.0 ml of chlorine-saturated carbon tetrachloride (1.72 mmol) was added. Aliquots of 0.70 ml were then added to each of five nitrogen-flushed ampules. Three of the ampules contained preweighed quantities, 2–3 mol % based on chlorine, of benzoyl peroxide, AIBN, and benzoquinone. The other two ampules contained no additional modifiers. All the ampules were sealed and those with modifiers and one without were irradiated at 0–5° for 5 min. The remaining ampule was wrapped in aluminum foil and stored in the dark at 5° for 24 hr.

The effect of oxygen was ascertained by saturating the solution of **1** with oxygen prior to addition of chlorine. The ampule and one treated with nitrogen were then irradiated for 10 min, at which time the nitrogen-treated sample was colorless.

**Product Analysis.** Samples were analyzed for **2** and **3** by analytical GLC using column B at 170°. Millimoles of product formed in each sample was determined by comparison of peak areas (planimetry integration) with standard solutions of **2** and **3**. Control experiments established that peak area was linear with respect to concentration and injection size within 1.5%. The minimum extent of reaction was determined by diluting the standards until a 40-$\mu$l injection gave a small but repeatable peak at recorder attenuation 2. A yield of **2** of 1.5%, based on chlorine, could have been detected and 1.9% of **3**.

When the irradiation of a series of samples was completed, they were stored at 3° in a darkened room prior to analysis. Standard solutions were injected, then each ampule was opened in a darkened room and the contents washed into a 1.0-ml volumetric flask and diluted to the mark with carbon tetrachloride. The solution was mixed thoroughly and a 25-$\mu$l injection made. In cases of severe inhibition a 40-$\mu$l injection was also made. Millimoles of **2** and **3** in each sample were calculated from the relative peak areas and standard solution concentrations.

Unreacted **1** in each sample was determined by $^1H$ NMR using *p*-xylene as an internal standard. A carefully weighed amount of *p*-xylene (ca. 0.10 g) and 0.50 ml of the sample solutions prepared for GLC analysis were mixed thoroughly and the singlets of **1** and methyl groups of *p*-xylene were scanned and integrated a minimum of five times, and millimoles of **1** calculated. All of the above operations were conducted in a darkened room and there was no evidence of chlorination of the xylene.

**B. Bromination.** The overall procedure was virtually identical with that described for the chlorination, except that irradiation times were 1 hr at 35 ± 2°. In each run a solution of 2.3 mmol of bromine in 22 mmol of **1** was used.

The amount of **5** in each sample was also determined by analytical GLC using column D at 170°. Peak areas were compared to those of standard solutions of **5** in carbon tetrachloride. Control experiments again verified the linearity, within ±1.0%, of peak areas with sample concentrations and injection size. It was also shown that as little as 0.70% of **5** could have been detected.

Attempts to determine unreacted **1**, however, were complicated by rapid bromination of *p*-xylene by residual bromine, even in a darkened room. The following general procedure was thus employed. At the completion of the GLC analysis the solution was added to 1.0 ml of 1 *M* sodium bisulfite and shaken until colorless. The organic layer was withdrawn and dried over potassium carbonate. Then 0.20-ml aliquots of the above were added to *p*-xylene and the integrals recorded, and the amount of unreacted **1** calculated. This procedure was checked by preparing a solution of **1** and bromine as if no reaction had occurred. Work-up and analysis indicated 98% of **1** present, indicating no loss due to reaction with bisulfite and/or solubility.

For both chlorination and bromination studies, at least two separate and independent studies of added modifiers were made. The averages of these runs are presented in Tables I and II.

**Acknowledgment.** The authors are indebted to Dr. Joseph Dadok of Mellon Institute for help in performing the 250-MHz $^1H$ NMR and deuterium decoupling studies, and to Dr. William Fately and Mr. David Pensenstadler, both formerly of Mellon Institute, and Dr. John Freeman of Monsanto Physical Sciences Center for their help in obtaining the laser Raman spectra.

**Registry No.**—**1**, 2088-35-9; **5**, 53074-35-4; **7**, 57325-47-0; **8**, 35293-28-8; **9**, 57377-84-1; **10**, 57325-48-1; **11**, 57325-49-2; **12**, 57325-50-5; **13**, 57325-51-6; **14** isomer A, 57377-85-2; **14** isomer B, 57377-86-3; **15** isomer A, 57377-87-4; **15** isomer B, 57377-88-5; **16**, 17760-13-3; **17** isomer A, 57325-52-7; **17** isomer B, 57325-53-8; **18** isomer A, 42292-07-9; **18** isomer B, 23153-23-3; **26**, 57325-54-9; (*E*)-ethylene-$d_2$, 1517-53-9; (*Z*)-ethylene-$d_2$, 2813-62-9; ethylene-$d_1$, 2680-00-4; chlorine, 7782-50-5; bromine, 7726-95-6.

## References and Notes

(1) For a preliminary report see J. H. Incremona and C. J. Upton, *J. Am. Chem. Soc.*, **92**, 301 (1972). Abstracted from the Ph.D. thesis of C.J.U., Duquesne University, 1973.
(2) Address correspondence to Detergent and Phosphates Division, Monsanto Co., St. Louis, Mo. 63166.
(3) W. A. Pryor, *Chem. Eng. News*, **49**, 34 (June 7, 1971).
(4) K. U. Ingold and B. P. Roberts, "Free Radical Substitution Reactions", Wiley, New York, N.Y., 1971.
(5) (a) E. Gorin, W. Kauzman, J. Walter, and H. Erying, *J. Chem. Phys.*, **7**, 633 (1939); (b) A. F. Trotman-Dickenson, *Adv. Free-Radical Chem.*, **1**, 1 (1965).
(6) J. A. Berson, *Angew. Chem., Int. Ed. Engl.*, **1**, 779 (1968).
(7) R. A. Ogg and M. Polanyi, *Trans. Faraday Soc.*, **31**, 482 (1935).
(8) (a) R. A. Herrman and R. M. Noyes, *J. Am. Chem. Soc.*, **78**, 5764 (1956); (b) J. E. Bujake, M. W. T. Pratt, and R. M. Noyes, *ibid.*, **83**, 1547 (1961); (c) N. Nakashima and R. M. Noyes, *Int. J. Chem. Kinet.*, **1**, 391 (1969).
(9) (a) For an overall discussion of this reaction see W. A. Pryor, "Free Radicals", McGraw-Hill, New York, N.Y., 1966, pp 190–191. (B) Also M. L. Poutsma in "Free Radicals", J. K. Kochi, Ed., Wiley, New York, N.Y., 1973, pp 142–143.
(10) Other pertinent references concerning atomic reactions of alkyl iodides include (a) J. H. Sullivan, *J. Phys. Chem.*, **65**, 722 (1961); (b) S. W. Benson and H. E. O'Neil, *J. Chem. Phys.*, **34**, 514 (1961); (c) S. W. Benson, *ibid.*, **38**, 1945 (1963).
(11) (a) A. J. Kassman and D. S. Martin Jr., *J. Am. Chem. Soc.*, **91**, 6237 (1969); (b) D. Clark, H. D. Pritchard, and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 2633 (1954).
(12) (a) N. Davidson and J. H. Sullivan, *J. Chem. Phys.*, **17**, 176 (1949); (b) J. H. Sullivan and N. Davidson, *ibid.*, **19**, 143 (1951).
(13) L. S. Slaugh, *J. Am. Chem. Soc.*, **83**, 2734 (1961).
(14) W. S. Trahanovsky and M. P. Doyle, *J. Org. Chem.*, **32**, 146 (1967).
(15) (a) L. S. Kaplan, *J. Am. Chem. Soc.*, **89**, 1753 (1967); (b) L. S. Kaplan and R. Drury, *ibid.*, **95**, 2213 (1973); (c) L. S. Kaplan, *J. Org. Chem.*, **32**, 4059 (1967). For alternative arguments see ref 4 and 9b.
(16) (a) G. Gustavson, *J. Prakt. Chem.*, **42**, 495 (1890); (b) J. D. Roberts and P. G. Dirstine, *J. Am. Chem. Soc.*, **67**, 1281 (1945); (c) P. G. Stevens, *ibid.*, **68**, 620 (1946); (d) C. Walling and P. S. Fredricks, *ibid.*, **84**, 3326 (1962); (e) A. J. Davidson and A. T. Bottini, *J. Org. Chem.*, **34**, 3642 (1969); (f) D. E. Applequist, G. P. Fanta, and B. Hendrickson, *J. Am. Chem. Soc.*, **82**, 2368 (1960).
(17) (a) R. A. Ogg and W. J. Priest, *J. Am. Chem. Soc.*, **60**, 217 (1938); (b) M. S. Kharasch, M. Z. Fineman, and F. R. Mayo, *ibid.*, **61**, 2139 (1939); (c) S. J. Cristol and R. T. LaLonde, *ibid.*, **80**, 4355 (1958); (d) R. T. LaLonde and A. D. Debboli, *J. Org. Chem.*, **37**, 1094 (1972).
(18) (a) R. A. Ogg and W. J. Priest, *J. Chem. Phys.*, **7**, 736 (1939); (b) *J. Am. Chem. Soc.*, **60**, 217 (1938).
(19) J. B. Levy and R. C. Kennedy, *J. Am. Chem. Soc.*, **96**, 4791 (1974).
(20) (a) J. Meinwald and J. K. Crandall, *J. Am. Chem. Soc.*, **88**, 1292 (1966); (b) S. J. Cristol, J. K. Harrington, and M. S. Singer, *ibid.*, **88**, 1529 (1966).
(21) (a) S. J. Cristol, W. Y. Lim, and A. R. Dahl, *J. Am. Chem. Soc.*, **92**, 4013 (1970), and references cited therein. (b) See also C. H. Depuy and R. H. McGirk, *ibid.*, **96**, 1121 (1974); C. H. Depuy, A. H. Andrist, and P. C. Funfschilling, *ibid.*, **96**, 948 (1974).
(22) D. E. Applequist and R. Searle, *J. Am. Chem. Soc.*, **86**, 1389 (1964).
(23) M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 4293 (1965).
(24) B. B. Jarvis, *J. Org. Chem.*, **35**, 924 (1970).
(25) (a) K. J. Shea and P. S. Skell, *J. Am. Chem. Soc.*, **95**, 6728 (1973). (b) See also A. C. Udding, J. Strating, and H. Wynberg, *Tetrahedron Lett.*, 1345 (1968).
(26) G. G. Maynes and D. E. Applequist, *J. Am. Chem. Soc.*, **95**, 856 (1973).
(27) (a) J. Z. Chrzastowski, C. J. Cooksey, M. D. Johnson, B. L. Lockman and P. N. Steggles, *J. Am. Chem. Soc.*, **97**, 932 (1975); (b) J. H. Espenson and T. D. Sellers, *ibid.*, **96**, 94 (1974); (c) J. H. Expenson and J. S. Shveima, *ibid.*, **95**, 4468 (1973).
(28) (a) M. S. Kharasch and E. V. Jensen, *J. Am. Chem. Soc.*, **69**, 1100 (1947); (b) M. Joyce, E. Hanford, and J. Harmon, *ibid.*, **70**, 2529 (1948); (c) H. G. Haring and G. Gerding, *Recl. Trav. Chim. Pays-Bas*, **74**, 841 (1955).
(29) (a) A. B. Dempster, K. Price and N. Sheppard, *Spectrochim. Acta, Part A*, **25**, 1381 (1969); (b) *ibid.*, **27**, 1563 (1971).
(30) Y. I. Rothstein and N. G. Sokolouskaya, *Zh. Org. Khim.*, **7**, 26 (1971); *J. Org. Chem. USSR (Engl. Transl.)*, **7**, 24 (1971).
(31) H. Hart and G. Levitt, *J. Org. Chem.*, **24**, 1261 (1959).
(32) See ref 9a, pp 129–133.
(33) (a)C. Walling, "Free Radicals in Solution", Wiley, New York, N.Y., 1957, pp 356–381; (b) M. S. Kharasch, P. C. White, and F. R. Mayo, *J. Org. Chem.*, **3**, 33 (1938).
(34) (a) W. Von E. Doering and W. A. Henderson, *J. Am. Chem. Soc.*, **80**, 5724 (1958); (b) G. C. Robinson, *Tetrahedron Lett.*, 1749 (1965); (c) W. Kirmse "Carbene Chemistry", Academic Press, New York, N.Y., 1964, pp 145–150.
(35) D. Seyferth, R. Minasz, A. J. H. Treiber, J. M. Burlitch, and S. R. Dowd, *J. Org. Chem.*, **28**, 1163 (1963).
(36) R. Fields, R. N. Haszeldine, and D. Peters, *J. Chem. Soc. C*, 167 (1969).
(37) A recent report indicates that toluene may not be necessary in preventing isomerization: J. M. Birchall, G. N. Gilmore, and R. N. Haszeldine, *J. Chem. Soc., Perkin Trans. 1*, 2530 (1975).
(38) P. P. Nicholas and R. T. Carroll, *J. Org. Chem.*, **33**, 2345 (1968).
(39) (a) G. Herzberg, "Infared and Raman Spectra of Polyatomic Molecules", Van Nostrand, Princeton, N.J., 1945, pp 288–293; (b) R. M. Talley and A. H. Neilson, *J. Chem. Phys.*, **22**, 2030 (1954); (c) H. C. Allen Jr., E. D. Tidwell, and E. K. Plyer, *J. Am. Chem. Soc.*, **78**, 3034 (1956).
(40) (a) W. J. Lehman, *J. Mol. Spectrosc.*, **7**, 1 (1961); (b) R. L. Arnett and B. L. Crawford, *J. Chem. Phys.*, **18**, 118 (1950).
(41) The lack of a significant infared spectral difference between **7–8** is in contrast to the 1,2-dideuterated cyclopropane isomers: E. W. Schlag and B. S. Rabinovitch, *J. Am. Chem. Soc.*, **82**, 5996 (1960).
(42) F. Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, N.Y., 1966, pp 132–141, and references cited therein.
(43) (a) C. Walling in "Molecular Rearrangements", P. DeMayo, Ed., Wiley-Interscience, New York, N.Y. 1963, pp 407–455; (b) J. C. Martin and J. W. Timberlake, *J. Am. Chem. Soc.*, **92**, 978 (1970), and references cited therein.
(44) (a) P. S. Skell and K. J. Shea in "Free Radicals", Vol. II, J. K. Kochi, Ed., Wiley, New York, N.Y., 1973, pp 809–849. (b) See also L. Kaplan, "Bridged Free Radicals", Marcel Dekker, New York, N.Y., 1972.
(45) Similar results have been reported for phenylcyclopropane; see R. T. LaLonde, P. B. Ferrara, and A. D. Debboli, *J. Org. Chem.*, **37**, 1094 (1972).
(46) J. L. Speier, *J. Am. Chem. Soc.*, **73**, 826 (1951).
(47) (a) K. Nozaki and P. D. Bartlett, *J. Am. Chem. Soc.*, **68**, 1686 (1946); (b) G. S. Hammond, L. S. Mahony, and U. S. Nandi, *ibid.*, **85**, 737 (1963).
(48) (a) V. Slabey, *J. Am. Chem. Soc.*, **74**, 4928 (1952); (b) J. M. Freeman and P. J. Robinson, *Can. J. Chem.*, **49**, 2533 (1971).
(49) D. Seyferth, *Org. Synth.* **39**, 10 (1959).
(50) P. A. DiGiorgio, L. H. Sommer, and F. C. Whitmore, *J. Am. Chem. Soc.*, **70**, 3512 (1948).
(51) R. Mueller, S. Reichel, and C. Dathe, *Chem. Ber.*, 1673 (1964).
(52) We experienced no difficulty or inconsistency with this modified procedure. Other workers[37] have reported some difficulty with the published procedure[51] and have devised an alternate synthesis.
(53) This reagent is now commercially available from PCR Inc., Gainesville, Fla.
(54) W. F. Linke, "Solubilities of Inorganic and Metal Organic Compounds", Vol. I., American Chemical Society, Washington, D.C., 1958, p 786.
(55) Y. N. Kost and R. Kh. Freidlina, *Izv. Akad. Nauk SSSR., Otd. Khim. Nauk.*, 1252 (1951); *Chem. Abstr.*, **56**, 1328 *i* (1963).
(56) M. S. Kharasch, O. Reinmuth, and W. H. Urry, *J. Am. Chem. Soc.*, **69**, 1105 (1947).

# Total Synthesis of 11β-Methyl-19-nor Steroids[1]

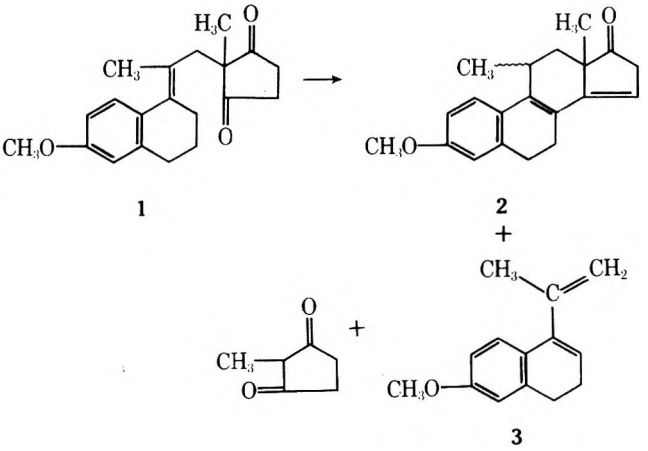
R. B. Garland,* J. R. Palmer, and R. Pappo*

*Department of Chemical Research, Searle Laboratories, A Division of G. D. Searle & Co., P.O. Box 5110, Chicago, Illinois 60680*

*Received September 8, 1975*

A total synthesis scheme for the preparation of 11β-methyl-19-nor steroids was developed. A key step in the synthesis involved the use of an allylic quaternary ammonium salt, **5**, to alkylate 2-methylcyclopentane-1,3-dione to produce the seco steroid, **6a**. Cyclization under mild conditions led to **7a** which after a series of stereospecific reductions produced racemic 11β-methylestradiol-3-methyl ether (**10a**). The method was also applied to the synthesis of previously inaccessible 11β,18-dimethyl-19-nor steroids.

The preparation of 11-methylated steroids from naturally available materials involves the reaction of an organometallic compound with a readily enolizable 11-ketone.[2] Attempts at applying the same series of reactions to the 18-homologues failed.[3] The problems encountered in the introduction of the 11β-methyl group as well as interest in obtaining the 13-ethyl analogues has prompted some efforts toward total synthesis. Because of the efficiency of the Smith-Torgov approach this method was tried but found unsuccessful for the 11-methyl derivatives.[3,4] The tricyclic compound, **1**, could be prepared with difficulty via the isothiouronium salt technique.[3,5] Various attempts at cyclization of **1** produced only traces of **2** (as a mixture of $C_{11}$ isomers) together with 98–100% of cleavage products, **3** and 2-methylcyclopentane-1,3-dione.



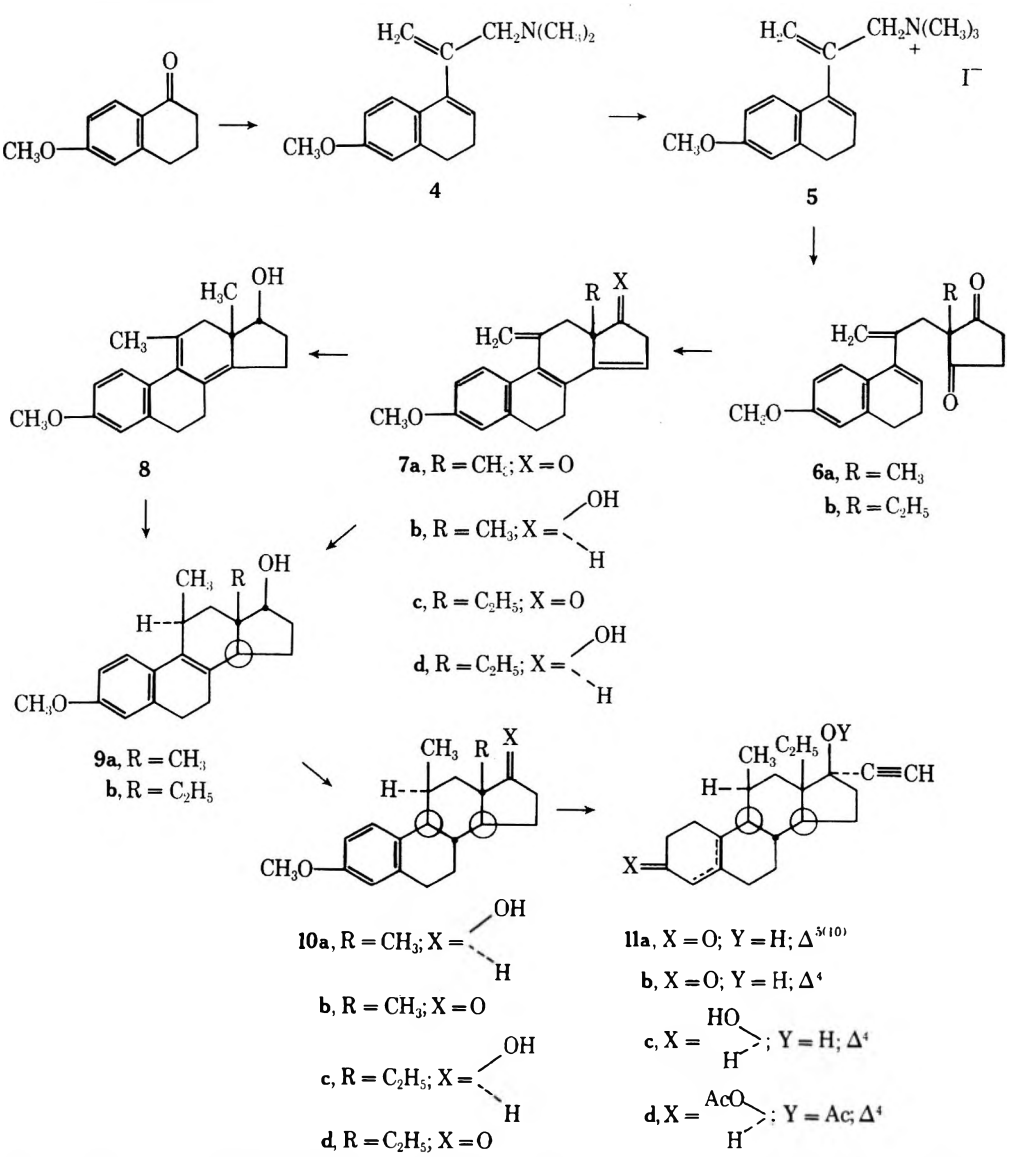
We postulated that if the 9,11 double bond could be forced into the 8,9 position the desired cyclization would become favorable and at the same time the cleavage reaction would become unlikely. Thus, we sought to prepare a diene such as **6a**.

Initially we approached this problem via the reaction of 3-dimethylaminopropen-2-yl magnesium bromide[6] with 6-methoxy-1-tetralone to produce **4** after acidic work-up. Subsequently we found it more convenient to utilize a lithium reagent prepared via halogen–metal interchange between 2-bromo-3-dimethylaminopropene and *n*-butyllithium.[7,8] In the course of our work we found that 2-chloro-3-dimethylaminopropene will also undergo exchange with *n*-butyllithium if the temperature is allowed to rise to 0°. (The bromo compound exchanges rapidly at −40°.) The use of the lithium reagent has the advantages of speed in preparation, easier work-up with a cleaner product, and more easily recovered 6-methoxy-1-tetralone. Owing to enolate formation there is always about 40% of the 6-methoxy-1-tetralone left at the end of the reaction. Presumably the high rate of enolate formation is due to the steric inhibition of the addition reaction. The crude product, **4**, could be quaternized directly with methyl iodide to form **5**.

Since the quaternary salt, **5**, is allylic, it was very likely that anionic attack would result in the displacement of trimethylamine. Most of the reported uses of quaternary ammonium salts for C-alkylation reactions involve quaternary salts of Mannich bases where an elimination–addition reaction mechanism is probable. The use of several benzylic quaternary ammonium salts to C-benzylate malonic ester or acetoacetic ester in up to 80% yield was the example closest to the reaction envisaged.[9,10] We treated the salt, **5**, with the sodium salt of 2-methylcyclopentane-1,3-dione in refluxing xylene with a trace of hexamethylphosphoric triamide (HMPT) and were able to isolate **6a** in 38% yield. The work-up was complicated by the presence of small amounts of complex amine by-products which were not readily removed by acid extraction and which hindered the crystallization of the product. We reasoned that these materials were formed by a dequaternization reaction induced by the iodide ion. This speculation was supported by the discovery of crystals of tetramethylammonium iodide high in the reflux condenser. In order to remove the iodide we converted **5** to a quaternary ammonium hydroxide, added the dione, and heated as before, thereby increasing the yield of **6a** to 55%. The use of more than 2% HMPT resulted in lowered yields as the amount of O-alkylation product and other undetermined by-products increased. The reaction of the amine, **4**, with 2-methylcyclopentane-1,3-dione with or without added base did not produce any of the desired product. In a similar manner 2-ethylcyclopentane-1,3-dione produced **6b**.

The tricyclic compounds, **6**, were indeed readily cyclized below 10° with 1 equiv of anhydrous *p*-toluenesulfonic acid in benzene or toluene. The tetracyclic hexaenes (**7a**, **7c**) were isolated with caution or more conveniently were reduced directly to the more stable hydroxy compounds (**7b**, **7d**). In both of these intermediates the 13-ethyl derivatives required somewhat greater caution in solution (low temperature, $N_2$ atmosphere, and avoidance of base) but all of these materials could be stored for extended periods in the crystalline state in a refrigerator.

Catalytic hydrogenation of **7b** led to **9a** as the major product. If the hydrogenation was stopped after 1 equiv of hydrogen the major product was **8** with the amount of material corresponding to structures **2** estimated at about 10% on the basis of NMR and uv analysis of the crude mixture. We can therefore presume that the hydrogenation proceeds by way of **8** with the entering hydrogen atoms going in by a 1,6 addition, followed by a 1,4 addition with both atoms on the same side of the molecule. In the ethyl series the yield of **9b** was slightly lower. This fact along with the decreased stability of **7c** and **7d** may be due to a slightly greater strain on the triene system caused by the bulkier ethyl group. This added strain could easily explain the decreased stabil-



ity and it might alter the route of hydrogenation leading to additional isomers.

Reduction of **9a** with sodium and aniline in ammonia[11] produced **10a**. The ir, uv, and NMR spectra of this material were identical with those of a sample of 3-methoxy-11$\beta$-methylestra-1,3,5(10)-trien-17$\beta$-ol from natural sources.[2] The 17-ketone, **10b**, was also prepared and again the spectra were identical with those of an authentic sample. The ethyl compounds, **10c** and **10d**, were likewise prepared. The similarity of the NMR bands corresponding to the 11-methyl protons in the methyl and ethyl series is evidence for the same relative stereochemistry.

The 3-methoxy-11$\beta$-methyl-13-ethylgona-1,3,5(10)-trien-17$\beta$-ol (**10c**) was converted by standard reactions to the progestational type compounds **11**.

## Experimental Section

Microanalyses were performed by Mr. Emmanuel Zielinski and associates and spectra were run by Mr. John Damascus and associates of Searle Laboratories. All uv spectra were run in methanol on a Beckman DK-2A spectrophotometer and are reported as wavelength in nanometers ($\epsilon$). Ir spectra were run in $CHCl_3$ on a Beckman IR-12 spectrophotometer and carbonyl region peaks are reported as wavelength in microns. NMR spectra were run in $CDCl_3$ except as noted on a Varian A-60A spectrometer and are reported in parts per million ($\delta$) downfield from $(CH_3)_4Si$ as an internal standard. (Notation: s, d, t, etc. refer to singlet, doublet, triplet, etc., and br refers to a broad peak.) Column chromatography was done by "dry column" technique[12] on Mallinckrodt SilicAR CC-7, 100–200 mesh. Hydrogenations were carried out by Mr. Mike Scaros and associates of Searle Laboratories. Melting points were determined on a Fisher-Johns block and are uncorrected.

**[2-(3,4-Dihydro-6-methoxy-1-naphthyl)-2-propenyl]trimethylammonium Iodide (5).** To a solution of 326 g (2 mol) of 2-bromo-3-dimethylaminopropene[6] in 1200 ml of *n*-hexane at −40° was added 2.0 mol of *n*-butyllithium in hexane over a 45-min period. After 30 min of additional stirring a solution of 300 g (1.7 mol) of 6-methoxy-1-tetralone in 1500 ml of benzene was added at a rate to keep the temperature at −40 to −30°. After 1 hr the temperature was allowed to rise to 0° and ice water was added. The organic layer was separated and washed again with ice water, then extracted with a total of 1200 ml of 10% HCl. Normal work-up of the residual organic layer returned 107 g of 6-methoxy-1-tetralone, mp 78–79° from cyclohexane. The acid solution was cooled to 0° and made strongly basic with 50% NaOH solution. The liberated amine was extracted with ether and the solution was washed well with water. After drying over sodium sulfate the mixture was thoroughly stripped of solvent at 65° on the water pump to remove low-boiling amines. [This product was adequately pure for quaternization. When the reaction was run similarly with a Grignard reagent[6] prepared from 310 g of 2-bromo-3-dimethylaminopropene and 260 g of 6-methoxy-1-tetralone the product contained dark impurities and was distilled to yield 121 g of **4**: bp 130–133° (0.2 mm); uv $\lambda_{max}$ 273 nm ($\epsilon$ 10800); NMR $\delta$ 2.25 (s, 6 H) superimposed on 2.1–2.9 (4 H), 3.06 (br s, 2 H), 3.79 (s, 3 H), 5.15–5.35 (2 H), 5.88 (t, $J$ = 4.4 Hz, 1 H), 6.5–7.2 (3 H).] The crude oil (160 g) was dissolved in 3 l. of benzene and 100 g of methyl iodide was added. After standing at room temperature overnight, the solid was collected and washed with benzene to give 242 g (37% conversion, 57% yield from 6-methoxy-1-tetralone) of **5**: mp 182–183°; uv $\lambda_{max}$ 218 nm ($\epsilon$ 27560), 268 (10000); NMR ($CD_3OD$) $\delta$ 2.1–2.9 (4 H), 3.15 (s, 9 H), 3.81 (s, 3 H), 4.32 (br s, 2 H), 5.84 (br s, 2 H), 6.25 (t, $J$ = 4.6 Hz, 1 H), 6.7–7.2 (3 H).

Anal Calcd for $C_{17}H_{24}NOI$: C, 52.99; H, 6.28; N, 3.64; I, 32.94. Found: C, 52.75; H, 6.24; N, 3.66; I, 32.81.

When 2-chloro-3-dimethylaminopropene (bp 32°, 20 mm), prepared from 2,3-dichloropropene in the same manner as the bromo compound,[6] was substituted and the reaction run on a 0.1-mol scale with the same temperature as above, the yield of **5** was only 10% and the neutral layer contained a significant amount of 1-butyl-6-methoxy-1-tetralol as indicated by NMR analysis. In another 0.1-mol run, the solution of 2-chloro-3-dimethylaminopropene and butyllithium was allowed to warm to 0° for 20 min before the 6-methoxy-1-tetralone was added. The rest of the sequence was unchanged and the yield of **5** was 53% based on consumed 6-methoxy-1-tetralone.

**13-Ethyl-3-methoxy-11-methylene-8,14-secogona-1,3,5(10),8-tetraene-14,17-dione (6b).** To a solution of 76 g (0.197 mol) of **5** in 800 ml of methanol and 40 ml of water at 15° was added 24 g (0.103 mol) of silver oxide. The mixture was stirred at 15–20° for 2 hr, when a silver nitrate test was negative. The solid was removed by filtration washing well with methanol. To the filtrate was added 30 g (0.238 mol) of 2-ethylcyclopentane-1,3-dione and the resulting solution was concentrated to dryness on the water pump. The residue was suspended in 1400 ml of xylene and 10 ml of triethylamine (to neutralize the excess dione). The resulting mixture was heated to distill out ca. 100 ml through a short Vigreux column to remove methanol, water, and excess triethylamine. After the addition of 5 ml of HMPT ca. 100 ml more distillate was collected and the heat was adjusted to cause refluxing in the column. After 18 hr slow distillation was resumed until little more amine was detected in the distillate (in 6 hr ca. 400 ml was collected). After cooling the solution was washed with water and 5% $NaHCO_3$ solution. After drying over sodium sulfate, the solvent was removed and the residue crystallized from methanol to yield 35.2 g (54%) of **6b:** mp 100–100.5°; ir 5.66 (weak), 5.79 μ; uv $\lambda_{max}$ 273 nm (ε 11000); NMR δ 0.73 (t, $J$ = 7.5 Hz, 3 H), 1.62 (q, $J$ = 7.5 Hz, 2 H), 1.9–2.4 ( 2 H), [2.60 (s, ca. 4 H) and 2.72 (br s, ca. 2 H) superimposed on 2.5–2.9 (ca. 2 H)], 3.81 (s, 3 H), 4.9–5.1 (2 H), 5.79 (t, $J$ = 4.6 Hz, 1 H), 6.6–7.1 (3 H).

Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.98; H, 7.64.

**3-Methoxy-11-methylene-8,14-secoestra-1,3,5(10),8-tetraene-14,17-dione (6a).** In a manner similar to the above 13.3 g of **5**, 4.1 g of silver oxide, and 4.0 g of 2-methylcyclopentane-1,3-dione with 1 ml of triethylamine, 5 ml of HMPT, and 500 ml of xylene yielded 5.9 g (55%) of **6a:** mp 82.5–83° from aqueous methanol; ir 5.65 (weak), 5.78 μ; uv $\lambda_{max}$ 274 nm (ε 10400); NMR δ 1.08 (s, 3 H), [2.67 (s, ca. 4 H) + 2.74 (br s, ca. 2 H) superimposed on 1.9–2.9 (ca. 4 H)], 3.81 (s, 3 H), 4.9–5.1 (2 H), 5.70 (t, $J$ = 4.5 Hz, 1 H), 6.4–7.1 (3 H).

Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.23; H, 7.27.

In a similar run with 2.8 g of **5**, 0.85 g of silver oxide, 1.0 g of 2-methylcyclopentane-1,3-dione, 1 ml of triethylamine, and 20 ml of HMPT in 250 ml of xylene, the crude product contained several impurities as evidenced by TLC. After chromatographic purification developing with 5% ethyl acetate in benzene the product fraction was crystallized from methanol to yield 256 mg of **6a** identical with the above. The major by-product fraction moving somewhat slower amounted to 430 mg of a crude oil believed to be the isomeric O-alkylation product: ir 5.74 (weak), 5.88; 6.10 μ; uv $\lambda_{max}$ 253 nm (ε 22650); NMR δ 1.66 (t, $J$ = 1.4 Hz, 3 H), 2.0–2.9 (ca. 8 H), 3.82 (s, 3 H), 4.79 (t, $J$ = 1.4 Hz, 2 H), 5.36 (d of t, $J$ = 7 + 1.4 Hz, 2 H), 5.91 (t, $J$ = 4.5 Hz, 1 H), 6.5–7.2 (3 H).

A solution of 2.25 g of 2-methylcyclopentane-1,3-dione and 1.08 g of sodium methylate in 10 ml of methanol was concentrated to dryness and 3.85 g of **5**, 250 ml of xylene, and 10 ml of HMPT were added. The mixture was slowly distilled over a 6-hr period adding xylene to maintain the volume at 200–250 ml. (From the stillhead a small amount of solid, mp ca. 330° dec, was identified as tetramethylammonium iodide, NMR in $D_2O$ single band δ 3.20.) After cooling the mixture was washed with water, 5% HCl, and 5% $NaHCO_3$ and dried over sodium sulfate. The solvent was removed and the mixture was chromatographed to give first 210 mg of a crude amine by-product with NMR bands at δ 3.10 and 2.22 in the ratio of 4:3 suggesting bis[2-(3,4-dihydro-6-methoxy-1-naphthyl)-2-propenyl]methylamine. This was followed by the crude product which on crystallization from aqueous methanol gave 1.17 g (38%) of **6a** identical with the above.

**Racemic 13-Ethyl-3-methoxy-11-methylenegona-1,3,5(10),-8,14-pentaen-17β-ol (7d).** A solution of 35.2 g (0.108 mol) of **6b** in 750 ml of toluene was dried by distillation of ca. 50 ml and then chilled under nitrogen to −30°. A solution, previously dried by reflux under a Dean-Stark type trap, from 20.5 g (0.108 mol) of $p$-toluenesulfonic acid monohydrate and 1.5 l. of benzene was added over a short period with vigorous stirring while keeping the temperature below 0°. The mixture was stirred at 0° for 15 min. The precipitate of $p$-toluenesulfonic acid hydrate was removed by rapid filtration through a Supercell cake in a nitrogen atmosphere rinsing the solid with dry benzene. The filtrate was diluted with 500 ml of dry ether and chilled in an ice bath under nitrogen while 35 ml of 1 $M$ $LiAlH_4$ in ether was added quickly with stirring. After 15 min the excess hydride was quenched and the mixture was washed with cold 5% HCl and then with ice water. After brief drying over sodium sulfate the solution was concentrated on the water pump to a small residue which was triturated with cold methanol. The solid was collected and recrystallized from methanol to yield 20.3 g of the hemimethanoloate of **7d**, mp 86–88°. (Other runs gave samples melting as low as 58–60° or as high as 102–104° with only slight variations in the amount of methanol as judged by the NMR spectrum.) Concentration of the mother liquors followed by quick chromatographic purification developing with 5% ethyl acetate in benzene and crystallization from methanol gave 6.3 g more material: mp 85–87°; uv $\lambda_{max}$ 248 nm (ε 13700), 257 (11300), 312 (19600), 324 (22600), 338 (17900); NMR δ 0.97 (t, $J$ = 7 Hz, 3 H), 1.61 (q, $J$ = 7 Hz, 2 H), 1.7–2.9 (ca. 9.5 H), 3.48 (s, ca. 1.5 H), 3.81 (s, 3 H), 4.23 (t, $J$ = 8.5 Hz, 1 H), 5.23 (d of t, $J$ = 6 + 1.5 Hz, 2 H), 5.64 (t, $J$ = 3 Hz, 1 H), 6.6–7.7 (3 H).

Anal. Calcd for $C_{21}H_{24}O_2 \cdot \frac{1}{2}CH_4O$: C, 79.59; H, 8.08. Found: C, 79.36; H, 7.99.

**Racemic 13-Ethyl-3-methoxy-11-methylenegona-1,3,5(10),-8,14-pentaen-17-one (7c).** Under similar conditions from 4.76 g of **6b** and 2.78 g of $p$-toluenesulfonic acid monohydrate, the intermediate was isolated by taking the filtrate after removal of tosyl acid hydrate, washing with ice water, and drying over sodium sulfate. After removal of solvents on the water pump the residue was triturated with methanol and the solid was recrystallized from $CH_2Cl_2$–$CH_3OH$ to yield 3.68 g (82%) of **7c:** mp 117.5–118°; ir 5.73 μ; uv $\lambda_{max}$ 248 nm (ε 12900), 257 (11000), 312 (16900), 325 (19000), 339 (15400); NMR δ 0.86 (t, $J$ = 7 Hz, 3 H), 1.64 (q, $J$ = 7 Hz, 2 H), 1.9–3.4 (ca. 8 H), 3.81 (s, 3 H), 5.31 (br d, $J$ = 7 Hz, 2 H), 5.92 (t, $J$ = 2.8 Hz, 1 H), 6.6–7.6 (3 H).

Anal. Calcd for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.22; H, 7.30.

**Racemic 3-Methoxy-11-methyleneestra-1,3,5(10),8,14-pentaen-17-one (7a).** In a manner similar to the preparation of **7c** above, 4.71 g of **6a** and 2.85 g of $p$-toluenesulfonic acid monohydrate yielded 3.80 g (86%) of **7a:** mp 161–163° from $CH_2Cl_2$–$CH_3OH$; ir 5.73 μ; uv $\lambda_{max}$ 246 nm (ε 15200), 255 (12700), 325 (23700), $\lambda_{shoulder}$ 313 (20400), 338 (19300); NMR δ 1.14 (s, 3 H) [2.43 (br s, ca. 2 H) superimposed on 2.1–2.9 (ca. 4 H)], 3.13 (d of d, $J$ = 12 + 3 Hz, 2 H), 3.80 (s, 3 H), 5.33 (br d, $J$ = 4 Hz, 2 H), 5.89 (t, $J$ = 3.3 Hz, 1 H), 6.6–7.6 (3 H).

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.15; H, 6.89. Found: C, 82.00; H, 7.13.

**Racemic 3-Methoxy-11-methyleneestra-1,3,5(10),8,14-pentaen-17β-ol (7b).** To a solution of 2.32 g of **7a** in 20 ml of benzene and 50 ml of ether under nitrogen was added 5 ml of 0.9 $M$ $LiAlH_4$ in ether. After 5 min the product was isolated in the normal manner to give 2.32 g (89%) of a methanol solvate, mp 102–110°. A portion was boiled in hexane and then recrystallized from ether to give a sample: mp 120–124°; uv $\lambda_{max}$ 247 nm (ε 13400), 257 (10900), 312 (20000), 324 (23300), 339 (18700); NMR δ 1.00 (s, 3 H), 1.78 (OH, 1 H), 2.0–2.8 (ca. 8 H), 3.81 (s, 3 H), 4.12 (br t, $J$ = 8.5 Hz, 1 H), 5.1–5.3 (2 H), 5.54 (t, $J$ = 3.3 Hz, 1 H), 6.6–7.7 (3 H).

Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60: H, 7.53. Found: C, 81.59; H, 7.59.

**Racemic 13-Ethyl-3-methoxy-11β-methylgona-1,3,5(10),8-tetraen-17β-ol (9b).** A solution of 7.55 g (23 mmol) of the hemimethanoloate of **7d** in 250 ml of ethanol was hydrogenated in the presence of 3.7 g of a 5% $Pd/Al_2O_3$ catalyst at 2 psi and room temperature. After 3 hr 49.5 mmol of $H_2$ had been taken up. The catalyst was removed by filtration and the filtrate was concentrated to a small residue which was triturated with methanol. The crude solid was recrystallized from $CH_2Cl_2$–$CH_3OH$ to yield 4.0 g of a solvate, mp 131–142°. Recrystallization from $CH_2Cl_2$–cyclohexane gave 3.47 g (48%) of **9b:** mp 147–148°; uv $\lambda_{max}$ 278 nm (ε 17600), $\lambda_{shoulder}$ 271 (17200); NMR δ [1.21 (d, $J$ = 7.5 Hz, ca. 3 H) + 1.52 (OH, ca. 1 H) superimposed on 0.9–2.9 (ca. 17 H)], 3.80 (s, 3 H) superimposed on 3.82 (br t, $J$ = 6 Hz, 1 H), 6.6–7.3 (3 H).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.59; H, 8.83.

**Racemic 3-Methoxy-11β-methylestra-1,3,5(10),8-tetraen-17β-ol (9a).** A solution of 1.48 g (5 mmol) of **7b** in 50 ml of benzene was hydrogenated over 0.74 g of 5% $Pd/Al_2O_3$ at 2 psi. After 4 hr 10 mmol of $H_2$ had been consumed. The catalyst was removed by filtration and the filtrate was concentrated to a small residue which was crystallized from aqueous methanol to give 870 mg (58%), mp 159–161°. A sample recrystallized from aqueous methanol melted at 162–163°; uv $\lambda_{max}$ 278 nm (ε 13900), $\lambda_{shoulder}$ 270 (13600); NMR δ 0.93 (s, 3 H), 1.21 (d, $J$ = 7.5 Hz, 3 H), 1.57 (OH, ca. 1 H) superimposed on 1.4–2.9 (ca. 13 H), 3.80 (s, 3 H) superimposed on 3.6–3.9 (ca. 1 H), 6.6–7.3 (3 H).

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.36; H, 8.74.

Concentration of the mother liquors led to 614 mg of an oil. A study of the methyl bands in the NMR spectrum indicated about 46% of the above material, δ 0.93 (s) and 1.21 (d, $J$ = 7.5 Hz) together with 25% of an isomeric component with δ 1.06 (s) and 0.69 (d, $J$ = 5 Hz) and 29% of a third component with δ 0.99 (s) and 0.83 (d, $J$ = 6 Hz). In some other runs very little of the third component was observed. On the basis of the ratios of the components from various runs, the third component may have arisen from the uptake of a third mole of hydrogen by the isomeric by-product.

**Racemic 3-Methoxy-11-methylestra-1,3,5(10),8(14),9(11)-pentaen-17β-ol (8).** A solution of 463 mg (1.5 mmol) of **7b** in 40 ml of benzene was hydrogenated over 50 mg of 5% $Pd/CaCO_3$ at atmospheric pressure. After 1 hr 1.55 mmol of $H_2$ had been consumed and uptake stopped. The catalyst was removed and the solution was concentrated to dryness. The residue was crystallized twice from aqueous methanol to yield 392 mg (63%) of **8**: mp 124–127°; uv $\lambda_{max}$ 244 nm (ε 20800), 285 (7600), $\lambda_{shoulder}$ 250 (20500); NMR δ 0.89 (s, 3 H), 1.61 (OH, 1 H), [2.00 (br s, ca. 3 H) + 2.24 (br s, ca. 2 H) superimposed on 1.7–2.8 (ca. 8 H)], 3.80 (s, 3 H), 3.8–4.1 (1 H), 6.7–7.4 (3 H).

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.06; H, 8.31.

Hydrogenation of this material over $Pd/Al_2O_3$ as described above resulted in an 80% yield of **9a** by an NMR analysis or 62% yield of crystallized **9a.**

Concentration of the mother liquors left 112 mg of a crude oil. The uv spectrum of this material was similar to the above with an additional maximum at 311 nm with shoulders at 300 and 324 nm. The NMR spectrum showed, in addition to the above (ca. 60%), bands at δ 0.83, 0.92, 0.99, 1.11, 1.20, 1.32, and 5.1–5.3 and 5.4–5.6 which may be accounted for by structures 2.

**Racemic 13-Ethyl-3-methoxy-11β-methylgona-1,3,5(10)-trien-17β-ol (10c).** To a solution of 2.0 g of sodium metal in ca. 250 ml of refluxing ammonia was added a solution of 6.117 g of **9b** in 15 ml of aniline and 100 ml of THF over a 5-min period. After 30 min the flask was cooled well in a dry ice bath and 10 g of solid ammonium chloride was added cautiously. The ammonia was allowed to evaporate under a nitrogen stream at room temperature and 50 ml of water was added. The mixture was concentrated on the water pump to remove most of the THF. The mixture was made acidic with 10% HCl and stirred until the supernatant liquid was clear. The solid was collected and washed well with water. After drying, recrystallization from methanol yielded 5.93 g of the hemimethanoloate of **10c**: mp 124–125°; uv $\lambda_{max}$ 220 nm (ε 8400), 278 (1970), 287 (1900); NMR δ [0.90 (d, $J$ = 7.5 Hz, ca. 3 H) + 1.50 (OH, ca. 1.5 H) superimposed on 0.8–2.9 (ca. 19 H)], 3.47 ($CH_3OH$, 1.5 H), 3.78 (s, 3 H) superimposed on 3.6–3.9 (1 H), 6.6–7.2 (3 H).

Anal. Calcd for $C_{21}H_{30}O_2 \cdot \frac{1}{2}CH_4O$: C, 78.13; H, 9.76. Found: C, 78.35; H, 9.85.

**Racemic 11β-Methylestradiol-3-methyl Ether (10a).** In a manner similar to the above procedure, 253 mg of **9a** and 500 mg of sodium metal yielded 2.2 mg of **10a**: mp 143–145° from aqueous methanol; uv $\lambda_{max}$ 279 nm (ε 1920), 288 (1960); NMR δ 0.89 (d, $J$ = 7.5 Hz, 3 H), 0.92 (s, 3 H), 1.58 (OH, 1 H) superimposed on 1.2–3.0 (ca. 14 H), 3.78 (s, 3 H) superimposed on 3.5–3.9 (1 H), 6.6–7.2 (3 H). These spectra and ir spectra are indistinguishable from those of a sample derived from natural sources.[2]

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.70; H, 9.40.

**Racemic 11β-Methylestrone-3-methyl Ether (10b).** Jones reagent oxidation[13] of 132 mg of **10a** produced 100 mg of **10b**: mp 150–153° from aqueous methanol; ir 5.74 μ; uv $\lambda_{max}$ 278 nm (ε 2000), 287 (1940); NMR δ 0.89 (d, $J$ = 7.5 Hz, 3 H), 1.00 (s, 3 H), 1.2–3.1 (ca. 14 H), 3.77 (s, 3 H), 6.6–7.3 (3 H). These spectra are indistinguishable from those of a sample derived from natural sources.[2]

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.43; H, 8.78.

**Racemic 13-Ethyl-3-methoxy-11β-methylgona-1,3,5(10)-trien-17-one (10d).** Jones reagent oxidation[13] of 560 mg of the hemimethanoloate of **10c** produced 453 mg of **10d**: mp 144.5–145° from aqueous methanol; ir 5.75 μ; uv $\lambda_{max}$ 220 nm (ε 8400), 278 (1970), 287 (1900); NMR δ 0.85 (t, $J$ = 5.5 Hz, ca. 3 H) superimposed on 0.90 (d, $J$ = 7 Hz, ca. 3 H), 1.1–3.0 (ca. 16 H), 3.77 (s, 3 H), 6.6–7.2 (3 H).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.68; H, 9.22.

**Racemic 13-Ethyl-17-hydroxy-11β-methyl-18,19-dinor-17α-pregn-5-en-20-yn-3-one (11a).** Under Birch reduction conditions,[14] 6.2 g of **10c** in 75 ml of THF and 75 ml of 2-propanol was treated with a total of 9.5 g of sodium metal in 150 ml of ammonia. The crude dry product (5.9 g, mp 155–158°) in 350 ml of dry toluene was oxidized by 60 ml of cyclohexanone in the presence of 6 g of aluminum isopropoxide during 1 hr at reflux. After some cooling 45 ml of a saturated Rochelle salt solution was added and the mixture was steam distilled under nitrogen until the distillate was clear. After cooling the mixture was extracted with ether. The extract was washed with water and dried over sodium sulfate and the solvent removed in vacuo. The residue was crystallized from benzene–cyclohexane to give 5.35 g of material melting at 142–144°. A solution of this material in 50 ml of dry THF was added to a solution previously prepared by addition of 25 ml of 3.1 $M$ ethylmagnesium bromide in ether to ca. 20 g of acetylene in 100 ml of THF at −78° and then allowed to warm to 10°. The resulting mixture was stirred for 4 hr at room temperature. After cooling in an ice bath, 100 ml of ice-cold saturated $NH_4Cl$ was added slowly with stirring. The mixture was extracted twice with ether and the extracts were washed with water, dried over sodium sulfate, and concentrated in vacuo. Crystallization from benzene–cyclohexane gave 3.79 g, mp 161–164°. This material was suspended in 150 ml of methanol and 10 ml of a 10% oxalic acid solution was added. After 30 min of stirring at room temperature the solution was complete and the mixture was diluted with 100 ml of water and concentrated on the water pump to remove most of the methanol. Normal extraction and crystallization from benzene-cyclohexane gave 3.38 g of **11a**: mp 135–136°; ir 5.81 μ; uv $\lambda_{max}$ 288 nm (ε 111); NMR δ 2.64 (s, 1 H), 2.77 (br s, 2 H), 0.8–2.6 (ca. 27 H including OH at 2.05 and strong bands at 0.84, 0.96, 1.08, 1.18, 2.02, and 2.40).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.79; H, 9.35.

**Racemic 13-Ethyl-17-hydroxy-11β-methyl-18,19-dinor-17α-preg-4-en-20-yn-3-one (11b).** To a solution of 860 mg of **11a** in 30 ml of methanol was added 10 ml of 4 $N$ HCl. After 6 hr at room temperature crystals had formed, and 10 ml more of 4 $N$ HCl was added. After 2 hr more the mixture was chilled an the solid collected and washed well with water. Recrystallization from aqueous methanol yielded 687 mg: mp 208–210°; ir 5.99, 6.17 μ; uv $\lambda_{max}$ 240.5 nm (ε 16700); NMR δ 2.61 (s, 1 H), 5.87 (br s, 1 H), 0.8–2.9 (ca. 34 H including OH at 2.15 and strong bands at 1.03, 1.17, 1.22, 2.02, 2.30, 2.39).

Anal Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 81.03; H, 9.31.

**Racemic 13-Ethyl-11β-methyl-18,19-dinor-17α-pregn-4-en-20-yne-3β,17-diol (11c).** To a solution of 909 mg of **11b** in 40 ml of THF was added 2 g of lithium tri-*tert*-butoxyaluminum hydride and the mixture was stirred at room temperature for 18 hr and worked up in the normal manner. After chromatographic purification developing with 5% ethyl acetate in benzene, the major fraction (faster moving) was crystallized twice from cyclohexane to yield 638 mg of **11c**: mp 176–178°; NMR δ 2.60 (s, 1 H), 3.98–4.32 (1 H), 5.3–5.5 (1 H), 0.7–2.5 (ca. 29 H including strong bands at 0.99, 1.10, 1.17, 1.46, 1.97, and 2.11).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.25; H, 9.63.

**Racemic 3β,17-Diacetoxy-13-ethyl-11β-methyl-18,19-dinor-17α-pregn-4-en-20-yne (11d).** A solution of 344 mg of **11c** and 11 mg of 4-dimethylaminopyridine in 5 ml of acetic anhydride and 5 ml of triethylamine was heated under nitrogen for 24 hr at 40° and then for 16 hr more at 45°. After cooling 20 ml of 2-propanol was added and after 30 min 100 ml of water was added and the mixture was extracted with ether. The extract was washed with water and dried over sodium sulfate and the solvent removed. The mixture was chromatographed developing with 2% ethyl acetate in benzene. The major fraction was crystallized from methanol to yield 230 mg of **11d**: mp 147–149°; NMR δ 2.05 (s, ca. 6 H) superimposed

on 0.9–2.4 (ca. 27 H), 2.63 (s, 1 H), 5.35–5.45 (ca. 1 H) superimposed on 5.0–5.6 (ca. 1 H).

Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80. Found: C, 75.97; H, 8.80.

**Registry No.**—**2** isomer A, 57346-08-4; **2** isomer B, 57346-09-5; **4**, 57346-10-8; **5**, 57346-11-9; **6a**, 57346-12-0; **6b**, 57346-13-1; **7a**, 57346-14-2; **7b**, 57346-15-3; **7c**, 57346-16-4; **7d** ½MeOH, 57346-18-6; **8**, 57346-19-7; **9a**, 57346-20-0; **9b**, 57346-21-1; **10a**, 57378-55-9; **10b**, 57346-22-2; **10c**, 57346-23-3; **10c** ½MeOH, 57427-66-4; **10d**, 17253-49-5; **11a**, 57362-17-1; **11b**, 57346-24-4; **11c**, 23163-43-1; **11d**, 23163-53-3; 2-bromo-3-dimethylaminopropene, 14326-14-8; 6-methoxytetralone, 1078-19-9; 2-ethylcyclopentane-1,3-dione, 823-36-9; 2-methylcyclopentane-1,3-dione, 765-69-5; (±)-13-ethyl-3-methoxy-11β-methylgona-2,5(10)-dien-17β-ol, 57346-25-5; (±)-13-ethyl-3-methoxy-11β-methylgona-2,5(10)-dien-17-one, 57346-26-6; (±)-13-ethyl-3-methoxy-11β-methyl-17-hydroxy-18,19-dinor-17α-pregna-2,5(10)-dien-20-yne, 53762-18-2.

## References and Notes


(1) Presented in part at the 4th International Congress on Hormonal Steroids, Mexico City, 1974; R. B. Garland and R. Pappo, *J. Steroid Biochem.*, **5**, 299 (1974).
(2) J. S. Baran, H. D. Lennon, S. E. Mares, and E. F. Nutting, *Experientia*, **26**, 762 (1970).
(3) J. S. Baran and C. D. Liang, private communication.
(4) R. V. Coombs and R. P. Danna, reported at the 4th International Congress on Hormonal Steroids, 1974. We also confirmed these results.
(5) C. H. Kuo, D. Taub, and N. L. Wendler, *Angew. Chem., Int. Ed. Engl.*, **4**, 1083 (1965).
(6) D. Bar, P. Marcinal, and A. Marcinal-Lefebvre, *Bull. Soc. Chim. Fr.*, 2484 (1972).
(7) E. J. Corey, D. E. Cane, and L. Libit, *J. Am. Chem. Soc.*, **93**, 7016 (1971).
(8) We are indebted to Dr. Robert Chorvat of these Laboratories for suggesting this reaction, which was discovered independently by him.
(9) H. R. Snyder, C. W. Smith, and J. M. Stewart, *J. Am. Chem. Soc.*, **66**, 200 (1944).
(10) See also the intramolecular alkylation of a ketone by a quaternary ammonium salt resulting in an *i*-steroid: R. Pappo, *J. Am. Chem. Soc.*, **81**, 1010 (1959).
(11) G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963).
(12) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).
(13) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).
(14) H. L. Dryden, Jr., G. M. Webber, R. R. Burtner, and J. A. Celia, *J. Org. Chem.*, **26**, 3237 (1961).


# Claisen Rearrangement with Hydroxymethylpyridines and Hydroxymethylpyridones

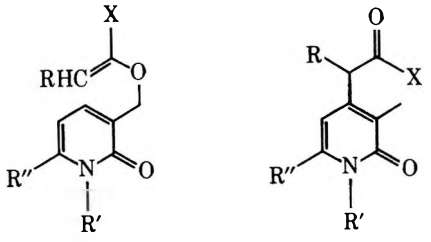

C. Richard Costin, Cary J. Morrow, and Henry Rapoport*

*Department of Chemistry, University of California, Berkeley, California 94720*


*Received August 19, 1975*


The Claisen rearrangement has been applied to 2-, 3-, and 4-hydroxymethylpyridines, using triethyl orthoacetate to generate the intermediate ketene acetals. In all three cases, the major products resulted from normal rearrangement, with the 3-hydroxymethylpyridine being the most reactive. Similar results were obtained using amide acetals in place of ortho esters. 3-Hydroxymethyl-1-methyl-2-pyridone took a different course in reaction with orthoesters, giving only thermal rearrangement to the corresponding propionates. This reaction path became minor with amide acetals and acid catalysis, normal Claisen rearrangement predominating. These rearrangements proceed more readily than with benzyl alcohols and are synthetically useful.


In the course of work directed toward the total synthesis of camptothecin, we were led to examine the Claisen rearrangement of substituted vinyl ethers prepared from 3-hydroxymethyl-2-pyridone systems, 1. As the products of



1

this reaction were found to be strongly dependent on the nature of R and X as well as on the presence or absence of acid catalysts, we decided to examine in some detail the general question of Claisen rearrangement in systems where the allylic double bond of the allyl vinyl ether is contained in a heterocyclic aromatic ring. In the extension of the Claisen rearrangement reported here, the allylic double bond is contained in a pyridine or pyridone nucleus. The method provides a convenient synthesis of alkyl-substituted pyridylacetates which are otherwise available by a rather tedious route.[1]

The Claisen rearrangement has been the subject of considerable research over six decades and has proved to be a highly versatile method in synthesis.[2] Most of this early work was concerned with the rearrangement of allyl phenyl ethers, and to date only a few, mostly unsuccessful, attempts have been made to extend the Claisen rearrangement to systems which have the allylic double bond incorporated in an aromatic ring. For example, benzyl vinyl ether was found[3] to rearrange to 3-phenylpropanal rather than *o*-tolylacetaldehyde. Similarly, α-benzyloxystyrene rearranges thermally to give β-phenylpropiophenone.[4] More recently, 5-benzyloxy-1,3-dimethyluracil was reported[5] not to undergo the Claisen rearrangement but to partially rearrange to 6-benzyl-1,3-dimethyl-5-hydroxyuracil. It is clear from these results that the thermal rearrangement of benzyl vinyl ethers does not proceed by a Claisen pathway, but may follow a free-radical scission–recombination mechanism[3] similar to that established for the thermal rearrangement of benzyl phenyl ether.[6]

Modification of the aromatic ring by substitution with electron-donating groups promotes the Claisen rearrangement. The thermal rearrangement of 3,5-dimethoxybenzyl isopropenyl ether provides 2,4-dimethoxy-6-methylphenylacetone and a minor amount of 3,5-dimethoxybenzylacetone.[7] Similarly, 3-methoxybenzyl isopropenyl ether gave a 1:1 mixture of the two corresponding ketones.[7]

In addition to the aromatic substituent effect, variations in the vinyl moiety also influence the course of the reaction. Whereas benzyl vinyl ether failed to give any Claisen product, the thermal rearrangement of benzyldiethyl orthoace-

Table I
Claisen Rearrangement of 3-Hydroxymethylpyridine and Triethyl Orthoacetate

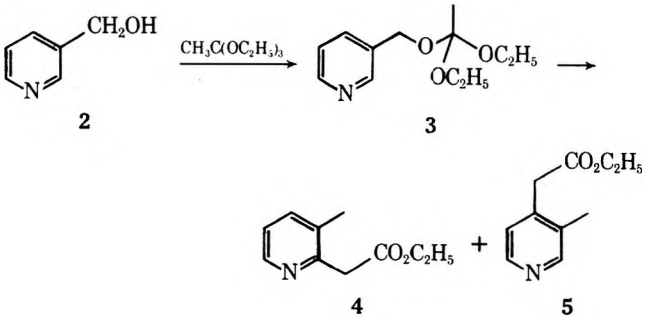
| 1, mol | $CH_3C(OEt)_3$, mol | Acid catalyst, mol % | Solvent | Reaction time, hr, temp, °C | Yield,[a] % | Ratio 4:5 |
|---|---|---|---|---|---|---|
| 1 | 8 | $CH_3CH_2CO_2H$, 1 | | 20, 190 | 42 | 61:39 |
| 1 | 8 | $CH_3CH_2CO_2H$, 110 | | 3, 195 | 48[c] | 56:44 |
| 1 | 8 | TsOH, 1 | | 3, 190[b] | 20 | 50:50 |
| 1 | 8 | $CH_3CH_2CO_2H$, 1 | *o*-Dichlorobenzene | 48, 180 | 32 | 57:43 |

[a] All yields were determined by GC using hexadecane as internal standard, unless noted otherwise. [b] Continued heating at 190° (15 hr) caused extensive tar formation. [c] Isolated yield.

tate gave a low yield of ethyl o-tolylacetate.[8] Similarly, treatment of dibenzyl bromoacetal with potassium *tert*-butoxide proceeded via a ketene acetal intermediate to give benzyl *o*-tolylacetate.[8] A more dramatic effect has been noted in the thermolysis of an α-aminovinyl benzyl ether.[9] This reagent, prepared in situ by the use of the acetal of *N,N*-dimethylacetamide and benzyl alcohol, was rearranged to give *N,N*-dimethyl-*o*-tolylacetamide.

## Results

Examination of rearrangement in the pyridine series was begun with treatment of 3-hydroxymethylpyridine (**2**) with triethyl orthoacetate and a catalytic amount of propionic acid under the conditions (140°, 15 hr) recently described.[10] These conditions failed to give Claisen rearrangement products but instead gave **3** resulting from 3-hydroxymethylpyridine exchange with the orthoacetate. Under similar conditions, benzyl alcohol reacts in the same manner giving benzyldiethyl orthoacetate. However, it has been reported[8] that at 200° benzyldiethyl orthoacetate rearranges to give a low yield of ethyl *o*-tolylacetate. Similar observations have been noted for the reaction of simple allylic alcohols and triethyl orthoacetate.[11] These reports suggest that higher temperatures might be necessary to effect the Claisen rearrangement in the pyridine series, and therefore a mixture of **2**, triethyl orthoacetate, and propionic acid was heated at 195°. A 48% yield of **4** and **5** in a ratio of 56:44 was obtained. Several additional reactions

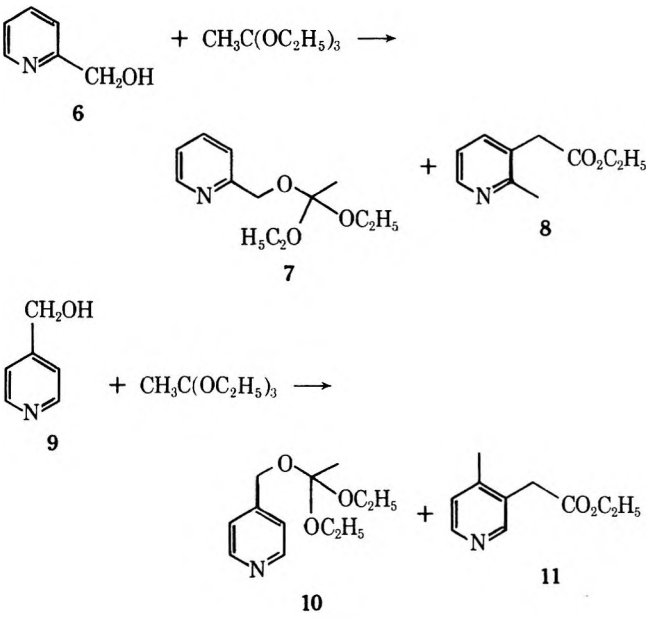


were conducted in an effort to increase the yield of **4** and **5**. The results are shown in Table I.

In each reaction the desired products, **4** and **5**, were accompanied by several minor products, whose identity has not been established. It was determined, however, that ethyl β-(3-pyridyl)propionate, an expected by-product resulting from 1,4 rearrangement, was not formed.

As shown in Table I, varying the amount of propionic acid (1 to 110 mol %) had no noticeable effect on the ratio or yield of **4** and **5**. However, when an excess of propionic acid was employed an additional unidentified by-product was formed. From these data we conclude that the preferred procedure for effecting the Claisen rearrangement in the 3-pyridyl system is heating **2** in triethyl orthoacetate containing 1 mol % of propionic acid at 195°.

Under these conditions 2- and 4-hydroxymethylpyridine also gave rise to rearranged products, but the reactivity was distinctly lower than in the 3-hydroxymethylpyridine case. Thus treatment of 2-hydroxymethylpyridine (**6**) with 8 mol of triethyl orthoacetate containing 1 mol % of propionic acid at 190° for 18 hr yielded, as the major products, the mixed ortho ester **7** (28%) and the pyridylacetate **8** (29%). Similar treatment of 4-hydroxymethylpyridine (**9**) afforded ortho ester **10** and pyridylacetate **11** in 62 and 22% yield, respectively.



As previously noted,[9] the amide acetal reagent has proved superior to ortho esters for effecting Claisen rearrangement in benzylic systems. Applying this method to 3-hydroxymethylpyridine, however, gave results comparable to those observed when the ortho ester method was employed. Treatment of 3-hydroxymethylpyridine (**2**) with a mixture of *N,N*-dimethylacetamide diethyl acetal (**12**) and 1-ethoxy-1-dimethylaminoethylene (**13**) in refluxing o-dichlorobenzene for 18 hr afforded a 44% yield of **14** and **15** in a ratio of 65:35.

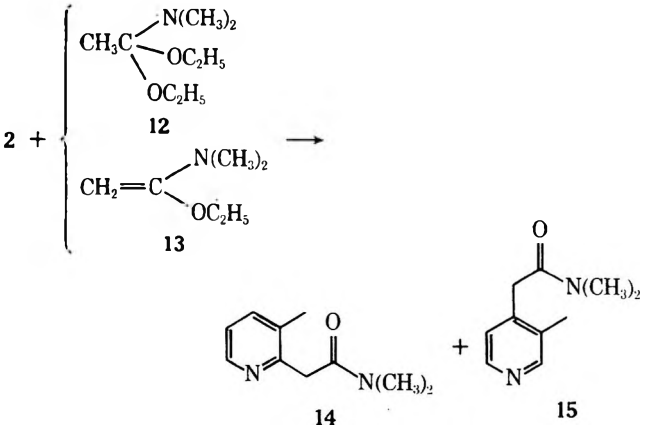
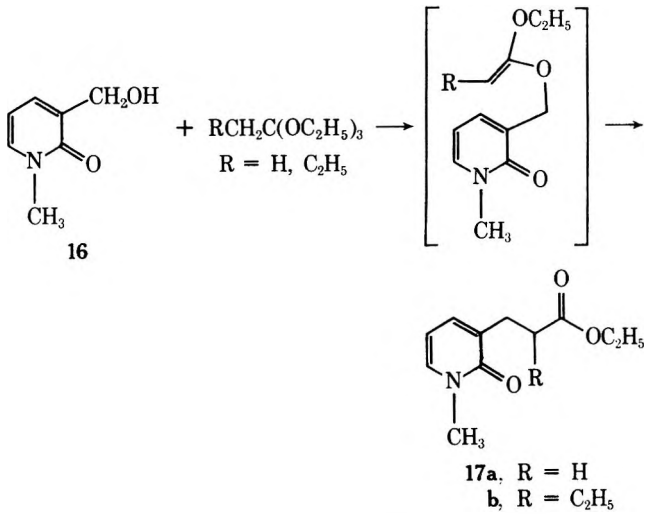


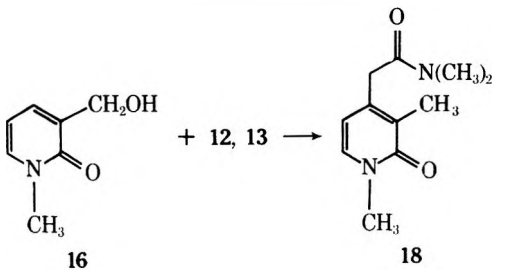
Table II
Claisen Rearrangement of 3-Hydroxymethyl-1-methyl-2-pyridone (16) with *N,N*-Dimethylbutyramide Diethyl Acetal (19)

| Expt | 16, mmol | 19, mmol[a] | Solvent,[b] ml | Temp, °C | Time, hr | $H^+$ catalyst[c] | Ratio 20:21 | Remarks |
|---|---|---|---|---|---|---|---|---|
| 1 | 3.0 | 4.5 | DCB, 6 | Reflux ~183 | 42 | | 36:64 | |
| 2 | 1.0 | 6.0 | | 145–150 | 17.5 | 6 mol % | 62.5:37.5 | Loss of peaks at 5 and 6.5 min first observed |
| 3 | 2.0 | 3.0 | DCB, 6 | 130<br>160 | 19<br>24 | | 38:62 | Added 12, 13 in 2 ml of DCB at 130° |
| 4 | 1.0 | 6.0 | | RT[f]<br>Reflux | 20<br>3 | 6.7 mol % | 75:25 | Predicted[e] ratio 80:20 at beginning of reflux |
| 5 | 0.5 | 3.0 | DCB, 3 | Reflux ~183 | 20 | | 41:59 | |
| 6 | 0.5 | 3.0 | DCB, 3 | 140–150 | 24 | 2.5 μl 6.7 mol % | 86:14[d] | Predicted[e] ratio 79:21 at 18.5 hr |
| 7 | 0.5 | 3.0 | | RT | 768 | 2.5 μl 6.7 mol % | 88:12 | |

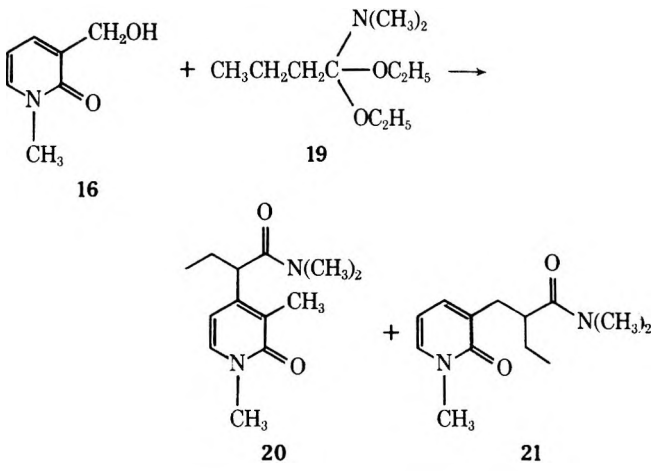
[a] Reported as if all 19. [b] DCB = *o*-dichlorobenzene. [c] Propionic acid was used in all reactions for which a catalyst is reported. [d] Failed to go to completion (~90% complete). [e] Prediction based on GC ratio of 22 to 23. [f] Room temperature.

Not surprisingly, the reaction of 3-hydroxymethyl-1-methyl-2-pyridone (16) with ortho esters and amide acetals gave results quite different from those just described for reactions of pyridinemethanols. Treatment of 16 with triethyl orthoacetate under the conditions described in the literature[10] (propionic acid catalyst, 140°) failed to give any product arising from Claisen rearrangement. Instead, the only stable product was found to be ethyl 1-methyl-2(1*H*)-oxo-3-pyridinepropionate (17a). When the reaction was repeated using 16 and triethyl orthobutyrate the product formed was ethyl α-ethyl-β-[1-methyl-2(1*H*)oxo-3-pyridine]propionate (17b). In view of these results, we again tried to capitalize on the reported[9] reactivity of amide acetals with benzyl alcohol to give Claisen rearranged products. Treatment of 16 with the acetamide diethyl acetal mixture 12, 13 under the conditions described indeed did provide the desired Claisen rearranged product 18 in 82% yield. No amide product analogous to 17 was obtained.




The successful application of this method to 16 encouraged additional experiments in this area. In an analogous reaction, 16 was treated with *N,N*-dimethylbutyramide diethyl acetal (19). In this case, however, a mixture of amides 20 and 21 was obtained in a ratio of 36:64, respectively (Table II, expt 1). From these experiments it is apparent that the products of such a reaction are strongly influenced by substitution on the amide acetal.




As our interest lay in the formation of Claisen rearranged product 20, further experiments were directed toward changing the 20:21 ratio in favor of 20. When the reaction was carried out in excess butyramide acetal with 6 mol % of propionic acid a reversal of the product distribution was observed giving 20 and 21 in a ratio of 63:37 (Table II, expt 2). The cause of this sudden change in the product ratio was not obvious as several factors had been changed from the initial experiment. To further determine which variables affect the product ratio a series of reactions was performed with systematic variation of the solvent, ratio of reactants, temperature, and presence of acid catalyst. The results are summarized in Table II, expt 3–7.

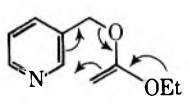
These results clearly show that the single factor most strongly favoring the formation of 20 is the presence of the acid catalyst (expt 2, 4, 6, 7). Variations in temperature influenced only the ratio of products but not the yield, while the presence of a solvent and the reactant ratios appear to have a minimal effect on the product ratio.

The explanation for this unexpected acid influence on the course of the reaction is not known. However, it appears that the formation of 20 and 21 occurs via two distinct intermediates, 22 and 23, respectively, clearly distin-

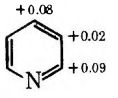
guishable by GC. The interchange between these intermediates appears slow, while their formation from starting material seems rapid. By assuming that the larger peak at 6.5-min retention time is a precursor **22** of **20** and the smaller peak at 5-min retention time is a precursor **23** of **21**, in the acid-catalyzed reactions one can predict with reasonable accuracy the final ratio of **20:21** several hours before the reaction is complete. Examples of these predictions are given under "Remarks" in expt 4 and 6, Table II. In expt 2, 6, and 7 the predicted fraction of **20** was low indicating that extended reaction times favored this product. This may be ascribed to a slow conversion of **23** to **22**, a suggestion supported by the high ratio **20:21** found in expt 7.

## Discussion

The mechanism of the Claisen rearrangement of benzyl vinyl ethers has not been clearly established; however, it appears that electron enrichment of the aromatic ring promotes the rearrangement of benzyl isopropenyl ether.[7] It is interesting that the pyridyl systems undergo rearrangement more readily than the corresponding benzylic compounds, since the $\pi$-electron density of pyridine is less than that of benzene. Perhaps one explanation is that the more electron-deficient pyridine ring promotes migration of the electron-rich ketene acetal moiety, facilitating the rearrangement as shown in **24**.




**24**

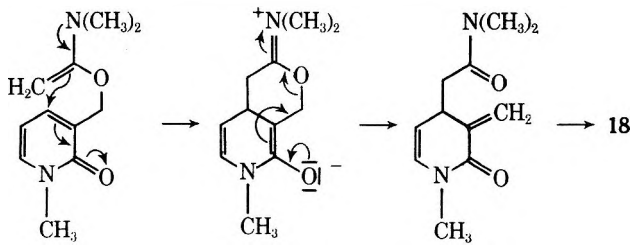



$\pi$-electron densities

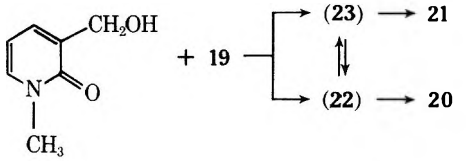
In addition this hypothesis helps explain the fact that the rearrangement is more facile in the 3-pyridyl system than in the 2- and 4-pyridyl systems. Molecular orbital calculations[12] show that the $\pi$-electron density at positions 2 and 4 of the pyridine ring is less than at position 3; therefore, migration of the electron-rich ketene acetal moiety to the 2 and 4 positions would be comparatively more favorable.

Another observation difficult to explain is the apparent 1,4 rearrangement of the ketene acetals formed from **16** and ortho esters. This is no doubt an example of the well-known thermal rearrangement of enol ethers to carbonyl compounds.[2a] Unfortunately the mechanism of this reaction is poorly understood and there is evidence for both radical and nonradical routes. The purely thermal reactions studied have been found second order in the enol ether, but none of these studies have provided a truly appropriate analogy for the present case.

Without some explanation for the formation of the 1,4-rearranged products found in the ortho ester reactions of **16**, it can certainly not be clearly determined why the amide acetal reactions with **16** lead to formation of Claisen products. One suggestion[9] is that the resonance stabilization of the carbonyl function by the dimethylamino group helps to favor product formation. Another possibility is that the enamine intermediate is providing a source of electrons and thereby promoting the rearrangement. In this regard, the observed rearrangement may be considered as Michael addition of an enamine to an $\alpha,\beta$-unsaturated amide followed in a second step by cleavage of the weakened ether bond. The first step would be facilitated by the presence of an acid to protonate the pyridone. The inability of a ketene acetal of **16** to undergo this Michael addition step would preclude the formation of Claisen rearranged products in these cases but does not explain why the 1,4 rearrangement occurs.

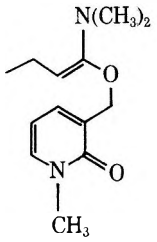



Either this mechanism or a true Claisen rearrangement is consistent with the assumption that the two peaks observed in the reaction of **16** with butyramide acetal may correspond to intermediates **22** and **23** leading to products **20** and **21**, respectively. The data suggest that the initially detected concentrations of **22** and **23** constitute a kinetically controlled distribution of the two products. As the reaction continues, the mixture of **22** and **23** slowly approaches the equilibrium concentration in which **22** is the thermodynamically stable product. Simultaneously with this interchange, **22** and **23** are being converted to **20** and **21** respectively at approximately equal rates. If product formation is more temperature dependent than the **22** $\rightleftarrows$ **23** equilibrium, the proportion of **23** converted to the more stable **22**, and hence to **20**, is increased at lower temperature, as is observed.

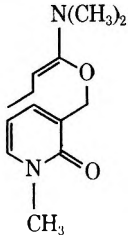



**16**

If one assumes that **22** and **23** are the trans and cis isomers of the ketene azacetal, their going to **20** and **21**, respectively, can be rationalized with molecular models




**22**




**23**

strictly on the basis of steric interactions in the transition state postulated for the Claisen rearrangement or the Michael addition. The trans isomer as **22** can assume either required conformation more readily than can **23** as the cis isomer. On the other hand, the cis isomer can more readily enter a bimolecular reaction in the alkenyl portion of the side chain. This is an observation of possible significance as in one case of thermal 1,4 rearrangement, product and kinetic evidence has been presented for a bimolecular reaction.[2a,13] The only data thus far presented for the relative rates of reaction of cis and trans isomers in the Claisen rearrangement are for $\gamma$-methylallyl phenyl ether, $\gamma$-phenylallyl phenyl ether, and substituted versions thereof. In every case, the data showed the trans isomer to rearrange 1.5–2 times as fast as the cis.[14]

## Experimental Section[15]

**Diethyl(3-pyridylmethyl) Orthoacetate (3). Procedure A.** A solution of 3-hydroxymethylpyridine[16] (**2**, 316.5 mg, 2.9 mmol), triethyl orthoacetate (3.8 g, 23.5 mmol), and propionic acid (1.5 mg, 0.02 mmol) was heated at 140° in a $N_2$ atmosphere while ethanol was continuously removed by distillation. GC analysis [5% Chromosorb W (CW) 20M, 145°, flow rate 160 ml/min] of aliquots

taken at 3-, 6-, and 15-hr intervals were essentially identical, showing one major and three minor peaks with retention times (min) of 3.52, 2.16, 4.44, and 5.20, respectively. Compound 3.52 was isolated by preparative GC (5% CW 20M, 145°) and identified as diethyl(3-pyridylmethyl) orthoacetate (3): NMR ($CCl_4$) $\delta$ 1.17 (6 H, t, $J$ = 7 Hz), 1.45 (3 H, s), 3.54 (4 H, q, $J$ = 7 Hz), 4.59 (2 H, broad d), 7.14 (1 H, m), 7.59 (1 H, m), and 8.40 (2 H, m).

Compound 5.20 had an identical retention time with that of 3-hydroxymethylpyridine. This product was not present in the reaction mixture as determined by NMR, and was apparently formed during GC analysis. The identity of the other minor components, 2.16 and 4.44, was not established.

**Ethyl 3-Methyl-2-pyridylacetate (4) and Ethyl 3-Methyl-4-pyridylacetate (5).** A solution of 3.46 g (31.6 mmol) of 3-hydroxymethylpyridine, 41 g (252 mmol) of triethyl orthoacetate, and 2.58 g (35.0 mmol) of propionic acid was heated at 195° for 5.5 hr under conditions for distillative removal of ethanol in a nitrogen atmosphere. The reaction mixture was chromatographed on Woelm neutral alumina (activity III). Elution with petroleum ether removed several non-pyridine-containing products. Further elution with petroleum ether–ether (1:1) gave 3.03 g (54%) of a mixture of products. GC analysis (5% CW 20M, 145°, flow rate 160 ml/min) showed the mixture to be primarily two components with retention times (min) of 2.94 and 4.20 in a ratio of 56:44, respectively. The products were isolated by preparative gc (10% QF-1, 150°).

Compound 2.94 was assigned the structure 4: ir ($CCl_4$) 1746, 1478, 1178, and 1025 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 1.25 (3 H, t, $J$ = 7 Hz), 2.29 (3 H, s), 3.74 (2 H, s), 4.12 (2 H, q, $J$ = 7 Hz), 7.00 (1 H, m), 7.39 (1 H, m), and 8.29 (1 H, broad d); mass spectrum (70 eV) $m/e$ (rel intensity) 179 (58), 134 (43), 133 (51), 107 (70), 106 (100), 92 (21), 79 (30), 77 (22), 65 (27), 39 (39), 29 (55).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3; N, 7.8. Found: C, 66.8; H, 7.2; N, 7.8.

Compound 4.20 was identified as 5: ir ($CCl_4$) 1746, 1587, 1198, and 1039 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 1.23 (3 H, t, $J$ = 7 Hz), 2.28 (3 H, s), 3.50 (2 H, s), 4.10 (2 H, q, $J$ = 7 Hz), 7.01 (1 H, d, $J$ = 5 Hz), and 8.29 (2 H, m); mass spectrum (70 eV) $m/e$ (rel intensity) 179 (79), 134 (30), 133 (30), 107 (45), 106 (100), 105 (52), 79 (22), 77 (28).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3; N, 7.8. Found: C, 66.8; H, 7.3; N, 7.9.

The identity of a minor component (ca. 6%) with a retention time of 2.60 min was not established.

**Variations of the Claisen Rearrangement of Diethyl(3-pyridylmethyl) Orthoacetate.** The following experiments were conducted using hexadecane as internal standard. The molar response factor for hexadecane was determined to be 0.54.

**A. Catalytic Amount of Propionic Acid.** A solution of 309.5 mg (2.84 mmol) of 3-hydroxymethylpyridine (2), 3.7 g (23 mmol) of triethyl orthoacetate, 2.3 mg (0.03 mmol) of propionic acid, and 70.7 mg (0.31 mmol) of hexadecane (internal standard) was heated at 190° in a nitrogen atmosphere while ethanol was continuously removed by distillation. Gc analysis (5% CW 20M, 145°, flow rate 160 ml/min) of the reaction mixture at 2-, 4-, and 20-hr intervals showed a mixture of 4 and 5 in a combined yield of 20, 31, and 42%, respectively.

**B. Catalytic Amount of *p*-Toluenesulfonic Acid.** A mixture of 218 mg (2.0 mmol) of 3-hydroxymethylpyridine (2), 2.5 g (15.5 mmol) of triethyl orthoacetate, 5.5 mg of *p*-toluenesulfonic acid, and 50.3 mg (0.22 mmol) of hexadecane (internal standard) was treated as in A. After 3 hr, GC analysis indicated that the yield of 4 and 5 was 20%. Continued heating at 190° (ca. 15 hr) results in considerable tar formation without any major improvement in yield.

**C. o-Dichlorobenzene as Solvent.** A mixture of 219.6 mg (2.01 mmol) of 3-hydroxymethylpyridine (2), 2.6 g (16 mmol) of triethyl orthoacetate, 1.5 mg (0.02 mmol) of propionic acid, and 49.2 mg (0.22 mmol) of hexadecane (internal standard) in 3 ml of *o*-dichlorobenzene was heated at reflux (bath temperature 185°) in a nitrogen atmosphere for 48 hr. GC analysis showed a 32% yield of 4 and 5 in a 57:47 ratio.

**Ethyl 2-Methyl-3-pyridylacetate (8).** A solution of 1.60 g (14.7 mmol) of 2-hydroxymethylpyridine (6),[17,18] 19.0 g (117 mmol) of triethyl orthoacetate, and 10.9 mg (0.15 mmol) of propionic acid was heated at 190° for 18 hr in a nitrogen atmosphere, while ethanol was continuously removed by distillation. Chromatography of the reaction mixture on Woelm neutral alumina (activity III), eluting with petroleum ether–ether (1:1), gave two major fractions. The faster moving fraction (0.94 g, 28%) was assigned the structure of the ortho ester 7: NMR ($CCl_4$) $\delta$ 1.19 (6 H, t, $J$ = 6 Hz), 1.53 (3 H, s), 3.59 (4 H, q, $J$ = 6 Hz), 4.73 (2 H, d), 7.21 (1 H, m), 7.48 (2 H, m), and 8.43 (1 H, m).

GC analysis (5% CW 20M, 125°, flow rate 160 ml/min) of the other fraction (0.76 g, 29%) showed only one peak with a retention time (min) of 4.48. This product was isolated by preparative GC (5% QF-1, 150°) and identified as the pyridylacetate 8: ir ($CCl_4$) 3071, 1746, 1436, 1359, 1323, 1140, and 1020 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 1.21 (3 H, t, $J$ = 6 Hz), 2.51 (3 H, s), 3.53 (2 H, s), 4.12 (2 H, q, $J$ = 6 Hz), 7.00 (1 H, m), 7.40 (1 H, m), and 8.31 (1 H, m); mass spectrum (70 eV) $m/e$ (rel intensity) 179 (78), 134 (26), 133 (47), 107 (71), 106 (100), 105 (43), 79 (58), 78 (18), 77 (27), 65 (50), 63 (18), 39 (67).

**Benzyldiethyl Orthoacetate.** A solution of 0.539 g (5.0 mmol) of benzyl alcohol, 6.50 g (40 mmol) of triethyl orthoacetate, and 15 $\mu$l (0.2 mmol) of propionic acid was refluxed in a nitrogen atmosphere for 26.5 hr. GC analysis (5% SE-30, 130°) showed one major peak with a retention time of 7.6 min. This product was isolated by preparative GC and identified as benzyldiethyl orthoacetate: ir ($CHCl_3$) 3020, 1733, 1496, 1450, 1375, 1206, 1152, 1041, 1021, 952, 926, and 684 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.22 (6 H, t, $J$ = 7 Hz), 1.53 (3 H, t, $J$ = 4 Hz), 3.55 and 3.60 (4 H, two overlapping q, $J$ = 7 Hz), 4.61 (2 H, d, $J$ = 4 Hz), and 7.33 (6 H, broad s); mass spectrum (70 eV) $m/e$ 179 (M − 45), 178 (M − 46), 150 (179 − 29), 149 (178 − 29), 132 (M − 92), 108 ($C_6H_5CH_2O$), 107, 105, 104, 91, 79, 77.

**Ethyl β-(1-Methyl-2(1*H*)-oxo-3-pyridine)propionate (17a).** A solution of 139 mg (1.0 mmol) of 1-methyl-3-hydroxymethyl-2-pyridone (16)[16] and 1.31 g (8.1 mmol) of triethyl orthoacetate containing a drop of propionic acid was refluxed for 3 hr in a nitrogen atmosphere. GC analysis (5% QF-1, 185°, flow rate 120 ml/min) showed two major peaks with retention times of 8.5 and 17.0 min. The products were isolated by preparative GC. Compound 8.5 was unstable and was slowly converted to a new material which has not been identified. Compound 17.0 was assigned the structure **17a**: ir ($CHCl_3$) 2950, 1706, 1640, 1586, 1547, 1430, 1391, 1358, 1332, 1310, 1281, 1200, 1176, 1150, 1092, 1030, and 870 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 1.20 (3 H, t, $J$ = 7 Hz), 2.67 and 2.76 (2 H, two overlapping d, $J$ = 7 Hz), 3.54 (3 H, s), 4.14 (2.5 H, q, $J$ = 7 Hz), 4.35–5.26 (0.5 H, m), 6.05 (1 H, t, $J$ = 6 Hz), and 7.00–7.33 (2 H, m).

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.1; H, 7.2; N, 6.7. Found: C, 63.2; H, 7.1; N, 6.5.

**Ethyl α-Ethyl-β-(1-methyl-2(1*H*)-oxo-3-pyridine)propionate (17b).** A mixture of 278 mg (2.0 mmol) of 1-methyl-3-hydroxymethyl-2-pyridone (16)[16] and 2.2 g (16 mmol) of triethyl orthobutyrate[19] containing 0.992 mg (0.125 mmol) of propionic acid was heated at 150° in a nitrogen atmosphere for 8 hr and then left at 25° for 60 hr. GC analysis (5% SE-30) showed two peaks with retention times of 8.0 and 16.0 min. The first product decomposed slowly and its identity was not established. The second product (16 min) was isolated by preparative GC and assigned the structure of **17b**: ir ($CHCl_3$) 3000, 1722, 1650, 1588, 1562, 1460, 1405, 1371, 1320, 1166, 1100, 1030, and 823 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.70–3.00 [11 H total, m, including 0.95 (t, $J$ = 7 Hz), 1.17 (t, $J$ = 7 Hz), and 2.72 (t, $J$ = 2 Hz)], 3.53 (3 H, s), 4.06 (2 H, q, $J$ = 7 Hz), 6.05 (1 H, t, $J$ = 7 Hz), and 7.17 (2 H, d, $J$ = 7 Hz); mass spectrum (70 eV) $m/e$ 237 (M), 222 (M − 15), 208 (M − 29), 205, 192 (M − 45), 176 (M − 61), 164 (M − 73), 163 (M − 74), 162 (M − 75), 148, 134, 123, 122 (M − $CH_3CH_2CHCO_2C_2H_5$).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.8; H, 8.1; N, 5.9. Found: C, 65.7; H, 8.1; N, 5.9.

**Reaction of 3-Hydroxymethylpyridine (2) with *N,N*-Dimethylacetamide Diethyl Acetal (12, 13).** A solution of 2.36 g (21.6 mmol) of 3-hydroxymethylpyridine (2) and 5.51 g of a mixture[20] of *N,N*-dimethylacetamide diethyl acetal (12) and 1-ethoxy-1-dimethylaminoethylene (13) in 30 ml of *o*-dichlorobenzene was refluxed for 18 hr in a nitrogen atmosphere. Fractional distillation afforded 0.589 g at 70–105° (0.05 mm) and 1.25 g at 105–123° (0.05 mm); GC analysis (5% CW 20M, 175°, flow rate 160 ml/min) of the lower boiling fraction showed one major component (75%) with a retention time of 3.28 min. Similar analysis of the higher boiling fraction showed that it contained the 3.28 peak and another peak at 8.35 in a ratio of 53:47, respectively. The yield of 3.28 and 8.35 was 44% in a ratio of 65:35, and the products were isolated by preparative GC (5% CW 20M, 175°).

Compound 3.28 was assigned the structure of amide 14: ir ($CCl_4$) 3009, 1657, 1645 (shoulder), 1437, 1378, and 1119 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 2.37 (3 H, s), 3.01 (6 H, d, $J$ = 16 Hz), 3.80 (2 H, s), 6.98 (1 H, m), 7.38 (1 H, m), and 8.27 (1 H, m); mass spectrum (70 eV) $m/e$ (rel intensity) 178 (61), 134 (36), 107 (100), 106 (67), 72 (85).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.3; H, 7.9; N, 15.7. Found: C, 67.2; H, 7.9; N, 15.5.

Compound 8.35 was identified as amide **15**: ir ($CCl_4$) 3007, 1666, 1381, and 1221 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 2.22 (3 H, s), 2.95 (6 H, s), 3.53 (2 H, s), 6.90 (1 H, m), and 8.27 (2 H, m); mass spectrum (70 eV) *m/e* (rel intensity) 178 (15), 162 (47), 147 (60), 133 (22), 120 (33), 119 (91), 106 (20), 105 (100), 91 (36), 79 (24), 77 (20), 72 (36), 41 (20), 39 (16).

Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.3; H, 7.9; N, 15.7. Found: C, 67.2; H, 7.9; N, 15.5.

***N,N*-Dimethyl(1,3-dimethyl-2(1*H*)-oxo-4-pyridine)acetamide (18).** A solution of 419 mg (3.0 mmol) of 3-hydroxymethyl-1-methyl-2-pyridone (**16**)[16] and 742 mg (4.6 mmol) of a mixture[20] of **12** and **13** in 6 ml of *o*-dichlorobenzene was refluxed under nitrogen for 24 hr. The mixture was chromatographed on silica gel. Elution with chloroform removed the o-dichlorobenzene. Further elution with 3% methanol in chloroform afforded 515 mg (82%) of product. GC analysis (5% QF-1, 220°, flow rate 150 ml/min) showed one major peak with a retention time of 11.0 min. This compound was identified as **18**: ir ($CHCl_3$) 2941, 1623, 1578, 1387, 1235, and 1127 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.10 (3 H, s), 2.97 and 3.02 (6 H together, two s), 3.50 and 3.57 (5 H together, two s), 6.03 (1 H, d, $J$ = 7 Hz), and 7.17 (1 H, d, $J$ = 7 Hz); mass spectrum (70 eV) *m/e* 208 ($M^+$), 189, 175, 174, 161, 160, 146, 132, 128, 118.

Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.4; H, 7.7; N, 13.4. Found: C, 63.6; H, 7.9; N, 13.0.

**Dimethylbutyramide Diethyl Acetal (19).** Triethyloxonium tetrafluoroborate (ca. 0.2 mol) was covered with 20.71 g (0.180 mol) of *N,N*-dimethylbutyramide while stirring mechanically. The salt failed to react until the mixture was heated sufficiently to reflux the liberated ether. Reflux was continued for 1 hr and the reaction mixture formed two layers; the upper was decanted, the lower was dissolved in 50 ml of methylene chloride (distilled from $P_2O_5$), and the solution was placed in a dropping funnel.

To 110 g of dry ethanol was added 5.478 g (0.238 daltons) of sodium. When the sodium had dissolved, the mixture was cooled in ice and to it was added the solution in the dropping funnel over 2 hr. A precipitate formed as the addition proceeded. After standing overnight, the solid was removed by centrifugation, the supernatant was distilled at reduced pressure, and the final oily fraction [bp 60–80° (20 mm)] was redistilled at atmospheric pressure through a 25-cm platinum spiral column. A fraction boiling at 145–153° was found to contain the product mixture and 5% of unreacted dimethylbutyramide: GC (5% QF-1 on CW 80/100, 10 ft × 0.25 in., flow rate 100 ml/min, 150°) retention time 1.1 min; ethanol, 0.9 min; dimethylbutyramide, 2.5 min.

**Reaction of 3-Hydroxymethyl-1-methyl-2-pyridone (16) with *N,N*-Dimethylbutyramide Diethyl Acetal–1-(*N,N*-Dimethylamino)-1-ethoxy-1-butene (19) (see Table II).** The series of reactions reported in Table II was performed by the following general procedure. In a 25-ml three-neck round-bottom flask fitted with condenser, serum cap, and nitrogen atmosphere were placed the 3-hydroxymethyl-1-methyl-2-pyridone,[16] solvent, amide acetal, and catalyst if any. The mixture was then heated at the specified temperature and time. The reactions were analyzed by GC (5% QF-1, 196°, flow rate 200 ml/min) and showed two peaks with retention times of 8.0 and 13.75 min. The products were isolated by preparative GC.

Compound 8.0 was identified as **21**: ir (film) 3550, 2960, 1637, 1585, 1559, 1400, 1222, 1143, 1104, and 760 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 0.87 (3 H, t, $J$ = 7 Hz), 1.13–2.00 (2 H, m), 2.57–3.43 (9 H, m, including singlets at 2.90 and 3.00), 3.54 (3 H, s), 6.05 (1 H, t, $J$ = 7 Hz), and 7.17 (2 H, d, $J$ = 7 Hz); mass spectrum (70 eV) *m/e* 236 ($M^+$), 192, 191 ($M - H - CH_3OCH_3$), 164 [$M - (CH_3)_2NCO$], 163, 162, 148, 122 [$M - (CH_3)_2NC(O)C_2H_6$].

Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.1; H, 8.5; N, 11.8. Found: C, 66.0; H, 8.5; N, 11.8.

Compound 13.75 was assigned the structure **20**: ir (film) 2963, 1632, 1594, 1385, 1229, 1150, and 785 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 2.20 (3 H, s), 2.85 and 2.93 (6 H together, two singlets), 3.50 (3 H, s), 3.72 (1 H, t, $J$ = 7 Hz), 6.16 (1 H, d, $J$ = 7 Hz), and 7.07 (1 H, d, $J$ = 7 Hz); mass spectrum (70 eV) *m/e* 236 ($M^+$), 191 ($M - H - CH_3OCH_3$), 176 (191 − $CH_3$), 164 [$M - CON(CH_3)_2$], 163, 162, 148.

Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.1; H, 8.5; N, 11.8. Found: C, 65.9; H, 8.5; N, 12.0.

**Acknowledgments.** C. R. Costin thanks the National Institutes of Health for a Postdoctoral Fellowship. Valuable experimental assistance was provided by D. S. Jones, P. D. Maestas, and R. K. Y. Ju.

**Registry No.**—**2,** 100-55-0; **3,** 57408-45-4; **4,** 5552-80-7; **5,** 57408-46-5; **6,** 586-98-1; **7,** 57408-47-6; **8,** 3654-30-6; **12,** 19429-85-7; **13,** 816-65-9; **14,** 57408-48-7; **15,** 57408-49-8; **16,** 36721-61-6; **17a,** 57408-50-1; **17b,** 57408-51-2; **18,** 57408-52-3; **19,** 55857-42-6; **20,** 57408-53-4; **21,** 57408-54-5; triethyl orthoacetate, 78-39-7; benzyldiethyl orthoacetate, 57408-55-6; benzyl alcohol, 100-51-6; triethyl orthobutyrate, 24964-76-9; triethyloxonium tetrafluoroborate, 368-39-8; *N,N*-dimethylbutyramide, 760-79-2.

## References and Notes

(1) J. C. Godfrey in "Pyridine and Its Derivatives", Part 3, E. Klingsberg, Ed., Interscience, New York, N.Y., 1962, p 353.
(2) For reviews of the Claisen rearrangement see (a) D. L. Dalrymple, T. L. Kruger, and W. N. White in "The Chemistry of the Ether Linkage", S. Patai, Ed., Interscience, New York, N.Y., 1967; (b) D. S. Tarbell, *Org. React.*, **2,** 1 (1944); (c) A. Jefferson and F. Scheinmann, *Q. Rev., Chem. Soc.*, 391 (1968); (d) D. J. Cram in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, pp 295–303; (e) S. J. Rhoads in "Molecular Rearrangements", Part I, P. de Mayo, Ed., Interscience, New York, N.Y., 1963, p 655.
(3) A. W. Burgstahler, L. K. Gibbons, and S. C. Nordin, *J. Chem. Soc.*, **4986** (1963).
(4) K. B. Wiberg, R. R. Kintner, and E. T. Motell, *J. Am. Chem. Soc.*, **85,** 450 (1963).
(5) B. A. Otter, A. Taube, and J. J. Fox, *J. Org. Chem.*, **36,** 1251 (1971).
(6) (a) T. M. Elkobaisi and W. J. Hickinbottom, *J. Chem. Soc.*, 1873 (1959); (b) *ibid.*, 1286 (1960).
(7) W. J. le Noble and P. J. Crean, *J. Am. Chem. Soc.*, **86,** 1649 (1964).
(8) S. M. McElvain, H. I. Anthes, and S. H. Shapiro, *J. Am. Chem. Soc.*, **64,** 2525 (1942).
(9) A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, **47,** 2425 (1964).
(10) W. S. Johnson, L. Wertheman, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Peterson, *J. Am. Chem. Soc.*, **92,** 741 (1970).
(11) R. K. Hill, R. Soman, and S. Saivada, *J. Org. Chem.*, **37,** 3737 (1972).
(12) R. A. Barnes in "Pyridine and Its Derivatives", Part 1, E. K. Klingsberg, Ed., Interscience, New York, N.Y., 1960, Chapter 1.
(13) M. Colonna and A. Risalti, *Boll. Sci. Fac. Chim. Ind. Bologna,* **10,** 157 (1952); reported in M. J. Kamlet, Ed., "Organic Electronic Spectra Data", Vol. 1, interscience, New York, N.Y., 1960.
(14) (a) E. R. Alexander and R. W. Kluiber, *J. Am. Chem. Soc.*, **73,** 4304 (1951); (b) E. N. Marvell and J. L. Stephenson, *J. Org. Chem.*, **25,** 676 (1960); (c) A. W. Burgstahler, *J. Am. Chem. Soc.*, **82,** 4681 (1960); (d) W. N. White and B. E. Norcross, *ibid.*, **83,** 1968, 3265 (1961); (e) L. D. Huestis and L. J. Andrews, *ibid.*, **83,** 1963 (1961).
(15) Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian T-60 spectrometer; chemical shifts are recorded as $\delta$ units, using tetramethylsilane as internal reference. Mass spectra were obtained on a Varian M-66 or a CEC-103 spectrometer. All boiling points are uncorrected. Elemental analyses were performed by the Microchemical Laboratory, University of California, and Berkeley, Calif.
(16) F. Bohlmann, N. Ottawa, and R. Keller, *Chem. Ber.*, **87,** 162 (1954).
(17) V. Boekelheide and W. L. Linn, *J. Am. Chem. Soc.*, **76,** 1286 (1954).
(18) O. H. Bullitt, Jr., and J. T. Maynard, *J. Am. Chem. Soc.*, **76,** 1370 (1954).
(19) S. M. McElvain and J. W. Nelson, *J. Am. Chem. Soc.*, **64,** 1825 (1942).
(20) H. Meerwein, W. Florian, N. Schon, and G. Stopp, *Justus Liebigs Ann. Chem.*, **641,** 1 (1961).

# Photochemical Codimerization of Benzofurans

Kuniaki Takamatsu, Hong-Son Ryang,* and Hiroshi Sakurai

*The Institute of Scientific and Industrial Research, Osaka University, Suita, Osaka, 565, Japan*

*Received April 7, 1975*

The photochemical codimerization of benzofuran with 2-substituted benzofurans has been examined. Irradiation of benzofuran with 2-(3-pyridyl)benzofuran or 2-phenylbenzofuran resulted in formation of the head-to-tail syn and anti cyclobutane codimers as main products. On the other hand, benzofuran with methyl benzofuran-2-carboxylate on irradiation gave the head-to-head syn codimer in addition to one homodimer of methyl benzofuran-2-carboxylate and two carbonyl compounds. It is suggested that the former proceeds via the excited singlet of benzofuran and the latter involves the excited singlet of methyl benzofuran-2-carboxylate.

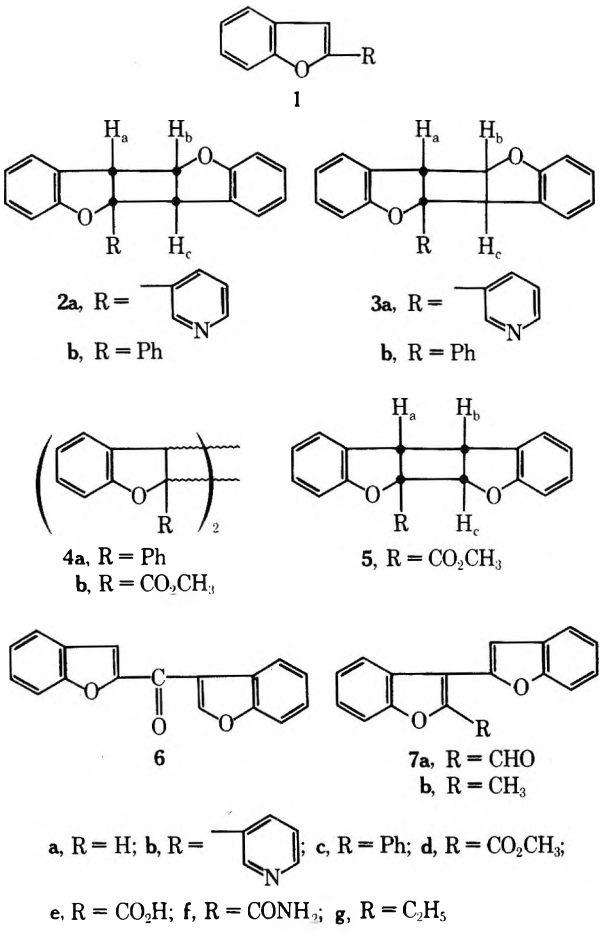
The connection between orientation and multiplicity of excited states in photoinduced dimerizations has attracted a great deal of attention.[1] With regard to the photochemistry of benzofurans, several examples including homodimerization in the presence of triplet sensitizers and addition reactions with carbonyl compounds and dimethylmaleic anhydride have been reported in the literature.[2-7] However, there has been no report on the photoreaction from the excited singlet of benzofurans. In this paper we would like to describe photoinduced codimerization of benzofuran with 2-substituted benzofurans, in which singlet excited states of benzofurans are involved.[8]

## Results and Discussion

All photochemical reactions described herein were carried out with a 350-W high-pressure mercury lamp in a nitrogen atmosphere. The products were isolated by chromatography over silica gel, and the structures were determined by analytical and spectroscopic data.

Irradiation of an acetonitrile solution of benzofuran (**1a**) and 2-(3-pyridyl)benzofuran (**1b**), derived from photoreaction of **1a** with 3-iodopyridine, gave two codimers **2a** and **3a** in good yields. The stereochemistry of these codimers is assigned mainly on the basis of their NMR spectra. The 100-MHz NMR spectrum of **2a** ($CCl_4$) showed three cyclobutane protons at $\delta$ 4.48 ($J$ = 6.0 and 3.8 Hz, $H_a$ or $H_c$), 4.59 ($J$ = 6.5 and 3.8 Hz, $H_a$ or $H_c$), and 5.54 ($J$ = 6.5 and 6.0 Hz, $H_b$). The large two coupling constants of $J_{ab}$ and $J_{bc}$ suggest that these three protons have a cis orientation. Furthermore, the observed strong upfield shift of the aromatic protons of the two benzofuran moieties can be attributed to long-range shielding by the $\pi$ electrons of the aromatic rings. Thus, **2a** was identified as the head-to-tail syn codimer. The large long-range coupling constant ($J_{ac}$) observed in **2a** relative to that in the literature (0.5–2.0 Hz) may be due to mutual repulsion of the two benzofuran moieties which results in a conformation permitting effective coupling through the cyclobutane ring.[9] The NMR spectrum of **3a** ($CCl_4$) contained signals of three methine protons at $\delta$ 4.40 ($J$ = 1.7 and <1.0 Hz, $H_a$), 4.57 ($J$ = 6.5 and <1.0 Hz, $H_c$), and 5.06 ($J$ = 6.5 and 1.7 Hz, $H_b$). In addition, the aromatic protons of the pyridine ring and one phenyl ring were shifted upfield from their normal positions. Thus, **3a** was assigned as the head-to-tail anti codimer. Pyrolysis of **2a** and **3a** at 220–240° in a degassed Pyrex tube leads in both cases to **1a** and **1b**.

Irradiation of a solution of **1a** and 2-phenylbenzofuran (**1c**) in acetonitrile through Pyrex glass afforded two codimers **2b** and **3b** and one homodimer **4a** as main products.[10] The stereochemistry of **2b** and **3b**, in analogy with **2a** and **3a**, is assigned mainly on the basis of their NMR spectra. The NMR spectrum of **2b** ($CDCl_3$) showed three methine protons at $\delta$ 4.43 ($J$ = 6.2 and 4.0 Hz, $H_a$ or $H_c$), 4.46 ($J$ = 7.6 and 4.0 Hz, $H_a$ or $H_c$), and 5.49 ($J$ = 7.6 and 6.2 Hz, $H_b$), eight aromatic protons of the two benzofuran moieties at $\delta$ 6.2–7.1, and five aromatic protons at $\delta$ 7.3–7.6. The NMR spectrum of **3b** ($CDCl_3$) contained signals of three cyclobutane protons at $\delta$ 4.40 ($J$ = 2.0 and 1.0 Hz, $H_a$), 4.46 ($J$ = 7.0 and 1.0 Hz, $H_c$), and 5.10 ($J$ = 7.0 and 2.0 Hz, $H_b$), and aromatic protons of the phenyl group and one of the two benzofuran moieties at higher field than the normal positions. These NMR spectra suggest that **2b** is the head-to-tail syn codimer and **3b** is the head-to-tail anti codimer. Pyrolysis of **2b** and **3b** at 220–240° gave **1a** and **1c** in quantitative yield.




Irradiation of an acetonitrile solution of **1a** and methyl benzofuran-2-carboxylate (**1d**) through Pyrex glass mainly gave a homodimer **4b**,[11] a codimer **5**, a ketone **6**,[12] and an aldehyde **7a**.[12] None of the other possible homodimers and codimers was detectable. **5** was identified as the head-to-head syn codimer on the basis of its NMR spectrum ($CDCl_3$): three methine protons at $\delta$ 4.42 ($J$ = 8.0 and 6.5 Hz, $H_b$), 4.49 ($J$ = 8.0 and 3.8 Hz, $H_a$), and 5.63 ($J$ = 6.5 and 3.8 Hz, $H_c$) as an ABX spectrum, one methyl group at $\delta$

3.80, and eight aromatic protons with the strong upfield shift at δ 6.6–7.0. Evidence for the structure **7a** has been obtained by the Wolff–Kishner reduction of **7a** to **7b**.

Solutions of **1a** and other 2-substituted benzofurans (**1e–g**) were also irradiated, but no detectable amount of cyclobutane dimers was obtained.

In order to try to clarify the excited state which is involved in these photocodimerization reactions, sensitization and quenching experiments were carried out. When an acetonitrile solution of **1a** (0.2 *M*) and **1c** (0.05 *M*) was irradiated through an *n*-hexane solution of naphthalene which cut out wavelengths shorter than 320 nm and assured absorption of **1c** alone, only **4a** was obtained as a main product. Irradiation (366 nm) of a solution in the presence of acetophenone (0.1 *M*) or benzophenone (0.1 *M*) as triplet sensitizers gave no detectable amount of codimers **2b** and **3b**. Furthermore, the formation of **2b** and **3b** was not quenched by 1,3-pentadiene (0.1 *M*), known as a triplet quencher. Similar results were obtained in the case of codimerization of **1a** with **1b**. These results suggest that the codimerization of **1a** with **1b** or **1c** proceeds via the excited singlet **1a**. The photocodimerization of **1a** and **1d** was also examined. When an acetonitrile solution of **1a** and **1d** was irradiated with 313-nm radiation, absorbed only by **1d**, the same products as obtained in the case of irradiation through Pyrex glass were mainly formed. The formation of these compounds was neither photosensitized by triplet sensitizer (acetophenone or benzophenone) nor quenched by 1,3-pentadiene. These results indicate that **5** is formed via addition of the excited singlet **1d** to the ground state **1a**, which contrasts with the case of the codimerization of **1a** with **1b** or **1c**.

With regard to the photochemical codimerization of **1a** with 2-substituted benzofurans, our present results indicate that the reactions obviously depend upon the benzofurans used, and two kinds of codimerization exist. One case is the codimerization of the excited singlet **1a** with the ground state of aryl-substituted benzofurans **1b** and **1c**, which leads to the head-to-tail syn and anti codimers. The other is the codimerization of the excited singlet **1d** with the ground state **1a**, which gives the head-to-head syn codimer. At the present state, it is difficult to state clearly the correlation between the orientation of addition and multiplicity of the excited states in the photodimerization of benzofurans. However, in view of the high substrate and orientational selectivity noted in these experimental results, it might be reasonable to consider that the reactions involve initial formation of a π complex between the excited singlet of one molecule and the ground state of another.[13]

## Experimental Section

Melting points are uncorrected. Nuclear magnetic resonance spectra were determined on a JEOL JNM JS-100 spectrometer using tetramethylsilane as a internal standard. Mass spectra were performed on a Hitachi Perkin-Elmer RMF-60 mass spectrometer. Infrared spectra were obtained on a Japan Spectroscopic DS-402G infrared spectrophotometer with samples prepared as KBr pellets.

**Photoreaction of 3-Iodopyridine with Benzofuran (1a).** A solution of 3-iodopyridine (4.1 g, 20 mmol) and **1a** (9.5 g, 80 mmol) in acetonitrile (180 ml) was prepared in a Pyrex doughnut-type vessel. The solution was flushed with nitrogen for several minutes before being irradiated. Irradiation was carried out using a 350-W high-pressure mercury lamp in a quartz immersion well with water-cooled jacket at room temperature for 48 hr. After removal of solvent in vacuo, the residue was dissolved in diethyl ether and washed with a diluted $NH_4OH$ solution. Evaporation of diethyl ether and recovery of unreacted **1a** and 3-iodopyridine (2.24 g) in vacuo afforded a crude product mixture (1.7 g). Chromatography on a column of silica gel (Merck) with benzene–diethyl ether (10:1) as eluent gave four fractions. The first fraction afforded **3a** (910 mg, 32% on the basis of consumed 3-iodopyridine) as colorless needles: mp 150° (from benzene); *m/e* 313 ($M^+$), 195, 166, 139, and 118; ir (KBr) 1592, 1480, 1460, 1420, 1235, 1004, 905, 763, 752, and 712 $cm^{-1}$; NMR ($CCl_4$) δ 4.40 (1 H, dd, *J* = 1.7 and <1.0 Hz), 4.57 (1 H, dd, *J* = 6.5 and <1.0 Hz), 5.06 (1 H, dd, *J* = 6.5 and 1.7 Hz), 6.40–6.68 (2 H, m), 6.12–6.72 (5 H, m), 7.20 (1 H, dd, *J* = 8.0 and 1.8 Hz), 7.27 (1 H, dd, *J* = 8.0 and 1.8 Hz), 7.35 (1 H, dt, *J* = 7.0 and 1.7 Hz), 8.31 (1 H, dd, *J* = 4.5 and 1.7 Hz), and 8.40 (1 H, d, *J* = 1.7 Hz).

Anal. Calcd for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.83; N, 4.47. Found: C, 80.39; H, 4.59; N, 4.18.

The second fraction from the column gave **1b** (90 mg, 5%) as colorless needles: mp 78° (from benzene); *m/e* 195 ($M^+$), 166, and 139; ir (KBr) 1578, 1445, 1253, 1163, 1110, 915, 797, 746, and 700 $cm^{-1}$; NMR ($CCl_4$) δ 7.03 (1 H, s), 7.12–7.36 (2 H, m), 7.27 (1 H, dd, *J* = 7.5 and 4.2 Hz), 7.44 (1 H, d, *J* = 8.0 Hz), 7.48 (1 H, d, *J* = 8.0 Hz), 8.03 (1 H, dt, *J* = 7.5 and 1.8 Hz), 8.46 (1 H, dt, *J* = 4.2 and 1.8 Hz), and 9.00 (1 H, d, *J* = 1.8 Hz).

Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65, N, 7.17. Found: C, 79.92; H, 4.51; N, 7.20.

The third fraction gave a mixture of pyridylbenzofuran isomers (90 mg, 5%): bp 120–130° (6 mmHg) (bath temperature); *m/e* 195 ($M^+$), 166, and 139. The NMR spectrum ($CCl_4$) of the mixture showed one major component (~85%): δ 6.84 (1 H, dd, *J* = 2.2 and 1.0 Hz), 7.28 (1 H, dd, *J* = 7.8 and 4.5 Hz), 7.18–7.34 (3 H, m, AB part of the ABX system), 7.39 (1 H, dt, *J* = 7.8 and 1.0 Hz, X part of the ABX system), 7.61 (1 H, d, *J* = 2.2 Hz), 7.80 (1 H, dt, *J* = 7.5 and 1.8 Hz), 8.51 (1 H, dd, *J* = 4.5 and 1.8 Hz), and 8.76 (1 H, d, *J* = 1.8 Hz). These NMR signals are probably attributed to 4-(3-pyridyl)benzofuran. Repeated recrystallizations of the HCl salt of the mixture from methanol–water afforded a white solid, mp 104°.

The fourth fraction gave **2a** (600 mg, 21%): mp 113° (from benzene); *m/e* 313 ($M^+$), 195, 166, 139, and 118; ir (KBr) 1592, 1480, 1460, 1235, 1062, 880, 752, and 712 $cm^{-1}$; NMR ($CCl_4$) δ 4.44 (1 H, dd, *J* = 6.0 and 3.8 Hz), 4.59 (1 H, dd, *J* = 6.5 and 3.8 Hz), 5.54 (1 H, dd, *J* = 6.5 and 6.0 Hz), 6.31 (1 H, dd, *J* = 8.0 and 1.5 Hz), 6.35 (1 H, dd, *J* = 8.0 and 1.5 Hz), 6.64 (1 H, dd, *J* = 8.0 and 7.0 Hz), 6.82 (2 H, dd, *J* = 8.0 and 7.0 Hz), 7.00 (1 H, dd, *J* = 7.0 and 1.5 Hz), 7.05 (1 H, dd, *J* = 7.0 and 1.5 Hz), 7.26 (1 H, dd, *J* = 7.5 and 4.5 Hz), 7.84 (1 H, dt, *J* = 7.5 and 1.8 Hz), 8.52 (1 H, dd, *J* = 4.5 and 1.8 Hz), and 8.81 (1 H, d, *J* = 1.8 Hz).

Anal. Calcd for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.83; N, 4.47. Found: C, 80.39; H, 4.57; N, 4.29.

Pyrolysis of **2a** (310 mg, 1 mmol) at 220–240° in a degassed Pyrex tube for 30 min, distillation of **1a**, and sublimation at 90–100° (6 mmHg) gave **1b** (190 mg). Similarly, pyrolysis of **3a** at 220–240° afforded **1b** quantitatively.

**Photoreaction of 1a and 2-(3-Pyridyl)benzofuran (1b).** A solution of **1a** (240 mg, 2 mmol) and **1b** (100 mg, 0.5 mmol) in acetonitrile (100 ml) was irradiated in a Pyrex vessel for 12 hr using a 350-W high-pressure mercury lamp. After removal of the solvent and **1a** in vacuo, sublimation of the residue at 150–160° (0.2 mmHg) gave 280 mg of a mixture of the codimer **2a, 3a**. The ratio of the codimers was determined by an NMR spectrum of the mixture (**2a: 3a** = 2:3).

**Photoreaction of 1a and 2-Phenylbenzofuran (1c).** A solution of **1a** (2.43 g, 20 mmol) and **1c** (1.0 g, 5.2 mmol) in acetonitrile (180 ml) in a Pyrex vessel was irradiated for 70 hr. During this time, colorless needles of **4a** (270 mg, 14% based on consumed **1c**) separated from the solution: mp 287–288°; *m/e* 388 ($M^+$), 194, and 165; NMR ($Me_2SO$-$D_6$) δ 5.04 (2 H, s), 6.64 (2 H, m), 7.00 (2 H, m), 7.10–7.55 (10 H, m).

Anal. Calcd for $C_{28}H_{20}O_2$: C, 86.57; H, 5.19. Found: C, 86.60; H, 5.10.

Evaporation of the filtrate to dryness and distillation of unreacted **1a** in vacuo gave a crude solid (1.26 g). Chromatography on a column of silica gel with *n*-hexane–benzene (6:1) as eluent gave three fractions. The first fraction gave **1c** (40 mg, 2 mmol). The second fraction afforded **3b** (1.06 g, 68%): mp 153–154° (from benzene); *m/e* 312 ($M^+$), 194, and 165; ir (KBr) 1594, 1480, 1460, 1245, 1002, 900, 745, and 700 $cm^{-1}$; NMR ($CDCl_3$) δ 4.40 (1 H, dd, *J* = 2.0 and 1.0 Hz), 4.60 (1 H, dd, *J* = 7.0 and 1.0 Hz), 5.11 (1 H, dd, *J* = 7.0 and 2.0 Hz), 6.56 (1 H, m), 6.74–7.06 (4 H, m), and 7.08–7.42 (7 H, m).

Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.90; H, 5.43.

The third fraction gave **2b** (190 mg, 12%): mp 130° (from diethyl ether); *m/e* 312 ($M^+$), 194, and 165; ir (KBr) 1586, 1570, 1455, 1220, 1060, 870, 793, 745, and 695 $cm^{-1}$; NMR ($CDCl_3$) δ 4.43 (1 H,

dd, $J$ = 6.2 and 4.0 Hz), 4.64 (1 H, dd, $J$ = 7.6 and 4.0 Hz), 5.49 (1 H, dd, $J$ = 7.6 and 6.2 Hz), 6.40 (2 H, d, $J$ = 7.5 Hz), 6.68 (2 H, d, $J$ = 6.7 Hz), 7.11 (2 H, d, $J$ = 6.7 Hz), and 7.24–7.68 (5 H, m).

Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.90; H, 5.43.

**Photoreaction of 1a with Methyl Benzofuran-2-carboxylate (1d).** A solution of **1a** (4.37 g, 37 mmol) and **1d** (1.6 g, 91 mmol) in acetonitrile (180 ml) was irradiated in a Pyrex vessel for 62 hr. After removal of solvent and unreacted **1a** in vacuo, chromatography of the residue on a column of silica gel gave five fractions. The first fraction (*n*-hexane–benzene, 10:1, as eluent) afforded **1d** (450 mg, 2.5 mmol). The second fraction (*n*-hexane–benzene, 10:1, as eluent) yielded **7a** (240 mg, 14%): mp 202–203° (from *n*-hexane–benzene); *m/e* 262 ($M^+$), 234, 205, and 176; ir (KBr) 1662, 1615, 1385, 1340, 1166, 1113, 1077, 876, 815, and 755 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.20–7.70 (7 H, m). 7.50 (1 H, s), 8.28 (1 H, m), and 10.88 (1 H, s).

Anal. Calcd for $C_{17}H_{10}O_3$: C, 77.85; H, 3.84. Found: C, 77.66; H, 3.59.

The third fraction (*n*-hexane–benzene, 10:1, as eluent) gave **6** (290 mg, 17%): mp 157–158° (from benzene); *m/e* 262 ($M^+$), 245, 234, 205, 145, and 117; ir (KBr) 1662, 1620, 1387, 1340, 1164, 1110, 1075, 870, 810, and 750 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.30–7.80 (7, H, m), 7.62 (1 H, s), 8.35 (1 H, m), and 8.84 (1 H, s).

Anal. Calcd for $C_{17}H_{10}O_3$: C, 77.85; H, 3.84. Found: C, 77.60; H, 3.59.

The fourth fraction (benzene as eluent) afforded **5** (540 mg, 28%): mp 99° (from benzene–diethyl ether); *m/e* 294 ($M^+$), 176, 145, 118, and 89; ir (KBr) 1750, 1476, 1460, 1232, 1126, 835, 755, and 742 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 3.80 (3 H, s), AB part of the ABX spectrum at 4.42 ($J$ = 8.0 and 6.6 Hz) and 4.49 ($J$ = 8.0 and 3.8 Hz), X part of the ABX spectrum at 5.63 (1 H, dd, $J$ = 6.6 and 3.8 Hz), and 6.4–7.0 (8 H, m).

Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.46; H, 4.80. Found: C, 73.18; H, 4.77.

The fifth fraction (diethyl ether as eluent) yielded **4b** (160 mg, 7%): mp 166° (from benzene–diethyl ether); *m/e* 352 ($M^+$), 176, 145, 118, and 89; ir (KBr) 1765, 1730, 1476, 1460, 1430, 1230, 1130, 1075, 1042, 1025, 982, 845, and 750 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 3.80 (6 H, s), 4.68 (3 H, s), and 6.5–7.0 (8 H, m).

Anal. Calcd for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found: C, 68.29; H, 4.38.

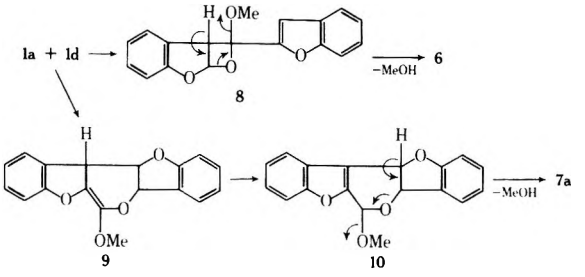
**Wolff–Kishner Reduction of 7a.** A mixture of **7a** (20 mg, 0.077 mmol), potassium hydroxide (50 mg), 90% hydrazine hydrate (50 mg), and diethylene glycol (5 ml) was heated to reflux for 1 hr. After refluxing, water was removed and refluxing was continued for an additional 2 hr. The mixture was then cooled and extracted with benzene. Evaporation of the dried solution and sublimation of the residue at 100–110° (6 mmHg) gave **7b** (17 mg, 88%): mp 126–127° (from *n*-hexane); *m/e* 248 ($M^+$); NMR ($CCl_4$) $\delta$ 2.60 (3 H, s), 7.04 (1 H, s), 7.10–7.30 (4 H, m), and 7.30–7.60 (4 H, m).

Anal. Calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.87. Found: C, 82.40, H, 4.90.

**Registry No.**—**1a**, 271-89-6; **1b**, 7035-06-5; **1c**, 1839-72-1; **1d**, 1646-27-1; **2a**, 52437-49-7; **2b**, 57237-76-0; **3a**, 52169-67-2; **3b**, 57287-76-0; **4a**, 57237-77-1; **4b**, 57237-78-2; **5**, 57237-79-3; **6**, 57237-80-6; **7a**, 57237-81-7; **7b**, 57237-82-8; 3-iodopyridine, 1120-90-7; 4-(3-pyridyl)benzofuran, 57237-83-9.

## References and Notes


(1) D. J. Trecker in "Organic Photochemistry", Vol. 2, O. L. Chapman, Ed., Marcel Dekker, New York, N.Y., 1969, pp 62–116.
(2) C. H. Krauch, S. Farid, and G. O. Schenck, *Chem. Ber.*, **98**, 3102 (1965).
(3) C. H. Krauch, W. Metzner, and G. O. Schenck, *Chem. Ber.*, **99**, 1723 (1966).
(4) C. D. DeBoer, *Tetrahedron Lett.*, 4977 (1971).
(5) S. Farid and S. E. Shealer, *J. Chem. Soc., Chem. Commun.*, 296 (1973).
(6) Y. Kawase, S. Yamaguchi, H. Ochiai, and H. Hirota, *Bull. Chem. Soc. Jpn.*, **47**, 2660 (1974).
(7) S. Farid, S. E. Hartman, and C. D. DeBoer, *J. Am. Chem. Soc.*, **97**, 808 (1975).
(8) For preliminary accounts of a portion of this work, see K. Takamatsu, H.-S. Ryang, and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 903 (1973).
(9) L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Oxford, 1969, p 334.
(10) The decrease in the yield of **2b** and the increase in the yield of **3b** were observed as irradiation time increased. Irradiations of **2b** and **3b** in acetonitrile through Pyrex glass resulted in formation of **1a** and **1c**. Thus, the observed variation in the ratio of **2b:3b** is probably due to the effective photodecomposition of **2b** relative to that of **3b**.
(11) The stereochemistry of **4b**, as well as that of **4a**, has not yet been established. However, **4b** is assigned as one of two possible syn dimers on the basis of its NMR spectrum, in which the strong upfield shift of the aromatic protons was observed. The formation of only one of four possible homodimers from **1d** shown in our present experiments contrasts with the results of the triplet sensitized homodimerization of **1d**, in which three isomers were obtained.[4]
(12) The formation of **6** can be envisaged as occurring via an oxetane intermediate **8** followed by elimination of MeOH. Similarly, a plausible pathway for the formation of **7a** is as follows: 1,4 cycloaddition of **1d** to **1a** followed by aromatization affords an acetal intermediate **10** that may readily lose MeOH to give **7a**.



(13) The possibility of the ground state charge-transfer complex between these benzofurans should be excluded by absorption studies in which no charge-transfer band was observed. In our preliminary mechanistic studies, we found that the fluorescence of **1a** (in cyclohexane) is completely quenched by **1c** ($10^{-3}$ *M*) at room temperature. However, no new emission suggesting the existence of an exciplex has been observed.


# Intramolecular Reorganization of Some Unsaturated 2*H*-Azirines[1]


Albert Padwa,* Joel Smolanoff, and Alan Tremper

*Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14214*


*Received August 12, 1975*

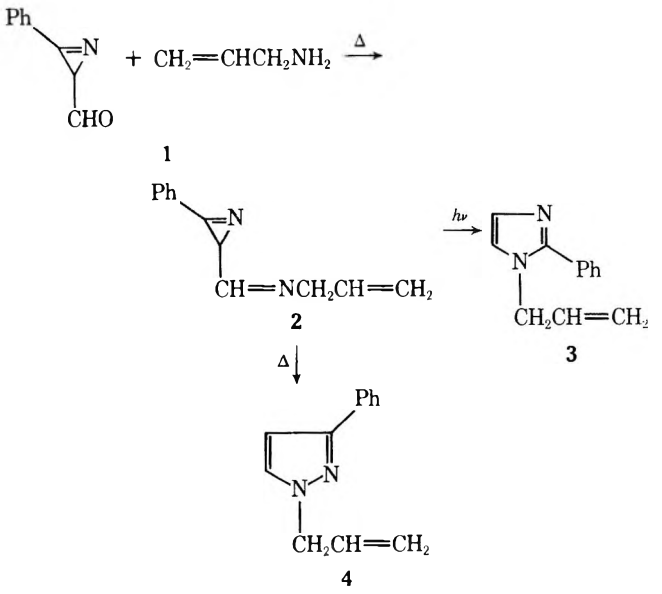

The thermal and photochemical expansion reactions of several unsaturated 2*H*-azirines have been examined. The azirines undergo thermal rearrangement by rupture of the C–N single bond to give a butadienyl nitrene which undergoes cyclization followed by a [1,5]-sigmatropic migration and subsequent tautomerization. The butadienyl nitrene was also found to insert into a neighboring allylic methyl group and the nitrene could also be trapped when the thermolysis was carried out in the presence of tris(dimethylamino)phosphine. The azirine derivatives were found to undergo photochemical reorganization via transient nitrile ylide intermediates which can be trapped with external dipolarophiles.


Previous papers from this laboratory have established that arylazirines undergo irreversible ring opening on electronic excitation to give nitrile ylides as reactive intermediates.[2–6] These species can be intercepted with a variety of

dipolarophiles to form five-membered rings.[1-7] As a result of these early studies, we became interested in determining whether the cycloaddition reaction would occur when the dipolarophile and the azirine ring were constrained to be within the same molecule. In a recent paper we reported that the intramolecular photochemical and thermal cycloadditions of 2-vinyl substituted 2*H*-azirines do indeed take place, the reactions providing clean transformations for the synthesis of five-membered nitrogen-containing heterocycles.[8] This study has now been extended to include other polyunsaturated 2*H*-azirines. The results of this investigation are reported in the present paper.

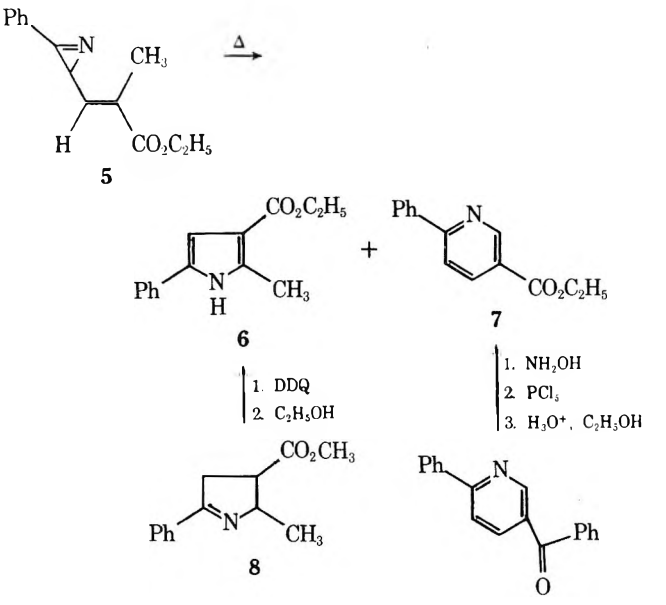
### Results and Discussion

2-Formyl-3-phenyl-2*H*-azirine-*N*-allylimine (**2**) was readily prepared by treating 2-formyl-3-phenyl-2*H*-azirine (**1**) with allyl amine in benzene which contained a trace of *p*-toluenesulfonic acid. Photolysis of azirine **2** in benzene afforded 2-phenyl-*N*-allylimidazole (**3**) as the only identifiable product in 85% yield. The structure of **3** is based on analytical and infrared, NMR, and mass spectral data as well as by comparison with an authentic sample synthesized by heating a mixture of 2-phenylimidazole with allyl chloride in the presence of sodium hydroxide. Thermolysis of azirine **2** was found to give *N*-allyl-3-phenylpyrazole (**4**)




as the exclusive thermal product. The structure of pyrazole **4** was readily established by comparison with an authentic sample prepared from the reaction of 3-phenylpyrazole with allyl bromide.

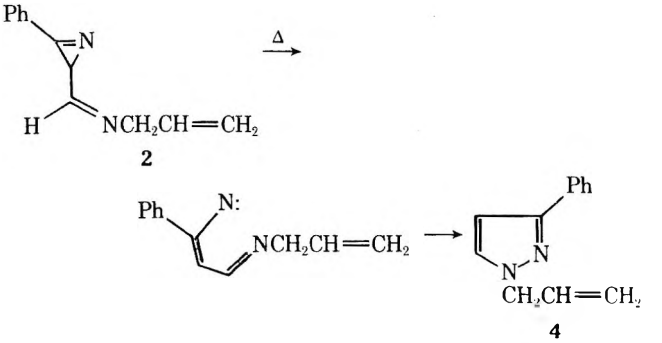
Attention was next turned to the thermal and photochemical behavior of ethyl 3-phenyl-2*H*-azirine-2-(2-methylacrylate) (**5**). This material was formed in high yield from the reaction of **1** with methylcarboethoxymethylenetriphenylphosphorane in benzene at 80°. Heating azirine **5** for 10 hr in xylene at 140° gave a mixture of two products. Separation of the mixture by thick layer chromatography afforded 2-methyl-3-carboethoxy-5-phenylpyrrole (**6**), mp 112–113° (60%), and 2-phenyl-5-carboethoxypyridine (**7**), mp 50–51° (40%). The structure of pyrrole **6** was established from its characteristic spectral data (see Experimental Section) and was further confirmed by its unequivocal synthesis from 2-phenyl-4-carbomethoxy-5-methyl-$\Delta^1$-pyrroline (**8**) by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) followed by transesterification with ethanol. The spectroscopic properties of pyridine **7** were perfectly consistent with the assigned structure (see Experimental Section). Further proof of structure **7** was obtained by comparison with an authentic sample.[9]

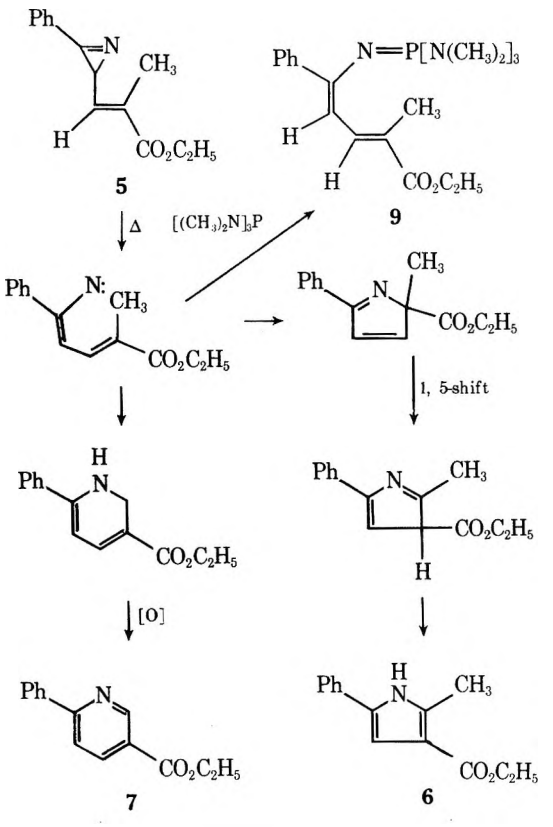



The thermal transformations observed with these systems can best be rationalized in terms of an equilibration of the 2*H*-azirine with a transient vinyl nitrene which subsequently rearranges to the final product. Several examples are available in the literature which provide good analogy for the cyclization of a butadienyl nitrene to a five-membered ring.[10,11]

The rearrangement of azirine **5** to pyrrole **6** is envisaged to occur by a related cyclization followed by a [1,5]-sigmatropic carboethoxy shift and subsequent tautomerization. The presumed carboethoxy shift in this reaction resembles the Van Alphen rearrangement[12] where 3,3,4,5-tetrasubstituted pyrazolenines rearrange into N-substituted pyrazoles, a reaction which was reported to be an uncatalyzed thermal rearrangement.[13] Recently, other examples of the pyrazolenine rearrangement were reported by Dürr and Sergio[14] and by Franck-Newmann and Buchecker,[15] who observed migrations of ester, acyl, and cyano groups which they also explained in terms of [1,5]-sigmatropic migrations.

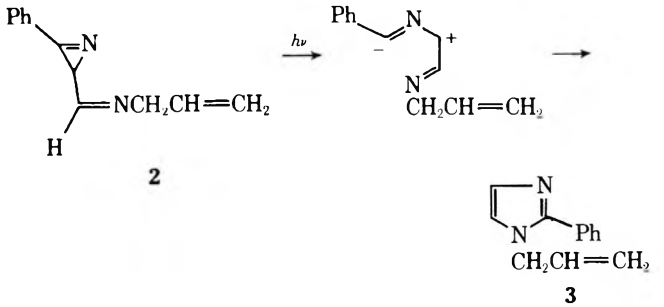
The formation of 2-phenyl-5-carboethoxypyridine (**7**) can be postulated to arise by insertion of the butadienyl nitrene into the neighboring allylic methyl group followed by oxidation of the transient dihydropyridine. Such a reaction pathway is supported by the fact that when the thermolysis of **5** was carried out in the presence of tris(dimethylamino)phosphine, the yield of both **6** and **7** was significantly diminished. Under these conditions, a new compound was obtained and identified as a 1:1 adduct of **5** and tris(dimethylamino)phosphine (i.e., structure **9**). Nishiwaki and



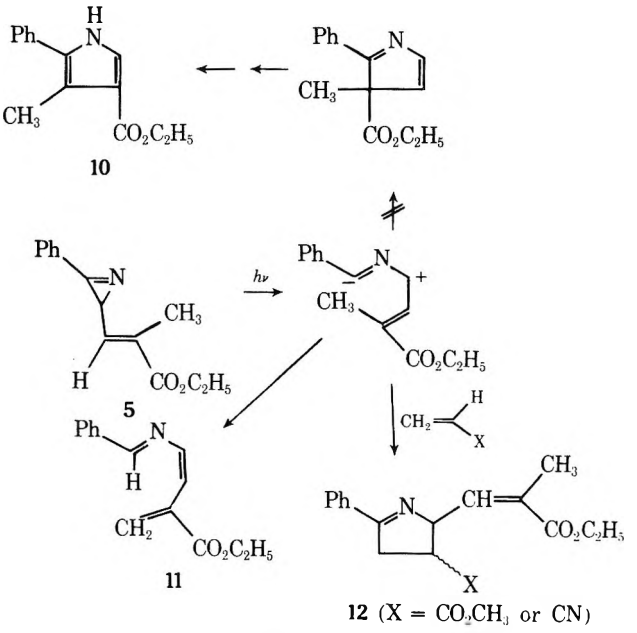


co-workers had previously demonstrated that vinyl nitrenes can be generated and trapped with phosphines during the thermolysis of substituted 2*H*-azirines.[16] Their results provide excellent precedence for the formation of structure **9**.

The photoisomerization of azirine **2** to 2-phenyl-*N*-allylimidazole (**3**) is explicable on the basis of a ring opening to

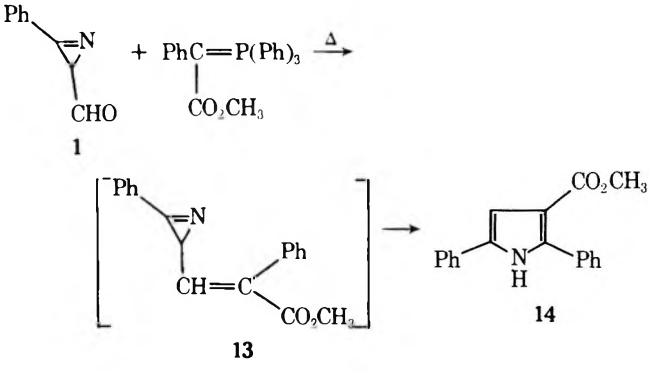


a nitrile ylide which subsequently undergoes intramolecular reorganization to the observed imidazole. Since the photolysis of 2*H*-azirines generally produces nitrile ylides, we anticipated the formation of 2-phenyl-3-methyl-4-carboethoxypyrrole (**10**) from the irradiation of azirine **5**. This pyrrole was expected to be formed by intramolecular reorganization of the initially generated nitrile ylide followed by a [1,5]-sigmatropic carboethoxy migration and subsequent tautomerization. However, all attempts to detect this pyrrole in the crude photolysate failed. Instead, the irradiation of **5** led to a complex mixture of products which resisted all attempts at purification. The crude NMR spectrum of the photolysate showed the presence of imine **11**, which can be envisaged to be formed by an intramolecular hydrogen transfer reaction. When the irradiation of **5** was carried out in the presence of methyl acrylate, a mixture of cis and trans cycloadducts **12** was formed in high yield. Similar results were obtained when acrylonitrile was used



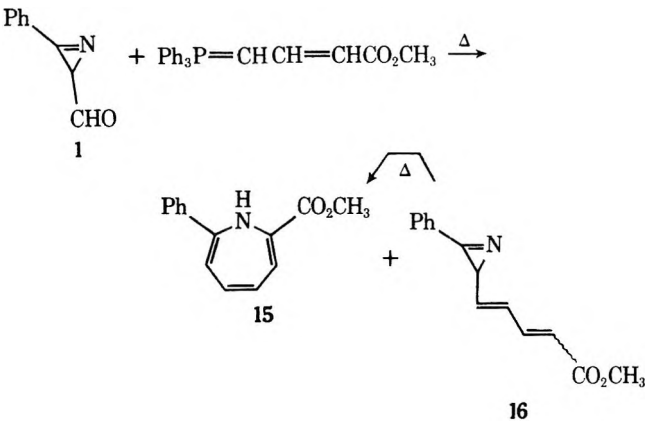
as the dipolarophile. The stereochemical assignments of the cycloadducts were made on the basis of the NMR data (see Experimental Section). The chemical shifts of the carbomethoxy groups are in the same direction as was previously observed for *cis*- and *trans*-2,5-diphenyl-4-carbomethoxy-$\Delta^1$-pyrrolines.[3] The formation of the cycloadducts and the reduction in the yield of the other products formed from the irradiation of **5** strongly argue for the involvement of a nitrile ylide in the photolysis of azirine **5**.

We next investigated the possibility of obtaining azirine **13** by treating 2-formyl-3-phenyl-2*H*-azirine (**1**) with phenylcarbomethoxymethylenetriphenylphosphorane. Photoly-

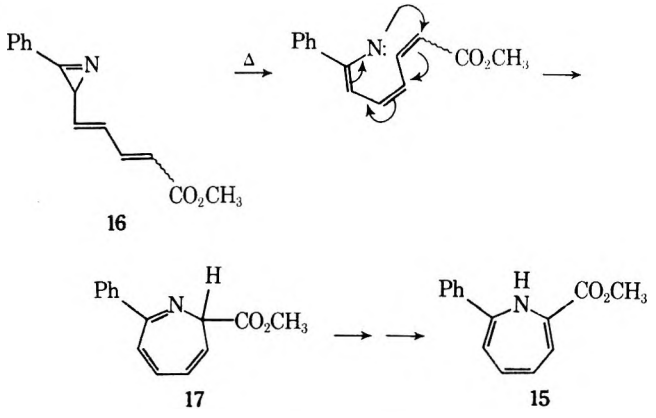


sis of this azirine would avoid the problem of an intramolecular hydrogen transfer. Unfortunately, in order to achieve the desired Wittig reaction between **1** and phenylcarbomethoxytriphenylphosphorane, it was necessary to use elevated temperatures. Under these conditions, we could only isolate 2,5-diphenyl-3-carbomethoxypyrrole (**14**). The formation of this pyrrole presumably proceeds through the intermediacy of azirine **13** followed by C–N ring opening and cyclization of the resulting vinyl nitrene in the same manner as had been previously observed with azirine **5**.

Further examples which would support the generality of intramolecular azirine cycloaddition reactions were sought. With this in mind, we decided to prepare an azirinyl diene system with the expectation that this system might undergo some interesting photochemical behavior. Reaction of 2-formyl-3-phenyl-2*H*-azirine **1** with 3-carbomethoxy-2-propenylidene-1-triphenylphosphorane[17] in benzene afforded a mixture of 2-phenyl-7-carbomethoxy-1*H*-azepine (**15**, 40%), mp 156–157°, as well as azirinyl diene **16** (60%).

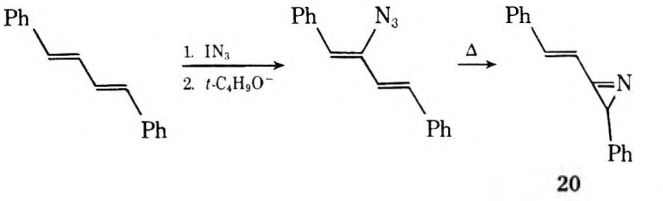


The azepine structure **15** was assigned on the basis of its spectroscopic data. The ultraviolet spectrum of this compound showed an absorption maximum at 388 nm ($\epsilon$ 29 300) indicating an extensively conjugated chromophore. The NMR spectrum showed signals at $\tau$ 6.28 (3 H, s), 3.70 (1 H, d), 3.40 (1 H, d), and 2.20–2.80 (7 H, m) and is compatible with the structure assignment. The mass spectrum showed the molecular ion peak at *m/e* 227. The azirinyl diene **16** was a mixture of the *EZ* and *EE* isomers which could not be purified since the mixture was extremely heat sensitive and rapidly undergoes isomerization to azepine **15** when allowed to stand at room temperature. The formation of azepine **15** may be formulated as proceeding through a vinyl nitrene intermediate. This species undergoes a subsequent intramolecular reorganization to generate **17**, which



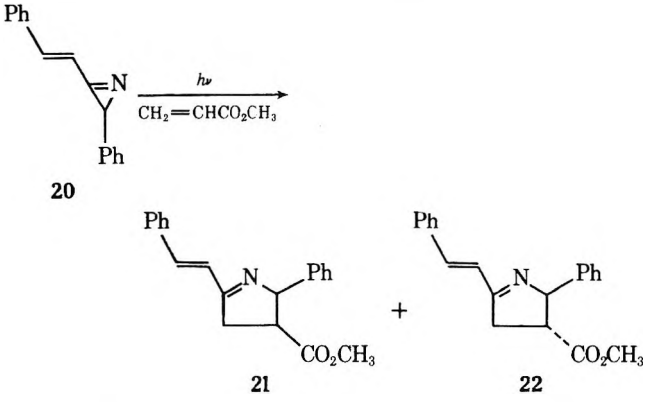
rearranges to the observed product by a series of 1,5-sigmatropic hydrogen shifts. Unlike the novel thermal chemistry encountered with azirine **16**, the photochemical behavior of this system was somewhat disappointing. Irradiation of a dilute solution of **16** through a Pyrex filter gave an extremely complex mixture from which no significant product could be isolated.

We had previously reported[8] an unusual aspect of the intramolecular photocyclization reaction of unsaturated azirines which was uncovered during our studies dealing with the photochemistry of (*Z*)-3-phenyl-2-styryl-2*H*-azirine (**18**). This styryl-substituted azirine was found to rearrange to 1-phenyl-3*H*-2-benzazepine (**19**) in high yield.[8] Our results with azirine **18** prompted an investigation of the chemical behavior of the isomeric 3-styryl-2-phenyl-2*H*-azirine (**20**) system. This compound was synthesized from 1,4-diphenyl-1,3-butadiene by the route shown below.[18]



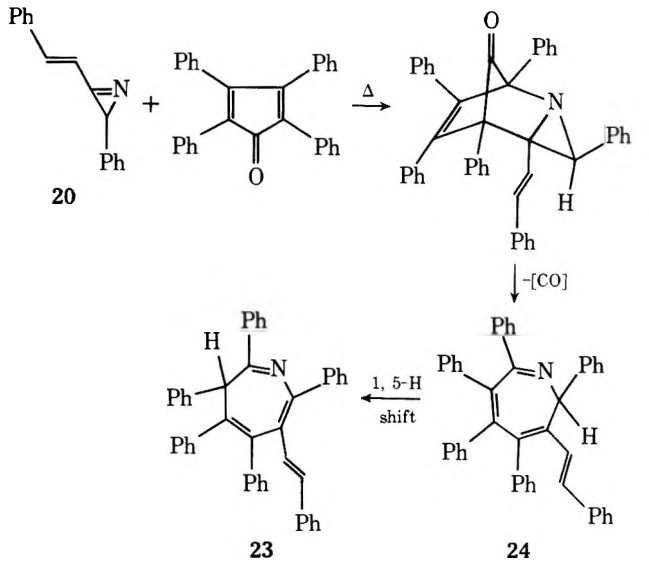
The structure of **20** was based on a parent peak at *m/e* 219 in the mass spectrum, an infrared band at 5.78 $\mu$, uv maximum at 293 nm ($\epsilon$ 26 000), and NMR signals at $\tau$ 6.92 (1 H, s) and 2.40–3.05 (12 H, m).

Whereas azirine **18** was smoothly converted to benzazepine **19** on irradiation, photolysis of the isomeric azirine **20** resulted in the formation of polymeric material. When the irradiation was carried out in the presence of methyl acrylate, cycloadducts **21** and **22** were isolated in good yield.



The major isomer (60%) was a crystalline solid, mp 133–134°, whose spectral properties were consistent with 2-styryl-5-phenyl-*cis*-4-carbomethoxy-$\Delta^1$-pyrroline (**21**). The assignment of stereochemistry was made on the basis of analogy to systems previously studied.[3,19] Photoadducts **21** and **22** exhibited absorptions for the carbomethoxy group at $\tau$ 6.28 and 6.84, respectively. The marked upfield shift of the carbomethoxy group in the cis adduct **21** can be attributed to shielding by the $\pi$ electrons of the neighboring phenyl ring.[19] This effect is absent in the trans adduct **22** and the carbomethoxy signal appears at a lower field relative to the signal for cis adduct **21**.

We also studied the thermal behavior of azirine **20** and found that it was perfectly stable in refluxing toluene. However, when azirine **20** was heated in toluene in the presence of 2,3,4,5-tetraphenylcyclopentadienone, a crystalline compound **23** was isolated in 38% yield. The mass spectrum and elemental analysis of this material were consistent with the formula $C_{44}H_{33}N$. The infrared spectrum was devoid of carbonyl and NH absorptions. The ultraviolet spectrum in methylene chloride showed absorption maxima at 283, 315, and 375 nm while the NMR spectrum showed signals at $\tau$ 3.80 (2 H, AB quartet, $J$ = 17.0 Hz), 3.72 (1 H, s), and 2.20–3.20 (30 H, m). The above data suggest that the structure of this compound is 6-styryl-2,3,4,5,7-pentaphenyl-3*H*-azepine (**23**). A reasonable mechanism for the formation of this azepine assumes that a normal Diels–Alder reaction initially occurs to produce a strained cycloadduct which then undergoes a chelotropic fragmentation with concomitant aziridine ring opening to give an azacycloheptatriene intermediate (i.e., **24**). This transient intermediate is converted to the thermodynamically more stable 3*H*-azepine by a 1,5-sigmatropic hydro-




gen shift. Such a sequence is closely related to reports by Hassner[20] and Nair,[21] who found that 2*H*-azirines react with substituted cyclopentadienones to give 3*H*-azepines in good yield.

## Experimental Section[22]

**Preparation of 2-Formyl-3-phenyl-2*H*-azirine-*N*-allylimine.** A solution containing 1.45 g of 2-formyl-3-phenyl-2*H*-azirine[8] (**1**) and 0.57 g of allylamine in 125 ml of benzene which contained a trace of *p*-toluenesulfonic acid was stirred in the presence of 15 g of anhydrous sodium sulfate for 1.5 hr. Addition of 1.0 g of sodium bicarbonate followed by filtration and removal of the solvent under reduced pressure left a dark oil. This material was taken up in pentane and separated from the insoluble portion. Removal of the solvent left 1.56 g (85%) of 2-formyl-3-phenyl-2*H*-azirine-*N*-allylimine (**2**) as a light yellow oil: ir (neat) 5.70 and 6.05 $\mu$; NMR ($CDCl_3$) $\tau$ 7.04 (1 H, d, $J$ = 7.0 Hz), 5.98 (2 H, m), 4.90 (2 H, m), 4.10 (1 H, m), 2.98 (1 H, d, $J$ = 7.0 Hz), 2.04–2.60 (5 H, m); MS *m/e* 184 ($M^+$), 183, 105, 90, 89, and 77.

**Irradiation of 2-Formyl-3-phenyl-2*H*-azirine-*N*-allylimine.** A solution containing 500 mg of *N*-allylimine **2** in benzene was irradiated for 90 min through a Corex filter sleeve. Removal of the solvent under reduced pressure left a dark oil which was distilled at 70° (0.005 mm) to give 425 mg (85%) of a colorless oil whose structure was assigned as 2-phenyl-*N*-allylimidazole (**3**) on the basis of its spectral properties and by an independent synthesis: ir (neat) 6.10 $\mu$; NMR ($CDCl_3$) $\tau$ 5.56 (2 H, m), 5.00 (2 H, m), 4.22 (1 H, m), 3.10 (1 H, s), 3.03 (1 H, s), 2.46–2.88 (5 H, m); MS *m/e* 184 ($M^+$, base), 143, 89, and 75. A picrate derivative was prepared and recrystallized from ethanol, mp 152–153°. An authentic sample of **3** was prepared by heating a mixture which contained 375 mg of 2-phenylimidazole,[23] 206 mg of allyl chloride, and 116 mg of sodium hydroxide in 5 ml of acetonitrile for 3 hr. The mixture was filtered and the solvent was removed under reduced pressure to give a dark oil which was distilled at 90° (0.005 mm) to give 325 mg (65%) of a colorless oil whose spectral properties were identical with those of the major product obtained from the photolysis of azirine **2**.

**Thermolysis of 2-Formyl-3-phenyl-2*H*-azirine-*N*-allylimine.** A solution containing 200 mg of azirine **2** in 50 ml of xylene was heated at reflux for 30 hr. Removal of the solvent under reduced pressure left a dark oil which was purified by thick layer chromatography using a 1:1 ether–pentane mixture as the eluent. The major band contained 168 mg (84%) of a yellow oil whose structure was assigned as *N*-allyl-3-phenylpyrazole (**4**) on the basis of its spectral properties and by comparison with an authentic sample: ir (neat) 5.96, 6.24 $\mu$; NMR ($CDCl_3$) $\tau$ 5.35 (2 H, m), 4.89 (2 H, m), 3.87–4.31 (1 H, m), 3.55 (1 H, d, $J$ = 2.0 Hz), 2.6–3.0 (4 H, m), 2.36 (1 H, m), 2.28 (1 H, d, $J$ = 2.0 Hz). An authentic sample of pyrazole **4** was prepared by treating 5-phenylpyrazole[24] with allyl bromide. To a solution containing 750 mg of 5-phenylpyrazole in 3 ml of absolute ethanol was added 0.28 g of potassium hydroxide in 2 ml of ethanol. The solution was allowed to stir for 30 min at room temperature and was then cooled to 0°. To this mixture was added a solution of 940 mg of allyl bromide in 4 ml of ethanol. After the addition was complete the mixture was heated at reflux for 1 hr. Filtration and removal of the solvent under reduced pressure left a dark oil. This material was purified by thick layer chromatography using a 1:1 ether–pentane mixture as the eluent. The major band corresponded to 626 mg (68%) of a yellow oil whose spectral properties were identical with those of *N*-allyl-3-phenylpyrazole (**4**) obtained from the thermolysis of azirine **2**.

**Preparation of Ethyl 3-Phenyl-2*H*-azirine-2-(2-methyl)acrylate.** A solution containing 1.45 g of 2-formyl-3-phenyl-2*H*-azirine (**1**) and 3.6 g of methylcarboethoxymethylenetriphenylphosphorane in 125 ml of benzene was heated at reflux for 12 hr. Removal of the solvent left an oily solid which was triturated with ether and filtered to remove triphenylphosphine oxide. The filtrate was concentrated under reduced pressure to leave an oil which was filtered through a short Florisil column with a 10% ethyl acetate–benzene mixture. Removal of the solvent left a light yellow oil which solidified on standing. This material was sublimed at 45° (0.005 mm) and recrystallized from pentane to give 2.0 g (89%) of ethyl 2-phenyl-2*H*-azirine-2-(2-methyl)acrylate (**5**) as a crystalline solid: mp 43–44°; ir (KBr) 5.73, 5.90, and 6.12 $\mu$; uv (cyclohexane) 243 nm ($\epsilon$ 27 400); NMR ($CDCl_3$) $\tau$ 8.84 (3 H, t, $J$ = 6.0 Hz), 7.95 (3 H, s), 7.06 (1 H, d, $J$ = 9.0 Hz), 5.90 (2 H, q, $J$ = 6.0 Hz), 3.94 (1 H, dq, $J$ = 9.0 and 1.0 Hz), 2.07–2.66 (5 H, m); MS *m/e* 229, 200, 184, 156, and 129.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.64; N, 6.06. Found: C, 73.29; H, 6.59; N, 6.11.

**Thermolysis of Ethyl 3-Phenyl-2*H*-azirine-2-(2-methyl)acrylate.** A solution containing 0.5 g of ethyl 3-phenyl-2*H*-azirine-2-(2-methyl)acrylate (**5**) in 500 ml of xylene was heated at reflux for 10 hr. Removal of the solvent under reduced pressure left a yellow oil which was chromatographed on silica gel using a 50% ether–pentane mixture as the eluent. The first material eluted from the column was a crystalline solid, mp 50–51° (40%), whose structure was assigned as 2-phenyl-5-carboethoxypyridine (**7**) on the basis of the following data: ir (KBr) 5.86 and 6.30 $\mu$; uv (95% ethanol) 290 nm ($\epsilon$ 29 000); NMR ($CDCl_3$) $\tau$ 8.59 (3 H, t, $J$ = 7.0 Hz), 5.59 (2 H, q, $J$ = 7.0 Hz), 1.55–2.45 (7 H, m), 0.7 (1 H, d, $J$ = 2.0 Hz); MS *m/e* 227 ($M^+$), 197, 180 (base), 153, 127, and 58. The structure of **7** was unambiguously verified by comparison with an authentic sample synthesized from the corresponding carboxylic acid according to the procedure of Benary and Psille.[9]

The second component isolated from the column was a crystalline solid, mp 112–113° (60%), whose structure was assigned as 2-methyl-3-carboethoxy-5-phenylpyrrole (**6**) on the basis of its spectral properties and by an independent synthesis: ir (KBr) 3.03, 6.02, and 6.29 $\mu$; uv (95% ethanol) 268 nm ($\epsilon$ 20 000); NMR ($CDCl_3$) 8.79 (3 H, t, $J$ = 7.0 Hz), 7.51 (3 H, s), 5.80 (2 H, q, $J$ = 7.0 Hz), 3.26 (1 H, d, $J$ = 3.0 Hz), 2.50–2.94 (5 H, m), and 1.26–1.56 (1 H, broad singlet); MS *m/e* 229 ($M^+$), 199 (base), 183, and 156. The structure of **6** was verified by comparison with an authentic sample synthesized in the manner described below. To a solution containing 1 g of 2-phenyl-4-carbomethoxy-5-methyl-$\Delta^1$-pyrroline[3] (**8**) in 50 ml of benzene was added 1 g of DDQ. The mixture was refluxed for 3 hr, filtered, and evaporated under reduced pressure. The dark oil obtained was purified by passing it through a short Florisil column with benzene. The crude solid obtained was identified as 2-methyl-3-carbomethoxy-5-phenylpyrrole: NMR ($CDCl_3$) $\tau$ 7.44 (s, 3 H), 6.20 (s, 3 H), 3.20 (d, 1 H, $J$ = 3.0 Hz), 2.4–2.8 (m, 5 H), 1.20 (NH, exchanged with $D_2O$). A solution containing 700 mg of the above carbomethoxypyrrole and a trace of sodium metal was heated at reflux in absolute ethanol for 4 hr. The mixture was diluted with water and extracted with ether. The ethereal layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 0.71 g (65%) of a white solid, mp 112–113°, which was identical with the sample of 2-methyl-3-carboethoxy-5-phenylpyrrole (**6**) obtained from the thermolysis of ethyl 3-phenyl-2*H*-azirine-2-(2-methyl)acrylate (**5**). A mixture melting point was undepressed at 112–113°.

The thermolysis of ethyl 3-phenyl-2*H*-azirine-2-(2-methyl)acrylate (**5**) was also carried out in the presence of tris(dimethylamino)phosphine. A solution containing 250 mg of **5** and 1 g of tris(dimethylamino)phosphine in 50 ml of xylene was heated at reflux for 12 hr. Removal of the solvent left an oily solid which was recrystallized from chloroform–ether to give 268 mg (62%) of a yellow solid (**9**): mp 230–235°; NMR ($CDCl_3$) $\tau$ 8.06 (3 H, s), 7.20–7.40 (18 H, 4 lines), 6.34 (3 H, 2 lines), 3.42 (1 H, dt, $J$ = 11.0 and 2.0 Hz), 2.12–2.86 (6 H, m). Azirine **5** was also heated in the presence of triphenylphosphine. A solution containing 0.5 g of **5** and 1.72 g of triphenylphosphine in 500 ml of xylene was heated at reflux for 15 hr. Removal of the solvent under reduced pressure gave a yellow oil. All attempts to purify this material resulted in the formation of tri-

phenylphosphine oxide. Under these conditions the normal thermal products (6 and 7) were formed in much lower yields.

**Irradiation of Ethyl 3-Phenyl-2*H*-azirine-2-(2-methyl)acrylate.** A solution containing 500 mg of ethyl 3-phenyl-2*H*-azirine-2-(2-methyl)acrylate (5) in 450 ml of benzene was irradiated for 1 hr using a Pyrex filter sleeve. The solvent was removed under reduced pressure to give a light yellow oil which was extremely sensitive to moisture and readily decomposed on standing at room temperature. The NMR spectrum of the crude photolysate was quite complex and showed a complex pattern of overlapping triplets for the carboethoxy methyl group at $\tau$ 8.90, a singlet at $\tau$ 8.12, a doublet at $\tau$ 6.71 ($J$ = 16.0 Hz), a complex pattern of overlapping quartets for the carboethoxy methylene group at $\tau$ 6.12, a triplet at $\tau$ 4.72 ($J$ = 10.0 Hz), a doublet at $\tau$ 4.26 ($J$ = 8.0 Hz), a doublet at $\tau$ 3.90 ($J$ = 10 Hz), a doublet at $\tau$ 3.48 ($J$ = 8.0 Hz), aromatic protons at $\tau$ 2.39–3.24 (multiplet), and a singlet at $\tau$ 2.39. All attempts to separate the mixture into its component parts failed as a result of the ready hydrolysis of the mixture to benzaldehyde and additional components which could not be characterized.

The irradiation of ethyl 3-phenyl-2*H*-azirine-2-(methyl)acrylate (5) was also carried out in the presence of a dipolarophile so as to trap the nitrile ylide. A solution containing 0.5 g of 5 and 10 ml of methyl acrylate in 450 ml of benzene was irradiated for 1 hr through a Pyrex filter sleeve. Removal of the solvent left a yellow oil which was chromatographed on a thick layer plate with a 1:1 mixture of ether–pentane as the eluent. The minor component isolated from the thick layer plate was a crystalline solid, mp 56–58° (38%), whose structure was assigned as *trans*-2-phenyl-4-carbomethoxy-$\Delta^1$-pyrroline-5-(2-methyl)acrylic acid ethyl ester (**12a**) on the basis of the following data: ir (KBr) 5.76, 5.82, 6.02, and 6.16 $\mu$; uv (95% ethanol) 248 nm ($\epsilon$ 20 300); NMR ($CDCl_3$) $\tau$ 8.79 (3 H, t, $J$ = 9.0 Hz), 8.08 (3 H, s), 6.86–7.18 (1 H, m), 6.56–6.78 (2 H, m), 6.33 (3 H, s), 5.85 (2 H, q, $J$ = 9.0 Hz), 4.79 (1 H, m), 3.40 (1 H, d, $J$ = 10.0 Hz), 2.07–2.80 (5 H, m). The major product isolated from the thick layer plate was a white, crystalline solid, mp 111–112° (62%), whose structure was assigned as *cis*-2-phenyl-4-carbomethoxy-$\Delta^1$-pyrroline-5-(2-methyl)acrylic acid ethyl ester (**12b**) on the basis of the following data: ir (KBr) 5.79, 5.87, 6.05, and 6.14 $\mu$; uv (95% ethanol) 248 nm ($\epsilon$ 23 000); NMR ($CDCl_3$) $\tau$ 8.78 (3 H, t, $J$ = 7.0 Hz), 8.01 (3 H, s), 6.26–7.08 (6 H, m), 5.87 (2 H, q, $J$ = 7.0 Hz), 4.02 (1 H, m), 3.54 (1 H, d, $J$ = 11.0 Hz), 2.06–2.78 (5 H, m).

The nitrile ylide was also trapped with acrylonitrile. A solution containing 300 mg of 5 and 10 ml of acrylonitrile in 450 ml of benzene was irradiated for 1 hr through a Corex filter sleeve. Removal of the solvent under reduced pressure gave a yellow oil which was chromatographed on a thick layer plate using a 1:1 ether–pentane mixture as the eluent. The minor component obtained (21%) from the thick layer plate was identified as *trans*-2-phenyl-4-cyano-$\Delta^1$-pyrroline-5-(2-methyl)acrylic acid ethyl ester: mp 72–73°; ir (KBr) 4.45, 5.83, 5.95, and 6.17 $\mu$; uv (95% ethanol) 247 nm ($\epsilon$ 14 700); NMR ($CDCl_3$) $\tau$ 8.70 (3 H, t, $J$ = 7.0 Hz), 7.87 (3 H, s), 6.19–7.20 (3 H, m), 5.78 (2 H, q, $J$ = 7.0 Hz), 4.67 (1 H, m), 3.38 (1 H, d, $J$ = 9.0 Hz), and 2.0–2.3 (5 H, m). The major isomer obtained was identified as *cis*-2-phenyl-4-cyano-$\Delta^1$-pyrroline-5-(2-methyl)acrylic acid ethyl ester: mp 109–110°; ir (KBr) 4.44, 5.72, 6.01, and 6.20 $\mu$; uv (95% ethanol) 247 nm ($\epsilon$ 14 900); NMR ($CDCl_3$) $\tau$ 8.69 (3 H, t, $J$ = 7.0 Hz), 7.89 (3 H, s), 6.26–7.18 (3 H, m), 5.80 (2 H, q, $J$ = 7.0 Hz), 4.68 (1 H, m), 3.38 (1 H, d, $J$ = 8.0 Hz), and 2.0–2.7 (5 H, m).

**Reaction of 2-Formyl-3-phenyl-2*H*-azirine with Phenylcarbomethoxymethylenetriphenylphosphorane.** A mixture containing 145 mg of 2-formyl-3-phenyl-2*H*-azirine (1) and 480 mg of phenylcarbomethoxymethylenetriphenylphosphorane[25] was heated in the solid state at 170° for 3 hr. Then 10 ml of ether was added to the mixture and the triphenylphosphine oxide which had precipitated was collected. The filtrate was concentrated under reduced pressure and the residue was filtered through a short Florisil column using a 10% ethyl acetate–benzene mixture as the eluent. The major component isolated from the column was a white solid, mp 169–170° (80%), whose structure was identified as 2,5-diphenyl-3-carbomethoxypyrrole (14): ir (KBr) 3.10, 6.05, and 6.27 $\mu$; NMR ($CDCl_3$) $\tau$ 6.40 (3 H, s), 2.50–3.0 (10 H, m), and 1.3–1.6 (1 H, m). The structure of this material was verified by comparison with an independently synthesized sample. A solution containing 0.35 g of 2,5-diphenyl-4-carbomethoxy-$\Delta^1$-pyrroline[3] and 0.8 g of DDQ in 50 ml of benzene was heated at reflux for 2.5 hr. The solvent was removed under reduced pressure and the residue was filtered through a short Florisil column with benzene. The major product (0.3 g) was identical in all respects with a sample of 2,5-diphenyl-3-carbomethoxypyrrole obtained from the reaction of 1 with phenylcarbomethoxymethylenetriphenylphosphorane. A mixture melting point was undepressed at 169–170°.

**Preparation of 3-Phenyl-2-(4-carbomethoxy-1,3-butadienyl)-2*H*-azirine.** A solution containing 0.84 g of 2-formyl-3-phenyl-2*H*-azirine (1) and 2.16 g of 3-carbomethoxy-2-propenylidene-1-triphenylphosphorane[17] in 100 ml of benzene was heated at 50° under a nitrogen atmosphere for 3 hr. The solvent was removed under reduced pressure and the residual oil was passed through a Florisil column using a 10% ethyl acetate–benzene mixture to give an oily solid. Addition of hexane gave 0.42 g (40%) of 2-phenyl-7-carbomethoxy-1*H*-azepine (**15**): mp 156–157°; ir (KBr) 3.00, 5.92, and 6.12 $\mu$; uv (95% ethanol) 388 nm ($\epsilon$ 29 300); NMR ($CDCl_3$) $\tau$ 6.28 (3 H, s), 3.70 (1 H, d), 3.40 (1 H, d), and 2.20–2.80 (6 H, m); *m/e* 227 ($M^+$).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.98; H, 5.70; N, 6.13.

The filtrate consisted of 3-phenyl-2-(4-carbomethoxy-1,3-butadienyl)-2*H*-azirine (16, 60%) as a dark oil which exhibited the following spectral characteristics: ir (neat) 5.75, 5.85, and 6.15 $\mu$; NMR ($CDCl_3$) $\tau$ 6.84 (1 H, d, $J$ = 10.0 Hz), 6.68 (1 H, d, $J$ = 12.0 Hz), 6.38 (3 H, s), 6.34 (3 H, s), a complex multiplet at $\tau$ 5.0–7.0, and aromatic absorptions centered at $\tau$ 2.60. The NMR spectrum indicated the presence of two geometric isomers in the ratio of 1.5:1. All attempts to separate and purify the isomeric azirines were unsuccessful as this material is extremely heat sensitive and underwent extensive decomposition on attempted purification. A solution containing 0.4 g of the impure azirines in 75 ml of benzene was heated at reflux for 1 hr. Removal of the solvent left 0.35 g (88%) of crystalline 2-phenyl-7-carbomethoxy-1*H*-azepine (15).

**Preparation of 3-Styryl-2-phenyl-2*H*-azirine.** To a stirred ice-cold solution of iodine azide (0.1 mol) in 200 ml of acetonitrile was added 20.6 g of *trans,trans*-1,4-diphenyl-1,3-butadiene. The mixture was allowed to warm to room temperature overnight prior to work-up. The resulting red-brown mixture was poured onto 500 ml of water and was extracted with ether. The combined organic extracts were washed successively with 700 ml of 5% aqueous sodium thiosulfate and 500 ml of water. The solvent was dried over magnesium sulfate and removed under reduced pressure to give a yellow oil which was passed through a neutral alumina column with a 1:1 ether–hexane mixture to give 13.6 g (37%) of a colorless oil. A solution containing 13 g of the iodine azide adduct in 300 ml of ether at 0° was treated with 23 g of potassium *tert*-butoxide. The reaction mixture was allowed to stir at 0° for 24 hr and was then diluted with 200 ml of water. The ethereal layer was dried over magnesium sulfate and concentrated under reduced pressure to give a yellow oil. This material was filtered through a column of neutral alumina and the resulting vinyl azide was heated in chloroform at 60° for 8 hr. Removal of the solvent left 4.6 g (21%) of a crude solid which was sublimed at 50° (0.05 mm) and recrystallized from hexane to give 3-styryl-2-phenyl-2*H*-azirine (**20**):[18] mp 66–67°; ir (KBr) 5.78 $\mu$; uv (95% ethanol) 293 nm ($\epsilon$ 26 000); NMR ($CDCl_3$, 100 MHz) $\tau$ 6.96 (1 H, s) and 2.40–3.00 (12 H, m); MS *m/e* 219, 218 (base), 217, 204, 191, 115, 108, 90, 89, and 77.

Anal. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.34; H, 5.96; N, 6.26.

**Irradiation of 3-Styryl-2-phenyl-2*H*-azirine.** A solution containing 0.5 g of 3-styryl-2-phenyl-2*H*-azirine (**20**) in 500 ml of benzene was irradiated through a Pyrex filter sleeve for 1 hr. Removal of the solvent under reduced pressure left a viscous oil which resisted all attempts at purification. No characterizable material could be obtained on extensive chromatography. The photolysis of **20** was also carried out in the presence of methyl acrylate. A solution containing 0.65 g of 2-styryl-3-phenyl-2*H*-azirine and 20 ml of methyl acrylate in 500 ml of benzene was irradiated through a Pyrex filter sleeve for 2.5 hr. Removal of the solvent and excess methyl acrylate under reduced pressure afforded a yellow oil. Liquid–liquid partition chromatography[26] of the oil indicated the presence of two adducts. The minor adduct (40%) was a pale yellow oil whose structure was assigned as 2-styryl-5-phenyl-*trans*-4-carbomethoxy-$\Delta^1$-pyrroline (**22**): ir (neat) 5.70, 6.05, and 6.18 $\mu$; NMR ($CDCl_3$) $\tau$ 6.80 (2 H, m), 6.28 (3 H, s), 4.56 (1 H, d), and 2.40–3.05 (12 H, m). A picrate derivative was prepared and recrystallized from ethanol, mp 171–172°.

Anal. Calcd for $C_{26}H_{22}N_4O_9$: C, 58.42; H, 4.15; N, 10.48. Found: C, 58.23; H, 4.18; N, 10.39.

The major adduct (60%) was assigned the structure of 2-styryl-5-phenyl-*cis*-4-carbomethoxy-$\Delta^1$-pyrroline (**21**) on the basis of the following data: mp 134–135°; ir (KBr) 5.70, 6.08, and 6.20 $\mu$; uv (95% ethanol) 287 nm ($\epsilon$ 22 000); NMR ($CDCl_3$) $\tau$ 6.84 (3 H, s), 6.40

(2 H, m), 4.32 (1 H, d), and 2.20–3.10 (12 H, m); MS *m/e* 305, 246, 218, 201 (base), 170, 169, 141, 115, 114, and 77.

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.63; H, 6.23; N, 4.59.

The combined yield of *cis*- and *trans*-$\Delta^1$-pyrrolines (**21** and **22**) was 68%.

**Thermolysis of 3-Styryl-2-phenylazirine in the Presence of Tetraphenylcyclopentadienone.** A solution containing 0.324 g of 3-styryl-2-phenylazirine and 0.538 g of tetraphenylcyclopentadienone in 50 ml of toluene was heated at reflux for 4 days. The toluene solution was concentrated under reduced pressure and the residual oil was chromatographed on a silica gel column with a 1:1 pentane–benzene mixture as the eluent to afford 0.31 g (38%) of a bright yellow, crystalline compound whose structure was assigned as 6-styryl-2,3,4,5,7-pentaphenyl-3*H*-azepine (**23**) on the basis of the following data: mp 229–231°; ir (KBr) 6.25 $\mu$; uv (methylene chloride) 283, 315, and 375 nm ($\epsilon$ 32 400, 18 200, and 14 500); NMR ($CDCl_3$) $\tau$ 3.80 (2 H, AB quartet, $J$ = 17.0 Hz), 3.72 (1 H, s), and 2.20–3.20 (30 H, m); *m/e* 369 (base).

Anal. Calcd for $C_{44}H_{33}N$: C, 91.18; H, 5.84; N, 2.44. Found: C, 91.08; H, 5.89; N, 2.37.

**Acknowledgment.** We gratefully acknowledge support of this work by the National Science Foundation (Grant PO-37550) and the National Institutes of Health (Grant CA-12195-09).

**Registry No.**—**1**, 42970-55-8; **2**, 57443-65-9; **3**, 14967-25-0; **3** picrate, 15139-33-0; **4**, 57443-66-0; **5**, 57443-67-1; **6**, 3652-48-0; **7**, 57443-68-2; **8**, 57443-69-3; **9**, 57443-70-6; *cis*-**12** (X = $CO_2CH_3$), 57443-71-7; *cis*-**12** (X = CN), 57443-72-8; *trans*-**12** (X = $CO_2CH_3$), 57443-73-9; *trans*-**12** (X = CN), 57443-74-0; **14**, 13901-74-1; **15**, 57443-75-1; (*EZ*)-**16**, 57443-76-2; (*EE*)-**16**, 57443-77-3; **20**, 57152-43-9; **21**, 57443-78-4; **22**, 57443-79-5; **23**, 57443-80-8; allylamine, 107-11-9; 2-methyl-3-carbomethoxy-5-phenylpyrrole, 28168-20-9; phenylcarbomethoxymethylenetriphenylphosphorane, 1106-06-5; 3-carbomethoxy-2-propenylidene-1-triphenylphosphorane, 53236-02-5; *trans,trans*-1,4-diphenyl-1,3-butadiene, 538-81-8; triphenylphosphine, 603-35-0; phenylcarbomethoxymethyltriphenylphosphonium bromide, 1106-05-4; methyl $\alpha$-bromophenylacetate, 3042-81-7.

## References and Notes

(1) Photochemical Transformations of Small Ring Heterocyclic Compounds. 71. For part 70, see A. Padwa, E. Chen, and A. Ku, *J. Am. Chem. Soc.*, **97**, 6484 (1975).
(2) A. Padwa and J. Smolanoff, *J. Am. Chem. Soc.*, **93**, 548 (1971).
(3) A. Padwa, M. Dharan, J. Smolanoff, and S. I. Wetmore, Jr., *J. Am. Chem. Soc.*, **94**, 1395 (1972); **95**, 1945, 1954 (1973); *Pure Appl. Chem.*, **33**, 269 (1973).
(4) A. Padwa and S. I. Wetmore, *J. Org. Chem.*, **38**, 1333 (1973); **39**, 1396 (1974); *J. Am. Chem. Soc.*, **96**, 2414 (1974).
(5) A. Padwa, D. Dean, and J. Smolanoff, *Tetrahedron Lett.*, 4087 (1972); A. Padwa, J. Smolanoff, and A. Tremper, *ibid.*, **29**, 33 (1974).
(6) A. Padwa and P. H. J. Carlsen, *J. Am. Chem. Soc.*, **97**, 3862 (1975).
(7) N. Gakis, M. Marky, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, **55**, 748 (1972); H. Giezendanner, M. Marky, B. Jackson, J. J. Hansen, and H. Schmid, *ibid.*, **55**, 745 (1972); B. Jackson, M. Marky, H. J. Hansen, and H. Schmid, *ibid.*, **55**, 919 (1972).
(8) A. Padwa, J. Smolanoff, and A. Tremper, *J. Am. Chem. Soc.*, **97**, 4682 (1975).
(9) A. E. Benary and H. Psille, *Ber.*, **57**, 828 (1924).
(10) P. A. Smith, "Arylnitrenes and Formation of Nitrenes by Rupture of Heterocyclic Rings", in "Nitrenes", W. Lwowski, Ed., Interscience, New York, N.Y., 1970, and references cited therein.
(11) P. Germeraad and H. W. Moore, *J. Org. Chem.*, **39**, 774 (1974).
(12) J. van Alphen, *Recl. Trav. Chim. Pays-Bas*, **62**, 485, 491 (1943).
(13) R. Huttel, K. Francke, H. Martin, and J. Riedl, *Chem. Ber.*, **93**, 1433 (1960).
(14) H. Durr and R. Sergio, *Tetrahedron Lett.*, 3479 (1972).
(15) M. Franck-Newmann and C. Buchecker, *Tetrahedron Lett.*, 937 (1972); *Angew. Chem., Int. Ed. Engl.*, 240, 259 (1973).
(16) T. Nishiwaki, A. Nakano, and H. Matsuoko, *J. Chem. Soc. C*, 1825 (1970); T. Nishiwaki and F. Fugiyama, *J. Chem. Soc., Perkin Trans. 1*, 1456 (1972).
(17) E. Buchta and F. Andree, *Chem. Ber.*, **92**, 3111 (1959).
(18) Since the completion of this work a report appeared describing the addition of iodine azide to noncyclic conjugated dienes; see A. Hassner and J. Keogh, *Tetrahedron Lett.*, 1575 (1975).
(19) For an additional example of this effect see J. H. Hall and R. Huisgen, *Tetrahedron Lett.*, 1187, 1188 (1971).
(20) D. J. Anderson and A. Hassner, *J. Am. Chem. Soc.*, **93**, 4339 (1971).
(21) V. Nair, *J. Org. Chem.*, **37**, 802 (1972).
(22) All melting points 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 MH-100 spectrometer. Mass spectra were determined with a Perkin-Elmer RMU6 mass spectrometer at an ionizing voltage of 70 eV. All irradiations were carried out using a 450-W Hanovia medium-pressure mercury arc.
(23) F. L. Pyman and R. G. Fargher, *J. Chem. Soc.*, 217 (1919).
(24) K. V. Auwers and W. Schmidt, *Ber.*, **58**, 537 (1925).
(25) A sample of phenylcarbomethoxymethylenetriphenylphosphorane was prepared by stirring 86.5 g of triphenylphosphine with 68.7 g of methyl $\alpha$-bromophenylacetate in 1 l. of anhydrous benzene for 30 hr at room temperature. The phosphonium bromide which crystallized out of solution (132 g, 89%) was filtered and dried to give a white solid, mp 154–155°. To a solution of 40 g of the above phosphonium salt in 1.75 l. of water was added 2 drops of methanolic phenolphthalein and the mixture was titrated to the end point with a 10% sodium hydroxide solution. The reaction mixture was cooled in an ice bath and filtered to give 30 g (75%) of phenylcarbomethoxymethylenetriphenylphosphorane: mp 151–152°; ir (KBr) 6.30, 8.05, and 10.21 $\mu$.
(26) A. Padwa and L. Hamilton, *J. Am. Chem. Soc.*, **89**, 102 (1967).

# Notes

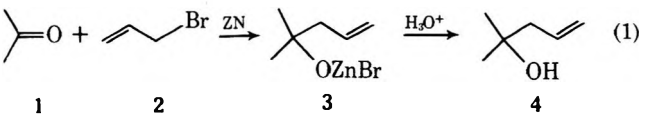
## Reaction of Allylzinc Bromides with Carbonyl Compounds in a Continuous Flow System. An Efficient Synthesis of Homoallyl Alcohols Including Artemisia Alcohol

John F. Ruppert and James D. White*

*Department of Chemistry, Oregon State University, Corvallis, Oregon 97331*

*Received July 1, 1975*

Recently we described a procedure in which the Reformatsky reaction is carried out by passing a mixture of an $\alpha$-bromo ester and an aldehyde or ketone through a heated column of granular zinc.[1] This continuous-flow adaptation of the conventional synthesis of $\beta$-hydroxy esters[2] was shown to give substantially improved yields. We have now found that a similar procedure is applicable to the synthesis of alcohols from an allylic bromide and an aldehyde or ketone (eq 1).

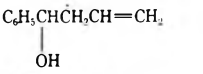
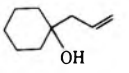
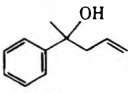
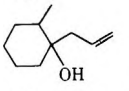
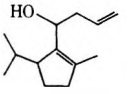
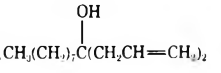
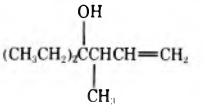
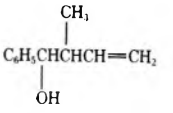
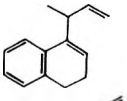
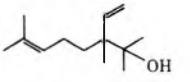
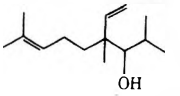



1 2 3 4 (1)

Optimized conditions require the slow addition of a 1:1.5 molar mixture of the carbonyl component (1) and allylic bromide (2) in tetrahydrofuran to a column of granular zinc, heated to just above the reflux temperature of the solvent. The apparatus is identical with that described previously.[1] After addition is complete, the column is flushed with tetrahydrofuran and the collected zinc alkoxide (3) is hydrolyzed with dilute sulfuric acid to yield homoallylic alcohol 4.

The results are summarized in Table I. Yields of alcohols (5–15) are consistently higher than those obtained from allylzinc bromides and aldehydes or ketones under conventional reaction conditions,[3] and are also superior to those obtained in the Barbier–Grignard reaction using allylmag-

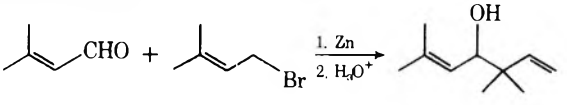
Table I
Reaction of Allylzinc Bromides with Carbonyl Compounds

| Carbonyl compd | Registry no. | Bromide | Registry no. | Product | | Registry no. | Bp, °C (mm)[a] | Yield, %[b] |
|---|---|---|---|---|---|---|---|---|
| Benzaldehyde | 100-52-7 | Allyl | 18925-10-5 |  | (5) | 936-58-3 | 50–54 (0.05) | 96 |
| Cyclohexanone | 108-94-1 | Allyl | |  | (6) | 1123-34-8 | 32–34 (0.05) | 97 |
| Acetophenone | 98-86-2 | Allyl | |  | (7) | 4743-74-2 | 54–56 (0.05) | 97 |
| 2-Methylcyclohexanone | 583-60-8 | Allyl | |  | (8) | 24580-51-6 | 40–42 (0.05) | 93 |
| 2-Methyl-5-isopropyl-cyclopent-1-enecarboxaldehyde | 54043-82-2 | Allyl | |  | (9) | 57256-47-0 | 65–67 (0.05) | 90 |
| Ethyl pelargonate | 123-29-5 | Allyl | |  | (10) | 57256-48-1 | 75–79 (0.03) | 94 |
| 3-Pentanone | 96-22-0 | Crotyl | 14735-44-5 |  | (11) | 25201-42-7 | 70–73 (16) | 96 |
| Benzaldehyde | | Crotyl | |  | (12) | 25201-44-9 | 65–67 (0.05) | 95 |
| $\alpha$-Tetralone | 529-34-0 | Crotyl | |  | (13) | 57256-49-2 | 79–83 (0.05) | 93 |
| Acetone | 67-64-1 | Geranyl | 57256-46-9 |  | (14) | 57256-50-5 | 63–67 (0.05) | 80 |
| Isobutyraldehyde | 78-84-2 | Geranyl | |  | (15) | 57256-51-6 | 71–75 (0.03) | 74 |

[a] Purity as determined by GLC was >95% except for 5 (92%), 9 (90%), 11 (93%), and 15 (93%). [b] Isolated yield following distillation.

nesium halides.[4] A noteworthy feature of the zinc column method is the absence of Wurtz coupling product derived from the allylic halide. Successive addition to the column of different mixtures of carbonyl components with allylic bromides gave, in each case, a product with no detectable contamination from preceding alcohols. Thus, the zinc in the column can simply be replenished as it is consumed. The method is especially well suited to the large-scale preparation of homoallylic alcohols and, as judged from **10**, is applicable to esters as well as aldehydes and ketones. However, the method is ineffective with allylic chlorides and with saturated bromides.

Product alcohols were purified by short-path distillation and were identified by means of infrared, NMR, and mass spectral data (Table II). (See paragraph at end of paper regarding supplementary material.) In the case of the alcohol derived from crotyl bromide and tetralone, dehydration occurred upon distillation, leading to diene **13**. The structures of products **11–15** from crotyl and geranyl halides reveal that attack on the allylic moiety takes place solely at the $\beta$ carbon in this reaction, in agreement with similar observations made with allylmagnesium[5] and allylzinc halides.[6] This feature ("allylic transposition") lends itself to an efficient, one-step synthesis of (±)-artemisia alcohol (**16**)[7]. Thus, passage through a heated zinc column of a mixture of 3-methyl-2-butenal[8] and 1-bromo-3-methyl-2-butene[9] gave, after hydrolysis, a 91% yield of **16**. The structure of artemisia alcohol was confirmed by oxidation with chromium trioxide in pyridine to the corresponding ketone.[10]




**16**

The continuous-flow, zinc column procedure appears to be a generally useful method for allylation at carbonyl functions where mild reaction conditions are necessary. The operational simplicity and high efficiency of the method afford significant advantages over the Grignard reaction in certain cases.

## Experimental Section

**Materials.** Geranyl bromide was prepared by the method of Eschenmoser.[11] 1-Bromo-3-methyl-2-butene was prepared by addition of hydrogen bromide to isoprene.[9] 3-Methyl-2-butenal was prepared by oxidation of 3-methyl-2-buten-1-ol with manganese dioxide in petroleum ether. 2-Methyl-5-isopropylcyclopent-1-enecarboxaldehyde was prepared by the method of van Tamelen.[12] All other materials were obtained from commercial sources. Granular zinc (10 mesh) was activated prior to use by the method described previously.[1] GLC analysis was carried out using (1) a 10 ft × 0.375 in. column of 30% Carbowax 20M on Chromosorb W, or (2) a 5 ft × 0.25 in. column of 20% SE-30 on Chromosorb W with an Aerograph Autoprep 700 instrument. Infrared spectra were measured on neat liquids using a Perkin-Elmer Model 137 spectrophotometer. NMR spectra were measured on $CDCl_3$ solutions using a Varian EM-360 spectrometer.

**Reactions Using Zinc Column.** The following procedure for the reaction of 3-pentanone with crotyl bromide to yield **11** is representative. To a heated column charged with activated zinc (10 mesh)[1] was added dropwise 25 ml of anhydrous tetrahydrofuran followed by a mixture of 3.05 g (35.4 mmol) of 3-pentanone and 7.16 g (53.0 mmol) of 1-bromo-2-butene in 50 ml of tetrahydrofuran. A low reflux was maintained at the head of the column during addition, which took 1 hr. The column was then flushed with 25 ml of tetrahydrofuran and the combined eluate, after dilution with 50 ml of ether, was treated with ice-cold 5% sulfuric acid, followed by sodium bicarbonate solution and saturated brine. The organic layer was dried ($MgSO_4$), the solvent was removed in vacuo, and the residue was purified by short-path distillation to give 4.81 g (95.6%) of **11**, bp 70–73° (16 mm).

**Artemisia Alcohol (16).** A mixture of 1.15 g (13.6 mmol) of 3-methylbut-2-enal and 3.05 g (20.4 mmol) of 1-bromo-3-methylbut-2-ene in 20 ml of tetrahydrofuran was passed through the heated column of granular zinc. After flushing the column, the eluate was diluted with 50 ml of ether and washed with 30 ml of cold 5% sulfuric acid, sodium bicarbonate solution, and brine. After drying and removal of the solvent in vacuo, distillation afforded 1.68 g (91.3%) of artemisia alcohol (**16**).

**Acknowledgments.** We are indebted to Mr. Mitchell Avery for the preparation of 2-methyl-5-isopropylcyclopent-1-enecarboxaldehyde. Financial support was provided by the National Science Foundation.

**Registry No.**—**16**, 29887-38-5; 3-methylbut-2-enal, 107-86-8; 1-bromo-3-methylbut-2-ene, 870-63-3.

**Supplementary Material Available.** Table II (2 pages). Ordering information is given on any current masthead page.

## References and Notes

(1) J. F. Ruppert and J. D. White, *J. Org. Chem.*, **39**, 269 (1974).
(2) M. W. Rathke, *Org. React.*, **22**, 423 (1975).
(3) For a summary, see G. Courtois and L. Miginiac, *J. Organomet. Chem.*, **69**, 1 (1974).
(4) M. P. Dreyfuss, *J. Org. Chem.*, **28**, 3269 (1963).
(5) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances", Prentice-Hall, Englewood Cliffs, N.J., 1954, p 1155.
(6) M. D. Abenhaim and E. Henry-Basch, *C. R. Acad. Sci., Ser. C*, **267**, 87 (1968).
(7) T. Takemoto and T. Nakajima, *Yakugaku Zasshi*, **77**, 1310 (1957).
(8) "Senecialdehyde" [R. Heilmann and R. Glénat, *Bull. Soc. Chim. Fr.*, 1586 (1955)].
(9) H. Staudinger, W. Kreis, and W. Schilt, *Helv. Chim. Acta*, **5**, 743 (1922).
(10) R. Ratcliffe and R. Rodenhorst, *J. Org. Chem.*, **35**, 4000 (1970).
(11) P. A. Stadler, A. Nechvatal, A. J. Frey, and A. Eschenmoser, *Helv. Chim. Acta*, **40**, 1373 (1957).
(12) E. E. van Tamelen, G. M. Milne, M. I. Suffiness, M. C. Rudler, R. J. Anderson, and R. S. Achiniv, *J. Am. Chem. Soc.*, **92**, 7702 (1970).
(13) M. Gaudemar, *Bull. Soc. Chim. Fr.*, **7**, 1475 (1963).
(14) J. Huet, *Bull. Soc. Chim. Fr.*, **10**, 2677 (1964).
(15) D. Abenhaim, E. Henry-Basch, and P. Freon, *Bull. Soc. Chim. Fr.*, 4038 (1969).

# Crystal and Molecular Structure of Cephalotaxine

Satish K. Arora, Robert B. Bates,* and Raymond A. Grady

*Department of Chemistry, University of Arizona, Tucson, Arizona 85721*

Gabriel Germain and Jean P. Declercq

Laboratoire de Chimie-Physique, Bâtiment Lavoisier, 1348, Louvain-la-Neuve, Belgium

Richard G. Powell

*Northern Regional Research Laboratory, Agricultural Research Service, USDA, Peoria, Illinois 61604*

*Received June 6, 1975*

The natural antileukemic esters of caphalotaxine (**1**) include homoharringtonine (**2**), which is undergoing preclinical testing.[1] As these esters are unfortunately noncrystalline, x-ray studies to reveal the conformational preferences of the cephalotaxine portion are limited to other derivatives, e.g., cephalotaxine *p*-bromobenzoate (**3**).[2] Prior to our study of the latter derivative (**3**), we had initiated an

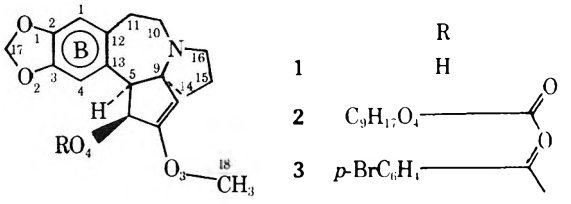


Table I
Fractional Coordinates and Estimated Standard Deviations in Molecules 1a and 1b

| Atom | x/a | | y/b | | z/c | |
|---|---|---|---|---|---|---|
| | 1a | 1b | 1a | 1b | 1a | 1b |
| O1 | 0.0676 (3) | 0.2427 (2) | −0.7615 (7) | 0.7842 (6) | 0.8860 (3) | 0.5325 (2) |
| O2 | 0.1050 (3) | 0.1730 (2) | −0.5379 (7) | 0.5584 (6) | 0.9689 (3) | 0.5008 (2) |
| O3 | −0.1110 (2) | 0.2329 (2) | 0.0883 (6) | 0.4723 (7) | 0.6009 (2) | 0.9492 (2) |
| O4 | −0.0946 (2) | 0.1988 (2) | −0.1699 (6) | 0.6433 (6) | 0.7088 (2) | 0.8074 (2) |
| N | 0.0802 (2) | 0.3768 (2) | −0.2399 (7) | 0.4027 (6) | 0.6729 (2) | 0.8377 (2) |
| C1 | 0.0219 (3) | 0.2948 (3) | −0.5985 (9) | 0.7432 (8) | 0.7651 (4) | 0.6742 (3) |
| C2 | 0.0526 (4) | 0.2538 (3) | −0.6162 (9) | 0.7009 (8) | 0.8426 (4) | 0.5997 (3) |
| C3 | 0.0758 (3) | 0.2135 (3) | −0.4850 (9) | 0.5654 (8) | 0.8927 (3) | 0.5807 (3) |
| C4 | 0.0686 (3) | 0.2127 (3) | −0.3273 (9) | 0.4637 (8) | 0.8656 (3) | 0.6353 (3) |
| C5 | 0.0282 (3) | 0.2493 (3) | −0.1268 (7) | 0.3975 (7) | 0.7564 (3) | 0.7739 (3) |
| C6 | −0.0440 (2) | 0.2116 (3) | −0.0581 (8) | 0.4708 (8) | 0.7193 (3) | 0.8166 (3) |
| C7 | −0.0522 (3) | 0.2573 (3) | 0.0116 (7) | 0.4318 (8) | 0.6444 (3) | 0.9000 (3) |
| C8 | −0.0007 (3) | 0.3125 (3) | −0.0041 (8) | 0.3599 (8) | 0.6322 (3) | 0.9124 (3) |
| C9 | 0.0557 (3) | 0.3177 (3) | −0.0917 (7) | 0.3319 (8) | 0.6977 (3) | 0.8387 (3) |
| C10 | 0.0302 (3) | 0.3936 (3) | −0.3560 (9) | 0.5740 (8) | 0.6213 (3) | 0.8613 (3) |
| C11 | −0.0190 (3) | 0.3352 (3) | −0.4088 (8) | 0.6904 (8) | 0.6498 (3) | 0.8162 (3) |
| C12 | 0.0139 (3) | 0.2940 (3) | −0.4374 (8) | 0.6443 (8) | 0.7360 (3) | 0.7322 (3) |
| C13 | 0.0367 (3) | 0.2532 (3) | −0.3038 (7) | 0.5039 (7) | 0.7863 (3) | 0.7134 (3) |
| C14 | 0.1191 (3) | 0.3279 (3) | 0.0087 (9) | 0.1469 (9) | 0.7331 (3) | 0.8259 (3) |
| C15 | 0.1520 (4) | 0.4027 (3) | −0.0181 (11) | 0.1200 (9) | 0.6814 (5) | 0.8676 (4) |
| C16 | 0.1196 (3) | 0.4318 (3) | −0.1755 (10) | 0.2929 (9) | 0.6362 (4) | 0.8888 (4) |
| C17 | 0.0948 (6) | 0.1983 (4) | −0.7137 (13) | 0.6846 (12) | 0.9640 (6) | 0.4711 (4) |
| C18 | −0.1182 (4) | 0.2746 (4) | 0.1529 (11) | 0.4315 (11) | 0.5280 (4) | 1.0292 (4) |
| HO4 | −0.111 (2) | 0.160 (2) | 0.875 (7) | 0.644 (7) | 0.730 (2) | 0.781 (3) |
| HC1 | 0.007 (2) | 0.327 (2) | 0.315 (7) | 0.818 (7) | 0.728 (2) | 0.681 (2) |
| HC4 | 0.085 (2) | 0.182 (2) | 0.773 (6) | 0.382 (6) | 0.896 (2) | 0.619 (2) |
| HC5 | 0.058 (2) | 0.224 (2) | 0.938 (6) | 0.300 (6) | 0.802 (2) | 0.749 (2) |
| HC6 | −0.048 (2) | 0.160 (2) | 0.029 (6) | 0.405 (6) | 0.750 (2) | 0.802 (3) |
| HC8 | 0.001 (2) | 0.349 (2) | 0.022 (6) | 0.325 (7) | 0.583 (2) | 0.962 (3) |
| H1C10 | 0.059 (2) | 0.441 (2) | 0.562 (7) | 0.613 (7) | 0.615 (2) | 0.857 (3) |
| H2C10 | 0.004 (2) | 0.410 (2) | 0.689 (7) | 0.586 (7) | 0.565 (3) | 0.912 (3) |
| H1C11 | −0.061 (2) | 0.299 (2) | 0.665 (7) | 0.680 (7) | 0.632 (3) | 0.841 (3) |
| H2C11 | −0.049 (2) | 0.361 (2) | 0.505 (7) | 0.800 (7) | 0.618 (3) | 0.812 (3) |
| H1C14 | 0.150 (2) | 0.308 (2) | 0.978 (7) | 0.063 (7) | 0.788 (3) | 0.856 (3) |
| H2C14 | 0.110 (2) | 0.311 (2) | 0.127 (7) | 0.119 (7) | 0.741 (3) | 0.776 (3) |
| H1C15 | 0.203 (2) | 0.425 (2) | 0.977 (8) | 0.056 (8) | 0.717 (3) | 0.828 (3) |
| H2C15 | 0.153 (2) | 0.412 (2) | 0.083 (8) | 0.054 (8) | 0.646 (3) | 0.924 (3) |
| H1C16 | 0.157 (2) | 0.451 (2) | 0.754 (7) | 0.316 (7) | 0.629 (3) | 0.946 (3) |
| H2C16 | 0.089 (2) | 0.475 (2) | 0.839 (7) | 0.323 (7) | 0.580 (3) | 0.886 (3) |
| HIC17 | 0.147 (3) | 0.230 (3) | 0.247 (10) | 0.603 (8) | 0.982 (4) | 0.449 (3) |
| H2C17 | 0.055 (3) | 0.169 (3) | 0.277 (10) | 0.709 (8) | 0.983 (4) | 0.420 (3) |
| H1C18 | −0.078 (3) | 0.327 (2) | 0.222 (8) | 0.487 (8) | 0.532 (3) | 1.053 (3) |
| H2C18 | −0.142 (3) | 0.279 (2) | 0.202 (8) | 0.327 (8) | 0.520 (3) | 1.039 (3) |
| H3C18 | −0.129 (3) | 0.250 (2) | 0.063 (8) | 0.472 (8) | 0.493 (3) | 1.062 (3) |

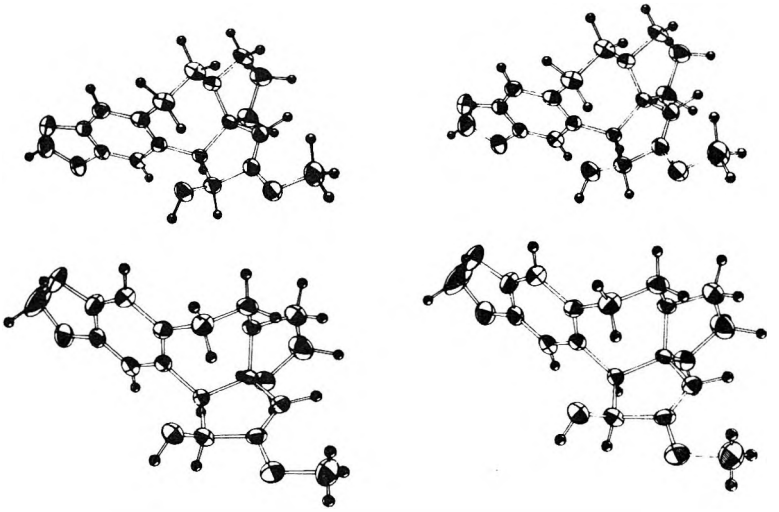


**Figure 1.** Stereoscopic view of cephalotaxine molecules **1a** (above) and **1b** (below). Hydrogen atoms are shown as spheres, and other atoms as 50% probability ellipsoids.

x-ray study on cephalotaxine (1) itself; after an uneventful data collection, we were unable to solve the phase problem by direct methods. Recently, vector search methods have revealed the structure, and we now wish to report the conformations of the two independent cephalotaxine molecules (**1a** and **1b**) in these crystals.

Table II
Bond Lengths in Molecules 1a and 1b

| Atoms | Distance, Å | | Atoms | Distance, Å | |
|---|---|---|---|---|---|
| | 1a | 1b | | 1a | 1b |
| 01–C2 | 1.402 (9) | 1.393 (8) | C12–C13 | 1.396 (8) | 1.411 (8) |
| 01–C17 | 1.409 (10) | 1.414 (8) | C14–C15 | 1.529 (11) | 1.529 (9) |
| 02–C3 | 1.387 (7) | 1.397 (5) | C15–C16 | 1.539 (10) | 1.533 (9) |
| 02–C17 | 1.447 (11) | 1.428 (10) | 04–H | 0.82 (6) | 0.80 (5) |
| 03–C7 | 1.362 (6) | 1.362 (9) | C1–H | 0.95 (5) | 0.92 (5) |
| 03–C18 | 1.457 (9) | 1.442 (7) | C4–H | 0.98 (5) | 0.90 (5) |
| 04–C6 | 1.410 (7) | 1.432 (8) | C5–H | 0.98 (4) | 0.97 (4) |
| N–C9 | 1.502 (8) | 1.478 (8) | C6–H | 0.97 (5) | 1.19 (6) |
| N–C10 | 1.463 (7) | 1.466 (8) | C8–H | 0.99 (6) | 0.98 (4) |
| N–C16 | 1.484 (10) | 1.487 (7) | C10–H1 | 0.99 (6) | 1.15 (6) |
| C1–C2 | 1.350 (9) | 1.359 (7) | C10–H2 | 1.05 (5) | 0.89 (5) |
| C1–C12 | 1.410 (9) | 1.397 (9) | C11–H1 | 1.05 (5) | 1.14 (6) |
| C2–C3 | 1.381 (9) | 1.373 (9) | C11–H2 | 0.97 (5) | 1.09 (6) |
| C3–C4 | 1.371 (9) | 1.360 (9) | C14–H1 | 1.01 (5) | 1.12 (6) |
| C4–C13 | 1.386 (8) | 1.406 (6) | C14–H2 | 1.02 (6) | 0.89 (5) |
| C5–C6 | 1.564 (7) | 1.570 (9) | C15–H1 | 1.05 (5) | 1.18 (7) |
| C5–C9 | 1.569 (9) | 1.577 (6) | C15–H2 | 1.08 (7) | 1.15 (6) |
| C5–C13 | 1.536 (8) | 1.502 (9) | C16–H1 | 1.09 (6) | 1.01 (5) |
| C6–C7 | 1.499 (8) | 1.501 (7) | C16–H2 | 0.99 (5) | 1.05 (6) |
| C7–C8 | 1.311 (9) | 1.306 (9) | C17–H1 | 1.11 (8) | 1.18 (7) |
| C8–C9 | 1.509 (6) | 1.514 (9) | C17–H2 | 1.18 (8) | 0.93 (5) |
| C9–C14 | 1.520 (8) | 1.565 (9) | C18–H1 | 1.06 (7) | 1.15 (6) |
| C10–C11 | 1.531 (10) | 1.536 (8) | C18–H2 | 0.74 (6) | 0.86 (6) |
| C11–C12 | 1.508 (8) | 1.514 (7) | C18–H3 | 0.95 (6) | 1.08 (7) |

Table III
Bond Angles in Molecules 1a and 1b with Estimated Standard Deviations[a]

| Atoms | Angle, deg | | Atoms | Angle, deg | |
|---|---|---|---|---|---|
| | 1a | 1b | | 1a | 1b |
| 01–C2–C1 | 128.5 | 128.2 | C14–C15–C16 | 104.2 | 104.5 |
| 01–C2–C3 | 108.8 | 109.4 | 01–C17–H1 | 97.6 | 104.8 |
| C2–01–C17 | 106.2 | 105.3 | 01–C17–H2 | 104.9 | 121.5 |
| 01–C17–02 | 108.9 | 109.6 | 02–C17–H1 | 98.9 | 104.4 |
| 02–C3–C2 | 110.7 | 110.4 | 02–C17–H2 | 99.5 | 111.8 |
| 02–C3–C4 | 128.2 | 127.5 | 03–C18–H1 | 115.5 | 113.3 |
| C3–02–C17 | 104.8 | 104.0 | 03–C18–H2 | 99.6 | 114.6 |
| 03–C7–C6 | 115.0 | 114.1 | 03–C18–H3 | 107.5 | 108.4 |
| 03–C7–C8 | 129.7 | 130.7 | 04–C6–H | 104.5 | 106.8 |
| C7–03–C18 | 114.0 | 115.5 | C6–04–H | 101.3 | 100.8 |
| 04–C6–C5 | 116.9 | 116.0 | N–C10–H1 | 109.1 | 111.1 |
| 04–C6–C7 | 112.4 | 110.1 | N–C10–H2 | 112.6 | 111.7 |
| N–C9–C5 | 115.0 | 115.2 | N–C16–H1 | 124.1 | 115.4 |
| N–C9–C8 | 114.0 | 115.4 | N–C16–H2 | 107.8 | 110.3 |
| N–C9–C14 | 99.5 | 99.8 | C2–C1–H | 125.9 | 115.5 |
| C9–N–C10 | 117.1 | 118.4 | C12–C1–H | 116.9 | 125.3 |
| N–C10–C11 | 113.7 | 112.2 | C3–C4–H | 126.8 | 117.1 |
| C9–N–C16 | 105.6 | 104.4 | C13–C4–H | 115.2 | 124.7 |
| C10–N–C16 | 110.5 | 110.3 | C5–C6–H | 111.6 | 115.3 |
| N–C16–C15 | 104.8 | 104.3 | C6–C5–H | 116.8 | 103.4 |
| C1–C2–C3 | 122.7 | 122.4 | C9–C5–H | 106.5 | 104.5 |
| C2–C1–C12 | 117.1 | 117.3 | C13–C5–H | 95.5 | 108.7 |
| C1–C12–C11 | 119.8 | 119.9 | C7–C6–H | 109.1 | 105.7 |
| C1–C12–C13 | 120.5 | 120.8 | C7–C8–H | 125.8 | 127.3 |
| C2–C3–C4 | 121.1 | 122.0 | C9–C8–H | 121.4 | 120.2 |
| C3–C4–C13 | 117.9 | 117.8 | C9–C14–H1 | 113.4 | 112.2 |
| C4–C13–C5 | 117.6 | 117.9 | C9–C14–H2 | 111.2 | 113.7 |
| C4–C13–C12 | 120.6 | 119.6 | C10–C11–H1 | 115.6 | 108.8 |
| C5–C6–C7 | 102.4 | 102.5 | C10–C11–H2 | 113.2 | 101.0 |
| C6–C5–C9 | 106.9 | 106.5 | C11–C10–H1 | 107.7 | 112.2 |
| C5–C9–C8 | 103.4 | 103.2 | C11–C10–H2 | 108.7 | 112.3 |
| C5–C9–C14 | 112.6 | 111.3 | C12–C11–H1 | 111.2 | 103.3 |
| C6–C5–C13 | 115.6 | 116.5 | C12–C11–H2 | 114.6 | 102.7 |
| C9–C5–C13 | 115.2 | 115.5 | C14–C15–H1 | 108.3 | 114.8 |
| C5–C13–C12 | 121.8 | 122.4 | C14–C15–H2 | 118.5 | 104.5 |
| C6–C7–C8 | 115.2 | 115.1 | C15–C14–H1 | 110.9 | 104.7 |
| C7–C8–C9 | 112.2 | 112.5 | C15–C14–H2 | 116.2 | 109.7 |
| C8–C9–C14 | 112.8 | 112.4 | C15–C16–H1 | 108.4 | 112.8 |
| C9–C14–C15 | 106.1 | 105.4 | C15–C16–H2 | 115.8 | 120.1 |
| C10–C11–C12 | 112.3 | 113.9 | C16–C15–H1 | 114.4 | 108.0 |
| C11–C12–C13 | 119.7 | 119.2 | C16–C15–H2 | 95.7 | 107.6 |

[a] The average estimated standard deviations in angles are 0.3° for angles involving nonhydrogen atoms and 2.0° for angles involving hydrogens.

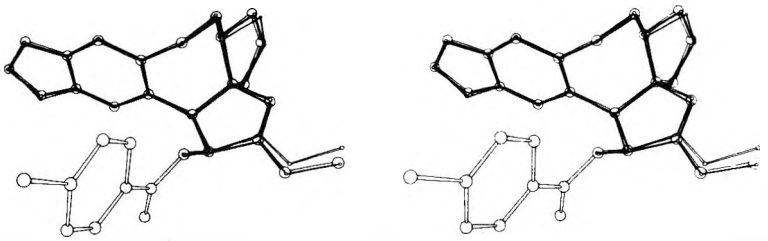


**Figure 2.** A stereoview comparing **1a**, **1b** (smallest atoms and bonds), and **3** (largest atoms and bonds) after least-squares fitting of the B rings.[5]

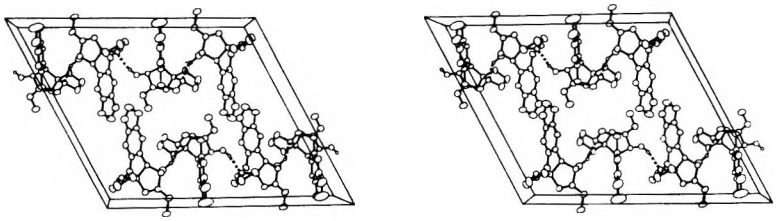


**Figure 3.** Stereoscopic view of a unit cell, *b* axis projection, with the *a* axis horizontal, the *c* axis approximately vertical, and dashed lines representing hydrogen bonds.

## Experimental Section

**Collection and Reduction of the Data.** Oscillation and Weissenberg photographs of a 0.3 × 0.3 × 0.5 mm needle of **1** grown from ether indicated space group *C*2. The cell parameters were found by least-squares fitting of the settings for four angles of eight reflections on a Picker-FACS-I diffractometer (Cu K$\alpha$, $\lambda$ = 1.54178 Å, graphite monochromator) to be $a$ = 22.834 (5), $b$ = 8.158 (3), $c$ = 19.534 (4) Å, $\beta$ = 117.7 (1)°, $\rho_c$ = 1.298 g/ml ($\rho_0$ = 1.291 g/ml), and $Z$ = 8. Intensity data were collected using a scintillation counter with pulse-height analyzer, $\theta$–2$\theta$ scan technique, 2°/min scan rate, 10-sec background counts, attenuators when the count rate exceeded $10^4$ counts/sec, and 2° scan range with a dispersion factor allowing for $\alpha_1$-$\alpha_2$ splitting at large 2$\theta$ values. Of 2910 independent reflections measured, 2690 > 3$\sigma$(I) were considered observed. Three standard reflections were monitored every 50 measurements to check crystal alignment and the stability; no decrease in the intensity of standards was observed. Lorentz and polarization corrections were applied to the data, but no correction was made for absorption.

**Solution and Refinement.** The structure was solved by the vector search method using the coordinates of the cephalotaxine part of cephalotaxine *p*-bromobenzoate;[2] two minima were obtained, corresponding to the two molecules in the asymmetric unit. The initial calculations of structure factors gave an $R$ value of 0.252. Two cycles of isotropic least-squares refinement of nonhydrogen atoms reduced $R$ to 0.122 and two more cycles of anisotropic least-squares refinement of nonhydrogen atoms brought $R$ to 0.077. A difference map at this stage revealed all the hydrogen atoms. One more cycle of least-squares refinement using anisotropic temperature factors for nonhydrogen atoms and isotropic temperature factors (of nonhydrogen atoms to which they were attached) for hydrogen atoms reduced $R$ to 0.052. The refinement was terminated at this stage with the ratios of shifts in parameters to estimated standard deviations all less than 0.3. Refinement was based on $F_0$, the quantity minimized being $\Sigma\omega(F_0 - F_c)^2$. Unit weights were used throughout the refinement. The scattering factors used were those of Hanson et al.[3] No correction was applied for extinction.

## Results and Discussion

Table I gives the observed fractional coordinates in **1a** and **1b**, and Figure 1 shows ORTEP[4] drawings of both molecules. Table II gives bond lengths and Table III bond angles. In Figure 2, the conformations of cephalotaxine molecules **1a** and **1b** and cephalotaxine *p*-bromobenzoate (**3**)[2] are compared after least-squares fitting of the aromatic ring carbons.[5] *The extreme similarity of the conformations of the cephalotaxine portion of these three molecules provides strong support for the view that the antileukemic esters of cephalotaxine, e.g.,* **2**, *share this conformation.*[2] It should be noted that Dreiding models permit considerable flexibility for the seven-membered ring, and from these models, it is not obvious that the observed conformation should be preferred.

Figure 3 shows the molecular packing, governed by hydrogen bonds between the alcohol proton in **1a** and the nitrogen in **1b** (2.92 Å between O4 and N) and the alcohol proton in **1b** and the nitrogen in **1a** (2.94 Å between O4 and N); these bonds form chains of molecules parallel to the diagonals of the *ab* face. Other short intermolecular distances between nonhydrogen atoms are O3–O2 (3.12 Å), O3–C3 (3.25 Å), O4–C16 (3.29 Å), and O3–C2 (3.21 Å).

**Acknowledgments.** We thank the Public Health Service (CA-10944) for financial aid and the University of Arizona Computer Center for computer time.

**Registry No.**—**1**, 24316-19-6.

**Supplementary Material Available.** Tables of temperature factors and torsion angles (4 pages). Ordering information is given on any current masthead page.

## References and Notes

(1) R. G. Powell, D. Weisleder, and C. R. Smith, Jr., *J. Pharm Sci.*, **61**, 1227 (1972), and references cited therein.
(2) S. K. Arora, R. B. Bates, R. A. Grady, and R. G. Powell, *J. Org. Chem.*, **39**, 1269 (1974); an x-ray study has also been carried out on racemic cephalotaxine methiodide [D. J. Abraham, R. D. Rosenstein, and E. L. McGandy, *Tetrahedron Lett.*, 4085 (1969)].
(3) H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Crystallogr., Sect. B.*, **17**, 1040 (1964).
(4) C. K. Johnson, ORTEP ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(5) Obtained with the aid of the program BMFIT: S. C. Nyburg, *Acta Crystallogr., Sect. B*, **30**, 251 (1974).

---

# Crystal Structure of 1-(*o*-Chlorophenyl)-1-(*p*-chlorophenyl)-2,2-dichloroethane

Satish K. Arora and Robert B. Bates*

*Department of Chemistry, University of Arizona, Tucson, Arizona 85721*

*Received June 6, 1975*

1,1-Dichloro-2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)ethane (I, *o,p'*-DDD), strikingly close in structure to the insecticides *o,p'*- (II) and *p,p'*-DDT (III), is used in the treatment of tumors of the adrenal cortex.[1] However, the mech-

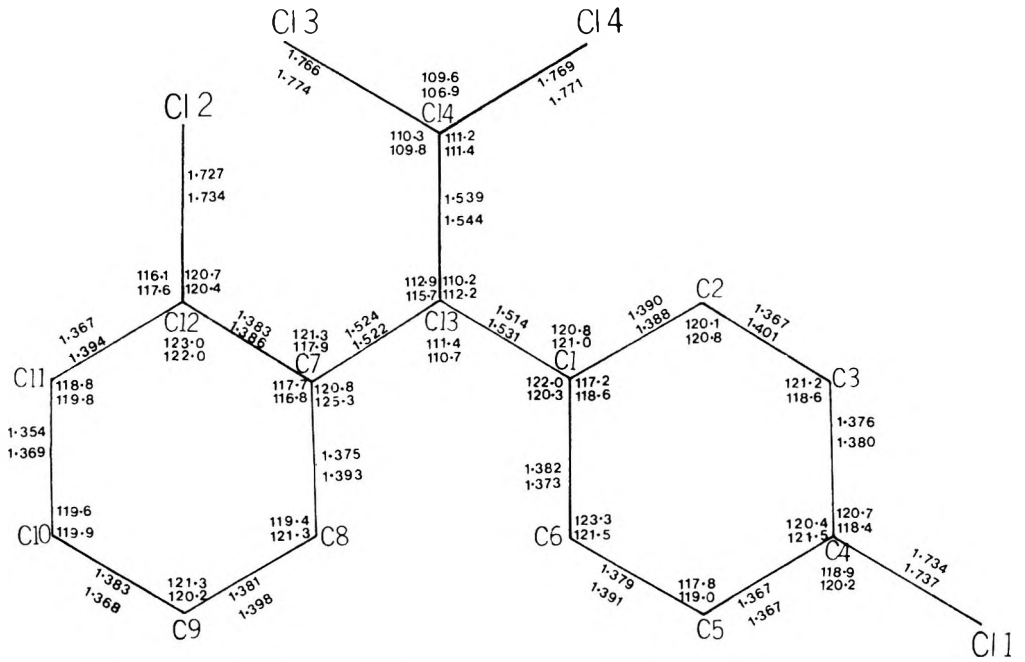



**Figure 1.** Bond distances (Å) and angles (°) in *o,p'*-DDD (I, above) and *o,p'*-DDT (II, below).[2]

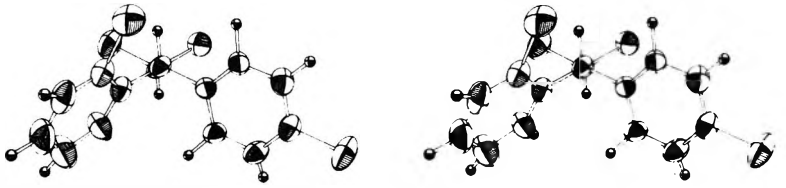
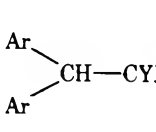


**Figure 2.** Stereoscopic view of an *o,p'*-DDD (I) molecule. Hydrogen atoms are depicted as spheres, and other atoms as 50% probability ellipsoids.

anism of its action and the reason why it acts so differently from the structurally related insecticides remain unknown. In the hope that a knowledge of the preferred conformation of *o,p'*-DDD (I) will aid in answering the above questions, an x-ray study was undertaken on the drug itself; similar studies had been carried out earlier on the insecticides II and III.[2]



| | | Ar | Ar′ | Y |
|---|---|---|---|---|
| I | | *o*-$ClC_6H_4$ | *p*-$ClC_6H_4$ | H |
| II | | *o*-$ClC_6H_4$ | *p*-$ClC_6H_4$ | Cl |
| III | | *p*-$ClC_6H_4$ | *p*-$ClC_6H_4$ | Cl |

## Experimental Section

Colorless crystals of *o,p'*-DDD (I, $C_{14}H_{10}Cl_4$) were grown from ethanol–water. A needle 0.2 × 0.2 × 0.3 mm was mounted with the *a* axis parallel to the goniostat $\phi$ axis. The space group was determined by film methods to be $P2_1/c$. The cell parameters were determined by least-squares fitting of the settings for the four angles of seven reflections on a Picker FACS-I diffractometer (Cu K$\alpha$, $\lambda$ = 1.54178 Å, graphite monochromator) to be $a$ = 6.136 (3), $b$ = 9.712 (5), c = 23.603 (9) Å, $\beta$ = 93.35 (3)°, and $Z$ = 4. The crystal density was measured by flotation as 1.49 g/ml, agreeing well with a calculated density of 1.50 g/ml. Intensity data were collected using a scintillation counter with pulse-height analyzer, $\theta$–$2\theta$ scan, 2°/min scan rate, 10-sec background counts, attenuators when the scan rate exceeded $10^4$ counts/sec, and 2° scan range with a dispersion factor allowing for $\alpha_1$–$\alpha_2$ splitting at large $2\theta$ values. Of 2474 independent reflections measured, 1881 > $3\sigma$(I) were considered observed. Three standard reflections were monitored every 50 measurements; no decrease in the intensity of standards was observed. Lorentz and polarization corrections were applied, but no correction was made for absorption ($\mu$ = 70.9 $cm^{-1}$).

Phases for reflections with normalized structure factor $E$ > 1.5 were generated using the direct method program MULTAN.[3] All nonhydrogen atoms were located on an $E$ map using calculated phases as coefficients. Full matrix least-squares refinement in which positional and isotropic thermal parameters were varied reduced $R$ to 0.166. Two more cycles of least-squares refinement using anisotropic thermal parameters reduced $R$ to 0.105. A difference map at this stage revealed all the hydrogen atoms. Two more cycles of least-squares refinement using anisotropic temperature factors for nonhydrogen atoms and isotropic temperature factors (of nonhydrogen atoms to which they were attached) for hydrogen atoms brought $R$ to 0.069. A difference map failed to show any unaccounted electron density, and refinement was terminated at this stage with the ratios of shifts in parameters to estimated standard deviations all less than 0.5. Refinements were based on $F_0$, the quantity minimized being $\Sigma w(F_0 - F_c)^2$. The weighting scheme used was based on counter statistics as defined by Corfield et al.,[4] the value of $p$ being 0.04. The scattering factors used were those of Hanson et al.[5] (anomalous scattering factors for Cl). No correction was applied for extinction.

## Results and Discussion

Table I shows the observed atomic coordinates. Figure 1 gives the bonds lengths and angles in I and II;[2] average standard deviations in I are 0.004, 0.006, and 0.04 Å for C–Cl, C–C, and C–H bonds, respectively, and 0.2, 0.3, and 1.2° for Cl–C–C, C–C–C, and H–C–C angles, respectively.

Figure 2 gives the conformation and thermal ellipsoids[6] of I, and Figure 3 compares the conformations of the antitumor agent I and the insecticide II. These conformations can be largely described in terms of the torsion angles about the C13–C14, C13–C1, and C13–C7 bonds. About C13–C14, I possesses almost perfect staggering with the hydrogens anti; in II and III, the deviation from perfect staggering in somewhat greater.[2] In all three structures, one aromatic ring is within a few degrees (2, 4, and 4° for I, II, and III, respectively) of the "butterfly" angle;[2] in the first two of these substances, it is the o-chlorophenyl ring, and the chlorine on this ring takes the position *away* from the other chlorines. The largest conformational difference

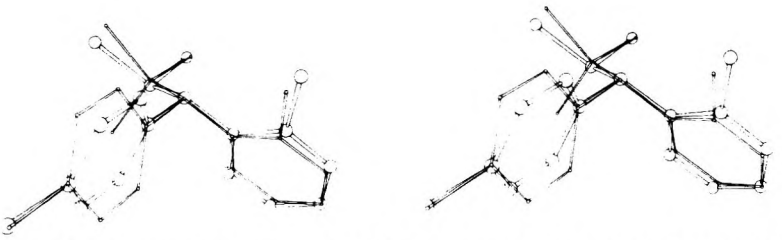


**Figure 3.** Stereoscopic view comparing I (larger atoms) and II,[2] with least-squares fitting of C1, C4, C7, C10, C13, and C11.[7]

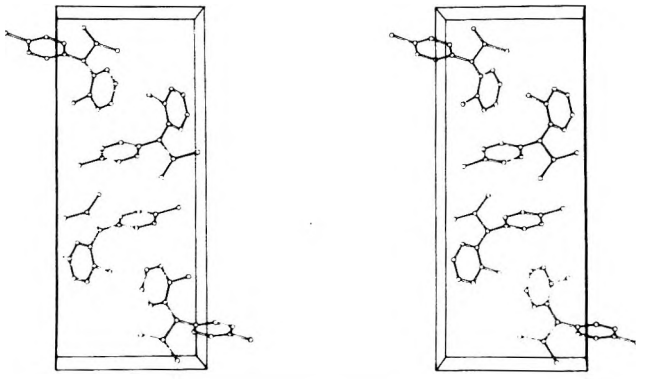


**Figure 4.** Stereoscopic view of a unit cell, *a* axis projection, *b* axis horizontal, *c* axis vertical.

Table I
Fractional Coordinates and Estimated Standard Deviations

| Atom | *x/a* | *y/b* | *z/c* |
|---|---|---|---|
| Cl1 | 0.5464 (3) | 0.1565 (2) | 0.4397 (1) |
| Cl2 | −0.0152 (3) | 0.6226 (2) | 0.2480 (1) |
| Cl3 | −0.0429 (2) | 0.6983 (2) | 0.4756 (1) |
| Cl4 | −0.0342 (3) | 0.9429 (2) | 0.4061 (1) |
| C1 | 0.2296 (8) | 0.5599 (5) | 0.3880 (2) |
| C2 | 0.4400 (8) | 0.5569 (5) | 0.4133 (2) |
| C3 | 0.5343 (9) | 0.4340 (6) | 0.4288 (2) |
| C4 | 0.4250 (9) | 0.3116 (5) | 0.4196 (2) |
| C5 | 0.2212 (9) | 0.3101 (5) | 0.3929 (2) |
| C6 | 0.1268 (8) | 0.4348 (5) | 0.3781 (2) |
| C7 | 0.2399 (8) | 0.7666 (5) | 0.3244 (2) |
| C8 | 0.4080 (10) | 0.8569 (6) | 0.3373 (2) |
| C9 | 0.5222 (12) | 0.9122 (7) | 0.2940 (3) |
| C10 | 0.4678 (12) | 0.8810 (7) | 0.2378 (3) |
| C11 | 0.3038 (11) | 0.7910 (6) | 0.2248 (2) |
| C12 | 0.1911 (9) | 0.7367 (5) | 0.2678 (2) |
| C13 | 0.1217 (8) | 0.6952 (5) | 0.3713 (2) |
| C14 | 0.1007 (8) | 0.7865 (5) | 0.4240 (2) |
| HC2 | 0.511 (6) | 0.645 (4) | 0.412 (2) |
| HC3 | 0.665 (6) | 0.434 (4) | 0.452 (2) |
| HC5 | 0.145 (6) | 0.235 (4) | 0.388 (2) |
| HC6 | −0.047 (6) | 0.442 (4) | 0.366 (2) |
| HC8 | 0.438 (6) | 0.899 (4) | 0.383 (2) |
| HC9 | 0.604 (6) | 1.005 (4) | 0.304 (2) |
| HC10 | 0.548 (6) | 0.927 (4) | 0.205 (2) |
| HC11 | 0.286 (6) | 0.769 (4) | 0.183 (2) |
| HC13 | −0.041 (6) | 0.679 (4) | 0.358 (2) |
| HC14 | 0.229 (6) | 0.811 (4) | 0.439 (2) |

comes in the rotation of the remaining *p*-chlorophenyl ring of each compound: the deviations from the "butterfly" angle are 24, 47, and 33° for I, II, and III, respectively. In I, the 24° rotation decreases repulsion between (a) the C14 hydrogen and the nearby ortho hydrogen on the *p*-chlorophenyl ring, and (b) the chlorine on the o-chlorophenyl ring and the other ortho hydrogen on the *p*-chlorophenyl ring. In II and III, a chlorine replaces the hydrogen on C14, and further rotation is required to minimize the energy. Thus, the conformation of the antitumor agent I in this crystal differs somewhat from those of the crystalline insecticides II and III.[2] The slight differences observed may be responsible for the difference in activity, but unfortunately neither activity is as yet well understood.[2,8]

Figure 4 shows the packing diagram for I. The only intermolecular distances less than 3.5 Å are 3.353 (Cl3–Cl5) and 3.434 Å (Cl1–Cl4).

**Acknowledgments.** We thank the Public Health Service (CA-10944) for financial aid and the University of Arizona Computer Center for computer time.

**Registry No.**—*o,p'*-DDD, 53-19-0.

**Supplementary Material Available.** Tables of temperature factors, bond distances and angles involving hydrogens, and torsion angles (3 pages). Ordering information is given on any current masthead page.

## References and Notes

(1) F. E. Knock, "Anticancer Agents", Charles C. Thomas, Springfield, Ill., 1967, pp 205–206.
(2) T. P. DeLacy and C. H. L. Kennard, *J. Chem. Soc., Perkin Trans. 2*, 2148 (1972).
(3) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970).
(4) P. W. R. Corfield, R. J. Deodens, and J. A. Ibers, *Inorg. Chem.*, **6**, 197 (1967).
(5) H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Crystallogr., Sect. B*, **17**, 1040 (1964).
(6) C. K. Johnson, ORTEP, ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(7) Calculated with the aid of the program BMFT: S. C. Nyburg, *Acta Crystallogr., Sect. B*, **30**, 251 (1974).
(8) For conflicting views on the reason for the insecticidal activity of II and III, see E. F. Rogers, H. D. Brown, I. M. Rasmussen, and R. E. Neal, *J. Am. Chem. Soc.*, **75**, 2991 (1953); R. Reimschneider and H. D. Otto, *Z. Naturforsch.*, **9b**, 95 (1954).

## An Improved Synthesis of Dichloromethylenetriphenylphosphorane

Beverly A. Clement and Robert L. Soulen*

*Department of Chemistry, Southwestern University, Georgetown, Texas 78626*

*Received July 1, 1975*

The phosphorus ylide, dichloromethylenetriphenylphosphorane (II), has been shown to be of good synthetic utility in the Wittig method of converting aldehydes,[1-3] ketones,[1,2] keto esters,[3] and acyl cyanides[4,5] to the corresponding 1,1-dichloroethylene derivatives.

Methods previously reported for the preparation of II include (a) the reaction of potassium *tert*-butoxide with chloroform in the presence of triphenylphosphine,[1] (b) the reaction of triphenylphosphine with $PhHgCCl_2X$, where X = Cl or Br,[6] and (c) the reaction of triphenylphosphine with carbon tetrachloride.[2] The last procedure offers several advantages, among which are simplicity and cost of the starting materials. It does have the disadvantage of being rather slow, i.e., several days at 0°. This time may be shortened by heating the reaction mixture to reflux; however, by-prod-

Table I
Conversion of Acyl Cyanides to 2-Substituted 3,3-Dichloroacrylonitriles

| RCOCN, R | $Cl_2C$=CRCN, % yield | |
|---|---|---|
| | $CCl_4$ [a] method | $CCl_3Br$ [b] |
| Ia, $CH_3$ | 61 | 90 |
| Ib, $CH_3CH_2$ | 45 [c] | 82 |
| Ic, $(CH_3)_2CH$ | 40 [c] | 87 |
| Id, $(CH_3)_3C$ | 48 | 91 |
| Ie, $p$-$ClC_6H_4$ | 20 | 43 |
| If, $p$-$CH_3OC_6H_4$ | 60 | 85 |

[a] The $CCl_4$, triphenylphosphine procedure is reported in ref 4 and 5. [b] Yield based on pure distilled or recrystallized product. [c] Yield based on VPC analysis of crude distillate.

ucts and lower yields result whenever more sensitive carbonyl components are added.[4,5]

We now wish to report on an improved method for the preparation of II and some reactions of II with acyl and aroyl cyanides. It has been found that the substitution of bromotrichloromethane for carbon tetrachloride allows the Wittig reagent II to be formed much faster and the concurrent reaction with the carbonyl component is significantly improved with higher yields and virtually no by-product formation. Gas chromatographic analysis of the crude reaction mixture does not show any of the bromochloroethylene derivative.

Although this procedure should be applicable toward the conversion of other carbonyl containing compounds to the dichlorovinyl group (=$CCl_2$) we have studied the carbonyl of acyl cyanides so that yields may be directly compared with our previous work.

$$2Ph_3P + Cl_3CBr \rightarrow Ph_3P{=}CCl_2 + Ph_3PBrCl$$

$$RCOCN + Ph_3P{=}CCl_2 \rightarrow Ph_3PO + Cl_2C{=}CRCN$$

In a typical reaction, excess dry bromotrichloromethane was added to 1.0 equiv of triphenylphosphine in sufficient dry benzene to produce a convenient volume. The mixture was stirred under a dry nitrogen atmosphere at 0° for 15–30 min, then 0.5 equiv of the acyl cyanide, Ia–f, was added and the mixture stirred at 0° for 2–4 hr. An immediate shift of the nitrile band as well as appearance of a strong =$CCl_2$ band in the 920–940-$cm^{-1}$ region was observed[7]. After approximately 30 min, large quantities of triphenylphosphine oxide began to precipitate from the reaction mixture. After 1–2 hr, the carbonyl stretching band was almost totally gone. Stirring the mixture for a longer period of time had little effect on the yield. In cases using aliphatic acyl cyanides, the reaction mixture was rapidly warmed and benzene, excess bromotrichloromethane, and liquid products were removed under vacuum. Unlike our previous report,[4] the 2-alkyl-3,3-dichloroacrylonitriles were virtually free of impurities and easily purified by simple distillation to give yields of 82–91% (Table I). With aroyl cyanides, the benzene and excess bromotrichloromethane was stripped from the reaction mixture and crude products extracted with boiling ligroin and the crude products recrystallized from anhydrous methanol to give yields of 43–85%.

## Experimental Section

All reactions were carried out under a dry nitrogen atmosphere. Boiling points and melting points are uncorrected. Infrared spectra were performed on a Beckman IR-8 and calibrated at 1601.0 $cm^{-1}$ with polystyrene film. Commercial triphenylphosphine was used without purification. The bromotrichloromethane and benzene were purified by atmospheric distillation, using only the center cuts.

**Acyl Cyanides.** The acyl cyanides used in this study were prepared according to procedures reported previously.[4,5]

**Reaction of II with Aliphatic Acyl Cyanides. General Procedure.** A mixture of triphenylphosphine (0.15 mol) and 80 ml of dry benzene was cooled in an ice bath and then 40 g of bromotrichloromethane was added. The mixture was stirred at 0° for 30 min and then 0.075 mol of the aliphatic acyl cyanide (Ia–d) was added rapidly. After maintaining the reaction at 0° for approximately 3 hr it was heated under vacuum (25–30 mm) to yield benzene, the excess bromotrichloromethane, and crude product. A second distillation of the crude product gave pure 2-alkyl-3,3-dichloroacrylonitriles with physical properties and ir spectra identical with those reported previously.[5]

**Reaction of II with Aryl Acyl Cyanides. General Procedure.** In a manner similar to that described above, the aryl acyl cyanide (Ie,f) was added rapidly to a mixture of benzene, triphenylphosphine, and bromotrichloromethane at 0°. After 3 hr, the mixture was vacuum stripped to remove the benzene and excess bromotrichloromethane. The solid residue was extracted three times with 100-ml portions of boiling ligroin. The combined extracts were cooled to remove most of the triphenylphosphine oxide. Concentration and cooling the extracts gave a crude product which was recrystallized twice from anhydrous methanol. The pure 2-aryl-3,3-dichloroacrylonitriles displayed physical properties and ir spectra identical with those reported previously.[4]

**Acknowledgment.** The support of this research by the Robert A. Welch Foundation is gratefully acknowledged.

**Registry No.**—Ia, 631-57-2; Ib, 4390-78-7; Ic, 42867-39-0; Id, 42867-40-3; Ie, 13014-48-7; If, 14271-83-1; II, 6779-08-4; triphenylphosphine, 603-35-0; bromotrichloromethane, 75-62-7; 2-methyl-3,3-dichloroacrylonitrile, 31413-58-8; 2-ethyl-3,3-dichloroacrylonitrile, 42791-06-0; 2-isopropyl-3,3-dichloroacrylonitrile, 42867-43-6; 2-*tert*-butyl-3,3-dichloroacrylonitrile, 42867-44-7; 2-(*p*-chlorophenyl)-3,3-dichloroacrylonitrile, 37447-52-2; 2-(*p*-methoxyphenyl)-3,3-dichloroacrylonitrile, 37447-53-3.

## References and Notes

(1) A. J. Speziale and K. W. Ratts, *J. Am. Chem. Soc.*, **84**, 854 (1962).
(2) R. Rabinowitz and R. Marcus, *J. Am. Chem. Soc.*, **84**, 1312 (1962).
(3) C. Raulet and E. Levas, *C. R. Acad. Sci., Ser. C*, **270**, 1467 (1970).
(4) B. A. Clement and R. L. Soulen, *J. Org. Chem.*, **39**, 97 (1974).
(5) R. L. Soulen, S. D. Carlson, and F. Lang, *J. Org. Chem.*, **38**, 479 (1973).
(6) D. Seyferth, H. D. Simmons, Jr., and G. Singh, *J. Organomet. Chem.*, **3**, 337 (1965).
(7) R. L. Soulen, D. B. Clifford, F. F. Crim, and J. A. Johnston, *J. Org. Chem.*, **36**, 3386 (1971).

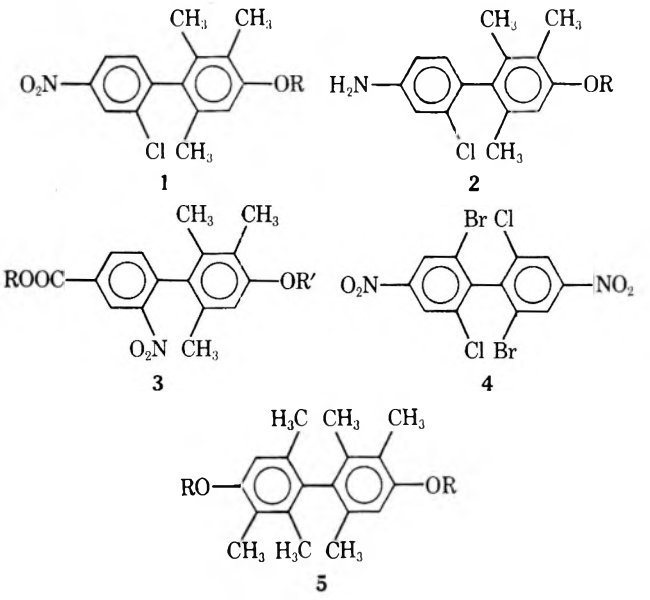
# Synthesis of Some New Hindered Biaryls

Harry W. Gibson* and F. C. Bailey

*Webster Research Center, Xerox Corporation, Webster, New York 14580*

*Received June 11, 1975*

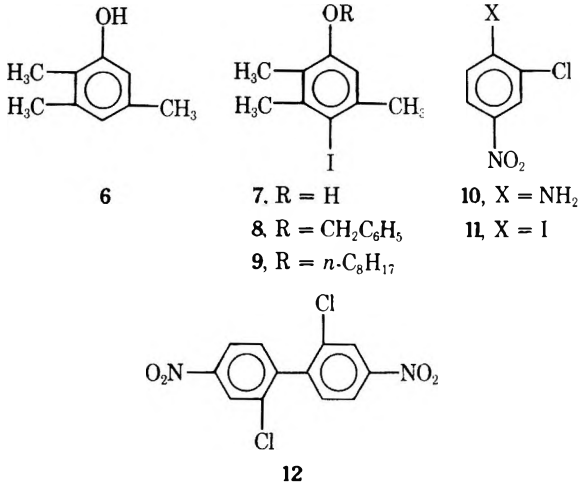
Our studies of the effects of chemical structure on molecular orbital energy levels and electron distributions[1–5] and associated electrical properties[6] have concerned themselves primarily with planar aromatic systems. Some such systems are subject to steric effects or nonbonded interactions which can lead to deviations from coplanarity and hence deviations from anticipated behavior. The biphenyl system is one whose susceptibility to these effects is well known.[7] The target structures **1–5** were designed with a view toward providing (1) a high rotational barrier about the biphenyl bond and (2) systems with an electron-rich ring and an electron-poor ring as well as ones with both rings electron poor or rich.



1 2 3 4 5

## Discussion

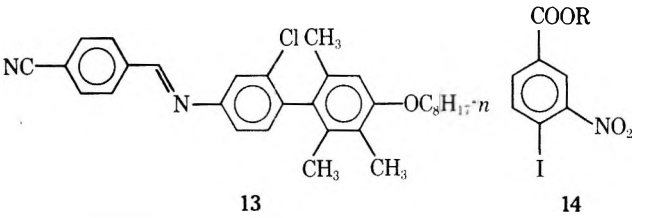
**A. Series 1.** The prime starting material in the synthesis of system 1 was 2,3,5-trimethylphenol (isopseudocumenol, **6**), which was converted to the known[8] **7** in 99% yield. Formation of the previously unreported benzyl ether **8** (85% yield) was accomplished by treatment of **7** with benzyl chloride in alkaline solution. Attempts to benzylate **7** without isolation from the reaction mixture were less efficient. Similarly the new *n*-octyl ether **9** was prepared in 97% yield using *n*-octyl iodide and **7**. A Sandmeyer reaction of diazotized **10** afforded a 71% yield of the desired 2-chloro-4-nitroiodobenzene (**11**).[9]



6 7, R = H 8, R = $CH_2C_6H_5$ 9, R = *n*-$C_8H_{17}$ 10, X = $NH_2$ 11, X = I 12

An Ullmann reaction of equimolar amounts of **8** and **11** led to the isolation of the desired 4-benzyloxy-2′-chloro-4′-nitro-2,3,6-trimethylbiphenyl (**1**, R = $CH_2C_6H_5$) in 36% yield (17% conversion) by means of column chromatography. Accompanying **1**, R = $CH_2C_6H_5$, was 2,2′-dichloro-4,4′-dinitrobiphenyl (**12**).[9] The desired **1**, R = H, was obtained in 88% yield by refluxing **1**, R = $CH_2C_6H_5$, with a 30% solution of HBr in acetic acid. Formation of octyl ether **1**, R = *n*-$C_8H_{17}$, was accomplished (89%) by treatment of **1**, R = H, with octyl iodide in alkaline medium. **1**, R = *n*-$C_8H_{17}$, can be obtained in a more direct manner via an Ullmann reaction of **9** and **11**. This transformation proceeded in 53% yield (17% conversion).

**B. Series 2.** The nitro group of **1**, R = *n*-$C_8H_{17}$, was reduced chemically with stannous chloride, affording a 97% yield of amine **2**, R = *n*-$C_8H_{17}$. Since **2**, R = *n*-$C_8H_{17}$, is an oil which could not be purified so as to afford satisfactory carbon analysis, it was derivatized. Condensation of **2**, R = *n*-$C_8H_{17}$, with *p*-cyanobenzaldehyde afforded anil **13** in 99% yield.



13 14

**C. System 3.** The approach to series **3** involves utilization of one of the starting materials used for series **1**, namely the benzyl ether **8**. The other starting material is of structure **14**, a 3 nitro-4-iodobenzoate ester. Nitration of ethyl *p*-iodobenzoate gives **14**, R = $C_2H_5$.[10] **9** and **14**, R = $C_2H_5$, were subjected to the conditions of the Ullmann reaction; by column chromatography **3**, R = $C_2H_5$, R′ = *n*-$C_8H_{17}$, was isolated in 8% yield. The ester was hydrolyzed to the desired acid **3**, R = H, R′ = *n*-$C_8H_{17}$, in 90% yield.

**D. Series 4.** Treatment of **12** with bromine in the presence of silver sulfate and sulfuric acid[11] led to the isolation of only dibromo derivative **4** in quantitative yield. Attempted brominations using organothallium intermediates were fruitless; apparently the aromatic rings of **12** are too deactivated for reaction with these species.

**E. Series 5.** Subjection of **8** to conditions of the Ullmann reaction for normal reaction times led primarily to recovery of starting material. Extended reaction times (60 hr) caused charring—no identifiable products were isolated. The procedure was that of previous workers who had succeeded in coupling 2,6-dimethyliodobenzene to form 2,2′,6,6′-tetramethylbiphenyl.[12] The present result is somewhat surprising, but can be explained by the presence of the deactivating benzyloxy group and increased steric hindrance at the 1-(iodo) position owing to the buttressing effect of the 3-methyl substituent.

As an alternative to the Ullmann synthesis of **5**, R = $CH_2C_6H_5$, a method previously employed for the synthesis of bimesityl[13] was utilized. The Grignard reagent derived from **8** was treated with cupric chloride in anhydrous ether. The hydrolysis product, 3-benzyloxy-1,2,5-trimethylbenzene, which was also synthesized from isopseudocumenol (**6**), was isolated in 80% yield. This result in light of the synthesis of bimesityl is surprising; it can be rationalized only in terms of the buttressing effect of the 3 and 4 substituents of the Grignard reagent prepared from 4-benzyloxy-2,3,6-trimethyliodobenzene. This apparently makes the 1 position very sterically hindered, even to a greater extent than in that derived from iodomesitylene (2,4,6-trimethyliodobenzene), so that the Grignard reagent does not couple. Thus, attempted syntheses of **5**, R = $CH_2C_6H_5$, were unsuccessful.

## Experimental Section

**General.** Melting points were taken in capillaries on a Thomas-Hoover apparatus and are corrected. Infrared (ir) spectra were recorded on a Perkin-Elmer Model 137; nuclear magnetic resonance (NMR) spectra were recorded on a Joelco C-60H unit and all shifts are relative to internal tetramethylsilane. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

**4-Iodo-2,3,5-trimethylphenol (7).** This compound, mp 110.0–110.5°, was prepared from 2,3,5-trimethylphenol (**6**) by the method of Cressman and Thirtle[8] using hydrogen peroxide–iodine in 98% yield: reported[8] mp 112–113°; yield 88%; NMR ($CD_3COOD$) s, δ 2.20 (3 H, 2-$CH_3$); s, 2.34 (3 H, 3-$CH_3$); s, 2.42 (3 H, 5-$CH_3$); s, 6.70 (1 H, 6-H); s, 11.1 (1 H, OH); ir (KBr) 3300 $cm^{-1}$ (OH).

**4-Benzyloxy-2,3,6-trimethyliodobenzene (8).** A solution of

63.4 g (0.243 mol) of phenol **7**, 19.5 g (0.348 mol) of 87% potassium hydroxide, 670 ml of ethanol, and 31.4 g (0.248 mol) of benzyl chloride was refluxed overnight, concentrated by distillation of 400 ml of ethanol, and then poured into 1200 g of ice. After filtration the solid was washed with 5 *M* sodium hydroxide and water, then dried and recrystallized from ethanol to give 62.8 g (73%) of material, mp 69–74°. Two more recrystallizations gave colorless crystals, mp 74.0–76.0°. Anal. Calcd for $C_{16}H_{17}IO$: C, 54.56; H, 4.87. Found: C, 54.67; H, 4.89. NMR ($CDCl_3$) s, δ 2.26 (3 H, 3-$CH_3$); s, 2.44 (3 H, 2-$CH_3$); s, 2.46 (3 H, 6-$CH_3$); s, 4.95 (2 H, $OCH_2$); s, 6.69 (1 H, 5-H); s, 7.30 (5 H, aromatic); ir (KBr) 1110, 1230, 1260 $cm^{-1}$ ($ArOCH_2$–), no OH.

**4-Octyloxy-2,3,6-trimethyliodobenzene (9).** A solution of 21.0 g (0.0800 mol) of phenol **7**, 19.2 g (0.0800 mol) of *n*-octyl iodide, 5.87 g (0.0900 mol) of 87% potassium hydroxide, 225 ml of ethanol, and 100 ml of dioxane was refluxed for 18 hr. Then most of the ethanol was removed and the resultant mixture was poured into ice–water. The hexane extract was dried and reduced in volume, whereupon 10.9 g (36%) of solid, mp 29–30°, precipitated. The filtrate was eluted through a column of neutral alumina and yielded 11.2 g (37%) more of the same material. Two recrystallizations from methanol–hexane yielded colorless crystals, mp 30.0–31.0°. Anal. Calcd for $C_{17}H_{27}IO$: C, 54.55; H, 7.27; I, 33.91. Found: C, 54.72; H, 7.18; I, 34.03. NMR ($CDCl_3$) m, δ 0.7–2.18 (15 H, OC–$C_7H_{15}$); s, 2.21 (3 H, 3-$CH_3$); s, 2.45 (6 H, 2-$CH_3$, 6-$CH_3$); t (*J* = 6 Hz), 3.88 (2 H, $OCH_2C$); s, 6.63 (1 H, 5-H); ir (KBr) 1050, 1230, 1270 $cm^{-1}$ ($ArOCH_2$), no OH.

**Activated Copper Powder.** Copper powder was prepared by reduction of copper sulfate with zinc[14] and stored under water. To "activate" it, 114 g of wet copper powder was stirred in a solution of 30 g of iodine in 200 ml of acetone. After washing with acetone it was dried in a vacuum oven to give 67.7 g of catalyst. This "activation" process was carried out just prior to each Ullmann reaction.

**4-Benzyloxy-2′-chloro-4′-nitro-2,3,6-trimethylbiphenyl (1, R = $CH_2C_6H_5$).** An intimately ground mixture of 40.5 g (0.115 mol) of 4-benzyloxy-2,3,6-trimethyliodobenzene (**8**) and 32.5 (0.115 mol) of 2-chloro-4-nitroiodobenzene (**11**)[9] was charged to a 400-ml stainless steel beaker containing 1 g of activated copper powder and 2 ml of pyridine and heated with stirring in an oil bath to 220° and a total of 66.7 g of activated copper was added at a rate of approximately 5 g/min. After heating for 1.5 hr, the mixture was cooled and exhaustively extracted with benzene. Concentration of the extract gave 37.8 g of a dark brown oil. This was chromatographed on neutral alumina with 1:1 benzene–hexane to yield 12.4 g of recovered **8** and 7.3 g of desired biphenyl **1**, R = $CH_2C_6H_5$, mp 155–160°. Elution with 3:1 benzene–methanol gave 7.54 g of **12** (see below). Based on unrecovered starting material **11**, the yield and conversion for **1**, R = $CH_2C_6H_5$, are 36 and 54% and for **12**, 17 and 54%. After three recrystallizations from ethanol–acetone the pale yellow crystals of **1**, R = $CH_2C_6H_5$, had mp 165.0–166.0°. Anal. Calcd for $C_{22}H_{20}ClNO_3$: C, 69.20; H, 5.28; N, 3.67; Cl, 9.29. Found: C, 69.74; H, 5.36; N, 3.72; Cl, 9.36. NMR ($CDCl_3$) s, δ 1.97 (3 H, 3-$CH_3$); s, 2.01 (3 H, 2-$CH_3$); 2.31 (3 H, 6-$CH_3$); s, 5.13 (2 H, $OCH_2$); s, 6.86 (1 H, 5-H); m, 7.5 (6 H, 6′-H, $CH_2C_6H_5$); m, 8.4 (2 H, 3′,5′-H); ir (KBr) 1520, 875 ($NO_2$); 1130, 1230, 1260 $cm^{-1}$ ($ArOCH_2$–).

**2,2′-Dichloro-4,4′-dinitrobiphenyl (12).** The crude product (above) after recrystallizations from benzene had mp 107.0–108.5° (reported[9] mp 107°), yield 44% from **11**. Using the same procedure as for the preparation of **1**, R = $CH_2C_6H_5$, 25.0 g (0.0877 mol) of **11** and 18 g of activated copper and column chromatography on neutral alumina in benzene, 2.0 g (15%) of authentic **12** was isolated.

**2′-Chloro-4-hydroxy-4′-nitro-2,3,6-trimethylbiphenyl (1, R = H).** A solution of 4.04 g (0.0103 mol) of benzyl ether **1**, R = $CH_2C_6H_5$, and 40 ml of 30–32% HBr in acetic acid was refluxed for 2.5 hr and then poured over 125 g of ice. The methylene chloride extract yielded 4.37 g of brown oil. Chromatography of a benzene solution by elution with hexane yielded 0.22 g (100%) of benzyl bromide; elution with 1:1 benzene–methanol gave 2.65 g (88%) of crude product. Recrystallization from ethyl acetate–hexane three times gave tan crystals, mp 140.5–142.0°. Anal. Calcd for $C_{15}H_{14}ClNO_3$: C, 61.75; H, 4.84; N, 4.80. Found: C, 61.62; H, 4.91; N, 4.56. NMR ($CDCl_3$) s, δ 1.90 (6 H, 2,3-$CH_3$); s, 2.22 (3 H, 6-$CH_3$); s, 5.15 (1 H, OH); s, 6.63 (1 H, 5-H); d (*J* = 10 Hz), 7.29 (1 H, 6′-H); q (*J* = 2, 10 Hz), 8.17 (1 H, 5′-H); d (*J* = 2 Hz), 8.37 (1 H, 3′-H); ir (KBr) 3550 (OH); 1350, 1520 $cm^{-1}$ ($NO_2$).

**2′-Chloro-4′-nitro-4-octyloxy-2,3,6-trimethylbiphenyl (1, R = *n*-$C_8H_{17}$). Method A.** Iodo compound **9** (4.47 g, 0.0119 mol), 3.38 g (0.0119 mol) of 2-chloro-4-nitroiodobenzene (**11**),[9] and 11.9 g of "activated" copper were allowed to react by the procedure given above for the preparation of **1**, R = $CH_2C_6H_5$. Elution of the crude product from neutral alumina with 1:1 benzene–hexane gave 2.22 g of recovered **9** and 0.83 g of **1**, R = *n*-$C_8H_{17}$. Elution with 2% methanol–benzene gave 0.96 g of symmetrical biphenyl **12**. Based on unrecovered starting material the yield of **1**, R = *n*-$C_8H_{17}$, was 53% and that of **12** 67%. The conversion of **9** and **11** to **1**, R = *n*-$C_8H_{17}$, was 17%. Upon standing **1**, R = *n*-$C_8H_{17}$, crystallized. Several recrystallizations from chloroform–methanol by use of seed crystals led to off-white crystals, mp 59.5–60.5°. Anal. Calcd for $C_{23}H_{30}ClNO_3$: C, 68.39; H, 7.49; Cl, 8.78; N, 3.47. Found: C, 67.93; H, 7.26; Cl, 9.07; N, 3.57. NMR ($CDCl_3$) m, δ 0.6–2.24 [24 H, $OC(CH_2)_6CH_3$ and $CH_3$'s including s, 1.77 (3-$CH_3$), s, 1.83 (2-$CH_3$), s, 2.05 (6-$CH_3$)]; t (*J* = 6 Hz), 3.73 (2 H, $OCH_2$); s, 6.24 (1 H, 5-H); d (*J* = 8 Hz), 6.84 (1 H, 6′-H); q (*J* = 2, 8 Hz), 7.67 (1 H, 5′-H); d (*J* = 2 Hz), 7.85 (1 H, 3′-H); ir (neat) 1070, 1240, 1260, 1290 ($ArOCH_2$); 1360, 1560 $cm^{-1}$ ($NO_2$).

**Method B.** A solution of 5.00 g (0.0171 mol) of phenol **1**, R = H, 4.12 g (0.0171 mol) of *n*-octyl iodide, 1.26 g (0.0193 mol) of 87% potassium hydroxide, 30 ml of ethanol, and 20 ml of dioxane was refluxed for 22 hr, concentrated to ~one-half volume, and diluted with water. The ether extract was washed with 10% sodium hydroxide, water, saturated salt solution, and water and dried over sodium sulfate. Evaporation gave 6.18 g (89%) of crude **1**, R = *n*-$C_8H_{17}$.

**4′-Amino-2′-chloro-4-octyloxy-2,3,6-trimethylbiphenyl (2, R = *n*-$C_8H_{17}$).** A mixture of 4.80 g (0.0119 mol) of nitro compound **1**, R = *n*-$C_8H_{17}$, 10.7 g (0.0475 mol) of stannous chloride dihydrate, 30 ml of concentrated hydrochloric acid, and 90 ml of ethanol was refluxed for 18.5 hr, cooled, and poured into excess cold sodium hydroxide solution. The methylene chloride extract was washed with water, dried (sodium sulfate), and evaporated to afford 4.33 g (97%) of yellow oil. The oil was chromatographed on neutral alumina by elution with hexane and benzene–hexane mixtures. None of the fractions could be induced to crystallize. Anal. Calcd for $C_{23}H_{32}ClNO$: C, 73.87; H, 8.63; Cl, 9.48; N, 3.74. Found: C, 72.82; H, 8.30; Cl, 8.72; N, 3.57. NMR ($CDCl_3$) m, δ 0.4–2.14 [(24 H, $OC(CH_2)_6CH_3$ and s, 1.80 (3-$CH_3$), s, 1.84 (2-$CH_3$), s, 2.02 (6-$CH_3$)]; broad s, 3.37 (2 H, $NH_2$); t (*J* = 6 Hz), 3.70 (2 H, $OCH_2$-$CH_2$–); m, 6.05–6.87 (4 H, aromatic H); ir (neat) 1070, 1240, 1270, 1290 ($ArOCH_2$); 3390, 3480 $cm^{-1}$ ($NH_2$).

**4′-(*p*-Cyanobenzylideneamino)-2′-chloro-4-octyloxy-2,3,6-trimethylbiphenyl (13).** The amine **2**, R = *n*-$C_8H_{17}$, and an equimolar amount of *p*-cyanobenzaldehyde were heated in absolute ethanol in the presence of a drop of acetic acid for 4 hr while the ethanol was allowed to boil off. The residue was purified by recrystallization from hexane as pale yellow crystals, mp 96.5–98.5°. Anal. Calcd for $C_{31}H_{35}ClN_2O$: C, 76.44; H, 7.24; N, 5.75. Found: C, 76.13; H, 7.18; N, 5.63. Ir (KBr) 2250 $cm^{-1}$ (CN); 1010, 1030, 1040, 1060, 1240, 1270 $cm^{-1}$ ($ArOCH_2$); no C=O or NH.

**Ethyl 4-Iodo-3-nitrobenzoate (14, R = $C_2H_5$).** Nitration of ethyl *p*-iodobenzoate[10] with nitric acid–sulfuric acid[10] afforded the desired compound, mp 78–81° (methanol), as orange crystals in 29% yield (reported[10] mp 88–89.5°, yield 85%): NMR ($CDCl_3$) t (*J* = 7 Hz), δ 1.44 (3 H, $CH_3$); q, 4.45 (2 H, $CH_2$); q (*J* = 2, 8 Hz), 7.86 (1 H, 6-H); d (*J* = 8 Hz), 8.17 (1 H, 5-H); d (*J* = 2 Hz), 8.41 (1 H, 2-H).

**4′-Carbethoxy-2′-nitro-4-octyloxy-2,3,6-trimethylbiphenyl (3, R = $C_2H_5$; R′ = *n*-$C_8H_{17}$).** An Ullmann reaction of 10.9 g (0.0291 mol) of **9**, 3.2 g (0.0100 mol) of **14**, R = $C_2H_5$, and 5.52 g of activated copper by the method described above for the preparation of **1**, R = $CH_2C_6H_5$, and column chromatography on acidic alumina gave 0.33 g (7.5%) of crude **3**, R = $C_2H_5$; R′ = *n*-$C_8H_{17}$ (1:1 benzene–hexane elution). This oil could not be crystallized: NMR ($CDCl_3$) m, δ 0.5–2.14 [24 H, $OC(CH_2)_6CH_3$ and s, 1.75 (3-$CH_3$), s, 1.80 (2-$CH_3$), s, 2.00 (6-$CH_3$)]; t (*J* = 5 Hz), 3.67 (2 H, $OCH_2CH_2$); s, 6.19 (1 H, 5-H); d (*J* = 8 Hz), 6.91 (1 H, 5′-H); q (*J* = 2, 8 Hz), 7.87 (1 H, 6′-H); d (*J* = 2 Hz), 8.14 (1 H, 3′-H); broad s, 9.59 (–COOH); ir (neat) 1370, 1530 ($NO_2$); 1030, 1250, 1290, 1310 ($ArOCH_2$); 1750 $cm^{-1}$ (C=O).

**4′-Carboxy-2′-nitro-4-octyloxy-2,3,6-trimethylbiphenyl (3, R = H; R′ = *n*-$C_8H_{17}$).** A solution of 0.33 g (0.749 mmol) of the ester **3**, R = $C_2H_5$; R′ = *n*-$C_8H_{17}$, 0.15 g of sodium hydroxide, 5 ml of dioxane, and 2 ml of water was refluxed for 2 hr and poured into cold dilute hydrochloric acid. The ether extract was washed with water, dried (sodium sulfate), and evaporated, leaving 0.28 g (90%) of crude product. Three recrystallizations from ethyl acetate–hexane gave yellow crystals, mp 175.6–176.1°. Anal. Calcd for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.95; H, 7.48; N, 3.38. Ir (KBr) 1030, 1090, 1260, 1295 ($ArOCH_2$); 1360, 1520 ($NO_2$); 1700 (C=O); 3000–2500 $cm^{-1}$ (OH).

**2,2'-Dibromo-6,6'-dichloro-4,4'-dinitrobiphenyl (4).** Bromination of 12 by the method used by Harris and Mitchell[11] led to a quantitative yield of 4 as light orange plates, mp 157.8–160.0° (ethanol). Anal. Calcd for $C_{12}H_{14}Br_2Cl_2N_2O_4$: C, 30.61; H, 0.86; Br, 33.94. Found: C, 30.30; H, 0.91; Br, 34.70. Ir (KBr) 1360, 1530 $cm^{-1}$ ($NO_2$).

**Attempted Self-Coupling of 4-Benzyloxy-2,3,6-trimethyliodobenzene (8) via the Grignard Reagent.** The reported procedure for preparation of bimesityl[13] was applied to 8; the only product, formed in about 80% yield, was 3-benzyloxy-1,2,5-trimethylbenzene (see below).

**3-Benzyloxy-1,2,5-trimethylbenzene.** Benzylation of the phenol 6 by the procedure described above for the preparation of 8 led to a 75% yield of the ether as an oil. Elution through neutral alumina and distillation gave a colorless oil, bp 165° (2.7 mm), which crystallized (mp 34.5–37.5°). Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 85.44; H, 7.97. NMR ($CDCl_3$) s, δ 2.13 (6 H, 1,2-$CH_3$); s, 2.20 (3 H, 5-$CH_3$); s, 5.14 (2 H, $OCH_2$); broad s, 6.50 (2 H, 4,6-H); m, 7.2 (5 H, $C_6H_5$); ir (neat) 1120, 1225, 1250, 1290 $cm^{-1}$ ($ArOCH_2$–); no OH.

**Registry No.**—**1** (R = $CH_2C_6H_5$), 57362-66-0; **1** (R = H), 57362-67-1; **1** (R = $n$-$C_8H_{17}$), 57362-68-2; **2** (R = $n$-$C_8H_{17}$), 57362-69-3; **3** (R = $C_2H_5$; R' = $n$-$C_8H_{17}$), 57362-70-6; **3** (R = H; R' = $n$-$C_8H_{17}$), 57362-71-7; **4**, 57362-72-8; **6**, 697-82-5; **7**, 7282-02-2; **8**, 57362-73-9; **9**, 57362-74-0; **11**, 41252-96-4; **12**, 57362-75-1; **13**, 57362-76-2; **14** (R = $C_2H_5$), 57362-77-3; benzyl chloride, 100-44-7; $n$-octyl chloride, 629-27-6; $p$-cyanobenzaldehyde, 105-07-7; ethyl $p$-iodobenzoate, 51934-41-9; 3-benzyloxy-1,2,5-trimethylbenzene, 57362-78-4.

## References and Notes


(1) H. W. Gibson, *Can. J. Chem.*, **51**, 3065 (1973).
(2) J. E. Kuder, H. W. Gibson, and D. Wychick, *J. Org. Chem.*, **40**, 875 (1975).
(3) H. W. Gibson and F. C. Bailey, *Tetrahedron*, **30**, 2043 (1974).
(4) H. W. Gibson and F. C. Bailey, *Can. J. Chem.*, **53**, 2162 (1975).
(5) H. W. Gibson and F. C. Bailey, *J. Chem. Soc., Perkin Trans. 2*, in press.
(6) H. W. Gibson, *J. Am. Chem. Soc.*, **97**, 3832 (1975).
(7) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, p 156 ff; "Steric Effects in Conjugated Systems", G. W. Gray, Ed., Academic Press, New York, N.Y., 1958.
(8) H. W. J. Cressman and J. R. Thirtle, *J. Org. Chem.*, **31**, 1279 (1966).
(9) L. M. Litvinenko, A. P. Grekov, N. N. Verkhovod, and V. P. Dzyuba, *Zh. Obshch. Khim.*, **26**, 2524 (1956); *Chem. Abstr.*, **51**, 5008e (1957).
(10) N. E. Searle and R. Adams, *J. Am. Chem. Soc.*, **55**, 1649 (1933).
(11) M. M. Harris and R. K. Mitchell, *J. Chem. Soc.*, 1905 (1960).
(12) R. B. Carlin, *J. Am. Chem. Soc.*, **67**, 928 (1945).
(13) W. W. Mayer and R. Adams, *J. Am. Chem. Soc.*, **51**, 630 (1929).
(14) "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 446.


---

# A New γ-Keto Aldehyde Synthesis


John C. Stowell

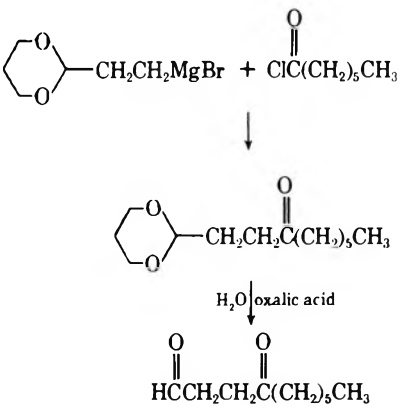
*Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70122*


*Received September 8, 1975*

γ-Keto aldehydes are an important class of compounds especially as intermediates for the preparation of cyclopentenones.[1] 1,4-Diketones have found wide application in the Paal–Knorr synthesis of pyrroles, furans, and thiophenes,[2] as well as in pyridazine synthesis,[3] which suggests that γ-keto aldehydes may be useful in the synthesis of these heterocycles as well. The available routes to γ-keto aldehydes include ring opening of substituted furans,[4] radical addition of an aldehyde to acrolein diethyl acetal,[5] oxidative cleavage of olefins,[6] alkylation of 2,4,4,6-tetramethyldihydrooxazine with 2-iodomethyl-1,3-dioxolane,[7] and alkylation of 2-ethoxyallyl vinyl sulfide followed by thio-Claisen rearrangement.[8] Recently a route using condensation of the dianion of γ-oxosulfone acetals with esters followed by removal of activating and protecting groups,[9] and another based on ring opening of cyclopropyl ketones followed by oxidation, were reported.[10] Most of these routes are either lengthy, require multistep preparation of a special reagent, or give low overall yields.

We have found a short route which begins with readily available materials, and gives high yields of γ-keto aldehyde, as outlined in Scheme I. Grignard reagents have

**Scheme I**




found occasional use for preparation of ketones from acid chlorides but the yields are usually low owing to reaction with the ketone, leading to tertiary alcohols.[11–13] Even at dry ice temperature and using inverse addition, the yields are not improved.[14] We have found that the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane is exceptional; it affords ketone in high yield with no more than a trace of tertiary alcohol at dry ice temperature.

Grignard reagents derived from β-halo ketals and acetals are known to be unstable[15] owing to their tendency to undergo intramolecular attack leading initially to cyclopropyl ethers. Büchi[16] and others[17] have used the reagent derived from 2-(2-bromoethyl)-1,3-dioxolane by preparing it at 30–35°. This reagent is destroyed if the solvent tetrahydrofuran (THF) is allowed to reflux. We chose to use the six-membered ring acetal and found that its greater stability allowed quick, high-yield preparation of the Grignard reagent at reflux in THF. This then gave 2-(3-oxononyl)-1,3-dioxane in 92% yield based on the bromo compound or the acid chloride.

The six-membered-ring acetal apparently has greater equilibrium stability than the five-membered ring, since boiling the intermediate in aqueous acid gives only partial hydrolysis to the keto aldehyde. However, the equilibrium is easily displaced toward hydrolysis with removal of the product by continuous steam distillation as it is formed. This gave γ-ketodecanal in 89% yield. This particular product is an intermediate in a synthesis of dihydrojasmone.[8] The Grignard reagent derived from 2-(2-bromoethyl)-4,4,6-trimethyl-1,3-dioxane also gives ketones in better than 90% yields but the acetal is more stable and therefore less readily removed with aqueous acid.

The usual technique for preventing overreaction is to first convert the Grignard to the zinc or cadmium reagent, which then affords ketones in better yields.[13,18] In our earlier efforts, we prepared the zinc reagent directly from 2-(2-iodoethyl)dioxolane at 51° in dimethylformamide (DMF);[19] however, we were unable to isolate any ketone products from reaction with acid chlorides. The formation of the organozinc iodide compounds could be followed in the NMR,[20] e.g., that from the iodoacetal gave a high-field triplet at δ 0.13 ppm, comparable with a quartet at δ 0.01 obtained from ethyl iodide and Zn in DMF. The Grignard

reagents may also be observed by NMR; that derived from 2-(2-bromoethyl )-1,3-dioxane in THF exhibits a high-field triplet at $\delta$-0.7 ppm.

## Experimental Section

**2-(2-Bromoethyl)-1,3-dioxane** was prepared from 1,3-propanediol, acrolein, and hydrogen bromide:[21] bp 67–70° (2.8 mm); 60-MHz NMR ($CCl_4$) $\delta$ 1.3 (m, 1 H), 2.1 (m, 3 H), 3.36 (t, 2 H), 3.9 (m, 4 H), 4.57 ppm (t, 1 H).

**2-(3-Oxononyl)-1,3-dioxane.** A 50-ml flask was equipped with a reflux condenser, nitrogen atmosphere, and magnetic stirring. In it was placed 0.97 g (0.040 mol) of magnesium turnings, 25 ml of dry THF, and 5.85 g (0.0300 mol) of 2-(2-bromoethyl)-1,3-dioxane. This was heated to reflux and the heat immediately removed. The exothermal reaction was moderated at reflux by occasional application of an ice bath. After 10 min, heat was applied to maintain refluxing for an additional 10 min. After cooling to room temperature the solution was drawn up into a 50-ml syringe, leaving the excess magnesium behind.

A 100-ml flask was equipped with a nitrogen atmosphere and magnetic stirring. In it was placed 4.46 g (0.0300 mol) of heptanoyl chloride and 25 ml of dry THF. This was cooled in a dry ice–2-propanol bath, and the Grignard reagent solution was added dropwise from the syringe with stirring over a 20-min period. It was warmed to room temperature over 45 min and then rotary evaporated to remove the THF. The residual oil was poured into 75 ml of water, and 20 ml of cyclohexane was added to extract the product. The organic layer was separated and washed with two 60-ml portions of aqueous sodium carbonate, dried with potassium carbonate, and rotary evaporated. The residual oil was passed through a short column of silica gel eluting with 10% ethyl acetate in cyclohexane. All volatile materials were then removed by evaporation at 0.3 mm in a warm water bath. This gave 6.29 g (92%) of pale yellow oil: homogeneous by TLC and GC; ir ($CCl_4$) 1720 $cm^{-1}$, no absorption for OH; 60-MHz NMR ($CCl_4$) $\delta$ 0.7–2.0 (overlapping m's, 15 H), 2.3 (m, 4 H), 3.8 (m, 4 H), 4.43 ppm (t, 1 H).

The semicarbazone was recrystallized from cyclohexane to mp 110–110.5°.

Anal. Calcd for $C_{14}H_{27}N_3O_3$: C, 58.92; H, 9.54; N, 14.72. Found: C, 59.14; H, 9.55; N. 14.68.

**4-Oxodecanal.** A Dean-Stark trap was modified to return the bottom layer and retain the upper layer, and fitted on a 50-ml flask. In the flask was placed 2.28 g (0.0100 mol) of the keto acetal, 1.00 g of oxalic acid, and 20 ml of water. The Dean-Stark trap was also filled with water. The mixture was heated at reflux with vigorous magnetic stirring for 3 hr, during which time the product continuously steam distilled into the trap. After cooling, the organic layer was taken up in ether, washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and rotary evaporated, giving 1.52 g (89%). Vacuum distillation gave 1.28 g of colorless liquid: bp 70° (0.25 mm); ir ($CCl_4$) 2730, 1735 (shoulder), 1712 $cm^{-1}$;[8,10] 60-MHz NMR ($CCl_4$) $\delta$ 0.70–2.0 (overlapping m's, 11 H), 2.40 (m, 2 H), 2.60 (s, 4 H), 9.58 ppm (s, 1 H).

Treatment with semicarbazide gave the bissemicarbazone, white crystals (ethanol), mp 180–181°.

Anal. Calcd for $C_{12}H_{24}N_6O_2$: C, 50.68; H, 8.51; N, 29.55. Found: C, 50.73; H, 8.66; N, 29.33.

**Registry No.**—2-(2-Bromoethyl)-1,3-dioxane, 33884-43-4; 2-(3-oxononyl)-1,3-dioxane, 57345-99-0; 2-(3-oxononyl)-1,3-dioxane semicarbazone, 57346-00-6; heptanoyl chloride, 2528-61-2; 4-oxodecanal, 43160-78-7; 4-oxodecanal bissemicarbazone, 57346-01-7.

## References and Notes


(1) R. A. Ellison, *Synthesis*, 397 (1973).
(2) G. M. Badger, "The Chemistry of Heterocyclic Compounds", Academic Press, New York, N.Y., 1961.
(3) M. Tisler and B. Stanovnik, *Adv. Heterocycl. Chem.*, **9**, 226 (1968).
(4) G. W. K. Cavill, B. S. Goodrich, and D. G. Laing, *Aust. J. Chem.*, **23**, 83 (1970).
(5) A. Mondon, *Angew. Chem.*, **64**, 224 (1952).
(6) C. Harries, *Chem. Ber.*, **36**, 1933 (1903); P. M. McCurry, Jr., and K. Abe, *Tetrahedron Lett.*, 1387 (1974); R. A. Ellison, E. R. Lukenbach, and C-w. Chiu, *ibid.*, 499 (1975); E. Brown and A. Bonte, *ibid.*, 2881 (1975).
(7) A. I. Meyers and N. Nazarenko, *J. Org. Chem.*, **38**, 175 (1973).
(8) K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **95**, 4446 (1973).
(9) K. Kondo and D. Tunemoto, *Tetrahedron Lett.*, 1397 (1975).
(10) T. Nakai, E. Wada, and M. Okawara, *Tetrahedron Lett.*, 1531 (1975).
(11) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances", Prentice-Hall, Englewood Cliffs, N.J., 1954, p 712.
(12) W. C. Percival, R. B. Wagner, and N. C. Cook, *J. Am. Chem. Soc.*, **75**, 3731 (1953).
(13) D. A. Shirley, *Org. React.*, **8**, 28 (1954).
(14) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).
(15) C. Feugeas, *Bull. Soc. Chim. Fr.*, 2568 (1963).
(16) G. Büchi and H. Wüest, *J. Org. Chem.*, **34**, 1122 (1969).
(17) H. J. J. Loozen, *J. Org. Chem.*, **40**, 520 (1975).
(18) K. Nützel in Houben-Weyl, "Methoden der Organischen Chemie", Vol. 13/2a, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1973, pp. 634, 779.
(19) R. Joly and R. Bucourt, U.S. Patent 3,040,079 (1962); *Chem. Abstr.*, **58**, 10238a (1963).
(20) D. F. Evans and J. P. Maher, *J. Chem. Soc.*, 5125 (1962).
(21) D. C. Kriesel and O. Gisvold, *J. Pharm. Sci.*, **60**, 1250 (1971).

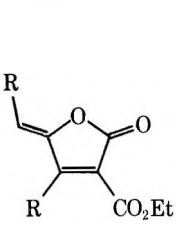

# Synthesis of α-Carbalkoxy-γ-alkylidene-$\Delta^{\alpha,\beta}$-butenolides


Arthur G. Schultz* and Ying K. Yee

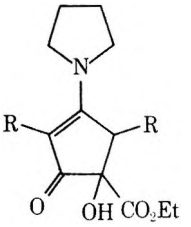
*Department of Chemistry, Cornell University, Ithaca, New York 14853*


*Received September 23, 1975*

In connection with a projected synthesis of certain sesquiterpenes, several α-carbalkoxy-γ-alkylidene-$\Delta^{\alpha,\beta}$-butenolides[1] were required, e.g., **1** and **10**. Although γ-arylidene analogues of **1** have been reported,[2] the methods employed did not seem compatible with an efficient synthesis of the desired butenolides.

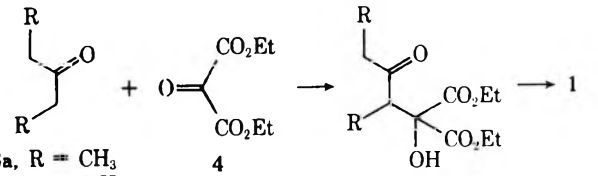


**1a**, R = $CH_3$
**b**, R = $C_6H_5$



**2a**, R = $CH_3$
**b**, R = $C_6H_5$

In principle, condensation of ketone **3** with diethyl ketomalonate (**4**) would give an α-hydroxy-γ-keto diester **5**, which might serve as a precursor to **1** via enol lactonization–dehydration. Direct condensation of diethyl ketomalonate (**4**) with tetrahydro-γ-pyrone in unspecified yield has been reported,[3] but we were unable to effectively react **3** with **4** under a variety of standard acid- or base-catalyzed conditions. Hence, we sought alternate methodology and now record a potentially general synthesis of α-carbalkoxy-γ-alkylidene-$\Delta^{\alpha,\beta}$-butenolides from diethyl ketomalonate (**4**) and describe simple reaction modifications which allow preparation of 3-dialkylamino-2-cyclopenten-1-ones **2** as well.



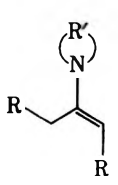
**3a**, R = $CH_3$
**b**, R = $C_6H_5$

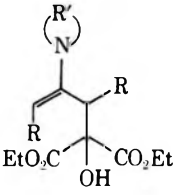
**4**

**5a**, R = $CH_3$
**b**, R = $C_6H_5$

Reaction of the morpholine enamine **6a**[4] of 3-pentanone with 1 equiv of diethyl ketomalonate (**4**) in benzene solution at 25°, followed by treatment with sodium acetate–aqueous acetic acid solution, gave α-hydroxy-γ-keto diester **5a** in excellent yield (80% isolated; analytically pure). In-

terestingly, when the pyrrolidine enamine **6b** was substituted for **6a**, the presence of keto diester **5a** could not be detected; rather, cyclopentenone **2a** was isolated in 68% yield. Presumably the greater reactivity of the pyrrolidine enamine intermediate **7a** toward internal acylation is responsible for this dramatic change in reaction. A high reactivity of pyrrolidine enamines toward acylation previously has been noted.[4]

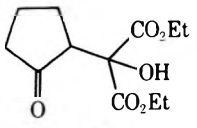




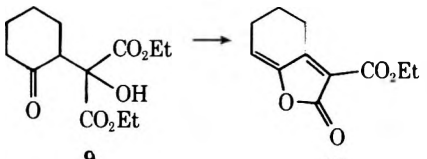
7

**6a**, R = $CH_3$; R′ = $CH_2CH_2OCH_2CH_2$
**b**, R = $CH_3$; R′ = $CH_2CH_2CH_2CH_2$
**c**, R = $C_6H_5$; R′ = $CH_2CH_2OCH_2CH_2$
**d**, R = $C_6H_5$; R′ = $CH_2CH_2CH_2CH_2$

In contrast to the conversion **3a** → **5a**, condensation of the morpholine enamine **6c** (as well as the pyrrolidine enamine) of 1,3-diphenylacetone with diethyl ketomalonate (**4**) did not give **5b**; cyclopentenone **2b** was isolated in high yield. Apparently the enamine $\beta$-carbon atom in intermediate **7c**, with a planar aryl substituent, is not sufficiently hindered to retard internal acylation. As was expected, with enamines derived from cycloalkanones, both the pyrrolidine enamine of cyclopentanone and cyclohexanone gave the respective $\alpha$-hydroxy-$\gamma$-keto diester **8** and **9** in excellent yields.



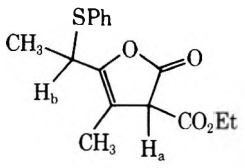
8



9 10

A variety of methods were explored for converting the $\alpha$-hydroxy-$\gamma$-keto diesters to the required butenolides; however, all proved radically inferior to a new technique for a one experimental step enol lactonization–dehydration effected with phosphorus pentoxide in methanesulfonic acid.[5] Thus, heating a solution of **5a** in a 1:10 solution by weight of phosphorus pentoxide in methanesulfonic acid at 50° for 5 hr followed by destruction of excess reagent by pouring into ice water gave $\alpha$-carbethoxy-$\beta$-methyl-$\gamma$-ethylidene-$\Delta^{\alpha,\beta}$-butenolide (**1a**) in 74% yield. Similarly, **9** was converted to butenolide **10** in 84% isolated yield. On the other hand, the butenolide desired from cyclopentanone **8** apparently is too unstable for preparation by methods outlined here (see Experimental Section).

Dehydration of $\alpha$-hydroxy diesters with phosphorus pentoxide–methanesulfonic acid reagent must be an exceedingly mild procedure, because butenolides **1a** and **10** are unusually reactive. For example, substantial decomposition of pure crystalline material to an uncharacterized polymeric substance occurs within hours at room temperature. Storage of crystalline material at −15° results in slow decomposition (~10% per week); methylene chloride solutions of **1a** or **10** have been stored at −15° for weeks with little decomposition. Rapid polymerization of ether solutions of **1a** occurs on treatment with aqueous bicarbonate or amines. On the other hand, a trace of triethylamine added to a methanolic solution of **1a** and 1 equiv of benzenethiol results in nearly instantaneous 1,6 addition to give substituted $\Delta^{\beta,\gamma}$ butenolide **11** in 81% isolated yield.[6]



11

We also have investigated the direct condensation of ketones with diethyl ketomalonate in phosphorus pentoxide–methanesulfonic acid reagent. Reaction of an equimolar mixture of 3-pentanone and diethyl ketomalonate in excess reagent gave **1a** in modest yield (19–23% isolated). Of even greater interest, 1,3-diphenylacetone and diethyl ketomalonate gave $\alpha$-carbethoxy-$\beta$-phenyl-$\gamma$-benzylidene-$\Delta^{\alpha,\beta}$-butenolide (**1b**) in 31% yield. Although the direct condensation suffers from low yield, it currently represents the only synthesis for certain butenolides (e.g., **1b**).

## Experimental Section

**General.** Proton NMR spectra were obtained on a Varian A-60A NMR spectrometer (tetramethylsilane internal standard, deuteriochloroform solvent). Proton spin decoupling experiments were performed on a Bruker HX-90 high-resolution NMR spectrometer. Chemical ionization and electron impact mass spectra were obtained on a Finnigan 3300 gas chromatograph–mass spectrometer and infrared spectra were recorded on a Perkin-Elmer Model 137B infrared spectrometer. Melting points were measured on a calibrated Thomas-Hoover capillary melting point apparatus, and all reactions were performed under a dry nitrogen atmosphere. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

**Ethyl 2-Hydroxy-2-carbethoxy-3-methyl-4-oxohexanoate (5a).** To an ice-cooled stirred solution of the morpholine enamine of 3-pentanone[4] (5.44 g, 35.0 mmol) in benzene (8 ml) was added diethyl ketomalonate (**4**,[7] 5.35 ml, 35.0 mmol). Stirring was continued at low temperature for 5 min and at 25° for 2.5 hr, after which a solution (14 ml) of sodium acetate (20%) in acetic acid–water (1:1)[4] was added and the resulting two-phase system was vigorously shaken for 15 min. Extraction with chloroform (2 × 25 ml) followed by water wash (2 × 25 ml) of the chloroform layer, drying over anhydrous magnesium sulfate, rotoevaporation of solvent, and distillation gave **5a** as a colorless liquid [7.19 g, 79%, bp 92–93° (0.07 mm)]: ir (neat) 3.10 (m) and 5.80 $\mu$ (s); $^1$H NMR $\delta$ 1.07 (3 H, triplet, $J$ = 7.0 Hz), 1.25 (3 H, doublet, $J$ = 7.0 Hz), 1.26 (3 H, triplet, $J$ = 7.0 Hz), 1.30 (3 H, triplet, $J$ = 7.0 Hz), 2.61 (2 H, quartet, $J$ = 7.0 Hz), 3.58 (1 H, quartet, $J$ = 7.0 Hz), 4.25 (2 H, quartet, $J$ = 7.0 Hz), 4.32 (2 H, quartet, $J$ = 7.0 Hz), and 4.48 (1 H, singlet, replaceable on addition of deuterium oxide); chemical ionization mass spectrum $m/e$ 261.

Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74; O, 36.88. Found: C, 55.33; H, 7.82.

**2,4-Dimethyl-3-pyrrolidinyl-5-hydroxy-5-carbethoxy-2-cyclopenten-1-one (2a).** Substitution of the pyrrolidine enamine of 3-pentanone **6b**[4] for **6a** in the preceding procedure gave after crystallization from ether **2a** (68%, mp 142.5–143.5°): ir (Nujol) 3.10 (m), 5.80 (s), and 6.00 $\mu$ (s); $^1$H NMR $\delta$ 1.17 (3 H, doublet, $J$ = 7.0 Hz), 1.26 (3 H, triplet, $J$ = 7.0 Hz), 1.94 (3 H, singlet), 1.75–2.20 (4 H, multiplet), 3.28 (1 H, quartet, $J$ = 7.0 Hz), 3.50–3.95 (4 H, multiplet), and 4.18 (2 H, quartet, $J$ = 7.0 Hz); chemical ionization mass spectrum $m/e$ 268.

Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24; O, 23.94. Found: C, 62.98; H, 7.88.

**2,4-Diphenyl-3-pyrrolidinyl-5-hydroxy-5-carbethoxy-2-cyclopenten-1-one (2b).** Reaction of the pyrrolidine enamine of 1,3-diphenylacetone **6d**[8] and diethyl ketomalonate by the procedure described for preparation of **5a** gave after crystallization from methylene chloride–ether **2b** (80%, mp 146–148°): ir (Nujol) 2.62 (m), 5.79 (s), 6.00 (s), 6.24 (m), and 6.41 $\mu$ (m); $^1$H NMR $\delta$ 1.32 (3 H, triplet, $J$ = 7.0 Hz), 1.50–1.95 (4 H, multiplet), 2.73–3.37 (4 H,

broad singlet), 3.63 (1 H, singlet, replaceable on addition of deuterium oxide), 4.31 (2 H, quartet, $J$ = 7.0 Hz), 4.64 (1 H, singlet), 7.35 (10 H, singlet).

**2-[Bis(carbethoxy)hydroxymethyl]cyclopentanone (8).** Reaction of the pyrrolidine enamine of cyclopentanone[4] and diethyl ketomalonate by the procedure described for preparation of **5a** gave after distillation **8** as a colorless oil [79%, bp 98–100° (0.07 mm)]: ir (neat) 2.80 (m) and 5.75 $\mu$ (s); $^1$H NMR $\delta$ 1.30 (3 H, triplet, $J$ = 7.0 Hz), 1.33 (3 H, triplet, $J$ = 7.0 Hz), 1.57–2.55 (6 H, multiplet), 3.24 (1 H, broad triplet, $J$ = 8.0 Hz), 4.12 (1 H, broad singlet, replaceable on addition of deuterium oxide), 4.29 (2 H, quartet, $J$ = 7.0 Hz), 4.38 (2 H, quartet, $J$ = 7.0 Hz).

**2-[Bis(carbethoxy)hydroxymethyl]cyclohexanone (9).** Reaction of the pyrrolidine enamine of cyclohexanone[4] and diethyl ketomalonate by the procedure described for preparation of **5a** gave after distillation **9** as a colorless oil [77%, bp 125–127° (0.07 mm)]; ir (neat) 2.85 (m) and 5.75 $\mu$ (s); $^1$H NMR $\delta$ 1.26 (3 H, triplet, $J$ = 7.0 Hz), 1.30 (3 H, triplet, $J$ = 7.0 Hz), 1.54–2.60 (8 H, multiplet), 3.34–3.82 (1 H, multiplet), 3.85–4.03 (1 H, broad singlet, replaceable on addition of deuterium oxide), 4.28 (4 H, quartet, $J$ = 7.0 Hz).

**α-Carbethoxy-β-methyl-γ-ethylidene-$\Delta^{\alpha,\beta}$-butenolide (1a).** To α-hydroxy-γ-keto diester **5a** (3.911 g, 15.0 mmol) was added a suspension of phosphorus pentoxide–methanesulfonic acid[5] (30 ml) and the mixture was heated to 50° for 5.2 hr, after which the mixture was cooled to 25° and added slowly to a mixture of water–ice (50:70 g). After stirring for 15 min, the yellow precipitate was filtered and dissolved in chloroform (60 ml). The aqueous filtrate was extracted with chloroform (15 ml). The chloroform solutions were combined and dried over anhydrous magnesium sulfate. Rotoevaporation of solvent and recrystallization from ether at −78° gave **1a** as a colorless solid (2.18 g, 74%, mp 83–84.5°): ir ($CHCl_3$) 5.65 (s), 5.86 (s), 6.01 (m), and 6.23 $\mu$ (s); $^1$H NMR $\delta$ 1.37 (3 H, triplet, $J$ = 7.0 Hz), 2.02 (3 H, doublet, $J$ = 7.0 Hz), 2.42 (3 H, singlet), 4.37 (2 H, quartet, $J$ = 7.0 Hz), 5.76 (1 H, quartet, $J$ = 7.0 Hz); chemical ionization mass spectrum $m/e$ 197.

**α-Carbethoxy-β-methyl-γ-ethylidene-$\Delta^{\alpha,\beta}$-butenolide (1a) from Diethyl Ketomalonate and 3-Pentanone.** To a stirred mixture of diethyl ketomalonate (1.44 ml, 9.42 mmol) and a suspension of phosphorus pentoxide–methanesulfonic acid (25 ml) was added 3-pentanone (0.5 ml, 4.72 mmol). After stirring for 1.5 hr at 25° another addition of 3-pentanone (0.5 ml, 4.72 mmol) was made. The mixture was stirred for another 1.5 hr and then heated to 50° for 9 hr, after which the mixture was cooled to 25° and added slowly to a mixture of water–ice (40:60 g) and stirred for 15 min. Extraction with chloroform (2 × 30 ml) followed by water wash (3 × 25 ml) of the chloroform layer, drying over anhydrous magnesium sulfate, rotoevaporation of solvent, and recrystallization from ether at −78° gave **1a** (19–23%).

**γ-Lactone of (2-Hydroxy-2-cyclohexeneylidene)carbethoxyacetic Acid (10).** Reaction of α-hydroxy-γ-keto diester **9** and phosphorus pentoxide–methanesulfonic acid by the procedure described for preparation of **1a** gave after crystallization from ether at −78° **10** (84%; mp 108–110°): ir ($CHCl_3$) 5.65 (s), 5.87 (s), 6.04 (m), and 6.20 $\mu$ (s); $^1$H NMR $\delta$ 1.38 (3 H, triplet, $J$ = 7.0 Hz), 1.90 (2 H, quintet, $J$ = 6.0 Hz), 2.49 (2 H, quartet, $J$ = 6.0 Hz), 3.09 (2 H, triplet, $J$ = 6.0 Hz), 4.36 (2 H, quartet, $J$ = 7.0 Hz), 6.18 (1 H, triplet, $J$ = 6.0 Hz); electron impact mass spectrum $m/e$ 208.0761.

**Attempted Synthesis of γ-Lactone of (2-Hydroxy-2-cyclopenteneylidene)carbethoxyacetic Acid.** Reaction of α-hydroxy-γ-keto diester **8** and phosphorus pentoxide–methanesulfonic acid by the procedure described for preparation of **1a** gave an uncharacterized polymeric substance.

**α-Carbethoxy-β-methyl-γ-(1-phenylmercaptoethyl)-$\Delta^{\beta,\gamma}$-butenolide (11).** To a stirred suspension of $\Delta^{\alpha,\beta}$-butenolide **1a**, (0.34 g, 1.74 mmol), phenyl mercaptan (177 $\mu$l, 1.72 mmol), ether (0.2 ml), and methanol (70 $\mu$l) was added triethylamine (2 $\mu$l, 0.014 mmol). After 0.5 hr, rotoevaporation of solvent and crystallization from methylene chloride–ether at −10° gave **11** (0.429 g, 81%, mp 90.5–93.0°): ir ($CHCl_3$) 5.61 (s), 5.81 (m), and 6.02 $\mu$ (m); $^1$H NMR $\delta$ 1.37 (3 H, triplet, $J$ = 7.0 Hz), 1.47 (3 H, doublet, $J$ = 7.0 Hz), 2.17 (3 H, singlet), 3.70 (1 H, doublet of quartets, $J$ = 7.0, $J_{ab}$ = 2.0 Hz), 4.38 (2 H, quartet, $J$ = 7.0 Hz), 4.94 (1 H, doublet, $J_{ab}$ = 2.0 Hz) [decoupling experiment—irradiation of doublet at $\delta$ 4.94 ($H_a$) results in collapse of doublet of quartets at $\delta$ 3.70 ($H_b$) to a quartet ($J$ = 7.0 Hz) and irradiation of doublet of quartets at $\delta$ 3.70 ($H_b$) results in collapse of doublet at $\delta$ 4.94 ($H_a$) to a singlet]; electron impact mass spectrum $m/e$ 306.

Anal. Calcd for $C_{16}H_{18}H_4S$: C, 62.74; H, 5.92; O, 20.89; S, 10.45. Found: C, 62.66; H, 5.99.

**α-Carbethoxy-β-phenyl-γ-benzylidene-$\Delta^{\alpha,\beta}$-butenolide (1b).** Reaction of 1,3-diphenylacetone, diethyl ketomalonate, and phosphorus pentoxide–methanesulfonic acid by the procedure described for preparation of **1a** gave after silica gel column chromatography with benzene–petroleum ether (1:1 by volume), followed by crystallization from ether at −78°, **1b** (31%, mp 104–106°): ir ($CHCl_3$) 5.65 (s), 5.84 (s), 6.10 (m), 6.21 (m), 6.31 (m), and 6.38 $\mu$ (m); $^1$H NMR $\delta$ 1.17 (3 H, triplet, $J$ = 7.0 Hz), 4.22 (2 H, quartet, $J$ = 7.0 Hz), 6.11 (1 H, singlet), 7.38 (8 H, multiplet), 7.78 (2 H, multiplet); electron impact mass spectrum $m/e$ 320.

Anal. Calcd for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03; O, 19.98. Found: C, 75.15; H, 4.99.

**Acknowledgment.** This work was supported by the National Institutes of Health (Grant CA16624-02).

**Registry No.**—**1a**, 57346-36-8; **1b**, 57346-37-9; **2a**, 57346-38-0; **2b**, 57346-39-1; **3a**, 96-22-0; **3b**, 102-04-5; **4**, 609-09-6; **5a**, 57379-34-7; **6a**, 13654-48-3; **6b**, 13750-57-7; **6d**, 10321-68-3; **8**, 57362-19-3; **9**, 57346-40-4; **10**, 57346-41-5; **11**, 57346-42-6; cyclopentanone pyrrolidine enamine, 7148-07-4; cyclohexanone pyrrolidine enamine, 1125-99-1.

## References and Notes

(1) For a review of the chemistry of butenolides, see Y. Shyamsunder Rao, *Chem. Rev.*, **64**, 353 (1964).
(2) M. Alguero, J. Bosch, J. Castaner, J. Castella, J. Castells, R. Metres, J. Pascual, and F. Serratoso, *Tetrahedron*, **18**, 1381 (1962).
(3) R. B. Woodward and G. B. Singh, *J. Am. Chem. Soc.*, **71**, 7581 (1949); **72**, 1428, 5351 (1950); R. B. Woodward and G. B. Singh, *Nature (London)*, **165**, 928 (1950).
(4) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963), and references cited therein.
(5) Recently, Eaton and co-workers have demonstrated that an uncharacterized reagent composed of a 1:10 solution by weight of phosphorus pentoxide in methanesulfonic acid was effective in the preparation of cyclopentanones by the intramolecular acylation of olefin acids and the preparation of amides by the Beckmann rearrangement: P. E. Eaton, G. R. Carlson, and J. T. Lee, *J. Org. Chem.*, **38**, 4071 (1973).
(6) It has been suggested that the cytotoxicity of sesquiterpene lactones may depend upon the ability of these compounds to react with biological thiols [S. M. Kupchan, D. C. Fessler, M. A. Eakin, and T. J. Giacobbe, *Science*, **168**, 376 (1970)]; however, a more recent report reveals that an attempt to find a direct correlation between the rate of cysteine addition and cytotoxicity was unsuccessful [S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971)].
(7) Diethyl ketomalonate (**4**) is commercially available; however, **4** may be conveniently prepared in at least 100-g amounts by nitrogen tetroxide oxidation of diethyl malonate: E. Gilman and T. B. Johnson, *J. Am. Chem. Soc.*, **50**, 3341 (1928).
(8) J. J. Looker, *J. Org. Chem.*, **31**, 2973 (1966).

---

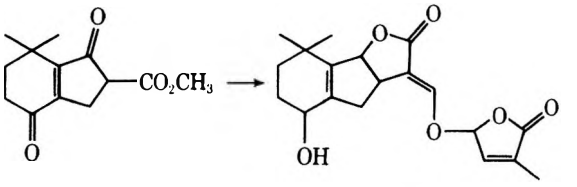
# A Convenient Synthesis of a Hydrindan Precursor to Strigol

Lloyd J. Dolby* and Gunnar Hanson[1]

*Department of Chemistry, University of Oregon, Eugene, Oregon 97403*

*Received August 5, 1975*

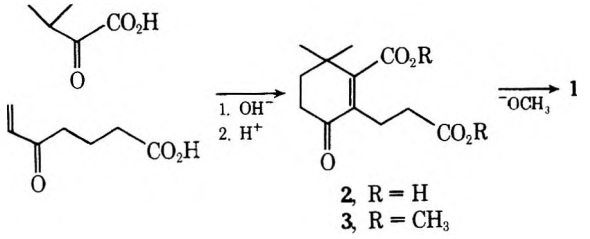
Strigol, a potent seed germination stimulant for the root parasite witchweed (*Striga lutea* Lour), has been an interesting synthetic problem since the structure of this material was reported in 1972.[2] Three syntheses which differ only in the construction of the hydrindan portion of strigol have been reported.[3,4] The ideal hydrindan precursor is the β-




1 strigol

keto ester **1**, which was the key intermediate in the first synthesis of strigol.[3]

Our synthesis of the β-keto ester **1** is outlined below. Two known compounds, dimethylpyruvic acid[5] and 5-oxo-6-heptenoic acid,[6] are condensed in aqueous base to give 70–80% yields of the dibasic acid **2**, which is converted to the methyl ester in quantitative yield by diazomethane. Diester **3** is cyclized to the nicely crystalline β-keto ester **1** in 98% yield by the action of sodium methoxide in methanol.




**2**, R = H
**3**, R = $CH_3$

This route to the hydrindan portion of strigol is much shorter than those previously reported and the yields are quite good. Moreover, the starting materials, dimethylpyruvic acid and 5-oxo-6-heptenoic acid, are easily obtained. Dimethylpyruvic acid may be conveniently prepared by an azlactone synthesis as described many years ago.[5] We prepared 5-oxo-6-heptenoic acid in modest yield by acylating ethylene with glutaric anhydride and aluminum chloride, although it and its esters have been prepared by other routes.[6–9] The crude material from the Friedel–Crafts acylation is quite satisfactory for the condensation with dimethylpyruvic acid.

## Experimental Section[10]

**5-Oxo-6-heptenoic Acid.** A mixture of aluminum chloride (66.7 g, 0.5 mol), glutaric anhydride (28.5 g, 0.25 mol), and methylene chloride (1 l.) was placed in a 2-l. three-necked flask equipped with a gas inlet tube, a drying tube, and a mechanical stirrer. Ethylene (44 g, 1.57 mol) was bubbled in during 4.5 hr with vigorous stirring, after which the reaction mixture was poured over a mixture of 5% hydrochloric acid (900 ml) and ice. The organic layer was separated and the aqueous portion was extracted once with ether (300 ml). The organic extracts were separately washed with water and evaporated under reduced pressure. The combined residues were warmed on the steam bath for 10 min with 100 ml of 10% potassium carbonate solution which resulted in a bright yellow suspension. This mixture was washed with ether until a colorless ether extract was obtained. The aqueous portion was acidified with hydrochloric acid and extracted with ether. The dried ($Na_2SO_4$) ether solution was evaporated to leave an orange oil (5.2 g, 14%) which crystallized on storage. A similar run gave a 34% yield of material with satisfactory spectroscopic properties. The material was triturated with carbon tetrachloride and collected. A sample of the crystalline material was purified by short-path distillation to produce a clear oil which gave crystalline material, mp 44–46°, after exposure to air (lit.[6] mp of the hydrate 45–46.5°): ir $\nu_{max}$ ($CHCl_3$) 1710, 1685, 1618 $cm^{-1}$; $^1H$ NMR 1.97 (p, 2 H, $J$ = 7 Hz), 2.44 (t, 2 H, $J$ = 7 Hz), 2.70 (t, 2 H, $J$ = 7 Hz), 5.8–6.6 ppm (m, 3 H).

**4,4-Dimethyl-2-(2-carboxyethyl)cyclohex-2-en-1-one-3-carboxylic Acid (2).** A solution of dimethylpyruvic acid (1.23 g, 0.0106 mol) and 5-oxo-6-heptenoic acid (1.509 g, 0.0106 mol) in 31.5 ml of 1.5 *N* aqueous potassium hydroxide was heated on the steam bath for 2 hr. The cooled solution was acidified with concentrated hydrochloric acid and the crystalline material (1.68 g) was collected by filtration. The $^1H$ NMR spectrum of this material was identical with that of the purified substance. The filtrate was extracted with ether to afford an additional 0.411 g of crude diacid **2** which was contaminated with ca. 50% by weight of dimethylpurivic acid as judged by its $^1H$ NMR spectrum. The total yield of crude diacid **2** (2.0 g) was 79%. The crude material was recrystallized from water to yield needles, mp 205–206.5°, with slight previous softening. Impure diacid is more conveniently recrystallized from ethyl acetate. The purified material showed $^1H$ NMR ($Me_2SO$-$d_6$–$CDCl_3$) 1.26 (s, 6 H), 1.95 (q, 2 H, $J$ = 6 Hz), 2.2–2.7 ppm (m, 6 H); ir $\nu_{max}$ (KBr) 1710, 1635 $cm^{-1}$; mass spectrum *m/e* calcd for $C_{12}H_{16}O_5$, 240.100; found, 240.100.

**4,4-Dimethyl-2-(2-carbomethyoxyethyl)-3-carbomethoxycyclohex-2-enone (3).** A sample of dibasic acid **2** in tetrahydrofuran was treated with excess ethereal diazomethane. The solvent was evaporated and the residue was sublimed to give a quantitative yield of **3**: mp 47–49°; $^1H$ NMR 1.23 (s, 6 H), 1.90 (t, 2 H, $J$ = 7 Hz), 2.40–2.7 (m, 6 H), 3.65 ppm (s, 3 H); ir $\nu_{max}$ ($CHCl_3$) 1730, 1675, 1619 $cm^{-1}$; uv $\lambda_{max}$ (EtOH) 237 nm (ε 12360); mass spectrum *m/e* calcd for $C_{14}H_{20}O_5$, 268.131; found, 268.129.

**5,5-Dimethyl-8-carbomethoxybicyclo[4.3.0]non-1(6)-ene-2,7-dione (1).** The diester **3** (0.20 g) was heated under reflux for 2 hr in a nitrogen atmosphere with 2 ml of 0.78 *N* sodium methoxide in methanol. The cooled solution was treated with 0.1 g of acetic acid and diluted with 1% hydrochloric acid. The crystalline material was collected by filtration and the aqueous portion was extracted with ether. The combined product was dried to give 0.173 g (98%) of **1**. A sample was crystallized from methanol and sublimed to give an analytical sample, mp 136.8–141°. The material is clearly a mixture of tautomers (ca. 1:1) in chloroform solution as previously indicated: $^1H$ NMR ($CDCl_3$) 1.32, 1.38 (s, 6 H), 1.96 m, 4 H), 2.67 (q, 2 H, $J$ = 7 Hz), 2.92 (m, 1 H), 3.28 (s, 1 H), 3.49 (m, 1 H), 3.78, 3.83 ppm (s, 3 H); ir $\nu_{max}$ ($CHCl_3$) 1740, 1715, 1680 sh, 1615, 1548 $cm^{-1}$; uv $\lambda_{max}$ (EtOH) 222 nm (ε 9170), 256 (7590), 325 (6478); mass spectrum *m/e* calcd for $C_{13}H_{16}O_4$, 236.105; found, 236.103.

**Registry No.**—**1**, 51799-98-5; **2**, 57304-91-3; **3**, 57304-92-4; dimethylpyruvic acid, 759-05-7; 5-oxo-6-heptenoic acid, 6934-67-4; glutaric anhydride, 108-55-4; ethylene, 74-85-1; diazomethane, 334-88-3; sodium methoxide, 124-41-4.

## References and Notes

(1) NSF Undergraduate Research Participant.
(2) C. E. Cook, L. P. Whichard, M. E. Wall, G. H. Egley, P. Coggon, P. A. Luhan, and A. T. McPhail, *J. Am. Chem. Soc.*, **94**, 6198 (1972).
(3) J. B. Heather, R. S. D. Miltol, and C. J. Shih, *J. Am. Chem. Soc.*, **96**, 1976 (1974).
(4) G. A. MacAlpine, R. A. Raphael, A. Shaw, A. W. Taylor, and H. Wild, *J. Chem. Soc., Chem Commun.*, 834 (1974).
(5) G. R. Ramage and J. L. Simonsen, *J. Chem. Soc.*, 532 (1935).
(6) S. Umezawa, Japanese Patent 1713 (1962); *Chem Abstr.*, **58**, 7833*a* (1963).
(7) G. P. Vig, A. S. Dhindsa, A. K. Vig, and O. P. Chugh, *J. Indian Chem. Soc.*, **49**, 163 (1972).
(8) L. B. Barkley, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *J. Am. Chem. Soc.*, **78**, 4111 (1956).
(9) N. Nazarov and S. I. Savyalov, *J. Gen. Chem. USSR* (*Engl. Transl.*), **23**, 1703 (1953).
(10) Infrared spectra were measured with either Beckman IR-5A or IR-7 Infrared spectrophotomers. Proton magnetic resonance spectra were determined at 100 MHz with a Varian Model XL-100 spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane internal standard. In the presentation of the $^1H$ NMR spectra the following notations are used: s = singlet, d = doublet, t = triplet, q = quartet, p = pentuplet, and m = multiplet.

---

## Synthesis of a Useful Spin Labeled Probe, 1-Oxyl-4-carboxyl-2,2,6,6-tetramethylpiperidine

Elmer J. Rauckman, Gerald M. Rosen,* and Mohamed B. Abou-Donia

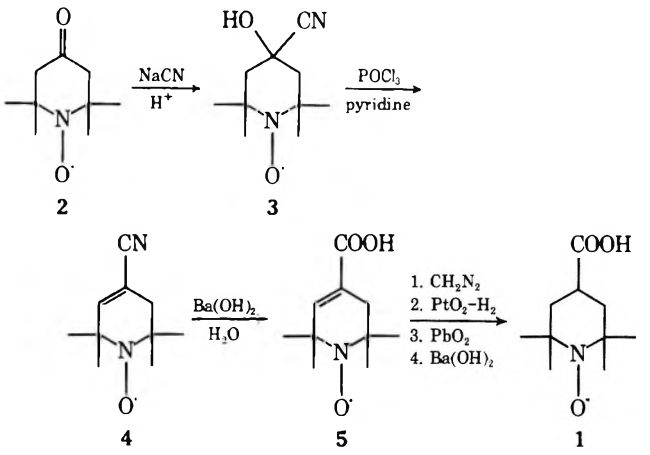
*Department of Physiology and Pharmacology, Duke University Medical Center, Durham, North Carolina 27710*

*Received September 3, 1975*

In our continuing study of the cholinergic receptor we found it necessary to prepare a variety of spin labeled analogues of acetylcholine, one of which required the preparation of 1-oxyl-4-carboxyl-2,2,6,6-tetramethylpiperidine (**1**). Unfortunately, the preparation of **1** proved to be of great difficulty because the nitroxyl group is sensitive to many synthetically useful techniques.

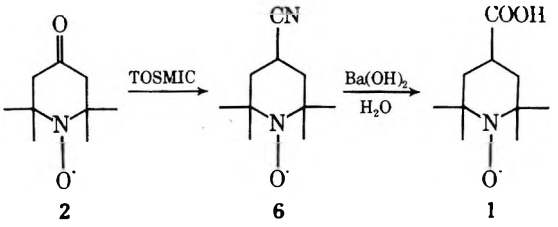
* Fellow of the Neurological Disease and Stroke Institute of the National Institutes of Health No. NS2697.

Scheme I




Recently Hsia et al.[1] reported the preparation of **1** as outlined in Scheme I. Using this reported procedure, we were unable to reduce 1-oxyl-4-carboxyl-2,2,6,6-tetramethyl-1,2,5,6-tetrahydropyridine (**5**) to the desired product (**1**). Palladium on charcoal, which we have found useful for other similar reductions, also failed to give a satisfactory yield of **1**.

Toward this goal, we have devised an unequivocal synthesis of **5** using tosylmethyl isocyanide as originally reported by Van Leusen.[2] Treatment of 1-oxyl-2,2,6,6-tetramethyl-4-piperidone (**2**) with tosylmethyl isocyanide in the presence of base resulted in a high yield of 1-oxyl-4-cyano-2,2,6,6-tetramethylpiperidine (**6**). Hydrolysis of **6** to the




acid gave a product melting 20°C lower than that reported by Hsia et al.[1] It may be noted that the unsaturated acid, **5**, has a reported melting point of 190–192°C, whereas the reduced (**1**) was reported to melt at 195–196°C. Furthermore, elemental analysis is unable to distinguish between the two compounds (**1** and **5**), given the generally accepted error of ±0.3%. To substantiate our findings, we performed a high-resolution mass spectral study of 1-oxyl-4-cyano-2,2,6,6-tetramethylpiperidine (**6**) and 1-oxyl-4-carboxyl-2,2,6,6-tetramethylpiperidine (**1**).

Field ionization mass spectra confirmed the molecular ions to be *m/e* 181 for **6** and *m/e* 200 for **1**.

## Experimental Section

Melting points were obtained on a Thomas-Hoover melting point apparatus and are corrected. The microanalysis was performed by M-H-W Laboratories, Garden City, Mich. Infrared spectra were recorded on a Perkin-Elmer Model 727 spectrophotometer. High-resolution mass spectra were recorded on a Varian CH-5 mass spectrometer.

**1-Oxyl-4-cyano-2,2,6,6-tetramethylpiperidine (6).** To a stirred solution of 1-oxyl-2,2,6,6-tetramethyl-4-piperidone (**2**, 1.0 g, 5.9 mmol) and tosylmethyl isocyanide (1.17 g, 6.0 mmol, Aldrich Chemical Co.) in 40 ml of dimethoxyethane at 0°C was added 2 equiv (1.34 g) of potassium *tert*-butoxide dissolved in 20 ml of a 1:1 mixture of dimethoxyethane and *tert*-butyl alcohol. The mixture was stirred at 0°C for 45 min, the temperature was then raised to 20°C, and the mixture was stirred for an additional 1 hr. At that time, 100 ml of water was added and the mixture was extracted three times with 25-ml portions of ether. The ether extracts were combined and dried over anhydrous magnesium sulfate. The ether was then removed in vacuo to give approximately 0.9 g of a red powder. A portion of this product was twice recrystallized from ether, giving red needles: mp 146.5–147°C; ir 2250 $cm^{-1}$ (–C≡N); *m/e* 181.1338.

Anal. Calcd for $C_{10}H_{17}N_2O$: C, 66.26; H, 9.45; N, 15.46. Found: C, 66.03; H, 9.63; N, 15.32.

**1-Oxyl-4-carboxyl-2,2,6,6-tetramethylpiperidine (1).** To a solution of 2 g of 1-oxyl-4-cyano-2,2,6,6-tetramethylpiperidine (**6**) in 25 ml of methanol was added a solution of 6 g of barium hydroxide and 0.5 g of sodium hydroxide in 100 ml of water. The mixture was refluxed for 24 hr, cooled, and extracted with chloroform. The remaining aqueous solution was cooled, acidified with 10% hydrochloric acid, and extracted exhaustively with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate and evaporated in vacuo, giving 1.9 g of a red powder: mp 171–172°C from hexane–benzene (1:2); ir 1680 (–C=O), 3300–3100 $cm^{-1}$ broad (–OH); *m/e* 200.1271.

Anal. Calcd for $C_{10}H_{18}NO_3$: C, 59.98; H, 9.06; N, 6.99. Found: C, 60.04; H, 9.19; N, 6.80.

**Acknowledgment.** This study was supported in part by a grant from NIH (NS 10823). We wish to thank Dr. Robert Harless for the mass spectral data.

**Registry No.**—**1**, 37149-18-1; **2**, 2896-70-0; **6**, 38078-71-6; tosylmethyl isocyanide, 36635-61-7.

## References and Notes

(1) L. T. Wong, R. Schwenk, and J. C. Hsia, *Can. J. Chem.*, **52**, 3381 (1974).
(2) A. M. Van Leusen, H. Siderius, B. E. Hoogenboom, and D. Van Leusen, *Tetrahedron Lett.*, 5337 (1972).

---

# A Convenient Preparation of *S*-Adenosylhomocysteine and Related Compounds

Ronald T. Borchardt,* [1] Joan A. Huber, and Yih Shiong Wu

*Department of Biochemistry, McCollum Laboratories, University of Kansas, Lawrence, Kansas 66044*

*Received June 30, 1975*

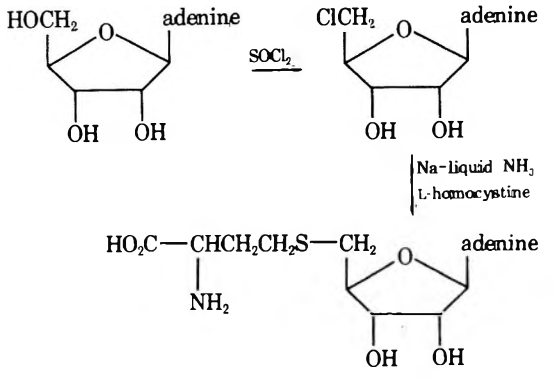
Since the discovery of *S*-adenosylmethionine,[2] a great variety of *S*-adenosylmethionine-dependent biological transmethylation reactions have been demonstrated.[3] A general feature of most *S*-adenosylmethionine-dependent methyltransferases is the inhibition produced by the demethylated product *S*-adenosyl-L-homocysteine. Because of its possible significance as a biological regulatory mechanism,[3b] this product inhibition has stimulated considerable research interest. Numerous compounds structurally related to *S*-adenosyl-L-homocysteine have been synthesized as potential inhibitors of this class of enzymes.[4]

Because of the high substrate specificity of the enzyme capable of synthesizing *S*-adenosylhomocysteine,[5] analogues of this compound have been prepared by chemical synthesis. The general route for the synthesis of *S*-adenosylhomocysteine analogues was modeled after the procedure first described by Baddiley and Jamieson.[6] This route involves (1) the synthesis of the parent nucleoside, if not commercially available; (2) protection of the 2′,3′-hydroxyl groups of the nucleoside using an isopropylidene protecting group; (3) activation of the nucleoside 5′ position by formation of the corresponding 5′-tosylate; (4) condensation of the intermediate 5′-tosylate with *S*-benzyl-L-homocysteine (or related compounds); and (5) removal of the isopropylidene protecting group using dilute acid. This standard procedure has proven quite successful for the synthesis of a broad spectrum of *S*-adenosylhomocysteine analogues.[4] A

variation of this procedure using a phenylboronate ester as a protecting group was recently reported.[4n] The general procedures outlined above suffer from several disadvantages which include (1) the necessity to protect the 2′,3′-hydroxyl groups of the nucleoside; and (2) a stability problem with the intermediate 5′-tosylate.

We have recently developed a shorter, more convenient procedure for the preparation of *S*-adenosyl-L-homocysteine and related compounds, which we feel has several advantages over the procedures outlined above. This new procedure involves the initial formation of the 5′-chloro-5′-deoxynucleoside from the corresponding nucleoside, followed by condensation with L-homocystine (Scheme I).

**Scheme I**




We have used the procedure outlined in Scheme I to synthesize *S*-adenosyl-L-homocysteine, *S*-adenosyl-D-homocysteine, and numerous base- or sugar-modified derivatives, some of which are listed in Table I. The appropriate 5′-chloro-5′-deoxynucleosides were prepared in 75–100% yields from the corresponding nucleosides using thionyl chloride and hexamethylphosphoramide according to a general procedure described by Kikugawa and Ichino.[7] The 5′-chloro-5′-deoxynucleosides were condensed with L-homocystine (or D-homocystine) in sodium and liquid ammonia to yield directly the desired *S*-adenosylhomocysteine derivatives. Use of L-homocystine, rather than the *S*-benzyl-L-homocysteine, was found to afford cleaner reaction products and higher yields (30–60%). In addition, since L-homocystine, D-homocystine, or DL-homocystine are commercially available, this makes the D isomer, L isomer, or DL mixture of *S*-adenosylhomocysteine or related compounds readily accessible.

We believe that this method has several advantages over previously described procedures. The route outlined in Scheme I is shorter, requiring only two steps to the desired product from the appropriate nucleoside. In addition, the overall yields from the appropriate nucleosides to the desired products are generally 30–60%, as compared to yields of 5–25% for the four-step conversion using the isopropylidene protecting group. We have also found that the 5′-chloro-5′-deoxynucleosides are relatively stable compounds, unlike the corresponding 5′-tosylates, which are unstable and unless properly stored (0°C) decompose. Most important, however, is the fact that by using this procedure we have been able to prepare in good yield several compounds, including the $N^6$-methyl-3-deazaadenine derivative **3**, which was prepared in very poor yield using the earlier procedures.

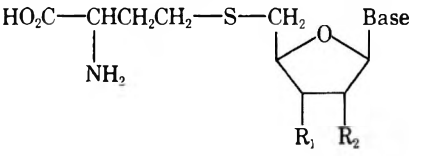
## Experimental Section

Melting points were obtained on a calibrated Thomas-Hoover Uni-Melt and were corrected. Microanalyses were conducted on an F & M Model 185 C, H, N analyzer, The University of Kansas, Lawrence, Kans. The ir, NMR, and uv data were consistent with the assigned structures. Ir data were recorded on a Beckman IR-33 spectrophotometer, NMR data on a Varian Associates Model T-60 spectrophotometer ($Me_4Si$), and uv data on a Cary Model 14 spectrophotometer.

The following compounds were commercially available from the indicated sources: adenosine, $N^6$-methyladenosine (Aldrich); 2′-deoxyadenosine, D-homocystine, L-homocystine, and tubercidin (7-deazaadenosine) (Sigma). $N^6$-Methyl-3-deazaadenosine was prepared by a modification[4b] of the procedure of Mizuno et al.[8]

**General Reaction Procedure for the Preparation of the 5′-Chloro-5′-deoxynucleosides.** The conversion of the appropriate nucleoside (e.g., adenosine) to the corresponding 5′-chloro-5′-deoxynucleoside (e.g., 5′-chloro-5′-deoxyadenosine) was modeled after a procedure previously described by Kikugawa and Ichino.[7] A solution of 0.75 ml of thionyl chloride and 5.0 ml of hexamethylphosphoramide was stirred under nitrogen while 0.50 g of the nucleo-

**Table I**
***S*-Adenosyl-L-homocysteine and Related Compounds Prepared by the Condensation of L-Homocystine and 5′-Chloro-5′-deoxynucleosides[a, b]**




| Compd | Base | $R_1$ | $R_2$ | Mp, °C | Lit. mp, °C | % yield from 5′-chloro-5′-deoxynucleoside[f] | % yield from nucleoside |
|---|---|---|---|---|---|---|---|
| 1 | Adenine[c] | OH | OH | 212 | 204[6] | 75 | 59 |
| 2 | $N^6$-Methyladenine | OH | OH | 208–210 | *d* | 45 | 39 |
| 3 | $N^6$-Methyl-3-deazaadenine | OH | OH | 222–224 | 214–215 | 67 | 56 |
| 4 | 7-Deazaadenine | OH | OH | 178–180 | *e* | 45 | 33 |
| 5 | Adenine | OH | H | 190–191 | 191[4c] | 45 | 31 |
| 6 | Adenine | H | OH | 213 | 211[4c] | 54 | 39 |

[a] The 5′-chloro-5′-deoxynucleosides were prepared from the corresponding nucleosides by the general procedure outlined in the Experimental Section. [b] The *S*-adenosylhomocysteine analogues were characterized by their NMR and uv spectra and their chromatographic properties against standard compounds. [c] *S*-Adenosyl-D-homocysteine was prepared in comparable yield by condensation of 5′-chloro-5′-deoxyadenosine and D-homocystine. [d] Previously prepared by Hildesheim et al.,[4k] but no melting point was reported. [e] Previously prepared by Coward et al.,[4g] but no melting point was reported. [f] Registry no. are, respectively, 892-48-8, 19254-36-5, 57274-13-2, 53458-85-8, 57274-14-3, 57274-15-4.

side was added. The mixture was allowed to stir for 15–20 hr at ambient temperature, then quenched with ca. 20 ml of water and concentrated in vacuo to 10 ml. For those less soluble 5′-chloronucleoside products, the aqueous solution was neutralized to pH 7–8 with 2 *N* aqueous ammonia. The resulting solution was cooled and crystals collected by filtration and washed thoroughly with ice water. The combined filtrates were applied to ca. 10 ml of ion exchange resin (Dowex 50W-X4, 50–100 mesh, $H^+$ form). The resin was washed well with water, then with 1 or 2 *N* $NH_4OH$ to remove the product. The ammonia solutions were concentrated to produce a second crop of crystals. For those samples which did not crystallize on neutralization, the entire original acidic solution was passed through a large column (100–150 ml) of Dowex 50W-X4. The product was again removed by elution with $NH_4OH$, after first washing the column thoroughly with water. Yields averaged in the 75–100% range. The products were identified by their ir and NMR spectra and their chromatographic properties.

**General Reaction Procedure for the Preparation of *S*-Adenosylhomocysteine Analogues from the 5′-Chloro-5′-deoxynucleoside and L-Homocystine.** A 0.75-mmol sample (1.4 equiv) of L-homocystine was dissolved in 25 ml of liquid ammonia and treated with sodium until the solution remained blue for at least 15 min. A stirring bar was introduced and enough $NH_4Cl$ was added to discharge the color. Then 1.05 mmol (1.0 equiv) of the appropriate 5′-chloro-5′-deoxynucleoside was added and stirring was continued for approximately 12 hr. After the ammonia had evaporated and the last traces were removed in vacuo, 5 ml of $H_2O$ was added and the solution neutralized to pH 6 with 5% HCl. The crude mixture was then applied to an ion exchange column (30 ml of Dowex 50W-X4, 50–100 mesh, $NH_4^+$ form) and eluted slowly with water. The first fractions contained the inorganic ions and homocystine. The desired product along with some starting 5′-chloro-5′-deoxynucleoside was removed either by further elution with water or by elution of the column with 1 *N* and/or 2 *N* $NH_4OH$. The fractions containing product were concentrated in vacuo and lyophilized. Where appropriate, impure samples were further purified by using preparative TLC [Avicel, 3:2 EtOH–$H_2O$, or silica gel, 9 (20EtOH:2$H_2O$:2HOAc) + 1 (0.5 *M* phosphate buffer pH 7.0)]. Yields averaged from 40 to 75% for this condensation step, giving overall yields of 30–60% of the products from the corresponding nucleoside. The *S*-adenosylhomocysteine analogues were characterized by their ir, NMR, and uv spectra, their chromatographic properties against standard samples, and chemical analyses.

**Acknowledgment.** The authors gratefully acknowledge support of this project by a Research Grant from the National Institute of Neurological Communicative Disorders and Stroke (NS-10918). The excellent technical assistance of Robert Miller is gratefully acknowledged.

**Registry No.**—**1**, 979-92-0; **2**, 53228-06-1; **3**, 53199-58-9; **4**, 57344-98-6; **5**, 57274-11-0; **6**, 57274-12-1; L-homocystine, 626-72-2; D-homocystine, 6027-15-2.

## References and Notes

(1) Established Investigator of the American Heart Association.
(2) G. L. Cantoni, *J. Am. Chem. Soc.*, **74**, 2942 (1952).
(3) (a) S. K. Shapiro and F. Schlenk, Ed., "Transmethylation and Methionine Biosynthesis", University of Chicago Press, Chicago, Ill., 1965; (b) E. Borek, Ed., "The Biochemistry of S-Adenosylmethionine", Columbia University Press, New York, N.Y., in press.
(4) (a) R. T. Borchardt and Y. S. Wu, *J. Med. Chem.*, **17**, 862 (1974); (b) R. T. Borchardt, J. A. Huber, and Y. S. Wu, *ibid.*, **17**, 868 (1974); (c) R. T. Borchardt and Y. S. Wu, *ibid.*, **18**, 300 (1975); (d) J. K. Coward, M. D'Urso-Scott, and W. D. Sweet, *Biochem. Pharmacol.*, **21**, 1200 (1972); (e) J. K. Coward and W. D. Sweet, *J. Med. Chem.*, **15**, 381 (1972); (f) J. K. Coward and E. P. Slisz, *ibid.*, **16**, 460 (1973); (g) J. K. Coward, O. L. Bussolotti, and C. D. Chang, *ibid.*, **17**, 1286 (1974); (h) V. Zappia, C. R. Zydek-Cwick, and F. Schlenk, *J. Biol. Chem.*, **244**, 4499 (1969); (i) J. Hildensheim, J. F. Goguillon, and E. Lederer, *FEBS Lett.*, **30**, 177 (1973); (j) J. Hildesheim, R. Hildesheim, J. Yon, and E. Lederer, *Biochimie*, **54**, 989 (1972); (k) J. Hildesheim, R. Hildesheim, P. Blanchard, G. Farrugia, and R. Michelot, *ibid.*, **55**, 541 (1973); (l) A. E. Pegg, *FEBS Lett.*, **16**, 13 (1971); (m) J. Hildesheim, R. Hildesheim, and E. Lederer, *Biochimie*, **54**, 431 (1972); (n) V. N. Rekunova, I. P. Rudakova, and A. M. Yurkevich, *Tetrahedron Lett.*, 2811 (1973); (o) J. A. Montgomery, A. T. Shortnacy, and H. J. Thomas, *J. Med. Chem.*, **17**, 1197 (1974).
(5) G. De La Haba and G. L. Cantoni, *J. Biol. Chem.*, **234**, 603 (1959).
(6) J. Baddiley and G. A. Jamieson, *J. Chem. Soc.*, 1085 (1955).
(7) K. Kikugawa and M. Ichino, *Tetrahedron Lett.*, 87 (1971).
(8) Y. Mizuno, S. Tazawa, and H. Kaguera, *Chem. Pharm. Bull.*, **16**, 2011 (1964).

## Synthesis and Characterization of 5-Hydroperoxymethyluracil (Thy$^{\alpha}$OOH)

Bo-Sup Hahn and Shih Yi Wang*

*Department of Biochemical and Biophysical Sciences, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Maryland 21205*

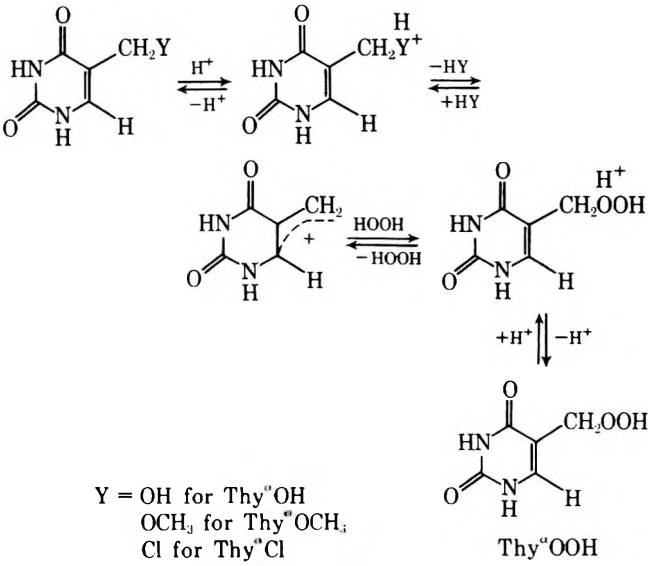
*Received August 22, 1975*

Cadet and Teoule[1] have shown that radiolysis of thymine (Thy)[2] and thymidine (dThd) in pH 1.7–7 aerated aqueous solutions results in the formation of Thy$^{\alpha}$OOH. Swinehart et al.[3] studied the $\gamma$-ray-induced production of [$^3$H]$H_2O$ from [$^3$H]Thy in single- and double-stranded DNA and suggested the formation of Thy$^{\bullet\alpha}$, a probable intermediate for the formation of Thy$^{\alpha}$OOH and other analogous products, to explain the observed [$^3$H] release. Earlier, the same suggestion was made by Wang and Alcantara[4] about the photooxidation of Thy in aqueous solutions. These findings indicate the possible importance of Thy$^{\alpha}$OOH in radiobiology and photobiology, and thus the study of the effects of Thy$^{\alpha}$OOH on biological compounds and systems seems to be warranted, especially in view of the effects of *cis*-5,6-dihydro-6-hydroperoxy-5-hydroxythymine (ho$^5$ho$_2$$^6$hThy, 6-TOOH)[5] on neighboring bases, cells, chromosomes, etc.[6]

Because access to sufficient quantities of Thy$^{\alpha}$OOH is necessary for similar studies, improved methods have been developed with analogous starting materials, two of which are novel for the preparation of Thy$^{\alpha}$OOH. These syntheses give Thy$^{\alpha}$OOH in yields of ~90%, which is considerably greater than in the previous method.[7] In addition, Thy$^{\alpha}$OOH exhibits some interesting photochemical and chemical behavior. Furthermore, purified Thy$^{\alpha}$OOH is in fact rather stable, contrary to the early belief,[1] and that is convenient for our intended studies.

### Results and Discussion

These syntheses are straightforward and give excellent yields of Thy$^{\alpha}$OOH. Considering the ease of reaction and the requirement of concentrated HCl, acid-catalyzed formation of an electrophilic center is probably involved as shown in the following scheme.




Because Cl is a much better leaving group than OH and $OCH_3$ under the present reaction condition, acid catalysis is necessary for the reactions of Thy$^{\alpha}$OH and Thy$^{\alpha}$$OCH_3$

but not for Thy$^{\alpha}$Cl. Also, the synthesis goes more readily and provides somewhat better yields when Thy$^{\alpha}$Cl is used as the reactant. However, whether these reactions proceed in a stepwise manner as shown has not yet been studied.

Our structural assignment of Thy$^{\alpha}$OOH is corroborated by the spectral data. The ir spectrum shows bands of $\nu$O–O (875 cm$^{-1}$) and $\nu$CH$_2$–O (973, 1033, and 1071 cm$^{-1}$). The last two bands also appear in the ir spectrum of CH$_2$OH-containing analogue, Thy$^{\alpha}$OH, but are in greatly reduced intensities. This reduction is to be expected[8,9] for C–OOH as compared to analogous C–OH compounds. In the NMR spectrum, the assignments are rather straightforward; however, the signal for OOH is absent. Similarly, the signal for OH in Thy$^{\alpha}$OH is also absent. On the other hand, we observed[9] the OOH signal as a sharp singlet in a similar compound, 6-TOOH. When Thy$^{\alpha}$OOH was allowed to stand in (CD$_3$)$_2$SO, it was reduced to the corresponding alcohol, Thy$^{\alpha}$OH [NMR in (CD$_3$)$_2$SO: $\delta$ 4.17 (s, 2, CH$_2$), 7.32 (d, 1, $J$ = 6 Hz, C$_6$H)]. However, in spite of its allylic hydroperoxide function, Thy$^{\alpha}$OOH is surprisingly stable in Me$_2$SO with an apparent half-life of approximately 14 days, whereas, 6-TOOH has an apparent half-life of 27 min at 35°C. No appreciable change can be detected when Thy$^{\alpha}$OOH is stored for 1 week at room temperature; however, in solution it is gradually converted to 5-formyluracil (5CHO-Ura). Because Thy$^{\alpha}$OOH and 5CHO-Ura are reactive species, they may interact with biomolecules and thus affect biological systems when they are formed directly or indirectly by radiation.

Furthermore, when Thy$^{\alpha}$OOH (0.1 m$M$) was irradiated with 254-nm light, it was quantitatively converted to 5CHO-Ura within 220 sec at a light intensity of 198 ergs/mm$^2$ sec$^{-1}$ (without filter) with $\phi$ = 0.47 (when Corning filter No. 954 is used, $\phi$ = 0.27). This efficacious photoconversion may have relevance in the study of radiobiology. In addition, 5CHO-Ura has been identified as a photoproduct of Thy.[4]

Thy$^{\alpha}$OOH can be easily reduced to Thy in H$_2$O by hydrogenation in the presence of 10% Pd/C at room temperature.

In short, the characteristics of Thy$^{\alpha}$OOH make it an interesting compound to be considered in the study of radiation effects of biological systems.

## Experimental Section

**Preparation of 5-Hydroperoxymethyluracil (Thy$^{\alpha}$OOH). From 5-Methoxymethyluracil (Thy$^{\alpha}$OCH$_3$).** The starting material was prepared according to the method of Santi and Pogolotti.[10] First, Thy$^{\alpha}$OCH$_3$ (62 mg, 40 mmol) was dissolved in 10 ml of 15% H$_2$O$_2$, then, dropwise, 50 $\mu$l of concentrated HCl in 5 ml of H$_2$O$_2$ was added. After standing at room temperature for 24 hr with stirring, the reaction solution was lyophilized. The residue was washed three times with cold water and the purified product (56 mg, 89%) was obtained by recrystallization from 10% methanol solution.

**From 5-Hydroxymethyluracil (Thy$^{\alpha}$OH).** The procedure is analogous to that described above. In this case, 57 mg (40 mmol) of Thy$^{\alpha}$OH was used and 57 mg (90%) of the purified Thy$^{\alpha}$OOH was obtained.

**From 5-Chloromethyluracil (Thy$^{\alpha}$Cl).** The starting material was synthesized according to the method of Giner-Sorolla and Medrek.[11] Thy$^{\alpha}$Cl (50 mg, 32 mmol) was added portionwise to 1 ml of 50% H$_2$O$_2$ solution with stirring. The product began to appear as fine crystals at the completion of the addition; however, the stirring was continued for an additional 30 min at room temperature. The product was collected by filtration and washed with 50% methanol until the washings gave a negative AgNO$_3$ test for Cl$^-$. Again, recrystallization was carried out in 10% MeOH solution and 45 mg (92%) of the purified product was obtained: mp >230° dec; $\lambda_{max}$ (H$_2$O) 261 nm ($\epsilon$ 7500); ir (KBr film) 11.43 $\mu$ for –O–O–, 10.28, 9.68, and 9.34 $\mu$ for C–OOH, respectively; NMR [(CD$_3$)$_2$SO] $\delta$ 4.52 (s, 2, CH$_2$), 7.52 (d, 1, $J$ = 6 Hz, C$_6$H), 9.47 (d, 1, $J$ = 6 Hz, N$_1$H), and 9.67 (b, 1, N$_3$H); mass spectrum $m/e$ 142 (M – 16). Anal. Calcd for C$_5$H$_6$N$_2$O$_4$: C, 38.00; H, 3.80; N, 17.71. Found: C, 37.88; H, 3.76; N, 17.79.

**Reduction of Thy$^{\alpha}$OOH to Thy.** Thy$^{\alpha}$OOH (31.7 mg, 20 mmol) and 10 mg of 10% Pd/C were suspended in 10 ml of water. The solution was shaken with H$_2$ at room temperature. A theoretical amount (9.6 ml, 2 molar equiv) of H$_2$ was taken up at the end of 4 hr. The catalyst was removed by filtration and the filtrate was evaporated until dry. The residue, after recrystallization from 20% methanol, gave 23.4 mg of thymine (~93% yield).

**Formation of 5CHO-Ura from Thy$^{\alpha}$OOH by Irradiation (254 nm).** Thy$^{\alpha}$OOH (5 mg, 36 $\mu$mol) was dissolved in 40 ml of water. The solution in a quartz tube was irradiated (254 nm) for 220 sec and evaporated until dry. The residue, after recrystallization from absolute methanol, gave 4.0 mg of 5CHO-Ura (88% yield), mp >300° dec, $\lambda_{max}$ (H$_2$O) 278 nm ($\epsilon$ 11850).[12]

**Acknowledgment.** The authors wish to express appreciation to ERDA (Contract E(11-1)-3286) and to NIH (Contract RO1-GM21146) for financial support. (This publication is identified as No. COO-3286-13.) Appreciation is also expressed to Dr. Catherine Fenselau and Mrs. Nancy Kan for the mass spectral determinations.

**Registry No.**—Thy$^{\alpha}$OOH, 33499-50-2; Thy$^{\alpha}$OCH$_3$, 57346-43-7; Thy$^{\alpha}$OH, 4433-40-3; Thy$^{\alpha}$Cl, 3590-48-5; 5CHO-Ura, 1195-08-0.

## References and Notes

(1) J. Cadet and R. Teoule, *Chem. Commun.*, 1269 (1971); *Tetrahedron Lett.*, 3225 (1972); *Int. J. Radiat. Biol. Relat. Stud. Phys., Chem. Med.*, 27, 211 (1975); *Bull. Soc. Chim. Fr.*, 891 (1975).
(2) The abbreviations system used is that proposed by W. E. Cohn, N. J. Leonard, and S. Y. Wang, *Photochem. Photobiol.*, **19**, 89 (1974).
(3) J. L. Swinehart, W. S. Lin, and P. A. Cerutti, *Radiat. Res.*, **58**, 166 (1974).
(4) S. Y. Wang and R. Alcantara, *Photochem. Photobiol.*, **4**, 477 (1965).
(5) *cis*-ho$^5$ho$_2$$^6$hThy is the abbreviation for this compound according to the system proposed in ref 2. However, TOOH has been used for various hydroperoxy thymine derivatives. Because we are dealing with ho$^5$ho$_2$$^6$hThy, ho$_2$$^5$ho$^6$hThy, and Thy$^{\alpha}$OOH at present, we propose that 6-TOOH, 5-TOOH, and $\alpha$-TOOH, respectively, be used for brevity and distinction.
(6) J. E. T. Kelley, B. S. Hahn, S. Y. Wang, and T. Merz, *Radiation Res.*, **59**, 283 (1974); S. Y. Wang and L. Parkhill, *ibid.*, **59**, 274 (1974); H. F. Thomas, R. M. Herriott, B. S. Hahn, and S. Y. Wang, *Nature*, in press.
(7) J. Cadet and R. Teoule, *Biochim. Biophys. Acta* **238**, 8 (1971).
(8) H. R. Williams and H. S. Mosher, *Anal. Chem.*, **27**, 517 (1955).
(9) B. S. Hahn and S. Y. Wang, *Biochem. Biophys. Res. Commun.*, **54**, 1224 (1973).
(10) D. V. Santi and A. L. Pogolotti, Jr., *J. Heterocycl. Chem.*, **8**, 265 (1971).
(11) A Giner-Sorolla and L. Medrek, *J. Med. Chem.*, **9**, 97 (1966).
(12) R. Alcantara and S. Y. Wang, *Photochem. Photobiol.*, **4**, 473 (1965).

---

# Allylic Rearrangement from O$^6$ to N-3 and N-7 of Guanine Blocked at C-8

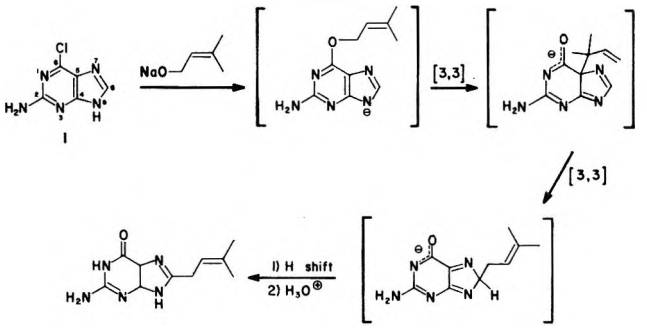
Brian N. Holmes[1] and Nelson J. Leonard*

*Roger Adams Laboratory, School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801*

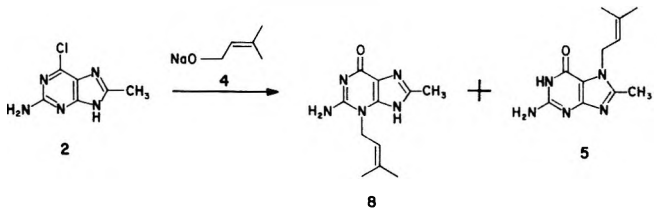
*Received September 25, 1975*

It was recently reported[2,3] from this laboratory that the displacement reaction of 2-amino-6-chloropurine (1) with the sodium salts of allylic alcohols proceeds through an O$^6$ ether to yield an 8-substituted guanine. The O$^6$ to C-8 rearrangement occurs intramolecularly and is judged to proceed by two anionic [3,3] sigmatropic shifts via C-5 (Scheme I). By blocking the 8 position of the purine ring with a methyl group, we sought to trap the C-5 intermediate or to redirect the migrating group. Thereby, another allylic rearrangement has been revealed in which the overall migration, with allylic retention, is from O$^6$ to the N-3 and N-7 positions of the guanine ring (Scheme II), with corresponding mechanistic implications.

Scheme I

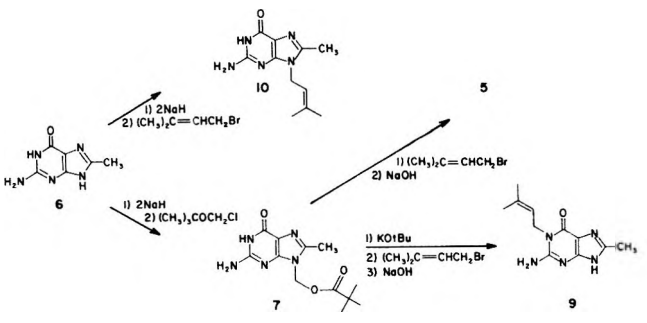


Scheme II



When 2-amino-6-chloro-8-methylpurine (**2**), prepared by reaction of 2-amino-6-mercapto-8-methylpurine (**3**)[4] with chlorine gas,[5] was allowed to react with sodium 3-methyl-2-butene 1-oxide (**4**) in refluxing dioxane (101°), a mixture of two *N*-isopentenyl-8-methylguanine products (2:1) was obtained in a total yield of 88%. After a separation by high-pressure liquid chromatography, the minor isomer was identified as 8-methyl-7-(3-methyl-2-butenyl)guanine (**5**) by comparison with an authentic sample prepared by independent synthesis. During consideration of possible synthetic routes to **5** we noted that 7-alkylguanine derivatives have, in general, been formed by alkylation of guanosine followed by hydrolytic removal of the ribose.[6] Since 8-methylguanosine is not readily available, a protecting group was sought that could be placed on N-9 of 8-methylguanine (**6**) and removed after alkylation at N-7. The pivaloyloxymethyl (POM) protecting group, employed for a similar purpose in the adenine series in the synthesis of cordycepin, for example,[7] was found satisfactory for the synthesis of **5**. Treatment of the disodium dianion of **6** with chloromethyl pivalate in dimethyl sulfoxide gave 8-methyl-9-pivaloyloxymethylguanine (**7**) in 92% yield. This compound was converted to isomer **5** by treatment with 3-methyl-2-butenyl bromide in dimethylformamide followed, without isolation, by basic hydrolysis of the POM protecting group in an overall yield of 55% (Scheme III). The

Scheme III

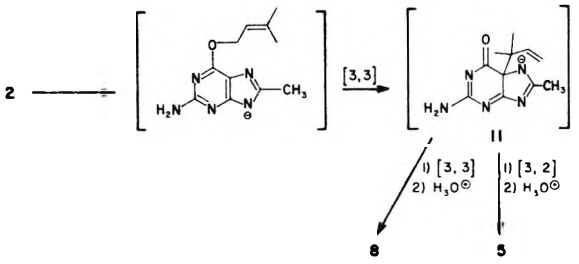


NMR, ultraviolet, and mass spectra of **5** prepared in this manner are identical with those of the minor isomer in the rearrangement mixture.

Although the ultraviolet spectrum strongly suggested that the major isomer was 8-methyl-3-(3-methyl-2-butenyl)guanine (**8**),[8] additional proof was obtained by synthesis of the remaining possible isomers, 8-methyl-1-(3-methyl-2-butenyl)guanine (**9**) and 8-methyl-9-(3-methyl-2-butenyl)guanine (**10**). Treatment of **7** with potassium *tert*-butoxide and 3-methyl-2-butenyl bromide followed by hydrolysis of the POM protecting group gave **9** in 13% yield. Derivative **10** was prepared in 36% yield by alkylation of the disodium dianion of **6** in dimethyl sulfoxide. The NMR and ultraviolet spectra for **9** and **10** do not correspond to those of the major rearrangement isomer, thus eliminating all but the N-3 isomer from consideration.

A mechanistic sequence for the formation of **8** and **5** can be formulated in terms of a C-5 bridgehead intermediate. Initial displacement on **2** followed by one [3,3] sigmatropic shift would yield the anionic bridgehead intermediate **11**. The major isomer **8** would then arise from a [3,3] sigmatropic rearrangement to N-3 (Scheme IV). The minor isomer **5**

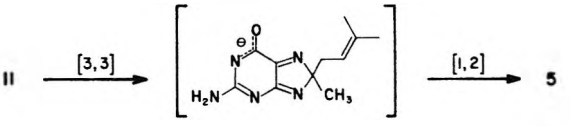
Scheme IV



could then arise by two possible routes. First, it might be formed directly by a [3,2] sigmatropic shift in the anion. Although it seems likely from steric considerations that the allylic migration to C-8 could occur to give a C-8 disubstituted derivative, the lack of a hydrogen for removal from C-8 as in Scheme I would favor reversal of the C-5 to C-8 rearrangement in the 8-methyl case. That the N-9 isomer (**10**) was not formed in the rearrangement is explicable on the basis of scale molecular models which show that the reactive end of the allylic moiety in the intermediate **11** is 15–20% further from N-9 than from either N-3 or N-7.

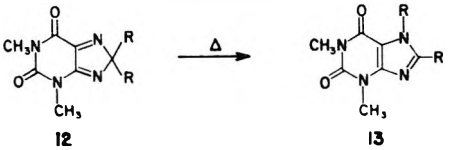
A second possible sequence is represented in Scheme V, in which a [3,3] sigmatropic shift from C-5 to C-8 would

Scheme V



produce a C-8 disubstituted intermediate that could then undergo a 1,2 migration to give **5**. The closest parallel is the thermal rearrangement of 1,3,8,8-tetrasubstituted pseudoxanthines (**12**) to 1,3,7,8-tetrasubstituted xanthines (**13**) exclusively.[9] The absence of any N-9 can be attributed to the energy barrier provided by the development of 3-8 peridialkyl interaction. In our system no such interaction would develop, and accordingly some N-9 isomer (**10**) would be expected. Since we were unable to detect the presence of any isomer **10** in the product resulting from the reaction of **2** and **4**, the [3,2] sigmatropic shift (Scheme IV) is favored for the conversion of the postulated intermediate **11** to 8-methyl-7-(3-methyl-2-butenyl)guanine (**5**).

Scheme VI



## Experimental Section

All melting points are uncorrected. The NMR spectra were recorded on Varian Associates A-60 or HA-100 spectrometers using tetramethylsilane as an internal standard. The ultraviolet spectra were obtained on a Beckman Acta Model MVI spectrometer. Microanalyses were performed by Mr. Josef Nemeth and associates, who also weighed samples for quantitative electronic absorption spectra. Low-resolution mass spectra were obtained on a Varian MAT CH-5 spectrometer and high resolution on a Varian-MAT 731 spectrometer, both coupled with a 620i computer and STATOS recorder.

**2-Amino-6-chloro-8-methylpurine (2).** Chlorine gas was introduced at a slow rate into a stirred suspension of 2-amino-6-mercapto-8-methylpurine[4] (6 g, 33 mmol) and acetonitrile (100 ml) for 1.5 hr at room temperature.[5] After purging the system with nitrogen for 1 hr, the bright yellow hydrochloride salt was filtered and washed with cold acetonitrile (150 ml).

The free base was obtained by suspending the hydrochloride salt in 100 ml of water and adjusting the pH to 6.5. The water was then removed in vacuo and the residue was extracted with chloroform for 6 hr in a Soxhlet extractor. The chloroform was removed in vacuo, and the residue was recrystallized from methanol: yield 4.25 g (70%); mp 205–215° dec; $\lambda_{max}$ ($H_2O$) 308 nm ($\epsilon$ 8070), 241.5 (6540), 217 (30200); ($H_2O$, 0.1 *N* HCl) 314 (8340), 237 (7960); ($H_2O$, 0.1 *N* NaOH) 302.5 (7740), 268 (3680); NMR (TFA) $\delta$ 3.00 (s, pu-$CH_3$); mass spectrum (10 eV) *m/e* 183 ($M^+$), 148 ($M - Cl$)$^+$.

Anal. Calcd for $C_6H_6ClN_5$: C, 39.25; H, 3.29; N, 38.15. Found: C, 39.14; H, 3.24; N, 38.12.

**8-Methyl-3-(3-methyl-2-butenyl)guanine (8) and 8-Methyl-7-(3-methyl-2-butenyl)guanine (5).** To a suspension of sodium hydride (0.5 g of a 51% oil dispersion, 12 mmol) in dry dioxane (40 ml), 3-methyl-2-buten-1-ol (1.00 g, 12 mmol) in dry dioxane (40 ml) was added under a nitrogen atmosphere. After evolution of hydrogen had ceased, 2-amino-6-chloro-8-methylpurine (**2**, 1.00 g, 5.9 mmol) was added and the mixture was heated at reflux for 20 hr. After cooling, the solvent was removed in vacuo, and the residue was dissolved in water (20 ml) and extracted five times with ether (50 ml). The aqueous layer was then acidified to pH 6 with 20% aqueous acetic acid. After cooling, the solid was removed by filtration, washed with acetone, and dried to yield 1.13 g (88%) of a mixture of 8 and 5. NMR [$(CD_3)_2SO$] of the mixture showed resonances at $\delta$ 1.65 (s, $CH_3$), 1.75 (s, $CH_3$), 2.30 (s, pu-$CH_3$), 2.31 (s, pu-$CH_3$), 4.62 (d, pu-$CH_2C$), 4.82 (d, pu-$CH_2C$), 5.18 (m, C–CH=C), 6.42 (broad, pu-$NH_2$).

High-performance liquid chromatographic separation of a 50-mg sample of the mixture was done on Bio-Rad Aminex A-5 cation exchange resin, packed in a 15 × 0.5 in. glass column maintained at a temperature of 50°. The column was eluted at a flow rate of 700 $\mu$l/min (ca. 275 psi) with 0.50 *M* ammonium formate–formic acid buffer containing 25% dimethylformamide, pH 4.10 (calculated). The retention volume of the minor isomer was 172 ml. See below for characterization.

The major isomer was eluted with a retention volume of 235 ml to give 30 mg of colorless needles of 8: mp >300°; $\lambda_{max}$ ($H_2O$) 271 nm ($\epsilon$ 13400), 236 (7900); ($H_2O$, 0.1 *N* HCl) 267 (12900), 245 sh (8200); ($H_2O$, 0.1 *N* NaOH) 277 (14800); NMR [$(CD_3)_2SO$] $\delta$ 1.65 (s, 3, $CH_3$), 1.75 (s, 3, $CH_3$), 2.31 (s, 3, pu-$CH_3$), 4.62 (d, 2, pu-$CH_2C$), 5.18 (m, 1, C–CH=C), 6.72 (broad, 2, pu-$NH_2$); mass spectrum (10 eV) *m/e* 233 ($M^+$) and 265 ($M - C_5H_8$)$^+$; high-resolution mass spectrum *m/e* 233.1278 (calcd, $C_{10}H_{15}N_5O$).

Anal. Calcd for $C_{11}H_{15}N_5O$: C, 56.64; H, 6.48; N, 30.02. Found: C, 56.94; H, 6.42; N, 29.96.

**8-Methyl-9-pivaloyloxymethylguanine (7).** Sodium hydride (3.00 g of a 51% oil dispersion, 60 mmol) was washed with two portions of dry hexane (30 ml). A solution of 8-methylguanine (**6**, 5.00 g, 30 mmol) in dry dimethyl sulfoxide (100 ml) was then added to the sodium hydride, and the mixture was stirred at 30° for 6 hr. Chloromethyl pivalate (5.00 g, 33 mmol) was added, and the reaction mixture was stirred at 30° for an additional 2 hr. The solution was treated with charcoal and filtered, and the $(CH_3)_2SO$ was removed in vacuo. To the residue was added 30 ml of 20% acetic acid, and the resulting suspension was stirred for 30 min with cooling. The product was removed by filtration, washed with water and then acetone, and dried to give 7.06 g (92%) of colorless solid. An analytical sample was obtained by an additional recrystallization from methanol: mp >350°; $\lambda_{max}$ ($H_2O$) 276 nm ($\epsilon$ 8900), 251 (13700); NMR [$(CD_3)_2SO$] $\delta$ 1.11 [s, 9, $C(CH_3)_3$], 2.35 (s, 3, pu-$CH_3$), 5.85 (s, 2, pu-$CH_2O$), 6.45 (broad, 2, pu-$NH_2$); mass spectrum (10 eV) *m/e* 255 ($M^+$), 170 ($M - C_5H_9O$)$^+$, and 140 ($M - C_6H_{10}O_2$)$^+$.

Anal. Calcd for $C_{12}H_{17}N_5O_3$: C, 51.61; H, 6.14; N, 25.07. Found: C, 51.61; H, 6.43; N, 25.18.

**8-Methyl-7-(3-methyl-2-butenyl)guanine (5).** To a suspension of 8-methyl-9-pivaloyloxymethylguanine (**7**, 150 mg, 0.59 mmol) in dry dimethylformamide (40 ml) was added isopentenyl bromide (175 mg, 12 mmol) and pyridine (0.5 ml). The mixture was stirred at room temperature for 200 hr. The DMF was removed in vacuo, and to the oily residue was added 20 ml of 2.0 *N* sodium hydroxide. This mixture was then heated on a steam bath for 1 hr. The basic solution was neutralized to pH 6, and the precipitate was collected and washed successively with ethanol and acetone. The light yellow solid was recrystallized from 80% ethanol–water to give 137 mg (55%) of yellow solid: mp >300°; $\lambda_{max}$ ($H_2O$) 283 nm ($\epsilon$ 8590), 248 sh (6690); ($H_2O$, 0.1 *N* HCl) 276 (8470), 247 (12600); ($H_2O$, 0.1 *N* NaOH) 278 (8570); NMR [$(CD_3)_2SO$] $\delta$ 1.65 (s, 3, $CH_3$), 1.75 (s, 3, $CH_3$), 2.30 (s, 3, pu-$CH_3$), 4.82 (d, 2, pu-$CH_2C$), 5.18 (m, 1, C–CH=C), 6.32 (broad, 2, pu-$NH_2$); mass spectrum (10 eV) *m/e* 233 ($M^+$) and 265 ($M - C_5H_8$)$^+$.

Anal. Calcd for $C_{11}H_{15}N_5O \cdot \frac{1}{2}H_2O$: C, 54.55, H, 6.65; N, 28.93. Found: C, 54.55; H, 6.47; N, 28.82.

**8-Methyl-9-(3-methyl-2-butenyl)guanine (10).** Sodium hydride (0.60 g of a 51% oil dispersion, 12 mmol) was added to a vigorously stirred suspension of 8-methylguanine (**6**, 1.00 g, 6 mmol) in dry DMF (50 ml). This mixture was stirred for 3 hr. A solution of isopentenyl bromide (1.2 g, 8 mmol) in dry DMF (40 ml) was then added dropwise over a period of 5 hr, and the mixture was stirred for an additional 30 min. The solvent was removed in vacuo, and to the residue was added 10 ml of 2 *N* sodium hydroxide. The solution was then washed with two portions of ether (10 ml). The aqueous layer was neutralized to pH 6 with 20% acetic acid and cooled. The precipitate was collected by filtration and washed successively with ethanol and ether to yield 481 mg (36%) of yellow solid: mp >300°; $\lambda_{max}$ ($H_2O$) 273 nm sh ($\epsilon$ 9670), 252 (13400); ($H_2O$, 0.1 *N* HCl) 277 (8770), 252 (1280); ($H_2O$, 0.1 *N* NaOH) 269 (11800), 255 sh (11300); NMR [$(CD_3)_2SO$] $\delta$ 1.65 (s, 3, $CH_3$), 1.75 (s, 3, $CH_3$), 2.27 (s, 3, pu-$CH_3$), 5.47 (d, 2, pu-$CH_2C$), 5.12 (m, 1, C–CH=C), 6.34 (broad, 2, pu-$NH_2$); mass spectrum (10 eV) 233 ($M^+$), and 165 ($M - C_5H_8$)$^+$.

Anal. Calcd for $C_{11}H_{15}N_5O$: C, 56.64; H, 6.48; N, 30.02. Found: C, 56.83; H, 6.22; N, 30.17.

**8-Methyl-1-(3,methyl-2-butenyl)guanine (9).** A solution of 8-methyl-9-pivaloyloxymethylguanine (**7**, 500 mg, 1.79 mmol) in dry dimethylformamide (200 ml) was treated with potassium *tert*-butoxide (250 mg, 2.23 mmol) under a nitrogen atmosphere. Isopentenyl bromide (425 mg, 2.85 mmol) was then added and the mixture stirred for 1 hr. Additional aliquots of potassium *tert*-butoxide (100 mg, 0.89 mmol) and isopentenyl bromide (100 mg, 0.67 mmol) were added, and the mixture was stirred for 1 hr. The dimethylformamide was then removed in vacuo, and the residue was dissolved in chloroform (100 ml) and filtered through a Celite pad. The chloroform solution was reduced in volume, applied to a 17-g silica gel column, and eluted with chloroform. The initial yellow fractions were discarded and the remaining fractions were concentrated to give 140 mg (23%) of crude 8-methyl-1-(3-methyl-2-butenyl)-9-pivaloyloxymethylguanine. This material was heated at reflux in 0.5 *N* sodium hydroxide–30% ethanol for 6 hr without further purification. After the solution was concentrated to 25 ml and made strongly acidic with 1 *N* HCl, it was extracted with three portions of $CHCl_3$ (30 ml). The aqueous layer was then neutralized with 1 *N* $NaHCO_3$ and the volume reduced to 5 ml. The resulting suspension was heated until the solid material dissolved and was treated with charcoal, filtered, and allowed to crystallize. The white crystals were filtered and dried to give 50 mg (53%) of 9. An analytical sample was obtained by recrystallization from water: mp >300°; $\lambda_{max}$ ($H_2O$) 275, 251 nm; ($H_2O$, 0.1 *N* HCl) 273 sh, 252; ($H_2O$, 0.1 *N* NaOH) 277, 262 sh; NMR [$(CD_3)_2SO$] $\delta$ 1.65 (s, 3, $CH_3$), 1.75 (s, 3, $CH_3$), 2.28 (s, 3, pu-$CH_3$), 4.56 (d, 2, pu-$CH_2C$), 5.10 (m, 1, C–CH=C), 6.50 (broad, 2, pu-$NH_2$); mass spectrum (10 eV) *m/e* 233 ($M^+$) and 265 ($M - C_5H_8$)$^+$.

Anal. Calcd for $C_{11}H_{15}N_5O \cdot \frac{1}{4}H_2O$: C, 55.51; H, 6.72; N, 29.44. Found: C, 55.55; H, 6.72; N, 29.18.

**Acknowledgment.** This work was supported by Research Grant MPS 74-05911 from the National Science Foundation. The authors are grateful to Dr. Charles R. Frihart for suggestions that stimulated this research.

**Registry No.**—**2**, 57346-44-8; **5**, 57346-45-9; **6**, 23662-75-1; **7**, 57346-46-0; **8**, 57346-47-1; **9**, 57346-48-2; **10**, 57346-49-3; 2-amino-

6-mercapto-8-methylpurine, 57379-36-9; 3-methyl-2-buten-1-ol, 556-82-1; chloromethyl pivalate, 18997-19-8.

### References and Notes


(1) Eli Lilly and Co. Fellow, 1974–1975.
(2) (a) C. R. Frihart and N. J. Leonard. *J. Am. Chem. Soc.*, **95**, 7174 (1973); (b) N. J. Leonard and C. R. Frihart, *ibid.*, **96**, 5894 (1974).
(3) For a review on allylic rearrangements of nitrogen heterocycles see B. S. Thyagarajan, *Adv. Heterocycl. Chem.*, **8**, 143 (1967); for a general review of the Claisen–Cope rearrangements see S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1 (1975).
(4) G. D. Davis, Jr., C. W. Noell, R. K. Robins, H. C. Koppel and A. G. Beaman, *J. Am. Chem. Soc.*, **82**, 2633 (1960).
(5) W. A. Nasutavicus and J. Love, *J. Heterocycl. Chem.*, **11**, 77 (1974).
(6) (a) J. W. Jones and R. K. Robins, *J. Am. Chem. Soc.*, **85**, 193 (1963); (b) J. A. Haines, C. B. Reese, and L. Todd, *J. Chem. Soc.*, 5281 (1962).
(7) (a) M. Rasmussen and N. J. Leonard, *J. Am. Chem. Soc.*, **89**, 5439 (1967); (b) N. J. Leonard and M. Rasmussen, *ibid.*, **33**, 2488 (1968).
(8) L. B. Townsend and E. K. Robins, *J. Am. Chem. Soc.*, **84**, 3008 (1962).
(9) V. H. Goldmer, G. Dietz, and E. Carstens, *Z. Chem.*, **4**, 454 (1964).


## Reaction of 7,7,8,8-Tetracyanoquinodimethane with Sodium Benzoate and Acetone

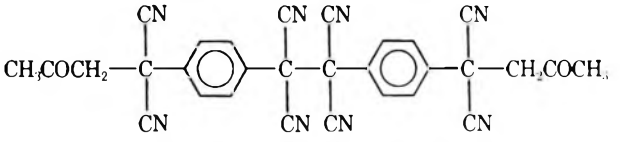

Malvina Farcasiu and Charlotte S. Russell*

*Department of Chemistry, City College of the City University of New York, New York, New York 10031*


*Received August 27, 1975*

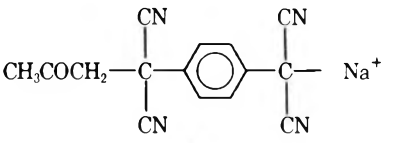
Complexes and anion radical salts of 7,7,8,8-tetracyanoquinodimethane (TCNQ) exhibit unusual electrical conductivity properties.[1] TCNQ forms $\pi$ complexes[1,2] with Lewis bases, simple anion radical salts ($M^+TCNQ\cdot^-$) with metal iodides [except for $Cs_2(TCNQ\cdot^-)_2(TCNQ)$], and complex salts with organic iodides. Tropylium iodide reacts with $Li^+TCNQ\cdot^-$ to yield $\alpha,\alpha'$-ditropyl-$\alpha,\alpha,\alpha',\alpha'$-tetracyano-*p*-xylene. TCNQ undergoes 1,6 addition with sulfurous acid and with chlorine. When TCNQ reacts with primary and secondary amines, one or two cyano groups are replaced by amine.[3]

Although acetone has been used as a solvent in some of these reactions, no reaction of TCNQ with acetone has been reported. This work describes a unique reaction which produces an acetone-substituted dimer of TCNQ, I. It appears that carboxylate anion is oxidized by TCNQ because sodium benzoate, sodium salicylate, and sodium acetate reduced TCNQ to $Na^+TCNQ\cdot^-$ in acetone and generated acetonyl radical. However, little or no $CO_2$ was evolved in these reactions.

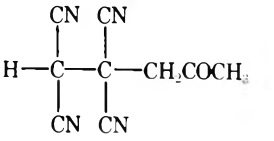


I

In a typical experiment TCNQ (20.0 mmol) and sodium benzoate (20.0 mmol) in 500 ml of dry acetone were stirred vigorously at room temperature in the dark for 48 hr. Results were the same in air and under nitrogen. $Na^+TCNQ\cdot^-$ (6.7 mmol) and benzoic acid (10.0 mmol) were obtained, as well as 0.319 g of compound I (dimer) and 1.736 g of compound II. The latter was soluble in ethyl acetate, ethanol, and acetonitrile with a light green color. II had strong absorption at 320 nm and very weak, broad absorption at 500–600 nm. II had strong infrared absorption (KBr disk) at 2130 and 2170 $cm^{-1}$ (substituted malononitrile anion as in sodium pentacyanoethane and potassium phenylmalononitrile),[4] weak absorption at 2250 $cm^{-1}$ (unconjugated nitrile with electronegative groups on carbon), strong absorption at 1720 $cm^{-1}$ (ketone), and peaks at 1610, 1520, 825 (para-substituted phenyl with strong $\pi$ overlap), 1420, 1360 $cm^{-1}$ (methyl and methylene). The NMR spectrum in acetone-$d_6$ showed two coupled doublets, 7.3 (2 H) and 7.0 ppm (2 H), and two singlets, 3.8 (2 H) and 2.3 ppm (3 H). When TCNQ was added to II, $Na^+TCNQ\cdot^-$ was formed. We assign to II the structure i on the basis of evidence described above, the conversion to dimer described below, and the fact that ii is formed from tetracyanoethylene and



i



ii

acetone by a free-radical mechanism.[5,6] II is also formed when sodium acetate and sodium salicylate were used instead of sodium benzoate.

An equimolar mixture of II and TCNQ in ethyl acetate yielded $Na^+TCNQ\cdot^-$ and I. I was purified by washing with ethanol and recrystallization from acetone, white needles, mp 279.9–280.1°C. I had a maximum at 320 nm in ethanol. The infrared spectrum (KBr disk) showed strong absorption at 1730 $cm^{-1}$ (ketone) and very weak absorption at 2250 and 2350 (unconjugated nitrile with electronegative groups on $\alpha$ carbon as in *p*-phenylenemalononitrile, which has a band at 2270 $cm^{-1}$), 1510 and 805 (para-substituted phenyl), and 1425 and 1355 $cm^{-1}$ (methyl and methylene). The NMR spectrum in acetone-$d_6$ showed two coupled doublets, 7.9 (2 H) and 7.6 ppm (2 H), and singlets at 4.0 (2 H) and 2.3 ppm (3 H). Anal. Calcd for $C_{30}H_{18}O_2N_8$: C, 69.0; H, 3.5; N, 21.5. Found: C, 68.8; H, 3.4; N, 21.4. Mol wt: calcd, 522; found, 483. The mass spectrum at high gain shows a peak at *m/e* 522.

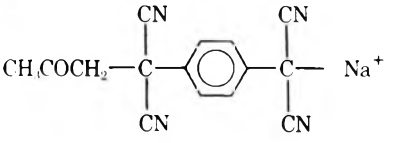
When acetonitrile was used as solvent in this reaction, $Na^+TCNQ\cdot^-$ was produced along with a material with broad absorption at 365 and 390 nm which resisted purification. With sodium carbonate and acetone or acetonitrile, TCNQ was converted to the sodium salt of $\alpha,\alpha$-dicyano-*p*-toluoyl cyanide.[3]

We assign to I the structure of the dimer rather than monomer primarily because of the molecular weight determination. We propose that the reaction proceeds in the following way.

$$C_6H_5COO^-Na^+ + TCNQ \longrightarrow C_6H_5COO\cdot + Na^+TCNQ\cdot^-$$

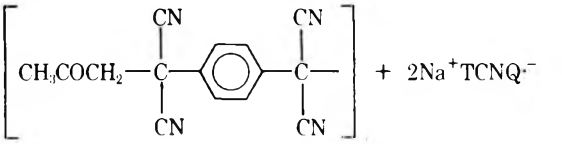
$$C_6H_5COO\cdot + CH_3COCH_3 \longrightarrow C_6H_5COOH + CH_3COCH_2\cdot$$

$$CH_3COCH_2\cdot + Na^+TCNQ\cdot^- \longrightarrow$$



II

$$2II + 2TCNQ \longrightarrow$$



I

While there are many examples of one-electron transfers from various donors to TCNQ, electron transfer from carboxylate ion is less common. In fact only the Kolbe synthesis unequivocally involves such a process. TCNQ appears to be a strong enough oxidant for carboxylate anion. Little or no decarboxylation is observed in agreement with the observation of others[7,8] on the fate of benzoyloxy radicals in solution. The isolation of dimer I suggests hydrogen abstraction from solvent, acetone.

**Acknowledgment.** One of the authors (M.F.) thanks Professor P. v. R. Schleyer for the opportunity to perform some experiments in his laboratory at Princeton University and for helpful discussions.

**Registry No.**—I, 57362-36-4; II, 57379-37-0; TCNQ, 1518-16-7; sodium benzoate, 532-32-1; acetone, 67-64-1; $Na^+TCNQ\cdot^-$, 12153-63-8; sodium acetate, 127-09-3; sodium salicylate, 54-21-7; sodium carbonate, 144-55-8; $\alpha,\alpha$-dicyano-*p*-toluoyl cyanide sodium salt, 57379-38-1.

## References and Notes

(1) L. R. Melby, R. J. Hader, W. R. Hertler, W. Mahler, R. E. Benson, and W. E. Mochel, *J. Am. Chem. Soc.*, **84**, 3374 (1962).
(2) D. S. Acker and W. R. Hertler, *J. Am. Chem. Soc.*, **84**, 3370 (1962).
(3) W. R. Hertler, H. D. Hartzler, D. S. Acker, and R. E. Benson, *J. Am. Chem. Soc.*, **84**, 3387 (1962).
(4) D. W. Webster, W. Mahler, and R. E. Benson, *J. Am. Chem. Soc.*, **84**, 3678 (1962).
(5) W. J. Middleton, R. E. Heckert, E. L. Little, and C. G. Kespan, *J. Am. Chem. Soc.*, **80**, 2783 (1958).
(6) C. L. Dickinson, *J. Am. Chem. Soc.*, **82**, 4367 (1960).
(7) J. L. Eberson, *Acta Chem. Scand.*, **17**, 2004 (1963).
(8) C. Walling, H. P. Waits, J. Milovanovic, and C. G. Paplaonnou, *J. Am. Chem. Soc.*, **92**, 4927 (1970).

---

# Photochemistry of 2,2,4,4-Tetraphenyloxetan-3-one. Intermediates in the Photofragmentation of Aryl Substituted Oxiranes

J. P. Wasacz[1] and M. M. Joullié*

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

U. Mende, I. Fuss, and G. W. Griffin*

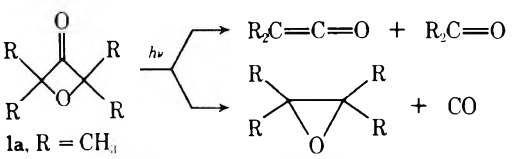
*Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70122*

*Received June 23, 1975*

The photochromic behavior of vicinally substituted aryloxiranes has been investigated in rigid glasses[2] and the intervention of ionic and free-radical intermediates has been proposed for the fragmentation of these oxiranes to arylcarbenes and carbonyl compounds.[3] During these investigations the development of a blue-colored species ($\lambda_{max}$ 610 nm) was observed upon irradiating tetraphenyloxirane (**2b**) at 254 nm in hydrocarbon glasses (77K). That carbon–carbon bond cleavage is associated with this phenomenon was confirmed by low-temperature rigid matrix studies on 2,2,4,4-tetraphenyloxetan-3-one (**1b**).[4] The colored intermediate that forms from the oxetanone on decarbonylation at 350 nm, under conditions in which the oxirane is photostable, was shown to be spectroscopically identical with that obtained from **2b** at 254 nm. We now wish to report additional photochemical results obtained on **1b** in solution.

Hammond and co-workers[5a,b] studied the solution photolysis of a related compound, 2,2,4,4-tetramethyloxetan-3-one (**1a**). In polar solvents, the principal reaction path involved cycloelimination to give dimethylketene and acetone, rather than decarbonylation to tetramethyloxirane. In nonpolar solvents, both reactions were found to occur (Scheme I). An acyl–alkyl biradical intermediate which decomposes by two different solvent-dependent paths was proposed for these processes, although complete product identification was not achieved.

Scheme I




**1a**, R = $CH_3$
**b**, R = $C_6H_5$

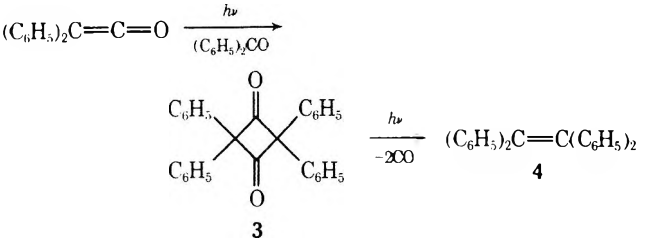
**2a**, R = $CH_3$
**b**, R = $C_6H_5$

The results with **1a** suggested that the tetraphenyl analogue **1b** would photolyze in a similar manner upon irradiation above 300 nm to give tetraphenyloxirane (**2b**). Under these conditions the oxirane is known to be photostable and, if formed, should be isolable.

Irradiation of **1b** in benzene (350 nm, Pyrex, c 20 mmol/l.) for 17 hr resulted in the conversion of the starting material (76%) to a mixture of the expected oxirane **2b** (36%), carbon monoxide (detected by gas-phase infrared spectroscopy), benzophenone (55%), and diphenylketene (Scheme I), as well as tetraphenylethylene (10%). Diphenylketene was shown to be present among the primary photoproducts by infrared spectroscopy ($\nu_{C=C=O}$ 2080 $cm^{-1}$) and was trapped as methyl diphenylacetate (13%) by quenching the benzene solution with methanol after irradiation. The benzophenone and methyl diphenylacetate were separated from unreacted **1b** and other photoproducts by elution chromatography on silica gel. The relative amounts of the two components were established by NMR.

The formation of tetraphenylethylene (**4**) was noted with great interest. 2,2,4,4-Tetraphenylcyclobutane-1,3-dione (**3**), the head-to-tail dimer of diphenylketene which is known to decarbonylate to **4**,[6] appeared to be a reasonable precursor[7a] (Scheme II). While benzene solutions of diphenylketene are stable to irradiation at 350 nm for prolonged periods (90 hr) in the absence of benzophenone (92% recovery), tetraphenylethylene (66%) and traces of biphenyl are formed when benzophenone is added to the solution. Since both benzophenone and diphenylketene are primary cycloelimination products obtained from **1b**, the proposed mechanism for the formation of **4** is clearly consistent with the experimental results. Benzophenone presumably behaves as a sensitizer for the dimerization of diphenylketene and experiments designed to test this proposal are in progress. An alternative route to **4** involving dimerization of diphenylcarbene, formed from diphenylketene in a sensitized process, is unlikely, at least in solution, at the wavelength employed.[7b,c]

Scheme II




**3** **4**

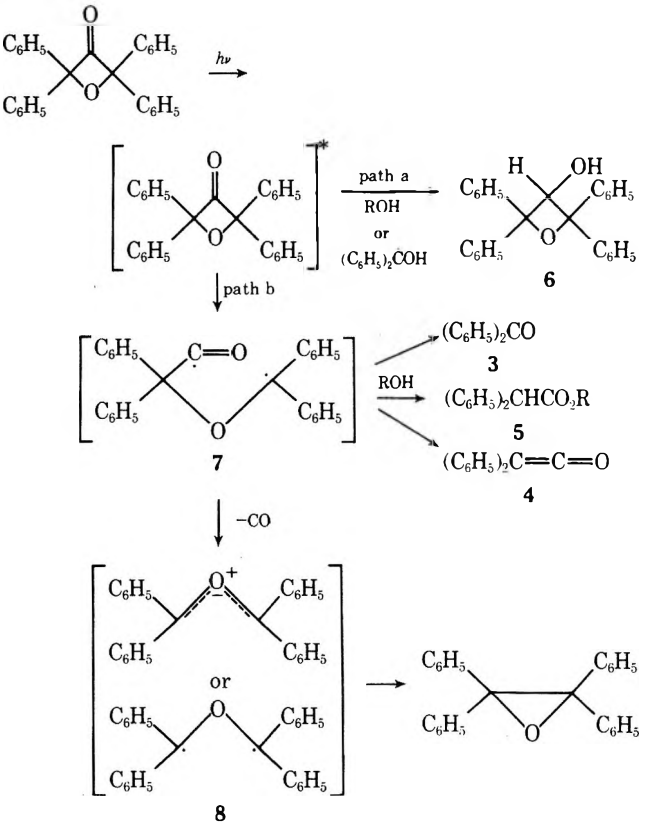
In an attempt to trap diphenylcarbene, a potential primary photoproduct of **1b**, irradiation of a solution of **1b** in methanol (c 3.3 mmol/l.) was undertaken.[8] After 18 hr ex-

posure and 99% conversion of **1b**, the only photoproducts found were carbon monoxide, tetraphenyloxirane (**2b**, 30%), methyl diphenylacetate (51%), and benzophenone (35%). Benzhydryl methyl ether, the product formed by the reaction of the carbene with methanol, could not be detected by GLC analysis, demonstrating, within the capabilities of our analytical technique (~1%), that no diphenylcarbene was formed either directly from **1b** or in secondary photoreactions involving diphenylketene or tetraphenyloxirane, both of which are possible precursors.[7c,9] Similar results were obtained even when **1b** was irradiated in methanol with a more intense source, provided that a Pyrex filter ($\lambda > 320$ nm) was employed; i.e., no benzhydryl methyl ether was formed, although, as observed earlier, **1b** fragments to give diphenylketene (as evidenced by isolation of methyl diphenylacetate, 52.3%) and benzophenone (16.2%), and also undergoes decarbonylation to afford the oxirane **2b** (39.5%). Irradiation of **1b** in methanol using a Corex filter (*c* 2.5 mmol/l.) resulted in the formation of substantial amounts of benzhydryl methyl ether (31%) and a concomitant decrease in the amount of oxirane (5.5%) produced. While direct fragmentation of a decarbonylation intermediate cannot be excluded as a source of diphenylcarbene, the oxirane **2b** is photolabile under the cited conditions and most, if not all, of the diphenylcarbene probably arises from a secondary photoreaction of the oxirane. We therefore conclude that oxirane **2b**, carbon monoxide, benzophenone, and diphenylketene are the primary photoproducts arising from fragmentation of **1b** at wavelengths above 320 nm.

Upon photolysis of **1b** in benzene–2-propanol solution (19:1), three reaction pathways were observed: decarbonylation to give tetraphenyloxirane (**2b**), cycloelimination to form benzophenone and diphenylketene [isolated as isopropyl diphenylacetate (**5**)], and reduction to 2,2,4,4-tetraphenyloxetan-3-ol (**6**). Although the photochemical ring expansion of cyclic ketones to cyclic acetals in hydroxylic solvents has been reported by several authors[10a–d] and is considered a general reaction for cyclobutanones,[10c] the photolysis of **1b** produced no detectable ring expanded products. Possible mechanisms consistent with these results are shown in Scheme III.

It is evident that the nonbonding orbital on oxygen in the n,$\pi^*$ excited state of ketones is a highly localized site of photochemical activity with radical characteristics[11] and, as a consequence, photoreduction of **2a** to give **6** (path a) may proceed by simple hydrogen abstraction from 2-propanol. Alternatively, however, some, if not all, of ketone **1b** may be reduced in a dark reaction by benzophenone ketyl generated, in turn, from triplet benzophenone and 2-propanol.[12] Path b involves a Norrish type I cleavage to give an acyl–alkyl diradical **7**[13] which, upon decarbonylation, produces **2b** via a diradical or zwitterion 8. The fragmentation of **7** yields diphenylketene and benzophenone. In the presence of alcohol, the diphenylketene is converted to an ester of diphenylacetic acid. It is noteworthy that no diphenylcarbene is formed by collapse of 8. Recently, Huisgen and co-workers reported that related oxo ylides produced by thermal cleavage of the oxirane carbon–carbon bond undergo typical dipolar additions without the elimination of carbenes.[14] These observations provide additional evidence that the mechanism for oxirane cycloelimination reactions leading to carbenes either requires initial carbon–oxygen bond cleavage or proceeds in a concerted fashion. All attempts to date to trap the oxo ylide 8 derived from **1b** or **2b** with electron-deficient dipolarophiles such as dimethyl fumarate, fumaronitrile, or their cis counterparts, which are effective in intercepting the corresponding ylides derived from stilbene oxides,[15] have proved unrewarding. We attribute this lack of reactivity to adverse steric factors in the addition complex.

Scheme III




## Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 521 double-beam spectrophotometer. NMR spectra were obtained on a Varian A-60A spectrometer. Chemical shifts are expressed in $\delta$ (parts per million) downfield from $Me_4Si$. The purity of liquid samples was verified by gas chromatography. If purification was required, the samples were distilled with a Nester-Faust NF-190 spinning band column (6 × 450 nm, 23 theoretical plates). Solid samples were purified by repeated recrystallizations from appropriate solvents until a constant melting point was obtained. Elemental analyses were carried out by Dr. A. Bernhardt Mikronalytische Laboratorium, West Germany, and Galbraith Laboratories, Knoxville, Tenn. Gas chromatographic analyses were conducted isothermally (180°) on a coated open-tubular capillary column available from Perkin-Elmer Corp., Norwalk, Conn., using a 900 Series Perkin-Elmer gas chromatograph. Yields are reported in terms of the weight of materials isolated assuming that only 1 mol of reactant is required for each mol of product formed regardless of the actual mechanism. Preparative VPC was achieved on a 20 ft × 0.25 in. column of 10% silicone rubber on 45-60 Chromosorb W at 100–110° (injection port, 180°) with a helium flow rate of 120 ml/min; retention times are reported relative to air coinjected as reference. The interpretation of VPC results was accomplished by standard calibration techniques.

2,2,4,4-Tetraphenyloxetan-3-one (**1b**) was prepared either by the method of Harper and Lester[5b] or Hoey, Dean, and Lester:[16] yield 50%; mp 198–199.5° (lit.[16] mp 199–201°); $\nu_{max}$ ($CHCl_3$) 1813 $cm^{-1}$ (C=O); NMR ($CDCl_3$) $\delta$ 7.26 (m).

All irradiations were conducted in serum-capped quartz or Pyrex test tubes. In each case, fluid solutions were degassed by sparging with nitrogen or argon prior to irradiation. A Rayonet Chamber Reactor (The Southern New England Ultraviolet Co., Middletown, Conn.) equipped with 16 G8T5 8-W low-pressure mercury lamps (254 nm) was used in some cases. The irradiation of **1b** in benzene in a Pyrex vessel for 17 hr was carried out with a source similar to that described above but fitted with F8T5 8-W lamps (350 nm) at 35°. The same source was used for the irradiation of **1b** in methanol. A quartz Hanovia probe, employing a 450-W high-pressure mercury lamp (Type 79A36), at 10° was also employed to irradiate **1b** in methanol. When a Pyrex filter ($\lambda > 320$

nm) was employed, the results were the same as in the previous irradiation of **1b** in methanol; however, with a Corex filter (λ <300 nm), substantial amounts of benzhydryl methyl ether and less oxirane were produced.

The irradiation of **1b** in benzene–2-propanol was carried out as follows. A solution of **1b** (0.74 g, 0.002 mol) in 190 ml of dry benzene and 10 ml of 2-propanol was irradiated for 45 min with a 450-W Hanovia (Type L, Model 679A-36) high-pressure quartz mercury-vapor lamp. After the removal of solvent, crystals of tetraphenylethylene oxide formed, mp 194–195.5°.

Anal. Calcd for $C_{26}H_{20}O$: C, 89.62; H, 5.79. Found: C, 89.37; H, 5.70.

The physical properties of this product were identical in every respect with those of an authentic sample prepared by the method of Mosher, Steffgen, and Lansbury.[17] Benzophenone (**3**), isopropyl diphenylacetate (**5**), and 2,2,4,4-tetraphenyloxetan-3-ol (**6**) were identified by comparing their NMR and ir spectra and their VPC retention times with those of authentic samples.

**Acknowledgment.** Acknowledgment (U.M., I.F., G.W.G.) is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and to the Army Research Office, Durham (ARO-D-31-124-73-G4). These authors also wish to thank Dr. K. Ishikawa for technical assistance and to acknowledge the assistance of Dr. E. Elder and Mrs. J. Thompson in the preparation of the manuscript.

**Registry No.**—**1b**, 40112-59-2; **2b**, 470-35-9.

## References and Notes

(1) Taken in part from the dissertation presented by J. P. Wasacz in partial fulfillment of the requirements of the Ph.D. degree at the University of Pennsylvania, 1969.
(2) R. S. Becker, J. Kolc, R. O. Bost, H. Dietrich, P. Petrellis, and G. W. Griffin, *J. Am. Chem. Soc.*, **90**, 3292 (1968); R. S. Becker, R. O. Bost, J. Kolc, N. R. Bertoniere, R. L. Smith, and G. W. Griffin, *ibid.*, **92**, 1302 (1970).
(3) P. Petrellis and G. W. Griffin, *Chem. Commun.*, 691 (1967); G. W. Griffin, *Angew. Chem., Int. Ed. Engl.*, **10**, 537 (1971).
(4) A. Trozzolo, T. Do-Minh, and G. W. Griffin, *J. Am. Chem. Soc.*, **92**, 1402 (1970).
(5) (a) P. J. Wagner, C. A. Stout, S. Searles, Jr., and G. S. Hammond, *J. Am. Chem. Soc.*, **88**, 1242 (1966); (b) J. L. Harper and C. T. Lester, *J. Org. Chem.*, **26**, 1294 (1961), and references cited therein.
(6) N. J. Turro and S. S. Edelson, personal communication.
(7) (a) H. Staudinger, *Chem. Ber.*, **44**, 521, 543 (1911). See L. A. Mileshina, R. N. Nurmukhameto, D. N. Shigorin, and Sh. Nadzhimuldinov, *Dokl. Akad. Nauk SSSR*, **182**, 684 (1968), for a discussion of the uv spectroscopy of diphenylketene. (b) H. Nozaki, M. Nakanc, and K, Kondo [*Tetrahedron*, **22**, 477 (1966)] have studied the solution photochemistry of diphenylketene. Diphenylcarbene appears to be among the products when a high-pressure mercury lamp (200 W) is used as a source and either cyclohexene, tetrahydrofuran, or ether is employed as a solvent. (c) H. E. Zimmerman and D. H. Paskovich [*J. Am. Chem. Soc.*, **86**, 2149 (1964)] observed that irradiation of dimesitylketene with a low-pressure mercury lamp gives tetramesitylethylene (19%) and dimesityl ketone. Tetraphenylethylene is not reported to be a photoproduct of diphenylketene photolysis.
(8) Alcohols previously have been used to trap the nucleophilic arylcarbenes as ethers. See W. Kirmse, L. Horner, and H. Hoffmann, *Justus Liebigs Ann. Chem.*, **614**, 19 (1958); W. Kirmse, *ibid.*, **666**, 9 (1963).
(9) (a) H. Kristinsson and G. W. Griffin, *J. Am. Chem. Soc.*, **88**, 1579 (1966); (b) A. M. Trozzolo, W. A. Yager, G. W. Griffin, H. Kristinsson, and I. Sarkar, *ibid.*, **89**, 3357 (1967).
(10) (a) P. Yates and L. Kilmurry, *Tetrahedron Lett.*, 1739 (1964); P. Yates and L. Kilmurry, *J. Am. Chem. Soc.*, **88**, 1563 (1966); (b) H. U. Hostettler, *Tetrahedron Lett.*, 687 (1965); H. U. Hostettler, *Helv. Chim. Acta*, **49**, 2417 (1966); (c) N. J. Turro and R. M. Southam, *Tetrahedron Lett.*, 545 (1967); D. R. Morton, E. Lee-Ruff, R. M. Southam, and N. J. Turro, *J. Am. Chem. Soc.*, **92**, 4349 (1970); (d) P. Yates and R. O. Loutfy, *Acc. Chem. Res.*, **8**, 209 (1975).
(11) N. J. Turro, "Molecular Photochemistry", R. Breslow and M. Karplus, Ed., W. A. Benjamin, New York, N.Y., 1967, p 137.
(12) H. Zimmerman and J. Hull, *J. Am. Chem. Soc.*, **92**, 6515 (1970).
(13) R. Srinivasan, *Adv. Photochem.*, **1**, 83 (1963).
(14) J. H. Hall and R. Huisgen, *Chem. Commun.*, 1187 (1971); J. H. Hall, R. Huisgen, C. H. Ross, and W. Scheer, *ibid.*, 1188 (1971); H. Hamberger and R. Huisgen, *ibid.*, 1190 (1971); A. Dahman, H. Hamberger, R. Huisgen, and V. Markowski, *ibid.*, 1192 (1971).
(15) G. W. Griffin, N. E. Brightwell, K. Ishikawa, I. Lev, and S. Satra, presented at VIII International Conference on Photochemistry, Edmonton, Alberta, Canada, August 7–15, 1975, Abstract I-1.
(16) G. B. Hoey, D. O. Dean, and C. T. Lester, *J. Am. Chem. Soc.*, **77**, 391 (1955).
(17) W. A. Mosher, F. W. Steffgen, and P. T. Lansbury, *J. Org. Chem.*, **26**, 670 (1961).

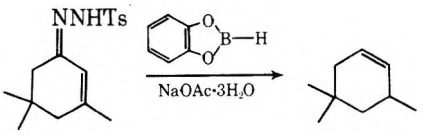
# Deoxygenation of α,β-Unsaturated Aldehydes and Ketones via the Catecholborane Reduction of the Corresponding Tosylhydrazones

George W. Kabalka,* Dominic T. C. Yang,[1] and John D. Baker, Jr.

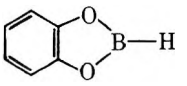
*Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37916*

*Received July 14, 1975*

The reduction of tosylhydrazones with boron hydrides offers a mild and convenient alternative to the Wolff–Kishner and Clemmensen reductions.[2–4] In the initial reports, it was observed that α,β-unsaturated systems were reduced with migration of the double bond.[2,5]




This migration offers exciting synthetic possibilities such as the formation of less stable positional isomers (exocyclic double bonds vs. endocyclic double bonds) and deconjugation of conjugated double bonds. Indeed these synthetic manipulations have been recently reported to occur (except in cyclohexenone derivatives) using sodium cyanoborohydride as the reducing agent.[6] This report[6] has prompted us to report our studies utilizing catecholborane (I) for the reductions of α,β-unsaturated tosylhydrazones.




I

We find that catecholborane (I) cleanly reduces the tosylhydrazones of α,β-unsaturated carbonyl compounds, including the cyclohexenone derivatives, in high yields. The catecholborane procedure offers a number of advantages over the current procedures in that (1) the reaction requires only 1 equiv of hydride (as opposed to 12 equiv in the $NaBH_3CN$ procedure); (2) it is carried out under mild conditions (temperature below 62°, pH near neutral); (3) common organic solvents are employed such as chloroform (as opposed to the DMF–sulfolane system utilized in the $NaBH_3CN$ procedure); and (4) clean isomerizations are obtained with no alkane formation. The reductions are practical for sensitive systems since the necessary tosylhydrazones are prepared at neutral pH in ethanol.

Our results are summarized in Table I.

The reaction most likely proceeds via the formation of an unstable diazene intermediate.[7] A reasonable mechanism is outlined in Scheme I which is based on analogy to known

**Scheme I**

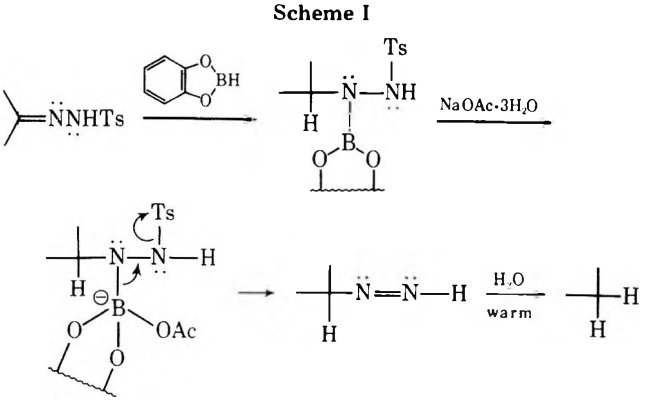
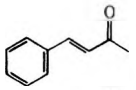
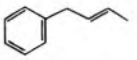
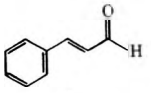
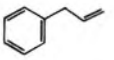
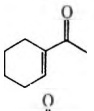
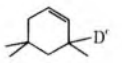


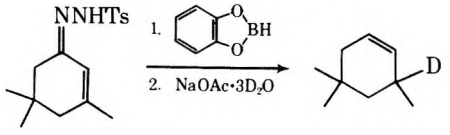
Table I
Conversion of Carbonyl Reagents to the Corresponding Methylene Derivatives[a]

| Carbonyl reagent[a] | Registry no. | Product[b] | Registry no. | Yield, % |
|---|---|---|---|---|
|  | 122-57-6 |  | 1560-06-1 | 72[c] |
|  | 104-55-2 |  | 300-57-2 | 53[c] |
|  | 141-79-7 |  | 4461-48-7 | 65[c] |
|  | 932-66-1 |  | 1003-64-1 | 77[c] (61)[f] |
|  | 78-59-1 |  | 933-12-0 | 66[d] (48)[f] |
|  | |  | 57325-57-2 | 66[d] |

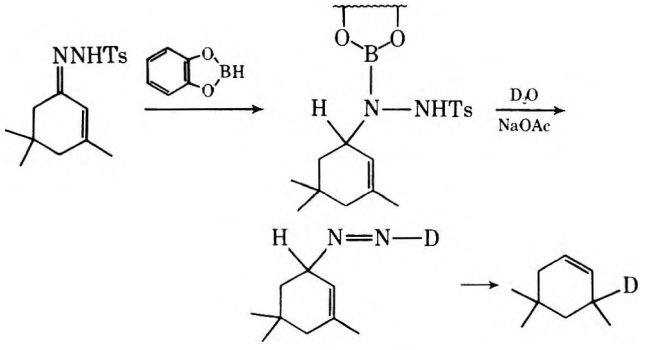
[a] The carbonyl reagents were first converted to the corresponding tosylhydrazone derivatives. [b] Products exhibited physical and spectral parameters in agreement with those of authentic samples and literature reports. [c] GLC analysis. [d] NMR analysis. [e] NaOAc·3$D_2O$ utilized rather than NaOAc·3$H_2O$. [f] Isolated yield.

borane reactions such as the elimination of a borane derivative when the boron is $\beta$ to an electronegative substituent.[8]

The reduction of the tosylhydrazone of isophorone followed by decomposition with NaOAc·3$D_2O$ led to the formation of 3,5,5-trimethylclohexene-*3-d*. This result, and




the observation that the least stable alkene is formed exclusively in a number of instances, strongly support a concerted decomposition of the diazene intermediate.[9] The available data do not differentiate between an intermolecular and an intramolecular decomposition however. Control experiments clearly demonstrate that deuterium–hydrogen exchange occurs rapidly in both the tosylhydrazones and the reduced intermediate.[10] Consequently it is likely that deuterium is incorporated prior to diazene decomposition.




## Experimental Section

**Materials.** The reagents, including catecholborane, were obtained from Aldrich Chemical Co. The tosylhydrazones were prepared according to the method of Hutchins[3,6] and exhibited melting points and spectral characteristics in accord with published values.[3,11]

**General Procedure for Reductions.** The reduction of isophorone is representative. The tosylhydrazone of isophorone, 2.5 mmol (0.768 g), was dissolved in 6 ml of chloroform at 0°C. Catecholborane (2.75 mmol, 0.31 ml) was added and the reduction allowed to proceed for 2 hr. Sodium acetate trihydrate (7.5 mmol, 1.02 g) was added and the reaction mixture was brought to a gentle reflux for 1 hr. NMR analysis indicated a 66% yield of 3,5,5-trimethylcyclohexene with no evidence of the corresponding alkane. The products were isolated via silica gel chromatography and preparative GLC. All exhibited physical and spectral characteristics in accord with published values.[3]

**Preparation of 3,5,5-Trimethylcyclohexene-*3-d*.** The reduction was carried out as described above except that NaOAc·3$D_2O$ was employed:[12] NMR ($CDCl_3$) $\delta$ 5.47 (m, 2), 1.73 (m, 2), 1.47 (m, 1), 1.35 (m, 1), 0.92 (m, 9); mass spectrum (70 eV) *m/e* (rel intensity) 125 (48, $M^+$), 110 (100), 69 (74), 56 (33).

**Acknowledgment.** We wish to thank Research Corporation for support of this work. We also wish to thank Professor R. O. Hutchins for helpful discussions.

**Registry No.**—Catecholborane, 274-07-7; 4-phenyl-3-buten-2-one tosylhydrazone, 17336-65-1; cinnamaldehyde tosylhydrazone, 7318-33-4; 4-methyl-3-penten-2-one tosylhydrazone, 5362-76-5; 1-acetylcyclohexene tosylhydrazone, 41780-85-2; 3,5,5-trimethyl-2-cyclohexen-1-one tosylhydrazone, 21195-62-0.

## References and Notes

(1) Visiting Professor, 1975, from the University of Arkansas at Little Rock.
(2) G. W. Kabalka and John D. Baker, *J. Org. Chem.*, **40**, 1834 (1975).
(3) R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973).
(4) L. Caglioti, *Tetrahedron*, **22**, 487 (1966).
(5) It was originally reported (in ref 3) that this was the major reaction when sodium cyanoborohydride was used to reduce the tosylhydrazone. It has since been noted that reduction to the hydrocarbon is the major reaction when sodium cyanoborohydride is utilized (see ref 6).
(6) R. O. Hutchins, M. Kacher, and L. Rua, *J. Org. Chem.*, **40**, 923 (1975).
(7) A similar mechanism has been proposed for the sodium cyanoborohydride reduction of tosylhydrazones of $\alpha,\beta$-unsaturated carbonyl reagents.
(8) (a) D. J. Pasto and R. Snyder, *J. Org. Chem.*, **31**, 2777 (1966); (b) H. C. Brown and R. M. Gallivan, *J. Am. Chem. Soc.*, **90**, 2906 (1968); (c) C. E. McKenna and T. G. Traylor, *ibid.*, **93**, 2313 (1971).
(9) The regiospecific incorporation of deuterium rules out a reduction–hydroboration–elimination sequence analogous to that observed in diborane reductions of $\alpha,\beta$-unsaturated ketones. See L. Caglioti, G. Cainella, G. Maina, and A. Selva, *Tetrahedron*, **20**, 957 (1964).
(10) In one experiment, the tosylhydrazone of isophorone was reduced with 1 equiv of catecholborane. Three equivalents of $D_2O$ were added which resulted in the immediate disappearance of the NMR signal due to NH.
(11) G. L. Closs, L. E. Closs, and W. A. Boll, *J. Am. Chem. Soc.*, **85**, 3796 (1963).
(12) The NaOAc·3$D_2O$ was prepared by dissolving anhydrous NaOAc in a slight excess of $D_2O$ and allowing the "hydrate" to crystallize.

## Carbon-13 Nuclear Magnetic Resonance Assignments in the Trichothecene Mycotoxins

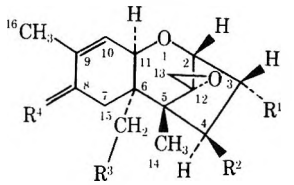
Robert A. Ellison* and Frank N. Kotsonis

*School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53706*

*Received June 13, 1975*

The trichothecenes (Chart I) are a family of at least 29 sesquiterpenes produced by several genera of fungi of which at least one is a notorious plant pathogen.[1] Most of these compounds are also very toxic to mammals and have been implicated in a number of epidemic disease states resulting from the ingestion of moldy foods and feeds.[2]

Chart I



1, $R_1$ = OAc; $R_2$ = OAc; $R_3$ = OAc; $R_4$ = α-$OCOCH_2CH(CH_3)_2$
2, $R_1$ = OH; $R_2$ = OAc; $R_3$ = OAc; $R_4$ = α-$OCOCH_2CH(CH_3)_2$
3, $R_1$ = OH; $R_2$ = OH; $R_3$ = OAc; $R_4$ = α-$OCOCH_2CH(CH_3)_2$
4, $R_1$ = OH; $R_2$ = OH; $R_3$ = OH; $R_4$ = α-$OCOCH_2CH(CH_3)_2$
5, $R_1$ = OH; $R_2$ = OH; $R_3$ = OH; $R_4$ = α-OH
6, $R_1$ = OH; $R_2$ = OAc; $R_3$ = OAc; $R_4$ = $H_2$
7, $R_1$ = H; $R_2$ = OCOCH=$CHCH_3$; $R_3$ = H; $R_4$ = 0
8, $R_1$ = H; $R_2$ = OCOCH=$CHCH_3$; $R_3$ = H; $R_4$ = α-H,β-7,8-epoxy

Owing to the relative complexity of the structure, particularly with regard to the variation in number and positioning of oxygen atoms, these compounds are not always readily distinguished from one another. Consequently carbon-13 magnetic resonance ($^{13}C$ NMR) was expected to be especially valuable in assigning structures. Recently $^{13}C$ NMR assignments have been proposed for two somewhat different group of trichothecenes.[3a,b]

It is anticipated that functional group variation on such a relatively condensed and interconnected skeleton could make assignments based on analogy or calculation somewhat tenuous. Indeed, examination of the recorded spectra showed that the lower field oxygenated methines in particular were difficult to differentiate. To avoid this problem we relied on a series of molecules (1–6) which permitted systematic and progressive alteration of functionality so as to restrict undesired chemical shift changes. Further, we employed the Birdsall technique[4a,b] to correlate the $^{13}C$ NMR spectrum of T-2 toxin (2) with that of the established proton spectrum[5,6] in order to provide a secure base from which to assign the series. This approach has resulted in reassignment of several lines proposed in one of the earlier studies.[3a]

Complete assignments for compounds 1–8 are listed in Table I. Because of its availability in quantity, T-2 toxin (2) was selected for Birdsall treatment. It is a member of a five-compound series which is characterized by successive deesterification. Results of the Birdsall plot for 2 are shown in Table II. The proton resonances were obtained from intersects with an error of ±0.25 ppm using nine off-resonance proton decoupling frequencies ranging from −4900 to −6100 Hz. The accuracy of the technique could be gauged by comparing the values obtained for easily assigned carbon atoms such as C-10, C-4′, and C-5′. Positions for the isovaleryl ester of 1–4 were verified by comparison with calculated values[7] and were absent in T-2 tetraol (5). With the chemical shifts of 2 now relatively secure, it remained to examine the other compounds. This was accomplished by placing the resonances in groups according to their multiplicity.

**Methyl Quartets.** The chemical shift for C-16 in 2 was corroborated by comparison with calculated values[7] which agreed remarkably well (calcd, 19.03 ppm; found, 19.40 ppm). This value remained constant in the series 1–5. On the other hand, the complex influence of the skeleton on chemical shift was evidenced by the lack of agreement between similar calculated values for C-14 and those which were found (13.27 and 6.38 ppm, respectively). While this

Table I
$^{13}C$ NMR Spectra of the Trichothecenes (δ in ppm from $Me_4Si$)

| | Carbon atom | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2 | 3[h] | 4[h] | 5 | 6 | 7 | 8 | 9 |
| Acyl T-2 toxin[a] (1) | 76.2 (d) | 78.7 (d) | 78.2 (d) | 47.7 (s) | 42.0 (s) | 26.7 (t) | 67.2 (d) | 135.0 (s) |
| T-2 toxin[b] (2) | 78.7 (d) | 76.0 (d) | 82.4 (d) | 48.2 (s) | 42.2 (s) | 26.7 (t) | 67.4 (d) | 134.6 (s) |
| HT-2 toxin[c] (3) | 78.7 (d) | 79.1 (d) | 79.8 (d) | 47.7 (s) | 41.8 (s) | 26.7 (t) | 68.9 (d) | 134.2 (s) |
| T-2 triol[d] (4) | 78.7 (d) | 79.3 (d) | 79.3 (d) | 47.5 (s) | 43.1 (s) | 27.4 (t) | 68.1 (d) | 133.7 (s) |
| T-2 tetraol (5) | 78.5 (d) | 79.1 (d) | 80.0 (d) | 48.0 (s) | 45.1 (s) | 28.5 (t) | 64.8 (d) | 138.1 (s) |
| Diacetoxyscirpenol[e] (6) | 79.3 (d) | 76.7 (d) | 83.1 (d) | 49.1 (s) | 44.0 (s) | 20.6 (t) | 27.4 (t) | 140.6 (s) |
| Trichothecin[f] (7) | 73.4 (d) | 35.8 (t) | 78.7 (d) | 48.2 (s) | 42.6 (s) | 41.3 (t) | 175.3 (s) | 138.8 (s) |
| Crotocin[g] (8) | 74.3 (d) | 36.2 (t) | 78.5 (d) | 47.7 (s) | 41.3 (s) | 58.1 (d) | 50.4 (d) | 137.2 (s) |
| | 10 | 11 | 12 | 13 | 14 | 15 | 16 | |
| Acyl T-2 toxin[a] (1) | 124.0 (d) | 66.3 (d) | 63.6 (s) | 41.4 (t) | 6.1 (q) | 63.6 (t) | 19.4 (q) | |
| T-2 toxin[b] (2) | 124.2 (d) | 66.3 (d) | 64.1 (s) | 46.2 (t) | 6.4 (q) | 63.9 (t) | 19.4 (q) | |
| HT-2 toxin[c] (3) | 124.6 (d) | 67.4 (d) | 64.3 (s) | 45.3 (t) | 6.6 (q) | 63.9 (t) | 19.4 (q) | |
| T-2 triol[d] (4) | 125.1 (d) | 66.3 (d) | 64.5 (s) | 45.3 (t) | 6.4 (q) | 61.7 (t) | 19.4 (q) | |
| T-2 tetraol (5) | 121.6 (d) | 67.6 (d) | 64.3 (s) | 45.1 (t) | 6.3 (q) | 61.0 (t) | 19.9 (q) | |
| Diacetoxyacirpenol[e] (6) | 119.8 (d) | 67.4 (d) | 64.5 (s) | 46.4 (t) | 6.4 (q) | 63.4 (t) | 22.5 (q) | |
| Trichothecin[f] (7) | 137.2 (d) | 69.2 (d) | 65.4 (s) | 46.4 (t) | 4.9 (q) | 14.4 (q) | 17.7 (q) | |
| Crotocin[g] (8) | 122.9 (d) | 69.4 (d) | 65.9 (s) | 46.8 (t) | 6.2 (q) | 15.9 (q) | 21.0 (q) | |

[a] C-1′, 172.2 (s); C-2′, 42.4 (t); C-3′, 25.2 (d); C-4′ and C-5′, 21.7 (q); three acetate methyls, 20.3 (q); three acetate carbonyls, 170.6 (s) and 170.1 (2 s). [b] C-1′, 172.0 (s); C-2′, 42.6 (t); C-3′, 25.0 (d); C-4′ and C-5′, 21.9 (q); two acetate methyls, 20.3 (q) and 20.8 (q); two acetate carbonyls, 170.4 (s) and 169.7 (s). [c] C-1′, C-2′, C-3′, C-4′, and C-5′ same as in *b*; acetate methyl, 20.8 (q); acetate carbonyl, 170.0 (s). [d] C-1′, C-2′, C-3′, C-4′, and C-5′ same as in *b*. [e] Two acetate methyls, 20.6 (q); and two acetate carbonyls, 171.9 (s) and 172.4 (s). [f] C-1′, 166.6 (s); C-2′, 120.7 (m); C-3′, 146.8 (d); and C-4′, 14.8 (q). [g] C-1′, 166.4 (s); C-2′, 120.2 (m); C-3′, 146.5 (d) and C-4′, 14.8 (q). [h] C-3 and C-4 assignments in 1, 3, and 5 could be reversed.

Table II
Birdsall Plot Determined $^1H$ Frequencies Compared to Known $^1H$ Frequencies in T-2 Toxin[a]

| Carbon atom | $^1H$ frequency, $\delta$[b] | | Carbon atom | $^1H$ frequency, $\delta$ | |
|---|---|---|---|---|---|
| | Known | Determined[c] | | Known | Determined |
| C-2 | 3.41 | 3.41 | C-14 | 0.58 | 0.79 |
| C-3 | 3.85–4.20 | 4.14 | C-15 | 3.85–4.20 | 3.70 |
| C-4 | 5.54 | 5.28 | C-16 | 1.65 | 1.74 |
| C-7 | | 2.16 | C-2′ | 2.47 | 2.58 |
| C-8 | 5.21 | 4.75 | C-3′ | | 1.62 |
| C-10 | 5.72 | 5.82 | C-4′ and C-5′ | 0.87 | 0.83 |
| C-11 | 3.85–4.20 | 3.91 | | | |
| | | | Acetate | | |
| C-13 | 2.88, 2.84 | 2.58 | methyls | 1.94, 2.01 | 1.74 |

[a] Concentration 600 mg/ml $Me_2SO$-$d_6$. [b] $\delta$ in parts per million from $Me_4Si$. [c] Error estimated to be ±0.25 ppm.

might be explained by steric compression,[8] it is difficult to assign an a priori value to this effect in these molecules. As expected, the chemical shift of C-14 also varies very little throughout the series. C-15 appears as a quartet in both **7** and **8** and resonates close to the crotonyl methyl in these compounds. The assignments for each were made on the assumption that the latter would not respond to the change in functionality in ring A although they are clearly reversible.

**Methylene Triplets.** All of the triplets in **2** were well separated. This reflected their different environments and each was identified by the Birdsall plot. The chemical shift of C-7 varied only slightly in **1–5** but suffered an upfield shift upon loss of the C-8 oxygen in **6**.[9] A shift downfield on going from **6** to **7** is expected for the oxidation at C-8[10] and this triplet is lost in crotocin (**8**). This permits assignment of the 36.24-ppm resonance in **8** to C-3. The resonance for C-13 varies very little across the series **2–8** with the exception of the conversion **1** to **2**, which was unexpected. The chemical shift for C-15 is corroborated by the shielding of 2.2 ppm upon deacylation of **3**[9] as well as conversion to an upfield quartet in **7** and **8**.

**Methine Doublets.** The difficulty in clearly assigning chemical shifts to the doublets of C-3 and C-11 with the Birdsall plot derives from the overlap of the corresponding proton resonances (Table II). While this may have been resolved by proton double resonance, assignments were reached by examining the effects of structural change. Thus, the doublet at 66.30 ppm in **2** is relatively constant during alteration to the bicyclooctane moiety and is therefore assigned to C-11. Of particular importance is the retention of this doublet upon loss of the C-3 hydroxyl in **7** and **8**.

Among the more difficult assignments are those of C-2, C-3, and C-4, which occur as a group of lower field doublets. While chemical shifts could be assigned in **2** with some confidence, assignment in the remaining molecules required careful attention to progressive changes in the series **1–6**. Given that acylation results in deshielding of the oxygenated carbon and shielding of the penultimate carbon,[9] the doublets at 79.78 and 79.12 ppm in **3** were assigned to C-4 and C-3, respectively. These coalesced to a single resonance at 79.34 ppm in **4**. This confirms the doublet at 78.68 ppm in **2** as being that of C-2 since it would not be expected to be responsive to changes at C-15. The expected shielding of C-2 in the **2** to **1** transition is also evident. The assignments in **5**, where all three doublets again become visible, was more difficult but C-4 was placed at lowest field under the assumption that this atom would be more likely than C-3 to respond to altered functionality at C-8. Similar shifts to those seen in **3** but in the opposite direction allow the lines in **1** at 78.68 and 78.24 ppm to be attributed to C-3 and C-4. Owing to the closeness of the resonances for C-3 and C-4 in **1**, **3**, and **5**, however, it is clear that our assignments for these could easily be reversed. The relative position of C-2 and C-4 is maintained in both **7** and **8** where the loss of hydroxyl at C-3 was expected to have a similar influence on both carbons.

Assignment of C-8 by using only the Birdsall plot is ambiguous owing to the discrepancy between deduced and actual proton chemical shifts at C-8. Although the carbon chemical shifts of C-8 and C-11 in **2** are relatively close, the latter had previously been assigned. Consequently, the lower doublet must be C-8. Further, the shielding (3.32 ppm) of C-8 upon deacylation of **4** is reasonable. In crotocin (**8**), the C-8 doublet moved upfield to become part of the ring A epoxide. The new doublet at 58.12 ppm was assigned to C-7. While no distinction between C-7 and C-8 could be made on the basis of model calculations, the higher field resonance was assigned to C-8 on the basis of comparison with epoxycyclohexene.[11] The assignment of C-8 in **5** is also corroborated by the 3.5-ppm upfield shift in the line attributed to C-10 upon deacylation of **4** which reflects operation of the allyl acetate rule.[12] Close examination of the spectrum reveals small (0.7 ppm) changes in the chemical shifts of C-2, C-3, and C-4 on esterification of **5**. These serve to again call attention to the subtle effects of structural modification on the chemical shifts of distant centers.

The chemical shift of the upfield olefinic carbon in **8** is readily distinguished from that of C-10 by the dramatic deshielding of the latter which occurs on conversion to **7**. The lowest field doublet in **7** and **8** would clearly be expected to be the $\beta$-olefinic carbon of the ester.

**Quaternary Singlets.** The assignments of C-9 are straightforward. Of the remainder, the low-field singlet was attributed to C-12 owing to its relative invariance with functional group alteration. The distinction between C-5 and C-6 was made on the basis of the 1.3-ppm deshielding of the high-field singlet which accompanied deacylation of **3**. The alternate line (C-5) also shifts but to a much lesser extent and in fact is shielded which is not consistent with being $\beta$ to a hydroxyl function.[9]

Partial relaxed Fourier transform (PRFT) spectra of **2** toxin were obtained by the inversion recovery method using a ($-180°-t-90°-T-$) sequence. The relative spin-lattice relaxation times ($T_1$'s) of the various assigned carbons were determined by altering $t$ (0.005 → 9.99 sec). At $t$ = 0.005 sec all carbons except C-15 [no signal; therefore, $t_1$ (C-15) ln 2 ~ 0.005 sec] gave inverted signals, while at $t$ = 1.00 sec all the carbons gave positive signals. However, at an intermediate $t$ (0.200 sec) only the unprotonated carbons (C-5, C-6, C-9, C-12, and the ester carbonyls) and the *gem*-dimethyl carbons of the isovaleroxy side chain gave negative signals. The longer relaxation times observed for the unprotonated carbons[13] and the *gem*-dimethyl carbons[14] were to be expected if our assignments were correct.

These observations, in addition to the general trend in the relaxation times of the other carbons, corroborated our carbon assignments in T-2 toxin.

## Experimental Section

All spectra were obtained with a Bruker HX-90E spectrophotometer operating at 22.624 MHz in the pulse Fourier transform mode. Field-frequency stabilization was obtained from the deuterium resonance of the solvent ($Me_2SO$-$d_6$). Proton decoupling was accomplished with a broad band modulator of Bruker design. Free induction decay (FID) data were averaged with a Nicolet 1080 computer.

In the case of spectra for the Birdsall plots, 25000 transients of T-2 toxin (600 mg/ml) were averaged before multiplication (TC = −1) of the accumulated FID.

Partially relaxed Fourier transform (PRFT) spectra of T-2 toxin (600 mg/ml) were obtained by the inversion recovery method using a $(-180°-t-90°-T-)_X$ sequence where $T$ (= 15 sec) was greater than $5T_1$ with the FID being accumulated after the 90° pulse. Different $t$ values were employed (0.005–9.99 sec) with $X$ = 1000 (sweeps) before multiplication (TC = −1) of the accumulated FID.

**Acknowledgments.** This work was funded by the Graduate School, University of Wisconsin, Madison. We thank Dr. P. A. Hart and Mr. J. Blackbourn, School of Pharmacy, for NMR spectra, and Dr. F. M. Strong, Department of Biochemistry, for samples of diacetoxyscirpenol and crotocin.

**Registry No.**—**1**, 21259-21-2; **2**, 21259-20-1; **3**, 26934-87-2; **4**, 34114-98-2; **5**, 34114-99-3; **6**, 2270-40-8; **7**, 637-96-7; **8**, 21284-11-7.

## References and Notes

(1) C. Booth, "The Genus Fusarium", Commonwealth Mycological Institute, Kew, Surrey, 1971.
(2) (a) J. V. Rodricks and R. M. Eppley in "Mycotoxins", I. F. H. Purchase, Ed., American Elsevier, New York, N.Y., 1974, Chapter 9; (b) E. B. Smalley and F. M. Strong, *ibid.*, Chapter 10; (c) A. Z. Joffe, *ibid.*, Chapter 11; D. M. Salto and K. Ohtsubo, *ibid.*, Chapter 12.
(3) (a) J. R. Hanson, T. Marten, and M. Siverns, *J. Chem. Soc., Perkin Trans. 1*, 1033 (1974); (b) W. Breitenstein and C. Tamm, *Helv. Chim. Acta*, **58**, 1172 (1975).
(4) (a) B. Birdsall, N. J. M. Birdsall, and J. Feeney, *J. Chem. Soc., Chem. Commun.*, 316 (1972); (b) N. J. Bach, M. E. Boaz, E. C. Kornfeld, C. J. Chang, H. G. Floss, E. W. Hagaman, and E. Wenkert, *J. Org. Chem.*, **39**, 1272 (1974).
(5) The published spectrum of **2** was taken with carbon tetrachloride as solvent.[6] Although some chemical shift changes were noted in the dimethyl sulfoxide spectrum, these could be reassigned without difficulty.
(6) (a) J. R. Bamburg, N. V. Riggs, and F. M. Strong, *Tetrahedron*, **24**, 3329 (1968); (b) B. K. Tidd, *J. Chem. Soc. C*, 218 (1967).
(7) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, p 38.
(8) Reference 7, p 43.
(9) Reference 7, p 47.
(10) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, Chapter 5, Section IIC, p 175.
(11) D. R. Paulson, F. Y. N. Tang, G. F. Moran, A. S. Murray, B. P. Pelka, and E. M. Vasquez, *J. Org. Chem.*, **40**, 184 (1975).
(12) N. J. Bach, M. E. Boaz, E. C. Kornfeld, C. J. Chang, H. G. Floss, E. W. Magaman, and E. Wenkert, *J. Org. Chem.*, **39**, 1272 (1974).
(13) Reference 7, p 7.
(14) A. Allerhand, D. Doddrell, and R. Komorowski, *J. Chem. Phys.*, **55**, 189 (1971).

# Organic Reactions at Alumina Surfaces. Elimination Reactions Effected by Dehydrated Chromatographic Alumina

Gary H. Posner* and George M. Gurria

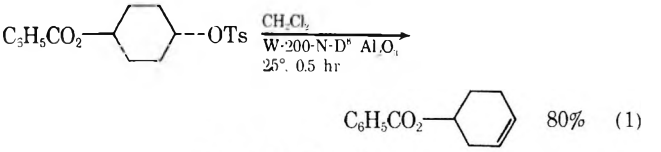
*Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218*

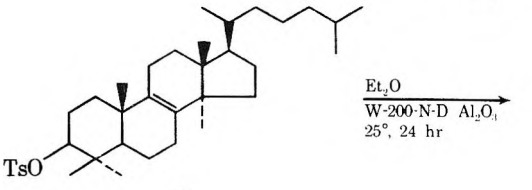
*Received July 22, 1975*

We have reported that stirring solutions of secondary *cyclic* *p*-toluenesulfonate esters over neutral, activity I, Woelm, chromatographic alumina at 25° produces olefins in high yields.[1] The simplicity and mildness of this procedure compare favorably with other methods for overall dehydration of alcohols,[2] and this method has been used recently in other laboratories to prepare some cycloalkenes.[3] Secondary *acyclic* tosylates, however, are converted by activity I alumina to 2:1 mixtures of olefins and alcohols. We reasoned that high temperature, vacuum dehydration of the alumina might form an activated alumina having some useful properties. We report here that Woelm W-200 (Brockmann activity super I),[4] neutral alumina dehydrated at 400° and 0.06 Torr for 24 hr is indeed a mild, effective, new reagent (1) for conversion of *acyclic* secondary tosylates and sulfamates to roughly 10:1 mixtures of olefins and alcohols, (2) for elimination of *cyclic* secondary tosylates to olefins even in presence of normally base and acid labile functionalities, and (3) for elimination of some rearrangement-prone tosylates and sulfamates to olefins *without any rearrangement*. The predominant mechanism of these alumina promoted reactions appears to be an anti elimination, with a syn elimination pathway occurring to some extent.

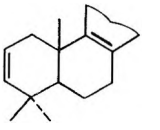
When 2-octyl tosylate or 2-octyl *N,N*-dimethylsulfamate was stirred in ether at 25° for 24 hr over neutral, dehydrated Woelm W-200 alumina, octenes and 2-octanol were formed in approximately 10:1 ratio and in 70–95% yields; the *cis*-2-octene predominated over the *trans*-2-octene and over the 1-octene.[5]

In contrast to activity I Woelm alumina, which transforms cyclohexyl tosylates to cyclohexenes (~90%) *and* cyclohexanols (~5%),[1] dehydrated W-200 alumina converts cyclohexyl tosylates to cyclohexenes without any detectable trace of cyclohexanols. Thus, 3β-cholestanyl tosylate was converted to 2-cholestene in 83% isolated yield with no cholestanol(s) being formed. This result should be compared with previous alumina-promoted reactions of 3β-tosyloxy sterols, which gave olefin and alcohol mixtures.[6] *p*-Toluenesulfonic acid elimination from *trans*-4-benzoyloxycyclohexyl tosylate illustrates the functional group selectivity of dehydrated W-200 alumina (eq 1).[7] Control experi-




1




2

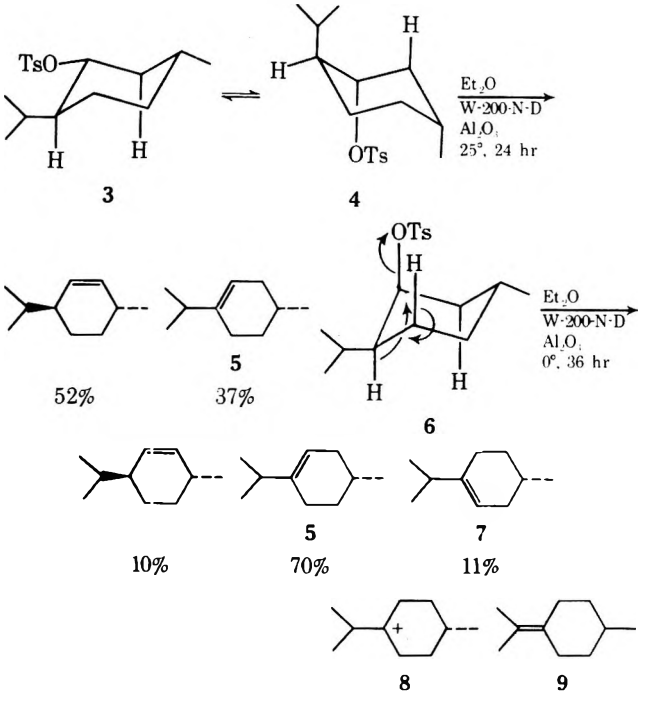
ments establish that the following compounds can be recovered in 70–90% yields after being stirred over dehydrated W-200 alumina for 24 hr at 25°: 1-iodooctane, 2-iodooctane, 5-nonanone, and diethyl dodecanedioate. Thus selective elimination of *p*-toluenesulfonic acid from bifunctional tosylates containing halo, keto, and carboxylic ester groups is practical with dehydrated alumina.

Neopentyl tosylates are known to undergo facile solvolytic rearrangements, and several 3-tosyloxy-4,4-dimethyl sterols suffer 4 → 3 methyl migration when exposed to alu-

mina.[9] We have found that stirring 3β-tosyloxy-4,4-dimethyl sterol **1** over dehydrated W-200 alumina produced $\Delta^2$ olefin **2** cleanly in 90% isolated yield with no detectable amount of alcohol or of rearranged material (eq 2). Likewise, cyclohexylmethyl *N,N*-dimethylsulfamate in acetonitrile reacted with dehydrated W-200 alumina to form methylenecyclohexane and 1-methylcyclohexene in 14:1 ratio; in a separate control experiment, methylenecyclohexane was found to be stable to the alumina reaction conditions.

Menthyl (**3**) and neomenthyl (**6**) tosylates reacted with dehydrated alumina to produce 2- and 3-menthenes as shown in Scheme I.[10] Formation of 3-menthenes from menthyl tosylate involves either a syn β-elimination[11] or an $E_1$ (carbonium ion) process. We have ruled out the $E_1$ process by using optically active (−)-menthyl tosylate and showing that only (+)-3-menthene (**5**) is formed; had carbonium ion **8** been an intermediate, both enantiomers **5** and **7** of 3-menthene should have been formed in equal amounts (i.e., racemic 3-menthene). Formation of 2-menthene from menthyl tosylate could be either an anti 1,2 elimination from conformer **4** or a syn 1,2 elimination from conformers **3** or **4**. Thus menthyl tosylate reacts at least to the extent of about 37% via a syn 1,2 elimination.[10] Formation of mainly (+)-3-menthene (**5**) from (+)-neomenthyl tosylate (**6**) involvss predominantly an anti 1,2 elimination, and production in small amount of (−)-3-menthene (**7**) involves either a syn 1,3 elimination or an $E_1$ process; although the $E_1$ mechanism cannot be ruled out by our data in this case, it seems unlikely because no tetrasubstituted olefin **9** was detected.[10,12] Thus neomenthyl tosylate reacts over dehydrated alumina predominantly but not exclusively via an anti 1,2 elimination. Control experiments showed that no menthene isomerization occurred under the alumina reaction conditions.

Scheme I




## Experimental Section

Analytical gas–liquid phase chromatography was performed on a Varian Aerograph Model 1200 chromatograph, and preparative gas–liquid phase chromatography was done on a Varian Aerograph Model 90-P3 chromatograph. Spectral data were obtained with a Perkin-Elmer 457-A infrared spectrometer and a Varian A-60 NMR spectrometer. Optical rotations were measured on chloroform solutions with a Perkin-Elmer Model 141 polarimeter.

All solvents were commercial reagent grade and were purified before use. The esters were prepared from the corresponding alcohols and acid chlorides in pyridine or from the alcoholates and acid chlorides in glyme and gave appropriate spectral and physical data. *trans*-4-Benzoyloxycyclohexyl tosylate was prepared by the method of Owen and Robins.[13]

**General Procedure for Alumina Dehydration.** Woelm W-200 (neutral, activity grade Super I) is activated by heating in a quartz tube at 400°C and 0.06 Torr for 24 hr, water condensing in a dry ice–acetone cooled trap (3–4% by weight water is removed). The quartz tube is then opened to nitrogen, removed from the vacuum line, and quickly stoppered while hot. The freshly prepared, dehydrated alumina is then transferred to the reaction flasks in the dry nitrogen atmosphere of a glove bag.

**General Procedure for Elimination Reactions.** To an amount (about 7 g of alumina per millimole of substrate) of dehydrated alumina plus magnetic stir bar in a stoppered round-bottom flask was added quickly via pipet the appropriate amount of substrate in solvent. The resultant thin slurry was rapidly stirred for the duration of the reaction period. At the end of the reaction, the alumina was then stripped of reaction materials by washing in a filter funnel with ether–methylene chloride (1:1); rotary evaporation yields products. (Note that the eliminated sulfonic acid is retained on the catalyst.)

**Octenes from 2-Octyl *N,N*-Dimethylsulfamate.** A solution of 124.4 mg (0.53 mmol) of 2-octyl *N,N*-dimethylsulfamate in 4 ml of dry ether was stirred over 2.98 g of dehydrated alumina at 25° for 1 day. Gas–liquid phase chromatography (7 ft × 0.125 in., 5% SE-30 on Chromosorb G 100/120 using *n*-nonane as calibrated, added internal standard) showed 82% octenes (1-octene:*cis*-2-octene:*trans*-2-octene, 1.5:3:1) and 9% 2-octanol.

**5α-Cholest-2-ene from 5α-Cholestan-3β-yl Tosylate.** A solution of 63.3 mg (0.12 mmol) of 5α-cholestan-3β-yl tosylate in 3 ml of carbon tetrachloride was stirred over 1.99 g of dehydrated alumina at 25° for 1 day. Rotary evaporation of the ether–methylene chloride filtrate gave 36 mg (83%) of 5α-cholest-2-ene: NMR ($CCl_4$) δ 0.60–2.4 (m, 44 H), 5.55 (m, 2 H, olefinic[14]); mp 72–74° (lit.[14] 74–75°) after passage through a silica gel column (29.1 mg, 68%).

**4-Benzoyloxycyclohexene from *trans*-4-Benzoyloxycyclohexyl Tosylate.** A solution of 66.0 mg (0.18 mmol) of *trans*-4-benzoyloxycyclohexyl tosylate in 3 ml of dry methylene chloride was stirred over 2.67 g of dehydrated alumina at 25° for 20 min. Filtering and rinsing the alumina with 30 ml of ether–methylene chloride (1:1) in a Hirsch funnel, followed by removal of solvent by rotary evaporation and Kugelrohr distillation, afforded 28.4 mg (80%) of 4-benzoyloxycyclohexene: ir (neat) 1712 (s, C=O), 1650 (w, C=C), 1275 $cm^{-1}$ (s, C–O); NMR ($CCl_4$) δ 1.7–2.5 (m, 6 H, methylenes), 5.21 (m, 1 H, carbinol), 5.66 (d, $J$ = 1.5 Hz, 2 H, olefinic), 7.25–8.10 ppm (m, 5 H, aromatic); $n^{22}D$ 1.5221 (lit.[7] $n^{26}D$ 1.5336).

**Lanosta-2,8-diene (2) from Lanost-8-en-3β-yl Tosylate (1).** A solution of 254.0 mg (0.43 mmol) of lanost-8-en-3β-yl tosylate in 4 ml of dry ether was stirred over 2.83 g of dehydrated alumina at 25° for 1 day. Rotary evaporation of the ether–methylene chloride filter gave 159 mg (90%) of a white solid, lanosta-2,8-diene: NMR ($CDCl_3$) δ 0.65–2.5 (m, 48 H), 5.45 ppm (m, 2 H, olefinic); 150 mg (85%), mp 77–81° (lit.[15] mp 79–81°), after passage through a silica gel column.

**Methylenecyclohexane from Cyclohexylmethyl *N,N*-Dimethylsulfamate.** A solution of 202.3 mg (0.91 mmol) of cyclohexylmethyl *N,N*-dimethylsulfamate and 44.8 mg of *trans*-2-octene (as internal, calibrated GLC standard) in 6.5 ml of dry acetonitrile was stirred over 7.43 g of dehydrated alumina at 50° for 1 day. Vapor phase chromatography (9 ft × 0.125 in., 5% SE-30 on Chromosorb G 100/140) showed 44% methylenecyclohexane and 3% 1-methylcyclohexene; these products were identified by preparative GLC isolation and comparison with known samples. Cyclohexyl *N,N*-dimethylsulfamate (43%) was also recovered.

**Menthenes from (−)-Menthyl Tosylate (3).** A solution of 223.7 mg (0.72 mmol) of (−)-menthyl tosylate (**3**) in 5 ml of dry ether was stirred over 5.26 g of dehydrated alumina at 25° for 1 day. Gas–liquid phase chromatography (10 ft × 0.25 in., 10% FFAP on Chromosorb W 60/80, using *p*-cymeme as added, calibrated, internal standard) showed 89% menthenes ($\Delta^2$ and $\Delta^3$ combined). Careful distillation removed most of the solvent and preparative GLC (20 ft × 0.375 in., 20% QF-1 on Chromosorb W 45/60) afforded 60 mg of pure menthenes ($\Delta^2$, $\Delta^3$ combined). Analysis of this

material by NMR and optical rotation showed 43% (+)-menth-3-ene ($[\alpha]^{23}_{589}$ + 106°, giving 97% optical purity) and 57% (+)-menth-2-ene.

**Menthenes from (+)-Neomenthyl Tosylate (6).** A solution of 99.0 mg (0.32 mmol) of (+)-neomenthyl tosylate (**6**) in 3 ml of dry ether was stirred over 2.72 g of dehydrated alumina at 0° for 1.5 days. Gas–liquid chromatography (10 ft × 0.25 in., 10% FFAP on Chromosorb W 60/80; using *p*-cymene as added, calibrated, internal standard) showed 91% menthenes ($\Delta^2$ and $\Delta^3$ combined). Careful distillation removed most of the solvent and preparative GLC (20 ft × 0.375 in., 20% QF-1 on Chromosorb W 45/60) afforded a pure sample of the $\Delta^2$- and $\Delta^3$-menthene mixture. Analysis of this material by NMR and optical rotation showed 89% (+)-menth-3-ene ($[\alpha]^{23}_{589}$ + 86.1°, giving 74% optical purity) and 11% (+)-menth-2-ene.

**Acknowledgment.** We thank the Research Corporation and NIH (CA 16068) for financial support.

**Registry No.**—**1,** 57346-50-6; **2,** 35652-87-0; **3,** 2230-82-2; **6,** 2230-77-5; alumina, 1344-28-1; 2-octyl *N,N*-dimethylsulfamate, 57346-51-7; 5α-cholest-2-ene, 570-73-0; 5α-cholestan-3β-yl tosylate, 3381-52-0; 4-benzoyloxycyclohexene, 36978-27-5; *trans*-4-benzoyloxycyclohexyl tosylate, 57346-52-8; cyclohexylmethyl *N,N*-dimethylsulfamate, 57346-53-9.

## References and Notes

(1) G. H. Posner, R. J. Johnson, and M. J. Whalen, *Chem. Commun*, 281 (1972); for other uses of dehydrated chromatographic alumina, see also G. H. Posner and A. W. Runquist, *Tetrahedron Lett.*, 3601 (1975), and G. H. Posner, D. Z. Rogers, C. M. Kinzig and G. M. Gurria, *ibid.*, 3597 (1975).
(2) (a) D. V. Banthorpe, "Elimination Reactions", American Elsevier, New York, N.Y., 1963; (b) E. M. Burgess, H. R. Penton, Jr., and E. A. Taylor, *J. Am. Chem. Soc.*, **92,** 5224 (1970); (c) P. Crabbé and C. León, *J. Org. Chem.*, **35,** 2594 (1970); (d) R. S. Monson, *Tetrahedron Lett.*, 567 (1971); (e) J. C. Martin and R. J. Arhart, *J. Am. Chem. Soc.*, **93,** 4327 (1971).
(3) (a) L. A. Paquette, S. V. Ley, and W. B. Farnham, *J. Am. Chem. Soc.*, **96,** 312 (1974); (b) C. Mercier, P. Soucy, W. Rosen, and P. Deslongchamps, *Synth. Commun.*, **3,** 161 (1973); (c) see also H. Mayr and R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **14,** 499 (1975).
(4) H. Brockmann and H. Schodder, *Chem. Ber.*, **74,** 73 (1941).
(5) A similar distribution of olefins was found in the dehydration of secondary alcohols over alumina at high temperature: H. Pines and W. P. Haag, *J. Am. Chem. Soc.*, **83,** 2947 (1961).
(6) (a) F. Chang and R. T. Blickenstaff, *Chem. Ind. (London)*, 590 (1958); (b) G. H. Douglas, P. S. Ellington, G. D. Meakins, and R. Swindells, *J. Chem. Soc.*, 1720 (1959); (c) D. Djerassi, R. D. H. Murray, and R. Villotti, *ibid.*, 1160 (1965); (d) R. J. W. Cremlyn and C. W. Shoppee, *ibid.*, 3515 (1954).
(7) Cf. D. A. Prins, *Helv. Chim. Acta*, **40,** 1621 (1957).
(8) "W-200-N-D" stands for "Woelm W-200 neutral, dehydrated".
(9) (a) F. Kohen, B. K. Patnaik, and R. Stevenson *J. Org. Chem.*, **29,** 2710 (1964); (b) J. F. McGhie, P. J. Palmer, M. Rosenberger, J. M. Birchenough, and J. F. Cavalla, *Chem. Ind. (London)*, 1221 (1959); (c) R. R. Sobti and S. Dev, *Tetrahedron Lett.*, 3939 (1966); (d) A. Bekaert, M. Devys, and M. Barbier, *Helv. Chim. Acta*, **58,** 1071 (1975).
(10) For a good discussion of the mechanism of dehydration of alcohols (including the menthols) over alumina catalysts, see H. Pines and J. Manassen, *Adv. Catal.*, **16,** 49 (1966); see also E. J. Blanc and H. Pines, *J. Org. Chem.*, **33,** 2035 (1968).
(11) A syn 1,2-elimination pathway for 2-octanol over alumina has recently been proposed: B. H. Davis, *J. Org. Chem.*, **37,** 1240 (1972).
(12) (a) W. Hückel and M. Hanack, *Angew. Chem., Int. Ed. Engl.*, **6,** 534 (1967); (b) W. Huckel and C.-M. Jennewein, *Justus Liebigs Ann. Chem.*, **683,** 100 (1965).
(13) L. N. Owen and P. A. Robins, *J. Chem. Soc.*, 320 (1949).
(14) G. M. L. Cragg, C. W. Davey, D. N. Hall, G. D. Meaklns, E. E. Richards, and T. L. Whateley, *J. Chem. Soc. C*, 1266 (1966).
(15) J. W. Huffman, *J. Org. Chem.*, **24,** 447 (1959).

---

## Reaction of Substituted Benzodioxoles with Methylmagnesium Iodide under Heterogeneous Conditions

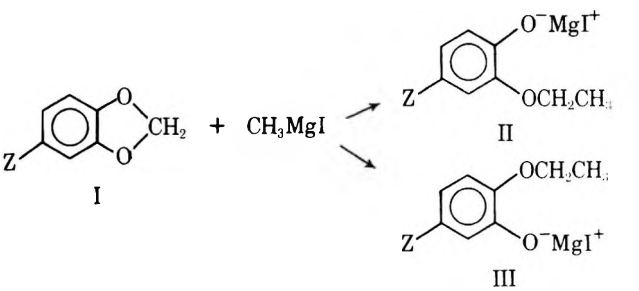
Paolo Beltrame,*[1] Gioanna Gelli, Adolfo Lai and Maura Monduzzi

*Istituto Chimico, Università, 09100 Cagliari, Italy*

*Received July 23, 1975*

Grignard reagents, when complexed and dissolved by the common ethers, are often unreactive toward C–O single bonds.[2] A typical case is the reaction of 1,3-benzodioxoles with methylmagnesium iodide, which had to be carried out under heterogeneous conditions, between the substrate dissolved in an aromatic hydrocarbon and the insoluble organomagnesium compound.[3]

Reinvestigating such reaction, it has now been found that it proceeds as follows.




a, Z = $CH_3$
b, Z = H
c, Z = Cl

A partial report has been given.[4]

## Results

**Stoichiometry.** By cleavage of one or the other of the two O–$CH_2$ bonds, different products, i.e., II and III, are obtained when Z is not hydrogen.

According to a previous report[3] Ia and Ic give only IIa and IIc, respectively. This claim was based on GLC analysis of the corresponding phenols in the hydrolyzed product. Both couples of possible phenolic products IIa–IIIa and IIc–IIIc have been now prepared and it has been shown that in the conditions of the GLC analysis (see Experimental Section) the isomers cannot be resolved. Therefore the reaction products, after hydrolysis and extraction of the phenolic fraction, were analyzed by NMR spectroscopy. Methylethoxyphenols exhibit slightly different $CH_2$ quartets and $CH_3$ triplets (at higher fields by 0.02 ppm for IIa); both isomers could be identified and determined in the product mixture from Ia. For the chloroethoxyphenols IIc and IIIc, besides an analogous pattern of the $CH_2$ and $CH_3$ signals, an additional difference was found in the peaks of the aromatic protons: an apparent singlet centered at δ 6.70 ppm for IIc and a multiplet with resonance bands centered at 6.77 and 6.59 ppm for IIIc. Both isomers were identified in the product from Ic; their determination was made using the aromatic region of the spectrum.

Ratios $x_p$ = II/(II + III) and $x_m = 1 - x_p$ were evaluated. Results at different conversions and temperatures (from 50 to 68°C) were identical within experimental error. For the reaction of Ia, $x_p \simeq 0.58$ and $x_m \simeq 0.42$, while for the case of Ic, $x_p \simeq 0.25$ and $x_m \simeq 0.75$ were found.

Ethers I and the Grignard reagent were consumed in a 1:1 molar ratio. However, a twofold excess of $CH_3MgI$ was required in order to complete the reaction with good yields of phenols. The formation of a stoichiometric compound between I and the Grignard reagent was not detected. In fact, the solution, separated from the solid phase after a short reaction time, contained the theoretical amount of I and did not evolve gas by water treatment. On the contrary, when phenetole was added to the solution, in the presence of excess $CH_3MgI$, some of the latter was carried over into the solution. Product IIb bound $CH_3MgI$ in an approximate 1:1 ratio.

Usually, the reactions were carried out on 6 mmol of I in 20 ml of toluene and 18 mmol of $CH_3MgI$. The latter was partially coordinated to diethyl ether (about 0.1 mol of

$Et_2O$/mol $CH_3MgI$) since it was obtained from an ethereal solution by applying heat, reduced pressure, and repeated toluene additions in order to strip out the ether.

The reaction was also carried out on Ib in the presence of $FeCl_3$. For Ib, $CH_3MgI$, and $FeCl_3$, initially present as 6, 24 and 6 mmol, respectively, the reaction proceeded at about the same rate as the standard reaction (without $FeCl_3$) at the same temperature. In blank experiments, $FeCl_3$ slowly decomposed $CH_3MgI$ with formation of methane and ethane.

## Discussion

The structure of solid Grignard reagents has been investigated by x rays in the case of $C_2H_5MgBr$ and $C_6H_5MgBr$, both crystalline when solvated by two diethyl ether molecules.[5] The same authors reported, in the case of $C_6H_5MgBr$,[5a] that at high temperature and low pressure the ether content can be lowered, obtaining amorphous polymer forms. The present results on the partial desolvation of $CH_3MgI$ are in agreement with that report.

The presence in the solid reactant, viewed as a polymer, of unsolvated $CH_3MgI$ units justifies its reactivity toward 1,3-benzodioxoles.

Product distribution ratios independent of conversion agree with a scheme of two parallel reactions, involving the oxygen atom para or meta to the substituent. A chloro substituent favors meta attack relative to para. The latter is slightly favored by a methyl substituent. Moreover, an approximate evaluation of reaction rates has shown that Ic is about half as reactive as Ia and Ib, which have nearly the same reactivity. Therefore, the prevailing character of this process can be identified as mildly electrophilic. The attack of magnesium (as a surface atom of the solid Grignard reagent) on one of the oxygen atoms of the substrate (from the solution) is probably involved.

The possibility that the reaction had radical character has been considered. To this purpose, the action of $FeCl_3$ has been tested, since this and similar halides are able to cleave Grignard reagents at low temperature to produce free radicals.[2a] The production of methyl radicals did not enhance the reaction rate enough to suggest a free-radical mechanism.

## Experimental Section

**Materials.** Methylmagnesium iodide was prepared from commercial methyl iodide and magnesium turnings in diethyl ether. The reagent was titrated by acidimetric and gas-volumetric methods.[6] The two methods gave coincident results provided that 1 mol of $CH_3MgI$ was taken to correspond to two acid equivalents (complete oxidation of HI to $I_2$).

Toluene was reagent grade and was kept over sodium. Sublimed anhydrous ferric chloride was employed.

5-Substituted 1,3-benzodioxoles (Ia–c) were prepared as described.[7,8] 4-Substituted 2-ethoxyphenols (IIa–c) were obtained as reported;[3] the melting point of 4-chloro-2-ethoxyphenol was found to be 57°C.[9] 5-Methyl-2-ethoxyphenol (IIIa) was prepared as described.[3]

**5-Chloro-2-ethoxyphenol (IIIc).** Concentrated HCl (100 ml) was carefully dropped, during ca. 30 min, into a stirred suspension of granular tin (45 g) in an ethanolic solution (80 ml) of 2-ethoxy-5-nitrophenol (40.3 g).[10] Several hours later, the tin was precipitated as sulfide; from the filtered solution, 5-amino-2-ethoxyphenol hydrochloride was obtained by evaporation. The last step was carried by diazotization and Sandmeyer reaction in the presence of $Cu_2Cl_2$, followed by steam distillation, extraction by diethyl ether, drying of the ether layer, and removal of the solvent. The product was purified by column chromatography on silica gel (170–230 mesh), eluting with petroleum ether (bp 40–60°C). A liquid was obtained, pure by GLC, bp 282–284°C (760 mm), $n^{27}D$ 1.5480 (yield 5%). Anal. Calcd for $C_8H_9ClO_2$: C, 55.66; H, 5.26; H, 5.26; Cl, 20.54. Found: C, 55.5; H, 5.3; Cl, 20.6. NMR spectrum: $CH_3$, $\delta$ 1.30 (t, 3 H); $CH_2$, 3.92 (q, 2 H); OH, 5.65 (s, 1 H); H aromatic 6.5–6.8 (m, 3 H).

In an attempt to isolate the undescribed 5-amino-2-ethoxyphenol only tar was obtained.

**Reaction Conditions.** A Pyrex glass cylindrical vessel (40 $cm^3$) was equipped with a thermostatted jacket, an outlet on the bottom, reflux condenser, thermometer, nitrogen inlet tube, and connection to rotary pump, besides a helicoidal stirrer, which was usually operated at 850 rpm.

Partial desolvation of the Grignard reagent was obtained by heating the ethereal solution (12–15 $cm^3$) up to about 90°C under stirring in the reaction vessel, applying a reduced pressure (5–10 Torr) and adding toluene (15–20 $cm^3$) under nitrogen. This stripping operation was repeated at least four times under continued stirring. A thick paste was finally obtained; the residual diethyl ether was determined by total decomposition of the organomagnesium compound, suspended in toluene, by a slight excess of $FeCl_3$ at 20°C, followed by GLC analysis. One mole of $CH_3MgI$ was found to correspond to 0.67, 0.31, 0.25, 0.10, and 0.10 mol of $Et_2O$ after successive stripping operations (from one to five, respectively).

For reaction, the 1,3-benzodioxolic derivative and toluene were added, usually thermostatting at a temperature in the range 50–70°C. After a time ranging from 2 min to 6 hr (conversion from 5 to 80%) the whole content of the vessel was discharged into ice–water, the mixture was made acidic by 10% aqueous $H_2SO_4$, the organic layer separated, and the aqueous layer extracted three times by diethyl ether. The combined organic layers were either analyzed by GLC in order to evaluate the conversion, or treated by alkaline extraction in order to isolate the phenolic product for NMR analysis.

**Reaction Products.** GLC analysis of hydrolyzed reaction products showed the following average yields: IIa + IIIa, 91%; IIb, 88%; IIc + IIIc, 68% of the theoretical.

The unhydrolyzed product from a reaction of Ib at 68°C in standard conditions was separated from the unreacted Grignard reagent, since the former was in the form of light flakes suspended in toluene and the latter in the form of thick paste. Such reaction product was examined by water decomposition and parallel gas-volumetric and GLC analyses; methane and 2-ethoxyphenol (IIb) were found in the molar ratio 1.08:1.

**GLC Analysis.** Quantitative analyses were performed on a preparative Perkin-Elmer F-21 flame-ionization chromatograph, fit for analytical GLC. The column (2 m i.d. 2 mm) contained 10% SE-301 and 5% neopentyl glycol adipate on Chromosorb P (30–60 mesh). Nitrogen (16 $cm^3$ $min^{-1}$) was used as carrier. Temperature was programmed from 50 to 150–170°C (heating rate 9°C $min^{-1}$). Cumene was used as internal standard and correction factors were determined for all substances.

**NMR Measurements.** The $^1H$ NMR spectra were recorded on a Varian HA-100 spectrometer operating at room temperature. Resonance shift values are reported in parts per million relative to hexamethyldisiloxane as internal reference. All samples were 0.1–0.2 $M$ $CCl_4$ solutions.

**Acknowledgment.** Financial support from Consiglio Nazionale delle Ricerche (Rome) is acknowledged.

**Registry No.**—Ia, 7145-99-5; Ib, 274-09-9; Ic, 7228-38-8; IIIc, 57428-47-4; methylmagnesium iodide, 917-64-6; 2-ethoxy-5-nitrophenol, 7260-32-4.

## References and Notes

(1) Istituto di Chimica Fisica, Università, 20133 Milano, Italy.
(2) (a) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances", Prentice-Hall, Englewood Cliffs, N.J., 1954, Chapter 15; (b) S. Patai, Ed., "The Chemistry of the Ether Linkage", Interscience, New York, N.Y., 1967.
(3) S. Cabiddu, A. Maccioni, and M. Secci, *Gazz. Chim. Ital.*, **98**, 800 (1968), and references cited therein.
(4) P. Beltrame, G. Gelli, A. Lai, and A. Loi, International Symposium on Nucleophilic Substitution, Pocono Manor, Pa., April 1975, Communication No. 16.
(5) (a) G. D. Stucky and R. E. Rundle, *J. Am. Chem. Soc.*, **85**, 1002 (1963); (b) L. J. Guggenberger and R. E. Rundle, *ibid.*, **86**, 5344 (1964).
(6) H. Gilman, P. D. Wilkinson, W. P. Fishel, and C. H. Meyers, *J. Am. Chem. Soc.*, **45**, 150 (1923).
(7) W. Bonthrone and J. W. Cornforth, *J. Chem. Soc. C*, 1202 (1969).
(8) E. Mameli, *Gazz. Chim. Ital.*, **36**, 382 (1906).
(9) A comparison with a sample of the product previously described[3] has confirmed this value of the melting point; the previously reported melting point of 164–166°C was a misprint.
(10) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, 933 (1917).

## Organic Structure Characterization by Natural-Abundance Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy. Penicillin and Cephalosporin Derivatives[1]

*Summary:* The $^{15}N$ resonances of a series of penicillin and cephalosporin derivatives have been detected at the natural-abundance level; crude structure–chemical shift correlations can be ascertained.

*Sir:* We report here (Table I) preliminary results of an examination of structurally complex organic molecules by $^{15}N$ NMR spectroscopy at the natural-abundance level (0.36%) of this isotope. Our results demonstrate the practicability of the technique as a complement to other types of NMR studies and illustrate some operational requirements for its success. Previous natural-abundance spectra of the insensitive (0.1% that of $^{1}H$ for an equal number of nuclei) $^{15}N$ nucleus have been of small molecules as neat liquids or as highly concentrated solutions, or have required very long total accumulation times.[2] Very recently, the natural-abundance spectrum of an amino sugar has been reported.[3]

To optimize signal strength, soluble ester derivatives of the title compounds were chosen; concentrations were in the range of 1–2.5 *M*.[4] The large molecular sizes and the high solution viscosity were expected to increase molecular correlation times and shorten $T_1$ values.[5] No paramagnetic complexes were used to further shorten $T_1$.[6] Noteworthy is the fact that, under the conditions used,[7] no signals were obtained from small molecules which did not have proton-bearing nitrogen atoms (e.g., nitrobenzenes, pyridines), even as pure liquids, in the absence of a paramagnetic additive. Additionally, the phases of the nitrogen resonances in most of the compounds studied here had the same polarity. Since the nuclear Overhauser effect (NOE) inverts a $^{15}N$ resonance because of the negative magnetic moment of $^{15}N$,[8] this observation suggests that even the nonprotonated lactam nitrogen experiences a NOE, although we do not know whether this leads to an intensity enhancement. In the most favorable cases, adequate signal-to-noise ratios were obtained in 2 hr (Figure 1), while at worst overnight runs were employed. Peak assignments were based on known $^{14}N$ shifts[9] and were confirmed for **1b** by increasing the pulse angle and repetition rate (Figure 2). As expected, the signal of the secondary amide nitrogen increased in intensity while that of the lactam disappeared, owing to its anticipated longer $T_1$ value.

Table I
$^{15}N$ Chemical Shifts of Antibiotic Derivatives[a]

| Compd | Concn, *M* | *t*,[b] hr | S/N[c] | $\delta_N$, ppm Lactam | Amide | Other |
|---|---|---|---|---|---|---|
| 1a | 1.0 | 10.9 | 15 | 134.77 | 80.52 | |
| 1b | 2.5[d] | 1.8[e] | 10[e] | 134.30 | 85.13 | |
| 2 | 1.4 | 2.1 | 11 | 106.10 | 78.03 | |
| 3 | 1.4 | 12.5 | 19 | 121.56 | 74.04 | |
| 4 | 2.0[f] | 10.2 | 12 | 130.78 | 85.89 | 185.95 |
| 5 | 1.7 | 10.9 | 22 | 117.29 | 78.91 | |
| 6 | 1.3[f] | 14.3 | 25 | 129.87 | 83.84 | 9.68 |

[a] In parts per million downfield from external 2.9 *M* $^{15}NH_4Cl$ in 1 *M* HCl contained in a 2-mm capillary. Experimental error was ±0.1 ppm. Solvent was dioxane except as noted. [b] Total accumulation time. [c] Signal-to-noise ratio of strongest peak. [d] In benzene. [e] For *t* 16.9, S/N 38. [f] In $D_2O$.

Structure-induced changes in the chemical shifts are

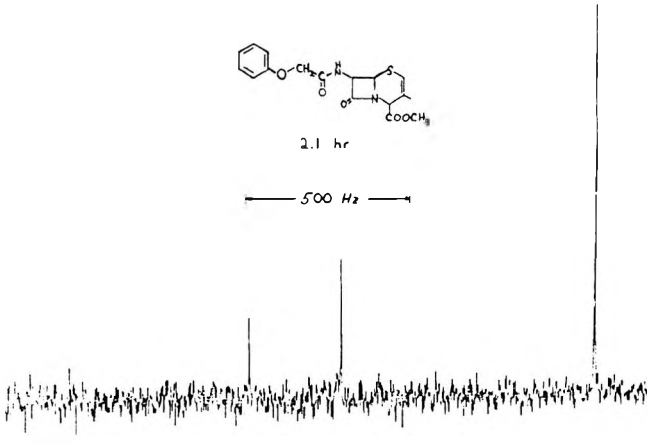



**Figure 1.** Natural-abundance $^{15}N$ spectrum of $\Delta^2$-cephalosporin V methyl ester, obtained after 2597 transients with a 30° pulse width and 2.9-sec repetition rate. The highest field signal is that of the ammonium chloride reference.

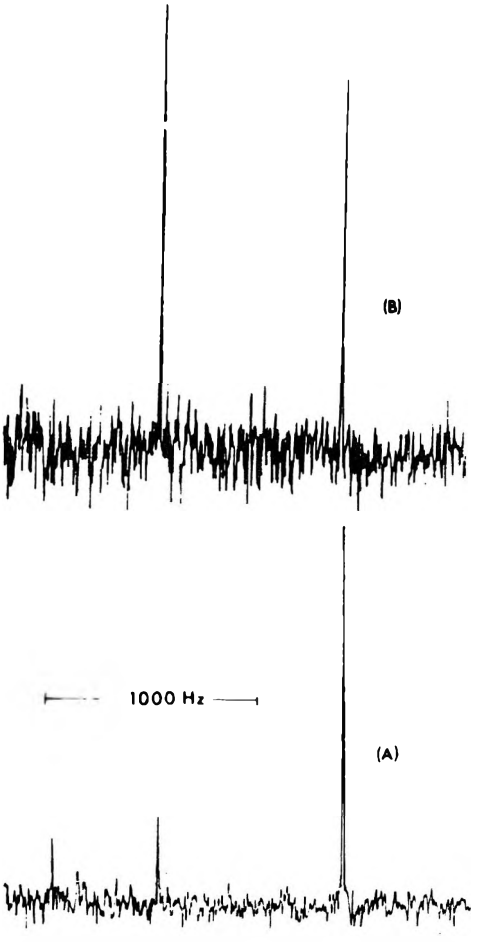
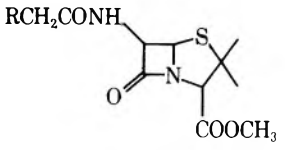
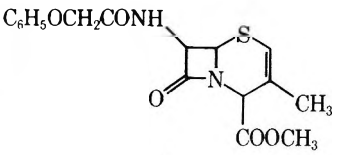



**Figure 2.** Natural-abundance $^{15}N$ spectra of penicillin G methyl ester (**1b**), obtained after 2000 transients with (a) a 30° pulse width and 3.2-sec repetition rate and (b) a 45° pulse width and 1.2-sec repetition rate. The highest field signal in each case is that of the ammonium chloride reference.

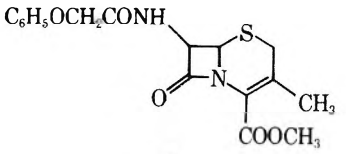
consistent with observations on small molecules.[2a] Thus, introduction of an oxygen $\gamma$ to a nitrogen causes an upfield shift (**1a** vs. **1b**) comparable with that observed in analogous $^{13}C$ spectra.[10] When **1a** is converted to its sulfoxide (**5**) both nitrogens experience upfield shifts but to different extents, probably reflecting both geometrical (cis vs. trans) and structural (sulfonyl vs. oxygen) contributions. Insofar as **3** and **6** are appropriate models, ionization of the 4-carboxyl group appears to have a larger effect on the chemical shift of the lactam nitrogen than would be observed for a carbon at the analogous position.[11]



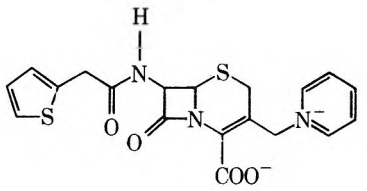

**1a**, R = $C_6H_5O$
**1b**, R = $C_6H_5$



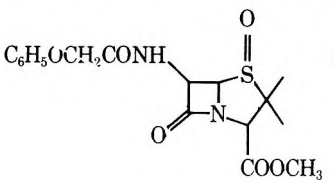

**2**



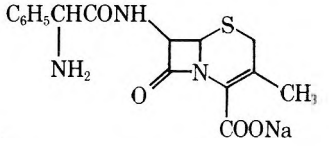

**3**




**4**




**5**




**6**

Of special interest are the lactam nitrogen resonance positions in **1–3**. The 30-ppm change in conversion from the five- to the six-membered ring (**1** vs. **2**) is not readily explicable. Because the lactam nitrogen in **2** is essentially planar,[12] increased amide conjugation would be expected to have induced a downfield shift. The corresponding nitrogen in **3** is less planar than in **2**, with concomitant decreased amide conjugation. Here, however, enamine-type conjugation is possible, and indeed the difference in resonance positions between **2** and **3** is comparable with that between cyclohexylamine and aniline.[2a] It may be that the nitrogen resonance position is insensitive to minor changes in the degree of amide delocalization.

Work is in progress to determine if the nitrogen chemical shifts of this class of compounds, including commercially available ones such as **4** and **6**, may be correlated with biological and pharmacological properties.

**Acknowledgments.** This work was supported by CUNY Faculty Research Award 10588 and by the U.S. Public Health Service, Grant 21148 from the Division of General Medical Sciences. Funds for the spectrometer were supplied in part by National Science Foundation Grant GP-37025. We are pleased to acknowledge the encouragement, advice, and samples provided by several research personnel of the Lilly Research Laboratories.

## References and Notes

(1) Reported in part at the 16th Annual Experimental NMR Conference, Asilomar, Pacific Grove, Calif., April 23, 1975, and at the 169th National Meeting of the American Chemical Society, Philadelphia, Pa., April 11, 1975.
(2) CW mode: (a) R. L. Lichter and J. D. Roberts, *J. Am. Chem. Soc.*, **94**, 2495, 4904 (1972); (b) R. L. Lichter and J. D. Roberts, *Org. Magn. Reson.*, **6**, 636 (1974). FT mode: (c) J. M. Briggs, L. F. Farnell, and E. W. Randall, *J. Chem. Soc. D*, 680 (1971); (d) P. S. Pregosin, A. I. White, and E. W. Randall, *ibid.*, 1602 (1971); (e) T. Suzuki, T. Yamaguchi, and M. Imamari, *Tetrahedron Lett.*, 1809 (1974); (f) G. Adler and R. L. Lichter, *J. Org. Chem.*, **39**, 3547 (1974); (g) D. W. Moore and W. M. Tolies, 15th Annual Experimental NMR Conference, Raleigh, N.C., April 29, 1974; (h) A. J. DiGioia, E. H. Cole, and R. L. Lichter, 15th Annual Experimental NMR Conference, Raleigh, N.C., 29 April 1974; (i) R. L. Lichter, *J. Magn. Reson.*, **18**, 367 (1975).
(3) B. Coxon, *Carbohydr. Res.*, **35**, C1 (1974).
(4) In the case of **6** the concentration in fact is not known because the substance precipitated during the course of the experiment.
(5) E.g., R. A. Goodman, E. Oldfield, and A. Allerhand, *J. Am. Chem. Soc.*, **95**, 7553 (1973).
(6) L. F. Farnell, E. W. Randall, and A. I. White, *J. Chem. Soc., Chem. Commun.*, 1159 (1972).
(7) Proton noise-decoupled spectra were obtained in 10-mm o.d. tubes using a JEOL PS/PFT-100 spectrometer equipped with the EC-100 data system and fitted with a probe insert designed to improve sensitivity.[2h] In general, a frequency range of 2 kHz with 8K words for FID accumulation was employed, using 30–45° pulses and repetition rates of 3–4.5 sec. No attempts were made to optimize these conditions, which were chosen because spectra could be obtained reliably.
(8) R. L. Lichter and J. D. Roberts, *J. Am. Chem. Soc.*, **93**, 3200 (1971).
(9) P. Hampson and A. Mathias, *Mol. Phys.*, **11**, 541 (1966).
(10) (a) R. A. Archer, R. D. G. Cooper, P. V. DeMarco, and L. F. Johnson, *Chem. Commun.*, 1291 (1970); (b) E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Am. Chem. Soc.*, **97**, 322 (1975).
(11) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, pp 147, 150.
(12) R. M. Sweet, in "Penicillins and Cephalosporins", E. H. Flynn, Ed., Academic Press, New York, N.Y., 1972, Chapter 7.

**Robert L. Lichter***
*Department of Chemistry*
*Hunter College of the City University of New York*
*New York, N.Y. 10021*

**Douglas E. Dorman**
*Lilly Research Laboratories, Eli Lilly and Company*
*Indianapolis, Indiana 46202*

*Received August 11, 1975*

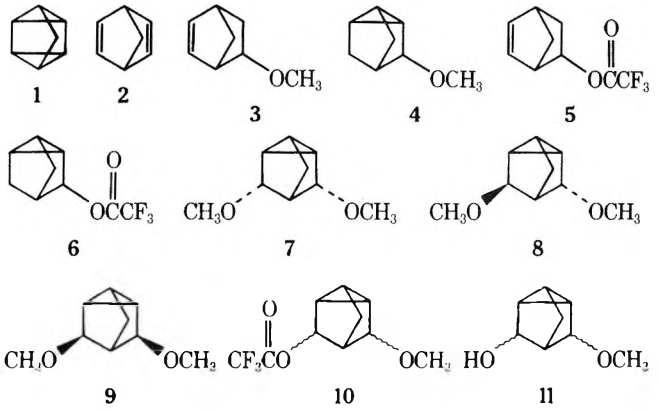
## Silver(I)-Promoted Reactions of Strained Hydrocarbons. Oxidation vs. Rearrangement

*Summary:* The reaction between silver trifluoroacetate and quadricyclene in methanol has been studied with the aid of an interfaced GC–MS data acquisition system. In addition to a Bronsted acid and silver metal, the products include norbornadiene (**2**), 3-methoxy-5-norbornene (**3**), 3-methoxynortricyclene (**4**), 3-trifluoroacetoxy-5-norbornene (**5**), 3-trifluoroacetoxynortricyclene (**6**), three isomeric 3,5-dimethoxynortricyclenes (**7**, **8**, and **9**), 3-methoxy-5-trifluoroacetoxynortricyclene (**10**), 3-methoxy-5-hydroxynortricyclene (**11**), and methyl trifluoroacetate. The formation of the various products as a function of time was monitored by gas chromatography. Finally, the formation of **7**, **8**, **9**, **10** and **11** along with acid and $Ag^0$ is interpreted as a two-electron redox reaction.

*Sir:* We wish to present evidence that oxidation occurs when certain strained hydrocarbons are treated with Ag(I) salts. Such a process was first proposed in 1971 by Kaiser, Childs, and Maitlis, who studied the action of various Lewis acids on tri-*tert*-butylprismane,[1] but their suggestion has since received little attention. We have been investigating some Ag(I)-promoted reactions of various quadri-

cyclenes and have been impressed by the ability of those compounds to reduce Ag(I) to the metallic state. For example, we recently reported that treatment of quadricyclene (1) with silver trifluoroacetate in methanol leads to 89% reduction of Ag(I) to $Ag^0$ and to Bronsted acid production.[2] Three organic products were tentatively identified (2, 3, and 4), but they provided no clue to the origin of silver metal. It is intriguing that while other strained hydrocarbons such as the bicyclo[1.1.0] butanes, cubanes, homocubanes, and tricyclo[4.1.0.$0^{2,7}$]heptanes undergo rearrangement in the presence of silver ion, they have not been reported to reduce Ag(I) to $Ag^0$.[3]

The reaction between silver trifluoroacetate (0.19 M) and 1 (0.24 M) in methanol at room temperature leads to a complex mixture of organic products. However, by utilization of an interfaced GC–MS data acquisition system, we have finally completed a detailed product study and have identified a group of materials which are intimately linked to Ag(I) reduction and to acid production. The products include norbornadiene (2), 3-methoxy-5-norbornene (3), 3-methoxynortricyclene (4), 3-trifluoroacetoxy-5-norbornene (5), 3-trifluoroacetoxynortricyclene (6), the isomeric 3,5-dimethoxynortricyclenes (7, 8, and 9), 3-methoxy-5-trifluoroacetoxynortricyclene (10), 3-methoxy-5-hydroxynortricyclene (11), and methyl trifluoroacetate.




All products were initially identified by GC–MS analysis of crude product mixtures. Molecular ions were observed for all compounds except 5 and 6, which yielded low quality spectra under the experimental conditions. The isomeric relationship between 7, 8, and 9 is clearly revealed in the similarity of their mass spectra, each of which exhibits a base peak at *m/e* 75 $(CH_3OCHOCH_3)\cdot^+$. The structures of 2, 3, 4, 5, 6, 8, and 9 were subsequently confirmed by comparison of their GC retention times and mass spectra (except for 5 and 6) with those of authentic materials. Further, a small quantity of 9 was isolated and subjected to NMR analysis (microcell), and the molecular formulas of 8 and 9 were rigorously established by mass measurement of their molecular ions: 8 (154.0990), 9 (154.0982). The structure assigned to 7 was inferred from its molecular formula (mol wt 154.0997), its obvious relationship to 8 and 9, and a GC demonstration that it is not the dimethyl ketal of nortricyclanone.[4] The structure of 11 was confirmed by mass measurement of its molecular ion (140.0820), and by ir and NMR analysis of a small collected sample. Finally, the structure assigned to 10, based initially on its mass spectrum, was verified by GC observation of its ultimate conversion, under the reaction conditions, to the alcohol 11. That this is possibly a transesterification reaction was indicated by GC–MS detection of methyl trifluoroacetate in the reaction mixture.

The progress of the reaction was followed by GC analysis of injected aliquots, peak areas being determined by electronic integration and taken from digital output. It was necessary to utilize two separate columns to resolve the product groups 1–6 (SE-30) and 7–11 (Carbowax). The results are summarized in Figure 1. It can be seen that 1 was largely reacted after 2 h and that 11 is clearly a secondary product. Further, some norbornadiene is consumed in secondary reactions, possibly through conversion to 5 and 6 by reaction with trifluoroacetic acid, also a reaction product.

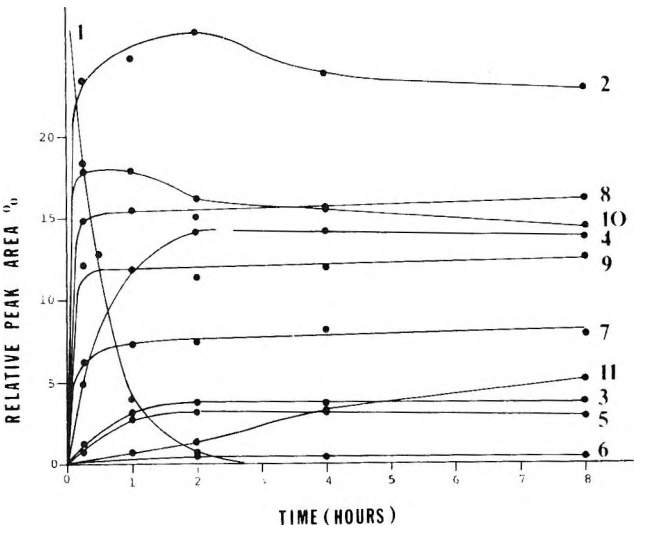
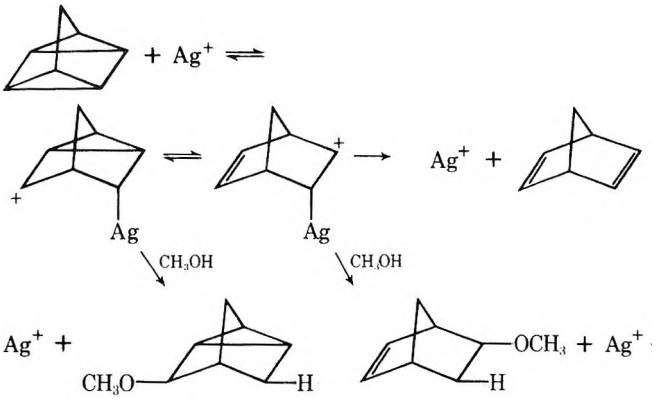
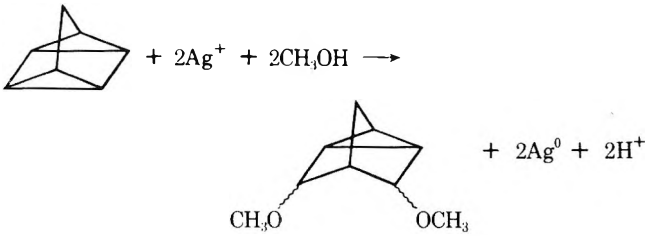



**Figure 1.** Product composition with time for the reaction of 1 with silver trifluoroacetate in methanol.

The formation of 2, 3, 4, 5, and 6 is consistent with the conventional argentation–deargentation pathway below. It




is significant, however, that this mechanism does not account for Ag(I) reduction or for acid production, but that Ag(I) is ultimately returned to the reaction medium. Moreover, the formation of 7, 8, 9, 10, and 11 cannot be so rationalized. Instead, a two-electron oxidation accounts for the precipitation of $Ag^0$, the production of protic acid, and for the observed organic products. A very recent study by




Brettle and his co-workers[5] of the anodic oxidation of 1 in methanolic sodium methoxide corroborates this view. Diethers 8 and 9 were identified as the major products.

Finally, inspection of *adiabatic* ionization potentials allows a prediction as to when oxidation of strained hydro-

carbons by Ag(I) should be important. For example, recently reported ionization potentials for 1,[6] cubane,[7] and tricyclo[4.1.0.0$^{2,7}$]heptane[6] are 7.40, 8.74, and 8.15 eV, respectively. Hence, the reduction of silver ion to $Ag^0$ (IP 7.57 eV) should be energetically favorable with 1 but not with the latter two hydrocarbons. We note, however, that oxidation potentials in methanol, when they are measured, may not follow the same trend as gas-phase ionization potentials, and the above data must be regarded as merely indicative.

### References and Notes


(1) K. L. Kaiser, R. F. Childs, and P. M. Maitlis, *J. Am. Chem. Soc.*, **93**, 1270 (1971).
(2) G. F. Koser, P. R. Pappas, and S.-M. Yu, *Tetrahedron Lett.*, 4943 (1973).
(3) For leading references, see L. A. Paquette, *Acc. Chem. Res.*, **4**, 280 (1971).
(4) We wish to thank Dr. Paul G. Gassman of the University of Minnesota for a sample of 3,3-dimethoxynortricyclene.
(5) A. J. Baggaley, R. Brettle, and J. R. Sutton, *J. Chem. Soc., Perkin Trans. 1*, 1055 (1975).
(6) G. N. Taylor, *Chem. Phys. Lett.*, **10**, 355 (1971).
(7) N. Bodor, M. J. S. Dewar, and S. O. Worley, *J. Am. Chem. Soc.*, **92**, 19 (1970).



**Gerald F. Koser,* J. Neil Faircloth**

*Department of Chemistry*
*The University of Akron, Akron, Ohio 44325*

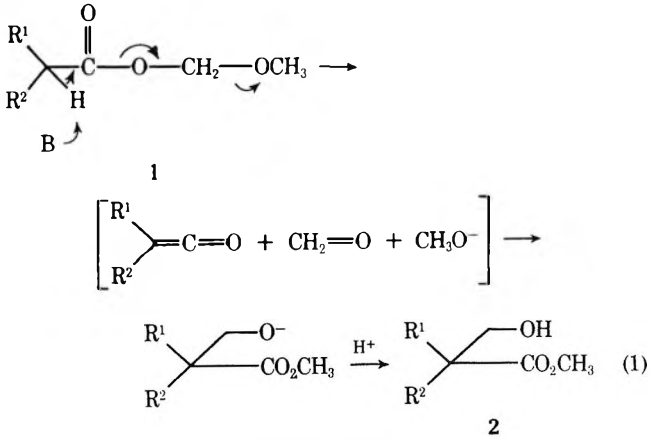

*Received October 1, 1975*

---

## Fragmentation–Recombination of Methoxymethyl Ester Enolates. A Novel Method for Preparation of Hydracrylic and Glycidic Esters

*Summary:* Methoxymethyl ester enolates undergo fragmentation to ketenes, formaldehyde, and methoxide ion which recombine to give hydracrylic and glycidic esters in good yield.

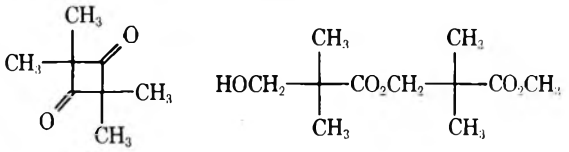
*Sir:* A variety of ester enolates have been prepared by reaction of lithium *N*-dialkylamides with esters at low temperature.[1] Although solutions of these ester enolates were considered to be stable even at room temperature, an interesting opportunity for reaction exists with enolates generated from methoxymethyl esters, (eq 1). Thus, heterolytic



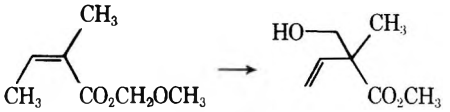
fragmentation[2] might be expected to occur as shown; in principle, recombination of the fragments should give the more stable hydracrylate ion. Herein, we report the realization of such a fragmentation–recombination and briefly discuss the mechanism and synthetic potential of the process.

Methoxymethyl esters were conveniently prepared in excellent yield by reaction of sodium carboxylates (sodium hydride + carboxylic acid) with chloromethyl methyl ether in refluxing tetrahydrofuran (THF)–hexamethylphosphoric triamide (HMPA, 1 equiv).

Addition of a THF solution of the methoxymethyl ester derived from isobutyric acid (**1**, $R^1 = R^2 = CH_3$) to 1.1 equiv of lithium diisopropylamide (LDA) in THF at −78° followed by quenching with $D_2O$ at −78° cleanly gave recovered **1** (50% D incorporation).[3] On the other hand, warming the solution of ester enolate to room temperature resulted in isolation of hydracrylate **2** ($R^1 = R^2 = CH_3$, 69% yield). Two minor reaction components were isolated and identified as dimethylketene dimer **3**[4] (~10%) and diester **4** (15%).[5] In similar fashion, except that HMPA was added to

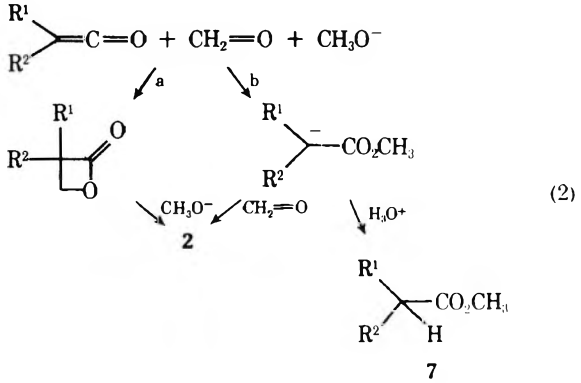


LDA before generation of the ester enolate,[6] the methoxymethyl ester derived from tiglic acid **5** gave the α-vinyl hydracrylate **6** in 61% isolated yield.



That a free alkoxide ion is involved in the process **1** → **2** was convincingly demonstrated by fragmentation–recombination of the ester enolate of **5** in the presence of ethoxymethyl ester enolate **1′** ($OCH_3$ replaced by $OCH_2CH_3$, $R^1 = R^2 = CH_3$); VPC comparison of the reaction components with previously isolated materials showed that four hydracrylic esters were present in about equal proportions and that these corresponded to the methyl and ethyl esters of **2** ($R^1 = R^2 = CH_3$) and **6**. Thus, intermediates derived from **1** and **5** must react indiscriminately with either methoxide or ethoxide generated in a fragmentation of the ester enolates (eq 1).[7]

At least two possible recombination paths to **2** have been considered (eq 2): a thermally allowed cycloaddition of ke-



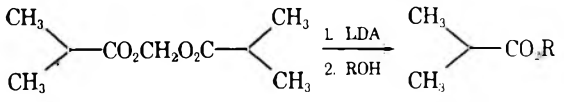
tene with formaldehyde and subsequent methoxide opening of the β-lactone (path a),[8] or ketene attack by methoxide to generate an ester enolate followed by trapping with formaldehyde (path b).

We do not favor path a for two important reasons. First, in all cases of fragmentation–recombination of **1**, trace to significant amounts of untrapped methyl ester **7** were detected; most dramatically, with **1** ($R^1 = CH_3$; $R^2 = OCOC_6H_5$), only methyl ester **7** ($R^1 = CH_3$; $R^2$ =

Table I
Preparation of 10 from 1 and 7 ($R^2$ = Br)

| No. | $R^1$ | % isolated yield: Fragmentation–recombination of 1 ($R^2$ = Br) | % isolated yield: Methyl ester 7 ($R^2$ = Br) enolate trapping with formaldehyde |
|---|---|---|---|
| 10a | $CH_3$ | 61 | 58 |
| 10b | $CH_2CH_3$ | 60 | 51 |
| 10c | $CH(CH_3)_2$ | 64 | 61 |

$OCOC_6H_5$) was isolated in 73% yield. Second, with methylene isobutyrate **8**, mainly isobutyric acid (**9a**) was isolated on quenching the LDA reaction with water and similarly methyl isobutyrate (**9b**) with methanol. These data indi-




**8** **9a**, R = H
**b**, R = $CH_3$

cate that nucleophilic attack of the ketene by methoxide precedes addition of formaldehyde (path b) and that, when the nucleophile generated in the fragmentation step is unreactive (isobutyrate), dimethyl ketene remains in solution to react with added water or methanol.

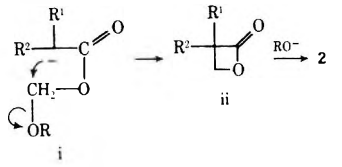
The viability of the second step in eq 2 (path b) was demonstrated by treatment of methyl ester lithium enolates (generated in the usual manner) with formaldehyde vapors and isolation of the corresponding hydracrylates **2** in yields comparable with those in the fragmentation–recombination process [2, $R^1 = R^2 = CH_3$, 60%; **6**, 60% (see Table I)]. Although the condensation of formaldehyde with regiospecifically generated ketone[9] and lactone[10] enolates has recently been reported, the analogous reaction described here with ester enolates seems not to have been previously cited. In any event, trapping ester enolates with formaldehyde and fragmentation–recombination of alkoxymethyl ester enolates should prove useful for preparation of many $\alpha,\alpha$-disubstituted hydracrylates.[11,12]

We also have shown that these two methods are especially attractive for preparation of glycidic esters **10** derived from formaldehyde and $\alpha$-bromo esters (Table I). Because the standard Darsens reaction of $\alpha$-halo esters with formaldehyde gives glycidic esters in low yield,[13] we feel that the methodology described here clearly represents a valuable alternative for preparation of these important synthetic intermediates.[14]

**Acknowledgment.** This work was supported by the National Institutes of Health (Grant No. CA 16624-02).

## References and Notes

(1) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 2318 (1971).
(2) C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, **6**, 1 (1967).
(3) Significantly less than quantitative deuterium incorporation has been reported to occur on treatment of presumably pure ester enolates with $D_2O$; see ref. 1.
(4) L. L. Miller and J. R. Johnson, *J. Org. Chem.*, **1**, 135 (1936).
(5) Isolated by preparative gas chromatography on a 6 ft × ¼ in. aluminum column filled with 10% SE-30 on Chromosorb WAW, 80–100 mesh size. Occasionally, a minor and unidentified reaction component which eluted with 3 was detected.
(6) J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973).
(7) Here, the operationally indistinguishable mechanism involving cyclization of ester enolate i to a $\beta$-lactone ii followed by methoxide opening of ii to give **2** was excluded by failure to detect $\beta$-lactones in reactions




of **1**, consideration of the highly unfavorable transition state required for closure i → ii, and further suggestive experimental results (vide infra).
(8) H. E. Zaugg, *Org. React.*, **8**, 305 (1954).
(9) G. Stork and J. d'Angelo, *J. Am. Chem. Soc.*, **96**, 7114 (1974).
(10) P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1317 (1972).
(11) Preliminary experiments indicate that $\alpha$-monosubstituted hydracrylates may not be attainable by the fragmentation–recombination method; indeed, reactions of LDA with $\alpha$-monosubstituted methoxymethyl esters have resulted in complex mixtures of products.
(12) Recent methods for synthesis of $\alpha$-substituted hydracrylates are outlined in the following: P. E. Pfeffer, E. Kinsel, and L. S. Silbert, *J. Org. Chem.*, **37**, 1256 (1972), and J. L. Herrmann and R. H. Schlessinger, *Tetrahedron Lett.*, 2429 (1973).
(13) M. S. Newman, *Org. React.*, **5**, 413 (1949). Darsens reaction to give the ethyl ester analog of **10a** has been reported to occur in 20–30% yield.
(14) Yields for all compounds reported in this paper are for isolated (distilled) material of near 100% purity (NMR and VPC analysis). Compounds previously reported are **2** ($R^1 = R^2 = CH_3$), J. Falbe and N. Huppes, *Brennst. Chem.*, **48**, 46 (1967); **10a**, R. W. White and W. D. Emmons, *Tetrahedron*, **17**, 31 (1962); **10b**, H. Loato and J. Ruohonen, *Suom. Kemistilehti (B)*, **42**, 466 (1969).

**Arthur G. Schultz,* Mitchell H. Berger**
*Department of Chemistry, Cornell University*
*Ithaca, New York 14853*

*Received November 4, 1975*

## Cleavage of Esters by Superoxide[1]

*Summary:* The reaction of carboxylic esters with potassium superoxide in benzene in the presence of 18-crown-6 ether produces, upon aqueous work-up, the corresponding carboxylic acid and alcohol in good to excellent yields by a process which appears to involve an initial nucleophilic attack of $O_2^-$ at the carbonyl carbon and by the subsequent formation of intermediate peroxo species.

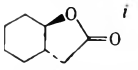
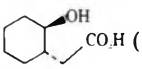
*Sir:* The beneficial and deleterious effects of superoxide in biological systems have become increasingly evident in recent years.[2] However, until recently,[3,4,5] virtually nothing was known of the reactivity of superoxide with common biological substrates.[6] Ester and peptide bonds are ubiquitous functionalities in biological systems. Here we wish to report that esters, but *not* amides or nitriles, undergo a reaction with superoxide which results in the cleavage of the ester functionality. Aqueous work-up affords the corresponding carboxylic acid in generally high yield. A summary of the results obtained on treatment of various representative substrates is given in Table I.

$$RCO_2R' \xrightarrow[2.\ H_3O^+]{1.\ KO_2\text{–}18\text{-crown-6},\ C_6H_6} RCO_2H + R'OH \quad (1)$$

In a typical experiment, a mixture of methyl octanoate (0.529 g, 3.34 mmol) and 18-crown-6 ether[7] (0.264 g, 1.00 mmol) dissolved in dry benzene (20 ml) was added to 0.710 g (10.0 mmol) of powdered potassium superoxide.[8] The resulting mixture was vigorously stirred for 24 h, then cautiously poured into 25 ml of water. The mixture was acidified with 6 M HCl and the organic layer separated. The remaining aqueous phase was extracted with an additional 25 ml of ether and the combined extracts dried ($MgSO_4$). GLC analysis indicated a 98% yield of *n*-octanoic acid.

The cleavage of carboxylate esters by superoxide seems applicable to a spectrum of esters including those of pri-

Table I
Reaction of Potassium Superoxide with Various Esters[a]

| Substrate[b] | Product(s) (%)[c] | Reaction time, h |
|---|---|---|
| $1\text{-}C_7H_{15}CO_2CH_3$ | 1-Octanoic acid (98) (68)[d] | 24 |
| $(CH_3)_3CCO_2CH_3$[e] | Pivalic acid (81) | 72 |
| $1\text{-}C_7H_{15}CO_2CH_2C_6H_5$ | 1-Octanoic acid (100)<br>Benzoic acid (55)[f] | 24 |
| $C_6H_5CO_2CH_2CH_3$ | Benzoic acid (88) | 24 |
| $1\text{-}C_7H_{15}CO_2CH(CH_3)_2$ | 1-Octanoic acid (98) | 72 |
| $CH_3CO_2CH(CH_3)C_6H_{13}$ | 2-Octanol (89) | 72 |
| $1\text{-}C_9H_{19}CO_2C_6H_5$ | 1-Decanoic acid (84)<br>Phenol (70)[g] | 8 |
| $1\text{-}C_7H_{15}CO_2C(CH_3)_3$[h] | 1-Octanoic acid (96) | 140 |
|  |  (85)[i] | 28 |
| $1\text{-}C_7H_{15}C(O)SC_4H_9$ | 1-Octanoic acid (93)<br>1-Butyl disulfide (33)[k] | 8 |
| $C_6H_5CH_2CH(NHCOCH_3)CO_2CH_2CH_3$[l] | *N*-Acetylphenylalanine (56)[m] | 24 |
| $(C_6H_5O)_3P(O)$ | Phenol (30)[g] | 24 |
| $(1\text{-}C_8H_{17}O)_3P(O)$ | 1-Octanol (<1)[n] | 72 |

[a] Unless otherwise indicated, all reactions were carried out at ambient temperature by adding a solution of ester (3.33 mmol) and 18-crown-6 ether (1.0 mmol) in dry benzene (20 ml) to powdered potassium superoxide. Vigorous stirring was maintained during addition and throughout the course of the reaction. [b] All esters, unless otherwise indicated, were prepared by adding the corresponding acid chloride to a solution of the appropriate alcohol or thiol in dry pyridine. [c] Yields were determined by GLC using a 6 ft × 0.25 in. column of 20% ethylene glycol adipate polyester–4% $H_3PO_4$ on Gas-Chrom Z [L. Metcalfe, *J. Gas Chromatogr.*, 1, 7 (1963)]. Yields are based on ester and were determined by the internal standard technique with response factors obtained from authentic samples. [d] Carried out in dry $Me_2SO$. [e] Purchased from Aldrich Chemical Co. [f] Control experiments established that under the reaction conditions, benzyl alcohol is oxidized to benzoic acid by superoxide in 62% yield. [g] Control experiments suggest that the low yield of phenol in this experiment results from the fact that this substance undergoes a subsequent reaction with an as yet undetermined reaction intermediate. [h] Prepared according to a procedure outlined by C. R. Hauser, B. E. Hudson, and B. Abramovitch, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 142. [i] M. S. Newman and C. A. VanderWerf, *J. Am. Chem. Soc.*, 67, 233 (1945). [j] Isolated yield after recrystallization from ethyl acetate–hexane, mp 105.0–105.5°C (lit.[i] 105.8–106.6°C). [k] Control experiments establish that superoxide reacts rapidly with alkyl thiols under these conditions. The resulting product, obtained in yields ranging from 60 to 75%, is the corresponding disulfide, RSSR. [l] Purchased from Sigma Chemical Co. [m] Isolated yield, after recrystallization from ethyl acetate, mp 151–153°C (lit.[18] 150–151°C). [n] Unreacted ester was recovered in 96% yield.

mary, secondary, and tertiary alcohols, as well as phenol and thiols. The use of dimethyl sulfoxide ($Me_2SO$) as a solvent resulted in shorter reaction times but reduced yields (cf. Table I). Reactions carried out in $Me_2SO$ in the absence of 18-crown-6 ether were slower than those performed in its presence. In all instances, ester cleavage is accompanied by the evolution of oxygen.

Although our understanding of the detailed course of this reaction is still incomplete, several observations allow a description of its general features. First, in view of the substantial nucleophilic character of the superoxide radical anion,[4] the possibility of oxygen–alkyl cleavage resulting in the nucleophilic displacement of a carboxylate anion was considered as a plausible pathway.[9] This mechanism is precluded, however, at least for esters of secondary and presumably other alcohols, by the fact that the reaction of superoxide with the acetate ester of (−)-(*R*)-2-octanol ($\alpha_{589}^{20}$ − 7.79°) yields (−)-(*R*)-2-octanol ($\alpha_{589}^{20}$ − 7.61°), corresponding to 99% net retention of configuration at the chiral carbon.

Second, an alternative mechanism involving the SN2 addition of $O_2^-$ to the carbonyl carbon remains reasonable and, moreover, is consistent with the apparent influence which the structure of the departing group exerts on the rate of reaction,[10] i.e., R′ = Ph > primary > secondary > tertiary, as indicated by a comparison of the half-life for reaction of phenyl, methyl, isopropyl, and *tert*-butyl *n*-octanoate under comparable conditions: $t_{1/2} \approx$ 1, 8, 15, and 26 h, respectively. Under similar conditions, the half-life of the reaction of potassium superoxide with the *n*-butanethiol ester of octanoic acid was 3 h. Understandably, the rate of these reactions can be enhanced by increasing the ratio of macrocyclic polyether to potassium superoxide. For example, the half-life for the reaction of *tert*-butyl *n*-octanoate decreased from 26 to 5 h when the ratio of 18-crown-6 ether to potassium superoxide was increased from 1:10 to 1:1.

Third, in addition to carboxylic esters, certain phosphate esters are also cleaved by superoxide. Thus, the reaction of triphenyl phosphate with potassium superoxide in benzene, in the presence of 18-crown-6 ether, proceeds to completion in less than 24 h. In contrast, tri-*n*-octyl phosphate showed no appreciable reactivity (96% recovery) after 72 h. Presumably this result is, at least in part, a reflection of the different leaving-group ability of phenoxide and *n*-alkoxide.

Finally, simple amides and nitriles seem largely unaffected by superoxide under conditions equivalent to those employed for ester cleavage.[11] As an example, benzamide and *N*-(α-phenylethyl)acetamide were recovered, respectively, in 84 and 99% yield after 8 days of treatment. Similar treatment of benzonitrile led to its recovery in 93% yield after 2 days. This yield was diminished to 73% when the reaction time was extended to 8 days.

Synthetically, the cleavage of carboxylate esters by superoxide is unexceptional since both we and others[12] have observed that under similar conditions, potassium hydroxide shows comparable reactivity. The significance of these observations, however, lies in their potential relevancy to the mechanism of certain biological oxidations. Thus, the observed cleavage of esters in these instances appears to involve nucleophilic substitution at the carbonyl carbon by $O_2^-$ and, although the precise nature of the subsequent intermediates involved in this reaction sequence remains uncertain, peroxo compounds are strongly implicated.[13] Indeed, similar species have been proposed as the oxygen-fix-

ing intermediates involved in several dioxygenase oxidations[14] and our own studies[15] show that the reactions of superoxide with such cosubstrates as, for example, α-ketoglutarate bear a resemblance to the action which certain dioxygenases have on these same substrates.[14]

## References and Notes


(1) Supported by the Research Corporation, Rutgers Research Council, Charles and Johanna Busch Memorial Fund, and Biomedical Sciences Support Grant.
(2) B. M. Babior, R. S. Kipnes, and J. T. Curnutte, *J. Clin. Invest.*, **52**, 741 (1973); J. T. Curnutte and B. M. Babior, *ibid.*, **53**, 1662 (1974); B. H. J. Bielski and P. C. Chan, *Arch. Biochem. Biophys.*, **159**, 873 (1973); P. C. Chan and B. H. J. Bielski, *J. Biol. Chem.*, **249**, 1317 (1974); **250**, 318 (1975).
(3) J. S. Valentine and A. B. Curtis, *J. Am. Chem. Soc.*, **97**, 224 (1975).
(4) J. San Filippo, Jr., C.-I. Chern, and J. S. Valentine, *J. Org. Chem.*, **40**, 1678 (1975); see also R. A. Johnson and E. G. Nidy, *ibid.*, **40**, 1680 (1975).
(5) For an application of these results to the synthesis of a naturally occurring prostaglandin, see E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Lett.*, 3183 (1975).
(6) I. Fridovich, *Annu. Rev. Biochem.*, **42**, 877 (1973).
(7) G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, *J. Org. Chem.*, **39**, 2445 (1974).
(8) Using a mortar and pestle and working in a glove bag under an atmosphere of dry nitrogen, lumps of potassium superoxide, purchased from K & K Chemicals, were ground to a fine consistency before use.
(9) Various nucleophilic reagents are capable of affecting *O*-alkyl cleavage of methyl and ethyl esters; see P. A. Bartlett and W. S. Johnson, *Tetrahedron Lett.*, 4459 (1970), and references cited therein.
(10) A similar influence and order has been observed in the rate of ester saponification, a second-order reaction involving nucleophilic substitution at the carbonyl carbon; see E. S. Gould, "Mechanism and Structure in Organic Chemistry", Holt, Rinehart and Winston, New York, N.Y., 1962, Chapter 9.
(11) This result is in strong contrast to the facile reaction that occurs between the hydroperoxide anion, $HO_2^-$, and nitriles; cf. K. Wiberg, *J. Am. Chem. Soc.*, **75**, 3961 (1953); **77**, 2519 (1955). This fact is surprising in view of the apparent nucleophilicity of superoxide. It may be a result of the considerable solvent differences (aprotic vs. protic) involved in these reactions.
(12) C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 7017 (1967).
(13) Several reaction sequences can be envisioned as pathways leading ultimately to the production of a carboxylate salt, for example

$$RCO_2R' + O_2^- \rightarrow RC(O)O_2\cdot + R'O^-$$

$$RC(O)O_2\cdot + O_2^- \rightarrow RC(O)O_2^- + O_2$$

$$RC(O)O_2^- \xrightarrow{H_2O} RCO_2^- \quad \text{(ref 16)}$$

$$RC(O)O_2^- + RCO_2R' \rightarrow RC(O)O_2(O)CR + R'O^-$$

$$RC(O)O_2(O)CR + O_2^- \rightarrow RCO_2^- + RC(O)O_2\cdot + O_2 \quad \text{(ref 17)}$$

(14) G. A. Hamilton, *Prog. Bioorg. Chem.*, **1**, 83 (1971).
(15) J. San Filippo, Jr., C.-I. Chern, and J. S. Valentine, *J. Org. Chem.*, submitted for publication.
(16) D. Swern, "Organic Peroxides", Vol. 1, D. Swern, Ed., Wiley, New York, N.Y., 1969, p 420.
(17) In this regard we have also noted that both acyl peroxides and peresters react readily with superoxide under the conditions cited in Table I. Thus, for example, reaction of benzoyl peroxide and *tert*-butyl perbenzoate with superoxide produced benzoic acid, isolated and recrystallized in yields, respectively, of 72 and 67% after 24 h.
(18) R. M. Herbst and D. Shemin, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 491.



**Joseph San Filippo, Jr.,* Louis J. Romano**
**Chuen-Ing Chern**
*School of Chemistry, Rutgers University*
*New Brunswick, New Jersey 08903*

**Joan S. Valentine**
*Department of Chemistry, Douglass College*
*Rutgers University, New Brunswick, New Jersey 08903*


*Received September 29, 1975*

## TOPICS IN CARBON-13 NMR SPECTROSCOPY, Volume 2

George C. Levy, *Florida State University, Tallahassee*

An up-to-date overview of research literature and available $^{13}C$ nuclear magnetic resonance texts and reviews written by researchers. Examines areas of interest to organic chemists, biochemists, biophys - cists, and molecular biologists, with investigations of organometallic chemistry, experimental methods, and the theory of spin-spin coupling.

Feb. 1976 approx. 496 pp. $27.50

## ORGANIC REACTIONS, Volume 23

Edited by William G. Dauben, *University of California, Berkeley*

Contents: Reduction and Related Reactions of $\alpha\beta$ Unsaturated Compounds with Metals in Liquid Ammonia. The Acyloin Condensation. Alkenes from Tosylhydrazones. Author Index, Volumes 1-23. Chapter and Topic Index, Volumes 1-23. Subject Index, Volume 23.

1975 approx. 528 pp. $27.50

# Solutions↔from↔Wiley

## ORGANIC SYNTHESES CUMULATIVE INDICES

Edited by Ralph L. Shriner, *Southern Methodist University, Dallas,* & Rachel H. Shriner

The time-saving, single reference source to the classified indices in all five Collective Volumes of Organic Syntheses.

Feb. 1976 approx. 464 pp. $22.50

## TECHNIQUES OF CHEMISTRY, Volume 8 Parts 1 & 2: Solutions and Solubilities

Michael R. J. Dack, *CSIRO, Central Communications Unit, Australia*

A collection of authoritative articles which examines the complex subject of solutions in terms of their industrial and biological significance. Material covers molecular thermodynamics, salvation of ions, influence of solvents on spectroscopy, chemical technology, molecular complex equilibria, gases, more.

| | | | |
|---|---|---|---|
| Part 1 | 1975 | 475 pp. | $29.50 |
| Part 2 | Feb. 1976 | approx. 528 pp. | $34.50 |

## ORGANIC ELECTRONIC SPECTRAL DATA, Volume XI, 1969

Edited by John P. Phillips, *University of Louisville,* Henry Feuer, *Purdue University,* Paul M. Laughton, *Carleton University, Canada,* & B. S. Thyagarajan, *University of Texas at San Antonio*

A compilation of data which serves as a quick, thorough reference on spectral maxima, extinction coefficients, and sources for ultraviolet and visible spectra of organic compounds. Extensively indexed.

1975 approx. 1057 pp. $42.00

## ORGANIC SYNTHESES, Volume 55

Edited by Sateru Masamune, *University of Alberta, Canada*

Thirty procedures which reflect the current interest of synthetic organic chemistry. Emphasis is on widely applicable, model procedures that illustrate important reactions.

Feb. 1976 approx. 160 pp. $11.95

## THE CHEMISTRY OF THE HYDRAZO, AZO AND AZOXY GROUPS, Parts 1 & 2

Edited by Saul Patai, *The Hebrew University, Jerusalem*

Partial Contents: Electronic Structures of the Azo, Azoxy, and Hydrazo Groups. Structural Chemistry. Thermochemistry of Hydrazo, Azo, and Azoxy Groups. Preparative Procedures. Mass Spectra of Hydrazo, Azo, and Azoxy compounds. Directing and Activating Effects. Formation and Fragmentation of Cyclic Azo Compounds. Author Index. Subject Index.

| | | | |
|---|---|---|---|
| Part 1 | 1975 | 597 pp. | $42.00 |
| Part 2 | 1975 | 591 pp. | $42.00 |

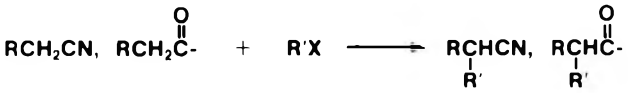
Available at your bookstore or write to Customer Information, Dept. A 5442

**WILEY-INTERSCIENCE**
a division of John Wiley & Sons, Inc.
605 Third Avenue
New York, N.Y. 10016
In Canada: 22 Worcester Rd., Rexdale, Ontario
Prices subject to change without notice. A 5442

# Phase-Transfer Catalysts

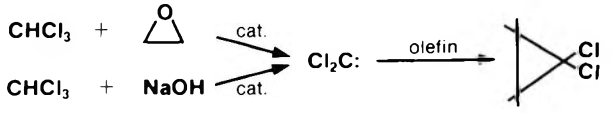
Phase-transfer catalysis has been applied to a great variety of organic reactions.[1,2] By this technique reactions are conducted in aqueous-organic two-phase systems in the presence of a phase-transfer catalyst, thus eliminating the necessity for anhydrous solvents. The most widely used phase-transfer catalysts are quaternary ammonium and phosphonium salts. The acceleration effects of these quaternary salts are so dramatic that they have become very important in preparative organic chemistry. Some successful applications of phase-transfer catalysts are:

**C-Alkylation**[1,2] (by *phase-transfer* or *ion-pair extraction*) of nitriles, ketones, malonates, β-diketones, β-cyanoacetates, β-ketoesters, β-ketosulfones, etc.

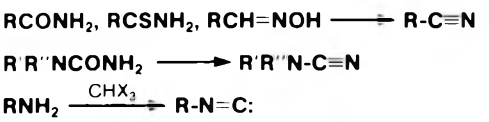


Alkylating reactivity: R'Cl > R'Br > R'I

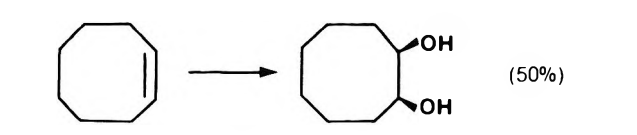
**Generation of Dichlorocarbene**[1,2] (in homogeneous or two-phase systems)



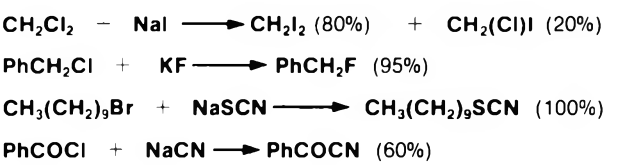
**Synthesis of Nitriles and Isonitriles**[2]



**Oxidation by $KMnO_4$**[1,2]



**Nucleophilic Displacements**[2-5]



Other Reactions:[1,2] **Hydrolysis of Esters and Sulfonyl Chlorides; Benzoin Condensation; Deuterium Exchange; $NaBH_4$ Reduction; Wittig Reaction.**


**References:**

1) **Review:** J. Dockx, *Synthesis*, 441 (1973).
2) **Review:** E.V. Dehmlow, *Angew. Chem., Intern. Ed. Engl.*, **13**, 170 (1974).
3) D. Landini and F. Rolla, *Chem. Ind.*, 534 (1974).
4) D. Landini, F. Montanari, and F. Rolla, *Synthesis*, 428 (1974).
5) K. E. Koenig and W. P. Weber, *Tetrahedron Lett.*, 2275 (1974).


**Quarternary Ammonium and Phosphonium Salts Useful as Phase-transfer Catalysts**

| | | |
|---|---|---|
| 85,657-6 | Adogen 464 | 100g $5.40; 500g $12.70 |
| 14,712-5 | Benzyltriethylammonium bromide | 25g $11.25; 100g $29.50 |
| 14,655-2 | Benzyltriethylammonium chloride | 25g $7.80; 100g $22.10 |
| 14,711-7 | Benzyltrimethylammonium bromide | 25g $10.90; 100g $28.75 |
| B3260-2 | Benzyltrimethylammonium hydroxide (Triton B), 40% in MeOH | 100g* $5.00 |
| B3280-7 | Benzyltriphenylphosphonium chloride | 25g $9.00; 38.9g† $15.00 100g $25.00 |
| 85,582-0 | Cetyltrimethylammonium bromide | 100g $7.35; 500g $24.50 |
| 14,111-9 | Methyltributylammonium iodide | 25g $8.40; 100g $22.00 |
| 17,242-1 | Tetrabutylammonium chloride | 25g $7.10; 100g $18.80 |
| 15,583-7 | Tetrabutylammonium hydrogen sulfate | 25g $11.15; 100g $29.40 |
| 17,878-0 | Tetrabutylammonium hydroxide, 40% in water | 50g* $10.20; 250g* $32.70 |
| 14,077-5 | Tetrabutylammonium iodide | 25g $4.50; 100g $11.00 |
| 14,002-3 | Tetraethylammonium bromide | 250g $10.35; 1kg $27.00 |
| 11,304-2 | Tetraethylammonium chloride | 25g $4.00; 100g $12.00 |
| 17,780-6 | Tetraethylammonium hydroxide, 20% in water | 100g* $6.05; 500g* $17.70 |

†Decimole unit
*Solution weights


## Aldrich Chemical Company, Inc.

Corporate Offices:
**Aldrich Chemical Co., Inc.**
**940 W. Saint Paul Ave.**
**Milwaukee, Wisconsin 53233**
**U. S. A.**

Great Britain:
**Aldrich Chemical Co., Ltd.**
**The Old Brickyard, New Road**
**Gillingham, Dorset SP8 4JL**
**England**

Belgium/
Continental Europe:
**Aldrich-Europe**
**B-2340 Beerse**
**Belgium**

West Germany/
Continental Europe:
**EGA-Chemie KG**
**7924 Steinheim am Albuch**
**West Germany**



15 CH.ED. 2519